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VAY736 (ianalumab)
CFZ533 (iscalimab)

Clinical Trial Protocol CVAY736X2208 / NCT03656562

A placebo-controlled, patient and investigator blinded, randomized parallel cohort study to assess pharmacodynamics, pharmacokinetics, safety, tolerability and preliminary clinical efficacy of VAY736 and CFZ533 in patients with systemic lupus erythematosus (SLE)

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Site Operations Manual (SOM)

A Site Operations Manual (SOM) accompanies this protocol amendment, providing the operational details for study procedures.

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List of abbreviations

ADA	anti-drug antibodies
AE	adverse event
ALP	alkaline phosphatase
ADCC	antibody-dependent cytotoxicity
ANA	anti-nuclear antibodies
APC	antigen presenting cell
aPTT	activated partial thromboplastin time
BAFF	B cell activating factor
BAFF-R	B cell activating factor receptor
BILAG	British Isles Lupus Assessment Group
BUN	blood urea nitrogen
BW	body weight
CD	cluster of differentiation
CD	cognitive dysfunction
CDC	complement-dependent cytotoxicity
CFR	U.S. Code of Federal Regulations
CK	creatinine kinase
CLASI	Cutaneous Lupus Erythematosus Disease Area and Severity Index
CMO&PS	Chief Medical Office & Patient Safety
CMV	cytomegalovirus
CRF	Case Report/Record Form (paper or electronic)
CRO	contract research organization
CS	corticosteroids
CTC	Common Toxicity Criteria
CV	coefficient of variation
d	day
DC	dendritic cell
DMARDs	disease modifying anti-rheumatic drugs
DNA	Deoxyribonucleic Acid
DSUR	Development Safety Update Report
ECG	electrocardiogram
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
ENA	extractable nuclear antigens
ELISA	enzyme-linked immunosorbent assay
EoS	End of Study
EOT	End of Treatment
eSAE	Electronic Serious Adverse Event
ESSDAI	EULAR Sjögren's Syndrome Disease Activity Index
eSource	Electronic Source

ESSPRI	EULAR Sjogren's Syndrome Patient Reported Index
FcRn	neonatal Fc receptor
FACIT-F	Functional Assessment of Chronic Illness Therapy-Fatigue Scale
FDA	Food and Drug Administration
FIH	first-in-human
GC	germinal center
GCP	Good Clinical Practice
h	hour
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCV	hepatitis C virus
HepBc Ab	hepatitis B core antibody
HIV	human immunodeficiency virus
IA	interim analysis
IB	Investigator's 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
Ig	immunoglobulin
INR	International Normalized Ratio
IRB	institutional review board
IRT	interactive response technology
LDH	lactate dehydrogenase
LLDAS	Lupus Low Disease Activity State
LLOQ	lower limit of quantification
LLN	lower limit of normal
LON	late onset neutropenia
MedDRA	Medical Dictionary for Regulatory Activities
MFI	Multi-dimensional Fatigue Index
mg	milligram(s)
mL	milliliter(s)
MTB	Mycobacterium tuberculosis
PCR	polymerase chain reaction
PD	pharmacodynamic(s)
PGA	Patient's Global Assessment
PhGA	Physicians' Global Assessment
PK	pharmacokinetic(s)
PoC	Proof of concept
PRO	Patient reported outcome
pSS	Primary Sjögren's syndrome

PT	prothrombin time
RA	rheumatoid arthritis
RBC	red blood cell(s)
RDC	Remote Data Capture
s.c.	subcutaneous
SAE	serious adverse event
SD	standard deviation
SF-36	36-Item Short Form Health Survey
SLE	systemic lupus erythematosus
SLEDAI	Systemic Lupus Erythematosus Disease Activity Index
SoC	standard of care
SOM	Site Operations Manual
SRI	SLE Responder Index
SUSAR	suspected unexpected serious adverse reactions
TB	tuberculosis
TBL	total bilirubin
TD	Study Treatment Discontinuation
TfH	T follicular helper cells
ULN	upper limit of normal
ULQ	upper limit of quantification
UPCR	urine protein creatinine ratio
US	ultrasound
VAS	visual analog scale
WBC	white blood cell(s)
WHO	World Health Organization
WoC	withdrawal of consent

Glossary of terms

Assessment	A procedure used to generate data required by the study
Cohort	A specific group of subjects fulfilling certain criteria
Control drug	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
Dosage	Dose of the study treatment given to the subject in a time unit (e.g. 100 mg once a day, 75 mg twice a day)
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.
eSource	eSource Direct Data Entry (DDE) refers to the capture of clinical study data electronically, at the point of care. eSource combines source documents and case report forms (eCRFs) into one application, allowing for the real time collection of clinical trial information to sponsors and other oversight authorities, as appropriate.
Healthy volunteer	A person with no known significant health problems who volunteers to be a study participant
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
Part	A single component of a study that contains different objectives or populations within that single study. Common parts within a study are: a single dose part and a multiple dose part, or a part in patients with established disease and in those with newly-diagnosed disease.
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
Run in Failure	A subject who is screened but not randomized/treated after the run-in period (where run-in period requires adjustment to subject’s medications or other intervention)
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.
Treatment number	A unique identifier assigned in non-randomized studies to each dosed subject, corresponding to a specific treatment arm
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 further collection personal data.

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Protocol summary

Protocol number	CVAY736X2208
Full Title	A placebo-controlled, patient and investigator blinded, randomized parallel cohort study to assess pharmacodynamics, pharmacokinetics, safety, tolerability and preliminary clinical efficacy of VAY736 and CFZ533 in patients with systemic lupus erythematosus (SLE)
Brief title	Study the efficacy and safety of VAY736 and CFZ533 in SLE patients
Sponsor **Clinical Phase**	Novartis Phase IIa
Investigation type	Biologics
Study type	Interventional
Purpose and rationale	This study is designed to evaluate the safety, tolerability, pharmacokinetics and therapeutic efficacy of treatment with either VAY736 or CFZ533 in patients with SLE to enable further development of these compounds as treatment in this disease population
Primary Objective(s)	The primary objective of this study is to determine the effect of VAY736 and of CFZ533 versus their respective placebo on disease activity in SLE patients using the SRI-4 index
Secondary Objectives	• To assess safety and tolerability of VAY736 and of CFZ533 in patients with SLE by recording all adverse events • To determine the change from baseline in the Physicians' Global Assessment (PhGA) at Week 29 in VAY736-, CFZ533- or their respective placebo-treated arms by using a visual analogue scale (VAS) • To determine the change from baseline in the Patient's Global Assessment (PGA) at Week 29 in VAY736, CFZ533 or their respective placebo-treated arms by using a patient VAS • To determine the pharmacokinetics (PK) of multiple doses of VAY736 (s.c.) and CFZ533 (i.v.) in SLE patients by analyzing PK concentrations in blood • To assess the effect of VAY736 and of CFZ533 versus their respective placebo to prevent disease flares in SLE patient's using BILAG (British Isles Lupus Assessment Group)-2004 score • To evaluate the immunogenicity of multiple doses of VAY736 (s.c.) or CFZ533 (i.v.) in SLE patients by analyzing anti-drug antibodies in blood • To evaluate the pharmacodynamics (PD; rate, extent and duration of target engagement) of multiple doses of CFZ533 in SLE patients by analyzing total soluble CD40 in plasma
Study design	This is an exploratory, randomized, patient- and investigator-blind, placebo-controlled, parallel-group study to assess the safety, tolerability, pharmacokinetics, immunogenicity, pharmacodynamics and preliminary clinical efficacy of multiple doses of VAY736 or of CFZ533 in patients with active SLE
Population	Approximately 120 male and female patients 18 to 75 years of age with active SLE disease will be randomized

Key Inclusion criteria	Fulfill ≥4 of the 11 American College of Rheumatology 1997 classification criteria for SLE at screening Patient diagnosed with SLE for at least 6 months prior to screening Elevated serum titers at screening of ANA (≥1:80) in a pattern consistent with an SLE diagnosis, including at a minimum anti-double stranded DNA (anti-ds DNA) or anti-Ro (SSA) or anti-La (SSB) or anti-nuclear ribonucleoprotein (anti-RNP) or anti-Smith (anti-Sm) Currently receiving corticosteroids and/or anti-malarial and/or thalidomide treatment and/or another DMARD according to the following: • Where corticosteroids are the single standard-of-care medication: an oral dose of ≤30 mg/d for a minimum of 8 weeks prior to randomization and at a stable dose for ≥2 weeks prior to randomization • Where oral corticosteroids are not as a single standard-of-care medication: a stable oral dose of ≤30 mg/d of prednisone or equivalent for a minimum of 8 weeks prior to randomization and at a stable dose for ≥2 weeks prior to randomization • An anti-malarial and/or thalidomide treatment and/or one of the following DMARDs: methotrexate or an imidazole derivative (e.g., azathioprine, mizoribine) or mycophenolic acid derivatives (e.g., mycophenolate mofetil) for a minimum of 12 weeks prior to screening and at a stable dose for ≥8 weeks prior to randomization. Combination of other DMARDs is not permitted SLEDAI-2K score of ≥6 at screening BILAG-2004 score at screening of • at least one “A” in either the mucocutaneous domain or in the musculoskeletal domain, OR • one “B” in either the mucocutaneous or musculoskeletal domain AND at least one “A” or “B” in a second domain Weigh at least 40 kg at screening

Key Exclusion criteria	Cohort 2 (CFZ533/Placebo) only: 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 significantly prolonged activated partial thromboplastin time (aPTT) consistent with co-existent anti-phospholipid syndrome and without concurrent prophylactic treatment with aspirin or anticoagulants as per local standard of care All Cohorts: History of receiving prior to screening: • Within 12 weeks: i.v. high dose corticosteroids, calcineurin inhibitors or other oral DMARD except as listed in inclusion criterion 6 • Within 24 weeks: cyclophosphamide, or biologics such as intravenous Ig, plasmapheresis, anti-TNF-α mAb, CTLA4-Fc Ig (abatacept) or BAFF targeting agents (e.g., belimumab) • Any B-cell depleting therapies (e.g., anti-CD20 mAb, anti-CD22 mAb, anti-CD52 mAb) or TACI-Ig (atacicept) administered within 52 weeks prior to screening and B-cell count <50 cells/μL at the time of screening Presence of severe lupus kidney disease as defined by proteinuria above 6 g / day or equivalent using spot urine protein to creatinine ratio, or serum creatinine greater than 2.5 mg/dL(221.05 μmol/L), or requiring immune suppressive induction or maintenance treatment exceeding protocol-defined limits Active viral, bacterial or other infections at the time of screening or enrollment, or history of recurrent, clinically significant infection or of recurrent bacterial infections with encapsulated organisms CMV IgM positive 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*) Receipt of live/attenuated vaccine within a 2-month period before first dosing Chronic infection with hepatitis B (HBV) or hepatitis C (HCV). A positive HBV surface antigen (HBsAg) test excludes a subject. HBsAg negative patients who are hepatitis B core antibody (HepBc Ab) positive are also excluded, except if both of the 2 following criteria are met: i) HBV DNA is negative, ii) hepatitis B monitoring is implemented (HBsAg and HBV DNA tested on a monthly basis). In addition, the following conditions must be fulfilled: • For Cohort 1 (VAY736/Placebo): prophylactic anti-viral treatment (e.g., lamivudine or entecavir) must be initiated at latest by Day 1 (start of study drug) and continued until at least 12 months after last treatment with VAY736. If Hepatitis B prophylaxis antiviral treatment is not recommended as per local guidelines for patients who are HepBc Ab positive and HBV DNA negative, ONLY HBsAg and HepBc Ab negative patients must be enrolled in the study. • For Cohort 2 (CFZ533/Placebo): anti-viral treatment (e.g., lamivudine or entecavir) must be initiated immediately in case of sero-conversion of either HBsAg or HBV DNA and continued until at least 6 months after last treatment with CFZ533.

	Any evidence of hepatitis B reactivation during monitoring (detectable serum levels of HBV DNA and/or HepBsAg seropositivity) require discontinuation of study medication. Subjects with a positive HCV antibody test should have HCV RNA levels measured. Subjects with positive (detectable) HCV RNA should be excluded. Pregnant or nursing (lactating) women
Study treatment	Commercially Confidential Information
Efficacy assessments	• SRI-4 (SLE responder index) • Physician Global Assessment Visual Analogue Scale (PhGA-VAS) • Patient Global Assessment (VAS) • Flare Rate by BILAG-2004 score • Lupus Low Disease Activity State (LLDAS)
Pharmacodynamic assessments	• Total soluble CD40 in Cohort 2
Pharmacokinetic assessments	• PK concentrations of VAY736 in Cohort 1 • PK concentrations of CFZ533 in Cohort 2
Key safety assessments	• Adverse event monitoring • Physical examinations • Monitoring of laboratory markers in blood and urine • Hepatitis B monitoring • CMV monitoring • ECG evaluation • Vital signs
Other assessments	Commercially Confidential Information

Data analysis	The primary endpoint will be analyzed using a Bayesian logistic regression model. The model will include treatment group, ENA status, baseline SLEDAI-2K (<10, ≥10) as fixed effects. Weakly informative priors will be used to obtain the posterior estimates. The primary analysis will be performed for each cohort separately. Bayesian posterior probabilities will be used to assess the following criteria as a guide for decision making (Fisch et al 2015). Efficacy criteria (for primary endpoint): Week 29 responder rate in active group better than that in placebo group with high confidence (90%), i.e., Prob (θ_active - θ _ placebo >0) >90%, AND Average magnitude of effect on Week 29 responder rate >15% over placebo, i.e., Prob (θ_active - θ _ placebo >15%) >50%. Where θ is the Week 29 responder rate, i.e., the proportion of responders per definition. Futility criteria Week 29 responder rate in active group worse than that in placebo with confidence higher than 60%, i.e., Prob (θ_active - θ _ placebo <0) >60%. The posterior estimates of the treatment effect of VAY736 and CFZ533 compared to their matching placebos (along with the 90% credible intervals) at Week 29 will be provided. The results will be reported in terms of difference in probability of responders. Descriptive statistics will be provided for the safety data (e.g., AEs, vital signs, ECGs, lab evaluations etc.).
Key words	Anti-CD40, anti-BAFF-receptor, B-cell depletion, systemic lupus erythematosus, SLE, VAY736, ianalumab, CFZ533, iscalimab, immunosuppression

1 Introduction

1.1 Background

1.1.1 Systemic lupus erythematosus

Systemic Lupus Erythematosus (SLE) is a chronic autoimmune disease of unknown etiology characterized by an inflammatory process that can target any organ. Most patients suffer from constitutional signs such as fever and weight loss. Other common manifestations include oral ulcers, skin rash, joint pain and neurocognitive impairment ranging from disabling fatigue to psychosis. Hematological complications can include anemia, leukopenia and thrombocytopenia, and anti-nuclear antibodies occur in the vast majority of patients. Renal involvement will occur at one point in the disease course of 40% of SLE patients; leading, in many, cases to renal failure. The disease can also affect the lungs, gastrointestinal tract and heart, and the risk of cardiovascular death is 3-10x higher in patients with SLE compared to the general population. Patients with SLE also have an increased risk for lymphoma.

The prevalence of SLE varies globally from 20 to 70 per 100,000. Approximately 90% of lupus patients are women, with a typical disease onset during the childbearing years. Lupus also occurs more often among certain populations such as African, Asian and Hispanic ethnic groups compared to frequency of the disease among Caucasians.

The pathobiology of SLE is complex and thought to begin with loss of tolerance by the immune system to nucleic acid self-antigens, possibly triggered by viral infection or other means of tissue damage. Subsequent immune amplification follows with generation of type 1 interferons activating anti-viral responses. Production of BAFF leads to B cell activation and expression of the co-stimulatory molecule CD40, which together with its ligand CD154 on activated T cells, drives B cell proliferation and maturation into autoantibody-producing plasmablasts and plasma cells. These autoantibodies form immune complexes that cause deposits in tissues throughout the body and cause end-organ injury. The activated T cells and macrophages can generate additional damaging inflammation. It is by this disease process that SLE patients can experience varied and diverse clinical manifestations.

Treatment of SLE depends on the severity and organ system involved. The anti-malarial agent hydroxychloroquine has been used since the 1960s for controlling milder disease manifestations. However, high dose steroids are required for treating more severe disease, and cytotoxic agents are used for steroid sparing and to treat severe disease involving the CNS and kidneys. Although these treatments have improved the overall SLE 10-year survival from 63% in the 1950s to 95% in the 1980s, there have been no further major improvements since. Approved targeted therapy for SLE is limited to the anti-soluble BAFF monoclonal antibody (mAb) belimumab, with clinical benefits primarily in patients with milder disease. Inconsistent clinical responses have been achieved in SLE patients with the B cell depleting agent rituximab, attributed in part to interference of B cell targeting by BAFF:BAFF-R signaling, leading to SLE trials evaluating combination therapy with rituximab induction followed by maintenance belimumab (Kraaij et al 2018; CALIBRATE, NCT02260934).

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1.1.2 VAY736 (ianalumab; anti-BAFF-R mAb)

VAY736 is a human IgG1/κ mAb designed to specifically bind to B cell activating factor receptor (BAFF-R) that is predominantly expressed on B cells, thereby preventing the binding of B cell activating factor (BAFF). BAFF:BAFF-R mediated signaling is critically involved in the maturation of transitional B cells, for survival and activation of mature B cells, and for isotype class switching in response to T cell-dependent antigens. The anti-BAFF-R mAb VAY736 was designed to eliminate BAFF-R+ B cells by a dual mechanism *in vivo*: (i) by antibody-dependent cytotoxicity (ADCC) and (ii) the induction of B cell apoptosis by preventing BAFF:BAFF-R interaction and blocking the prominent BAFF-induced survival pathway in B cells. Expression of BAFF-R is limited to immature and mature B cells up to the lymphoblast stage, and thus earlier stage pro- and pre-B cells are not directly affected by VAY736

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This unique, dual mode-of-action supports the therapeutic hypothesis of increased efficacy of VAY736 over single targeting of B cell functions by either CD20 depletion (e.g., rituximab) or soluble BAFF blockade (e.g., belimumab).

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As of 07-Dec-2021, an estimated total of 480 patients have been exposed to VAY736 at various doses in 11 clinical studies, including four phase 1 studies CVAY736X2101 (n=55), CVAY736A2101 (n=43) both in patients with rheumatoid arthritis (RA), CVAY736Y2101 (n=3) and CVAY736Y2102 (n=37), both in chronic lymphocytic leukemia (CLL). In addition, there have been five phase 2a studies that include primary Sjögren's syndrome (pSS; CVAY736X2201, n=23), multiple sclerosis (MS; CVAY736X2202, n=8), pemphigus vulgaris (PV; CVAY736X2203, n=12), idiopathic pulmonary fibrosis (IPF; CVAY736X2207, n=14) and systemic lupus erythematosus (SLE; CVAY736X2208, n=50). One ongoing phase 2b in pSS (CVAY736A2201, n= 188, enrollment completed) and one phase 2b/3 study in autoimmune hepatitis (AIH; CVAY736B2201, n=47). Out of the 480 subjects treated with VAY736 across these clinical trials up until the above cut-off date, data from 289 patients have been analyzed and included in the IB (dated 14-May-2021), including the FIH study CVAY736X2201 in RA, VAY736Y2101 in CLL and the phase 2a studies in PV, MS, CLL and pSS; the other trials remain ongoing.

Clinically, acute infusion reactions (CTCAE 4.03 grade 1-2) as a consequence of rapid, ADCC-depletion of circulating B cells and unrelated to dosage were observed in the phase 1 studies in the absence of any pre-medication, resolving with administration of paracetamol. There have been no significant differences observed between VAY736- and placebo-treated patients, with the exception of dose-related increases in the occurrence of local injection-related site reactions. There were no notable differences in infection, although increases were observed in the incidence of upper respiratory tract infections in patients receiving VAY736. In the

CVAY736A2201 study (Bowman et al 2022), common infections reported included respiratory tract infections, urinary tract infections, oral herpes and conjunctivitis. In contrast to other high dose B-cell depleting agents, VAY736 so far has not shown increased occurrence of severe infections or cases of rare infections (please refer to the IB). Overall, VAY736 is considered as having an acceptable risk/benefit profile and therefore considered adequate for development in SLE.

Efficacy: The 12-week efficacy results in pSS clinical outcomes observed in the proof-of-concept study CVAY736X2201 with single infusions of two different i.v. doses of VAY736 (3 mg/kg and 10 mg/kg) in 27 patients suggest early and clinically meaningful improvements in signs and symptoms compared to placebo (Dörner et al 2019). These were measured using patient reported outcomes (PROs) including EULAR Sjogren's Syndrome Patient Reported Index (ESSPRI), 36-Item Short Form Health Survey (SF-36) physical component score, Multi-dimensional Fatigue Index (MFI), and global assessments of disease activity by physicians (PhGA) and patients (PGA). Moreover, numerical improvements were seen in the EULAR Sjögren's Syndrome Disease Activity Index (ESSDAI), a disease activity score that measures 12 domains across multiple organ and body systems. Full tissue-level PD effects provided by sustained receptor occupancy with multiple VAY736 dosing have yet to be evaluated. The shared clinical characteristics and pathobiology elements between pSS and SLE suggest potential for efficacy of VAY736 in SLE.

1.1.3 CFZ533 (iscalimab; anti-CD40 mAb)

CFZ533 is a non-agonistic, fully human, Fc-silent, antagonistic IgG1 anti-CD40 mAb 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 ADCC or complement-dependent cytotoxicity (CDC).

CD40 is a transmembrane glycoprotein constitutively expressed on B cells and antigen presenting cells (APCs) such as monocytes, macrophages, and dendritic cells (DCs). CD40 is also expressed on platelets and, under certain conditions, can be expressed on eosinophils, and inflamed parenchymal cells. Binding of the ligand for CD40, CD154 (also known as CD40 ligand or CD40L), results in cellular activation and provides an important signal for DC maturation as well as monocyte survival and cytokine secretion. In addition, CD40 pathway stimulation is required for many B cell effector functions including germinal center (GC) formation, memory B cell development, immunoglobulin (Ig) isotype switching, antibody production and affinity maturation.

CFZ533 inhibits CD154-induced activation in vitro and T cell-dependent antibody 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.

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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 target activated platelets expressing CD154. The hypothesis that BG9588 induced thromboembolism via targeting CD154 on activated platelets has been supported by recent data with CDP7657 (dapirolizumab pegol) showing no platelet activation (Chamberlain et al 2017; Tocoian et al 2015).

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As of 15 Nov 2021, 88 healthy volunteers and 1106 patients have been enrolled into the clinical development program that includes one phase 1 study in rheumatoid arthritis (CCFZ533X2101, n=20) and 11 phase 2a/2b studies, including renal transplant (CCFZ533X2201, n=59), primary Sjögren's syndrome (CCFZ533X2203, n=69), myasthenia gravis (CCFZ533X2204, n=44), Graves` disease (CCFZ533X2205, n=15), hidradenitis suppurativa (CCFZ533H12201BC, n=45), kidney transplant (CCFZ533A2201, n=406), liver transplant (CCFZ533A2202, n=113), Sjögren's syndrome (CCFZ533B2201, n=240), systemic lupus erythematosus (CVAY736X2208, n=41) and lupus nephritis (CCFZ533X2202, n=43) and type 1 diabetes mellitus (CCFZ533X2207, n=11). In total from these aforementioned studies, approximately 888 subjects received CFZ533. In these patients, CFZ533 was generally well tolerated and specifically not associated with an increased risk of infection or neutropenia, nor was there evidence for an increased risk of drug-related thromboembolic events in dosed subjects.

Based on preliminary data, multiple i.v. doses of 10 mg/kg CFZ533 were safe and improved the signs and symptoms of pSS as measured by relevant clinical endpoints, including the ESSDAI. With the similarities in B cell and T cell involvement in pSS and in SLE, such as circulating autoantibodies and CD40 pathway-related abnormalities, this clinical efficacy in pSS by CFZ533 may further strengthen the rationale for targeting CD40 in patients with SLE.

In summary, experience with VAY736 and with CFZ533 suggest that their respective mechanisms-of-action represent safe and efficacious therapeutic approaches for the treatment of SLE for which no approved disease modifying therapy exists and where the unmet medical need is high.

1.2 Purpose

This study is designed to evaluate the safety, tolerability, pharmacokinetics and therapeutic efficacy of treatment with either VAY736 or CFZ533 in patients with SLE to enable further development of these compounds as treatment in this disease population.

2 Objectives and endpoints

Table 2-1 Objectives and related endpoints

Objective(s)	Endpoint(s)
Primary objective(s)	**Endpoint(s) for primary objective(s)**
• To determine the effect of VAY736 and of CFZ533 versus their respective placebo on disease activity in SLE patients at Week 29 compared to baseline	• SRI-4 response status at Week 29 with reduced steroid dose maintained between Weeks 17 and 29
Secondary objective(s)	**Endpoint(s) for secondary objective(s)**
• To assess safety and tolerability of VAY736 and of CFZ533 in patients with SLE	• Adverse events and other safety data such as vital signs, ECG and laboratory results recorded during study
• To determine the change from baseline in the Physicians' Global Assessment (PhGA) at Week 29 in VAY736-, CFZ533- or their respective placebo-treated arms	• Changes between baseline and Week 29 in the PhGA visual analog scale (VAS) assessing patient's overall disease activity
• To determine the change from baseline in the Patient's Global Assessment (PGA) at Week 29 in VAY736, CFZ533 or their respective placebo-treated arms	• Changes between baseline and Week 29 in the patients' VAS assessing their global disease activity
• To determine the pharmacokinetics (PK) of multiple doses of VAY736 (s.c.) and CFZ533 (i.v.) in SLE patients	• PK Cohort 1 (VAY736): free VAY736 serum concentration (Cmax,ss, Ctrough,ss) • PK Cohort 2 (CFZ533): free CFZ533 concentration in plasma (Cmax,ss, Ctrough,ss)
• To assess the effect of VAY736 and of CFZ533 versus their respective placebo to prevent disease flares in SLE patients	• Flare rate and time to first flare, with flare defined as one new 'A' score or two or more 'B' score using BILAG -2004
• To evaluate the immunogenicity of multiple doses of VAY736 (s.c.) or CFZ533 (i.v.) in SLE patients	• Anti-VAY736 (Cohort 1) or anti-CFZ533 (Cohort 2) antibodies and incidence of ADA-positive patients
• To evaluate the pharmacodynamics (PD; rate, extent and duration of target engagement) of multiple doses of CFZ533 in SLE patients	• PD Cohort 2 (CFZ533): total soluble CD40 in plasma

Objective(s)	Endpoint(s)
Exploratory objective(s)	**Endpoint(s) for exploratory objective(s)**

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3 Study design

This is a randomized, patient- and investigator-blind, placebo-controlled, parallel-group, non-confirmatory study to assess the safety, tolerability, pharmacokinetics, immunogenicity, pharmacodynamics and preliminary clinical efficacy of multiple doses of VAY736 or of CFZ533 in patients with active SLE (see Figure 3-1).

Figure 3-1 Study design

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Key study design features are as follows:

- Patient randomization into one of two treatment cohorts (VAY736 or CFZ533) and to either active or placebo
- Seven-month, placebo-controlled, blinded treatment
- Guided corticosteroid taper from Study Week 5 to Study Week 17
- A 5-month, open label treatment followed by a final outcomes assessment
- Four-month follow up for safety/PK/PD, with additional follow up for VAY736-treated patients until B cell recovery criteria are met

Screening and randomization

The study will randomize approximately 120 patients to test two active treatments against their matching placebo in parallel cohorts. After a 28-day screening period, eligible patients will be enrolled and stratified according to serum extractable nuclear antigens (ENA) status (positive or negative) and baseline SLEDAI-2K score (<10, ≥10). At the baseline visit, patients who are eligible for both cohorts will be randomly assigned to one of the four treatment arms. Patients who are eligible for only one cohort will be randomly assigned to either of the two

treatment arms in that cohort. Randomization across the cohorts will be implemented via central randomization aiming for randomization ratio of 1:1:1:1.

Blinded treatment phase

Within the treatment cohort, blinded treatment with the investigational drug (VAY736 or CFZ533) or placebo will be administered on top of patients' stable standard of care therapy for SLE. Visits to assess safety and/or efficacy are scheduled at 4-week intervals. An additional safety visit is scheduled at Week 3 (within the placebo-controlled period) and Week 31 (within the open label period) where patients in Cohort 2 (CFZ533) will receive an additional treatment dose (see Section 4.2.2).

At the baseline visit Day 1, following patient eligibility confirmation and completion of all assessments, first dose of study drug/placebo will be administered. The last treatment in the blinded treatment period will be given at the Week 25 visit. The readout for the blinded treatment period will be performed at Week 29. Study drug will be administered every 4 weeks. Unless otherwise stated, all assessments must be completed BEFORE the next dose of study drug is administered.

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Guided corticosteroid (CS) reduction

- Patients entering the study on a stable CS regimen are required to undergo a guided CS taper from baseline levels starting at Week 5 in order to achieve by Week 17:
  - a daily CS dose of ≤5 mg/day prednisone or equivalent,
  - or a CS dose that is less than the baseline dose, whichever is the lower dose.
- In addition, the patient should remain at the lowered CS dose achieved at Week 17 through to Week 29.
- Patients entering the study without background CS therapy should remain free of any CS regimen or increase in SoC DMARDs through to Week 29.
- Patients exceeding the rescue therapy allowances may continue in trial but will be labeled a non-responder for primary endpoint.
- During the open label phase, further reductions in patients' SoC CS and DMARDs may be made on an individual basis as deemed appropriate by the investigator. For details on the guided CS tapering please refer to Section 6.2.2

Open-label treatment phase

At the end of the Week 29 visit, after all assessments have been performed, the first -open label treatment will be administered. Patients in Cohort 1 will receive VAY736 and patients in Cohort 2 will receive CFZ533. Study drug will be administered every 4 weeks. The last treatment will be given at the Week 49 visit, and the End-of-Treatment (EoT) visit will be performed 4 weeks thereafter, at Week 53.

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Follow-Up period

After completion of the open-label treatment period, all patients will enter a Follow-Up period in order to monitor safety and efficacy up to Week 69. The Week 69 visit is the End of Study (EoS) visit for patients in Cohort 2 (CFZ533). Study duration for patients in Cohort 2 will be approximately 18 months.

For Cohort 1 (VAY736). Patients who do not achieve B-cell recovery by Week 69 Visit will enter into a Secondary Follow-Up period until achieving B cell recovery criteria (B-cell count is at ≥50 cells/µl or at least 80% of baseline levels). Safety follow-up visits will be scheduled as deemed appropriate until the patient achieves the B cell recovery criteria, followed by an EoS 4 weeks later.

Please also refer to the Assessment Schedule.

4 Rationale

4.1 Rationale for study design

This study design is based on published randomized clinical trials in SLE (Furie et al 2017; Kalunian et al 2017) and the latest EMA 2015 guidelines for evaluation of medicinal products intended for the treatment of this patient population. Two different study treatments are tested against placebo in the same study setting for better comparability and possibility to stop or adapt the individual cohorts independently if needed. In the open-label period, all patients will receive active treatment. Blinded randomization to active versus placebo in each cohort is employed during the blinded-treatment phase to provide an unbiased assessment of efficacy in this patient population known for a high placebo response rate.

Patients are selected for a disease activity level sufficient to require systemic therapy. Stratification for high disease severity will reduce imbalances of this parameter between the different arms. In addition, patients are stratified based on ENA seropositivity, based on

evidence that patients tested positive for ENA autoantibodies may have distinct resistance or response to B cell depleting therapy (Cambridge et al 2006 and Cambridge et al 2007).

Patients with resolved hepatitis B infection who remain seropositive for the hepatitis B core antibody (HepBc Ab) are at increased risk for viral re-activation under immune suppressed conditions. Over half the clinical sites participating in this study are located in Asian-Pacific countries for which adult prevalence rates for HepBc Ab positivity range from 20% in Japan to up to 80% in target populations of Thailand, Taiwan and China mainland. Given that such patients with potentially latent hepatitis B infection represent a substantial proportion of the world SLE population, it is important in this study to demonstrate effective application of current clinical practice guidelines for use of immune suppressive agents in these patients (EASL 2017, Terrault et al 2018). Therefore, enrolled HepBc Ab+ patients with inactive infection (i.e., negative for both hepatitis B surface antigen (HBsAg) and blood viral DNA) will require monitoring during study participation. In accordance with the guidelines in reference to B cell depleting agents, patients randomized to the VAY736 treatment arm will additionally require anti-viral prophylaxis during study participation. Evidence of viral reactivation will result in termination of study treatment.

To reduce potential interference in the effects of the study drugs upon the SLE disease mechanisms, specific limitations are placed on patients' concomitant use of corticosteroids and other immunosuppressive therapies. Patients are excluded who require higher dose corticosteroids (>30 mg/day of prednisone or equivalent), cytotoxic or immune suppressive induction/maintenance therapies for severe organ dysfunction (e.g., proliferative renal disease, CNS lupus).

The impact of study treatment on reducing background corticosteroid dosing will be demonstrated by including a guided corticosteroid taper followed by a sustained period at the lower dosing level prior to assessment of primary and key secondary outcomes. Enrolled patients who require additional corticosteroid dosing beyond the limited rescue therapy (see Section 6.2.4, Rescue medication and Table 6-3 Prohibited medicine) through to Week 29 may remain in study but are considered non-responder for primary endpoint.

4.1.1 Rationale for choice of SoC therapy

The antimalarial agent hydroxychloroquine has been used since the 1960s for controlling milder SLE disease manifestations (reviewed in Kaul et al 2016). More severe disease manifestations often require systemic CS therapy and cytotoxic therapies leading to numerous adverse effects common with chronic exposure to this drug class. Disease modifying anti-rheumatic drugs (DMARDs) such as methotrexate or an imidazol derivative (e.g., azathioprine, mizoribine) or mycophenolic acid derivatives (e.g., mycophenolate mofetil) are typically added as steroid-sparing agents to allow reduction of daily CS dosage. Thalidomide has emerged as second line treatment for severe, refractory mucocutaneous disease (Chasset et al 2018). Background therapy with CS and DMARDs in this trial will be limited to prevent potential over-immune suppression in patients receiving VAY736 or CFZ533. In addition, this study in SLE patients limits the severity of active kidney involvement, thus reducing potential for requiring higher corticosteroid dosing or addition of other cytotoxic drugs such as cyclophosphamide.

To reduce the high placebo responder rate typical of SLE trials, patients will be assessed for primary outcomes only after a defined period at a lowered CS dose achieved by a guided taper (Merrill et al 2017, Thanou and Merrill 2018).

4.2 Rationale for dose/regimen and duration of treatment

4.2.1 Study treatment duration

The 28 weeks of blinded treatment are considered appropriate to show clinical effects of the study treatments on the underlying SLE disease mechanism. The 5-month open label period, starting at Study Week 29, offers patients on placebo the potential benefit of active treatment. The overall treatment duration of up to 48 weeks will demonstrate effects on disease flare rate and sustainability of clinical effects.

4.2.2 VAY736 dosing

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4.2.3 CFZ533 dosing

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

Placebo use in this blinded trial is justified by providing it as add-on to standard-of-care background therapy along with use of rescue glucocorticoid therapy if required. Placebo arms respective to the VAY736 and to the CFZ533 cohorts are required due to the different dosing requirements for these two experimental treatments that include s.c. versus i.v., pre-medication and loading regimen; all factors that could affect the known high placebo response rate typically seen in SLE trials.

4.4 Purpose and timing of interim analyses/design adaptations

A first interim analysis (IA1) is planned after approximately 50% of randomized patients have completed all Week 29 assessments. The efficacy endpoints up to Study Week 29 along with relevant safety data will be examined as a preliminary evaluation of therapeutic effects. A second IA (IA2) is planned after all enrolled patients have completed their Week 29 assessments.

An ongoing blinded review of safety data will be conducted at frequent intervals.

Additional interim analyses may be conducted to support decision making concerning the current clinical study or project, the sponsor's clinical development projects in general or in case of any safety concerns.

4.5 Risks and benefits

Initially, patients have a 50% chance of being treated with a potentially efficacious treatment, VAY736 or CFZ533, for a chronic disease with possible long-term outcomes that include serious disabilities. All patients who received placebo in the blinded treatment phase up to Study Week 25 will receive active treatment in the open-label treatment phase starting at Week 29, respective to their cohort (either VAY736 or CFZ533), for the subsequent 5 months. All patients are permitted to stay on their stable standard-of-care therapy.

Both VAY736 and CFZ533 are systemic immune-suppressive therapies and thus the study population is limited to patients with moderate-to-severe SLE who are most likely to benefit from such treatment. However, to avoid over-immune suppression and reduce potential

interference with the effects of the study drugs upon SLE disease mechanisms, patients with severe disease requiring high corticosteroid dosing (prednisone >30 mg/day or equivalent) or immune suppressive induction/maintenance therapies for severe organ dysfunction (e.g., proliferative renal disease, CNS lupus) should not be included in this initial trial, and thus concurrent use of these medications are not permitted.

Allergic reactions. Although no allergic or anaphylactic reactions following i.v. or s.c. administration were observed to date in patients receiving either VAY736 or CFZ533, the potential to develop an allergic reaction to either compound in a predisposed subject cannot be ruled out. Routine monitoring as for other biologic treatments is warranted as described in the respective IBs.

Anti-drug antibodies (ADAs) are assessed in all VAY736- or CFZ533-treated subjects across all clinical trials involving these compounds. Only limited signs and symptoms of immunogenicity have been observed thus far in patients exposed to VAY736 or CFZ533. Other potential clinical manifestations of immunogenicity can include local skin reactions at the injection site, pyrexia and an influenza-like syndrome.

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- Of about 435 subjects treated with CFZ533 (up to 15 November 2019), only 2 cases were reported: one healthy volunteer and one patient in the Sjögren's syndrome study CCFZ533X2203 have tested positive for immunogenicity with no consequences on PK, PD or safety. Nonetheless, administration of monoclonal antibodies, independent of the antibody specificity carries the risk of immune reactions such as acute anaphylaxis, serum sickness and the generation of anti-drug antibodies (ADAs).

Vaccinations. In immune suppressed patients, live vaccinations may cause serious adverse events and success with any form of vaccination may be attenuated. No data exist on the effect of VAY736 or CFZ533 on response to vaccinations in general, but vaccinations prior to clearance of the mAbs and, in the case of VAY736, during marked B cell depletion, are likely to result in failure to produce protective antibody titers. Study subjects should therefore receive appropriate vaccinations before entering the study in accordance with current immunization guidelines at least 4 weeks prior to study medication administration (>2 months before dosing for live/attenuated vaccines).

Infections. Both VAY736 and CFZ533 target one or more elements of the immune system and thus effect immune suppression that can increase risks of infection. The Investigator should remind the patient of the potential increased risk of infection and instruct them to promptly report any symptoms of infections to the Investigator. An increase in mild -to -moderate upper respiratory tract infections compared to placebo has been associated with use of VAY736. The available data for CFZ533 (cut-off date 15 November 2021) in over 888 treated subjects suggest

no overall increased risk of infection in CFZ533-treated subjects compared to placebo or standard of care in patients with autoimmune diseases and those with kidney transplant. A Phase 1 study of CFZ533 did not reveal evidence for T cell or B cell lymphopenia or increased rate or severity of infections versus placebo in healthy volunteers.

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In the completed (CCFZ533X2201) and ongoing (CCFZ533A2201) study in kidney transplant patients, the rate of infections in CFZ533-treated patients was not increased compared to patients receiving tacrolimus. However, the risk of infection with VAY736 or with CFZ533 may increase if either agent is combined with steroids or other strong immune suppressive agents. In the current study, concurrent background therapy of patients is restricted to CS dosing ≤30 mg prednisone or equivalent and to drugs with low-to-moderate risk for immune suppression. Stronger immune suppressive drugs such as cyclophosphamide and cyclosporine A are prohibited. In addition, patients with current, active or latent infection susceptible to reactivation will be excluded from entry into study CVAY736X2208.

In the CCFZ533X2202 phase 2 study in lupus nephritis, a patient presented with a gastrointestinal infection suspected for CMV disease. During hospitalization, the patient developed a respiratory infection that progressed to a fatal outcome.

Currently the causal effect of CFZ533 remains unclear, however, active viral infections do remain a potential risk. Therefore, CMV screening and monitoring have been implemented to mitigate the risk across the clinical development program for CFZ533.

Overall, the risk-benefit remains unchanged since the latest updated IB and is considered favorable to support investigation of CFZ533 patients with autoimmune diseases and in solid organ transplant patients.

For the most up-to-date information on infections, please refer to the latest edition of the respective IB.

Safety monitoring. Patients enrolled in both VAY736 and CFZ533 treatment cohorts will be monitored at all scheduled site visits for safety risks standard for this study population by routine assessments, including complete physical examination and general laboratory assessments. The risk for patients in this trial will be minimized by compliance with the eligibility criteria and study procedures, close clinical monitoring and compliance with criteria for treatment interruption outlined in the protocol. The IB's respective to the two study compounds provide specific advice on monitoring for and diagnosing infections. Additional, cohort-specific risks and safety monitoring are detailed in the following Section 4.5.1 and Section 4.5.2. Women of child-bearing potential must be informed that taking the study treatment may involve unknown risks to the fetus if pregnancy were to occur during the study and agree that in order to participate in the study they must adhere to the contraception requirements outlined in the exclusion criteria. If there is any question that the subject will not reliably comply with, they should not be entered or continue in the study.

4.5.1 VAY736: specific risks

The identified safety risks of BAFF receptor blockade and ADCC with VAY736 are systemic injection reactions and upper respiratory tract infections. Potential risks include infections and neutropenia related to B cell depletion. Since B cell depletion can persist for several months or even years after the last treatment with B cell depleting agents, monitoring requirements are in place for patients receiving VAY736 over an extended follow up period.

Injection-related reactions. Consistent with VAY736 mode of action, mild-to-moderate, non-allergic systemic reactions, including symptoms such as headache, fever/pyrexia, shivering/chills, nausea, dizziness, rash, flushing, myalgia, fatigue, tachycardia and hypotension have occurred in VAY736 single and multiple dose administrations. Symptoms were most often observed after the first VAY736 dose, but new-onset and recurrent reactions after repeated dosing have occasionally been reported. Reactions typically occurred within a range of 30 minutes up to 24 hours after initial VAY736 dosing and were manageable by treatment with paracetamol, antihistamines and corticosteroids, or in case of i.v. administration of the drug, by short-term cessation of the mAb infusion and restarting the infusion at a slower rate. In severe cases, the associated signs and symptoms may be indistinguishable from those of allergic reactions, although the required treatment is similar for both of these conditions. Pre-medication with paracetamol alone has been ineffective to prevent these acute injection reactions. Orallyor i.v. administered corticosteroids may be used to prevent or treat these reactions.

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For safety monitoring, patients in Cohort 1 are required to stay at the clinic until at least 2 hours after first study medication on Day 1 and on the Week 29 visit. Patients should remain at the study site under observation during this period. Patients should be instructed to promptly report symptoms occurring within 24 hours after study drug administration.

Potential side effects of the methylprednisolone pre-medication are short term and may include sodium retention-related weight gain and fluid accumulation, hyperglycemia and glucose intolerance, hypokalemia and gastrointestinal upset. These symptoms are generally self-limited and do not require treatment. Patients with uncontrolled diabetes or hypertension will be excluded from the trial.

In the study CVAY736A2201, local injection-related reactions (site reactions) were the most commonly reported AEs.

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Symptoms included erythema, swelling, pain, itching/pruritus, rash and tenderness

around the injection site. Some local injection reactions have been reported with a delayed onset and lasted up to several weeks. The majority of local reactions did not require treatment or were managed symptomatically as warranted.

Neutropenia. Neutropenia occurring during the B cell recovery period (>16 weeks post treatment) has been associated with rituximab-mediated B cell depletion, termed 'late onset neutropenia' (LON), which remains of unclear etiology, is typically self-resolving and has only rarely been associated with infections (Wolach et al 2012; Tesfa et al 2011). Adverse events of neutropenia with VAY736 exposure have been reported which have been primarily transient CTC Grades 1 (1500/mm^3 to LLN) and 2 (1000/mm^3 to 1500/mm^3) (see IB). As VAY736 is expected to similarly induce B cell depletion followed by recovery, SLE patients enrolled in the VAY736 cohort will have regular monitoring of neutrophil counts throughout the treatment and follow up periods for potential occurrence of both early and late onset of neutropenia.

Hypoimmunoglobulinemia. In patients treated with VAY736, a trend toward reduction in IgM levels was observed with VAY736 in pSS patients and in RA patients; a finding consistent with reported experiences with other B cell depleting agents targeting CD20 such as rituximab (Marco et al 2014) and ocrelizumab. In the Ph2b study (CVAY736A2201) in pSS patients. For IgG, the proportion of patients below normal reference range at any time was low (2.1% in 4/188 patients) and there were no serious infections reported in these 4 patients. While this study is ongoing, the observations of sustained IgG below normal reference range ≥ 12 weeks thus far is low (1.1%, 2/187) (refer to IB). There were no disseminated infections with opportunistic pathogens to date in patients treated with VAY736. Patients enrolled into the VAY736 cohort will have IgG and IgM levels monitored regularly during the study and follow up periods.

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In humans, transient peripheral B-cell depletion and lymphocytopenia have been reported in infants born to mothers exposed to anti-CD20 antibodies during pregnancy. The potential duration of B-cell depletion in infants following maternal exposure to VAY736 in utero, and the impact of B-cell depletion on the safety and effectiveness of vaccines, are both unknown. Women of child-bearing potential should be informed that taking the study treatment may involve unknown risks to the fetus if pregnancy were to occur during the study, and then should agree that in order to participate in the study, they must adhere to the contraception requirements required during the period of study treatment administration and the period after discontinuation of study drug as outlined in the protocol's exclusion criteria.

Malignancies: There is no evidence to suggest that VAY736 increases the risk of malignancy to date. However, there is a risk of malignancies in immunocompromised patients in general, including those patients receiving immunosuppressive therapies and/or those patients who were

immunocompromised from prior therapies. Patients with autoimmune disorders are also prone to develop specific types of cancer, depending on type of autoimmune disease. Based on the description of the individual cases reported from the VAY736 clinical trials and the confounding factors present (e.g., underlying disease, prior/concomitant treatment with immunosuppressants), a causal association with VAY736 cannot be established at this time. However, given that patients receiving immunosuppressive therapies are at increased risk of malignancies, and based on the safety information from other anti-CD20 mAb and soluble BAFF-inhibitor therapies, 'Malignancy' is considered as an Important Potential risk for VAY736. Based on overall data analysis to date, it does not alter the benefit-risk profile of VAY736/ianalumab. In ongoing non-oncology studies, there exists long-term treatment-free safety follow-up of patients until B-cell count recovery thresholds are met (up to 2 years post-treatment). During this time all SAEs, including any malignant neoplasm, are collected to provide for further evaluation of this important potential risk of malignancy.

Please refer to Section 7 in the VAY736 IB current edition for additional information on details of the above specific risks and other potential adverse effects of the compound.

4.5.2 CFZ533 specific risks

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 immune suppression with a decreased capacity to mount a response to novel immunogens, including those of bacterial, viral, fungal and parasitic origin. However, although the ability to mount a primary immune response will be affected by CFZ533, the memory B cell and plasma cell repertoire should remain intact and protective. In addition, subjects will have adequate preformed serum antibody to maintain protective humoral response for extended periods of time. Infections in patients treated with CFZ533 in clinical trials involving healthy volunteers or patients with RA or other rheumatic diseases are overall mild-to-moderate in severity.

Thrombosis. Thromboembolic events have been reported in clinical trials with CD154 (CD40 ligand) blocking antibodies, but not with CD40 blocking antibodies. The risk of thromboembolic events with CFZ533 is considered minimal.

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Investigation in human FcγR transgenic mice revealed the absence of thromboembolic activity of a blocking, non-depleting anti-CD40 mAb, whereas anti-CD154 mAb caused thrombocytopenia and thrombi formation. *In vitro* whole blood aggregation assays also demonstrated platelet activation liabilities of anti-CD154 but not anti-CD40 mAbs. Clinical data for CFZ533 available to date do not suggest an increased risk of thromboembolism. Furthermore, there have been no reports of thromboembolic complications with other anti-CD40 antibodies, including dapirolizumab, lucatumumab or ASKP1240 (anti-CD40 antibody by Astellas Pharma). Although risk of thromboembolism is theoretical, hematologic and coagulation parameters will be monitored in the current study. Furthermore, patients with conditions such as anti-phospholipid syndrome who are at a higher risk for thromboembolism will be excluded from the CFZ533 arm unless they are receiving anti-thrombotic prophylaxis.

Please refer to Section 7 in the CFZ533 IB current edition for further information, further details on the above specific risks and other potential adverse effects of the compound.

4.5.3 Benefits of VAY736 and CFZ533

There is a large, unmet need in SLE for new immunosuppressive treatments with less severe adverse effects. The expected benefit profiles in patients with SLE for VAY736 and CFZ533 are anticipated to provide reductions in disease activity and improved quality of life along with reduced toxicities compared to existing treatments. Additionally, these clinical benefits from VAY736 and from CFZ533 are expected to reduce dependence on chronic corticosteroid use and prevent long term organ damage.

4.5.4 Blood sample volume

A total blood volume of approximately 790 mL will be collected over the course of the initial 13-month screening / treatment phase up to Study Week 53. Approximately 205 mL of additional blood will be collected during the 4-month Follow-up period (Study Week 57 to Week 69). Thus, for the entire study from Screening until the Week 69 visit, an overall total blood volume of approximately 995 mL over 18 months will be collected.

For patients tested positive for HepBc Ab, an additional overall blood volume of approximately 140 mL will be taken up to V399 (Month 18) for both Cohorts. Monthly hepatitis B monitoring will be continued after V399 to V400 (12 months after last treatment) for all patients in Cohort 1 who tested positive for HepBc Ab. For patients who do not achieve B-cell recovery, testing will continue at every visit (8 mL at each visit) until EoS visit Cohort 1.

For patients randomized to the CFZ533 cohort, an additional blood volume of approximately 115 mL from Baseline until Week 69 will be collected for local CMV monitoring.

Patients in Cohort 1 (VAY736) who do not achieve B-cell recovery criteria at the Week 69 visit will continue the study and enter into a secondary Follow-Up period starting after the Week 69 visit has been completed. At each of the safety follow-up visits in the secondary Follow-Up period, approximately 15 mL of blood (plus 8 mL if HepB monitoring is required) will be collected to monitor safety laboratory and B-cell recovery. At EoS visit for Cohort 1 approximately 60 mL of blood will be collected. Since each patient in Cohort 1 (VAY736) will have an individual follow-up time to achieve B cell recovery criteria, a total blood volume taken throughout the study cannot be given. Additional samples may be required for safety monitoring or repeat measures.

Timings of blood sample collection are outlined in the Assessment Schedule.

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.

4.6 Rationale for Public Health Emergency mitigation procedures

During a public health emergency as declared by local or regional authorities e.g., pandemic, epidemic or natural disaster, mitigation procedures to ensure participant safety and trial integrity are listed in relevant sections. Notification of the public health emergency should be discussed with Novartis prior to implementation of mitigation procedures, which should be then permitted/approved by local or regional Health Authorities and Ethics Committees as appropriate.

5 Population

The patient population will be comprised of adult male and female patients with active SLE.

The investigator must ensure that all patients being considered for the study 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 patients.

Patient selection is to be established by checking through all eligibility criteria at screening. A relevant record (e.g., checklist) of the eligibility criteria must be stored with the source documentation at the study site.

Deviation from **any** entry criterion excludes a subject from enrollment into the study.

Patient re-screening will be allowed in the study.

5.1 Inclusion criteria

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

1. Written informed consent must be obtained before any assessment is performed
2. Male and female patients 18 to 75 years of age
3. Fulfill ≥4 of the 11 American College of Rheumatology 1997 classification criteria for SLE (Hochberg 1997; Tan et al 1982) at screening
4. Patient diagnosed with SLE for at least 6 months prior to screening
5. Elevated serum titers at screening of ANA (≥1:80) of a pattern consistent with an SLE diagnosis, including at a minimum either anti-double stranded DNA (anti-ds DNA) or anti-Ro (SSA) or anti-La (SSB) or anti-nuclear ribonucleoprotein (anti-RNP) or anti-Smith (anti-Sm)
6. Currently receiving corticosteroids and/or anti-malarial and/or thalidomide treatment and/or another DMARD :

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7. SLEDAI-2K score of ≥6 (Gladman et al 2002) at screening
8. BILAG-2004 score at screening of:
   - at least one "A" in either the mucocutaneous domain or in the musculoskeletal domain,
     OR
   - one "B" in either the mucocutaneous or musculoskeletal domain AND at least one "A" or "B" in a second domain (Isenberg et al 2005, Isenberg et al 2011, Yee et al 2006, Yee et al 2010)
9. Able to communicate well with the investigator, to understand and comply with the requirements of the study
10. Weigh at least 40 kg at screening

5.2 Exclusion criteria

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

1. **Cohort 2 (**CFZ533/Placebo**) only:** 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 significantly prolonged activated partial thromboplastin time (aPTT) consistent with co-existent anti-phospholipid syndrome and without concurrent prophylactic treatment with aspirin or anticoagulants as per local standard of care
2. History of receiving prior to screening:
   - Within 12 weeks: high dose corticosteroids (i.e., ≥500 mg Solumedrol or equivalent), calcineurin inhibitors, or other oral DMARD except as listed in inclusion criterion 6
   - Within 24 weeks: cyclophosphamide or biologics such as intravenous Ig, plasmapheresis, anti-TNF-a mAb, CTLA4-Fc Ig (abatacept) or BAFF-targeting agents (e.g., belimumab)
   - Any B-cell depleting therapies (e.g., anti-CD20 mAb, anti-CD22 mAb, anti-CD52 mAb) or TACI-Ig (atacicept) administered within 52 weeks prior to screening, and a B-cell count <50 cells/µL at the time of screening.
3. Evidence of past exposure to tuberculosis (TB) as assessed by Quantiferon testing at screening. Patients with history of latent TB infection may be eligible if they have received and completed appropriate anti-TB treatment according to national guidelines
4. Presence of human immunodeficiency virus (HIV) infection at screening
5. Any of the following abnormal laboratory values:
   - Platelets < 50,000/mm^3 (< 50 x 10^9/L)
   - Hemoglobin (Hgb) < 8.0 g/dL (< 5 mmol/L)

- Neutrophil count (< 1,000/mm^3) (< 1.0 X 10^9/L)

6. Have donated blood or experienced a loss of blood > 400 mL within 3 months prior study entry, or longer if required by local regulations
7. Severe organ dysfunction or life-threatening disease
8. Presence of severe lupus kidney disease as defined by proteinuria above 6 g/day or equivalent using spot urine protein creatinine ratio, or serum creatinine greater than 2.5 mg/dL (221.05 µmol/L), or requiring immune suppressive induction or maintenance treatment exceeding protocol defined limits
9. Active viral, bacterial or other infections at the time of screening or enrollment, or history of recurrent clinically significant infection or of recurrent bacterial infections with encapsulated organisms.

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10. Receipt of live/attenuated vaccine within a 2-month period before first dosing
11. Uncontrolled, co-existing serious disease, e.g., uncontrolled hypertension, heart failure, type I diabetes, thyroid disease within 3 months prior to first dosing, or significant, unresolved illness within 2 weeks prior to first dosing
12. History of hypersensitivity to drugs of similar chemical class (e.g., IgG biologics)

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13. History of non-compliance with medical regimens or considered potentially unreliable
14. Use of other investigational drugs at the time of enrollment, or within 5 half-lives of enrollment, or until the expected PD effect has returned to baseline, whichever is longer; or longer if required by local regulations.
15. Chronic infection with hepatitis B (HBV) or hepatitis C (HCV). A positive HBV surface antigen (HBsAg) test excludes a subject. HBsAg negative patients who are HepBc Ab positive are also excluded, except if both of the 2 following criteria are met: i) HBV DNA is negative, ii) Hepatitis B monitoring is implemented (HBsAg and HBV DNA tested on a monthly basis).

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Subjects with a positive HCV antibody test should have HCV RNA levels measured. Subjects with positive (detectable) HCV RNA should be excluded.

16. History of malignancy of any organ system (other than localized basal cell carcinoma or squamous cell carcinoma of the skin or *in-situ* cervical cancer), treated or untreated,

within the past 5 years, regardless of whether there is evidence of local recurrence or metastases.

17. Pregnant or nursing (lactating) women.
18. Women of child-bearing potential, defined as all women physiologically capable of becoming pregnant, **unless** they are using highly effective (for Cohort 1 VAY736/Placebo) or effective (for Cohort 2 CFZ533/Placebo) methods of contraception during dosing and for 6 months (for Cohort 1 VAY736/Placebo) or 14 weeks (for Cohort 2 CFZ533/Placebo) after stopping of investigational drug (or longer if required by concomitant medications).

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19. Any surgical, medical, psychiatric or additional physical condition that the Investigator feels may potentially jeopardize the patient in case of participation in this study
20. Subjects who are committed to an institution by way of official or judicial order

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

6 Treatment

6.1 Study treatment

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 SOM and the Pharmacy Manual.

6.1.1 Investigational and control drugs

Table 6-1 Investigational and control drug

Investigational/ Control Drug (Name and Strength)	Pharmaceutical Dosage Form	Route of Administration

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Clinical supplies are to be dispensed only in accordance with the specified study procedures.

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 treatments

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6.1.3 Treatment arms/group

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6.2 Other treatment(s)

6.2.1 Concomitant therapy

Permitted standard-of-care co-medications include oral CS and/or an anti-malarial agent (e.g., hydroxychloroquine) and/or thalidomide and/or one of the listed DMARDs: (see Inclusion criteria Section 5.1).

Table 6-2 Allowed concomitant medications

Medication	Condition
Ad hoc use of oral analgesics (NSAIDs, acetylsalicyclic acid, paracetamol)	All use must be recorded in the concomitant medications / significant non-drug therapies
Corticosteroids	If CS is patient's single, SoC medication, an oral dose ≤30 mg/d ≥8 weeks prior randomization and stable dose for ≥ 2 weeks prior to randomization If CS is not patient's single SoC medication, an oral, stable dose of ≤30 mg/d for ≥2 weeks prior to randomization Commercially Confidential Information Maintain baseline CS dosing from Study Week 1 to Week 5
Anti-malarials	Anti-malarial drugs (i.e., hydroxychloroquine, chloroquine, quinacrine) and/or thalidomide at stable dosing ≥8 weeks prior screening and remaining stable throughout blinded treatment period. Substitution between anti-malarial drugs is permitted if equivalent dosing is maintained.
DMARDS	Methotrexate or an imidazole derivative (e.g., azathioprine, mizoribine) or a mycophenolic acid derivative (e.g., mycophenolate mofetil) if at stable dosing ≥8 weeks prior to randomization and remaining stable throughout blinded treatment period. Any DMARDs that will be discontinued by the patient prior to study entry will require a minimum wash-out period of 4 weeks (methotrexate requires 8 weeks) or 5 half-lives, whichever is longer, unless noted otherwise in the protocol

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

All medications, procedures and significant non-drug therapies (including physical therapy and blood transfusions) administered after the subject was enrolled into the study must be recorded in the concomitant medications / significant non-drug therapies

6.2.2 Permitted concomitant therapy requiring action (guided CS tapering)

Corticosteroids. Patients on stable, maintenance dosing of oral corticosteroids (≤30 mg/day prednisone or equivalent) prior to randomization should continue this dosing level until Week 5. From Week 5 visit onwards, patients will undergo a guided CS dose reduction from baseline levels according to the following schedule:

- Achieve by Week 17 a prednisone dose or equivalent of ≤5 mg/day or less than CS dose at Baseline, whichever dose is lower.
- Any remaining corticosteroid dosing at Week 17 should subsequently be kept stable up to the Week 29 visit.

- Patients who are unable to reach these reduced CS dose level goals by week 17 or maintain these achieved CS dose levels through to Week 29 will be considered a non-responder for primary endpoint.
- Limited adjustments in CS dosing after Week 17 are provided (see Section 6.2.4 Rescue medication and Table 6-3 Prohibited medication).
- Further adjustments of corticosteroids and of other DMARD co-medications may take place during the open label period after Week 29 according to PI discretion.

6.2.3 Prohibited medication

Use of the treatments displayed in the below Table 6-3 are not allowed after the start of the study.

Table 6-3 Prohibited medication

Medication	Prohibition period	Action taken
Other immune suppressive agents and biologics: • Calcineurin inhibitors • Cyclophosphamide, intravenous Ig, plasmapheresis, anti-TNF-α mAb, CTLA4-Fc Ig (abatacept) or BAFF targeting agents (e.g., belimumab) • Any B-cell depleting therapies (e.g., anti-CD20 mAb, anti-CD22 mAb, anti-CD52 mAb), atacicept, (TACI-Ig)	Throughout treatment period through EoS	Withdrawal may be required on a case-by-case basis
• Total CS >30 mg/d prednisone or equivalent	Throughout treatment period through Week 29	Designated non-responder for primary endpoint
• Changes in CS dose	Within 2 weeks of Study Visit Week 29	Designated non-responder for primary endpoint
• Other experimental therapies	Throughout treatment period through to EoS	Withdrawal may be required on a case-by-case basis
• Live/ attenuated vaccines	• For Cohort 1 (VAY736): Throughout treatment period and follow up period until achieving B cell recovery • For Cohort 2 (CFZ533): Throughout treatment period and up to 14 weeks after last CFZ533 dosing	Study treatment discontinuation; patient should remain in study and follow visit schedule for safety monitoring until achieving EoS visit for their respective cohorts

6.2.4 Rescue medication

Corticosteroids may be administered to patients for SLE clinical disease flares after enrollment into this study as determined necessary by the responsible PI. However, patients receiving increased CS dose will be considered non-responders for primary study endpoint if any of following criteria was met:

- total daily CS dose is >30 mg/d prednisone or equivalent, or
- increased daily CS dose is administered >2 days within a 4-week treatment cycle from Week 17 to Week 29, or
- daily CS dose is increased within 2 weeks of Study Visit Week 29.

Where acute corticosteroid administration occurs for purposes other than the treatment of SLE disease activity, such as short-acting hydrocortisone dosed peri-operatively in patients with suppressed hypothalamic-pituitary-adrenal axis, patient responder status will be discussed on a case-by-case basis.

All Concomitant Medications as well as their dose changes must be recorded in the eCRF.

6.3 Subject numbering, treatment assignment, randomization

6.3.1 Subject numbering

The subject number will be assigned through the eCRF capture system to a patient at the screening visit and remains the unique identifier for the patient throughout the study. For more detailed information on subject numbering, please see 'Subject numbering' section in the Site Operations Manual.

6.3.2 Treatment assignment, randomization

Randomization has to be performed via the IRT system at the Baseline visit at the latest. All eligible participants will be randomized to one of the available treatment arms using the IRT system. The Investigator or his/her delegate will contact the IRT system after confirming that the participant satisfies all the inclusion/exclusion criteria. The IRT system will specify a unique medication number for the package of investigational drug to the participant. The randomization number will not be communicated to the requester.

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

If study participants are only eligible for VAY736 Cohort (i.e., meeting exclusion criterion 1), they will be randomized to either active arm or placebo arm of Cohort 1. Otherwise, the participants will be randomized to one of four treatment arms of two cohorts.

Randomization will be stratified by ENA status (positive vs. negative) and SLEDAI-2K <10, ≥10 status at Baseline, based on screening results, in order to remove any possible confounding impact on treatment effects.

6.4 Treatment blinding

This is a patient and investigator-blinded study. Patients and investigators will remain blinded to study treatment throughout the blinded treatment phase of the study, except where indicated below.

Patients, investigator staff, persons performing the assessments, and the clinical trial team (CTT) will remain blind to the identity of the treatment from the time of randomization until end of the Week 29 visit applying the following rules:

- Randomization data are kept strictly confidential until the time of unblinding,
- Unblinding will occur in the case of subject emergencies and at the conclusion of the study.
- Unblinding of the CTT members may occur at the time of the interim analyses.

Site staff

With the exception of any unblinded site staff identified below, all site staff (including study investigator and study nurse) will be blinded to study treatment throughout the blinded treatment phase of the study.

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

Drug product will be supplied in open label medication packs; therefore an unblinded pharmacist who is independent of the study team will be required in order to maintain the blind. The unblinded pharmacist will receive the appropriate treatment allocation numbers via the IRT system. Appropriate measures must be taken by the unblinded pharmacist to ensure that the treatment assignments are concealed from the rest of the site staff.

Sponsor staff or delegate

The following unblinded sponsor roles are required for this study:

The randomization codes associated with subjects from whom PK samples are taken will be disclosed to PK analysts who will keep PK results confidential until data base lock.

- Unblinded sample analysts

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- Unblinded Clinical Trial Associate role to have oversight of randomization in IRT system
- Unblinded field monitors

The unblinded field monitors are required to review drug accountability and allocation at site. The unblinded monitors are not provided with a randomization list directly but will be unblinded through review of source documentation compiled by the unblinded pharmacist, which details treatment allocation to individual subjects. The unblinded monitors will also be able to review the randomization list provided to the unblinded pharmacist.

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 Table 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 CCI 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 6-4 Blinding and unblinding plan (up to Study Week 29)

	Time or Event			
Role	**Randomi-zation list generated**	**Treatment allocation & dosing**	**Safety event (single subject unblinded)**	**Interim Analysis**
Patients	B	B	UI	B
Site staff	B	B	UI	B
Unblinded site staff e.g., pharmacy staff	UI	UI	UI	UI
Drug Supply and Randomization Office	UI	UI	UI	UI
Unblinded sponsor staff e.g., for study treatment re-supply, unblinded monitor(s), sample analyst(s),	UI	UI	UI	UI
Statistician/statistical programmer/ data analysts CCI	B	B	UI	UI
All other sponsor staff not identified above (trial team, project team, management & decision boards, support functions)	B	B	UI	UI

UI: Allowed to be unblinded on individual subject level
B: Remains blinded

6.5 Dose modification

Investigational study treatment dose adjustments and/or interruptions are not allowed and must be discussed with the sponsor on a case-by-case basis if considered appropriate by the investigator.

Study drug dose adjustments are not permitted in this study; in case of an AE or for any reason (e.g., non-compliance, operational issue) resulting in a deviation from the required dosing

scheme, consultation and agreement with Novartis will be necessary to decide whether the patient can continue or needs to be withdrawn from the treatment.

If not avoidable, dosing can be brought forward or delayed by up to 1 week for administrative reasons. The subsequent dose should be given according to the original schedule (i.e., do not move subsequent dose dates).

Any change in dosing must be recorded on the Dosage Administration Record eCRF.

6.6 Additional treatment guidance

6.6.1 Treatment compliance

Study treatment will be administered at the clinical sites for all patients; therefore, treatment compliance is monitored by the clinical staff and recorded in the eCRF.

Serum/plasma concentrations for VAY736 and CFZ533 will be obtained, and pharmacokinetic parameters (measures of treatment exposure) will be determined in all patients treated with VAY736 and CFZ533, as detailed in Section 8.5.1.

6.6.2 Recommended treatment of adverse events

Patients experiencing disease signs and symptoms may receive symptomatic care with over-the-counter, anti-inflammatory/analgesic agents such as NSAIDs and paracetamol.

For patients with SLE disease signs and symptoms not adequately controlled by symptomatic care and/or have more severe SLE disease manifestations not suitable for such treatment may receive rescue therapy with corticosteroids if determined by the PI to be medically necessary. However, any increases in corticosteroid dosing during the blinded treatment period to treat increased SLE disease activity may result in the patient labeled as a non-responder for primary endpoint (see Table 6-2 and Table 6-3 for allowed and prohibited concomitant medications, respectively).

Any medication used to treat AEs must be recorded on the Concomitant Medications/ Significant non-drug therapies CRF.

6.6.3 Emergency breaking of assigned treatment code

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

It is the investigator's responsibility to ensure that there is an appropriate procedure in place to allow access to the IRT system at any time in case of emergency.

In addition, oral and written information to the subject must be provided on how to contact his/her backup in cases of emergency, or when he/she is unavailable, to ensure that 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 patient. In case the study drug will be discontinued, patients should continue the study without receiving study treatment in order to monitor their safety, wherever possible.

6.7 Preparation and dispensation

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

Preparation of both study drugs is described in detail in a separate Pharmacy Manual.

A unique medication number is printed on the study medication label.

Investigator staff will identify the study medication kits to dispense to the patient by contacting the IRT system and obtaining the medication number(s).

Each study site will be supplied with study drug in packaging as described in Section 6.1.

An unblinded pharmacist at each site will identify the study medication kits to dispense to the patient by contacting the IRT system and obtaining the medication number(s), and will prepare the study medication accordingly. VAY736, CFZ533 and corresponding placebos will be administered to the patient via s.c. injection or i.v. infusion, respectively, at the study site by trained and competent site personnel. Please refer to the respective Pharmacy Manuals for further details.

7 Informed consent procedures

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

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

Novartis will provide to investigators in a separate document a proposed model informed consent form (ICF) that complies with the ICH GCP guidelines and regulatory requirements and is considered appropriate for this study. Any changes to the proposed model consent form suggested by the investigator must be agreed by Novartis before submission to the IRB/IEC. The model ICFs will be adapted locally to comply with local regulations.

Information about common side effects already known about the investigational drug can be found in the IB. This information will be included in the subject informed consent and should be discussed with the patient before and during the study as needed. Any new information regarding the safety profile of the investigational drug 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 patient.

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

For patients receiving SoC background therapy, contraception requirements and pregnancy warnings must be discussed with the PI, as per local practices.

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

8 Visit schedule and assessments

The Assessment schedule lists all assessments and indicates with an "X" at which visits they are to be performed. All data obtained from these assessments must be entered into the eCRF and must be supported in the patient's source documentation.

Patients should be seen for all visits/assessments as outlined in the assessment schedule or as close to the designated day/time as possible. Missed or rescheduled visits should not lead to automatic discontinuation. Patients who prematurely discontinue the study for any reason should be scheduled for a visit as soon as possible, at which time all of the assessments listed for the final visit will be performed. At this final visit, all dispensed investigational product should be reconciled, and the adverse event and concomitant medications recorded on the CRF. Patients who prematurely discontinue the treatment with study drug for any reason should be encouraged to continue their study participation and complete all safety study visits as deemed necessary by the investigator, if possible.

As per Section 4.6, during a public health emergency as declared by local or regional authorities e.g., pandemic, epidemic or natural disaster that limits or prevents on-site study visits, alternative methods of providing continuing care may be implemented by the investigator as the situation dictates. If allowed by local Health Authority and depending on operational capabilities, phone calls and virtual contacts (e.g., tele consult) or visits by site staff/ home nursing staff to the participant´s home can replace on-site study visits for the duration of the disruption and until it is safe for the participant to visit the site again.

Table 8-1 Assessment Schedule, Cohort 1 & 2 – Treatment period

Epoch	Screening		Treatment																EoT
Visit Name	Screen	Base-line [2]	Treatment – blinded period									Treatment – open label period							EoT
Visit Numbers[1]	1	20	110	120	130	140	150	160	170	180	190	200	210	220	230	240	250	260	299
Days	-28 ±2	-1 to 1	1	15 ±2	29 ±2	57 ±2	85 ±2	113 ±2	141 ±2	169 ±3	197 ±3	211 ±2	225 ±3	253 ±3	281 ±3	309 ±3	337 ±4	340 ±1	365 ±5
Weeks	-4	-1 to 1	1	3	5	9	13	17	21	25	29	31	33	37	41	45	49	49	53
Months	-1	-1 to 1	1	1	2	3	4	5	6	7	8	8	9	10	11	12	13	13	14
Informed consent	X																		

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In/Exclusion criteria	X	X																	
Medical history	X																		
Demography	X																		
Vital signs [3]	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		X
Electrocardiogram (ECG)	X	X			X		X		X		X			X		X			X
Corticosteroid induction [4]			X[4]								X[4]								
SLEDAI-2K	X	X			X	X	X	X	X	X	X		X	X	X	X	X		X
BILAG-2004	X	X			X	X	X	X	X	X	X		X	X	X	X	X		X

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PhGA - VAS (physician)	X	X			X	X	X	X	X	X	X		X	X	X	X	X		X
PGA – VAS (patient)	X	X			X	X	X	X	X	X	X		X	X	X	X	X		X
Hepatitis & HIV Screen [7]	X																		
CMV Monitoring[6,25]	X		X		X	X	X	X	X	X	X		X	X	X	X	X		X

Epoch	Screening		Treatment																EoT
Visit Name	Screen	Base-line [2]	Treatment – blinded period								Treatment – open label period								EoT
Visit Numbers[1]	1	20	110	120	130	140	150	160	170	180	190	200	210	220	230	240	250	260	299
Days	-28 ±2	-1 to 1	1	15 ±2	29 ±2	57 ±2	85 ±2	113 ±2	141 ±2	169 ±3	197 ±3	211 ±2	225 ±3	253 ±3	281 ±3	309 ±3	337 ±4	340 ±1	365 ±5
Weeks	-4	-1 to 1	1	3	5	9	13	17	21	25	29	31	33	37	41	45	49	49	53
Months	-1	-1 to 1	1	1	2	3	4	5	6	7	8	8	9	10	11	12	13	13	14
HepB monitoring[7,24]					X	X	X	X	X	X	X		X	X	X	X	X		X
Tuberculosis test [7]	X																		X
Pregnancy test [5]	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X		X
Hematology [7]	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X		X
Clinical Chemistry [7]	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X		X

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Coagulation Panel [7]	X	X[6]					X[6]				X[6]								X[6]
Autoantibodies [7]	X	X					X				X				X				X

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IMI blood sample [7, 16]		X			X					X									
IMI urine sample [7, 16]		X			X					X									

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Steroid taper [11]					X	X	X	X											
PK Cohort 1 [12]			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
PK Cohort 2 [12]			X[13]	X	X[13]	X	X[13]	X	X	X	X[13]	X	X[13]	X	X[13]	X	X[13]		X
Immunogenicity [12, 14]		X		X			X				X	X			X				X

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Epoch	Screening		Treatment																EoT
Visit Name	Screen	Base-line [2]	Treatment – blinded period									Treatment – open label period							**EoT**
Visit Numbers[1]	1	20	110	120	130	140	150	160	170	180	190	200	210	220	230	240	250	260	299
Days	**-28 ±2**	**-1 to 1**	**1**	**15 ±2**	**29 ±2**	**57 ±2**	**85 ±2**	**113 ±2**	**141 ±2**	**169 ±3**	**197 ±3**	**211 ±2**	**225 ±3**	**253 ±3**	**281 ±3**	**309 ±3**	**337 ±4**	**340 ±1**	**365 ±5**
Weeks	-4	-1 to 1	1	3	5	9	13	17	21	25	29	31	33	37	41	45	49	49	53
Months	**-1**	**-1 to 1**	**1**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**8**	**9**	**10**	**11**	**12**	**13**	**13**	**14**

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IRT	X	X[23]		X	X	X	X	X	X	X	X	X	X	X	X	X	X		X
Dose administration [21]			X[22]	X[6]	X	X	X	X	X	X	X[22]	X[6]	X	X	X	X	X		

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Adverse Events	As required
Concomitant Treatment	As required
Comments	As required

[X] Assessment to be recorded in the clinical database, EoT – End of Treatment

[1] Visit structure given for internal programming purpose only

[2] Baseline visit may be combined with Visit 110 at Day 1

[3] Body Weight, Height (screening only), Temperature, Blood Pressure, Pulse Rate

[4] Only for Cohort 1 (VAY736); i.v. CS to be applied approximately 1 hour before first dose

[5] Pregnancy test on Visit 1 (Screening) in serum, all other visits in urine, only females

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[7] Central Lab

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[11] Corticosteroids should be tapered down to 5 mg/day or lower

[12] Samples are collected pre-dose unless otherwise stated

[13] Cohort 2 (CFZ533): take one PK sample at pre-dose and another sample 90 min AFTER THE START of i.v. infusion

[14] Cohort 1 (VAY736): serum Cohort 2 (CFZ533): plasma

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[16] Only selected sites

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[21] Dosing must be done after all assessments are completed, except for PK blood sampling in Cohort 2 (CFZ533) at visits V110, 130, 150, 190, 210, 230 and 250 where pre and post dose blood sampling is required

[22] Post-dose observation time of 2 hours after first dose for Cohort 1 (VAY736), only

[23] Randomization assignment at Baseline

[24] This test will only be applied as follows: for HepBc Ab positive patients at screening, followed by monthly HBV DNA and HBsAg testing

[25] CMV test (CMV serologies IgM and IgG and CMV DNA by PCR) will be performed in the local laboratory at screening for all patients. Starting from visit 110 this testing will be repeated on a monthly basis only for patients randomized to Cohort 2 (CFZ533).

Table 8-2 Assessment Schedule, Cohort 1 & 2 - Follow up period

Epoch	Follow Up - Cohort 1&2				Secondary Follow-Up					EoS Disposition
Visit Name	Follow Up			FU 1 Cohort 1/ EoS Cohort 2	FU 2 Cohort 1 [3]					EoS Disposition[2]
Visit Numbers[1]	300	310	320	399	400	410	420	430	440	1999
Days	393 ±5	421 ±5	449 ±5	477 ±5	645 ±10	813 ±10	981 ±10	1233 ±10	1569 ±10	-
Weeks	57	61	65	69	93	117	141	177	225	0
Months	15	16	17	18	24	30	36	45	57	0
Vital signs [4]		X		X						X
Physical Examination		X		X						X
Electrocardiogram (ECG)		X		X						X
SLEDAI		X		X						X
BILAG-2004		X		X						X
PhGA-VAS (physician)	X	X	X	X	X	X	X	X	X	X
PGA-VAS (patient)	X	X	X	X	X	X	X	X	X	X
HepB monitoring[7,15,16]	X	X	X	X	X	X	X	X	X	X
CMV monitoring[6, 17]	X	X	X	X						
Tuberculosis test				X						
Pregnancy test [5]	X	X	X	X	X					X
Hematology [7]	X	X	X	X	X	X	X	X	X	X
Clinical Chemistry [7]	X	X	X	X	X	X	X	X	X	X
Coagulation Panel [6]		X[6]		X[6]						
Autoantibodies [7]		X		X						X

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Epoch	Follow Up - Cohort 1&2				Secondary Follow-Up					EoS Disposition
Visit Name	Follow Up			FU 1 Cohort 1/ EoS Cohort 2	FU 2 Cohort 1 [3]					EoS Disposition[2]
Visit Numbers[1]	300	310	320	399	400	410	420	430	440	1999
Days	393 ±5	421 ±5	449 ±5	477 ±5	645 ±10	813 ±10	981 ±10	1233 ±10	1569 ±10	-
Weeks	57	61	65	69	93	117	141	177	225	0
Months	15	16	17	18	24	30	36	45	57	0

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PK Cohort 1	X	X	X	X						X
PK Cohort 2	X	X	X	X						
Immunogenicity		X		X						X

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Adverse Events	As required
Concomitant Treatment	As required
Comments	As required

[X] Assessment to be recorded in the clinical database, EoS – End of Study

[1] Visit structure given for internal programming purpose only

[2] Cohort 1 (VAY736), only: End of study visit will be performed within 4 weeks after the visit where B-cell depletion is no longer persistent. If a patient B-cells recovery is confirmed at Week 69, no additional follow-up or EOS visit is needed, and therefore Week 69, FU 1 Cohort 1/ EoS Cohort 2 will be the last visit.

[3] Cohort 1 (VAY736), only: Follow-up visits in Cohort 1 have to be performed until B-cell count is at ≥50 cells/ul or at least 80% of baseline levels. If a patient B-cells recovery is confirmed at Week 69 no additional follow-up or EOS visit is needed, and therefore Week 69, FU 1 Cohort 1/ EoS Cohort 2 will be the last visit.

[4] Body Weight, Temperature, Blood Pressure, Pulse Rate

[5] Pregnancy test on Visit 1 (Screening) in serum, all other visits in urine, only women

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[7] Central Lab

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[15] Monthly HepB monitoring will be continued after V399 to V400 for all patients in Cohort 1 who tested positive for HepB core Ab. For patients who do not achieve B-cell recovery, testing will continue at every visit until EoS visit Cohort 1.

[16] This test will only be applied for HepBc Ab positive patients at screening; followed by monthly HBV DNA and HBsAg testing.

[17] CMV test (CMV serologies IgG and IgM and CMV DNA by PCR) will be continued at the local laboratory after V300 to V399 on a monthly basis only for patients randomized to Cohort 2 (CFZ533)

8.1 Screening

8.1.1 Re-Screening

It is permissible to re-screen a patient if s/he fails the initial screening; however, each case must be discussed and agreed with the Sponsor on a case-by-case basis. In case a new ICF version is available, the patient needs to sign the updated ICF. In a situation where information/data from procedures that have been previously performed as part of the patients' routine disease care (prior to enrolling in the trial) will need to be used for inclusion this also needs to be agreed with the Sponsor on a case-by-case basis.

In the event a patient is being re-screened a new subject-ID will be assigned.

In the case where a safety laboratory assessment at screening is outside of the range specified in the exclusion criteria, the assessment may be repeated once prior to randomization. If the repeat value remains outside of the specified ranges, the patient must be excluded from the study.

8.1.2 Eligibility screening

Following registering in the IRT system for screening, patient eligibility will be checked once all screening procedures are completed.

Patients who sign an informed consent but fail to be started on treatment for any reason will be considered a screen failure. The reason for not being started on treatment will be entered on the screening phase disposition page. The demographic information, informed consent, and Inclusion/Exclusion pages must also be completed for screen failure patients. No other data will be entered into the clinical database for patients who are screen failures, unless the patient experienced a serious adverse event during the screening phase (see SAE section (Section 10.1.2 and Section 10.1.3) for reporting details). If the patient fails to be randomized, the IRT system must be notified within 2 days of the screen fail that the patient was not randomized.

8.2 Subject demographics/other baseline characteristics

Demographic and baseline characteristic data will be collected on all patients. Patients' race and ethnicity are collected to assess the diversity of the study population as required by Health Authorities. Relevant medical history/current medical conditions data will also be collected until the time/date of the signature of informed consent. 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. Additional screening occurs for potential, underlying diseases that may compromise safety, including latent or active infections (*Mycobacterium tuberculosis*, viral hepatitis, HIV). Date of the original diagnosis of SLE should be recorded.

Serology for autoimmunity is obtained for diagnostic purposes, and both ENA status and the screening SLEDAI score will be used as stratification factors.

8.3 Efficacy/ Pharmacodynamics

8.3.1 Pharmacodynamics

Pharmacodynamic samples will be collected at the time points defined in the Assessment schedule. Follow instructions outlined in the Central Lab 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 need to remain blinded during the study.

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

Soluble CD40

In Cohort 2 (CFZ533) blood samples will be collected for soluble CD40 concentrations in plasma (baseline, during treatment and follow-up) in order to assess the rate, extent and duration of target engagement. Blood samples will be obtained from all patients to protect blinding, but analysis may be performed only for patients receiving active treatment.

In Cohort 1 (VAY736) blood samples will be collected for soluble CD40 concentration in plasma (baseline, end of placebo-controlled period, and end of follow-up period) to explore if VAY736 treatment has the ability to modulate the expression of CD40 levels. Blood samples will be obtained from all patients to protect blinding, but analysis may be performed only for patients receiving active treatment

8.3.2 Clinical efficacy

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8.3.3 Patient reported outcomes (PRO)

The following PROs are not disease specific but applied conventionally to assess SLE and other chronic diseases. A detailed training manual relating to the administrative procedures of the questionnaires will be provided to the sites.

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8.4 Safety/ Tolerability

Safety assessments are specified below with the Assessment Schedule detailing when each assessment is to be performed.

For details on AE collection and reporting, refer to Section 10.1.1.

Assessment	Specification
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 pelvic exams may be performed. Information for all physical examinations must be included in the source documentation at the study site. Clinically relevant findings that are present prior to signing informed consent must be included in the Medical History part of the CRF. Significant findings made after first administration of investigational drug which meets the definition of an Adverse Event must be recorded on the Adverse Event section of the eCRF.
Vital signs	Vital signs include body temperature (recorded in °C), blood pressure (BP) and pulse measurements. The location of the temperature measurement (e.g., otic, oral) should be the same at every visit and will be documented in the Source data. After the patient has been sitting for three minutes, with back supported and both feet placed on the floor, systolic and diastolic blood pressure will be measured three times using a validated device, (e.g., OMRON) with an appropriately sized cuff. The repeat sitting measurements will be made at 1- to 2-minute intervals. In case the cuff sizes available are not large enough for the patient's arm circumference, a sphygmomanometer with an appropriately sized cuff may be used. If vital signs are out-of-range additional readings can be obtained. **At least the last reading must be within the specified ranges in order for the patient to qualify.**

Assessment	Specification
	In case of repeated vital assessments, the CRF should contain all repeat measurements.
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.

As per Section 4.6, during a public health emergency as declared by local or regional authorities e.g., pandemic, epidemic or natural disaster, that limits or prevents on-site study visits, regular phone or virtual calls can occur (every 4 weeks or more frequently if needed) for safety monitoring and discussion of the participant´s health status until it is safe for the participant to visit the site again. If participants cannot visit the site for protocol-specified safety lab assessments, an alternative lab (local) collection site may be used, as applicable.

8.4.1 Laboratory evaluations

A central laboratory will be used for analysis of specimens collected that are listed below. Details on the collections, shipment of samples and reporting of results by the central laboratory are provided to investigators in a separate Central Laboratory manual. For timing of the blood sampling please refer to the Assessment Schedule.

Clinically significant abnormalities must be recorded on the relevant section of the medical history/Current medical conditions/AE e(CRF) pages as appropriate

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.

Clinical chemistry

Albumin, alkaline phosphatase, total bilirubin (TBL), bicarbonate/CO_2, calcium, cholesterol, chloride, creatinine, creatinine kinase (CK), γ-GT, glucose, LDH, inorganic phosphorus, lipase, amylase, magnesium, potassium, total protein, AST, ALT, sodium, triglycerides, blood urea nitrogen/BUN and uric acid.

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

Urinalysis

A midstream urine sample will be obtained, in order to avoid contamination with epithelial cells and sediments. The sample will be analyzed for specific gravity, creatinine, pH, glucose, protein, bilirubin, ketones, nitrite, leucocytes or blood, and microscopic analysis of white blood cells, red blood cells, and casts will be performed.

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Coagulation panel

Prothrombin time (PT) and activated partial thromboplastin time (aPTT) will be measured for characterization of SLE disease (e.g., anti-phospholipid (aPL) syndrome) and general safety. Additional parameters, e.g., INR, may be assessed at the Investigator's discretion.

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Serum immunoglobulins

Serum levels of immunoglobulins (Ig) may be reduced by B cell-targeted interventions and so both IgG and IgM levels will be assessed.

8.4.2 Electrocardiogram (ECG)

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.

8.4.3 Pregnancy and assessments of fertility

Pregnancy tests are required in all women of child-bearing potential.

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 study drug must be discontinued, and 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.

8.4.4 Other safety evaluations

Quantiferon test

Both VAY736 and CFZ533 suppress the immune system and thus have potential for increasing susceptibility to mycobacterial infection. To identify patients exposed to *Mycobacterium tuberculosis* (MTb), a QuantiFeron test will be performed and read at screening (or within 6 months prior to randomization). 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 of ELISPOT assays based on interferon-gamma release may also be used for MTb diagnosis as per local practice.

Precautions against TB 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 MTb infection 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.

Hepatitis, HIV and CMV

Hepatitis

The immune suppressive effects of VAY736 and CFZ533 may exacerbate disease in patients with active viral hepatitis. All subjects will be screened for HBsAg and for HepBc Ab.

Table 8-3 Hepatitis screening

HBsAg	HepBc Ab	HBV DNA	Eligible	Comment
-	-	-	Yes	
-	+	-	Yes	Cohort 1 (VAY736/Placebo): monitoring required, prophylactic anti-viral treatment Cohort 2 (CFZ533/Placebo): monitoring only required
-	+	+	No	
+	+	+	No	

In case of HepBc Ab positivity:

- **Cohort 1 (VAY736/Placebo):** HBsAg negative patients who are HepBc Ab positive are also excluded except if all 3 following criteria are met: i) HBV DNA is negative, ii) prophylactic anti-viral treatment (e.g., lamivudine or entecavir) initiated latest on day 1 and continued until 12 months after last treatment. and iii) hepatitis B monitoring at study is implemented (HBsAg and HBV DNA) at study visits until EoS. In case of sero-conversion (i.e., if either HBsAg or HBV DNA turn positive), second line anti-viral treatments (e.g., tenofovir) will be initiated.

  If Hepatitis B prophylaxis antiviral treatment is not recommended as per local guidelines for patients who are HepBc Ab positive and HBV DNA negative, ONLY HBsAG and HepBc Ab negative patients must be enrolled in the study

- **Cohort 2 (CFZ533/Placebo):** HBsAg negative patients who are HepBc Ab positive are also excluded except if both following criteria are met: 1) HBV DNA is negative and 2) monthly hepatitis B monitoring is implemented (HBsAg and HBV DNA). In case of sero-conversion (i.e., if either HBsAg or HBV DNA turn positive), anti-viral treatment (e.g., lamivudine or entecavir) must be initiated immediately, and continued until EoS of Cohort 2.

Any evidence of hepatitis B reactivation during monitoring (detectable serum levels of hepatitis B viral DNA and/or HBsAg seropositivity) require discontinuation of study medication.

Screening for Hepatitis C will be based on HCV antibodies. Subjects with a positive HCV antibody test should have HCV RNA levels measured. Subjects with positive (i.e., detectable) HCV RNA should be excluded.

This protocol guidance is the minimum required. If individual countries have additional criteria or applicable local guidelines, these must be adhered to.

HIV

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

CMV

Detection during Screening and monitoring

At 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. However, a patient at screening with CMV serologies positive for IgM and negative for IgG with no detectable viral DNA may be determined to have a false positive IgM and thus to be study eligible if, upon repeat testing ≥4 weeks later, CMV serologies remain unchanged and viral DNA is still undetectable.

Patients randomized into the CFZ533 cohort will be monitored for potential CMV reactivation or primary infections by measurements at baseline and monthly thereafter for CMV serologies (IgG and IgM) and for the presence of viral DNA using PCR.

Management of asymptomatic, confirmed or probable disease

- During the study, for patients who develop evidence of 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 consult with an expert.

Guidance to investigators

CMV infections will be recorded as Adverse Events and on the CMV-specific CRF. CMV infection is identified by assessments of laboratory and/or clinical signs/symptoms (Ljungman et al 2017).

- Laboratory-defined CMV (antigenemia-positive, PCR positive).
- CMV syndrome (fever for 2 days, neutropenia, leucopenia, viral syndrome)
- CMV disease (organ involvement).

Infections

All occurrences of infections must be carefully monitored by the Investigator.

Significant findings meeting the definition of infection must be recorded in the Adverse Event eCRF.

IMI samples

Novartis is a member of a consortium of the European Innovative Medicines Initiative (IMI). Novartis will contribute blood and urine samples from placebo-treated patients enrolled in this SLE study from selected sites to the IMI biobank for additional research within this IMI project.

8.5 Additional assessments

8.5.1 Pharmacokinetics

For Cohort 1 (VAY736) and Cohort 2 (CFZ533), PK blood samples will be collected at the time points defined in the Assessment Schedule. Follow instructions outlined in the SOM regarding sample collection, numbering, processing and shipment.

PK samples will be obtained from all patients (CFZ533-, VAY736-, and placebo-treated) to maintain blinding, but the analysis (free CFZ533 concentration in plasma, free VAY736 in serum) will only be conducted for CFZ533- and VAY736-treated patients.

8.5.2 Immunogenicity

The immunogenicity of multiple i.v. doses of CFZ533 and of multiple s.c. doses of VAY736 will be assessed via the quasi-quantitative analysis of anti-CFZ533 antibodies in plasma, and anti-VAY736 antibodies in serum, respectively.

Blood samples collected for immunogenicity testing will be obtained from all patients and analysis will be performed for CFZ533-, VAY736-, and placebo-treated patients (to assess the rate of pre-existing ADAs). The details of sample processing, handling, storage, shipment and analytical method will be described in a separate laboratory manual.

The SOM is providing operational details including 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.

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9 Study discontinuation and completion

9.1 Discontinuation

9.1.1 Discontinuation of study treatment

Discontinuation of study treatment for a subject occurs when study treatment is stopped earlier than the protocol planned duration and can be initiated by either the subject or the investigator. The investigator must discontinue study treatment for a given patient if, on balance, he/she believes that continuation would negatively impact the risk/benefit of trial participation.

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
- Severe injection-related reactions (Cohort 1, VAY736) or infusion-related reactions (Cohort 2, CFZ533). Immediate interruption of the study drug administration is required where possible in such cases
- Severe hypersensitivity reaction e.g., anaphylaxis. Immediate interruption of the infusion/injection is required in such cases.
- Pregnancy (see Section 10.1.4 (Pregnancy reporting))
- Patient received a live/ attenuated vaccine
- Reactivation of hepatitis B infection (e.g., seroconversion of HBsAg or detection of viral DNA); suspected or confirmed active CMV infection (see Section 8.4.4, Hepatitis, HIV and CMV screening)
- Any situation or protocol deviation that may result in a significant safety risk to the patient
- Patient withdraws his/her consent (when patients also must be withdrawn from the study)
- Adverse events, abnormal laboratory values or abnormal test results that indicate a safety risk to the patient.
- Use of prohibited treatment as outlined in Table 6-3
- In addition, in case of emergence of the following adverse events, discontinuation must be considered jointly by the investigator and Novartis:
    - Persistent neutropenia ≤1,000/µl that may preclude further administration of a B cell depleting agent (Cohort 1, only: VAY736/Placebo)

- Cohort 2 (CFZ533/Placebo) only: significant changes in standard coagulation parameters, including prothrombin time (PT) and activated partial prothrombin time (aPTT) suggesting an increased risk for hypercoagulability or any sign or symptom of a thromboembolic event
- SAEs or severe AEs of infection that are suspected to be related to study treatment

Discontinuations from study treatment may be considered jointly by the investigator and the sponsor on a case-by-case basis if individual treatment doses are missed. 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, investigator must determine the primary reason for the subject's premature discontinuation of study treatment and record this information on the Dosage Administration eCRF.

Subjects who discontinue study treatment or 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 (see Section 9.1.3, Withdrawal of Informed Consent).

Patients who discontinue after having received at least one study drug administration should continue the study as planned but without receiving further study treatment, if possible. If they fail to return to the sites for unknown reasons, every effort (e.g., telephone, e-mail, or letter) should be made to contact the subject/pre-designated contact as specified in Section 9.1.4 (Lost to follow-up). This contact should preferably be done according to the study visit schedule.

Patients receiving at least one dose of study drug with subsequent study treatment stopped prematurely and who do not withdraw their consent should stay in the study and continue to come to the study visits as per Assessment Schedule for safety monitoring. Premature study discontinuation should be discussed with the investigator and the sponsor on a case-by-case basis.

The investigator must also contact the IRT system to report the patient's discontinuation from study treatment.

9.1.2 Replacement policy

Over-recruitment of approximately 10% will be allowed to compensate for early dropouts.

9.1.3 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 communication 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 Japan and 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.

9.1.4 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 must show "due diligence" by documenting in the source documents steps taken to contact the subject, e.g., dates of telephone calls, registered letters, etc. A subject should not be considered as lost to follow-up until due diligence has been completed.

9.1.5 Study/ Cohort stopping rules

The relevant study cohort will be put on hold for further enrollment pending further safety data analysis if any of the following criteria occur in patients receiving VAY736 or CFZ533:

- Any death or life-threatening event suspected to be related to study treatment
- Persisting changes from baseline in vital signs, electrocardiograms of potentially life-threatening severity, or relevant, persistent changes in laboratory parameters which are not consistent with existing co-morbidities or the desired experimental compound mechanism-of-action (e.g., B cell depletion by VAY736), in >1 patient within the first 5 treated subjects or an incidence of >20% thereafter
- Three (3) or more patients per cohort with a similar adverse event of severe intensity with the following exceptions:
  - Events of Special Interest, including injection-related (hypersensitivity, cytokine release), decreased neutrophil or leukocyte counts not requiring treatment, and diagnostic procedures involving elective or non-urgent hospital admission
  - Disease-Specific Events that are due to the patient's underlying SLE diagnosis
  - AEs/SAEs clearly unrelated to the experimental compound as determined by the investigator or Novartis
- Two (2) or more patients per cohort presenting with active treatment-suspected toxicities, including:

  - Severe systemic infection or severe opportunistic infection that requires treatment, e.g., sepsis, urosepsis, mycoses, pneumonia
- *Cohort 1, VAY736 treatment arm only:* more than one (1) injection-related reaction of severe intensity within the first five (5) treated patients or an incidence of >20% thereafter
- *Cohort 2, CFZ533 treatment arm only:* one (1) patient presenting with suspected CFZ533-related thromboembolic event that is at least of moderate severity and is unrelated to pre-existing co-morbidities

The investigator must also contact the IRT to register the patient's discontinuation from study treatment and/or from study.

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

The study may resume following the safety review, if the Investigators and Sponsor agree it is safe to proceed.

9.1.6 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. In taking the decision to terminate, Novartis will always consider the subject welfare and safety. Should early termination be necessary, subjects must be seen as soon as possible (provide instruction for contacting the subject, when the subject should stop taking drug, when the subject should come for a final visit) and treated as a prematurely withdrawn subject. The investigator may be informed of additional procedures to be followed in order to ensure that adequate consideration is given to the protection of the subject's interests. The investigator or sponsor depending on the local regulation will be responsible for informing IRBs/IECs of the early termination of the trial.

9.2 Study completion and post-study treatment

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

Each patient will be required to complete the study in its entirety and thereafter no further study treatment will be made available to them, unless required by local regulations.

10 Safety monitoring and reporting

10.1 Definition of adverse events and reporting requirements

10.1.1 Adverse events

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

The investigator has the responsibility for managing the safety of individual subject and identifying adverse events.

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

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 findings, laboratory test findings, or other assessments.

Adverse events must be recorded in the Adverse Events CRF under the signs, symptoms or diagnosis associated with them, accompanied by the following information (as far as possible) (if the event is serious refer to Section 10.1.2*)*:

1. the severity grade
   - mild: usually transient in nature and generally not interfering with normal activities
   - moderate: sufficiently discomforting to interfere with normal activities
   - severe: prevents normal activities
2. its relationship to the study treatment. If the event is due to lack of efficacy or progression of underlying illness (i.e., progression of the study indication) the assessment of causality will usually be 'Not suspected'. The rationale for this guidance is that the symptoms of a lack of efficacy or progression of underlying illness are not caused by the trial drug, they happen in spite of its administration and/or both lack of efficacy and progression of underlying disease can only be evaluated meaningfully by an analysis of cohorts, not on a single subject
3. its duration (start and end dates) or if the event is ongoing, an outcome of not recovered/not resolved must be reported.
4. whether it constitutes a SAE (see Section 10.1.2 for definition of SAE) and which seriousness criteria have been met
5. action taken regarding with the study treatment.

All adverse events must be treated appropriately. Treatment may include one or more of the following:

- Dose not changed
- Dose reduced/increased

- Drug interrupted/withdrawn

6. its outcome:
   a. not recovered/not resolved;
   b. recovered/resolved;
   c. recovering/resolving,
   d. recovered/resolved with sequelae;
   e. fatal, or
   f. unknown.

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

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

Adverse event monitoring should be continued until the EoS visit.

Once an adverse event is detected, it must be followed until its resolution or until it is judged to be permanent (e.g., continuing at the end of the study), and assessment must be made at each visit (or more frequently, if necessary) of any changes in severity, the suspected relationship to the interventions required to treat it, and the outcome.

Information about adverse drug reactions for the investigational drug can be found in the Investigator Brochures (IBs).

Any new information regarding the safety profile of the medicinal product that is identified between IB updates will be communicated as appropriate, for example, via an Investigator Notification. New information might require an update to the informed consent and has then to be discussed with the subject.

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

10.1.2 Serious adverse events

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

- fatal
- life-threatening:

  life threatening in the context of a SAE refers to a reaction in which the subject was at risk of death at the time of the reaction; it does not refer to a reaction that hypothetically might have caused death if it were more severe (please refer to the ICH-E2D Guidelines 2004).
- results in persistent or significant disability/incapacity
- constitutes a congenital anomaly/birth defect

- requires inpatient hospitalization or prolongation of existing hospitalization, unless hospitalization is for:
  - routine treatment or monitoring of the studied indication, not associated with any deterioration in condition
  - elective or pre-planned treatment for a pre-existing condition that is unrelated to the indication under study and has not worsened since signing the informed consent
  - social reasons and respite care in the absence of any deterioration in the subject's general condition
  - treatment on an emergency outpatient basis for an event not fulfilling any of the definitions of a SAE given above and not resulting in hospital admission
- is medically significant, e.g. defined as an event that jeopardizes the subject or may require medical or surgical intervention to prevent one of the outcomes listed above

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

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

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

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

10.1.3 SAE reporting

To ensure subject safety, every SAE, regardless of causality, occurring after the subject has provided informed consent and until 30 days after the last study visit must be reported to Novartis safety immediately, without undue delay, but under no circumstances later than within 24 hours of obtaining knowledge of the events (Note: If more stringent, local regulations regarding reporting timelines prevail). Detailed instructions regarding the submission process and requirements are to be found in the investigator folder provided to each site.

1. **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.
2. **Randomized** OR **Treated Subjects**: SAEs collected between time subject signs ICF until the subject has discontinued or stopped the study. 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.

All follow-up information for the SAE including information on complications, progression of the initial SAE and recurrent episodes must be reported as follow-up to the original episode immediately, without undue delay, but under no circumstances later than within 24 hours of the Investigator receiving the follow-up information (Note: If more stringent, local regulations regarding reporting timelines prevail). An SAE occurring at a different time interval or otherwise considered completely unrelated to a previously reported one must be reported separately as a new event.

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

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

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

10.1.4 Pregnancy reporting

Pregnancies

All childbearing women will have a local serum β-hCG test (serum pregnancy test) performed at screening. From baseline onwards monthly local urine pregnancy tests will be performed as indicated in the Assessment schedule. A positive urine pregnancy test requires immediate interruption of study drug until serum β-hCG is performed and found to be negative. Additional pregnancy testing might be performed if requested by local requirements.

If a female trial participant becomes pregnant, the patient must be asked to read and sign pregnancy consent form to allow the Study Doctor ask about her pregnancy.

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. The follow-up for pregnant participants should be done 1 month, 3 months (for a live birth only) and 12 months (for a live birth only) after estimated date of delivery.

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

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.

10.1.5 Reporting of study treatment errors including misuse/abuse

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

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

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

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

Table 10-1 Guidance for capturing the study treatment errors including misuse/abuse

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

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

10.2 Additional Safety Monitoring

Not applicable.

11 Data Collection and Database management

11.1 Data collection

Designated investigator staff will enter the data required by the protocol into the Electronic Case Report Forms (eCRF). The eCRFs have been built using fully validated secure web-enabled software that conforms to 21 CFR Part 11 requirements, Investigator site staff will not be given access to the EDC system until they have been trained. Automatic validation programs check for data discrepancies in the eCRFs, allow modification and/or verification of the entered data by the investigator staff.

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

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

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

11.2 Database management and quality control

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

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

Randomization codes and data about all study treatment (s) dispensed to the subject and all dosage changes will be tracked using an Interactive Response Technology (IRT) system. The data will be sent electronically to Novartis/ at specific timelines.

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

Once all the necessary actions have been completed and the database has been declared to be complete and accurate, it will be locked and the treatment codes will be unblinded and made available for data analysis. Any changes to the database after that time can only be made after written agreement by Novartis development management.

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11.3 Site monitoring

Before study initiation, at a site initiation visit or at an investigator's meeting, a Novartis representative will review the protocol and data capture requirements with the investigators and their staff. During the study, Novartis employs several methods of ensuring protocol and GCP

compliance and the quality/integrity of the sites' data. The field monitor will visit the site to check the completeness of subject records, the accuracy of data capture / data entry, the adherence to the protocol and to Good Clinical Practice, the progress of enrollment, and to ensure that study treatment is being stored, dispensed, and accounted for according to specifications. Key study personnel must be available to assist the field monitor during these visits. Continuous remote monitoring of each site's data may be performed by a centralized Novartis Clinical Research Associate (CRA) organization. Additionally, a central analytics organization may analyze data and identify risks and trends for site operational parameters and provide reports to Novartis clinical teams to assist with trial oversight.

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

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

12 Data analysis and statistical methods

The analyses will be conducted on all subject data at the time when interim analyses occur and when the trial ends. The analyses will be performed on Cohort 1 and Cohort 2 separately unless otherwise specified. Any data analysis carried out independently by the investigator should be submitted to Novartis before publication or presentation.

12.1 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 who 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 primary PD analysis set will include all subjects who received any study drug having no protocol deviations with relevant impact on PD data.

12.2 Subject demographics and other baseline characteristics

Demographic and baseline characteristics (e.g., SLEDAI-2K, BILAG-2004, Physician Global Assessment, Patient Global Assessment, Commercially Confidential Information and baseline steroid dose) will be listed by subject and summarized by treatment group. Categorical

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

Relevant medical histories and current medical conditions at baseline will be summarized separately by system organ class and preferred term, and by treatment group. They will also be listed by subject and treatment group.

12.3 Treatments

The safety set will be used for the analyses in this section. Categorical data will be summarized as frequencies and percentages. For continuous data, mean, standard deviation, median, minimum, and maximum will be presented.

The duration of exposure in weeks to study drug will be summarized by treatment group. The listing by subject and by treatment group will also be provided.

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

12.4 Analysis of the primary endpoint(s)

For either investigational drug, the primary analysis will compare active treatment with its matching placebo based on the PD analysis set within either cohort independently.

12.4.1 Definition of primary endpoint(s)

The primary endpoint is a composite of SRI-4 response at Week 29 with sustained reduction in oral corticosteroid from Week 17 through Week 29.

SRI-4 response is defined as below:

- having ≥4 points reduction from baseline in SLEDAI-2K score AND
- no new BILAG-2004 A and no more than one new BILAG-2004 B domain scores AND
- no worsening, i.e., <10mm increase from baseline if scaled 0-100mm or 0.3-point increase from baseline if scaled 0 to 3 in the Physician's Global Assessment

Sustained reduction in oral corticosteroid is defined as below:

- ≤5 mg/day or ≤ baseline dose, whichever is lower, at Week 17

AND

- No increase of that dose from Week 17 through Week 29 according to all of the following conditions.
    - total daily CS dose remains ≤30 mg/d prednisone or equivalent
    - any increased daily CS dose administered is ≤2 days within a 4-week treatment cycle from Week 17 to Week 29
    - daily CS dose is not increased within 2 weeks of Week 29 study visit

When all these criteria are met, the patient is a responder. Patients who receive rescue medication (see Section 6.2.4) will be considered as non-responder.

12.4.2 Statistical model, hypothesis, and method of analysis

The primary endpoint will be analyzed using a Bayesian logistic regression model. The model will include treatment group, ENA status, baseline SLEDAI-2K (<10, ≥10) as fixed effects. Weakly informative priors will be used to obtain the posterior estimates. The primary analysis will be performed for each cohort separately.

Bayesian posterior probabilities will be used to assess the following criteria as a guide for decision making (Fisch et al 2015).

Efficacy criteria (for primary endpoint):

- Week 29 responder rate in active group better than that in placebo group with high confidence (90%), i.e., Prob (θ_active - θ _ placebo >0) >90%, AND
- Average magnitude of effect on Week 29 responder rate >15% over placebo, i.e., Prob (θ_active - θ _ placebo >15%) >50%.

Where θ is the Week 29 responder rate, i.e. the proportion of responders per definition.

Futility criteria:

- Week 29 responder rate in active group worse than that in placebo with confidence higher than 60%, i.e., Prob (θ_active - θ _ placebo <0) >60%.

The posterior estimates of the treatment effect of VAY736 and CFZ533 compared to their matching placebos (along with the 90% credible intervals) at Week 29 will be provided. The results will be reported in terms of difference in probability of responders.

12.4.3 Supportive analyses

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Further details of these analyses will be specified in the Statistical Analysis Plan (SAP).

12.5 Analysis of secondary endpoints

Data will be listed by treatment group, period (blinded vs. open label), subject and visit/time as appropriate. Details of statistical methodologies for secondary endpoints will be described in the SAP. Graphical presentation of the data will be performed where applicable.

12.5.1 Efficacy and/or Pharmacodynamic endpoint(s)

The PD analysis set will be used for analyses in this section.

Physician's global assessment in visual analog scale (VAS)

Physician's global assessment (PhGA) in VAS will be listed by treatment group, subject, and visit. The change from baseline in physician's VAS will be listed by treatment group, subject and visit, and summarized by treatment group and visit. Summary statistics will include mean, SD, median, minimum and maximum. A Bayesian MMRM will be applied to this endpoint, as a continuous response variable. The model will include treatment group, ENA status, baseline SLEDAI-2K (<10, ≥10) and visit as fixed effects and baseline PhGA as continuous covariate. Weakly informative priors will be used to obtain the posterior estimates and unstructured covariance will be assumed.

Patient's global assessment in visual analog scale (VAS)

Patient's global assessment (PGA) in VAS will be analyzed the same way as physician's global assessment (PhGA) in VAS.

Flare

Flare determined by BILAG-2004 as below (Isenberg et al 2005, Isenberg et al 2011):

- Severe flare: developing a BILAG-2004 "A" score in any system due to items that are new or worse
- Moderate flare: having two or more "B" score due to items that are new or worse

The number of flare and the rate of flare will be summarized by treatment group for different severities.

The proportion of patients with flare will be summarized by treatment group. The time to first flare will be summarized by treatment group, and listed by treatment group and subject.

12.5.2 Safety endpoints

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

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

summarize only on-treatment events, with a start date during the on-treatment period (*treatment-emergent* AEs).

The on-treatment period lasts from the date of first administration of study treatment until end of study (EoS).

Adverse events

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

The number (and percentage) of subjects with treatment emergent adverse events (events started after the first dose of study medication or events present prior to start of double-blind treatment but increased in severity based on preferred term) will be summarized in the following ways:

1) by treatment group, primary system organ class and preferred term.
2) by treatment group, primary system organ class, preferred term and maximum severity.

Separate summaries will be provided for study medication related adverse events, death, serious adverse events, other significant adverse events leading to discontinuation and adverse events leading to dose adjustment.

The number (and proportion) of subjects with adverse events of special interest will be summarized by treatment group. A subject with multiple adverse events within a primary system organ class is only counted once towards the total of the primary system organ class.

Vital signs

All vital signs data will be listed by treatment group, subject, and visit and if ranges are available, abnormalities will be flagged. Summary statistics (e.g., change from baseline and shift tables) will be provided by treatment group and visit.

12-lead ECG

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

1. PR, QRS, QT, QTcF, and RR intervals will be obtained from 12-lead ECGs for each subject during the study. ECG data will be read and interpreted (/locally).
2. Categorical Analysis of QT/QTc interval data based on the number of subjects meeting or exceeding predefined limits in terms of absolute QT/QTc intervals or changes from baseline will be presented. In addition, a listing of these subjects will be produced by treatment group.

Clinical laboratory evaluations

All laboratory data will be listed by treatment group, subject, and visit and if normal ranges are available abnormalities will be flagged. Summary statistics will be provided by treatment group and visit. Shift tables using the low/normal/high/ (low and high) classification will be used to compare baseline to the worst on-treatment value.

Immunogenicity

All immunogenicity results will be listed by treatment group, subject and visit/time. Anti-VAY736 antibody and anti-CFZ533 antibody results will be listed by treatment group, subject and visit. The proportion of ADA-positive patients will be listed by treatment group and visit.

12.5.3 Pharmacokinetics

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Pharmacokinetic parameters for VAY736 and CFZ533 (Cmax,ss - The highest concentration observed during a dosing interval at steady-state, and Ctrough,ss - The trough observed analyte concentration at the end of a dosing interval) will be listed by treatment group and subject. Descriptive summary statistics will include mean (arithmetic and geometric), SD, and CV (arithmetic and geometric), median, minimum and maximum.

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12.5.4 PK/PD relationships

Relationships between PK and PD variables may be explored by graphical approach and descriptive statistics will be provided. Additional statistical analysis such as analysis of variance (ANOVA) or regression analysis may be performed, if necessary. Modeling of the PK and PD data may be performed as appropriate. During modeling of the PK of the study drug, the broad principles outlined in the FDA, *Guidance for Industry: Population Pharmacokinetics*, will be followed. As the PK and PD data from the current study may be pooled with data from previous study, the PK/PD analysis will be described and reported separately in a modeling plan and modelling report respectively.

12.6 Analysis of exploratory endpoints

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12.6.1 Clinical Outcome Assessment

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12.7 Interim analyses

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12.8 Sample size calculation

12.8.1 Primary endpoint(s)

In total 120 patients are to be randomized to 4 treatment arms, aiming at 30 patients per treatment arm. The sample size may be re-estimated based on results of interim analysis 1 based on observed response rate in placebo arm.

With 30 patients in either active or the matching placebo arm, there is 84% chance that the predefined efficacy criteria (Section 12.4.2) will be met, assuming the true difference in proportion of responders is 25% in favor of active arm and placebo responder rate is 17% (Furie et al 2017). If the true different from placebo is zero, the chance of meeting efficacy criteria is around 10%. The same assumption is made for either VAY736 or CFZ533 cohort.

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12.8.2 Secondary endpoint(s)

Not applicable.

13 Ethical considerations and administrative procedures

13.1 Regulatory and ethical compliance

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

13.2 Responsibilities of the investigator and IRB/IEC

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

IRBs/IECs, and regulatory authorities as required. If an inspection of the clinical site is requested by a regulatory authority, the investigator must inform Novartis immediately that this request has been made.

13.3 Publication of study protocol and results

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

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

13.4 Quality Control and Quality Assurance

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

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

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

14 Protocol adherence

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

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

14.1 Protocol Amendments

Any change or addition to the protocol can only be made in a written protocol amendment that must be approved by Novartis, health authorities where required, and the IRB/IEC prior to implementation.

Only amendments that are required for subject safety may be implemented immediately provided the health authorities are subsequently notified by protocol amendment and the reviewing IRB/IEC is notified.

Notwithstanding the need for approval of formal protocol amendments, the investigator is expected to take any immediate action required for the safety of any subject included in this study, even if this action represents a deviation from the protocol. In such cases, Novartis should be notified of this action and the IRB/IEC at the study site should be informed according to local regulations.

15 References

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16 Appendices

16.1 1997 Update of the 1982 ACR Revised Criteria for Classification of Systemic Lupus Erythematosus

(Tan et al 1982; Hochberg 1997)

Table 16-1 ACR Revised Criteria for Classification of SLE

Criterion	Definition
• **Malar rash**	Fixed erythema, flat or raised, over the malar eminences, tending to spare the nasolabial folds
• **Discoid rash**	Erythematous raised patches with adherent keratoric scaling and follicular plugging; atrophic scarring may occur in older lesions
• **Photosensitivity**	Skin rash as a result of unusual reaction to sunlight, by patient history or physician observation
• **Oral ulcers**	Oral or nasopharyngeal ulceration, usually painless, observed by a physician
• **Arthritis**	Non-erosive arthritis involving two or more peripheral joints, characterized by tenderness, swelling, or effusion
• **Serositis**	a) Pleuritis - convincing history for 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
• **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
• **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
• **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

Criterion	Definition
• **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
• **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 is 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

16.2 The Systemic Lupus Erythematosus Disease Activity Index 2000 (SLEDAI-2K)

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Site No. Subject No.

Date of Assessment

day month year

Visit Number

♦ Only record manifestations/items due to SLE Disease Activity occurring in the last 4 weeks

♦ TO BE USED IN CONJUCTION WITH THE SLEDAI 2000 GLOSSARY (Please refer to the following pages)

Descriptor		Weight	Score	Not Present	Not Known
1.	Seizure	8			
2.	Psychosis	8			
3.	Organic brain syndrome	8			
4.	Visual disturbance	8			
5.	Cranial nerve disorder	8			
6.	Lupus headache	8			
7.	CVA	8			
8.	Vasculitis	8			
9.	Arthritis	4			
10.	Myositis	4			
11.	Urinary casts	4			
12.	Hematuria	4			
13.	Proteinuria	4			
14.	Pyuria	4			
15.	Rash	2			
16.	Alopecia	2			
17.	Mucosal ulcers	2			
18.	Pleurisy	2			
19.	Pericarditis	2			
20.	Low complement	2			
21.	Increased DNA binding	2			
22.	Fever	1			
23.	Thrombocytopenia	1			
24.	Leukopenia	1			
	TOTAL SCORE				

(Petri et al 2005, Gladman et al 2002)

16.3 British Isles Lupus Activity Group (BILAG) score

BILAG 2004 Scoring Index

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CVAY736X2208 | Site No. | Subject No. | Date of Assessment (day / month / year) | Visit Number

- Only record manifestations/items due to SLE Disease Activity
- Score manifestations occurring in the last 4 weeks, as compared with the previous 4 weeks, and based on the principles of the physician's intention to treat
- TO BE USED IN CONJUCTION WITH THE BILAG 2004 GLOSSARY

Record: ND Not Done
0 Not present
1 Improving
2 Same
3 Worse
4 New
Yes/No OR Value (where indicated)

CONSTITUTIONAL

1. Pyrexia - documented > 37.5ºC	(	)
2. Weight loss - unintentional > 5%	(	)
3. Lymphadenopathy/splenomegaly	(	)
4. Anorexia	(	)

MUCOCUTANEOUS

5. Skin eruption - severe	(	)
6. Skin eruption - mild	(	)
7. Angio-oedema - severe	(	)
8. Angio-oedema - mild	(	)
9. Mucosal ulceration - severe	(	)
10. Mucosal ulceration - mild	(	)
11. Panniculitis/Bullous lupus - severe	(	)
12. Panniculitis/Bullous lupus - mild	(	)
13. Major cutaneous vasculitis/thrombosis	(	)
14. Digital infarcts or nodular vasculitis	(	)
15. Alopecia - severe	(	)
16. Alopecia - mild	(	)
17. Peri-ungual erythema/chilblains	(	)
18. Splinter haemorrhages	(	)

NEUROPSYCHIATRIC

19. Aseptic meningitis	(	)
20. Cerebral vasculitis	(	)
21. Demyelinating syndrome	(	)
22. Myelopathy	(	)
23. Acute confusional state	(	)
24. Psychosis	(	)
25. Acute inflammatory demyelinating polyradiculoneuropathy	(	)
26. Mononeuropathy (single/multiplex)	(	)
27. Cranial neuropathy	(	)
28. Plexopathy	(	)
29. Polyneuropathy	(	)
30. Seizure disorder	(	)
31. Status epilepticus	(	)
32. Cerebrovascular disease (not due to vasculitis)	(	)
33. Cognitive dysfunction	(	)
34. Movement disorder	(	)
35. Autonomic disorder	(	)
36. Cerebellar ataxia (isolated)	(	)
37. Lupus headache - severe unremitting	(	)
38. Headache from IC hypertension	(	)

MUSCULOSKELETAL

39. Myositis - severe	(	)
40. Myositis - mild	(	)
41. Arthritis (severe)	(	)
42. Arthritis (moderate)/Tendonitis/Tenosynovitis	(	)
43. Arthritis (mild)/Arthralgia/Myalgia	(	)

CARDIORESPIRATORY

44. Myocarditis - mild	(	)
45. Myocarditis/Endocarditis + Cardiac failure	(	)
46. Arrhythmia	(	)
47. New valvular dysfunction	(	)
48. Pleurisy/Pericarditis	(	)
49. Cardiac tamponade	(	)
50. Pleural effusion with dyspnoea	(	)
51. Pulmonary haemorrhage/vasculitis	(	)
52. Interstitial alveolitis/pneumonitis	(	)
53. Shrinking lung syndrome	(	)
54. Aortitis	(	)
55. Coronary vasculitis	(	)

GASTROINTESTINAL

56. Lupus peritonitis	(	)
57. Abdominal serositis or ascites	(	)
58. Lupus enteritis/colitis	(	)
59. Malabsorption	(	)
60. Protein losing enteropathy	(	)
61. Intestinal pseudo-obstruction	(	)
62. Lupus hepatitis	(	)
63. Acute lupus cholecystitis	(	)
64. Acute lupus pancreatitis	(	)

OPHTHALMIC

65. Orbital inflammation/myositis/proptosis	(	)
66. Keratitis - severe	(	)
67. Keratitis - mild	(	)
68. Anterior uveitis	(	)
69. Posterior uveitis/retinal vasculitis - severe	(	)
70. Posterior uveitis/retinal vasculitis - mild	(	)
71. Episcleritis	(	)
72. Scleritis - severe	(	)
73. Scleritis - mild	(	)
74. Retinal/choroidal vaso-occlusive disease	(	)
75. Isolated cotton-wool spots (cytoid bodies)	(	)
76. Optic neuritis	(	)
77. Anterior ischaemic optic neuropathy	(	)

Ensure that lab values are reported in the correct unit
*Y/N Only select No if value is not due to SLE activity

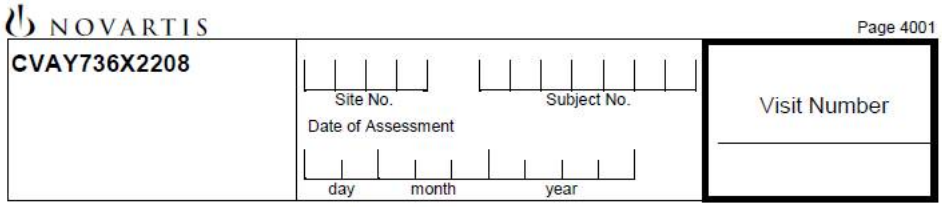
RENAL			Due to SLE
78. Systolic blood pressure (mm Hg)	value	( )	
79. Diastolic blood pressure (mm Hg)	value	( )	
80. Accelerated hypertension	Yes/No	( )	
81. Urine dipstick protein (+=1, ++=2, +++=3)		( )	
82. Urine albumin-creatinine ratio	mg/mmol	( )	
83. Urine protein-creatinine ratio	mg/mmol	( )	-Y/N*
84. 24 hour urine protein	g/24hrs	( )	
85. Nephrotic syndrome	Yes/No	( )	
86. Creatinine (plasma/serum)	µmol/l	( )	Y/N*
87. GFR (calculated)	ml/min/1.73 m²	( )	Y/N*
88. Active urinary sediment	Yes/No	( )	
89. Active nephritis	Yes/No	( )	

HAEMATOLOGICAL			Due to SLE
90. Haemoglobin (g/dl)	value	( )	Y/N*
91. Total white cell count (GI/L = 10^9/l)	value	( )	Y/N*
92. Neutrophils (GI/L = 10^9/l)	value	( )	Y/N*
93. Lymphocytes (GI/L = 10^9/l)	value	( )	Y/N*
94. Platelets (GI/L = 10^9/l)	value	( )	Y/N*
95. TTP	0,1,2,3,4	( )	
96. Evidence of active haemolysis	Yes/No	( )	
97. Coombs Test Positive (Yes/No/Not Required)		( )	

End of BILAG 2004 Assessment

(Yee et al 2006; Yee et al 2010; Castrejón et al 2014)

Flare determined by BILAG-2004 as below (Isenberg et al 2005; Isenberg et al 2011):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Site No. Subject No.

Date of Assessment

day month year

Visit Number

BILAG Flare, as defined below, determined by Investigator from BILAG-2004 scores

Ref : (Isenberg et al 2005; Isenberg et al 2011):

BILAG 2004 Moderate Flare

Two or more B scores, due to items which are 'New' or 'Worse' :

BILAG 2004 Severe Flare

One or more A scores, due to items which are 'New' or 'Worse' :

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