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Secukinumab (AIN457)

Clinical Trial Protocol CAIN457Q12301E1

A three-year, open-label extension study of subcutaneous secukinumab to evaluate the long-term efficacy, safety and tolerability in patients with active lupus nephritis

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List of abbreviations

ACE	Angiotensin-converting enzyme
ACR	American College of Rheumatology
AE	Adverse Event
ALP	Alkaline Phosphatase
ALT	Alanine Aminotransferase
aPTT	activated Partial Thromboplastin Time
ARBs	Angiotensin receptor blocker(s)
AST	Aspartate Aminotransferase
axSpA	Axial spondyloarthritis
BAFF	B-cell activating factor
BMI	Body Mass Index
CFR	Code of Federal Regulation
CHMP	Committee for Medicinal Products for Human Use
CKD	Chronic Kidney Disease
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
CMO&PS	Novartis Chief Medical Office and Patient Safety
CNIs	Calcineurin inhibitors
CO	Country Organization
CRA	Clinical Research Associate
CRF	Case Report/Record Form (paper or electronic)
CRO	Clinical Research Organization
CRR	Complete Renal Response
CS	Corticosteroid(s)
CSR	Clinical study report
CYC	Cyclophosphamide
DBP	Diastolic Blood Pressure
DLT	Dose Limiting Toxicity
DMC	Data Monitoring Committee
DNA	Deoxyribonucleic acid
dsDNA	double stranded DNA
ECG	Electrocardiogram
EDC	Electronic Data Capture
eGFR	estimated Glomerular Filtration Rate
EMA	European Medicines Agency
EOS	End of Study
EOT	End of Treatment
ERA-EDTA	European Renal Association – European Dialysis and Transplant Association
eSAE	Electronic Serious Adverse Event
eSource	Electronic Source
ESRD	End Stage Renal Disease
EU	European Union
EULAR	European League Against Rheumatism
F/U	Follow up
FAS	Full Analysis Set
FDA	Food and Drug Administration

FMV	First Morning Void
GCP	Good Clinical Practice
GCS	Global Clinical Supply
GGT	Gamma-glutamyl transferase
h	Hour
HbA1c	Hemoglobin A1c
HDL	High Density Lipoprotein
i.v.	intravenous
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use
IEC	Independent Ethics Committee
IFU	Instructions for Use
IgG1	Immunoglobulin G1
IL-17	Interleukin 17
IMP	Investigational Medicinal Product
IN	Investigator Notification
INR	International Normalized Ratio
IRB	Institutional Review Board
IRT	Interactive Response Technology
ISN	International Society of Neurology
IUD	Intrauterine device
IUS	Intrauterine system
kg	Kilogram
LDL	Low Density Lipoprotein
LFT	Liver function test
LLN	lower limit of normal
LN	Lupus Nephritis
MCV	Mean corpuscular volume
MedDRA	Medical dictionary for regulatory activities
mg	milligram(s)
mL	milliliter(s)
MMF	Mycophenolate Mofetil
MPA	Mycophenolic Acid
MRA	Magnetic resonance angiography
MUGA	Multiple gated acquisition
NSAIDs	Nonsteroidal Anti-Inflammatory Drug(s)
OHP	Off-site Healthcare Professional
p.o.	oral(ly)
PFS	Prefilled syringe
PRR	Partial Renal Response
PsA	Psoriatic arthritis
PsO	Psoriasis
PSW	Premature Participant/Subject Withdrawal
PT	prothrombin time
PY	Patient Year

QMS	Quality Management System
QTcF	QT interval corrected by Fridericia's formula
R Value	ALT/ALP x ULN
RBC	Red Blood Cell(s)
RPS	Renal Pathology Society
s.c.	subcutaneous
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SBP	Systolic Blood Pressure
SD	standard deviation
SGOT	Serum Glutamic Oxaloacetic Transaminase
SGPT	Serum Glutamic Pyruvic Transaminase
SLE	Systemic Lupus Erythematosus
SoC	Standard of Care
SOP	standard operating procedure
SUSAR	Suspected Unexpected Serious Adverse Reaction
TBL	Total bilirubin
TD	Treatment Discontinuation
TEAE	Treatment-emergent adverse event
TH17	T helper type 17
[redacted]	[redacted]
ULN	upper limit of normal
UPCR	Urine Protein-to-Creatinine Ratio
WBC	White Blood Cell(s)
WHO	World Health Organization
WoC	Withdrawal of Consent
β-hCG	β-subunit of human chorionic gonadotropin

Glossary of terms

Additional treatment	Medicinal products that may be used during the clinical trial as described in the protocol, but not as an investigational medicinal product (e.g. any background therapy)
Assessment	A procedure used to generate data required by the study
Biologic Samples	A biological specimen including, for example, blood (plasma, serum), saliva, tissue, urine, stool, etc. taken from a study participant
Clinical Trial Team	A group of people responsible for the planning, execution and reporting of all clinical trial activities. Examples of team members include the Study Lead, Medical Monitor, Trial Statistician etc.
Coded Data	Personal Data which has been de-identified by the investigative center team by replacing personal identifiers with a code.
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 (active or placebo) used as a comparator to reduce assessment bias, preserve blinding of investigational drug, assess internal study validity, and/or evaluate comparative effects of the investigational drug
Cycles	Number and timing or recommended repetitions of therapy are usually expressed as number of days (e.g., q28 days)
Discontinuation from study	Point/time when the participant permanently stops receiving the study treatment and further protocol required assessments or follow-up, for any reason. No specific request is made to stop the use of their samples or data.
Discontinuation from study treatment	Point/time when the participant permanently stops receiving the study treatment for any reason (prior to the planned completion of study drug administration, if any). Participant agrees to the other protocol required assessments including follow-up. No specific request is made to stop the use of their samples or data.
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)
Electronic Data Capture (EDC)	Electronic data capture (EDC) is the electronic acquisition of clinical study data using data collection systems, such as Web-based applications, interactive voice response systems and clinical laboratory interfaces. EDC includes the use of Electronic Case Report Forms (eCRFs) which are used to capture data transcribed from source data/documents used at the point of care
End of the clinical trial	The end of the clinical trial is defined as the last visit of the last participant
Enrollment	Point/time of participant entry into the study at which informed consent must be obtained. The action of enrolling one or more participants
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/ treatment	The drug whose properties are being tested in the study
Medication number	A unique identifier on the label of medication kits
Off-site	Describes trial activities that are performed at remote location by an off-site healthcare professional, such as procedures performed at the participant's home.
Off-site healthcare Professional (OHP)	A qualified healthcare professional, such as include those used in the study e.g. Nurse, Phlebotomist, Physician, who performs certain protocol procedures for the participant in an off-site location such as a participant's home.

Other treatment	Treatment that may be needed/allowed during the conduct of the study (i.e., concomitant or rescue therapy)
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
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	The subdivisions of the trial design (e.g., Screening, Treatment, Follow-up) which are described in the Protocol. Periods define the study phases and will be used in clinical trial database setup and eventually in analysis
Personal data	Participant information collected by the Investigator that is coded and transferred to Novartis for the purpose of the clinical trial. This data includes participant identifier information, study information and biological samples.
Randomization	The process of assigning trial participants to investigational drug or control/comparator drug using an element of chance to determine the assignments in order to reduce bias.
Randomization number	A unique identifier assigned to each randomized participant
Remote	Describes any trial activities performed at a location that is not the investigative site where the investigator will conduct the trial, but is for example a home or another appropriate location
Screen Failure	A participant who did not meet one or more criteria that were required for participation in the study
Source Data/Document	Source data refers to the initial record, document, or primary location from where data comes. The data source can be a database, a dataset, a spreadsheet or even hard-coded data, such as paper or eSource
Start of the clinical trial	The start of the clinical trial is defined as the signature of the informed consent by the first participant
Study treatment	Any drug or combination of drugs or intervention administered to the study participants as part of the required study procedures; includes investigational drug(s), control(s) or background therapy
Treatment arm/group	A treatment arm/group defines the dose and regimen or the combination and may consist of 1 or more cohorts.
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 study consent (WoC) / Opposition to use of data /biological samples	Withdrawal of consent from the study occurs when the participant explicitly requests to stop 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 in writing (depending on local regulations) and recorded in the source documentation. Opposition to use data/biological samples occurs in the countries where collection and processing of personal data is justified by a different legal reason than consent.

Protocol summary

Protocol number	CAIN457Q12301E1
Full Title	A three-year, open-label extension study of subcutaneous secukinumab to evaluate the long-term efficacy, safety and tolerability in patients with active lupus nephritis
Brief title	Open-label extension study of efficacy, safety and tolerability of secukinumab in patients with active lupus nephritis
Sponsor and Clinical Phase	Novartis, Phase III
Investigation type	Biological
Study type	Interventional
Purpose	The purpose is to provide treatment with secukinumab delivered subcutaneously (s.c.) via pre-filled syringe (PFS) for participants who complete study treatment until the Week 104 of the core study and to obtain long term efficacy, safety and tolerability data
Primary Objective(s)	The primary objective is to assess long-term efficacy of secukinumab with respect to Complete Renal Response (CRR) over time up to Week 260 in adult participants with Lupus Nephritis (ISN/RPS Class III or IV, with or without co-existing class V features) on background SoC therapy
[redacted]	[redacted]
Study design	A multicenter, open-label, extension study of s.c. secukinumab to evaluate long-term efficacy, safety and tolerability up to three years in patients with Lupus Nephritis
Rationale	This three-year open-label extension study will offer continuous secukinumab therapy to eligible participants from the core study CAIN457Q12301 and will provide long-term efficacy and safety data. The proposal to continue treatment with subcutaneous (s.c.) doses of 300 mg administered every four weeks, is based on the need for long-term treatment exposure in participants suffering from a chronic illness such as LN with relapsing and remitting course. The regular assessments of disease activity would ensure that participants who are experiencing worsening of disease can exit the study upon their own decision or based on the advice of the investigator at any time.
Study population	The study population will consist of male and female participants aged from 18 to 75 years (at time of Core Study Screening) who were diagnosed with active LN-World Health Organization (WHO) or International Society of Nephrology/Renal Pathology Society (ISN/RPS) Class III or IV [excluding III (C), IV-S (C) and IV-G (C)], with or without co-existing class V features at SCREENING in the core study CAIN457Q12301, and who have completed the entire treatment period up to and including Week 104 of the core study.
Key Inclusion criteria	● Participant must have both participated in core study and completed the entire treatment period up to and including Week 104 of the core study CAIN457Q12301. ● Participant must be deemed by the investigator to benefit from secukinumab therapy. ● Signed informed consent must be obtained prior to participation in the study
Key Exclusion criteria	● Any participant taking other concomitant biologic immunomodulating agent(s) except secukinumab. ● Pregnant or nursing (lactating) women, where pregnancy is defined as the state of a female after conception and until the termination of gestation, confirmed by a positive human chorionic gonadotropin (hCG)laboratory test. ● Women of 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 methods of contraception are recommended due to the known teratogenic effect of SoC (MPA)
Study treatment	Secukinumab 300 mg solution for s.c. injection in a 2mL Pre-Filled Syringe (PFS)

Treatment of interest	Secukinumab 300 mg every 4 weeks along with Standard of Care (MPA and low dose corticosteroids)
Efficacy assessments	CRR is a composite endpoint based on: ● estimated Glomerular Filtration Rate (eGFR) ● Urine Protein-to-Creatinine Ratio (UPCR)
Key safety assessments	Adverse events/Serious adverse events Laboratory evaluations Physical Examination Vital Signs Weight Pregnancy test Tolerability of secukinumab
Data analysis	All data will be summarized descriptively for all participants by core study treatment groups in Full Analysis Set. Summary statistics for continuous variables will generally include the number of subjects (N), mean, standard deviation (SD), median, minimum and maximum. For categorical or binary variables, the frequency and percent of subjects in each category will be presented. All details of statistical analyses will be specified in Statistical Analysis Plan (SAP).
Key words	Lupus Nephritis, secukinumab (AIN457), estimated glomerular filtration rate (eGFR), Urine Protein-to-Creatinine Ratio (UPCR), Standard of care (SoC) background therapy

1 Introduction

1.1 Background

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

Immune complex formation in LN is related to a plethora of autoantibodies, especially anti-double stranded deoxyribonucleic acid (dsDNA) and -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 interleukin 17 (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 six 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 antimalarials 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.

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 (Faurschou et al 2010, Tektonidou et al 2016). In addition, current immunosuppressive therapies carry substantial infectious as well as other mid/long-term toxicity risks. Despite recent advances in treatment for LN, including two recent approvals of belimumab [intravenous (i.v.) and subcutaneous (s.c.)], a B-cell activating factor (BAFF) inhibitor and voclosporin

(p.o.), a calcineurin inhibitor, it continues to remain a major cause of morbidity and mortality (Furie et al 2020, Rovin et al 2021).

The European League Against Rheumatism/European Renal Association – European Dialysis and Transplant Association (EULAR/ERA-EDTA) and American College of Rheumatology (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 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 30% 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.

In addition to animal models, 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 (Crispín et al 2008, Zhang et al 2009). 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 et al 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.

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.

A recent case report of a childbearing age women with SLE, who developed refractory LN despite all indicated therapeutic options, reported that treatment with IL-17A inhibitor secukinumab showed improvement in clinical and biological features and complete renal response was achieved Costa R et al 2021.

Secukinumab is a recombinant high-affinity fully human monoclonal anti-human IL-17A antibody of the Immunoglobulin G1 (IgG1)/kappa isotype. The product is indicated in Psoriasis

(PsO), Axial Spondyloarthritis (axSpA) and Psoriatic Arthritis (PsA) and has shown to offer 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 axSpA, supporting its long-term use in these chronic inflammatory conditions.

Participants from the core trial CAIN457Q12301 study can participate in this optional open-label extension study as described in Section 1.2. The total duration of the extension study is estimated to last about three years providing up to five years of total treatment exposure including core study CAIN457Q12301.

1.2 Purpose

This study is an up to three-year open-label extension study to the core study CAIN457Q12301 (a two-year, phase III study that enrolled participants aged 18 to 75 years with active Lupus Nephritis). The aim is to provide treatment with secukinumab delivered subcutaneously (s.c.) via pre-filled syringe (PFS) for participants who complete study treatment until the Week 104 of the core study and opt to continue in to the extension study and to obtain further long-term efficacy, safety and tolerability information.

Background SoC will consist of maintenance 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) and oral corticosteroids at the minimal dose (could be zero) required by the participant's status to maintain response.

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, endpoints and estimands

Table 2-1 Objectives and related endpoints

Objective(s)	Endpoint(s)
Primary objective(s)	**Endpoint(s) for primary objective(s)**
● To assess the long-term efficacy of secukinumab with respect to CRR over time up to Week 260 in adults with Lupus Nephritis (ISN/RPS class III or IV, with or without co-existing class V features) participant on background of SoC therapy	● Proportion of participants achieving CRR CRR is a composite endpoint defined as: ● Normal estimated Glomerular Filtration Rate (eGFR) or no less than 85% of core Baseline values and ● 24-hour Urine-to-Protein Creatinine Ratio (UPCR) ≤ 0.5mg/mg
[redacted]	

2.1 Primary estimands

The estimand is the precise description of the treatment effect and reflects strategies to address events occurring during trial conduct which could impact the interpretation of the trial results (e.g., premature discontinuation of treatment).

The attributes of the estimand are:

- Population: All participants who completed secukinumab 300 mg up to Week 104 in core study and satisfy the inclusion/exclusion criteria to reflect the targeted LN population
- Variable: Complete renal response up to Week 260
- Treatment of interest: secukinumab 300 mg every four weeks and with low dose steroids
- Remaining intercurrent events: Treatment discontinuation/rescue treatment: composite (non-responder)
- Population level summary: Proportion of responders summarized over time.

2.2 Secondary estimands

Not applicable

3 Study design

A multicenter, optional, open-label, extension study of s.c. secukinumab to evaluate the long-term efficacy, safety and tolerability up to three years in patients with lupus nephritis.

The aim of this three-year extension study is to provide treatment with secukinumab for participants who complete core study treatment in CAIN457Q12301 and to obtain further long-term efficacy, safety and tolerability information.

Investigators will use their clinical judgement to decide if it might be beneficial, in terms of overall improvement and response to therapy, for participants to enter the extension study. The total combined duration for the core study and this extension study is five years.

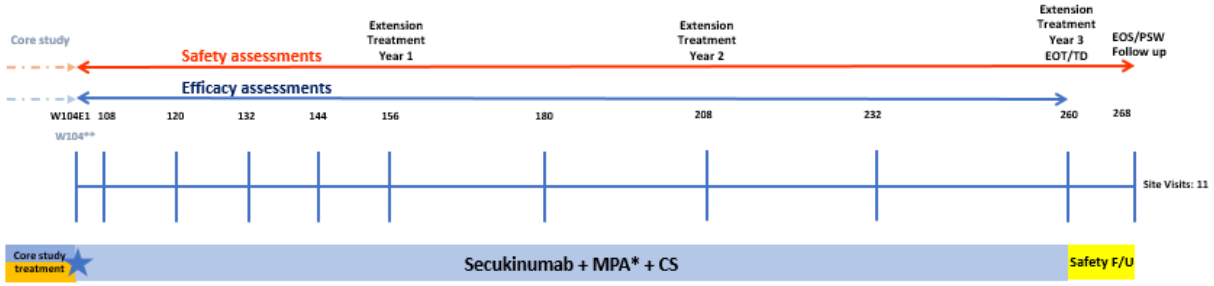
At Week 104 of the core study CAIN457Q12301, eligible participants will complete the assessments associated with the core study visit and will subsequently continue in the extension study on the dose of secukinumab 300 mg administered every four weeks.

Of note, as this is an extension study, Baseline always refers to the core study CAIN457Q12301 Baseline.

An outline of study design is presented in Figure 3-1 and a detailed visit and assessment schedule in Table 8-1.

Additional unscheduled follow-up visits in person and/or by phone may be performed as per investigator's clinical judgement.

Figure 3-1 Study Design



EOT: End Of treatment
TD: Treatment Discontinuation
EOS: End Of Study
PSW: Premature Participant/Subject Withdrawal
F/U: Follow up

4 Rationale

4.1 Rationale for study design

This three-year open-label extension study will offer continuous secukinumab therapy to eligible participants from the core study CAIN457Q12301 and will provide long-term efficacy and safety data. The regular assessments of disease activity would ensure that participants who are experiencing worsening of disease can exit the study upon their own decision or based on the advice of the investigator at any time.

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 maintenance therapy for participants 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).

SoC background regimen will consist of MPA along with oral corticosteroids at the minimum dose (could be zero) required by the participant status to maintain response and shall not exceed >7.5 mg/day (prednisone or equivalent).

4.2 Rationale for dose/regimen and duration of treatment

The doses and regimen selected for the core study CAIN457Q12301 are projected to deliver efficacy while at the same time ensuring participant safety.

The proposal to continue treatment with subcutaneous (s.c.) doses of 300 mg administered every four weeks, is based on the need for long-term treatment exposure in participants suffering from a chronic illness such as LN with relapsing and remitting course.

Subcutaneous injection through PFS offers the option of self-administration by the participant and is likely to provide a better treatment experience and added convenience. Participants with chronic diseases who are able to self-inject their medication gain control of their treatment schedule and their treatment setting, thus allowing greater independence, better adherence, improved therapeutic outcomes and freedom in their social, domestic, and professional lives, which can result in economic benefits to both participants and the healthcare system (Kivitz et al 2006, Chilton and Collett 2008). Self-injection may also offer psychological benefits over administration by healthcare professionals, including improved self-esteem Hamm R et al 2000.

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

There is no placebo control group or active comparator in this study given the purpose and main objectives.

4.4 Purpose and timing of interim analyses/design adaptations

Interim analyses may be performed for purposes of publication and/or to support health authority interactions, as necessary.

4.5 Risks and benefits

To date, belimumab and voclosporin are two recently approved drugs 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 nephritis, 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, axSpA 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.

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.

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 Data Monitoring Committee (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

During a Public Health emergency as declared by Local or Regional authorities i.e. pandemic, epidemic or natural disaster, mitigation procedures to ensure participant safety and trial integrity are listed in relevant sections. 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 Study Population

The study population will consist of male and female participants aged from 18 to 75 years who were diagnosed with active LN-World Health Organization (WHO) or ISN/RPS Class III or IV [excluding III (C), IV-S (C) and IV-G (C)], with or without co-existing class V features

at SCREENING in the core study CAIN457Q12301, and who have completed the entire treatment period up to and including Week 104 of the core study.

5.1 Inclusion criteria

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

1. Participant must have both participated in core study and completed the entire treatment period up to and including Week 104 of the core study CAIN457Q12301.
2. Participant must be deemed by the investigator to benefit from secukinumab therapy.
3. Signed informed consent must be obtained prior to participation in the study.

5.2 Exclusion criteria

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

1. Any participant taking other concomitant biologic immunomodulating agent(s) except secukinumab.
2. Pregnant or nursing (lactating) women, where pregnancy is defined as the state of a female after conception and until the termination of gestation, confirmed by a positive hCG laboratory test.
3. 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 methods are recommended due to the known teratogenic effect of SoC (MPA).

   Highly effective contraception methods include:

   - Total abstinence, when this 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. In case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow-up hormone level assessment
   - Male sterilization (at least 6 months prior to screening). For female participants on the study, the vasectomized male partner should be the sole partner for that participant
   - 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 of childbearing potential should have been stable on the same pill for a minimum of 3 months before taking study treatment.

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 maintenance standard of care medications, they must be followed.

Note: Women are considered post-menopausal if they have had 12 months of natural (spontaneous) amenorrhea with an appropriate clinical profile (e.g., age appropriate, history of vasomotor symptoms). Women are considered not of child bearing potential if they are post-menopausal or have had surgical bilateral oophorectomy (with or without hysterectomy), total hysterectomy or tubal ligation at least six weeks ago. In the case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow-up hormone level assessment is she considered not of child bearing potential.

6 Treatment

6.1 Study treatment

Before enrollment in this extension study, all participants electing to continue will sign an ICF.

Detailed instructions, based on the Instructions for Use (IFU), for self-administration of the s.c. injection using the PFS formulation will be provided to each participant. Each injection will be administered into an appropriate injection site of the body. For the first visit at Week 104E1, s.c. administration will be performed at site under the supervision of the site staff. Starting from Week 112, participants will have the choice of self-administration at home or continuing with administration at site, based on personal preference and the investigator's clinical judgment. Site staff will administer the injection to participants who are not able or feel insecure to self-administer the PFS injection.

At Week 104, all eligible participants from the core study can opt to be enrolled in the extension study via Interactive Response Technology (IRT) and will receive secukinumab dosing, 300 mg every four weeks until Week 256. The Week 104E1 will be performed on the same day once the participant completes Week 104 of the core study.

The investigator or his/her delegate will contact the IRT after confirming that the participant fulfills all the inclusion/exclusion criteria. The IRT will then specify a unique medication number for the first package of investigational treatment to be dispensed to the participant for Week 104E1.

6.1.1 Investigational and control drugs

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

Table 6-1 Investigational drug and Control drug

Investigational (Name and Strength)	Pharmaceutical Dosage Form	Route of Administration	Presentation	Sponsor (global or local)
AIN457300 mg /2mL	Solution for injection in pre-filled syringe	Subcutaneous use	Open label prefilled syringes (PFS)	Novartis Pharma AG

The PFSs are packed in an open-label 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 two-part label. A unique medication number is printed on each part of this label.

The study treatments will be labeled as follows: AIN457 300mg/2mL.

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 maintenance therapy.

Background SoC medications will **not** be provided by Novartis GCS and must be handled at the country level. Oral doses of MPA or corticosteroids will be taken by the participant at home.

Table 6-2 Background therapy

Name of medication	Dosage form	Route of administration	Availability
MMF/MPA	Tablet	Oral	Open-label participant packs
Corticosteroids	Tablets	Oral	Open-label participant packs

6.1.3.1 Maintenance therapy

The participants shall continue the same dose of MPA as administered in the core study. 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.

Oral corticosteroids shall continue at the minimum dose (could be zero) required by the participant status to maintain response and shall not exceed >7.5 mg/day (prednisone or equivalent).

6.1.4 Treatment arms/group

All participants will be treated with open label secukinumab 300 mg every four weeks until Week 256.

6.1.5 Treatment duration

The total duration of the extension study is estimated to last up to three years, providing up to five years of total treatment exposure including core study CAIN457Q12301.

Participants may be discontinued from treatment earlier due to unacceptable toxicity, disease progression and/or treatment is discontinued at the discretion of the investigator or the participant, or if the clinical trial is discontinued for any reason. Participants who the investigator believes will continue to receive benefit from treatment may also have post-trial access until secukinumab is available for LN following product launch/subsequent reimbursement (where applicable), or treatment discontinuation, or the benefit-risk profile is no longer positive.

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 Forms (CRFs).

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 allowing a new medication to be started or to determine if the participant 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 if prescribed in the core 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 electronic Case Report Form (eCRF) at every visit, including the dose changes when appropriate.

Anti-malarial medications

Concomitant treatment with anti-malarial (e.g., hydroxychloroquine) will continue if prescribed in the core study and will be recorded in the eCRF.

Anti-hypertensive medications

Participants already taking angiotensin-converting enzyme (ACE) inhibitors or angiotensin receptor blockers (ARBs) in the core study 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.

Cholesterol-lowering drugs

Concomitant treatment with cholesterol-lowering drugs (e.g., statins) will continue if prescribed in the core 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 not be used during the trial with the following exceptions:

- treatment of pleuritis and pericarditis if deemed necessary by the Investigator.
- treatment of arthritis pain that is unresponsive to other treatment modalities (e.g., analgesics, intra-articular steroid treatment)

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) in the core study are allowed to start these medications, at the investigator's discretion (see ACR Ad Hoc Committee 2001).

Other Permitted Therapy

Low dose aspirin for cardioprotection may be used at Investigator's discretion.

Participants who use oral contraceptives or hormone-replacement therapy should continue their use.

All other concomitant medications deemed necessary will be reviewed by the Investigator in consultation with the Novartis Clinical Team 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 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 cyclophosphamide, CNI, rituximab and belimumab therapy
- Use of any other systemic biologic/non-biologic immunomodulatory treatment
- Administration of live vaccines
- Any investigational treatment or participation in any interventional trial.

6.2.3 Rescue medication

Rescue medication is defined as any new medication used because the participant's disease is not adequately controlled by secukinumab 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 medication 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.

If study investigational treatment is discontinued, participants may take study prohibited medication under the Investigator's guidance and as per locally approved prescribing information.

Participant will be discontinued from the study and complete Week 260/End of Treatment (EOT) visit if treated with prohibited medications (as described in Section 6.2.2) and should complete the End of Treatment (EOT) visit at the earliest possible time point and enter the Post-treatment follow-up period.

A follow-up visit is to be done 12 weeks after last study treatment administration for all participants, regardless of whether they complete the entire study as planned or discontinue prematurely.

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

6.3 Preparation and dispensation

Each study site will be supplied with study drug in packaging as described under investigational section.

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.

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, delivery of investigational medicinal product (IMP) directly to a participant's home may be permitted (if allowed by Local or Regional Health Authorities and Ethics Committees as appropriate) in the event the Investigator has decided that an on-site visit by the participant is no longer appropriate or possible, and that it is in the interest of the participant's health to administer the study treatment even without performing an on-site visit. The dispatch of IMP from the site to the participant's home remains under the accountability of the Investigator. Each shipment/provisioning will be for a maximum of 24 weeks supply. In this case, regular phone calls or virtual contacts (every four weeks or more frequently if needed) will occur between the site and the participant for instructional purposes, safety monitoring, investigation of any adverse events, ensuring participants continue to benefit from treatment, and discussion of the participant's health status until the participants can resume visits at the study site.

6.3.1 Handling of study treatment and other treatment

6.3.1.1 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.

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 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.

If the participant will be self-administering treatment at home, the investigator should ensure the participants can store the medication according to these conditions before allowing the participant to self-administer at home.

If required for certain participants, treatment might be administered at home by an off-site healthcare professional (OHP).

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 field monitors during site or remote monitoring visits, and at the completion of the trial.

If study treatment is administered at home, participants will be asked to return all unused study treatment and packaging at the next site visit, at the end of the study or at the time of discontinuation of study treatment.

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. If participant chooses the abdomen, a two-inch (5 cm) 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.

The site may destroy and document destruction of unused study treatment, drug labels and packaging as appropriate in compliance with site processes, monitoring processes and per local regulation/guidelines, and after approval by the Novartis Clinical Team. Otherwise, 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.

The treatment for remote administration might be handled by off-site healthcare provider such as off-site research nurse, in line with the IFU.

6.3.1.2 Handling of other treatment

The following non-study treatment has to 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-malarial medications, ACE inhibitors or ARBs.

6.4 Participant numbering, treatment assignment, randomization

6.4.1 Participant numbering

This being an extension study, the participant numbers will remain same as that of core study CAIN457Q12301, new numbers will **not** be assigned.

Each participant is identified in the study by a Participant Number (Participant No.), that is assigned when the participant is first enrolled in the core study CAIN457Q12301 and is retained for the participant throughout his/her participation in the trial. The Participant No. consists of

the Center Number (Center No.) (as assigned by Novartis to the investigative site) with the sequential participant number suffixed to it assigned in the core study, so that each participant's participation is numbered uniquely across the entire database.

6.4.2 Treatment assignment, randomization

At visit Week 104E1, all eligible participants from core study CAIN457Q12301 will be enrolled via Interactive Response Technology (IRT). The investigator or his/her delegate will contact the IRT after confirming that the participant fulfills all the inclusion/exclusion criteria. The IRT will specify a unique medication number for the first package of study treatment to be dispensed to the participant.

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 assignment of medication numbers to packs containing the study treatment.

6.5 Treatment blinding

There is no treatment blinding in this study. Participants, investigator staff and persons performing the assessments will remain blinded to the identity of the treatment that participants were randomized to within the core study CAIN457Q12301 from the time of enrollment in the extension study until the final database lock of the core study.

6.6 Dose escalation and dose modification

While no study treatment dose adjustments are permitted, interruptions are allowed as described below in Section 6.6.2.

6.6.1 Definitions of dose limiting toxicities (DLTs)

Not applicable.

6.6.2 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 CRF.

6.6.3 Follow-up for toxicities

Participants whose treatment is interrupted or permanently discontinued due to an adverse event or clinically significant laboratory value, must be followed up in accordance with what is clinically indicated per the investigator until resolution or stabilization of the event. Appropriate clinical experts such as ophthalmologist, endocrinologist, dermatologist, psychiatrists, etc., should be consulted as deemed necessary. All participants must be followed up for adverse events and serious adverse events for 84 days following the last dose of study treatment.

6.7 Additional treatment guidance

6.7.1 Treatment compliance

The first study treatment administration will occur at the Week 104E1 visit only after eligibility criteria have been confirmed, all study assessments have been performed, and the scheduled blood samples have been drawn.

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

6.7.1.1 Study treatment compliance

Compliance is expected to be 100% unless temporary interruption is needed for safety reasons as described in Section 6.6.3.

For home administration, the investigator must promote compliance by instructing the participant to take the study 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 study treatment as prescribed. Compliance will be assessed by the investigator and/or study personnel at each visit checking the Participant Dosing Record, unused syringes with boxes and empty syringe boxes and reviewing information provided by the participant.

Detailed instructions, based on the Participant Instructions for Home Administration, for self-administration at home of the s.c. injection using the PFS formulation will be provided to each participant. This information should be captured in the source document at each visit.

All study treatment dispensed and returned must be recorded in the Drug Accountability Log.

6.7.1.2 Standard of care treatment compliance

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

Doses administered and dates (MPA/Corticosteroids) should be recorded on the appropriate eCRF pages.

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.

6.7.2 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.

At present there is insufficient information to provide specific recommendations regarding treatment of adverse events (AEs).

Medication used to treat adverse events (AEs) must be recorded on the appropriate CRF.

6.7.3 Emergency breaking of assigned treatment code

Not applicable

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)/Independent Ethics Committee (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 level of 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 source documents.

Novartis will provide to investigators in a separate document a proposed informed consent form that complies with the International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use (ICH) E6 Good Clinical Practice (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 treatment 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.

The following informed consents are included in this study:

- Main study consent, which also included:
  - A subsection that requires a separate signature for the ‘Optional Consent for Additional Research’ to allow future research on data/samples collected during this study
- As applicable, Pregnancy Outcomes Reporting Consent for female participants t

Women of child bearing potential must be informed that taking the study treatment may involve unknown risks to the fetus if pregnancy were to occur during the study and agree that in order to participate in the study they must adhere to the contraception requirements.

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

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 may challenge the ability to obtain a standard written informed consent due to limits that prevent an on-site visit, Investigator may conduct the informed consent discussion remotely (e.g. telephone, videoconference) if allowable by a local Health Authority.

Guidance issued by local regulatory bodies on this aspect prevail and must be implemented and appropriately documented (e.g., the presence of an impartial witness, sign/dating separate ICFs by trial participant and person obtaining informed consent, etc.).

8 Visit schedule and assessments

The 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 Table 8-1 or as close to the designated day/time as possible. Missed or rescheduled visits should not lead to automatic discontinuation.

Participants who discontinue from study treatment are to return for the end of treatment visit as soon as possible and attend the follow-up visits as indicated in the Assessment Schedule.

Participants who discontinue from study or withdraw their consent/oppose the use of their data/biological samples should be scheduled for a final evaluation visit if they agree, as soon as possible, at which time all assessments listed for the final visit will be performed. At this final visit, all dispensed investigational product should be reconciled, and the adverse event and concomitant medications not previously reported must be recorded on the CRF.

The "X" in the table denotes the assessments to be recorded in the clinical database or received electronically from a vendor. The "S" in the table denotes the assessments that are only in the participant's source documentation and do not need to be recorded in the clinical database.

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, alternative methods of providing continuing care may be implemented by the investigator as the situation dictates. If allowable by a local Health Authority and depending on operational capabilities, phone calls, virtual contacts (e.g., tele consult) or visits by site staff/ home nursing staff to the participant´s home, can replace on-site study visits, for the duration of the disruption until it is safe for the participant to visit the site again.

Table 8-1 Assessment Schedule

Period	Extension Treatment Year 1													
Visit Name	**W104E1**	**W108**	**W112**	**W116**	**W120**	**W124**	**W128**	**W132**	**W136**	**W140**	**W144**	**W148**	**W152**	**W156**
Visit Numbers[1]	**100**	**110**	**120**	**130**	**140**	**150**	**160**	**170**	**180**	**190**	**200**	**210**	**220**	**230**
Days	**0**	**28**	**56**	**84**	**112**	**140**	**168**	**196**	**224**	**252**	**280**	**308**	**336**	**364**
Informed consent	X													
Inclusion / Exclusion criteria	X													
Participant details entry in extension database	X													
Site Visit (mandatory)	X	X			X			X			X			X
Study Drug Administration at site[2]	X	X			X			X			X			X
Study Drug Administration at home[2,3]			X	X		X	X		X	X		X	X	
Standard of Care administration	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant medications/non-drug therapies	Update as necessary													
Physical Examination		S			S			S			S			S
Vital Signs		X			X			X			X			X
Body Weight[9]		X			X			X			X			X
12-Lead ECG (local)	X													
Hematology		X			X			X			X			X
Clinical Chemistry		X			X			X			X			X
Coagulation Panel		X			X			X			X			X
Fasting lipid panel[4]		X			X			X			X			X
24-hr urine collection (UPCR[redacted])								X[5]						X[5]
FMV urine collection (central/local assessments)[6]		X			X			X			X			X
Pregnancy test (urine)[7]		S	S	S	S	S	S	S	S	S	S	S	S	S
Adverse Events[8]	Update as necessary													

Period	**Extension Treatment Year 2**												
Visit Name	**W160**	**W164**	**W168**	**W172**	**W176**	**W180**	**W184**	**W188**	**W192**	**W196**	**W200**	**W204**	**W208**
Visit Numbers[1]	**240**	**250**	**260**	**270**	**280**	**290**	**300**	**310**	**320**	**330**	**340**	**350**	**360**
Days	**392**	**420**	**448**	**476**	**504**	**532**	**560**	**588**	**616**	**644**	**672**	**700**	**728**
Site Visit (mandatory)						X							X
Study Drug Administration at site[2]						X							X
Study Drug Administration at home[2,3]	X	X	X	X	X		X	X	X	X	X	X	
Standard of Care administration	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant medications/non-drug therapies	Update as necessary												
Physical Examination						S							S
Vital Signs						X							X
Body Weight[9]						X							X
Hematology						X							X
Clinical Chemistry						X							X
Coagulation Panel						X							X
Fasting lipid panel[4]						X							X
24-hr urine collection (UPCR[redacted])						X[5]							X[5]
FMV urine collection (central/local assessments)[6]						X							X
Pregnancy test (urine)[7]	S	S	S	S	S	S	S	S	S	S	S	S	S
Adverse Events[8]	Update as necessary												

Period		**Extension Treatment Year 3**													
Visit Name	**W212**	**W216**	**W220**	**W224**	**W228**	**W232**	**W236**	**W240**	**W244**	**W248**	**W252**	**W256**	**W260/EOT**	**Unscheduled**[10]	**W268/EOS/Follow up**[11]
Visit Numbers[1]	**370**	**380**	**390**	**400**	**410**	**420**	**430**	**440**	**450**	**460**	**470**	**480**	**490**	**500**	**1999**
Days	**756**	**784**	**812**	**840**	**868**	**896**	**924**	**952**	**980**	**1008**	**1036**	**1064**	**1092**	**1093**	**1148**
Site Visit (mandatory)						X							X	X	X
Study Drug Administration at site[2]						X									
Study Drug Administration at home[2,3]	X	X	X	X	X		X	X	X	X	X	X			
Standard of Care administration	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant medications/non-drug therapies	Update as necessary														
Physical Examination						S							S	S	S
Vital Signs						X							X	X	X
Body Weight[9]						X							X	X	X
Hematology						X							X	X	X
Clinical Chemistry						X							X	X	X
Coagulation Panel						X							X	X	X
Fasting lipid panel[4]						X							X	X	X
24-hr urine collection (UPCR[redacted])						X[5]							X[5]	X	
FMV urine collection (central/local assessments)[6]						X							X	X	X
Pregnancy test (urine)[7]	S	S	S	S	S	S	S	S	S	S	S	S	S	S	S
Adverse Events[8]	Update as necessary	Update as necessary												X	X

[X] Assessment to be recorded in the clinical database or received electronically from a vendor
[S] Assessment to be recorded in the source documentation only
[1] Visit structure given for internal programming purpose only
[2] IRT to be contacted based on type of visit •For site administration: Contact IRT every visit • For home administration: Contact IRT at the previous visit and collect drug for subsequent home visits
[3] Participants who are unable to self-administer the PFS injection at home, will visit the site and site staff will administer PFS injection for them or get administration at home by an off-site healthcare provider
[4] Samples for lipid panel should be obtained after an overnight fast (10hrs or more)
[5] Site to ensure that a urine container is dispensed at previous site visit
[6] First morning void urine sample will be collected for 1) local determination of urinary sediment and standard safety evaluation 2) central determination of UPCR 3) pregnancy test where applicable. Jugs for the Urine collection will be dispensed at previous visit
[7] Pregnancy tests will be conducted for women of childbearing potential. Only if positive pregnancy urine dipstick test, samples to be collected and shipped to central lab
[8] AEs/SAEs occurring after the participant has provided informed consent must be reported
[9] Body Mass Index (BMI) to be automatically calculated by Novartis
[10] As per site requirements
[11] If participant decides to discontinue study at any point of time, the participant would need to complete the follow up visit 12 weeks after the last dose

8.1 Enrollment

At Week 104 all eligible participants from the core study can opt to be enrolled in the extension study via Interactive Response Technology (IRT).

The Week 104E1 will be performed on the same day once the Week 104 is completed by the participant. Participant must be able to understand and communicate with investigator and comply with the requirements of the study and must give a written, dated and signed informed consent before any extension study assessments are performed.

The investigator or his/her delegate will contact IRT after confirming that participant fulfills all inclusion/exclusion criteria. The IRT will then specify a unique medication number for the first package of the investigational treatment to be dispensed to a participant at Week 104E1.

8.2 Screening

8.2.1 Information to be collected on screening failures

Not Applicable

8.3 Participant demographics/other Baseline characteristics

Participant's demographic and Baseline characteristics will not be separately captured in the extension database, participant number from the core study CAIN457Q12301 will be the only information captured.

Of note, as this is an extension study, Baseline always refers to the core study CAIN457Q12301 Baseline.

8.4 Efficacy

Clinical efficacy measurements related to primary [redacted] are described in the subsections below.

8.4.1 Complete Renal Response (CRR)

The CRR will be used to determine efficacy. A participant is defined as a CRR 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 urinary protein to creatinine ratio (UPCR) ≤ 0.5 mg/mg

[redacted]

[redacted]

8.4.3 Estimated Glomerular Filtration Rate (eGFR)

The glomerular filtration rate will be estimated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation Martínez-Martínez MU 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.

8.4.4 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 participant's home.

[redacted]

8.4.6 Appropriateness of efficacy assessments

The proposed primary endpoint is in line with the Committee for Medicinal Products for Human Use 2015 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) and absence of urinary sediment. 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 six months of enrollment in core study CAIN457Q12301.

[redacted]

In addition, both CRR [redacted] have been previously used in clinical trials in LN, as a measure of the renal activity and are the endpoints used in the core study CAIN457Q12301, allowing an evaluation of long-term efficacy, safety and tolerability.

8.5 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
- Weight
- Laboratory evaluations (Hematology, Clinical Chemistry, Lipid Panel, Urinalysis)
- Evaluation of AEs/SAEs
- Electrocardiogram
- Local tolerability (Injection site reactions)
- Pregnancy
- Tolerability of secukinumab

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 four 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.

Table 8-2 Assessments specifications

Assessment	Specification
Physical examination	A complete physical examination done at Week 104E1 visit will include the examination of general appearance, skin, neck (including thyroid), eyes, ears, nose, throat, lungs, heart, abdomen, back, lymph nodes, extremities, vascular, and neurological systems. At subsequent visits, a short physical exam will include the examination of general appearance and vital signs (systolic and diastolic blood pressure [SBP and DBP] and pulse). If indicated 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 made after signing informed consent which meet the definition of an Adverse Event must be recorded as an adverse event on the Adverse Event eCRF.
Vital signs	Vital signs including blood pressure and pulse measurements will be assessed 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, systolic and diastolic blood pressure will be measured three times using an automated validated device, e.g., OMRON devices, with an appropriately sized cuff. The repeat sitting measurements will be made at 1-2 minute intervals and the mean of the three measurements will be used. 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 CRF.

Assessment	Specification
Weight	Body weight (to the nearest 0.1 kilogram (kg) in indoor clothing, but without shoes) will be measured as specified in Table 8-1. If possible, body weight assessments should be performed by the same study site staff member and using the same scale throughout the study.

8.5.1 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.

As per Section 4.6, changes in safety assessments can be added as one of the risk mitigation procedure during public health emergency declared by local or regional authorities.

If participants cannot visit the site for safety lab assessments conducted through central labs, local lab collection may be used 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.

Clinically notable laboratory findings are defined in Section 16.1.

Clinically significant abnormalities must be recorded as current medical conditions or adverse events as appropriate.

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

Table 8-3 Test categories and names

Test Category	Test Name
Hematology	Hematocrit, hemoglobin, Ery. Mean Corpuscular Volume (MCV), Erythrocytes, Leucocytes, platelets, Erythrocyte Cell Morphology, differential (basophils, eosinophils, lymphocytes, monocytes, neutrophils, bands)
Chemistry	Albumin, alkaline phosphatase (ALP), alanine aminotransferase (ALT) Serum Glutamic Pyruvic Transaminase (SGPT), aspartate aminotransferase (AST) ,Serum Glutamic Oxaloacetic Transaminase (SGOT) , gamma-glutamyl-transferase (GGT), bicarbonate, calcium, phosphate, sodium, potassium, creatinine, total bilirubin (TBL), total cholesterol, low density lipoprotein (LDL) cholesterol, high density lipoprotein (HDL) cholesterol, total protein, triglycerides, urea, uric acid, amylase, lipase, hemoglobin A1c (HbA1c).
Urinalysis	Specific gravity, protein, glucose, pH, blood, urine blood dipstick (non-hemolyzed), urine blood dipstick (hemolyzed), bilirubin, ketones and white blood cells (WBCs).
Coagulation	Prothrombin time (PT), International normalized ratio [INR]), activated Partial Thromboplastin Time (aPTT).
Additional tests	24 hr UPCR [redacted] First morning void (FMV) UPCR
Pregnancy Test	Serum / Urine pregnancy test (refer to 'Pregnancy and assessments of fertility' Section 8.5.3)

8.5.1.1 Coagulation panel

Coagulation panel will be evaluated **locally** for general safety and additional characterization of the disease.

8.5.1.2 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.

8.5.1.3 Urinary analysis

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 days preceding specific visits, as outlined in Table 8-1.
- First morning void (FMV) urine collection on the day of visits as specified in Table 8-1.

8.5.1.3.1 Local urinalysis

The participant's FMV urine sample will be used as outlined below.

- **local** determination of urinary sediment: Presence of red blood cells (RBCs), white blood cells (WBCs), epithelial cells, and cellular casts will be determined by microscopic evaluation or automatic analyzer 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) ,
- **central** determination of UPCR, as outlined in Efficacy Section 8.4.4
- Where required, FMV urine sample will be used for urine pregnancy tests.

Material for the FMV urine collection will be dispensed at participant's previous visit. Please refer to the central laboratory manual for additional details.

8.5.1.3.2 24-hour urine collection

A 24-hour urine collection is done 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 [redacted] as mentioned in Section 8.4.4 and Section 8.4.5.

8.5.2 Electrocardiogram (ECG)

Electrocardiograms (ECGs) will be locally collected and evaluated at Visit Week 104E1. ECGs must be recorded after 10 minutes rest in the supine position to ensure a stable measurement. A single 12-lead ECG is collected. The Fridericia QT correction formula (QTcF) must be used for clinical decisions. The investigator must calculate QTcF if it is not auto-calculated by the ECG machine. 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.

Interpretation of the tracing must be made by a qualified physician and documented on the appropriate CRF. Each ECG tracing should be labeled with the study number, participant initials (where regulations permit), participant number, date, and kept in the source documents at the study site. Clinically significant abnormalities should be reported on the appropriate CRF. Clinically significant findings must be discussed with Novartis prior to investigational treatment administration.

The preferred sequence of cardiovascular data collection during study visits is ECG collection first, followed by vital signs, blood sampling, and any remaining assessments for that visit (refer to flow diagram below).

Additional, unscheduled, safety ECGs may be repeated at the discretion of the investigator at any time during the study as clinically indicated. For any ECGs with participant safety concerns, two additional ECGs must be performed to confirm the safety finding. ECG safety monitoring, or a review process, should be in place for clinically significant ECG findings at Week 104E1 before administration of study treatment and during the study.

Clinically significant abnormalities must be recorded on the CRF as adverse events.

Figure 8-1 Timing of study procedures

8.5.2.1 Cardiac imaging - MRA (magnetic resonance angiography), MUGA (multiple gated acquisition) scan or echocardiogram

Not Applicable

8.5.2.2 Cardiac enzymes

Not Applicable

8.5.3 Pregnancy and assessments of fertility

All pre-menopausal women who are not surgically sterile will have monthly local urine pregnancy testing as indicated in Table 8-1. Urine pregnancy kits would be provided to participants to perform the test at home and would report the result to site. A simple diary to record dates and outcome of home urinary test would be provided. Additional pregnancy testing might be performed if requested by local requirements. A serum β-hCG test will be performed only if there is positive urine dipstick test. A positive urine pregnancy test during the treatment periods of the study requires immediate interruption of study treatment until a serum β-subunit of human chorionic gonadotropin (β-hCG) is performed and found to be negative. If the serum β-hCG test is positive, the participant must be discontinued from the study treatment.

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

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

1. Surgical bilateral oophorectomy without a hysterectomy

2. Reported 12 months of natural (spontaneous) amenorrhea with an appropriate clinical profile.

8.5.4 Appropriateness of safety measurements

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

8.6 Additional assessments

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

9 Discontinuation and completion

9.1 Discontinuation from study treatment and from study

9.1.1 Discontinuation from study treatment

Discontinuation of study treatment for a participant occurs when study treatment is permanently stopped for any reason (prior to the planned completion of study drug administration, if any) and 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.

Discontinuation from study treatment is required 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
- 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 from study treatment occurs, the investigator should make a reasonable effort to understand the primary reason for the participant's discontinuation from study treatment and record this information in eCRF.

Participants who discontinue from study treatment agree to return for the end of treatment and follow-up visits indicated in the Assessment Schedule (refer to Section 8).

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.

All participants who prematurely discontinue study treatment should perform the EOT study visit four weeks after their last study treatment administration. Adverse event monitoring should be continued for at least 84 days following the last dose of study treatment.

An End of Study (EOS) visit is to be done 12 weeks after last study treatment administration for all participants, regardless of whether they complete the entire study as planned or discontinue prematurely.

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

9.1.2 Discontinuation from study

Discontinuation from study is when the participant permanently stops receiving the study treatment, and further protocol-required assessments or follow-up, for any reason.

If the participant agrees, a final evaluation at the time of the participant's study discontinuation should be made as detailed in the assessment table (refer to Section 8).

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 from study treatment or discontinue from study or withdraw consent/oppose to the use of their data/biological samples, 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.

9.2 Withdrawal of informed consent/Opposition to use data/biological samples

Withdrawal of consent/opposition to use data/biological samples occurs when a participant:

- Explicitly requests to stop use of their biological samples and/or data (opposition to use participant's data and biological samples)

and

- No longer wishes to receive study treatment

and

- Does not want any further visits or assessments (including further study-related contacts)

This request should be in writing (depending on local regulations) and recorded in the source documentation.

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 their consent/opposition to use data/biological samples and record this information.

Where consent to the use of Personal and Coded Data is not required in a certain country's legal framework, the participant therefore cannot withdraw consent. However, they still retain the right to object to the further collection or use of their Personal Data.

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.

If the participant agrees, a final evaluation at the time of the participant's withdrawal of consent/opposition to use data/biological samples should be made as detailed in the assessment table (refer to Section 8).

Further details on withdrawal of consent or the exercise of participants' data privacy rights are included in the corresponding informed consent form.

9.3 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.

All enrolled and/or treated participants should have a safety follow-up call conducted 84 days after last administration of study treatment. The information collected is kept as source documentation. All SAEs reported during this time period must be reported as described in Section 10.1.3 SAE reporting. Documentation of attempts to contact the participant should be recorded in the source documentation.

9.4 Early study termination by the sponsor

The study can be terminated by Novartis at any time. This may include reasons related to the benefit/risk assessment of participating in the study (e.g., outcome of planned core study CAIN457Q12301 futility analysis), practical reasons (including slow enrollment), or for regulatory or medical reasons.

In taking the decision to terminate, Novartis will always consider participant welfare and safety. Should early termination be necessary, participants must 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 local regulation will be responsible for informing IRBs/IECs of the early termination of the trial.

10 Safety monitoring, reporting and committees

10.1 Definition of adverse events and reporting requirements

10.1.1 Adverse events

An adverse event (AE) is any untoward medical occurrence (e.g. any unfavorable and unintended sign [including abnormal laboratory findings], symptom or disease) in a 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 adverse events.

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

Adverse events must be recorded under the signs, symptoms, or diagnosis associated with them, accompanied by the following information (as far as possible) (if the event is serious refer to Section 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 ongoing) and the outcome 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 adverse events must be treated appropriately. Treatment may include one or more of the following:

- Dose not changed
- Dose Reduced/increased
- Drug interrupted/permanently discontinued

6. Its outcome (not recovered/not resolved; recovered/resolved; recovered/resolved with sequelae; fatal; or unknown)

Adverse events (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 adverse events only if they fulfill at least one of the following criteria:

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

Clinically significant abnormal laboratory values or test results must be identified through a review of values outside of normal ranges/clinically notable ranges, significant changes from Baseline or the previous visit, or values which are considered to be non-typical in participant with the underlying disease. Alert ranges for laboratory and other test abnormalities are included in Section 16.1.

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 (refer to the ICH E2D 2003 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 (refer to the ICH E2D 2003 Guidelines).

All new 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 immediately, without undue delay, but under no circumstances later than within 24 hours of obtaining knowledge of the events (Note: If more stringent, local regulations regarding reporting timelines prevail). Detailed instructions regarding the submission process and requirements are to be found in the investigator folder provided to each site. Information about all SAEs is collected and recorded on the eSAE with paper backup. Serious Adverse Event Report Form; all applicable sections of the form must be completed in order to provide a clinically thorough report.

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 immediately, without undue delay, but under no circumstances later than within 24 hours of the investigator receiving the follow-up information (Note: If more stringent, local regulations regarding reporting timelines prevail). 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.

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 Novartis Chief Medical Office and Patient Safety (CMO&PS) Department associate may urgently require further information from the investigator for health authority reporting. Novartis may need to issue an Investigator Notification (IN) to inform all investigators involved in any study with the same study treatment that this SAE has been reported.

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

Any SAEs experienced after the 84 days following the last administration of study treatment/should only be reported to Novartis Safety if the investigator suspects a causal relationship to study treatment, unless otherwise specified by local law/regulations.

10.1.4 Pregnancy reporting

Pregnancies

If a female trial participant becomes pregnant, the study treatment should be stopped, and the pregnancy consent form should be presented to the trial participant. The participant must be given adequate time to read, review and sign the pregnancy consent form. This consent form is necessary to allow the investigator to collect and report information regarding the pregnancy. 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 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. After consent is provided, the pregnancy reporting will occur up to one year after the estimated date of delivery.

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, participant 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 CRF irrespective of whether or not associated with an AE/SAE and reported to Safety only if associated with an SAE. Misuse or abuse will be collected and reported in the safety database irrespective of it being associated with an AE/SAE 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 CRF (Yes/No)	Document in AE eCRF	Complete SAE form
Unintentional study treatment error	Yes	Only if associated with an AE	Only if associated with an SAE
Misuse/Abuse	Yes	Yes	Yes, even if not associated with a SAE

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

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.

Please refer to Table 16-2 in Section 16.2 for complete definitions of liver laboratory triggers.

Once a participant is exposed to study treatment, every liver event defined in Table 16-3 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, total bilirubin (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 CRF.
- 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), if appropriate.
- Hospitalization of the participant, if appropriate.

- Causality assessment of the liver event.
- Thorough follow-up of the liver event should include investigations based on investigator's discretion: 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

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

10.3 Committees

10.3.1 Data Monitoring Committee

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

10.3.2 Steering Committee

The Steering Committee (SC) will be established comprising 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

Designated investigator staff will enter the data required by the protocol into the eCRFs. The eCRFs have been built using fully validated secure web-enabled software that conforms to the Code of Federal Regulation (CFR) 21 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.

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

11.2 Database management and quality control

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

Concomitant treatments and prior medications entered into the database will be coded using the WHO Drug Reference List, which employs the Anatomical Therapeutic Chemical classification system. Medical history/current medical conditions and adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) terminology.

Dates of enrollment and study completion, as well as data about all study treatment dispensed to the participant and all dosage regimen changes, will be tracked using an 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.

Once all the necessary actions have been completed and the database has been declared to be complete and accurate, it will be locked. 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 (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 Clinical Research Associate (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.

12 Data analysis and statistical methods

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

12.1 Analysis sets

The Full Analysis Set (FAS) will be comprised of all analyzable subjects from the FAS of core study to whom study treatment has been assigned. Subjects will be analyzed according to the study treatment received.

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 Participant demographics and other Baseline characteristics

Demographic and other Baseline data including disease characteristics will be summarized descriptively by core study treatment groups in FAS.

Categorical data will be presented as frequencies and percentages. For continuous data, mean, standard deviation, median, minimum, and maximum will be presented. .

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

12.3 Treatments

The analysis of study treatment data will be based on the safety set. The number of active injections received will be presented by core study treatment group. The duration of exposure to study treatment will also be summarized by core study 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.

12.4 Analysis supporting primary objectives

The primary endpoint CRR at Week 260 will be summarized using descriptive statistics including proportion of responders with 95% confidence interval.

12.4.1 Definition of primary endpoint(s)

Primary endpoint for this study is CRR at Week 260.

CRR is defined as:

- eGFR is within the normal range or no less than 85% of Baseline,

and

- 24-hour UPCR ≤ 0.5 mg/mg.

12.4.2 Statistical model, hypothesis, and method of analysis

No formal statistical testing will be applied for the primary variable.

The primary variable will be summarized by treatment group in FAS, using descriptive statistics and 95% confidence interval for proportion of responders.

12.4.3 Handling of intercurrent events of primary estimand

Composite strategy (non-responder imputation) will be used for treatment discontinuation and rescue treatment.

12.4.4 Handling of missing values not related to intercurrent event

Non responder imputation will be used for missing data in primary estimand analysis. Data will also be analyzed descriptively as observed.

12.4.5 Sensitivity analyses

Sensitivity analyses may be specified in statistical analysis plan.

12.4.6 Supplementary analysis

Supplementary analyses may be specified in statistical analysis plan.

12.5 Analysis supporting secondary objectives

Not applicable

12.7 Interim analyses

Interim analyses may be performed for purposes of publication and/or to support health authority interactions, as necessary.

12.8 Sample size calculation

Not applicable. Sample size is based on participants continuing from core study to extension study.

12.8.1 Primary endpoint(s)

Not applicable.

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 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 standard operating procedures (SOPs), and are performed according to written Novartis processes.

13.5 Participant Engagement

The following participant engagement initiatives are included in this study and will be provided, as available, for distribution to study participants

- Thank You letter
- Plain language trial summary - after clinical study report (CSR) publication

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.

15 References

References are available upon request

Allam R, Anders HJ (2008) The role of innate immunity in autoimmune tissue injury. Curr Opin Rheumatol p. 538-44.

Anon (2001) Recommendations for the prevention and treatment of glucocorticoid-induced osteoporosis: 2001 update. American College of Rheumatology Ad Hoc Committee on Glucocorticoid-Induced Osteoporosis. Arthritis Rheum; 44(7):1496-503

Anon (2015). Committee for Medicinal Products for Human Use (CHMP) (2015) guidance document: https://www.ema.europa.eu/documents/scientific-guideline/guideline-clinical-investigation-medicinal-products-treatment-systemic-lupus-erythematosus-lupus_en.pdf (Accessed 02 Dec 2021)..

Appel GB, Contreras G, Dooley MA, et al (2009) Mycophenolate mofetil versus cyclophosphamide for induction treatment of lupus nephritis. J Am Soc Nephrol p. 1103-12.

Bertsias GK, Tektonidou M, Amoura Z, et al (2012) Joint European League Against Rheumatism and European Renal Association-European Dialysis and Transplant Association (EULAR/ERA-EDTA) recommendations for the management of adult and paediatric lupus nephritis. Ann Rheum Dis p. 1771-82.

Cervera R, Khamashta MA, Font J, et al (2003) Morbidity and mortality in systemic lupus erythematosus during a 10-year period: a comparison of early and late manifestations in a cohort of 1,000 patients. Medicine (Baltimore) p. 299-308.

Chilton F, Collett RA (2008) Treatment choices, preferences and decision-making by patients with rheumatoid arthritis. Musculoskeletal Care p. 1-14.

Costa R, Antunes P, Salvador P, et al (2021) Secukinumab on Refractory Lupus Nephritis. Cureus; 13(8): e17198

Crispín JC, Oukka M, Bayliss G, et al (2008) Expanded double negative T cells in patients with systemic lupus erythematosus produce IL-17 and infiltrate the kidneys. J Immunol p. 8761-6.

Faurschou M, Dreyer L, Kamper AL, et al (2010) Long-term mortality and renal outcome in a cohort of 100 patients with lupus nephritis. Arthritis Care Res (Hoboken) p. 873-80.

Feldman CH, Hiraki LT, Winkelmayer WC, et al (2015) Serious infections among adult Medicaid beneficiaries with systemic lupus erythematosus and lupus nephritis. Arthritis Rheumatol p. 1577-85.

Furie R, Rovin BH, Houssiau F, et al (2020) Two-Year, Randomized, Controlled Trial of Belimumab in Lupus Nephritis. N Engl J Med p. 1117-1128.

Grootscholten C, Berden JH (2006) Discontinuation of immunosuppression in proliferative lupus nephritis: is it possible? Nephrol Dial Transplant p. 1465-9.

Hahn BH, McMahon M, Wilkinson A, et al (2012) American College of Rheumatology guidelines for screening, treatment, and management of lupus nephritis. Arthritis Care Res (Hoboken) p. 797-808.

Hamm R, Patel B, Whittlestone T, et al (2000) Patient self-injection: a new approach to administering luteinizing hormone-releasing hormone analogues. BJU International; 86: 840-2

ICH E2D (2003) Clinical Safety Data Management: Definitions and Standards for expedited reporting. Accessed from: https://www.ema.europa.eu/en/ich-e2d-post-approval-safety-data-management (Accessed 02 Dec 2021).

Kivitz A, Cohen S, Dowd JE, et al (2006) Clinical assessment of pain, tolerability, and preference of an autoinjection pen versus a prefilled syringe for patient self-administration of the fully human, monoclonal antibody adalimumab: the TOUCH trial. Clin Ther p. 1619-29.

Krebs CF, Schmidt T, Riedel JH, et al (2017) T helper type 17 cells in immune-mediated glomerular disease. Nat Rev Nephrol p. 647-659.

Levey AS, Stevens LA, Schmid CH, et al (2009) A new equation to estimate glomerular filtration rate. Ann Intern Med p. 604-12.

Markowitz GS, D'Agati VD (2007) The ISN/RPS 2003 classification of lupus nephritis: an assessment at 3 years. Kidney Int p. 491-5.

Martínez-Martínez MU, Mandeville P, Llamazares-Azuara L, et al (2013) CKD-EPI is the most reliable equation to estimate renal function in patients with systemic lupus erythematosus.

Nowling TK, Gilkeson GS (2011) Mechanisms of tissue injury in lupus nephritis. Arthritis Res Ther p. 250.

Palmer SC, Tunnicliffe DJ, Singh-Grewal D, et al (2017) Induction and Maintenance Immunosuppression Treatment of Proliferative Lupus Nephritis: A Network Meta-analysis of Randomized Trials. Am J Kidney Dis p. 324-336.

Rovin BH, Parikh SV (2014) Lupus nephritis: the evolving role of novel therapeutics. Am J Kidney Dis p. 677-90.

Rovin BH, Teng YKO, Ginzler EM, et al (2021) Efficacy and safety of voclosporin versus placebo for lupus nephritis (AURORA 1): a double-blind, randomised, multicentre, placebo-controlled, phase 3 trial. Lancet p. 2070-2080.

Satoh Y, Nakano K, Yoshinari H, et al (2018) A case of refractory lupus nephritis complicated by psoriasis vulgaris that was controlled with secukinumab. Lupus p. 1202-1206.

Schwartz N, Goilav B, Putterman C (2014) The pathogenesis, diagnosis and treatment of lupus nephritis. Curr Opin Rheumatol p. 502-9.

Tektonidou MG, Dasgupta A, Ward MM (2016) Risk of End-Stage Renal Disease in Patients With Lupus Nephritis, 1971-2015: A Systematic Review and Bayesian Meta-Analysis. Arthritis Rheumatol p. 1432-41.

Waldman M, Madaio MP (2005) Pathogenic autoantibodies in lupus nephritis. Lupus p. 19-24.

Wang H, Ren YL, Chang J, et al (2018) A Systematic Review and Meta-analysis of Prevalence of Biopsy-Proven Lupus Nephritis. Arch Rheumatol p. 17-25.

Weening JJ, D'Agati VD, Schwartz MM, et al (2004) The classification of glomerulonephritis in systemic lupus erythematosus revisited. Kidney Int p. 521-30.

Yu F, Haas M, Glassock R, et al (2017) Redefining lupus nephritis: clinical implications of pathophysiologic subtypes. Nat Rev Nephrol p. 483-495.

Zhang Z, Kyttaris VC, Tsokos GC (2009) The role of IL-23/IL-17 axis in lupus nephritis. J Immunol p. 3160-9.

Zickert A, Amoudruz P, Sundström Y, et al (2015) IL-17 and IL-23 in lupus nephritis - association to histopathology and response to treatment. BMC Immunol p. 7.

16 Appendices

16.1 Appendix 1: Clinically notable laboratory values and vital signs

The following criteria will be used to define expanded limits and notable abnormalities of key laboratory tests. Clinically notable values will be forwarded to Novartis at the same time that they are sent to investigators. Any action based on these laboratory values should be discussed with Novartis personnel.

Table 16-1 Safety Analyses: Expanded limits and Notable Criteria

Laboratory variable	Notable Criteria Standard Units	SI units
LIVER FUNCTION VARIABLE		
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 VARIABLE		
Hemoglobin: 20 g/L decrease from Baseline		
Platelet count: < 50 x 10 E^9/L		
White Blood Cell Count: < 0.8 x LLN		
Neutrophil: < 0.9 x LLN		

16.2 Appendix 2: Liver event and laboratory trigger definitions & follow-up requirements

Table 16-2 Liver event and laboratory trigger definitions

	Definition/ threshold
Liver laboratory triggers If ALT, AST and total bilirubin normal at Baseline:	● 3 × ULN <ALT/AST ≤ 5×ULN ● 1.5 × ULN < TBL × ULN ● ALT or AST > 5 × ULN ● ALP > 2 × ULN (in the absence of known bone pathology) ● Total bilirubin > 3 × 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 Total bilirubin > 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
If ALT or AST abnormal at Baseline:	● ALT or AST > 3x Baseline or > 300 U/L (whichever occurs first)

Table 16-3 Follow up requirements for liver 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)
AST or ALT		
> 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 (participant is asymptomatic)	1. Repeat LFT within the next week 2. If elevation is confirmed, initiate close observation of the participant	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 (participant is asymptomatic)	1. Repeat LFT within the next week 2. If elevation is confirmed, initiate close observation of the participant	Investigator discretion Monitor LFT within 1 to 4 weeks or at next visit
Jaundice	1. Discontinue the study treatment immediately 2. Hospitalize the participant 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
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.

16.3 Appendix 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)