Official Title: A Two-year, Phase III Randomized, Double-blind, Parallel-group, Placebo-controlled Trial to Evaluate the Safety, Efficacy, and Tolerability of 300 mg s.c. Secukinumab Versus Placebo, in Combination With SoC Therapy, in Patients With Active Lupus Nephritis

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Secukinumab (AIN457)

Clinical Trial Protocol CAIN457Q12301

A two-year, phase III randomized, double-blind, parallel-group, placebo-controlled trial to evaluate the safety, efficacy, and tolerability of 300 mg s.c. secukinumab versus placebo, in combination with SoC therapy, in patients with active lupus nephritis

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List of abbreviations

[redacted]	[redacted]
ACR	American College of Rheumatology
AE	adverse event
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ANA	anti-nuclear antibodies
ANCOVA	analysis of covariance
anti-dsDNA	Anti-double stranded DNA
[redacted]	[redacted]
aPTT	activated partial thromboplastin time
AST	aspartate aminotransferase
[redacted]	[redacted]
BMI	Body Mass Index
BAFF	B-cell activating factor
CFR	Code of Federal Regulation
CHMP	Committee for Medicinal Products for Human Use
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
[redacted]	[redacted]
CNIs	calcineurin inhibitors
COAs	Clinical Outcome Assessments
CRF	Case Report/Record Form (paper or electronic)
CRO	Clinician reported outcomes
CRR	Complete Renal Response
CT	computed tomography scan
CYC	cyclophosphamide
[redacted]	[redacted]
DMC	Data Monitoring Committee
DNA	deoxyribonucleic acid
EC	Ethics committee
ECG	Electrocardiogram
EDC	Electronic Data Capture
eGFR	estimated glomerular filtration rate
ELISA	Enzyme-linked immunosorbent assay
EMA	European Medicines Agency
ERA	Enthesitis-Related Arthritis
ERA-EDTA	European Renal Association – European Dialysis and Transplant Association
ESRD	end-stage renal disease
EULAR	European League Against Rheumatism
FACIT-Fatigue©	Functional Assessment of Chronic Illness Therapy - Fatigue

FDA	Food and Drug Administration
GCP	Good Clinical Practice
GGT	gamma-glutamyl transferase
h	hour
HbA1c	Hemoglobin A1c
HDL	High Density Lipoprotein
HIV	human immunodeficiency virus
HRQoL	health-related quality of life
hsCRP	High sensitivity C-reactive protein
i.v.	intravenous
ICH	International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use
IEC	Independent Ethics Committee
[redacted]	[redacted]
INR	International Normalized Ratio
IRB	Institutional Review Board
IRR	Individual Research Results
IRT	Interactive Response Technology
ISN	International Society of Nephrology
JIA	Juvenile idiopathic arthritis
JPsA	Juvenile psoriatic arthritis
[redacted]	[redacted]
LDL	Low Density Lipoprotein
LFT	Liver function test
[redacted]	[redacted]
LLN	lower limit of normal
LLQ	lower limit of quantification
LN	lupus nephritis
mAb	Monoclonal antibody
[redacted]	[redacted]
mCRR	modified Complete Renal Response
MedDRA	Medical dictionary for regulatory activities
mg	milligram(s)
mL	milliliter(s)
ml	milliliter(s)
MMF	Mycophenolate mofetil
MMRM	Mixed-Effect Model Repeated Measure
MPA	mycophenolic acid
MRI	Magnetic resonance imaging
mRNA	Messenger ribonucleic acid
nr-axSpA	non-radiographic axial spondyloarthritis

o.d.	once a day
p.o.	per oral
PA	Posterior / Anterior view
PCS	physical component summary
PD	pharmacodynamic(s)
PFS	Prefilled syringe
[redacted]	[redacted]
PK	pharmacokinetic(s)
PRR	partial renal response
PRO	Patient reported outcomes
PsA	Psoriatic arthritis
PsO	Plaque psoriasis
PT	Prothrombin time
PY	Patient Year
QoL	Quality of Life
RBC	red blood cell(s)
RNA	ribonucleic acid
RPS	Renal Pathology Society
s.c.	subcutaneous
SAE	serious adverse event
SARS-CoV2	Severe acute respiratory syndrome coronavirus 2
SD	standard deviation
SF-36	Medical Outcome Short Form (36) Health Survey
SGOT	serum glutamic oxaloacetic transaminase
SGPT	serum glutamic pyruvic transaminase
SLE	systemic lupus erythematosus
[redacted]	[redacted]
SoC	standard of care
SUSAR	Suspected Unexpected Serious Adverse Reactions
TBL	total bilirubin
TEAE	Treatment-emergent adverse event
TFQ	Trial Feedback Questionnaire
[redacted]	[redacted]
[redacted]	[redacted]
ULN	upper limit of normal
ULQ	upper limit of quantification
UPCR	Urine Protein-to-Creatinine Ratio
WBC	white blood cell(s)
WHO	World Health Organization

Glossary of terms

Assessment	A procedure used to generate data required by the study
Cohort	A group of individuals who share a common exposure, experience or characteristic, or a group of individuals followed-up or traced over time
Control drug	A study drug 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 participant in a time unit (e.g., 100 mg once a day, 75 mg twice a day)
Enrollment	Point/time of participant entry into the study at which informed consent must be obtained (i.e., prior to starting any of the procedures described in the protocol)
Estimand	As defined in the ICH E9(R1) addendum, estimand is a precise description of the treatment effect reflecting the clinical question posed by the trial objective. It summarizes at a population-level what the outcomes would be in the same participants under different treatment conditions being compared. Attributes of an estimand include the population, variable (or endpoint) and treatment of interest, as well as the specification of how the remaining intercurrent events are addressed and a population-level summary for the variable.
Intercurrent events	Events occurring after treatment initiation that affect either the interpretation or the existence of the measurements associated with the clinical question of interest.
Investigational drug	The study drug whose properties are being tested in the study; this definition is consistent with US CFR 21 Section 312.3 and Directive 2001/20/EC and is synonymous with “investigational new drug” or “test substance”
Investigational treatment	All investigational drug(s) whose properties are being tested in the study as well as their associated treatment controls. This includes any placebos, any active controls, as well as approved drugs used outside of their indication/approved dosage or tested in a fixed combination. Investigational treatment generally does not include other treatments administered as concomitant background therapy required or allowed by the protocol when used within approved indication/dosage.
Medication number	A unique identifier on the label of each study drug package in studies that dispense study drug using an IRT system.
Part	A single component of a study, which contains different objectives or populations within that single study. Common parts within a study are: a single dose part and a multiple dose part, or a part in patients with established disease and in those with newly-diagnosed disease.
Participant	A trial participant (can be a healthy volunteer or a patient). "Participant" terminology is used in the protocol whereas term "Subject" is used in data collection and for data analysis
Participant number	A unique number assigned to each participant upon signing the informed consent. This number is the definitive, unique identifier for the participant and should be used to identify the participant throughout the study for all data collected, sample labels, etc.
Period	A minor subdivision of the study timeline; divides phases into smaller functional segments such as Screening, Baseline, titration, washout, etc.
Randomization number	A unique identifier assigned to each randomized subject, corresponding to a specific treatment arm assignment
Screen Failure	A subject who is screened but is not treated or randomized
Stage	A major subdivision of the study timeline; begins and ends with major study milestones such as enrollment, randomization, completion of treatment, etc.
Study completion	Point/time at which the subject came in for a final evaluation visit or when study drug was discontinued whichever is later.
Study treatment	Any drug administered to the study participants as part of the required study procedures; includes investigational drug (s), control(s) or non-investigational medicinal product(s)

Study treatment discontinuation	Point/time when subject permanently stops taking study treatment for any reason; may or may not also be the point/time of premature subject withdrawal.
Treatment of interest	The treatment of interest and, as appropriate, the alternative treatment to which comparison will be made. These might be individual interventions, combinations of interventions administered concurrently, e.g., as add-on to standard of care, or might consist of an overall regimen involving a complex sequence of interventions. This is the treatment of interest used in describing the related clinical question of interest, which might or might not be the same as the study treatment.
Variable (or endpoint)	The variable (or endpoint) to be obtained for each participant that is required to address the clinical question. The specification of the variable might include whether the participant experiences an intercurrent event.
Withdrawal of consent (WoC)	Withdrawal of consent from the study occurs when the participant explicitly requests to stop the use of their data and biological samples (opposition to use data and biological samples) AND no longer wishes to receive study treatment AND does not agree to further protocol required assessments. This request should be made in writing (depending on local regulations) and recorded in the source documentation.

Amendment 1 (17-Feb-2023)

Amendment rationale

The key purposes of Amendment 1 are to:

Decrease the overall study sample size from 460 to 400 participants based on recent literature reporting results of Phase 3 studies in adult lupus nephritis populations (Furie et al 2020, Rovin et al 2021). In those two Phase 3 clinical trials (comparing voclosporin or belimumab versus placebo in combination with standard of care therapy with tapered doses of corticosteroids) with a study design similar to this current protocol, the complete renal response (CRR) rates at Week 52 for the placebo groups are lower than those reported in previous clinical trials in the same population (CRR rates at Week 52 in placebo arms were 23-25% versus a previously reported rate of 30% (Mysler et al 2013, Rovin et al 2012)). The placebo response rate in this study is therefore expected to be lower than originally assumed, which allows for a smaller sample size while retaining adequate statistical power.

1. Replace the O'Brien-Fleming method with the Pocock method for alpha spending so that the superiority analysis (at the second interim analysis) can utilize more alpha and achieve higher power. This adjustment is made to compensate for the delay of the study triggered by the COVID-19 pandemic.
2. Incorporate the estimand framework based on the ICH E9(R1) guideline "addendum on estimands and sensitivity analysis in clinical trials: to the guideline on statistical principles for clinical trials", adopted in November 2019, after the release of the original study protocol (version 00, dated 11-Oct-2019).
3. Address a Health Authority recommendation which was received for this study in 2020, pointing at the potential of corticosteroid overuse to confound the primary endpoint. The intercurrent event of "overuse of corticosteroid" was clearly defined and the strategy to handle it is specified as the non-responder composite endpoint strategy.
4. Clarify the normal estimated glomerular filtration rate as (eGFR) ≥ 60mL/min/1.73m2, which is a component of the primary endpoint.

In addition, further clarifications and corrections are made as specified below:

5. Add clarifying details to the secondary efficacy analyses.
6. Update the intercurrent event strategies for certain secondary estimands.
7. Re-calculate the power for the secondary analyses based on the new sample size.
8. Categorize the interim analyses as the first and second interim analyses. The first interim analysis includes the first futility analysis [redacted]. The second interim analysis contains the superiority interim analysis and a second futility analysis.

[redacted]

10. Removal of barrier method of contraception, which does not fulfill the criteria for highly effective contraception, and clarify that highly effective contraception is required during the study for any woman of childbearing potential due to Standard of Care background medications.

Lastly, Amendment 1 addresses commitments and comments received from EC/HAs to the original protocol, and introduces additional minor clarifications and administrative changes.

Changes to the protocol

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

The following sections have been changed in the amended protocol:

- Protocol Summary: Changes made to study participant number, and definition of active urinary sediment.
- Section 1: Information on recently approved treatments for LN and newly approved secukinumab indications were added.
- Section 2: The estimand framework has been added. Intercurrent events and the strategies to handle them were added in the endpoint definition.
- Section 2: Estimated glomerular filtration rate (eGFR) was clarified.
- Section 2: Exploratory objective endpoints was clarified.
- Section 3: Guidance added for retest of inclusion / exclusion assessments.
- Section 3: Information on the extension study was added.
- Section 4.4: Interim analyses were categorized as first and second interim analyses. Another futility analysis would be performed at the second interim analysis.
- Section 4.5: Reference for exposure- adjusted incidence rate of SAEs was added.
- Section 4.6: was added to address public health emergency mitigation procedures.
- Section 5: Total study sample size was updated from 460 to 400.
- Section 5: Definition of "active urinary sediment" as presence of cellular casts (white blood cell or red blood cell casts) or hematuria (> 5 red blood cells per high power field or above the laboratory reference range) was clarified
- Section 5.2: Exclusion criteria for barrier method of contraception removed, and guidance for country specific contraception requirements clarified.
- Section 5.2: Timeframe for chest X-ray, CT or MRI clarified.
- Section 6.1.4: Number of participants was updated from 230 to 200 per treatment arm
- Section 6.1.5: Information on extension study was added.
- Section 6.2.2: Updated information on administration of vaccines was added
- [redacted]
- Section 6.4: Details regarding return of Individual Results to Patients were added.
- Section 8.1: Clarification on screening period was added.
- Section 8.2.4: Clarification on Central Pathologist Charter for renal biopsy was added.
- Section 8.4: Verbiage on safety assessment in Public Health emergency was added.

- Section 8.5: Verbiage on Clinical outcome assessment in Public Health emergency was added.
- Section 8.5: Verbiage on additional spot urine was added for optional biomarker informed consent.
- [redacted]
- Section 11.4: Data Protection section was added to describe how data will be handled.
- Section 12.4: Components of the primary endpoint were clarified and intercurrent event strategies, sensitivity analysis, modified complete renal response and treatment policy estimand sections were updated.
- Section 12.5: Estimand definitions for the secondary variables removed.
- Section 12.6: Secondary efficacy endpoints were clearly stated.
- Section 12.7: Interim analyses were categorized as first and second interim analyses. Another futility analysis would be performed at the second interim analysis.
- Section 12.7: O'Brien-Fleming method was replaced with Pocock method for alpha spending so that the superiority analysis (at the second interim analysis) could utilize more alpha and achieve higher power. Note that the overall Type I error rate is still controlled.
- Section 12.7: The information proportion of the first and second interim analyses were altered due to the change of the overall sample size.
- Section 12.8: The overall sample size was changed from 460 to 400 based on an updated lower placebo response rate.
- Section 12.8: The powers for primary and secondary efficacy analyses were updated with the new sample size.
- Section 15: New references were added.

This protocol amendment also includes editorial revisions, corrections, and clarifications throughout the protocol to improve consistency. In addition, the term 'subject' is replaced throughout the protocol with the term 'participant' and 'patient'.

IRBs/IECs

A copy of this amended protocol will be sent to Institutional Review Boards (IRBs)/ Independent Ethic Committees (IECs) and Health Authorities.

The changes described in this amended protocol are substantial and require IRB/IEC and Health Authority approval according to local regulations prior to implementation.

The changes herein affect the Informed Consent. Sites are required to update and submit for approval a revised Informed Consent (Global Model) that takes into account the changes described in this protocol amendment.

Protocol summary

Protocol number	CAIN457Q12301
Full Title	A two-year, phase III randomized, double-blind, parallel-group, placebo-controlled trial to evaluate the safety, efficacy, and tolerability of 300 mg s.c. secukinumab versus placebo, in combination with SoC therapy, in patients with active lupus nephritis
Brief title	Study of safety, efficacy and tolerability of secukinumab versus placebo, in combination with SoC therapy, in patients with active lupus nephritis
Sponsor and Clinical Phase	Novartis Phase III
Investigation type	Biological
Study type	Interventional
Purpose and rationale	The purpose of this trial is to evaluate the efficacy and safety of subcutaneous secukinumab 300 mg compared to placebo, in combination with standard of care therapy (SoC), in patients with active lupus nephritis (ISN/RPS Class III or IV, with or without co-existing class V features). Background SoC will consist of induction therapy with mycophenolic acid (MPA) (which refers to Mycophenolate mofetil (MMF) (Cellcept® or generic equivalent), or enteric-coated MPA sodium (Myfortic® or generic equivalent) at equivalent doses (oral), or Cyclophosphamide (CYC) (i.v.), followed by maintenance therapy with MPA (MMF, enteric-coated MPA sodium, or their generics). In addition, all participants will receive i.v. and/or oral corticosteroids. The aim of the study is to demonstrate the efficacy and safety of secukinumab in LN that will enable registration for the indication of lupus nephritis.
Primary Objective(s)	The primary objective is to demonstrate that secukinumab 300 mg is superior to placebo in Complete Renal Response (CRR) rate at Week 52 in active lupus nephritis (ISN/RPS Class III or IV, with or without co-existing Class V features) patients on a background of SoC therapy
Secondary Objectives	Objective 1: To demonstrate superiority of secukinumab compared to placebo in change from Baseline in 24-hour UPCR at Week 52 Objective 2: To demonstrate superiority of secukinumab compared to placebo in proportion of patients achieving partial renal response (PRR) at Week 52 Objective 3: To demonstrate superiority of secukinumab compared to placebo in average daily dose of oral corticosteroids administered between Week 16 and Week 52 Objective 4: To demonstrate superiority of secukinumab compared to placebo in proportion of patients achieving PRR at Week 24 Objective 5: To demonstrate superiority of secukinumab compared to placebo in time to achieve CRR Objective 6: To demonstrate superiority of secukinumab compared to placebo in time to achieve PRR Objective 7: To demonstrate superiority of secukinumab compared to placebo in time to achieve first morning void Urine Protein-to-Creatinine Ratio (UPCR) ≤ 0.5 mg/mg Objective 8: To demonstrate superiority of secukinumab compared to placebo in change in Functional Assessment of Chronic Illness Therapy – Fatigue (FACIT-Fatigue©) score at Week 52 Objective 9: To demonstrate superiority of secukinumab compared to placebo in patient's health related quality of life via Medical Outcome Short Form Health Survey (SF-36 Physical Component Summary (PCS)) score at Week 52 Objective 10: To demonstrate superiority of secukinumab compared to placebo in change of LupusQoL (Physical Health) score at Week 52 Objective 11: To evaluate the safety and tolerability of secukinumab s.c. as an add-on therapy to Standard of Care in lupus nephritis patients Objective 12: To estimate the proportion of patients with maintained renal response at Week 104

	Objective 13: To estimate the proportion of patients with improved or maintained renal response at Week 104
Study design	This is a pivotal, randomized, double-blind, placebo-controlled trial evaluating at Week 52 the efficacy and safety of secukinumab versus placebo in patients with active lupus nephritis also receiving background SoC regimen. In addition, long-term efficacy, safety and tolerability will be collected up to 2 years.
Population	The study population will be comprised of adult male and female participants in the age range of 18-75 years with a renal biopsy (results current or within the 6 months prior to Screening) showing active glomerulonephritis WHO or ISN/RPS Class III or IV LN [excluding III (C), IV-S (C) and IV-G (C)], with or without co-existing class V features, who are inadequately controlled with previous SoC defined as having UPCR ≥1 mg/mg and active urinary sediment defined as hematuria (presence of >5 red blood cells (RBC)/ high power field (hpf) or above the laboratory reference range) OR presence of cellular casts (RBC or WBC casts). Approximately 400 participants, randomized into two treatment arms (1:1 active: placebo), are planned. At randomization, participants will be stratified on the basis of the SoC induction therapy they will receive during the study, MPA or CYC-based, to ensure a balanced representation in each of the treatment arms (secukinumab or placebo). The target will be to have a maximum of 25% of randomized participants receiving CYC-based induction therapy.
Key Inclusion criteria	Participants eligible for inclusion in this study must meet **all** of the following criteria: 1. Adult male and female participants aged 18 - 75 years old at the time of Baseline 2. Confirmed diagnosis of: - SLE with documented history of at least 4 of the 11 criteria for SLE as defined by the American College of Rheumatology (ACR). [NOTE: The 4 criteria do not have to be present at the time of Screening], OR - Lupus nephritis as the sole clinical criterion in the presence of ANA or anti-dsDNA antibodies. 3. Active lupus nephritis, as defined by meeting the 4 following criteria: - Biopsy within 6 months prior to Screening visit indicating active glomerulonephritis WHO or ISN/RPS Class III or IV LN [excluding III (C), IV-S (C) and IV-G (C)]; participants are permitted to have co-existing Class V. If no biopsy was performed within 6 months of Screening, a biopsy will need to be performed during the Screening period, after all other inclusion/exclusion criteria would have been verified. - UPCR ≥ 1 mg/mg at Screening - eGFR > 30 mL/min/1.73m^2 by Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) - Active urinary sediment as defined by at least 1 of the following: - Hematuria >5 RBC/hpf or above the laboratory reference range. - Presence of cellular casts (RBC or WBC). 4. Participants must be currently on MPA, or willing to initiate SoC induction therapy for LN according to the institutional practices using MPA (MMF or enteric-coated MPA sodium) or low-dose CYC in addition to corticosteroids. 5. If the participant is on cholesterol-lowering agents, the dose must be stable for at least 7 days prior to Randomization. 6. Participants must be treated with anti-malarials (e.g., hydroxychloroquine), unless contra-indicated, and the dose must be stable for at least 10 days prior to Randomization. 7. Able to provide signed informed consent.
Key Exclusion criteria	Participants meeting any of the following criteria are not eligible for inclusion in this study.

	1. Severe renal impairment as defined by i.) Stage 4 CKD, or ii.) presence of oliguria (defined as a documented urine volume < 400 mL/24 h), or iii.) ESRD requiring dialysis or transplantation 2. Known intolerance/hypersensitivity to MPA (MMF or enteric-coated MPA sodium), or oral corticosteroids, or any component of the study treatment 3. Participants having received any other biologic immunomodulatory therapy within 6 months prior to Screening, excluding belimumab where 3 months are acceptable 4. Previous exposure to secukinumab (AIN457) or any other biologic drug targeting IL-17 or the IL-17 receptor 5. Participants having received any investigational drug within 1 month or five times the half-life, whichever is longer 6. Receipt of more than 3000 mg i.v. pulse methylprednisolone (cumulative dose) within the 12 weeks prior to Baseline 7. Treatment with a systemic calcineurin inhibitor (e.g., cyclosporine, tacrolimus) within 12 weeks prior to Baseline 8. CYC use (i.v. or oral) within the month prior to Baseline 9. Participants requiring dialysis within the previous 12 months before Screening 10. History of renal transplant 11. Any severe progressive or uncontrolled concurrent medical condition, including recent severe thromboembolic events, that, in the opinion of the principal investigator, renders the participant unsuitable for the trial 12. Active ongoing inflammatory diseases that might confound the evaluation of the benefit of secukinumab therapy, including inflammatory bowel disease 13. Presence of investigator-identified significant medical problems which at the investigator's discretion will prevent the patient from participating in the study, including but not limited to the following: myocarditis, pericarditis, poorly controlled seizure disorder, acute confusional state, depression, severe manifestations of neuropsychiatric SLE (NPSLE) 14. Chest X-ray, computerized tomography (CT) scan, or MRI with evidence of ongoing infectious or malignant process, obtained within three months prior to Screening and evaluated by a qualified physician 15. History of chronic, recurrent systemic infections, active tuberculosis infection, or active systemic infections during the last two weeks (exception: common cold) prior to Randomization 16. Known infection with human immunodeficiency virus (HIV), hepatitis B or hepatitis C at Screening or Randomization 17. History of lymphoproliferative disease or any known malignancy or history of malignancy of any organ system treated or untreated within the past 5 years, regardless of whether there is evidence of local recurrence or metastases (except for skin Bowen's disease or basal cell carcinoma or actinic keratoses that have been treated with no evidence of recurrence in the past 12 weeks, carcinoma *in situ* of the cervix or non-invasive malignant colon polyps that have been removed) 18. Any of the following abnormal laboratory values on Screening evaluations as reported by Central Laboratory: · Aspartate aminotransferase (AST), alanine aminotransferase (ALT), or amylase > 2.5xULN · Hemoglobin < 8g/dL · Neutrophils < 1.0 x 10^9/L · Platelet count < 50 x 109/L 19. Inability or unwillingness to undergo repeated venipuncture (e.g., because of poor tolerability or lack of venous access) 20. History or evidence of ongoing alcohol or drug abuse, within the last six months before Randomization 21. Pregnant or lactating women

	22. Women of childbearing potential, defined as all women physiologically capable of becoming pregnant, unless they are using highly effective methods of contraception during the entire study or longer if required by locally approved prescribing information (e.g., in European Union (EU) 20 weeks). Of note: the highly effective methods of contraception are mandated due to SoC medications used as per protocol (MPA and CYC).
Study treatment	At Baseline, all eligible participants will be randomized to one of the two treatment arms in a 1:1 ratio via Interactive Response Technology (IRT): • Arm 1: approximately 200 participants with LN will receive secukinumab 300 mg s.c. (2 x 1.0 mL PFS of 150 mg dose) at Randomization, Weeks 1, 2 and 3, and every 4 weeks from Week 4 until Week 100 • Arm 2: approximately 200 participants with LN will receive placebo s.c. (2 x 1.0 mL PFS of 0 mg dose) at Randomization, Weeks 1, 2 and 3, and every 4 weeks from Week 4 until Week 100 At Randomization, participants will be stratified on the basis of the SoC induction therapy they will receive during the study, MPA or CYC-based, to ensure a balanced representation in each of the treatment arms (secukinumab or placebo).
Efficacy assessments	• Assessment of CRR • Time to achieve UPCR ≤ 0.5 mg/mg • Assessment of PRR • Average daily dose of oral corticosteroids • Time to achieve CRR • Time to achieve PRR • FACIT-Fatigue© score • SF-36 PCS score • LupusQoL Physical Health score
Key safety assessments	• Physical examinations • Vital signs • Height and weight • Laboratory evaluations (hematology, clinical chemistry, coagulation panel, local urinalysis, 24-hour urine collection, lipid panel, [redacted] and pregnancy test) • Chest X-ray • Evaluation of AEs and SAEs
Other assessments	[redacted] • Biomarkers (urine and serum) • Pharmacogenetics; DNA and RNA analysis
Data analysis	The primary efficacy endpoint is the CRR at Week 52 with the consideration of intercurrent events. See Section 2.1 for detail.

	The statistical hypothesis tested for the primary objective is that there is no difference in the proportion of patients fulfilling the response criteria at Week 52 between the secukinumab regimen and placebo regimens. Let p_j denote the proportion of responders at Week 52 for treatment regimens j, j = 0, 1 where · 0 corresponds to placebo regimen, · 1 corresponds to secukinumab, In statistical terms, H_1: p1 = p0, H_{A1}: p1 ≠ p0, i.e., H1: secukinumab is not different to placebo regimen with respect to CRR at Week 52 Logistic regression model adjusting for SoC, race and Baseline UPCR will be used for the primary analysis. Difference in marginal response proportions with p-value and respective 95% confidence interval will be estimated from the logistic regression model. Safety analyses will include summaries of AEs, laboratory measurements, and vital signs. Full details of all data analyses will be specified in the statistical analysis plan.
Key words	Systemic Lupus Erythematosus (SLE), Lupus Nephritis (LN), secukinumab, renal biopsy, estimated glomerular filtration rate (eGFR), Urine Protein-to-Creatinine Ratio (UPCR), Standard of care (SoC) background therapy

1 Introduction

1.1 Background

1.1.1 Lupus nephritis

Lupus nephritis is estimated to affect more than one-half of SLE patients and is a severe manifestation in SLE (Cervera et al 2003).

Immune complex formation in LN related to a plethora of autoantibodies, especially anti-dsDNA and anti-nucleosome antibodies, is the result of systemic autoimmunity and is a hallmark of the disease (Waldman and Madaio 2005, Nowling and Gilkeson 2011) that is generally treated by systemic immunosuppression. Once formed, immune complexes activate complement, which can injure renal cells leading to either mesangial LN (class I, II), proliferative LN (class III, IV), membranous LN (class V) and advanced sclerotic LN (class VI). However, pathogenesis of LN is complex and involves both the innate and adaptive immune systems; various cytokines, immune tissues and cell types are involved in its pathogenesis. Intra-renal inflammation is maintained via local cytokine and chemokine production, and by cells of the innate immune system such as neutrophils, that are attracted into the glomerulus and interstitium. Targeting local release of proinflammatory cytokines by blocking single cytokine pathways may enhance treatment efficacy in autoimmunity without increasing systemic immunosuppression (Allam and Anders 2008).

Lupus nephritis is characterized by glomerular endothelium, podocyte, tubulointerstitial and vascular injury. Specific leukocyte subsets, including IL-17-producing T helper type 17 (T_H17) cells, drive inflammation and contribute to renal immunopathology (Yu et al 2017).

Lupus nephritis is categorized histologically into 6 classes by the International Society of Nephrology/Renal Pathology Society (ISN/RPS) classification system (Weening et al 2004, Markowitz and D'Agati 2007). Treatments include management with corticosteroids together with anti-malarials for lower stage disease, followed by more aggressive immunosuppressive therapies for more severe disease, and ultimately renal transplant.

Class III and IV LN are detected in approximately 39 to 71.9% of LN patients, and from the deposition of immune complexes in the subendothelial space of the glomerular capillaries (Wang et al 2018). Both these classes of LN are considered to have similar lesions that differ by severity and distribution. Class IV diffuse LN is distinguished from class III on the basis of involvement of more than 50% of glomeruli with endocapillary lesions. Patients with class III and IV LN require aggressive therapy with glucocorticoids and immunosuppressive agents including cyclophosphamide (CYC), mycophenolate mofetil (MMF), rituximab as well as calcineurin inhibitors (CNIs) (Hahn et al 2012).

Lupus nephritis is associated with significant morbidity and mortality, even with current treatments. With current induction and maintenance therapies, the risk of developing LN-related end-stage renal disease (ESRD) at 5, 10, and 15 years remained at 11%, 17%, and 22%, respectively, for the last decade (Tektonidou et al 2016, Faurschou et al 2010). Two new therapeutic options for LN patients on top of SoC include the calcineurin inhibitor (CNI) voclosporin (Rovin et al 2021) and the soluble B-cell activating factor (BAFF) blocking monoclonal antibody (mAb) belimumab (Furie et al 2020). However, there remains a high

unmet medical need and the effects of these agents on long-term outcomes are unknown. Therefore, despite those recent drug approvals, LN continues to be associated with significant morbidity and mortality (Lichtnekert et al 2022).The European League Against Rheumatism (EULAR)/European Renal Association – European Dialysis and Transplant Association (ERA-EDTA) and ACR guidelines are uniform in their recommendations for therapy for class III and IV LN and include a sequence of induction and maintenance phases. For patients with class III or IV proliferative glomerulonephritis, the guidelines recommend induction therapy with MPA (MMF or enteric-coated MPA sodium) or intravenous (i.v.) CYC, with or without initial pulses of i.v. methylprednisolone. With current induction regimens, less than 60% of class III to V patients achieve a complete or partial response (Appel et al 2009). Among those who attain a complete renal response (CRR) with current standard-of-care (SoC), nearly half of the patients had a relapse. The incidence rate of relapse in these patients was 5 to 15 per 100 patient year (PY) (Grootscholten and Berden 2006).

Despite the aggressive nature of SoC treatment, and the addition of voclosporin and belimumab as further treatment options available for LN, only up to 40% of patients achieve a CRR after 1 year (Rovin and Parikh 2014, Furie et al 2020, Rovin et al 2021). In addition, current LN treatment regimens have substantial side effects from glucocorticoids and prolonged immunosuppression (Schwartz et al 2014). Immunosuppressed LN patients are at significant risk of developing serious infections. In a multiethnic Medicaid cohort, the incidence rate of serious infections was more than 2-fold higher in LN than in SLE patients (Feldman et al 2015).

Thus, given the severity of the condition, there is a high unmet medical need for more effective therapies with a favorable benefit:risk profile for the treatment of LN patients.

1.1.2 Scientific rationale for targeting IL-17 in lupus nephritis

Animal model studies have demonstrated that the IL-17 and upstream IL-23 pathways contribute to renal injury in experimental models of LN or glomerulonephritis. IL-23 receptor deficiency decreased the number of IL-17A-producing double-negative (DN) T cells, produced less anti-DNA antibodies and prevented glomerulonephritis in lupus-prone C57BL/6-lpr/lpr mice (Kyttaris et al 2010); treatment with an anti-IL-23 antibody in the same mouse model ameliorated nephritis and was accompanied by a reduction of IL-17A produced by *in vitro* stimulated splenocytes post-treatment (Kyttaris et al 2013). Both IL-23p19 and IL-17A knock-out mice developed less severe nephritis in a T cell-mediated murine model of nephrotoxic nephritis (Paust et al 2009). Elevated expression of IL-17A was observed in lupus-prone Fcgr2b knock-out mice, which develop fatal lupus glomerulonephritis, while mice lacking IL-17 displayed increased survival and protection from glomerulonephritis (Pisitkun et al 2014). Additional support for a role of IL-17A in LN has been provided in the pristane-induced LN mouse model, in which absence of IL-17A led to decreased renal inflammation and renal injury, along with reduced levels of anti-DNA antibodies (Summers et al 2014). In this model, macrophages as well as neutrophils were the main producers of IL-17A. Thus, based on these animal data, blocking IL-17A in LN may prove beneficial in limiting glomerular inflammation and renal damage.

A growing number of studies in patients with LN indicate that IL-17A and Th17 cells play important roles in the pathogenesis of LN, contributing to glomerular injury and the persistence of inflammation and renal damage (Zhang et al 2009, Crispín et al 2008) and high levels of IL-

17 predict poor histopathological outcomes after immunosuppressive therapy in patients with LN (Zickert et al 2015). A set of T cells infiltrates the kidneys of patients with LN and represent the major source for IL-17 (Crispín and Tsokos 2008). IL-17 has the potential to induce the production of additional inflammatory cytokines and chemokines and to promote recruitment of inflammatory cells such as monocytes and neutrophils to inflamed organs. Higher levels of glomerular IL-17 and IL-23 expression are observed in renal biopsies from class IV LN patients as compared with those from minimal change nephropathy patients and normal controls. Both glomerular IL-17 and IL-23 expression levels positively correlate with renal histological activity index scores for LN patients (Chen et al 2012). The urinary expression of Th17-related genes, including those for IL-17 and IL-23, is increased and associated with the activity of LN (Kwan et al 2009).

Additional evidence shows that neutrophil recruitment to the kidney starts several hours after the induction of nephrotoxic nephritis and is partly mediated by IL-17A-producing γδ T cells (Kurts et al 2013). Th17 cells promote intra-renal IL-17A expression in LN (Crispín and Tsokos 2008). IL-17 can also drive T cells away from maturing into a regulatory T cell phenotype that can suppress autoantibody production and attenuate the systemic immune response (Bettelli et al 2006).

An imbalance between inflammatory Th17 and regulatory T cells and the secretion of inflammatory cytokines including IL-17A amplify the immune response in LN by inducing the local production of chemokines and cytokines, as well as the recruitment of neutrophils and monocytes. This ultimately contributes to persistent inflammation and kidney damage in LN (Koga et al 2017). IL-17A can also act directly on kidney cells such as mesangial cells (Paust et al 2009), tubular epithelial cells (Hirai et al 2012) and podocytes (Yan et al 2018), thereby increasing inflammation, T cell and neutrophil infiltration, and disruption of renal function leading to proteinuria. Therefore, a pathogenic model for glomerulonephritis is emerging in which Th17 cells infiltrate the kidney and IL-17A (as well as potentially other cytokines) produced by Th17 cells acts directly on resident kidney cells to induce cytokines and chemokines that lead to further recruitment of Th17 cells and neutrophils into the tissue, resulting in renal tissue damage (Krebs et al 2017).

A case report of a patient with refractory LN and concomitant psoriasis vulgaris suggests that treatment with the IL-17A inhibitor secukinumab may have contributed to an improvement in renal function and a decrease in urine protein levels in this patient (Satoh et al 2018). An additional case was reported of a childbearing woman with SLE who developed refractory LN despite use of all standard therapeutic options. After starting secukinumab, clinical and biological features improved, and complete renal response was achieved (Costa et al 2021).

1.1.3 Secukinumab

Secukinumab is a recombinant high-affinity fully human monoclonal anti-human IL-17A antibody of the IgG1/kappa isotype.

Secukinumab is currently approved in more than 100 countries worldwide. The product is indicated for the treatment of adults and children aged 6 years and above with moderate to severe plaque psoriasis (PsO), as well as adults with psoriatic arthritis (PsA), ankylosing spondylitis (AS), and non-radiographic axial spondyloarthritis (nr-axSpA). It is also approved

for two juvenile idiopathic arthritis (JIA) subtypes (juvenile PsA (JPsA) and enthesitis-related arthritis (ERA)).

The outcome of the extensive Novartis clinical program comprising more than 25 Phase III studies and at least 17,000 participants studied over a period of up to 5 years in these indications has shown that secukinumab offers robust and clinically meaningful efficacy to these patients and is complemented by a consistently favorable benefit:risk profile. The safety profile of secukinumab was indeed consistent and comparable across all indications supporting its long-term use in these chronic inflammatory conditions.

Based on the available data suggesting that IL-17 is an appropriate therapeutic target for patients with LN, secukinumab has the potential to be an effective therapy for patients with active LN (ISN/RPS Class III or IV, with or without co-existing Class V features), when used in combination with SoC therapy.

1.2 Purpose

The purpose of this trial is to evaluate the efficacy and safety of subcutaneous secukinumab 300 mg compared to placebo, in combination with standard of care therapy (SoC), in patients with active lupus nephritis (ISN/RPS Class III or IV, with or without co-existing class V features).

Background SoC will consist of induction therapy with mycophenolic acid (MPA) (which refers to Mycophenolate mofetil (MMF) (Cellcept® or generic equivalent), or enteric-coated MPA sodium (Myfortic® or generic equivalent) at equivalent doses (oral)), or Cyclophosphamide (CYC) (i.v.), followed by maintenance therapy with MPA. In addition, all participants will receive i.v. and/or oral corticosteroids.

The aim of the study is to demonstrate the efficacy and safety of secukinumab in LN that will enable registration for the indication of lupus nephritis.

Within this document, at each time MPA will be mentioned without further information, it will refer to Cellcept®, Myfortic® or generic equivalent at equivalent doses.

2 Objectives and endpoints

Table 2-1 Objectives and related endpoints

Objective(s)	Endpoint(s)
Primary objective(s)	**Endpoint(s) for primary objective(s)**
• To demonstrate that secukinumab 300 mg is superior to placebo in Complete Renal Response (CRR) rate at Week 52 in active lupus nephritis (ISN/RPS Class III or IV, with or without co-existing Class V features) patients on a background of SoC therapy.	• Proportion of participants achieving CRR at Week 52 CRR at Week 52 is an endpoint defined as meeting all of the following: • Estimated glomerular filtration rate (eGFR) ≥ 60 mL/min/1.73 m^2 or no less than 85% of Baseline • 24-hour urine protein-to-creatinine ratio (UPCR) ≤ 0.5 mg/mg • No treatment discontinuation before Week 52

Objective(s)	Endpoint(s)
	• The participant did not receive more than 10 mg/day prednisone equivalent for ≥ 3 consecutive days or for ≥ 7 days in total during Week 44 through Week 52

Secondary objective(s)	Endpoint(s) for secondary objective(s)*
• To demonstrate superiority of secukinumab compared to placebo in change from baseline in 24-hour UPCR at Week 52	• Change from Baseline in 24-hour UPCR at Week 52
• To demonstrate superiority of secukinumab compared to placebo in proportion of patients achieving partial renal response (PRR) at Week 52	• Proportion of participants achieving PRR at Week 52 defined as: • ≥ 50% reduction in 24-hour UPCR to sub-nephrotic levels (≤ 3 mg/mg) and • eGFR ≥ 60 mL/min/1.73 m^2 or no less than 85% of Baseline
• To demonstrate superiority of secukinumab compared to placebo in average daily dose of oral corticosteroids administered between Week 16 and Week 52	• Average daily dose of oral corticosteroids administered between Week 16 and Week 52 compared to placebo
• To demonstrate superiority of secukinumab compared to placebo in proportion of patients achieving PRR at Week 24	• Proportion of participants achieving PRR at Week 24 defined as: • ≥ 50% reduction in 24-hour UPCR to sub-nephrotic levels (≤ 3 mg/mg) and • eGFR ≥ 60 mL/min/1.73 m^2 or no less than 85% of Baseline
• To demonstrate superiority of secukinumab compared to placebo in time to achieve CRR	• Time to achieve CRR up to Week 52
• To demonstrate superiority of secukinumab compared to placebo in time to achieve PRR	• Time to achieve PRR up to Week 52
• To demonstrate superiority of secukinumab compared to placebo in time to achieve first morning void UPCR ≤ 0.5 mg/mg	• Time to achieve first morning void UPCR ≤ 0.5 mg/mg up to Week 52
• To demonstrate superiority of secukinumab compared to placebo in change in Functional Assessment of Chronic Illness Therapy – Fatigue (FACIT-Fatigue©) score at Week 52	• Improvement in FACIT-Fatigue© mean change of score from Baseline at Week 52 compared to placebo
• To demonstrate superiority of secukinumab compared to placebo in patient's health related quality of life via Medical Outcome Short Form Health Survey (SF-36 Physical Component Summary (PCS)) score at Week 52	• Improvement in SF-36 PCS mean change from Baseline at Week 52 compared to placebo
Secondary objective(s)	**Endpoint(s) for secondary objective(s)***
• To demonstrate superiority of secukinumab compared to placebo in change of LupusQoL (Physical Health) score at Week 52	• Improvement in LupusQoL Physical Health mean change of score from Baseline at Week 52 compared to placebo
• To evaluate the safety and tolerability of secukinumab s.c. as an add-on therapy to Standard of Care in lupus nephritis patients	• Incidence of Treatment-emergent AEs (TEAEs) / SAEs from Baseline to Week 52; vital signs and body measurements, standard chemistry and hematology up to Week 52

• To estimate the proportion of patients with maintained renal response at Week 104	• Estimate the proportion of participants with CRR at Week 104 within participants who had achieved CRR at Week 52 in the secukinumab group
• To estimate the proportion of patients with improved or maintained renal response at Week 104	• Estimate the proportion of participants with improved or maintained response (PRR or CRR) in participants who had achieved at least PRR at Week 52 in the secukinumab group

Exploratory objective(s)	**Endpoint(s) for exploratory objective(s)**
[redacted]	

• To perform exploratory pharmacogenomic analysis based on blood samples for DNA and RNA analysis (optional assessments)	• Evaluate the relationship of genetic polymorphisms and transcriptomic data with treatment response

*Intercurrent events of the secondary efficacy endpoints and the strategies to handle these are specified in Section 2.2.

2.1 Primary estimand

The **primary clinical question of interest** to be answered in the trial is:

What is the effect of subcutaneous secukinumab 300 mg compared with placebo on achieving CRR at Week 52, in patients with active LN (ISN/RPS Class III or IV, with or without co-existing class V features), on a background of SoC therapy?

CRR is defined as

1. eGFR $\geq$ 60 mL/min/1.73m^2 or no less than 85% of Baseline

AND

2. 24-hour UPCR $\leq$ 0.5 mg/mg

This question gives rise to the primary estimand, which has the following attributes with respect to the primary question:

- **Population**: Participants with active LN (ISN/RPS Class III or IV, with or without co-existing class V features), as defined by the inclusion and exclusion criteria of the study Section 5.
- **Treatment**: The randomized treatment (the investigational therapy subcutaneous secukinumab 300 mg or the placebo), in combination with SoC. More details about the treatment are provided in Section 6.
- **Endpoint**: An endpoint meeting all of the following:
  - CRR at Week 52;
  - If the participant discontinues the treatment before Week 52, then the participant will be considered as a non-responder (composite endpoint strategy);
  - If the participant has overuse of corticosteroid (> 10 mg/day prednisone equivalent for ≥ 3 consecutive days or ≥ 7 days in total) between Week 44 and Week 52, then the participant will be considered as a non-responder (composite endpoint strategy).
- **Summary measure**: Difference in marginal response proportions of achieving CRR at Week 52, between secukinumab and placebo.

2.2 Secondary estimands

The **secondary clinical questions of interest** to be answered in the trial are:

What are the effects of subcutaneous secukinumab 300 mg compared with placebo in patients with active LN (ISN/RPS Class III or IV, with or without co-existing class V features), on a background of SoC therapy, in the following variables?

1. Change from Baseline in 24-hour UPCR at Week 52
2. Proportion of patients achieving PRR at Week 52
3. Average daily dose of oral corticosteroids administered between Week 16 and Week 52 compared to placebo
4. Proportion of patients achieving PRR at Week 24
5. Time to achieve CRR up to Week 52
6. Time to achieve PRR up to Week 52
7. Time to achieve first morning void UPCR ≤ 0.5 mg/mg up to Week 52
8. Improvement in FACIT-Fatigue© mean change from Baseline at Week 52
9. Improvement in SF-36 PCS mean change from Baseline at Week 52
10. Improvement in LupusQoL Physical Health mean change from Baseline at Week 52

The estimands for secondary objectives are described by the following attributes:

- **Population**: Participants with active LN (ISN/RPS Class III or IV, with or without co-existing class V features), as defined by the inclusion and exclusion criteria of the study in Section 5.
- **Treatment**: The randomized treatment (the investigational therapy subcutaneous secukinumab 300 mg or placebo), in combination with SoC. More details about the treatment are provided in Section 6.

For **binary** variables (PRR at Week 52, and PRR at Week 24):

PRR is an endpoint defined as:

1. eGFR ≥ 60 mL/min/1.73m^2 or no less than 85% of Baseline

AND

2. ≥ 50% reduction in 24-hour UPCR to sub-nephrotic level (≤ 3 mg/mg) compared to Baseline.

- **Endpoint**: An endpoint meeting all of the following:
  - PRR at the time point of interest;
  - (*For both PRR at Week 52 and Week 24*) if the participant discontinues the treatment before the timepoint of interest, the participant will be considered as a non-responder (composite endpoint strategy);
  - (For *PRR at Week 52 only*) if the participant experiences overuse of corticosteroid (> 10 mg/day prednisone equivalent for ≥ 3 consecutive days or ≥ 7 days in total) between Week 44 and Week 52, then the participant will be considered as a non-responder (composite endpoint strategy).
- **Summary measure**: Difference in marginal response proportions of achieving PRR at the time point of interest, between secukinumab and placebo.

For **continuous** variables (24-hour UPCR, average daily dose of oral corticosteroids, SF-36 PCS, FACIT-Fatigue©, and LupusQoL physical health):

- **Endpoint**: An endpoint meeting all of the following:
  - Variable (e.g., change from Baseline in UPCR) of interest at timepoint of interest;
  - If the participant discontinues the treatment before the timepoint of interest, the observed value of the variable will be used (treatment policy strategy);
  - (*For 24-hour UPCR, SF-36 PCS, FACIT-Fatigue©, and LupusQoL physical health only*) if the participant experiences overuse of corticosteroid, the observed value will still be used (treatment policy strategy).
- **Summary measure**: Difference in variable means between the secukinumab and placebo arms.

For **time-to-event** variables (time to achieve CRR, time to achieve PRR, and time to achieve first morning void UPCR ≤ 0.5 mg/mg):

- **Endpoint**: An endpoint meeting all of the following:
  - Time to response of interest (e.g., CRR);
  - If the participant discontinues the treatment before achieving the event, then the time to response will be censored at Week 52 (composite endpoint strategy);
- **Summary measure**: Hazard ratio of secukinumab vs placebo.

3 Study design

This is a pivotal, randomized, double-blind, placebo-controlled trial evaluating at Week 52 the efficacy and safety of secukinumab versus placebo in patients with active LN also receiving background SoC regimen. Long-term efficacy, safety and tolerability will be collected up to 2 years.

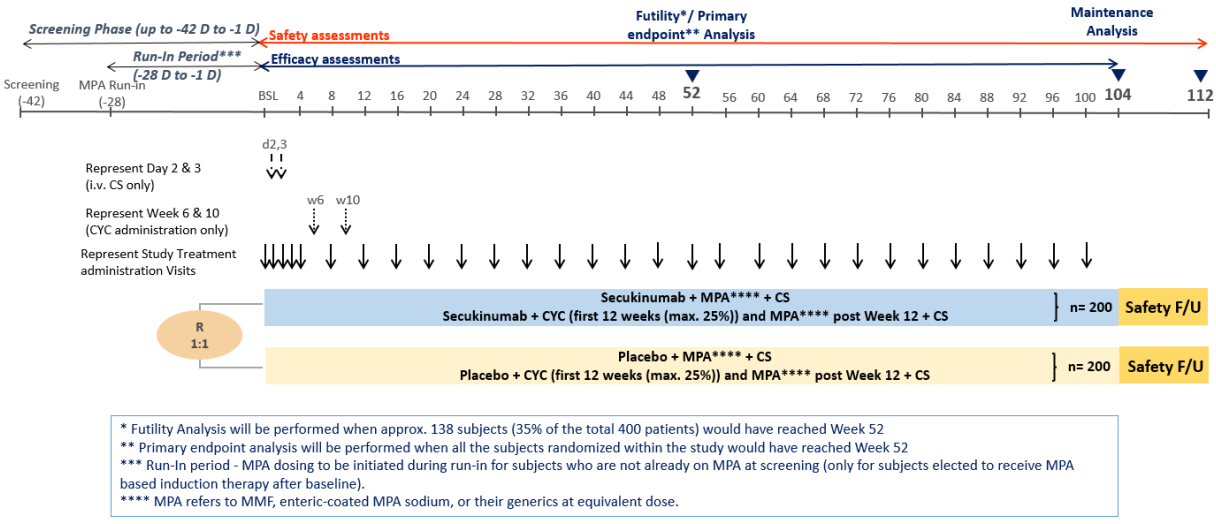
The SoC regimen will consist of induction therapy with MPA or CYC, followed by maintenance therapy with MPA. The choice of background SoC induction therapy will be at investigator's discretion. At Randomization, participants will be stratified on the basis of the SoC induction therapy they will receive during the study, MPA or CYC-based, to ensure a balanced representation in each of the treatment arms (secukinumab or placebo). The target will be to have a maximum of 25% of randomized participants receiving CYC-based induction therapy.

In addition, steroids will be administered through i.v. pulses followed by oral daily doses as described in Section 6.1.3 SoC background therapy.

The primary endpoint analysis will be performed after all participants have completed the visit associated with the primary endpoint (Week 52). Although the unblinding of selected members of the Novartis Global Clinical Team will occur after the Week 52 database lock, original randomization to active treatment versus placebo will continue to remain blinded to all investigators, site personnel, participants, and monitors until the final database lock. The study consists of the following parts:

a. Screening (up to 42 days/6 weeks)
b. Run-in period (optional): For participants who will receive MPA as SoC induction therapy as per investigator's decision and who are not already on MPA at Screening, MPA dosing will be initiated during a run-in period before Randomization (for up to 4 weeks prior to the first dose of secukinumab)
c. Treatment Period: Duration of 104 weeks of treatment with secukinumab/placebo in addition to SoC treatment (with last dose given at Week 100)
d. Follow-up period: Duration of 8 weeks (last visit performed 12 weeks after last dose of study medication)

Figure 3-1 Study design



Screening to Randomization (Screening and Run-in period):

A Screening period of up to 6 weeks will be used to assess participant´s eligibility and to adjust for concomitant medication(s) (Day -42 to -1). While this duration should provide enough time to evaluate eligibility of the participant, including renal biopsy evaluation, it could be extended

on a case-by-case basis, to be discussed with the Sponsor, to allow for a retest of inclusion/exclusion assessments. If participants do not have a renal biopsy obtained within 6 months of the Screening visit, a renal biopsy should be performed. This renal biopsy should be performed after confirming that the participant meets all other inclusion/exclusion criteria.

Participants who will receive MPA-based SoC induction therapy for the treatment of active LN as per investigator's decision, and not already on MPA when entering Screening, will be initiated on MPA during the run-in period (-28 to -1) as described in Section 6.1.3 SoC background therapy.

Treatment period: Treatment period covers time between Randomization (Baseline) through EOT.

At Baseline, eligible participants will be randomized in a 1:1 ratio to secukinumab 300 mg s.c. or placebo. Approximately 200 participants will be randomized to each of the two treatment arms. A blinded, weekly, s.c. secukinumab or placebo loading regimen will be administered for the first 4 weeks followed by a monthly maintenance dose in all randomized participants thereafter. At the end of the treatment period at Week 104, the planned End of Treatment (EOT) visit will be performed.

Participants who discontinue study treatment prematurely for any reason other than withdrawal of informed consent before Week 104 will not be considered as discontinued from the study. Those participants should perform the EOT study visit 4 weeks after their last study treatment administration. Thereafter, participants should continue attending all subsequent scheduled site visits for study assessments. Participants who are unwilling to continue attending further study visits after prematurely discontinuing the study treatment, should attend the End of Study (EOS) visit 12 weeks after the last administration of study treatment. Please refer to Section 9.1.1 Discontinuation of study treatment for further details.

In addition, starting at Week 52, participants who are not deemed, by the investigator, to achieve the desired benefit from the study treatment, should be considered for rescue medication. In case a prohibited medication (as defined in Section 6.2.2 Prohibited medication) is used as rescue medication, the participant should be discontinued from study treatment.

Follow-up period: An EOS visit is to be done for all participants. The EOS visit will be performed 12 weeks after last study treatment administration for all participants who complete the 104 weeks treatment period, or who discontinue prematurely from study treatment and study. For participants who discontinue study treatment prematurely but continue attending study visits, please refer to Section 9.1.1 Discontinuation of study treatment for detailed guidelines. Participants enrolling into the extension study CAIN457Q12301E1 will not be required to complete the follow-up period, as their ongoing safety information will be recorded in the extension trial.

Safety assessments will include physical examinations, vital signs, standard clinical laboratory evaluations, hematology (including blood coagulation assays), blood chemistry, urinalysis, adverse and serious adverse event monitoring.

4 Rationale

4.1 Rationale for study design

The double-blind, randomized, placebo-controlled, parallel-group design will enable the evaluation of the benefit-risk of the proposed secukinumab dose regimen in an adequate and well-controlled setting, minimizing potential bias in reporting of safety and efficacy data.

A recommended steroid tapering regimen will be initiated in all randomized participants during the treatment period. The tapering schedule (timing and dose decrease) will depend on the Baseline corticosteroid dose. The tapering regimen, as described in Section 6.1.3 SoC Background therapy, is in alignment with common medical practice in LN and is designed to minimize steroid-related toxicity and avoid confounding the primary efficacy assessment.

CRR is a preferred primary outcome for induction and maintenance therapy in LN. It is demonstrated as clinically significant improvement of renal function during the induction phase, shown by improvement of eGFR and signs and symptoms of renal injury like protein excretion. The primary endpoint assessment is planned at Week 52 as recommended by various guidelines. The two-year duration (104 weeks) will provide additional safety and efficacy data as well as the durability of response.

An assessment of PRR will be conducted as a secondary endpoint in the trial and will evaluate the proportion of participants who improved while not achieving a CRR. Considering the long duration of the study (104 weeks), maintenance of CRR and prevention of renal flares are also secondary outcomes that may be evaluated. [redacted]

4.1.1 Rationale for choice of background therapy

The SoC background therapy that all participants will receive was selected as it corresponds to the treatment recommendations of the ACR and EULAR/ERA-EDTA guidelines for induction and maintenance therapy for patients with ISN/RPS Class III or IV LN, with or without co-existing class V features, (Bertsias et al 2012), (Hahn et al 2012), (Palmer et al 2017).

The choice of background SoC regimen for induction will be left at investigator's discretion, with a maximum of 25% of randomized participants receiving CYC-based induction therapy (stratification at Randomization will ensure balanced representation in both groups, secukinumab or placebo). SoC background regimen will consist of induction therapy with MPA or low-dose CYC regimen, followed by maintenance therapy with MPA, along with glucocorticoids:

- MPA and CYC are considered equivalent for the induction of remission in patients with ISN/RPS Class III or IV LN, with or without co-existing class V features
- The low dose intravenous CYC regimen for induction was selected, as it presents a better efficacy/toxicity ratio than high-dose intravenous CYC
- Corticosteroid administration as per the above-mentioned guidelines are considered a mainstay in LN treatment

4.2 Rationale for dose/regimen and duration of treatment

Secukinumab dosing will start with initial dosing of 300 mg s.c. injections at Baseline, Weeks 1, 2, 3, and 4, followed by dosing every 4 weeks. This dosing regimen is approved for treatment of other autoimmune diseases (PsO, PsA). Available data in PsO and PsA strongly suggest that secukinumab operates at the plateau of the dose-exposure-response curve in these autoimmune diseases, which is one of the reasons to select this dose level in LN as well. As clearly demonstrated in the development program for PsO, it is expected that the initial weekly dosing during the first month will enable rapid achievement of effective drug concentrations and lead to a more rapid onset of clinical response.

It has to be noted that due to kidney damage, proteinuria is commonly observed in patients with LN. The effect of renal impairment on the PK of biologics is dependent on the ability of the compound to undergo glomerular filtration, which is largely driven by molecular weight (MW). Secukinumab has a MW of ca. 148 kDa, and renal clearance usually plays a minimal role in the elimination of biologics with MW greater than 69 kDa (Meibohm and Zhou H 2012). An association between increased Baseline proteinuria and increased clearance was observed in the population PK analysis of belimumab (a human mAb that inhibits B-cell activating factor, BAFF) in SLE (Struemper et al 2013). Also, there is evidence that in some forms of renal disease, such as diabetic nephropathy, there may be an increase in the renal elimination of IgGs (Bakoush et al 2002). However, slight changes in distribution volume or increased clearance of secukinumab in LN patients will probably not dramatically change the PK characteristics of secukinumab.

In addition, the secukinumab dosing regimen used in the study is associated with a reassuring safety profile, as confirmed in multiple clinical trials (up to 5 years) and in the post-marketing setting.

4.3 Rationale for choice of control drugs (comparator/placebo) or combination drugs

A placebo arm is included for the whole duration of the study treatment. Due to the nature of the disease and the primary outcome measure used (CRR), a placebo arm is necessary to obtain reliable efficacy measurements for comparison between the active treatment and the placebo. In addition, all participants, including those assigned to the placebo arm, will receive background SoC therapy as recommended within the EULAR/ERA-EDTA and ACR guidelines for the induction and maintenance treatment of patients with active ISN/RPS class III or IV LN [excluding III (C), IV-S (C) and IV-G (C)], with or without co-existing class V features.

As recommended by the same guidelines, all participants will also receive hydroxychloroquine (HCQ) as adjunctive medication unless contraindicated. Treatment with lipid-lowering statin and of renin-angiotensin-aldosterone system inhibitors (ACE inhibitors /ARBs) is allowed.

The FDA (FDA 2018) and the Committee for Medicinal Products for Human Use (CHMP) recommend double blind, parallel-group, randomized trial designs. Per the CHMP guideline (Committee for Medicinal Products for Human use (CHMP) 2015), a superiority trial design against an active comparator or placebo is preferred in LN. Placebo-controlled trials are acceptable provided that placebo is given as add-on to SoC therapy.

4.4 Purpose and timing of interim analyses/design adaptations

The study team, site staff, investigators and participants will remain blinded to the interim data and results of the analysis for both the first and second interim analyses described below. These analyses will be conducted by independent statisticians and programmers from a contract research organization (CRO) and will be evaluated by an independent data monitoring committee (DMC).

In addition to those interim analyses, the primary endpoint analysis will be performed after **all** participants have completed the visit associated with the primary endpoint (Week 52). At time of the primary endpoint analysis, although the unblinding of selected members of the Novartis Global Clinical Team will occur, investigators/site personnel, participants and monitors will remain blinded until the final study analyses are completed. Additional safety analyses may be performed between the second interim analysis and the Week 52 final analysis if needed to support health authority interactions following a statistically significant result at the second interim analysis.

4.4.1 First interim analysis

The first interim analysis will be performed when approximately 138 participants (approximately 35% of the total 400 participants) are expected to complete 52 weeks of treatment (including those who discontinue the treatment early).

Futility analysis

A futility analysis will be performed at the first interim analysis. A Go/No-Go decision will be taken at this futility analysis based on predictive probability of achieving statistical significance for the primary estimand. Futility stopping rules will be defined in the DMC charter.

[redacted]

4.4.2 Second interim analysis

The second interim analysis will be performed when approximately 308 participants (approximately 77% of all 400 participants) complete 52 weeks of treatment. The results from this interim analysis will support the decision-making concerning the current clinical study, i.e., to continue or to stop the trial based on efficacy (superiority or futility) and/or safety findings.

Superiority analysis

An alpha spending function will be used to calculate the nominal p-value threshold for the superiority analysis. This method will maintain the overall type-I error rate for the primary and secondary endpoints. Further details are provided in Section 12.8.2.

Futility analysis

A second futility analysis will also be conducted at the time of the second interim analysis. Futility stopping rules will be specified in the DMC charter.

4.5 Risks and benefits

Current standard of care therapies comprise of conventional immunosuppressants which are not fully efficacious in all patients and associated with significant toxicities. Based on the scientific rationale for targeting IL-17 pathway in lupus, and the data available on secukinumab, IL-17 inhibition by secukinumab has a potential therapeutic benefit for lupus nephritis patients who are clinically active despite standard of care treatment.

Secukinumab has demonstrated positive benefit risk in the treatment of multiple chronic inflammatory diseases, including e.g., PsA, AS, PsO, nr-axSpA and JIA (ERA and JPsA subtypes).

Secukinumab therapy has a well-established and well-described safety profile based on extensive post-marketing experience and continued clinical trial patient exposure since its approval for the first indication of moderate to severe plaque psoriasis. Details of the risk and benefits are outlined in the current version of the Investigator's Brochure (IB).

The safety and tolerability of secukinumab as an add-on to SoC will be evaluated. Based on the favorable safety profile of secukinumab and the known safety profile of the SoC treatments for LN, it is unlikely that the addition of secukinumab to the LN SoC regimens will result in unacceptably high risks, particularly for serious infections. In a pooled analysis of psoriasis clinical trial data from 3993 patients, the crude incidence of severe AEs of infections was 2.6% for any 300 mg and 2.2% for any 150 mg [IB 26 Jun 2021 – 25 Jun 2022, data on file]. A published meta-analysis found that, in patients treated for lupus nephritis, the crude incidence rates of serious infections have been reported at 26.7% with high-dose glucocorticoids, 15.1% with cyclophosphamide, and 11.6% with MMF (Singh et al 2016). Additionally, in the pooled secukinumab psoriasis trial data, the exposure-adjusted incidence rate of SAEs of infections was 1.4/100 PY for any 300 mg (N=1410) and 1.1/100 PY (N=1395) [IB 26 Jun 2021 – 25 Jun 2022, data on file], while the risk of serious infections with a combined regimen of MMF and corticosteroids was reported at 19/100 PY (Rovin et al 2012, Mysler et al 2013).

The risk to participants in this trial may be minimized by compliance with the eligibility criteria and study procedures, as well as close clinical monitoring, and periodic review of safety data by an independent DMC. Additional information can be found in the IB for secukinumab.

Women of childbearing 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 must agree that in order to participate in the study, they must adhere to the contraception requirements outlined in the exclusion criteria. If there is any question that the participant will not reliably comply, they should not be entered or continue in the study.

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

4.6 Rationale for public health emergency mitigation procedures

In the event of a public health emergency as declared by local or regional authorities (i.e., pandemic, epidemic or natural disaster), mitigation procedures may be required to ensure participant safety and trial integrity and are listed in relevant sections of the study protocol. Notification of the public health emergency should be discussed with Novartis prior to implementation of mitigation procedures and permitted/approved by local or regional health authorities and ethics committees as appropriate.

5 Population

The study population will be comprised of adult male and female participants in the age range of 18-75 years with a renal biopsy (current or within the 6 months prior to Screening) showing active glomerulonephritis WHO or ISN/RPS Class III or IV LN [excluding III (C), IV-S (C) and IV-G (C)], with or without co-existing class V features, who are inadequately controlled with previous SoC defined as having UPCR ≥ 1 mg/mg and active urinary sediment (presence of hematuria (> 5 RBC/ hpf or above the laboratory reference range)) OR presence of cellular casts (RBC or WBC casts).Approximately 400 participants, randomized into two treatment arms (1:1 active: placebo), are planned. At Randomization, participants will be stratified on the basis of the SoC induction therapy they will receive during the study, MPA or CYC-based, to ensure a balanced representation in each of the treatment arms (secukinumab or placebo). The target will be to have a maximum of 25% of randomized participants receiving CYC-based induction therapy.

5.1 Inclusion criteria

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

1. Adult male and female participants aged 18 - 75 years old at the time of Baseline.
2. Confirmed diagnosis of:
   - SLE with documented history of at least 4 of the 11 criteria for SLE as defined by the American College of Rheumatology (ACR) (Tan et al 1982) revised by (Hochberg 1997). [NOTE: The 4 criteria do not have to be present at the time of Screening],

   OR
   - LN as the sole clinical criterion in the presence of ANA or anti-dsDNA antibodies.
3. Active lupus nephritis, as defined by meeting the 4 following criteria:
   - Biopsy within 6 months prior to Screening visit indicating active glomerulonephritis WHO or ISN/RPS Class III or IV LN [excluding III (C), IV-S (C) and IV-G (C)]; patients are permitted to have co-existing Class V. If no biopsy was performed within 6 months of Screening, a biopsy will need to be performed during the Screening period, after all other inclusion/exclusion criteria would have been verified.
   - UPCR ≥ 1 mg/mg at Screening.

- eGFR > 30 mL/min/1.73 m^2 by Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI).
- Active urinary sediment (presence of cellular casts (RBC or WBC casts)) or hematuria (> 5 red blood cells per high power field or above the laboratory reference range).

4. Participants must be currently on MPA, or willing to initiate SoC induction therapy for LN according to the institutional practices using MPA or low-dose CYC in addition to corticosteroids. For guidance, see published guidelines such as by (Bertsias et al 2012, Hahn et al 2012).
5. If the participant is on cholesterol-lowering agents, the dose must be stable for at least 7 days prior to Randomization.
6. Participants must be treated with anti-malarials (e.g., hydroxychloroquine), unless contra-indicated, and the dose must be stable for at least 10 days prior to Randomization.
7. Able to provide signed informed consent.

5.2 Exclusion criteria

Participants meeting any of the following criteria are not eligible for inclusion in this study.

1. Severe renal impairment as defined by i.) Stage 4 CKD, or ii.) presence of oliguria (defined as a documented urine volume < 400 mL/24 h), or iii.) ESRD requiring dialysis or transplantation.
2. Known intolerance/hypersensitivity to MPA, or oral corticosteroids, or any component of the study drug(s).
3. Participants having received any other biologic immunomodulatory therapy within 6 months prior to Screening, excluding belimumab where 3 months are acceptable.
4. Previous exposure to secukinumab (AIN457) or any other biologic drug targeting IL-17 or the IL-17 receptor.
5. Participants having received any investigational drug within 1 month or five times the half-life of enrollment, whichever is longer.
6. Receipt of more than 3000 mg i.v. pulse methylprednisolone (cumulative dose) within the 12 weeks prior to Baseline.
7. Treatment with a systemic calcineurin inhibitor (e.g., cyclosporine, tacrolimus) within 12 weeks prior to Baseline
8. CYC use (i.v. or oral) within the month prior to Baseline.
9. Participants requiring dialysis within the previous 12 months before Screening.
10. History of renal transplant.
11. Any severe progressive or uncontrolled concurrent medical condition, including recent severe thromboembolic events, that, in the opinion of the principal investigator, renders the participant unsuitable for the trial.
12. Active ongoing inflammatory diseases that might confound the evaluation of the benefit of secukinumab therapy, including inflammatory bowel disease.
13. Presence of investigator-identified significant medical problems which at the investigator's discretion will prevent the patient from participating in the study, including but not limited

to the following: myocarditis, pericarditis, poorly controlled seizure disorder, acute confusional state, depression, severe manifestations of neuropsychiatric SLE (NPSLE).

14. Chest X-ray, computerized tomography (CT) scan, or MRI with evidence of ongoing infectious or malignant process, obtained within 3 months preceding the Screening visit and evaluated by a qualified physician.
15. History of chronic, recurrent systemic infections, active tuberculosis infection, or active systemic infections during the last two weeks (exception: common cold) prior to Randomization.
16. Known infection with human immunodeficiency virus (HIV), hepatitis B or hepatitis C at Screening or Randomization.
17. History of lymphoproliferative disease or any known malignancy or history of malignancy of any organ system treated or untreated within the past 5 years, regardless of whether there is evidence of local recurrence or metastases (except for skin Bowen's disease or basal cell carcinoma or actinic keratoses that have been treated with no evidence of recurrence in the past 12 weeks, carcinoma *in situ* of the cervix or non-invasive malignant colon polyps that have been removed).
18. Any of the following abnormal laboratory values on Screening evaluations as reported by Central Laboratory:
    - Aspartate aminotransferase (AST), alanine aminotransferase (ALT), or amylase > 2.5xULN
    - Hemoglobin < 8g/dL
    - Neutrophils < 1.0 x 10^9/L
    - Platelet count < 50 x 10^9/L
19. Inability or unwillingness to undergo repeated venipuncture (e.g., because of poor tolerability or lack of venous access).
20. History or evidence of ongoing alcohol or drug abuse, within the last six months before Randomization.
21. Pregnant or lactating women.
22. Women of childbearing potential, defined as all women physiologically capable of becoming pregnant, unless they are using highly effective methods of contraception during the entire study or longer if required by locally approved prescribing information (e.g., in European Union (EU) 20 weeks). Of note: the highly effective methods of contraception are mandated due to SoC medications used as per protocol (MPA and CYC).

    Highly effective contraception methods include:

    - Total abstinence, when this is in line with the preferred and usual lifestyle of the participant. Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception.
    - Female sterilization (have had surgical bilateral oophorectomy [with or without hysterectomy], total hysterectomy or tubal ligation at least six weeks before taking study treatment). In case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow-up hormone level assessment.
    - Male sterilization (at least 6 months prior to Screening). The vasectomized male partner should be the sole partner for that participant.

- Use of oral (estrogen and progesterone), injected or implanted hormonal methods of contraception or other forms of hormonal contraception that have comparable efficacy (failure rate < 1%), for example hormone vaginal ring or transdermal hormone contraception or placement of an intrauterine device (IUD) or intrauterine system (IUS). In case of use of oral contraception, women should have been stable on the same treatment for a minimum of 3 months prior to Randomization.

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

If stricter female or male contraception requirements are specified in the country-specific label for induction and maintenance standard of care medications, they must be followed.

Note: Women are considered post-menopausal and not of childbearing potential if they have had 12 months of natural (spontaneous) amenorrhea with an appropriate clinical profile (e.g., age appropriate, history of vasomotor symptoms) or have had surgical bilateral oophorectomy (with or without hysterectomy), total hysterectomy or tubal ligation at least six weeks prior to enrollment. 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 childbearing potential.

6 Treatment

6.1 Study treatment

6.1.1 Investigational and control drugs

Novartis Global Clinical Supply (GCS) will supply the following study treatments:

Table 6-1 Investigational and control drug

Investigational/ Control Drug (Name and Strength)	Pharmaceutical Dosage Form	Route of Administration	Supply Type	Sponsor (global or local)
AIN457 150mg / 1mL	Solution for Injection	Subcutaneous use	Double blinded prefilled syringes (PFS)	Novartis Pharma AG
AIN457 0 mg / 1mL (Placebo)	Solution for Injection	Subcutaneous use	Double blinded prefilled syringes (PFS)	Novartis Pharma AG

The PFSs are packed in a double blinded fashion and do not need to be prepared.

Each study site will be supplied by Novartis with investigational treatment in packaging of identical appearance. The investigational treatment packaging has a 2-part label. A unique Randomization number is printed on each part of this label, which corresponds to placebo or active treatment.

The study treatments will be labeled as follows: Double blind secukinumab and placebo PFS will be labeled AIN457 150 mg/1 mL/Placebo.

6.1.2 Additional study treatments

No other study treatment beyond investigational drug and control drug are included in this trial.

6.1.3 SoC background therapy

All participants will receive SoC background regimen for induction and maintenance therapy.

Table 6-2 Background therapy

Name of the medication	Dosage Form	Route of administration	Availability
MMF/MPA	Tablet	Oral	Open-label participant packs
CYC	Powder for solution for infusion	Intravenous	Open-label participant packs
Corticosteroids	Tablets and/or Solution for injection	Oral and/or Intravenous use	Open-label participant packs

Background SoC medications will NOT be provided by Novartis GCS and must be handled at the country level.

6.1.3.1 Induction therapy

The induction therapy will consist of either MPA or low-dose CYC, in combination with corticosteroids. The choice of the induction SoC therapy, MPA or low-dose CYC will be left at the investigator's discretion. To ensure a balanced representation in both treatment arms (secukinumab or placebo), participants will be stratified at time of Randomization according to their SoC induction therapy. A maximum of 25% of participants receiving CYC-based SoC induction therapy will be allowed to be randomized in the study (maximum of 100 participants in the study).

MPA:

Target dose during the first six-month treatment period (MPA induction period) is 2 g/day of MMF or equivalent dosage of enteric-coated MPA of 1440 mg/day. If required, a dose up to 3 g/day of MMF or equivalent dosage of enteric-coated MPA of 2160 mg/day is allowed, based on Investigator’s judgement. A reduction of MPA dose is only allowed in case of toxicity, as per Investigator's decision.

Optional Run-in period

Participants not already on MPA at study entry will be initiated, after verification of eligibility, on an MMF dose of 1 g/day (divided q12h or an equivalent dosage of enteric-coated MPA of 720 mg/day. The dose must be increased to 2 g/day of MMF or equivalent dosage of enteric-coated MPA in the second week, and up to 3 g/day of MMF or equivalent dosage of enteric-coated MPA in the third week when required. If participants experience adverse effects that prevent up-titration as described, an additional 1 week of titration is permitted. If MMF/MPA dose escalation is clinically inappropriate as judged by the investigator, or inconsistent with local treatment guidelines, participants can take a dose of 1-2 g/day MMF or equivalent dosage of enteric-coated MPA in the absence of observed toxicity.

Low-dose CYC:

The low-dose CYC induction treatment consists of 6 administrations of 500 mg i.v. CYC every 2 weeks. All i.v. CYC administration will be performed according to the site and/or local guidelines, including the administration of any medication for prophylaxis of potential toxicities.

The first i.v. CYC administration will be performed at Baseline visit, after all inclusion/exclusion criteria would have been verified.

Corticosteroids:

Pulse i.v. corticosteroid should be initiated at Baseline visit (500–1000 mg methylprednisolone daily) for a maximum of 3 doses. This will be followed by daily administration of oral glucocorticoids at initial dose of 0.3 to 0.5 mg/kg/day to be tapered within 16 weeks to the minimal dose necessary to control disease (see recommended guidance on Table 6-3).

Participants who cannot take the pulse i.v. corticosteroid therapy should directly start on 0.3-0.5 mg/kg/day oral dose of glucocorticoid followed by the above-described tapering.

Participants having already received pulse i.v. corticosteroids up to a cumulative dose of 3000 mg within 12 weeks prior to Baseline do not need to repeat the i.v. pulse. For these participants already on corticosteroids at Baseline, a predefined steroid taper regimen (see Table 6-3) should be implemented.

In all cases, from Week 16 onward, the target dose of oral corticosteroids is 5 mg daily (prednisone equivalent).

Table 6-3 Guidance for corticosteroid (prednisone equivalent) taper

Initial Dose	40 mg	30 mg	20 mg
Week 2	30	25	15
Week 4	25	20	15
Week 6	20	15	10
Week 8	15	10	10
Week 12	10	10	10
Week 16 and thereafter maintain at 5 mg where possible * acceptable dose range	5 *7.5 – 2.5	5 *7.5 – 2.5	5 *7.5 – 2.5

6.1.3.2 Maintenance therapy

After the induction period (6 months for MPA-based induction; 12 weeks for CYC-based induction), all participants must receive MPA-based maintenance therapy.

The target dose during the maintenance period is 1-2 g/day of MMF or of equivalent dosage of enteric-coated MPA. Further reduction of MMF to 0.5 g/day or of equivalent dosage of enteric-coated MPA is allowed as per Investigator's decision.

In addition, all participants will receive a maintenance dose of oral corticosteroids as per Table 6-3 above, with a target dose of 5 mg/day prednisone equivalent (2.5-7.5 mg/day acceptable dose range) from Week 16.

A recommended diagram for administration of SoC background therapy from the Run-In period until Week 24 is provided in Appendix 16.4.

6.1.4 Treatment arms/group

At Baseline, all eligible participants will be randomized to one of the two treatment arms in a 1:1 ratio via Interactive Response Technology (IRT):

- Arm 1: approximately 200 participants with LN will receive secukinumab 300 mg s.c. (2 x 1.0 mL PFS of 150 mg dose) at Randomization (i.e., Baseline).
- Arm 2: approximately 200 participants with LN will receive placebo s.c. (2 x 1.0 mL PFS of 0 mg dose) at Randomization (i.e., Baseline).

At Randomization, participants will be stratified on the basis of the SoC induction therapy they will receive during the study, MPA or CYC-based, to ensure a balanced representation in each of the treatment arms (secukinumab or placebo).

6.1.5 Treatment duration

Participants will receive investigational treatment at Baseline, Weeks 1, 2 and 3, followed by administration every 4 weeks starting at Week 4, until Week 100. Participants will self-administer all secukinumab or placebo doses at the investigational site. Participants, who have completed the entire treatment period of this study up to and including Week 104 will be offered participation in the extension study CAIN457Q12301E1, if the investigator deems secukinumab therapy beneficial for these patients.

6.2 Other treatment(s)

6.2.1 Concomitant therapy

All medications, procedures, and significant non-drug therapies (including physical therapy and blood transfusions) administered after the participant was enrolled into the study must be recorded on the appropriate Case Report Form (CRF).

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 participant or allowing a new medication to be started. If the participant is already enrolled, contact Novartis to determine if the patient should continue participation in the study.

6.2.1.1 Permitted concomitant therapy requiring caution and/or action

Guidelines for the use of specific medications are provided below.

Participants may continue on the concomitant medication listed below provided they are on a stable dosage as described below and until the end of study. However, investigators may change the dose of concomitant medications during the study for safety reasons based on their clinical judgement. Each concomitant medication should be captured/recorded in the eCRF at every visit, including the dose changes when appropriate.

Anti-malarials

Participants will remain on one stable background anti-malarial medication (e.g., hydroxychloroquine) in addition to the SoC medication. Participants who have not taken previously anti-malarial medication should be initiated on an anti-malarial at least 10 days prior to Randomization (unless contraindicated) and remain on a stable dose throughout the trial. Refer to Section 5.1 Inclusion Criteria.

Anti-hypertensive medication

Participants already taking angiotensin-converting enzyme (ACE) inhibitors or angiotensin receptor blockers (ARBs) at Screening should remain on the same dose throughout the study unless precluded by toxicity or if dose adjustment is required for hypertensive control. Combination therapy with an ACE inhibitor and an ARB will not be allowed. For participants not already receiving one of these agents, it is recommended that treatment with an ACE inhibitor or ARB should be initiated during Screening (unless contraindicated) and be given at a stable dose for at least 7 days prior to Randomization. These therapies should not be initiated after study Baseline.

Cholesterol-lowering drugs

Concomitant treatment with cholesterol-lowering drugs (e.g., statins) will continue if prescribed prior to the study and will be recorded in the eCRF. Statin treatment can be initiated during the course of the study if considered required by the Investigator. If the participant is on a cholesterol-lowering agent already at the time of Screening, the dose must be stable for at least 7 days prior to Randomization.

Nonsteroidal Anti-Inflammatory Drugs (NSAIDs)

NSAIDs may have impact upon renal function and therefore should only be used during the trial if deemed necessary by the Investigator, e.g., in cases such as the following:

- treatment of pleuritis and pericarditis.
- treatment of arthritis pain that is unresponsive to other treatment modalities (e.g., analgesics)

Osteoporosis Prevention /Treatment

Participants not already taking vitamin D (400 IU/day) and calcium supplements (1200 mg/day of calcium citrate or 1500 mg/day calcium carbonate) are allowed to start these medications, at the investigator's discretion (see ACR 2001). The above dosages can be modified as per local medical practice, to adhere to the dosage commonly used in each country.

Other Permitted Therapy

- Low dose aspirin for cardio-protection may be used at Investigator's discretion.
- Participants who use oral contraceptives or hormone-replacement therapy should continue their use.
- Any prophylaxis for CYC-induced toxicities, as per site and or local guidelines, if participant is to receive low-dose CYC-based induction treatment.

All other concomitant medications deemed necessary will be reviewed by the Investigator and decisions made on a case-by-case basis.

Note: Concomitant medications will not be provided by Novartis and must be supplied by the study center.

6.2.2 Prohibited medication

The following treatments are prohibited after Screening and during the course of the trial due to their mechanisms of action that can confound the study results. If administered, the participant is to be withdrawn from the study treatment:

- Initiation of CYC treatment (oral or i.v.) outside of the protocol planned low-dose CYC induction therapy for participants elected to receive CYC-based induction
- Initiation of rituximab or belimumab therapy
- Use of any other systemic biologic/non-biologic immunomodulatory treatment, including use of *i.v.* corticosteroids as rescue medication
- Administration of live vaccines

  Of note, the administration of other vaccines is acceptable, including the use of an inactivated, viral-vector- or mRNA-based SARS-CoV2 vaccine that is approved or the use of which has been authorized by the Health Authority in the respective country. The decision for vaccinating patients participating in this study against SARS-CoV2 is at the discretion of the Investigator, taking into consideration the individual patient's characteristics such as the presence of co-morbidities, prior and concomitant medications, as well as further risk factors applying to the patient.

6.2.3 Rescue medication

Rescue medication is defined as any new medication used because the participant's disease is not adequately controlled by the investigational study treatment in addition to the SoC background therapy.

Although no participant will be restricted from receiving necessary rescue medications for lack of benefit or worsening of the disease (e.g., experiencing a renal flare), participants will be discontinued from the study treatment if they are treated with prohibited medications (as described in Section 6.2.2). The choice of the rescue medication will be based on the treating Investigator's assessment and applicable regulatory guidelines.

Participants who discontinue investigational treatment can continue to attend all subsequent scheduled visit assessments unless informed consent is withdrawn as described in Section 9.1.1 Discontinuation of study treatment. If study investigational treatment is discontinued, participants may take study-prohibited medication under the investigator's guidance and as per locally approved prescribing information.

Use of rescue medication must be recorded on the appropriate eCRF page.

6.3 Participant numbering, treatment assignment, randomization

6.3.1 Participant numbering

Each participant is identified in the study by a Subject Number (Subject No.) that is assigned when the participant is first enrolled for Screening and is retained as the primary identifier for the participant throughout his/her entire participation in the trial. The Subject No. consists of

the Center Number (Center No.) (as assigned by Novartis to the investigative site) with a sequential participant number suffixed to it, so that each participant is numbered uniquely across the entire database. Upon signing the informed consent form, the participant is assigned to the next sequential Subject No. available.

6.3.2 Treatment assignment, randomization

At Baseline visit, all eligible participants will be randomized via Interactive Response Technology (IRT) to one of the treatment arms. The investigator or his/her delegate will contact the IRT after confirming that the participant fulfills all the inclusion/exclusion criteria. The IRT will assign a randomization number to the participant, which will be used to link the participant to a treatment arm and will specify a unique medication number for the first package of study treatment to be dispensed to the participant.

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

Randomization will be stratified by the SoC induction therapy participants will receive (MPA or CYC-based). A maximum of 25% of the randomized participants will receive low-dose CYC induction therapy (up to 50 participants per treatment arm). This will ensure that participants can be treated with SoC therapy as per site and/or local guidelines, and a balanced repartition within the two treatment arms.

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

6.4 Treatment blinding

This is a double-blind, randomized treatment trial.

Participants, investigator staff, persons performing the assessments will remain blinded to the identity of the treatment from the time of Randomization until final 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 with the following exceptions:

- Specific vendors whose role in the clinical trial requires their unblinding (e.g., IRT)
- Global Clinical Supply
- The designated Novartis study team members involved in the primary endpoint analysis
- [redacted]

(2) The identity of the treatments will be concealed by the use of study treatments in the form of PFS, filled with secukinumab or placebo, that are all identical in packaging, labeling, appearance and schedule of administration.

[redacted]

As the primary endpoint analysis will be performed at Week 52, there will be a database lock when all participants have completed Week 52 assessments. Summary results may be shared internally and externally; additionally, after the study is completed and study results are made publicly available, upon request by participants, the Study Doctor will ensure individual research results (IRR) are returned to participants.

If the DMC provides a positive recommendation after the second interim analysis, designated members from the Novartis Global Team may have access to unblinded results. However, subjects and site staff directly involved in the conduct of the trial, i.e., investigator staff and persons performing the assessments, will remain blinded to individual treatment allocation until the conclusion of the study to ensure study integrity is maintained. For details regarding the planned Interim Analyses, refer to Section 4.4 Purpose and timing of interim analyses/design adaptation, and Section 12.7 Interim analyses.

A final database lock will occur when all participants have completed the study. After the Week 104 analysis has been conducted, the Novartis clinical team will notify the investigative staff and the IRT system and site personnel and the participant will be unblinded to the originally assigned treatment arms.

The high sensitivity C-reactive protein (hsCRP) results from samples collected during the treatment period will be revealed only after database lock and analyses are completed.

6.5 Dose escalation and dose modification

Investigational study treatment dose adjustments are not permitted.

6.5.1 Dose modifications

Study treatment interruption is only permitted if, in the opinion of the investigator, a participant 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 appropriate eCRF.

6.5.2 Follow-up for toxicities

Participants whose treatment is interrupted or permanently discontinued due to an adverse event or clinically significant abnormal laboratory value, must be followed up in accordance with what is clinically indicated per the investigator until resolution or stabilization of the event, whichever comes first. Appropriate clinical experts such as ophthalmologist, endocrinologist, dermatologist, psychiatrist, etc., should be consulted as deemed necessary.

6.6 Additional treatment guidance

6.6.1 Treatment compliance

6.6.1.1 Study treatment compliance

Administration of study treatment will occur at the study site through Week 100. The first study treatment administration will occur at the Baseline/Randomization visit only after eligibility criteria have been confirmed, all study Baseline assessments have been performed, and the scheduled blood samples have been drawn.

Compliance is expected to be 100% unless temporary interruption is needed for safety reasons as described in Section 6.5.1. Compliance will also be assessed by a Novartis monitor using information provided by authorized site personnel.

All doses of study treatment administration will be recorded on the appropriate eCRF page.

6.6.1.2 Standard of care treatment compliance

All intravenous administration of SoC, like CYC or pulses of glucocorticoids as specified in Section 6.1.3 SoC background therapy, must be administered at the study site under the supervision of appropriate personnel. Doses administered and dates should be recorded on the appropriate eCRF pages.

Oral doses of MPA or corticosteroids, as specified in Section 6.1.3, will be taken by the participant at home.

The investigator must promote compliance by instructing the participant to take the SoC treatment exactly as prescribed and by stating that compliance is necessary for the participant's safety and the validity of the study. The participant must also be instructed to contact the investigator if he/she is unable for any reason to take the SoC treatment as prescribed. Compliance will be assessed by the investigator and/or study personnel at each visit by reviewing the information provided by the participant. This information should be captured in the source document at each visit.

6.6.2 Recommended treatment of adverse events

Treatments for AEs are at the discretion of the investigator or treating physician. Refer to the Investigator's Brochure for AEs related to secukinumab.

Medication used to treat AEs must be recorded on the appropriate eCRF.

6.6.3 Emergency breaking of assigned treatment code

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

automatically inform the Novartis monitor for the site and the study team that the code has been broken.

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

- protocol number
- study drug name
- subject number

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

Study drug should be discontinued after emergency unblinding.

6.7 Preparation and dispensation

Each study site will be supplied with investigational study drug in packaging as described under investigational and control drugs Section 6.1.1.

Secukinumab solution for s.c. injection or placebo secukinumab solution (active or placebo, respectively) will be provided in prefilled syringes (PFS).

Each participant will require one box with PFS per dose throughout the study:

· One secukinumab 300 mg (2 x 1.0 mL PFS of 150 mg dose) OR

· One secukinumab placebo (2 x 1.0 mL PFS)

All study treatment kits assigned to the participant by IRT during the study will be captured in the IRT system.

The first study treatment administration will occur at the Baseline/Randomization visit after the inclusion/exclusion criteria have been confirmed and all study scheduled assessments have been performed, including completion of PRO and blood withdrawal.

All doses of study treatment (secukinumab and/or placebo) will be self-administered by the participant/trained caregiver at the study site after the study assessments for the visits have been completed.

At the Baseline visit, participants will be instructed by the site staff on how to self-inject via the PFS (Instructions for Use (IFU) containing detailed information about self-administration of study treatment should be provided to each participant at the beginning of the study). After providing detailed explanations/instructions, participants will then be asked to raise any questions.

Thereafter, they will proceed with self-injection. At Week 1, participants will be asked to refer to the IFU and to proceed with self-injection of the study treatment (i.e., without a detailed explanation/instruction on handling the syringe).

A unique medication number is printed on the study medication label. Investigator staff will identify the study medication kits to dispense to the participant by contacting the IRT and

obtaining the medication number(s). The study medication has a 2-part label (base plus tear-off label), immediately before dispensing the medication kit to the participant, site personnel will detach the outer part of the label from the packaging and affix it to the source document.

6.7.1 Handling of study treatment and additional treatment

6.7.1.1 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 designated site personnel have access. Upon receipt, all study treatment must be stored according to the instructions specified on the labels and in the Investigator's Brochure. Clinical supplies are to be dispensed only in accordance with the protocol. Technical complaints are to be reported to the respective Novartis Country Organization (CO) Quality Assurance.

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

The PFS (150 mg active/placebo) sealed in their outer box must be stored in an access controlled/locked refrigerator between 2°C and 8°C (36°F and 46°F) (Do Not Freeze) and protected from light. They must be carefully controlled in accordance with regulations governing investigational medicinal products and local regulations.

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.

Subcutaneous administration with PFSs

The study treatment solution **must** be injected into **non-affected** areas of the skin.

The injections will be self-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 participant chooses the abdomen, a 2-inch/5-centimeter area around the navel should be avoided. Investigational drug should not be injected into areas where the skin is tender, bruised, red, or hard, or where participant has scars or stretch marks.

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

Destruction of the unused drug should be done according to local requirements and after approval by the Novartis Clinical Team.

6.7.1.2 Handling of additional treatment

The following non-study treatment will be monitored specifically:

- SoC background therapy, as described in Section 6.1.3
- Concomitant therapy as described in Section 6.2.1, e.g., anti-malarials, ACE or ARBs

7 Informed consent procedures

Eligible participants may only be included in the study after providing (witnessed, where required by law or regulation) Institutional Review Board (IRB)/IEC-approved informed consent.

If applicable, in cases where the participant's representative(s) gives consent (if allowed according to local requirements), the participant must be informed about the study to the extent possible given his/her understanding. If the participant is capable of doing so, he/she must indicate agreement by personally signing and dating the written informed consent document.

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 participant's source documents.

Novartis will provide to investigators in a separate document a proposed informed consent form that complies with the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use - Good Clinical Practice (ICH GCP) guidelines and regulatory requirements and is considered appropriate for this study. Any changes to the proposed consent form suggested by the investigator must be agreed by Novartis before submission to the IRB/IEC.

Information about common side effects already known about the investigational drug can be found in the Investigator's Brochure (IB). This information will be included in the participant informed consent and should be discussed with the participant during the study as needed. Any new information regarding the safety profile of the investigational drug 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 then must be discussed with the participant.

Women of childbearing 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.

The study includes two optional components, namely a biomarker component and a deoxyribonucleic acid (DNA)/ribonucleic acid (RNA)/Pharmacogenetics component. Each of them requires a separate signature if the patient agrees to participate. It is required as part of this protocol that the Investigator presents these options to the participants, as permitted by local governing regulations. The process for obtaining consent should be exactly the same as described above for the main informed consent.

Declining to participate in these optional assessments (DNA/RNA/Pharmacogenetics or biomarkers) will in no way affect the participant's ability to participate in the main research study.

A copy of the approved version of all consent forms must be provided to Novartis/sponsor after IRB/IEC approval.

Participants might be asked to complete an optional questionnaire to provide feedback on their clinical trial experience.

8 Visit schedule and assessments

Assessment schedule (Table 8-1) lists all of the assessments when they are performed. All data obtained from these assessments must be supported in the participant's source documentation.

Participants should be seen for all visits/assessments as outlined in the assessment schedule (able 8-11or as close to the designated day/time as possible. Missed or rescheduled visits should not lead to automatic discontinuation of study investigational treatment or study. Handling of participants who discontinue study treatment or study prematurely is described in Section 9.1 Discontinuation.

Table 8-1 Assessment Schedule

Period	Screening	Extension Run-In	Treatment Year 1																			
Visit Name	Screening[2]	Optional MPA run-in[3]	Treatment Baseline	Day 2 (i.v. CS)	Day 3 (i.v. CS)	Week 1	Week 2	Week 3	Week 4	Week 6 (CYC)	Week 8	Week 10 (CYC)	Week 12	Week 16	Week 20	Week 24	Week 28	Week 32	Week 36	Week 40	Week 44	Week 48	Week 52
Visit Numbers[1]	1	20	100	110	120	130	140	150	160	170	180	190	200	210	220	230	240	250	260	270	280	290	300
Days	-42 to -1	-28 to -1	1	2	3	8	15	22	29	43	57	71	85	113	141	169	197	225	253	281	309	337	365
Informed consent	X																						
Pharmacogenetic Informed Consent	X																						
Biomarker Informed Consent	X																						
Demography	X																						
Inclusion / Exclusion criteria	X[4]	X[4]	X																				
Medical history/current medical conditions[5]	X		X																				
SLE and LN medical history and previous therapies	X																						
Tuberculosis test[6]	X																						
Smoking history	X																						
Chest X-ray[7]	X																						
Body Height	X																						
Serology[8]	X																						
Randomization			X																				
Physical Examination[9]	X		X			X	X	X	X		X		X	X	X	X	X	X	X	X	X	X	X
Body Weight & BMI[10]	X		X			X	X	X	X		X		X	X	X	X	X	X	X	X	X	X	X
Vital Signs	X		X			X	X	X	X		X		X	X	X	X	X	X	X	X	X	X	X
12-Lead ECG[11]			X																				
Renal biopsy[12]	X																						
Record of Menses	X		X			X	X	X	X		X		X	X	X	X	X	X	X	X	X	X	X
Hematology	X		X			X	X	X	X		X		X	X	X	X	X	X	X	X	X	X	X
Clinical Chemistry	X		X			X	X	X	X		X		X	X	X	X	X	X	X	X	X	X	X
Coagulation Panel	X		X			X	X	X	X		X		X	X	X	X	X	X	X	X	X	X	X
Fasting lipid panel[13]			X								X		X			X							X
[redacted]																							
24-hr urine collection (UPCR [redacted][14])			X[16]										X[16]			X[16]			X[16]				X[16]
FMV urine collection [redacted] (central/local assessments)[17]	X		X			X	X	X	X		X		X	X	X	X	X	X	X	X	X	X	X
Pregnancy Test[18]	X		X			X	X	X	X		X		X	X	X	X	X	X	X	X	X	X	X
CRP and ESR	X		X								X		X			X			X				X
[redacted]																							

Period	Screening	Extension Run-In	Treatment Year 1																				
Visit Name	Screening [2]	Optional MPA run-in [3]	Treatment Baseline	Day 2 (i.v. CS)	Day 3 (i.v. CS)	Week 1	Week 2	Week 3	Week 4	Week 6 (CYC)	Week 8	Week 10 (CYC)	Week 12	Week 16	Week 20	Week 24	Week 28	Week 32	Week 36	Week 40	Week 44	Week 48	Week 52
Visit Numbers [1]	1	20	100	110	120	130	140	150	160	170	180	190	200	210	220	230	240	250	260	270	280	290	300
Days	-42 to -1	-28 to -1	1	2	3	8	15	22	29	43	57	71	85	113	141	169	197	225	253	281	309	337	365
FACIT-Fatigue			X										X			X			X				X
SF36 [19]			X										X			X			X				X
LupusQoL			X										X			X			X				X
Prior/Concomitant medications	X	X	X			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Adverse Events [20]	X	X	X			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
[redacted]																							
Blood collection for DNA/RNA (optional)			X																				
Study drug administration			X			X	X	X	X		X		X	X	X	X	X	X	X	X	X	X	X
Standard of Care administration [23]		X	X	X [24]	X [24]	X	X	X	X	X [25]	X	X [25]	X	X	X	X	X	X	X	X	X	X	X
Trial Feedback Questionnaire			X																				X

X Assessment to be recorded in the clinical database or received electronically from a vendor

[1] Visit structure given for internal programming purpose only

[2] Screening period will be up to 42 days depending on the MPA Run-in need. The duration of the Screening period must be kept at a minimum.

[3] For participants not yet on MPA at Screening, a Run-in period can optionally be considered

[4] These assessments are source documentation only and will not be entered into the eCRF. However, data regarding to which inclusion/exclusion criteria are not met are captured on the Inclusion/Exclusion eCRF.

[5] Included in Medical History and recorded in the eCRF on the corresponding page.

[6] PPD/QuantiFERON®

[7] not required if chest X-ray, CT or MRI of the chest have been taken in the past three months prior to Screening that show no clinically significant abnormality

[8] Hepatitis B and/or C and/or HIV serology testing performed during Screening period only if required as per local medical practice or regulators prior to initiation of therapy. These assessments will be documented in source records only and will not be entered into eCRF

[9] These assessments are source documentation only and will not be entered into the eCRF. However, data regarding to which inclusion/exclusion criteria are not met should be captured on the Inclusion/Exclusion eCRF. After the Baseline visit, the investigator should do an abbreviated physical exam focusing on relevant clinical areas

[10] Body Mass Index (BMI) to be automatically calculated by Novartis

[11] performed locally

[12] To enter the study, participants must have a biopsy demonstrating active glomerulonephritis WHO or ISN/RPS class III or IV LN [excluding III (C), IV-S (C) and IV-G (C)]; participants are permitted to have co-existing class V. Renal biopsy must have been performed within 6 months prior to Screening. Otherwise, a new renal biopsy must be performed during Screening, once all other eligibility criteria have been confirmed. Any subsequent biopsies (e.g., upon disease flare) may be performed where considered appropriate by the investigator

[13] Samples for Lipid panel should be obtained after an overnight fast (10hr or more)

[redacted]

[15] Including central determination of UPCR [redacted] calculation

[16] Site to ensure that a urine container is dispensed at previous site visit

[17] First morning void urine sample will be collected for 1) local determination of urinary sediment and standard safety evaluation and 2) central determination of UPCR. Jugs for the Urine collection will be dispensed at previous visit
[18] Pregnancy tests will be conducted for women of child bearing potential; serum pregnancy test at Screening and Urine pregnancy test at all other time points
[19] SF-36 v2 performed (both PCS and MCS)
[20] AEs/SAEs occurring after the participant has provided informed consent must be reported.
[redacted]
[23] Background SoC therapy will be administered during the whole treatment period on a daily basis for MPA and Corticosteroids, cyclophosphamide induction every 2 weeks for 3 months
[24] for site administration of i.v. corticosteroids only
[25] for site administration of i.v. cyclophosphamide only
[26] planned End of Treatment (EOT) period visit will be performed at Week 104. Participants who discontinue study treatment prematurely for any reason other than withdrawal of informed consent before Week 104 will not be considered as discontinued from the study. Please refer to Section 9.1 Discontinuation for detailed instructions.

Period	Treatment Year 2													
Visit Name	Week 56	Week 60	Week 64	Week 68	Week 72	Week 76	Week 80	Week 84	Week 88	Week 92	Week 96	Week 100	EOT[26]	EOS
Visit Numbers[1]	310	320	330	340	350	360	370	380	390	400	410	420	430	1999
Days	393	421	449	477	505	533	561	589	617	645	673	701	729	785
Physical Examination[9]	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Body Weight & BMI[10]	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Vital Signs	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Record of Menses	X	X	X	X	X	X	X	X	X	X	X	X	X	
Hematology	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Clinical Chemistry	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Coagulation Panel	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Fasting lipid panel[13]						X							X	
[redacted]														
24-hr urine collection (UPCR/[redacted])[15]						X[16]							X[16]	
FMV urine collection (central/local assessments)[17]	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Pregnancy Test[18]	X	X	X	X	X	X	X	X	X	X	X	X	X	X
CRP and ESR						X							X	
[redacted]														
FACIT-Fatigue						X							X	
SF36[19]						X							X	
LupusQoL						X							X	
Prior/Concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Adverse Events[20]	X	X	X	X	X	X	X	X	X	X	X	X	X	X
[redacted]														
Study drug administration	X	X	X	X	X	X	X	X	X	X	X	X		
Standard of Care administration[23]	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Trial Feedback Questionnaire														X

[X] Assessment to be recorded in the clinical database or received electronically from a vendor
[1] Visit structure given for internal programming purpose only
[9] These assessments are source documentation only and will not be entered into the eCRF. After the Baseline visit, the investigator should do an abbreviated physical exam focusing on relevant clinical areas
[10] Body Mass Index (BMI) to be automatically calculated by Novartis
[11] performed locally
[13] Samples for Lipid panel should be obtained after an overnight fast (10hr or more)
[redacted]
[15] including central determination of UPCR [redacted] calculation
[16] site to ensure that a urine container is dispensed at previous site visit
[17] First morning void urine sample will be collected for 1) local determination of urinary sediment and standard safety evaluation and 2) central determination of UPCR. Jugs for the Urine collection will be dispensed at previous visit
[18] Pregnancy tests will be conducted for women of childbearing potential; serum pregnancy test at Screening and Urine pregnancy test at all other time points
[19] SF-36 v2 performed (both PCS and MCS)
[20] AEs/SAEs occurring after the participant has provided informed consent must be reported.
[redacted]
[23] Background SoC therapy will be administered during the whole treatment period on a daily basis for MPA and Corticosteroids, cyclophosphamide induction every 2 weeks for 3 months
[26] Planned End of Treatment (EOT) period visit will be performed at Week 104. Participants who discontinue study treatment prematurely for any reason other than withdrawal of informed consent before Week 104 will not be considered as discontinued from the study. Please refer to Section 9.1 Discontinuation for detailed instructions

8.1 Screening

A Screening period of up to 6 weeks will be used to assess participant´s eligibility (Day -42 to Day -1). While this duration should provide enough time to evaluate eligibility of the participant, including renal biopsy evaluation, it could be extended on a case-by-case basis, to be discussed with the Sponsor, to allow for retest of inclusion/exclusion assessments.

Once eligibility is confirmed, participants elected to receive MPA-based induction SoC therapy and not already on this background therapy will be initiated on MPA (MMF or enteric-coated MPA sodium) during the run-in period (Day-28 to Day-1). These participants will be initiated on an MMF dose of 1 g/day (divided q 12 h.)/equivalent dosage of enteric-coated MPA. Doses are to be increased to 2 g/day of MMF/equivalent dosage of enteric-coated MPA in the second week and up to 3 g/day of MMF/equivalent dosage of enteric-coated MPA in the third week, if tolerability allows. If participants experience adverse effects, which prevent up-titration as described, an additional 1 week of titration is permitted. If MMF dose escalation is clinically inappropriate as judged by the investigator or inconsistent with local treatment guidelines, participants can take a dose of 1.5-2 g/day MMF/equivalent dosage of enteric-coated MPA in the absence of observed toxicity.

All participants evaluated at Screening for eligibility should not be screen failed on the basis of a medication requiring washout, unless the participant will be unable to complete the washout in the appropriate time frame before Randomization.

Participants who prematurely withdraw from the study treatment will not be replaced.

In the case where a safety laboratory assessment at Screening and/or Baseline is outside of the range specified in the exclusion criteria, the assessment may be repeated once prior to Randomization. If the repeat value remains outside of the specified ranges, the participant must be excluded from the study.

8.1.1 Information to be collected on Screening failures

Participants who sign an informed consent form 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 Screening visit date, demographic information, informed consent, Inclusion/Exclusion, participant re-screening (for re-screened participants) pages must also be completed for screen failure participants. No other data will be entered into the clinical database for participants who are screen failures, unless the participant experienced a serious adverse event during the Screening phase (see SAE Section 10.1.3 for reporting details).

AEs that are not SAEs will be followed up by the investigator and collected only in source data.

If the participant fails to be randomized, the IRT must be notified within 2 days of the screen fail that the participant was not randomized.

Participants who are randomized and fail to start treatment, e.g., participants randomized in error, will be considered as early terminated. The reason for early termination should be recorded on the appropriate eCRF. If consent was withdrawn during the Screening period before the participant was randomized, complete the appropriate eCRF.

8.1.2 Re-screening

It is permissible to re-screen a participant 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.

If a participant re-screens for the study, the participant must sign a new ICF and be issued a new subject number prior to any Screening assessments being conducted under the new subject number. For all re-screened participants, the investigator/qualified site staff will record if the participant was re-screened on the re-screening eCRF and the original Screening number the participant was issued prior to the current Screening number. The date of the new informed consent signature must be entered in the Informed Consent eCRF corresponding to the new subject number.

For re-screening, all Screening assessments must be performed per protocol, except the tuberculosis (TB) work up (if applicable). If the date of the TB work up is less than 12 weeks from the projected Baseline date, then it is not required that the TB work up be repeated; however, the re-screened participant must repeat PPD skin test or the QuantiFERON TB-Gold performed by the central laboratory.

Participants who are mis-randomized cannot be re-screened.

8.2 Participant demographics/other Baseline characteristics

Country-specific regulations should be considered for the collection of demographic and Baseline characteristics in alignment with eCRF.

8.2.1 Demography

Demographics data to be collected on all participants and recorded in the eCRF include

- age,
- sex,
- race, and ethnicity

8.2.2 SLE/LN medical history/diagnosis

The following information should be collected and entered in the relevant eCRF:

- the date of first diagnosis for SLE and/or LN
- SLE/LN family history

8.2.3 Prior SLE/LN medications and therapy

Any treatment for SLE/ LN since initial diagnosis (as determined through medical history records or through participant interview) prior to study entry will be collected and recorded in the eCRF, along with the duration of the prior therapy, the response to the therapy and the reason for discontinuation.

8.2.4 Renal biopsy

An important criterion to be fulfilled for a participant to be randomized within the study is a renal biopsy showing active glomerulonephritis WHO or ISN/RPS Class III or IV LN [excluding III (C), IV-S (C) and IV-G (C)], with or without co-existing class V features. The

biopsy must have been performed within 6 months prior to Screening, or during Screening period if not available.

The local pathologist report confirming Class III or IV LN with active lesions must be kept as a source document at the site. In addition, it should be used to complete the Renal Biopsy Report eCRF page.

While the classification of the patient's LN for randomization will be based on the local pathologist report, a central reading of electronic images of the local biopsy slides will be performed for confirmation of the classification. The slides used for determination of the classification by the local pathologist shall be collected to allow for their digitalization. For this purpose, several slides, preferably representing the use of the three most important types of staining (e.g., H&E, PAS, silver staining), wherever available, should be collected. Details regarding collection of local biopsy slides will be outlined in the Central Laboratory Manual. Details regarding central reading of electronic images process, responsibilities and membership is described in a separate Central Pathologist Charter. All slides will be returned to the site after their digitalization.

8.2.5 Standard of care induction therapy

Before Randomization, during the Screening period, the investigator must define the SoC induction therapy that the participant will receive, MPA or CYC-based. (see Section 6.1.3 Standard of Care background therapy).

This will ensure that participants can be treated with SoC therapy as per site and/or local guidelines, and a balanced repartition within the two treatment arms (secukinumab and placebo).

The target will be to have a maximum of 25% of randomized participants receiving CYC-based induction therapy.

The choice of SoC induction therapy must be reported in the eCRF and confirmed at time of Randomization within the IRT system.

8.2.6 Smoking history

The current and /or previous use of tobacco will be recorded, as well as the estimate number of pack-years based on the approximate consumption per year.

8.2.7 Cardiovascular medical history

Protocol-solicited cardiovascular medical history will be collected on the appropriate eCRF page.

8.2.8 Relevant medical history/ current medical conditions

Relevant medical history and current medical conditions not related to the study indication, and which were present prior to signing of the informed consent, should be recorded in the Medical History eCRF. This includes surgical sterilization for females, if applicable.

Whenever possible, diagnoses and not symptoms should be recorded.

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

Significant findings that are observed after the participant has signed the ICF and that meet the definition of an AE must be recorded in the AE eCRF.

8.2.9 Prior and concomitant medications

Concomitant medications and prior medications taken over 6 months preceding study enrollment for reasons other than SLE/ LN will be captured at the Screening visit and updated as necessary in the relevant eCRF.

Any new medication taken during the course of the study should be collected on the relevant eCRF.

8.2.10 Determination of the tuberculosis status

Either a QuantiFERON TB-Gold test **or** a PPD skin test must be performed at the Screening visit for the determination of the participant's tuberculosis status. Participants with a positive test may participate in the study if further work up (according to local practice/guidelines) establishes conclusively that the participant has no evidence of active tuberculosis, or, if presence of latent tuberculosis is established, then treatment according to local country guidelines must have been initiated.

8.2.10.1 QuantiFERON TB-Gold test

A QuantiFERON TB-Gold test is to be performed at the Screening visit and the results to be known prior to Randomization to determine the participant’s eligibility for the trial. The test will be used to screen the participant population for latent tuberculosis infection.

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

8.2.10.2 PPD skin test

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

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

8.2.11 Hepatitis and human immunodeficiency virus (HIV) screen

Screening for hepatitis and HIV is optional, based on the judgment of the investigator or if required by local regulations. If hepatitis testing is performed, testing will include hepatitis B surface antigen (HBsAg) and anti-HCV antibodies. If HIV testing is performed, positive HIV

screening will be confirmed by a second technique available at the respective local laboratory, e.g., Western blot.

8.2.12 Electrocardiogram (ECG)

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

The ECG tracing must be labeled with study number, participant initials, subject number, date and time, and filed in the study site source documents. Any identifier details must be redacted, e.g., obscuring participant initials, date of birth.

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

For any ECGs with participant safety concerns, two additional ECGs must be performed to confirm the safety finding. Clinically significant ECG findings at Baseline must be discussed with the sponsor before administration of investigational treatment. Clinically significant abnormalities must be recorded on the relevant section of the medical history/Current medical conditions/AE eCRF as appropriate.

8.3 Efficacy

Clinical efficacy measurements related to primary and secondary objectives are described in the subsections below.

8.3.1 Complete Renal Response (CRR)

The CRR will be used to determine efficacy. CRR is a composite endpoint defined as:

- eGFR $\geq$ 60 mL/min/1.73m^2 or no less than 85% of Baseline

and

- 24-hour UPCR $\leq$ 0.5 mg/mg

In addition, the estimand definition for primary endpoint is specified in Section 12.4.1.

8.3.1.1 Estimated glomerular filtration rate (eGFR)

The glomerular filtration rate will be estimated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation (Martínez-Martínez et al 2013) (see appendix Section 16.3) based on participant gender, age (years) and serum creatinine (mg/dL).

Central laboratory serum creatinine values will be used for all renal function data analysis.

8.3.1.2 Urine Protein-to-Creatinine Ratio (UPCR)

Urine Protein-to-Creatinine Ratio (UPCR), expressed in mg/mg, will be determined by a central laboratory by dividing the protein concentration by the creatinine concentration as measured in the urine collected.

Depending on the objective to be assessed, the UPCR will be determined using one of the following two types of urine collection, 24-hour urine collection or first morning void urinary sample, as indicated in Section 2, Table 2-1 Objectives and related endpoints.

Both the 24-hour urine collection and the first morning void will be collected in the participants' home.

8.3.2 Partial Renal Response (PRR)

PRR is a composite endpoint defined as:

- eGFR ≥ 60 mL/min/1.73m^2 or no less than 85% of Baseline

and

- ≥50 % reduction in 24-hour UPCR to sub-nephrotic level (≤ 3 mg/mg) compared to Baseline

8.3.3 Average daily dose of corticosteroids

Average daily dose of oral corticosteroids doses will be used to demonstrate superiority of secukinumab compared to placebo in the averaged daily dose of oral corticosteroids administered between Week 16 and Week 52.

8.3.4 Functional Assessment of Chronic Illness Therapy – Fatigue (FACIT-Fatigue©)

The FACIT-Fatigue© is a 13-item questionnaire (Cella et al 1993), (Yellen et al 1997) that assesses self-reported fatigue and its impact upon daily activities and function over the past week. The purpose of the FACIT-Fatigue© in this study is to assess the impact of fatigue on patients with LN.

The level of fatigue is measured on a 5-point Likert scale (0 = not at all, 1 = a little bit, 2 = somewhat, 3 = quite a bit, 4 = very much).

The purpose of FACIT-Fatigue© in this study is to demonstrate superiority of secukinumab compared to placebo on the mean change of score.

8.3.5 Short Form Health Survey (SF-36)

The Medical Outcome Short Form Health Survey (SF-36) Version 2 (Acute Form) is a survey evaluating individual participants' health status, which also monitors and compares participants' disease burden. This has been widely used to assess physical, psychological and social impact of chronic disease like LN (Holloway et al 2014).

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 et al 1993). Two overall summary scores, the Physical Component Summary (PCS) and the Mental Component Summary (MCS) also can be computed (Ware et al 1994). In this trial, SF-36-PCS responder (improvement of ≥ 2.5 points, (Lubeck 2004)) will be evaluated. 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 participants. The

purpose of the SF-36 in this study is to assess the HRQoL of participants with active LN. Given the acute nature of this disease, version 2, with a one-week recall period, will be used in this study.

8.3.6 Lupus Quality of Life (LupusQoL)

The LupusQoL is a disease-specific, 34-item, self-report questionnaire designed to measure the health-related quality of life (HRQoL) of patients with SLE within 8 domains (i.e., physical health (8 items), emotional health (6 items), body image (5 items), pain (3 items), planning (3 items), fatigue (4 items), intimate relationships (2 items), and burden to others (3 items). Responses are based on a 5-point Likert scale where 0 (all of the time) to 4 (never) (Yazdany 2011), (RWS Life).

Each domain of the LupusQoL is scored separately.

8.3.7 Urinary sediment

Urinary sediment will be determined at site at each visit using the first morning void sample.

Presence of red blood cells (RBCs), white blood cells (WBCs), epithelial cells, and cellular casts (RBC and WBC casts) will be determined by microscopic evaluation or through automated evaluation performed at local laboratory. Results must be recorded on the appropriate eCRF.

Active urinary sediment is defined as the presence of cellular casts (RBC or WBC casts), or hematuria (> 5 RBCs per high power field or above the laboratory reference range).

8.3.8 Appropriateness of efficacy assessments

The proposed primary endpoint is in line with the CHMP guideline, which recommends that studies conducted in patients with LN should be aimed for the control of renal activity with primary outcome focusing on renal specific endpoints such as induction of CRR.

The CRR is demonstrated as a clinically significant improvement of renal function as measured by improvement of eGFR ((≥ 60 mL/min/1.73 m2)/return to Baseline eGFR), and a reduction in renal injury as measured by reduction in proteinuria (<0.5 mg/mg in 24-hour) [redacted] The urinary sediment was removed from the components of the primary endpoint CRR after consultation of Food and Drug Administration (FDA) and European Medicines Agency (EMA), due to the difficulty to standardize methods of evaluation for urinary sediment across a multicenter study, and because the selection of the appropriate population (active class III or IV LN) is ensured by renal biopsies performed within 6 months of enrollment.

The proposed secondary endpoints, such as the composite PRR, or laboratory indices of the activity of renal diseases such as proteinuria, are in line with the CHMP guidelines.

In addition, both CRR and PRR have been previously used in clinical trials in LN, as a measure of renal activity.

As chronic fatigue and participant's disease burden may interfere with daily activities and quality of life, additional patient reported outcome measures (PROs) of physical functioning and health-related quality of life (HRQoL) tools will be used for assessing participant's perception of the impact of the disease and treatment on daily life. While FACIT-Fatigue© and

SF36 PCS are not disease specific, it has been widely used to assess physical, psychological and social impact of chronic diseases including SLE. The lupus specific quality of life instrument LupusQoL will be evaluated to further evaluate the impact of the disease during the study.

8.4 Safety

All blood draws and safety assessments should be done prior to study treatment administration.

- Physical examination
- Vital signs
- Height and weight
- Laboratory evaluations (Hematology, Clinical Chemistry, Lipid Panel, coagulation panel, Urinalysis)
- Evaluation of AEs/SAEs
- Local tolerability (Injection site reactions)
- Pregnancy
- Tolerability of secukinumab
- [redacted]

As per Section 4.6, during a public health emergency as declared by local or regional authorities, i.e., pandemic, epidemic or natural disaster, that limits or prevents on-site study visits, regular phone or virtual calls can occur (every 4 weeks or more frequently if needed) for safety monitoring and discussion of the participant´s health status until it is safe for the participant to visit the site again.

8.4.1 Physical examination

A physical examination, including general appearance, skin, neck, eyes, ears, nose, throat, lungs, heart, abdomen, back, lymph nodes, extremities, and vascular and neurological systems will be performed as indicated in Table 8-1.

If necessary, based on medical history and/or symptoms, additional exams will be performed at the discretion of the investigator.

Whenever possible, assessments for an individual participant should be performed by the same member of the study site staff throughout the study.

Information for all physical examinations must be included in the source documentation at the study site. Significant findings that are present prior to the start of study treatment must be included in the Medical History eCRF. Significant findings made after signing informed consent, which meet the definition of an Adverse Event, must be recorded on the Adverse Event eCRF.

8.4.2 Vital signs

Vital signs (including blood pressure and pulse measurements) will be assessed at every scheduled visit as indicated in Table 8-1. Whenever possible, assessments should be performed by the same study site staff member throughout the study.

After the participant has been sitting for five minutes, with back supported and both feet placed on the floor, heart rate, systolic and diastolic blood pressure will be measured twice (measurements separated by 1 to 2 minutes) using a validated device, with an appropriately sized cuff. In case the cuff sizes available are not large enough for the participant's arm circumference, a sphygmomanometer with an appropriately sized cuff may be used. Measurements will be recorded in the source documentation and the average of the two measurements will be entered on the Vital Signs eCRF.

No specific action is pre-defined within this protocol to respond to specific abnormal vital signs, as it will be decided by the investigator whether and which specific action needs to be taken to respond to any abnormal values, taking into account the overall status of the participant.

8.4.3 Height and weight

Height and body weight will be measured as indicated in Table 8-1.

Height in centimeter (cm) and body weight (to the nearest 0.1 kilogram (kg)) will be measured in indoor clothing, but without shoes. If possible, body weight assessments should be performed by the same study site staff member and using the same scale throughout the study.

8.4.4 Laboratory evaluations

A central laboratory will be used for analysis of all specimens listed below, unless noted otherwise. Details on the collections, shipment of samples and reporting of results by the central laboratory are provided to investigators in the laboratory manual. Refer to the Laboratory Manual for identification of laboratory reference range values and the schema for notification of site staff and Novartis for out-of-range values.

For the identification of clinically notable values, see Section 16.10. All participants with laboratory tests containing clinically significant abnormal values are to be followed until the values return to normal ranges or until a valid reason, other than treatment related AE, is defined.

Blood withdrawals and safety assessments should be done prior to study treatment administration and should be taken as shown in Table 8-1.

8.4.4.1 Hematology

Hemoglobin, hematocrit, red blood cell count, white blood cell count with differential (neutrophils including bands, lymphocytes, monocytes, eosinophils, basophils) and platelet count will be measured.

8.4.4.1.1 Erythrocyte sedimentation rate (ESR)

The ESR test will be performed using the ESR Supplies kit provided by the central laboratory. A laboratory manual will be provided with detailed information on sample collection and handling. ESR results will be reported in the appropriate eCRF page.

8.4.4.2 Clinical chemistry

Serum chemistry will include urea, creatinine, hemoglobin A1c (HbA1c), total bilirubin (TBL), AST (serum glutamic oxaloacetic transaminase (SGOT)), ALT (serum glutamic pyruvic transaminase (SGPT)), gamma-glutamyl transferase (GGT), alkaline phosphatase (ALP),

sodium, potassium, bicarbonate, calcium, phosphorous, total protein, albumin, lipase, amylase, and uric acid.

High sensitivity C-reactive protein (hsCRP) will also be assessed. In order to preserve the blind, results of hsCRP will not be communicated to the study site staff, including the investigator, or to Novartis during the study.

8.4.4.2.1 Lipid panel

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

8.4.4.2.2 High sensitivity C-reactive protein

High sensitivity C-reactive protein (hsCRP) will be assessed as indicated in Table 8-1. In order to preserve the blind, results of hsCRP will not be communicated to the study site staff, including the investigator, or to Novartis during the study.

8.4.4.3 Coagulation panel

Prothrombin time (PT), activated partial thromboplastin time (aPTT) and International Normalized Ratio (INR) will be evaluated locally for general safety and additional characterization of the disease.

8.4.4.4 Urinalysis

There will be two types of urinary collection, both performed at participants' home:

- 24-hour urine collection, corresponding to the 24-hour collection of the urine the day preceding the Baseline, Week 12, Week 24, Week 36, Week 52, Week 76 and EOT visits, as outlined in Table 8-1.
- first morning void urine collection on the day of visits as specified in Table 8-1.

8.4.4.4.1 Local urinalysis

The participant's first morning void urine sample will be used for **local** urinalysis assessments performed for standard safety evaluation.

Those standard assessments will include specific gravity, protein, glucose, pH, blood, urine blood dipstick (non-hemolyzed), urine blood dipstick (hemolyzed), bilirubin, ketones and WBC.

Please refer to the central laboratory manual for additional details.

In addition, participant's first morning void urine sample will also be used for **local** determination of urinary sediment, as outlined in Efficacy Section 8.3.7 and **central** determination of UPCR, as outlined in Efficacy Section 8.3.1.2.

Jugs for the first morning void urine collection will be dispensed at participant's previous visit.

8.4.4.4.2 24-hour urine collection

A 24-hour urine collection is done at selected time point by collecting urine in a special container over a full 24-hour period.

Instructions regarding the timing, the collection and the storage of the 24-hour urine collection will be detailed within the laboratory manual.

This 24-hour urine collection will be used for central determination of the UPCR, as mentioned in Efficacy Section 8.3.1.2 .

8.4.4.5 Autoantibodies

8.4.4.5.1 ANA and anti-dsDNA

[redacted]

In addition, ANA or anti-dsDNA must be tested positive for a participant being eligible in this study in case of confirmed diagnosis of lupus nephritis as the sole criterion as per inclusion criteria 2 (refer to Section 5.1 Inclusion criteria).

[redacted]

8.4.5 Pregnancy and assessments of fertility

All pre-menopausal women who are not surgically sterile will have a serum β-hCG test (serum pregnancy test) performed at the Screening visit, and local urine pregnancy tests as indicated in Table 8-1. A positive urine pregnancy test requires immediate interruption of study drug until serum β-hCG is performed and found to be negative. Additional pregnancy testing might be performed if requested by local requirements.

Secukinumab, MPA, CYC and corticosteroids should not be given to pregnant women; therefore, effective methods of birth control must be used for women of childbearing potential (see exclusion criteria definitions, Section 5.2).

In addition, menses will be recorded on the appropriate eCRF page for all pre-menopausal women, as indicated in Table 8-1.

8.4.6 Other safety evaluations

Chest X-ray

Standard chest X-ray (PA view) will be performed except for those who have had a valid X-ray done within 3 months preceding the Screening visit. If participants do not have a chest X-ray, CT or MRI obtained within 3 months preceding the Screening visit, a standard chest X-ray (PA view) should be performed. In order to minimize unnecessary exposure to radiation, the chest X-ray should only be performed after confirming that the participant meets all inclusion/exclusion criteria (apart from renal biopsy which would be undertaken after a chest x-ray, if applicable). In some sites selected by Novartis, the X-ray assessment may be replaced by CT or MRI assessment.

8.4.7 Appropriateness of safety measurements

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

8.5 Additional assessments

The other assessments planned for the study are:

- Clinical Outcome Assessments (COAs): This includes Patient reported outcomes (PRO) [redacted]
- Trial Feedback Questionnaires

[redacted]

As per Section 4.6, during a public health emergency as declared by local or regional authorities i.e., pandemic, epidemic or natural disaster, that limits or prevents on-site study visits, COA data may be collected remotely *(e.g., web portal, telephone interviews) depending on local regulations, technical capabilities, and following any applicable training in the required process.*

8.5.1 Patient reported outcomes (PRO)

Participants will be asked to complete the following PRO measures in e-devices provided by the site:

1. FACIT-Fatigue©

2. SF-36 v2

3. LupusQoL

[redacted]

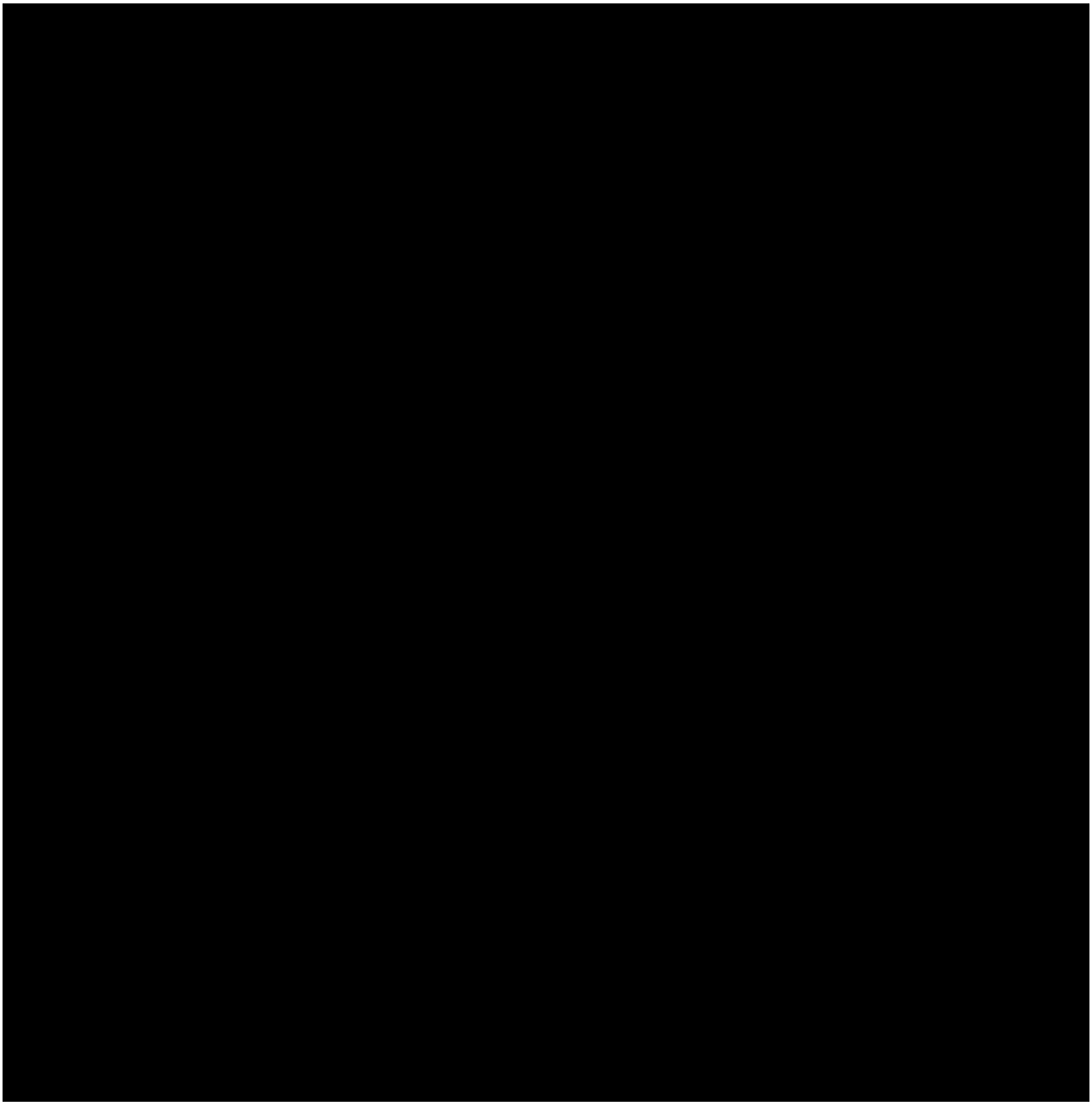
The participant must be given the PRO measure(s) to be completed at the scheduled visit before any clinical assessments are conducted. Participant's refusal to complete all or any part of a PRO measure should be documented in the study data capture system and should not be captured as a protocol deviation.

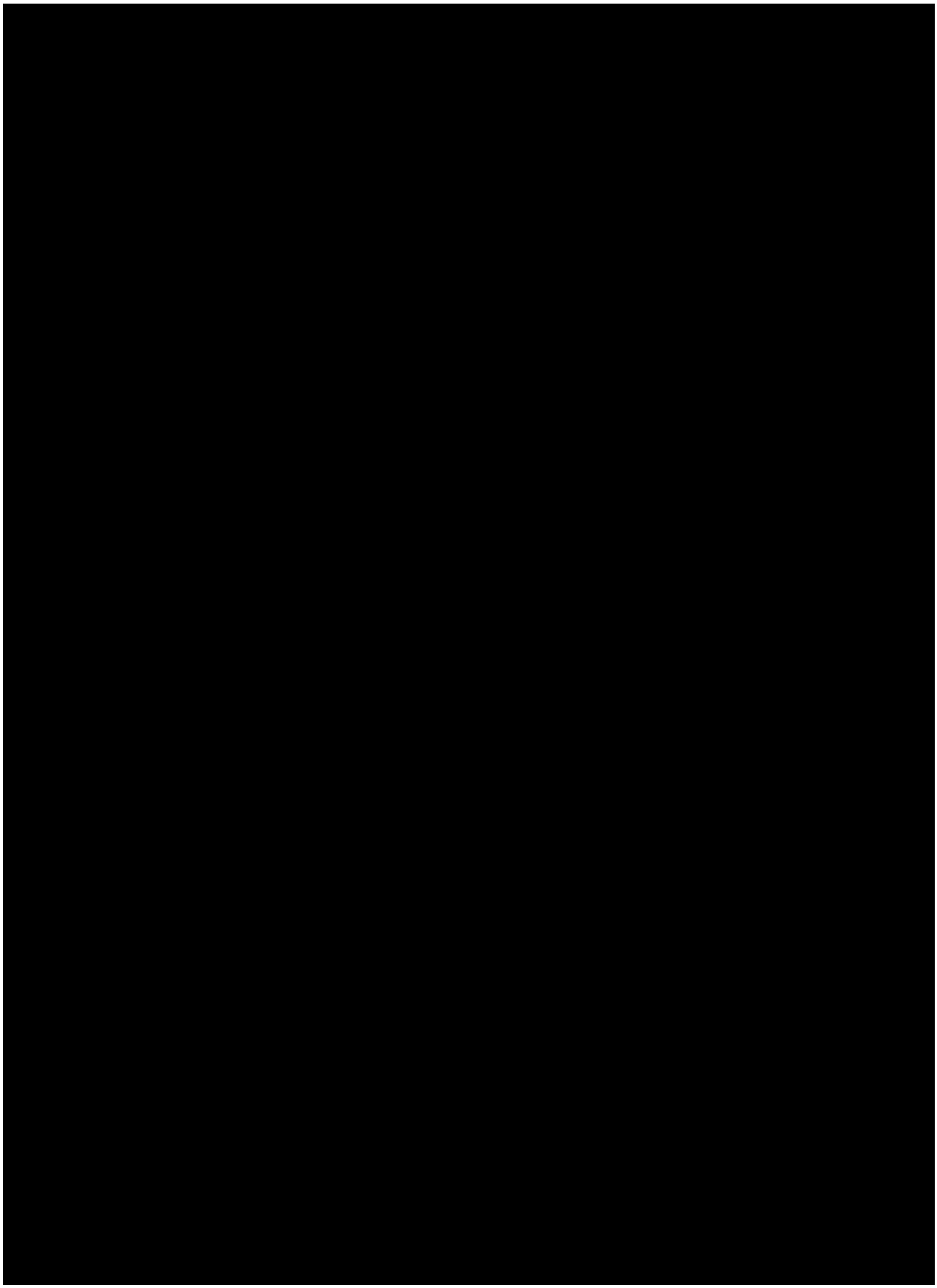
The participant should be given sufficient space and time to complete the PRO measures.

The site personnel should check PRO measures for completeness and ask the participant to complete any inadvertently missing responses.

The participant should be made aware that completed measures are not reviewed by the investigator/study personnel.

FACIT-Fatigue©, SF-36 v2 Physical Component Summary and Lupus QoL are already described in Efficacy Section 8.3.4, Section 8.3.5, Section 8.3.6, respectively.



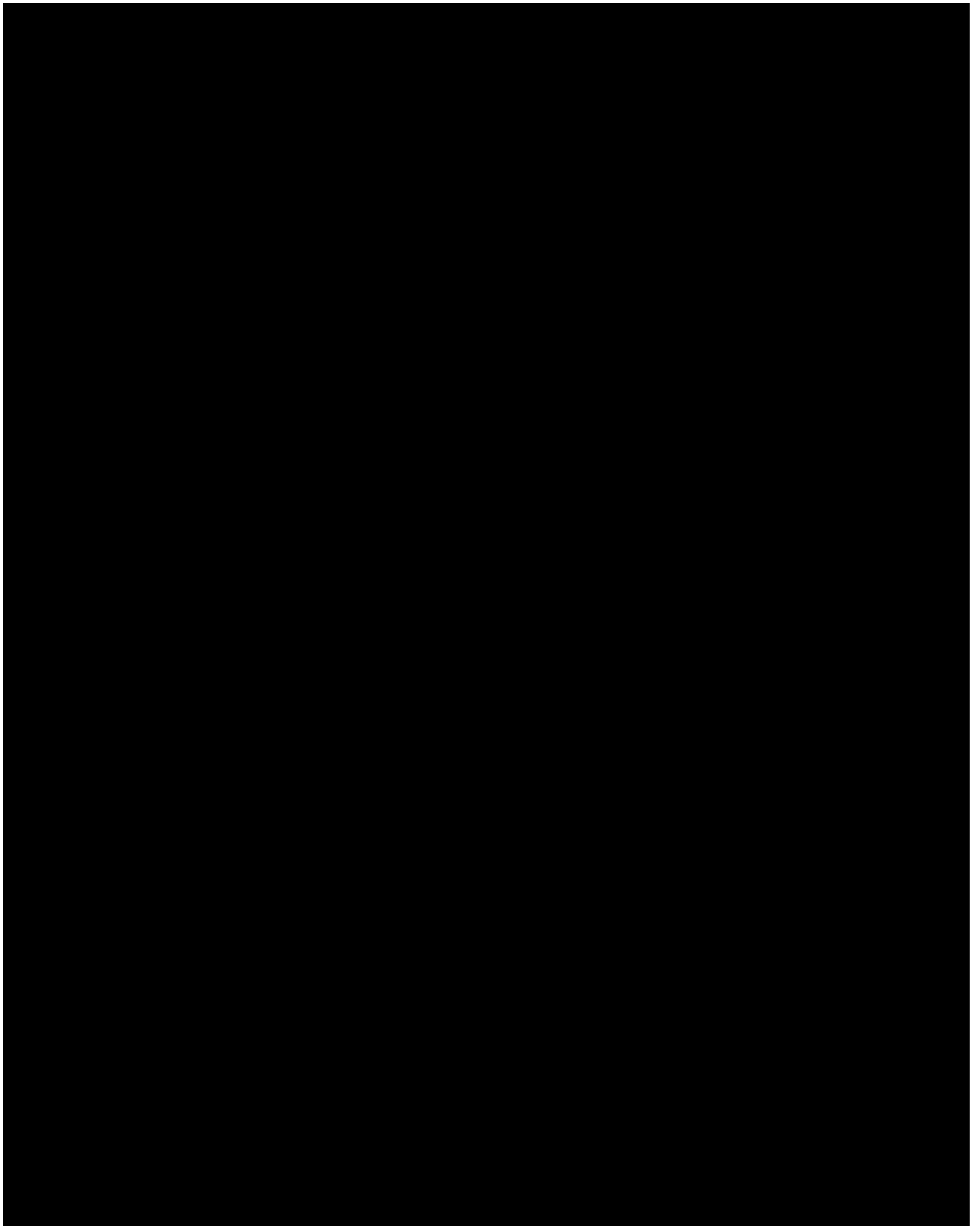


[redacted]

8.5.3 Trial Feedback Questionnaire (TFQ)

This study is including an optional questionnaire, the “Trial Feedback Questionnaire” for trial participants to provide feedback on their clinical trial experience. Individual trial participant responses will not be reviewed by investigators. Responses may be used by the sponsor (Novartis) to understand where improvements can be made in future clinical trial processes. This questionnaire does not ask questions about the trial participant's disease, symptoms, treatment effect, or AEs, and, therefore is not considered as trial data.

[redacted]



[redacted]

8.5.6 Biomarkers

This clinical study includes additional, **optional** biomarker components supported by an exploratory objective. These studies are hypothesis generating (i.e., discovery-based research) and optional to the participant.

Exploratory biomarker assessments

Biomarkers are objectively measured and evaluated indicators of normal biological processes, pathogenic processes or pharmacologic responses to a therapeutic intervention (Biomarkers Definitions Working Group 2001). This search for biomarkers of disease and drug response will involve an integrated molecular approach examining gene expression in blood and protein profiles in serum.

These optional assessments aim to identify potential markers of response and/or loss of response, and to characterize molecular mechanisms of treatment with secukinumab.

Any biomarker samples may be stored for up to 15 years (depending on local regulations) to research scientific questions related to secukinumab, LN and related diseases with a potential involvement of IL-17A. The material can be destroyed on participant's request at any time point.

Any results from these exploratory biomarker assessments will be reported separately.

[redacted] The final selection of analytes will be driven by assay availability, new information from the public domain, results obtained in other secukinumab clinical studies, as well as by hypotheses generated by other exploratory biomarker assessments. In addition, selected markers exploring the effect of secukinumab treatment on co-morbidities may be assessed.

[redacted]

DNA/RNA sampling / Pharmacogenetics

The study includes an optional genetic research component, which requires a separate informed consent signature if the patient agrees to participate as stated in Section 7. As permitted by local governing regulations and by IRB/EC, it is required as part of this protocol that the Investigator presents these options to the participant.

The purpose of genetic research is to evaluate the effect of genetic polymorphisms on treatment response and to better understand the safety and efficacy of secukinumab.

As technology changes over time, the most appropriate technology will be used at the time the exploratory genetic research is performed. This may include the study of the entire genome.

Follow instructions for sample collection, numbering, processing, and shipment provided in the laboratory manual.

DNA/RNA samples

The use of DNA/RNA to search for biomarkers of disease and drug action is exploratory. Any results from this DNA/RNA study will not be placed in the participant's medical records.

To maximize confidentiality, all samples and the information associated with the samples will be double-coded to prevent the exposure of the participant's information and identity. This double-coding process allows Novartis to go back and destroy the sample at the participant's request. In addition, sample information is stored in one secured database while genetic data is stored in an independent secured database.

RNA

The activity (the expression) of genes will be examined using RNA (or other nucleic acid) analytical technologies, which may include expression microarrays, PCR, Nanostring, Next Generation Sequencing techniques, or others. These analyses will be used to examine the effect of secukinumab on transient RNA expression in serum and may support the identification of pathways/markers that characterize the disease or response of treatment with secukinumab.

9 Study discontinuation and completion

9.1 Discontinuation

9.1.1 Discontinuation of study treatment

Discontinuation of study treatment for a participant occurs when study treatment is stopped earlier than the protocol planned duration, i.e., before Week 100 last planned study treatment administration. Discontinuation of study treatment can be initiated by either the participant or the investigator.

The investigator must discontinue study treatment for a given participant if, he/she believes that continuation would negatively impact the participant's well-being.

Study treatment must be discontinued under the following circumstances:

- Participant/guardian decision - participants may choose to discontinue study treatment for any reason at any time
- Pregnancy (see Section 10.1.4 Pregnancy reporting)
- Participant received a live vaccine
- Use of prohibited treatment as outlined in Section 6.2.2 prohibited medication
- Any situation or protocol deviation in which study participation might result in a safety risk to the participant
- Following an emergency unblinding
- Emergence of the following AEs:
    - Any AE that in the judgment of the investigator, taking into account the participant's overall status, prevents the participant from continuing study treatment (for example sepsis)
    - Any severe or serious AE that requires treatment with an unacceptable co-medication
    - Severe hypersensitivity reaction or anaphylactic reaction
- Any laboratory abnormalities that in the judgment of the investigator, taking into account the participant's overall status, prevents the participant from continuing study treatment
- Unsatisfactory therapeutic effect

If discontinuation of study treatment occurs, the investigator should make a reasonable effort to understand the primary reason for the participant’s premature discontinuation of study treatment and record this information in the eCRF.

Participants who discontinue study treatment prematurely for any reason should NOT be considered as discontinued from the study UNLESS they withdrew their consent (see Section 9.1.2 Withdrawal of Informed Consent). **Where possible, they should continue attending site visits.**

All participants who prematurely discontinue study treatment should perform the EOT study visit 4 weeks after their last study treatment administration. For example, if study treatment discontinuation decision is taken at time of planned Week 16 visit, the participant should perform the EOT visit assessments instead of Week 16 visit assessments.

Thereafter, different possibilities may arise, for which guidelines are outlined below:

- **Participants unwilling to continue attending further study visits** after prematurely discontinuing the study treatment should also perform an EOS visit 12 weeks after the last administration of the study treatment.
- **Participants willing to continue attending study visits** should continue attending all subsequent scheduled site visits for clinical and safety study assessments. For the example taken above, next visit should be Week 20 during which visit assessments as outlined in Visit Schedule Table 8-1 will be performed, except study treatment administration. The EOS visit should be performed 12 weeks after the Week 100 visit.
- **Participants initially continuing attending site visits after premature study treatment discontinuation may decide to discontinue study at any time**. For those participants, the EOS visit will be performed at time of study discontinuation. Of note, the EOS visit must always be completed at least 12 weeks after the last study treatment administration.

Finally, if the participant is failing to return for these assessments for unknown reasons, every effort (e.g., telephone, e-mail, letter) should be made to contact the participant/pre-designated contact as specified in the lost to follow-up section. This contact should preferably be done according to the study visit schedule.

If the participant cannot or is unwilling to attend any visit(s), the site staff should maintain regular telephone contact with the participant, or with a person pre-designated by the participant. This telephone contact should preferably be done according to the study visit schedule.

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

If discontinuation occurs because treatment code has been broken, please refer to Emergency breaking of treatment code section.

9.1.2 Withdrawal of informed consent

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

- 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 participant'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 participant 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 participant's study withdrawal should be made as detailed in the assessment table.

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

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

For EU and RoW: 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.

9.1.3 Lost to follow-up

For participants 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 participant, e.g., dates of telephone calls, registered letters, etc. A participant should not be considered as lost to follow-up until due diligence has been completed.

9.1.4 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 (including slow enrollment), or for regulatory or medical reasons. In taking the decision to terminate, Novartis will always consider the participant welfare and safety. Should early termination be necessary, participants must be contacted by the sites to be seen as soon as possible and treated as a prematurely withdrawn participant. 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 participant's interests. The investigator or sponsor, depending on the local regulation, will be responsible for informing IRBs/IECs of the early termination of the trial.

9.2 Study completion and post-study treatment

Study completion is defined as when the last participant finishes their Study Completion 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.

A participant will be considered to have completed the study when she/he has completed the last planned visit in the protocol.

The investigator must provide follow-up medical care for all participants, including participants who are prematurely withdrawn from the study, or must refer them for appropriate ongoing care. This care may include initiating another treatment outside of the study, as deemed appropriate by the investigator.

10 Safety monitoring and reporting

10.1 Definition of adverse events and reporting requirements

10.1.1 Adverse events

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

The investigator has the responsibility for managing the safety of individual participant 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 participant at each visit during the study. AEs also may be detected when they are volunteered by the participant during or between visits or through physical examination findings, laboratory test findings, or other assessments.

AEs 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 10.1.2):

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 study treatment and other investigational treatment. 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 participant
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 10.1.2 for definition of SAE) and which seriousness criteria have been met
5. action taken regarding with study treatment

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; recovered/resolved with sequelae; fatal; or unknown)

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

AEs (including lab 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 84 days following the last dose of study treatment.

Once an adverse event 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 must be made at each visit (or more frequently, if necessary) of any changes in severity, the suspected relationship to the interventions required to treat it, and the outcome.

Information about adverse drug reactions for the investigational drug can be found in the Investigator's Brochure (IB).

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. Alert ranges for laboratory test abnormalities are included in Section 16.10.

10.1.2 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 participant 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 the ICH-E2D Guidelines).

- 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
- social reasons and respite care in the absence of any deterioration in the participant's general condition
- 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

- is medically significant, e.g., defined as an event that jeopardizes the participant or may require medical or surgical intervention to prevent one of the outcomes listed 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 participant or might require intervention to prevent one of the other outcomes listed above. Such events should be considered as "medically significant." 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 the ICH-E2D Guidelines).

All malignant neoplasms will be assessed as serious under "medically significant" if other seriousness criteria are not met and the malignant neoplasm is not a disease progression of the study indication.

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 product are also considered serious adverse event irrespective if a clinical event has occurred.

10.1.3 SAE reporting

To ensure participant safety, every SAE, regardless of causality, occurring after the participant has provided informed consent and until 12 weeks (84 days) following the last administration of study treatment, or 30 days after the participant has stopped study participation (whichever is later), 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.

Any SAEs experienced after the 30-day period after the last study visit should only be reported to Novartis Safety if the investigator suspects a causal relationship to study treatment.

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

Information about all SAEs is collected and recorded on the Serious Adverse Report Form; all applicable sections of the form must be completed in order to provide a clinically thorough report. The investigator must assess the relationship of each SAE to study treatment, 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.

If the SAE is not previously documented in the Investigator's Brochure or Package Insert (new occurrence) and is thought to be related to the study treatment, a 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.

10.1.4 Pregnancy reporting

Pregnancies

To ensure participant 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 Chief Medical Office and Patient Safety (CMO&PS). Pregnancy follow-up should be recorded on the same form and should include an assessment of the possible relationship to the study treatment and any pregnancy outcome. Any SAE experienced during pregnancy must be reported.

10.1.5 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 recorded on 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 10-1 Guidance for capturing the study treatment errors including misuse/abuse

Treatment error type	Document in Dosing eCRF (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.

10.2 Additional Safety Monitoring

10.2.1 Liver safety monitoring

To ensure participant safety and enhance reliability in determining the hepatotoxic potential of an investigational drug, a standardized process for identification, monitoring and evaluation of liver events has to be followed.

The following two categories of abnormalities / AEs have to be considered during the course of the study (irrespective of whether classified/reported as AE/SAE):

- Liver laboratory triggers, which will require repeated assessments of the abnormal laboratory parameter
- Liver events, which will require close observation, follow-up monitoring and contributing factors are recorded on the appropriate eCRFs

Please refer to Table 16-1 of appendix Section 16.9 for complete definitions of liver laboratory triggers and liver events.

Every liver event defined in Table 16-2 should be followed up by the investigator or designated personnel at the trial site, as summarized below. Additional details on actions required in case of liver events are outlined in Table 16-2. Repeat liver chemistry tests (i.e., ALT, AST, TBL, PT/INR, ALP and GGT) to confirm elevation.

- These liver chemistry repeats will be performed using the central laboratory. If results will not be available from the central laboratory, then the repeats can also be performed at a local laboratory to monitor the safety of the participant. If a liver event is subsequently reported, any local liver chemistry tests previously conducted that are associated with this event should have results recorded on the appropriate eCRF.
- If the initial elevation is confirmed, close observation of the participant will be initiated, including consideration of treatment interruption if deemed appropriate.
- Discontinuation of the investigational drug (refer to the Section 9.1.1 Discontinuation of study treatment section), if appropriate
- Hospitalization of the participant if appropriate
- Causality assessment of the liver event
- Thorough follow-up of the liver event should include

- These investigations can include based on investigator's discretion: serology tests, imaging and pathology assessments, hepatologist consultancy; obtaining more detailed history of symptoms and prior or concurrent diseases, history of concomitant drug use, exclusion of underlying liver disease

All follow-up information and procedures performed must be recorded as appropriate in the eCRF.

10.2.2 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 data from the interim analyses, as well as the progress of the clinical trial, safety data, and critical efficacy variables and it will 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 described in a separate charter that is established between the sponsor and the DMC.

10.2.3 Steering Committee

A Steering Committee (SC) will be established comprising disease area experts, investigators participating in the trial, i.e., not being members of the DMC, and Novartis representatives from the Clinical Trial Team.

The SC will ensure transparent management of the study according to the protocol through recommending and approving modifications as circumstances require. The SC will review protocol amendments as appropriate. Together with the clinical trial team, the SC will also develop recommendations for publications of study results including authorship rules. The details of the role of the steering committee will be defined in the steering committee charter.

11 Data Collection and Database management

11.1 Data collection

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

Designated investigator staff will enter the data required by the protocol into the Electronic Case Report Forms (eCRF). The eCRFs have been built using fully validated secure web-enabled software that conforms to 21 Code of Federal Regulation (CFR) Part 11 requirements, Investigator site staff will not be given access to the Electronic Data Capture (EDC) 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 (recorded on CRFs) (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 participant data for archiving at the investigational site.

11.2 Database management and quality control

Novartis personnel (or designated 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 treatment(s) dispensed to the participant and all dosage changes will be tracked using an Interactive Response Technology (IRT). The system will be supplied by a vendor, who will also manage the database. The data will be sent electronically to Novartis (or a designated CRO) at specific timelines.

Each occurrence of a code break via IRT will be reported to the clinical team and monitor. The code break functionality will remain available until study shut down or upon request of Novartis.

Once all the necessary actions have been completed and the database has been declared to be complete and accurate, it will be locked **and the treatment codes will be unblinded** and made available for data analysis/moved to restricted area to be accessed by independent programmer, [redacted] statistician. Any changes to the database after that time can only be made after written agreement by Novartis development management.

11.3 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., eSource DDE or 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 participant 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 & identify risks & trends for site operational parameters, and provide reports to Novartis clinical teams to assist with trial oversight.

The investigator must maintain source documents for each participant in the study, consisting of case and visit notes (hospital or clinic medical records) containing demographic and medical information, laboratory data, electrocardiograms, and the results of any other tests or assessments. All information on CRFs must be traceable to these source documents in the

participant's file. The investigator must also keep the original informed consent form signed by the participant (a signed copy is given to the participant).

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 CRFs are performed according to the study-specific monitoring plan. No information in source documents about the identity of the participants will be disclosed.

11.4 Data protection

Participants will be assigned a unique identifier by Novartis. Any participant records or datasets that are transferred to Novartis will contain the identifier only; participant names or any information which would make the participant identifiable will not be transferred.

The participant must be informed that his/her personal study-related data will be used by Novartis in accordance with local data protection law. The level of disclosure must also be explained to the participant who will be required to give consent for their data to be used as described in the informed consent

The participant must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by Novartis, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

Novartis has appropriate processes and policies in place to handle personal data breaches according to applicable privacy laws.

12 Data analysis and statistical methods

Summary statistics for continuous variables include N, mean, standard deviation (SD), minimum, lower quartile, median, upper quartile, and maximum. For binary or discrete variables, the absolute number of participants in each category and relative frequencies will be provided.

Unless otherwise specified, p-values will be presented as 2-sided p-values and the type I error rate (alpha) will be 5%.

Efficacy and safety data for Treatment Period will be presented by the following two treatment groups.

- Secukinumab 300 mg
- Placebo

Any data analysis carried out independently by the investigator should be submitted to Novartis before publication or presentation.

12.1 Analysis sets

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

The Full Analysis Set (FAS) will be comprised of all analyzable participants from the randomized set to whom study treatment has been assigned. According to the intent to treat principle, participants will be analyzed according to the treatment they have been assigned to during the randomization procedure, but according to actual stratum.

The Safety Set includes all participants who received at least one dose of study treatment. Participants will be analyzed according to the study treatment received.

12.2 Subject demographics and other Baseline characteristics

Summary statistics will be presented for continuous demographic and Baseline characteristic variables for each treatment group and for all participants in the randomized set. The number and percentage of participants in each category will be presented for categorical variables for each treatment group and all participants.

Any significant prior or active medical condition at the time of signing informed consent will be coded using the MedDRA dictionary. These medical conditions will be summarized by primary system organ class and preferred term. SLE and LN specific medical history will be summarized by treatment group.

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

12.3 Treatments

Study treatment

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

Prior and concomitant medication

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

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

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

The number and percentage of participants receiving prior and concomitant LN therapy will be presented by randomized treatment group.

12.4 Analysis of the primary endpoint(s)/estimand(s)

12.4.1 Definition of primary endpoint(s)

The primary efficacy endpoint is the complete renal response (CRR) at Week 52 with the consideration of intercurrent events, which is defined in detail at Section 2.1 .

12.4.2 Statistical model, hypothesis, and method of analysis

The statistical hypothesis tested for the primary objective is that there is "no difference in the proportion" of patients fulfilling the response criteria at Week 52 between the secukinumab and placebo regimens.

Let pj denote the proportion of responders at Week 52 for treatment regimens j, j=0, 1 where

- 0 corresponds to placebo regimen,
- 1 corresponds to secukinumab,

In statistical terms, H_1: p1 = p0, H_{A1}: p1 ≠ p0, i.e.,

H_1: secukinumab is not different from placebo regimen with respect to CRR at Week 52

Logistic regression model adjusting for SoC, race and Baseline UPCR will be used for the primary analysis. Difference in marginal response proportions with p-value and respective 95% confidence interval will be estimated from the logistic regression model.

12.4.3 Handling of intercurrent events of primary estimand

Major intercurrent events of primary estimand will be addressed with the following strategies (considering that these events occur before the assessments at Week 52):

1. Treatment discontinuation for any reason: non-responder (composite endpoint strategy)
2. Overuse of corticosteroid (> 10mg/day prednisone equivalent for ≥ 3 consecutive days or ≥ 7 days in total) between Week 44 and Week 52: non-responder (composite endpoint strategy)

12.4.4 Handling of missing values not related to intercurrent events

Participants who do not have the required data to compute CRR at Week 52 will be classified as non-responders.

12.4.5 Sensitivity analyses

The impact of missing data on the analysis results of CRR will be assessed by repeating the logistic regression model using different ways to handle missing data.

These may include, but are not limited to:

- Multiple imputation
- Observed data analysis
- Tipping point analysis

12.4.6 Supplementary analyses

12.4.6.1 Modified complete renal response

As a supplementary analysis to primary endpoint modified Complete Renal Response (mCRR) will be analyzed.

A participant is defined as a mCRR responder when the following two conditions are met:

- Estimated glomerular filtration rate (eGFR) ≥ 60 mL/min/1.73 m^2 or no less than 85% of Baseline and
- 24-hour UPCR ≤ 0.7 mg/mg

Intercurrent events will be handled in the same way as for the primary estimand.

12.4.6.2 Treatment policy estimand

A supplementary analysis of the primary endpoint will be performed using a treatment policy strategy, i.e., regardless of study treatment discontinuation or corticosteroid overuse.

12.4.6.3 Components of the primary endpoint

All components of the endpoint CRR will be tabulated separately by treatment group. This will include:

- Number of participants with eGFR ≥ 60 mL/min/1.73 m^2 or no less than 85% of Baseline at Week 52
- Number of participants with 24-hour UPCR ≤ 0.5 mg/mg at Week 52
- Number of participants without study treatment discontinuation before Week 52
- Number of participants without corticosteroid overuse before Week 52

12.5 Analysis of secondary endpoints/estimands

12.5.1 Secondary efficacy endpoints

The secondary efficacy variables and the method for adjusting for multiplicity are described below.

H_2: Secukinumab 300 mg is not different to placebo with respect to change from Baseline in 24-hour UPCR at Week 52 compared to Baseline

H_3: Secukinumab 300 mg is not different to placebo with respect to proportion of patients achieving PRR at Week 52

H_4: Secukinumab 300 mg is not different to placebo with respect to average daily dose of oral corticosteroids administered between Week 16 and Week 52

H_5: Secukinumab 300 mg is not different to placebo with respect to proportion of patients achieving PRR at Week 24

H_6: Secukinumab 300 mg is not different to placebo with respect to time to achieve CRR

H_7: Secukinumab 300 mg is not different to placebo with respect to time to achieve PRR

H_8: Secukinumab 300 mg is not different to placebo with respect to time to achieve first morning void UPCR $\leq$ 0.5 mg/mg

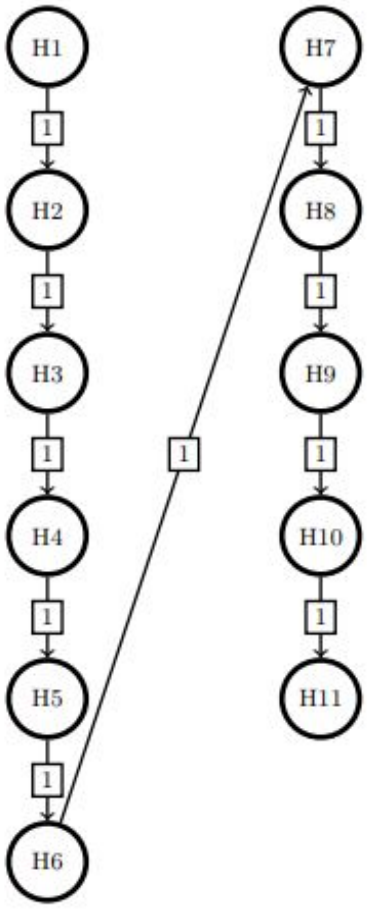
H_9: Secukinumab 300 mg is not different to placebo with respect to FACIT-Fatigue©, mean change of score from Baseline at Week 52

H_{10}: Secukinumab 300 mg is not different to placebo with respect to improvement in SF-36 PCS mean change from Baseline at Week 52

H_{11}: Secukinumab 300 mg is not different to placebo with respect to improvement in LupusQoL physical health score mean change from Baseline at Week 52

A sequential testing strategy will be used in order to control for multiplicity of testing. The graphical approach of (Bretz et al 2009) for sequentially rejective testing procedures is used to illustrate the testing strategy:

Figure 12-1 Testing strategy



The family-wise error will be set to two-sided $\alpha = 5\%$ and it will be controlled with the proposed hierarchical testing strategy.

The hypotheses (H1) for the primary objective (CRR at Week 52) for the secukinumab vs. placebo will be tested at α. If H1 is rejected, then the hypothesis H2 will be tested at α. If H2 is rejected, then the hypothesis H3 will be tested and so on.

UPCR at Week 52

For the change in UPCR, analysis will be performed on the $\log_e$ ratio of the treatment value vs Baseline value (calculated by dividing the post-Baseline value by the Baseline value and then applying the $\log_e$ transformation) to normalize the distribution of UPCR at each analysis visit. Between-treatment differences in the change in UPCR relative to Baseline will be evaluated using MMRM with treatment group, stratification factor (SoC), race, and analysis visit as factors and $\log_e$ Baseline UPCR as continuous covariates. Treatment by analysis visit and $\log_e$ Baseline UPCR by analysis visit will be included as interaction terms in the model. An unstructured covariance structure will be assumed for the model. The significance of the

treatment effect for secukinumab will be determined from the pairwise comparisons performed between secukinumab and placebo at the appropriate analysis visits.

PRR at Week 24 or at Week 52

Logistic regression model adjusting for SoC, race and baseline UPCR will be used for the analysis. Difference in marginal response proportions with p-value and respective 95% confidence interval will be estimated from the logistic regression model.

Average daily dose of oral corticosteroids administered between Week 16 and Week 52

Between-treatment differences for average daily dose of oral corticosteroids administered between Week 16 and Week 52 will be evaluated with analysis of covariance (ANCOVA) model including treatment group, race, Baseline dose and SoC as covariates. Missing data will be handled using multiple imputation.

Time to achieve CRR

For time to achieve CRR, between treatment differences will be evaluated using log-rank test stratified by race and SoC. The hazard ratios for these comparisons for achieving response and their corresponding 95% confidence intervals will be computed using a stratified Cox proportional hazards regression model with treatment group and $\log_e$ Baseline UPCR as explanatory variable and stratified by race and SoC. Participants who have not achieved response up to Week 52 will be considered as censored observations. Kaplan-Meier curves will be presented for each treatment.

Time to achieve PRR

For time to achieve PRR, between treatment differences will be evaluated using log-rank test stratified by race and SoC. The hazard ratios for these comparisons for achieving response and their corresponding 95% confidence intervals will be computed using a stratified Cox proportional hazards regression model with treatment group and $\log_e$ Baseline UPCR as explanatory variable and stratified by race and SoC. Participants who have not achieved response up to Week 52 will be considered as censored observations. Kaplan-Meier curves will be presented for each treatment.

Time to achieve first morning void UPCR ≤ 0.5 mg/mg

For time to achieve first morning void UPCR ≤ 0.5 mg/mg; between treatment differences will be evaluated using log-rank test stratified by race and SoC. The hazard ratios for these comparisons for achieving response and their corresponding 95% confidence intervals will be computed using a stratified Cox proportional hazards regression model with treatment group and $\log_e$ Baseline UPCR as explanatory variable and stratified by race and SoC. Participants who have not achieved response up to Week 52 will be considered as censored observations. Kaplan-Meier curves will be presented for each treatment.

FACIT-Fatigue© change from Baseline at Week 52

Between-treatment differences in the change from Baseline in FACIT-Fatigue© will be evaluated using MMRM with treatment group, stratification factor (SoC), race, and analysis visit as factors and Baseline FACIT-Fatigue© as continuous covariates. Treatment by analysis visit and Baseline FACIT-Fatigue© by analysis visit will be included as interaction terms in the model. An unstructured covariance structure will be assumed for the model. The significance

of the treatment effect for secukinumab will be determined from the pairwise comparisons performed between secukinumab and placebo at the appropriate analysis visits.

SF-36 PCS change from Baseline at Week 52

Between-treatment differences in the change from Baseline in SF-36 PCS will be evaluated using MMRM with treatment group, stratification factor (SoC), race, and analysis visit as factors and Baseline SF-36 PCS as continuous covariates. Treatment by analysis visit and Baseline by analysis visit will be included as interaction terms in the model. An unstructured covariance structure will be assumed for the model. The significance of the treatment effect for secukinumab will be determined from the pairwise comparisons performed between secukinumab and placebo at the appropriate analysis visits.

LupusQoL physical health score change from Baseline at Week 52

Between-treatment differences in the change from Baseline in LupusQoL physical health score will be evaluated using MMRM with treatment group, stratification factor (SoC), race, and analysis visit as factors and Baseline LupusQoL physical health score as continuous covariates. Treatment by analysis visit and Baseline LupusQoL physical health score by analysis visit will be included as interaction terms in the model. An unstructured covariance structure will be assumed for the model. The significance of the treatment effect for secukinumab will be determined from the pairwise comparisons performed between secukinumab and placebo at the appropriate analysis visits.

Maintained renal response at Week 104

A patient with maintained renal response at Week 104 is one who achieves CRR at Week 104 after already achieving CRR at Week 52. Response rate with 95% confidence interval will be presented for the secukinumab group.

Improved or maintained renal response at Week 104

A patient with improved or maintained renal response at Week 104 is one who achieves CRR or PRR at Week 104 after achieving at least PRR at Week 52. Response rate with 95% confidence interval will be presented for the secukinumab group.

12.5.2 Safety endpoints

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

Adverse events

Treatment-emergent adverse events (i.e., events started after the first dose of study treatment or events present prior to the first dose of study treatment but increased in severity based on preferred term and on or before last dose + 84 days) will be summarized.

Adverse events will be summarized by presenting, for each treatment group, the number and percentage of participants having any AE, having an AE in each primary system organ class and having each individual AE (preferred term). Summaries will also be presented for AEs by severity and for study treatment related AEs. If a participant reported more than one adverse event with the same preferred term, the adverse event with the greatest severity will be presented.

If a participant reported more than one adverse event within the same primary system organ class, the participant will be counted only once with the greatest severity at the system organ class level, where applicable. Serious adverse events will also be summarized.

As appropriate, the incidence of AEs will be presented per 100 participant-years of exposure (exposure-adjusted incidence rates).

Separate summaries will be provided for deaths, SAEs, and AEs leading to study treatment discontinuation.

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

Vital signs

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

12-lead ECG

Summary statistics will be presented for ECG variables.

Clinical laboratory evaluations

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

[redacted]

12.6 Analysis of exploratory endpoints

[redacted]

[redacted]

[redacted]

12.6.1 Patient reported outcomes

Health-related Quality of Life assessments will be evaluated based on FAS unless otherwise specified.

SF-36

The following variables will be evaluated:

• SF-36 domain scores (based on a scale of 0-100)

• SF-36 PCS and MCS scores (norm-based scores)

• SF-36 PCS and MCS responder (improvement of ≥ 2.5 points, (Lubeck 2004))

For the change in SF-36 summary scores (PCS and MCS), summary statistics will be provided using observed data for each treatment regimen. Between-treatment differences will be evaluated using MMRM.

The SF-36 domain scores will be summarized by treatment.

FACIT-Fatigue©

For the change in FACIT-Fatigue© scores, summary statistics of observed data by visit and change from Baseline in FACIT-Fatigue© will be provided for each treatment. Between-treatment differences will be evaluated using MMRM.

LupusQoL

For the change in LupusQoL domain scores, summary statistics of observed data by visit and change from Baseline will be provided for each treatment. Between-treatment differences will be evaluated using MMRM.

[redacted]

[redacted]

12.6.3 DNA and RNA

Exploratory DNA and RNA studies are designed to investigate the association between genetic factors (genotypes) and clinical assessments (phenotypes) which are collected during the clinical trial. Without prior evidence of a strong association, a number of possible associations are evaluated with exploratory analyses. A range of statistical tests is used for the analyses. Additional data, from other clinical trials, are often needed to confirm associations. Alternatively, if the number of participants enrolled in the study is too small to complete proper statistical analyses, the data may be combined, as appropriate, with those from other studies to enlarge the dataset for analysis.

Data generated on hypothesis-free platforms will be reported separately (e.g., CSR addendum).

12.6.4 Biomarkers

Soluble marker panel studies investigate differences in the level of expression of proteins or peptides between individuals in a given biofluid. The goal of such studies is to allow the identification of potential protein or peptide biomarkers of treatment action or disease and to better understand the associated underlying molecular mechanisms. By applying statistical analysis methods (e.g., principal component analysis) between participant groups, distinct study time points, or between study groups from other clinical trials, it may be possible to identify patterns, which are associated with disease state or response to drug treatment. However, the exact type of data analysis method will depend on the type of data obtained in the study, and thus, the analysis of these data will be data-driven and, hence, not part of the Clinical Study Report (CSR).

[redacted]

12.7 Interim analyses

12.7.1 First interim analysis

The first interim analysis will be performed when approximately 138 participants (approximately 35% of the total 400 participants) are expected to complete 52 weeks of treatment (including those who discontinue the treatment early).

Futility analysis

A futility analysis will be conducted at the first interim analysis. A Go/No-Go decision will be taken at this futility analysis based on the predictive probability of achieving statistical significance for the primary estimand. Futility stopping rules will be defined in the DMC charter.

[redacted]

12.7.2 Second interim analysis

Based on the group sequential design applied in the study, the second interim analysis is planned when approximately 308 participants (approximately 77 % of the total 400 participants) complete 52 weeks of treatment. The results from this interim analysis will support the decision-making concerning the current clinical study, i.e., to continue or to stop the trial based on efficacy (superiority or futility) and/or safety findings.

Superiority analysis

A Lan-De Mets alpha spending function (Lan and DeMets 1983) with Pocock type stopping boundary (Pocock 1977) (as implemented in the software East 6.5) will be used to maintain the overall type-I error rate for the primary and secondary endpoints at Week 52.

Based on the choice of α-spending function described above, the efficacy boundary in terms of p-value scale at the superiority analysis is calculated as p = 0.042 for a two-sided test. The observed (i.e., nominal) p-value has to be smaller than 0.042 to conclude superior efficacy at the interim analysis. If a hypothesis is not rejected at the superiority analysis, it will be tested again at the Week 52 final analysis. The efficacy boundary for the final analysis in terms of p-value scale is p = 0.024.

The exact rejecting boundaries will be calculated after the exact number of participants in each treatment arm is available.

A sequential testing hierarchy will be used to test the secondary hypotheses. The secondary hypotheses will be tested at the superiority analysis only if the primary hypothesis is rejected. This guarantees the 5% overall level of significance for the primary and secondary hypotheses (Glimm et al 2010). For Week 52 secondary endpoints the same rejecting boundaries will be used as for the primary endpoint.

Futility analysis

A second futility analysis will also be conducted at the time of the second interim analysis. Futility stopping rules will be specified in the DMC charter.

12.8 Sample size calculation

12.8.1 Primary endpoint(s)

The total planned sample size is 400 participants. Based on literature (Mysler et al 2013, Rovin et al 2012, Furie et al 2020, Rovin et al 2021), the control response rate was assumed to

be approximately 25%. Assuming 15% treatment difference with 40% response rate for secukinumab, the power for rejecting the null hypothesis for primary endpoint (CRR) is 87%. The assumptions are summarized in Table 12-1 below.

Table 12-1 Power for primary endpoint

Analysis	Control response rate	Secukinumab response rate	Sample size	Cumulative power for primary endpoint
Superiority Interim analysis	25%	40%	308	79%
Final analysis	25%	40%	400	87%

12.8.2 Secondary endpoint(s)

Using published data for control (Mysler et al 2013, Rovin et al 2012, Deng et al 2018, Wallace et al 2017, McElhone et al 2016) and assuming given treatment effects for secukinumab, a summary for power for secondary efficacy parameters is shown in Table 12-2 for binary endpoints, Table 12-3 for continuous endpoints and Table 12-4 for time to event endpoints. Power for the secondary endpoints was calculated with the group sequential design and the total cumulative power, to reject either at the superiority interim or final analysis, is presented.

Table 12-2 Summary of power for binary secondary endpoints

Endpoint	Response rate		Power
	Secukinumab 300 mg (N = 200)	Placebo (N = 200)	
PRR at Week 52	75%	60%	87%
PRR at Week 24	75%	60%	87%

Table 12-3 Summary of power or continuous endpoints

Endpoint	Mean values		Common standard deviation	Power
	Secukinumab 300 mg (N = 200)	Placebo (N = 200)		
Change from baseline in UPCR at Week 52	-3.5	-2.68	2.69	83%
Average daily dose of corticosteroids between Week 16 and Week 52	5	5.52	1.67	84%
FACIT-Fatigue© change from baseline at Week 52	7.0	2.82	10.0	98%
SF-36 PCS change from baseline at Week 52	6.1	3.1	8.0	95%

Endpoint	Mean values		Common standard	Power
LupusQoL Physical Health change from baseline at Week 52	9.6	5.6	14	78%

Table 12-4 Summary of power for time to event endpoints

Endpoint	Event rates and hazard ratios		Power
	Placebo (N = 200) Event rate at Week 52	Hazard Ratio Secukinumab (N = 200)	
Time to CRR	30%	1.67	85%
Time to PRR	60%	1.67	98%
Time to UPCR ≤ 0.5 mg/mg	35%	1.67	89%

13 Ethical considerations and administrative procedures

13.1 Regulatory and ethical compliance

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

13.2 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, written informed consent form, consent form updates, participant recruitment procedures (e.g., advertisements) and any other written information to be provided to participants. 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.

13.3 Publication of study protocol and results

The protocol will be registered in a publicly accessible database such as clinicaltrials.gov and as required in EudraCT. In addition, after study completion (defined as last patient last visit) and finalization of the study report the results of this trial will be submitted for publication and posted in a publicly accessible database of clinical trial results, such as the Novartis clinical trial results website and all required Health Authority websites (e.g., Clinicaltrials.gov, EudraCT etc.).

For details on the Novartis publication policy including authorship criteria, please refer to the Novartis publication policy training materials that were provided to you at the trial investigator meetings.

13.4 Quality Control and Quality Assurance

Novartis maintains a robust Quality Management System (QMS) that includes all activities involved in quality assurance and quality control, to ensure compliance with written Standard Operating Procedures as well as applicable global/local GCP regulations and ICH Guidelines.

Audits of investigator sites, vendors, and Novartis systems are performed by auditors, 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.

14 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 participants 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 prohibition, 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.

14.1 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 required for participant safety 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 participant included in this study, even if this action represents a deviation from the protocol. In such cases, Novartis should be notified of this action and the IRB/IEC at the study site should be informed according to local regulations.

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16 Appendices

16.1 ACR Criteria for Diagnosis of SLE

1997 Update of the 1982 American College of Rheumatology Revised Criteria for Classification of Systemic Lupus Erythematosus

Criterion	Definition
1. Malar Rash	Fixed erythema, flat or raised, over the malar eminences, tending to spare the nasolabial folds
2. Discoid rash	Erythematous raised patches with adherent keratotic scaling and follicular plugging; atrophic scarring may occur in older lesions
3. Photosensitivity	Skin rash as a result of unusual reaction to sunlight, by patient history or physician observation
4. Oral ulcers	Oral or nasopharyngeal ulceration, usually painless, observed by physician
5. Nonerosive Arthritis	Involving 2 or more peripheral joints, characterized by tenderness, swelling, or effusion
6. Pleuritis or Pericarditis	1. Pleuritis--convincing history of pleuritic pain or rubbing heard by a physician or evidence of pleural effusion 1. *OR* 2. Pericarditis--documented by electrocardigram or rub or evidence of pericardial effusion
7. Renal Disorder	1. Persistent proteinuria > 0.5 grams per day or > than 3+ if quantitation not performed 1. *OR* 2. Cellular casts--may be red cell, hemoglobin, granular, tubular, or mixed
8. Neurologic Disorder	1. Seizures--in the absence of offending drugs or known metabolic derangements; e.g., uremia, ketoacidosis, or electrolyte imbalance 1. *OR* 2. Psychosis--in the absence of offending drugs or known metabolic derangements, e.g., uremia, ketoacidosis, or electrolyte imbalance
9. Hematologic Disorder	1. Hemolytic anemia--with reticulocytosis 1. *OR*

Criterion	Definition
	2. Leukopenia--< 4,000/mm^3 on ≥ 2 occasions 1. *OR* 3. Lyphopenia--< 1,500/ mm^3 on ≥ 2 occasions 1. *OR* 4. Thrombocytopenia--<100,000/ mm^3 in the absence of offending drugs
10. Immunologic Disorder	1. Anti-DNA: antibody to native DNA in abnormal titer 1. *OR* 2. Anti-Sm: presence of antibody to Sm nuclear antigen 1. *OR* 3. Positive finding of antiphospholipid antibodies on: 1. 1. an abnormal serum level of IgG or IgM anticardiolipin antibodies, 2. 2. a positive test result for lupus anticoagulant using a standard method, or 3. 3. a false-positive test result for at least 6 months confirmed by Treponema pallidum immobilization or fluorescent treponemal antibody absorption test
11. Positive Antinuclear Antibody	An abnormal titer of antinuclear antibody by immunofluorescence or an equivalent assay at any point in time and in the absence of drugs

16.2 International Society of Nephrology/Renal Pathology Society (ISN/RPS) 2003 classification of LN

Class I	**Minimal mesangial lupus nephritis** Normal glomeruli by light microscopy, but mesangial immune deposits by immunofluorescence
Class II	**Mesangial proliferative lupus nephritis** Purely mesangial hypercellularity of any degree or mesangial matrix expansion by light microscopy, with mesangial immune deposits May be a few isolated subepithelial or subendothelial deposits visible by immunofluorescence or electron microscopy, but not by light microscopy
Class III	**Focal lupus nephritis**[a] Active or inactive focal, segmental or global endo- or extracapillary glomerulonephritis involving <50% of all glomeruli, typically with focal subendothelial immune deposits, with or without mesangial alterations
Class III (A)	Active lesions: focal proliferative lupus nephritis
Class III (A/C)	Active and chronic lesions: focal proliferative and sclerosing lupus nephritis
Class III (C)	Chronic inactive lesions with glomerular scars: focal sclerosing lupus nephritis
Class IV	**Diffuse lupus nephritis**[b] Active or inactive diffuse, segmental or global endo- or extracapillary glomerulonephritis involving ≥50% of all glomeruli, typically with diffuse subendothelial immune deposits, with or without mesangial alterations. This class is divided into diffuse segmental(IV-S) lupus nephritis when ≥50% of the involved glomeruli have segmental lesions, and diffuse global (IV-G) lupus nephritis when ≥50% of the involved glomeruli have global lesions. Segmental is defined as a glomerular lesion that involves less than half of the glomerular tuft. This class includes cases with diffuse wire loop deposits but with little or no glomerular proliferation
Class IV-S (A)	Active lesions: diffuse segmental proliferative lupus nephritis
Class IV-G (A)	Active lesions: diffuse global proliferative lupus nephritis
Class IV-S (A/C)	Active and chronic lesions: diffuse segmental proliferative and sclerosing lupus nephritis Active and chronic lesions: diffuse global proliferative and sclerosing lupus nephritis
Class IV-S (C)	Chronic inactive lesions with scars: diffuse segmental sclerosing lupus nephritis
Class IV-G (C)	Chronic inactive lesions with scars: diffuse global sclerosing lupus nephritis
Class V	**Membranous lupus nephritis** Global or segmental subepithelial immune deposits or their morphologic sequelae by light microscopy and by immunofluorescence or electron microscopy, with or without mesangial alterations Class V lupus nephritis may occur in combination with class III or IV in which case both will be diagnosed Class V lupus nephritis show advanced sclerosis
Class VI	**Advanced sclerosis lupus nephritis** ≥90% of glomeruli globally sclerosed without residual activity

[a] Indicate the proportion of glomeruli with active and with sclerotic lesions.
[b] Indicate the proportion of glomeruli with fibrinoid necrosis and/or cellular crescents.
Indicate and grade (mild, moderate, severe) tubular atrophy, interstitial inflammation and fibrosis, severity of arteriosclerosis or other vascular lesions.

16.3 Estimation of eGFR by the CKD-EPI

The CKD-EPI creatinine equation uses a 2-slope spline to model the relationship between estimated GFR and serum creatinine, and a different relationship for age, sex and race. The equation was reported to perform better and with less bias than the MDRD Study equation, especially in patients with higher GFR. This results in reduced misclassification of CKD (Levey et al 2009)

The CKD-EPI creatinine equation is:

$$GFR = 141 \times \min(Scr/\kappa, 1)^{\alpha} \times \max(Scr/\kappa, 1)^{-1.209} \times 0.993^{Age} \times 1.018[\text{if female}] \times 1.159[\text{if black}]$$

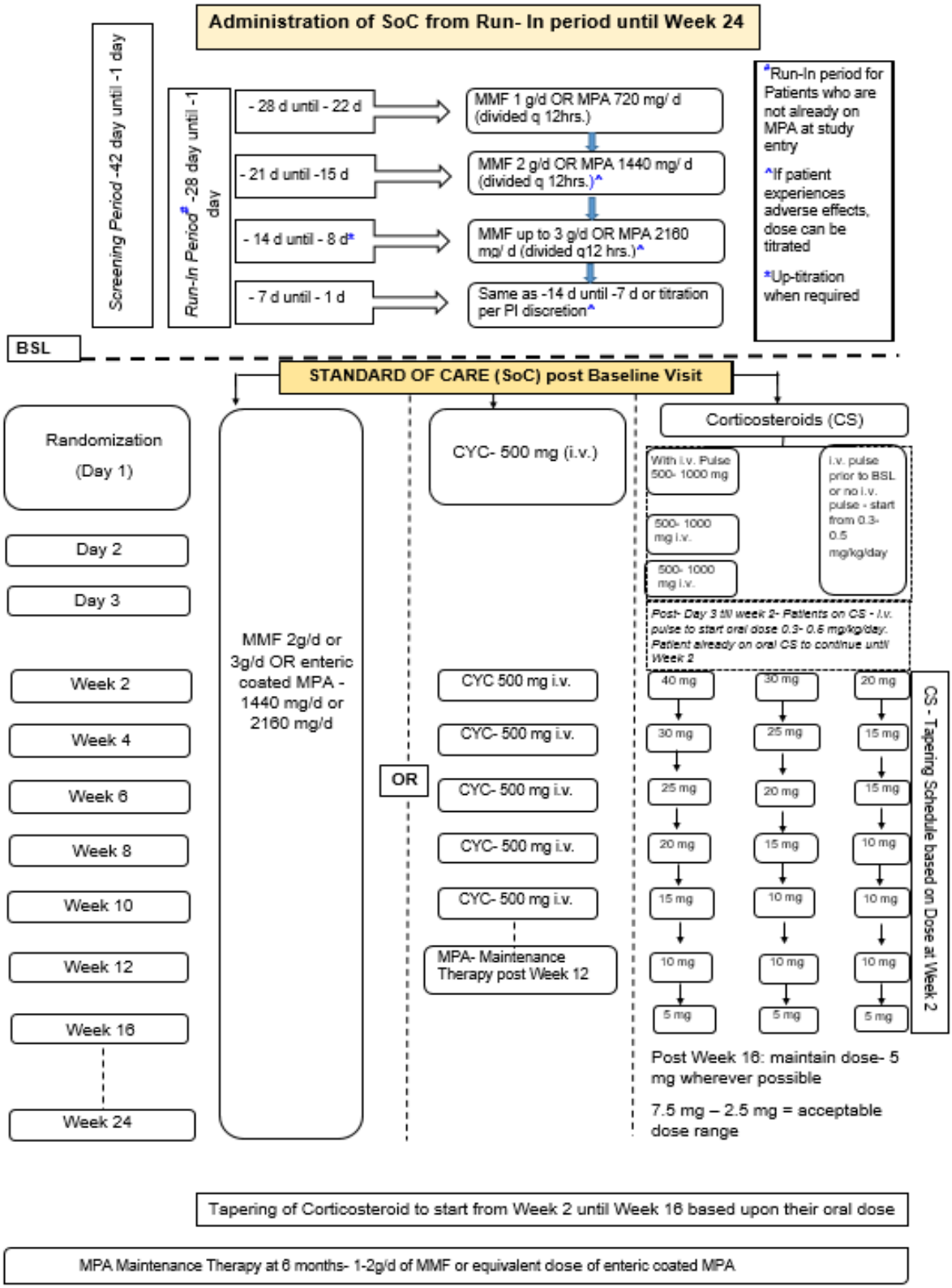
$\kappa = 0.7$ if female
$\kappa = 0.9$ if male

$\alpha = -0.329$ if female
$\alpha = -0.411$ if male

min = The minimum of Scr/κ or 1
max = The maximum of Scr/κ or 1

Scr = serum creatinine (mg/dL)

16.4 Recommended Diagram for administration of Standard of Care



16.5 Guidelines for administering PROs

All questionnaires will be completed on an electronic device at the scheduled study visit prior to the participant seeing the investigator for any clinical assessment or evaluation. The study coordinator should check the questionnaire for completeness and encourage the participant to complete any missing responses.

The participant should be made aware that completed measures are not reviewed by the investigator/study personnel.

Before trial begin

Study coordinators should familiarize themselves with the PRO questionnaires in the trial.

Before completion

1. Participants should be provided with the correct questionnaire at the appropriate visits, and in the appropriate language
2. Participants should be given sufficient instructions, space, time and privacy to complete the questionnaires
3. Questionnaire should be administered before the clinical examination

During completion

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

After completion

1. Check for completeness
2. Check for multiple responses that were made in error
3. Data should be transcribed from the completed questionnaire to the appropriate web portal

Addressing Problems and Concerns

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

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

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

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

In these instances, the coordinator may obtain participant responses by reading out loud each question, followed by the corresponding response categories, and entering the participant’s response. No help should be provided to the participant by any person other than the designated

study coordinator. The coordinator should not influence participant responses. The study coordinator cannot translate the question into simpler language and has to be read verbatim.

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

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

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

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

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

Emphasize that all responses are to be kept confidential. Point out that their names do not appear anywhere on the questionnaire, so that their results will be linked with an ID number and not their name. Tell the participant that his/her answers will be pooled with other participants' answers and that they will be analyzed as a group rather than as individuals. Tell the participant that completed forms are not routinely shared with treating staff, and that their responses will only be seen by you (to check for completeness), and possibly the investigator. Any response which may directly impact on or reflect their medical condition (e.g., noting of severe depression) will be communicated by the coordinator to the physician.

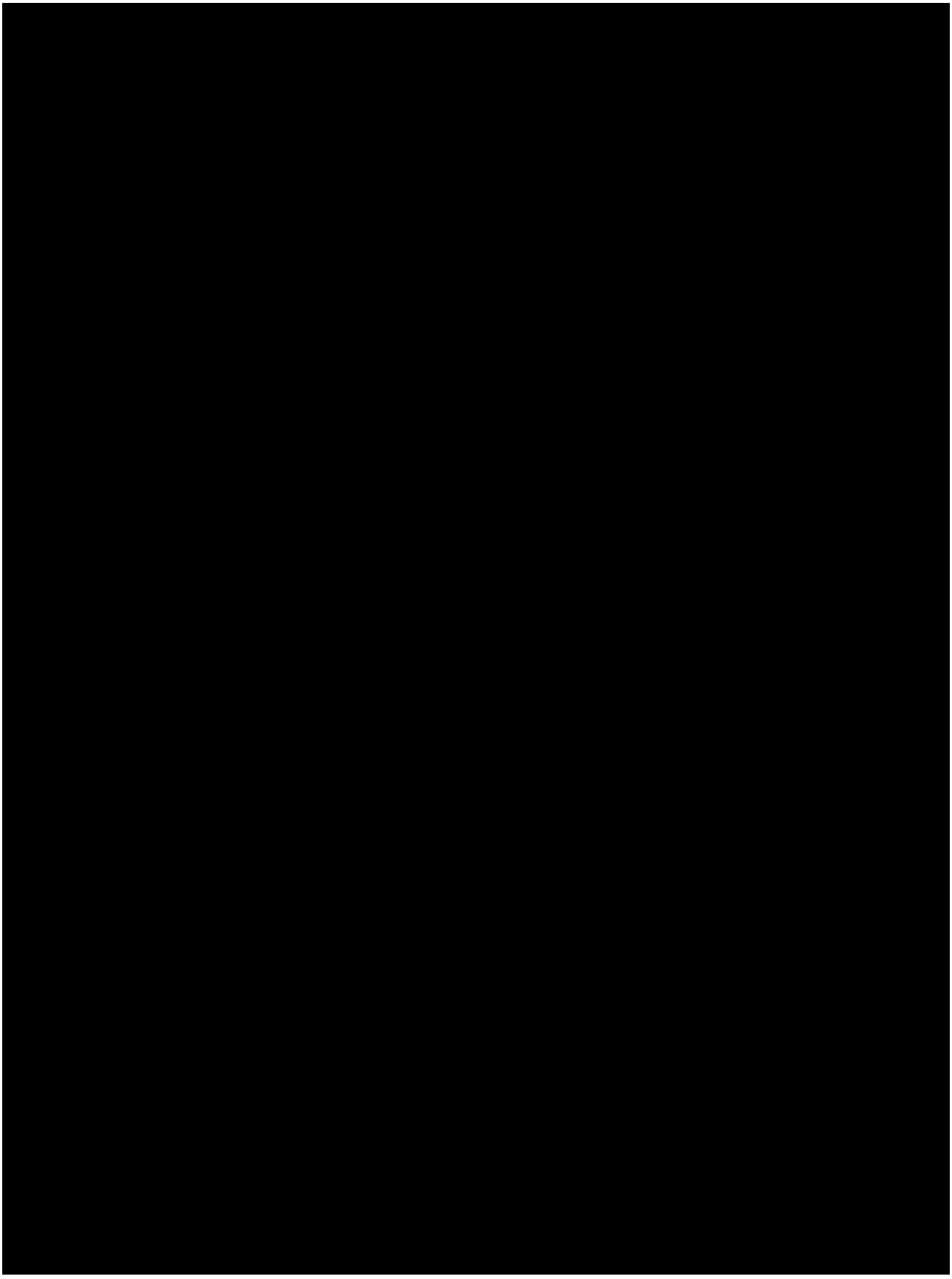
The patient asks the meaning of a question/item

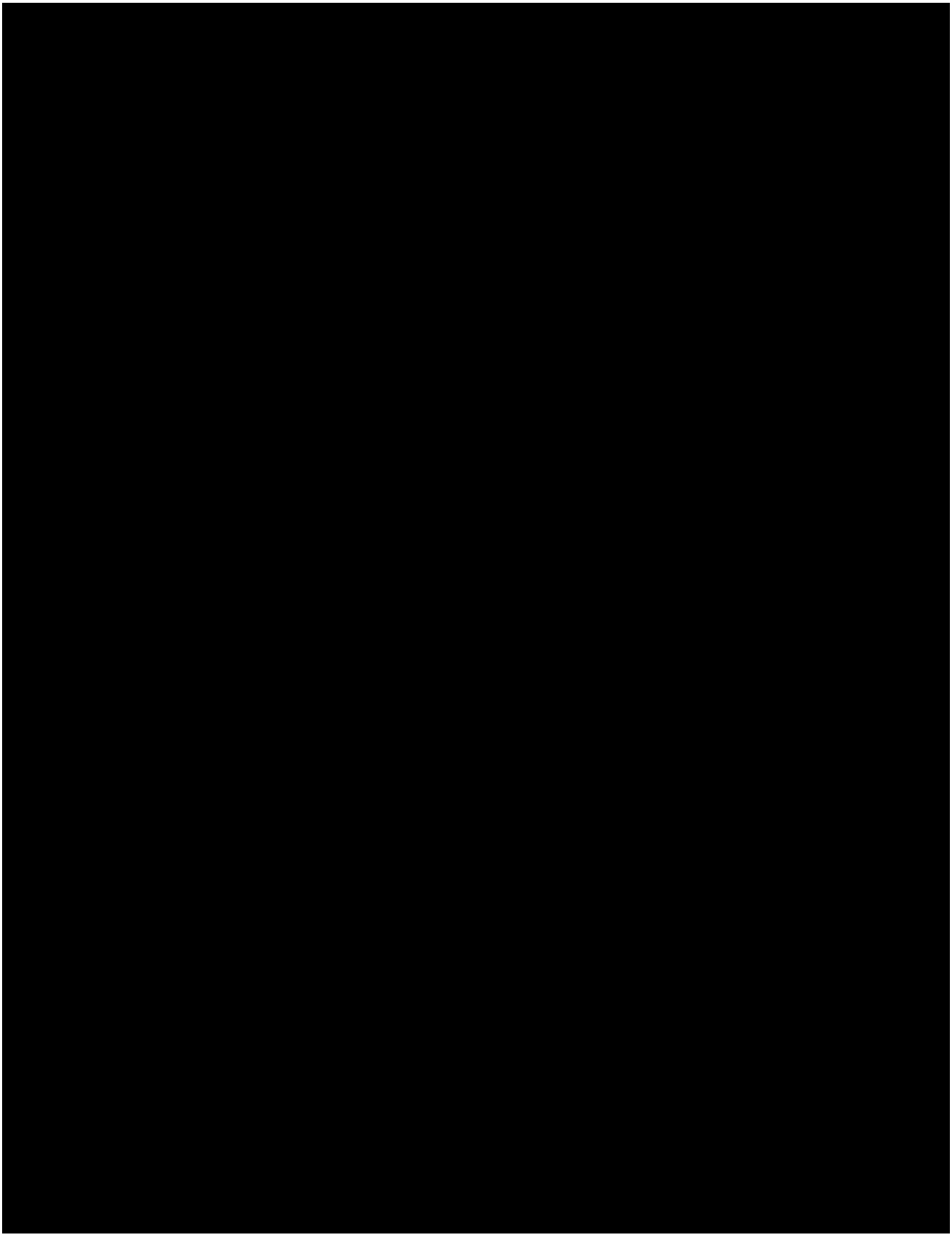
While completing the questionnaire, some participants might ask the meaning of specific items so that they can better understand and respond. If this happens, assist the participant by rereading the question for them *verbatim.* If the participant asks to interpret the meaning of an item, do not try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

General information about all questionnaire(s):

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

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





[redacted]

16.9 Liver event and Laboratory trigger Definitions and Follow-up Requirements

Table 16-1 Liver event and laboratory trigger definitions

	Definition/ threshold
LIVER LABORATORY TRIGGERS	3 x ULN < ALT / AST ≤ 5 x ULN
	1.5 x ULN < TBL ≤ 2 x ULN
LIVER EVENTS	ALT or AST > 5 × ULN
	ALP > 2 × ULN (in the absence of known bone pathology)
	TBL > 2 × ULN (in the absence of known Gilbert syndrome)
	ALT or AST > 3 × ULN and INR > 1.5
	Potential Hy's Law cases (defined as ALT or AST > 3 × ULN and TBL > 2 × ULN [mainly conjugated fraction] without notable increase in ALP to > 2 × ULN)
	Any clinical event of jaundice (or equivalent term)
	ALT or AST > 3 × ULN accompanied by (general) malaise, fatigue, abdominal pain, nausea, or vomiting, or rash with eosinophilia
	Any adverse event potentially indicative of a liver toxicity*

*These events cover the following: Hepatic failure, fibrosis and cirrhosis, and other liver damage-related conditions; the non-infectious hepatitis; the benign, malignant and unspecified liver neoplasms TBL: total bilirubin; ULN: upper limit of normal

Table 16-2 Follow up requirements for liver events and laboratory triggers

Criteria	**Actions required**	**Follow-up monitoring**
Potential Hy's Law case[a]	1. Discontinue the study treatment immediately 2. Hospitalize, if clinically appropriate 3. Establish causality 4. Record the AE and contributing factors (e.g., conmeds, med hx, lab) in the appropriate CRF	ALT, AST, TBL, Alb, PT/INR, ALP and GGT until resolution[c] (frequency at investigator discretion)

Criteria	Actions required	Follow-up monitoring
ALT or AST		
> 8 × ULN	1. Discontinue the study treatment immediately 2. Hospitalize if clinically appropriate 3. Establish causality 4. Record the AE and contributing factors (e.g., conmeds, med hx, lab) in the appropriate CRF	ALT, AST, TBL, Alb, PT/INR, ALP and GGT until resolution[c] (frequency at investigator discretion)
> 3 × ULN and INR > 1.5	1. Discontinue the study treatment immediately 2. Hospitalize, if clinically appropriate 3. Establish causality 4. Record the AE and contributing factors (e.g., conmeds, med hx, lab) in the appropriate CRF	ALT, AST, TBL, Alb, PT/INR, ALP and GGT until resolution[c] (frequency at investigator discretion)
> 5 to ≤ 8 × ULN	1. Repeat Liver function test (LFT) within 48 hours 2. If elevation persists, continue follow-up monitoring 3. If elevation persists for more than 2 weeks, discontinue the study drug 4. Establish causality 5. Record the AE and contributing factors (e.g., conmeds, med hx, lab) in the appropriate CRF	ALT, AST, TBL, Alb, PT/INR, ALP and GGT until resolution[c] (frequency at investigator discretion)
> 3 × ULN accompanied by symptoms[b]	1. Discontinue the study treatment immediately 2. Hospitalize if clinically appropriate 3. Establish causality 4. Record the AE and contributing factors (e.g., conmeds, med hx, lab) in the appropriate CRF	ALT, AST, TBL, Alb, PT/INR, ALP and GGT until resolution[c] (frequency at investigator discretion)
> 3 to ≤ 5 × ULN (patient is asymptomatic)	1. Repeat LFT within the next week 2. If elevation is confirmed, initiate close observation of the patient	Investigator discretion Monitor LFT within 1 to 4 weeks
ALP (isolated)		
> 2 × ULN (in the absence of known bone pathology)	1. Repeat LFT within 48 hours 2. If elevation persists, establish causality 3. Record the AE and contributing factors (e.g., conmeds, med hx, lab) in the appropriate CRF	Investigator discretion Monitor LFT within 1 to 4 weeks or at next visit

Criteria	Actions required	Follow-up monitoring
TBL (isolated)		
> 2 × ULN (in the absence of known Gilbert syndrome)	1. Repeat LFT within 48 hours 2. If elevation persists, discontinue the study drug immediately 3. Hospitalize if clinically appropriate 4. Establish causality 5. Record the AE and contributing factors (e.g., conmeds, med hx, lab) in the appropriate CRF	ALT, AST, TBL, Alb, PT/INR, ALP and GGT until resolution[c] (frequency at investigator discretion) Test for hemolysis (e.g., reticulocytes, haptoglobin, unconjugated [indirect] bilirubin)
> 1.5 to ≤ 2 × ULN (patient is asymptomatic)	1. Repeat LFT within the next week 2. If elevation is confirmed, initiate close observation of the patient	Investigator discretion Monitor LFT within 1 to 4 weeks or at next visit
Jaundice	1. Discontinue the study treatment immediately 2. Hospitalize the patient 3. Establish causality 4. Record the AE and contributing factors (e.g., conmeds, med hx, lab) in the appropriate CRF	ALT, AST, TBL, Alb, PT/INR, ALP and GGT until resolution[c] (frequency at investigator discretion)
Any AE potentially indicative of a liver toxicity*	1. Consider study treatment interruption or discontinuation 2. Hospitalization if clinically appropriate 3. Establish causality 4. Record the AE and contributing factors (e.g., conmeds, med hx, lab) in the appropriate CRF	Investigator discretion

[a]Elevated ALT/AST > 3 × ULN and TBL > 2 × ULN but without notable increase in ALP to > 2 × ULN [b](General) malaise, fatigue, abdominal pain, nausea, or vomiting, or rash with eosinophilia [c]Resolution is defined as an outcome of one of the following: (1) return to Baseline values, (2) stable values at three subsequent monitoring visits at least 2 weeks apart, (3) remain at elevated level after a maximum of 6 months, (4) liver transplantation, and (5) death.

Based on investigator's discretion investigation(s) for contributing factors for the liver event can include: Serology tests, imaging and pathology assessments, hepatologist's consultancy; obtaining more detailed history of symptoms and prior or concurrent diseases, history of concomitant drug use, exclusion of underlying liver disease.

16.10 Clinically notable laboratory values

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

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

Table 16-3 Safety Analyses: Expanded Limits and Notable Criteria

	Notable Criteria	
Laboratory Variable	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

HEMATOLOGY VARIABLES

Hemoglobin: 20 g/L decrease from Baseline

Platelet count: < 50 x 10E9/L

White blood cell count: < 0.8 x LLN

Neutrophils: < 0.9 x LLN

NOVARTIS

Novartis Research and Development

Secukinumab (AIN457)

Clinical Trial Protocol CAIN457Q12301

A two-year, phase III randomized, double-blind, parallel-group, placebo-controlled trial to evaluate the safety, efficacy, and tolerability of 300 mg s.c. secukinumab versus placebo, in combination with SoC therapy, in patients with active lupus nephritis

Document type:	Clinical Trial Protocol
EUDRACT number:	2019-003211-57
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Clinical Trial Phase:	III
Release date:	11-Oct-2019

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List of abbreviations

[redacted]	[redacted]
ACR	American College of Rheumatology
AE	adverse event
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ANA	anti-nuclear antibodies
ANCOVA	analysis of covariance
anti-dsDNA	Anti-double stranded DNA
[redacted]	[redacted]
aPTT	activated partial thromboplastin time
AST	aspartate aminotransferase
[redacted]	[redacted]
BMI	Body Mass Index
CFR	Code of Federal Regulation
CHMP	Committee for Medicinal Products for Human Use
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
[redacted]	[redacted]
CNIs	calcineurin inhibitors
COAs	Clinical Outcome Assessments
CRF	Case Report/Record Form (paper or electronic)
CRO	Clinician reported outcomes
CRR	Complete Renal Response
CYC	cyclophosphamide
[redacted]	[redacted]
DMC	Data Monitoring Committee
DNA	deoxyribonucleic acid
EC	Ethics committee
ECG	Electrocardiogram
EDC	Electronic Data Capture
eGFR	estimated glomerular filtration rate
ELISA	Enzyme-linked immunosorbent assay
EMA	European Medicines Agency
ERA-EDTA	European Renal Association – European Dialysis and Transplant Association
ESRD	end-stage renal disease
EULAR	European League Against Rheumatism
FACIT-Fatigue©	Functional Assessment of Chronic Illness Therapy - Fatigue
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GGT	gamma-glutamyl transferase
h	hour

HbA1c	Hemoglobin A1c
HDL	High Density Lipoprotein
HIV	human immunodeficiency virus
HRQoL	health-related quality of life
hsCRP	High sensitivity C-reactive protein
i.v.	intravenous
ICH	International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use
IEC	Independent Ethics Committee
[redacted]	[redacted]
INR	International Normalized Ratio
IRB	Institutional Review Board
IRT	Interactive Response Technology
ISN	International Society of Neurology
[redacted]	[redacted]
LDL	Low Density Lipoprotein
LFT	Liver function test
[redacted]	[redacted]
LLN	lower limit of normal
LLQ	lower limit of quantification
LN	lupus nephritis
[redacted]	[redacted]
mCRR	modified Complete Renal Response
MedDRA	Medical dictionary for regulatory activities
mg	milligram(s)
mL	milliliter(s)
ml	milliliter(s)
MMF	Mycophenolate mofetil
MMRM	Mixed-Effect Model Repeated Measure
MPA	mycophenolic acid
[redacted]	[redacted]
o.d.	once a day
p.o.	per oral
PCS	physical component summary
PD	pharmacodynamic(s)
PFS	Prefilled syringe
[redacted]	[redacted]
PK	pharmacokinetic(s)
PRR	partial renal response
PT	Prothrombin time
PY	Patient Year
RBC	red blood cell(s)

RNA	ribonucleic acid
RPS	Renal Pathology Society
s.c.	subcutaneous
SAE	serious adverse event
SD	standard deviation
SF-36	Medical Outcome Short Form (36) Health Survey
SGOT	serum glutamic oxaloacetic transaminase
SGPT	serum glutamic pyruvic transaminase
SLE	systemic lupus erythematosus
[redacted]	[redacted]
SoC	standard of care
SUSAR	Suspected Unexpected Serious Adverse Reactions
TBL	total bilirubin
TEAE	Treatment-emergent adverse event
TFQ	Trial Feedback Questionnaire
[redacted]	[redacted]
[redacted]	[redacted]
ULN	upper limit of normal
ULQ	upper limit of quantification
UPCR	Urine Protein-to-Creatinine Ratio
WBC	white blood cell(s)
WHO	World Health Organization

Glossary of terms

Assessment	A procedure used to generate data required by the study
Cohort	A specific group of subjects fulfilling certain criteria
Control drug	A study drug used as a comparator to reduce assessment bias, preserve blinding of investigational drug, assess internal study validity, and/or evaluate comparative effects of the investigational drug.
Dosage	Dose of the study treatment given to the subject in a time unit (e.g., 100 mg once a day, 75 mg twice a day)
Enrollment	Point/time of subject entry into the study at which informed consent must be obtained (i.e. prior to starting any of the procedures described in the protocol)
Investigational drug	The study drug whose properties are being tested in the study; this definition is consistent with US CFR 21 Section 312.3 and Directive 2001/20/EC and is synonymous with “investigational new drug” or “test substance”
Investigational treatment	All investigational drug(s) whose properties are being tested in the study as well as their associated treatment controls. This includes any placebos, any active controls, as well as approved drugs used outside of their indication/approved dosage or tested in a fixed combination. Investigational treatment generally does not include other treatments administered as concomitant background therapy required or allowed by the protocol when used within approved indication/dosage.
Medication number	A unique identifier on the label of each study drug package in studies that dispense study drug using an IRT system.
Part	A single component of a study, which contains different objectives or populations within that single study. Common parts within a study are: a single dose part and a multiple dose part, or a part in patients with established disease and in those with newly-diagnosed disease.
Period	A minor subdivision of the study timeline; divides phases into smaller functional segments such as Screening, Baseline, titration, washout, etc.
Randomization number	A unique identifier assigned to each randomized subject, corresponding to a specific treatment arm assignment
Screen Failure	A subject who is screened but is not treated or randomized
Stage	A major subdivision of the study timeline; begins and ends with major study milestones such as enrollment, randomization, completion of treatment, etc.
Study completion	Point/time at which the subject came in for a final evaluation visit or when study drug was discontinued whichever is later.
Study treatment	Any drug administered to the study participants as part of the required study procedures; includes investigational drug (s), control(s) or non-investigational medicinal product(s)
Study treatment discontinuation	Point/time when subject permanently stops taking study treatment for any reason; may or may not also be the point/time of premature subject withdrawal.
Subject	An individual who has consented to participate in this study. The term Subject may be used to describe either a healthy volunteer or a patient.
Subject number	A unique number assigned to each subject upon signing the informed consent. This number is the definitive, unique identifier for the subject and should be used to identify the subject throughout the study for all data collected, sample labels, etc.
Variable	Information used in the data analysis; derived directly or indirectly from data collected using specified assessments at specified timepoints.

Withdrawal of consent (WoC)	Withdrawal of consent from the study is defined as when a subject does not want to participate in the study any longer, and does not allow further collection of personal data

Protocol summary

Protocol number	CAIN457Q12301
Full Title	A two-year, phase III randomized, double-blind, parallel-group, placebo-controlled trial to evaluate the safety, efficacy, and tolerability of 300 mg s.c. secukinumab versus placebo, in combination with SoC therapy, in patients with active lupus nephritis
Brief title	Study of safety, efficacy and tolerability of secukinumab versus placebo, in combination with SoC therapy, in patients with active lupus nephritis
Sponsor and Clinical Phase	Novartis Phase III
Investigation type	Biological
Study type	Interventional
Purpose and rationale	The purpose of this trial is to evaluate the efficacy and safety of subcutaneous secukinumab 300 mg compared to placebo, in combination with standard of care therapy (SoC), in subjects with active lupus nephritis (ISN/RPS Class III or IV, with or without co-existing class V features). Background SoC will consist of induction therapy with mycophenolic acid (MPA) (which refers to Mycophenolate mofetil (MMF) (Cellcept® or generic equivalent), or enteric-coated MPA sodium (Myfortic® or generic equivalent) at equivalent doses (oral), or Cyclophosphamide (CYC) (i.v.), followed by maintenance therapy with MPA (MMF, enteric-coated MPA sodium, or their generics). In addition, all subjects will receive i.v. and/or oral corticosteroids. The aim of the study is to demonstrate the efficacy and safety of secukinumab in LN that will enable registration for the indication of lupus nephritis.
Primary Objective(s)	The primary objective is to demonstrate that secukinumab 300 mg is superior to placebo in Complete Renal Response (CRR) rate at Week 52 in active lupus nephritis (ISN/RPS Class III or IV, with or without co-existing Class V features) subjects on a background of SoC therapy
Secondary Objectives	Objective 1: To demonstrate superiority of secukinumab compared to placebo in change from Baseline in 24-hour UPCR at Week 52 Objective 2: To demonstrate superiority of secukinumab compared to placebo in proportion of subjects achieving partial renal response (PRR) at Week 52 Objective 3: To demonstrate superiority of secukinumab compared to placebo in average daily dose of oral corticosteroids administered between Week 16 and Week 52 Objective 4: To demonstrate superiority of secukinumab compared to placebo in proportion of subjects achieving PRR at Week 24 Objective 5: To demonstrate superiority of secukinumab compared to placebo in time to achieve CRR Objective 6: To demonstrate superiority of secukinumab compared to placebo in time to achieve PRR

	Objective 7: To demonstrate superiority of secukinumab compared to placebo in time to achieve first morning void Urine Protein-to-Creatinine Ratio (UPCR) ≤ 0.5 mg/mg Objective 8: To demonstrate superiority of secukinumab compared to placebo in change in Functional Assessment of Chronic Illness Therapy – Fatigue (FACIT-Fatigue©) score at Week 52 Objective 9: To demonstrate superiority of secukinumab compared to placebo in patient's health related quality of life via Medical Outcome Short Form Health Survey (SF-36 Physical Component Summary (PCS)) score at Week 52 Objective 10: To demonstrate superiority of secukinumab compared to placebo in change of LupusQoL (Physical Health) score at Week 52 Objective 11: To evaluate the safety and tolerability of secukinumab s.c. as an add-on therapy to Standard of Care in lupus nephritis subjects Objective 12: To estimate the proportion of subjects with maintained renal response at Week 104 Objective 13: To estimate the proportion of subjects with improved or maintained renal response at Week 104
Study design	This is a pivotal, randomized, double-blind, placebo controlled trial evaluating at Week 52 the efficacy and safety of secukinumab versus placebo in subjects with active lupus nephritis also receiving background SoC regimen. In addition, long-term efficacy, safety and tolerability will be collected up to 2 years.
Population	The study population will be comprised of adult male and female subjects in the age range of 18-75 years with a renal biopsy (results current or within the 6 months prior to Screening) showing active glomerulonephritis WHO or ISN/RPS Class III or IV LN [excluding III (C), IV-S (C) and IV-G (C)], with or without co-existing class V features, who are inadequately controlled with previous SoC defined as having UPCR ≥1 and active urinary sediment (presence of cellular casts which are granular casts or red blood cells) or hematuria (>5 red blood cells per high power field)). Approximately 460 subjects, randomized into two treatment arms (1:1 active: placebo), are planned. At randomization, subjects will be stratified on the basis of the SoC induction therapy they will receive during the study, MPA or CYC-based, to ensure a balanced representation in each of the treatment arms (secukinumab or placebo). The target will be to have a maximum of 25% of randomized subjects receiving CYC-based induction therapy.
Key Inclusion criteria	Subjects eligible for inclusion in this study must meet **all** of the following criteria: 1. Adult male and female subjects aged 18 - 75 years old at the time of Baseline 2. Confirmed diagnosis of: · SLE with documented history of at least 4 of the 11 criteria for SLE as defined by the American College of Rheumatology (ACR). [NOTE: The 4 criteria do not have to be present at the time of Screening], OR · Lupus nephritis as the sole clinical criterion in the presence of ANA or anti-dsDNA antibodies. 3. Active lupus nephritis, as defined by meeting the 4 following criteria:

	· Biopsy within 6 months prior to Screening visit indicating active glomerulonephritis WHO or ISN/RPS Class III or IV LN [excluding III (C), IV-S (C) and IV-G (C)]; subjects are permitted to have co-existing Class V. If no biopsy was performed within 6 months of Screening, a biopsy will need to be performed during the Screening period, after all other inclusion/exclusion criteria would have been verified. · UPCR ≥1 at Screening · Estimated eGFR >30 mL/min/1.73 m^2 by Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) · Active urinary sediment (presence of cellular casts (granular or red blood cell casts) or hematuria (>5 red blood cells per high power field)) 4. Subjects must be currently on, or willing to initiate SoC induction therapy for LN according to the institutional practices using MPA (MMF or enteric-coated MPA sodium) or low-dose CYC in addition to corticosteroids. 5. If the subject is on cholesterol-lowering agents, the dose must be stable for at least 7 days prior to Randomization. 6. Subjects must be treated with anti-malarials (e.g., hydroxychloroquine), unless contra-indicated, and the dose must be stable for at least 10 days prior to Randomization. 7. Able to provide signed informed consent.
Key Exclusion criteria	Subjects meeting any of the following criteria are not eligible for inclusion in this study. 1. Severe renal impairment as defined by i.) Stage 4 CKD, or ii.) presence of oliguria (defined as a documented urine volume < 400 mL/24 hrs), or iii.) ESRD requiring dialysis or transplantation 2. Known intolerance/hypersensitivity to MPA (MMF or enteric-coated MPA sodium), or oral corticosteroids, or any component of the study treatment 3. Subjects having received any other biologic immunomodulatory therapy within 6 months prior to Screening, excluding belimumab where 3 months are acceptable 4. Previous exposure to secukinumab (AIN457) or any other biologic drug targeting IL-17 or the IL-17 receptor 5. Subjects having received any investigational drug within 1 month or five times the half-life, whichever is longer 6. Receipt of more than 3000 mg i.v. pulse methylprednisolone (cumulative dose) within the 12 weeks prior to Baseline 7. Treatment with a systemic calcineurin inhibitor (e.g., cyclosporine, tacrolimus) within 12 weeks prior to Baseline 8. CYC use (i.v. or oral) within the month prior to Baseline 9. Subjects requiring dialysis within the previous 12 months before Screening 10. History of renal transplant 11. Any severe progressive or uncontrolled concurrent medical condition, including recent severe thromboembolic events, that, in the opinion of the principal investigator, renders the subject unsuitable for the trial

	12. Active ongoing inflammatory diseases that might confound the evaluation of the benefit of secukinumab therapy, including inflammatory bowel disease 13. Presence of investigator-identified significant medical problems which at the investigator's discretion will prevent the subject from participating in the study, including but not limited to the following: myocarditis, pericarditis, poorly controlled seizure disorder, acute confusional state, depression, severe manifestations of neuropsychiatric SLE (NPSLE) 14. Chest X-ray, computerized tomography (CT) scan, or MRI with evidence of ongoing infectious or malignant process, obtained within 12 weeks prior to Randomization and evaluated by a qualified physician 15. History of chronic, recurrent systemic infections, active tuberculosis infection, or active systemic infections during the last two weeks (exception: common cold) prior to Randomization 16. Known infection with human immunodeficiency virus (HIV), hepatitis B or hepatitis C at Screening or Randomization 17. History of lymphoproliferative disease or any known malignancy or history of malignancy of any organ system treated or untreated within the past 5 years, regardless of whether there is evidence of local recurrence or metastases (except for skin Bowen's disease or basal cell carcinoma or actinic keratoses that have been treated with no evidence of recurrence in the past 12 weeks, carcinoma *in situ* of the cervix or non-invasive malignant colon polyps that have been removed) 18. Any of the following abnormal laboratory values on Screening evaluations as reported by Central Laboratory : · Aspartate aminotransferase (AST), alanine aminotransferase (ALT), or amylase > 2.5xULN · Hemoglobin <8g/dL · Neutrophils <1.0 x 10^9/L · Platelet count <50 x 10^9/L 19. Inability or unwillingness to undergo repeated venipuncture (e.g., because of poor tolerability or lack of venous access) 20. History or evidence of ongoing alcohol or drug abuse, within the last six months before Randomization 21. Pregnant or lactating women 22. Women of childbearing potential, defined as all women physiologically capable of becoming pregnant, unless they are using highly effective methods of contraception during the entire study or longer if required by locally approved prescribing information (e.g., in European Union (EU) 20 weeks)
Study treatment	At Baseline, all eligible subjects will be randomized to one of the two treatment arms in a 1:1 ratio via Interactive Response Technology (IRT): • Arm 1: approximately 230 LN subjects will receive secukinumab 300 mg s.c. (2 x 1.0 mL PFS of 150 mg dose) at Randomization, Weeks 1, 2 and 3, and every 4 weeks from Week 4 until week 100 • Arm 2: approximately 230 LN subjects will receive placebo s.c. (2 x 1.0 mL PFS of 0 mg dose) at Randomization, Weeks 1, 2 and 3, and every 4 weeks from Week 4 until week 100

	At Randomization, subjects will be stratified on the basis of the SoC induction therapy they will receive during the study, MPA or CYC-based, to ensure a balanced representation in each of the treatment arms (secukinumab or placebo).
Efficacy assessments	• Assessment of CRR, defined as eGFR within the normal range or no less than 85% of Baseline AND 24-hour UPCR ≤ 0.5 mg/mg • Time to achieve UPCR ≤ 0.5 mg/mg • Assessment of PRR, defined as ≥50% reduction in 24-hour UPCR to sub-nephrotic levels AND normal eGFR or no less than 85% of Baseline • Average daily dose of oral corticosteroids • Time to achieve CRR • Time to achieve PRR • FACIT-Fatigue© score • SF-36 PCS score • LupusQoL Physical Health score
Key safety assessments	• Physical examinations • Vital signs • Height and weight • Laboratory evaluations (hematology, clinical chemistry, coagulation panel, local urinalysis, 24-hour urine collection, lipid panel, [redacted] and pregnancy test) • Chest X-ray • Evaluation of AEs and SAEs
Other assessments	[redacted] • Biomarkers (urine and serum) • Pharmacogenetics; DNA and RNA analysis
Data analysis	The primary efficacy endpoint is the CRR at Week 52. The statistical hypothesis tested for the primary objective is that there is no difference in the proportion of subjects fulfilling the response criteria at Week 52 between the secukinumab regimen and placebo regimens. Let p_j denote the proportion of responders at Week 52 for treatment regimens j, j=0, 1 where · 0 corresponds to placebo regimen, · 1 corresponds to secukinumab , In statistical terms, H1: p1 = p0, HA1: p1 ≠ p0, i.e.,

	H1: secukinumab is not different to placebo regimen with respect to CRR at Week 52 Logistic regression model adjusting for SoC, race and Baseline UPCR will be used for the primary analysis. Difference in marginal response proportions with p-value and respective 95% confidence interval will be estimated from the logistic regression model. Safety analyses will include summaries of AEs, laboratory measurements, and vital signs. Full details of all data analyses will be specified in statistical analysis plan.
Key words	Systemic Lupus Erythematosus (SLE), Lupus Nephritis (LN), secukinumab, renal biopsy, estimated glomerular filtration rate (eGFR), Urine Protein-to-Creatinine Ratio (UPCR), Standard of care (SoC) background therapy

1 Introduction

1.1 Background

1.1.1 Lupus nephritis

Lupus nephritis is estimated to affect more than one-half of SLE patients and is a severe manifestation in SLE (Cervera et al 2003).

Immune complex formation in LN related to a plethora of autoantibodies, especially anti-dsDNA and anti-nucleosome antibodies, is the result of systemic autoimmunity and is a hallmark of the disease (Waldman and Madaio 2005), (Nowling and Gilkeson 2011) that is generally treated by systemic immunosuppression. Once formed, immune complexes activate complement, which can injure renal cells leading to either mesangial LN (class I, II), proliferative LN (class III, IV), membranous LN (class V) and advanced sclerotic LN (class VI). However, pathogenesis of LN is complex and involves both the innate and adaptive immune systems; various cytokines, immune tissues and cell types are involved in its pathogenesis. Intra-renal inflammation is maintained via local cytokine and chemokine production, and by cells of the innate immune system such as neutrophils, that are attracted into the glomerulus and interstitium. Targeting local release of proinflammatory cytokines by blocking single cytokine pathways may enhance treatment efficacy in autoimmunity without increasing systemic immunosuppression (Allam and Anders 2008), (Yu et al 2017).

Lupus nephritis is characterized by glomerular endothelium, podocyte, tubulointerstitial and vascular injury. Specific leukocyte subsets, including IL-17-producing T helper type 17 (T_H17) cells, drive inflammation and contribute to renal immunopathology (Yu et al 2017).

Lupus nephritis is categorized histologically into 6 classes by the International Society of Nephrology/Renal Pathology Society (ISN/RPS) classification system (Weening et al 2004), (Markowitz and D'Agati 2007). Treatments include management with corticosteroids together with anti-malarials for lower stage disease, followed by more aggressive immunosuppressive therapies for more severe disease, and ultimately renal transplant.

Class III and IV LN are detected in approximately 39 to 71.9 % of LN patients, and from the deposition of immune complexes in the subendothelial space of the glomerular capillaries (Wang et al 2018). Both these classes of LN are considered to have similar lesions that differ by severity and distribution. Class IV diffuse LN is distinguished from class III on the basis of involvement of more than 50% of glomeruli with endocapillary lesions. Patients with class III and IV LN require aggressive therapy with glucocorticoids and immunosuppressive agents cyclophosphamide (CYC), mycophenolate mofetil (MMF), rituximab as well as calcineurin inhibitors (CNIs) (Hahn et al 2012).

Lupus nephritis is associated with significant morbidity and mortality, even with current treatments. With current induction and maintenance therapies, the risk of developing LN-related end-stage renal disease (ESRD) at 5, 10, and 15 years remained at 11%, 17%, and 22%, respectively for the last decade (Tektonidou et al 2016), (Faurschou et al 2010). In addition, current immunosuppressive therapies carry substantial infectious as well as other mid/long-term toxicity risks.

Despite recent advances in treatment for several autoimmune diseases, there are currently no specific Food and Drug Administration (FDA) or European Medicines Agency (EMA)-approved therapies for LN. Current treatments are non-specific, aimed at slowing progression with general immunosuppression. Renal response rates remain suboptimal, underscoring the persistent high unmet medical need in the treatment of patients with LN. Thus, there is still a substantial proportion of LN patients with ESRD within 5 years (Houssiau et al 2010).

The European League Against Rheumatism (EULAR)/European Renal Association – European Dialysis and Transplant Association (ERA-EDTA) and ACR guidelines are uniform in their recommendations for therapy for class III and IV LN and include a sequence of induction and maintenance phases. For patients with class III or IV proliferative glomerulonephritis, the guidelines recommend induction therapy with MPA (MMF or enteric-coated MPA sodium) or intravenous (i.v.) CYC, with or without initial pulses of i.v. methylprednisolone. With current induction regimens, less than 60% of class III to V patients achieve a complete or partial response (Appel et al 2009). Among those who attain a complete renal response (CRR) with current standard-of-care (SoC), nearly half of the patients had a relapse. The incidence rate of relapse in these patients was 5 to 15 per 100 patient year (PY) (Grootscholten and Berden 2006).

Despite the aggressive nature of SoC treatment, only up to 40% of patients achieve a CRR after 1 year (Rovin and Parikh 2014). In addition, current LN treatment regimens have substantial side effects from glucocorticoids and prolonged immunosuppression (Schwartz et al 2014). Immunosuppressed LN patients are at significant risk of developing serious infections. In a multiethnic Medicaid cohort, the incidence rate of serious infections was more than 2-fold higher in LN than in SLE patients (Feldman et al 2015).

Given the severity of the condition and the lack of approved therapy, there is a high unmet medical need for efficacious therapies, which also have a favorable benefit:risk profile, for the treatment of LN patients.

1.1.2 Scientific rationale for targeting IL-17 in lupus nephritis

Animal model studies have demonstrated that the IL-17 and upstream IL-23 pathways contribute to renal injury in experimental models of LN or glomerulonephritis. IL-23 receptor deficiency decreased the number of IL-17A-producing double-negative (DN) T cells, produced less anti-DNA antibodies and prevented glomerulonephritis in lupus-prone C57BL/6-lpr/lpr mice (Kyttaris et al 2010); treatment with an anti-IL-23 antibody in the same mouse model ameliorated nephritis and was accompanied by a reduction of IL-17A produced by *in vitro* stimulated splenocytes post-treatment (Kyttaris et al 2013). Both IL-23p19 and IL-17A knock-out mice developed less severe nephritis in a T cell-mediated murine model of nephrotoxic nephritis (Paust et al 2009). Elevated expression of IL-17A was observed in lupus-prone Fcgr2b knock-out mice, which develop fatal lupus glomerulonephritis, while mice lacking IL-17 displayed increased survival and protection from glomerulonephritis (Pisitkun et al 2014). Additional support for a role of IL-17A in LN has been provided in the pristane-induced LN mouse model, in which absence of IL-17A led to decreased renal inflammation and renal injury, along with reduced levels of anti-DNA antibodies (Summers et al 2014). In this model, macrophages as well as neutrophils were the main

producers of IL-17A. Thus, based on these animal data, blocking IL-17A in LN may prove beneficial in limiting glomerular inflammation and renal damage.

A growing number of studies in patients with LN indicate that IL-17A and Th17 cells play important roles in the pathogenesis of LN, contributing to glomerular injury and the persistence of inflammation and renal damage (Zhang et al 2009), (Crispín and Tsokos 2008). High levels of IL-17 predict poor histopathological outcomes after immunosuppressive therapy in patients with LN (Zickert et al 2015). A subset of T cells infiltrates the kidneys of patients with LN and represent the major source for IL-17 (Crispín and Tsokos 2008). IL-17 has the potential to induce the production of additional inflammatory cytokines and chemokines and to promote recruitment of inflammatory cells such as monocytes and neutrophils to inflamed organs. Higher levels of glomerular IL-17 and IL-23 expression are observed in renal biopsies from class IV LN patients as compared with those from minimal change nephropathy patients and normal controls. Both glomerular IL-17 and IL-23 expression levels positively correlate with renal histological activity index scores for LN patients (Chen et al 2012). The urinary expression of Th17-related genes, including those for IL-17 and IL-23, is increased and associated with the activity of LN (Kwan et al 2009).

Additional evidence shows that neutrophil recruitment to the kidney starts several hours after the induction of nephrotoxic nephritis and is partly mediated by IL-17A-producing γδ T cells (Kurts et al 2013). Th17 cells promote intra-renal IL-17A expression in LN (Crispín and Tsokos 2008). IL-17 can also drive T cells away from maturing into a regulatory T cell phenotype that can suppress autoantibody production and attenuate the systemic immune response (Bettelli et al 2006).

An imbalance between inflammatory Th17 and regulatory T cells and the secretion of inflammatory cytokines including IL-17A amplify the immune response in LN by inducing the local production of chemokines and cytokines, as well as the recruitment of neutrophils and monocytes. This ultimately contributes to persistent inflammation and kidney damage in LN (Koga et al 2017). IL-17A can also act directly on kidney cells such as mesangial cells (Paust et al 2009), tubular epithelial cells (Hirai et al 2012) and podocytes (Yan et al 2018), thereby increasing inflammation, T cell and neutrophil infiltration, and disruption of renal function leading to proteinuria. Therefore, a pathogenic model for glomerulonephritis is emerging in which Th17 cells infiltrate the kidney and IL-17A (as well as potentially other cytokines) produced by Th17 cells acts directly on resident kidney cells to induce cytokines and chemokines that lead to further recruitment of Th17 cells and neutrophils into the tissue, resulting in renal tissue damage (Krebs et al 2017).

A recent report of a patient with refractory LN and concomitant psoriasis vulgaris suggests that treatment with the IL-17A inhibitor secukinumab may have contributed to an improvement in renal function and a decrease in urine protein levels in this patient (Satoh et al 2018).

1.1.3 Secukinumab

Secukinumab is a recombinant high-affinity fully human monoclonal anti-human IL-17A antibody of the IgG1/kappa isotype.

Secukinumab is currently approved in more than 94 countries worldwide. The product is indicated for the treatment of three inflammatory/autoimmune diseases, moderate to severe

plaque psoriasis (PSO), psoriatic arthritis (PsA) and ankylosing spondylitis (AS), and is being evaluated in other inflammatory conditions such as non-radiographic axial spondyloarthritis, juvenile idiopathic arthritis and pediatric psoriasis.

The outcome of the extensive Novartis clinical program comprising more than 25 Phase III studies and at least 17,000 subjects studied over a period up to 5 years in these indications has shown that secukinumab offers robust and clinically meaningful efficacy to these patients and is complemented by a consistently favorable benefit:risk profile. The safety profile of secukinumab was indeed consistent and comparable across PsO, PsA and AS, supporting its long-term use in these chronic inflammatory conditions.

Based on the available data suggesting that IL-17 is an appropriate therapeutic target for patients with LN, secukinumab has the potential to be an effective therapy for the active LN patients (ISN/RPS Class III or IV, with or without co-existing Class V features), when used in combination with SoC therapy.

1.2 Purpose

The purpose of this trial is to evaluate the efficacy and safety of subcutaneous secukinumab 300 mg compared to placebo, in combination with standard of care therapy (SoC), in subjects with active lupus nephritis (ISN/RPS Class III or IV, with or without co-existing class V features).

Background SoC will consist of induction therapy with mycophenolic acid (MPA) (which refers to Mycophenolate mofetil (MMF) (Cellcept® or generic equivalent), or enteric-coated MPA sodium (Myfortic® or generic equivalent) at equivalent doses (oral), or Cyclophosphamide (CYC) (i.v.), followed by maintenance therapy with MPA. In addition, all subjects will receive i.v. and/or oral corticosteroids.

The aim of the study is to demonstrate the efficacy and safety of secukinumab in LN that will enable registration for the indication of lupus nephritis.

Within this document, at each time MPA will be mentioned without further information, it will refer to Cellcept®, Myfortic® or generic equivalent at equivalent doses.

2 Objectives and endpoints

Table 2-1 Objectives and related endpoints

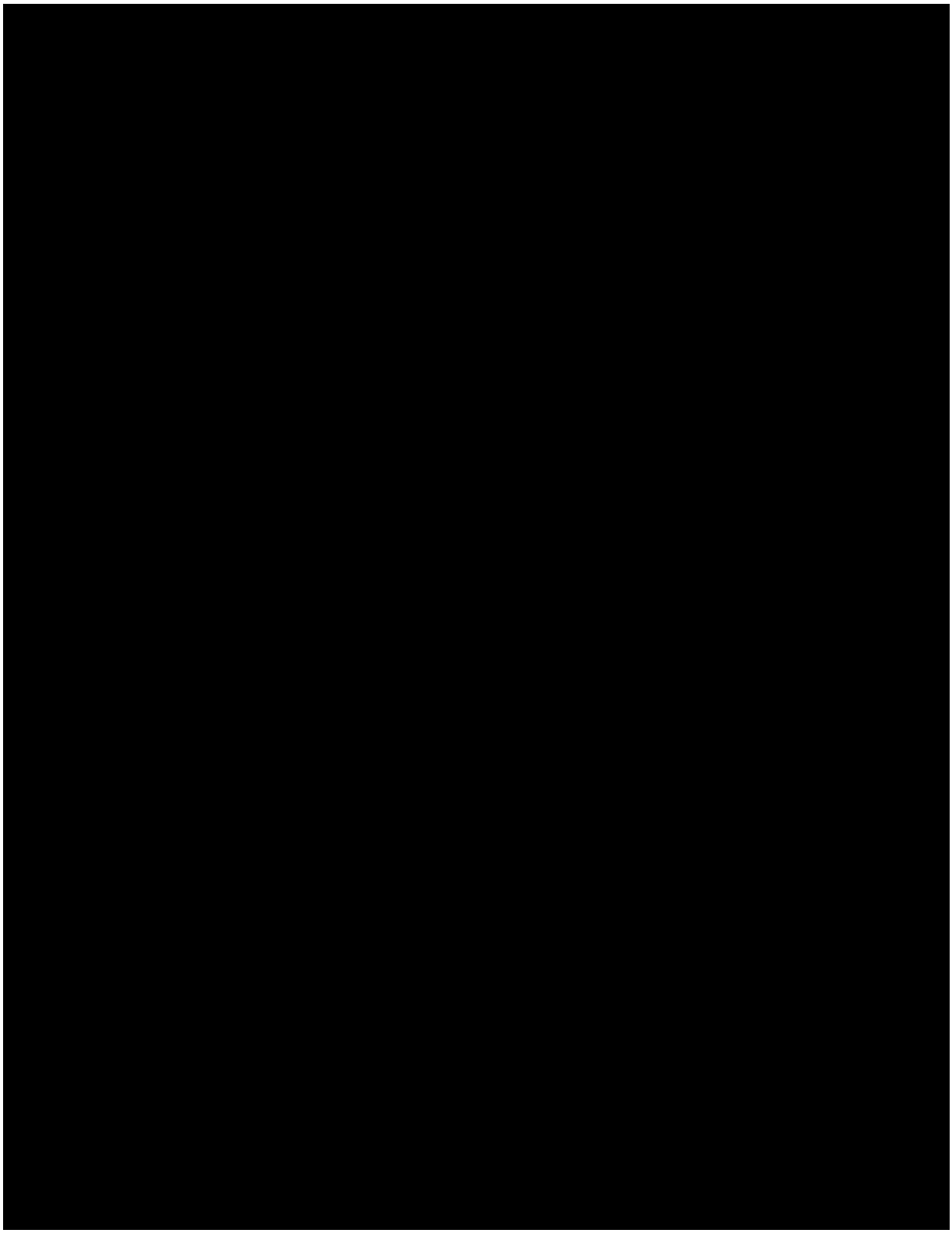
Objective(s)	Endpoint(s)
Primary objective(s)	**Endpoint(s) for primary objective(s)**
• To demonstrate that secukinumab 300 mg is superior to placebo in Complete Renal Response (CRR) rate at Week 52 in active lupus nephritis (ISN/RPS Class III or IV, with or without co-existing Class V features) subjects on a background of SoC therapy.	• Proportion of subjects achieving CRR at Week 52 CRR is a composite endpoint defined as meeting the following: • Estimated glomerular filtration rate (eGFR) within

Objective(s)	Endpoint(s)
	the normal range or no less than 85% of Baseline and • 24-hour urine protein-to-creatinine ratio (UPCR) ≤0.5 mg/mg

Secondary objective(s)	Endpoint(s) for secondary objective(s)
• To demonstrate superiority of secukinumab compared to placebo in change from baseline in 24-hour UPCR at Week 52	• Change from Baseline in 24-hour UPCR at Week 52
• To demonstrate superiority of secukinumab compared to placebo in proportion of subjects achieving partial renal response (PRR) at Week 52	• Proportion of subjects achieving PRR at Week 52 defined as: • ≥50% reduction in 24-hour UPCR to sub-nephrotic levels and • Normal eGFR or no less than 85% of Baseline
• To demonstrate superiority of secukinumab compared to placebo in average daily dose of oral corticosteroids administered between Week 16 and Week 52	• Average daily dose of oral corticosteroids administered between Week 16 and Week 52 compared to placebo
• To demonstrate superiority of secukinumab compared to placebo in proportion of subjects achieving PRR at Week 24	• Proportion of subjects achieving PRR at Week 24 defined as: • ≥50% reduction in 24-hour UPCR to sub-nephrotic levels and • Normal eGFR or no less than 85% of Baseline
• To demonstrate superiority of secukinumab compared to placebo in time to achieve CRR	• Time to achieve CRR up to Week 52
• To demonstrate superiority of secukinumab compared to placebo in time to achieve PRR	• Time to achieve PRR up to Week 52
• To demonstrate superiority of secukinumab compared to placebo in time to achieve first morning void UPCR ≤ 0.5 mg/mg	• Time to achieve first morning void UPCR ≤ 0.5 mg/mg up to Week 52
• To demonstrate superiority of secukinumab compared to placebo in change in Functional Assessment of Chronic Illness Therapy – Fatigue (FACIT-Fatigue©) score at Week 52	• Improvement in FACIT-Fatigue© mean change of score from Baseline at Week 52 compared to placebo
• To demonstrate superiority of secukinumab compared to placebo in patient's health related quality of life via Medical Outcome Short Form Health Survey (SF-36 Physical Component Summary (PCS)) score at Week 52	• Improvement in SF-36 PCS mean change from Baseline at Week 52 compared to placebo

Secondary objective(s)	Endpoint(s) for secondary objective(s)
• To demonstrate superiority of secukinumab compared to placebo in change of LupusQoL (Physical Health) score at Week 52	• Improvement in LupusQoL Physical Health mean change of score from Baseline at Week 52 compared to placebo
• To evaluate the safety and tolerability of secukinumab s.c. as an add-on therapy to Standard of Care in lupus nephritis subjects	• Incidence of Treatment-emergent AEs (TEAEs) / SAEs from Baseline to Week 52; vital signs and body measurements, standard chemistry and hematology up to Week 52
• To estimate the proportion of subjects with maintained renal response at Week 104	• Estimate the proportion of subjects with CRR at Week 104 within subjects who had achieved CRR at Week 52 in the secukinumab group
• To estimate the proportion of subjects with improved or maintained renal response at Week 104	• Estimate the proportion of subjects with improved or maintained response (PRR or CRR) in subjects who had achieved at least PRR at Week 52 in the secukinumab group

Exploratory objective(s)	Endpoint(s) for exploratory objective(s)
[redacted]	



- To perform exploratory pharmacogenomic analysis based on blood samples for DNA and RNA analysis (optional assessments)
- Evaluate the relationship of genetic polymorphisms and transcriptomic data with treatment response

3 Study design

This is a pivotal, randomized, double-blind, placebo controlled trial evaluating at Week 52 the efficacy and safety of secukinumab versus placebo in subjects with active LN also receiving background SoC regimen. Long-term efficacy, safety and tolerability will be collected up to 2 years.

The SoC regimen will consist of induction therapy with MPA or CYC, followed by maintenance therapy with MPA. The choice of background SoC induction therapy will be at investigator's discretion. At Randomization, subjects will be stratified on the basis of the SoC induction therapy they will receive during the study, MPA or CYC-based, to ensure a balanced representation in each of the treatment arms (secukinumab or placebo). The target will be to have a maximum of 25% of randomized subjects receiving CYC-based induction therapy.

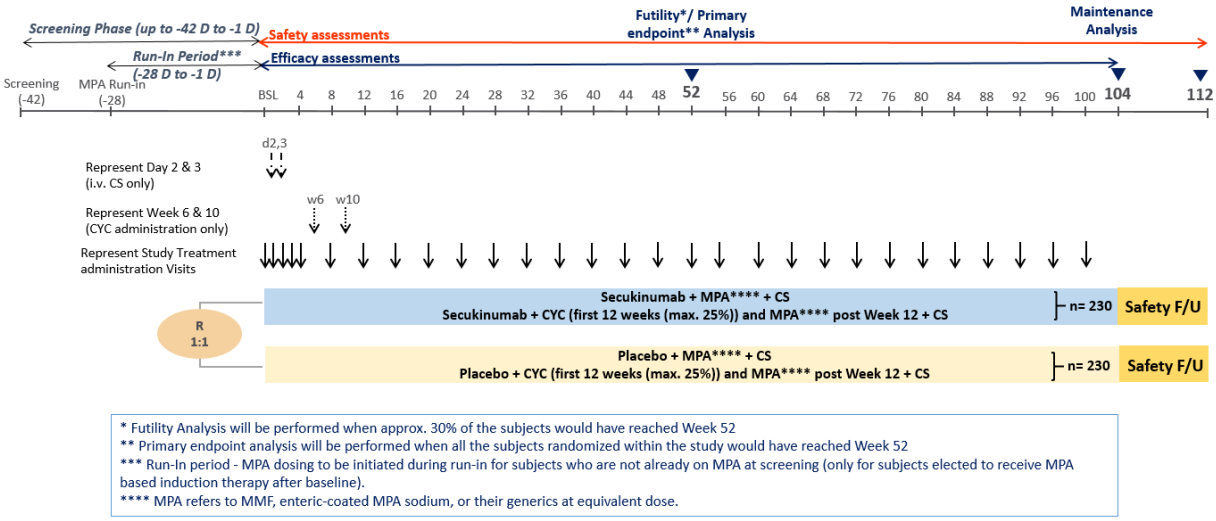
In addition, steroids will be administered through i.v. pulses followed by oral daily doses as described in Section 6.1.3 SoC background therapy.

The primary endpoint analysis will be performed after all subjects have completed the visit associated with the primary endpoint (Week 52). Although the unblinding of selected members of the Novartis Global Clinical Team will occur after the Week 52 database lock, original randomization to active treatment versus placebo will continue to remain blinded to all investigators, site personnel, subjects, and monitors until the final database lock and analyses are completed.

The study consists of the following parts:

a. Screening (up to 42 days/6 weeks)
b. Run-in period (optional): For subjects who will receive MPA as SoC induction therapy as per investigator's decision and who are not already on MPA at Screening, MPA dosing will be initiated during a run-in period before Randomization (for up to 4 weeks prior to the first dose of secukinumab)
c. Treatment Period: Duration of 104 weeks of treatment with secukinumab/placebo in addition to SoC treatment (with last dose given at Week 100)
d. Follow-up period: Duration of 8 weeks (last visit performed 12 weeks after last dose of study medication)

Figure 3-1 Study design



* Futility Analysis will be performed when approx. 30% of the subjects would have reached Week 52
** Primary endpoint analysis will be performed when all the subjects randomized within the study would have reached Week 52
*** Run-In period - MPA dosing to be initiated during run-in for subjects who are not already on MPA at screening (only for subjects elected to receive MPA based induction therapy after baseline).
**** MPA refers to MMF, enteric-coated MPA sodium, or their generics at equivalent dose.

Screening to Randomization (Screening and Run-in period):

A Screening period of up to 6 weeks will be used to assess subject´s eligibility and to adjust for concomitant medication(s) (-42 to -1 day). This flexible duration will provide enough time to evaluate eligibility of the subject, including renal biopsy evaluation. If subjects do not have a renal biopsy obtained within 6 months of the Screening visit, a renal biopsy should be performed. This renal biopsy should be performed after confirming that the subject meets all other inclusion/exclusion criteria.

Subjects who will receive MPA-based SoC induction therapy for the treatment of active LN as per investigator's decision, and not already on MPA when entering Screening, will be initiated on MPA during the run-in period (-28 to -1) as described in Section 6.1.3 SoC background therapy.

Treatment period: Treatment period covers time between Randomization (Baseline) through EOT.

At Baseline, eligible subjects will be randomized in a 1:1 ratio to secukinumab 300 mg s.c. or placebo. Approximately 230 subjects will be randomized to each of the two treatment arms. A blinded, weekly, s.c. secukinumab or placebo loading regimen will be administered for the first 4 weeks followed by a monthly maintenance dose in all randomized subjects thereafter. At the

end of the treatment period at Week 104, the planned End of Treatment (EOT) visit will be performed.

Subjects who discontinue study treatment prematurely for any reason other than withdrawal of informed consent before Week 104 will not be considered as discontinued from the study. Those subjects should perform the EOT study visit 4 weeks after their last study treatment administration. Thereafter, subjects should continue attending all subsequent scheduled site visits for study assessments. Subjects who are unwilling to continue attending further study visits after prematurely discontinuing the study treatment, should attend the End of Study (EOS) visit 12 weeks after the last administration of study treatment. Please refer to Section 9.1.1 Discontinuation of study treatment for further details.

In addition, starting at Week 52, subjects who are not deemed, by the investigator, to achieve the desired benefit from the study treatment, should be considered for rescue medication. In case a prohibited medication (as defined in Section 6.2.2 Prohibited medication) is used as rescue medication, the subject should be discontinued from study treatment.

Follow-up period: An EOS visit is to be done for all subjects. The EOS visit will be performed 12 weeks after last study treatment administration for all subjects who complete the 104 weeks treatment period, or who discontinue prematurely study treatment and study. For subjects who discontinue study treatment prematurely but continue attending study visits, please refer to Section 9.1.1 Discontinuation of study treatment for detailed guidelines.

Safety assessments will include physical examinations, vital signs, standard clinical laboratory evaluations, hematology (including blood coagulation assays), blood chemistry, urinalysis, adverse and serious adverse event monitoring.

4 Rationale

4.1 Rationale for study design

The double-blind, randomized, placebo-controlled, parallel-group design will enable the evaluation of the benefit-risk of the proposed secukinumab dose regimen in an adequate and well-controlled setting, minimizing potential bias in reporting of safety and efficacy data.

A recommended steroid tapering regimen will be initiated in all randomized subjects during the treatment period. The tapering schedule (timing and dose decrease) will depend on the Baseline corticosteroid dose. The tapering regimen, as described in Section 6.1.3 SoC Background therapy, is in alignment with common medical practice in LN and is designed to minimize steroid-related toxicity and avoid confounding the primary efficacy assessment.

CRR is a preferred primary outcome for induction and maintenance therapy in LN. It is demonstrated as clinically significant improvement of renal function during the induction phase, shown by improvement of eGFR and signs and symptoms of renal injury like protein excretion. The primary endpoint assessment is planned at Week 52 as recommended by various guidelines. The two-year duration (104 weeks) will provide additional safety and efficacy data as well as the durability of response.

An assessment of PRR will be conducted as a secondary endpoint in the trial and will evaluate the proportion of subjects who improved while not achieving a CRR. Considering the long

duration of the study (104 weeks), maintenance of CRR and prevention of renal flares are also secondary outcomes that may be evaluated. [redacted]

4.1.1 Rationale for choice of background therapy

The SoC background therapy that all subjects will receive was selected as it corresponds to the treatment recommendations of the ACR and EULAR/ERA-EDTA guidelines for induction and maintenance therapy for subjects with ISN/RPS Class III or IV LN, with or without co-existing class V features, (Bertsias et al 2012), (Hahn et al 2012), (Palmer et al 2017).

The choice of background SoC regimen for induction will be left at investigator's discretion, with a maximum of 25% of randomized subjects receiving CYC-based induction therapy (stratification at Randomization will ensure balanced representation in both groups, secukinumab or placebo). SoC background regimen will consist of induction therapy with MPA or low-dose CYC regimen, followed by maintenance therapy with MPA, along with glucocorticoids:

- MPA and CYC are considered equivalent for the induction of remission in patients with ISN/RPS Class III or IV LN, with or without co-existing class V features
- The low dose intravenous CYC regimen for induction was selected, as it presents a better efficacy/toxicity ratio than high-dose intravenous CYC
- Corticosteroid administration as per the above mentioned guidelines are considered a mainstay in LN treatment

4.2 Rationale for dose/regimen and duration of treatment

Secukinumab dosing will start with initial dosing of 300 mg s.c. injections at Baseline, Weeks 1, 2, 3, and 4, followed by dosing every 4 weeks. This dosing regimen is approved for treatment of other autoimmune diseases (PsO, PsA). Available data in PsO and PsA strongly suggest that secukinumab operates at the plateau of the dose-exposure-response curve in these autoimmune diseases, which is one of the reasons to select this dose level in LN as well. As clearly demonstrated in the development program for PsO, it is expected that the initial weekly dosing during the first month will enable rapid achievement of effective drug concentrations and lead to a more rapid onset of clinical response.

It has to be noted that due to kidney damage, proteinuria is commonly observed in patients with LN. The effect of renal impairment on the PK of biologics is dependent on the ability of the compound to undergo glomerular filtration, which is largely driven by molecular weight (MW). Secukinumab has a MW of ca. 148 kDa, and renal clearance usually plays a minimal role in the elimination of biologics with MW greater than 69 kDa (Meibohm and Zhou H 2012). An association between increased Baseline proteinuria and increased clearance was observed in the population PK analysis of belimumab (a human mAb that inhibits B-cell activating factor, BAFF) in SLE (Struemper et al 2013). Also, there is evidence that in some forms of renal disease, such as diabetic nephropathy, there may be an increase in the renal elimination of IgGs (Bakoush et al 2002). However, slight changes in distribution volume or increased clearance of secukinumab in LN patients will probably not dramatically change the PK characteristics of secukinumab.

In addition, the secukinumab dosing regimen used in the study is associated with a reassuring safety profile, as confirmed in multiple clinical trials (up to 5 years) and in the post-marketing setting.

4.3 Rationale for choice of control drugs (comparator/placebo) or combination drugs

A placebo arm is included for the whole duration of the study treatment. Due to the nature of the disease and the primary outcome measure used (CRR), a placebo arm is necessary to obtain reliable efficacy measurements for comparison between the active treatment and the placebo. In addition, all subjects, including those assigned to the placebo arm, will receive background SoC therapy as recommended within the EULAR/ERA-EDTA and ACR guidelines for the induction and maintenance treatment of patients with active ISN/RPS class III or IV LN [excluding III (C), IV-S (C) and IV-G (C)] ,with or without co-existing class V features.

As recommended by the same guidelines, all subjects will also receive hydroxychloroquine (HCQ) as adjunctive medication unless contraindicated. Treatment with lipid-lowering statin and of renin-angiotensin-aldosterone system inhibitors (ACE inhibitors /ARBs) is allowed.

The FDA (FDA 2018) and the Committee for Medicinal Products for Human Use (CHMP) recommend double blind, parallel-group, randomized trial designs. Per the CHMP guideline (Committee for Medicinal Products for Human use (CHMP) 2015), a superiority trial design against an active comparator or placebo is preferred in LN. Placebo-controlled trials are acceptable provided that placebo is given as add-on to SoC therapy.

4.4 Purpose and timing of interim analyses/design adaptations

The study team, site staff, investigators and subjects will remain blinded to the interim data and results of the analysis for both the futility and interim analysis described below.

In addition to those interim analysis, the primary endpoint analysis will be performed after **all** subjects have completed the visit associated with the primary endpoint (Week 52). At time of the primary endpoint analysis, although the unblinding of selected members of the Novartis Global Clinical Team will occur, investigators/site personnel, subjects and monitors will remain blinded until the final study analyses are completed.

Futility Analysis

A futility analysis will be performed when approximately 30% of the subjects have completed the first 52 weeks of treatment. A Go/No-Go decision will be taken at this futility analysis based on predictive probability calculated from the CRR achieved at Week 52.

The analysis will be conducted by an independent statistician and programmer supporting an independent data monitoring committee (DMC). Futility stopping rules will be defined in the DMC charter.

[redacted]

[redacted]

Interim analysis

Based on the group sequential design applied in the study, an Interim Analysis is planned when 2/3 or approximately 67% subjects complete 52 weeks of treatment. The interim analysis will be performed by independent DMC. The results from this interim analysis will support the decision to continue or to stop the trial based on efficacy and/or safety findings.

4.5 Risks and benefits

To date, no evidence-based, systemic therapy has been available for lupus nephritis patients. Current standard of care therapies comprise conventional immunosuppressants which are not fully efficacious in all patients and associated with significant toxicities. Based on the scientific rationale for targeting IL-17 pathway in lupus, and the data available on secukinumab, IL-17 inhibition by secukinumab has a potential therapeutic benefit for lupus nephritis patients who are clinically active despite standard of care treatment.

Secukinumab has demonstrated positive benefit risk in the treatment of multiple chronic inflammatory diseases, including PsA, AS and PsO.

Secukinumab therapy has a well-established and well-described safety profile based on extensive post-marketing experience and continued clinical trial patient exposure since its approval for the first indication of moderate to severe plaque psoriasis. Details of the risk and benefits are outlined in the current version of the Investigator's Brochure (IB).

The safety and tolerability of secukinumab as an add-on to SoC will be evaluated. Based on the favorable safety profile of secukinumab and the known safety profile of the SoC treatments for LN, it is unlikely that the addition of secukinumab to the LN SoC regimens will result in unacceptably high risks, particularly for serious infections. In a pooled analysis of clinical trial data, including multiple indications and nearly 18,000 patients exposed to any dose of secukinumab, the crude incidence of severe AEs of infections was 2.7% [PSUR – data on file]. In comparison, a recent meta-analysis found that, in patients with lupus nephritis treated, the crude incidence rates of serious infections have been reported at 26.7% with high-dose glucocorticoids, 15.1% with cyclophosphamide, and 11.6% with MMF (Singh et al 2016). Additionally, in secukinumab trials, the exposure-adjusted incidence rate of SAEs of infections have been reported at 1.6/100 PY [PSUR – data on file], while the risk of serious infections with a combined regimen of MMF and corticosteroids was reported at 19/100 PY (Rovin et al 2012), (Mysler et al 2013).

The risk to subjects in this trial may be minimized by compliance with the eligibility criteria and study procedures, as well as close clinical monitoring, and periodic review of safety data by an independent DMC. Additional information can be found in the IB for secukinumab.

Women of childbearing 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 must agree that in order to participate in the study, they must adhere to the contraception requirements outlined in the exclusion criteria. If there is any question that the subject will not reliably comply, they should not be entered or continue in the study.

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

5 Population

The study population will be comprised of adult male and female subjects in the age range of 18-75 years with a renal biopsy (current or within the 6 months prior to Screening) showing active glomerulonephritis WHO or ISN/RPS Class III or IV LN [excluding III (C), IV-S (C) and IV-G (C)], with or without co-existing class V features, who are inadequately controlled with previous SoC defined as having UPCR ≥1 and active urinary sediment (presence of cellular casts which are granular casts or red blood cells or hematuria (>5 red blood cells per high power field)).

Approximately 460 subjects, randomized into two treatment arms (1:1 active: placebo), are planned. At Randomization, subjects will be stratified on the basis of the SoC induction therapy they will receive during the study, MPA or CYC-based, to ensure a balanced representation in each of the treatment arms (secukinumab or placebo). The target will be to have a maximum of 25% of randomized subjects receiving CYC-based induction therapy.

5.1 Inclusion criteria

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

1. Adult male and female subjects aged 18 - 75 years old at the time of Baseline.
2. Confirmed diagnosis of:
   - SLE with documented history of at least 4 of the 11 criteria for SLE as defined by the American College of Rheumatology (ACR) (Tan et al 1982) revised by (Hochberg 1997). [NOTE: The 4 criteria do not have to be present at the time of Screening],

   OR
   - LN as the sole clinical criterion in the presence of ANA or anti-dsDNA antibodies.
3. Active lupus nephritis, as defined by meeting the 4 following criteria:
   - Biopsy within 6 months prior to Screening visit indicating active glomerulonephritis WHO or ISN/RPS Class III or IV LN [excluding III (C), IV-S (C) and IV-G (C)]; subjects are permitted to have co-existing Class V. If no biopsy was performed within 6 months of Screening, a biopsy will need to be performed during the Screening period, after all other inclusion/exclusion criteria would have been verified.
   - UPCR ≥1 at Screening.
   - Estimated eGFR >30 mL/min/1.73 m^2 by Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI).
   - Active urinary sediment (presence of cellular casts (granular or red blood cell casts) or hematuria (>5 red blood cells per high power field)).
4. Subjects must be currently on, or willing to initiate SoC induction therapy for LN according to the institutional practices using MPA or low-dose CYC in addition to corticosteroids. For guidance, see published guidelines such as by (Bertsias et al 2012), (Hahn et al 2012).

5. If the subject is on cholesterol-lowering agents, the dose must be stable for at least 7 days prior to Randomization.
6. Subjects must be treated with anti-malarials (e.g., hydroxychloroquine), unless contra-indicated, and the dose must be stable for at least 10 days prior to Randomization.
7. Able to provide signed informed consent.

5.2 Exclusion criteria

Subjects meeting any of the following criteria are not eligible for inclusion in this study.

1. Severe renal impairment as defined by i.) Stage 4 CKD, or ii.) presence of oliguria (defined as a documented urine volume < 400 mL/24 hrs), or iii.) ESRD requiring dialysis or transplantation.
2. Known intolerance/hypersensitivity to MPA, or oral corticosteroids, or any component of the study drug(s).
3. Subjects having received any other biologic immunomodulatory therapy within 6 months prior to Screening, excluding belimumab where 3 months are acceptable.
4. Previous exposure to secukinumab (AIN457) or any other biologic drug targeting IL-17 or the IL-17 receptor.
5. Subjects having received any investigational drug within 1 month or five times the half-life of enrollment, whichever is longer.
6. Receipt of more than 3000 mg i.v. pulse methylprednisolone (cumulative dose) within the 12 weeks prior to Baseline.
7. Treatment with a systemic calcineurin inhibitor (e.g., cyclosporine, tacrolimus) within 12 weeks prior to Baseline
8. CYC use (i.v. or oral) within the month prior to Baseline.
9. Subjects requiring dialysis within the previous 12 months before Screening.
10. History of renal transplant.
11. Any severe progressive or uncontrolled concurrent medical condition, including recent severe thromboembolic events, that, in the opinion of the principal investigator, renders the subject unsuitable for the trial.
12. Active ongoing inflammatory diseases that might confound the evaluation of the benefit of secukinumab therapy, including inflammatory bowel disease.
13. Presence of investigator-identified significant medical problems which at the investigator's discretion will prevent the subject from participating in the study, including but not limited to the following: myocarditis, pericarditis, poorly controlled seizure disorder, acute confusional state, depression, severe manifestations of neuropsychiatric SLE (NPSLE).
14. Chest X-ray, computerized tomography (CT) scan, or MRI with evidence of ongoing infectious or malignant process, obtained within 12 weeks prior to Randomization and evaluated by a qualified physician.
15. History of chronic, recurrent systemic infections, active tuberculosis infection, or active systemic infections during the last two weeks (exception: common cold) prior to Randomization.
16. Known infection with human immunodeficiency virus (HIV), hepatitis B or hepatitis C at Screening or Randomization.

17. History of lymphoproliferative disease or any known malignancy or history of malignancy of any organ system treated or untreated within the past 5 years, regardless of whether there is evidence of local recurrence or metastases (except for skin Bowen's disease or basal cell carcinoma or actinic keratoses that have been treated with no evidence of recurrence in the past 12 weeks, carcinoma *in situ* of the cervix or non-invasive malignant colon polyps that have been removed).
18. Any of the following abnormal laboratory values on Screening evaluations as reported by Central Laboratory:
    - Aspartate aminotransferase (AST), alanine aminotransferase (ALT), or amylase > 2.5xULN
    - Hemoglobin <8g/dL
    - Neutrophils $<1.0 \times 10^9$/L
    - Platelet count $<50 \times 10^9$/L
19. Inability or unwillingness to undergo repeated venipuncture (e.g., because of poor tolerability or lack of venous access).
20. History or evidence of ongoing alcohol or drug abuse, within the last six months before Randomization.
21. Pregnant or lactating women.
22. Women of childbearing potential, defined as all women physiologically capable of becoming pregnant, unless they are using highly effective methods of contraception during the entire study or longer if required by locally approved prescribing information (e.g., in European Union (EU) 20 weeks).

    Highly effective contraception methods include:
    - Total abstinence, when this is in line with the preferred and usual lifestyle of the subject. Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception.
    - Female sterilization (have had surgical bilateral oophorectomy [with or without hysterectomy], total hysterectomy or tubal ligation at least six weeks before taking study treatment). In case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow-up hormone level assessment.
    - Male sterilization (at least 6 months prior to Screening). The vasectomized male partner should be the sole partner for that subject.
    - Barrier methods of contraception: Condom or occlusive cap (diaphragm or cervical/vault caps). NOTE: for United Kingdom: with spermicidal foam/gel/film/cream/vaginal suppository.
    - Use of oral (estrogen and progesterone), injected or implanted hormonal methods of contraception or other forms of hormonal contraception that have comparable efficacy (failure rate <1%), for example hormone vaginal ring or transdermal hormone contraception or placement of an intrauterine device (IUD) or intrauterine system (IUS). In case of use of oral contraception, women should have been stable on the same treatment for a minimum of 3 months prior to Randomization.

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

Note: Women are considered post-menopausal and not of childbearing potential if they have had 12 months of natural (spontaneous) amenorrhea with an appropriate clinical profile (e.g., age appropriate, history of vasomotor symptoms) or have had surgical bilateral oophorectomy (with or without hysterectomy), total hysterectomy or tubal ligation at least six weeks prior to enrollment. 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 childbearing potential.

6 Treatment

6.1 Study treatment

6.1.1 Investigational and control drugs

Novartis Global Clinical Supply (GCS) will supply the following study treatments:

Table 6-1 Investigational and control drug

Investigational/ Control Drug (Name and Strength)	Pharmaceutical Dosage Form	Route of Administration	Supply Type	Sponsor (global or local)
AIN457 150mg / 1mL	Solution for Injection	Subcutaneous use	Double blinded prefilled syringes (PFS)	Novartis Pharma AG
AIN457 0 mg / 1mL (Placebo)	Solution for Injection	Subcutaneous use	Double blinded prefilled syringes (PFS)	Novartis Pharma AG

The PFSs are packed in a double blinded fashion and do not need to be prepared.

Each study site will be supplied by Novartis with investigational treatment in packaging of identical appearance. The investigational treatment packaging has a 2-part label. A unique Randomization number is printed on each part of this label, which corresponds to placebo or active treatment.

The study treatments will be labeled as follows: Double blind secukinumab and placebo PFS will be labeled AIN457 150 mg/1 mL/Placebo

6.1.2 Additional study treatments

No other study treatment beyond investigational drug and control drug are included in this trial.

6.1.3 SoC background therapy

All subjects will receive SoC background regimen for induction and maintenance therapy.

Table 6-2 Background therapy

Name of the medication	Dosage Form	Route of administration	Availability
MMF/MPA	Tablet	Oral	Open-label subject packs
CYC	Powder for solution for infusion	Intravenous	Open-label subject packs
Corticosteroids	Tablets and/or Solution for injection	Oral and/or Intravenous use	Open-label subject packs

Background SoC medications will NOT be provided by Novartis GCS and must be handled at the country level.

6.1.3.1 Induction therapy

The induction therapy will consists of either MPA or low-dose CYC, in combination with corticosteroids. The choice of the induction SoC therapy, MPA or low-dose CYC will be left at the investigator's discretion. To ensure a balanced representation in both treatment arms (secukinumab or placebo), subjects will be stratified at time of Randomization according to their SoC induction therapy. A maximum of 25% of subjects receiving CYC-based SoC induction therapy will be allowed to be randomized in the study (maximum of 116 subjects in the study).

MPA:

Target dose during the first six-month treatment period (MPA induction period) is 2 g/day of MMF or equivalent dosage of enteric-coated MPA of 1440 mg/day. If required, a dose up to 3 g/day of MMF or equivalent dosage of enteric-coated MPA of 2160 mg/day is allowed, based on Investigator’s judgement. A reduction of MPA dose is only allowed in case of toxicity, as per Investigator's decision.

Optional Run-in period

Subjects not already on MPA at study entry will be initiated, after verification of eligibility, on an MMF dose of 1 g/day (divided q 12 hrs) or an equivalent dosage of enteric-coated MPA of 720 mg/day. The dose must be increased to 2 g/day of MMF or equivalent dosage of enteric-coated MPA in the second week, and up to 3 g/day of MMF or equivalent dosage of enteric-coated MPA in the third week when required. If subjects experience adverse effects that prevent up-titration as described, an additional 1 week of titration is permitted. If MMF/MPA dose escalation is clinically inappropriate as judged by the investigator, or inconsistent with local treatment guidelines, subjects can take a dose of 1-2 g/day MMF or equivalent dosage of enteric-coated MPA in the absence of observed toxicity.

Low-dose CYC:

The low-dose CYC induction treatment consists of 6 administrations of 500 mg i.v. CYC every 2 weeks. All i.v. CYC administration will be performed according to the site and /or local

guidelines, including the administration of any medication for prophylaxis of potential toxicities.

The first i.v. CYC administration will be performed at Baseline visit, after all inclusion/exclusion criteria would have been verified.

Corticosteroids:

Pulse i.v. corticosteroid should be initiated at Baseline visit (500–1000 mg methylprednisolone daily) for a maximum of 3 doses. This will be followed by daily administration of oral glucocorticoids at initial dose of 0.3 to 0.5 mg/kg/day to be tapered within 16 weeks to the minimal dose necessary to control disease (see recommended guidance on Table 6-3).

Subjects who cannot take the pulse i.v. corticosteroid therapy should directly start on 0.3-0.5 mg/kg/day oral dose of glucocorticoid followed by the above-described tapering.

Subjects having already received pulse i.v. corticosteroids up to a cumulative dose of 3000 mg within 12 weeks prior to Baseline do not need to repeat the i.v. pulse. For these subjects already on corticosteroids at Baseline, a predefined steroid taper regimen (see Table 6-3) should be implemented.

In all cases, from Week 16 onward, the target dose of oral corticosteroids is 5 mg daily (prednisone equivalent).

Table 6-3 Guidance for corticosteroid (prednisone equivalent) taper

Initial Dose	40 mg	30 mg	20 mg
Week 2	30	25	15
Week 4	25	20	15
Week 6	20	15	10
Week 8	15	10	10
Week 12	10	10	10
Week 16 and thereafter maintain at 5 mg where possible * acceptable dose range	5 *7.5 – 2.5	5 *7.5 – 2.5	5 *7.5 – 2.5

6.1.3.2 Maintenance therapy

After the induction period (6 months for MPA-based induction; 12 weeks for CYC-based induction), all subjects must receive MPA-based maintenance therapy.

The target dose during the maintenance period is 1-2 g/day of MMF or of equivalent dosage of enteric-coated MPA. Further reduction of MMF to 0.5 g/day or of equivalent dosage of enteric-coated MPA is allowed as per Investigator's decision.

In addition, all subjects will receive a maintenance dose of oral corticosteroids as per Table 6-3 above, with a target dose of 5 mg/day prednisone equivalent (2.5-7.5 mg/day acceptable dose range) from Week 16.

A recommended diagram for administration of SoC background therapy from the Run-In period until Week 24 is provided in Appendix 16.4.

6.1.4 Treatment arms/group

At Baseline, all eligible subjects will be randomized to one of the two treatment arms in a 1:1 ratio via Interactive Response Technology (IRT):

- Arm 1: approximately 230 LN subjects will receive secukinumab 300 mg s.c. (2 x 1.0 mL PFS of 150 mg dose) at Randomization (i.e., Baseline).
- Arm 2: approximately 230 LN subjects will receive placebo s.c. (2 x 1.0 mL PFS of 0 mg dose) at Randomization (i.e., Baseline).

At Randomization, subjects will be stratified on the basis of the SoC induction therapy they will receive during the study, MPA or CYC-based, to ensure a balanced representation in each of the treatment arms (secukinumab or placebo).

6.1.5 Treatment duration

Subjects will receive investigational treatment at Baseline, Weeks 1, 2 and 3, followed by administration every 4 weeks starting at Week 4, until Week 100. Subjects will self-administer all secukinumab or placebo doses at the investigational site.

6.2 Other treatment(s)

6.2.1 Concomitant therapy

All medications, procedures, and significant non-drug therapies (including physical therapy and blood transfusions) administered after the subject was enrolled into the study must be recorded on the appropriate Case Report Form (CRF).

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 subject or allowing a new medication to be started. If the subject is already enrolled, contact Novartis to determine if the subject should continue participation in the study.

6.2.1.1 Permitted concomitant therapy requiring caution and/or action

Guidelines for the use of specific medications are provided below.

Subjects may continue on the concomitant medication listed below provided they are on a stable dosage from seven days prior to Screening to the end of study. However investigators may change the dose of concomitant medications during the study for safety reasons based on their clinical judgement. Each concomitant medication should be captured/recorded in the eCRF at every visit, including the dose changes when appropriate.

Anti-malarials

Subjects will remain on one stable background anti-malarial medication (e.g., hydroxychloroquine) in addition to the SoC medication. Subjects who have not taken previously anti-malarial medication should be initiated on an anti-malarial at least 10 days prior to

Randomization (unless contraindicated) and remain on a stable dose throughout the trial. Refer to Section 5.1 Inclusion Criteria.

Anti-hypertensive medication

Subjects already taking angiotensin-converting enzyme (ACE) inhibitors or angiotensin receptor blockers (ARBs) at Screening should remain on the same dose throughout the study unless precluded by toxicity or if dose adjustment is required for hypertensive control. Combination therapy with an ACE inhibitor and an ARB will not be allowed. For subjects not already receiving one of these agents, it is recommended that treatment with an ACE inhibitor or ARB should be initiated during Screening (unless contraindicated) and be given at a stable dose for at least 7 days prior to Randomization. These therapies should not be initiated after study Baseline.

Cholesterol-lowering drugs

Concomitant treatment with cholesterol-lowering drugs (e.g., statins) will continue if prescribed prior to the study and will be recorded in the eCRF. Statin treatment can be initiated during the course of the study if considered required by the Investigator.

Nonsteroidal Anti-Inflammatory Drugs (NSAIDs)

NSAIDs may have impact upon renal function and therefore should only be used during the trial if deemed necessary by the Investigator, e.g. in cases such as the following:

- treatment of pleuritis and pericarditis.
- treatment of arthritis pain that is unresponsive to other treatment modalities (e.g., analgesics)

Osteoporosis Prevention /Treatment

Subjects not already taking vitamin D (400 IU/day) and calcium supplements (1200 mg/day of calcium citrate or 1500 mg/day calcium carbonate) are allowed to start these medications, at the investigator's discretion (see ACR 2001).

Other Permitted Therapy

- Low dose aspirin for cardio-protection may be used at Investigator's discretion.
- Subjects who use oral contraceptives or hormone-replacement therapy should continue their use.
- Any prophylaxis for CYC-induced toxicities, as per site and or local guidelines, if patient is to receive low-dose CYC-based induction treatment.

All other concomitant medications deemed necessary will be reviewed by the Investigator and decisions made on a case-by-case basis.

Note: Concomitant medications will not be provided by Novartis and must be supplied by the study center.

6.2.2 Prohibited medication

The following treatments are prohibited after Screening and during the course of the trial due to their mechanisms of action that can confound the study results. If administered, the subject is to be withdrawn from the study treatment:

- Initiation of CYC treatment (oral or i.v.) outside of the protocol planned low-dose CYC induction therapy for subjects elected to receive CYC-based induction
- Initiation of rituximab or belimumab therapy
- Use of any other systemic biologic /non-biologic immunomodulatory treatment
- Administration of live vaccines

6.2.3 Rescue medication

Rescue medication is defined as any new medication used because the subject's disease is not adequately controlled by the investigational study treatment in addition to the SoC background therapy.

Although no subject will be restricted from receiving necessary rescue medications for lack of benefit or worsening of the disease (e.g., experiencing a renal flare), subjects will be discontinued from the study treatment if they are treated with prohibited medications (as described in Section 6.2.2). The choice of the rescue medication will be based on the treating Investigator's assessment and applicable regulatory guidelines.

Subjects who discontinue investigational treatment can continue to attend all subsequent scheduled visit assessments unless informed consent is withdrawn as described in Section 9.1.1 Discontinuation of study treatment. If study investigational treatment is discontinued, subjects may take study-prohibited medication under the investigator's guidance and as per locally approved prescribing information.

Use of rescue medication must be recorded on the appropriate eCRF page.

6.3 Subject numbering, treatment assignment, randomization

6.3.1 Subject numbering

Each subject is identified in the study by a Subject Number (Subject No.) that is assigned when the subject is first enrolled for Screening and is retained as the primary identifier for the subject throughout his/her entire participation in the trial. The Subject No. consists of the Center Number (Center No.) (as assigned by Novartis to the investigative site) with a sequential subject number suffixed to it, so that each subject is numbered uniquely across the entire database. Upon signing the informed consent form, the subject is assigned to the next sequential Subject No. available.

6.3.2 Treatment assignment, randomization

At Baseline visit, all eligible subjects will be randomized via Interactive Response Technology (IRT) to one of the treatment arms. The investigator or his/her delegate will contact the IRT after confirming that the subject fulfills all the inclusion/exclusion criteria. The IRT will assign a randomization number to the subject, which will be used to link the subject to a treatment arm

and will specify a unique medication number for the first package of study treatment to be dispensed to the subject.

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

Randomization will be stratified by the SoC induction therapy subjects will receive (MPA or CYC-based). A maximum of 25% of the randomized subjects will receive low-dose CYC induction therapy (up to 58 subjects per treatment arm). This will ensure that subjects can be treated with SoC therapy as per site and/or local guidelines, and a balanced repartition within the two treatment arms.

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

6.4 Treatment blinding

This is a double-blind, randomized treatment trial.

Subjects, investigator staff, persons performing the assessments will remain blinded to the identity of the treatment from the time of Randomization until final 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 with the following exceptions:

- Specific vendors whose role in the clinical trial requires their unblinding (e.g., IRT)
- Global Clinical Supply
- The designated Novartis study team members involved in the primary endpoint analysis

[redacted]

(2) The identity of the treatments will be concealed by the use of study treatments in the form of PFS, filled with secukinumab or placebo, that are all identical in packaging, labeling, appearance and schedule of administration.

[redacted]

As the primary endpoint analysis will be performed at Week 52, there will be a database lock when all subjects have completed Week 52 assessments. Summary results may be shared internally and externally; however, individual unblinded subject data will not be disclosed. For details regarding the planned Interim Analyses, refer to Section 4.4 Purpose and timing of interim analyses/design adaptation, and Section 12.7 Interim analyses.

A final database lock will occur when all subjects have completed the study. After the Week 104 analysis has been conducted, the Novartis clinical team will notify the investigative staff and the IRT system and site personnel and the subject will be unblinded to the originally assigned treatment arms.

The high sensitivity C-reactive protein (hsCRP) results from samples collected during the treatment period will be revealed only after database lock and analyses are completed.

6.5 Dose escalation and dose modification

Investigational study treatment dose adjustments are not permitted.

6.5.1 Dose modifications

Study treatment interruption is only permitted if, in the opinion of the investigator, a subject 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 appropriate eCRF.

6.5.2 Follow-up for toxicities

Subjects whose treatment is interrupted or permanently discontinued due to an adverse event or clinically significant abnormal laboratory value, must be followed up in accordance with what is clinically indicated per the investigator until resolution or stabilization of the event, whichever comes first. Appropriate clinical experts such as ophthalmologist, endocrinologist, dermatologist, psychiatrist, etc., should be consulted as deemed necessary.

6.6 Additional treatment guidance

6.6.1 Treatment compliance

6.6.1.1 Study treatment compliance

Administration of study treatment will occur at the study site through Week 100. The first study treatment administration will occur at the Baseline/Randomization visit only after eligibility criteria have been confirmed, all study Baseline assessments have been performed, and the scheduled blood samples have been drawn.

Compliance is expected to be 100% unless temporary interruption is needed for safety reasons as described in Section 6.5.1. Compliance will also be assessed by a Novartis monitor using information provided by authorized site personnel.

All doses of study treatment administration will be recorded on the appropriate eCRF page.

6.6.1.2 Standard of care treatment compliance

All intravenous administration of SoC, like CYC or pulses of glucocorticoids as specified in Section 6.1.3 SoC background therapy, must be administered at the study site under the

supervision of appropriate personnel. Doses administered and dates should be recorded on the appropriate eCRF pages.

Oral doses of MPA or corticosteroids, as specified in Section 6.1.3, will be taken by the patient at home.

The investigator must promote compliance by instructing the subject to take the SoC treatment exactly as prescribed and by stating that compliance is necessary for the subject's safety and the validity of the study. The subject must also be instructed to contact the investigator if he/she is unable for any reason to take the SoC treatment as prescribed. Compliance will be assessed by the investigator and/or study personnel at each visit by reviewing the information provided by the subject. This information should be captured in the source document at each visit.

6.6.2 Recommended treatment of adverse events

Treatment for AEs are at the discretion of the investigator or treating physician. Refer to the Investigator's Brochure for AEs related to secukinumab.

Medication used to treat AEs must be recorded on the appropriate eCRF.

6.6.3 Emergency breaking of assigned treatment code

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

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

- protocol number
- study drug name
- subject number

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

Study drug should be discontinued after emergency unblinding.

6.7 Preparation and dispensation

Each study site will be supplied with investigational study drug in packaging as described under investigational and control drugs Section 6.1.1.

Secukinumab solution for s.c. injection or placebo secukinumab solution (active or placebo, respectively) will be provided in prefilled syringes (PFS).

Each subject will require one box with PFS per dose throughout the study:

· One secukinumab 300 mg (2 x 1.0 mL PFS of 150 mg dose) OR

· One secukinumab placebo (2 x 1.0 mL PFS)

All study treatment kits assigned to the subject by IRT during the study will be captured in the IRT system.

The first study treatment administration will occur at the Baseline/Randomization visit after the inclusion/exclusion criteria have been confirmed and all study scheduled assessments have been performed, including completion of PRO and blood withdrawal.

All doses of study treatment (secukinumab and/or placebo) will be self-administered by the subject/trained caregiver at the study site after the study assessments for the visits have been completed.

At the Baseline visit, subjects will be instructed by the site staff on how to self-inject via the PFS (Instructions for Use (IFU) containing detailed information about self-administration of study treatment should be provided to each subject at the beginning of the study). After providing detailed explanations/instructions, subjects will then be asked to raise any questions.

Thereafter, they will proceed with self-injection. At Week 1, subjects will be asked to refer to the IFU and to proceed with self-injection of the study treatment (i.e., without a detailed explanation/instruction on handling the syringe).

A unique medication number is printed on the study medication label. Investigator staff will identify the study medication kits to dispense to the subject by contacting the IRT and obtaining the medication number(s). The study medication has a 2-part label (base plus tear-off label), immediately before dispensing the medication kit to the subject, site personnel will detach the outer part of the label from the packaging and affix it to the source document.

6.7.1 Handling of study treatment and additional treatment

6.7.1.1 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 designated site personnel have access. Upon receipt, all study treatment must be stored according to the instructions specified on the labels and in the Investigator's Brochure. Clinical supplies are to be dispensed only in accordance with the protocol. Technical complaints are to be reported to the respective Novartis Country Organization (CO) Quality Assurance.

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

The PFS (150 mg active/placebo) sealed in their outer box must be stored in a access controlled/locked refrigerator between 2°C and 8°C (36°F and 46°F) (Do Not Freeze) and

protected from light. They must be carefully controlled in accordance with regulations governing investigational medicinal products and local regulations.

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.

Subcutaneous administration with PFSs

The study treatment solution **must** be injected into **non-affected** areas of the skin.

The injections will be self-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 subject chooses the abdomen, a 2-inch area around the navel should be avoided. Investigational drug should not be injected into areas where the skin is tender, bruised, red, or hard, or where subject has scars or stretch marks.

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

Destruction of the unused drug should be done according to local requirements and after approval by the Novartis Clinical Team.

6.7.1.2 Handling of additional treatment

The following non-study treatment will be monitored specifically:

- SoC background therapy, as described in Section 6.1.3
- Concomitant therapy as described in Section 6.2.1, e.g., anti-malarials, ACE or ARBs

7 Informed consent procedures

Eligible subjects may only be included in the study after providing (witnessed, where required by law or regulation), Institutional Review Board (IRB)/IEC-approved informed consent.

If applicable, in cases where the subject's representative(s) gives consent (if allowed according to local requirements), the subject must be informed about the study to the extent possible given his/her understanding. If the subject is capable of doing so, he/she must indicate agreement by personally signing and dating the written informed consent document.

Informed consent must be obtained before conducting any study-specific procedures (e.g., all of the procedures described in the protocol). The process of obtaining informed consent must be documented in the subject source documents.

Novartis will provide to investigators in a separate document a proposed informed consent form that complies with the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use - Good Clinical Practice (ICH GCP) guidelines and regulatory requirements and is considered appropriate for this study. Any

changes to the proposed consent form suggested by the investigator must be agreed by Novartis before submission to the IRB/IEC.

Information about common side effects already known about the investigational drug can be found in the Investigator's Brochure (IB). This information will be included in the subject informed consent and should be discussed with the subject during the study as needed. Any new information regarding the safety profile of the investigational drug 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 then must be discussed with the subject.

Women of childbearing 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.

The study includes two optional components, namely a biomarker component and a deoxyribonucleic acid (DNA)/ribonucleic acid (RNA)/Pharmacogenetics component. Each of them requires a separate signature if the subject agrees to participate. It is required as part of this protocol that the Investigator presents these options to the subjects, as permitted by local governing regulations. The process for obtaining consent should be exactly the same as described above for the main informed consent.

Declining to participate in these optional assessments (DNA/RNA/Pharmacogenetics or biomarkers) will in no way affect the subject’s ability to participate in the main research study.

A copy of the approved version of all consent forms must be provided to Novartis/sponsor after IRB/IEC approval.

Subjects might be asked to complete an optional questionnaire to provide feedback on their clinical trial experience.

8 Visit schedule and assessments

Assessment schedule (Table 8-1) lists all of the assessments when they are performed. All data obtained from these assessments must be supported in the subject’s source documentation.

Subjects should be seen for all visits/assessments as outlined in the assessment schedule (Table 8-1) or as close to the designated day/time as possible. Missed or rescheduled visits should not lead to automatic discontinuation of study investigational treatment or study. Handling of subjects who discontinue study treatment or study prematurely is described in Section 9.1 Discontinuation.

Table 8-1 Assessment Schedule

Period	Screening	Extension Run-In	Treatment Year 1																				
Visit Name	Screening [2]	Optional MPA run-in [3]	Treatment Baseline	Day 2 (i.v. CS)	Day 3 (i.v. CS)	Week 1	Week 2	Week 3	Week 4	Week 6 (CYC)	Week 8	Week 10 (CYC)	Week 12	Week 16	Week 20	Week 24	Week 28	Week 32	Week 36	Week 40	Week 44	Week 48	Week 52
Visit Numbers [1]	1	20	100	110	120	130	140	150	160	170	180	190	200	210	220	230	240	250	260	270	280	290	300
Days	-42 to -1	-28 to -1	1	2	3	8	15	22	29	43	57	71	85	113	141	169	197	225	253	281	309	337	365
Informed consent	X																						
Pharmacogenetic Informed Consent	X																						
Biomarker Informed Consent	X																						
Demography	X																						
Inclusion / Exclusion criteria	X [4]	X [4]	X																				
Medical history/current medical conditions [5]	X		X																				
SLE and LN medical history and previous therapies	X																						
Tuberculosis test [6]	X																						
Smoking history	X																						
Chest X-ray [7]	X																						
Body Height	X																						
Serology [8]	X																						
Randomization			X																				
Physical Examination [9]	X		X			X	X	X	X		X		X	X	X	X	X	X	X	X	X	X	X
Body Weight & BMI [10]	X		X			X	X	X	X		X		X	X	X	X	X	X	X	X	X	X	X
Vital Signs	X		X			X	X	X	X		X		X	X	X	X	X	X	X	X	X	X	X
12-Lead ECG [11]			X																				
Renal biopsy [12]	X																						
Record of Menses	X		X			X	X	X	X		X		X	X	X	X	X	X	X	X	X	X	X
Hematology	X		X			X	X	X	X		X		X	X	X	X	X	X	X	X	X	X	X
Clinical Chemistry	X		X			X	X	X	X		X		X	X	X	X	X	X	X	X	X	X	X
Coagulation Panel	X		X			X	X	X	X		X		X	X	X	X	X	X	X	X	X	X	X
Fasting lipid panel [13]			X								X		X			X							X
[redacted]																							
24-hr urine collection [15]			X [16]										X [16]			X [16]			X [16]				X [16]
Urinalysis [17]	X		X			X	X	X	X		X		X	X	X	X	X	X	X	X	X	X	X
Pregnancy Test [18]	X		X			X	X	X	X		X		X	X	X	X	X	X	X	X	X	X	X
CRP and ESR	X		X								X		X			X			X				X
[redacted]																							

Period	Screening	Extension Run-In	Treatment Year 1																				
Visit Name	Screening [2]	Optional MPA run-in [3]	Treatment Baseline	Day 2 (i.v. CS)	Day 3 (i.v. CS)	Week 1	Week 2	Week 3	Week 4	Week 6 (CYC)	Week 8	Week 10 (CYC)	Week 12	Week 16	Week 20	Week 24	Week 28	Week 32	Week 36	Week 40	Week 44	Week 48	Week 52
Visit Numbers [1]	1	20	100	110	120	130	140	150	160	170	180	190	200	210	220	230	240	250	260	270	280	290	300
Days	-42 to -1	-28 to -1	1	2	3	8	15	22	29	43	57	71	85	113	141	169	197	225	253	281	309	337	365
FACIT-Fatigue			X										X			X			X				X
SF36 [19]			X										X			X			X				X
LupusQoL			X										X			X			X				X
Prior/Concomitant medications	X	X	X			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Adverse Events [20]	X	X	X			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
[redacted]																							
Blood collection for DNA/RNA (optional)			X																				
Study drug administration			X			X	X	X	X		X		X	X	X	X	X	X	X	X	X	X	X
Standard of Care administration [23]		X	X	X [24]	X [24]	X	X	X	X	X [25]	X	X [25]	X	X	X	X	X	X	X	X	X	X	X
Trial Feedback Questionnaire			X																				X

[X] Assessment to be recorded in the clinical database or received electronically from a vendor
[1] Visit structure given for internal programming purpose only
[2] Screening period will be up to 42 days depending on the MPA Run-in need. The duration of the Screening period must be kept at a minimum.
[3] For subjects not yet on MPA at Screening, a Run-in period is necessary
[4] These assessments are source documentation only and will not be entered into the eCRF. However, data regarding to which inclusion/exclusion criteria are not met are captured on the Inclusion/Exclusion eCRF.
[5] Included in Medical History and recorded in the eCRF on the corresponding page.
[6] PPD/QuantiFERON®
[7] not required if chest X-rays have been taken in the past 12 weeks that show no clinically significant abnormality
[8] Hepatitis B and/or C and/or HIV serology testing performed during Screening period only if required as per local medical practice or regulators prior to initiation of therapy. These assessments will be documented in source records only and will not be entered into eCRF
[9] These assessments are source documentation only and will not be entered into the eCRF. However, data regarding to which inclusion/exclusion criteria are not met are captured on the Inclusion/Exclusion eCRF. After the Baseline visit, the investigator should do an abbreviated physical exam focusing on relevant clinical areas
[10] Body Mass Index (BMI) to be automatically calculated by Novartis
[11] performed locally
[12] To enter the study, subjects must have a biopsy demonstrating active glomerulonephritis WHO or ISN/RPS class III or IV LN [excluding III (C), IV-S (C) and IV-G (C)]; subjects are permitted to have co-existing class V. Renal biopsy must have been performed within 6 months prior to Screening. Otherwise, a new renal biopsy must be performed during Screening, once all other eligibility criteria have been confirmed. Any subsequent biopsies (e.g., upon disease flare) may be performed where considered appropriate by the investigator
[13] Samples for Lipid panel should be obtained after an overnight fast (10hr or more)
[redacted]
[15] Including central determination of UPCR [redacted] calculation
[16] Site to ensure that a urine container is dispensed at previous site visit
[17] First morning void urine sample will be collected for 1) local determination of urinary sediment and standard safety evaluation and 2) central determination of UPCR. Jugs for the Urine collection will be dispensed at previous visit
[18] Pregnancy tests will be conducted for women of child bearing potential; serum pregnancy test at Screening and Urine pregnancy test at all other time points
[19] SF-36 v2 performed (both PCS and MCS), SF-36-PCS responder will be evaluated
[20] AEs/SAEs occurring after the patient has provided informed consent must be reported.
[21] at pre-dose
[redacted]
[23] Background SoC therapy will be administered during the whole treatment period on a daily basis for MPA and Corticosteroids, cyclophosphamide induction every 2 weeks for 3 months
[24] for site administration of i.v. corticosteroids only
[25] for site administration of i.v. cyclophosphamide only
[26] planned End of Treatment (EOT) period visit will be performed at Week 104. Subjects who discontinue study treatment prematurely for any reason other than withdrawal of informed consent before Week 104 will not be considered as discontinued from the study. Please refer to Section 9.1 Discontinuation for detailed instructions.

Period	Treatment Year 2													
Visit Name	Week 56	Week 60	Week 64	Week 68	Week 72	Week 76	Week 80	Week 84	Week 88	Week 92	Week 96	Week 100	EOT[26]	EOS
Visit Numbers[1]	310	320	330	340	350	360	370	380	390	400	410	420	430	1999
Days	393	421	449	477	505	533	561	589	617	645	673	701	729	785
Physical Examination[9]	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Body Weight & BMI[10]	X	X	X	X	X	X	X	X	X	X	X	X	X[27]	X
Vital Signs	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Record of Menses	X	X	X	X	X	X	X	X	X	X	X	X	X	
Hematology	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Clinical Chemistry	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Coagulation Panel	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Fasting lipid panel[13]						X							X	
[redacted]														
24-hr urine collection[15]						X[16]							X[16]	
Urinalysis[17]	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Pregnancy Test[18]	X	X	X	X	X	X	X	X	X	X	X	X	X	X
CRP and ESR						X							X	
[redacted]														
FACIT-Fatigue						X							X	
SF36[19]						X							X	
LupusQoL						X							X	
Prior/Concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Adverse Events[20]	X	X	X	X	X	X	X	X	X	X	X	X	X	X
[redacted]														
Study drug administration	X	X	X	X	X	X	X	X	X	X	X	X		
Standard of Care administration[25]	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Trial Feedback Questionnaire														X

[X] Assessment to be recorded in the clinical database or received electronically from a vendor

[1] Visit structure given for internal programming purpose only

[9] These assessments are source documentation only and will not be entered into the eCRF. After the Baseline visit, the investigator should do an abbreviated physical exam focusing on relevant clinical areas

[10] Body Mass Index (BMI) to be automatically calculated by Novartis

[11] performed locally

[13] Samples for Lipid panel should be obtained after an overnight fast (10hr or more)
[redacted]

[15] including central determination of UPCR [redacted] calculation

[16] site to ensure that a urine container is dispensed at previous site visit

[17] First morning void urine sample will be collected for 1) local determination of urinary sediment and standard safety evaluation and 2) central determination of UPCR. Jugs for the Urine collection will be dispensed at previous visit

[18] Pregnancy tests will be conducted for women of childbearing potential; serum pregnancy test at Screening and Urine pregnancy test at all other time points

[19] SF-36 v2 performed (both PCS and MCS), SF-36-PCS responder will be evaluated

[20] AEs/SAEs occurring after the patient has provided informed consent must be reported.

[21] at pre-dose
[redacted]

Background SoC therapy will be administered during the whole treatment period on a daily basis for MPA and Corticosteroids, cyclophosphamide induction every 2 weeks for 3 months

[26] Planned End of Treatment (EOT) period visit will be performed at Week 104. Subjects who discontinue study treatment prematurely for any reason other than withdrawal of informed consent before Week 104 will not be considered as discontinued from the study. Please refer to Section 9.1 Discontinuation for detailed instructions

8.1 Screening

A Screening period of up to 6 weeks will be used to assess subject´s eligibility (-42 to -29). This flexible duration will provide enough time to evaluate eligibility of the subject, including renal biopsy evaluation.

Once eligibility is confirmed, subjects elected to receive MPA-based induction SoC therapy and not already on this background therapy will be initiated on MPA (MMF or enteric-coated MPA sodium) during the run-in period (-28 to -1). These subjects will be initiated on an MMF dose of 1 g/day (divided q 12 hrs.)/equivalent dosage of enteric-coated MPA. Doses are to be increased to 2 g/day of MMF/equivalent dosage of enteric-coated MPA in the second week and up to 3 g/day of MMF/equivalent dosage of enteric-coated MPA in the third week, if tolerability allows. If subjects experience adverse effects, which prevent up-titration as described, an additional 1 week of titration is permitted. If MMF dose escalation is clinically inappropriate as judged by the investigator or inconsistent with local treatment guidelines, subjects can take a dose of 1.5-2 g/day MMF/equivalent dosage of enteric-coated MPA in the absence of observed toxicity.

All subjects evaluated at Screening for eligibility should not be screen failed on the basis of a medication requiring washout, unless the subject will be unable to complete the washout in the appropriate time frame before Randomization.

Subjects who prematurely withdraw from the study treatment will not be replaced.

In the case where a safety laboratory assessment at Screening and/or Baseline is outside of the range specified in the exclusion criteria, the assessment may be repeated once prior to Randomization. If the repeat value remains outside of the specified ranges, the subject must be excluded from the study.

8.1.1 Information to be collected on Screening failures

Subjects who sign an informed consent form 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 Screening visit date, demographic information, informed consent, Inclusion/Exclusion, subject re-screening (for re-screened subjects) pages must also be completed for screen failure subjects. No other data will be entered into the clinical database for subjects who are screen failures, unless the subject experienced a serious adverse event during the Screening phase (see SAE Section 10.1.3 for reporting details).

AEs that are not SAEs will be followed up by the investigator and collected only in source data.

If the subject fails to be randomized, the IRT must be notified within 2 days of the screen fail that the subject was not randomized.

Subjects who are randomized and fail to start treatment, e.g., subjects randomized in error, will be considered as early terminated. The reason for early termination should be recorded on the appropriate eCRF. If consent was withdrawn during the Screening period before the subject was randomized, complete the appropriate eCRF.

8.1.2 Re-screening

It is permissible to re-screen a subject 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.

If a subject re-screens for the study, the subject must sign a new ICF and be issued a new subject number prior to any Screening assessments being conducted under the new subject number. For all re-screened subjects, the investigator/qualified site staff will record if the subject was re-screened on the re-screening eCRF and the original Screening number the subject was issued prior to the current Screening number. The date of the new informed consent signature must be entered in the Informed Consent eCRF corresponding to the new subject number.

For re-screening, all Screening assessments must be performed per protocol, except the tuberculosis (TB) work up (if applicable). If the date of the TB work up is less than 12 weeks from the projected Baseline date, then it is not required that the TB work up be repeated; however, the re-screened subject must repeat PPD skin test or the QuantiFERON TB-Gold performed by the central laboratory.

Subjects who are mis-randomized cannot be re-screened.

8.2 Subject demographics/other Baseline characteristics

Country-specific regulations should be considered for the collection of demographic and Baseline characteristics in alignment with eCRF.

8.2.1 Demography

Demographics data to be collected on all subjects and recorded in the eCRF include

- age,
- sex,
- race, and ethnicity
- source of referral

8.2.2 SLE/LN medical history/diagnosis

The following information should be collected and entered in the relevant eCRF:

- the date of first diagnosis for SLE and/or LN
- SLE/LN family history

8.2.3 Prior SLE/LN medications and therapy

Any treatment for SLE/ LN since initial diagnosis (as determined through medical history records or through subject interview) prior to study entry will be collected and recorded in the eCRF, along with the duration of the prior therapy, the response to the therapy and the reason for discontinuation.

8.2.4 Renal biopsy

An important criteria to be fulfilled for a subject to be randomized within the study is a renal biopsy showing active glomerulonephritis WHO or ISN/RPS Class III or IV LN [excluding III

(C), IV-S (C) and IV-G (C)], with or without co-existing class V features. The biopsy must have been performed within 6 months prior to Screening, or during Screening period if not available.

The local pathologist report confirming Class III or IV LN with active lesions must be kept as a source document at the site. In addition, it should be used to complete the Renal Biopsy Report eCRF page.

While the classification of the subject's LN for randomization will be based on the local pathologist report, a central reading of electronic images of the local biopsy slides will be performed for confirmation of the classification. For this purpose, the slides used for determination of the classification by the local pathologist, representing at least the three most important types of staining (H&E, PAS, silver staining) will be collected to allow for their digitalization. Details regarding collection of local biopsy slides will be outlined in the Central Laboratory Manual. Details regarding central reading of electronic images process, responsibilities and membership is described in a separate Central Biopsy Reading Charter. All slides will be returned to the site after their digitalization.

8.2.5 Standard of care induction therapy

Before Randomization, during the Screening period, the investigator must define the SoC induction therapy that the subject will receive, MPA or CYC-based. (see Section 6.1.3 Standard of Care background therapy).

This will ensure that subjects can be treated with SoC therapy as per site and/or local guidelines, and a balanced repartition within the two treatment arms (secukinumab and placebo).

The target will be to have a maximum of 25% of randomized subjects receiving CYC-based induction therapy.

The choice of SoC induction therapy must be reported in the eCRF and confirmed at time of Randomization within the IRT system.

8.2.6 Smoking history

The current and /or previous use of tobacco will be recorded, as well as the estimate number of pack-years based on the approximate consumption per year.

8.2.7 Cardiovascular medical history

Protocol-solicited cardiovascular medical history will be collected on the appropriate eCRF page.

8.2.8 Relevant medical history/ current medical conditions

Relevant medical history and current medical conditions not related to the study indication, and which were present prior to signing of the informed consent, should be recorded in the Medical History eCRF. This includes surgical sterilization for females, if applicable.

Whenever possible, diagnoses and not symptoms should be recorded.

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

Significant findings that are observed after the subject has signed the ICF and that meet the definition of an AE must be recorded in the AE eCRF.

8.2.9 Prior and concomitant medications

Concomitant medications and prior medications taken over 6 months preceding study enrollment for reasons other than SLE/ LN will be captured at the Screening visit, and updated as necessary in the relevant eCRF.

Any new medication taken during the course of the study should be collected on the relevant eCRF.

8.2.10 Determination of the tuberculosis status

Either a QuantiFERON TB-Gold test **or** a PPD skin test must be performed at the Screening visit for the determination of the subject's tuberculosis status. Subjects with a positive test may participate in the study if further work up (according to local practice/guidelines) establishes conclusively that the subject has no evidence of active tuberculosis, or, if presence of latent tuberculosis is established, then treatment according to local country guidelines must have been initiated.

8.2.10.1 QuantiFERON TB-Gold test

A QuantiFERON TB-Gold test is to be performed at the Screening visit and the results to be known prior to Randomization to determine the subject’s eligibility for the trial. The test will be used to screen the subject population for latent tuberculosis infection.

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

8.2.10.2 PPD skin test

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

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

8.2.11 Hepatitis and human immunodeficiency virus (HIV) screen

Screening for hepatitis and HIV is optional, based on the judgment of the investigator or if required by local regulations. If hepatitis testing is performed, testing will include hepatitis B surface antigen (HBsAg) and anti-HCV antibodies. If HIV testing is performed, positive HIV

screening will be confirmed by a second technique available at the respective local laboratory, e.g., Western blot.

8.2.12 Electrocardiogram (ECG)

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

The ECG tracing must be labeled with study number, subject initials, subject number, date and time, and filed in the study site source documents. Any identifier details must be redacted, e.g., obscuring subject initials, date of birth.

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

For any ECGs with subject safety concerns, two additional ECGs must be performed to confirm the safety finding. Clinically significant ECG findings at Baseline must be discussed with the sponsor before administration of investigational treatment. Clinically significant abnormalities must be recorded on the relevant section of the medical history/Current medical conditions/AE eCRF as appropriate.

8.3 Efficacy

Clinical efficacy measurements related to primary and secondary objectives are described in the subsections below.

8.3.1 Complete Renal Response (CRR)

The CRR will be used to determine efficacy. CRR is a composite endpoint defined as:

- eGFR is within the normal range or no less than 85% of Baseline

and

- 24-hour UPCR $\leq$ 0.5 mg/mg

In addition, the estimand definition for primary endpoint is specified in Section 12.4.1.

8.3.1.1 Estimated glomerular filtration rate (eGFR)

The glomerular filtration rate will be estimated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation (Martínez-Martínez et al 2013) (see appendix Section 16.3) based on subject gender, age (years) and serum creatinine (mg/dL).

Central laboratory serum creatinine values will be used for all renal function data analysis.

8.3.1.2 Urine Protein-to-Creatinine Ratio (UPCR)

Urine Protein-to-Creatinine Ratio (UPCR), expressed in mg/mg, will be determined by a central laboratory by dividing the protein concentration by the creatinine concentration as measured in the urine collected.

Depending on the objective to be assessed, the UPCR will be determined using one of the following two types of urine collection, 24-hour urine collection or first morning void urinary sample, as indicated in Section 2, Table 2-1 Objectives and related endpoints.

Both the 24-hour urine collection and the first morning void will be collected in the subjects' home.

8.3.2 Partial Renal Response (PRR)

PRR is a composite endpoint defined as:

- eGFR is within the normal range or no less than 85% of Baseline

and

- ≥50 % reduction in 24-hour UPCR to sub-nephrotic level compared to Baseline

8.3.3 Average daily dose of corticosteroids

Average daily dose of oral corticosteroids doses will be used to demonstrate superiority of secukinumab compared to placebo in the averaged daily dose of oral corticosteroids administered between Week 16 and Week 52.

8.3.4 Functional Assessment of Chronic Illness Therapy – Fatigue (FACIT-Fatigue©)

The FACIT-Fatigue© is a 13-item questionnaire (Cella et al 1993), (Yellen et al 1997) that assesses self-reported fatigue and its impact upon daily activities and function over the past week. The purpose of the FACIT-Fatigue© in this study is to assess the impact of fatigue on subjects with LN.

The level of fatigue is measured on a 5-point Likert scale (0 = not at all, 1 = a little bit, 2 = somewhat, 3 = quite a bit, 4 = very much).

The purpose of FACIT-Fatigue© in this study is to demonstrate superiority of secukinumab compared to placebo on the mean change of score.

8.3.5 Short Form Health Survey (SF-36)

The Medical Outcome Short Form Health Survey (SF-36) Version 2 (Acute Form) is a survey evaluating individual subjects' health status, which also monitors and compares subjects' disease burden. This has been widely used to assess physical, psychological and social impact of chronic disease like LN (Holloway et al 2014).

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 et al 1993). Two overall summary scores, the Physical Component Summary (PCS) and the Mental Component Summary (MCS) also can be computed (Ware et al 1994). In this trial, SF-36-PCS responder (improvement of ≥ 2.5 points, (Lubeck 2004)) will be evaluated. 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 subjects. The purpose of the SF-36 in this study is to assess the HRQoL of subjects with active LN. Given

the acute nature of this disease, version 2, with a one-week recall period, will be used in this study.

8.3.6 Lupus Quality of Life (LupusQoL)

The LupusQoL is a disease-specific, 34-item, self-report questionnaire designed to measure the health-related quality of life (HRQoL) of subjects with SLE within 8 domains (i.e., physical health (8 items), emotional health (6 items), body image (5 items), pain (3 items), planning (3 items), fatigue (4 items), intimate relationships (2 items), and burden to others (3 items). Responses are based on a 5-point Likert scale where 0 (all of the time) to 4 (never) (Yazdany 2011), (RWS Life).

Each domain of the LupusQoL is scored separately.

8.3.7 Urinary sediment

Urinary sediment will be determined at site at each visit using the first morning void sample.

Presence of red blood cells (RBCs), white blood cells (WBCs), epithelial cells, and cellular casts will be determined by microscopic evaluation and recorded on the appropriate eCRF.

Active urinary sediment is defined as the presence of cellular casts which are granular casts or red blood cells, or hematuria (>5 RBCs per high power field).

8.3.8 Appropriateness of efficacy assessments

The proposed primary endpoint is in line with the CHMP guideline, which recommends that studies conducted in patients with LN should be aimed for the control of renal activity with primary outcome focusing on renal specific endpoints such as induction of CRR.

The CRR is demonstrated as a clinically significant improvement of renal function as measured by improvement of eGFR (normalization/return to Baseline eGFR), and a reduction in renal injury as measured by reduction in proteinuria (<0.5 mg/mg in 24-hour) [redacted]. The urinary sediment was removed from the components of the primary endpoint CRR after consultation of Food and Drug Administration (FDA) and European Medicines Agency (EMA), due to the difficulty to standardize methods of evaluation for urinary sediment across a multicenter study, and because the selection of the appropriate population (active class III or IV LN) is ensured by renal biopsies performed within 6 months of enrollment.

The proposed secondary endpoints, such as the composite PRR, or laboratory indices of the activity of renal diseases such as proteinuria, are in line with the CHMP guidelines.

In addition, both CRR and PRR have been previously used in clinical trials in LN, as measure of the renal activity.

As chronic fatigue and subject's disease burden may interfere with daily activities and quality of life, additional patient reported outcome measures (PROs) of physical functioning and health-related quality of life (HRQoL) tools will be used for assessing subject's perception of the impact of the disease and treatment on daily life. While FACIT - Fatigue and SF36 PCS are not disease specific, it has been widely used to assess physical, psychological and social impact of chronic diseases including SLE. The lupus specific quality of life instrument LupusQoL will be evaluated to further evaluate the impact of the disease during the study.

8.4 Safety

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

- Physical examination
- Vital signs
- Height and weight
- Laboratory evaluations (Hematology, Clinical Chemistry, Lipid Panel, coagulation panel, Urinalysis)
- Evaluation of AEs/SAEs
- Local tolerability (Injection site reactions)
- Pregnancy and assessment of fertility
- Tolerability of secukinumab
- [redacted]

8.4.1 Physical examination

A physical examination, including general appearance, skin, neck, eyes, ears, nose, throat, lungs, heart, abdomen, back, lymph nodes, extremities, and vascular and neurological systems will be performed as indicated in Table 8-1.

If necessary, based on medical history and/or symptoms, additional exams will be performed at the discretion of the investigator.

Whenever possible, assessments for an individual subject should be performed by the same member of the study site staff throughout the study.

Information for all physical examinations must be included in the source documentation at the study site. Significant findings that are present prior to the start of study treatment must be included in the Medical History eCRF. Significant findings made after signing informed consent, which meet the definition of an Adverse Event, must be recorded on the Adverse Event eCRF.

8.4.2 Vital signs

Vital signs (including blood pressure and pulse measurements) will be assessed at every scheduled visit as indicated in Table 8-1. Whenever possible, assessments should be performed by the same study site staff member throughout the study.

After the subject has been sitting for five minutes, with back supported and both feet placed on the floor, heart rate, systolic and diastolic blood pressure will be measured twice (measurements separated by 1 to 2 minutes) using a validated device, with an appropriately sized cuff. In case the cuff sizes available are not large enough for the subject's arm circumference, a sphygmomanometer with an appropriately sized cuff may be used. Measurements will be recorded in the source documentation and the average of the two measurements will be entered on the Vital Signs eCRF.

No specific action is pre-defined within this protocol to respond to specific abnormal vital signs, as it will be decided by the investigator whether and which specific action needs to be taken to respond to any abnormal values, taking into account the overall status of the subject.

8.4.3 Height and weight

Height and body weight will be measured as indicated in Table 8-1.

Height in centimeters (cm) and body weight (to the nearest 0.1 kilogram (kg)) will be measured in indoor clothing, but without shoes. If possible, body weight assessments should be performed by the same study site staff member and using the same scale throughout the study.

8.4.4 Laboratory evaluations

A central laboratory will be used for analysis of all specimens listed below, unless noted otherwise. Details on the collections, shipment of samples and reporting of results by the central laboratory are provided to investigators in the laboratory manual. Refer to the Laboratory Manual for identification of laboratory reference range values and the schema for notification of site staff and Novartis for out of range values.

For the identification of clinically notable values, see Section 16.10. All subjects with laboratory tests containing clinically significant abnormal values are to be followed until the values return to normal ranges or until a valid reason, other than treatment related AE, is defined.

Blood withdrawals and safety assessments should be done prior to study treatment administration and should be taken as shown in Table 8-1.

8.4.4.1 Hematology

Hemoglobin, hematocrit, red blood cell count, white blood cell count with differential (neutrophils including bands, lymphocytes, monocytes, eosinophils, basophils) and platelet count will be measured.

8.4.4.1.1 Erythrocyte sedimentation rate (ESR)

The ESR test will be performed using the ESR Supplies kit provided by the central laboratory. A laboratory manual will be provided with detailed information on sample collection and handling. ESR results will be reported in the appropriate eCRF page.

8.4.4.2 Clinical chemistry

Serum chemistry will include urea, creatinine, hemoglobin A1c (HbA1c), total bilirubin (TBL), AST (serum glutamic oxaloacetic transaminase (SGOT)), ALT (serum glutamic pyruvic transaminase (SGPT)), gamma-glutamyl transferase (GGT), alkaline phosphatase (ALP), sodium, potassium, bicarbonate, calcium, phosphorous, total protein, albumin, lipase, amylase, and uric acid.

High sensitivity C-reactive protein (hsCRP) will also be assessed. In order to preserve the blind, results of hsCRP will not be communicated to the study site staff, including the investigator, or to Novartis during the study.

8.4.4.2.1 Lipid panel

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

8.4.4.2.2 High sensitivity C-reactive protein

High sensitivity C-reactive protein (hsCRP) will be assessed using a fasting blood sample as indicated in Table 8-1. In order to preserve the blind, results of hsCRP will not be communicated to the study site staff, including the investigator, or to Novartis during the study.

8.4.4.3 Coagulation panel

Prothrombin time (PT), activated partial thromboplastin time (aPTT) and International Normalized Ratio (INR) will be evaluated locally for general safety and additional characterization of the disease.

8.4.4.4 Urinary analysis

There will be two types of urinary collection, both performed at subjects' home:

- 24-hour urine collection, corresponding to the 24-hour collection of the urine the day preceding the Baseline, Week 12, Week 24, Week 36, Week 52, Week 76 and EOT visits, as outlined in Table 8-1.
- first morning void urine collection on the day of visits as specified in Table 8-1.

8.4.4.4.1 Local urinalysis

The subject's first morning void urine sample will be used for **local** urinalysis assessments performed for standard safety evaluation.

Those standard assessments will include specific gravity, protein, glucose, pH, blood, urine blood dipstick (non-hemolyzed), urine blood dipstick (hemolyzed), bilirubin, ketones and WBC.

Please refer to the central laboratory manual for additional details.

In addition, subject's first morning void urine sample will also be used for **local** determination of urinary sediment, as outlined in Efficacy Section 8.3.7 and **central** determination of UPCR, as outlined in Efficacy Section 8.3.1.2.

Jugs for the first morning void urine collection will be dispensed at subject's previous visit.

8.4.4.4.2 24-hour urine collection

A 24-hour urine collection is done at selected time point by collecting urine in a special container over a full 24-hour period.

Instructions regarding the timing, the collection and the storage of the 24-hour urine collection will be detailed within the laboratory manual.

This 24-hour urine collection will be used for central determination of the UPCR, as mentioned in Efficacy Section 8.3.1.2 .

8.4.4.5 Autoantibodies

8.4.4.5.1 ANA and anti-dsDNA

[redacted]

In addition, ANA or anti-dsDNA must be tested positive for a patient being eligible in this study in case of confirmed diagnosis of lupus nephritis as the sole criterion as per inclusion criteria 2 (refer to Section 5.1 Inclusion criteria).

[redacted]

8.4.5 Pregnancy and assessments of fertility

All pre-menopausal women who are not surgically sterile will have a serum β-hCG test (serum pregnancy test) performed at the Screening visit, and local urine pregnancy tests as indicated in Table 8-1. A positive urine pregnancy test requires immediate interruption of study drug until serum β-hCG is performed and found to be negative. Additional pregnancy testing might be performed if requested by local requirements.

Secukinumab, MPA, CYC and corticosteroids should not be given to pregnant women; therefore, effective methods of birth control must be used for women of childbearing potential (see exclusion criteria definitions, Section 5.2).

In addition, menses will be recorded on the appropriate eCRF page for all pre-menopausal women, as indicated in Table 8-1.

8.4.6 Other safety evaluations

Chest X-ray

Standard chest X-ray (PA view) will be performed except for those who have had a valid X-ray done within 3 months of first dosing. If subjects do not have a chest X-ray obtained within 3 months preceding the Screening visit, a chest X-ray should be performed. In order to minimize unnecessary exposure to radiation, the chest X-ray should only be performed after confirming that the subject meets all inclusion/exclusion criteria. In some sites selected by Novartis, the X-ray assessment may be replaced by MRI assessment.

8.4.7 Appropriateness of safety measurements

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

8.5 Additional assessments

The other assessments planned for the study are:

- Clinical Outcome Assessments (COAs): This includes Patient reported outcomes (PRO) [redacted]
- Trial Feedback Questionnaires
- [redacted]
- Optional Biomarkers

8.5.1 Patient reported outcomes (PRO)

Subjects will be asked to complete the following PRO measures in e-devices provided by the site:

1. FACIT-Fatigue©
2. SF-36 v2
3. LupusQoL

[redacted]

The subject must be given the PRO measure(s) to be completed at the scheduled visit before any clinical assessments are conducted. Subject's refusal to complete all or any part of a PRO measure should be documented in the study data capture system and should not be captured as a protocol deviation.

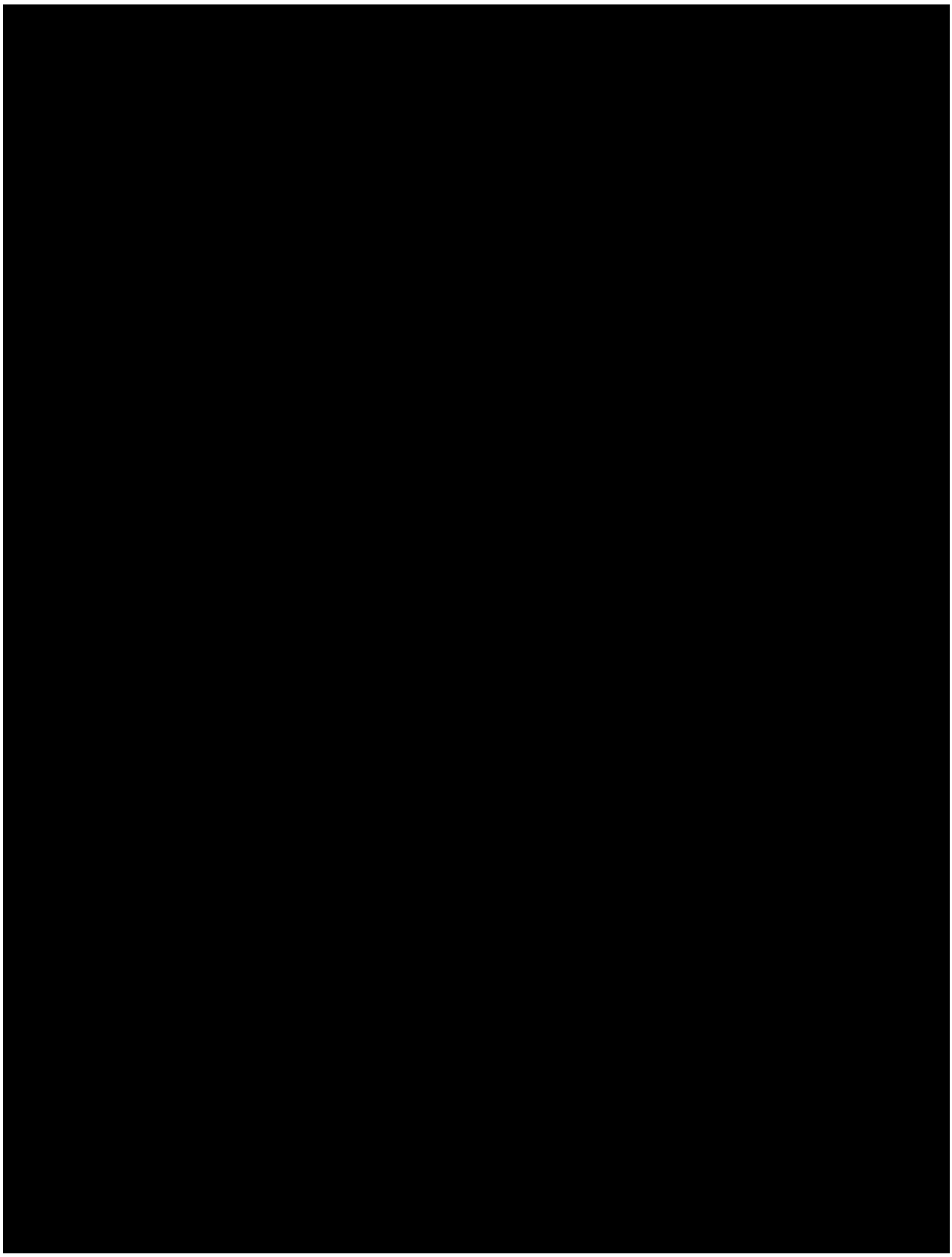
The subject should be given sufficient space and time to complete the PRO measures.

The site personnel should check PRO measures for completeness and ask the subject to complete any inadvertently missing responses.

The patient should be made aware that completed measures are not reviewed by the investigator/study personnel.

FACIT-Fatigue©, SF-36 v2 Physical Component Summary and Lupus QoL are already described in Efficacy Section 8.3.4, Section 8.3.5, Section 8.3.6, respectively.

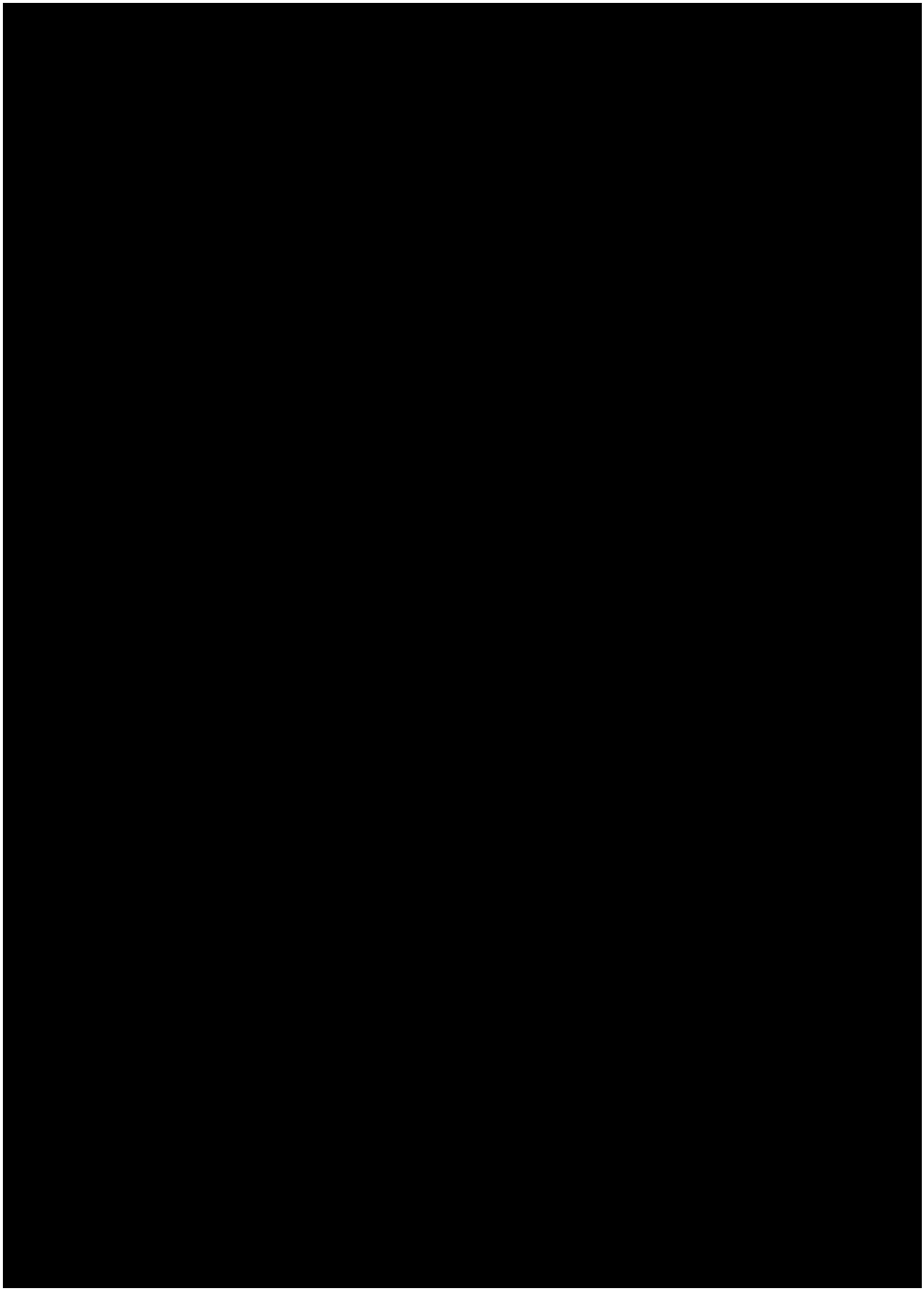
[redacted]

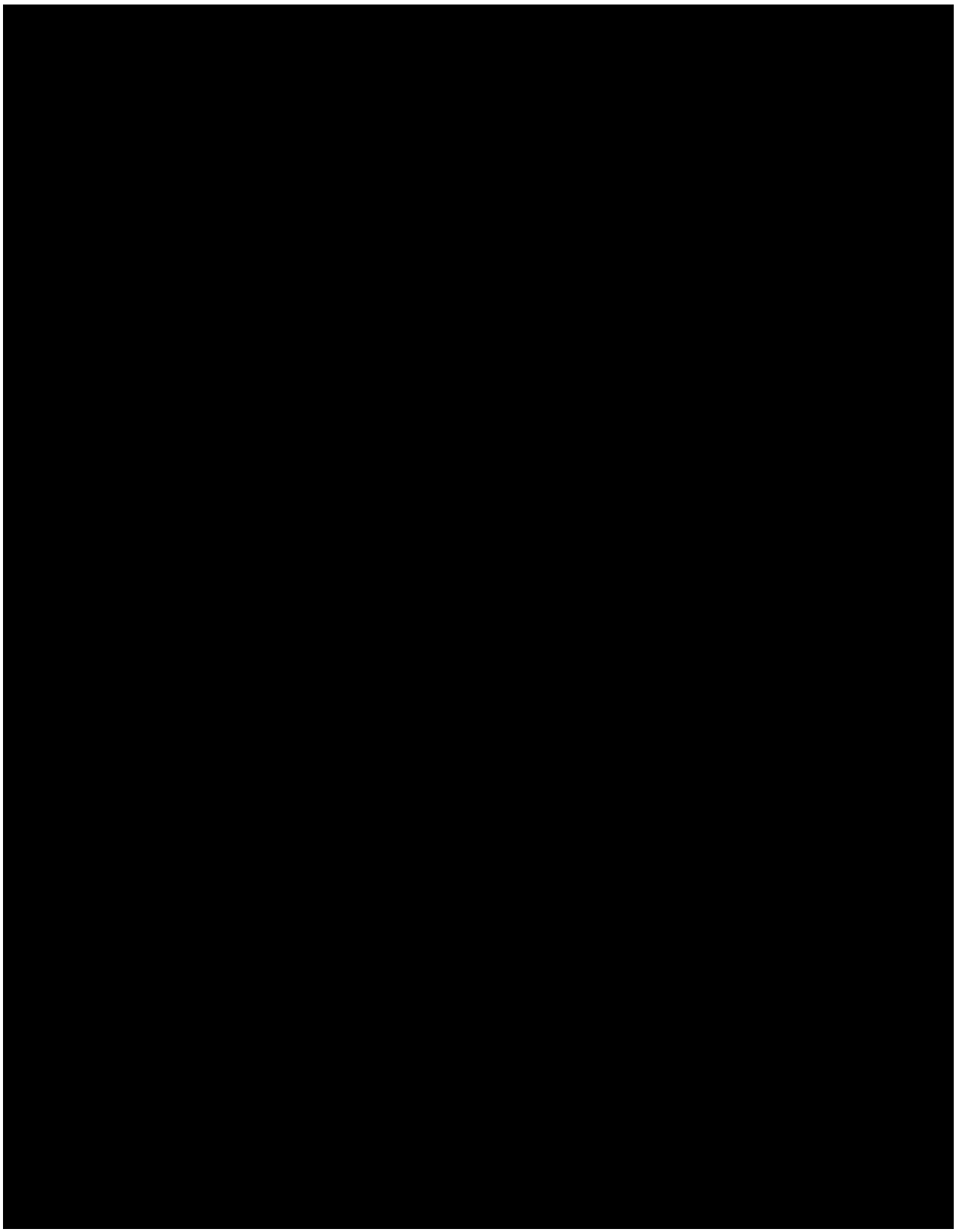


[redacted]

8.5.3 Trial Feedback Questionnaire (TFQ)

This study is including an optional questionnaire, the “Trial Feedback Questionnaire” for trial subjects to provide feedback on their clinical trial experience. Individual trial subject responses will not be reviewed by investigators. Responses may be used by the sponsor (Novartis) to understand where improvements can be made in future clinical trial processes. This questionnaire does not ask questions about the trial subject's disease, symptoms, treatment effect, or AEs, and, therefore is not considered as trial data.





8.5.6 Biomarkers

This clinical study includes additional, **optional** biomarker components supported by an exploratory objective. These studies are hypothesis generating (i.e., discovery based research) and optional to the subject.

Exploratory biomarker assessments

Biomarkers are objectively measured and evaluated indicators of normal biological processes, pathogenic processes or pharmacologic responses to a therapeutic intervention (Biomarkers Definitions Working Group 2001). This search for biomarkers of disease and drug response will involve an integrated molecular approach examining gene expression in blood and protein profiles in serum.

These optional assessments aim to identify potential markers of response and/or loss of response, and to characterize molecular mechanisms of treatment with secukinumab.

Any biomarker samples may be stored for up to 15 years (depending on local regulations) to research scientific questions related to secukinumab, LN and related diseases with a potential involvement of IL-17A. The material can be destroyed on subject's request at any time point.

Any results from these exploratory biomarker assessments will be reported separately.

[redacted] The final selection of analytes will be driven by assay availability, new information from the public domain, results obtained in other secukinumab clinical studies, as well as by hypotheses generated by other exploratory biomarker assessments. In addition, selected markers exploring the effect of secukinumab treatment on co-morbidities may be assessed.

[redacted]

[redacted]

DNA/RNA sampling / Pharmacogenetics

The study includes an optional genetic research component, which requires a separate informed consent signature if the subject agrees to participate as stated in Section 7. As permitted by local governing regulations and by IRB/EC, it is required as part of this protocol that the Investigator presents these options to the subject.

The purpose of genetic research is to evaluate the effect of genetic polymorphisms on treatment response and to better understand the safety and efficacy of secukinumab.

As technology changes over time, the most appropriate technology will be used at the time the exploratory genetic research is performed. This may include the study of the entire genome.

Follow instructions for sample collection, numbering, processing, and shipment provided in the laboratory manual.

DNA/RNA samples

The use of DNA/RNA to search for biomarkers of disease and drug action is exploratory. Any results from this DNA/RNA study will not be placed in the subject's medical records.

To maximize confidentiality, all samples and the information associated with the samples will be double-coded to prevent the exposure of the subject's information and identity. This double-coding process allows Novartis to go back and destroy the sample at the subject's request. In addition, sample information is stored in one secured database while genetic data is stored in an independent secured database.

RNA

The activity (the expression) of genes will be examined using RNA (or other nucleic acid) analytical technologies, which may include expression microarrays, PCR, Nanostring, Next Generation Sequencing techniques, or others. These analyses will be used to examine the effect of secukinumab on transient RNA expression in serum and may support the identification of pathways/markers that characterize the disease or response of treatment with secukinumab.

9 Study discontinuation and completion

9.1 Discontinuation

9.1.1 Discontinuation of study treatment

Discontinuation of study treatment for a subject occurs when study treatment is stopped earlier than the protocol planned duration, i.e., before Week 100 last planned study treatment

administration. Discontinuation of study treatment can be initiated by either the subject or the investigator.

The investigator must discontinue study treatment for a given subject if, he/she believes that continuation would negatively impact the subject's well-being.

Study treatment must be discontinued under the following circumstances:

- Subject/guardian decision - subjects may choose to discontinue study treatment for any reason at any time
- Pregnancy (see Section 10.1.4 Pregnancy reporting)
- Patient received a live vaccine
- Use of prohibited treatment as outlined in Section 6.2.2 prohibited medication
- Any situation or protocol deviation in which study participation might result in a safety risk to the subject
- Following an emergency unblinding
- Emergence of the following AEs:
    - Any AE that in the judgment of the investigator, taking into account the subject's overall status, prevents the subject from continuing study treatment (for example sepsis)
    - Any severe or serious AE that requires treatment with an unacceptable co-medication
    - Severe hypersensitivity reaction or anaphylactic reaction
- Any laboratory abnormalities that in the judgment of the investigator, taking into account the subject's overall status, prevents the subject from continuing study treatment
- Unsatisfactory therapeutic effect

If discontinuation of study treatment occurs, the investigator should make a reasonable effort to understand the primary reason for the subject's premature discontinuation of study treatment and record this information in the eCRF.

Subjects who discontinue study treatment prematurely for any reason should NOT be considered as discontinued from the study UNLESS they withdrew their consent (see Section 9.1.2 Withdrawal of Informed Consent). **Where possible, they should continue attending site visits.**

All subjects who prematurely discontinue study treatment should perform the EOT study visit 4 weeks after their last study treatment administration. For example, if study treatment discontinuation decision is taken at time of planned Week 16 visit, the subject should perform the EOT visit assessments instead of Week 16 visit assessments.

Thereafter, different possibilities may arise, for which guidelines are outlined below:

- **Subjects unwilling to continue attending further study visits** after prematurely discontinuing the study treatment should also perform an EOS visit 12 weeks after the last administration of the study treatment.
- **Subjects willing to continue attending study visits** should continue attending all subsequent scheduled site visits for clinical and safety study assessments. For the example

taken above, next visit should be Week 20 during which visit assessments as outlined in Visit Schedule Table 8-1 will be performed, except study treatment administration. The EOS visit should be performed 12 weeks after the Week 100 visit.

- **Subjects initially continuing attending site visits after premature study treatment discontinuation may decide to discontinue study at any time**. For those subjects, the EOS visit will be performed at time of study discontinuation. Of note, the EOS visit must always be completed at least 12 weeks after the last study treatment administration.

Finally, if the subject is failing to return for these assessments for unknown reasons, every effort (e.g., telephone, e-mail, letter) should be made to contact the subject/pre-designated contact as specified in the lost to follow-up section. This contact should preferably be done according to the study visit schedule.

If the subject cannot or is unwilling to attend any visit(s), the site staff should maintain regular telephone contact with the subject, or with a person pre-designated by the subject. This telephone contact should preferably be done according to the study visit schedule.

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

If discontinuation occurs because treatment code has been broken, please refer to Emergency breaking of treatment code section.

9.1.2 Withdrawal of informed consent

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

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

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

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

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

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

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

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

For EU and RoW: 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.

9.1.3 Lost to follow-up

For subjects whose status is unclear because they fail to appear for study visits without stating an intention to discontinue or withdraw, the investigator must show "due diligence" by documenting in the source documents steps taken to contact the subject, e.g., dates of telephone calls, registered letters, etc. A subject should not be considered as lost to follow-up until due diligence has been completed.

9.1.4 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 (including slow enrollment), or for regulatory or medical reasons. In taking the decision to terminate, Novartis will always consider the subject welfare and safety. Should early termination be necessary, subjects must be contacted by the sites to be seen as soon as possible and treated as a prematurely withdrawn subject. The investigator may be informed of additional procedures to be followed in order to ensure that adequate consideration is given to the protection of the subject's interests. The investigator or sponsor depending on the local regulation will be responsible for informing IRBs/IECs of the early termination of the trial.

9.2 Study completion and post-study treatment

Study completion is defined as when the last subject finishes their Study Completion 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.

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

The investigator must provide follow-up medical care for all subjects, including subjects who are prematurely withdrawn from the study, or must refer them for appropriate ongoing care. This care may include initiating another treatment outside of the study, as deemed appropriate by the investigator.

10 Safety monitoring and reporting

10.1 Definition of adverse events and reporting requirements

10.1.1 Adverse events

An AE is any untoward medical occurrence (e.g., any unfavorable and unintended sign [including abnormal laboratory findings], symptom or disease) in a subject or clinical investigation subject after providing written informed consent for participation in the study.

Therefore, an AE may or may not be temporally or causally associated with the use of a medicinal (investigational) product.

The investigator has the responsibility for managing the safety of individual subject 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 subject at each visit during the study. AEs also may be detected when they are volunteered by the subject during or between visits or through physical examination findings, laboratory test findings, or other assessments.

AEs 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 10.1.2):

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 study treatment and other investigational treatment. 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 subject
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 10.1.2 for definition of SAE) and which seriousness criteria have been met
5. action taken regarding with study treatment

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; recovered/resolved with sequelae; fatal; or unknown)

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

AEs (including lab 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 30 days following the last dose of study treatment.

Once an adverse event 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 must be made at each visit (or more frequently, if necessary) of any changes in severity, the suspected relationship to the interventions required to treat it, and the outcome.

Information about adverse drug reactions for the investigational drug can be found in the Investigator's Brochure (IB).

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 subjects with the underlying disease. Alert ranges for laboratory test abnormalities are included in Section 16.10.

10.1.2 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 the ICH-E2D Guidelines).

- 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
    - social reasons and respite care in the absence of any deterioration in the subject’s general condition
    - 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

- is medically significant, e.g., defined as an event that jeopardizes the subject or may require medical or surgical intervention to prevent one of the outcomes listed 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 subject or might require intervention to prevent one of the other outcomes listed above. Such events should be considered as "medically significant." 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 the ICH-E2D Guidelines).

All malignant neoplasms will be assessed as serious under "medically significant" if other seriousness criteria are not met and the malignant neoplasm is not a disease progression of the study indication.

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 product are also considered serious adverse event irrespective if a clinical event has occurred.

10.1.3 SAE reporting

To ensure subject safety, every SAE, regardless of causality, occurring after the subject has provided informed consent and until 12 weeks (84 days) following the last administration of study treatment, or 30 days after the subject has stopped study participation (whichever is later), 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.

Any SAEs experienced after the 30-day period after the last study visit should only be reported to Novartis Safety if the investigator suspects a causal relationship to study treatment.

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

Information about all SAEs is collected and recorded on the Serious Adverse Report Form; all applicable sections of the form must be completed in order to provide a clinically thorough report. The investigator must assess the relationship of each SAE to study treatment, 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.

If the SAE is not previously documented in the Investigator's Brochure or Package Insert (new occurrence) and is thought to be related to the study treatment, a 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.

10.1.4 Pregnancy reporting

Pregnancies

To ensure subject 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 Chief Medical Office and Patient Safety (CMO&PS). Pregnancy follow-up should be recorded on the same form and should include an assessment of the possible relationship to the study treatment any pregnancy outcome. Any SAE experienced during pregnancy must be reported.

10.1.5 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, subject or consumer (EMA definition).

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

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

Study treatment errors and uses outside of what is foreseen in the protocol will be recorded on 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 10-1 Guidance for capturing the study treatment errors including misuse/abuse

Treatment error type	Document in Dosing eCRF (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.

10.2 Additional Safety Monitoring

10.2.1 Liver safety monitoring

To ensure subject safety and enhance reliability in determining the hepatotoxic potential of an investigational drug, a standardized process for identification, monitoring and evaluation of liver events has to be followed.

The following two categories of abnormalities / AEs have to be considered during the course of the study (irrespective of whether classified/reported as AE/SAE):

- Liver laboratory triggers, which will require repeated assessments of the abnormal laboratory parameter
- Liver events, which will require close observation, follow-up monitoring and contributing factors are recorded on the appropriate eCRFs

Please refer to Table 16-1 of appendix Section 16.9 for complete definitions of liver laboratory triggers and liver events.

Every liver event defined in Table 16-2 should be followed up by the investigator or designated personnel at the trial site, as summarized below. Additional details on actions required in case of liver events are outlined in Table 16-2. Repeat liver chemistry tests (i.e., ALT, AST, TBL, PT/INR, ALP and GGT) to confirm elevation.

- These liver chemistry repeats will be performed using the central laboratory. If results will not be available from the central laboratory, then the repeats can also be performed at a local laboratory to monitor the safety of the subject. If a liver event is subsequently reported, any local liver chemistry tests previously conducted that are associated with this event should have results recorded on the appropriate eCRF.
- If the initial elevation is confirmed, close observation of the subject will be initiated, including consideration of treatment interruption if deemed appropriate.
- Discontinuation of the investigational drug (refer to the Section 9.1.1 Discontinuation of study treatment section), if appropriate
- Hospitalization of the subject if appropriate
- Causality assessment of the liver event
- Thorough follow-up of the liver event should include
    - These investigations can include based on investigator's discretion: serology tests, imaging and pathology assessments, hepatologist consultancy; obtaining more detailed history of symptoms and prior or concurrent diseases, history of concomitant drug use, exclusion of underlying liver disease

All follow-up information and procedures performed must be recorded as appropriate in the eCRF.

10.2.2 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 data from interim analysis, as well

as the progress of the clinical trial, safety data, and critical efficacy variables and it will recommend to the sponsor whether to continue, modify, or terminate a trial.

Specific details regarding composition, responsibilities, data monitoring, and meeting frequency, and documentation of DMC reports, minutes, and recommendations will be described in a separate charter that is established between the sponsor and the DMC.

10.2.3 Steering Committee

A Steering Committee (SC) will be established comprising disease area experts, investigators participating in the trial, i.e., not being members of the DMC, and Novartis representatives from the Clinical Trial Team.

The SC will ensure transparent management of the study according to the protocol through recommending and approving modifications as circumstances require. The SC will review protocol amendments as appropriate. Together with the clinical trial team, the SC will also develop recommendations for publications of study results including authorship rules. The details of the role of the steering committee will be defined in the steering committee charter.

11 Data Collection and Database management

11.1 Data collection

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

Designated investigator staff will enter the data required by the protocol into the Electronic Case Report Forms (eCRF). The eCRFs have been built using fully validated secure web-enabled software that conforms to 21 Code of Federal Regulation (CFR) Part 11 requirements, Investigator site staff will not be given access to the Electronic Data Capture (EDC) 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 (recorded on CRFs) (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 subject data for archiving at the investigational site.

11.2 Database management and quality control

Novartis personnel (or designated 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 treatment(s) dispensed to the subject and all dosage changes will be tracked using an Interactive Response Technology (IRT). The system will be supplied by a vendor, who will also manage the database. The data will be sent electronically to Novartis (or a designated CRO) at specific timelines.

Each occurrence of a code break via IRT will be reported to the clinical team and monitor. The code break functionality will remain available until study shut down or upon request of Novartis.

Once all the necessary actions have been completed and the database has been declared to be complete and accurate, it will be locked **and the treatment codes will be unblinded** and made available for data analysis/moved to restricted area to be accessed by independent programmer and statistician. Any changes to the database after that time can only be made after written agreement by Novartis development management.

11.3 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., eSource DDE or 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 subject 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 & identify risks & trends for site operational parameters, and provide reports to Novartis clinical teams to assist with trial oversight.

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

The investigator must give the monitor access to all relevant source documents to confirm their consistency with the 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 CRFs are performed according to the study-specific monitoring plan. No information in source documents about the identity of the subjects will be disclosed.

12 Data analysis and statistical methods

Summary statistics for continuous variables include N, mean, standard deviation (SD), minimum, lower quartile, median, upper quartile, and maximum. For binary or discrete variables, the absolute number of subjects in each category and relative frequencies will be provided.

Unless otherwise specified, p-values will be presented as 2-sided p-values and the type I error rate (alpha) will be 5%.

Efficacy and safety data for Treatment Period will be presented by the following two treatment groups.

- Secukinumab 300 mg
- Placebo

Any data analysis carried out independently by the investigator should be submitted to Novartis before publication or presentation.

12.1 Analysis sets

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

The Full Analysis Set (FAS) will be comprised of all analyzable subjects from the randomized set to whom study treatment has been assigned. According to the intent to treat principle, subjects will be analyzed according to the treatment they have been assigned to during the randomization procedure, but according to actual stratum.

The Safety Set includes all subjects who received at least one dose of study treatment. Subjects will be analyzed according to the study treatment received.

12.2 Subject demographics and other Baseline characteristics

Summary statistics will be presented for continuous demographic and Baseline characteristic variables for each treatment group and for all subjects in the randomized set. The number and percentage of subjects in each category will be presented for categorical variables for each treatment group and all subjects.

Any significant prior or active medical condition at the time of signing informed consent will be coded using the MedDRA dictionary. These medical conditions will be summarized by primary system organ class and preferred term. SLE and LN specific medical history will be summarized by treatment group.

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

12.3 Treatments

Study treatment

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

Prior and concomitant medication

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

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

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

The number and percentage of subjects receiving prior and concomitant LN therapy will be presented by randomized treatment group.

12.4 Analysis of the primary endpoint(s)

12.4.1 Definition of primary endpoint(s)

The primary efficacy endpoint is the complete renal response at Week 52.

The estimand definition for the primary endpoint is as follows:

1. Population: defined through appropriate inclusion/exclusion criteria to reflect the targeted LN population
2. Variable: composite of remaining on the study and on randomized treatment through 52 weeks and achieving CRR response at 52 weeks
3. Intercurrent event: the intercurrent event is captured through the variable definition
4. Population-level summary: difference in proportions of responders between the secukinumab and placebo arms

12.4.2 Statistical model, hypothesis, and method of analysis

The statistical hypothesis tested for the primary objective is that there is no difference in the proportion of subjects fulfilling the response criteria at Week 52 between the secukinumab and placebo regimens.

Let pj denote the proportion of responders at Week 52 for treatment regimens j, j=0, 1 where

- 0 corresponds to placebo regimen,
- 1 corresponds to secukinumab,

In statistical terms, H1: p1 = p0, HA1: p1 ≠ p0, i.e.,

H1: secukinumab is not different to placebo regimen with respect to CRR at Week 52

Logistic regression model adjusting for SoC, race and Baseline UPCR will be used for the primary analysis. Difference in marginal response proportions with p-value and respective 95% confidence interval will be estimated from the logistic regression model.

12.4.3 Handling of missing values/censoring/discontinuations

Non-responder imputation will be used for handling missing data for the primary endpoint and other binary endpoints. For the continuous secondary and exploratory variables Mixed-Effect Model Repeated Measure (MMRM) model, which is valid under the missing at random assumption, will be used. For average daily dose of oral corticosteroids multiple imputation will be used for handling missing data.

12.4.4 Sensitivity and Supportive analyses

Sensitivity analyses and supportive analyses will be conducted in order to provide evidence that the results seen from the primary analysis are robust. These analyses will center on the deviations in model assumptions and the treatment of missing data.

Sensitivity analyses

The impact of missing data on the analysis results of CRR will be assessed as well by repeating the logistic regression model using different ways to handle missing data.

These may include, but are not limited to:

- Multiple imputation
- Observed data analysis
- Tipping point analysis

Supportive analyses

As a sensitivity analysis to primary endpoint modified Complete Renal Response (mCRR) will be analyzed.

A subject is defined as a mCRR responder when the following two conditions are met:

· Estimated glomerular filtration rate (eGFR) is within the normal range or no less than 85% of Baseline and

· 24-hour UPCR ≤ 0.7 mg/mg

12.5 Analysis of secondary endpoints

12.5.1 Testing strategy

The secondary efficacy variables and the method for adjusting for multiplicity are described below.

H_2: Secukinumab 300mg is not different to placebo with respect to change from Baseline in 24-hour UPCR at Week 52 compared to Baseline

H_3: Secukinumab 300mg is not different to placebo with respect to proportion of subjects achieving PRR at Week 52

H_4: Secukinumab 300mg is not different to placebo with respect to average daily dose of oral corticosteroids administered between Week 16 and Week 52

H_5: Secukinumab 300mg is not different to placebo with respect to proportion of subjects achieving PRR at Week 24

H_6: Secukinumab 300mg is not different to placebo with respect to time to achieve CRR,

H_7: Secukinumab 300mg is not different to placebo with respect to time to achieve PRR

H_8: Secukinumab 300mg is not different to placebo with respect to time to achieve first morning void UPCR $\leq$ 0.5 mg/mg

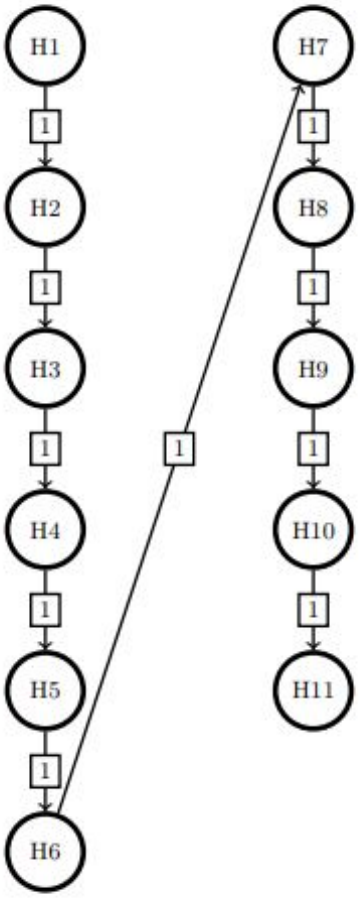
H_9:Secukinumab 300mg is not different to placebo with respect to FACIT-Fatigue©, mean change of score from Baseline at Week 52

H_{10}: Secukinumab 300mg is not different to placebo with respect to improvement in SF-36 PCS mean change from Baseline at Week 52

H_{11}: Secukinumab 300mg is not different to placebo with respect to improvement in LupusQoL physical health score mean change from Baseline at Week 52

A sequential testing strategy will be used in order to control for multiplicity of testing. The graphical approach of (Bretz et al 2009) for sequentially rejective testing procedures is used to illustrate the testing strategy:

Figure 12-1 Testing strategy



The family-wise error will be set to two-sided α=5% and it will be controlled with the proposed hierarchical testing strategy.

The hypotheses (H1) for the primary objective (CRR at Week 52) for the secukinumab vs. placebo will be tested at α. If H1 is rejected, then the hypothesis H2 will be tested at α. If H2 is rejected, then the hypothesis H3 will be tested and so on.

Estimand definitions for the secondary variables

Estimand definition for the secondary binomial variables is the following:

A. Population: defined through appropriate inclusion/exclusion criteria to reflect the targeted LN population, unless otherwise specified.

B. Variable: composite of remaining on the study and on randomized treatment through 16 weeks and achieving *variable* (e.g., PRR) response at 52 (or 24) weeks

C. Intercurrent event: the intercurrent event is captured through the variable definition

D. Population-level summary: Difference in marginal response proportions between treatments

The estimand of binary variables is (secukinumab vs placebo) obtained from a logistic regression model adjusting for covariates in the FAS population. Difference in marginal response proportions will be computed for comparisons of secukinumab vs. placebo regimen utilizing the logistic regression model fitted. In the analysis subjects dropping out or being unblinded before the time point of interest or having missing response data at the time point of interest are considered as non-responders.

Estimand definition for the secondary continuous variables except average daily dose of oral corticosteroids is the following:

A. Population: defined through appropriate inclusion/exclusion criteria to reflect the targeted LN population

B. Variable: *variable* (e.g., change from Baseline in UPCR) of interest

C. Intercurrent event: had no intercurrent events occurred before Week 52

D. Population-level summary: difference in variable means between the treatment conditions

The estimand of continuous variables at Week 52 is (secukinumab vs placebo) obtained from a repeated measures model in the FAS population assuming subjects dropping out or having missing data at Week 52 are missing-at-random (MAR).

Estimand definition for the average daily dose of oral corticosteroids is the following:

A. Population: defined through appropriate inclusion/exclusion criteria to reflect the targeted LN population

B. Variable: *variable* (e.g., average daily dose of oral corticosteroids) of interest

C. Intercurrent event: observed data regardless of intercurrent events

D. Population-level summary: difference in variable means between the treatment conditions

Estimand definition for the secondary time-to-event variables is the following:

A. Population: defined through appropriate inclusion/exclusion criteria to reflect the targeted LN population

B. Variable: time to *response of interest* (e.g., CRR)

C. Intercurrent event: had no intercurrent events occurred before Week 52

D. Population-level summary: hazard ratio of secukinumab vs placebo

For all secondary endpoints, supplementary estimands of interest may be specified in statistical analysis plan.

UPCR at Week 52

For the change in UPCR analysis will be performed on the $\log_e$ ratio of the treatment value vs Baseline value (calculated by dividing the post-Baseline value by the Baseline value and then applying the $\log_e$ transformation) to normalize the distribution of UPCR at each analysis visit. Between-treatment differences in the change in UPCR relative to Baseline will be evaluated using MMRM with treatment group, stratification factor (SoC), race, and analysis visit as factors and $\log_e$ Baseline UPCR as continuous covariates. Treatment by analysis visit and $\log_e$ Baseline UPCR by analysis visit will be included as interaction terms in the model. An

unstructured covariance structure will be assumed for the model. The significance of the treatment effect for secukinumab regimens at different analysis visits will be determined from the pairwise comparisons performed between secukinumab and placebo at the appropriate analysis visits

PRR at Week 24 or at Week 52

Logistic regression model adjusting for SoC, race and baseline UPCR will be used for the analysis. Difference in marginal response proportions with p-value and respective 95% confidence interval will be estimated from the logistic regression model.

Average daily dose of oral corticosteroids administered between Week 16 and Week 52

Between-treatment differences for average daily dose of oral corticosteroids administered between Week 16 and Week 52 will be evaluated with analysis of covariance (ANCOVA) model including treatment group, race, Baseline dose and SoC as covariates. Missing data will be handled using multiple imputation.

Time to achieve CRR

For time to achieve CRR between treatment differences will be evaluated using log-rank test stratified by race and SoC. The hazard ratios for these comparisons for achieving response and their corresponding 95% confidence intervals will be computed using a stratified Cox proportional hazards regression model with treatment group and $\log_e$ Baseline UPCR as explanatory variable and stratified by race and SoC. Subjects who have not achieved response up to Week 52 will be considered as censored observations. Kaplan-Meier curves will be presented for each treatment.

Time to achieve PRR

For time to achieve PRR between treatment differences will be evaluated using log-rank test stratified by race and SoC. The hazard ratios for these comparisons for achieving response and their corresponding 95% confidence intervals will be computed using a stratified Cox proportional hazards regression model with treatment group and $\log_e$ Baseline UPCR as explanatory variable and stratified by race and SoC. Subjects who have not achieved response up to Week 52 will be considered as censored observations. Kaplan-Meier curves will be presented for each treatment.

Time to achieve first morning void UPCR ≤ 0.5 mg/mg

For time to achieve first morning void UPCR ≤ 0.5 mg/mg between treatment differences will be evaluated using log-rank test stratified by race and SoC. The hazard ratios for these comparisons for achieving response and their corresponding 95% confidence intervals will be computed using a stratified Cox proportional hazards regression model with treatment group and $\log_e$ Baseline UPCR as explanatory variable and stratified by race and SoC. Subjects who have not achieved response up to Week 52 will be considered as censored observations. Kaplan-Meier curves will be presented for each treatment.

FACIT-Fatigue© change from Baseline at Week 52

Between-treatment differences in the change from Baseline in FACIT-Fatigue© will be evaluated using MMRM with treatment group, stratification factor (SoC), race, and analysis visit as factors and Baseline FACIT-Fatigue© as continuous covariates. Treatment by analysis

visit and Baseline FACIT-Fatigue© by analysis visit will be included as interaction terms in the model. An unstructured covariance structure will be assumed for the model. The significance of the treatment effect for secukinumab regimens at different analysis visits will be determined from the pairwise comparisons performed between secukinumab and placebo at the appropriate analysis visits.

SF-36 PCS change from Baseline at Week 52

Between-treatment differences in the change from Baseline in SF-36 PCS will be evaluated using MMRM with treatment group, stratification factor (SoC), race, and analysis visit as factors and Baseline SF-36 PCS as continuous covariates. Treatment by analysis visit and Baseline by analysis visit will be included as interaction terms in the model. An unstructured covariance structure will be assumed for the model. The significance of the treatment effect for secukinumab regimens at different analysis visits will be determined from the pairwise comparisons performed between secukinumab and placebo at the appropriate analysis visits.

LupusQoL physical health score change from Baseline at Week 52

Between-treatment differences in the change from Baseline in LupusQoL physical health score will be evaluated using MMRM with treatment group, stratification factor (SoC), race, and analysis visit as factors and Baseline LupusQoL physical health score as continuous covariates. Treatment by analysis visit and Baseline LupusQoL physical health score by analysis visit will be included as interaction terms in the model. An unstructured covariance structure will be assumed for the model. The significance of the treatment effect for secukinumab regimens at different analysis visits will be determined from the pairwise comparisons performed between secukinumab and placebo at the appropriate analysis visits.

12.5.2 Safety endpoints

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

Adverse events

Treatment-emergent adverse events (i.e., events started after the first dose of study treatment or events present prior to the first dose of study treatment but increased in severity based on preferred term and on or before last dose + 84 days) will be summarized.

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

As appropriate, the incidence of AEs will be presented per 100 subject-years of exposure (exposure-adjusted incidence rates).

Separate summaries will be provided for deaths, SAEs, other significant AEs leading to discontinuation and AEs leading to study treatment discontinuation.

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

Vital signs

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

12-lead ECG

Summary statistics will be presented for ECG variables.

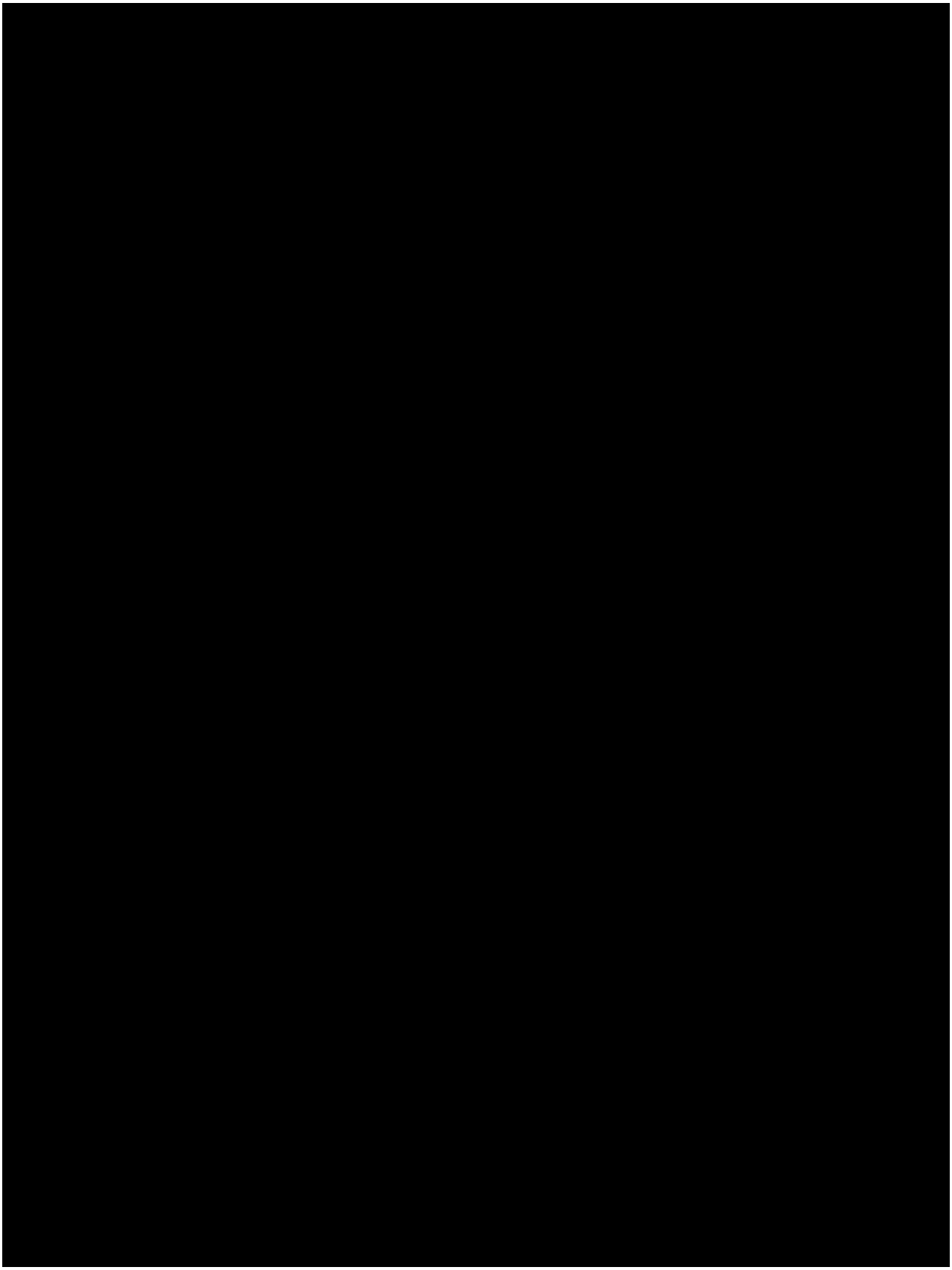
Clinical laboratory evaluations

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

[redacted]

12.6 Analysis of exploratory endpoints

[redacted]



12.6.1 Patient reported outcomes

Health-related Quality of Life assessments will be evaluated based on FAS unless otherwise specified.

SF-36

The following variables will be evaluated:

• SF-36 domain scores (based on a scale of 0-100)

• SF-36 PCS and MCS scores (norm-based scores)

• SF-36 PCS and MCS responder (improvement of ≥ 2.5 points, (Lubeck 2004))

For the change in SF-36 summary scores (PCS and MCS), summary statistics will be provided using observed data for each treatment regimen. Between-treatment differences will be evaluated using MMRM.

The SF-36 domain scores will be summarized by treatment.

FACIT-Fatigue

For the change in FACIT-Fatigue scores, summary statistics of observed data by visit and change from Baseline in FACIT will be provided for each treatment. Between-treatment differences will be evaluated using MMRM.

LupusQoL

For the change in LupusQoL domain scores, summary statistics of observed data by visit and change from Baseline will be provided for each treatment. Between-treatment differences will be evaluated using MMRM.

[redacted]

[redacted]

12.6.3 DNA and RNA

Exploratory DNA and RNA studies are designed to investigate the association between genetic factors (genotypes) and clinical assessments (phenotypes) which are collected during the clinical trial. Without prior evidence of a strong association, a number of possible associations are evaluated with exploratory analyses. A range of statistical tests is used for the analyses. Additional data, from other clinical trials, are often needed to confirm associations. Alternatively, if the number of subjects enrolled in the study is too small to complete proper statistical analyses, the data may be combined, as appropriate, with those from other studies to enlarge the dataset for analysis.

Data generated on hypothesis-free platforms will be reported separately (e.g., CSR addendum).

12.6.4 Biomarkers

Soluble marker panel studies investigate differences in the level of expression of proteins or peptides between individuals in a given biofluid. The goal of such studies is to allow the identification of potential protein or peptide biomarkers of treatment action or disease and to better understand the associated underlying molecular mechanisms. By applying statistical analysis methods (e.g., principal component analysis) between subject groups, distinct study time points, or between study groups from other clinical trials, it may be possible to identify patterns, which are associated with disease state or response to drug treatment. However, the exact type of data analysis method will depend on the type of data obtained in the study, and thus, the analysis of these data will be data-driven and, hence, not part of the Clinical Study Report (CSR).

[redacted]

12.7 Interim analyses

Futility Analysis

A futility analysis will be performed when approximately 30% of subjects will have completed the first 52 weeks of treatment. A Go/No-Go decision will be taken at this futility analysis based on predictive probability calculated from the CRR achieved at Week 52. The analysis will be conducted by an independent statistician and programmer supporting an external DMC. Futility stopping rules will be defined in the DMC charter.

[redacted]

[redacted]

Interim analysis

Based on the group sequential design applied in the study, an interim analysis is planned when 2/3 or 67% of the subjects complete 52 weeks of treatment. The results from this interim analysis will support the decision-making concerning the current clinical study, i.e., to continue or to stop the trial based on efficacy and/or safety findings.

A Lan-De Mets alpha spending function with O'Brien Fleming type stopping boundary (as implemented in the software East 6.3) will be used to maintain the overall type-I error rate for the primary and secondary endpoints at Week 52 (O'Brien and Fleming 1979).

Based on the choice of α-spending function described above, the efficacy boundary in terms of p-value scale at the interim analysis is calculated as p=0.012 for a two-sided test. The observed (i.e., nominal) p-value has to be smaller than 0.012 to conclude superior efficacy at the interim analysis. If a hypothesis is not rejected at the interim analysis, it will be tested again at the Week 52 analysis. The efficacy boundary for the final analysis in terms of p-value scale is p=0.046.

The exact rejecting boundaries will be calculated after the exact number of subjects in each treatment arm is available.

A sequential testing hierarchy will be used to test the secondary hypotheses. The secondary hypotheses will be tested at the interim analysis only if the primary hypothesis is rejected. This guarantees the 5% overall level of significance for the primary and secondary hypotheses (Glimm et al 2010). For Week 52 secondary endpoints the same rejecting boundaries will be used as for the primary endpoint.

12.8 Sample size calculation

12.8.1 Primary endpoint(s)

The total planned sample size is 460 subjects. Based on literature (Mysler et al 2013), (Rovin et al 2012) the control response rate was assumed approximately 30%. Assuming 15% treatment difference with 45% response rate for secukinumab, the power for rejecting the null hypothesis for primary endpoint (CRR) is 92%. The assumptions are summarized in the Table 12-1 below.

Table 12-1 Power for primary endpoint

Analysis	Control response rate	Secukinumab response rate	Sample size	Cumulative power for primary endpoint
Interim analysis	30%	45%	306	60%
Final analysis	30%	45%	460	92%

12.8.2 Secondary endpoint(s)

Using published data for control (Mysler et al 2013), (Rovin et al 2012), (Deng et al 2018) (Wallace et al 2017), (McElhone et al 2016) and assuming given treatment effects for secukinumab, a summary for power for secondary efficacy parameters is shown in Table 12-2 for binary endpoints, Table 12-3 for continuous endpoints and Table 12-4 for time to event endpoints. Power for the secondary endpoints was calculated with the group sequential design and the total cumulative power, to reject either at the interim or final analysis, is presented.

Table 12-2 Summary of power for binary secondary endpoints

Endpoint	Response rate		Power
	Secukinumab 300 mg (N = 230)	Placebo (N = 230)	
PRR at Week 52	75%	60%	93%
PRR at Week 24	75%	60%	93%

Table 12-3 Summary of power or continuous endpoints

Endpoint	Mean values		Common standard deviation	Power
	Secukinumab 300 mg (N = 230)	Placebo (N = 230)		
Change from baseline in UPCR at Week 52	-3.5	-2.68	2.69	90%
Average daily dose of corticosteroids between Week 16 and Week 52	5	5.52	1.67	91%
FACIT-Fatigue© change from baseline at Week 52	7.0	2.82	10.0	99%
SF-36 PCS change from baseline at Week 52	6.1	3.1	8.0	98%
LupusQoL Physical Health change from baseline at Week 52	9.6	5.6	14	86%

Table 12-4 Summary of power for time to event endpoints

Endpoint	Event rates and hazard ratios		Power
	Placebo (N = 230) Event rate at Week 52	Hazard Ratio Secukinumab (N = 230)	
Time to CRR	30%	1.67	92%
Time to PRR	60%	1.67	99%
Time to UPCR ≤ 0.5 mg/mg	35%	1.67	95%

13 Ethical considerations and administrative procedures

13.1 Regulatory and ethical compliance

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

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

13.3 Publication of study protocol and results

The protocol will be registered in a publicly accessible database such as clinicaltrials.gov and as required in EudraCT. In addition, after study completion (defined as last patient last visit) and finalization of the study report the results of this trial will be submitted for publication and posted in a publicly accessible database of clinical trial results, such as the Novartis clinical trial results website and all required Health Authority websites (e.g., Clinicaltrials.gov, EudraCT etc.).

For details on the Novartis publication policy including authorship criteria, please refer to the Novartis publication policy training materials that were provided to you at the trial investigator meetings.

13.4 Quality Control and Quality Assurance

Novartis maintains a robust Quality Management System (QMS) that includes all activities involved in quality assurance and quality control, to ensure compliance with written Standard Operating Procedures as well as applicable global/local GCP regulations and ICH Guidelines.

Audits of investigator sites, vendors, and Novartis systems are performed by auditors, 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.

14 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 subjects 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 prohibition, 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.

14.1 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 required for subject safety may be implemented immediately, provided the health authorities are subsequently notified by protocol amendment and the reviewing IRB/IEC is notified.

Notwithstanding the need for approval of formal protocol amendments, the investigator is expected to take any immediate action required for the safety of any subject included in this study, even if this action represents a deviation from the protocol. In such cases, Novartis should be notified of this action and the IRB/IEC at the study site should be informed according to local regulations.

15 References

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16 Appendices

16.1 ACR Criteria for Diagnosis of SLE

1997 Update of the 1982 American College of Rheumatology Revised Criteria for Classification of Systemic Lupus Erythematosus

Criterion	Definition
1. Malar Rash	Fixed erythema, flat or raised, over the malar eminences, tending to spare the nasolabial folds
2. Discoid rash	Erythematous raised patches with adherent keratotic scaling and follicular plugging; atrophic scarring may occur in older lesions
3. Photosensitivity	Skin rash as a result of unusual reaction to sunlight, by patient history or physician observation
4. Oral ulcers	Oral or nasopharyngeal ulceration, usually painless, observed by physician
5. Nonerosive Arthritis	Involving 2 or more peripheral joints, characterized by tenderness, swelling, or effusion
6. Pleuritis or Pericarditis	1. Pleuritis--convincing history of pleuritic pain or rubbing heard by a physician or evidence of pleural effusion 1. *OR* 2. Pericarditis--documented by electrocardigram or rub or evidence of pericardial effusion
7. Renal Disorder	1. Persistent proteinuria > 0.5 grams per day or > than 3+ if quantitation not performed 1. *OR* 2. Cellular casts--may be red cell, hemoglobin, granular, tubular, or mixed
8. Neurologic Disorder	1. Seizures--in the absence of offending drugs or known metabolic derangements; e.g., uremia, ketoacidosis, or electrolyte imbalance 1. *OR* 2. Psychosis--in the absence of offending drugs or known metabolic derangements, e.g., uremia, ketoacidosis, or electrolyte imbalance
9. Hematologic Disorder	1. Hemolytic anemia--with reticulocytosis 1. *OR*

Criterion	Definition
	2. Leukopenia--< 4,000/mm^3 on ≥ 2 occasions 1. *OR* 3. Lyphopenia--< 1,500/ mm^3 on ≥ 2 occasions 1. *OR* 4. Thrombocytopenia--<100,000/ mm^3 in the absence of offending drugs
10. Immunologic Disorder	1. Anti-DNA: antibody to native DNA in abnormal titer 1. *OR* 2. Anti-Sm: presence of antibody to Sm nuclear antigen 1. *OR* 3. Positive finding of antiphospholipid antibodies on: 1. 1. an abnormal serum level of IgG or IgM anticardiolipin antibodies, 2. 2. a positive test result for lupus anticoagulant using a standard method, or 3. 3. a false-positive test result for at least 6 months confirmed by Treponema pallidum immobilization or fluorescent treponemal antibody absorption test
11. Positive Antinuclear Antibody	An abnormal titer of antinuclear antibody by immunofluorescence or an equivalent assay at any point in time and in the absence of drugs

16.2 International Society of Nephrology/Renal Pathology Society (ISN/RPS) 2003 classification of LN

Class I	**Minimal mesangial lupus nephritis** Normal glomeruli by light microscopy, but mesangial immune deposits by immunofluorescence
Class II	**Mesangial proliferative lupus nephritis** Purely mesangial hypercellularity of any degree or mesangial matrix expansion by light microscopy, with mesangial immune deposits May be a few isolated subepithelial or subendothelial deposits visible by immunofluorescence or electron microscopy, but not by light microscopy
Class III	**Focal lupus nephritis**[a] Active or inactive focal, segmental or global endo- or extracapillary glomerulonephritis involving <50% of all glomeruli, typically with focal subendothelial immune deposits, with or without mesangial alterations
Class III (A)	Active lesions: focal proliferative lupus nephritis
Class III (A/C)	Active and chronic lesions: focal proliferative and sclerosing lupus nephritis
Class III (C)	Chronic inactive lesions with glomerular scars: focal sclerosing lupus nephritis
Class IV	**Diffuse lupus nephritis**[b] Active or inactive diffuse, segmental or global endo- or extracapillary glomerulonephritis involving ≥50% of all glomeruli, typically with diffuse subendothelial immune deposits, with or without mesangial alterations. This class is divided into diffuse segmental(IV-S) lupus nephritis when ≥50% of the involved glomeruli have segmental lesions, and diffuse global (IV-G) lupus nephritis when ≥50% of the involved glomeruli have global lesions. Segmental is defined as a glomerular lesion that involves less than half of the glomerular tuft. This class includes cases with diffuse wire loop deposits but with little or no glomerular proliferation
Class IV-S (A)	Active lesions: diffuse segmental proliferative lupus nephritis
Class IV-G (A)	Active lesions: diffuse global proliferative lupus nephritis
Class IV-S (A/C)	Active and chronic lesions: diffuse segmental proliferative and sclerosing lupus nephritis Active and chronic lesions: diffuse global proliferative and sclerosing lupus nephritis
Class IV-S (C)	Chronic inactive lesions with scars: diffuse segmental sclerosing lupus nephritis
Class IV-G (C)	Chronic inactive lesions with scars: diffuse global sclerosing lupus nephritis
Class V	**Membranous lupus nephritis** Global or segmental subepithelial immune deposits or their morphologic sequelae by light microscopy and by immunofluorescence or electron microscopy, with or without mesangial alterations Class V lupus nephritis may occur in combination with class III or IV in which case both will be diagnosed Class V lupus nephritis show advanced sclerosis
Class VI	**Advanced sclerosis lupus nephritis** ≥90% of glomeruli globally sclerosed without residual activity

[a] Indicate the proportion of glomeruli with active and with sclerotic lesions.
[b] Indicate the proportion of glomeruli with fibrinoid necrosis and/or cellular crescents.
Indicate and grade (mild, moderate, severe) tubular atrophy, interstitial inflammation and fibrosis, severity of arteriosclerosis or other vascular lesions.

16.3 Estimation of eGFR by the CKD-EPI

The CKD-EPI creatinine equation uses a 2-slope spline to model the relationship between estimated GFR and serum creatinine, and a different relationship for age, sex and race. The equation was reported to perform better and with less bias than the MDRD Study equation, especially in patients with higher GFR. This results in reduced misclassification of CKD (Levey et al 2009)

The CKD-EPI creatinine equation is:

$$GFR = 141 \times \min(Scr/\kappa, 1)^{\alpha} \times \max(Scr/\kappa, 1)^{-1.209} \times 0.993^{Age} \times 1.018[\text{if female}] \times 1.159[\text{if black}]$$

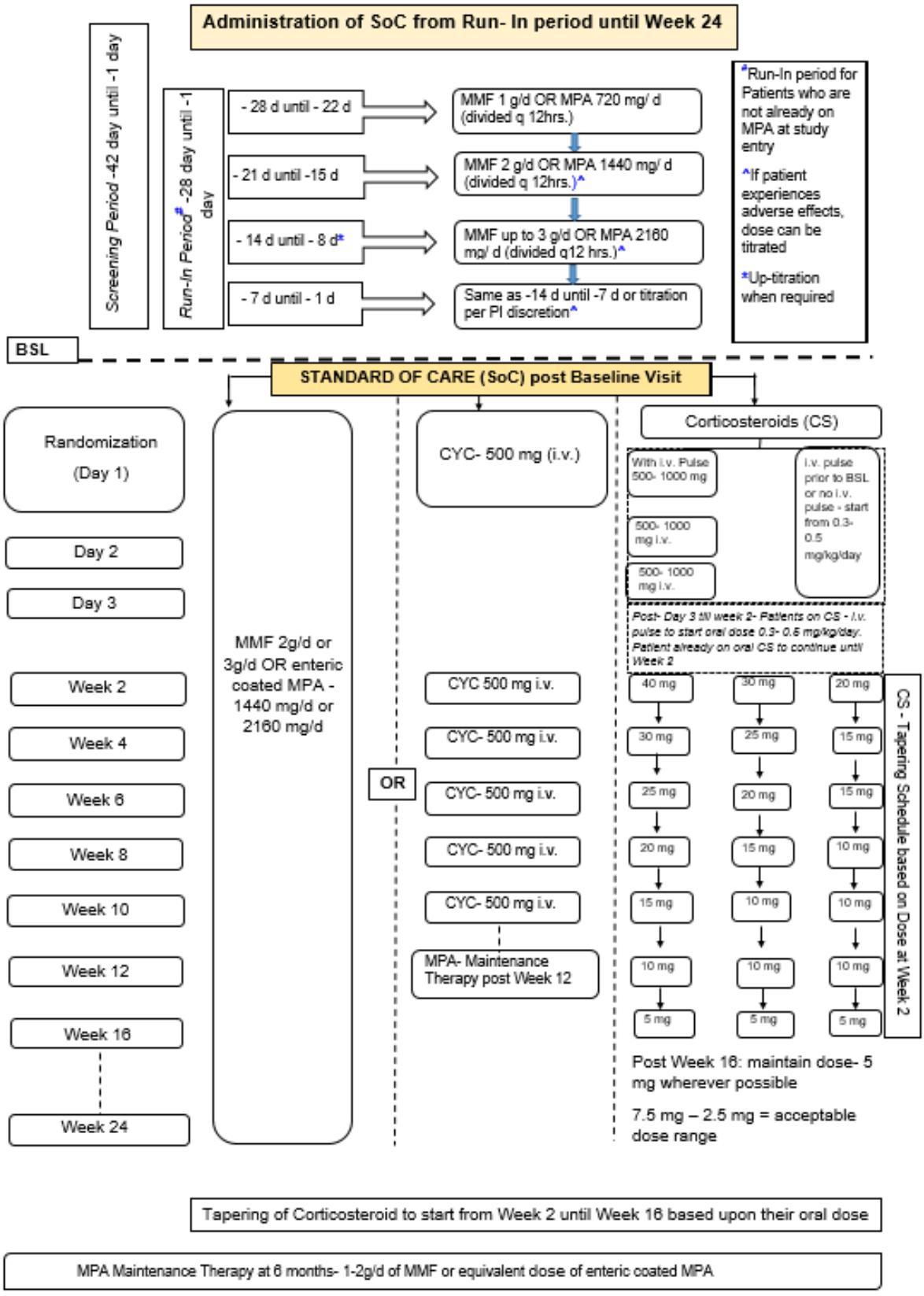
$\kappa = 0.7$ if female
$\kappa = 0.9$ if male

$\alpha = -0.329$ if female
$\alpha = -0.411$ if male

min = The minimum of Scr/κ or 1
max = The maximum of Scr/κ or 1

Scr = serum creatinine (mg/dL)

16.4 Recommended Diagram for administration of Standard of Care



16.5 Guidelines for administering PROs

All questionnaires will be completed on an electronic device at the scheduled study visit prior to the subject seeing the investigator for any clinical assessment or evaluation. The study coordinator should check the questionnaire for completeness and encourage the subject to complete any missing responses.

The subject should be made aware that completed measures are not reviewed by the investigator/study personnel.

Before trial begin

Study coordinators should familiarize themselves with the PRO questionnaires in the trial.

Before completion

1. Subjects should be provided with the correct questionnaire at the appropriate visits, and in the appropriate language
2. Subjects should be given sufficient instructions, space, time and privacy to complete the questionnaires
3. Questionnaire should be administered before the clinical examination

During completion

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

After completion

1. Check for completeness
2. Check for multiple responses that were made in error
3. Data should be transcribed from the completed questionnaire to the appropriate web portal

Addressing Problems and Concerns

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

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

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

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

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

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

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

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

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

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

Emphasize that all responses are to be kept confidential. Point out that their names do not appear anywhere on the questionnaire, so that their results will be linked with an ID number and not their name. Tell the subject that his/her answers will be pooled with other subjects' answers and that they will be analyzed as a group rather than as individuals. Tell the subject that completed forms are not routinely shared with treating staff, and that their responses will only be seen by you (to check for completeness), and possibly the investigator. Any response which may directly impact on or reflect their medical condition (e.g., noting of severe depression) will be communicated by the coordinator to the physician.

The patient asks the meaning of a question/item

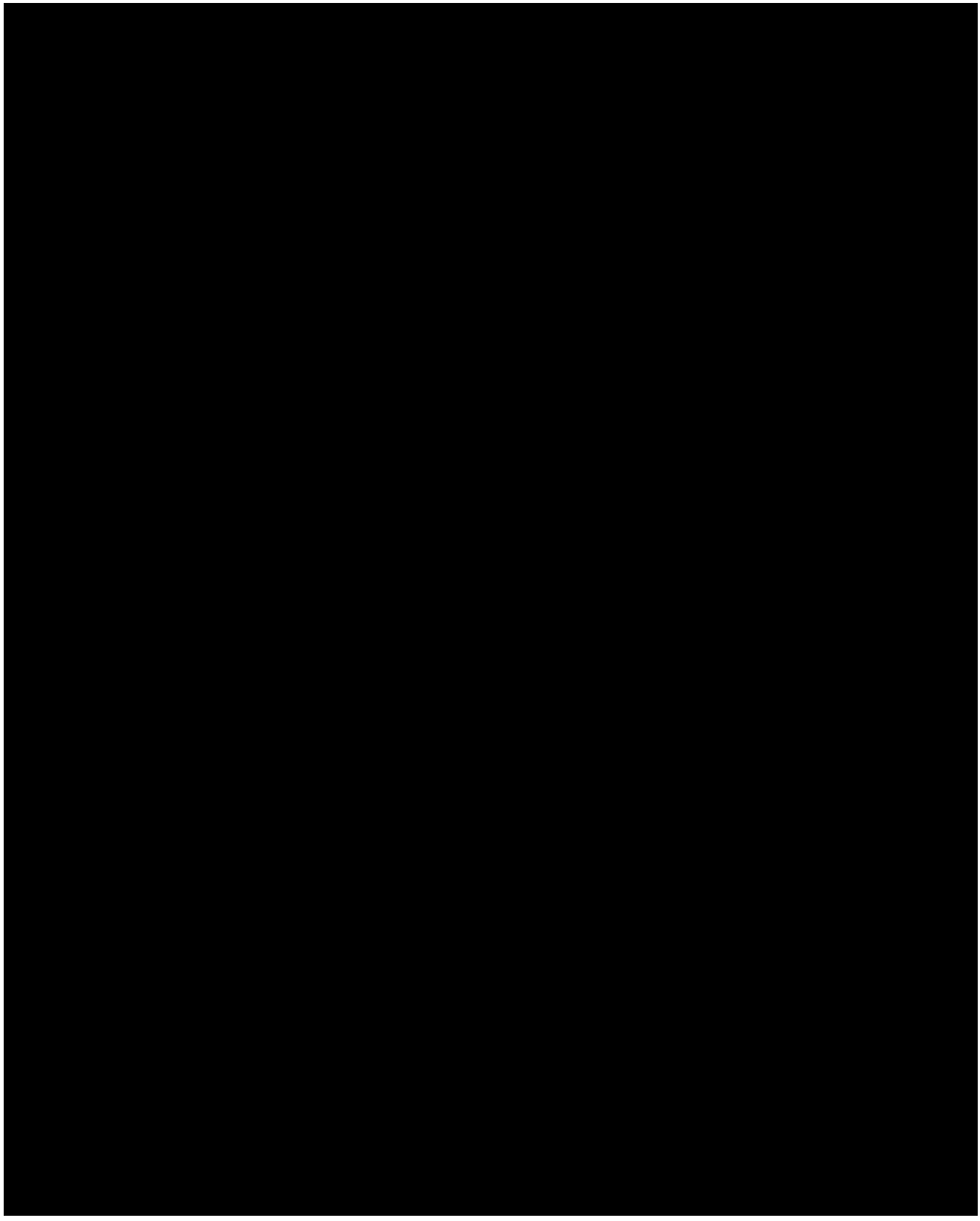
While completing the questionnaire, some subjects might ask the meaning of specific items so that they can better understand and respond. If this happens, assist the subject by rereading the question for them *verbatim.* If the subject asks to interpret the meaning of an item, do not try to explain it,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

General information about all questionnaire(s):

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

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

[redacted]



16.9 Liver event and Laboratory trigger Definitions and Follow-up Requirements

Table 16-1 Liver event and laboratory trigger definitions

	Definition/ threshold
LIVER LABORATORY TRIGGERS	3 x ULN < ALT / AST ≤ 5 x ULN
	1.5 x ULN < TBL ≤ 2 x ULN
LIVER EVENTS	ALT or AST > 5 × ULN
	ALP > 2 × ULN (in the absence of known bone pathology)
	TBL > 2 × ULN (in the absence of known Gilbert syndrome)
	ALT or AST > 3 × ULN and INR > 1.5
	Potential Hy's Law cases (defined as ALT or AST > 3 × ULN and TBL > 2 × ULN [mainly conjugated fraction] without notable increase in ALP to > 2 × ULN)
	Any clinical event of jaundice (or equivalent term)
	ALT or AST > 3 × ULN accompanied by (general) malaise, fatigue, abdominal pain, nausea, or vomiting, or rash with eosinophilia
	Any adverse event potentially indicative of a liver toxicity*

*These events cover the following: Hepatic failure, fibrosis and cirrhosis, and other liver damage-related conditions; the non-infectious hepatitis; the benign, malignant and unspecified liver neoplasms TBL: total bilirubin; ULN: upper limit of normal

Table 16-2 Follow up requirements for liver events and laboratory triggers

Criteria	Actions required	Follow-up monitoring
Potential Hy's Law case[a]	1. Discontinue the study treatment immediately 2. Hospitalize, if clinically appropriate 3. Establish causality 4. Record the AE and contributing factors (e.g., conmeds, med hx, lab) in the appropriate CRF	ALT, AST, TBL, Alb, PT/INR, ALP and GGT until resolution[c] (frequency at investigator discretion)
ALT or AST		
> 8 × ULN	1. Discontinue the study treatment immediately 2. Hospitalize if clinically appropriate 3. Establish causality 4. Record the AE and contributing factors (e.g., conmeds, med hx, lab) in the appropriate CRF	ALT, AST, TBL, Alb, PT/INR, ALP and GGT until resolution[c] (frequency at investigator discretion)
> 3 × ULN and INR > 1.5	1. Discontinue the study treatment immediately 2. Hospitalize, if clinically appropriate 3. Establish causality 4. Record the AE and contributing factors (e.g., conmeds, med hx, lab) in the appropriate CRF	ALT, AST, TBL, Alb, PT/INR, ALP and GGT until resolution[c] (frequency at investigator discretion)
> 5 to ≤ 8 × ULN	1. Repeat Liver function test (LFT) within 48 hours 2. If elevation persists, continue follow-up monitoring 3. If elevation persists for more than 2 weeks, discontinue the study drug 4. Establish causality 5. Record the AE and contributing factors (e.g., conmeds, med hx, lab) in the appropriate CRF	ALT, AST, TBL, Alb, PT/INR, ALP and GGT until resolution[c] (frequency at investigator discretion)

Criteria	Actions required	Follow-up monitoring
> 3 × ULN accompanied by symptoms[b]	1. Discontinue the study treatment immediately 2. Hospitalize if clinically appropriate 3. Establish causality 4. Record the AE and contributing factors (e.g., conmeds, med hx, lab) in the appropriate CRF	ALT, AST, TBL, Alb, PT/INR, ALP and GGT until resolution[c] (frequency at investigator discretion)
> 3 to ≤ 5 × ULN (patient is asymptomatic)	1. Repeat LFT within the next week 2. If elevation is confirmed, initiate close observation of the patient	Investigator discretion Monitor LFT within 1 to 4 weeks
ALP (isolated)		
> 2 × ULN (in the absence of known bone pathology)	1. Repeat LFT within 48 hours 2. If elevation persists, establish causality 3. Record the AE and contributing factors (e.g., conmeds, med hx, lab) in the appropriate CRF	Investigator discretion Monitor LFT within 1 to 4 weeks or at next visit
TBL (isolated)		
> 2 × ULN (in the absence of known Gilbert syndrome)	1. Repeat LFT within 48 hours 2. If elevation persists, discontinue the study drug immediately 3. Hospitalize if clinically appropriate 4. Establish causality 5. Record the AE and contributing factors (e.g., conmeds, med hx, lab) in the appropriate CRF	ALT, AST, TBL, Alb, PT/INR, ALP and GGT until resolution[c] (frequency at investigator discretion) Test for hemolysis (e.g., reticulocytes, haptoglobin, unconjugated [indirect] bilirubin)
> 1.5 to ≤ 2 × ULN (patient is asymptomatic)	1. Repeat LFT within the next week 2. If elevation is confirmed, initiate close observation of the patient	Investigator discretion Monitor LFT within 1 to 4 weeks or at next visit

Criteria	Actions required	Follow-up monitoring
Jaundice	1. Discontinue the study treatment immediately 2. Hospitalize the patient 3. Establish causality 4. Record the AE and contributing factors (e.g., conmeds, med hx, lab) in the appropriate CRF	ALT, AST, TBL, Alb, PT/INR, ALP and GGT until resolution[c] (frequency at investigator discretion)
Any AE potentially indicative of a liver toxicity*	1. Consider study treatment interruption or discontinuation 2. Hospitalization if clinically appropriate 3. Establish causality 4. Record the AE and contributing factors (e.g., conmeds, med hx, lab) in the appropriate CRF	Investigator discretion

[a]Elevated ALT/AST > 3 × ULN and TBL > 2 × ULN but without notable increase in ALP to > 2 × ULN
[b](General) malaise, fatigue, abdominal pain, nausea, or vomiting, or rash with eosinophilia
[c]Resolution is defined as an outcome of one of the following: (1) return to Baseline values, (2) stable values at three subsequent monitoring visits at least 2 weeks apart, (3) remain at elevated level after a maximum of 6 months, (4) liver transplantation, and (5) death.

Based on investigator's discretion investigation(s) for contributing factors for the liver event can include: Serology tests, imaging and pathology assessments, hepatologist's consultancy; obtaining more detailed history of symptoms and prior or concurrent diseases, history of concomitant drug use, exclusion of underlying liver disease.

16.10 Clinically notable laboratory values

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

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

Table 16-3 Safety Analyses: Expanded Limits and Notable Criteria

	Notable Criteria	
Laboratory Variable	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

HEMATOLOGY VARIABLES

Hemoglobin: 20 g/L decrease from Baseline

Platelet count: < 50 x 10E9/L

White blood cell count: < 0.8 x LLN

Neutrophils: < 0.9 x LLN