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CFZ533 (iscalimab)

Clinical Trial Protocol CCFZ533X2202

A randomized, placebo-controlled, patient and investigator blinded study investigating the safety, tolerability, pharmacokinetics and preliminary efficacy of multiple doses of CFZ533 in patients with moderately active proliferative lupus nephritis

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Site Operations Manual (SOM)

A Site Operations Manual (SOM) accompanies this protocol, providing the operational details for study conduct. Note: The SOM will not form part of the Clinical Study Report.

Notification of serious adverse events

Dear Investigator,

You must report a serious adverse event (SAE) (initial or follow-up) to Novartis as summarized below. Refer to Section 9.2 of the protocol for SAE criteria and additional requirements. See also page 2 of the Site Operations Manual for further details on the method of reporting a SAE.

- Complete SAE report
- Submit SAE report to Novartis Chief Medical Office & Patient Safety (CMO&PS) **within 24 hours after awareness of the SAE**
- Notify the Novartis Medical Lead
- The fax number(s) and email address(es) are located in the Site Operations Manual.

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List of abbreviations

AE	adverse event
AESI	Adverse events of special interest
ADA	Anti-drug antibodies
ADCC	Antibody dependent cell-mediated cytotoxicity
α-GST	Alpha-glutathione S-transferase
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ANA	Antinuclear autoantibody
aPTT	Activated partial thromboplastin time
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BMI	Body Mass Index
BP	Blood pressure
BUN	Blood Urea Nitrogen
BW	Body weight
CDC	Complement dependent cytotoxicity
CFR	U.S. Code of Federal Regulation
CM	Centimeters
CMO&PS	Chief Medical Office & Patient Safety
CMV	Human cytomegalovirus
COVID-19	Coronavirus disease of 2019
CNS	Central nervous system
CRF	Case Report/Record Form (paper or electronic)
CRO	Contract Research Organization
CRP	C-reactive protein
CRR	Complete renal remission
CSF	Cerebrospinal fluid
CTA	Clinical trial application
CTC	Common Toxicity Criteria
CV	coefficient of variation
CysC	Cystatin C

DAR	Dose administration record
DMC	Data Monitoring Committee
EBV	Epstein-Barr virus
ECG	electrocardiogram
eCRF	Electronic case report forms
EDC	Electronic Data Capture
EFD	embryo-fetal development
eGFR	estimated glomerular filtration rate
ELISA	enzyme-linked immunosorbent assay
eSAE	electronic Serious Adverse Event
ESR	Erythrocyte Sedimentation Rate
FDA	Food and Drug Administration
FMV	First morning void
GCP	Good Clinical Practice
GGT	gamma-glutamyl transferase
h	hour
HbA1c	Hemoglobin A1c
HBsAg	hepatitis B surface antigen
Anti-HBc	Hepatitis B core antibody
HBV	hepatitis B virus
HCV	hepatitis C virus
HIV	human immunodeficiency virus
IB	Investigators brochure
i.v.	intravenous
ICF	Informed Consent Form
ICH	International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use
IEC	Independent Ethics Committee
IgG	Immunoglobulin G
IgM	Immunoglobulin M
IN	Investigator Notification

INR	International Normalized Ratio
IRB	Institutional Review Board
IRT	Interactive Response Technology
ISG	Interferon gene signature
IUD	Intrauterine device
IUS	Intrauterine system
Kg	Kilogram
KLH	Keyhole limpet hemocyanin
LDH	lactate dehydrogenase
LLN	lower limit of normal
LN	Lupus nephritis

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MABEL	minimum anticipated biological effect level
MAR	Missing at random
MAS	Macrophage activation syndrome
MedDRA	medical dictionary for regulatory activities
mg	milligram(s)
mL	milliliter(s)
MMF	mycophenolate mofetil
MRSD	maximum recommended starting dose
NCA	Non-compartmental analysis
NCDS	Novartis Clinical Data Standards
NGAL	neutrophil gelatinase-associated lipocalin
NSAIDs	Nonsteroidal anti-inflammatory drugs
PBMC	peripheral blood mononuclear cells
p.o.	oral
PCR	Polymerase chain reaction
PD	pharmacodynamic(s)

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PK	pharmacokinetic(s)

pSS	primaru Sjögren' s syndrome
PT	prothrombin time
QM	Quality Management
QTcF	QT correction formula
RA	Rheumatoid arthritis
RBC	red blood cell(s)
RF	Rheumatoid factor
RNA	Ribonucleic acid
s.c.	Subcutaneous
SAE	serious adverse event
SAP	Statistical analysis plan
sCR	serum creatinine
SD	standard deviation
SELENA	Safety of Estrogens in Lupus Erythematosus National Assessment
SGOT	serum glutamic oxaloacetic transaminase
SGPT	serum glutamic pyruvic transaminase
SLE	Systemic Lupus Erythematosus

SoC	Standard of care
SOM	Site Operations Manual
SOPs	Standard operating procedures
SUSAR	Suspected Unexpected Serious Adverse Reactions
TB	Tuberculosis
TBL	total bilirubin
TE	Thromboembolic
TEG	Thromboelastography
TME	target mediated elimination
TTx	Tetanus toxoid
ULN	upper limit of normal
UPCR	urinary protein creatinine ratio

WBC	white blood cell(s)
WHO	World Health Organization
WoC	Withdrawal of Consent

Pharmacokinetic definitions and symbols

AUClast	AUClast is the area under the plasma concentration-time curve calculated to the last quantifiable concentration point (or to 0, in situations where concentrations below the limit of quantification (BLQ) are treated as zero)
Cmax	The observed maximum plasma (or serum or blood) concentration following drug administration [mass / volume]
Cmin	The observed minimum plasma concentration following drug administration
Ctrough	The observed plasma concentration that is just prior to the beginning of, or at the end of a dosing interval
Cmax,ss	The observed maximum plasma (or serum or blood) concentration following drug administration at steady state [mass / volume]
Cmin,ss	The lowest plasma (or serum or blood) concentration observed during a dosing interval at steady state [mass / volume]
Tmax	The time to reach the maximum concentration after drug administration [time]

Glossary of terms

Assessment	A procedure used to generate data required by the study
Clinic spot urine	Urine sample collected at the clinic during site visit
Control drug	Any drug(s) (an active drug or an inactive drug, such as a placebo) which is used as a comparator to the investigational drug being tested in the trial
Electronic Data Capture (EDC)	Electronic data capture (EDC) is the electronic acquisition of clinical study data using data collection systems, such as Web-based applications, interactive voice response systems and clinical laboratory interfaces. EDC includes the use of Electronic Case Report Forms (eCRFs) which are used to capture data transcribed from paper source forms used at the point of care.
Enrollment	Point/time of subject entry into the study at which informed consent must be obtained (i.e. prior to starting any of the procedures described in the protocol)
Epoch	Interval of time in the planned conduct of a study. An epoch is associated with a purpose (e.g. screening, randomization, treatment, follow-up) which applies across all arms of a study.
First morning void urine	First morning void urine sample collected at patient's home
Investigational drug	The study drug whose properties are being tested in the study; this definition is consistent with US CFR 21 Section 312.3 and Directive 2001/20/EC and is synonymous with "investigational new drug," "Investigational Medicinal Product," or "test substance"
Medication pack number	A unique identifier on the label of each drug package in studies that dispense study treatment using an IRT system
Patient	An individual with the condition of interest
Personal Data	Subject information collected by the Investigator that is transferred to Novartis for the purpose of the clinical trial. This data includes subject identifier information, study information and biological samples.
Randomization number	A unique identifier assigned to each randomized subject, corresponding to a specific treatment arm assignment
Screen Failure	A subject who is screened but is not treated or randomized

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
Study treatment	Any drug or combination of drugs administered to the study participants as part of the required study procedures; includes investigational drug(s), control(s) or background therapy
Study treatment discontinuation	When the subject permanently stops taking study treatment prior to the defined study treatment completion date
Subject	A trial participant (can be a healthy volunteer or a patient)
Subject number	A unique number assigned to each subject upon signing the informed consent. This number is the definitive, unique identifier for the subject and should be used to identify the subject throughout the study for all data collected, sample labels, etc.
Variable	A measured value or assessed response that is determined in specific assessments and used in data analysis to evaluate the drug being tested in the study
Withdrawal of consent (WoC)	Withdrawal of consent from the study occurs only when a subject does not want to participate in the study any longer, and does not allow any further collection of personal data

Protocol summary

Protocol number	CCFZ533X2202
Full Title	A randomized, placebo-controlled, patient and investigator blinded study investigating the safety, tolerability, pharmacokinetics and preliminary efficacy of multiple doses of CFZ533 in patients with moderately active proliferative lupus nephritis
Brief title	Safety, pharmacokinetics and preliminary efficacy study of CFZ533 in patients with lupus nephritis
Sponsor and Clinical Trial Phase	Novartis Phase II
Intervention type	Drug
Study type	Interventional
Purpose and rationale	This study is to evaluate the safety, tolerability, pharmacokinetics, pharmacodynamics, and preliminary therapeutic efficacy of multiple doses of CFZ533 anti-CD40 monoclonal antibody in patients with moderately active lupus nephritis (LN)
Primary Objective(s)	• To evaluate the safety and tolerability of 24 weeks of treatment with multiple intravenous (IV) doses of 10 mg/kg CFZ533 as an add-on therapy of CFZ533 to standard of care in moderately active lupus nephritis (LN) patients • To assess the effect of CFZ533 on renal proteinuria using urinary protein creatinine ratio (UPCR) in moderately active LN patients after 24 weeks of treatment as an add-on therapy to standard of care as compared to placebo
Secondary Objectives	• To assess the effect of CFZ533 on relevant renal outcomes at different time points • To evaluate the pharmacokinetics (PK) and pharmacodynamics (PD) of CFZ533 in LN patients after multiple 10 mg/kg IV doses • To evaluate the immunogenicity of CFZ533 in LN patients after multiple 10 mg/kg IV doses
Study design	Randomized, double-blind, placebo-controlled, non-confirmatory study in approximately 60 subjects, up to a maximum of 75 subjects
Population	Female and male subjects with moderately active lupus nephritis at the age of ≥ 18 years and ≤ 75 years
Key Inclusion criteria	• Men and women with systemic lupus erythematosus (see below), aged ≥ 18 years and ≤ 75 years at screening, fulfilling at least 4 out of 11 criteria for SLE as defined by the American College of Rheumatology (Tan et al 1982, revised by Hochberg 1997) • Subjects must have a body mass index (BMI) within the range of 18 - 40 kg/m^2. (BMI = Body weight (kg) / [Height (m)]^2) at screening visit • Histological diagnosis of proliferative lupus nephritis World Health Organization (WHO) ISN/RPS (Weening et al 2004) Class III or IV within 5 years of screening • Presence of antinuclear autoantibody (ANA titer ≥1:80 at screening)

	• First morning void or spot urine UPCR ≥ 0.5 mg/mg (56.52 mg/mmol) at screening visit and baseline visit • At least one of the following: a) low complement level (C3 < 0.9 g/L) or C4 < 0.1 g/L), and/or b) elevated anti-dsDNA (≥30 IU/mL), and/or c) urine sediment consistent with active proliferative lupus nephritis such as presence of cellular (granular or red blood cell) casts or hematuria (>5 red blood cells per high power field) if other causes such as menstrual bleeding are excluded • Patient must have sufficient kidney function as estimated by eGFR > 30 mL/min/1.73 m^2 at screening and baseline visits (Levey et al 2009) • Patients must have active disease as defined by proteinuria and additional symptoms as above despite standard of care therapy for lupus nephritis as considered appropriate by the treating physician (e.g., corticosteroids and/or immunosuppressive or immunomodulatory treatments such as mycophenolate, azathioprine, methotrexate or hydroxychloroquine) . For guidance, see published guidelines such as by Bertsias et al 2012 and Hahn et al 2012 • Women of child-bearing potential (defined as all women physiologically capable of becoming pregnant) must use highly effective methods of contraception during dosing and until study completion.
Key Exclusion criteria	• Any glomerulonephritis other than WHO Class III or IV lupus nephritis. Patients with proliferative nephritis (Class III or IV) who, in addition, have overlapping histological signs for other glomerulonephritis, e.g., Class V, are eligible at the investigator`s discretion • Hypoalbuminemia (serum albumin of less than 2.0 g/dL) • Patients who have received a) oral or i.v. cyclophosphamide within 3 months prior to randomization b) i.v. corticosteroid bolus (dose > 1mg/kg) within 3 months prior to randomization c) rituximab or other B cell depleting agent received prior to randomization within ▪ ≤ 6 months: no inclusion ▪ > 6 but ≤12 months: B cell count must be within normal range ▪ >12 months prior to randomization: no special requirements d) belimumab within 6 months prior to randomization e) any other biologic drug or an investigational drug within three (3) months or five times the half-life, whichever is longer from randomization f) any calcineurin inhibitors (e.g., tacrolimus or cyclosporin A) within 3 months prior to randomization [For China, Hong Kong, and Korea only: calcineurin inhibitors, except tacrolimus (≤ 3mg/day), within 3 months prior to randomization]

	• Patients who are at significant risk for thromboembolic events based on the following: a) History of either thrombosis or 3 or more spontaneous abortions b) Presence of lupus anticoagulant or prolonged activated partial thromboplastin time (aPTT) and no prophylactic treatment with aspirin or anticoagulants as per local standard of care • Positive serology for • HIV antibodies, • CMV IgM in the absence of positive CMV IgG, or quantifiable CMV DNA by PCR (patients with detectable but NOT quantifiable DNA test result may be eligible for the study), • Or hepatitis B surface antigen (HBsAg) or hepatitis B core antibody (anti-HBc), except if HBV DNA is negative and hepatitis B monitoring (HBsAg and HBV DNA tested every 4 weeks until the end of study) is implemented; and hepatitis C antibodies confirmed by an appropriate licensed test at screening. • Have had signs or symptoms of a clinically significant systemic viral, bacterial or fungal infection within 30 days prior to randomization • Live vaccines within 8 weeks of first study drug infusion
Study treatment	• CFZ533 150 mg or placebo Liquid in vial for injection o CFZ533 10 mg/kg administered by intravenous infusion o placebo administered by intravenous infusion Intravenous infusion will be administered at Days 1, 15, 29, 57, 85, 113, and 141
Pharmacokinetic assessments	• Free CFZ533 in plasma
Efficacy/PD assessments	• Urinary protein creatinine ratio (UPCR) • Total soluble CD40 (target engagement) in plasma
Key safety assessments	• Adverse events/Serious adverse events • Vital signs • ECG evaluation • Standard hematology and chemistry evaluations • Immunogenicity
Other assessments	Commercially Confidential Information

Data analysis	The primary variable is the ratio from baseline in urinary protein creatinine ratio (UPCR) at Week 25, using first morning void. This ratio will be log transformed prior to the analysis. A repeated measures mixed model will be fitted with factors for treatment group (CFZ533 or placebo) and visit (e.g. Week 5, 9, 13 etc.). The model will also include a factor for the prednisone dose-equivalent at baseline (≤ 10 mg, >10 mg), which is a stratification factor for the randomization. Log-transformed baseline UPCR will be included in the model as a covariate along with the interactions between visit and all of the fixed effects. A normal errors model will be assumed with an unstructured covariance matrix to account for the correlation within subjects. At each of the visits, the difference between the CFZ533 and placebo group will be estimated (along with its corresponding 95% confidence interval) and then back-transformed to provide an estimate of the ratio between treatment groups. Descriptive statistics will be provided for the safety data (e.g. AEs, vital signs, ECGs, hematology and chemistry evaluations etc.). For serious adverse events and adverse events of special interest, statistical analyses comparing the event rates in the two treatment groups will be performed.
Key words	CFZ533, anti-CD40, moderately active lupus nephritis

1 Introduction

1.1 Background

Systemic Lupus Erythematosus (SLE) is a chronic inflammatory disease characterized by autoantibody production and other distinct immunological abnormalities (Frieri 2013, Gurevitz et al 2013). It may affect the skin, joints, kidneys, lungs, heart, serous membranes, nervous system or other organs. Lupus Nephritis (LN) is a common manifestation of SLE clinically affecting approximately 60% of patients with greater representation in children and young adults. Despite recent advances in the treatment of many autoimmune diseases including SLE, , LN remains a major cause of morbidity and mortality in SLE patients with 5-20% of LN patients progressing to end stage renal disease within 10 years of diagnosis (Faurschou et al 2010). Intensive induction therapies with intravenous (IV) and/or oral corticosteroids combined with IV cyclophosphamide or oral mycophenolate mofetil (MMF) achieve a satisfactory renal response only in about half of the patients and carry a significant burden of toxicity. Maintenance therapies with lower doses of oral corticosteroids, azathioprine, or MMF often fail to maintain remission (Waldman and Appel 2006).

1.1.1 Scientific rationale for targeting CD40/CD154 co-stimulation in lupus nephritis

Pharmacological inhibition of CD40-CD154 interactions using anti-CD40 or anti-CD154 antibodies reduced autoimmune disease pathology in numerous pre-clinical and clinical studies and prolonged allograft survival in non-human primates (Aoyagi et al 2009; Watanabe et al 2013). CD40-CD154 interactions have been shown to be involved in the pathology of SLE and LN. Anti-CD154 treatment of lupus prone animals was found to ameliorate renal disease (Mohan et al 1995). Elevated sCD154 levels in SLE sera has also been documented, and activated T and B cells from the periphery of active SLE patients were found to express CD154 (Desai-Mehta et al 1996). Additionally, augmented CD40 expression was observed on renal parenchymal cells from patients suffering proliferative lupus nephritis (Yellin et al 1997), potentially linking CD40 signaling to organ-specific pathology. When lupus patients with active proliferative lupus nephritis were treated with rituximab and oral prednisolone, remission was preceded by down-regulation of CD154 on CD4+ T cells (Sfikakis et al 2005). In addition, an anti-CD154 antibody, BG9588, improved serologic activity and decreased hematuria in patients with proliferative lupus nephritis in an open-label phase 2 study (Boumpas et al 2003). Treatment of SLE patients with BG9588 led to the disappearance of $CD38^{high}$ Ig-secreting plasma cells from the periphery (Grammer et al 2003) and reduced the frequency of anti-dsDNA antibody-producing B cells in the peripheral blood (Huang et al 2002). However, treatment with BG9588 (due to its platelet activating effects) provoked life-threatening thromboembolic (TE) events precluding further clinical development (Kawai et al 2000). An alternative approach that targets the CD40 signaling pathway but is devoid of TE events would have a great potential for the safe and efficacious treatment of lupus nephritis.

1.1.2 CFZ533 overview

CFZ533 (iscalimab) is a non-agonistic, fully human, non-depleting (Fc-silencing mutation N297A), antagonistic IgG1 anti-CD40 antibody that binds to the CD154 binding site on CD40 and prevents the binding of CD154 to CD40. Since it is Fc-silent, CFZ533 binding is able to block the CD40/CD154 costimulatory pathway and inhibit cellular proliferation and other effector functions, but does not cause antibody-dependent cell-mediated cytotoxicity (ADCC) or complement dependent cytotoxicity (CDC).

CFZ533 inhibits CD154-induced activation in vitro and T cell-dependent Ab formation and germinal center formation in vivo. CFZ533 was able to prolong non-human primate renal allograft survival alone or in combination with sub-therapeutic doses of cyclosporine. In addition, CFZ533 was able to completely suppress primary and secondary antibody responses to immunization with a T cell-dependent antigen.

CFZ533 is expected to be devoid of the thromboembolic risk characteristic of the Fc active anti-CD154 antibodies such as BG9588 as CFZ533 does not activate platelets. The hypothesis that BG9588-induced TE in an Fc-dependent manner was supported by recent data with CDP7657 (dapirolizumab pegol), an anti-CD154 Fab fragment, that showed no evidence of platelet activation (Chamberlain et al 2017, Tocoian et al 2015). Comprehensive preclinical studies, specifically exploring whether there is a propensity of CFZ533 to cause thrombosis using the most sensitive species for TE events showed no sign or event of TE.

As of November 2020, a total of approximately 837 subjects have been enrolled into the CFZ533 clinical program: 88 healthy subjects (CCFZ533X1101 and CCFZ533X2101), 20 patients with rheumatoid arthritis (CCFZ533X2101), 59 patients with renal transplant (CCFZ533X2201), 155 patients with Sjögren's syndrome (CCFZ533X2203 and CCFZ533B2201), 44 patients with myasthenia gravis (CCFZ533X2204), 15 patients with Graves` disease (CCFZ533X2205), 19 patients with hidradenitis suppurativa (CCFZ533H12201BC), 340 patients with kidney transplant (CCFZ533A2201), 39 with liver transplant (CCFZ533A2202), 26 patients with systemic lupus erythematosus (CVAY736X2208), 30 patients with lupus nephritis (CCFZ533X2202), 2 patients with Type 1 Diabetes (CCFZ533X2207) of which approximately 608 subjects received CFZ533. Based on this CFZ533 is well-tolerated, with no increased risk for drug-related thromboembolic events in dosed subjects.

Based on preliminary data, multiple doses of 10 mg/kg IV CFZ533 were safe and improved the signs and symptoms of primary Sjögren's syndrome (pSS) as measured by relevant clinical endpoints. As pSS is, in many aspects, similar to SLE (also characterized by circulating autoantibodies and CD40 pathway-related abnormalities), efficacy in pSS may further strengthen the rationale for targeting CD40 in lupus nephritis.

Collectively, these results suggest that inhibition of the CD40/CD154 pathway by CFZ533 may represent a safe and efficacious novel therapeutic approach for the treatment of lupus nephritis and where, despite progress, the unmet medical need is high.

1.1.3 Relevant data summary

The most relevant data for the present study are summarized in the sections below. For detailed information, please refer to the IB .

1.2 Nonclinical data

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1.3 Clinical data

1.3.1 Human safety and tolerability data

As of November 2020, a total of approximately 837 subjects have been enrolled into the CFZ533 clinical program. The program has included Phase 1 trials in healthy volunteers (CCFZ533X1101 and CCFZ533X2101, n=88) and in rheumatoid arthritis patients (CCFZ533X2101, n=20); and Phase 2 trials in patients undergoing renal transplant (CCFZ533X2201, n=59), with primary Sjögren's syndrome (CCFZ533X2203, and CCFZ533B2201, 155 patients), with myasthenia gravis (CCFZ533X2204, n=44), with Graves` disease (CCFZ533X2205, n=15), with hidradenitis suppurativa (CCFZ533H12201BC, n=19), with kidney transplant (CCFZ533A2201, n=340), with liver transplant (CCFZ533A2202, n=39), with Sjögren's syndrome (CCFZ533B2201, n=86), with systemic lupus erythematosus (CVAY736X2208, n=26), and with lupus nephritis (CCFZ533X2202, n=30), with Type 1 diabetes (CCFZ533X2207, n=2). Results from two clinical trials relevant for the proposed study in lupus nephritis are summarized below; more details are included in the Investigator`s Brochure.

1.3.1.1 Study CCFZ533X2101: First in human trial

This was a First-in-Human, non-confirmatory, randomized, double-blind, placebo-controlled, single-ascending dose study. The study was conducted in 7 centers and utilized a 2 part design. Part 1 evaluated single ascending doses of CFZ533 (0.03, 0.1, 0.3, 1 and 3 mg/kg) and placebo administered as an IV infusion over approximately 1-2 hours in non-Chinese healthy subjects (Cohorts 1 through 5), healthy subjects of Chinese descent (3 mg/kg and placebo, Cohort 9) and patients with rheumatoid arthritis (10 and 30 mg/kg and placebo, Cohorts 6 and 7). Part 2 evaluated a single SC dose of 3 mg/kg CFZ533 and placebo in healthy subjects (Cohort 8). A total of 76 subjects were enrolled including 56 healthy subjects (Cohorts 1 to 5, and 8 and 9) and 20 patients with rheumatoid arthritis (Cohorts 6 and 7).

Overall, single doses of CFZ533 from 0.03 to 3 mg/kg IV and 3 mg/kg SC in healthy subjects, and from 10 to 30 mg/kg IV in patients with rheumatoid arthritis, appeared to be safe and well tolerated. There was no evidence of any dose-related increases in the incidence of AEs or notable differences between non-Chinese and Chinese healthy subjects (3 mg/kg) or between IV and SC (3 mg/kg) administration in non-Chinese healthy subjects. There were no deaths and no subjects withdrew due to AEs. There were no SAEs in healthy subjects. Two patients with rheumatoid arthritis experienced a total of 3 SAEs (due to hospitalization), none of which were considered to be treatment-related. Of note, no thromboembolic event occurred.

There were no apparent differences between CFZ533 treatment groups and placebo for any hematology, biochemistry or urinalysis parameters. No notable changes were observed for EBV/CMC surveillance parameters, coagulation parameters, total IgG and IgM, cytokine parameters, or renal function parameters. There was no evidence of a dose-related effect of CFZ533 on any rheumatoid arthritis markers. There were also no clinically relevant changes in vital signs or changes in ECG parameters.

1.3.1.2 Study CCFZ533X2203: Proof of Concept in primary Sjögren`s syndrome

A multi-center, randomized, double-blind, placebo controlled, parallel group study to assess the safety, tolerability, pharmacokinetics and preliminary efficacy of CFZ533 in patients with primary Sjögren's syndrome (pSS) has been completed.

The study comprised three sequential cohorts. Cohorts 1 (3 mg/kg SC) and 2 (10 mg/kg IV) applied a design with two periods where Period 1 was a 12-week, double blind, placebo controlled period followed by Period 2 which was an additional open label (all-CFZ533) 12 week extension. Cohort 3 was open label with two active (CFZ533) parallel arms.

Twelve (12) patients were included in Cohort 1, 32 in Cohort 2, and 25 patients were included in Cohort 3. In Cohorts 1 and 2, CFZ533 or placebo was administered at Weeks 1, 3, 5 and 9 in Period 1 followed by Period 2 when CFZ533 was administered at Weeks 13, 15, 17 and 21. The doses of CFZ533 administered in Cohort 1 and Cohort 2 were 3 mg/kg SC and 10 mg/kg IV, respectively. In Cohort 3 Arm 1 (N=13), CFZ533 was administered at 600 mg SC weekly on 4 occasions (loading doses), followed by 300 mg SC weekly on 9 occasions (maintenance regimen starting on Day 29). In Cohort 3 Arm 2 (N=12), the loading dose of 10 mg/kg IV CFZ533 on Day 1 was followed by 300 mg SC weekly on 12 occasions (maintenance regimen starting on Day 8).

Overall, based on final data of this study, repeated dosing with different dose levels of CFZ533 over 21 weeks was safe and well tolerated in patients with Sjögren's syndrome. Multiple doses of 10 mg/kg IV. CFZ533 improved the signs and symptoms of Sjögren's syndrome as measured by ESSDAI.

1.3.2 Human pharmacokinetic and pharmacodynamic data

1.3.2.1 Study CCFZ533X2101

In healthy subjects as well as in patients with rheumatoid arthritis, after single IV or SC administration, CFZ533 PK profiles were consistent with target mediated disposition resulting in non-linear PK profiles and more rapid clearance when CD40 receptor occupancy dropped below approximately 90%.

Despite some inter-individual variability in the PK profiles from the Chinese subjects, the disposition of CFZ533 in Chinese subjects was generally similar as for non-Chinese subjects, and the target engagement was also similar (about 4 weeks) after 3 mg/kg IV CFZ533. At this dose level, similar PK/PD profiles were demonstrated through free CFZ533 profiles in plasma, CD40 occupancy on peripheral B cells measuring free CD40 and total CD40, and total sCD40 concentrations in plasma.

In patients with rheumatoid arthritis at 10 mg/kg IV, as measured by free CD40 on whole blood B cells compared to mean pre-dose, and total sCD40 profiles in plasma, full CD40 occupancy was generally maintained for 8 weeks. At 30 mg/kg IV, PK and total sCD40 profiles in plasma are consistent with a duration of target engagement of 16 weeks.

In healthy subjects CD40 engagement by CFZ533 generally led to a decrease in total CD40 on peripheral B cells by about 50%, tracking CD40 occupancy on B cells as measured by free CD40 on B cells. This is likely due to internalization and/or shedding of the membrane bound

CD40 upon binding to CFZ533. In patients with rheumatoid arthritis the decrease in total CD40 on peripheral B cells was not confirmed.

The relationship between CFZ533 in plasma and CD40 occupancy on whole blood B cells (free CD40 on B cells) was defined, and CFZ533 concentrations of 0.3-0.4 μg/mL were associated with full (defined as ≥90%) CD40 occupancy on whole blood B cells.

More generally, non-specific and specific elimination pathways have been identified for CFZ533. The non-specific and high capacity pathway mediated by FcRn receptors is commonly shared by endogenous IgGs. The specific target mediated disposition of CFZ533 led to the formation of CFZ533-CD40 complexes that were partially internalized (with subsequent lysosomal degradation) and/or shed from the membrane. Target-mediated processes resulted in saturable and nonlinear disposition of CFZ533. The formation of CFZ533-CD40 complexes was dose/concentration-dependent, with saturation occurring at high concentrations of CFZ533.

Overall, the disposition of CFZ533 is dependent on the relative contribution of the specific (target mediated) and non-specific elimination pathways to the overall clearance of CFZ533. Nonlinear PK behavior was observed when CFZ533 concentrations were lower than that of the target, while at higher concentrations with CD40 receptors being saturated, the non-specific pathways predominate and the elimination of CFZ533 was linear.

As expected for a typical IgG1 antibody targeting a membrane bound receptor and demonstrating target mediated disposition, the extent of exposure of CFZ533 (AUClast) increased more than the increase in dose (hyper-proportionality). Consequently, this is expected to be associated with a decrease in the volume of distribution and clearance of CFZ533 at higher doses.

One subject at 1 mg/kg IV CFZ533 (1 week full CD40 occupancy) developed specific antibodies to CFZ533 detected 6 weeks after CFZ533 plasma concentrations were below the limit of quantification, and definitively too low to block any CD40 pathway-relevant effects in tissue. The presence of anti-drug antibodies (ADAs) in this subject did not compromised exposure, and was not associated with an immune related safety signal. This corresponds to an ADA incidence of 2% in this study.

A single dose of 3 mg/kg (IV and SC) of CFZ533 transiently suppressed anti-KLH responses to the first KLH immunization, at CFZ533 concentrations corresponding to full (≥90%) receptor occupancy (for about 3-4 weeks). Anti-KLH primary responses were detected in all subjects as CFZ533 concentration, and accompanying receptor occupancy, declined. All subjects were able to mount recall responses to a second KLH immunization (administered after loss of receptor occupancy was anticipated).

Data suggest that CD40 engagement by CFZ533 prevented recombinant human CD154 (rCD154) mediated B cell activation in human whole blood. The rCD154-induced-CD69 expression on B cells was generally suppressed during a period corresponding to full CD40 occupancy on B cells. When CD40 occupancy was incomplete, the functional activity of rCD154 was restored.

There was no evidence of any effect of CFZ533 on immunophenotyping data.

1.3.2.2 Study CCFZ533X1101

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1.4 Study purpose

This study is designed to explore the safety, tolerability, pharmacokinetics and preliminary efficacy of CFZ533 compared with placebo as add-on to standard of care therapy in patients with moderately active proliferative lupus nephritis.

2 Objectives and endpoints

2.1 Primary objective(s)

Primary objective(s)	*Endpoints related to primary objective(s)*
• To evaluate the safety and tolerability of 24 weeks of treatment with CFZ533 as an add-on therapy to standard of care in moderately active lupus nephritis (LN) patients	• AEs/SAEs • Vital signs • ECG evaluation • Standard hematology and chemistry evaluations
• To assess the effect of CFZ533 on renal proteinuria in moderately active lupus nephritis patients after 24 weeks of treatment as an add-on therapy to standard of care as compared to placebo	• Ratio from baseline in urinary protein creatinine ratio (UPCR) at Week 25 (using first morning void)

2.2 Secondary objective(s)

Secondary objective(s)	*Endpoints related to secondary objective(s)*
• To assess the effect of CFZ533 on relevant renal outcomes at different time points	• Ratio from baseline in the following parameters: o UPCR (first morning void) o hematuria and cellular casts • Proportion of patients who fulfill the criteria for complete renal remission (CRR) according to ACR recommendation (Wofsy et al 2012)
• To evaluate the pharmacokinetics (PK) and pharmacodynamics (PD) of CFZ533 in LN patients, after multiple 10 mg/kg IV doses	• PK: Free CFZ533 concentrations in plasma. • Parameters (free CFZ533): Ctrough,ss or Cmin,ss, Cmax,ss, and AUClast (after last dose) • PD: Total soluble CD40 concentrations in plasma: pre-dose, during treatment and follow up. Rate, extent and duration of target engagement.
• To evaluate the immunogenicity of CFZ533 in LN patients, after multiple 10 mg/kg IV doses	• Anti-CFZ533 antibodies in plasma: baseline, during treatment and follow-up, incidence of ADA-positive patients

2.3 Exploratory objective(s)

Exploratory objective(s)	***Endpoints related to exploratory objective(s)***

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Exploratory objective(s)	***Endpoints related to exploratory objective(s)***

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3 Investigational plan

3.1 Study design

This is an exploratory, randomized (2:1 active:placebo), subject- and investigator-blind, placebo-controlled, multicenter study evaluating the safety, tolerability, pharmacokinetics and preliminary efficacy of multiple doses of 10 mg/kg CFZ533 administered intravenously (IV) in lupus nephritis patients.

The study will randomize approximately 60 subjects with moderately active lupus nephritis. The study comprises two periods. The 24-week treatment period will be followed by a 24-week safety follow-up period (starting on Day 169). The duration of the study (including a screening period of up to 4 weeks) for each subject will be approximately 53 weeks. The investigational drug or placebo will be administered on top of standard of care therapy for lupus nephritis. The randomization will be stratified by baseline daily dose equivalent of prednisone (≤10 mg, >10 mg). Patients who do not receive corticosteroids at baseline will be included in the ≤10 mg stratum.

Subjects will be screened within 29 days of the first study drug infusion. Eligibility will be confirmed at the baseline visit within one week before the first dose. All baseline safety evaluation results must be available prior to dosing, and meeting eligibility criteria. Eligible subjects will enter the treatment period, and will be randomized at a 2:1 ratio to receive treatment with either CFZ533 or placebo. Subjects will receive the intravenous infusion on Day 1 within seven days of the baseline visit, followed by PK, PD, and safety assessments until one hour after completed infusion.

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All infusions will take place in a monitored facility with assessment of vital signs ahead of the infusion. Subjects will be discharged 1 hour post-dose following satisfactory review of safety data (AE events, vital signs) by the Investigator.

Each patient will come to the study site for the follow-up evaluations on Day 169, Day 197, Day 225, Day 253, Day 281, Day 309, and Day 337, respectively. Patients should remain on their standard of care therapies. Dose of standard of care (SoC) therapies (see eligibility criteria and permitted co-medications) must remain unchanged during the study. However, in case of SoC related toxicities, doses of concomitant medications may be adjusted at the investigator's discretion.

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Safety assessments will include physical examinations, ECGs, vital signs, standard clinical laboratory evaluations (also including serum amylase and lipase), hematology (including blood coagulation assays), blood chemistry, urinalysis, adverse event, serious adverse event and AEs of special interest monitoring.

Proteinuria will be assessed using urine samples collected in the patients' home (first morning void sample) and at the clinic (clinic spot urine sample).

PK/PD and immunogenicity assessments at pre-dose, and during treatment and follow up periods include (i) free CFZ533 in plasma (Ctrough or Cmin, and Cmax in steady state conditions), total soluble CD40 in plasma, and (iii) anti-CFZ533 antibodies in plasma.

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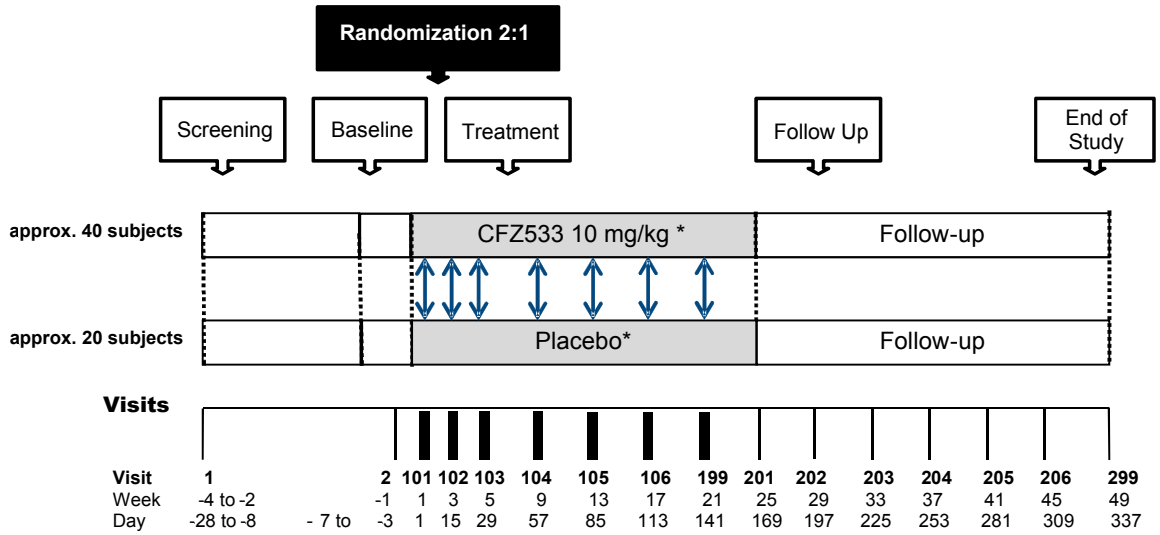
For a detailed outline of safety assessments, please refer to the Assessment schedule.

Figure 3-1 Study Design



* CFZ533 or placebo 10 mg/kg i.v. on Day 1, 15, 29, 57, 85, 113, and 141

3.2 Rationale of study design

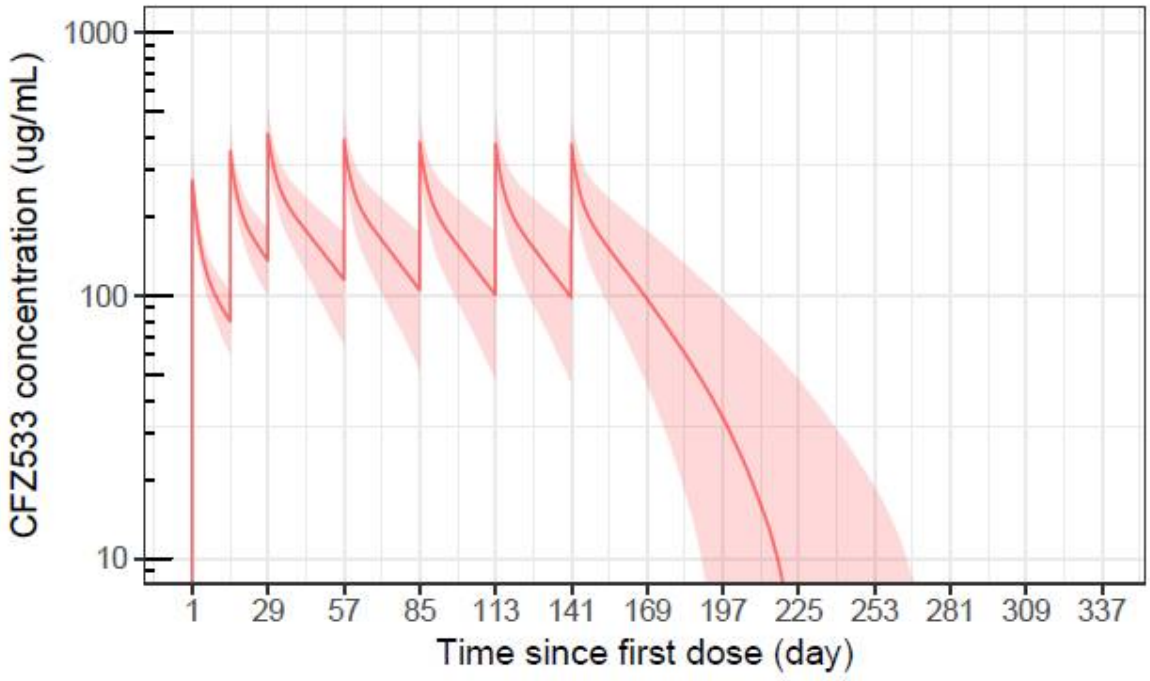
A randomized, placebo-controlled, subject and investigator blind approach is planned to minimize potential bias in reporting safety and clinical efficacy data in this exploratory study with CFZ533 in lupus nephritis patients. Patients will be randomized to CFZ533 or placebo in a 2:1 ratio in order to minimize exposure to placebo and to gather more data on CFZ533. Stratified randomization is planned in order to limit imbalances between active and placebo arms in baseline intake of oral corticosteroids. Placebo will be used as comparator to provide objective evaluation of potential AEs and other safety data, as well as of clinical efficacy. Use of placebo will be administered on top of standard of care therapy so patients remain on an established treatment regimen with the study medication added.

This study will use first morning void urine protein to creatinine ratio (UPCR), an established renal endpoint, as the key efficacy outcome measure. Based on internal data (Novartis Study CERL080A2420 testing mycophenolate (Myfortic) in lupus nephritis patients), as well as published evidence (Zeher et al 2011), this endpoint is expected to be sufficiently sensitive to provide preliminary evidence for efficacy after 24 weeks of treatment.

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

Figure 3-2 displays the predicted time-course of CFZ533 concentrations in plasma, following the intravenous dosing regimen described in Section 3.1, and assuming similar kinetics of the drug and its target in LN and primary Sjögren's Syndrome patients (ongoing study CCFZ533X2203).

Figure 3-2 Predicted time-course of CFZ533 concentration



The line represents the predicted time-course of CFZ533 concentration for the typical patient; the band represents the 90% prediction interval, meaning that 90% of the patients' concentration is expected in that area.

3.3.1 Loading regimen

Renal CD40 expression is up-regulated in World Health Organization (WHO) class III and class IV LN patients (proliferative LN; Yellin et al 1997), potentially linking CD40 signaling to organ-specific pathology. The levels of soluble CD40 (sCD40) are also significantly increased in patients with SLE, and an association between the levels of sCD40 and the rs1883832 C/T polymorphism of CD40 gene was observed (Chen et al 2015). Additionally, in SLE patients (Vakkalanka et al 1999) the concentration of soluble CD154 was higher than in disease controls or healthy subjects, and segregation of SLE patients by severe, moderate, or mild extent of

disease showed a relationship between disease severity and sCD154 concentration, denoting up-regulation/activation of the CD40-CD154 pathway in SLE.

In this study CFZ533 will be administered at 10 mg/kg IV every 4 weeks (Q4W; from Day 1 to Day 141), plus an additional dose of 10 mg/kg IV at Day 15.

The initial Q2W (every 2 weeks) loading regimen (for the first 3 doses) is justified because CFZ533 is subject to target mediated elimination, and elevated CD40 expression in the body is associated with high elimination (clearance) rate of CFZ533, loss of target engagement and loss of CD40 pathway blockade in target tissues, if CD40 is not fully saturated. The Q2W regimen for the first 3 doses is expected to provide full CD40 occupancy at start of treatment. In these conditions, the contribution of CD40 to the overall clearance of CFZ533 is minimal, and the disposition of CFZ533 is mainly the consequence of CFZ533 binding to FcRn receptors (a high capacity receptor responsible for IgG homeostasis by recycling/salvage). This was clearly demonstrated through PK/PD data collected in HVs and RA patients (CCFZ533X2101), kidney transplant patients (CCFZ533X2201), primary Sjögren's Syndrome patients (CCFZ533X2203) and Grave's disease patients (CCFZ533X2205) patients.

Generally, patients with systemic autoimmune diseases present with an increase CD40 expression compared to healthy subjects. Elevated serum/plasma sCD40 levels have been reported in RA (Study CCFZ533X2101, and MacDonald et al 1997), Systemic Sclerosis (Komura et al 2007), and Graves' ophthalmopathy/GD (Study CCFZ533X2205, Mysliwiec et al 2007). In salivary glands biopsies obtained from pSS patients, CD40 was constitutively expressed by lymphocytes, ductal epithelial cells and endothelial cells (Dimitriou et al 2002), which is in line with elevated plasma levels noted in Study CCFZ533X2203. In Type 1 Diabetes patients, elevated sCD40 correlated well with patients' inflammatory state (Chatzigeorgiou et al 2010), and in diabetic patients, cellular CD40 (on peripheral blood mononuclear cells) showed a significantly positive correlation with plasma concentrations of sCD40, interleukin-6 (IL-6), C-reactive protein (CRP) and hemoglobin A1c (HbA1c). Additionally, elevated levels of soluble CD40 ligand (sCD154) in serum of patients with systemic autoimmune diseases were noted (Goules et al 2006).

These additional data in patients with systemic autoimmune diseases further justify the need for a Q2W regimen for the first 3 doses to provide full target saturation at start of treatment, in conditions where CD40 expression is enhanced.

Due to kidney damage, proteinuria is commonly observed in patients with SLE/LN. The effect of renal impairment on the PK of biologics is dependent on the ability of the compound to undergo glomerular filtration, which is largely driven by molecular weight (MW). CFZ533 has a MW of *ca*. 146 kD, and renal clearance usually plays a minimal role in the elimination of biologics with MW greater than 69 kDa (Meibohm and Zhou 2012).

An association between increased baseline proteinuria and increased clearance was observed in the population PK of belimumab (a human mAb that inhibits B-cell activating factor, BAFF) in SLE (Struemper et al 2013). Also, there is evidence that in some forms of renal disease, such as diabetic nephropathy, there may be an increase in the renal elimination of IgGs (Bakoush et al 2002). This is further justifying the need for a loading regimen for CFZ533.

3.3.2 Maintenance regimen

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3.3.3 Bodyweight-adjusted dosing

While a fixed dosing regimen would be favored for its ease of use, a bodyweight (BW)-adjusted dosing is justified in this study.

Whether CFZ533 should be administered as a flat (fixed) dose or based on BW mainly depends on the effect of BW on the PK/PD of CFZ533. At this point in time the effect of BW on the disposition of CFZ533 is not fully characterized, especially in the low BW range.

The LN population is predominantly represented by female patients, and it is anticipated that patients within a BW range of 40-150 kg will be enrolled in this study. While, no gender effect is expected for the disposition of CFZ533 (the effect of sex on the exposure of IgG-type antibodies is often insignificant after the difference in BW has been taken into account),

a BW-adjusted dosing is likely to reduce the interpatient variability in exposure in the proposed BW range.

Only subjects with a body mass index (BMI) within the range of 18 to 40 kg/m^2 will be eligible to participate in the study.

3.4 Rationale for choice of comparator

Placebo to CFZ533 will be used as comparator to provide objective evidence of potential AEs and other safety data, as well as clinical efficacy and PD data generated from subjects exposed to the experimental therapy. Since there is no established, clinically effective disease modifying treatment for lupus nephritis patients who are clinically active despite conventional immunosuppressive therapies, treatment with placebo on top of standard of care therapy is justified.

3.5 Purpose and timing of interim analyses/design adaptations

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3.6 Risks and benefits

3.6.1 Potential benefit

Despite progress, unmet medical need in lupus nephritis patients remains high. Current standard of care therapies comprise conventional immunosuppressive which are not fully efficacious in all patients and associated with significant toxicities. Based on the scientific rationale for targeting CD40 pathway in lupus and the data available for CFZ533, CD40 inhibition by CFZ533 has a potential therapeutic benefit for lupus nephritis patients who are clinically active despite standard of care.

3.6.2 Potential risks associated with exposure to CFZ533 and their mitigation

Currently, limited data exists regarding the use of agents that block the CD40/CD154 pathway. Preclinical and data from the Phase 1 and 2 programs for CFZ533 as well as data from compounds acting on the same pathway (CD40-CD154) have been taken into account to estimate the potential risks associated with CFZ533. The current IB (Section 6, Investigator Guidance) also provides detailed instructions regarding the risks and their mitigation.

3.6.2.1 Infections

Subjects treated with CFZ533 may be at an increased risk of infection. CD40 ligation is linked to the functional activity of antigen presentation, as well as T-cell priming, B-cell differentiation, antibody production and immune memory. Administration of CFZ533 is expected to result in general immunosuppression with a decreased capacity to mount a response to novel immunogens, including those of bacterial, viral, fungal and parasitic origin when full receptor occupancy has been achieved.

Although the ability to mount a primary immune response will be affected by CFZ533, the memory B-cell repertoire and immune recall response should remain intact and protective. In addition, subjects will have adequate preformed antibody to maintain protective humoral response for extended periods of time (months).

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No T-cell or B-cell lymphopenia or infection was noted in the Phase 1 study. In patients receiving weekly to bi-monthly administration of the parent antibody lucatumumab, the rate of infection was very low and similar to control, supporting this above hypothesis. Subjects with current, active or latent infection susceptible to reactivation will be excluded from entry into this clinical study.

The risk of infection may increase if CFZ533 is combined with steroids or strong immunosuppressive drugs. In the current study, low dose steroid (up to 30 mg prednisone or equivalent per day) and drugs with low to moderate risk for immunosuppression will be allowed in combination with CFZ533. Strong immune-suppressive drugs such as cyclophosphamide or cyclosporine A will be prohibited.

During the conduct of the current study, a fatal SAE was reported (Investigator Notification case ID: NVSC2019TN015399) in Nov 2019.

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Subjects enrolled in the current study will be monitored regularly and carefully for signs and symptoms which might indicate a severe infection. All subjects will be screened and regularly monitored for CMV infection (also see Section 8.6.8.2.). Subjects will be informed to contact

the study physician if they present with signs and symptoms of an infection such as fever, nausea, myalgia, headache, arthralgia, chills, diarrhea, stiff neck, and malaise for further assessment and treatment if necessary.

3.6.2.2 Vaccination

Vaccination of subjects during treatment with CFZ533 and prior to clearance of the antibody is likely to result in therapeutic failure (i.e., non-protective antibody titers) due to the pharmacologic activity of the antibody. For subjects participating in this study, all vaccinations should be up to date based on local guidelines. Reduced or absent immunization effectiveness may be expected for both live (attenuated) and non-live (e.g. inactivated (killed), viral-vector, mRNA) vaccines. For further information refer to the Investigator's Brochure Section 4.2.7.

Administration of live (attenuated) SARS-CoV-2 vaccines is prohibited within 8 weeks of the first infusion of CFZ533, while receiving CFZ533 treatment and for at least 14 weeks after the last dose of the study medication.

While there is no absolute contraindication for the use of non-live (e.g. inactivated (killed), viral-vector, mRNA) SARS-CoV-2 vaccines, reduced or absent immunization effectiveness may be expected during treatment with CFZ533 and until 14 weeks after the last dose.

If treatment with CFZ533 is stopped, insufficient humoral immune response is likely to persist until 14 weeks after the last dose (until CFZ533 exposure decreases in the blood and tissues below the pharmacologically relevant level).

If SARS-CoV-2 vaccine is considered mandatory by local governance, administration of the vaccine should be provided at least 4 weeks before randomization or postponed for at least 14 weeks following the last dose of study drug, due to anticipated reduced or absent immunization effectiveness in treated patients.

Although there is no mandate to vaccinate clinical trial participants against SARS-CoV-2 prior to entry into the trial, patients will be advised to have completed vaccination series (if multi-dose regimen) against SARS-CoV-2 at least 4 weeks prior to randomization (or as long as needed before the first dose of CFZ533 based on when the protective immune response is expected to develop as indicated for the specific vaccine), if available, and according to local practice.

Patients who have decided not to get vaccinated may enter the trial if they have been informed that, should they receive a SARS-CoV-2 vaccination during the trial, the vaccination would likely be ineffective, and maximizing vaccine effectiveness would require study drug discontinuation and a waiting period of at least 14 weeks before vaccination.

For patients already in the study, the decision of vaccination for SARS-CoV-2 should be done on a case-by-case basis and in consultation between the treating physician and patient. Vaccination failure is a known risk.

For patients enrolled in Novartis clinical trials who do receive a SARS-CoV-2 vaccine which has been permitted* for use by a local Health Authority, vaccine documentation will be recorded as a concomitant medication. Institutional Review Board/Ethics Committee (IRB/EC) approval and inclusion in Informed Consent are not required. [*Permitted includes full approval, conditional approval, emergency use authorization, provisional/temporary/interim

authorization by Health Authority i.e., outside of a COVID- 19 clinical trial to evaluate the effectiveness/safety of a SARS-CoV-2 vaccine.]

3.6.2.3 Immunogenicity

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3.6.2.4 Thrombophilia

Currently, a theoretical risk without clinical evidence exists for CFZ533 to cause thromboembolic events based on previous experience with monoclonal antibodies that bind to CD154 (CD40L). Such antibodies have been associated with a risk of thrombophilia in both clinical and non-clinical studies in primates. These thromboembolic events have been linked to the direct activation of platelets which express both CD154 and a low affinity, activating Fc receptor FcγRIIA. Upon binding to CD154, the Fc-domains of the anti-CD154 mAb may interact with the platelet FcγRIIA receptors, and induce cross-linking and aggregation. While anti-CD154 antibodies are clearly associated with a high risk for thrombophilia, both preclinical and clinical data from an extensive phase 2 clinical program across healthy subjects and patients across different indications have not indicated an associated risk with CFZ533. Detailed information can be found in the current IB version.

Although the risk is theoretical, hematologic and coagulation parameters will be regularly monitored in the current study. Furthermore, patients with conditions such as anti-phospholipid syndrome where the risk is already high will be excluded unless they are on a stable anti-thrombotic prophylaxis.

3.6.2.5 Malignancy including lymphoproliferative disorders

A hypothetical risk for lymphoproliferative disorders for some patients under strong immunosuppression cannot be excluded for CFZ533. To date, however, no lymphoproliferative disorders have been detected in NHP studies, or in clinical trials in healthy volunteers or patients where CFZ533 was evaluated. In the ASKP1240 trials, no lymphoproliferative disorders were reported to date. In the renal transplant study (CCFZ533X2201) the incidence of malignancies were comparable among the treatment groups with 5.9% in the CFZ533 group and 5.6% in the control group. Epstein-Barr virus (EBV) infection is commonly associated with

lymphoproliferative disorders in transplant and immunosuppressed patients. Inclusion of patients who are EBV negative will be defined by the specific clinical trial protocol where applicable. The clinician should monitor hematology regularly for changes consistent with a lymphoproliferative disorder. Patients with history of malignancy of any organ system, treated or untreated, within the past 5 years are excluded from the clinical trials.

3.6.3 Blood sample volumes

A maximum of 650 mL of blood is planned to be collected over a period of 53 weeks from each subject as part of the study. Additional samples may be required for safety monitoring.

Timings of blood sample collection are outlined in the Assessment schedule (Section 8.1).

A summary blood log is provided in the Site Operations Manual (SOM). Instructions for all sample collection, processing, storage and shipment information is also available in the SOM and central Laboratory Manual.

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4 Population

The study population will be comprised of female and male subjects (in the age range of 18 to 75 years) with moderately active lupus nephritis who are on a stable dose of immunosuppressive treatment and demonstrate moderate disease activity despite standard of care therapy. Moderate disease activity is defined as having clinical signs of renal disease activity such as proteinuria (≥ 0.5) but without an immediate need for induction therapy or for whom standard induction therapy with high dose corticosteroids and mycophenolate or cyclophosphamide is not an option. A total of approximately 60 subjects will be randomized (2:1 ratio active:placebo) to participate in the study.

The Investigator must ensure that all subjects being considered for participation in the study will meet the following eligibility criteria. No additional criteria should be applied by the Investigator, in order that the study population will be representative of all eligible subjects.

Subject selection is to be established by checking through all inclusion and exclusion criteria at screening and baseline. A relevant record (e.g., checklist) of the eligibility criteria must be filed with the subject's source documentation at the study site.

Deviation from any eligibility criterion excludes a subject from enrollment into the study, and randomization to study treatment.

4.1 Inclusion criteria

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

1. Understand the study procedures and provide written informed consent before any study-related assessment is performed.
2. Men and women with systemic lupus erythematosus (see below), aged ≥18 years and ≤75 years at screening, fulfilling at least 4 out of 11 criteria for SLE as defined by the American College of Rheumatology (Tan et al 1982, revised by Hochberg 1997).

3. Subjects must have a body mass index (BMI) within the range of 18 - 40 kg/m^2. (BMI = Body weight (kg) / [Height (m)]^2) to participate in the study at Screening visit.
4. Histological diagnosis of proliferative lupus nephritis World Health Organization (WHO) ISN/RPS (Weening et al 2004) Class III or IV within 5 years of screening.
5. Presence of antinuclear autoantibody (ANA titer ≥1:80 at screening)
6. First morning void or spot urine UPCR ≥0.5 mg/mg (56.52 mg/mmol) at Screening visit and Baseline visit
7. At least one of the following at Screening visit:
   a. low complement level (C3 < 0.9 g/L or C4 < 0.1 g/L), and/or
   b. elevated anti-dsDNA (≥30 IU/mL), and/or
   c. urine sediment consistent with active proliferative lupus nephritis such as presence of cellular (granular or red blood cell) casts or hematuria (>5 red blood cells per high power field) if other causes such as menstrual bleeding are excluded
8. Patient must have sufficient kidney function as estimated by eGFR > 30 mL/min/1.73m^2 at screening and baseline visits
9. Patients must have active disease as defined by proteinuria and additional symptoms as defined above (criterion 7) despite standard of care therapy for lupus nephritis as considered appropriate by the treating physician (e.g., corticosteroids and/or immunosuppressive or immunomodulatory treatments such as mycophenolate, azathioprine, methotrexate or hydroxychloroquine). For guidance, see published guidelines such as by Bertsias et al 2012 and Hahn et al 2012
10. If the patient is taking oral corticosteroid treatment at screening, the dose (max. 30 mg prednisone or equivalent per day) must be stable for at least 2 weeks prior to randomization

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14. Women of child-bearing potential (defined as all women physiologically capable of becoming pregnant) must use highly effective methods of contraception before entering the study, during dosing and until study completion.

    Highly effective contraception methods include:

    - Total abstinence from heterosexual intercourse (when this is in line with the preferred and usual lifestyle of the subject). Periodic abstinence (e.g. calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception.
    - Female sterilization (have had surgical bilateral oophorectomy with or without hysterectomy), total hysterectomy or tubal ligation at least six weeks before taking

investigational drug. In case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment.

- Male-partner sterilization (at least 6 months prior to screening). For female subjects in the study, the vasectomized male partner should be the sole partner for that subject.
- Use of oral, injected or implanted hormonal methods of contraception or placement of an intrauterine device (IUD) or intrauterine system (IUS) or other forms of hormonal contraception that have comparable efficacy (failure rate < 1%), for example hormone vaginal ring or transdermal hormone contraception. Women should have been stable on their chosen method of OC for a minimum of 3 months before entering the trial.
- Postmenopausal females must have had no regular menstrual bleeding for at least one (1) year prior to initial dosing. Menopause will be confirmed by a plasma FSH level of >20 IU/L at screening.

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

All female patients of childbearing potential must have negative pregnancy test results at Screening and Baseline visits.

4.2 Exclusion criteria

Eligible Population fulfilling any of the following criteria are <u>not</u> eligible for inclusion in this study:

1. Any glomerulonephritis other than WHO Class III or IV lupus nephritis. Patients with proliferative nephritis (Class III or IV) who, in addition, have overlapping histological signs for other glomerulonephritis, e.g. Class V are eligible at the investigator`s discretion.
2. Hypoalbuminemia (serum albumin of less than 2.0 g/dL).
3. Patients who have received
   a) oral or IV cyclophosphamide within 3 months prior to randomization.
   b) IV corticosteroid bolus (dose higher than 1 mg/kg) within 3 months prior to randomization.
   c) rituximab or other B cell depleting agent received prior to randomization within
      - ≤ 6 months: no inclusion
      - > 6 but ≤12 months: B cell count must be within normal range
      - >12 months prior to randomization: no special requirements
      - .
   d) belimumab within 6 months prior to randomization.
   e) any other biologic drug or an investigational drug within three (3) months or five times the half-life, whichever is longer prior to randomization.

f) calcineurin inhibitor (e.g., tacrolimus, cyclosporin A) within 3 months prior to randomization.
[For China, Hong Kong, and Korea only: calcineurin inhibitors except tacrolimus (≤ 3 mg/day) within 3 months prior to randomization.]

4. Patients who are at significant risk for thromboembolic events based on the following:
   - History of either thrombosis or 3 or more spontaneous abortions
   - Presence of lupus anticoagulant or prolonged aPTT and no prophylactic treatment with aspirin or anticoagulants as per local standard of care

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7. Have had signs or symptoms of a clinically significant systemic viral, bacterial or fungal infection within 30 days prior to randomization

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13. Live vaccines within 8 weeks of study drug infusion

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

5 Restrictions for Study Subjects

For the duration of the study, the subjects should be informed and reminded of the restrictions outlined in this section.

5.1 Contraception requirements

Women of child bearing potential must be informed that taking the study treatment may involve unknown risks to the fetus if pregnancy were to occur during the study, and agree that in order to participate in the study they must adhere to the contraception requirement outlined in the Section 4.1 (Inclusion Criteria). If there is any question that the subject will not reliably comply, they should not be entered or continue in the study.

5.2 Prohibited treatment

The following treatments are prohibited during the course of the trial and before the first dosing, due to their mechanisms of action that can act as a confounder for the study objectives and results:

- Oral or i.v. cyclosphosphamide treatment within 3 months prior to first dosing with study drug.
- I.V. corticosteroid bolus (dose higher than 1 mg/kg) within 3 months prior of first dosing with study drug.

- Rituximab or other B cell depleting agent received prior to randomization within
  - ≤ 6 months
- > 6 but ≤12 months, *and* B cell count *not* within normal range
- Belimumab within 6 month of first dosing with study drug.
- Any other biologic or an investigational drug within 3 months or five times the half-life before the first dosing with study drug, whichever is longer

- Calcineurin inhibitors (e.g., tacrolimus, cyclosporin A) within 3 months of first dosing with study drug.
  [For China, Hong Kong, and Korea only: Calcineurin inhibitors except tacrolimus (≤ 3mg/day) within 3 months of first dosing with study drug.]

In case of any of the above therapies becomes necessary during the trial, (e.g. cyclophosphamide rescue due to major disease worsening), the washout period for CFZ533 (approximately 16 weeks) and potential interactions need to be considered by the Investigator.

5.3 Dietary restrictions and smoking

Subjects should maintain their usual diet and life habits during the entire study.

5.4 Other restrictions

No strenuous physical exercise (e.g. weight training, aerobics, football) until after Study Completion evaluation. Patients may otherwise continue with their usual level of physical activity.

6 Treatment

6.1 Study treatment

The investigational drug, CFZ533 and matching placebo, will be prepared by Novartis and supplied to the Investigator site as double-blinded medication kits.

Details on the requirements for storage and management of study treatment, and instructions to be followed for subject numbering, prescribing/dispensing and taking study treatment are outlined in the Site Operations Manual.

6.1.1 Investigational treatment and control drug(s)

The dosage form of the supplied drug is a "ready to use" aqueous buffered sterile solution also referred to as CFZ533 Concentrate for infusion (liquid in vial). The solution contains 150 mg/ml CFZ533 and the excipients L-histidine, sucrose, and polysorbate 20, pH 6.0 ± 0.5. The placebo control selected for this study is a solution with matching composition of inactive excipients.

Table 6-1 Overview of study medication

Study drug name	Formulation	Appearance	Unit dose	Packaging	Provided by
CFZ533	Solution for infusion	Opalescent to clear, colorless solution	150 mg/mL*	6 ml Type I glass vials, double blind	Novartis
Placebo	Solution for infusion	Opalescent to clear, colorless solution	0 mg/mL*	6 ml Type I glass vials, double blind	Novartis

*The vials contain a 20% overfill to allow a complete withdrawal of the labeled amount of CFZ533 or placebo.

Clinical supplies are to be dispensed only in accordance with the pharmacy manual.

A pharmacist or authorized designee is required to prepare the study drug. Instructions for storage and handling of study medication vials, and preparation of infusion solution are described in the Pharmacy Manual (which is provided as a separate document).

6.1.2 Additional study treatment

No additional treatment beyond investigational drug (CFZ533 and placebo) are included in this trial.

6.2 Treatment arms

Subjects will be assigned to one of the following two treatment arms in a ratio of 2:1:

- CFZ533: multiple doses of 10 mg/kg CFZ533 IV infusion
- Placebo: multiple doses of placebo IV infusion

6.3 Treatment assignment and randomization

If the subject's eligibility is confirmed at the Baseline visit, the subject will be randomized, and treatment will be assigned, via the IRT system that will be set up for the randomization of eligible subjects, and for distribution and assignment of the study medication. Eligible subjects will be assigned to a treatment arm (see Site Operations Manual for details).

The Subject number assigned to a subject at screening remains the unique identifier for the subject throughout the study. The randomization number is only used to identify which treatment the subjects have been randomized to receive. For information on subject numbering, please see 'Subject numbering' section in the SOM.

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

The randomization will be stratified by baseline daily dose equivalent of prednisone (≤ 10mg, >10mg). Patients who do not receive corticosteroids at baseline will be included in the ≤10mg stratum.

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

Follow the details outlined in the Site Operations Manual regarding the process and timing of treatment assignment and randomization of subjects.

6.4 Treatment blinding

This is a subject and investigator-blinded study. Subjects and investigators will remain blinded to study treatment throughout the study, except where indicated below.

The identity of the treatments will be concealed by the use of study drugs that are all identical in packaging, labeling, schedule of administration, appearance, and odor.

Site staff

All site staff (including study investigator and study nurse) will be blinded to study treatment throughout the study.

Unblinding a single subject at site for safety reasons (necessary for subject management) will occur via an emergency system in place at the site (see Section 6.7).

Sponsor staff or delegate

The following unblinded sponsor roles are required for this study amend as appropriate:

Unblinded sample analysts for PK, PD and IG.

The sample analysts will receive a copy of the randomization schedule (via request to the Randomization Office), to facilitate analysis of the samples. The sample analysts will provide the sample data to the study team under blinded conditions unless otherwise allowed.

The study statistician will be able to access the randomization list for interim analyses and is allowed to share unblinded information with the rest of the clinical team as appropriate for internal decision purposes, as outlined in Section 6.4. For example, unblinded summaries and unblinded individual data can be shared with the team for interim analyses.

Study programmers and other personnel involved in study data analysis (e.g. biomarker expert) are allowed to access treatment assignment information for the purpose of conducting interim analyses.

The clinical trial team is allowed to share unblinded results with other sponsor staff (e.g. decision boards) as required for internal decision making on the study or the project at the time of interim analyses while the study is ongoing.

All unblinded personnel will otherwise keep randomization lists and data or information that could unblind other study team members confidential and secure except as described above.

Following final database lock all roles may be considered unblinded.

Table 6-2 Blinding and unblinding plan

Role	Randomization list generated	Treatment allocation & dosing	Safety event (single subject unblinded)	Interim Analysis
Subjects/Patients	B	B	UI	B
Site staff	B	B	UI	B
Drug Supply and Randomization Office	UI	UI	UI	UI
Statistician/statistical programmer/ data analysts (e.g. PK)	B	B	UI	UI
Independent committees used for assessing interim results, if required (e.g. DMC)	B	B	UI	UI
All other sponsor staff not identified above (trial team, project team, management & decision boards, support functions)	B	B	UI	UI

Key:

UI: Allowed to be unblinded on individual patient level

B: Remains blinded

6.5 Treating the subject

CFZ533 10 mg/kg or placebo will be administered to the subject as an intravenous infusion at the study site. See the Site Operations Manual and Pharmacy Manual for further details.

6.6 Permitted dose adjustments and interruptions of study treatment

Study drug dose adjustments and/or interruptions are not permitted in this study; in case of an AE or for any reason (e.g., non-compliance, operational hurdle) resulting in a deviation from the required dosing scheme, consultation and agreement with Novartis will be necessary to decide whether the subject can continue or needs to be withdrawn from the study. Any change in dosing must be recorded on the Dosage Administration Record eCRF. In case of notable adverse events, SAEs including loss of efficacy and/or associated PK/PD data collected during the study, changes to a different dosing scheme level may be considered and implemented via a protocol amendment.

Upon review data at interim analysis, dose adjustment for study drug may occur. This will be implemented via a protocol amendment.

6.7 Emergency breaking of assigned treatment code

Emergency code breaks must only be undertaken when it is required to in order to treat the subject safely. Most often, study treatment discontinuation and knowledge of the possible treatment assignments are sufficient to treat a study subject who presents with an emergency condition. Emergency treatment code breaks are performed using the IRT. When the investigator contacts the system to break a treatment code for a subject, he/she must provide the

requested subject identifying information and confirm the necessity to break the treatment code for the subject. The investigator will then receive details of the investigational drug treatment for the specified subject and a fax or email confirming this information. The system will automatically inform the study monitor for the site and the Study Team that the code has been broken.

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

- protocol number
- study drug name
- subject number.

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

An assessment will be done by the appropriate site personnel and sponsor after an emergency unblinding to assess whether or not study treatment should be discontinued for a given subject.

6.8 Treatment exposure and compliance

Pharmacokinetic data and parameters (measures of treatment exposure) will be determined in all subjects treated with CFZ533, as detailed in Section 8.7.

6.9 Recommended treatment of adverse events

Parenteral administration of monoclonal antibodies can be associated with acute, severe reactions (occurring within the first few hours post dose) secondary to hypersensitivity, immunogenicity, or ADCC-mediated cell depletion.

In this study, CFZ533 will be administered as intravenous infusion. No infusion reactions have been noted in the Phase 1 and Phase 2 clinical program with CFZ533 so far; however, investigators should be aware of the possibility and be prepared to treat such events.

Subjects will be monitored at the site for at least 1 hour post dose or longer, at the discretion of the Investigator, to ensure adequate safety monitoring. In case of any signs of an acute reaction, clinical treatment will be provided as determined by the treating physician on a case-by-case basis and depending on the severity, using symptomatic treatment, anti-histamines, Nonsteroidal anti-inflammatory drugs (NSAIDs), acetaminophen, intravenous fluids, corticosteroids, or adrenaline.

For the severity evaluation of allergic reaction, anaphylaxis and cytokine release and any other adverse event which may potentially lead to treatment discontinuation, it is recommended to follow the guidelines by the National Cancer Institute Common Toxicity Criteria version 4.03 (NCI-CTCAE 2010).

Use of rescue medication must be recorded on the Concomitant medications / Significant non-drug therapies eCRF after start of study drug.

6.10 Rescue medication

Standard of care treatment for lupus nephritis includes conventional immunomodulatory therapy (e.g. antimalarials), non-steroidal anti-inflammatory drugs, and immuno-suppressive agents such as corticosteroids, cyclophosphamide, calcineurin inhibitors, mycophenolate, or azathioprine. B cell depleting agent rituximab is also used for certain cases. Medication for SLE is similar, but often including further immunosuppressives such as methotrexate, and recently, also the anti-BAFF monoclonal antibody, belimumab.

In case of severe, clinically significant flare of nephritis or any other SLE manifestations (based on investigator's judgment), introduction or dose increase of any standard of care therapies (e.g. corticosteroids) will be at the discretion of the treating physician. Rescue medicine is to be provided by the study center or personal physician. Use of rescue medication (after start of CFZ533 or placebo) must be recorded in the eCRF at the Concomitant medications/Significant non-drug therapies section.

6.11 Concomitant treatment

Certain standard of care therapies (corticosteroids, mycophenolate, azathioprine, methotrexate, antimalarials) in a stable dose are permitted, while others like cyclophosphamide, rituximab, belimumab, calcineurin inhibitors [For China, Hong Kong, and Korea only: (except tacrolimus ≤ 3 mg/day)] are prohibited, as defined in the eligibility criteria. Corticosteroids and antimalarials may be combined with maximum one further permitted standard of care medication (as listed above), to minimize the risk of over-immunosuppression.

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The Investigator must instruct the subject to notify the study site about any new medications he/she takes after the subject was enrolled into the study.

All prescription medications, over-the-counter drugs and significant non-drug therapies (including physical therapy and blood transfusions) administered or taken within the timeframe defined in the entry criteria prior to the start of the study and during the study, must be recorded on the Concomitant medications/Significant non-drug therapies CRF.

Medication entries should be specific to trade name, the single dose and unit, the frequency and route of administration, the start and discontinuation date and the reason for therapy.

Each concomitant drug must be individually assessed against all exclusion criteria/prohibited medication. If in doubt, the Investigator should contact Novartis before randomizing a subject or, if the subject is already enrolled, to determine if the subject should continue participation in the study.

7 Study completion and discontinuation

7.1 Study completion and post-study treatment

Each subject will be required to complete the study in its entirety and thereafter no further study treatment will be made available to them.

Study completion is defined as when the last subject completes 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.

7.2 Discontinuation of study treatment

Discontinuation of study treatment for a subject occurs when study treatment is stopped earlier than the protocol planned duration. Discontinuation of study treatment can be decided by either the subject or the investigator. For CTCAE grading, version 4.03 will be used (NCI CTCAE).

Study treatment must be discontinued under the following circumstances:

- Subject/guardian decision - subjects may choose to discontinue study treatment for any reason at any time
- The investigator believes that continuation would negatively impact the safety of the subject or the risk/benefit ratio of trial participation.
- CTCAE Grade 3 or higher adverse event unless it can be conclusively shown that AE is not related to study treatment
- Severe hypersensitivity reaction, infusion reaction, including any of the following: anaphylaxis, fever, chills, urticaria, dyspnea, headache, myalgia, hypotension. Immediate interruption of the infusion to administer study treatment is required in such cases.
- Any protocol deviation that results in a significant risk to the subject's safety.
- Pregnancy
- Major worsening of renal function (e.g. >40% increase from Baseline creatinine level)
- Major worsening of proteinuria (e.g. confirmed 3-fold increase from Baseline)
- Acute infection as a severe AE as judged by the investigator
- In case of suspected or confirmed active CMV infection - see Section 8.6.8.2.
- Significant increase in extra-renal SLE disease activity (e.g. new onset severe CNS lupus)
- Significant changes in standard coagulation test results, including prothrombin time (PT), activated partial thromboplastin time (aPTT) and thromboelastography (TEG) suggesting an increased risk for hypercoagulability or any sign or symptom of a thromboembolic event
- Any other AE or complication where continued dosing of the patient is considered to be placing them at excess risk
- Patient withdraws consent (when patient must also be withdrawn from the study)
- Use of prohibited treatment as outlined in Section 5.2.
- If a liver or renal event occurs, follow guidelines outlined in protocol Appendix 1 and Appendix 2 regarding discontinuation of study treatment.

The appropriate personnel from the site and Novartis will assess whether investigational drug treatment should be discontinued for any subject whose treatment code has been broken inadvertently for any reason.

If discontinuation of study treatment occurs, the investigator must determine the primary reason for the subject's premature discontinuation of study treatment and record this information on the Dosage Administration CRF. The investigator must also contact the IRT to register the subject's discontinuation from study treatment.

Patients who discontinue study treatment are to continue their study participation, and to complete all study visits.

Patients who decide they do not wish to participate in the study further should NOT be considered withdrawn from the study UNLESS they withdraw their consent. If they fail to return for the study visits for unknown reasons, every effort (e.g. telephone, e-mail, letter) should be made to contact the subject. This contact should preferably be done according to the study visit schedule.

The following data should be collected at minimum via telephone/email contact:

- new / concomitant treatments
- adverse events/Serious Adverse Events

Any unresolved AEs will be followed with additional post-study visits as determined appropriate by the study site investigator and sponsor.

Patients who discontinue the study must be reminded not to become pregnant for 14 weeks after the last dose of study medication.

7.3 Withdrawal of informed consent

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

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

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

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

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

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

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

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

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

7.4 Lost to follow-up

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

7.5 Study stopping rules

Stopping Rules

The study can be terminated at any time for any reason by Novartis. Should this be necessary, the patient should be seen as soon as possible and treated as a prematurely withdrawn subject. The investigator may be informed of additional procedures to be followed in order to ensure that adequate consideration is given to the protection of the patient's interests. The investigator will be responsible for informing IRBs and/or ECs of the early termination of the trial. The study will be paused with no further dosing, and recruitment on hold, pending full safety review if patient(s) experience(s) the following events if related to treatment of CFZ533:

1. One (1) patient with CFZ533-related death
2. Three (3) or more patients with a serious adverse event that is suspected to be related to CFZ533 by the Investigator
3. One (1) patient presenting with suspected CFZ533-related cytokine release syndrome,
4. One (1) patient presenting with a suspected CFZ533-related thromboembolic event that is at least of moderate severity
5. More than one (1) patient with allergic reaction of CTCAE Grade 3 or higher severity
6. Any treatment-related, CTCAE Grade 3 or higher adverse event Criteria considered drug related by the Investigator with the following exceptions:
   - Events not requiring treatment, and diagnostic procedures involving elective or non-urgent hospital admission,
   - Disease Specific Events due to the patients underlying LN diagnosis,
   - AEs/SAEs unrelated to the experimental compound as determined by the Investigator or Novartis
7. Two (2) or more patients presenting with:
   - Progressive renal insufficiency or acute kidney injury defined as a Grade 2 increase in serum creatinine (1.5 x ULN) in the setting of euvolemia at any time during the study related to CFZ533
   - Emergent hypogammaglobulinemia defined as total serum IgG below 5.65 g/L or IgM below 0.40 g/L and a reduction in total serum IgG or IgM concentration by 50% or more from baseline, considered clinically significant by the investigator
   - Severe systemic infection or severe opportunistic infection that requires treatment, e.g., sepsis, urosepsis, mycoses, pneumonia.

8. Clinically significant (according to the Investigator) and study drug-related, persisting changes from baseline in vital signs, electrocardiograms, or relevant, persistent changes in laboratory parameters, which are not consistent with existing co-morbidities, in more than one (1) subject within the first 5 treated patients or an incidence of >20% thereafter.
9. Other clinically significant changes or effects in the opinion of the Sponsor that are deemed unsafe to continue dosing.

In addition, all blinded safety data, including disease specific events, will be evaluated by the Sponsor continuously. The study may be paused pending further data analysis and the decision to adjust the dose or modify the medication if the following criteria occur:

- The Sponsor considers that the number and/or severity of AEs justify discontinuation of the study.
- Other clinically significant changes or effects in the opinion of Sponsor that are deemed unsafe to continue dosing.

Furthermore, a Data Monitoring Committee will be established to monitor safety and based on their recommendation the study may be put on hold or modified.

7.6 Early study termination by the sponsor

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

8 Procedures and assessments

8.1 Assessment schedule

Subjects should be seen for all visits/assessments as outlined in the assessment schedule or as close to the designated day/time as possible.

Missed or rescheduled visits should not lead to automatic discontinuation. Subjects who prematurely discontinue the study drug for any reason should be continuing their study participation, i.e., to complete all study visits.

If an epidemic or pandemic (e.g. COVID-19 pandemic) limits or prevents on-site study visits, alternative methods of providing continuing care may be implemented. Phone calls, virtual contacts (e.g. teleconsult) or visits by site staff to the participant´s home depending on local regulations and capabilities, can replace on-site study visits, for the duration of the pandemic until it is safe for the participant to visit the site again.

Table 8-1 Assessment schedule

Epoch	Screening		Treatment														Follow Up						
Visit Name	SCR	BL	Treatment														Follow Up						EOS
Visit Numbers	**1**	**2**	**101**		**102**		**103**		**104**		**105**		**106**		**199**		**201**	**202**	**203**	**204**	**205**	**206**	**299**
Week	-4 to -1		1		3		5		9		13		17		21		25	29	33	37	41	45	49
Day	**-28 to -8**	**-7 to -3**	**1**		**15** ±1		**29** ±2		**57** ±2		**85** ±2		**113** ±2		**141** ±2		**169** ±3	**197** ±3	**225** ±3	**253** ±3	**281** ±3	**309** ±3	**337** +3
Pre/Post[1]			Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post							
Informed consent	X																						
Genetic consent	X																						
Eligibility criteria	X	X																					
Medical history/current conditions	X																						
Demography	X																						
Body height	X																						
Body weight	X	X	X		X		X		X		X		X		X		X	X	X	X	X	X	X
Body temperature	X	X	X		X		X		X		X		X		X		X	X	X	X	X	X	X
Blood pressure/pulse rate	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Physical examination	X	X	X		X		X		X		X		X		X		X	X	X	X	X	X	X
Electrocardiogram	X	X	X		X		X		X		X		X		X		X	X	X	X	X	X	X

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Hematology/Clinical Chemistry/ Urinanalysis[9]	X	X	X		X		X		X		X		X		X		X	X	X	X	X	X	X
Hepatitis, CMV, HIV screen	X[2]		X[8]				X[8]		X[8]		X[8]		X[8]		X[8]		X[8]	X[8]	X[8]	X[8]	X[8]	X[8]	X[8]
TB screen	X																						
FSH[3]	X																						
Pregnancy test[3]	X	X	X		X		X		X		X		X		X		X	X	X	X	X	X	X
ESR, CRP	X	X			X		X		X		X		X		X		X	X	X	X	X	X	X
IgG, IgM	X	X					X				X						X			X			X
C3, C4 Complement	X	X					X				X						X			X			X
Lupus anticoagulant	X		X												X								X
Coagulation test	X	X			X		X		X		X		X		X		X	X	X	X	X	X	X
PK collection[1]			X	X			X	X			X	X	X	X	X	X		X	X	X	X		
PD collection (total soluble CD40)			X				X						X						X		X		
Immunogenicity			X				X						X						X		X		

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Drug administration			X		X		X		X		X		X		X								
Study completion																							X
Concomitant meds/Therapies	As required																						
Adverse Events	As required																						
Comments	As required																						

[1] Pre-dose collection: ahead of drug administration; post-dose collection: 1h AFTER completion of the i.v. infusion

[2] HIV and Hepatitis results to be available in Source data, will not be recorded within the eCRF

[3] FSH level and serum pregnancy test at Visit 1 for female subjects, all other visits pregnancy test in urine (if FSH ≤ 20)

[8] CMV IgG, IgM and DNA (by PCR) done for all subjects. Hepatitis B monitoring done in subjects with positive serology for anti-HBc at screening (results to be available in Source data, will not be recorded within the eCRF). .

[9] A first morning void urine sample will be collected in the patients' home and a second spot urine sample will be collected at the investigational site for the analysis of UPCR, albumin, and creatinine.

8.2 Informed consent procedures

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

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

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

Novartis will provide to investigators a proposed informed consent form that complies with the ICHE6 Good Clinical Practice (GCP) guideline and regulatory requirements and is considered appropriate for this study. The informed consent form will also include a section related to optional future research which will require a separate signature if the subject agrees to future research. The procedures set out in the main consent form concerning the storage, maintenance of privacy, and release of the data or specimens for the main study will also be adhered to for any future research. Any changes to the proposed consent form suggested by the investigator must be agreed to by Novartis before submission to the IRB/IEC.

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

Ensure subjects are informed of the contraception requirements outlined in the Section 4.2 (Exclusion criteria) and in Section 5.1 (Contraception requirements).

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

Refer to the Site Operations Manual for a complete list of Informed Consent Forms included in this study.

8.3 Subject screening

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

Information on what data should be collected for screening failures is outlined in the Site Operations Manual.

8.4 Subject demographics/other baseline characteristics

Subject demographic and baseline characteristic data will be collected on all subjects. Relevant medical history/current medical conditions data will also be collected until signature of informed consent. Details are outlined in the Site Operations Manual.

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

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8.5 Efficacy / Pharmacodynamics

Pharmacodynamic (PD) samples will be collected at the timepoints defined in the Assessment schedule. Follow instructions outlined in the Site Operations Manual regarding sample collection, numbering, processing and shipment.

In order to better define the PD profile, the timing of the sample collection may be altered based on emergent data. The number of samples/blood draws and total blood volume collected will not exceed those stated in the protocol. The results of the sample analyses needs to remain blinded during the study.

Generally, PD samples will be obtained and evaluated in all subjects, including the placebo group.

8.5.1 Total soluble CD40 in plasma

Blood samples collected for total soluble CD40 in plasma (target engagement) will be obtained from all patients to protect blinding, but analysis will be performed only for CFZ533 treated patients.

A SOM accompanies this protocol, providing operational details for study conduct (incl. subject numbering, blood log with sample numbers). Further details on sample collection, processing and shipment will be provided in the Central Lab Manual. The detailed methods and analysis will be described in the Bioanalytical Data Report.

8.5.2 Urinary protein creatinine ratio (UPCR)

Urinary protein creatinine ratio (UPCR) as routine measurement by Central Lab will be assessed on dedicated visit days. The first morning void will be collected in the patients' home and a second spot urine sample will be collected at the investigational site.

8.6 Safety

Safety assessments are specified below; methods for assessment and recording are specified in the Site Operations Manual, with the Assessment schedule detailing when each assessment is to be performed.

During an epidemic or pandemic (e.g. COVID-19 pandemic) that limits or prevents on-site study visits regular phone or virtual calls will occur for safety monitoring and discussion of the participant´s health status until the participant can again visit the site.

8.6.1 Physical examination

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

Information for all physical examinations must be included in the source documentation at the study site and will not be recorded the eCRF. Significant findings that are present prior to informed consent are included in the Relevant Medical History eCRF. Significant' findings observed after informed consent signature which meet the definition of an Adverse Event must be appropriately recorded on the Adverse Event eCRF.

8.6.2 Vital signs

Vital signs include blood pressure (BP) and pulse measurements. After the subject has been sitting for at least 3 minutes, with back supported and both feet placed on the floor, systolic and diastolic BP will be measured using a validated device, with an appropriately sized cuff. In case the cuff sizes available are not large enough for the subject's arm circumference, a sphygmomanometer with an appropriately sized cuff may be used.

If heart-rate or blood pressure is out-of-range at screening or baseline, the Investigator may obtain two additional readings**,** so that a total of up to three consecutive assessments are made, with the subject seated quietly for approximately five minutes preceding each repeat assessment.

8.6.3 Height and weight

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

8.6.4 Laboratory evaluations

In the case where a laboratory assessment that is listed in the inclusion/exclusion criteria is outside of a **protocol-specified range** at screening or baseline, the assessment may be repeated once prior to randomization. If the repeat value remains outside of protocol-specified ranges, the subject is excluded from the study.

In the case where a laboratory range is **not specified by the protocol**, but is outside the reference range for the laboratory at screening or baseline, a decision regarding whether the result is of clinical significance or not shall be made by the Investigator and shall be based, in

part, upon the nature and degree of the observed abnormality. The assessment may be repeated once prior to randomization.

Further retests at screening or baseline could be permitted if deemed necessary by the investigator; however, each case must be discussed and agreed with the Sponsor on a case-by-case basis.

In all cases, the Investigator must document in the source documents, the clinical considerations (i.e., result was/was not clinically significant and/or medically relevant) in allowing or disallowing the subject to continue in the study.

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

8.6.4.1 Hematology

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

8.6.4.2 Clinical chemistry

Albumin, alkaline phosphatase, total bilirubin, bicarbonate/CO_2, calcium, cholesterol, chloride, creatinine, CK, GGT, glucose, LDH, inorganic phosphorus, lipase, amylase, magnesium, potassium, total protein, AST, ALT, sodium, triglycerides, urea/BUN and uric acid.

If the total bilirubin concentration is increased above 1.5 times the upper limit of normal, direct and indirect reacting bilirubin should be differentiated.

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8.6.4.4 Complement

C3 and C4 will be measured to assess complement activity.

8.6.4.5 Coagulation test

Prothrombin time (PT) and activated partial thromboplastin time (aPTT) will be measured. Additional parameters, e.g., INR, may be assessed at Investigator's discretion.

8.6.4.6 C-reactive protein (CRP) and ESR

C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) will be assessed.

8.6.4.7 Auto-antibodies

Anti-nuclear antibodies (ANA), rheumatoid factor (RF), anti-ds DNA antibodies, Anti-Smith antibody, anticardiolipin IgG and anticardiolipin IgM will be assessed.

8.6.4.8 Serum and plasma immunoglobulins

Serum total immunoglobulin G (IgG) and M (IgM) will be assessed. Lupus anticoagulant will also be assessed from plasma.

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8.6.5 Immunogenicity

The immunogenicity of multiple IV doses of CFZ533 will be assessed via the quasi-quantitative analysis of anti-CFZ533 antibodies in plasma.

Blood samples collected for immunogenicity testing will be obtained from all patients and analysis will be performed for CFZ533 and placebo-treated patients (assess pre-existing ADAs). The details of sample processing, handling, storage, shipment and analytical method will be described in a separate laboratory manual.

8.6.6 Electrocardiogram

The Fridericia QT correction formula (QTcF) should be used for clinical decisions.

Single 12 lead ECGs are collected. The original ECGs, appropriately signed, should be collected and archived at the study site.

Each ECG tracing should be labeled with study number, subject initials, subject number, date and time, be appropriately signed and dated to confirm review and filed in the study site source documents. For any ECGs with subject safety concerns, two additional ECGs should be performed to confirm the safety finding. Clinically significant ECG findings prior to dosing with investigational treatment must be discussed with the Sponsor.

Clinically significant abnormalities should be recorded on the relevant section of the medical history/Current medical conditions/AE eCRF page as appropriate.

The eCRF will contain:

- date and time of ECG
- heart rate
- PR interval
- QT uncorrected
- QTcF
- QRS duration.

8.6.7 Pregnancy

Pregnancy tests are required of all women of childbearing potential. Female subjects with documented post-menopausal status (as confirmed by FSH > 20 at screening) are not required to be tested for pregnancy.

Serum pregnancy tests will be performed at screening. At all other times urine pregnancy tests may be used.

If a urine pregnancy test is performed and is found to be positive, this will require immediate performing a serum β-hCG test. If positive, the Sponsor and Investigator will decide if discontinuation from the trial is required or whether study assessments can continue without compromising the patient's safety.

8.6.8 Other safety assessments

8.6.8.1 Quantiferon test

A QuantiFeron test will be performed and read at screening (or within 6 months prior to randomization) in order to evaluate the infection with tuberculosis (TB). Test may be repeated if test result is not unambiguous. A positive QuantiFeron test at screening will exclude the subjects from participation in the study.

T-SPOT or other types ELISPOT assays based on interferon-gamma release may also be used for tuberculosis diagnosis as per local practice.

Precautions against tuberculosis should be handled according to the best medical practice consistent to the local standards in each country with prior consultation with Novartis. Patients requiring administration of antibiotics against latent tuberculosis should complete their treatment and should be considered cured prior to being re-considered for entry into this study (consultation with Novartis must occur before allowing the patient to enter the study).

Results will be available as source data and will not be recorded within the eCRF.

8.6.8.2 Hepatitis, CMV, HIV screening

Hepatitis

All subjects will be screened for Hepatitis B surface antigen (HBsAg) and Hepatitis B core antibody (anti-HBc); HBV DNA testing will be performed if needed.

- If HBsAg is positive then the patient is **not eligible**, regardless of other test results, and HBV DNA test is not required.
- If HBsAg and anti-HBc are both negative, then the patient is **eligible** and HBV DNA test is not required.
- If HBsAg is negative and anti-HBc is positive then HBV DNA test has to be performed to confirm eligibility: the subject is only eligible if HBV DNA is negative.
  - For such subjects an expert in hepatitis must be consulted and recommendations followed. If enrolled, hepatitis B monitoring must be implemented: HBsAg and HBV DNA tested every 4 weeks until the end of study.

- In case of sero-conversion (i.e., if either HBsAg or HBV DNA turn positive) preemptive anti-viral treatment (e.g., lamivudine or entecavir) must be initiated immediately.

For subjects who are ineligible for the study based on hepatitis B screening, appropriate treatment should be considered.

Table 8-2 Hepatitis screening

HBsAg	Anti-HBc	HBV DNA	Eligible	Comment
-	-	not required	Yes	
-	+	-	Yes	Monitoring required
-	+	+	No	Consider treatment
+	+ or -	not required	No	Consider treatment

Screening for Hepatitis C will be based on HCV antibodies and HCV RNA.

CMV

Guidance to investigators:

CMV infections will be recorded as Adverse Events and on the CMV-specific CRF page. CMV infection is identified by assessments of laboratory and/or clinical sign/symptoms.

Cytomegalovirus disease is defined according to published criteria (Ljungman et al 2017; Choo et al 2019) as described below.

a. ACTIVE CYTOMEGALOVIRUS INFECTION is defined as a detectable cytomegalovirus viral load in the absence of signs or symptoms attributable to cytomegalovirus. Active cytomegalovirus infection can be the result of cytomegalovirus reactivation or primary cytomegalovirus infection.
b. PROVEN DISEASE: For pneumonia, central nervous system (CNS) disease, gastrointestinal disease, hepatitis, nephritis, cystitis, myocarditis, pancreatitis, and disease in other organs, definite tissue-invasive disease requires the correct clinical syndrome combined with the detection of cytomegalovirus in tissue samples (or in bronchoalveolar lavage fluid for pneumonia) by virus isolation, immunohistochemical analysis, in situ hybridization, or conventional histologic features. Detection of cytomegalovirus by PCR alone is not sufficient.
   - Cytomegalovirus viral syndrome requires fever (oral temperature >38°C) for two or more days within a 4-day period, neutropenia or thrombocytopenia, and the detection of cytomegalovirus in the blood by culture or the detection of antigen, DNA, or RNA. Human herpes virus -6 (HHV-6) infection needs to be excluded.
   - For central nervous system (CNS) disease, detection of cytomegalovirus in cerebrospinal fluid (CSF) samples by culture or PCR is sufficient.
   - For retinitis, typical cytomegalovirus lesions must be confirmed by an ophthalmologist; detection of cytomegalovirus is not required.
c. PROBABLE DISEASE requires the correct clinical syndrome but the detection of cytomegalovirus cannot be confirmed as outlined above.

Detection During Screening and monitoring:

1. At study screening, patients with active viral infections (quantifiable CMV DNA by PCR or positive IgM in the absence of a positive IgG) will not be eligible for randomization
2. All patients will be monitored for potential CMV reactivation or new primary infections by CMV (IgG and IgM) serology and viral DNA using PCR from randomization visit and monthly thereafter
3. In case of suspicion CMV infection, CMV serology will be performed as soon as possible, i.e. not waiting for the next scheduled CMV monitoring.
4. For patients currently ongoing in the study (i.e. patients enrolled under Protocol version 02 dated 22May2019 and continuing with study follow up period), CMV monitoring should be implemented at the next scheduled visit as per protocol

Table 8-3 CMV screening

IgM	IgG	DNA (PCR) detectable	DNA (PCR) quantifiable	Eligible	Comment
+	-			No	Regardless of DNA results: patient *not* eligible.
			+	No	Regardless of any other results: patient *not* eligible.
Examples of non-eligibility					
+	-	-	-	No	IgM positive and IgG negative: patient *not* eligible.
-	-	+	+	No	DNA quantifiable: patient *not* eligible
If the patient has neither (IgM+ and IgG-) nor quantifiable DNA: patient eligible					
+	+	+	-	Yes	IgM positive. but IgG positive, too. DNA not quantifiable.
	+	+	-	Yes	IgM negative, DNA not quantifiable.
-	-	+	-	Yes	DNA detectable but not quantifiable.
	-	-	-	Yes	All negative.

The patient is NOT eligible if **either** [DNA by PCR is quantifiable] **or** [IgM is positive **and** IgG is negative].

If there is suspicion of false positive result, the test can be repeated.

Management of asymptomatic, confirmed or probable disease

- During the study, for patients who develop evidence of an asymptomatic active CMV infection based on viral load measurement (quantifiable CMV DNA in copies/mL or IU equivalent), it is required that:
  - CMV monitoring is increased to at least weekly intervals of DNA monitoring by serial PCR assessments as well as clinical monitoring for early signs of CMV end organ disease until resolution
  - Consider initiation of pre-emptive anti-CMV therapy when PCR-determined viral load is >1,000 copies/mL, in consultation with an infectious disease expert
  - Consider reducing or stopping the dose of other immunosuppressive agents

  - Consider stopping the study drug
  - If primary CMV infection is suspected based on confirmed prior negative serology CMV IgG, repeat CMV IgG serology after resolution of primary infection and after completion of study treatment
- During the study, for patients with confirmed or probable CMV disease activity who develop clinical symptoms, it is required that:
  - Appropriate anti-CMV therapy is initiated
  - The study drug is stopped
  - Consider stopping or reducing the dose of other immunosuppressive agents.
- For patients with potential infectious symptoms during the trial in the absence of laboratory support of CMV etiology, consider age- and country-appropriate infectious exposure risks; consider direct isolation of pathogens, virology, and/or serology and initiating appropriate targeted anti-viral or anti-bacterial therapies as indicated in consultation with an expert.

HIV

Evaluation for HIV sero-positivity will be performed, and, if positive, confirmation by a second technique available at the laboratory site, e.g., Western blot.

Appropriate subject counseling will be made available by the Investigator in the event of a positive finding. Notification of state and federal authorities, as required by law, will be the responsibility of the Investigator.

Results will be available as source data and will not be recorded within the eCRF.

8.6.8.3 Infections

All occurrences of infections must be carefully monitored by the Investigator. Significant findings, which meet the definition of infection, must be recorded in the Adverse Event eCRF.

8.7 Pharmacokinetics

PK blood samples will be collected at the timepoints defined in the Assessment schedule (Section 8.1). Follow instructions outlined in the Site Operations Manual regarding sample collection, numbering, processing and shipment.

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Pharmacokinetic (PK) samples will be obtained from all patients (CFZ533 and placebo-treated) to maintain blinding, but the analysis (free CFZ533 concentration in plasma) will only be conducted for CFZ533 treated patients.

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For standard pharmacokinetic abbreviations and definitions see the list provided at the beginning of this protocol. PK samples will be collected at pre-dose and 1-hour after the end of the intravenous infusion on dosing days, and at time of the scheduled visit during the Follow-up Period.

The following pharmacokinetic parameters will be determined for free CFZ533 in plasma (i) Ctrough,ss or Cmin,ss, and Cmax,ss will be directly derived from the bioanalytical data and listings, and (ii) AUClast from the last dose at Day 141 will be determined using the actual recorded sampling times and non-compartmental methods with Phoenix WinNonlin (Version 8.0 or higher). The linear trapezoidal rule will be used for AUClast calculation.

No other parameters (e.g. clearance, volume of distribution, or half-life) will be derived using non-compartmental analysis (NCA). The pharmacokinetics of CFZ533 is non-linear and characterized by target-mediated disposition where CD40 binding by CFZ533 is leading to CFZ533 elimination (this includes receptor-mediated endocytosis by the membrane bound CD40, and subsequent metabolism of the CFZ533-CD40 complexes). As such, it is expected that:

- The amount of drug-target complex does influence the pharmacokinetics of CFZ533,
- Tissue metabolism may have a significant impact on the disposition of CFZ533 (the volume of distribution will be dependent on clearance),
- The volume of distribution may not be accurately inferred from plasma concentration alone, and the values for the volume of distribution obtained from a NCA may be incorrect,
- Volume of distribution and clearance parameters (as inferred from NCA analysis) would decrease when the dose increases.

The NCA approach is not appropriate due to violations of the assumptions that the disposition of the drug is linear, and that the elimination is from sites that are in rapid equilibrium with blood.

For each PK and total soluble CD40 (PD; Section 8.5.1) samples, the actual recorded sampling time will captured, and the elapsed time since the first and since the last dose will be calculated.

8.8 Other assessments

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9 Safety monitoring

9.1 Adverse events

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

In addition, all reports of intentional misuse and abuse of the study treatment are also considered an adverse event irrespective if a clinical event has occurred. See Section 9.6 for an overview of the reporting requirements.

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

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

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

Clinically significant abnormal laboratory values or test results should be identified through a review of values outside of normal ranges/clinically notable ranges, significant changes from baseline or the previous visit, or values which are considered to be non-typical in patients with underlying disease. Investigators have the responsibility for managing the safety of individual subject and identifying adverse events. Alert ranges for liver and kidney related events are included in Appendix 1 and Appendix 2, respectively.

All adverse events should be recorded on the Adverse Events CRF under the signs, symptoms or diagnosis associated with them, and accompanied by the following information:

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
   - Yes or
   - No
3. its duration (start and end dates) or if the event is ongoing an outcome of not recovered/not resolved must be reported
4. whether it constitutes a SAE (see Section 9.3 for definition of SAE) and which seriousness criteria have been met
5. Action taken regarding investigational treatment
   All adverse events must be treated appropriately. Treatment may include one or more of the following:
   - no action taken (e.g. further observation only)
   - investigational treatment dosage increased/reduced
   - investigational treatment interrupted/withdrawn
   - concomitant medication or non-drug therapy given
   - hospitalization/prolonged hospitalization (see Section 9.3 for definition of SAE)

6. its outcome (not recovered/not resolved; recovered/resolved; recovering/resolving, recovered/resolved with sequelae; fatal; or unknown). Information about common side effects already known about the investigational drug can be found in the Investigator's Brochure (IB) or will be communicated between IB updates in the form of Investigator Notifications. Once an adverse event is detected, it must be followed until its resolution or until it is judged to be permanent, and assessment should be made at each visit (or more frequently, if necessary) of any changes in severity, the suspected relationship to the investigational drug, the interventions required to treat it, and the outcome.

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

Adverse events potentially leading to treatment discontinuation should also be assessed using the CTCAE grading, version 4.03. CTCAE grading will not be recorded into the eCRF.

9.2 Adverse event of special interest

Adverse events of special interest (AESI) are defined, based on potential risks associated with exposure to CFZ533 (see Section 3.6.2), as any of the following adverse events:

- Infections (see Section 3.6.2.1)
- Immunogenicity (see Section 3.6.2.3)
- Thrombophilia (see Section 3.6.2.4)
- Malignancy including lymphoproliferative disease (see Section 3.6.2.5)

For AESI, statistical analyses comparing the event rates in two treatment groups will be performed.

9.3 Serious adverse event reporting

9.3.1 Definition of SAE

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

- is fatal or life-threatening
- results in persistent or significant disability/incapacity
- constitutes a congenital anomaly/birth defect
- requires inpatient hospitalization or prolongation of existing hospitalization, unless hospitalization is for:
  - routine treatment or monitoring of the studied indication, not associated with any deterioration in condition
  - elective or pre-planned treatment for a pre-existing condition (that is unrelated to the indication under study and has not worsened since the start of study drug

- treatment on an emergency outpatient basis for an event not fulfilling any of the definitions of a SAE given above and not resulting in hospital admission
- social reasons and respite care in the absence of any deterioration in the subject's general condition

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

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

Life-threatening in the context of a SAE refers to a reaction in which the subject was at risk of death at the time of the reaction; it does not refer to a reaction that hypothetically might have caused death if it were more severe (please refer to ICH-E2D Guideline 2004).

Medical and scientific judgment should be exercised in deciding whether other situations should be considered serious reactions, such as important medical events that might not be immediately life threatening or result in death or hospitalization but might jeopardize the subject or might require intervention to prevent one of the other outcomes listed above. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization or development of dependency or abuse (please refer to ICH-E2D Guideline 2004).

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

All AEs (serious and non-serious) are captured on the CRF; SAEs also require individual reporting to Novartis Chief Medical Office and Patient Safety (CMO&PS) as per Section 9.3.2.

9.3.2 SAE reporting

Screen Failures

Note the following requirement for Screen Failures: SAEs occurring after the subject has provided informed consent until the time the subject is deemed a Screen Failure must be reported to Novartis.

Randomized Subjects

To ensure subject safety, every SAE, regardless of causality, occurring after the subject has provided informed consent and until 30 days after the last study visit must be reported to Novartis within 24 hours of learning of its occurrence as described below.

Any SAEs experienced after this period should only be reported to Novartis if the investigator suspects a causal relationship to study treatment.

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

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

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 Chief Medical Office and Patient Safety (CMO& PS) Department associate may urgently require further information from the investigator for Health Authority reporting. Novartis may need to issue an Investigator Notification (IN) to inform all investigators involved in any study with the same study treatment that this SAE has been reported. Suspected Unexpected Serious Adverse Reactions (SUSARs) will be collected and reported to the competent authorities and relevant ethics committees in accordance with EU Guidance 2011/C 172/01 or as per national regulatory requirements in participating countries.

Follow the detailed instructions outlined in the Site Operations Manual regarding the submission process for reporting SAEs to Novartis. Note: SAEs must be reported to Novartis within 24 hours of the investigator learning of its occurrence/receiving follow-up information.

9.4 Liver safety monitoring

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

Please refer to Table 15-1, Appendix 1 for complete definitions of liver events.

Follow-up of liver events

Once a participant is exposed to study treatment, every liver event defined in Table 15-1, Appendix 1 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 15-2, Appendix 1.

- Repeating liver chemistry tests (ALT, AST, TBL, PT/INR, ALP and GGT) to confirm elevation within 48-72 hours.

These liver chemistry repeats should always be performed using the central laboratory, with the results provided via the standard electronic transfer. If results will not be available from the central laboratory within 24 hours, then the repeats can also be performed at a local laboratory to monitor the safety of the subject. If a liver event is subsequently reported, any local liver chemistry tests previously conducted that are associated with this event should have results reported on the unscheduled local laboratory CRF.

- If the initial elevation is confirmed, close observation of the subject will be initiated, including consideration of treatment interruption if deemed appropriate.
- Discontinuation of the investigational drug (refer to Section 7.2 (Discontinuation of study treatment), if appropriate
- Hospitalization of the subject if appropriate

- Causality assessment of the liver event
- Thorough follow-up of the liver event should include
- Repeating liver chemistry tests two or three times weekly. Testing should include ALT, AST, ALP, PT/INR, and GGT. If total bilirubin is elevated > 2 x ULN, fractionation into direct and indirect bilirubin is required. To rule out muscular origin of transaminase elevations, CPK should be measured along with liver chemistry tests. Frequency of retesting can decrease to once a week or less if abnormalities stabilize or the study drug has been discontinued and the subject is asymptomatic. Retesting should be continued up to resolution.
- Obtaining a more detailed history of symptoms and prior or concurrent diseases.
- Obtaining a history of concomitant drug use (including nonprescription medications and herbal and dietary supplement preparations), alcohol use, recreational drug use, and special diets.
- Exclusion of underlying liver disease, as specified in Table 15-3.
- Imaging such as abdominal US, CT or MRI, as appropriate
- Obtaining a history of exposure to environmental chemical agents.
- Considering gastroenterology or hepatology consultations.

All follow-up information, and the procedures performed must be recorded as appropriate in the CRF. Refer to the Site Operations Manual for additional details.

9.5 Renal safety monitoring

Once a participant is exposed to study treatment, every renal laboratory trigger or renal event must be followed up by the investigator or designated personnel at the trial site. Recommended follow-up assessments are listed in Appendix 2.

All follow-up information, and the procedures performed must be recorded as appropriate in the CRF. Refer to the Site Operations Manual for additional details.

9.6 Reporting of study treatment errors including misuse/abuse

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

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

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

All study treatment errors and uses outside of what is foreseen in the protocol will be collected in the dose administration record (DAR) CRF. Study treatment errors are only to be reported to CMO&PS department if the treatment error is associated with an SAE.

All instances of misuse or abuse must be documented in the adverse event (AE) CRF irrespective of the misuse/abuse being associated with an AE/SAE. In addition, all instances of misuse or abuse must be reported to Novartis Chief Medical Office and Patient Safety (CMO&PS). As such, instances of misuse or abuse are also to be reported using the SAE form/CRF. Table 9-1 summarizes the reporting requirements.

Table 9-1 Guidance for capturing study treatment errors

Treatment error type	Document in Dose Administration (DAR) CRF	Document in AE CRF	Complete SAE form/CRF
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 Section 9.1 and Section 9.2, respectively.

9.7 Pregnancy reporting

Reproductive toxicity and teratogenicity data are not available for the investigational drug at this time, therefore no guidelines on therapeutic recommendations in case of pregnancy are available. This study enrolls women who are either considered to be of non-child-bearing potential or who use highly effective methods of contraception, thus pregnancy is not an expected outcome for any female study participant. However, in the case that a pregnancy in a female study participant should occur, please follow the below reporting guidelines.

To ensure subject safety, each pregnancy occurring after signing the informed consent must be **reported to Novartis within 24 hours** of learning of its occurrence. The pregnancy should be followed up to determine outcome, including spontaneous or voluntary termination, details of the birth, and the presence or absence of any birth defects, congenital abnormalities, or maternal and/or newborn complications.

Pregnancy must be recorded on the Pharmacovigilance Pregnancy Form and reported by the investigator to the local Novartis Chief Medical Office and Patient Safety (CMO& PS) Department. Pregnancy follow-up should be recorded on the same form and should include an assessment of the possible relationship to the study treatment.

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

The study drug must be discontinued, though the subject may stay in the study, if she wishes to do so. All assessments that are considered as a risk during pregnancy must not be performed. The subject may continue all other protocol assessments.

If a trial participant becomes pregnant, the trial participant must be asked to read and sign the pregnancy consent form to allow the study doctor to ask about her pregnancy.

9.8 Early phase safety monitoring

The Investigator will monitor adverse events in an ongoing manner and inform the Sponsor of any clinically relevant observations. Any required safety reviews will be made jointly between medically qualified personnel representing the Sponsor and Investigator. Such evaluations may occur verbally, but the outcome and key discussion points will be summarized in writing (e-mail) and made available to both Sponsor and all Investigator(s). Criteria pertaining to stopping the study/treatment or adapting the study design are presented above.

When two or more clinical site(s) are participating in the clinical study, the Sponsor will advise the Investigator(s) at all sites in writing (e-mail) (and by telephone if possible) of any new, clinically relevant safety information reported from another site during the conduct of the study in a timely manner.

10 Data review and database management

10.1 Site monitoring

Before study initiation, at a site initiation visit or at an investigator's meeting, a Novartis representative will review the protocol and data capture requirements (i.e. eSource or eCRFs) with the investigators and their staff. During the study Novartis employs several methods of ensuring protocol and GCP compliance and the quality/integrity of the sites' data. The monitor will visit the site to check the completeness of subject records, the accuracy of data capture / data entry, the adherence to the protocol and to Good Clinical Practice, the progress of enrollment, and ensure that study drug is being stored, dispensed, and accounted for according to specifications. Key study personnel must be available to assist the monitor during these visits.

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

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

10.2 Data collection

Designated investigator staff will enter the data required by the protocol into the electronic Case Report Forms (eCRF) using fully validated software that conforms to 21 CFR Part 11 requirements. Designated investigator site staff will not be given access to the EDC system until they have been trained. Automatic validation programs check for data discrepancies and, by generating appropriate error messages, allow the data to be confirmed or corrected before

transfer of the data to the CRO working on behalf of Novartis. The Investigator must certify that the data entered into the eCRFs are complete and accurate. After database lock, the Investigator will receive copies of the subject data for archiving at the investigational site.

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

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

10.3 Database management and quality control

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

Concomitant medications entered into the database will be coded using the 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.

Laboratory samples will be processed centrally and the results will be sent electronically to Novartis (or a designated CRO).

Randomization codes and data about all study drug(s) dispensed to the subject and all dosage changes will be tracked using an Interactive Response Technology (IRT). The system will be supplied by a vendor, who will also manage the database. The database will be sent electronically to Novartis (or a designated CRO).

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

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

10.4 Data Monitoring Committee

A Data Monitoring Committee (DMC) will be established (according to Novartis Standard Operating Procedures) with the primary task to perform ongoing review of safety. The DMC is an unblinded board comprised of specialists with specific knowledge on the disease area, drug development and issues related to conducting clinical trials. Specific details on the composition and the scope of its mandate will be presented in a DMC charter document.

The DMC will be responsible for the following:

- Ongoing review of study data; the triggering events will be defined in the DMC charter
- To advise the clinical team of a need for protocol modifications/amendments in order to minimize potential risk for subjects
- To request additional information or make recommendation including stopping of enrolment, if needed.
- The chair of the DMC will be responsible for providing summaries/executive reports of each DMC meeting to the clinical team, arranging ongoing communication between members of the DMC, and maintaining files with all correspondence pertaining to the study.

10.5 Adjudication Committee

Not required.

11 Data analysis

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

11.1 Analysis sets

For all analysis sets, subjects will be analyzed according to the study treatment(s) received.

The safety analysis set will include all subjects that received any study drug.

The PK analysis set will include all subjects with at least one available valid (i.e. not flagged for exclusion) PK concentration measurement, who received any study drug and with no protocol deviations that impact on PK data.

The PD analysis set will include all subjects with available PD data and no protocol deviations with relevant impact on PD data.

11.2 Subject demographics and other baseline characteristics

All data for background and demographic variables will be listed by treatment group and subject. Summary statistics will be provided by treatment group.

Relevant medical history, current medical conditions, results of laboratory screens, drug tests and any other relevant information will be listed by treatment group and subject.

11.3 Treatments

Data for study drug administration (rescue medication) and concomitant therapies will be listed by treatment group and subject.

11.4 Analysis of the primary variable(s)

11.4.1 Primary Variable(s)

The primary variable is the ratio from baseline in first morning void urinary protein creatinine ratio (UPCR) at Week 25.

11.4.2 Statistical model, hypothesis, and method of analysis

The ratio from baseline in first morning void UPCR will be log transformed prior to the analysis. A repeated measures mixed model will be fitted with factors for treatment group (CFZ533 or placebo) and visit (e.g. Week 5, 9, 13 etc.). The model will also include a factor for the prednisone dose-equivalent at baseline (≤10 mg, >10 mg), which is a stratification factor for the randomization. Log-transformed baseline first morning void UPCR will be included in the model as a covariate along with the interactions between visit and all of the fixed effects. A normal errors model will be assumed with an unstructured covariance matrix to account for the correlation within subjects. The model will be estimated using maximum likelihood techniques.

At each of the visits, the difference between the CFZ533 and placebo group will be estimated (along with its corresponding 95% confidence interval) and then back-transformed to provide an estimate of the ratio between treatment groups.

11.4.3 Handling of missing values/censoring/discontinuations

Data from patients taking rescue medication during the trial (or failing to tolerate steroid taper, for patients receiving oral corticosteroid at baseline) will be excluded from the date of rescue medication intake. Data from patients who discontinue study treatment will also be excluded, from the date of study drug discontinuation. The primary analysis is unbiased under the assumption that the missing data are missing at random (MAR).

If the UPCR from the first morning void sample is not available, then the UPCR from the corresponding spot sample taken at the investigator site will be used in the analyses.

11.4.4 Summary statistics of safety

Vital signs

All vital signs data will be listed by treatment group, subject, and visit/time and if ranges are available abnormalities (and relevant orthostatic changes) will be flagged. Summary statistics will be provided by treatment and visit/time.

ECG evaluations

All ECG data will be listed by treatment group, subject and visit/time, abnormalities will be flagged. Summary statistics will be provided by treatment and visit/time.

Clinical laboratory evaluations

All laboratory data will be listed by treatment group, subject, and visit/time and if normal ranges are available abnormalities will be flagged. Summary statistics will be provided by treatment and visit/time.

Adverse events

All information obtained on adverse events will be displayed by treatment group and subject.

The number and percentage of subjects with adverse events will be tabulated by body system and preferred term with a breakdown by treatment. A subject with multiple adverse events within a body system is only counted once towards the total of this body system.

For serious adverse events and adverse events of special interest (AESI), statistical analyses comparing the event rates in two treatment groups will be performed.

11.4.5 Sensitivity analyses

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11.5 Analysis of secondary variable(s)

11.5.1 Efficacy / Pharmacodynamics

11.5.1.1 Total soluble CD40 in plasma

Total soluble CD40 concentration in plasma will be listed by treatment, subject, and visit/sampling time point.

Descriptive summary statistics will be provided by treatment and visit/sampling time point. Summary statistics will include mean (arithmetic and geometric), SD, CV (arithmetic and geometric), median, minimum and maximum.

11.5.1.2 UPCR, hematuria and cellular casts

First morning void and clinic spot urine sample UPCR, hematuria and cellular casts will be listed by treatment, subject and visit/sampling time-point. Descriptive statistics will be provided by treatment and visit/sampling time.

11.5.1.3 Complete renal remission (CRR)

A patient will be defined as being in complete renal remission if they fulfill all the following criteria (as per the ACR definition described in Wofsy et al 2012):

- First morning void UPCR $\leq$ 0.2 mg/mg
- eGFR within 25% of baseline value
- Normal urine sediment

The proportion of patients fulfilling the definition of complete renal remission will be listed and summarized by treatment and visit.

If the UPCR from the first morning void sample is not available, then the UPCR from the corresponding spot sample taken at the investigator site will be used in the derivation of complete renal remission.

11.5.2 Pharmacokinetics

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Pharmacokinetic parameters will be directly derived from the PK concentration data or using non-compartmental analysis, as described in Section 8.7. These parameters will be listed by treatment and subject. Descriptive summary statistics will include mean (arithmetic and geometric), SD, and CV (arithmetic and geometric), median, minimum and maximum.

11.5.3 Pharmacokinetic / pharmacodynamic relationships

PK/PD analysis (incl. free CFZ533 and total soluble CD40 in plasma) will be explored graphically. Modeling of PK/PD data using a population approach may be performed as appropriate and will be reported if necessary in a separate, standalone modeling and simulation report.

11.5.4 Other assessments

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11.6 Analysis of exploratory variables

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11.7 Sample size calculation

The sample size is based on the number of patients required to meet the efficacy criteria comparing CFZ533 to placebo in the primary analysis of the ratio from baseline in UPCR at Week 25. The efficacy criteria are:

- Statistically significant decrease in UPCR at week 25 of the treatment period compared to placebo (at the one-sided 10% level)
- Estimated mean reduction in UPCR at week 25 of at least 20% more than on placebo (i.e. ratio of UPCR for CFZ533:placebo $\leq$0.80 or equivalently difference in log UPCR for CFZ533 – placebo $\leq$-0.223).

With complete data from 51 patients (34 patients on CFZ533 and 17 patients on placebo), there will be approximately 80% power to achieve the efficacy criteria assuming a true reduction of 36% in UPCR on CFZ533 treatment compared to placebo. This calculation assumes that the standard deviation of the change from baseline in UPCR at 24 weeks is 0.7.

In order to account for a dropout rate of 15%, approximately 60 patients will be enrolled (40 patients on CFZ533 and 20 patients on placebo).

The sample size will be re-assessed based on interim analysis performed approx. 1 to 3 months before the completion of enrollment of 60 patients. The sample size may be increased based on the results of the analysis, up to a maximum of 75 randomized patients.

The sample size calculations were performed using a custom-made R package run in R version 2.13.0.

11.8 Power for analysis of key secondary variables

Not applicable

11.9 Interim analyses

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12 Ethical considerations

12.1 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 Code of Federal Regulations Title 21, and Japanese Ministry of Health, Labor, and Welfare), and with the ethical principles laid down in the Declaration of Helsinki.

12.2 Responsibilities of the investigator and IRB/IEC

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

For multi-center trials, a Coordinating Investigator will be selected by Novartis by the time of Last Patient Last Visit to be a reviewer and signatory for the clinical study report.

12.3 Publication of study protocol and results

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

12.4 Quality Control and Quality Assurance

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

Audits of investigator sites, vendors, and Novartis systems are performed or overseen by Novartis Pharma Auditing and Compliance Quality Assurance (or CRO working on behalf of Novartis), a group independent from those involved in conducting, monitoring or performing

quality control of the clinical trial. The clinical audit process uses a knowledge/risk based approach.

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

13 Protocol adherence

This protocol defines the study objectives, the study procedures and the data to be collected on study participants. Additional assessments required to ensure safety of subjects should be administered as deemed necessary on a case by case basis. Under no circumstances is an investigator allowed to collect additional data or conduct any additional procedures for any research related purpose involving any investigational drugs under the protocol.

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.

13.1 Protocol Amendments

Any change 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.

Amendments that are intended to eliminate an apparent immediate hazard to subjects may be implemented immediately, provided the Health Authorities are subsequently notified by protocol amendment and the reviewing IRB/IEC is notified.

Notwithstanding the need for approval of formal protocol amendments, the investigator is expected to take any immediate action required for the safety of any subject included in this study, even if this action represents a deviation from the protocol. In such cases, the reporting requirements identified in Section 9 *(*Safety Monitoring) must be followed and the Study Lead informed.

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15 Appendix 1: Liver Event Definitions and Follow-up Requirements

Table 15-1 Liver Event Definitions

Definition	Thresholds
Potential Hy's law cases	• ALT or AST > 3 × ULN and TBL > 2 × ULN without initial increase in ALP to > 2 × ULN
ALT or AST elevation with coagulopathy	• ALT or AST > 3 × ULN and INR > 1.5 (in the absence of anticoagulation)
ALT or AST elevation accompanied by symptoms	• ALT or AST > 3 × ULN accompanied by (general) malaise, fatigue, abdominal pain, nausea, or vomiting, or rash, or eosinophilia
Isolated ALT or AST elevation	• ALT or AST > 8 × ULN • 5 x ULN < ALT/AST ≤ 8 x ULN • 3 x ULN < ALT/AST ≤ 5 x ULN
Isolated ALP elevation	• ALP > 2 × ULN (in the absence of known bone pathology)
Others	• Any clinical event of jaundice (or equivalent term) • Any adverse event potentially indicative of liver toxicity

Table 15-2 Actions required for Liver Events

Criteria	Actions required
Potential Hy's Law case ALT or AST elevation with coagulopathy ALT or AST elevation accompanied by symptoms Isolated ALT or AST elevation > 8 × ULN Jaundice	• Discontinue the study treatment immediately • Hospitalize, if clinically appropriate • Establish causality • Complete CRFs per liver event guidance*
Isolated ALT or AST elevation > 5 to ≤ 8 × ULN	• If confirmed, consider interruption or discontinuation of study drug • If elevation persists for more than 2 weeks, discontinue the study drug • Establish causality • Complete CRFs per liver event guidance*
Isolated ALT or AST elevation > 3 to ≤ 5 × ULN (patient is asymptomatic)	• Monitor liver chemistry tests two or three times weekly
Isolated ALP elevation	• Repeat liver chemistry tests within 48-72 hours • If elevation is confirmed, measure fractionated ALP; if >50% is of liver origin, establish hepatic causality • Complete CRFs per liver event guidance*
Any AE potentially indicative of liver toxicity	• Consider study treatment interruption or discontinuation • Hospitalize if clinically appropriate • Complete CRFs per liver event guidance*

*Liver event guidance for CRF completion is available in the Site Operations Manual

Table 15-3 Exclusion of underlying liver disease

Disease	Assessment
Hepatitis A, B, C, E	• IgM anti-HAV; HBSAg, IgM anti-HBc, HBV DNA; anti-HCV, HCV RNA, IgM & IgG anti-HEV, HEV RNA
CMV, HSV, EBV infection	• IgM & IgG anti-CMV, IgM & IgG anti-HSV; IgM & IgG anti-EBV
Autoimmune hepatitis	• ANA & ASMA titers, total IgM, IgG, IgE, IgA
Alcoholic hepatitis	• Ethanol history, GGT, MCV, CD-transferrin
Nonalcoholic steatohepatitis	• Ultrasound or MRI
Hypoxic/ischemic hepatopathy	• Medical history: acute or chronic CHF, hypotension, hypoxia, hepatic venous occlusion. Ultrasound or MRI.
Biliary tract disease	• Ultrasound or MRI, ERCP as appropriate.
Wilson disease	• Caeruloplasmin
Hemochromatosis	• Ferritin, transferrin
Alpha-1-antitrypsin deficiency	• Alpha-1-antitrypsin

16 Appendix 2: Specific Renal Alert Criteria and Actions

Table 16-1 Specific Renal Alert Criteria and Actions

The following criteria and actions (intended for subjects without significant kidney disease) should be followed considering both potential investigational drug related toxicity and abnormalities that are underlying features of proliferative lupus nephritis (e.g. proteinuria, hematuria, decreased renal function).

Specific Renal Alert Criteria and Actions

Criteria	Action required
Serum creatinine (sCr) increase 25 – 49% compared to baseline	• Consider causes and possible interventions • Follow up within 2-5 days
Serum creatinine increase ≥ 50%	• Consider causes and possible interventions • Repeat assessment within 24-48h if possible • Consider drug interruption or discontinuation unless other causes are diagnosed and corrected • Consider hospitalization and specialized treatment
Protein-creatinine or albumin-creatinine ratio increase ≥ 2-fold or new onset dipstick proteinuria ≥ 1+ or Albumin-creatinine ratio (ACR) ≥ 30 mg/g or ≥ 3 mg/mmol; or Protein-creatinine ratio (PCR)≥ 150 mg/g or >15 mg/mmol	• Consider causes and possible interventions • Assess serum albumin & serum protein • Repeat assessment to confirm • Consider drug interruption or discontinuation unless other causes are diagnosed and corrected
New onset glucosuria on urine dipstick (unless related to concomitant treatment, diabetes)	Assess & document: • Blood glucose (fasting) • Serum creatinine • Urine albumin-creatinine ratio
New hematuria on dipstick	Assess & document: • Urine sediment microscopy • Assess sCr and urine albumin-creatinine ratio • Exclude infection, trauma, bleeding from the distal urinary tract/bladder, menstruation • Consider bleeding disorder

Additional specialized assessments are available to assess renal function or renal pathology. (Note: In exceptional cases when a nephrologist considers a renal biopsy, it is strongly recommended to make specimen slides available for evaluation by Novartis to potentially identify project-wide patterns of nephrotoxicity.)

Whenever a renal event is identified, a detailed subject history and examination are indicated to identify, document and potentially eliminate risk factors that may have initiated or contributed to the event:

- Blood pressure assessment (after 5 min rest, with an appropriate cuff size)
- Signs and symptoms such as fever, headache, shortness of breath, back or abdominal pain, dysuria, hematuria, dependent or periorbital edema
- Changes in blood pressure, body weight, fluid intake, voiding pattern, or urine output
- Concomitant events or procedures such as trauma, surgical procedures, cardiac or hepatic failure, contrast media or other known nephrotoxin administration, or other potential causes of renal dysfunction, e.g., dehydration, hemorrhage, tumor lysis

Table 16-2 Follow-up of renal events

Action	Follow up
Assess*, document and record in the Case Report Form (CRF) or via electronic data load. Review and record possible contributing factors to the renal event (co-medications, other co-morbid conditions) and additional diagnostic procedures (MRI etc) in the CRF.	• Urine dipstick and sediment microscopy • Blood pressure and body weight • Serum creatinine, electrolytes (sodium, potassium, phosphate, calcium), bicarbonate and uric acid • Urine output
Monitor subject regularly (frequency at investigator's discretion) until:	• Event resolution: (sCr within 10% of baseline or protein-creatinine ratio within 50% of baseline) or • Event stabilization: sCr level with ±10% variability over last 6 months or protein-creatinine ratio stabilization at a new level with ±50% variability over last 6 months.

* Urine osmolality: in the absence of diuretics or chronic kidney disease this can be a very sensitive metric for integrated kidney function that requires excellent tubular function. A high urinary osmolality in the setting of an increase in sCr will point toward a "pre-renal" cause rather than tubular toxicity.

17 Appendix 3: 1997 Update of the 1982 ACR Revised Criteria for Classification of Systemic Lupus Erythematosus

Table 17-1 ACR Revised Criteria for Classification of SLE

Criterion	Definition
1. Malar rash	Fixed erythema, flat or raised, over the malar eminences, tending to spare the nasolabial folds
2. Discoid rash	Erythematous raised patches with adherent keratoric scaling and follicular plugging; atrophic scarring may occur in older lesions
3. Photosensitivity	Skin rash as a result of unusual reaction to sunlight, by patient history or physician observation
4. Oral ulcers	Oral or nasopharyngeal ulceration, usually painless, observed by a physician
5. Arthritis	Non-erosive arthritis involving two or more peripheral joints, characterized by tenderness, swelling, or effusion
6. Serositis	a) Pleuritis - convincing history fo pleuritic pain or rub heard by a physician or evidence of pleural effusion OR b) Pericarditis – documented by ECG or rub or evidence of pericardial effusions
7. Renal disorder	a) Persistent proteinuria greater than 0.5 grams per day or greater than 3+ if quantitation not performed OR b) Cellular casts – may be red cell, hemoglobin, granular, tubular, or mixed
8. Neurologic disorder	a) Seizures – in the absence of offending drugs or known metabolic derangements OR b) Psychosis – in the absence of offending drugs or known metabolic derangements
9. Hematologic disorder	a) Hemolytic anemia – with reticulocytosis OR b) Leukopenia – less than 4,000/mm^3 total on two or more occasions OR c) Lymphopenia – less than 1,500/ mm^3 on two or more occasions OR d) Thrombocytopenia – less than 100,000 mm^3 in the absence of offending drugs
10. Immunologic disorder	a) Anti-DNA: antibody to native DNA in abnormal titer OR b) Anti-Sm: presence of antibody to Sm or nuclear antigen OR c) Positive finding of antiphospholipid antibodies based on (1) abnormal serum level of IgG or IgM anti-cardiolipin antibodies; (2) a positive test result for lupus anticoagulant using a standard method; or (3) a false positive serologic test for syphilis known to be positive for at least 6 months and confirmed by Treponema pallidum immobilization or fluorescent treponemal antibody absorption test
11. Antinuclear antibody	An abnormal titer of antinuclear antibody by immunofluorescence or an equivalent assay at any point in time and in the absence of drugs known to be associated with “drug-induced lupus” syndrome

The proposed classification os based on 11 criteria. For the purpose of identifying patients in clinical studies, a person shall be said to have SLE if any 4 or more of the 11 criteria are present, serially or simultaneously, during any interval of observation

(Tan et al 1982, Hochberg 1997)

18 Appendix 4: Classification of Lupus nephritis

Table 18-1 Classification of Lupus nephritis

Class		Definition
I		Minimal mesangial LN
II		Mesangial proliferative LN
III		Focal LN (<50% of glomeruli)
	III (A)	Active lesions
	III (A/C)	Active and chronic lesions
	III (C)	Chronic lesions
IV		Diffuse LN (≥50% of glomeruli)
	IV (A)	Active lesions
	IV (A/C)	Active and chronic lesions
	IV (C)	Chronic lesions
V		Membranous LN
VI		Advanced sclerosing LN (≥90% globally sclerosed glomeruli without residual activity)

From ACR guidelines (Hahn et al 2012)

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