A MULTICENTER, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED, PARALLEL-GROUP STUDY TO EVALUATE THE EFFICACY AND SAFETY OF DAPIROLIZUMAB PEGOL IN STUDY PARTICIPANTS WITH MODERATELY TO SEVERELY ACTIVE SYSTEMIC LUPUS ERYTHEMATOSUS

PROTOCOL SL0043 AMENDMENT 4

PHASE 3

SHORT TITLE:

A randomized placebo-controlled study to evaluate the efficacy and safety of dapirolizumab pegol in study participants with moderately to severely active systemic lupus erythematosus

Sponsor:
UCB Biopharma SRL
Allée de la Recherche 60
1070 Brussels
BELGIUM

Regulatory agency identifying number(s):

Eudra CT Number:	2019-003406-27
IND Number:	100807

PROTOCOL AMENDMENT SUMMARY OF CHANGES TABLE

Protocol/Amendment number	Date	Type of amendment
Protocol Amendment 4	16 Mar 2023	Substantial
Protocol Amendment 3	14 Jan 2022	Substantial
Protocol Amendment 2.3 (UK)	07 Jul 2021	Substantial
Protocol Amendment 2.2 (Hungary)	06 Jul 2021	Nonsubstantial
Protocol Amendment 2.1 (Germany)	06 Jul 2021	Nonsubstantial
Protocol Amendment 2	29 Jun 2021	Nonsubstantial
Protocol Amendment 1.4 (Denmark)	08 Apr 2021	Nonsubstantial
Protocol Amendment 1.3 (UK)	15 Oct 2020	Substantial
Protocol Amendment 1.2 (Hungary)	15 Oct 2020	Substantial
Protocol Amendment 1.1 (Germany)	15 Oct 2020	Substantial
Protocol Amendment 1	14 Oct 2020	Substantial
Protocol Amendment 0.5 (Italy)	25 Sep 2020	Nonsubstantial
Protocol Amendment 0.4 (Portugal)	08 Sep 2020	Nonsubstantial
Protocol Amendment 0.3 (UK)	26 Aug 2020	Nonsubstantial
Protocol Amendment 0.1 (Hungary)	21 Jul 2020	Nonsubstantial
Protocol Amendment 0.1 (Germany)	29 Jun 2020	Nonsubstantial
Original Protocol	03 Dec 2019	Not applicable

Amendment 4: 16 Mar 2023

This amendment is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.

Overall Rationale for the Amendment

The primary purpose of this amendment is to reduce the sample size and consequently remove the interim analysis. Other updates have been incorporated based on Investigators, the independent data monitoring committee (IDMC) and regulatory feedback, to provide further clarity on the protocol or to correct errors. The table below does not include correction of minor typographical errors and formatting/stylistic changes.

Section # and Name	Description of Change	Brief Rationale
Seious Adverse Event Reporting	Text was added on how all SAEs are to be reported.	Updated to provide further clarity.
1.1 Synopsis, Overall design 4.1 Overall design	IDMC review information was removed.	Due to reduced sample size no interim analysis will be conducted.

Section # and Name	Description of Change	Brief Rationale
1.1 Synopsis, Number of participants 1.2 Schema	Participant numbers were updated.	Updated for consistency within the protocol.
1.3 Schedule of activities	The following text has been added to footnote f: In case of a pregnancy after initiation of study treatment, weight measurement will be performed at every study visit. Footnote x was updated with the option of administering paracetamol.	Updated to enhance monitoring of a pregnant study participant. Clarification.
2.3 Benefit/risk assessment	Text describing the important risks was amended.	To ensure consistency with the content of the Investigator's Brochure (IB, section 6, Summary of Data and Guidance for Investigator).
6.1 Treatments administered	Text was added to emphasize the potential risk of infusion reactions and the potential benefit of using premedication under certain circumstances at the discretion of the Investigator.	To align with other sections of the protocol referring to study medication administration and preparation and to ensure awareness.
6.5.1.3 Other immunosuppressants/ immunomodulatory agents	The list after the first paragraph in the section was removed. Tacrolimus was added to Table 6-6.	Information in the bulleted list is the same as in Table 6-6 so duplication removed. Correction. Tacrolimus was deleted from Table 6-7 during Protocol Amendment 3 and was not added to Table 6-6.
7.1.3 Permanent and temporary study drug discontinuation due to other reasons	Bullet 5 was updated to remove the word "severe". Text was added about the timing of upcoming surgery after last infusion of study medication.	Updated to align with therapeutic guidances and the Sampson criteria in Appendix 10.14. Updated to provide further clarity.
8.1.1.1 BILAG 2004	Text was added on grading being subject to adjudication.	To clarify that centralized grading includes adjudication.

Section # and Name	Description of Change	Brief Rationale
8.1.3.1 BILAG 2004-based Composite Lupus Assessment	Text was added that if a treatment change represents an intercurrent event, it will be confirmed by a blinded independent adjudicator.	Additional clarification on how the intercurrent event of use of escape medication is handled.
8.1.3.2 Severe BILAG flare	Clarification that flares will be seen as such only if there was at least 1 period with stable or improving disease activity and that flares will be adjudicated.	Updated to provide clarity based on regulatory feedback.
8.2.2 Vital signs	Text was added for the option of taking blood pressure and pulse readings in a sitting position. The requirements for 3 blood pressure measurements was removed.	Updated to simplify the study procedure and to clarify current practice.
8.2.7 SARS-CoV-2/COVID-19	Text regarding COVID-19 was updated.	Addition of IDMC recommended language and updated text regarding risks of the COVID-19 infection for study participants to reflect emerging evidence.
8.3 AEs and SAEs	Text was added regarding disclosure of results on public registries.	Updated to align with current practice.
8.3.8 Anticipated SAEs, Table 8-4 Anticipated SAEs for study participants with SLE	[redacted] was removed from the table.	Correction.
8.6.1 Assessment of PK variables	Text regarding the [redacted] Text regarding the [redacted]	[redacted] Correction.
9.3.1 Analysis of the primary efficacy/primary endpoint	Details regarding the null and alternative hypotheses were updated. Primary estimand information was updated.	Based on regulatory feedback, the primary estimand was updated to estimate and test the difference between proportions meeting the primary endpoint, instead of the odds ratio.

Section # and Name	Description of Change	Brief Rationale
9.3.1.1 Sensitivity analysis	Text was added on how a logistic regression model will be used to analyze BICLA.	Given the change in the primary estimand to analysis of the difference between proportions, the originally planned analysis of odds ratio via a logistic regression model was added as a sensitivity analysis.
9.4.2.1 Pharmacokinetic analyses	Text was added to make clear that [redacted] data will be generated if required.	Clarification.
9.7 Planned interim analysis and data monitoring	Added text that there will be no interim analysis.	There will no longer be an interim analysis since the sample size is reduced.
9.8 Determination of sample size	The sample size was reduced.	This section was updated to provide the power calculation for the reduced sample size.
10.2 Appendix 2: Clinical laboratory tests 10.15 Appendix 15: Suggested management guidelines for suspected infusion reactions	Serum tryptase was added to the table and a new section was added with tryptase information.	Updated to enhance monitoring of a suspected infusion reaction.
10.4 Appendix 4: Contraceptive guidance and collection of pregnancy information	Information to be collected by Investigators from participants who become pregnant was updated.	Updated to align with current practice.
10.11 Appendix 11: Protocol Amendment History	Added a summary of the changes made in Amendment 3.	Intra-document cross-reference.
Section 10.15, Appendix 15: Suggested management guidelines for suspected infusion reactions	Text regarding suspected infusion reactions, [redacted] and anaphylactic reactions was updated.	Clarification.
11 References	The following 2 references were added: Muraro et al, 2022 Platzgummer et al, 2020	Update.

SERIOUS ADVERSE EVENT REPORTING

Serious adverse event reporting (24h)	
All serious adverse events (SAEs) will be reported and transmitted to Patient Safety through the electronic Case Report form (eCRF) system. The numbers below are to be used to send ancillary documentation only (eg, discharge summaries, death certificates) or in the event that the eCRF is not available.	
Fax	**Europe and Rest of the World:** +32 2 386 24 21 **US and Canada:** +1 800 880 6949 or +1 866 890 3175
Email	**Global:** DS_ICT@ucb.com

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

1 PROTOCOL SUMMARY

1.1 Synopsis

Protocol title

A multicenter, randomized, double-blind, placebo-controlled, parallel-group study to evaluate the efficacy and safety of dapirolizumab pegol in study participants with moderately to severely active systemic lupus erythematosus

Short Title

A randomized placebo-controlled study to evaluate the efficacy and safety of dapirolizumab pegol in study participants with moderately to severely active systemic lupus erythematosus

Rationale

Systemic lupus erythematosus (SLE) is a chronic autoimmune inflammatory disease which can present with a chronic disease course but has more often a relapsing-remitting disease course. The majority of patients develop tissue and organ damage over time with current standard of care (SOC) medication due to either lack of well-controlled disease activity or due to toxicities of the SOC medications. Therefore, new therapies are needed to achieve long-term control of the disease activity of SLE with well-tolerated SLE medication. The study aims to evaluate the efficacy of dapirolizumab pegol (DZP) in study participants who have persistent active or frequently relapsing-remitting SLE with moderate to severe disease activity despite being on stable non-biological SOC medication and therefore have an unmet medical need for a treatment intervention with new therapies.

Objectives and endpoints

Table 1-1: Objectives and endpoints

Objectives	Endpoints
Primary	
• To evaluate the ability of DZP as an add-on treatment to SOC medication to achieve clinically relevant long-term improvement of moderate to severe disease activity	• Achievement of BICLA response at Week 48
Key Secondary	
• To evaluate the ability of DZP as an add-on treatment to SOC medication to achieve fast, clinically relevant improvement of moderate to severe disease activity	• Achievement of BICLA response at Week 24 • Achievement of BICLA response at Week 12
• To evaluate the ability of DZP as an add-on treatment to SOC medication	• Achievement of prevention of severe BILAG flares (severe BILAG flare-free) through Week 48

Objectives	Endpoints
to achieve long-term control of disease activity	
• To evaluate the ability of DZP as an add-on treatment to SOC medication to achieve and maintain the treat-to-target goal: low disease activity with low/acceptable corticosteroid dose over time	• Achievement of LLDAS in ≥50% of post-Baseline visits through Week 48
• To evaluate the ability of DZP as an add-on treatment to SOC medication to achieve improvement of disease activity as measured by numerical disease state score commonly used in clinical practice	• Change from Baseline in SLEDAI-2K at Week 48
Secondary	
• To evaluate the ability of DZP as an add-on treatment to SOC medication to achieve components of the composite primary endpoints	• Achievement of BILAG improvement without worsening at Week 48
	• Change from Baseline in PGA at Week 48
• To evaluate the ability of DZP as an add-on treatment to SOC medication to achieve alternative responder endpoint	• Achievement of SRI4 response at Week 48
• To evaluate the ability of DZP as an add-on treatment to SOC medication to achieve endpoints supporting other key secondary endpoints	• Achievement of prevention of moderate/severe BILAG flares (moderate/severe BILAG flare-free) through Week 48
	• Time to severe BILAG flare through Week 48
	• Time to moderate/severe BILAG flare through Week 48
• To evaluate the safety and tolerability of DZP as add-on treatment to SOC medication	• TEAEs, serious TEAEs, TEAEs of special interest, and TEAEs of special monitoring
Tertiary	
• To evaluate the ability of DZP as add-on treatment to SOC to achieve endpoints which support the primary and secondary objectives and/or	• Achievement of reduction of corticosteroid dose from >7.5mg/day prednisone equivalent dose at start of study to ≤7.5mg/day prednisone equivalent by visit

Objectives	Endpoints
support the interpretation of the primary and secondary endpoints	• Achievement of reduction of corticosteroid dose from >7.5mg/day prednisone equivalent dose at start of study to ≤7.5mg/day prednisone equivalent at Week 24 and maintaining low corticosteroid dose afterwards and achievement of BICLA response at Week 48
	• Achievement of reduction of corticosteroid dose from >7.5mg/day prednisone equivalent dose at start of study to ≤7.5mg/day prednisone equivalent at Week 24 and maintaining low corticosteroid dose and achievement of prevention of moderate/severe BILAG flares (moderate/severe BILAG flare-free) at Week 48
	• Achievement of reduction in corticosteroid dose from ≥7.5mg/day prednisone equivalent dose at start of study to ≤5mg/day prednisone equivalent at Week 24 and maintaining low corticosteroid dose and achievement of BICLA response at Week 48
	• Achievement of reduction of corticosteroid dose from ≥7.5mg/day prednisone equivalent dose to ≤5mg/day prednisone equivalent at Week 24 and maintaining low corticosteroid dose and achievement of prevention of moderate/severe BILAG flares (moderate/severe BILAG flare-free) at Week 48
	• Total corticosteroid dose through Week 24, through Week 48, and from Week 24 through Week 48
	• Achievement of BICLA response by visit
	• Achievement of BILAG 2004 improvement without worsening by visit
	• Change from Baseline in BILAG 2004 score by visit

Objectives	Endpoints
	• Achievement of BILAG 2004 shifts by visit
	• Achievement of BILAG 2004 improvement by organ system by visit
	• Achievement of maintained BICLA response by visit
	• Achievement of persistent BICLA response between Week 24 and Week 48
	• Worsening of any organ system with a BILAG 2004 B, C, D, E at Baseline to BILAG 2004 A or worsening of >1 organ system with a BILAG 2004 C, D, E at Baseline to BILAG 2004 B by visit
	• Achievement of BILAG 2004 C, D, E in all organ systems by visit
	• Change from Baseline in SLEDAI-2K by visit
	• Achievement of SRI 4, 6, 8 response by visit
	• Change from prior visits in S2K RI50 by visit
	• Change from Baseline in PGA by visit
	• Achievement of LLDAS status by visit
	• Cumulative number of visits in LLDAS through Week 48
	• Achievement of LLDAS Variant (demand for ≤5mg/day prednisone equivalent) in >50% of post-Baseline visits through Week 48
	• Achievement of prednisone equivalent dose ≤7.5mg/day by visit
	• Prednisone equivalent dose by visit
	• Occurrence of severe BILAG 2004 flares by visit
	• Occurrence of moderate BILAG flares by visit
	• Occurrence of severe SFI flares by visit
	• Occurrence of moderate SFI flares by visit

Objectives	Endpoints
	• Time to severe SFI flare
	• Time to moderate SFI flare
	• Change from Baseline in ACR/SLICC damage score by visit
	• Achievement of DORIS remission by visit
• To evaluate the ability of DZP as an add-on treatment to SOC medication to achieve organ specific endpoints	• Change from Baseline in CLASI activity score by visit for all study participants and for subset of study participants with high CLASI score
	• Achievement of a meaningful improvement in CLASI activity score by visit for all study participants and for subset of participants with high CLASI score
	• Change from Baseline in TJC and SJC by visit for all study participants and for subset of participants with moderate to severe arthritis
	• Achievement of a meaningful decrease in TJC/SJC by visit for all study participants and for a subset of participants with moderate to severe arthritis
	• Change from Baseline in Lupus Arthritis and Musculoskeletal Disease Activity score by visit
• To evaluate the ability of DZP as an add-on treatment to SOC medication to achieve important patient reported outcomes	• Change from Baseline in FACIT-F by visit
	• Change from Baseline in PHQ-9 score by visit
	• Change from Baseline in FATIGUE-PRO 'Physical Fatigue', 'Mental Fatigue' and 'Fatigability' scores by visit
	• Change from Baseline in LupusQoL by visit
	• Change from Baseline in EQ-5D-5L by visit
• To evaluate the PK	[redacted]

Objectives	Endpoints
• To evaluate immunogenicity of DZP as an add-on treatment to SOC medication	• Incidence of anti-drug antibodies: [redacted]
• To evaluate the PD and immunological parameters of DZP as an add-on treatment to SOC medication	• Observed values and change from baseline in [redacted] in all study participants by visit and in study participants 'positive' at Baseline by visit
	• Seroconversion of: [redacted] status by visit
• To evaluate the safety and tolerability of DZP as an add-on treatment to SOC medication	• TEAEs leading to study withdrawal, TEAEs leading to permanent study medication discontinuation, TEAEs with start day on day or up to 1 day after infusion, other identified TEAE clusters
	• Summary of participants withdrawn from the study due to TEAEs • Summary of participants who permanently discontinued study medication
	• Change from Baseline in vital sign parameters by visit
	• Observed values and change from Baseline in safety laboratory tests (hematology, serum chemistry, urinalysis) by visit, % study participants achieving critical threshold for selected lab parameters by visits
• To evaluate changes in exploratory biomarkers	• Change from Baseline in biomarkers selected for analysis • [redacted]

Objectives	Endpoints
• To evaluate risk for anti-phospholipid associated events	• Change from Baseline in APS score by visit

ACR/SLICC=American College of Rheumatology/Systemic Lupus International Collaborating Clinics; [redacted]; APS=antiphospholipid antibody syndrome; BICLA=BILAG 2004-based Composite Lupus Assessment; BILAG= British Isles Lupus Assessment Group Disease Activity Index 2004; CLASI=Cutaneous Lupus Erythematosus Disease Area and Severity Index; DORIS=definitions of remission in SLE; DZP=dapirolizumab pegol; [redacted] EQ-5D-5L=Euro Quality of life 5-Dimensions 5-Level; Fab'=fragment antigen-binding; FACIT-F=Functional Assessment of Chronic Illness Therapy Fatigue; FATIGUE-PRO=Fatigue patient reported outcome; Ig=immunoglobulin; LLDAS=low lupus disease activity state; PD=pharmacodynamics; PEG=polyethylene glycol; PGA=Physician's Global Assessment of Disease; PHQ-9=Patient Health Questionnaire-9; PK=pharmacokinetic(s); QoL=quality of life; RNA=ribonucleic acid; SFI=SELENA Flare Index; SJC=swollen joint count; SLE=systemic lupus erythematosus; SLEDAI-2K=Systemic Lupus Erythematosus Disease Activity Index 2000; sm=Smith antigen; SOC=standard of care; SRI=Systemic Lupus Erythematosus Responder Index; [redacted]; S2K RI50=Systemic Lupus Erythematosus Disease Activity Index-2000 Responder Index-50; TEAE=treatment-emergent adverse event; TJC=tender joint count

Overall design

The study will be conducted to assess the efficacy, safety and tolerability of DZP in study participants with active SLE despite standard therapy and its results will support regulatory filing.

This study is a randomized, double-blind, placebo-controlled, parallel group, Phase 3 study in study participants 16 years of age and older with moderately to severely active SLE who are receiving stable SOC medication (ie, antimalarials, corticosteroids, and/or immunosuppressants) in line with local and international guidances at Screening Visit (V1). It will primarily investigate the improvement of SLE disease activity in study participants treated with DZP as add-on to nonbiological SOC treatment over 48 weeks. Key secondary objectives will be to investigate early improvement at Weeks 12 and 24, long-term disease control as evidenced by prevention of severe British Isles Lupus Assessment Group Disease Activity Index 2004 (BILAG) flares (severe BILAG flare-free) through Week 48, achievement of a treat-to-target endpoint (low disease activity state in conjunction with low/acceptable corticosteroid dose [low lupus disease activity state LLDAS]) through Week 48, and long-term improvement of disease activity as assessed with an instrument commonly used in clinical practice (Systemic Lupus Erythematosus Disease Activity Index 2000 [SLEDAI-2K]) at Week 48.

The study consists of a 2-week Screening Period, 48-week Treatment Period, and 6-week Safety Follow-up (SFU) Period. Due to the required moderate to severe disease activity at screening visit (V1), a short Screening Period is planned. At the start of the study, eligible study participants will be randomized (2:1) to DZP 24mg/kg or to placebo administered by intravenous (iv) infusion every 4 weeks (Q4W). The initial dose will be administered as a 2-hour infusion while each subsequent dose will be administered as a 1-hour infusion. Study participants who complete the 48-week Treatment Period may be eligible to participate in the open-label extension (OLE) study (SL0046). Study participants who withdraw early from the 48-week Treatment Period or choose not to enter the OLE will be followed up for at least 10 weeks after

their final dose of study medication (also referred to as investigational medicinal product [IMP] in the document).

Eligible study participants will have persisting active or relapsing-remitting SLE at screening visit (V1) despite stable SOC treatment (ie, antimalarials, corticosteroids, and/or immunosuppressants), in line with local and international guidance at screening visit (V1). Study participants considered to have a monophasic or an infrequent relapsing-remitting disease course (defined as no evidence for frequently flaring disease course and low risk to have frequent flares) will be excluded as their disease likely does not correspond to a persistent active or frequently relapsing SLE despite SOC treatment.

During the study, participants with a corticosteroid dose above a long-term tolerable level (7.5mg/day prednisone equivalent) will have to start corticosteroid tapering no later than the Week 8 Visit (Visit 4) to reach a target of 7.5mg/day or below. Investigators will be encouraged to start steroid tapering earlier if the condition of the study participant suggests improvement. Guidance will be provided on how to taper but the exact tapering regimen will be at the discretion of the Investigator to be adapted to the individual study participant's disease activity. Other SLE SOC treatment will have to be kept stable unless a reduction is indicated due to side effects. In case of insufficient improvement of disease activity, or a clinically relevant worsening of the disease activity, Investigators may initiate an escape treatment (Section 6.6.2) by increasing the dose of concomitant SOC medication. Depending on the nature of an escape treatment intervention, DZP may have to be discontinued if there is a safety concern. Investigators should discuss the impact of escape treatment use on study conduct with the Medical Monitor before initiation. In case of an initiation of escape treatment, study participants may be declared as **nonresponders** for the primary endpoint; however, they do not have to be withdrawn from the study.

Study participants will be encouraged to stay in the study under observation even if the study medication is discontinued (see Section 7.1). A study participant will have to be withdrawn from the study only if the study participant withdraws consent or a regulator, Institutional Review Board/Independent Ethics Committee (IRB/IEC), or the independent data monitoring committee (IDMC) requests a withdrawal for justified reasons (see Section 7.2).

An IDMC will be established to monitor the benefit-risk profile of study participants during the study. The IDMC will regularly review data and will have access to unblinded data as needed. The review will include observations in the BILAG 2004 neuropsychiatric body organ system in order to monitor potential neuropsychiatric events falsely assigned to SLE. Details are described in the IDMC charter. The IDMC will provide recommendation if the study should be stopped, should be adapted or can proceed as planned.

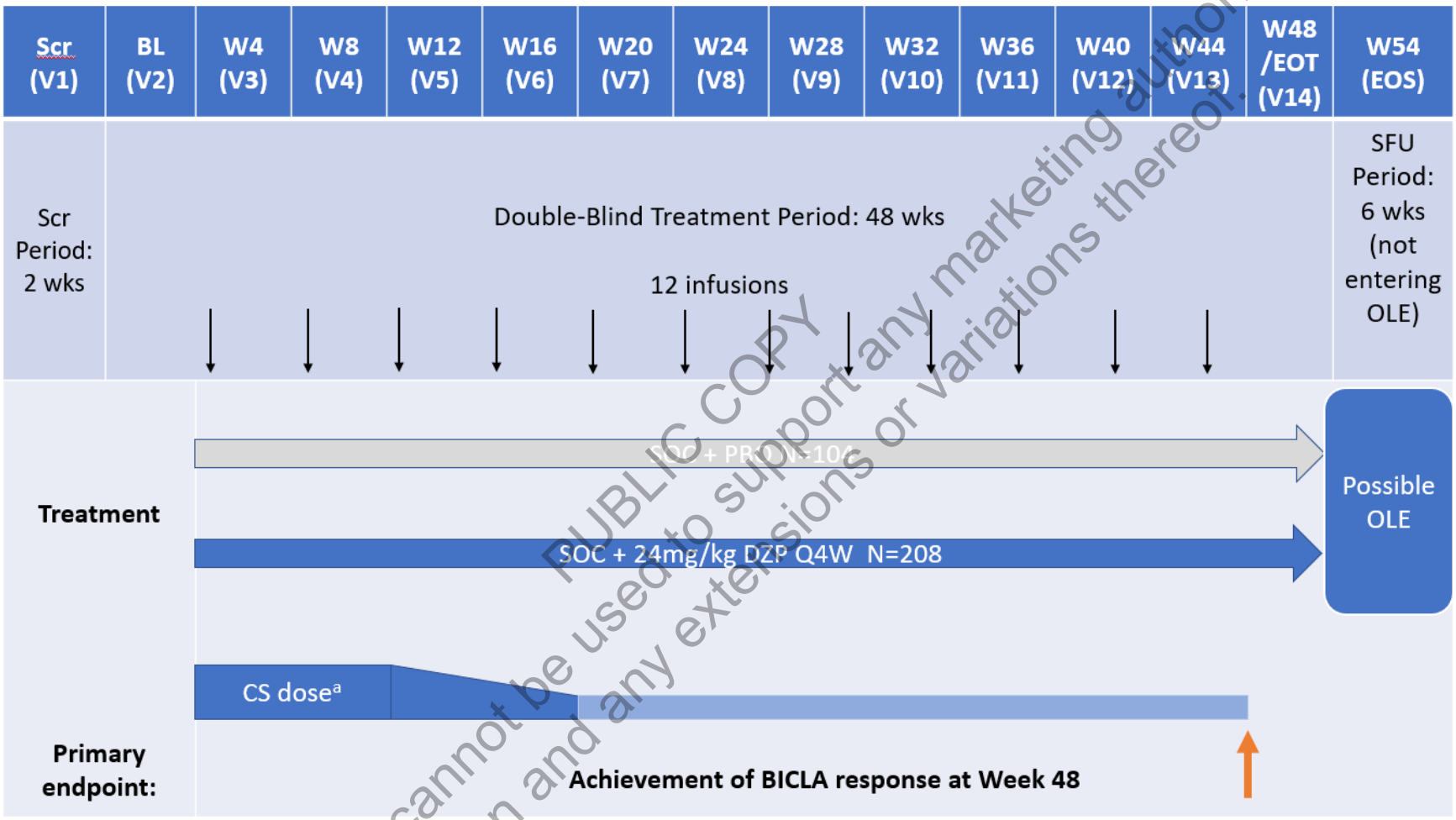
Number of participants

Approximately 700 participants will be screened at approximately 230 sites in approximately 31 countries to achieve approximately 312 participants randomly assigned (2:1) to DZP 24mg/kg or to placebo for an estimated total of 208 and 104 participants in the DZP 24mg/kg and placebo groups, respectively.

Treatment groups and duration

This study consists of a 2-week Screening Period, a 48-week Placebo-controlled Period, and a 6-week SFU Period after Week 48 (>60 days [5 half-lives] after the final dose at Week 44), for a total of up to 56 weeks for study participants not entering the OLE study.

1.2 Schema



BICLA=BILAG 2004-based Composite Lupus Assessment; BILAG=British Isles Lupus Assessment Group Disease Activity Index; BL=Baseline; CS=corticosteroid; DZP=dapirolizumab; EOS=End of Study; EOT=End of Treatment; N=number of study participants planned; OLE=open-label extension; PBO=placebo; Q4W=every 4 weeks; Scr=Screening; SFU=Safety Follow-up; SOC=standard of care; V=Visit; W/wk=week

[a] The CS tapering should start no later than the Week 8 Visit (V4) with a targeted prednisone equivalent dose ≤7.5mg/day (in line with current treatment guidelines), guidance on how to taper will be provided but dynamic of dose-reduction is finally in the discretion of the Investigators to be adapted to the patient's individual needs.

1.3 Schedule of activities

Table 1-2: Schedule of activities

Period	Scr	Treatment (all visits in Treatment Period ±3 days)													SFU[a]
Visit	V1	V2	V3	V4	V5	V6	V7	V8	V9	V10	V11	V12	V13	V14	V15
Week	Scr	Bsl	W4	W8	W12	W16	W20	W24	W28	W32	W36	W40	W44	EOT[b] W48	EOS W54
Day [c]	D-14 to -1[d]	D1[c]	D28	D56	D84	D112	D140	D168	D196	D224	D252	D280	D308	D336	D378
Procedures															
Written informed consent	X														
Genetic informed consent [e]	X														
Demographics and Baseline characteristics [f]	X							X							
Thrombophilia diagnostic [g,dd]		X													
Inclusion/exclusion criteria [h]	X	X [i]													
General medical/procedures history	X														
Medication history [j]	X														
Vaccination history [j]	X														
Concomitant medications (inc. vaccines)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Pregnancy serum test	X														

Table 1-2: Schedule of activities

Period	Scr	Treatment (all visits in Treatment Period ±3 days)													SFU[a]
Visit	V1	V2	V3	V4	V5	V6	V7	V8	V9	V10	V11	V12	V13	V14	V15
Week	Scr	Bsl	W4	W8	W12	W16	W20	W24	W28	W32	W36	W40	W44	EOT[b] W48	EOS W54
Day [c]	D-14 to -1[d]	D1[c]	D28	D56	D84	D112	D140	D168	D196	D224	D252	D280	D308	D336	D378
Procedures															
Pregnancy urine test (for WOCBP) [k,dd]		X	X	X	X	X	X	X	X	X	X	X	X	X	X
Antimalarial blood levels[dd]	X	X						X						X	
Chest x-ray [l]	X														
12-lead ECG [m]	X	X	X					X						X	
Vital signs	X	X[n]	X[n]	X[n]	X[n]	X[n]	X[n]	X[n]	X[n]	X[n]	X[n]	X[n]	X[n]	X	X
Study participant Identification Card assigned		X													
Randomization		X													
Infection serology [o]	X														
IGRA TB Test (QuantiFERON® at central lab)[dd]	X[p]												X		
TB questionnaire	X	X			X			X			X			X	
Complete physical examination and anamnesis [q]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

Table 1-2: Schedule of activities

Period	Scr	Treatment (all visits in Treatment Period ±3 days)													SFU[a]
Visit	V1	V2	V3	V4	V5	V6	V7	V8	V9	V10	V11	V12	V13	V14	V15
Week	Scr	Bsl	W4	W8	W12	W16	W20	W24	W28	W32	W36	W40	W44	EOT[b] W48	EOS W54
Day [c]	D-14 to -1[d]	D1[c]	D28	D56	D84	D112	D140	D168	D196	D224	D252	D280	D308	D336	D378
Procedures															
Study withdrawal and study medication discontinuation criteria review			X	X	X	X	X	X	X	X	X	X	X		
BILAG 2004 [r]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
SLEDAI-2K [r]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
S2K-RI50			X	X	X			X			X			X	
PGA [r]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
CLASI	X	X	X	X	X			X			X			X	
TJC/SJC	X	X	X	X	X			X			X			X	
Lupus Arthritis and Musculoskeletal Disease Activity (LAMDA) score	X	X	X	X	X			X			X			X	
SFI	X				X			X			X			X	
SLICC Damage Index		X												X	
FATIGUE-PRO [s]	X	X	X	X	X			X			X			X	X
FACIT-F [s]	X	X			X			X			X			X	
LupusQOL [s]		X			X			X			X			X	

Table 1-2: Schedule of activities

Period	Scr	Treatment (all visits in Treatment Period ±3 days)													SFU[a]
Visit	V1	V2	V3	V4	V5	V6	V7	V8	V9	V10	V11	V12	V13	V14	V15
Week	Scr	Bsl	W4	W8	W12	W16	W20	W24	W28	W32	W36	W40	W44	EOT[b] W48	EOS W54
Day [c]	D-14 to -1[d]	D1[c]	D28	D56	D84	D112	D140	D168	D196	D224	D252	D280	D308	D336	D378
Procedures															
PGI-S, PGI-S Fatigue[s]	X	X			X			X			X			X	
PGI-C, PGI-C Fatigue[s]					X			X			X			X	
EQ-5D-5L [s]		X			X			X			X			X	
PHQ-9	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
C-SSRS	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
[redacted]															
Coagulation assay (pTT, INR, quick), if indicated[dd]	X	X[u]	X[u]	X[u]	X[u]	X[u]	X[u]	X[u]	X[u]	X[u]	X[u]	X[u]	X[u]	X[u]	
Adhoc diagnostic as clinically appropriate, including SARS-CoV-2 testing [v,dd]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
[redacted]															

Table 1-2: Schedule of activities

Period	Scr	Treatment (all visits in Treatment Period ±3 days)													SFU[a]
Visit	**V1**	**V2**	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9**	**V10**	**V11**	**V12**	**V13**	**V14**	**V15**
Week	**Scr**	**Bsl**	**W4**	**W8**	**W12**	**W16**	**W20**	**W24**	**W28**	**W32**	**W36**	**W40**	**W44**	**EOT[b] W48**	**EOS W54**
Day [c]	**D-14 to -1[d]**	**D1[c]**	**D28**	**D56**	**D84**	**D112**	**D140**	**D168**	**D196**	**D224**	**D252**	**D280**	**D308**	**D336**	**D378**
Procedures															
TSH, T3, T4[dd]	X														
[redacted]															
IMP infusion [x]		X	X	X	X	X	X	X	X	X	X	X	X		
[redacted]															

Table 1-2: Schedule of activities

Period	Scr	Treatment (all visits in Treatment Period ±3 days)													SFU[a]
Visit	V1	V2	V3	V4	V5	V6	V7	V8	V9	V10	V11	V12	V13	V14	V15
Week	Scr	Bsl	W4	W8	W12	W16	W20	W24	W28	W32	W36	W40	W44	EOT[b] W48	EOS W54
Day [c]	D-14 to -1[d]	D1[c]	D28	D56	D84	D112	D140	D168	D196	D224	D252	D280	D308	D336	D378
Procedures															
[redacted]															
Study participant diary completion/review [cc]			X	X	X	X	X	X	X	X	X	X	X	X	
Recording of AEs/medical procedures	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

Table 1-2: Schedule of activities

Period	Scr	Treatment (all visits in Treatment Period ±3 days)													SFU[a]
Visit	V1	V2	V3	V4	V5	V6	V7	V8	V9	V10	V11	V12	V13	V14	V15
Week	Scr	Bsl	W4	W8	W12	W16	W20	W24	W28	W32	W36	W40	W44	EOT[b] W48	EOS W54
Day [c]	D-14 to -1[d]	D1[c]	D28	D56	D84	D112	D140	D168	D196	D224	D252	D280	D308	D336	D378
Procedures															
Contact IWRS	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Study medication accountability		X	X	X	X	X	X	X	X	X	X	X	X		

AE=adverse event; [redacted]
BILAG 2004=British Isles Lupus Assessment Group Disease Activity Index 2004; BMI=body mass index; Bsl=Baseline; CD=cluster of differentiation antigen; CK-MB=creatine kinase- myocardial band; CLASI=Cutaneous Lupus Erythematosus Disease Area and Severity Index; COVID-19=Coronavirus disease 2019; [redacted]; C-SSRS=Columbia Suicide Severity Rating Scale; CT=computerized tomography; CXR=chest x-ray; D=Day; DZP=dapirolizumab; [redacted]; ECG=electrocardiogram; [redacted]; EOS=End of Study; EOT=End of Treatment; EQ-5D-5L=Euro Quality of life 5-Dimensions 5-Level; Fab'=fragment antigen-binding; FACIT-F=Functional Assessment of Chronic Illness Therapy-Fatigue; FATIGUE-PRO=Fatigue patient reported outcome; F/U=follow-up; HIV=human immunodeficiency virus; ICF=Informed Consent form; IEC=Independent Ethics Committee; Ig=immunoglobulin; IGRA= interferon-γ release assay; IMP=investigational medicinal product; INR=international normalized ratio; IWRS= Interactive Web Response System; LAMDA= Lupus Arthritis and Musculoskeletal Disease Activity; LLDAS=low lupus disease activity state; LTBI=latent tuberculosis infection; PEG=polyethylene glycol; PGA=Physician's Global Assessment of Disease; PGI-C= Patient Global Impression of Change; PGI-S=Patient Global Impression of Severity; PHQ-9=Patient Health Questionnaire-9; PK=pharmacokinetic; pTT=partial thromboplastin time; Q4W=every 4 weeks; QoL=quality of life; RNA=ribonucleic acid; Scr=Screening; SFI=SELENA Flare Index; SFU=safety follow-up; SJC=swollen joint count; SLE=systemic lupus erythematosus; SLEDAI-2K=Systemic Lupus Erythematosus Disease Activity Index 2000; SLICC =Systemic Lupus International Collaborating Clinics; S2K RI50=Systemic Lupus Erythematosus Disease Activity Index-2K Responder Index-50; TB=tuberculosis; TJC=tender joint count; TSH=thyroid-stimulating hormone; V=Visit; VAS=visual analog scale; W=Week; WOCBP=women of childbearing potential

Note: If study participants have a missed or delayed visit, they should return to their original visit schedule.

Note: For study participants prematurely terminating or completing the study, final disposition is recorded at Week 48 (V14, EOT). All study participants prematurely terminating from the study should be encouraged to undergo final evaluation procedures, in accordance with the Week 48 (V14, EOT) schedule as soon as possible after the final dose of study medication.

Note: Pandemic Situation: In case a study participant is unable to attend a scheduled visit due to pandemic related situations, all efforts will be taken by the Investigator to maintain contact with study participant remotely through telephone/video contact, monitor and support participant's safety and collect relevant study data.

The data collected during telephone/video contact will be recorded in the medical records and/or the electronic data capture system (EDC), accordingly. The procedures which cannot be performed will be recorded in EDC as "not done".

[a] If the study drug is discontinued >10 weeks before Week 48/EOT visit and the study participant attends the Week 48/EOT visit, no SFU is required.

[b] In the case of early study termination.

[c] Day 1 is the first day of Week 1; for all other weeks, the day shown is the final day of the week indicated.

[d] If the 14 day Screening Period is exceeded, an additional 7 days may be allowed after consultation with the Medical Monitor.

[redacted]

[f] Collected data includes information about lifestyle, childbearing potential (as applicable), height, weight, and BMI. Weight will be measured again at Week 24. For study participants screened under the initial protocol (ie, before Amendment 1), the Baseline (Visit 2) body weight is to be used to determine study drug dosing (Section 6.1) through Week 20 (Visit 7). In case of a pregnancy after initiation of study treatment, weight measurement will be performed at every study visit.

[g] Thrombophilia diagnostic includes assessment of protein C, S, antithrombin deficiency, homocysteine, factor V Leiden, and prothrombin Gene G20210A.

[h] Inclusion/exclusion criteria will be reviewed in addition centrally in accordance with the Central Eligibility Review Plans. Laboratory values obtained within 4 weeks of the Screening Visit will be considered for BILAG 2004.

[i] Confirmation of inclusion/exclusion criteria will be limited to the clinical assessments (eg, SLEDAI without laboratory assessments). Laboratory assessments will not be available and therefore will not be considered.

[j] All medications, vaccinations and SLE medication history. For SLE medications, record all biologic treatment and antimalarials the study participant has ever taken and all other nonbiologic SLE treatments (ie, corticosteroids, immunosuppressants) taken in the prior 6 months. Record known vaccinations (including vaccinations against COVID-19) received by study participant.

[k] If a study participant is pregnant and stays in the study for observation, no pregnancy testing will be performed as long as the pregnancy lasts.

[l] Unless a CXR or chest CT scan is available within 3 months prior to Screening.

[m] The 12—lead ECGs at Baseline, Week 4, Week 24, and Week 48 will be read centrally. Screening ECGs will be assessed by Investigators to determine eligibility. Post screening ECGs will be assessed by Investigators to detect change from the baseline and significant abnormalities.

[n] Will be assessed predose; then every 15 min from start of infusion to end of infusion; then every 30 min until 1 hour after the end of infusion. Refer to Section 8.2.2 and Section 10.15 Appendix 15.

[o] HIV, hepatitis B, and hepatitis C.

[p] In the case of rescreening due to prior LTBI diagnosis and initiation of prophylactic treatment, the IGRA TB test does not have to be performed.

[q] To include lung and heart auscultation. If a participant has cutaneous SLE manifestations at V1, photodocumentation as part of source documents may be needed at V1, V2, V8, and V14 for adjudication of BILAG 2004 grading. Photodocumentation of cutaneous SLE manifestations may also be needed at other visits.

[r] To be conducted after physical examination and before study participant questionnaire. The PGA should be re-evaluated after review of laboratory parameters. To minimize bias, the same Investigator should perform the key efficacy assessments whenever possible and this will be documented in the database.

[s] To be conducted after efficacy assessments are completed.

[redacted]

[u] Only performed if study participant receives anticoagulant therapy or in the case of significantly increased liver enzymes.

[v] Adhoc diagnostic(s) may include but are not limited to the following as medically indicated: procalcitonin, thrombophilia diagnostic, hepatitis/liver injury diagnostic, CK-MB, and troponin I. These diagnostics will only be performed in the event of a specified medical event(s), which will be discussed with the Investigator and Medical Monitor. SARS-CoV-2 testing will be performed in participants when SARS-CoV-2 infection is suspected by Investigator (in line with Section 8.2.7).

[redacted]

[x] The initial dose (Baseline; Day 1) will be administered as a 2-hour infusion as this will be the initial exposure to DZP. All other doses will be administered as a 1-hour infusion. Study participants will remain in the clinic for 1 hour post-infusion for observation. In study participants with an increased risk for allergic reactions premedication with antihistamines with or without paracetamol can be applied at the discretion of the Investigator. In case a study participant cannot attend a scheduled study visit or drug cannot be administered as planned at a scheduled visit the study drug should be administered as soon as possible but not less than 14 days before the next scheduled visit at a separate day. If procedures assigned to a certain visit have to be done on 2 separate days both days will be assigned to the same visit.

[redacted]

[cc] Study participants will receive a smart phone with the MyUCB4me tool to enter their corticosteroid use.

[redacted]

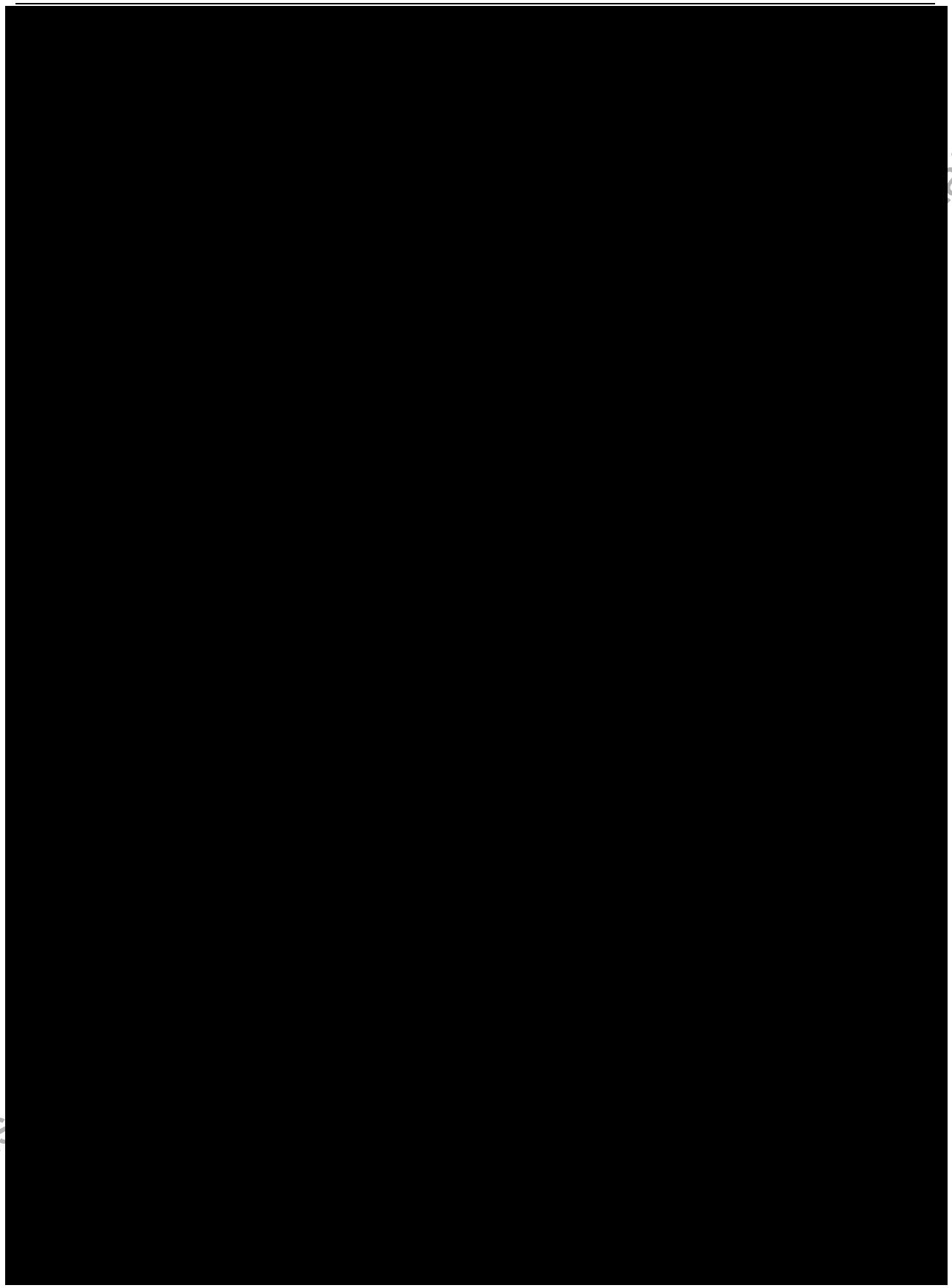
2 INTRODUCTION

2.1 Study rationale

Systemic lupus erythematosus (SLE) is a chronic autoimmune inflammatory disease which can present with a chronic disease course but has more often a relapsing-remitting disease course. The majority of patients develop tissue and organ damage over time with current SOC medication due to either lack of well controlled disease activity or due to toxicities of the SOC medications. Therefore, new therapies are needed to achieve long-term control of the disease activity of SLE with well tolerated SLE medication. The study aims to evaluate the efficacy of DZP in study participants who have persistent active or frequently relapsing-remitting SLE with moderate to severe disease activity despite being on stable non-biological SOC medication and therefore have an unmet medical need for a treatment intervention with new therapies.

2.2 Background

[redacted]



[redacted]

2.3 Benefit/risk assessment

The totality of the evidence from studies with clinical and immunological outcome parameters suggests a signal of superior efficacy of DZP in combination with SOC as compared with SOC alone in patients with persisting active or frequent relapsing-remitting SLE.

[redacted]

Risks from taking part in the studies will be minimized through the selection of an appropriate dose level, selection of appropriate study participants defined by the inclusion/exclusion criteria, an independent data monitoring committee (IDMC), regular safety monitoring, and regular blinded assessments of study data assessments.

Overall, the benefit-risk profile of DZP is considered favorable for further clinical development in a Phase 3 program. Further information can be found in the Investigator's Brochure (IB).

3 OBJECTIVES AND ENDPOINTS

Table 3-1: Objectives and endpoints

Objectives	Endpoints
Primary	
• To evaluate the ability of DZP as an add-on treatment to SOC medication to achieve clinically relevant long term improvement of moderate to severe disease activity	• Achievement of BICLA response at Week 48
Key Secondary	
• To evaluate the ability of DZP as an add-on treatment to SOC medication to achieve fast, clinically relevant improvement of moderate to severe disease activity	• Achievement of BICLA response at Week 24 • Achievement of BICLA response at Week 12
• To evaluate the ability of DZP as an add-on treatment to SOC medication to achieve long term control of disease activity	• Achievement of prevention of severe BILAG flares (severe BILAG flare-free) through Week 48
• To evaluate the ability of DZP as an add-on treatment to SOC medication to achieve and maintain the treat-to-target goal: low disease activity with low/acceptable corticosteroid dose over time	• Achievement of LLDAS in ≥50% of post Baseline visits through Week 48
• To evaluate the ability of DZP as an add-on treatment to SOC medication to achieve improvement of disease activity as measured by numerical disease state score commonly used in clinical practice	• Change from Baseline in SLEDAI-2K at Week 48
Secondary	
• To evaluate the ability of DZP as an add-on treatment to SOC medication to achieve components of the composite primary endpoints	• Achievement of BILAG improvement without worsening at Week 48
	• Change from Baseline in PGA at Week 48
• To evaluate the ability of DZP as an add-on treatment to SOC medication to achieve alternative responder endpoint	• Achievement of SRI4 response at Week 48

Objectives	Endpoints
• To evaluate the ability of DZP as an add-on treatment to SOC medication to achieve endpoints supporting other key secondary endpoints	• Achievement of prevention of moderate/severe BILAG flares (moderate/severe BILAG flare-free) through Week 48
	• Time to severe BILAG flare through Week 48
	• Time to moderate/severe BILAG flare through Week 48
• To evaluate the safety and tolerability of DZP as add-on treatment to SOC medication	• TEAEs, serious TEAEs, TEAEs of special interest, and TEAEs of special monitoring
Tertiary	
• To evaluate the ability of DZP as add-on treatment to SOC to achieve endpoints which support the primary and secondary objectives and/or support the interpretation of the primary and secondary endpoints	• Achievement of reduction of corticosteroid dose from >7.5mg/day prednisone equivalent dose at start of study to ≤7.5mg/day prednisone equivalent by visit
	• Achievement of reduction of corticosteroid dose from >7.5mg/day prednisone equivalent dose at start of study to ≤7.5mg/day prednisone equivalent at Week 24 and maintaining low corticosteroid dose afterwards and achievement of BICLA response at Week 48
	• Achievement of reduction of corticosteroid dose from >7.5mg/day prednisone equivalent dose at start of study to ≤7.5mg/day prednisone equivalent at Week 24 and maintaining low corticosteroid dose and achievement of prevention of moderate/severe BILAG flares (moderate/severe BILAG flare-free) at Week 48
	• Achievement of reduction in corticosteroid dose from ≥7.5mg/day prednisone equivalent dose at start of study to ≤5mg/day prednisone equivalent at Week 24 and maintaining low corticosteroid dose and achievement of BICLA response at Week 48
	• Achievement of reduction of corticosteroid dose from ≥7.5mg/day prednisone equivalent

Objectives	Endpoints
	dose to ≤5mg/day prednisone equivalent at Week 24 and maintaining low corticosteroid dose and achievement of prevention of moderate/severe BILAG flares (moderate/severe BILAG flare-free) at Week 48
	• Total corticosteroid dose through Week 24, through Week 48, and from Week 24 through Week 48
	• Achievement of BICLA response by visit
	• Achievement of BILAG 2004 improvement without worsening by visit
	• Change from Baseline in BILAG 2004 score by visit
	• Achievement of BILAG 2004 shifts by visit
	• Achievement of BILAG 2004 improvement by organ system by visit
	• Achievement of maintained BICLA response by visit
	• Achievement of persistent BICLA response between Week 24 and Week 48
	• Worsening of any organ system with a BILAG 2004 B, C, D, E at Baseline to BILAG 2004 A or worsening of >1 organ system with a BILAG 2004 C, D, E at Baseline to BILAG 2004 B by visit
	• Achievement of BILAG 2004 C, D, E in all organ systems by visit
	• Change from Baseline in SLEDAI-2K by visit
	• Achievement of SRI 4, 6, 8 response by visit
	• Change from prior visits in S2K RI50 by visit
	• Change from Baseline in PGA by visit
	• Achievement of LLDAS status by visit

Objectives	Endpoints
	• Cumulative number of visits in LLDAS through Week 48
	• Achievement of LLDAS Variant (demand for ≤5mg/day prednisone equivalent) in >50% of post-Baseline visits through Week 48
	• Achievement of prednisone equivalent dose ≤7.5mg/day by visit
	• Prednisone equivalent dose by visit
	• Occurrence of severe BILAG 2004 flares by visit
	• Occurrence of moderate BILAG flares by visit
	• Occurrence of severe SFI flares by visit
	• Occurrence of moderate SFI flares by visit
	• Time to severe SFI flare
	• Time to moderate SFI flare
	• Change from Baseline in ACR/SLICC damage score by visit
	• Achievement of DORIS remission by visit
• To evaluate the ability of DZP as an add-on treatment to SOC medication to achieve organ specific endpoints	• Change from Baseline in CLASI activity score by visit for all study participants and for subset of study participants with high CLASI score
	• Achievement of a meaningful improvement in CLASI score by visit for all study participants and for subset of study participants with high CLASI score
	• Change from Baseline in TJC and SJC by visit for all participants and for subset of participants with moderate to severe arthritis
	• Achievement of a meaningful decrease in TJC/SJC by visit for all participants and for a subset of participants with moderate to severe arthritis

Objectives	Endpoints
	• Change from Baseline in Lupus Arthritis and Musculoskeletal Disease Activity score by visit
• To evaluate the ability of DZP as an add-on treatment to SOC medication to achieve important patient reported outcomes	• Change from Baseline in FACIT-F by visit
	• Change from Baseline in PHQ-9 score by visit
	• Change from Baseline in FATIGUE-PRO 'Physical Fatigue', 'Mental Fatigue' and 'Fatigability' scores by visit
	• Change from Baseline in LupusQoL by visit
	• Change from Baseline in EQ-5D-5L by visit
• To evaluate the PK	[redacted]
• To evaluate immunogenicity of DZP as an add-on treatment to SOC medication	• Incidence of anti-drug antibodies: [redacted]
• To evaluate the PD and immunological parameters of DZP as an add-on treatment to SOC medication	• Observed values and change from baseline in [redacted] in all study participants by visit and in study participants 'positive' at Baseline by visit
	• Seroconversion of: [redacted] status by visit
• To evaluate the safety and tolerability of DZP as an add-on treatment to SOC medication	• TEAEs leading to study withdrawal, TEAEs leading to permanent study medication discontinuation, TEAEs with start day on day or up to 1 day after infusion, other identified TEAE clusters
	• Summary of participants withdrawn from the study due to TEAEs

Objectives	Endpoints
	• Summary of participants who permanently discontinued study medication
	• Change from Baseline in vital sign parameters by visit
	• Observed values and change from Baseline in safety laboratory tests (hematology, serum chemistry, urinalysis) by visit, % study participants achieving critical threshold for selected lab parameters by visits
• To evaluate changes in exploratory biomarkers	• Change from Baseline in biomarkers selected for analysis [redacted]
• To evaluate risk for anti-phospholipid associated events	• Change from Baseline in APS score by visit

ACR/SLICC=American College of Rheumatology/Systemic Lupus International Collaborating Clinics; [redacted]; APS=antiphospholipid antibody syndrome; BICLA=BILAG 2004-based Composite Lupus Assessment; BILAG=British Isles Lupus Assessment Group Disease Activity Index 2004; CLASI=Cutaneous Lupus Erythematosus Disease Area and Severity Index; DORIS=definitions of remission in SLE; DZP=dapirolizumab pegol; [redacted]; EQ-5D-5L=Euro Quality of life 5-Dimensions 3-Level; Fab'=fragment antigen-binding; FACIT-F=Functional Assessment of Chronic Illness Therapy Fatigue; FATIGUE-PRO=Fatigue patient reported outcome; Ig=immunoglobulin; LLDAS=low lupus disease activity state; PD=pharmacodynamics; PEG=polyethylene glycol; PGA=Physician's Global Assessment of Disease; PHQ-9=Patient Health Questionnaire-9; PK=pharmacokinetic(s); SFI=SELENA Flare Index; SJC=swollen joint count; SLE=systemic lupus erythematosus; SLEDAI-2K=Systemic Lupus Erythematosus Disease Activity Index 2000; sm=Smith antigen; SOC=standard of care; SRI4, 6, 8=Systemic Lupus Erythematosus Responder Index-4, 6, 8; [redacted];S2K RI50=Systemic Lupus Erythematosus Disease Activity Index-2000 Responder Index-50; TEAE=treatment-emergent adverse event; TJC=tender joint count

4 STUDY DESIGN

4.1 Overall design

The study will be conducted to assess the efficacy, safety and tolerability of DZP in study participants with active SLE despite standard therapy and its results will support regulatory filing.

This study is a randomized, double-blind, placebo-controlled, parallel group, Phase 3 study in study participants 16 years of age and older with moderately to severely active SLE who are receiving stable SOC medication (ie, antimalarials, corticosteroids, and/or immunosuppressants) in line with local and international guidances at screening visit (V1). It will primarily investigate the improvement of SLE disease activity in study participants treated with DZP as add-on to nonbiological SOC treatment over 48 weeks. Key secondary objectives will be to investigate early improvement at Weeks 12 and 24, long-term disease control as evidenced by prevention of severe BILAG flares (severe BILAG flare-free) through Week 48, achievement of a

treat-to-target endpoint (low disease activity state in conjunction with low/acceptable corticosteroid dose [LLDAS]) through Week 48, and long-term improvement of disease activity as assessed with an instrument commonly used in clinical practice (SLEDAI-2K) at Week 48.

The study consists of a 2-week Screening Period, 48-week Treatment Period, and 6-week SFU Period (if the participant completes the study but decides not to enter the open-label extension study SL0046). Due to the required moderate to severe disease activity at screening visit (V1) and limited allowed treatment possibilities during the screening phase, a short Screening Period is planned. At the start of the study, eligible study participants will be randomized (2:1) to DZP 24mg/kg or to placebo administered by iv infusion Q4W. The initial dose will be administered as a 2-hour infusion while each subsequent dose will be administered as a 1-hour infusion. Study participants who complete the 48-week Treatment Period may be eligible to participate in the OLE study (SL0046). Study participants who withdraw early from the 48-week Treatment Period or choose not to enter the OLE will be followed up for at least 10 weeks SFU after their final dose of study medication.

Eligible study participants will have persisting active or relapsing-remitting SLE at screening visit (V1) despite stable SOC treatment (ie, antimalarials, corticosteroids, and/or immunosuppressants), in line with local and international guidance at screening visit (V1). Study participants considered to have a monophasic or an infrequent relapsing-remitting disease course (defined as no evidence for frequently flaring disease course and low risk to have frequent flares) will be excluded as their disease likely does not correspond to a persistent active or frequently relapsing SLE despite SOC treatment.

During the study, participants with a corticosteroid dose above a long-term tolerable level (7.5mg/day prednisone equivalent) will have to start corticosteroid tapering no later than the Week 8 Visit (Visit 4) to reach a target of 7.5mg/day or below. Investigators will be encouraged to start steroid tapering earlier if the condition of the study participant suggests improvement. Guidance will be provided on how to taper but the exact tapering regimen will be at the discretion of the Investigator to be adapted to the individual study participant's disease activity. Other SLE SOC treatment will have to be kept stable unless a reduction is indicated due to side effects. In case of insufficient improvement of disease activity, or a clinically relevant worsening of the disease activity, Investigators may initiate an escape treatment (Section 6.6.2) by increasing the dose of concomitant SOC medication. Depending on the nature of an escape treatment intervention, DZP may have to be discontinued if there is a safety concern. Investigators should discuss the impact of escape treatment use on study conduct with the Medical Monitor before initiation. In case of an initiation of escape treatment, study participants may be declared as **nonresponders** for the primary endpoint; however, they do not have to be withdrawn from the study.

Study participants will be encouraged to stay in the study under observation even if the study medication is discontinued (see Section 7.1). A study participant will have to be withdrawn from the study only if the study participant withdraws consent or a regulator, Institutional Review Board/Independent Ethics Committee (IRB/IEC), or the independent data monitoring committee (IDMC) requests a withdrawal for justified reasons (see Section 7.2).

An IDMC will be established to monitor the benefit-risk profile of study participants during the study. The IDMC will regularly review data and will have access to unblinded data as needed. The review will include observations in the BILAG 2004 neuropsychiatric body organ system in

order to monitor potential neuropsychiatric events falsely assigned to SLE. Details are described in the IDMC charter. The IDMC will provide recommendation if the study should be stopped, should be adapted or can proceed as planned.

4.2 Scientific rationale for study design

A randomized, double-blind, placebo-controlled, parallel-group study design has been selected to demonstrate efficacy and safety of DZP to support regulatory filing. The study population will include study participants 16 years of age and older with moderately to severely active SLE who are receiving stable SOC medication (ie, antimalarials, corticosteroids, and/or immunosuppressants) at screening visit (V1). The primary efficacy outcome measures and other efficacy assessments included in this study are consistent with those used for some other SLE studies and are considered appropriate for establishing efficacy of DZP. Clinically relevant improvement of moderate to severe disease activity over 48 weeks will be used to demonstrate the efficacy of DZP over placebo long term. Early clinically relevant improvement from moderate to severe disease activity will be assessed after 12 and 24 weeks. Long-term disease control will be demonstrated by assessment of flare prevention (flare-free), the achievement of the treat-to-target endpoint LLDAS, and the reduction in SLEDAI-2K score.

4.3 Justification for dose

The selection of the dose is based on the Phase 2b study, SL0023. Efficacy and safety of DZP was assessed in 3 dose arms in SL0023. The lowest dose of 6mg/kg was selected based on non-clinical data on a non-human primate tetanus toxoid (TT) model showing minimal reduction of [redacted] titers suggesting some immunomodulation. [redacted].

SL0023 Study participants who received 24mg/kg or 45mg/kg DZP showed overall similar clinical response rates across all clinical endpoints and majority of time points as well as similar reduction in [redacted], therefore the 45mg/kg dose is not considered to provide added benefit as compared to the 24mg/kg. This was also applicable in subgroups of participants with higher disease activity and/or more severe disease. While similarities were seen between 24mg/kg and 45mg/kg doses, response rates in study participants receiving 6mg/kg were inconsistent. Moreover, generation of anti-drug antibodies was increased in study participants receiving 6mg/kg as compared to study participants receiving 24mg/kg or 45mg/kg. Therefore, 6mg/kg is considered as a dose with inferior efficacy while 24mg/kg is considered as dose with maximum observed effect. As doses between 6mg/kg and 24mg/kg overlap pharmacokinetically with the 24mg/kg dose, a clear assignment of benefit/risk to dosages below 24mg/kg is difficult. Therefore, in view of the aforementioned information, 24mg/kg was selected as a dose with a maximum effect and an acceptable safety profile.

4.4 End of study definition

A study participant is considered to have completed the study if she/he has completed the Week 48 Visit.

The end of the study is defined as the date of the final visit of the last study participant in the study.

5 STUDY POPULATION

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, is not permitted.

5.1 Inclusion criteria

Rescreening will be allowed once during the study in case there is new evidence for an inclusion criterion that was not fulfilled at the first screening or in case a study participant no longer meets an exclusion criterion (Section 5.4) or screening period exceeded the maximum duration due to delays in screening processes.

Study participants are eligible to be included in the study only if all of the following criteria apply:

Age

1. Study participant must be ≥16 years of age, unless restricted by local regulation, at the time of signing the Informed Consent form (ICF).

Type of participant and disease characteristics

2. Study participants who have moderate to severe disease activity due to either persisting active SLE or due to an acute worsening of SLE in the scope of frequent flaring/relapsing-remitting SLE despite stable SOC medication defined as:
   - a1. Diagnosed with SLE at least 24 weeks before the Screening Visit (Visit 1) by a qualified physician (eg, rheumatologist, internal medicine expert, nephrologist, or dermatologist)
   - b. Classified by 2019 SLE European League Against Rheumatism/American College of Rheumatology (EULAR/ACR) classification criteria for SLE
   - c1. With serological evidence for SLE at Screening as demonstrated by at least 1 of the following:
     - i) Evidence for [redacted] (defined as evidence for [redacted] in central laboratory)
     - ii) Either [redacted] < lower limit of normal (LLN) OR [redacted] <LLN OR elevated erythrocyte-bound complement [redacted] (where available) as measured by central laboratory
     - iii) [redacted] with a titer of at least 1:80 confirmed by central laboratory in combination with evidence of at least 1 of the following SLE typical autoantibodies:
       1. [redacted] (central laboratory)

2. [redacted] (central laboratory)
3. Historic evidence for anti-dsDNA antibodies (at least 2 historical positive tests [>upper limit of normal (ULN) of lab assay with an interval of at least 12 weeks between tests])

d. Moderately to severely active defined as
-British Isles Lupus Assessment Group Disease Activity Index 2004 (BILAG 2004) Grade B in ≥2 organ systems and/or a BILAG 2004 Grade A in ≥1 organ systems at Screening and Baseline Visit AND
-SLEDAI-2K ≥6 at Screening Visit AND
-SLEDAI-2K without labs ≥4 at Baseline Visit

e3. Receiving the following SOC medication at stable dose:

- Antimalarial treatment in combination with corticosteroids and/or immunosuppressants or as stand-alone treatment if justified (ie, if for other SLE SOC medications there is documented intolerance in medical history, documented lack of efficacy, contraindications, or lack of availability) OR
- Treatment with corticosteroids and/or immunosuppressants if anti-malarial treatment is not possible (ie, documented intolerance in medical history or antimalarials not available locally)

Stable dose is defined for:

- Antimalarials as no change to dose within 8 weeks prior to Screening and during Screening Period and a start date at least 12 weeks before Screening. Maximum doses are described in Section 6.5.1.2.
- Corticosteroids as no change in dose for 2 weeks prior to Screening, no change during Screening Period, and no iv pulse therapy (>500mg x 1 to 3 days) within 4 weeks prior to screening. The maximum dose allowed at screening is 40mg/day prednisone or equivalent (see Section 6.5.1.1).
- Immunosuppressants as no change in dose for 12 weeks prior to Screening Visit and during Screening Period. Maximum doses are described in Section 6.5.1.3.

Weight

3. Body weight ≥40kg and ≤160kg.

Sex

4a. Female and/or male

- A male study participant must agree to use contraception, as detailed in Section 10.4, during the Treatment Period and for at least 17 weeks after the final dose of study medication and refrain from donating sperm during this period.
- A female study participant is eligible to participate if she is not pregnant, not breastfeeding (including pumping breast milk to feed to a child), and at least 1 of the following conditions applies:

– Not a woman of childbearing potential (WOCBP) as defined in Section 10.4 of the protocol, or

– A WOCBP who agrees to follow the contraceptive guidance in Section 10.4 of the final protocol during the treatment period and for at least 17 weeks after the final dose of study medication.

Informed consent

5. Capable of giving signed informed consent as described in Section 10.1.3, which includes compliance with the requirements and restrictions listed in the ICF and in this protocol.

5.2 Exclusion criteria

Study participants are excluded from the study if any of the following criteria apply:

Medical conditions

General

1. Study participant has any medical or psychiatric condition (including conditions due to neuropsychiatric SLE) that, in the opinion of the Investigator, could jeopardize or would compromise the study participant's ability to participate in this study. This includes study participants with a life threatening condition (eg, CTCAE grade 4 conditions, CAPS, acute severe renal failure, acute severe central nervous system [CNS] manifestations)

2a. Study participant has moderate to severe disease activity (as defined per inclusion criterion 2.d) at the Screening Visit (V1) due to an acute flare but **does not fulfill at least one** of the following criteria in addition to the Screening Visit:

– ≥1 additional disease flare within the last 24 weeks prior to Screening (as per medical record) OR

– [redacted] positivity in combination with [redacted] <LLN as per central laboratory OR

– [redacted] <LLN as per central laboratory OR

– African-American OR

– Age <25 years

3. Study participant has a history of chronic alcohol or drug abuse within the previous 24 weeks.

4. Study participant has a known [redacted] to any components of DZP including PEG or comparative drugs (and/or an investigational device) as stated in this protocol.

5a. Study participant has a history of an anaphylactic reaction to parenteral administration of contrast agents, human or murine proteins, or monoclonal antibodies. This includes systemic reactions due to latex allergy.

6a. Study participant has a history of malignancy, except the following treated cancers: cervical carcinoma in situ (after complete resection [eg, curettage, electrodesiccation] not later than 4 weeks prior to the Screening Visit [V1]), basal cell carcinoma, or dermatological

squamous cell carcinoma (after complete resection not later than 24 weeks prior to the Screening Visit [V1]).

7. Study participants who have had major surgery (including joint surgery) within the 24 weeks prior to Screening, or planned surgery within 24 weeks after entering the study.
8. Study participants who have had significant blood loss or have donated or received 1 or more units (450mL) of blood within 30 days prior to the Screening Visit or have donated plasma or platelets within 14 days prior to the Screening Visit.
9. Study participants with a history of thromboembolic events within 52 weeks of Screening (Visit 1), including but not limited to the following: deep venous thrombosis, pulmonary embolism, cortical sinus thrombosis, myocardial infarction, stroke, transient ischemic attack, or arterial insufficiency causing digital gangrene or tissue necrosis.

   Note:
   1) In case of anti-phospholipid antibodies present at the Screening Visit, a prophylactic treatment should be considered in line with local or international guidelines and considering the individual risk profile of the patient for thromboembolic events
   2) Study participants with antiphospholipid syndrome (APS) can be enrolled if they are on stable anticoagulation therapy at an effective dose (eg, International Normalized Ratio [INR] target 2 to 3 depending on clinical situation) and did not have a thromboembolic event and/or obstetric morbidity within the 52 weeks prior to Screening (Visit 1).Obstetric morbidity is defined as 1 or more unexplained deaths of a morphologically normal fetus at or beyond the tenth week of gestation with the latest incidence within 52 weeks prior to Screening (Visit 1) OR 1 or more preterm births of a morphologically normal neonate before the 34th week of: (i) eclampsia or severe pre-eclampsia or (ii) recognized features of placental insufficiency with the latest incidence within 52 weeks prior to Screening (Visit 1).
10. Study participants with a history of catastrophic APS or saddle pulmonary embolism.
11a. Study participant has an increased risk for thromboembolic events due to an ongoing heart disease or due to a medical device, including but not limited to vascular graft, valvular heart disease, atrial fibrillation, or a heart rhythm disorder.
12. Study participant has a BILAG 2004 Grade A in the musculoskeletal system due to severe arthritis only AND no BILAG 2004 Grade A or B in any other organ system AND no current (within the past 4 weeks) evidence for synovitis based on imaging methods such as magnetic resonance imaging or doppler-sonography.
13a. Study participant has a mixed connective tissue disease, scleroderma, and/or overlap syndrome of these diseases with SLE.
   - Clarification: Study participants with rheumatoid arthritis in their medical history are not considered as having an overlap syndrome and are therefore eligible.

Infection related risks:

14. Study participant has evidence of human immunodeficiency virus infection, agammaglobulinemias, T-cell deficiencies, or human T-cell lymphotropic virus-1 infection at any time prior to or during the study.

15a. Study participant has clinically significant active or latent infection (eg, chronic viral hepatitis B or C, or SARS CoV-2 infection [see Section 8.2.7]).

16a. Study participant has a history of a serious infection within the last 60 days prior to the first study medication infusion (Visit 2) that required iv/intramuscular antibiotics, systemic antiviral treatment or required hospitalization/prolonged hospitalization. Study participants must have completed any prior anti-infective therapy for serious infections prior to the first study medication infusion.

17b. Study participant had a reactivated latent infection (eg, cytomegalovirus, herpes simplex virus, or herpes zoster infection) or opportunistic infection (including but not limited to pneumocystis, cytomegalovirus, or severe herpes zoster infection) within 12 weeks prior to the first study medication infusion (Visit 2), or is currently receiving suppressive therapy for an opportunistic infection.

18. Study participant has a clinically relevant recurrent (more than 3 times a year) infection.

19. Study participant with any of the following tuberculosis (TB) exclusion criteria:

- Known active TB infection.
- History of active TB infection involving any organ system or findings in other organ systems consistent with TB, unless adequately treated according to WHO/CDC therapeutic guidance and proven to be fully recovered upon consult with a TB specialist.
- Latent TB infection (LTBI) unless appropriate prophylaxis is initiated at least 4 weeks prior to study medication dosing and will be continued to completion of prophylaxis.
- High risk of acquiring TB infection, eg, known close exposure to another person with active TB infection within 3 months prior to Screening or significant time spent in a health care delivery setting or institution where individuals infected with TB are housed and where the risk of transmission is high within 3 months prior to Screening.
- Current nontuberculous mycobacterial (NTM) infection or history of NTM infection unless proven to have fully recovered upon consult with a TB specialist.

20a. Study participants who have received live/live attenuated vaccines within 6 weeks prior to the first study medication infusion (Visit 2) or who plan to receive these vaccines during the study or up to 12 weeks after the final dose of study medication will be excluded. Use of nonlive vaccines is allowed during the study; however, based on current evidence, it cannot be excluded that the effectiveness of these vaccines may be compromised by the study medication. Investigator should consider local and international guidance on vaccination in immunosuppressed patients and discuss risks, benefits and administration options with participants (for more details see also Section 6.6.1 and Section 8.2.7).

Prior/Concomitant therapy

21. Study participant has active lupus that, in the opinion of the Investigator or according to local or international guidances, requires an increase in SOC therapy outside of that permitted in Section 6.5.1.

22. Study participants requiring plasma exchange or immunoadsorption in the 16 weeks prior to Visit 2 or at any time during the study.

23. Study participant has used the prohibited medications listed in Table 6-7, regardless of route (with the exception of eye drops), within the time frame (Wash-Out Period) listed in the table prior to Screening (Visit 1). Study participant has used investigational agents not included in Table 6-7, including other investigational or recently approved biologics, off-label use of immunomodulators, or device products, within 12 weeks or 5 times the half-life prior to Screening (Visit 1), whichever is longer. Concomitant participation in studies where no product or device is administered/used may be allowed if discussed and approved by the Medical Monitor/UCB. If there are any questions regarding acceptable wash-out periods not mentioned, the Investigator should contact the Medical Monitor.
24. Hormone replacement therapy is allowed provided it is not initiated within the 4 weeks prior to Screening (Visit 1) or during the study. The hormone replacement therapy may be decreased and/or discontinued at any time during the study.
25. Study participant should, if possible, stay on stable doses of the following other concomitant medications for the treatment of SLE during the study unless changes in these treatments are clinically indicated: analgesics, non-steroidal anti-inflammatory drugs (NSAIDs), 3-hydroxy-3-methyl-glutaryl-coenzyme A (HMG-CoA) reductase inhibitors (statins), angiotensin converting enzyme (ACE) inhibitors, and other anti-hypertensive drugs.

Prior/Concurrent clinical study experience

26a. Study participant has previously been randomized within this study or has previously been assigned to treatment with DZP in a study evaluating DZP.
27. Study participant has participated in another study of an IMP (and/or an investigational device) within the previous 12 weeks or 5 half-lives of the IMP whatever is longer (see Table 6-7) or is currently participating in another study of an IMP.

Diagnostic assessments

28a. Study participant has history of a suicide attempt within the 5 years prior to the Screening Visit or has had suicidal ideation in the past 6 months as indicated by a positive response ("Yes") to either Question 4 or Question 5 of the "Screening/Baseline" version of the Columbia Suicide Severity Rating Scale (C-SSRS) at Screening.

Note:

- In case a study participant responds to Question 9 in Patient Health Questionnaire-9 (PHQ-9) [redacted] the severity of the suicidal ideation needs to be adequately assessed with the C-SSRS rating scale.
- In case of history of a suicide attempt more than 5 years ago the absence of concurrent suicidal ideation and/or severe depression should be confirmed by a mental healthcare practitioner before enrolling into the study.

29a. Study participant has ≥3x the ULN alanine aminotransferase (ALT), aspartate aminotransferase (AST), or alkaline phosphatase (ALP), or >ULN bilirubin (≥1.5xULN

bilirubin if known Gilbert's syndrome), except in the case where the abnormal test values are ascribed to SLE hepatitis

- If study participant only has >ULN, but <1.5xULN bilirubin, fractionate bilirubin to identify possible undiagnosed Gilbert's syndrome (ie, direct bilirubin<35%) should be assessed, except in the case where the abnormal test values are ascribed hemolytic anemia, in the opinion of the Investigator.
- In case of a suspected SLE hepatitis, eligibility must be discussed with the Medical Monitor.
- If study participant has a result of ALT, AST, or ALP that is >ULN but that does not meet the exclusion limit at Screening, a repetition of the lab assessment is recommended to judge the dynamic of the increase, but is in the Investigator's discretion, considering the medical history of the participant. In case of a further clinically relevant increase (with a value that still doesn't meet the exclusion limit), inclusion of the study participant must be discussed with the Medical Monitor.

30a. Study participant has chronic kidney failure stage 4, manifested by estimated glomerular filtration rate (eGFR) <30mL/min/1.73m^2, or serum creatinine >2.5mg/dL, or participant has proteinuria >3g/day, or protein:creatinine ratio >340mg/mmol at the Screening Visit.

31a. Study participant has any significant hematologic abnormalities at the Screening Visit (Visit 1) as follows:

a. Hemoglobin <7.0g/dL
b. [redacted] T-lymphocytes <200/mm^3
c. Absolute neutrophil count <500/mm^3
d. [redacted] T lymphocytes <500/mm^3 in combination with neutrophil count <1000/mm^3
e. Platelets <25,000/mm^3. Study participants with a higher platelet count should also be excluded if they have a clinical risk of bleeding for reasons other than SLE.

Note: Study participants with an isolated laboratory parameter outside of the normal range at the Screening Visit may have a repeat test. If the repeat laboratory parameter is within normal range, the study participant may be randomized at the Baseline Visit, provided they meet all other eligibility criteria.

5.3 Lifestyle restrictions

No restrictions required.

5.3.1 Meals and dietary restrictions

No restrictions required.

5.3.2 Caffeine, alcohol, and tobacco

No restrictions required.

5.3.3 Activity

No restrictions required.

5.4 Screen failures

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently randomly assigned to study medication. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the Consolidated Standards of Reporting Trials publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any serious adverse event (SAE).

Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened once, in this case the study participant will be assigned a new number; information on the previous number must be recorded.

Study participants who require prophylaxis for LTBI must be on treatment for at least 4 weeks prior to initiation of IMP. These study participants may be rescreened once they have completed the first 4 weeks of prophylaxis treatment after consultation with the Medical Monitor.

Study participants who initiated treatment for latent TB infection (LTBI) during the Screening Period will be screening failures as TB treatment needs to be stable at least 4 weeks prior to first DZP dose. In the scope of rescreening the study participant must repeat initial screening laboratory parameters (except the interferon-γ release assay [IGRA] TB test), all physical examinations, and questionnaires (after completing at least 4 weeks of treatment for LTBI) at the rescreening visit prior to randomization in the study and must continue the full course of TB prophylactic therapy.

The Investigator must assess that the study participant's likelihood of completing the full course of TB prophylactic therapy is high and duly record their opinion in the study participant's record prior to randomizing the study participant.

6 STUDY TREATMENTS

Study treatment is defined as any investigational treatment(s), marketed product(s), placebo, or medical device(s) intended to be administered to a study participant according to the study protocol.

6.1 Treatments administered

Study participants will receive IMP by iv administration as a 2-hour infusion at the first administration Visit (V2, Baseline Visit), and then as a 1-hour infusion Q4W thereafter. Study participants will be observed for at least 1 hour after dosing for safety surveillance.

Serious [redacted] reactions (including [redacted]) and other infusion-related reactions have been reported following the initial and subsequent DZP and blinded study medication administrations [see IB Section 6.2.2]. Consider premedication by administration of an antihistamine, with or without paracetamol, before infusion of study medication, specifically before the first infusion and for study participants with a history of these reactions (see also Section 8.3.7 and Table 1-2, footnote x). However, available evidence is insufficient to determine to what extent premedication diminishes the frequency or severity of [redacted] reactions. Study medication must be administered by healthcare providers prepared to manage [redacted] reactions, including [redacted], and infusion-related reactions (see Table 1-2, footnote x). If a serious infusion-related or [redacted] reaction (eg, [redacted]) occurs,

immediately interrupt the administration of study medication and initiate appropriate therapy. In case of a suspected infusion reaction, blood samples should be obtained for a serum tryptase test (see Section 10.15.1).

Body weight will be measured at Screening to determine dosing through Week 20 and will be measured again at Week 24 to determine dosing for the rest of the study. (Exceptions: For participants screened under the initial protocol [ie, before Amendment 1], dosing through Week 20 will be determined using the Baseline body weight.)

Characteristics of the IMP are provided in Table 6-1.

Table 6-1: Characteristics of IMP

ARM Name	DZP	PBO
Intervention name	DZP	PBO
Type	Biologic	PBO
Dose formulation	Lyophilized drug product in vial	Liquid
Dosage level(s)	24 mg/kg	NA
Route of administration	iv infusion	iv infusion
Infusion duration	Initial dose: 2 hours Follow up doses: 1 hour	Initial dose: 2 hours Follow up doses: 1 hour
Use	Experimental	Placebo comparator
Sourcing	Provided centrally by Sponsor	Provided centrally by Sponsor
Packaging and labeling	Packaging will be described in the IP Handling Manual Labeling will be as per country requirements	Packaging will be described in the IP Handling Manual Labeling will be as per country requirements
Current/Former name(s) or alias(es)	CDP7657	NA

DZP=dapirolizumab pegol; IMP=investigational medicinal product; IP=investigational product; iv=intravenous; NA=not applicable; PBO=placebo

6.2 Preparation, handling, storage, and accountability requirements

In order to maintain blinding, an unblinded pharmacist or other suitably qualified site personnel will prepare each dose of IMP and provide the blinded and sealed infusion bag to the qualified site personnel performing the administration. The used blinded and sealed infusion bag is to be returned to the pharmacy or other unblinded designee to confirm the seal is not broken and blind is ensured outside the pharmacy. Complete preparation instructions will be outlined in the IP Handling Manual.

The Investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study medication received and any discrepancies are reported and resolved before use of the study medication.

Only participants randomized in the study may receive study medication and only authorized site staff may supply or administer study medication. All study medication must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the Investigator and authorized site staff.

The Investigator, institution, or the head of the medical institution (where applicable) is responsible for study treatment accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records).

In case an out-of-range temperature is noted, it must be immediately reported as per instructions contained in the IP Handling Manual.

Further guidance and information for the final disposition of unused study treatment are provided in the IP Handling Manual.

6.2.1 Drug accountability

The electronic Case Report Form (eCRF) will be used to record study medication dispensing and return information on a by-participant basis. Details of any study medication lost, damaged (due to breakage or wastage), not used, partially used, disposed of at the study site, or returned to the Sponsor or designee must also be recorded on the appropriate forms. All supplies and pharmacy documentation must be made available throughout the study for UCB (or designee) to review.

The Investigator (or designee) is responsible for retaining all used, unused, and partially used containers of study medication until returned or destroyed.

The Investigator may assign some of the Investigator's duties for drug accountability at the study site to an appropriate pharmacist/designee.

The Investigator must ensure that the study medication is used only in accordance with the protocol.

Periodically, and/or after completion of the clinical phase of the study, all used (including empty containers)/partially used, unused, damaged, and/or expired study medication must be reconciled and either destroyed at the site according to local laws, regulations, and UCB standard operating procedures or returned to UCB (or designee). Investigational medicinal product intended for the study cannot be used for any other purpose than that described in this protocol.

6.3 Measures to minimize bias: randomization and blinding

All participants will be centrally assigned to randomized study medication using an Interactive Web Response System (IWRS). Before the study is initiated, the log in information and directions for the IWRS will be provided to each site.

The IWRS will assign eligible participants to a treatment regimen based on a predetermined production randomization and/or packaging schedule provided by UCB (or designee). The randomization schedule will be produced by the IWRS vendor. The IWRS will generate individual assignments for participant kits of IMP, as appropriate, according to the visit schedule. Participants' treatment assignment will be stratified by Pooled Region (North America vs Western Europe/Asia-Pacific vs Latin America/Eastern Europe), Screening disease activity (chronic active vs acute flaring) and Screening SLEDAI score (<10 vs ≥10), to ensure balanced

treatment allocation across the 12 subgroups. Each site enrollment of study participants will be limited to 5% of the total study population.

At Screening, each candidate participant will be assigned a 5-digit number that serves as the participant identifier throughout the study. The participant number will be required in all communication between the Investigator or designee and the IWRS regarding a particular participant.

Eligible participants will be randomized to treatment groups at the Baseline Visit (Day 1). The IWRS will allocate kit numbers to the participant based on the participant number during the course of the study. Participant numbers and kit numbers will be tracked via the IWRS.

Study medication will be dispensed at the study visits summarized in Schedule of Activities (Section 1.3).

To minimize bias, the same Investigator should perform the key efficacy assessments BILAG 2004 and SLEDAI-2K whenever possible and this will be documented in the database.

6.3.1 Procedures for maintaining and breaking the treatment blind

6.3.1.1 Maintenance of study treatment blind

All study participant treatment details will be allocated and maintained by the IWRS.

The following individuals will receive the randomization code at the start of the study:

- Sponsor and designated contract research organization (CRO) bioanalytical staff analyzing pharmacokinetic (PK) and ADA samples.
- Sponsor clinical trial supply staff
- IWRS provider

Study site pharmacists or other suitably qualified site personnel who are responsible for preparation of IMP treatments and any necessary assistants will have access to treatment allocations for individual study participants via the IWRS. The unblinded pharmacy monitors from the CRO, the Clinical Supply Manager, and the unblinded Clinical Project Manager (CPM) (or designee) will also have access to the treatment allocations and to the drug accountability records, if applicable.

The following individuals may have access to the randomization code as indicated:

- Sponsor Drug Safety staff as needed for reporting SAEs to regulatory authorities.
- On request, members of the IDMC (Section 9.7) who participate in unblinded (closed) sessions will be given information about the IMP allocation for those study participants for whom data are provided at these sessions.
- Sponsor and/or CRO staff supporting preparation of the initial biomarker analysis.
- Sponsor and/or CRO staff supporting preparation of the data outputs for the IDMC review.
- A Quantitative Clinical Pharmacologist/Modeling & Simulation Scientist may have access to the randomization code if PK data are requested for review by the IDMC.

Beside the exception of emergency unblinding of individual participants as described in Section 6.3.1.2, the following individuals will be unblinded to the treatment assignment. All other study personnel will remain blinded to the treatment assignment until the end of the study.

Key unblinded study personnel include:

- Study site pharmacists or other qualified site personnel who are responsible for the preparation and handling of IMP treatments
- Unblinded pharmacy monitors from the CRO
- Clinical Supply Manager
- Unblinded CPM
- Members of the IDMC who participate in unblinded sessions, and statistical team members who provide unblinded outputs (and are not involved in the study in any other way)
- A Quantitative Clinical Pharmacologist/Modeling & Simulation Scientist (separate from study team)
- Laboratory staff analyzing blood samples for [redacted] and ADA
- Sponsor pharmacovigilance staff reporting SUSARs to regulatory authorities

Should other study with DZP be performed at the same site, all efforts will be made to maintain the blinding at the site level as defined in this protocol as long as the study will be performed.

Under normal circumstances, the blinded treatment must not be revealed. It will be possible to break the blind, if medically indicated (Section 6.3.1.2). The impact on study conduct of this should be discussed in advance with the Medical Monitor or the Sponsor's Study Physician whenever possible.

6.3.1.2 Breaking the treatment blind in an emergency situation

If a situation arises in which it is medically indicated to determine the treatment (ie, knowledge of the nature and/or dose of the applied study medication determines decisions on further diagnostic procedures or treatment), it will be possible to determine to which treatment arm the study participant has been allocated during the Double-Blind Treatment Period by contacting the IWRS. All sites will be provided with details of how to contact the system for code breaking at the start of the study. Unblinding can be initiated by the Investigator at any time as medically indicated; however, whenever possible, the Medical Monitor or the Sponsor's Study Physician should be consulted prior to unblinding to discuss the impact on the study conduct.

The study team will be informed immediately via the IWRS when a code is broken, but will remain blinded to specific treatment information. Any unblinding of the IMP performed by the Investigator must be recorded in the source documents and on the Study Termination eCRF page.

6.4 Treatment compliance

The IMP will be administered by designated study site staff. The unblinded monitor will review the pharmacy records at each site, including the Drug Dispensing Record Form. The unblinded

monitor will compare the dispensing record and vials to the individual study participant's identifiers and visit schedule to assure that the study participant received the correct treatment and dose, and that the dosing schedule is correct. The unblinded monitor's report will include details of any missed doses, errors in dose, treatment errors or schedule errors, and reasons for these. All supplies and pharmacy documentation must be made available throughout the study for the unblinded monitor to review.

Study participants are expected to receive all doses of IMP as detailed in the schedule of assessments. Any study participants who deviate from the dosing schedule or miss any scheduled treatment should be reported to the Medical Monitor as soon as possible for determination of possible schedule adjustments and continued eligibility; these study participants should return to their original visit schedule. These instances will be handled on a case-by-case basis.

6.5 Concomitant medication(s)/treatment(s)

6.5.1 Permitted concomitant treatments (medications and therapies)

6.5.1.1 Corticosteroids

Corticosteroids are permitted during the study at any dose in the sense of escape medication, if medically indicated (see Section 6.6.2). At the screening visit (V1) corticosteroid dose must not exceed 40mg/day prednisone equivalent and must be stable for 2 weeks prior to Screening (approximately 4 weeks prior to Baseline Visit). Further, the dose must remain stable during Screening Period and should be kept stable onwards, if possible, or tapered. In case of a high corticosteroid dose (>20mg/day) an early start of tapering should be considered depending on the individual patient's condition. If the corticosteroid dose exceeds 7.5mg/day prednisone equivalent, it should be tapered in line with international treatment guidance as soon as possible, but must be initiated at the latest at Week 8 (V4). The timepoint and speed of tapering should be adapted to the individual study participant's condition (see below). Steroid doses should be converted to prednisone equivalent doses prior to the assessment of study participant inclusion criteria and initiation of corticosteroid tapering (regardless of route, except for intraocular, nasal, and topical). The list of corticosteroids and their corresponding prednisone equivalent doses can be found in Table 6-2.

Table 6-2: Prednisone equivalent doses of systemic corticosteroids

Corticosteroids	Prednisone equivalent dose to 1mg of the listed corticosteroid dose
Cortisone	0.2mg
Hydrocortisone	0.25mg
Deflazacort	0.75mg
Prednisolone	1mg
Prednisone	1mg
Methylprednisolone	1.25mg
Triamcinolone	1.25mg
Dexamethasone	6.7mg

Table 6-2: Prednisone equivalent doses of systemic corticosteroids

Betamethasone	8.3mg

To determine the prednisone equivalent dose of the corticosteroids shown on the left, multiply the mg dose of corticosteroid on the left by the dose amount in the corresponding right hand column. For example, a 0.8mg dose of methylprednisolone is equivalent to 1mg (0.8mg × 1.25) of prednisone.

The dose of a specified corticosteroid that is equivalent to 1mg prednisone is given in Table 6-3.

Table 6-3: Corticosteroid dose equivalent to 1mg prednisone

Corticosteroids	**Corticosteroid dose equivalent to 1mg prednisone**
Cortisone	5mg
Hydrocortisone	4mg
Deflazacort	1.3mg
Prednisolone	1mg
Prednisone	1mg
Methylprednisolone	0.8mg
Triamcinolone	0.8mg
Dexamethasone	0.15mg
Betamethasone	0.12mg

A pulse dose (>500mg x 1 to 3 days) of iv corticosteroids should not have been given within the 4 weeks before screening.

Study participants not receiving concomitant corticosteroids or who were previously receiving corticosteroids on an as-needed basis must have stopped the treatment or been assigned to a continuous corticosteroid dose at least 2 weeks prior to Screening (Visit 1).

In study participants receiving concomitant corticosteroid doses >7.5mg/day prednisone or equivalent, a mandatory corticosteroid taper must be initiated as early as possible but no later than 8 weeks after the first study medication infusion (Day 56). The tapering regimen will aim to reduce the daily prednisone equivalent dose to 7.5mg/day or lower by Week 18.

If such a rapid tapering is not considered by the Investigator to be appropriate for the individual study participant, a slower tapering regimen can be used.

Study participants achieving a dose of 7.5mg/day or lower may remain on this dose or continue to taper at the discretion of the Investigator. It is recommended to reduce the dose further in a slow manner.

Study participants whose disease is worsening after initiation of tapering and therefore cannot fulfill the taper based on the Investigator's judgment or whose corticosteroid dose has to be increased, if indicated, should remain in the study and receive corticosteroids at an appropriate

dose as determined by the Investigator. Study participants will be considered nonresponders for the primary endpoint in case of the intercurrent event escape treatment intervention with corticosteroids as outlined in Section 8.1.3.1.

Study participants will be issued a daily diary in which to record corticosteroid doses taken on a daily basis at home in between visits. Investigators are advised to contact the Medical Monitor or Sponsor's Study Physician upfront, if possible, to discuss the potential impact on the further study conduct in case use of oral or parenteral steroids for non-SLE related conditions is needed.

In case the corticosteroid dose at screening visit (V1) is not shown in the recommended tapering regimen table (Table 6-4), the tapering regimen of the next higher dose in the table should be used. Reduction of corticosteroids between Weeks 44 and 48 should be avoided.

Table 6-4: Recommended corticosteroid tapering schedule

Week	Day	Corticosteroid dose[a] (mg/day; prednisone equivalent)										
Starting Dose		**40** [a]	**35** [a]	**30** [a]	**25** [a]	**20** [a]	**15** [a]	**10** [a]	**7.5** [b]	**5** [b]	**2.5** [b]	**0**
1	Day 1 to Day 7	30	30	30	25	20	15	10	7.5	5	2.5	0
2	Day 8 to Day 14	30	20	30	25	20	15	10	7.5	5	2.5	0
3	Day 15 to Day 21	20	20	20	20	20	15	10	7.5	5	2.5	0
4	Day 22 to Day 28	20	15	20	20	20	15	10	7.5	5	2.5	0
5	Day 29 to Day 35	15	15	15	15	15	10	10/7.5 [b,c]	7.5[b]	5[b]	NA[b]	NA[b]
6	Day 36 to Day 42	15	10	15	15	15	10	10/7.5 [b,c]	7.5[b]	5[b]	NA[b]	NA[b]
7	Day 43 to Day 49	10	10	10	10	10	10[b]	10/7.5 [b,c]	7.5/5[b,c]	5[b]	NA[b]	NA[b]
8	Day 50 to Day 56	10	10	10	10	10	10[b]	10/7.5 [b,c]	7.5/5[b,c]	5[b]	NA[b]	NA[b]
9	Day 57 to Day 63	10	10/7.5[b,c]	10	10	10	10/7.5[b,c]	7.5[b]	7.5/5[b,c]	5[b]	NA[b]	NA[b]
10	Day 64 to Day 70	10/7.5[b,c]	10/7.5[b,c]	10/7.5[b,c]	10/7.5[b,c]	10/7.5[b,c]	10/7.5[b,c]	7.5[b]	7.5/5[b,c]	5[b]	NA[b]	NA[b]
11	Day 71 to Day 77	10/7.5[b,c]	10/7.5[b,c]	10/7.5[b,c]	10/7.5[b,c]	10/7.5[b,c]	10/7.5[b,c]	7.5[b]	7.5/5[b,c]	5[b]	NA[b]	NA[b]
12	Day 78 to Day 84	10/7.5[b,c]	10/7.5[b,c]	10/7.5 [b,c]	10/7.5[b,c]	10/7.5[b,c]	10/7.5[b,c]	7.5[b]	7.5/5[b,c]	5[b]	NA[b]	NA[b]

Table 6-4: Recommended corticosteroid tapering schedule

Week	Day	Corticosteroid dose[a] (mg/day; prednisone equivalent)										
13	Day 85 to Day 91	10/7.5[b,c]	7.5[b]	10/7.5 [b,c]	10/7.5[b,c]	10/7.5[b,c]	7.5[b]	7.5/5[b,c]	5[b]	5[b]	NA[b]	NA[b]
14	Day 92 to Day 98	7.5[b]	7.5[b]	7.5[b]	7.5[b]	7.5[b]	7.5[b]	7.5/5[b,c]	5[b]	5[b]	NA[b]	NA[b]
15	Day 99 to Day 105	7.5[b]	7.5[b]	7.5[b]	7.5[b]	7.5[b]	7.5[b]	7.5/5[b,c]	5[b]	5[b]	NA[b]	NA[b]
16	Day 106 to Day 112	7.5[b]	7.5[b]	7.5[b]	7.5[b]	7.5[b]	7.5[b]	7.5/5[b,c]	5[b]	5[b]	NA[b]	NA[b]
17	Day 113 to Day 119	7.5[b]	7.5/5[b,c]	7.5[b]	7.5[b]	7.5[b]	7.5/5[b,c]	7.5/5[b,c]	5[b]	5[b]	NA[b]	NA[b]
18	Day 120 to Day 126	7.5/5[b,c]	7.5/5[b,c]	7.5/5[b,c]	7.5/5[b,c]	7.5/5[b,c]	7.5/5[b,c]	7.5/5[b,c]	5[b]	5[b]	NA[b]	NA[b]
19	Day 127 to Day 133	7.5/5[b,c]	7.5/5[b,c]	7.5/5[b,c]	7.5/5[b,c]	7.5/5[b,c]	7.5/5[b,c]	5[b]	5[b]	5[b]	NA[b]	NA[b]
20	Day 134 to Day 140	7.5/5[b,c]	7.5/5[b,c]	7.5/5[b,c]	7.5/5[b,c]	7.5/5[b,c]	7.5/5[b,c]	5[b]	5[b]	5[b]	NA[b]	NA[b]
21	Day 141 to Day 147	7.5/5[b,c]	5[b]	7.5/5[b,c]	7.5/5[b,c]	7.5/5[b,c]	5[b]	5[b]	5[b]	5[b]	NA[b]	NA[b]
22	Day 148 to Day 154	5[b]	5[b]	5[b]	5[b]	5[b]	5[b]	5[b]	5[b]	5[b]	NA[b]	NA[b]

Table 6-4: Recommended corticosteroid tapering schedule

Week	Day	Corticosteroid dose[a] (mg/day; prednisone equivalent)										
23	Day 155 to Day 161	5[b]	5[b]	5[b]	5[b]	5[b]	5[b]	5[b]	5[b]	5[b]	NA[b]	NA[b]
24	Day 162 to Day 168	5[b]	5[b]	5[b]	5[b]	5[b]	5[b]	5[b]	5[b]	5[b]	NA[b]	NA[b]

NA=not applicable

[a] Corticosteroid tapering is only required in those study participants receiving continuous corticosteroids at doses >7.5/day prednisone equivalent at the time of enrollment into the study.

[b] Study participants starting at or achieving a dose of 7.5mg/day or lower may remain on this dose or taper at the discretion of the Investigator. This is indicated by cells with light grey font.

[c] Alternating dosing every other day recommended to allow slow reduction based on standard tablet sizes

6.5.1.2 Antimalarials

Antimalarials (eg, hydroxychloroquine, chloroquine, and quinacrine) are permitted during the study (see inclusion criteria and maximum dose restrictions in Table 6-5).

Treatment with antimalarials must have been started or stopped at least 12 weeks prior to screening visit (V1). In study participants receiving concomitant antimalarials used for the treatment of SLE, doses must have been stable for at least 8 weeks prior to screening visit (V1) and should be kept stable through the study. Increases in doses of antimalarials are not permitted during the study, unless absolutely clinically indicated (dose reductions are allowed, if medically indicated [eg, due to toxicity], per the Investigator's discretion). Investigators are advised to contact the Medical Monitor or Sponsor's Study Physician, upfront if possible, to discuss the potential impact on the further study conduct in case a dose change is needed.

Table 6-5: Maximum doses of permitted concomitant antimalarials

Antimalarial (generic name)	Maximum dose allowed
Hydroxychloroquine	400mg/day
Chloroquine	500mg/day
Quinacrine	200mg/day
Quinine	Any dose allowed

Antimalarial blood levels will be measured at Screening and at selected visits during the study to serve as source for drug intake adherence in order to verify the documented dose of antimalarials.

If blood levels are inconsistent with the dose taken as reported by the participant this must be discussed with the participant and documentation of concomitant antimalarials must be adapted accordingly. In this case eligibility of the study participant must be reevaluated with respect to if the study participant indeed took a stable antimalarial dose as described in inclusion criterion 2.e3. If the dose is not considered as stable in the past 8 weeks prior to screening the study participant is not eligible at this time point.

In case a participant reports based on the conversation about antimalarial blood levels to have stopped or reduced intake of antimalarials due to intolerance more than 12 weeks before Screening, the actual intake needs to be documented appropriately. Based on the adequately documented concomitant medications it must be evaluated if the participant fulfills the inclusion criterion 2.e3. and no exclusion criterion before randomization. In case the participant is eligible they should be clearly instructed not to restart or increase antimalarial intake in this case. Investigators are advised to contact the Medical Monitor or Sponsor's Study Physician upfront, if possible, to discuss the potential impact on the further study conduct in case a dose change is needed.

In case blood levels suggest a change in intake during the study, which was not reported by the participant, this should be discussed with the participant and the true intake should be documented on the concomitant medication page.

6.5.1.3 Other immunosuppressants/immunomodulatory agents

Other immunosuppressant or immunomodulatory agents are permitted during the study (see inclusion criteria and maximum dose restrictions in Table 6-6).

In study participants receiving concomitant immunosuppressants for the treatment of SLE, doses must have been stable for at least 12 weeks prior to the screening visit (V1) and should be kept stable through the study. If immunosuppressants permitted during the study were stopped before study entry, they must have been stopped no later than 8 weeks prior to the Screening Visit. Increases in doses of immunosuppressant or immunomodulatory agents are not permitted during the study, unless absolutely clinically indicated, per the Investigator's discretion but should not occur between Week 44 and Week 48. A temporary hold or dose reduction is allowed if medically indicated (eg, due to vaccination [ACR 2021] or due to toxicity), per the Investigator's discretion. Investigators are advised to contact the Medical Monitor or Sponsor's Study Physician, upfront, if possible, to discuss the potential impact on the further study conduct in case a dose change is needed.

Table 6-6: Maximum doses of permitted concomitant immunosuppressants

Immunosuppressant (generic name)	Maximum dose allowed
Azathioprine	300mg/day oral
Mycophenolate mofetil (including mycophenolate mofetil hydrochloride)	3000mg/day oral
Coated mycophenolate sodium	2200mg/day
Leflunomide	40mg/day oral
Methotrexate	25mg/week any route
Cyclosporine	4mg/kg/day
Voclosporin	47.4mg/day
Tacrolimus	3mg/day

Caution should be exercised in the co-administration of calcineurin inhibitors (cyclosporine and voclosporin) and the study drug. Local guidance(s) should be followed regarding monitoring of plasma levels when calcineurin inhibitors are administered. Additionally, when calcineurin inhibitors are administered concomitantly with DZP, special benefit-risk considerations and enhanced monitoring for infections are advised since the potential for synergistic immunomodulatory effects on T-cells (affecting both efficacy and safety) cannot be excluded. Please refer to Section 7.1.3 regarding recommended temporary discontinuation of study drug in case of infection.

It cannot be excluded that mycophenolate mofetil (MMF) could reduce effectiveness of combined hormonal contraceptives including levonorgestrel. Investigators are advised to regularly counsel patients who are of childbearing potential on the risk of MMF treatment for adverse pregnancy outcomes and the possibility of reduced effectiveness of hormonal contraceptives due to interaction with MMF. Please refer to Section 10.4 for further information.

6.5.1.4 Analgesics, medications including natural or synthetic cannabinoids (approved in line with local regulations), NSAIDs, HMG-CoA reductase inhibitors (statins), ACE inhibitors, and other anti-hypertensive drugs.

Study participants should stay on stable doses of the following other concomitant medications for the treatment of SLE during the study including the Screening Period, unless changes in these treatments are clinically indicated: analgesics, NSAIDs, medications including natural or synthetic cannabinoids (approved in line with local regulations), HMG-CoA reductase inhibitors (statins), ACE inhibitors, and other anti-hypertensive drugs.

6.6 Dose modification

Not applicable for the IMP.

6.6.1 Prohibited concomitant treatments (medications and therapies)

The following concomitant medications will be prohibited at screening visit (V1) and as concomitant medication to the IMP during the study (Table 6-7) with the exception of immunoglobulins which are allowed to be used concomitantly with DZP after randomization if medically indicated. In case one of these medications has to be initiated during the study the IMP needs to be permanently discontinued (with the exception of immunoglobulins).

The impact of initiation of prohibited medications on the study conduct should be discussed upfront, if possible, with the Medical Monitor and/or Sponsor's Study Physician.

Table 6-7: Prohibited medications and required wash-out periods prior to Screening (Visit 1)

Generic (trade) names	Wash-out period prior to Screening[a]	Generic (trade) names	Wash-out period prior to Screening
Biologics (mAbs and Fusion Proteins)		**Immunosuppressants**	
Abatacept (CTLA4-Ig) (Orencia®)		High-dose cyclophosphamide (Cytoxan®)	
Belimumab (Benlysta™) (iv and sc)		Pimecrolimus (Elidel®)	
Blisibimod		Sirolimus (Rapamune®)	
Eculizumab (Soliris®)		---	
ETI–201 (Elusys Heteropolymer Product)		**Others**	
Rituximab (Rituxan®), Ofatumumab (Arzerra®), Obinutuzimab (Gazyva®), Ocrelizumab, Veltuzumab		Intravenous immunoglobulin	
		Rigerimod (Lupuzor™)	
		Minocycline	
Natalizumab (Tysabri®)		Thalidomide or lenalidomide (Thalomid®, Revlimid®)	
Vedolizumab (Entyvio®)			
Tabalumab		JAK inhibitors (eg, Baricitinib)	
TACI-Ig (atacicept)		TYK 2 Inhibitors (eg, BMS-986165)	
Tocilizumab (Actemra®, MRA)			
BIIB059 (anti-BDCA2)		IFN kinoid	
Anifrolumab			
Sifalimumab (MEDI 545)			
Ustekinumab (Stelara)			

Table 6-7: Prohibited medications and required wash-out periods prior to Screening (Visit 1)

Generic (trade) names	Wash-out period prior to Screening[a]	Generic (trade) names	Wash-out period prior to Screening
Any other investigational drug or off-label drug used to treat SLE, cutaneous Lupus or [redacted] but not mentioned in this table	**Contact Medical Monitor before using**		

[a] The wash-out period refers to the last administration of the relevant medication.
BDACA2=blood dendritic cell antigen 2; IFN=interferon; JAK=Janus kinase; mAbs=monoclonal antibodies; MRA=myeloma receptor antibody; SLE=systemic lupus erythematosus; TYK 2=tyrosine kinase 2
Note: Topical formulations (eg, eye drops) are permitted without wash-out, unless otherwise indicated.

Vaccines

Administration of live vaccines should not occur during the conduct of the study. If a study participant receives a live vaccine, temporary or permanent discontinuation of study medication may be needed. In case of considered application of live vaccines the Medical Monitor and/or Sponsor's Study Physician should be contacted to discuss the impact on further study conduct.

Administration of non-live vaccines is allowed during the study at the discretion of the Investigator and should be documented. Local and international guidance on vaccination in immunocompromised patients (Furer et al, 2020; Van Assen et al, 2011; Murdaca et al 2016; Mason et al, 2021, ACR 2021, Geisen et al, 2021) should be considered.

According to local and international guidance approved SARS-CoV-2 vaccines are endorsed to be used in patients receiving immunosuppressant treatment (ACR 2021; EULAR 2021).

It cannot be excluded that the effectiveness of some vaccines may be compromised by DZP or any other concomitant immunosuppressant drug as part of standard of care. Therefore, blood samples will be collected to be able to determine the effect of DZP on the immune response to vaccines, eg, [redacted] as indicated.

The potential benefits and risks and vaccine administration options should be discussed with the study participant.

In case of administration of investigational Coronavirus Disease 2019 (COVID-19) vaccine (vaccines without regulatory authorization or emergency authorization) study medication should not be administered within 2 weeks after vaccination.

6.6.2 Escape medication

Although the use of escape medications is allowed at any time of the study, it should be delayed, if possible, for at least 8 weeks following the first administration of study treatment. Data from Phase 1 and Phase 2 studies suggest that DZP has a fast onset of action however it can take several weeks until the potential therapeutic effect of DZP fully develops. Escape treatment should be initiated as clinically indicated by the Investigator or other qualified physicians

treating the participant. Investigators should discuss the impact of escape treatment use on study conduct with the Medical Monitor before initiation.

Initiation of escape treatment may be handled as intercurrent event in estimands, which will be detailed in the statistical analysis plan (SAP) as described in Section 9.3.1. For the primary endpoint, specification of how escape treatment will be handled as an intercurrent event is detailed in Section 8.1.3.1, Section 9.3.1, and Section 9.6.

The date and time of escape medication administration as well as the name and dosage regimen of the escape medication must be recorded.

In case of use of escape treatment the study medication does not have to be automatically discontinued, however if the escape treatment in combination with DZP represents a safety concern (see Section 6.6) for the study participant the study medication should be discontinued but the study participant should remain in the study under observation. Investigators are advised to contact the Medical Monitor upfront if possible, to discuss the potential impact on the further study conduct in case study medications should be permanently discontinued.

The following escape medications may be used as indicated:

- Corticosteroids (new initiation or increase in dose)
- Immunosuppressants (new initiation or increase in dose):
  - azathioprine
  - methotrexate
  - mycophenolate mofetil
  - tacrolimus
  - low dose cyclophosphamide
  - cyclosporine
  - voclosporin

6.7 Criteria for study hold or dosing stoppage

UCB will hold further dosing if the following criteria are met during the course of the study and following case review to confirm causality and seriousness and/or severity of reported events:

- If regulators request a study hold.

If the IDMC recommends a study hold, UCB will consider the study hold as outlined in the IDMC charter.

6.8 Treatment after the end of the study

Study participants who complete the 48-week Treatment Period may be eligible to participate in an OLE study.

7 DISCONTINUATION OF STUDY MEDICATION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

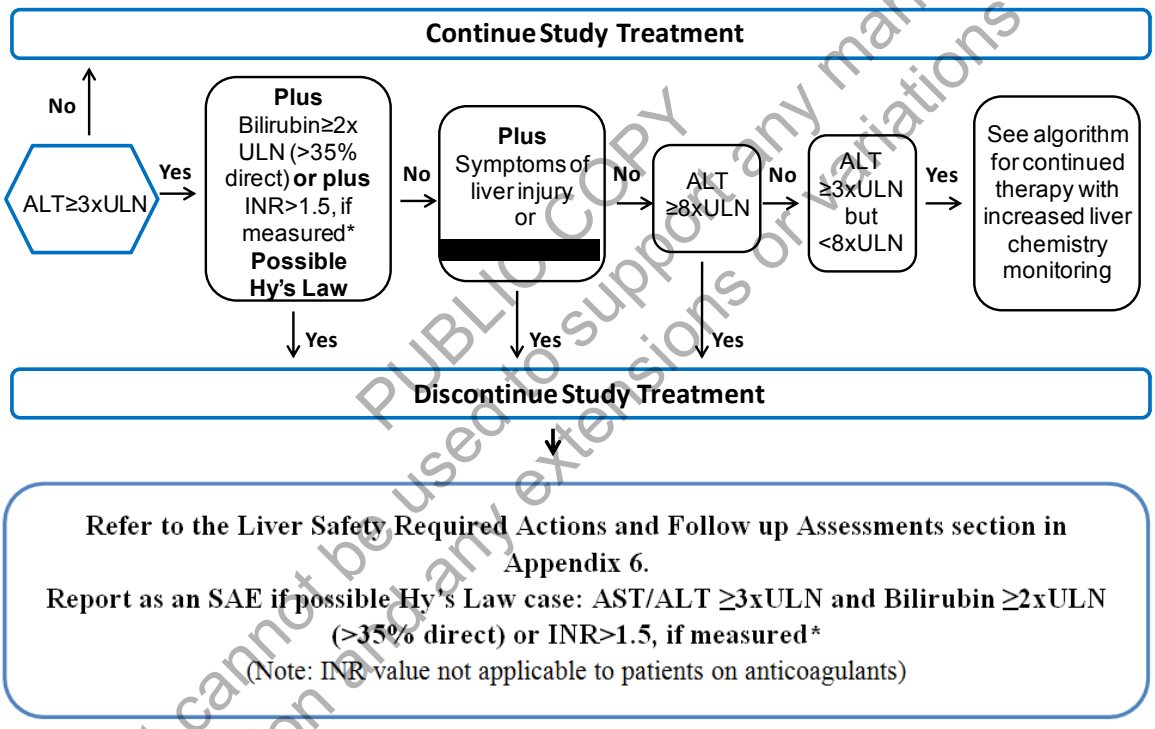
7.1 Discontinuation of study medication

Study participants who discontinue study medication will be encouraged to stay in the study under observation. They should continue to be followed for all regularly scheduled visits for safety and efficacy assessments.

7.1.1 Liver chemistry stopping criteria

Discontinuation of study treatment for abnormal liver function should be considered by the Investigator when a participant meets one of the conditions outlined in Figure 7-1 or if the Investigator believes that it is in best interest of the participant.

Figure 7-1: Phase 3-4 Liver Chemistry Stopping Criteria and Increased Monitoring Algorithm



Abbreviations: ALT=alanine aminotransferase; AST=aspartate aminotransferase; INR=international normalized ratio; SAE=serious adverse event; ULN=upper limit of normal.

Specific assessments and follow up actions for potential drug-induced liver injury are provided in Section 10.6.

7.1.2 QTc stopping criteria

If a clinically significant finding is identified (including, but not limited to changes from Baseline in QT interval corrected using Fridericia's formula [QTcF]) after enrollment, the Investigator or qualified designee will determine if the participant can continue in the study and if any change in participant management is needed. This review of the electrocardiogram (ECG)

printed at the time of collection must be documented. Any new clinically relevant finding should be reported as an AE.

A participant who develops an ECG finding which meets the bulleted criterion based on the ECG readings after first study drug application will be withdrawn from study medication.

- QTcF >500 msec OR Uncorrected QT >600 msec

For participants with underlying bundle branch block, follow the discontinuation criteria listed below:

Baseline QTcF with Bundle Branch Block	Discontinuation QTcF Threshold with Bundle Branch Block
< 450 msec	> 500 msec
450 to 480 msec	≥ 530 msec

See the Schedule of Activities (Section 1.3) for data to be collected at the time of treatment discontinuation and follow-up and for any further evaluations that need to be completed.

7.1.3 Permanent and temporary study drug discontinuation due to other reasons

Study participants must be permanently discontinued from study medication (but not necessarily from the study) if any of the following occurs:

1. Study participant experiences a thromboembolic event.
2. Study participant requires an induction therapy with cyclophosphamide for management of acute flare of [redacted] or other severe manifestation of SLE, in the opinion of the Investigator.
3. Study participant requires an induction of therapy with an approved biological immune response modifier or an investigational drug (see Section 6.6).
4. Potential drug-induced liver injury (pDILI) and related to study medication in the opinion of the Investigator, regulators, or the Sponsor. Discontinuation of study treatment for abnormal liver function should be considered by the Investigator when a participant meets one of the conditions outlined in Figure 7-1 or if the Investigator believes that it is in best interest of the participant.
5. Study participant has an anaphylactic reaction related to study medication (fulfilling Sampson criteria as described in Section 10.14).
6. Study participant develops an active TB or NTM (see Section 8.2.6.3).

Study participants may be temporarily discontinued from study medication (but not necessarily from the study) if any of the following occurs, but may be restarted. Consultation with the Medical Monitor is advised before restart:

1. Study medication will be stopped if the study participant develops a medical condition (or laboratory abnormality or ECG change) that, in the opinion of the Investigator, compromises the study participant's ability to proceed with study medication or compromises the study

participant's safety. This includes clinically significant infections such as SARs-Cov-2 (see Section 8.2.7) and tuberculosis (Section 8.2.6.3). Caution should be taken to exclude a clinically significant infection in case of symptoms (see Section 8.3). Study participants must be closely followed up. In case of resolution of the event leading to interruption, study medication can be restarted after consultation with the Medical Monitor unless the event fulfils the criteria for permanent study drug discontinuation. In case of upcoming surgery, the time between the last infusion of study medication administered to the participant and the surgery should be at least 4 weeks (if possible 6 weeks). After surgery, study medication can be restarted once the proliferative phase of wound healing is completed.

2. If there is a positive pregnancy test, study medication will be held. If there is confirmed pregnancy, study medication must be discontinued until end of the pregnancy. In case the participant intends to breastfeed after a pregnancy, study medication must be further discontinued until end of breastfeeding (including pumping breast milk to feed to a child).
3. In case a study participant answers Question 9 of the PHQ-9 with [redacted] and active suicidal ideation is confirmed as indicated by a positive response ("Yes") to Question 4 or 5 of the C-SSRS study medication application must be discontinued and study participant must be referred immediately to a mental health care professional for further clarification. Permanent study medication discontinuation should be considered based upon the Investigator's judgment of benefit/risk. Consultation with the Medical Monitor and/or the Sponsor Study Physician is advised upfront to restart.

In addition, a participant may discontinue study medication administration at any time at the discretion of the Investigator for safety, behavioral, compliance, or administrative reasons. However, the participant should be encouraged to stay in the study under observation, continuing to be followed for all regularly scheduled safety and efficacy assessments.

Investigators are advised to contact the Medical Monitor, whenever possible in advance, to discuss the potential impact on the further study conduct in case of study drug discontinuation.

7.2 Participant discontinuation/withdrawal from the study

Participants are free to withdraw at her/his own request from the study at any time, without prejudice to their continued care.

If the participant withdraws consent for disclosure of future information, the Sponsor may retain and continue to use any data collected before such a withdrawal of consent.

If a participant withdraws from the study, he/she may request destruction of any samples taken and not tested, and the Investigator must document this in the site study records.

See the Schedule of Activities (Section 1.3) for data to be collected at the time of study discontinuation and follow-up and for any further evaluations that need to be completed.

Participants should be withdrawn from the study if any of the following events occur:

1. Participant withdraws his/her consent.
2. The IDMC, the responsible IRB/IEC, or a regulatory agency requests withdrawal of the participant for safety, behavioral, compliance, or administrative reasons.

Investigators should contact the Medical Monitor, whenever possible, to discuss the withdrawal of a participant in advance.

7.3 Lost to follow up

A participant will be considered lost to follow-up if she/he repeatedly fails to return for scheduled visits and is unable to be contacted by the study site.

The following actions must be taken if a participant fails to return to the clinic for a required study visit:

- The site must attempt to contact the participant and reschedule the missed visit as soon as possible and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain whether or not the participant wishes to and/or should continue in the study.
- Before a participant is deemed lost to follow up, the Investigator or designee must make every effort to regain contact with the participant (at least 1 phone call and 1 written message to the participant), and document his/her effort (date and summary of the phone call and copy of the written message in the source documents), to complete the final evaluation. All results of these evaluations and observations, together with a narrative description of the reason(s) for removing the participant, must be recorded in the source documents. The eCRF must document the primary reason for withdrawal.

Should the participant continue to be unreachable, he/she will be considered to have withdrawn from the study with a primary reason of lost to follow-up documented in the eCRF.

8 STUDY ASSESSMENTS AND PROCEDURES

Study procedures and their timing are summarized in the Schedule of Activities (Table 1-2).

Protocol waivers or exemptions are not allowed.

Immediate safety concerns should be discussed with the Medical Monitor or the Sponsor Study Physician immediately upon occurrence or awareness to determine if the participant should continue or discontinue study treatment.

Adherence to the study design requirements, including those specified in the Schedule of Activities, is essential and required for study conduct.

All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The Investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.

Procedures conducted as part of the participant's routine clinical management (eg, blood count) and obtained before signing of the ICF may be utilized for screening or baseline purposes provided the procedures met the protocol-specified criteria and were performed within the time frame defined in the Schedule of Activities.

The amount of blood collected from each participant over the duration of the study will be approximately 900mL. Additional extra assessments that may be required for re-screening, technical issues with the collected samples or safety evaluations may result in additional blood volume to be collected.

8.1 Efficacy assessments

8.1.1 Clinical assessments of disease activity

8.1.1.1 BILAG 2004

The BILAG 2004 will be used as a clinical assessment of SLE disease activity (Tsokos et al, 2007).

The Investigators will perform an anamnesis and physical examination at every visit and will record present symptoms corresponding to the BILAG 2004 components in the electronic clinical outcomes assessment (eCOA). Clinical features attributable to SLE are to be recorded and based on the study participant's condition in the last 4 weeks compared with the previous 4 weeks. For vital signs and laboratory parameters, Investigators must indicate whether or not values are outside the normal range and, if outside the normal range, whether or not they are due to SLE.

Nine body/organ-based systems will be assessed if SLE symptoms are present:

- Constitutional (fatigue, fever, anorexia, weight loss, etc)
- Mucocutaneous (rash, alopecia, mucosal ulcers, etc)
- Neuropsychiatric (headache, seizure, psychosis, etc)
- Musculoskeletal [redacted] etc)
- Cardiorespiratory (coronary vasculitis, cardiac failure, effusion, etc)
- Gastrointestinal (lupus enteritis, hepatitis, peritonitis, etc)
- Ophthalmic (keratitis, scleritis, optic neuritis, etc)
- Renal (proteinuria, urine microscopy for red blood cells, casts, etc)
- Hematology (cytopenias, coagulopathy, etc)

The Investigator must maintain/provide independent supporting source documents (eg, chart, worksheet, clinic notes, labs, and photodocumentation of cutaneous SLE manifestations) capable of withstanding audit:

- For each SLE symptom present at the visit or present within the past 4 weeks before the visit
- Indicating if symptom had a new onset, was improving, same, or worse in the past 4 weeks as compared to the prior 4 weeks
- Sufficient descriptive detail to support changes (improved, worsening); eg, number/location of arthritic joints, size/location of rashes, etc
- Information indicating that other symptoms relevant for BILAG were not present at the time point of the visit and within the 4 weeks prior to the visit

The Sponsor will provide centralized grading (A, B, C, D, and E) based on BILAG 2004 eCOA pages completed by the Investigator, eCRF pages completed by Investigators, laboratory parameters, and may be subject to adjudication. Prior to Visit 2, the site must have received

confirmation from the central efficacy reader for BILAG 2004 data that the study participant has met BILAG 2004 eligibility for randomization.

The BILAG 2004 grading is anchored in the physician's intention to treat. Disease activity is graded separately for 9 body systems to 5 different grades (A to E) as follows:

A ("Active")	=	Severely active disease (sufficient to require systemic immunosuppressant or anticoagulant therapy; eg, >20mg/day prednisone, immunosuppressants, or cytotoxics)
B ("Beware")	=	Moderately active disease (requires low dose or local immunosuppressant therapy or symptomatic therapy; eg, prednisone ≤20mg/day prednisone, or antimalarials)
C ("Contentment")	=	Mild stable disease (no indication for changes in treatment)
D ("Discount")	=	Inactive now but previously active
E ("Excluded")	=	Never affected

An SLE Assessment Reference Guide will be provided to all study personnel, which contains detailed protocol-specific clarifications and extensions of BILAG 2004 clinical parameter definitions and guidance for correlating SLEDAI-2K and BILAG 2004 clinical parameters. Important extensions of selected BILAG 2004 glossary definitions are included as follows:

[redacted]

[redacted]

A shift from BILAG 2004 Grade A or B to a lower grade indicates a clinically relevant change in disease activity as the BILAG 2004 grades mirror the decision points for treatment interventions.

Investigators must complete full certified training on BILAG 2004 assessments ≤2 years before conducting their initial BILAG 2004 assessment in this study. Investigators who perform BILAG 2004 assessments on an ongoing basis (either in this study or another DZP study) are not required to repeat this training unless ≥2 years have elapsed since they last conducted a BILAG 2004 assessment. Preferably, the same Investigator should evaluate the study participant at each BILAG 2004 assessment from Screening to study completion. The assessor will be documented in the eCOA and dataset.

8.1.1.2 SLEDAI-2K

The SLEDAI-2K (30 days) measures disease activity. Disease activity in the 30 days prior to and at the time point of the assessment shall be considered. It is a global index and includes 24 clinical symptoms and laboratory variables that are weighted by the type of manifestation, but not by severity or dynamic of the individual item. The SLEDAI-2K includes scoring for antibodies [redacted] positive or negative) and low complement, as well as some renal and hematologic parameters. The total score falls between 0 and 105, with higher scores representing increased disease activity. The SLEDAI-2K has been shown to be a valid and reliable disease activity measure in multiple study participant groups (Gladman et al, 2002).

To confirm study participant eligibility at Baseline (Visit 2), the SLEDAI-2K score without any laboratory values is calculated based on all the clinical variables only, without factoring in the laboratory variables. At Screening (Visit 1), the SLEDAI-2K will include laboratory parameters.

8.1.1.3 S2K RI-50

The S2K RI-50 is comprised of the same 24 descriptors covering 9 organ systems as the SLEDAI-2K and describes the improvement in disease activity of at least 50% compared with the previous assessment; the S2K RI-50 reflects disease activity over the 30 days prior to the assessment (Touma et al, 2011).

The S2K RI-50 score corresponds to the sum of each of the 24 descriptor scores on the S2K RI-50 data retrieval form. The method of scoring is simple, cumulative, and intuitive and similar to the SLEDAI-2K. One of 3 situations could have resulted when a descriptor was present at the previous assessment:

1. The descriptor has achieved complete remission, in which case the score would be “0”;
2. The descriptor has not achieved a minimum of 50% improvement, in which case the score would be identical to its corresponding SLEDAI-2K value; or
3. The descriptor has improved by ≥50% (according to the S2K RI-50 definition) but has not achieved complete remission, in which case the score was evaluated as one-half the score that would be assigned for SLEDAI-2K.

If a descriptor was not present at the previous assessment, the value for the S2K RI-50 was the same as that for SLEDAI-2K. This process was repeated for each of the 24 descriptors.

8.1.1.4 Physician's Global Assessment

The Investigator will rate the overall status of the study participant in response to the following statement:

> "Please mark a vertical line on the scale below to assess the overall status of the study participant's Systemic Lupus Erythematosus signs and symptoms and the functional capacity of the study participant. The very far left end is 'very good, asymptomatic and no limitation of normal activities'; the very far right end indicates 'severe disease'. This refers to the most severe possible disease, and does not reflect the most severe ever seen in a particular patient, but the most severe disease ever seen in all SLE patients."

When scoring the Physician's Global Assessment (PGA), the assessor should always look back at the score from the previous visit.

8.1.1.5 SELENA Flare Index (2009 revision)

The SELENA (Safety of Estrogens in Lupus National Assessment) Flare Index in its 2009 revision evaluates increases in SLE disease activity within eight organ systems: mucocutaneous, musculoskeletal, cardiopulmonary, hematological, constitutional, renal, neurological, and gastrointestinal. The Investigator assesses different clinical manifestations within each organ system, treatment recommendations and the need for hospitalization. The observed manifestations map into a flare categorization as no flare, mild flare, moderate flare, or severe flare. In case the assessment of a clinical manifestation and the recommendation for a treatment change are discrepant the treatment choice takes precedence in the direction of a higher flare definition. Treatment changes recommended because of intolerance, toxicity or safety do not count towards a flare definition.

8.1.1.6 Cutaneous Lupus Erythematosus Disease Area and Severity Index

The Cutaneous Lupus Erythematosus Disease Area and Severity Index (CLASI) consists of 2 scores; the first summarizes the activity of the disease and the second is a measure of the damage done by the disease (Table 8–1) (Albrecht et al, 2005). Activity is scored on the basis of erythema, scale/hypertrophy of skin and mucous membranes, acute hair loss, and nonscarring alopecia. Damage is scored in terms of dyspigmentation and scarring, including scarring alopecia. Study participants are asked whether dyspigmentation due to cutaneous lupus erythematosus lesions usually remains visible for more than 12 months, which is taken to be permanent. Symptoms representing damage can not disappear. If so, the dyspigmentation score is doubled. The scores are calculated by simple addition based on the extent of the symptoms. The extent of involvement for each of the skin symptoms is documented according to specific anatomic areas that are scored according to the worst affected lesion within that area for each symptom.

Table 8–1: Cutaneous Lupus Erythematosus Disease Area and Severity Index activity and damage scoring

Activity		Damage	
Erythema	0=absent 1=pink; faint erythema 2=red 3=dark red; purple/ violaceous/ crusted/ hemorrhagic	**Dyspigmentation**	0=absent 1=dyspigmentation
Scale/ Hypertrophy	0=absent 1=scale 2=verrucous/hypertrophic	**Scarring/Atrophy/ Panniculitis**	0=absent 1=scarring 2=severely atrophic scarring or panniculitis
Mucous Membrane Involvement	0=absent 1=lesion or ulceration	**Duration of Dyspigmentation** (after active lesions have resolved)	0=dyspigmentation usually lasts <12 months 1=dyspigmentation usually lasts ≥12 months
Alopecia [a]		**Alopecia** [a]	
Recent Hair Loss (within the last 30 days)	0=no 1=yes	Scarring of the Scalp (judged clinically)	0=absent 3=in 1 quadrant 4=2 quadrants 5=3 quadrants 6=affects the whole skull
Alopecia (clinically not obviously scarred)	0=absent 1=diffuse; noninflammatory 2=focal or patchy in 1 quadrant 3=focal or patchy in >1 quadrant		

CLASI=Cutaneous Lupus Erythematosus Disease Area and Severity Index
[a] If scarring and nonscarring aspects seem to coexist in 1 lesion, both should be scored.

8.1.1.7 Tender and Swollen Joint Counts

The joint assessment will be carried out on 28 joints, including the shoulders, elbows, wrists (radiocarpal, carpal, and carpometacarpal bones were considered as a single unit), metacarpophalangeal (MCP) joints (MCP 1, 2, 3, 4, and 5), thumb interphalangeal joint, proximal interphalangeal (PIP) joints (PIP 2, 3, 4, and 5), and the knees and must be performed by the Investigator, a Subinvestigator or a qualified joint assessor.

Artificial and ankylosed joints will be excluded from tenderness and swelling assessments.

Study participants taking maintenance NSAIDs/analgesics, medications including natural or synthetic cannabinoids (approved inline with local regulations), or approved narcotics should not take a dose of these medications within 12 hours prior to the tender joint count/swollen joint count (TJC/SJC) assessment visits in order to allow a true assessment of the joint tenderness and swelling to be conducted.

Tenderness and swelling will be graded on a 2-point scale as described in Table 8–2.

Table 8–2: Joint tenderness and swelling grades

Grade	Swelling Response	Tenderness Response (28)
0	Not swollen	Not tender
1	Detectable synovial thickening with or without loss of bony contours, or bulging synovial proliferation with or without cystic characteristics	Positive response to questioning (tender), spontaneous response elicited (tender and winced), or withdrawal by study participant on examination (tender, winced, and withdrew)

Every effort should be made to ensure each study participant is evaluated by the same Investigator (or qualified assessor) during all study visits.

The total TJC and SJC are the sum of all individual respective tenderness and swelling grades. If there are missing observations in the TJC or SJC, then the remaining observations are assessed and weighted by dividing by the number of nonmissing values and multiplying by 28. If a joint is not evaluable at Baseline, then that joint is set to missing throughout the study. If more than 50% of the tenderness or swelling grades are missing, then no imputation is done and the total TJC or SJC are set to missing. The total scores are used to assess the percentage change from Baseline.

8.1.1.8 Lupus Arthritis and Musculoskeletal Disease Activity score

Three different VAS scales will be used to assess musculoskeletal disease activity. The participant will be asked to rate their musculoskeletal pain on a first VAS scale, and their early morning stiffness on a second VAS scale, and the physician will be asked to rate the overall musculoskeletal disease activity on a third VAS scale.

8.1.1.9 SLICC/ACR Damage Index

The Systemic Lupus International Collaborating Clinics (SLICC)/ACR Damage Index (version 1996) for SLE measures irreversible, accumulated organ damage from either the disease process or disease treatment, which has been present for at least 6 months, in 12 organ systems. It is an important predictor of long-term mortality and is an independent outcome measure separate from the BILAG 2004 and SLEDAI-2K. Only nonreversible change that has occurred since the onset of SLE is to be included, rather than change related to active inflammation. Consequently, a damage/feature once documented cannot disappear. Otherwise, the original grading must be reassessed.

Definition of damage:

- Nonreversible change
- Occurring since onset of lupus
- Not related to active inflammation
- Present for at least 6 months
- Ascertained by clinical assessment/x-rays

The Investigator (or qualified designee) will perform the SLICC/ACR Damage Index assessment for the 12 different organ systems (Table 8–3), and check "Yes" if the criterion is present (and

tick the appropriate box if there is more than 1 choice); or check "No," or "Unknown," as appropriate.

Table 8–3: SLICC/ACR Damage Index organ system scoring

ACR=American College of Rheumatology; SLICC=Systemic Lupus International Collaborating Clinics

8.1.2 Patient-reported outcomes

Study participants will complete 9 patient-reported outcomes (PROs) as per time points mentioned in the schedule of study assessments in Section 1.3.

Study personnel other than the treating physician should administer the PROs. The PROs should be completed by the study participants themselves in a quiet place.

The PROs should be completed in the following order: FATIGUE-PRO, Functional Assessment of Chronic Illness Therapy (FACIT-F), PGI-S Fatigue, PGI-C Fatigue, PGI-S, PGI-C, Lupus quality of life (QoL), Euro Quality of life 5-Dimensions 5-Level (EQ-5D-5L), and PHQ-9.

The PROs should only be checked for completeness. If a PRO is incomplete, the study personnel may check with the participant that any missing data is involuntary. On dosing days, the PROs will be completed prior to dosing.

8.1.2.1 FATIGUE-PRO

The FATIGUE-SLE (Short Form) was renamed recently to FATIGUE-PRO. It consists of 31 items across 3 scales: Physical Fatigue (items 1-9), Mental Fatigue (items 10-20), and Fatigability (items 21-31). The study participant is asked to score each fatigue item based on how frequently they experienced the item during the past 7◦days using the following response options: 1=none of the time; 2=a little of the time; 3=some of the time; 4=most of the time; 5=all of the time. For each scale, a score ranging from 0 to 100 is calculated, with 100 indicating a higher level of fatigue.

8.1.2.2 FACIT-F

Functional Assessment of Chronic Illness Therapy-Fatigue Scale is a 13-item, self-reported tool that measures an individual's level of fatigue during their usual daily activities over the past week (Cella, 2002). The level of fatigue is measured on a four-point Likert scale (4=not at all fatigued to 0 = very much fatigued). Clinically important difference (CID) estimates of 3.0 points were determined using anchor-based and distribution-based methods in three patient samples (affected by cancer).

8.1.2.3 PGI

Patient Global Impression of Severity (PGI-S) is a single-state, self-report measure that rates a participant's severity of their symptoms over the past week. The PGI-S is a 5-point scale ("none", "mild", "moderate", "severe", "very severe").

Patient Global Impression of Fatigue Severity (PGI-S Fatigue) is a single-state, self-report measure that rates a participant's severity of their fatigue over the past week. The PGI-S is a 5-point scale ("none", "mild", "moderate", "severe", "very severe").

Patient Global Impression of Change (PGI-C) is a single-state, self-report measure that reflects a participant's belief about the efficacy of treatment. The PGI-C is a 7-point scale ("much improved", "moderately improved", "a little bit improved", "no change", "a little bit worse", "moderately worse", "much worse").

Patient Global Impression of Change in Fatigue (PGI-C Fatigue) is a single-state, self-report measure that reflects a participant's belief about the efficacy of treatment on their experience of fatigue. The PGI-C is a 7-point scale ("much improved", "moderately improved", "a little bit improved", "no change", "a little bit worse", "moderately worse", "much worse").

8.1.2.4 LupusQoL

The LupusQoL (version 2007) is a disease-specific health-related QoL (HRQoL) instrument developed with SLE patient qualitative input (McElhone et al, 2007). It consists of 8 domains: physical health (8 items), pain (3 items), planning (3 items), intimate relationships (2 items), burden to others (3 items), emotional health (6 items), body image (5 items), and fatigue (4 items). Scores are calculated independently for each domain and transformed to a 0 to 100 point scale with higher scores denoting better HRQoL. A recent study has suggested minimal clinically important difference scores for minimally improved (ranging from 1.1 to 9.2 points) and minimally worse (ranging from -0.5 to -6.4 points) for each of the 8 domains of LupusQoL (Devilliers et al, 2015).

8.1.2.5 EQ-5D-5L

The EQ-5D-5L health questionnaire provides a descriptive profile and a single index value for health status. The instrument is comprised of a 5-item health status measure and a VAS. The EQ-5D-5L VAS records the respondent's self-rated health status on a vertical 20cm scale, graduated from 0 to 100 (0=worst imaginable health status, 100=best imaginable health status).

8.1.2.6 PHQ-9

The PHQ-9 is a validated patient outcome tool for screening depression and is not sufficiently accurate to establish a definitive diagnosis for depression. The PHQ-9 is scored 0 to 27, with

scores ≥10 indicating a possible depressive disorder. The sensitivity and specificity of the tool is 88%. It is also used to determine treatment response.

8.1.3 Derived endpoints

8.1.3.1 BILAG 2004-based Composite Lupus Assessment

A study participant is considered to be a BILAG 2004-based Composite Lupus Assessment (BICLA) responder if all of the following is fulfilled:

1. BILAG 2004 improvement without worsening, defined as BILAG 2004 Grade As at Baseline Visit improved to B/C/D, and BILAG 2004 Grade Bs at Baseline Visit improved to C/D, and no BILAG 2004 worsening in other BILAG 2004 organ systems (that had BILAG 2004 Grade C, D, or E at Baseline) such that there are no new BILAG 2004 Grades A nor greater than 1 new BILAG 2004 Grade(s) B; and
2. No worsening in the SLEDAI-2K total score compared to Baseline Visit (defined as no increase in SLEDAI-2K total score); and
3. No worsening in the PGA compared to Baseline Visit ("no worsening" is defined as either no worsening or worsening <10% of the full 100mm VAS, equivalent to less than a 10mm increase in the PGA compared to Baseline Visit (V2) score).

Escape treatment intervention as indicated by Investigator until the assessment time point will be defined as intercurrent event for the primary endpoint leading to non-response from the day after the event onward.

Escape treatment intervention is defined as:

1. Any dose increase or new start of systemic antimalarials or immunosuppressants from Screening Visit and during Treatment Period
2. Any increase in dose or new start of a moderate to high potency topical immunosuppressant (eg, Tacrolimus) used for an organ system with SLE disease activity during the study
3. Any increase of prednisone equivalent dose within the first 4 weeks (up to Week 4) that is above the Baseline level by >50% of the Baseline level or of >10mg/day, whichever is higher, which does not return to the Baseline level within 7 days after increase above Baseline level
4. Any increase of prednisone equivalent dose for a SLE indication above Baseline level after Week 4
5. Any increase of prednisone equivalent dose by >50% or 5mg/day, whichever is lower, for more than 1 day within 8 weeks prior to an assessment for any indication after Week 4.
6. More than 1 corticosteroid intra-articular injection up to Week 12
7. Any corticosteroid intra-articular injection after Week 12 for an SLE indication
8. Any intramuscular administration of corticosteroid for an SLE indication
9. Any iv administration of corticosteroid for an SLE indication

If a treatment change represents an intercurrent event, it will be confirmed by a blinded independent adjudicator.

In addition, study participants who permanently discontinue study medication prematurely or are withdrawn from the study are categorized as non-responders for the primary analysis (see Section 9.3.1).

8.1.3.2 Severe BILAG flare

BILAG severe flare is defined as a BILAG 2004 Grade A in any system due to individual items that are new or worse and are qualifying for the Grade A (Isenberg et al, 2011). Determination of items that are new or worse qualifying for the Grade A will be according to the supplementary information for the numerical scoring of the BILAG-2004 index (Yee et al, 2010). Worsening of symptoms after the Baseline Visit will only be considered as a flare if there was at least 1 post-Baseline Visit, prior to the worsening, where the symptom remained the same or improved. BILAG flares will be confirmed by a blinded review by independent adjudicators.

8.1.3.3 Moderate BILAG flare

BILAG moderate flare is defined as 2 or more BILAG 2004 Grade Bs due to individual items that are new or worse and are qualifying for the Grade B in any system (Isenberg et al, 2011). Determination of items that are new or worse qualifying for the Grade B will be according to the supplementary information for the numerical scoring of the BILAG-2004 index (Yee et al, 2010).

8.1.3.4 LLDAS

LLDAS is defined as

- No significant disease activity as per SLEDAI-2K:
  - SLEDAI-2K score ≤4 with no activity in major organ systems (renal, CNS, cardiopulmonary, vasculitis, fever)
- No new and/or worsening disease activity defined as no SLEDAI-2K component documented as present that was not documented present at previous visit
- PGA ≤33mm
- Prednisone equivalent systemic dose for SLE indication ≤7.5mg per day
- Stable standard maintenance doses of immunosuppressive drugs as allowed by protocol defined as no increase in dose in the past 12 weeks, and no dose higher than allowed as per protocol.

8.1.3.5 Systemic Lupus Erythematosus Responder Index-4

The Systemic Lupus Erythematosus Responder Index (SRI)-4 define responders as (ie, all criteria must be met):

- Reduction in SLEDAI-2K score of ≥4
- No shift from BILAG 2004 Grade B, C, D, or E to A post-Baseline
- No more than 1 shift from BILAG 2004 Grade C, D, or E to B post-Baseline

- No worsening in the PGA compared to Baseline Visit (V2) ("no worsening" is defined as either no worsening or worsening <10% of the full 100mm VAS, equivalent to less than a 10mm increase in the PGA compared to Baseline Visit (V2) score);

The analysis will be repeated using a cut-off of 6 (SRI-6) and 8 (SRI-8) for reduction in SLEDAI.

8.1.3.6 DORIS (Definitions of Remission in SLE) complete remission on treatment

SLEDAI-based remission is defined as:

- Clinical SLEDAI-2K score = 0 (SLEDAI-2K without serology: [redacted] items) and
- PGA ≤16mm and
- Prednisone equivalent systemic dose for SLE indication ≤5mg per day and
- [redacted] ≤ULN and
- [redacted] ≥ LLN.

Other tertiary endpoints will be described in the SAP.

8.2 Safety assessments

Planned time points for all safety assessments are provided in the Schedule of Activities (Section 1.3).

8.2.1 Physical examination

The physical examination and the interim medical history (anamnesis) are an important base for recognition and appropriate documentation of AEs and is a critical part of disease activity assessment instruments, such as the BILAG 2004 or the SLEDAI-2K and will be performed at every visit.

Physical examination findings will be recorded in the eCRF at Screening. Clinically relevant changes in subsequent physical examinations will be recorded as AEs if not related to SLE. If physical examination findings are considered to be related to SLE, they will be documented within the BILAG 2004 and/or SLEDAI-2K assessment eCOA. The outcome of physical examinations and the interim medical history must be documented in source documentation.

A complete physical examination will include, at a minimum, general appearance; ear, nose, mouth, and throat; eyes, hair, and skin; and assessments of the respiratory, cardiovascular, gastrointestinal, musculoskeletal, hepatic, and neurological (including focused assessment of reflexes, sensitivity, and muscle strength) systems and mental status. Height (only at Screening) and weight (at applicable visits and if deemed necessary by the Investigator) will also be measured and recorded.

Investigators should pay special attention to clinical signs related to previous serious illnesses.

Clinically relevant findings or worsening of previous findings will be recorded as AEs.

8.2.2 Vital signs

Oral, tympanic, or temporal artery temperature, pulse rate, respiratory rate, and blood pressure will be assessed.

Blood pressure and pulse measurements will be assessed in a supine or sitting position with a completely automated device. Manual techniques will be used only if an automated device is not available.

Blood pressure and pulse measurements should be preceded by at least 10 minutes of rest for the participant in a quiet setting without distractions.

Vital signs (to be taken before blood collection for laboratory tests) will include oral, tympanic, or temporal artery temperature, pulse and blood pressure measurements.

8.2.3 ECG

Single 12-lead ECG will be obtained prior to dosing and prior to obtaining PK or other laboratory samples (if applicable) using an ECG machine that automatically calculates the heart rate and measures PR, QRS, QT, and QTc intervals. Refer to Section 7 for QTc withdrawal criteria and any additional QTc readings that may be necessary.

All ECG recordings should be taken with the study participant resting in the supine position for at least 15 minutes prior to the recording and should be motionless during the recording.

The Investigator or designee will determine whether the results of the ECG are normal or abnormal. All important findings and abnormalities (including their specification) should be reported as AEs. Data will be electronically transferred to a third-party vendor.

8.2.4 Clinical safety laboratory assessments

See Section 10.2 for the list of clinical laboratory tests to be performed. Some laboratory parameters may be subject to blinding. In case a blinded laboratory parameter is considered safety relevant, alert notifications in case of clinically significant levels or changes from baseline will be established.

Some immune system markers (Section 8.9) may also be considered safety markers.

The Investigator must review the laboratory report, document this review, and record the underlying disease or condition of clinically relevant laboratory changes occurring during the study or, in case an underlying disease or condition cannot be identified, the laboratory change itself in the AE section of the eCRF. The laboratory reports must be filed with the source documents. Clinically significant abnormal laboratory findings are those which are not associated with the underlying disease, unless judged by the Investigator to be more severe than expected for the participant's condition.

All laboratory tests with values considered clinically significantly abnormal during participation in the study or within 5 half-lives (10 Weeks) after the final dose of study medication should be repeated until the values return to normal or baseline or are no longer considered clinically significant by the Investigator or Medical Monitor.

If such values do not return to normal/Baseline within a period of time judged reasonable by the Investigator, the etiology should be identified and the Sponsor notified.

All protocol-required laboratory assessments, as defined in Section 10.2, must be conducted in accordance with the laboratory manual and the Schedule of Activities.

If laboratory values from non-protocol specified laboratory assessments performed at the institution's local laboratory require a change in participant management or are considered clinically significant by the Investigator (eg, SAE or AE or dose modification), then the results must be recorded in the eCRF.

8.2.5 Suicidal risk monitoring

Suicidal ideation and behavior will be assessed by trained study personnel (preferably the Investigator or Subinvestigator in the scope of the mandatory anamnesis) using the C-SSRS. This scale will be used for screening as well as to assess suicidal ideation and behavior that may occur during the study. All information available to the assessor at the time of assessment should be considered.

8.2.6 Assessment and management of TB and TB risk factors

Appropriate rigorous precautions are being taken within this protocol to monitor the risk of TB infection in this study (see Section 5.2 [Exclusion Criterion 19] and Section 7.1 [discontinuation of study medication]). Any presumptive diagnosis or diagnosis of a TB infection is a reportable event. Confirmed active TB must be reported as an SAE (Section 8.3). The Investigator is to complete and submit the TB follow-up form provided.

For the purposes of this study, TB definitions are as follows:

a. Known TB infection
   - Active TB infection or clinical signs and symptoms suspicious for TB (pulmonary or extra-pulmonary).
   - History of active TB infection involving any organ system or findings in other organ systems consistent with TB infection, unless adequately treated and proven to be fully recovered upon consult with a TB specialist.
   - Any evidence by radiography or other imaging modalities consistent with previously active TB infection that is not reported in the study participant's medical history.

b. High risk of acquiring TB infection:
   - Known close exposure to another person with active TB infection within the 3 months prior to Screening.
   - Time spent in a healthcare delivery setting or institution where individuals infected with TB are housed and where the risk of transmission of infection is high.

c. Latent TB infection (unless appropriate prophylaxis is initiated at least 4 weeks prior to study medication dosing and continued to completion of prophylaxis):
   - The absence of signs, symptoms, or physical findings suggestive of TB infection with a positive IGRA test (or 2 indeterminate IGRA test results) and a chest x-ray (or other imaging) without evidence of TB infection. If the result of the IGRA test is indeterminate, the particular IGRA test previously performed may be repeated once; if positive or indeterminate on retest, the study participant may not be randomized to IMP

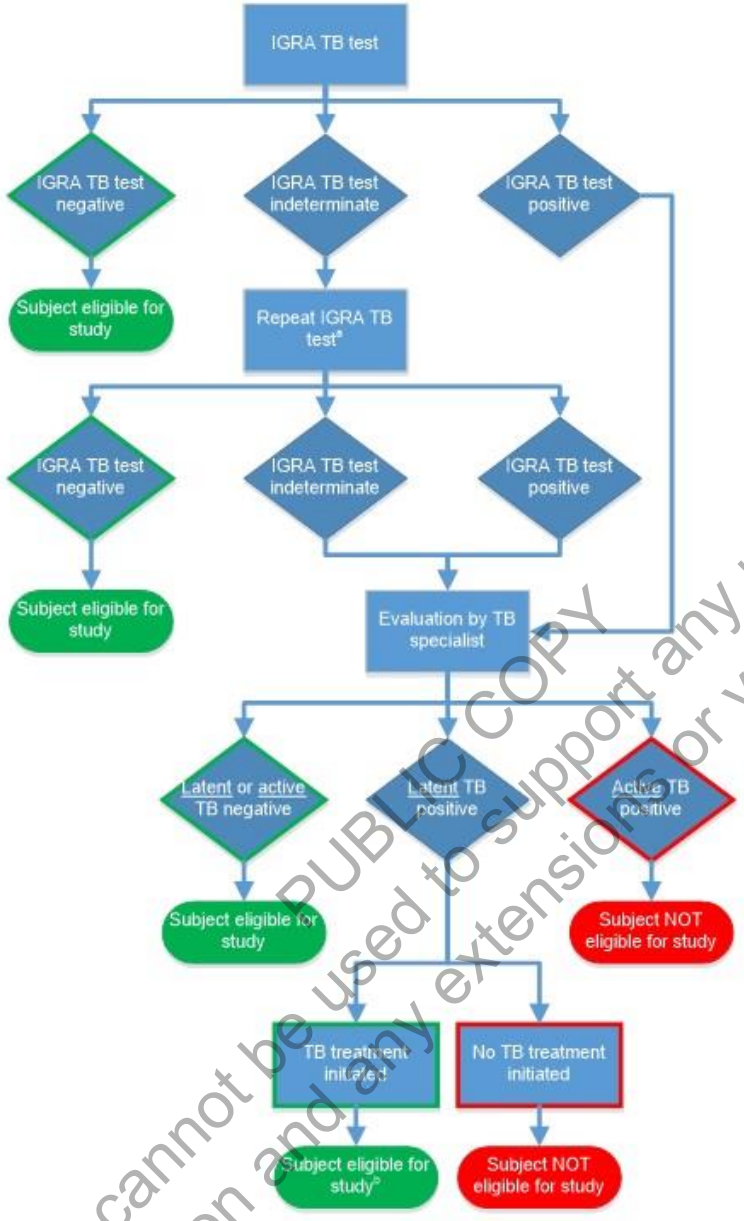
without further evaluation by a TB specialist and discussion with the Study Physician, if LTB infection is identified. The retest must be done during the protocol-defined Screening window.

Note: If available, respiratory or other specimens must also be smear and culture negative for TB (CDC diagnosis of LTB infection) http://www.cdc.gov/TB/topic/testing/default.htm).

d. Pulmonary NTM infection is defined as a clinical infection caused by mycobacterial species other than those belonging to the Mycobacterium TB complex.

Study participant eligibility, retesting requirements, and treatment requirements are depicted in Figure 8-1.

Figure 8-1: Schematic diagram of TB test results and study eligibility



IGRA=interferon gamma release assay; TB=tuberculosis
[a]IGRA retest must be done during the protocol-defined Screening window
[b]Study participants with LTB1 may enter the study only after they have completed least 4 weeks of appropriate prophylactic therapy and thereafter, will continue and complete the entire regimen.

8.2.6.1 Assessment and reporting of TB and TB risk factors during the study

8.2.6.1.1 Physical examination

The Investigator should consider all potential sites of infection when assessing for TB during the physical examination, and other evaluations, and based on the study participant's medical or social history.

The most common primary focus of TB is the lung. Other sites may include gastrointestinal system, bone/joints, lymph glands and meninges etc. However, in immune compromised patients, study participants, and/or patients treated with biologics (especially TNF inhibitors) extra-pulmonary manifestations of TB are common compared with the normal population.

Some common symptoms that the study participant may present are dependent on the primary focus of infection and may include cough, blood in sputum, night sweats, lymphadenitis, joint pain/swelling, spinal deformity, headache/confusion, abdominal pain (mimicking inflammatory bowel disease), etc. Unusual presentations should always be considered.

8.2.6.1.2 IGRA test conversion

Tuberculosis test conversion is defined as a positive or indeterminate (and confirmed indeterminate on repeat) IGRA result for the current test when previous IGRA test results were negative. All study participants with positive or indeterminate IGRA test results must immediately stop study medication administration. In case of an IGRA test conversion, the study participant must be considered as having either a suspected new latent or an active TB infection and be promptly referred to an appropriate specialist (eg, pulmonologist, infectious disease specialist) for further evaluation. Additional assessments (eg, blood tests or IGRA, chest X-rays, or other imaging) should be performed where medically relevant and documented. Such conversions should be reported as AEs as described in the protocol. The AE term would need to be updated with final diagnosis once available.

8.2.6.1.3 Latent TB

In case the evaluation by the appropriate specialist diagnoses a new LTBI, a TB prophylactic therapy in accordance with applicable clinical guidelines should be immediately initiated. Study medication can be restarted no sooner than 4 weeks after the start of TB prophylactic therapy if it is deemed likely that the TB prophylactic therapy will be continued to full completion. If no TB prophylactic therapy is initiated for the newly diagnosed LTBI, the study participant must permanently stop study medication. Every related action should be discussed in advance with the Medical Monitor.

Study participants who prematurely discontinue treatment for LTBI or who, in the opinion of the Investigator or Sponsor, are noncompliant with anti-TB therapy must discontinue further intake of study medication immediately. Even though withdrawn from study treatment, study participants should still be encouraged to regularly attend scheduled visits (but without IMP administration) and in any case should return for the End of Treatment Visit, complete all end of treatment assessments, and complete an End of Study Visit (as applicable). LTBI must be reported as an AE. Follow-up reports should be completed as per protocol requirement until such time as the LTBI resolves.

8.2.6.1.4 Active TB or non-TB mycobacterium infection

Study participants who develop active TB or NTM infection during the study must immediately permanently discontinue study medication. Treatment for active TB or NTMB should be started immediately.

Confirmed active TB is always considered an SAE. UCB's process requires that these must be captured on an SAE report form and provided to the Sponsor in accordance with SAE reporting

requirements. Follow-up reports should be completed as per protocol requirement until such time as the TB infection resolves.

8.2.6.2 TB questionnaire

The questionnaire "Evaluation of signs and symptoms of tuberculosis" should be used as a source document. The questionnaire will assist with the identification of study participants who may require therapy for TB. A study participant who answers "Yes" to the question "Has the study participant been in close contact with an individual with active TB, or an individual who has recently been treated for TB?" at Screening is excluded. A "Yes" response to any of the other questions within the questionnaire at Screening should trigger further careful assessment to determine if study participant has LTB or active TB. A "Yes" response to any of the questions during the study should trigger further assessments to determine if the study participant has either LTB or active TB infection.

8.2.6.3 TB management

During the study, study participants who develop evidence of LTBI, active TB or NTM infection must immediately stop further administration of study medication and will be referred to TB specialist (pulmonologist or infectious disease specialist) for further evaluation. Study participants diagnosed with active TB or LTBI should receive appropriate TB or prophylaxis therapy. If a TB specialist excludes active TB, the study participant can restart the study medication no earlier than 4 weeks after the start of an appropriate TB prophylactic therapy. The study participant should be transferred to the care of their physician and managed according to the standard of care.

Study participants identified as having active TB during the study must permanently discontinue study medication.

If infection with NTM is identified during the study, the same procedure as for active TB acquired during the study and compliant TB treatment shall be followed.

8.2.7 SARS-CoV-2/COVID-19

While the SARS-CoV-2 outbreak coincides with the conduct of the study, and study participants are at risk of developing the COVID-19 disease caused by the SARS-CoV-2 virus, to date study participants do not appear to be at an increased risk for severe disease. Nevertheless, this experience is based on a small number of individual cases, and careful monitoring of study participants for SARS-CoV-2 infection is recommended.

Records on the history of COVID-19 vaccination should be collected and best medical practice and applicable local healthcare guidance should be followed to exclude active SARS-CoV-2 infection for evaluating Exclusion Criterion 15a and to validate the criteria for the temporary study drug discontinuation as described in Section 7.1.

Prior to or at any regular study visit participants need to be evaluated by the Investigator if they are at risk for having an active SARS-CoV-2 infection. If participants are considered as at risk to have an active SARS-CoV-2 infection adequate testing (polymerase chain reaction [PCR] or antigen test) is indicated.

This is applicable at:

- The Baseline Visit (V2) to confirm eligibility

- All post Baseline visits

Among the factors described in the literature and in healthcare guidance as increasing the possibility to have contracted an active SARS-CoV-2 infection are:

1. Participant is not vaccinated against SARS-CoV-2
2. Signs and symptoms suggestive of COVID-19
3. A close contact with a person diagnosed with SARS-CoV-2 infection/COVID-19 within the preceding 14 days
4. The participant resided or visited an area (county, city) with high prevalence of active infection (in line with local guidance).

Investigators are further advised to carefully consider risk factors for a severe COVID-19 course, the individual life situation as well as a potential immunity against SARS-CoV-2 (post infection, post vaccination) in the decision for diagnostic measures.

Among the factors described in the literature as representing an increased risk for severe course of COVID-19 are: elder age (>65y), obesity (body mass index [BMI] ≥35), comorbidities such as diabetes mellitus, chronic kidney disease, hypertension, significant cardiac or pulmonal disease and concurrent treatment with a high dose corticosteroid (≥ 10mg/day prednisone equivalent) (Haberman et al 2020, Fernandez et al 2020, Gianfrancesco et al 2020, Pablos et al 2020, Fredi et al 2020). However, these factors appear not to represent an increased risk to contract a SARS-CoV-2 infection.

In case of a suspected SARS-CoV-2 infection, samples for SARS-CoV-2 test should be drawn as close as possible, preferably within 72 hours before the planned dosing, to obtain the most up-to-date status of the suspected infection prior to the study drug administration. If the test sample was collected over 72 hours prior to the study drug administration, risks of a new SARS-CoV-2 virus exposure since sample collection, should be considered and the arguments for proceeding with the dosing recorded in the source documentation.

In case of a positive test result, study drug administration should be temporarily discontinued. Study drug application can be resumed ≥ 7 days after recovery of symptoms or, in case of an asymptomatic course, ≥ 14 days after the positive test result.

In case of a known exposure to a person with COVID-19 study drug administration should be suspended until ≥ 14 days after the contact.

Study drug should be only resumed after consultation with the Medical Monitor (see Section 7.1.3).

In case of a positive test result Investigators are advised to recommend quarantine measures to the study participants and report the infection according to the local guidance.

Investigators are strongly advised to discuss with participants the potential risks associated with COVID-19 and to encourage them to take special caution to self-protect – this includes wearing of masks in public, following social distancing best practices and early medical consultation in case of symptoms of an infection, and reporting such symptoms to the Investigator.

Local and international guidance on vaccination of immunocompromised patients (Furer et al, 2020; Van Assen et al, 2011; Murdaca et al 2016; Mason et al, 2021, ACR 2021, Geisen et al,

2021) should be considered. Applicable guidance, benefits and risks of COVID-19 vaccination as well as the option of being vaccinated during the study (including the screening period) should be discussed with the study participant during the informed consent process. In case a patient is deciding to be vaccinated during the screening period, the screening period may be prolonged to 3 weeks (ie, prolonged by 1 extra week).

8.3 AEs and SAEs

Adverse events will be reported by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's legally authorized representative).

The study participant will be given the opportunity to report AEs spontaneously. A general prompt will also be given at each study visit to detect AEs. For example:

"Did you notice anything unusual about your health (since your last visit)?"

In addition, the Investigator should review any self-assessment procedures (eg, diary cards) employed in the study for potential AEs.

The Investigator and any designees are responsible for detecting, documenting, and recording events that meet the definition of an AE or SAE and remain responsible for following up AEs that are serious, considered related to the study treatment or study procedures, or that caused the participant to discontinue the study treatment (see Section 7).

New or worsening manifestations of SLE should be recorded as AEs only if they are assessed as serious.

All efforts should be taken to clarify the origin of the AE. This may require at any time point additional assessments including but not limited to additional laboratory assessments, imaging methods, EMGs and ECGs as medically indicated. Special caution should be taken on signs and symptoms of severe infections such as COVID-19.

For results disclosure on public registries (eg, ClinicalTrials.gov), TEAEs and treatment-emergent SAEs will be published.

8.3.1 Time period and frequency for collecting AE and SAE information

All AEs and SAEs will be collected from the signing of the ICF until the follow-up visit at the time points specified in the Schedule of Activities (Section 1.3).

In order to ensure complete safety data collection, all AEs occurring during the study (ie, after the signing of the ICF), including any pretreatment and posttreatment periods required by the protocol, must be reported in the eCRF even if no study medication was taken but specific study procedures were conducted. This includes all AEs not present prior to the initial visit and all AEs that recurred or worsened after the initial visit.

All SAEs will be recorded and reported to the Sponsor or designee within 24 hours, as indicated in Section 10.3. The Investigator will submit any updated SAE data to the Sponsor within 24 hours of it being available.

The Investigator is specifically requested to collect and report to UCB (or its representative) any SAEs (even if the Investigator is certain that they are in no way associated with the study medication), up to from the end of the study for each participant, and to also inform participants of the need to inform the Investigator of any SAE within this period. Serious AEs that the

Investigator thinks may be associated with the study medication must be reported to UCB regardless of the time between the event and the end of the study.

The method of recording, evaluating, and assessing causality of AE and SAE and the procedures for completing and transmitting SAE reports are provided in Section 10.3.

8.3.2 Method of detecting AEs and SAEs

Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and non-leading verbal questioning of the participant is the preferred method to inquire about AE occurrences.

8.3.3 Follow-up of AEs and SAEs

After the initial AE/SAE report, the Investigator is required to proactively follow each participant at subsequent visits/contacts. All SAEs, treatment-emergent adverse events (TEAEs) of special interest and non-serious AEs of special monitoring (as defined in Section 8.3.6 and Section 8.3.7, respectively), will be followed until resolution, stabilization, the Investigator determines that it is no longer clinically significant, the event is otherwise explained, or the participant is lost to follow-up (as defined in Section 7.3). Further information on follow-up procedures is given in Section 10.3.

8.3.4 Regulatory reporting requirements for SAEs

Prompt notification by the Investigator to the Sponsor of a SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study treatment under clinical investigation are met.

The Sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study treatment under clinical investigation. The Sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, the IRB/IEC, and Investigators.

Investigator safety reports must be prepared for suspected unexpected serious adverse reactions (SUSAR) according to local regulatory requirements and Sponsor policy and forwarded to Investigators as necessary.

An Investigator who receives an Investigator safety report describing a SAE or other specific safety information (eg, summary or listing of SAEs) from the Sponsor will review and then file it along with the IB and will notify the IRB/IEC, if appropriate according to local requirements.

8.3.5 Pregnancy

Details of all pregnancies in female participants and female partners of male participants will be collected after the start of study treatment and until 12 months after the delivery date.

If a pregnancy is reported, the Investigator must immediately inform the Sponsor within 24 hours of learning of the pregnancy and should follow the procedures outlined in Section 10.4.

Study medication must be discontinued as soon as a pregnancy is suspected (eg, by positive urine pregnancy test). Study participants can remain in the study under observation and should attend to scheduled visits regularly as their condition allows. Blood sample collection will be adapted as indicated considering the study participant's condition during the study and at the end of the study visit. Caution is required with respect to concomitant medication if not contraindicated in

pregnancy. As indicated Investigators are advised to discuss the case with medical monitors or the sponsor's study physician to gain feedback on protocol defined actions.

Abnormal pregnancy outcomes (eg, spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs.

8.3.6 AEs of special interest

An AE of special interest is any AE that a regulatory authority has mandated be reported on an expedited basis, regardless of the seriousness, expectedness, or relatedness of the AE to the administration of a UCB product/compound.For DZP, the following events require immediate reporting (within 24 hours regardless of seriousness) to UCB:

- Hy's Law
  - Potential Hy's Law, defined as ≥3xULN ALT or AST with coexisting ≥2xULN total bilirubin in the absence of ≥2xULN ALP, with no alternative explanation for the biochemical abnormality (ie, without waiting for any additional etiologic investigations to have been concluded). Follow-up information should be reported if an alternative etiology is identified during investigation and monitoring of the participant.
  - Malignancies

8.3.7 AEs of special monitoring

[redacted]

[redacted]

8.3.8 Anticipated SAEs

[redacted]

8.3.9 Suspected transmission of an infection agent via a medicinal product

For the purposes of reporting, any suspected transmission of an infectious agent via a medicinal product should be considered as an SAE (Section 8.3); such cases must be reported immediately, recorded in the AE module of the eCRF, and followed as any other SAE. Any organism, virus, or infectious particle (eg, prion protein transmitting transmissible spongiform encephalopathy), pathogenic or nonpathogenic, is considered an infectious agent.

8.4 Safety signal detection

Selected data from this study will be reviewed periodically to detect as early as possible any safety concern(s) related to the study medication so that Investigators, clinical study participants, regulatory authorities, and IRBs/IECs will be informed appropriately and as early as possible.

The Study Physician or medically qualified designee/equivalent will conduct an ongoing review of SAEs and perform ongoing SAE reconciliations in collaboration with the Patient Safety representative.

As appropriate for the stage of development and accumulated experience with the study medication, medically qualified personnel at UCB may identify additional safety measures (eg, AEs, vital signs, laboratory or ECG results) for which data will be periodically reviewed during the course of the study.

8.5 Treatment of overdose

For this study, any dose of DZP greater than that prescribed in the protocol will be considered an overdose. Overdose events are only considered AEs or SAEs if there are associated clinical signs and symptoms or if the act of taking the excess study medication itself is an AE or SAE (eg, suicide attempt).

UCB does not recommend specific treatment for an overdose.

In the event of an overdose, the Investigator should:

1. Contact the Medical Monitor immediately.
2. Closely monitor the participant for any AE/SAE and laboratory abnormalities until study treatment can no longer be detected systemically (at least 84 days).
3. Obtain a plasma sample for PK analysis within 84 days from the date of the final dose of study medication if requested by the Medical Monitor (determined on a case-by-case basis).
4. Document the quantity of the excess dose as well as the duration of the overdose in the eCRF.

Decisions regarding dose interruptions or modifications will be made by the Investigator in consultation with the Medical Monitor based on the clinical evaluation of the participant.

8.6 Pharmacokinetics

[redacted]. Additional samples may be collected at additional time points during the study if warranted and agreed upon between the Investigator and the Sponsor.

Instructions for the collection and handling of biological samples will be provided in the Laboratory Manual. The actual date and time (24-hour clock time) of each sample will be recorded. [redacted]

Drug concentration information that would unblind the study will not be reported to investigative sites or blinded personnel until the study has been unblinded.

Any changes in the timing or addition of time points for any planned study assessments must be documented and approved by the relevant study team member and then archived in the Sponsor and site study files, but will not constitute a protocol amendment. The IRB/IEC will be informed of any safety issues that require alteration of the safety monitoring scheme or amendment of the ICF.

Study participants are to rest in a supine position for at least 10 min before blood samples are taken. Blood samples are to be taken in the arm opposite the one used for infusion and be drawn at the time points and sampling windows designated in Table 1-2. Blood samples must not be drawn through the infusion cannula.

Samples may be stored for a maximum of 20 years (or according to local regulations) following the last participant's last visit for the study at a facility selected by the Sponsor to enable further analysis of PK of DZP and PEG.

8.6.1 Assessment of PK variables

[redacted]

8.7 Immunogenicity assessments

[redacted]

[redacted]

8.8 Pharmacodynamics

Some immune system markers (Section 8.9) may also be considered pharmacodynamic (PD) markers.

8.9 Immune system markers

[redacted]

8.10 Biomarkers

[redacted]

If samples are not used immediately, they will be stored frozen for later analysis (reflected in a separate report as applicable) for a maximum of 20 years (or according to local regulations) following the last participant's last visit for the study at a facility selected by the Sponsor. They will only be used in the context of understanding the molecular taxonomy of SLE and/or response to treatment with DZP.

As required, unused PK back-up samples may also be used for research to develop methods and to further investigate the biology of SLE and its treatment with DZP.

Some immune system markers (Section 8.9) may also be considered biomarkers.

8.11 Genetics

A blood sample for potential future exploratory DNA analysis/genetics research will be collected and stored from consenting participants in the study. This sampling is optional for study participants and requires a separate informed consent. A decision not to consent does not exclude the study participant from the study.

These samples will only be used to further our understanding of SLE and/or how genetic variation may affect response or be affected by treatment with DZP and/or concomitant medications on SLE. Blood samples will be stored frozen in a UCB-appointed secure Biobank and they may be stored for up to 20 years.

See Section 10.5 for Information regarding genetic research. Details on processes for collection and shipment of these samples can be found in the Laboratory Manual.

8.12 Medical resource utilization and health economics

Not applicable.

9 STATISTICAL CONSIDERATIONS

A description of statistical methods follows and will be described in more detail in the SAP.

9.1 Definition of analysis sets

The Enrolled Set (ES) will consist of all study participants who have given informed consent.

The Full Analysis Set (FAS) will consist of all study participants randomized into the study. The FAS is the primary analysis set for efficacy analyses.

The Safety Set (SS) will consist of all study participants who are randomized and have received at least 1 dose (any amount) of study medication. Safety variables will be analyzed using the SS.

The Per-Protocol Set (PPS) will consist of study participants in the FAS who have received at least 1 full dose of study medication and have no important protocol deviations (such as not under stable SOC treatment at Baseline) during the Treatment Period that may influence the validity of the data for the primary efficacy variable.

The Pharmacokinetic Per-Protocol Set (PK-PPS) consists of all study participants who received at least 1 dose of study medication and provided at least one quantifiable plasma concentration post-dose without important protocol deviations that would affect the concentration.

9.2 General statistical considerations

9.2.1 General presentation of summaries and analyses

Statistical analysis and generation of tables, figures, study participant data listings, and statistical output will be performed using SAS® Version 9.4 or higher.

All original and derived parameters will be listed and described using summary statistics. For continuous parameters, number of participants with available measurements, mean, standard deviation (SD), median, minimum and maximum and for categorical parameters, number of participants and percentages (to one decimal place) in each category will be presented.

All descriptive statistics will be presented by treatment where applicable, including columns for all treated participants and all participants on demographics, baseline characteristics, and AE displays, and using the available data for the study population as observed. Summaries of concentration data will be based on geometric mean and geometric standard deviation instead of arithmetic versions. All tabulations will be sorted by treatment, parameter and visit (including time relative to dosing if applicable, unless otherwise stated). Only scheduled visits and times relative to dosing will be included in the tabulation.

Categorical data will be summarized by visit and treatment group, including columns for all treated study participants and all study participants on demographics, baseline characteristics, and AE displays, using the number and percent of study participants in each category. Percentages will be based on the corresponding population size (ie, the denominator of percentages should match the sample size in the column header), unless otherwise noted via footnote in the applicable summary table.

Statistical tests of efficacy variables will be presented as 2-sided p-values. P-values will be rounded to 4 decimal places. P-values less than 0.0001 will be presented as "<0.0001" and p-values greater than 0.9999 will be presented as ">0.9999."

Handling of multiplicity for the primary and key secondary efficacy variables is discussed in Section 9.4. All other efficacy variables will be considered secondary or exploratory and will be assessed at a nominal 2-sided α=0.05 significance level.

9.2.2 Analysis time points

The timeframe for this protocol compasses the entire study, which extends from Screening to 10 weeks after the final dose, ie, 48 weeks of Double-Blind Treatment Period and 6 weeks of SFU Period.

The following study periods will be included in the analysis:

- Screening Period: up to 14 days (Day -14 through Day -1).
- Double-Blind Treatment Period: 48 weeks, starts with the randomization (1:2) of eligible participants to 1 of 2 treatment arms (SOC+PBO or SOC+DZP 24mg/kg), stratified in accordance with the 3 stratification factors. Study medication will be administered by iv infusion every 4 weeks, starting on Day 1.
- Safety Follow-up Period: 6 weeks, participants who complete the 48-week Double-Blind Treatment Period will continue into this 6-week SFU Period. During this period, participants will not receive study medication but will be able to receive SOC treatment, as indicated.

The time points for individual assessments are provided in Table 1-2.

Analyses conducted by visit will include each planned study visit at which the assessment was scheduled. Data for planned study visits will be based on the nominal time point and will not include any unplanned visits. Usually, efficacy data will not be obtained at unscheduled visits, with the following exceptions: labs in BILAG and SLEDAI-2K. Here labs that are obtained up to 2 weeks after the original visit are used to replace missing lab data.

Study participant data listings will include all time points for collected data, including all assessments (planned or unplanned). Data for derived time points Last Visit and Early Withdrawal will be included in study participant data listings.

9.2.3 Definition of Baseline values

Unless otherwise specified, the last value obtained prior to the first infusion of study medication (Visit 2) will be used as the Baseline value. If a Baseline measurement is missing, and a Screening value available, the Screening value will be utilized as Baseline instead.

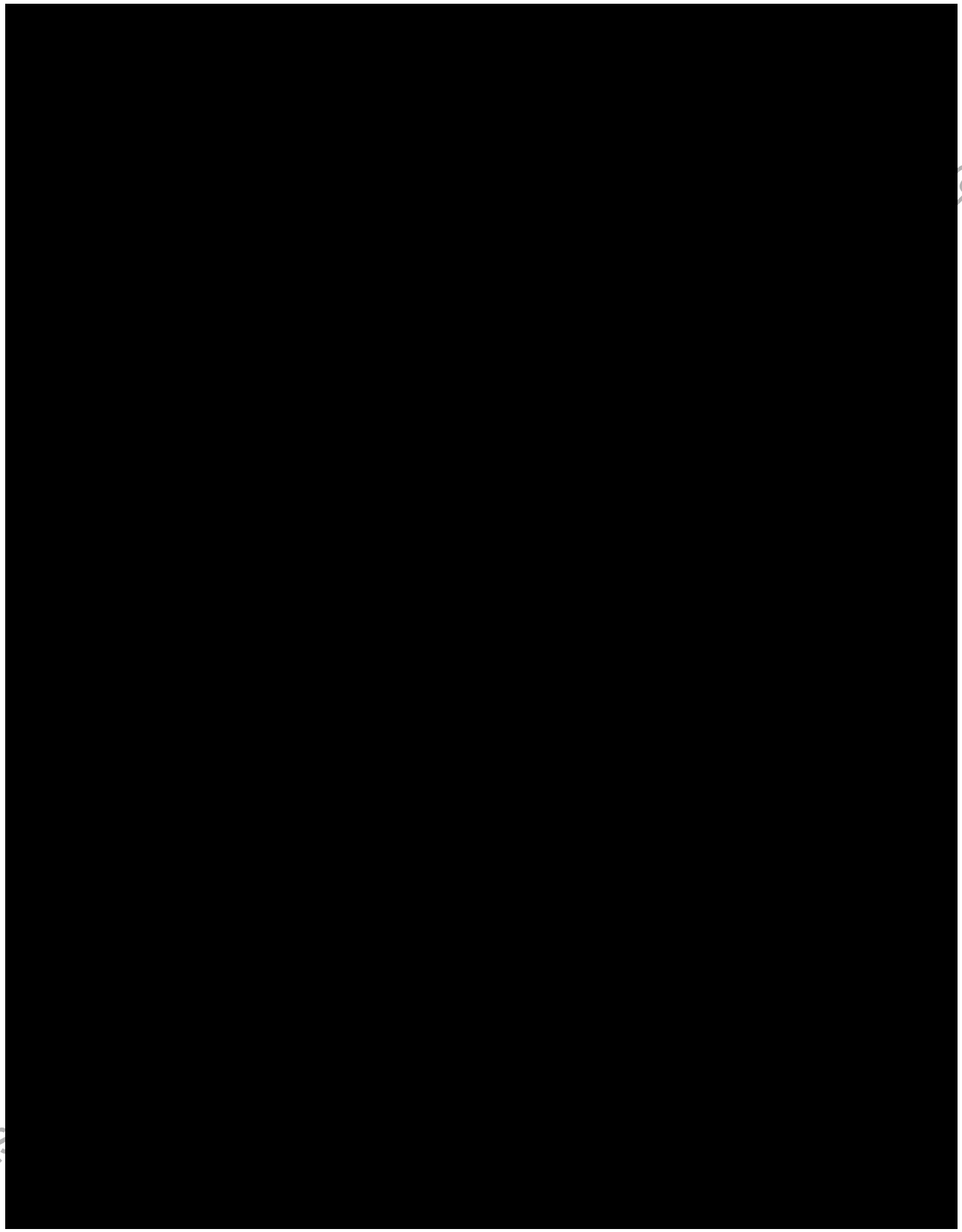
For vital signs, a measurement prior to, or at the moment of, the start of the first infusion will be available for each visit. The last measurement prior to, or at the moment of, the start of the first infusion of study medication will be used as the baseline value. An additional analysis will be performed using the pre-infusion values as baseline values and determine the changes from pre-infusion to post-infusion for each infusion visit. At each post-Baseline Visit, the pre-infusion value will be one taken prior to, or at the moment of, the start of the infusion of study medication.

For Baseline assessments, if the BILAG 2004 is completed, but the grade for 1 or more individual system(s) is missing, the grade for the system will be set to a grade of BILAG 2004 D if no value can be imputed from the Screening Visit. This is a conservative approach for study participants on active doses, since no improvement can occur following a baseline grade of BILAG 2004 D level disease.

9.3 Planned efficacy/outcome analyses

9.3.1 Analysis of the primary efficacy/primary endpoint

[redacted]



9.3.1.1 Sensitivity analysis

The primary analysis described in Section 9.3.1 will be repeated using the PPS as a sensitivity analysis. In addition to this, the following sensitivity analyses will also be performed.

The primary endpoint will also be analyzed using a logistic regression model for BICLA response at Week 48 as a function of treatment group, controlling for randomization stratification factors. Odds ratio, 95% CI, and 2-sided p-value based on the Wald Chi-square statistic will be presented.

Study participants who have a missing value for the Week 48 treatment response assessment (including those who withdraw/dropout prior to the Week 48 Visit), will be included in the primary efficacy analysis as non-responders. To examine the impact of such missing data on the primary analysis, tipping point analyses that systematically vary assumptions about the missing outcomes on the two treatment groups will be performed as a sensitivity analysis.

The details of all of the above sensitivity analyses and any additional sensitivity analyses will be included in the SAP.

9.3.2 Analysis of secondary efficacy endpoints

The handling of intercurrent events for all secondary efficacy endpoints will be described in the SAP.

9.3.2.1 Analysis of key secondary endpoints

[redacted]

[redacted]

9.3.2.1.1 Multiplicity control strategy

The multiplicity control strategy of the overall Type-I error rate α (2-sided 5%) is described below and presented in Figure 9-1.

Step 1: First perform the primary endpoint comparison of BICLA responder rate at Week 48 comparison for SOC+DZP 24mg/kg versus SOC+PBO at the α level (2-sided 0.05), this serves as a gatekeeping step.

If it is not significant at the α level, then stop the rest of the comparison procedure, that is, no other formal comparisons will be performed.

If it is significant at the α level, then proceed to perform key secondary endpoint comparisons as follows.

Step 2: Perform the first key secondary efficacy endpoint comparison of BICLA responder rate at Week 24 for SOC+DZP 24mg/kg versus SOC+PBO.

If it is not significant at the α level, then stop the rest of the comparisons.

If it is significant at the α level, then continue to:

Step 3: Perform the second key secondary efficacy endpoint comparison of severe BILAG 2004 flare prevention responder rate at Week 48 for SOC+DZP 24mg/kg versus SOC+PBO.
If it is not significant at the α level, then stop the rest of comparisons.

If it is significant at the α level, continue to:

Step 4: Apply Hochberg Method for the next 2 key secondary endpoint comparisons in parallel (concurrently).

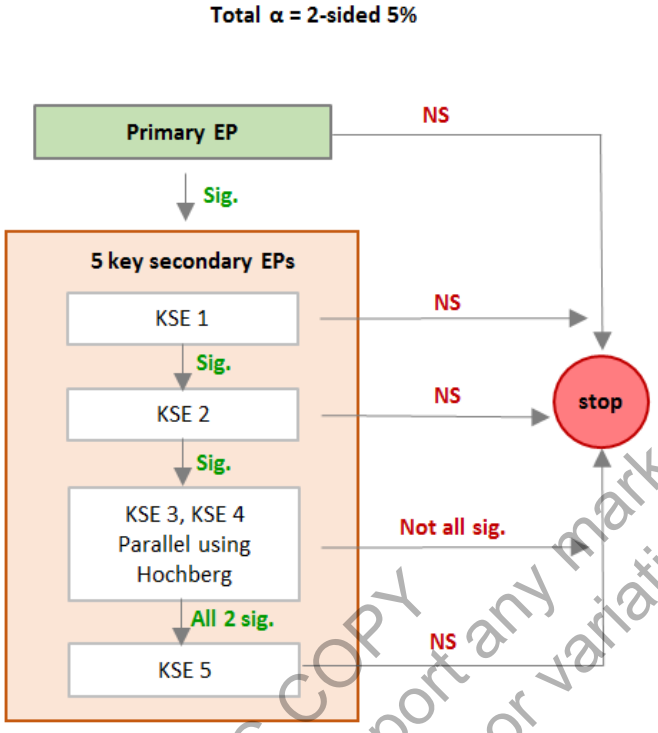
If the larger p-value is ≤α, then both comparisons are statistically significant.

Otherwise (ie, the larger p-value is > α), if the smaller p-value is ≤ α/2, then the corresponding comparison is statistically significant.

Otherwise (ie, the smaller p-value is > α/2), then neither comparison is statistically significant.

Step 5: Only if both of these 2 key secondary endpoint comparisons are significant (ie, the larger p-value is ≤ α), will proceed to the fifth key secondary endpoint BICLA responder rate at Week 12 and it will be tested at the α significance level.

Figure 9-1: Multiplicity strategy figure



EP=endpoint; KSE=key secondary endpoint; NS=not significant; sig=significant.

This strategy combines gatekeeping procedures and the Hochberg method to assure the overall Type-I error rate is controlled at the α (2-sided 0.05) level.

All other efficacy/outcome analyses will either be other-secondary or exploratory in nature without multiplicity adjustments.

9.3.2.2 Analysis of other secondary endpoints

Other secondary efficacy endpoints are the following:

- Achievement of BILAG improvement without worsening at Week 48
- Change from Baseline in PGA at Week 48
- Achievement of SRI4 response at Week 48
- Achievement of prevention of moderate/severe BILAG flares (moderate/severe BILAG flare-free) through Week 48
- Time to severe BILAG flare through Week 48
- Time to moderate/severe BILAG flare through Week 48

The analysis methods for these endpoints are described below and details will be included in the SAP.

For response rate type of endpoints such as achievement of BILAG improvement without worsening at Week 48, they will be analyzed the same way as for the primary efficacy endpoint without sensitivity analyses.

For change from Baseline in PGA at Week 48, it will be analyzed the same way as for the key secondary endpoint of change from Baseline in SLEDAI-2K at Week 48.

Time to event endpoints (eg, time to severe BILAG flare through Week 48) will be analyzed using statistical survival analysis methods. The time to event will be defined as the time until the start of the event. Participants who do not achieve an event by Week 48 or the early termination visit will be censored at the date of the last assessment during study period. Survival curves will be generated using the Kaplan-Meier product limit estimate. The treatment difference between SOC+DZP and SOC+PBO will be analyzed using the stratified log-rank statistic, adjusting for stratification factors (if feasible). Median time to event values for each treatment group will be summarized and Kaplan-Meier survival curves will be presented by treatment group on a single graph.

9.3.3 Analysis of tertiary efficacy endpoints

The tertiary efficacy endpoints are listed Table 3-1. The analysis methods for these endpoints are briefly described by categories below and more details will be included in the SAP.

For response rate type of endpoints such as achievement of BICLA response by visit, they will be analyzed the same way as for the primary efficacy endpoint without sensitivity analyses.

For change from Baseline type of endpoints where the continuous variable analysis methods can be applied, they will be analyzed the same way as for the key secondary endpoint of change from Baseline in SLEDAI-2K at Week 48.

For time to event endpoints, they will be analyzed using statistical survival analysis methods as described for time to severe BILAG flare through Week 48.

9.3.4 Primary efficacy subgroup analyses

The following subgroup analyses are intended to be performed for the primary efficacy endpoint using descriptive statistics, however the list of pre-specified subgroup analyses will be finalized in the SAP:

- Subgroups defined by prior use of biological response modifier vs no prior use
- Subgroups defined by prior use of belimumab vs. no prior use
- Subgroups representing stratification factors (Pooled regions, chronic active vs. acute flaring, SLEDAI-2K <10 vs ≥10)
- Subgroups defined by study participants on antimalarials and corticosteroids vs. other (EULAR treatment guidance subgroup)
- Subgroups defined by [redacted] positive AND low complement vs. other
- Subgroups defined by [redacted] positive AND low complement AND SLEDAI ≥10 vs other
- Subgroups defined by activity (grade) in BILAG organ systems

- Subgroups defined by region
- Subgroups defined by ethnicity
- Subgroups by presence of any organ system with a BILAG A vs. other
- Subgroups defined by low complement vs. other
- Subgroup defined by young age (<25) vs. other
- Subgroups defined by gender
- Subgroup by evidence for at least 1 additional flare in medical history within the past 24 weeks vs. other
- Subgroups defined by:
  - Antimalarials at Baseline: yes/no
  - Immunosuppressants at Baseline: yes/no
  - Corticosteroid dose at Baseline: >7.5mg/day yes/no

9.4 Planned safety and other analyses

9.4.1 Safety analyses

Safety variables will be analyzed for all study participants in the SS.

Adverse events will be coded according to the Medical Dictionary for Regulatory Activities (MedDRA®). The frequency of all AEs during the study period will be presented for each treatment group separately by System Organ Class, high level term, and preferred term. The data will be displayed as number of study participants experiencing the AEs, percentage of study participants, and number of AEs. Data will also be corrected for exposure and reported by 100 patient-years.

The incidence of study participants with AEs will be presented by treatment group and total treatment. Additional tables will summarize AEs leading to permanent discontinuation of study medication, AEs by maximum intensity, AEs by intensity, and AEs by relationship to study medication by treatment group and total treatment. Adverse events will be categorized by severity. The countermeasures taken for each AE, the time of onset of AEs after dosing, and AE duration will be listed. Additional tables with respect to all categories of AEs will also include the numbers of study participants who experienced the respective AE.

All TEAEs (serious and nonserious), including TEAEs of special interest, TEAEs of special monitoring, and deaths will also be tabulated and listed. Other laboratory safety parameters will also be tabulated and listed.

Laboratory evaluations, vital signs, and ECGs will be analyzed in the SS for observed cases. Descriptive statistics will be presented by treatment group at each time point: change from Baseline in vital signs, serum chemistry, hematology, and urinalysis. For laboratory data, changes between the Baseline (predose) or, if missing, Screening value and each posttreatment assessment may be presented in shift tables or using other summaries as detailed in the SAP.

9.4.2 Other analyses

9.4.2.1 Pharmacokinetic analyses

Pharmacokinetic variables will be analyzed for all study participants in the PK-PPS.

Individual study participant concentrations of DZP and PEG will be displayed graphically. They will be summarized using the statistics described for continuous variables (number of available observations, mean, median, standard deviation, minimum, and maximum) and in addition by the geometric mean and the geometric coefficient of variation (assuming log normally distributed data).

[redacted]

If data merit, a population PK analysis and PK/PD analyses may be conducted for the clinical efficacy endpoints and PD variables of interest. All population PK and PK/PD analyses will be described in more detail in a separate Data Analysis Plan, and results will be reported in a separate report.

9.4.2.2 Immunogenicity analyses

[redacted] incidence will be tabulated. More detailed specifications will be presented in the SAP.

9.5 Handling of protocol deviations

Important protocol deviations are a subset of protocol deviations that may significantly impact the completeness, accuracy, and/or reliability of the study data or that may significantly affect a study participant's rights, safety, or well-being. The criteria for identifying important protocol deviations will be defined within the appropriate protocol-specific document. Important protocol deviations will be reviewed as part of the ongoing data cleaning process and data evaluation. All important deviations will be identified and documented prior to unblinding to confirm exclusion from analysis sets.

9.6 Handling of dropouts or missing data

As the primary efficacy variable is treatment responder rate in BICLA at Week 48, the handling of missing data, dropouts and intercurrent events is described as follows.

- In case of the use of escape treatment as an intercurrent event prior to the Week 48 Visit (ie, the escape treatment initiation is at least 1 day before), study participants will be included for the primary analysis as non-responders per the composite strategy handling of this intercurrent event.
- Study participants who prematurely withdraw from the study or permanently discontinue study medication prior to the Week 48 Visit, will be included for the primary analysis as non-responders per the composite strategy handling of this intercurrent event.
- Study participants who have a missing BICLA response for the Week 48 assessment for any other reason besides defined intercurrent events will be imputed as non-responders for the primary efficacy analysis.

- A modified non-responder imputation (mNRI)for missing data will be applied to its components, in order to obtain the BICLA response. If the Week 48 assessment was performed but the value for a single component (BILAG 2004, SLEDAI-2K, or PGA) is not available, then the missing component value will be imputed from the respective previous visit value prior to computing the BICLA treatment response variable (limited to 1 visit back). In the case where the predose laboratory result is missing (at Screening and at Baseline and there is no other unscheduled predose laboratory result), the BILAG 2004 body/organ system Baseline score for the body system requiring the missing laboratory result will be set to a score of BILAG 2004 D level disease. More details will be included in the SAP.

9.7 Planned interim analysis and data monitoring

There will be an IDMC that will meet periodically to monitor safety on an ongoing basis. In addition to safety data, this IDMC will review disposition, demographics and other Baseline characteristics, protocol deviations and compliance, as well as efficacy data to allow for benefit-risk assessment. The IDMC can recommend terminating enrollment and stopping dosing if it is in the interest of patient safety, but the study cannot be stopped prematurely for overwhelmingly positive efficacy results. Thus, there will be no risk of increasing the false positive (Type I error) rate due to IDMC monitoring, and no alpha-level adjustment for the final analysis will be made. Further details of the IDMC will be specified in the IDMC Charter.

There is no planned interim analysis.

9.8 Determination of sample size

The statistical power and sample size consideration is based on the objective to detect a 20% improvement in BICLA responder rate compared with SOC+PBO at Week 48. Given 104 study participants in SOC+PBO and 208 study participants in SOC+DZP 24mg/kg groups and an assumed SOC+PBO responder rate of 0.32, there will be 90% power to confirm an SOC+DZP 24mg/kg responder rate of 0.52 (ie, a 0.20 improvement), corresponding to a 2-sided 0.05 significance level test (SAS® v9.4 POWER procedure, Fisher's exact). The sample size assumptions for SOC+PBO and SOC+DZP 24mg/kg responder rates are based on the Phase 2b study SL0023 responder data at Week 24.

Participants who withdraw from the study prior to the Week 48 Visit will be included in the primary efficacy analysis as non-responders. Therefore, no additional participants are planned to be randomized in order to make up for early withdrawers.

10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1 Appendix 1: Regulatory, ethical, and study oversight considerations

10.1.1 Regulatory and ethical considerations

The study will be conducted under the auspices of an IRB/IEC, as defined in local regulations, International Council on Harmonisation-Good Clinical Practice (ICH-GCP), and in accordance with the ethical principles that have their origin in the Declaration of Helsinki.

The Investigator/UCB will ensure that an appropriately constituted IRB/IEC that complies with the requirements of the current ICH-GCP version or applicable country-specific regulations will be responsible for the initial and continuing review and approval of the clinical study. Prior to initiation of the study, the Investigator/UCB will forward copies of the protocol, ICF, IB, Investigator's curriculum vitae (if applicable), advertisement (if applicable), and all other participant-related documents to be used for the study to the IRB/IEC for its review and approval.

Before initiating a study, the Investigator will have written and dated full approval from the responsible IRB/IEC for the protocol.

The Investigator will also promptly report to the IRB/IEC all changes in the study, all unanticipated problems involving risks to participants or others, and any protocol deviations, to eliminate immediate hazards to participants.

The Investigator will not make any changes in the study or study conduct without IRB/IEC approval, except where necessary to eliminate apparent immediate hazards to the participants. For minor changes to a previously approved protocol during the period covered by the original approval, it may be possible for the Investigator to obtain an expedited review by the IRB/IEC as allowed.

As part of the IRB/IEC requirements for continuing review of approved studies, the Investigator will be responsible for submitting periodic progress reports to the IRB/IEC (based on IRB/IEC requirements), at intervals appropriate to the degree of participant risk involved, but no less than once per year. The Investigator should provide a final report to the IRB/IEC following study completion.

UCB (or its representative) will communicate safety information to the appropriate regulatory authorities and all active Investigators in accordance with applicable regulatory requirements. The appropriate IRB/IEC will also be informed by the Investigator or the Sponsor, as specified by the applicable regulatory requirements in each concerned country. Where applicable, Investigators are to provide the Sponsor (or its representative) with evidence of such IRB/IEC notification.

10.1.2 Financial disclosure

Insurance coverage will be handled according to local requirements.

Finance and insurance are addressed in the Investigator and/or CRO agreements, as applicable.

10.1.3 Informed consent process

Participant's informed consent/assent must be obtained and documented in accordance with local regulations, ICH-GCP requirements, and the ethical principles that have their origin in the principles of the Declaration of Helsinki.

Prior to obtaining informed consent, information should be given in a language and at a level of complexity understandable to the participant in both oral and written form by the Investigator (or designee). Each participant will have the opportunity to discuss the study and its alternatives with the Investigator.

Prior to participation in the study, the ICF should be signed and personally dated by the participant, or his/her legal representative, and by the person who conducted the informed

consent discussion (Investigator or designee). The participant or his/her legal representative must receive a copy of the signed and dated ICF. The study participant of legal age who is incapable of comprehending the nature, significance and implications of the clinical trial and of determining his/her will in the light of these facts, must not be included in the study. The ICF should be signed and personally dated by the participant, or, in case of minors, the informed assent must be obtained in addition to his/her legal representative's consent.

As part of the consent process, each participant must consent to direct access to his/her medical records for study-related monitoring, auditing, IRB/IEC review, and regulatory inspection.

If the ICF is amended during the study, the Investigator (or the Sponsor, if applicable) must follow all applicable regulatory requirements pertaining to the approval of the amended Informed Consent form by the IRB/IEC and use of the amended form.

All studies conducted at centers in the United States must include the use of a Health Insurance Portability and Accountability Act Authorization form.

The participant may withdraw his/her consent to participate in the study at any time. A participant is considered as enrolled in the study when he/she has signed the ICF. An eCRF must not be started, nor may any study specific procedure be performed for a given participant, without having obtained his/her written consent to participate in the study.

10.1.4 Data protection

UCB staff (or designee) will affirm and uphold the participant's confidentiality. Throughout this study, all data forwarded to UCB (or designee) will be identified only by the participant number assigned at Screening.

The Investigator agrees that representatives of UCB, its designee, representatives of the relevant IRB/IEC, or representatives of regulatory authorities will be allowed to review that portion of the participant's primary medical records that directly concerns this study (including, but not limited to, laboratory test result reports, ECG reports, admission/discharge summaries for hospital admissions occurring during a participant's study participation, and autopsy reports for deaths occurring during the study).

The participant must be informed that his/her personal study-related data will be used by the Sponsor in accordance with local data protection law. The level of disclosure must also be explained to the participant.

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

10.1.5 Committees structure

The IDMC regularly reviewing data snapshots will be comprised of 3 independent medical experts (voting), an unblinded statistician, and the Sponsor's medical representatives (not voting and not part of open session). Other experts may be included in this group as voting or non-voting members or consulted at the discretion of the Sponsor. Further details are described in the IDMC Charter.

10.1.6 Data quality assurance

All participant data relating to the study will be recorded on printed, eCOA or eCRF unless transmitted to the Sponsor or designee electronically (eg, laboratory data). The Investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the eCRF or eCOA.

The Investigator must maintain accurate documentation (source data) that supports the information entered in the eCRF or eCOA.

The Investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.

The Sponsor or designee is responsible for the data management of this study including quality checking of the data.

Study monitors will perform ongoing source data verification to confirm that data entered into the eCRF by authorized site personnel are accurate, legible, contemporaneous, original, and attributable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH-GCP, and all applicable regulatory requirements.

All essential documents must be retained by the Investigator for the minimum retention period mandatory under the applicable local laws and regulations. The Investigator will contact UCB for authorization prior to the destruction of any study records or in the event of accidental loss or destruction of any study records. The Investigator will also notify UCB should he/she relocate or move the study-related files to a location other than that specified in the Sponsor's trial master file.

Quality tolerance limits will be established for the study using parameters related to patient safety reporting and reliability of study results. The parameters will be monitored throughout the study to identify systemic issues. Parameters used, parameter values, important deviations from the quality tolerance limits, and actions taken will be summarized in the clinical study report.

10.1.6.1 Case Report form completion

The Investigator is responsible for prompt reporting of accurate, complete, and legible data in the eCRFs or eCOA and in all required reports.

Any change or correction to the eCRF or eCOA after saving must be accompanied by a reason for the change.

Corrections made after the Investigator's review and approval (by means of a password/electronic signature) will be reapproved by the Investigator.

The Investigator should maintain a list of personnel authorized to enter data into the eCRF or eCOA.

Detailed instructions will be provided in the eCRF/eCOA Completion Guidelines.

10.1.6.2 Apps

Study participants will be given a smart phone with the MyUCB4me tool to enter their corticosteroid use.

The data recorded in the MyUCB4me tool are not intended to be used to influence the treatment decisions of study participants during the conduct of this study. Rather, the data will be analyzed at the end of the study to determine whether the design of the app enables the collection of information that has potential benefit in the future treatment of SLE.

Furthermore, this app is designed to only record data associated with the participant's disease state, and therefore it is neither designed nor intended to be used to collect or report safety-related information about the participant.

To ensure the confidence in the reliability, quality, and integrity of the data, several security measures have been put in place. The MyUCB4me tool itself is protected by a Personal Identification Number that is known only to the participant in SL0043. Furthermore, the MyUCB4me tool also allows for qualified and trained site personnel to personalize the configuration for each participant. The access to the personalized configuration within the MyUCB4me tool is password protected, and the password is only known to the site personnel.

All data entered by the study participant are fully encrypted within the MyUCB4me tool and its transmission to UCB Systems.

The participant responds to the questions and acts on the requested activities in the MyUCB4me tool. All data collected as part of these activities will be stored locally in the MyUCB4me tool. All data are reviewable for the Investigator while the participant is at the site. The data collected are synchronized with UCB Systems. All data in the MyUCB4me tool will be erased upon configuration for a new participant. All data collected will be provided back to the sites in a human readable way.

10.1.7 Source documents

All source documents must be accurate, clear, unambiguous, permanent, and capable of being audited. They should be made using some permanent form of recording (ink, typing, printing, optical disc). They should not be obscured by correction fluid or have temporary attachments (such as removable self-stick notes). Photocopies and/or printouts of eCRFs are not considered acceptable source documents.

Source documents are original records in which raw data are first recorded. These may include hospital/clinic/general practitioner records, charts, diaries, x-rays, laboratory results, printouts, pharmacy records, care records, ECG or other printouts, completed scales, QoL questionnaires, or video, for example. Source documents should be kept in a secure, limited access area.

Source documents that are computer generated and stored electronically must be printed for review by the monitor (eg, ECG reports). Once printed, these copies should be signed and dated by the Investigator and become a permanent part of the participant's source documents. The Investigator will facilitate the process for enabling the monitor to compare the content of the printout and the data stored in the computer to ensure all data are consistent.

Electronic data records, such as Holter monitor records or electroencephalogram records, must be saved and stored as instructed by UCB (or designee).

Source documents including clinical notes, doctor's letters, histology reports, reports of technical medical assessments (ie, imaging, electrography, ultrasound, laboratory reports), or photographs of cutaneous SLE manifestations may be requested in indicated cases and provided after

pseudonymization to a medical team established by the Sponsor for central source review of AEs and efficacy outcomes (see Section 8.1.1 and Section 10.3).

10.1.8 Study and site closure

The Sponsor designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the Sponsor. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study-site closure visit has been performed.

The Investigator may initiate study-site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a study site by the Sponsor or Investigator may include but are not limited to:

- Failure of the Investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the Sponsor's procedures, or GCP guidelines
- Inadequate recruitment of participants by the Investigator
- Discontinuation of further study medication development

10.1.9 Publication policy

The results of this study may be published or presented at scientific meetings. If this is foreseen, the Investigator agrees to submit all manuscripts or abstracts to the Sponsor before submission. This allows the Sponsor to protect proprietary information and to provide comments.

The Sponsor will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the Sponsor will generally support publication of multicenter studies only in their entirety and not as individual site data. In this case, a coordinating Investigator will be designated by mutual agreement.

Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

10.2 Appendix 2: Clinical laboratory tests

- The tests detailed in the table below will be performed by the central laboratory with the exception of urine pregnancy tests and ESR.
- Local laboratory results are only required in the event that the central laboratory results are not available in time for either study treatment administration and/or response evaluation. If a local sample is required, it is important that the sample for central analysis is obtained at the same time. Additionally, if the local laboratory results are used to make either a study treatment decision or response evaluation, the results must be entered into the eCRF.
- Protocol-specific requirements for inclusion or exclusion of participants are detailed in Section 5.1 and Section 5.2.
- Additional tests may be performed at any time during the study as determined necessary by the Investigator or required by local regulations.
- Study participants are to rest in a supine position for at least 10min before blood samples are taken. Blood samples are to be taken in the arm opposite the one used for infusion. **Blood samples must not be drawn through the infusion cannula.**

[redacted]

- At visits for which serum creatinine values are available, eGFR will be calculated using the Modification of Diet in Renal Disease formula modified for race.

Protocol-Required Safety Laboratory Assessments

Laboratory Assessments	**Parameters**		
Hematology	Platelet Count	RBC Indices:	WBC Count with Differential:
	RBC Count	MCV	Neutrophils
	Hemoglobin	MCH	Lymphocytes
	Hematocrit	%Reticulocytes	Monocytes
	Erythrocyte sedimentation rate	MCH concentration	Eosinophils
			Basophils
			[redacted]

Laboratory Assessments	Parameters			
Clinical Chemistry[a]	Blood Urea Nitrogen (BUN)	Potassium Sodium Chloride Calcium Phosphate	Aspartate Aminotransferase (AST)/ Serum glutamic-oxaloacetic transaminase (SGOT)	Total and direct bilirubin
	Creatinine		Alanine (ALT)/ serum glutamic-pyruvic transaminase (SGPT)	Total protein and albumin
	Glucose (nonfasting)		Alkaline phosphatase GGT LDH Lipase	Total cholesterol and triglycerides Lipase Creatine phosphokinase, CK-MB and Troponine I from serum in case of increased CPK
Routine Urinalysis	• Specific gravity • pH, glucose, protein, blood, ketones, bilirubin, urobilinogen, nitrite, leukocyte esterase by dipstick • Protein, albumin, and creatinine (for protein:creatinine ratio [mg/mmol] and albumin:creatinine [mg/mmol] ratios) • Microscopy of sediment for RBCs, RBC casts, WBCs, and WBC casts			
Other Screening Tests	• Follicle-stimulating hormone and estradiol (as needed in women of non-childbearing potential only) • Serum or urine human chorionic gonadotropin (hCG) pregnancy test (as needed for women of childbearing potential)[b] • Serology (hepatitis B surface antigen, hepatitis B core antibody, and hepatitis C virus antibody), plasma HIV antibody, and reflex testing • Tuberculosis test (IGRA): Quantiferon test All study-required laboratory assessments will be performed by a central laboratory.			

Laboratory Assessments	Parameters
Additional assessments	[redacted]

NOTES :

[a] Details of liver chemistry stopping criteria and required actions and follow-up assessments after liver stopping or monitoring event are given in Section 10.6. All events of ALT ≥3×upper limit of normal (ULN) and bilirubin ≥2 ×ULN (>35% direct bilirubin) or ALT ≥3×ULN and international normalized ratio (INR) >1.5, if INR measured, may indicate severe liver injury (possible Hy's Law) and must be reported as an SAE (excluding studies of hepatic impairment or cirrhosis).

[b] Local urine testing will be standard for the protocol (for all assessments after Screening) unless serum testing is required by local regulation or IRB/IEC.

[redacted]

Investigators must document their review of each laboratory safety report.

Laboratory results that could unblind the study will not be reported to investigative sites or other blinded personnel until the study has been unblinded.

10.3 Appendix 3: AEs – definitions and procedures for recording, evaluating, follow-up, and reporting

Definition of AE

AE Definition
• An AE is any untoward medical occurrence in a patient or clinical study participant, temporally associated with the use of study medication, whether or not considered related to the study medication. • NOTE: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of study medication.

Events Meeting the AE Definition
• Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) not related to SLE or other safety assessments (eg, ECG, radiological scans, vital signs measurements not related to SLE, including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the Investigator (ie, not related to progression of underlying disease). • Exacerbation of a chronic or intermittent pre-existing condition other than SLE including either an increase in frequency and/or intensity of the condition. • New conditions not SLE related detected or diagnosed after study medication administration even though it may have been present before the start of the study. • Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction. • Signs, symptoms, or the clinical sequelae of a suspected overdose of either study medication or a concomitant medication. Overdose per se will not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae. • "Lack of efficacy" or "failure of expected pharmacological action" per se will not be reported as an AE or SAE. Such instances will be captured in the efficacy assessments. However, the signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as SAE if they fulfil the definition of a SAE.

Events NOT Meeting the AE Definition

- Any clinically significant abnormal laboratory findings or other abnormal safety assessments which are associated with the underlying disease (SLE) except it fulfills seriousness criteria.
- SLE or expected progression, signs, or symptoms of the SLE except they fulfill seriousness criteria.
- Medical or surgical procedure (eg, endoscopy, appendectomy): the condition that leads to the procedure is the AE.
- Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).
- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

Definition of SAE

If an event is not an AE per definition above, then it cannot be an SAE even if serious conditions are met (eg, hospitalization for signs/symptoms of the disease under study, death due to progression of disease).

An SAE is defined as any untoward medical occurrence that, at any dose:
a. Results in death
b. Is life-threatening The term 'life-threatening' in the definition of 'serious' refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.
c. Requires inpatient hospitalization or prolongation of existing hospitalization In general, hospitalization signifies that the participant has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious. Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.
d. Results in persistent disability/incapacity • The term disability means a substantial disruption of a person's ability to conduct normal life functions. • This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, [redacted], and accidental trauma (eg, sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.
e. Is a congenital anomaly/birth defect
f. Important medical events: • Medical or scientific judgment should be exercised in deciding whether SAE reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious. • Examples of such events include, but are not limited to, potential Hy's law, invasive or malignant cancers, 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 drug dependency or drug abuse.

Recording and Follow-Up of AE and/or SAE

AE and SAE Recording

- When an AE/SAE occurs, it is the responsibility of the Investigator to review all documentation (eg, hospital progress notes, laboratory reports, and diagnostics reports) related to the event.
- The Investigator will then record all relevant AE/SAE information in the eCRF.
- It is **not** acceptable for the Investigator to send photocopies of the participant's medical records to UCB in lieu of completion of the UCB/AE/SAE eCRF page.
- There may be instances when copies of medical records for certain cases are requested by UCB. In this case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission to UCB.
- The Investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

Assessment of Intensity

The Investigator will make an assessment of intensity for each AE and SAE reported during the study and assign it to 1 of the following categories:

- Mild: An event that is easily tolerated by the participant, causing minimal discomfort and not interfering with everyday activities.
- Moderate: An event that causes sufficient discomfort and interferes with normal everyday activities.
- Severe: An event that prevents normal everyday activities. An AE that is assessed as severe should not be confused with a SAE. Severe is a category utilized for rating the intensity of an event; and both AEs and SAEs can be assessed as severe.
- An event is defined as 'serious' when it meets at least 1 of the predefined outcomes as described in the definition of an SAE, NOT when it is rated as severe (eg, a severe AE may be either serious or not serious, depending on whether these criteria are also met).

The National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) or the Rheumatology Common Terminology Criteria (RCTC) should be used as a supportive standardization instrument to evaluate AEs and SAEs but the final intensity grading by the Investigator must be mild, moderate, or severe.

Assessment of Causality

- The Investigator is obligated to assess the relationship between study medication and each occurrence of each AE/SAE.
- A "reasonable possibility" of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.
- The Investigator will use clinical judgment to determine the relationship.
- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study medication administration will be considered and investigated.
- The Investigator will also consult the IB and/or Product Information, for marketed products, in his/her assessment.
- For each AE/SAE, the Investigator **must** document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.
- There may be situations in which an SAE has occurred and the Investigator has minimal information to include in the initial report to UCB. However, **it is very important that the Investigator always make an assessment of causality for every event before the initial transmission of the SAE data to UCB.**
- The Investigator may change his/her opinion of causality in light of follow-up information and send a SAE follow-up report with the updated causality assessment.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.

Follow-up of AEs and SAEs

- The Investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by UCB to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.
- An AE should be followed until it has resolved, has a stable sequelae, the Investigator determines that it is no longer clinically significant, or the participant is lost to follow up. This follow-up requirement applies to AEs, SAEs, and AEs of special interest.
- If a participant dies during participation in the study or during a recognized follow-up period, the Investigator will provide UCB with a copy of any post-mortem findings including histopathology.
- New or updated information will be recorded in the originally completed eCRF.
- The Investigator will submit any updated SAE data to the Sponsor within 24 hours of receipt of the information.

Reporting of SAEs

SAE Reporting to UCB via an Electronic Data Collection Tool

- The primary mechanism for reporting an SAE to UCB will be the electronic data collection tool.
- If the electronic system is unavailable for more than 24 hours, then the site will use the paper SAE data collection tool (see next section).
- The site will enter the SAE data into the electronic system as soon as it becomes available.
- After the study is completed at a given site, the electronic data collection tool will be taken off-line to prevent the entry of new data or changes to existing data.
- If a site receives a report of a new SAE from a study participant or receives updated data on a previously reported SAE after the electronic data collection tool has been taken off-line, then the site can report this information on a paper SAE form (see next section) or to the UCB Study Physician by telephone.
- Contacts for SAE reporting can be found in SERIOUS ADVERSE EVENT REPORTING.

SAE Reporting to UCB via Paper CRF

- Facsimile transmission of the SAE paper CRF is the preferred method to transmit this information to the UCB Study Physician.
- In rare circumstances and in the absence of facsimile equipment, notification by telephone is acceptable with a copy of the SAE data collection tool sent by overnight mail or courier service.
- Initial notification via telephone does not replace the need for the Investigator to complete and sign the SAE CRF pages within the designated reporting time frames.
- Contacts for SAE reporting can be found in SERIOUS ADVERSE EVENT REPORTING.

AEOIs and AESMs should be reported to UCB within 24 hours irrespective of seriousness using the same procedures as reporting SAEs.

10.4 Appendix 4: Contraceptive guidance and collection of pregnancy information

Definitions

Woman of Childbearing Potential (WOCBP)

A woman is considered fertile following menarche and until becoming post-menopausal unless permanently sterile (see below).

Women in the following categories **are not considered WOCBP**:

1. Premenarchal
2. Premenopausal female with 1 of the following:
   - Documented hysterectomy
   - Documented bilateral salpingectomy
   - Documented bilateral oophorectomy

   Note: Documentation can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview.
3. Postmenopausal female
   - A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. A high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy (HRT). However, in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient.
   - Females on HRT and whose menopausal status is in doubt will be required to use one of the non-estrogen hormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

Contraception Guidance

Male participants

Male participants with female partners of childbearing potential (including partners who are pregnant or breastfeeding [including pumping breast milk to feed to a child]) must use contraception if any of the following criteria are met:

- Genotoxic study medication
- Study medication where reproductive toxicology studies have not yet been conducted
- Study medication with demonstrated or suspected human teratogenicity/fetotoxicity at subtherapeutic exposure levels if relevant systemic concentrations may be achieved in WOCBP from exposure to seminal fluid

Male participants with female partners of childbearing potential are eligible to participate if they agree to ONE of the following during the protocol-defined time frame in Section 5.1:

- Are abstinent from penile-vaginal intercourse as their usual and preferred lifestyle (abstinent on a long-term and persistent basis) and agree to remain abstinent.
- Agree to use a male condom plus partner use of a contraceptive method with a failure rate of <1% per year as described in the table below when having penile-vaginal intercourse with a WOCBP who is not currently pregnant.
- Agree to use a male condom when having penile-vaginal intercourse WOCBP who is currently pregnant.

In addition male participants must refrain from donating sperm for the duration of the study and for 17 weeks after the final dose of study medication.

Male participants with a pregnant or breastfeeding (including pumping breast milk to feed to a child) partner must agree to remain abstinent from penile-vaginal intercourse or use a male condom during each episode of penile penetration during the study and for at least 17 weeks after the final dose of study medication.

Female participants

Female participants of childbearing potential are eligible to participate if they agree to use a highly effective method of contraception consistently and correctly as described in the table below. If the Investigator considers another contraception method not listed below but is proven to have a failure rate <1/100 patient-years (PEARL index) or participants use a combination of contraceptives with a failure rate <1/100 patient-years, then this method may be considered as effective contraception after discussion with the Medical Monitor or Sponsor Study Physician.

Highly Effective Contraceptive Methods[a]

Highly Effective Contraceptive Methods That Are User Dependent[b] Failure rate of <1% per year when used consistently and correctly.
Combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation[c] • Oral • Intravaginal • Transdermal
Progestogen only hormonal contraception associated with inhibition of ovulation • Oral • Injectable
Highly Effective Methods That Are User Independent
Implantable progestogen only hormonal contraception associated with inhibition of ovulation • Intrauterine device (IUD) • Intrauterine hormone-releasing system (IUS) • Bilateral tubal occlusion
Vasectomized partner A vasectomized partner is a highly effective contraception method provided that the partner is the sole male sexual partner of the WOCBP and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used.
Sexual abstinence Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study medication. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.

NOTES:
a) In case of newly started contraception pills/IUDs, PI should consider the correct timing of starting/applying such methods in relation to the menstrual cycle and the manufacturing instruction as when these newly started methods would become effective.
b) Typical use failure rates may differ from those when used consistently and correctly. Use should be consistent with local regulations regarding the use of contraceptive methods for participants participating in clinical studies.

Potential drug-drug interactions of medicinal products or medical conditions (eg, gastrointestinal disturbances like diarrhea, vomiting) which could impact the effectiveness of oral contraceptives need to be considered as well. Respective prescribing information of concomitant medications needs to be consulted and guidance (SmPC, local/national or international guidance) on the need of additional contraceptive methods be followed.

Female participants using mycophenolate treatment

As per current EMA recommendations for contraception for men and women during mycophenolate treatment (EMA/828208/2017) patients who can get pregnant must use at least

one reliable form of contraception before, during, and for 6 weeks after stopping treatment. Two forms of contraception are preferred.

As per current FDA label information (Cellcept [package insert] 2019), females of reproductive potential taking mycophenolate must receive contraceptive counseling and use acceptable contraception. Patients must use acceptable birth control during the entire mycophenolate therapy, and for 6 weeks after stopping mycophenolate, unless the patient chooses abstinence.

Unless patients are abstinent, acceptable contraceptive methods for females of reproductive potential during, and for 6 weeks after, treatment with mycophenolate are shown below (Cellcept [package insert] 2019, Table 7):

Option 1 Methods to use alone	Intrauterine devices (IUDs) Tubal sterilization Patient's partner vasectomy

OR

Option 2	Hormone Methods Choose 1		Barrier Methods Choose 1
Choose one hormone method AND one barrier method	Estrogen and progesterone • Oral contraceptive pill • Transdermal patch • Vaginal ring Progesterone-only • Injection • Implant	AND	Diaphragm with spermicide Cervical cap with spermicide Contraceptive sponge Male condom Female condom

OR

Option 3	Barrier Methods choose 1		Barrier Methods choose 1
Choose one barrier method from each column (must choose two methods)	Diaphragm with spermicide Cervical cap with spermicide Contraceptive sponge	AND	Male condom Female condom

Pregnancy testing

- Women of childbearing potential should only be included after a confirmed menstrual period and a negative highly sensitive serum pregnancy test.
- Additional urine pregnancy testing should be performed at monthly intervals during the treatment period and at End of Treatment/End of Study, after the final dose of study medication and as required locally.

- Pregnancy testing will be performed when pregnancy is suspected
- Pregnancy testing will be performed at Screening and at every post-Screening visit before study medication application.
- If a study participant is pregnant and stays in the study for observation no pregnancy testing will be performed as long as the pregnancy lasts.

Male participants with partners who become pregnant

- The Investigator will attempt to collect pregnancy information on any male participant's female partner who becomes pregnant while the male participant is in this study. This applies only to male participants who receive study medication. If the study participant is later found to be on placebo, then pregnancy data collection can stop.
- After obtaining the necessary signed informed consent from the pregnant female partner directly, the Investigator will record pregnancy information on the appropriate form and submit it to the Sponsor within 1 working day of learning of the partner's pregnancy. The female partner will also be followed to determine the outcome of the pregnancy. Information on the status of the mother and child will be forwarded to the Sponsor. Generally, the follow-up will be at least 12 months after the delivery date. Any termination of the pregnancy will be reported regardless of fetal status (presence or absence of anomalies) or indication for the procedure.

Female Participants who become pregnant

- Any female participant who becomes pregnant while participating in the study will discontinue study medication.
- The Investigator will collect pregnancy information on any female participant who becomes pregnant while participating in this study. Information will be recorded on the appropriate form and submitted to the Sponsor within 1 working day of learning of a participant's pregnancy. The participant will be followed to determine the outcome of the pregnancy. The Investigator will collect follow-up information on the participant and the neonate and the information will be forwarded to the Sponsor. Generally, the follow-up will be at least 12 months after the delivery date. Any termination of pregnancy will be reported, regardless of fetal status (presence or absence of anomalies) or indication for the procedure.
- While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy will be reported as an AE or SAE. A spontaneous abortion is always considered to be an SAE and will be reported as such. Any post-study pregnancy related SAE considered reasonably related to the study medication by the Investigator will be reported to the Sponsor as described in Section 8.3.5. While the Investigator is not obligated to actively seek this information in former study participants, he or she may learn of an SAE through spontaneous reporting.
- The Investigator should obtain obstetric history of the study participant, outcomes of prior pregnancies, complications of pregnancy and parturition, birth defects and health problems in infancy in earlier offspring and known family history of birth defects.

10.5 Appendix 5: Genetics

Use and Analysis of DNA

- Genetic variation may impact a participant's response to study medication, susceptibility to, and severity and progression of disease. Variable response to study medication may be due to genetic determinants that impact drug absorption, distribution, metabolism, and excretion; mechanism of action of the drug; disease etiology; and/or molecular subtype of the disease being treated. Therefore, where local regulations and IRB/IEC allow, a blood sample will be collected for DNA analysis from participants who have provided a separate informed consent.
- DNA samples may be used for research related to DZP or SLE and related diseases. They may also be used to develop tests/assays including diagnostic tests related to DZP and/or interventions of this drug class and SLE. Genetic research may consist of the analysis of one or more candidate genes or the analysis of genetic markers throughout the genome (as appropriate).
- The samples may be analyzed as part of a multi-study assessment of genetic factors involved in the response to DZP or study medications of this class to understand study disease or related conditions.
- The results of genetic analyses will be reported separately from the clinical study report or in a separate study summary.
- The Sponsor will store the DNA samples in a secure storage space with adequate measures to protect confidentiality.
- The samples will be retained while research on DZP or SLE continues but no longer than 20 years or other period as per local requirements.

10.6 Appendix 6: Liver safety – suggested actions and follow-up assessments

Participants with potential drug-induced liver injury must be assessed to determine if study medication must be discontinued. In addition, all concomitant medications and herbal supplements that are not medically necessary should also be discontinued.

Investigators should attempt to obtain information on study participants in the case of study medication discontinuation to complete the final evaluation.

Study participants with potential drug-induced liver injury should not be withdrawn from the study until investigation and monitoring are complete. All results of these evaluations and observations, as well as the reason(s) for study medication discontinuation and/or participant withdrawal (if applicable), must be recorded in the source documents. The eCRF must document the primary reason for discontinuation of study medication.

A specific monitoring plan must be agreed between the UCB study physician and the Investigator for study participants who have ALT >5 ULN. The monitoring plan should include any necessary follow-up assessments (until resolution of the abnormal lab values).

Table 10-1: Phase 3-4 liver chemistry stopping criteria and follow-up assessments

Liver Chemistry Stopping Criteria	
ALT-absolute	ALT ≥8xULN
ALT Increase	ALT ≥5xULN but <8xULN persists for ≥2 weeks ALT ≥3xULN but <5xULN persists for ≥4 weeks
Bilirubin[a,b]	ALT ≥3xULN **and** bilirubin ≥2xULN (>35% direct bilirubin)
INR [b]	ALT ≥3xULN **and** international normalized ratio (INR) >1.5, if INR measured
Cannot Monitor	ALT ≥5xULN but <8xULN and cannot be monitored weekly for ≥2 weeks ALT ≥3xULN but <5xULN and cannot be monitored weekly for ≥4 weeks
Symptomatic[c]	ALT ≥3xULN associated with symptoms (new or worsening) believed to be related to liver injury or [redacted]
Suggested Actions and Follow up Assessments	
Actions	**Follow Up Assessments**
• **Immediately** discontinue study medication. • Report the event to the UCB within **24 hours.** • Complete the liver event case report form (eCRF), and complete a serious adverse event (SAE) data collection tool if the event also met the criteria for an SAE. [b] • Perform liver chemistry follow-up assessments.	• Viral hepatitis serology[d] • Obtain INR and recheck with each liver chemistry assessment until the transaminases values show downward trend • Only in those with underlying chronic hepatitis B at screening visit (V1) (identified by positive hepatitis B surface antigen or hepatitis B core antibodies), quantitative

Liver Chemistry Stopping Criteria	
• Monitor the participant until liver chemistry test abnormalities resolve, stabilize, or return to baseline (see **MONITORING**). • **Do not restart/rechallenge** participant with study medication unless allowed per protocol and UCB approval is granted. • If restart/rechallenge **not allowed per protocol or not granted**, permanently discontinue study medication and continue participant in the study for any protocol specified follow up assessments.Consider the need for a toxicology screening. **MONITORING:** **<u>For bilirubin or INR criteria</u>** • Repeat liver chemistry tests (include ALT, aspartate transaminase [AST], alkaline phosphatase, bilirubin) and perform liver event follow-up assessments within **24 hours.** • Monitor participant twice weekly until liver chemistry test abnormalities resolve, stabilize, or return to baseline. • A specialist or hepatology consultation is recommended. **<u>For all other criteria</u>** • Repeat liver chemistry tests (include ALT, AST, alkaline phosphatase, bilirubin) and perform liver chemistry follow-up assessments within **24 to 72 hours.** • Monitor participants weekly until liver chemistry abnormalities resolve, stabilize, or return to baseline.	hepatitis B deoxyribonucleic acid (DNA) and hepatitis delta antibody[e] • Obtain blood sample for pharmacokinetic (PK) analysis after the most recent dose[f] • Serum creatine phosphokinase (CPK) and lactate dehydrogenase (LDH) • Fractionate bilirubin, if total bilirubin ≥ 2xULN • Obtain complete blood count with differential to assess eosinophilia • Record the appearance or worsening of clinical symptoms of liver injury (eg, fatigue, nausea, vomiting, right upper quadrant pain), or [redacted], on the adverse event (AE) report form • Record use of concomitant medications (including acetaminophen, herbal remedies, and other over-the-counter medications) on the concomitant medications eCRF. • Record alcohol use on the liver event alcohol intake eCRF • Exclude pregnancy **<u>For bilirubin or INR criteria:</u>** • Anti-nuclear antibody, anti-smooth muscle antibody, Type 1 anti-liver kidney microsomal antibodies, and quantitative total [redacted] • Serum acetaminophen adduct high performance liquid chromatography (HPLC) assay (quantifies potential acetaminophen contribution to liver injury in participants with definite or likely acetaminophen use in the preceding week [James, 2009]). **NOTE: Not required in China**. • Liver imaging (ultrasound, magnetic resonance, or computerized tomography) and or liver biopsy to evaluate liver disease; complete Liver Imaging and/or Liver Biopsy eCRFs.

[a] Serum bilirubin fractionation should be performed if testing is available. If serum bilirubin fractionation is not immediately available, discontinue study medication if ALT ≥3xULN **and** bilirubin ≥2xULN. Additionally, if serum bilirubin fractionation testing is unavailable, **record the absence/presence of detectable urinary bilirubin on dipstick** which is indicative of direct bilirubin elevations suggesting liver injury.

[b] All events of ALT ≥3xULN and bilirubin ≥2xULN (>35% direct bilirubin) or ALT ≥3xULN and INR >1.5 may indicate severe liver injury **(possible 'Hy's Law') and must be reported as an SAE (excluding studies of**

hepatic impairment or cirrhosis). The INR measurement is not required and the stated threshold value will not apply to participants receiving anticoagulants.

[c] New or worsening symptoms believed to be related to liver injury (such as fatigue, nausea, vomiting, right upper quadrant pain or tenderness, or jaundice) or [redacted] (such as fever, rash or eosinophilia).

[d] Includes: Hepatitis A [redacted]; HBsAg and HBcAb; hepatitis C RNA; cytomegalovirus [redacted] Epstein-Barr viral capsid antigen [redacted] (or if unavailable, heterophile antibody or monospot testing); and hepatitis E [redacted]

[e] If hepatitis delta antibody assay cannot be performed, it can be replaced with a polymerase chain reaction (PCR) of hepatitis D RNA virus (where needed) (Le Gal, 2005).

[f] PK sample may not be required for participants known to be receiving placebo or non-comparator interventions. Record the date/time of the PK blood sample draw and the date/time of the last dose of study medication prior to the PK blood sample draw on the eCRF. If the date or time of the last dose is unclear, provide the participant's best approximation. If the date/time of the last dose cannot be approximated OR a PK sample cannot be collected in the time period indicated above, do not obtain a PK sample. Instructions for sample handling and shipping are in the Laboratory Manual.

10.7 Appendix 7: Medical device AEs, ADEs, SAEs and device deficiencies: definition and procedures for recording, evaluating, follow-up, and reporting

Not applicable.

10.8 Appendix 8: Rapid alert procedures

Not applicable.

10.9 Appendix 9: Country-specific requirements

10.9.1 Poland

The Polish Health Authority's and Clinical Trial Facilitation Group have made recommendations related to contraception and pregnancy testing in a clinical study with IMP where the human data for exposure at pregnancy and nonclinical reproductive toxicology data are not available. As a mitigation measure, pregnancy testing is to be implemented monthly up to 2 months after the final dose of study medication. A urine pregnancy test is added at 4 weeks after final study medication administration at Week 44 (Visit 13) for sites located in Poland, thus it meets the above requirement. Based on the short half-life of the study medication and because genotoxicity is not a class effect of the monoclonal antibody, it is considered [redacted] to reduce the duration of post-study medication administration requirement on contraception for female study participants of childbearing potential from 3 months to 2 months, with implementation of monthly pregnancy testing during this period.

10.9.2 Romania

The Romanian authorities introduced the following specific requirement for Romania: change in duration for the use of permitted oral corticosteroids (prednisolone) from a stable dose of 2 weeks to 4 weeks prior to the Baseline Visit (Visit 2). It is recommended for sites located in Romania, that oral corticosteroids (prednisolone) need to be stable for 4 weeks, rather than 2 weeks as mentioned in Section 5.1 of this protocol.

10.10 Appendix 10: Abbreviations and trademarks

ACR	American College of Rheumatology
ACE	angiotensin converting enzyme
ADL	activities of daily living
AE	adverse event
ALP	alkaline phosphatase
ALT	alanine aminotransferase
[redacted]	
aPL	antiphospholipid
APS	antiphospholipid syndrome
[redacted]	
AST	aspartate aminotransferase
BICLA	BILAG 2004-based Composite Lupus Assessment
BILAG 2004	British Isles Lupus Assessment Group Disease Activity Index 2004
CAPS	catastrophic APS
[redacted]	
CI	confidence interval
CLASI	Cutaneous Lupus Erythematosus Disease Area and Severity Index
CNS	central nervous system
COVID-19	Coronavirus disease 2019
CPM	Clinical Project Manager
CRO	contract research organization
C-SSRS	Columbia Suicide Severity Rating Scale
DNA	deoxyribonucleic acid

DZP	dapirolizumab pegol
[redacted]	[redacted]
ECG	electrocardiogram
eCOA	electronic clinical outcomes assessment form
eCRF	electronic Case Report Form
EQ-5D-5L	Euro Quality of life 5-Dimensions 5-Level
eGFR	estimated glomerular filtration rate
ES	Enrolled Set
EULAR/ACR	European League Against Rheumatism/American College of Rheumatology
Fab′	fragment antigen-binding
FAS	Full Analysis Set
Fc	fragment crystallizable
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GEE	Generalized Estimating Equation
HIV	human immunodeficiency virus
HMG-CoA	3-hydroxy-3-methyl-glutaryl-coenzyme A
HRQoL	health-related quality of life
[redacted]	[redacted]
IB	Investigator's Brochure
ICF	Informed Consent form
ICH	International Council for Harmonisation
IDMC	independent data monitoring committee
IEC	Independent Ethics Committee
Ig	immunoglobulin
IGRA	interferon-γ release assay
IMP	investigational medicinal product
INR	International Normalized Ratio
IP	investigational product
IRB	Institutional Review Board
iv	intravenous(ly)
IWRS	interactive web response system

LLDAS	low lupus disease activity state
LLN	lower limit of normal
LTBI	latent tuberculosis infection
LupusQoL	Lupus Quality of Life questionnaire
MCP	metacarpophalangeal
MMF	mycophenolate mofetil
NHP	nonhuman primate
NSAID	nonsteroidal anti-inflammatory drug
NTM	non-tuberculosis mycobacterial
OLE	open label extension
PBO	placebo
PCR	polymerase chain reaction
PD	pharmacodynamics(s)
PEF	peak expiratory flow
PEG	polyethylene glycol
PGA	Physician's Global Assessment of Disease
PHQ-9	Patient Health Questionnaire-9
PIP	proximal interphalangeal
PK	pharmacokinetic(s)
PK-PPS	Pharmacokinetic Per Protocol Set
PPS	Per Protocol Set
PRO	patient-reported outcome
QoL	quality of life
qSOFA	Quick Sequential Organ Failure Assessment
Q4W	every 4 weeks
[redacted]	[redacted]
RNA	ribonucleic acid
RS	Randomized Set
SAE	serious adverse event
SAP	Statistical Analysis Plan
SARS CoV-2	severe acute respiratory syndrome coronavirus 2
SFI	SELENA (Safety of Estrogens in Lupus National Assessment) Flare Index

SFU	Safety Follow-up
SJC	swollen joint count
SLE	systemic lupus erythematosus
SLEDAI-2K	Systemic Lupus Erythematosus Disease Activity Index 2000
SLICC	Systemic Lupus International Collaborating Clinics
SOC	standard of care
SRI	Systemic Lupus Erythematosus Responder Index
SS	Safety Set
TB	tuberculosis
TEAE	treatment-emergent adverse event
TJC	tender joint count
TT	tetanus toxoid
ULN	upper limit of normal
VAS	visual analog scale
WOCBP	woman of childbearing potential

10.11 Appendix 11: Protocol amendment history

Amendment 3: 14 Jan 2022

This amendment is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.

Overall Rationale for the Amendment

The primary purpose of this amendment is to provide recommendations for contraception during mycophenolate treatment, as requested by regulatory authorities. Additional guidance on Coronavirus disease 2019 (COVID-19) vaccinations in immunosuppressed patients has been added, as recommend by the Independent Data Monitoring Committee. Other updates have been incorporated based on Investigators feedback, to provide further clarity on the protocol or to correct errors. The table below does not include correction of minor typographical errors and formatting/stylistic changes.

Section # and Name	Description of Change	Brief Rationale
1.3 Schedule of activities	"COVID-19=Coronavirus disease 2019;" has been added to the table of abbreviations.	Updated for consistency within the table.
1.3 Schedule of activities	Footnote j: "(including vaccinations against COVID-19)" has been added.	Updated for consistency within the protocol.
1.3 Schedule of activities	The following text has been added to [redacted]	Updated to provide clarification of collection specifications.
1.3 Schedule of Activities		Clarification of when blood samples are collected.
5.2 Exclusion criteria	Exclusion criterion #20a: "Investigator should consider local and international guidance on vaccination in immunosuppressed patients and discuss risks, benefits and administration options with participants (for more details see also Section 6.6.1 and Section 8.2.7)." has been added.	To provide additional guidance on COVID-19 vaccinations in immunosuppressed patients.
6.5.1.3 Other immunosuppressants/ immunomodulatory agents	The following text has been added to: Other immunosuppressant or immunomodulatory agents **are permitted during the study** (see	Updated to provide further clarity.

	inclusion criteria and maximum dose restrictions in Table 6-6)	
6.5.1.3 Other immunosuppressants/ immunomodulatory agents	"If immunosuppressants permitted during the study were stopped before study entry, they must have been stopped no later than 8 weeks prior to the Screening Visit." has been added.	Updated to provide clarity and consistency with other systemic lupus erythematosus medications, as so far for immunosuppressants only a required minimum time interval participants had to be on a stable dose was defined, but no timeframe was defined in case immunosuppressants were stopped before screening.
6.5.1.3 Other immunosuppressants/ immunomodulatory agents	New wording was included to clarify that if a participant has a vaccination a temporary hold or a reduction in dose of concomitant immunosuppressant or immunomodulatory agents are permitted.	Updated to provide clarity.
6.5.1.3 Other immunosuppressants/ immunomodulatory agents	Table 6-6: Maximum doses of permitted concomitant immunosuppressants: "Coated mycophenolate mofetil" changed to "Coated mycophenolate sodium".	Correction.
6.5.1.3 Other immunosuppressants/ immunomodulatory agents	"It cannot be excluded that mycophenolate mofetil (MMF) could reduce effectiveness of combined hormonal contraceptives including levonorgestrel. Investigators are advised to regularly counsel patients who are of childbearing potential on the risk of MMF treatment for adverse pregnancy outcomes and the possibility of reduced effectiveness of hormonal contraceptives due to interaction with MMF. Please refer to Section 10.4 for further information." has been added.	To address a regulatory authority request.
6.5.1.4 Analgesics, medications including natural or synthetic cannabinoids (approved in line with local regulations), NSAIDs, HMG-CoA reductase inhibitors (statins), ACE inhibitors, and other anti-hypertensive drugs	The sub-heading number (6.5.1.4) was added.	Editorial correction.

6.6.1 Prohibited concomitant treatments (medications and therapies)	"with the exception of immunoglobulins which are allowed to be used concomitantly with DZP after randomization if medically indicated." has been added to the end of the first sentence.	To clarify that use of immunoglobulins in parallel to DZP does not represent a safety concern (in difference to other drugs) and is thereby not prohibited.
6.6.1 Prohibited concomitant treatments (medications and therapies)	The following text has been added to: In case one of these medications has to be initiated during the study, the IMP needs to be permanently discontinued **(with the exception of immunoglobulins)**.	Updated to provide further clarity.
6.6.1 Prohibited concomitant treatments (medications and therapies)	Table 6-7: Prohibited medications and required wash-out periods prior to the Screening Visit (V1): Updates were made to some of the prohibited medications and their wash-out periods.	To adapt washout periods based on recent pharmacokinetic and pharmacodynamic data for approved biologics (see Section 10.13).
6.6.1 Prohibited concomitant treatments (medications and therapies)	Table 6-7: Prohibited medications and required wash-out periods prior to the Screening Visit (V1): The routes of administration (iv and sc) have been added for Belimumab (Benlysta™).	Added to provide further clarity.
6.6.1 Prohibited concomitant treatments (medications and therapies)	Table 6-7: Prohibited medications and required wash-out periods prior to the Screening Visit (V1): Tacrolimus (FK506) (Prograf®) has been removed from the table.	Tacrolimus is approved and is a permitted escape medication (see Section 6.6.2).
6.6.1 Prohibited concomitant treatments (medications and therapies)	Table 6-7: Prohibited medications and required wash-out periods prior to the Screening Visit (V1): Footnote a has been added: The wash-out period refers to the last administration of the relevant medication.	Added to provide further clarity.
6.6.1 Prohibited concomitant treatments (medications and therapies)	Table 6-7: Prohibited medications and required wash-out periods prior to the Screening Visit (V1): the definition for MRA in the footnote has been changed to "myeloma receptor antibody".	Correction.
6.6.1 Prohibited concomitant treatments (medications and therapies)	Details have been added to provide vaccination guidance for non-live vaccines.	To provide additional guidance on COVID-19 vaccinations in immunosuppressed patients.
6.6.1 Prohibited concomitant treatments (medications and therapies)	"In case of administration of investigational Coronavirus Disease 2019 (COVID-19) vaccine (vaccines without regulatory authorization or	To clarify how DZP administration should be handled in case of administration of

	emergency authorization) study medication should not be administered within 2 weeks after vaccination." has been added to the vaccines subsection.	investigational COVID-19 vaccines.
8.1.3.2 Severe BILAG flare	The definition of a severe flare was amended.	Corrected to be aligned with the definition as published by Isenberg et al, 2011.
8.1.3.3 Moderate BILAG flare	The definition of a moderate flare was amended.	Corrected to be aligned with the definition as published by Isenberg et al, 2011.
8.2.6.1.3 Latent TB	Wording was modified to clarify that study participants who prematurely discontinue treatment for LTBI or who, in the opinion of the Investigator or Sponsor, are noncompliant with anti-TB therapy are withdrawn from study treatment, but are still encouraged to regularly attend scheduled visits (but without IMP administration).	Updated for consistency within the protocol.
8.2.7 SARS-CoV-2/ Coronavirus Disease 2019	Details have been added to provide reference to local and international guidance on vaccination of immunocompromised patients.	To provide additional guidance on COVID-19 vaccinations in immunosuppressed patients.
8.3.8 Anticipated SAEs	New wording was included to provide clarity for the Investigators regarding anticipated SAEs and reporting of SAEs.	Updated to reduce ambiguity and considerations from the recently released FDA guidance.
9.3.1 Analysis of the primary efficacy/primary endpoint	Details regarding the covariate "corticosteroid dose at Baseline (≤7.5mg/day vs >7.5mg/day)" have been removed.	To clarify that any covariate be described and justified in the Statistical Analysis Plan before unblinding.
9.7 Planned interim analysis and data monitoring	Noted that other key secondary and secondary efficacy endpoints will be provided at the interim analysis for consideration by the IDMC in the recommendation regarding futility. In addition, stated that the SAP will address considerations around ensuring the blind with regards to the interim futility analysis.	Correction to data provided to IDMC, and to approach for documentation of ensuring the blind with regards to the interim futility analysis.
10.2 Appendix 2: Clinical laboratory tests	Protocol-required safety laboratory assessments: Footnote a removed from the Additional assessment: aPL antibodies including [redacted]	Correction.

	[redacted] Footnote a added to the Additional assessment: Hepatitis/liver injury diagnostic.	
10.4 Appendix 4: Contraceptive guidance and collection of pregnancy information	Female participants: Clarified that the PEARL index is used.	Updated to correct an error and provide clarity.
10.4 Appendix 4: Contraceptive guidance and collection of pregnancy information	Details added to note that potential drug-drug interactions of medicinal products or medical conditions could impact the effectiveness of oral contraceptives and therefore prescribing information and guidance's should be followed.	Updated to provide clarity and reference to guidances and labels.
10.4.1 Female participants using mycophenolate treatment	A section has been added to provide contraceptive guidance for female participants using mycophenolate treatment.	To address a regulatory authority request.
10.10 Appendix 10: Abbreviations and Trademarks	One addition (MMF) was made to the list of abbreviations.	Updated to reflect the parameters measured in the study.
10.11 Appendix 11: Protocol Amendment History	Added a summary of the changes made in Amendment 2.	Intra-document cross-reference.
10.13 Appendix 13: Inclusion and exclusion criteria rationale	Exclusion criterion #20a: "Investigator should consider local and international guidance on vaccination in immunosuppressed patients and discuss risks, benefits and administration options with participants (for more details see also Section 6.6.1 and Section 8.2.7)." has been added.	To provide additional guidance on COVID-19 vaccinations in immunosuppressed patients.
10.13 Appendix 13: Inclusion and exclusion criteria rationale	The following text has been added to the justification for exclusion criteria #23: [redacted]	To adapt washout periods based on recent pharmacokinetic and pharmacodynamic data for approved biologics.

	[redacted]	
11 REFERENCES	Nine new references have been added.	Updated to reflect the additional publications used within the document.

Amendment 2: 29 Jun 2021

Overall Rationale for the Amendment

The primary purpose of this amendment is to clarify that repeat certified BILAG 2004 training for Investigators who have used the assessment within 2 years in any DZP study that requires BILAG 2004 assessments is not required as continued use supports maintenance of skills; to clarify that photodocumentation of cutaneous SLE manifestations as part of source documents may be needed for adjudication of BILAG 2004 grading; to update the recommendations about the concomitant use of calcineurin inhibitors (including newly authorized voclosporin) and to add cautionary statements about co-administration of these products with the study drug; and to remove references to the IF-IDMC as a group separate from the IDMC, as the members are the same. These and other secondary changes are summarized in the following table. The table does not include correction of minor typographical errors and formatting/stylistic changes.

Section # and Name	Description of Change	Brief Rationale
1.1 Synopsis 4.1 Overall design 9.7 Planned interim analysis and data monitoring	Removed text referring to and describing IF-IDMC as a group separate from the IDMC.	Clarification that IF-IDMC and IDMC members are the same and function under 1 charter (ie, the IDMC charter).
1.3 Schedule of activities 6.1 Treatments administered	Added that Baseline body weight is used to determine dosing through Week 20 for study participants screened under the initial protocol (ie, before Amendment 1).	Clarification. Baseline body weight was specified in the protocol prior to Amendment 1 and changed to Screening with Amendment 1.

1.3 Schedule of activities 8.1.1.1 BILAG 2004 10.1.7 Source documents	Added text regarding photodocumentation of cutaneous SLE manifestations.	Clarification regarding need for source documentation to support external adjudication of BILAG 2004 grading.
5.1 Inclusion criteria 7.1.3 Permanent and temporary study drug discontinuation due to other reasons 10.4 Appendix 4: Contraceptive guidance and collection of pregnancy information 10.13 Appendix 13: Inclusion and exclusion criteria rationale	Added "including pumping breast milk to feed to a child" to "breastfeeding" (Criterion 4; with amendment "4" becomes "4a").	Clarification.
5.2 Exclusion criteria 10.13 Appendix 13: Inclusion and exclusion criteria rationale	Reordered examples of latent and opportunistic infections. (Criterion 17a; with amendment "17a" becomes "17b").	Clarification that herpes simplex virus and, unless severe, herpes zoster are not considered as opportunistic infections but rather as latent infections.
5.2 Exclusion criteria 10.13 Appendix 13: Inclusion and exclusion criteria rationale	Clarification of criteria for fractionation of bilirubin. (Criterion 29; with amendment becomes 29a).	Consistency with existing Gilbert's syndrome text in this criterion.
6.3.1.2 Breaking the treatment blind in an emergency situation	Addition of text stating that unblinding can be initiated by the Investigator at any time as medically indicated.	Clarification and emphasis.
6.5.1.3 Other immunosuppressants/immunomodulatory agents 6.6.2 Escape medication	Added voclosporin.	Voclosporin approved for active renal SLE in US.
6.5.1.3 Other immunosuppressants/immunomodulatory agents	Added cautionary text about administration of calcineurin inhibitors.	To emphasize the need for compliance with local guidance(s) and caution for concomitant use with study drug due to potential risks that cannot be excluded at this time.
6.6.1 Prohibited concomitant treatments (medications and therapies)	Clarified that only high-dose cyclophosphamide is prohibited.	Correction.
8.1.1.1 BILAG 2004	Eliminated the requirement for repeat certified BILAG	Investigators who have completed full certified

	2004 training for Investigators who have used the assessment within 2 years in any DZP study that requires BILAG 2004 assessments.	BILAG 2004 training, and who have ongoing and recent (within 2 years) use of the BILAG 2004 assessment are considered to be in continuous training.
9.7 Planned interim analysis and data monitoring	Removed reference to interim SAP.	Plans for the interim futility analysis are included in the main SAP.
10.11 Appendix 11: Protocol Amendment History	Added a summary of the changes made in Amendment 1.	Intra-document cross-reference.

Amendment 1: 14 Oct 2020

This amendment is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.

Overall Rationale for the Amendment

This amendment addresses questions and comments from regulators, Investigators, and other reviewers. Included are updates to the planned analysis, addition of exploratory biomarker analysis on the [redacted] clarification regarding handling of protocol-defined criteria and actions respect to the SARS-CoV-2 pandemic, clarification of unclear or miss-interpretable text, and resolution/clarification of inconsistencies between different sections. In addition, minor editorial changes have been made and minor errors corrected.

Section # and Name	Description of Change	Brief Rationale
The following changes were made throughout the protocol:	Added BILAG 2004 score of B at baseline to be included in assessments of worsening Clarified that "prevention of severe BILAG flares" means severe BILAG flare-free Clarified that "prevention of moderate/severe BILAG flares" means moderate/severe BILAG flare-free	To clarify based on regulator feedback
1.1 Synopsis – Objectives and Endpoints 3 Objectives and Endpoints 10.12 Endpoint rationale	Tertiary endpoints: FATIGUE-SLE replaced with FATIGUE-PRO throughout document Changes in exploratory biomarkers updated:	Name of scale recently changed. To add exploratory biomarker analysis to be able to assess

	[redacted] added.	[redacted]
1.1 Synopsis and 4.1 Overall design 9.7 Planned interim analysis and data monitoring	BILAG 2004 neuropsychiatric body organ system to monitor potential neuropsychiatric events falsely assigned to SLE added to IDMC review Clarification added on IF-IDMC determination if the study should be stopped. Details added of regular IDMC meetings	Additional text to clarify that the IDMC will also review neuropsychiatric outcomes as defined by BILAG 2004 in line with the Investigator's Brochure. Editorial change to provide more details on the planned interim analysis.
1.3 Schedule of Activities, Table 1-1	Updated schedule of events table and footnotes	Editorial change to provide more information and/or correct errors
2.2 Background	Data from the 3 clinical studies (SL0013, SL0014, and SL0023) added.	To provide information included in the IB
5.1 Inclusion criteria and Appendix 13: Inclusion and exclusion criteria rationale	Clarified timing of the "study entry" as appeared in the original protocol. (number changed from 2.a to 2.a1)	To clarify that in the original criterion "study entry" was intended to mean at the Screening Visit, not the signature date of the ICF
5.1 Inclusion criteria and Appendix 13: Inclusion and exclusion criteria rationale	Added that serological evidence for SLE is only applicable for the Screening Visit (number changed from 2.c to 2.c1) Clarification that [redacted] will be measured where available (number changed from 2.c to 2.c1)	To clarify that serological evidence for SLE only applies for Screening Visit data as blood samples for baseline will not be available at time point of randomization To clarify that [redacted] will be only available in certain regions due to logistic reasons
5.1. Inclusion criteria Appendix 13: Inclusion and exclusion criteria rationale	Added clarification for when antimalarial monotherapy is acceptable (number changed from 2.e to 2.e3)	Clarification
5.1 Inclusion criteria and Appendix 13: Inclusion and exclusion criteria rationale	Added maximum corticosteroid doses and no iv pulse therapy (>500 mg x 1-3 days) within 4 weeks prior to screening and no change in CS allowed during the Screening period (number changed from 2.e to 2.e3)	To clarify additional rules regarding corticosteroid pulse iv treatment, originally not defined, and to provide maximum doses in alignment with other sections of the protocol

5.2 Exclusion criteria and Appendix 13: Inclusion and exclusion criteria rationale	Added clarification for anti-dsDNA positivity and measurements as per central laboratory (number changed from 2 to 2a)	Editorial changes to provide more clarity, based on feedback from investigators
5.2 Exclusion criteria and Appendix 13: Inclusion and exclusion criteria rationale	Added systemic reactions due to latex allergy (number changed from 5 to 5a)	To clarify that systemic reactions to latex (eg, contact allergy) was the intent of the original inclusion criterion
5.2 Exclusion criteria and Appendix 13: Inclusion and exclusion criteria rationale	Clarified timing of the "study entry" as appeared in the original protocol. (number changed from 6 to 6a)	To clarify that in the original criterion "study entry" was intended to mean at the Screening Visit, not the signature date of the ICF
5.2 Exclusion criteria and Appendix 13: Inclusion and exclusion criteria rationale	Added clarification for thromboembolic events (number changed from 11 to 11a)	Editorial change to clarify that this exclusion criteria is generally linked to heart diseases with an increased risk for thromboembolic events based on feedback from Investigators
5.2 Exclusion criteria and Appendix 13: Inclusion and exclusion criteria rationale	Deleted text referring to erosive arthritis (number changed from 13 to 13a)	Editorial change as erosive arthritis is not a symptom
5.2 Exclusion criteria and Appendix 13: Inclusion and exclusion criteria rationale	Added "or SARS CoV-2" (number changed from 15 to 15a)	To clarify that SARS CoV-2 infection is considered a clinically significant infection
5.2 Exclusion criteria and Appendix 13: Inclusion and exclusion criteria rationale	Added systemic antiviral treatment (number changed from 16 to 16a)	To include systemic antiviral treatment (eg, for SARS CoV-2)
5.2 Exclusion criteria and Appendix 13: Inclusion and exclusion criteria rationale	Added reactivated latent infection (number changed from 17 to 17a)	Change to clarify this refers to reactivated latent and not to silent latent infections (eg, herpes zoster, herpes simplex)
5.2 Exclusion criteria and Appendix 13: Inclusion and exclusion criteria rationale	Added clarification on study participant previously randomized within this study (number changed from 26 to 26a)	Change to clarify that study participants gave consent but were a screening failure can be rescreened, however, study participants who were randomized before cannot.
5.2 Exclusion criteria and Appendix 13: Inclusion and exclusion criteria rationale	Added text to include absence of concurrent suicidal ideation and/or severe depression (number changed from 28 to 28a)	Clarification added to diagnostic assessment
5.2 Exclusion criteria and Appendix 13: Inclusion and exclusion criteria rationale	Updated chronic kidney failure to stage 4 (number changed from 30 to 30a)	Clarification added to chronic kidney failure
5.2 Exclusion criteria and Appendix 13: Inclusion and exclusion criteria rationale	Clarification that all assessments are per Screening (Visit 1)	Clarification

	(number changed from 31 to 31a)	
6.2 Preparation, handling, storage, and accountability requirements	Clarification to blinding of the infusion bag and maintenance of blind.	To provide clarity on the process of IMP preparation and to clarify that study participant will not store study medication.
6.4 Treatment compliance	Deleted text referring to 'blinded fashion'	To clarify as Investigators and medical monitors are usually blinded
6.5.1.1 Corticosteroids	Corticosteroid tapering scheme revised, including update of Table 6-3 and Table 6-4	To clarify that tapering for participants receiving high dose corticosteroid therapy should be initiated as soon as possible and to clarify that no maximum dose of corticosteroid treatment is defined for its administration as escape treatment in the study
6.5.1.2 Antimalarials	Additional wording added in case a dose change is needed and to provide details on antimalarial intake.	To clarify that Investigators are advised to contact medical monitors to discuss the potential impact of an intervention on the future study conduct not the intervention itself, based on feedback from a regulator
6.5.1.3 Other immunosuppressants/immunomodulatory agents	Use of concomitant immunosuppressants clarified and wording added in case a dose change is needed. Updated text to include natural and synthetic cannabinoids	Change to provide clarification consistent with other sections of the protocol and to clarify that Investigators are advised to contact medical monitors to discuss the potential impact of an intervention on the future study conduct not the intervention itself, based on feedback from a regulator
6.6 Dose modification	Added clarification that dose modification was not applicable	Change to clarify that no dose change to the study drug is foreseen, based on feedback from Investigators
6.6.1 Prohibited concomitant treatments (medications and therapies	Clarification added for prohibited medications Vaccines:Text added on blood collection to determine immune response to vaccines.	Changes to be consistent with other sections of the protocol and to describe additional sample collection for potential future analysis of the impact of DZP on the immune response to infectious antigens

6.6.2 Escape medication	Wording added to clarify when escape treatment represents a safety risk	Change to clarify that study drug only needs to be discontinued if escape treatment in combination with DZP could represent a safety risk based on Investigator feedback.
7.1 Discontinuation of study medication	Added clarification on study medication discontinuation and observation	Change to be consistent with other sections and to underline the need to keep participants in the study based on feedback from a regulator
7.1.2 QTc stopping criteria	Clarification on single ECG collection	Change to align with other sections of the protocol describing that only single ECGs are foreseen and to clarify that this withdrawal criteria applies for new findings after eligibility review/randomization.
7.1.3 Permanent and temporary study drug discontinuation due to other reasons	New sub-section created to include clinically significant infections, impact on study conduct and observation for study participants who discontinue study drug Addition of text to clarify discontinuation of study medication in case of a new tuberculosis infection	Changes to provide more clarity under which considerations a study participant should discontinue study drug, stay in the study and be withdrawn, based on feedback from a regulator and Investigators. To clarify existing guidance in Section 8.2.6.3
8 Study assessments and procedures	Changed blood volume to 900mL	Change to fix error due to wrong calculation
8.1.1.1 BILAG 2004	Corrected reference guide title	Change to reflect correct title of the document
8.1.1.2 SLEDAI 2K	Updated SLEDAI 2K definition.	Change to fix error on the exact definition of the SLEDAI 2K to be used
8.1.1.3 S2K RI 50	Updated S2K RI 50 assessment	Change to fix error and to be consistent with the published way how to analyze the data
8.1.1.6 Cutaneous Lupus Erythematosus Disease Area and Severity Index	Updated CLASI assessment	Change to fix error as VAS scores described here are not part of CLASI
8.1.1.7 Tender and Swollen Joint Counts	Clarification added on qualification of assessor Updated text on cannabinoids	Change to provide clarification on who is qualified to do the assessment, based on Investigator feedback. Change to provide clarity that only locally approved drugs

	Clarification on assessments to be performed by the same Investigator (or qualified assessor)	including cannabinoids are allowed but not illegal drugs, based on feedback from a regulator Change to underline that key efficacy assessments should be done by same assessor through the study
8.1.1.8 Lupus Arthritis and Musculoskeletal Disease Activity score	Updated VAS scale	Change to provide more clarity on exploratory endpoint
8.1.2.1 FATIGUE-PRO (Short Form)	Updated to FATIGUE-PRO	Change to update naming convention
8.1.3.1 BILAG 2004-based Composite Lupus Assessment	Updated BICLA assessment	Change to the planned analysis based on feedback from a regulator
8.1.3.4 LLDAS	Deleted 'BILAG 2004'	Change to clarify that no BILAG items are part of the referenced definition of LLDAS
8.1.3.5 Systemic Lupus Erythematosus Responder Index-4	Updated assessment	Change to provide more clarity on planned exploratory analysis
8.1.3.6 DORIS (Definitions of Remission in SLE) complete remission on treatment	New sub-section added to describe analysis	Change to add only exploratory endpoint which was not described in the protocol
8.2.1 Physical examination	Clarification on weight measurement collection	Change to clarify that in case of certain SLE specific symptoms (weight loss) weight may have to be also measured at other Visits than BL and Week 24
8.2.2 Vital signs	Updated assessment procedure	Change to provide more details on vitals assessment based on feedback from Investigators
8.2.4 Clinical safety laboratory assessments	Clarification added on blinding	Change to clarify, consistent with other section
8.2.5 Suicidal risk monitoring	Updated assessment procedure	Change to provide clarity about the expected qualification of assessor
8.2.6 Assessment and management of TB and TB risk factors	Clarification that prophylactic therapy for LTB1 should be initiated 4 weeks prior to study medication.	Change to fix error, consistent with other section
8.2.7 SARS-CoV-2/COVID-19	New section added to include monitoring of study participants for SARS-CoV-2 infection.	Change to provide more clarity on monitoring of study

		participants for SARS-CoV-2 infection
8.3 AEs and SAEs	Clarification on additional assessments assess infections such as COVID-19.	Change to provide more clarity on expected actions to report adverse events
8.3.5 Pregnancy	Updated assessment	Change to clarify that concomitant medications need to be assessed in case a study participant becomes pregnant
8.3.7 AEs of special monitoring	[redacted]	
8.6.1 Assessment of PK variables	Added wording on [redacted]	Change to clarify details of planned analysis
8.9 Immune system markers	[redacted] added	Change to clarify that [redacted] is part of the assessed autoantibodies consistent with other section of the protocol
8.10 Biomarkers	Clarification on analysis of the immune response against vaccines or infection related antigens and stored samples.	Change to describe planned additional exploratory analysis on impact of DZP on the immune response to infectious antigens
9.1 Definition of analysis sets	Updated to clarify the FAS	Change to planned analysis based on feedback from a regulator
9.2.2 Analysis time points	Updated timepoints to remove Early Withdrawal Visit (EWV)	Change to clarify that study participants who withdrew their consent and therefore leave the study do not have to return for another visit. Last visit is the EOT visit.
9.3.1 Analysis of the primary efficacy/primary endpoint	Updated analysis	Change to provide clarity as sensitivity analysis using the PPS is described elsewhere
9.3.1.1 Sensitivity analysis	Updated analysis	Changes to provide clarity on analysis based on feedback from a regulator
9.3.2.1 Analysis of key secondary endpoints	Updated to remove Early Withdrawal Visit (EWV)	Change as no EWV is foreseen. The final visit if a patient withdrew consent and

		leaves the study will be the EOT (End of treatment) visit
9.5 Handling of protocol deviations	Updated section	Change to fix error and duplication text
9.6 Handling of dropouts or missing data	Text updated to clarify study participants who will be considered non-responders.	Change to planned analysis based on feedback from a regulator
10.1.3 Informed consent process	Updated process.	Change to clarify informed consent process based on feedback from a regulator
10.1.6 Data quality assurance	Wording added to clarify the quality tolerance limits.	Change to describe the process of planned quality management.
10.2 Clinical laboratory tests	Section updated to match tests in the Schedule of Activities Addition of hepatitis B core antibody testing	Change to reflect planned laboratory analysis and fix errors
10.3 Appendix 3: AEs – definitions and procedures for recording, evaluating, follow-up, and reporting	Additional text added to clarify reporting of AEOIs and AESMs.	Change to describe details of the process to report AESMs and AESIs
10.4 Appendix 4: Contraceptive guidance and collection of pregnancy information	Clarification added to pregnancy testing	Change to clarify that a pregnancy test is not required in study participants who are known to be pregnant and editorial change create consistency with other sections of the protocol
10.6 Appendix 6: Liver safety – suggested actions and follow-up assessments	Addition of hepatitis B core antibody testing	To improve sensitivity of chronic hepatitis B screening
10.17 Appendix 17: Criteria for Antiphospholipid Syndrome (APS)	New appendix for criteria for APS syndrome	Change to provide clarity on criteria recommend to classify APS
6.5. Permitted concomitant medication(s)/treatments(s)	Rearrangement of headers with movement of associated text, as applicable	Editorial change to improve presentation
1.1 Synopsis 4.1 Overall design 6.3.1.1 Maintenance of study treatment blind 6.3.1.2 Breaking the treatment blind in an emergency situation 6.6.1 Prohibited concomitant treatments (medications and therapies) 6.6.2 Escape medication	Wording added to specify impact of study conduct	Change to clarify that Investigators are advised to contact medical monitors to discuss the potential impact of an intervention on the future study conduct not the intervention itself, based on feedback from a regulator
Global	Minor administrative, formatting, and typographical changes have been made.	To provide clarity and be consistent with remainder of protocol.

10.12 Appendix 12: Endpoint rationale

Objectives	Endpoints	Rationale
Primary		
To evaluate the ability of DZP as an add-on treatment to SOC medication to achieve clinically relevant long-term improvement of moderate to severe disease activity	Achievement of BICLA response at Week 48	BICLA is a composite endpoint which measures improvement of disease activity based on improvement by BILAG 2004 grades across all organ systems with relevant disease activity at screening visit (V1)/start of treatment. BILAG 2004 is developed and validated based on intention to treat principles. A change (improvement or worsening) by at least 1 grade represents a change in the need for and nature of a therapeutic intervention as determined by SLE experts and therefore represents a clinically relevant change in disease activity. This can be either a clinically relevant improvement as demanded by BICLA or a clinically relevant worsening (flare) as demanded to not occur by BICLA. As the BICLA demands improvement across all organ systems with disease activity suggesting the need for a therapeutic intervention, it represents clinically relevant improvement as to be demanded from a potent systemic immune response modifier. BICLA is inline with EMA regulatory guidance. BILAG as the driving component of the BICLA is in line with FDA regulatory guidance.
Key Secondary		
To evaluate the ability of DZP as an add-on treatment to SOC medication to achieve fast, clinically relevant improvement of moderate to severe disease activity	Achievement of BICLA response at Week 24 Achievement of BICLA response at Week 12	Phase 2 data suggest a fast onset of response within 12-24 weeks. This is relevant for study participants/prescribers to make informed treatment decisions as soon as possible including further change in therapy or further escalation of treatment.

Objectives	Endpoints	Rationale
To evaluate the ability of DZP as an add-on treatment to SOC medication to achieve long-term control of disease activity	Achievement of prevention of severe BILAG flares (severe BILAG flare-free) through Week 48	Phase 2 data suggest a substantial prevention of severe flares. Prevention of disease flares is an intuitive measure if the disease is well controlled over time which is one of the primary objectives of treatment in SLE according to international treatment guidances. Severe flares are associated with poor long-term prognosis.
To evaluate the ability of DZP as an add-on treatment to SOC medication to achieve and maintain the treat-to-target goal: low disease activity with low/acceptable corticosteroid dose over time	Achievement of LLDAS in ≥50% of post-Baseline visits through Week 48	Phase 2 data suggest that more patients achieve and maintain over time the treat-to-target endpoint LLDAS. LLDAS represents low disease activity at a low/acceptable corticosteroid background medication dose level. It appears to be correlated with long-term outcomes including damage prevention and flare prevention. It is therefore considered as highly clinically relevant. The LLDAS is based on achievement of a low SLEDAI-2K score which is a commonly used instrument to measure disease activity state in clinical practice. As it combines the achievement of a steroid tapering target with the demand for a well-controlled disease, it represents clinically successful steroid sparing. International treatment guidances refer to LLDAS as treatment target.
To evaluate the ability of DZP as an add-on treatment to SOC medication to achieve improvement of disease activity as measured by numerical disease state score commonly used in clinical practice	Change from Baseline in SLEDAI-2K at Week 48	While the BILAG 2004 as the main component of BICLA adequately describes clinically relevant improvement across all organ systems, the BILAG 2004 instrument is not broadly used in clinical practice due to its complexity. The SLEDAI-2K is an often-used instrument in clinical practice. Information on this endpoint will provide valuable information to prescribers based on an instrument they are familiar with from daily practice. Further SLEDAI-2K represents a component of the BICLA and the LLDAS.

Objectives	Endpoints	Rationale
Secondary		
To evaluate the ability of DZP as an add-on treatment to SOC medication to achieve components of the composite primary endpoints	Achievement of BILAG improvement without worsening at Week 48	This endpoint represents the first and driving component of BICLA. Analysis of the components of composite endpoints like the BICLA are recommended by regulatory guidance
	Change from Baseline in PGA at Week 48	This endpoint represents a component of BICLA. Analysis of the components of composite endpoints like the BICLA are recommended by regulatory guidance.
To evaluate the ability of DZP as an add-on treatment to SOC medication to achieve alternative responder endpoint	Achievement of SRI4 response at Week 48	This endpoint represents the primary endpoint of the only approved drug in SLE in the past decades. It is added to allow indirect comparison.
To evaluate the ability of DZP as an add-on treatment to SOC medication to achieve endpoints supporting other key secondary endpoints	Achievement of prevention of moderate/severe BILAG flares (moderate/severe BILAG flare-free) through Week 48	Support to Key secondary endpoint prevention of severe flares, recommended by regulatory guidance.
	Time to severe BILAG flare through Week 48	Support to key secondary endpoint prevention of severe flares, recommended by regulatory guidance.
	Time to moderate/severe BILAG flare through Week 48	Support to Key secondary endpoint prevention of severe flares, recommended by regulatory guidance.
To evaluate the safety and tolerability of DZP as add-on treatment to SOC medication	TEAEs, serious TEAEs, TEAEs of special interest, and TEAEs of special monitoring	To evaluate the safety profile of DZP.

Objectives	Endpoints	Rationale
Tertiary		
To evaluate the ability of DZP as add-on treatment to SOC to achieve endpoints which support the primary and secondary objectives and/or support the interpretation of the primary and secondary endpoints	Achievement of reduction of corticosteroid dose from >7.5mg/day prednisone equivalent dose at start of study to ≤7.5mg/day prednisone equivalent by visit	Support to all primary and key secondary endpoints, component of LLDAS, recommended by regulatory guidance
	Achievement of reduction of corticosteroid dose from >7.5mg/day prednisone equivalent dose at start of study to ≤7.5mg/day prednisone equivalent at Week 24 and maintaining low corticosteroid dose afterwards and achievement of BICLA response at Week 48	Support to primary endpoint, recommended by regulatory guidance
	Achievement of reduction of corticosteroid dose from >7.5mg/day prednisone equivalent dose at start of study to ≤7.5mg/day prednisone equivalent at Week 24 and maintaining low corticosteroid dose and achievement of prevention of moderate/severe BILAG flares (moderate/severe BILAG flare-free) at Week 48	Support to key secondary endpoint, recommended by regulatory guidance
	Achievement of reduction in corticosteroid dose from ≥7.5mg/day prednisone equivalent dose at start of study to ≤5mg/day prednisone equivalent at Week 24 and maintaining low corticosteroid dose and achievement of BICLA response at Week 48	Support to key secondary endpoint, recommended by regulatory guidance
	Achievement of reduction of corticosteroid dose from ≥7.5mg/day prednisone equivalent dose to ≤5mg/day prednisone equivalent at Week 24 and maintaining low corticosteroid dose and achievement of prevention of moderate/severe BILAG flares (moderate/severe BILAG flare-free) at Week 48	Support to primary endpoint, recommended by regulatory guidance

Objectives	Endpoints	Rationale
	Total corticosteroid dose through Week 24, through Week 48, and from Week 24 through Week 48	Support to all primary and key secondary endpoints, component of LLDAS, recommended by regulatory guidance
	Achievement of BICLA response by visit	To provide supportive information for better understanding of the primary and key secondary endpoints
	Achievement of BILAG 2004 improvement without worsening by visit	To provide supportive information for better understanding of the primary and key secondary endpoints
	Change from Baseline in BILAG 2004 score by visits	To provide supportive information for better understanding of the primary and key secondary endpoints
	Achievement of BILAG 2004 shifts by visit	To provide supportive information for better understanding of the primary and key secondary endpoints
	Achievement of BILAG 2004 improvement by organ system by visit	To provide supportive information for better understanding of the primary and key secondary endpoints
	Achievement of maintained BICLA response by visit	To evaluate if achieved BICLA response is maintained for more than one visit, to provide supportive information for better understanding of the primary and key secondary endpoints, due to regulatory guidance
	Achievement of persistent BICLA response between Week 24 and Week 48	To evaluate if achieved BICLA response is maintained from Week 24 on through end of study in majority of visits, to provide supportive information for better understanding of the primary and key secondary endpoints, due to regulatory guidance
	Worsening of any organ system with a BILAG 2004 B, C, D, E at Baseline to BILAG 2004 A or worsening of >1 organ system with a BILAG 2004 C, D, E at baseline to BILAG 2004 B by visit	To provide supportive information for better understanding of the primary and key secondary endpoints
	Achievement of BILAG 2004 C, D, E in all organ systems by visit	To provide supportive information for better understanding of the primary and key secondary endpoints

Objectives	Endpoints	Rationale
	Change from Baseline in SLEDAI-2K by visit	To provide supportive information for better understanding of the primary and key secondary endpoints
	Achievement of SRI 4, 6, 8 response by visit	To provide supportive information for better understanding of the primary and key secondary endpoints and to provide information on alternative definitions of the SRI
	Change from prior visits in S2K RI50 by visit	To provide information on from visit to visit dynamic of disease activity and to provide supportive information for better understanding of the primary and key secondary endpoints
	Change from Baseline in PGA by visit	To provide information on a global assessment of disease activity and to provide supportive information for better understanding of the primary and key secondary endpoints
	Achievement of LLDAS status by visit	To provide supportive information for better understanding of the primary and key secondary endpoints
	Cumulative number of visits in LLDAS through Week 48	To provide supportive information for better understanding of the primary and key secondary endpoints
	Achievement of LLDAS Variant (demand for ≤5mg/day prednisone equivalent) in >50% of post-Baseline visits through Week 48	To provide supportive information for better understanding of the primary and key secondary endpoints
	Achievement of prednisone equivalent dose ≤7.5 mg/day by visit	To provide supportive information for better understanding of the primary and key secondary endpoints
	Prednisone equivalent dose by visit	To provide supportive information for better understanding of the primary and key secondary endpoints
	Occurrence of severe BILAG 2004 flares by visit	To provide supportive information for better understanding of the primary and key secondary endpoints
	Occurrence of moderate BILAG flares by visit	To provide supportive information for better understanding of the primary and key secondary endpoints

Objectives	Endpoints	Rationale
	Occurrence of severe SFI flares by visit	To provide supportive information for better understanding of the primary and key secondary endpoints
	Occurrence of moderate SFI flares by visit	To provide supportive information for better understanding of the primary and key secondary endpoints
	Time to severe SFI flare	To provide supportive information for better understanding of the primary and key secondary endpoints
	Time to moderate SFI flare	To provide supportive information for better understanding of the primary and key secondary endpoints
	Change from Baseline in ACR/SLICC damage score by visit	To provide supportive information for better understanding of the primary and key secondary endpoints
	Achievement of DORIS remission by visit	To provide supportive information for better understanding of the primary and key secondary endpoints
To evaluate the ability of DZP as an add-on treatment to SOC medication to achieve organ specific endpoints	Change from Baseline in CLASI activity score by visit for all study participants and for subset of study participants with high CLASI score	To provide information on organ specific improvement of disease activity
	Achievement of a meaningful improvement in CLASI score by visit for all study participants and for subset of study participants with high CLASI score	To provide information on organ specific improvement of disease activity
	Change from Baseline in Tender joint count (TJC), swollen joint count (SJC) by visit for all study participants and for subset of study participants with moderate to severe arthritis	To provide information on organ specific improvement of disease activity
	Achievement of a meaningful decrease in TJC/SJC by visit for all study participants and for a subset of participants with moderate to severe arthritis	To provide information on organ specific improvement of disease activity
	Change from Baseline in Lupus Arthritis and Musculoskeletal Disease Activity score by visit	To provide information on organ specific improvement of disease activity

Objectives	Endpoints	Rationale
To evaluate the ability of DZP as an add-on treatment to SOC medication to achieve important patient reported outcomes	Change from baseline in Functional Assessment of Chronic Illness Therapy Fatigue (FACIT-F) by visit	To provide information on organ specific improvement of disease activity
	Change from Baseline in PHQ-9 score by visit	To provide information on depression as important comorbidity, regulatory guidance
	Change from Baseline in FATIGUE PRO 'Physical Fatigue', 'Mental Fatigue' and 'Fatigability' scores by visit	To provide information on study participants' perception on their disease activity.
	Change from Baseline in LupusQoL by visit	To provide information on study participants' perception on their disease activity.
	Change from Baseline in EQ-5D-5L by visit	To provide information on study participants' perception on their disease activity.
To evaluate the pharmacokinetics (PK)	[redacted]	
To evaluate immunogenicity of DZP as an add-on treatment to SOC medication	Incidence of anti-drug antibodies: [redacted]	To provide information on antibody generation against components of DZP with possible impact on efficacy and study participant's safety
To evaluate the PD and immunological parameters of DZP as an add-on treatment to SOC medication	Observed values and change from baseline in [redacted] in all study participants by visit and in study participants 'positive' at Baseline by visit	To provide information on pharmacodynamic, information on important biomarkers of SLE possible predictive of clinical outcomes, likely important information for study participant's safety
	Seroconversion of: [redacted]	To provide information on PD, information on important biomarkers of SLE possible predictive of clinical outcomes, likely important

Objectives	Endpoints	Rationale
	[redacted] status by visit	information for study participant's safety
To evaluate the safety and tolerability of DZP as an add-on treatment to SOC medication	TEAEs leading to study withdrawal, TEAEs leading to permanent study medication discontinuation, TEAEs with start day on day or up to 1 day after infusion, other identified TEAE clusters	To provide information on study participants' safety outcomes
	Summary of participants withdrawn from the study due to TEAEs Summary of participants who permanently discontinued study medication	To provide information number of participants who were withdrawn from study or whose study medication was discontinued
	Change from Baseline in vital sign parameters by visit	To provide information on study participants' safety outcomes
	Observed values and change from Baseline in safety laboratory tests (hematology, serum chemistry, urinalysis) by visit, % study participants achieving critical threshold for selected lab parameters by visits	To provide information on study participants' safety outcomes
To evaluate changes in exploratory biomarkers	Change from Baseline in biomarkers selected for analysis [redacted]	To provide information on biomarkers of SLE comorbidity and potential additional PD endpoints, possibly predictive of clinical outcomes
To evaluate risk for anti-phospholipid associated events	Change from Baseline in APS score by visit	To provide information on change in risk profile for thromboembolic events. Antiphospholipid antibodies are common in SLE and substantially contribute to comorbidity such as cardiovascular events, other thromboembolic events, adverse pregnancy outcomes. Phase 2 data suggest a reduction of these antibodies which would be of substantial value for study participants.

10.13 Appendix 13: Inclusion and exclusion criteria rationale

Criterion	N	Content	Justification
Inclusion	1	Study participant must be ≥16 years of age, unless restricted by local regulation, at the time of signing the Informed Consent form (ICF).	SLE is a disease with a common onset with puberty. It is estimated that up to 30% of study participants have first symptoms before they are 18 years old. The unmet medical need is high in this young population due to the high toxicity of existing standard of care (high dose corticosteroids, cyclophosphamide, MTX, Azathioprine). Further SLE in adolescents has a similar etiology, pathogenesis, clinical manifestations, and laboratory findings but is often described to have a more severe disease course. Study participants ≥16 years of age are expected to have a comparable pharmacokinetic as study participants ≥18 years of age. Therefore, the risk-benefit is considered as comparable to adults
Inclusion	2	Study participants who have moderate to severe disease activity due to either persisting active SLE or due to an acute worsening of SLE in the scope of frequent flaring/relapsing-remitting SLE despite stable SOC medication defined as:	DZP is intended to provide a treatment option for study participants whose disease is not well controlled on SOC treatment at a well-tolerated dose. SLE is considered not well controlled over time if there is residual disease activity and/or frequently flaring/relapsing remitting disease despite SOC. Sporadic flares need a short time treatment intervention but do not need automatically modification of long-term immunomodulatory therapy if not occurring frequently.
Inclusion	2.a1	Diagnosed with SLE at least 24 weeks before the Screening Visit (Visit 1) by a qualified physician (eg, rheumatologist, internal medicine expert, nephrologist, or dermatologist)	SLE is a highly complex disease which can involve almost all organs and is therefore covering the full spectrum of internal medicine. However due to its complexity diagnosis should be done by a well-trained expert in the field with a specialty training in rheumatology, dermatology, or any specialty within the spectrum of internal medicine including nephrology. The diagnosis should have been done at least 24 weeks prior to screening visit (V1) to ensure that there was an appropriate attempt to keep the disease well-controlled on conventional

Criterion	N	Content	Justification
			standard of care treatment at well-tolerated dose.
Inclusion	2.b	Classified by 2019 European League Against Rheumatism/American College of Rheumatology (EULAR/ACR) classification criteria for SLE	The 2019 EULAR/ACR criteria are considered to have high sensitivity, specificity and a high positive predictive value, and represent the state of the art of current clinical and scientific knowledge
Inclusion	2.c1	With serological evidence for SLE at Screening as demonstrated by at least 1 of the following: i) Evidence for [redacted] (defined as evidence for [redacted] in central laboratory) ii) Either [redacted] < lower limit of normal (LLN) OR [redacted] <LLN OR elevated erythrocyte-bound complement [redacted] (where available) as measured by central laboratory iii) [redacted] with a titer of at least 1:80 confirmed by central laboratory in combination with evidence of at least 1 of the following SLE typical autoantibodies: 1. [redacted] (central laboratory) 2. [redacted] autoantibodies (central laboratory) 3. Historic evidence for [redacted] (at least 2 historical positive tests [>upper limit of normal (ULN) of lab assay with an interval of at least 12 weeks between tests])	The 2019 EULAR/ACR criteria are demanding evidence for anti-nuclear antibodies at any time as mandatory. These criteria shall assure that there is also sufficient evidence for SLE typical autoantibodies or a decrease in complement, which is also typical for SLE and an important risk factor at screening visit (V1). [redacted] and low complement are also part of EULAR/ACR criteria.
Inclusion	2.d	Moderately to severely active defined as - British Isles Lupus Assessment Group Disease Activity Index 2004 (BILAG 2004) Grade B in ≥2 organ systems and/or a BILAG	Study participant should have an indication for a systemic treatment intervention with a biotherapeutic immunomodulator. A BILAG A represents the medical indication for a treatment intervention with high potent immunomodulatory therapy, a BILAG B

Criterion	N	Content	Justification
		2004 Grade A in ≥1 organ systems at Screening and Baseline Visit AND - SLEDAI-2K ≥6 at Screening Visit AND - SLEDAI-2K without labs ≥4 at Baseline Visit	represents also an indication to change the immunomodulatory therapy; however, could also indicate local therapy. When at least 2 BILAG Bs are present this medically indicates to alter the immunomodulatory therapy with a systemic treatment to cover all affected organ systems. SLEDAI ≥6 also represent moderately to severely active disease and is an entry criteria which is in line with other programs to define study participants with the need for a treatment intervention with investigational immunomodulatory. As both BILAG 2004 and SLEDAI-2K are partially depending on lab parameters which are not available at baseline, the disease activity shall be performed at baseline by considering only clinical symptoms to assure that indication for treatment intervention is still present when the investigational drug is first applied.
Inclusion	2.e3	Receiving the following SOC medication at stable dose: • Antimalarial treatment in combination with corticosteroids and/or immunosuppressants or as stand-alone treatment if justified (ie, if for other SLE SOC medications there is documented intolerance in medical history, documented lack of efficacy, contraindications, or lack of availability) OR • Treatment with corticosteroids and/or immunosuppressants if antimalarial treatment is not possible (ie, documented intolerance in medical history or antimalarials not available locally) Stable dose is defined for: • Antimalarials as no change to dose within 8 weeks prior to Screening and during Screening Period and a start date at least 12 weeks before Screening.	DZP is intended to provide a treatment option for study participants with residual disease and/or frequently flaring/relapsing-remitting SLE despite SOC treatment. Therefore, study participants should be on optimized but also stable SOC medication to judge adequately how well the study participants' disease is controlled and therefore to judge if there is a need for a treatment intervention at all which is the prerequisite to qualify for an interventional study. In line with international and local treatment guidance documents and overall expert opinion, antimalarials are accepted as the cornerstone of treatment in study participants with SLE accompanied with corticosteroids at the lowest dose possible and/or immunosuppressants (if corticosteroids cannot be reduced to a well-tolerated level). However, some study participants do not tolerate corticosteroids and/or conventional immunosuppressants due to side effects and are therefore treated by antimalarials as stand-alone treatment.

Criterion	N	Content	Justification
		Maximum doses are described in Section 6.5.1.2 • Corticosteroids as no change in dose for 2 weeks prior to Screening, no change during Screening Period, and no iv pulse therapy (>500mg x 1 to 3 days) within 4 weeks prior to screening. The maximum dose allowed at screening is 40mg/day prednisone or equivalent (see Section 6.5.1.1). Immunosuppressants as no change in dose for 12 weeks prior to Screening Visit and during Screening Period. Maximum doses are described in Section 6.5.1.3	Further a certain proportion of study participants do have to stop antimalarial treatment or are not intake adherent due to side effects. In rare cases antimalarials may also be not available to study participants. In this case study participants should still be on either corticosteroids or immunosuppressants or both. In terms of dosage for these treatments, changes in corticosteroid therapy can influence significantly and short term the disease activity in both direction - worsening and improvement of disease activity. Antimalarials and Immunosuppressants have a treatment effect with more latency, changes could interfere with the disease activity also longer after changes to the medication itself. The demand for stable corticosteroid therapy at least 2 weeks before screening visit (V1) and consequently approx. 4 weeks before randomization (Baseline Visit) as well as the demand for stable antimalarial and immunosuppressant therapy longer term shall ensure the adequate qualification for this interventional trial (residual disease and/or frequent flaring disease despite SOC) and at the same time rescue bias on the assessment of the investigational drug. Any treatment intervention with SOC treatment will be possible at any time during the study if medically indicated. However, if this is needed during the Screening Period study participants will be considered as not eligible. If it occurs during the study participants may be considered as non-responders but should remain in the study.
Inclusion	3	Body weight ≥40kg and ≤160kg	Weight range as usually in this population and based on toxicity margins
Inclusion	4a	Female and/or male • A male study participant must agree to use contraception, as	As DZP lacks a Fc' part it is expected analogue to other drugs with the same structure not to pass the placental barrier.

Criterion	N	Content	Justification
		detailed in Section 10.4, during the Treatment Period and for at least 17 weeks after the final dose of study treatment and refrain from donating sperm during this period. • A female study participant is eligible to participate if she is not pregnant, not breastfeeding (including pumping breast milk to feed to a child), and at least 1 of the following conditions applies: - Not a woman of childbearing potential (WOCBP) as defined in Section 10.4 of the final protocol, or - A WOCBP who agrees to follow the contraceptive guidance in Section 10.4 of the final protocol during the treatment period and for at least 17 weeks after the final dose of study medication.	However, there is no evidence, neither from in vitro experiments, nor from animal experiments, nor from humans if DZP can pass the placental barrier or can do any harm to embryos or fetus. Therefore, a substantial contraception is needed at this point in time.
Inclusion	5	Capable of giving signed informed consent as described in Section 10.1.3, which includes compliance with the requirements and restrictions listed in the ICF and in this protocol.	To protect study participants' rights
Exclusion	1	Study participant has any medical or psychiatric condition (including conditions due to neuropsychiatric SLE) that, in the opinion of the Investigator, could jeopardize or would compromise the study participant's ability to participate in this study. This includes study participants with a life threatening condition (eg, CTCAE grade 4 conditions, CAPS, acute severe renal failure, acute severe central nervous system [CNS] manifestations)	To protect study participants' well-being as under this conditions adherence to study procedures are expected to be affected which could put study participants at risk
Exclusion	2a	Study participant has moderate to severe disease activity (as defined per Inclusion Criterion 2.d) at the Screening Visit (V1) due to an acute	Study participants are required to have signs and symptoms of SLE qualifying for moderate to severe disease activity at screening visit (V1) defined as at least 2

Criterion	N	Content	Justification
		flare but **does not fulfill at least one** of the following criteria in addition to the Screening Visit: • ≥1 additional disease flare within the last 24 weeks prior to Screening (as per medical record) OR • [redacted] positivity in combination with [redacted] < LLN as per central laboratory OR • [redacted] < LLN as per central laboratory OR • African-American OR • Age <25 years	organ systems with a BILAG B or at least 1 organ system with a BILAG A in combination with a SLEDAI ≥6. Participants could have these signs and symptoms due to residual/chronic disease activity or due to an acute worsening of disease activity (acute flare). If signs and symptoms at screening visit (V1) are due to an acute flare, it cannot be distinguished if these occurred in the setting of frequent flares or is a sporadic flare in a study participant who is indeed overall well controlled on SOC treatment. In fact, the sporadic flare can occur due to external events such as UV irradiation, infections, drug intake or in adherence to SOC treatment but may not represent an overall not controlled disease state. To avoid introducing a biological treatment in study participants that may be controlled with SOC, an assessment is needed to ensure a well-documented medical history of multiple flares. In case no substantial documentation of the medical history is available (eg, in case of referrals to investigational site), several risk factors for frequent flares have been well described and would also be used to assess the need for biologic treatment (Fanouriakis, 2019).
Exclusion	3	Study participant has a history of chronic alcohol or drug abuse within the previous 24 weeks.	To protect patents' well-being as under this conditions adherence to study procedures are expected to be affected which could put study participants at risk
Exclusion	4	Study participant has a known [redacted] to any components of DZP including PEG or comparative drugs (and/or an investigational device) as stated in this protocol.	To protect study participants' well-being. DZP is a PEGylated fab' fragment. Both PEG as well as the fab' fragment are proteins which can cause allergic reactions under certain circumstances. Study participants who have a history for such reactions are considered as having a high risk to have a severe allergic reactions again.
Exclusion	5a	Study participant has a history of an anaphylactic reaction to parenteral administration of contrast agents,	To protect study participants' well-being. Study participants who had severe reactions against proteins or other

Criterion	N	Content	Justification
		human or murine proteins, or monoclonal antibodies. This includes systemic reactions due to latex allergy.	molecules have a high risk to react again against a molecule such as DZP
Exclusion	6a	Study participant has a history of malignancy, except the following treated cancers: cervical carcinoma in situ (after complete resection [eg, curettage, electrodessication] not later than 4 weeks prior to the Screening Visit [V1]), basal cell carcinoma, or dermatological squamous cell carcinoma (after complete resection not later than 24 weeks prior to the Screening Visit [V1]).	to protect study participants" well-being as any immunomodulation could interfere with the capability of the immune system to keep preexisting tumors under control which could lead to exacerbation of the tumor
Exclusion	7	Study participants who have had major surgery (including joint surgery) within the 24 weeks prior to Screening, or planned surgery within 24 weeks after entering the study.	To protect study participants' well-being as major surgeries, increase the risk of infections and as an immunomodulator DZP could increase the risk of such infections further.
Exclusion	8	Study participants who have had significant blood loss or have donated or received 1 or more units (450mL) of blood within 30 days prior to the Screening Visit or have donated plasma or platelets within 14 days prior to the Screening Visit.	To protect study participants' well-being as a relevant amount of blood will be taken at the Screening and Baseline Visit
Exclusion	9	Study participants with a history of thromboembolic events within 52 weeks of Screening (Visit 1), including but not limited to the following: deep venous thrombosis, pulmonary embolism, cortical sinus thrombosis, myocardial infarction, stroke, transient ischemic attack, or arterial insufficiency causing digital gangrene or tissue necrosis. Note: 1) In case of anti-phospholipid antibodies present at the Screening Visit, a prophylactic treatment should be considered in line with local or international guidelines and considering the	To protect study participants' well-being. In vitro, animal data and limited data in humans suggest no increased risk for thromboembolic events in contrast to the full antiCD40 antibody including the Fc' part (see DZP IB). However, the data so far in humans are still limited. Study participants with recent thromboembolic events in the medical history are considered to be of increased risk to have an adverse event such as another thromboembolic event or a bleeding event (if on anti-coagulation). As an increased risk for such events associated with DZP cannot be excluded at this time exposure to DZP could increase the risk further.

Criterion	N	Content	Justification
		individual risk profile of the patient for thromboembolic events 2) Study participants with antiphospholipid syndrome (APS) can be enrolled if they are on stable anticoagulation therapy at an effective dose (ie, International Normalized Ratio [INR] target 2 to 3 depending on clinical situation) and did not have a thromboembolic event and/or obstetric morbidity within the 52 weeks prior to Screening (Visit 1). Obstetric morbidity is defined as 1 or more unexplained deaths of a morphologically normal fetus at or beyond the tenth week of gestation with the latest incidence within 52 weeks prior to Screening (Visit 1) OR 1 or more preterm births of a morphologically normal neonate before the 34th week of: (i) eclampsia or severe pre-eclampsia or (ii) recognized features of placental insufficiency with the latest incidence within 52 weeks prior to Screening (Visit 1).	
Exclusion	10	Study participants with a history of catastrophic APS or saddle pulmonary embolism	To protect study participants' well-being. In vitro, animal data and limited data in humans suggest no increased risk for thromboembolic events in contrast to the full antiCD40 antibody including the Fc' part. However, the data so far in humans are still limited. If DZP does promote thromboembolism, then the combination of a history of thromboembolism and DZP may be too high risk.
Exclusion	11a	Study participant has an increased risk for thromboembolic events due to an ongoing heart disease or due to a medical device, including but not limited to vascular graft, valvular heart disease, atrial fibrillation, or a heart rhythm disorder.	To protect study participants' well-being. In vitro, animal data and limited data in humans suggest no increased risk for thromboembolic events in contrast to the full antiCD40 antibody including the Fc' part. However, the data so far in humans are still limited. If DZP does promote thromboembolism, then the combination of a history of thromboembolism and DZP may be too high risk.

Criterion	N	Content	Justification
Exclusion	12	Study participant has a BILAG 2004 Grade A in the musculoskeletal system due to severe arthritis only AND no BILAG 2004 Grade A or B in any other organ system AND no current (within the past 4 weeks) evidence for synovitis based on imaging methods such as magnetic resonance imaging or doppler-sonography	To ensure study participants have an unmet medical need for a treatment intervention with a systemic potent immunomodulator. Severe arthritis as defined by BILAG is defined as active synovitis ≥ 2 joints with marked loss of functional range of movements and significant impairment of activities of daily living, that has been present on several days (cumulatively) over the last 4 weeks. As the latter is based on a subjective and not well-defined assessment, the reproducibility and generalizability of the assessment in study participants who have no other objective symptoms of SLE present could be impaired, specifically if synovitis is only based on a subjective joint assessment by the assessor either.
Exclusion	13a	Study participant has a mixed connective tissue disease, scleroderma, and/or overlap syndrome of these diseases with SLE. - Clarification: Study participants with rheumatoid arthritis in their medical history are not considered as having an overlap syndrome and are therefore eligible.	To assure study participants indeed have the indicated disease
Exclusion	14	Study participant has evidence of human immunodeficiency virus infection, agammaglobulinemias, T-cell deficiencies, or human T-cell lymphotropic virus-1 infection at any time prior to or during the study.	To protect study participants' well-being as DZP as a potent immunomodulator can increase the risk for severe exacerbations of preexisting chronic infections.
Exclusion	15a	Study participant has clinically significant active or latent infection (eg, chronic viral hepatitis B or C, or SARS CoV-2 infection [see Section 8.2.7]).	To protect study participants' well-being as DZP as a potent immunomodulator can increase the risk for severe exacerbations of ongoing or preexisting chronic infections.
Exclusion	16a	Study participant has a history of a serious infection within the last 60 days prior to the first study medication infusion (Visit 2) that required iv/intramuscular antibiotics, systemic antiviral treatment or	To protect study participants' well-being as DZP as a potent immunomodulator can increase the risk for severe exacerbations of preexisting chronic or ongoing acute infections.

Criterion	N	Content	Justification
		required hospitalization/prolonged hospitalization. Study participants must have completed any prior anti-infective therapy for serious infections prior to the first study medication infusion.	
Exclusion	17b	Study participant had a reactivated latent infection (eg, cytomegalovirus, herpes simplex virus, or herpes zoster infection) or opportunistic infection (including but not limited to pneumocystis, cytomegalovirus, or severe herpes zoster infection) within 12 weeks prior to the first study medication infusion (Visit 2) or is currently receiving suppressive therapy for an opportunistic infection.	To protect study participants' well-being as DZP as a potent immunomodulator can increase the risk for severe exacerbations of preexisting chronic or ongoing acute infections.
Exclusion	18	Study participant has a clinically relevant recurrent (more than 3 times a year) infection	To protect study participants' well-being as DZP as a potent immunomodulator can increase the risk for severe exacerbations of preexisting chronic or ongoing acute infections.
Exclusion	19	Study participant with any of the following tuberculosis (TB) exclusion criteria: • Known active TB infection. • History of active TB infection involving any organ system or findings in other organ systems consistent with TB, unless adequately treated according to WHO/CDC therapeutic guidance and proven to be fully recovered upon consult with a TB specialist. • Latent TB infection (LTBI) unless appropriate prophylaxis is initiated at least 4 weeks prior to study medication dosing and will be continued to completion of prophylaxis. • High risk of acquiring TB infection eg. known close exposure to another person with active TB infection within 3	To protect study participants' well-being as DZP as a potent immunomodulator can increase the risk for severe exacerbations of preexisting chronic or ongoing acute infections.

Criterion	N	Content	Justification
		months prior to Screening or significant time spent in a health care delivery setting or institution where individuals infected with TB are housed and where the risk of transmission is high within 3 months prior to Screening • Current nontuberculous mycobacterial (NTM) infection or history of NTM infection unless proven to fully recovered upon consult with a TB specialist.	
Exclusion	20a	Study participants who have received live/live attenuated vaccines within 6 weeks prior to the first study medication infusion (Visit 2) or who plan to receive these vaccines during the study or up to 12 weeks after the final dose of study medication will be excluded. Use of nonlive vaccines is allowed during the study; however, based on current evidence, it cannot be excluded that the effectiveness of these vaccines may be compromised by the study medication. Investigator should consider local and international guidance on vaccination in immunosuppressed patients and discuss risks, benefits and administration options with participants (for more details see also Section 6.6.1 and Section 8.2.7).	To protect study participants' well-being as DZP as potent immunomodulator could lead to exacerbation of infection by live vaccines
Exclusion	21	Study participant has active lupus that, in the opinion of the Investigator or according to local or international guidances, requires an increase in SOC therapy outside of that permitted in Section 6.5.1.	To protect study participants' well-being by assuring that study participants receive adequate and indicated treatment for their SLE if prohibited by this study.
Exclusion	22	Study participants requiring plasma exchange or immunoadsorption in the 16 weeks prior to Visit 2 or at any time during the study.	To protect study participants' well-being as plasma exchange or immunoadsorption leads to significant immunosuppression which could be further exacerbated by DZP and therefore increase the risk for serious infections.

Criterion	N	Content	Justification
Exclusion	23	Study participant has used the prohibited medications listed in Table 6-7, regardless of route (with the exception of eye drops), within the time frame (Wash-Out Period) listed in the table prior to Screening (Visit 1). Study participant has used investigational agents not included in Table 6-7, including other investigational or recently approved biologics, off-label use of immunomodulators, or device products, within 12 weeks or 5 times the half-life prior to Screening (Visit 1), whichever is longer. Concomitant participation in studies where no product or device is administered/used may be allowed if discussed and approved by the Medical Monitor/UCB. If there are any questions regarding acceptable wash-out periods not mentioned, the Investigator should contact the Medical Monitor.	To protect study participants' well-being as prohibited medications as mentioned lead to significant immunosuppression which could be further exacerbated by DZP and therefore increase the risk for serious infections. [redacted]
Exclusion	24	Hormone replacement therapy is allowed provided it is not initiated within the 4 weeks prior to Screening (Visit 1) or during the study. The hormone replacement therapy may be decreased and/or discontinued at any time during the study	To ensure the diagnostic value of the FSH test to determine if a study participant is of childbearing potential
Exclusion	25	Study participant should, if possible, stay on stable doses of the following other concomitant medications for the treatment of SLE during the study unless changes in these treatments are clinically indicated: analgesics, non-steroidal anti-inflammatory drugs (NSAIDs), 3-hydroxy-3-methyl-glutaryl-coenzyme A (HMG-	To assure integrity of data by reducing bias by other background medication. Study participants should receive treatment which is indicated at any time, however if this happens before randomization it should be considered to not include the study participant in the study.

Criterion	N	Content	Justification
		CoA) reductase inhibitors (statins), angiotensin converting enzyme (ACE) inhibitors, and other anti-hypertensive drugs.	
Exclusion	26a	Study participant has previously been randomized within this study or participant has previously been assigned to treatment with DZP in a study evaluating DZP.	To protect study participants' well-being as prior participation in a study by which the study participants received DZP could increase the risk for severe allergic reactions.
Exclusion	27	Study participant has participated in another study of an IMP (and/or an investigational device) within the previous 12 weeks or 5 half-lives of the IMP whatever is longer (see Table 6-7) or is currently participating in another study of an IMP.	To protect study participants' well-being as prohibited medication as mentioned lead to significant immunosuppression which could be further exacerbated by DZP and therefore increase the risk for serious infections. Also, to ensure integrity of data controlling for bias by medication with impact on SLE.
Exclusion	28a	Study participant has history of a suicide attempt within the 5 years prior to the Screening Visit or has had suicidal ideation in the past 6 months as indicated by a positive response ("Yes") to either Question 4 or Question 5 of the "Screening/Baseline" version of the Columbia Suicide Severity Rating Scale (C-SSRS) at Screening. Note: • In case a study participant responds to Question 9 in PHQ9 [redacted]' the severity of the suicidal ideation needs to be adequately assessed with the C-SSRS rating scale • In case of history of a suicide attempt more than 5 years ago the absence of concurrent suicidal ideation and/or severe depression should be confirmed by a mental healthcare practitioner before enrolling into the study.	To protect study participants' well-being. Study participants with SLE have an increased risk for depression and suicidality. Some biotherapeutic immunomodulators are suspected to increase the risk for suicidality.

Criterion	N	Content	Justification
Exclusion	29a	Study participant has ≥3x the ULN alanine aminotransferase (ALT), aspartate aminotransferase (AST), or alkaline phosphatase (ALP), or >ULN bilirubin (≥1.5xULN bilirubin if known Gilbert's syndrome), except in the case where the abnormal test values are ascribed to SLE hepatitis. • If study participant only has >ULN, but <1.5xULN bilirubin, fractionate bilirubin to identify possible undiagnosed Gilbert's syndrome (ie, direct bilirubin <35%) should be assessed, except in the case where the abnormal test values are ascribed to SLE hepatitis or hemolytic anemia, in the opinion of the Investigator. • In case of a suspected SLE hepatitis, eligibility must be discussed with the Medical Monitor. • If study participant has a result of ALT, AST, or ALP that is >ULN but that does not meet the exclusion limit at Screening, a repetition of the lab assessment is recommended to judge the dynamic of the increase but is in the Investigator's discretion considering the medical history of the study participant. In case of a further clinically relevant increase (with a value that still doesn't meet the exclusion limit), inclusion of the study participant must be discussed with the Medical Monitor.	To protect study participants' well-being. Severe liver dysfunction could impact the metabolization of DZP
Exclusion	30a	Study participant has chronic kidney failure stage 4, manifested by estimated glomerular filtration rate (eGFR) <30mL/min/1.73m^2, or serum creatinine >2.5mg/dL, or participant has proteinuria >3g/day, or protein:creatinine ratio >340mg/mmol at the Screening Visit.	To protect study participants' well-being. Components of DZP are secreted through the renal system. So far there are only data up to a creatinine clearance of ≥45mL/min/1.73m^2 and proteinuria ≤3g/day and no impact could be detected. As Proteinuria is common in SLE study participants this was extended to not

Criterion	N	Content	Justification
			exclude study participants with high unmet medical need but only by a justifiable range
Exclusion	31a	Study participant has any significant hematologic abnormalities at the Screening Visit (V1) as follows: a. Hemoglobin <7.0g/dL b. [redacted] T-lymphocytes <200/mm^3 c. Absolute neutrophil count <500/mm^3 d. [redacted] T lymphocytes <500/mm^3 in combination with neutrophil count <1000/mm3 e. Platelets <25,000/mm^3. Study participants with a higher platelet count should also be excluded if they have a clinical risk of bleeding for reasons other than SLE.	To protect study participants' well-being. Hematological alterations are common in SLE however severe anemia (Hb <7g/dL) and/or thrombopenia (CTCAE grade 4, <25,000/µL) is associated with an increased risk for cardiovascular, constitutional and bleeding events. Severe lymphopenia and granulocytopenia or combination is increasing the risk for serious infections which could be exacerbated by DZP.

10.14 Appendix 14: Criteria for diagnosis of anaphylaxis

Anaphylaxis is highly likely when any of the following 3 criteria is fulfilled (Sampson et al, 2006):

1. Acute onset of an illness (minutes to several hours) with involvement of the skin, mucosal tissue, or both (eg, generalized hives, pruritus or flushing, swollen lips-tongue-uvula)

   AND at least 1 of the following:

   - Respiratory compromise (eg, dyspnea, wheeze-bronchospasm, stridor, reduced peak expiratory flow [PEF], hypoxemia)
   - Reduced blood pressure or associated symptoms of end-organ dysfunction (eg, hypotonia [collapse], syncope, incontinence)

2. Two or more of the following that occur rapidly after exposure to a likely allergen for that study participant (minutes to several hours):

   - Involvement of the skin-mucosal tissue (eg, generalized hives, itch-flush, swollen lips-tongue-uvula)
   - Respiratory compromise (eg, dyspnea, wheeze-bronchospasm, stridor, reduced PEF, hypoxemia)
   - Reduced blood pressure or associated symptoms (eg, hypotonia [collapse], syncope, incontinence)
   - Persistent gastrointestinal symptoms (eg, crampy abdominal pain, vomiting)

3. Reduced blood pressure after exposure to known allergen for that study participant (minutes to several hours): systolic blood pressure of <90mmHg or >30% decrease from the study participant's Baseline.

10.15 Appendix 15: Suggested management guidelines for suspected infusion reactions

Type of reaction	Sponsor recommendations for management
Acute – Mild Eg, flushing; dizziness; headache; sweating; palpitations; nausea	Slow infusion rate to 5mL/h Infuse 0.9% NaCl 500-1000mL/h iv Antihistamine iv/im Paracetamol 1g po Monitor vital signs every 10min until back to baseline Wait 20min, then increase infusion rate to 8mL/h for 15min, then 16mL/h, 20mL/h, 25mL/h every 15min, as tolerated until intended dose has been given
Acute – Moderate eg, flushing; chest tightness; dyspnea; hypo/hypertension (change >20mmHg in SBP); raised temperature; palpitations; urticaria	Stop infusion Infuse 0.9% NaCl 500-1000mL/h iv Antihistamine iv/im Paracetamol 1g po Monitor vital signs every 5min until back to baseline Wait 20min If there is no indication of anaphylaxis (eg, generalized urticaria and/or bronchospasm), and if clinically appropriate, consider restarting the infusion at a lower rate following this suggested regimen: Restart infusion at 5mL/h for 15min Increase infusion rate to 8mL/h for 15min, then 16mL/h, 20mL/h, 25mL/h every 15min, as tolerated until intended dose has been given
Acute – Severe Eg, hypo/hypertension (change >40mmHg in SBP); raised temperature with rigors; chest tightness; dyspnoea with wheezing; stridor	Stop infusion definitively Alert crash team Maintain airway, ensure oxygen is available If wheezing, give epinephrine 0.5mg im (0.5mL 1:1000 epinephrine) Antihistamine iv/im Corticosteroids iv Monitor vital signs every 2min until back to baseline

im=intramuscular; NaCl=sodium chloride; iv=intravenous; po=oral; SBP=systolic blood pressure

10.15.1 Tryptase

In case of a suspected infusion reaction, samples should be taken as follows to determine serum tryptase levels to support the differential diagnosis (Muraro et al, 2022; Platzgummer et al, 2020):

- The first blood sample should be taken 30 minutes to 2 hours after the start of the reaction (if not feasible during this time period, a sample may be taken up to 6 hours after the start of the reaction).
- The second blood sample should be taken 24 or more hours after complete resolution of symptoms. If obtaining the second blood sample on one of the following days after the

suspected infusion reaction is not feasible, a sample should be taken at the next regular contact with the study participant (eg, next study visit).

10.16 Appendix 16: Criteria for diagnosis of sepsis

In line with the 2016 Society of Critical Care Medicine/European Society of Intensive Care Medicine recommendation, Quick Sequential Organ Failure Assessment (qSOFA) scoring should be used to determine if a participant likely has a sepsis. Study participants with suspected infection can be rapidly identified as being more likely to have poor outcomes typical of sepsis if they have at least 2 of the following clinical criteria:

- Respiratory rate ≥22/min
- Altered mentation
- Systolic blood pressure ≥100mmHg

In a hospital setting, the more comprehensive qSOFA score should be considered to determine if an event meets the criteria for sepsis.

10.17 Appendix 17: Criteria for Antiphospholipid Syndrome (APS)

Clinical criteria (1 or more of the following)	**Laboratory criteria (1 or more of the following present on 2 or more occasions at least 12 weeks apart using recommended procedures)**
Vascular thrombosis: 1 or more objectively confirmed episodes of arterial, venous or small vessel thrombosis occurring in any tissue or organ	[redacted] detected according to the guidelines of the ISTH
Pregnancy morbidity: 1 or more unexplained deaths of a morphologically normal fetus at or beyond the 10th week of gestation; or 1 or more premature births of a morphologically normal neonate before the 34th week of gestation because of eclampsia, preeclampsia, or placental insufficiency; or 3 or more unexplained consecutive spontaneous abortions before the 10th week of gestation	ACL antibody of [redacted] isotype, present in medium or high titer (> 40 [redacted] phospholipid units or > the 99th percentile) measured by a standardized ELISA [redacted] isotype present in titer > the 99th percentile measured by a standardized ELISA

ACL = anticardiolipin; APS= antiphospholipid syndrome; [redacted] I; ELISA= enzyme-linked immunosorbent assay; [redacted] M; ISTH= International Society on Thrombosis and Haemostasis; [redacted]
Adapted from Lim, 2013

11 REFERENCES

ACR 2021. https://www.COVID-19-Vaccine-Clinical-Guidance-Rheumatic-Diseases-Summary.pdf (rheumatology.org). Accessed 28 October 2021.

Albrecht J, Taylor L, Berlin JA, Dulay S, Ang G, Fakharzadeh S, et al. The CLASI (Cutaneous LE Disease Area and Severity Index): an outcome instrument for cutaneous lupus erythematosus. J Invest Dermatol. 2005;125(5):889–94.

Borchers AT, Naguwa SM, Shoenfeld Y, Gershwin ME. The geoepidemiology of systemic lupus erythematosus. Autoimmunity Reviews. 2010;9:A277-A287.

Cella D, Eton DT, Lai JS, Peterman AH, Merkel DE. Combining anchor and distribution-based methods to derive minimal clinically important differences on the Functional Assessment of Cancer Therapy (FACT) anemia and fatigue scales. J Pain Symptom Manage. 2002; 24(6): 547-61.

Cellcept (package insert). South San Francisco, CA: Genentech USA, Inc; 2019.

Cervera R, Khamashta MA, Font J, Sebastiani GD, Gil A, Lavilla P, et al. Morbidity and mortality in systemic lupus erythematosus during a 10-year period: a comparison of early and late manifestations in a cohort of 1,000 patients. Medicine (Baltimore). 2003;82:299-308.

Chambers SA, Allen E, Rahman A, Isenberg D. Damage and mortality in a group of British patients with systemic lupus erythematosus followed up for over 10 years. Rheumatology. 2009;48:673-675.

Costedoat-Chalumeau N, Pouchot J, Guettrot-Imbert G, Le Guern V, Leroux, G, Marra D, et al. Adherence to treatment in systemic lupus erythematosus patients. Best Practice & Research Clinical Rheumatology. 2013;027:329-340.

CPMP/ICH/135/95 Note for guidance on Good Clinical Practice (EMEA) Jul 2002.

Devilliers H, Amoura Z, Besancenot JF, Bonnotte B, Pasquali JL, Wahl D, et al. Responsiveness of the 36-item Short Form Health Survey and the Lupus Quality of Life questionnaire in SLE. Rheumatol (Oxford). 2015;54(5):940-9.

EMA/828208/2017 Mycophenolate: updated recommendations for contraception for men and women. 2017.

EULAR 2021. Recommendations for the management of rheumatic and musculoskeletal diseases in the context of SARS-CoV-2: The July 2021 update. https://www.eular.org/myUploadData/files/eular_recommendations_for_the_management_of_rheumatic_and_musculoskeletal_diseases_in_the_context_of_sars_cov_2_(07_21).pdf

Fanouriakis A, Kostopoulou M, Alunno A, Aringer M, Bajema I, Boletis JN, et al. 2019 update of the EULAR recommendations for the management of systemic lupus erythematosus. Ann Rheum Dis. 2019;38(6); 736-745.

Fernandez-Ruiz R, Masson M, Kim MY, Myers B, Haberman RH, Castillo R, et al. Leveraging the United States Epicenter to Provide Insights on COVID-19 in Patients with Systemic Lupus Erythematosus. Arthritis Rheumatol. 2020 Jul 26. doi: 10.1002/art.41450.

Food and Drug Administration. Guidance for Industry. Drug-induced liver injury: premarketing clinical evaluation. US Dept of Health and Human Services, Center for Drug Evaluation and Research, Center for Biologics Evaluation and Research, 07/2009.

Fredi M, Cavazzana I, Moschetti L, Andreoli L, Franceschini F, on behalf of the Brescia Rheumatology COVID-19 Study Group. COVID-19 in patients with rheumatic diseases in northern Italy: a single-centre observational and case–control study. The Lancet Rhematol. 2020; 2(9):549-56.

Furer V, Rondaan C, Heijstek MW, et al. 2019 update of EULAR recommendations for vaccination in adult patients with autoimmune inflammatory rheumatic diseases. Ann Rheum Dis. 2020;79(1):39–52.

Geisen UM, Berner DK, Tran F, et al. Immunogenicity and safety of anti-SARS-CoV-2 mRNA vaccines in patients with chronic inflammatory conditions and immunosuppressive therapy in a monocentric cohort. Ann Rheum Dis. 2021;80(10):1306-11.

Gianfrancesco M, Hyrich KI Al-Adely S, Carmona L, Danila MI, Gossec L, et al. Characteristics associated with hospitalisation for COVID-19 in people with rheumatic disease: data from the COVID-19 Global Rheumatology Alliance physician- reported registry. Ann Rheum Dis. 2020;79(7):859-866.

Gladman DD, Ibañez D, Urowitz MB. Systemic lupus erythematosus disease activity index 2000. J Rheumatol. 2002;29:288-91.

Gladman DD, Urowitz MB, Rahman P, Ibañez D, Tam LS. Accrual of organ damage over time in patients with systemic lupus erythematosus. J Rheumatol. 2003;30:1955-9.

Haberman RH, Castillo R, Chen A, Yan D, Ramirez D, Sekar V, et al. COVID-19 in Patients with Inflammatory Arthritis: A Prospective Study on the Effects of Comorbidities and DMARDs on Clinical Outcomes. Arthritis Rheumatol. 2020 Jul 28. doi: 10.1002/art.41456.

Isenberg DA, Allen E, Farewell V, D'Cruz D, Alarcon GS, Aranow C, et al. An assessment of disease flare in patients with systemic lupus erythematosus: a comparison of BILAG 2004 and the flare version of SELENA. Ann Rheum Dis. 2011;70(1):54-59.

ISO 14155:2011 Clinical Investigations of medical devices for human study participants – Good Clinical Practice.

James LP, Letzig L, Simpson PM, Capparelli E, Roberts DW, Hinson JA, et al. Pharmacokinetics of acetaminophen-adduct in adults with acetaminophen overdose and acute liver failure. Drug Metab Dispos 2009;37:1779-84.

Kimball AB, Yu AP, Signorovitch J, Xie, J, Tsaneva M, Gupta SR, et al. The effects of adalimumab treatment and psoriasis severity on self-reported work productivity and activity impairment for patients with moderate to severe psoriasis. J Am Acad Dermatol. 2012;66(2):e67-e75.

Le Gal F, Gordien E, Affolabi D, Hanslik T, Alloui C, Dény P, Gault E. Quantification of Hepatitis Delta Virus RNA in Serum by Consensus Real-Time PCR Indicates Different Patterns of Virological Response to Interferon Therapy in Chronically Infected Patients. J Clin Microbiol. 2005;43:2363–2369.

Lim W. Antiphospholipid Syndrome. Hematology Am Soc Hematol Educ Program 2013;2013:675-80.

Mason A, Anver H, Lwin M, Holroyd C, Faust SN, Edwards CJ. Lupus, vaccinations and COVID-19: What we know now. Lupus. 2021;30(10):1541-52.

Maruish, ME (Ed.). User's manual for the SF-36v2 Health Survey (3rd ed.). Lincoln, RI: QualityMetric Incorporated. 2011.

McElhone K, Abbott J, Shelmerdine J, Bruce IN, Ahmad Y, Gordon C, et al. Development and validation of a disease-specific health-related quality of life measure, the LupusQol, for adults with systemic lupus erythematosus. Arthritis Rheum. 2007;57:972-9.

Muraro A, Worm M, Alviani C, et al. EAACI guidelines: Anaphylaxis (2021 update). Allergy. 2022;77(2):357-77.

Murdaca G, Orsi A, Spanò F, et al. Vaccine-preventable infections in Systemic Lupus Erythematosus. Hum Vaccin Immunother. 2016;12(3):632-43.

Nightingale AL, Farmer RD, de Vries CS. Incidence of clinically diagnosed systemic lupus erythematosus 1992-1998 using the UK General Practice Research Database. Pharmacoepidemiol Drug Saf. 2006;15:656-61.

Pablos JL, Galindo M, Carmona L, Lledó A, Retuerto M, Blanco R, et al. Clinical outcomes of hospitalised patients with COVID-19 and chronic inflammatory and autoimmune rheumatic diseases: a multicentric matched cohort study. Ann Rheum Dis. 2020;79:1544-9.

Platzgummer S, Bizzaro N, Bilò MB, Pravettoni V, Cecchi L, Sargentini V, et al. Recommendations for the use of tryptase in the diagnosis of anaphylaxis and clonal mastcell disorders. Eur Ann Allergy Clin Immunol. 2020;52(2):51-61.

Reilly MC, Zbrozek AS, Dukes EM. The Validity and Reproducibility of a Work Productivity and Activity Impairment Instrument. PharmacoEconomics. 1993:4(5):353-65.

Thamer M, Hernán MA, Zhang Y, Cotter D, Petri M. Prednisone, lupus activity, and permanent organ damage. J Rheumatol. 2009;36:560-4.

Touma Z, Gladman DD, Ibañez D, Taghavi-Zadeh S, Urowitz MB. Systemic Lupus Erthematosus Disease Activity Index 2000 Responder Index-50 enhances the ability of SLE Responder Index to identify responders in clinical trials. J Rheumatol. 2011:38(11):2395-9.

Tsokos GC, Gordon C, Smolen JS, editors. Systemic Lupus Erythematosus: A companion to Rheumatology. Pennsylvania: Mosby Elsevier; 2007.

Van Assen S, Elkayam O, Agmon-Levin N, et al. Vaccination in adult patients with auto-immune inflammatory rheumatic diseases: a systematic literature review for the European League Against Rheumatism evidence-based recommendations for vaccination in adult patients with auto-immune inflammatory rheumatic diseases. Autoimmun Rev. 2011;10(6):341-52.

Vender R, Lynde C, Ho V, Chau D, Poulin-Costello M. Work Productivity and Healthcare Resource Utilizatioin Outcomes for Patients on Etanercept for Moderate-to-Severe Plaque Psoriasis: Results from a 1-Year, Multicentre, Open-Lable, Single-Arm Study in a Clinical Setting. Appl Health Econ Health Policy. 2012:10(5):343-53.

Yee CS, Cresswell L, Farewell V, Rahman A, Teh LS, Griffiths B, et al. Numerical scoring for the BILAG-2004 index. Rheumatology (Oxford) 2010;49(9):1665-9.

Yurkovich M, Vostretsova K, Chen W, Aviña-Zubieta JA. Overall and cause-specific mortality in patients with systemic lupus erythematosus: a meta-analysis of observational studies. Arthritis Care Res. 2014;66(4):608–616.

SPONSOR DECLARATION

I confirm that I have carefully read and understand this protocol and agree to conduct this clinical study as outlined in this protocol and according to current Good Clinical Practice.

Approval Signatures

Name: sl0043-protocol-amend-4-16Mar2023

Version: 1.0

Document Number: CLIN-000213926

Title: SL0043 Protocol - Amendment 4 - Placebo-controlled Double-blind

Approved Date: 16 Mar 2023

Document Approvals	
Approval Verdict: Approved	Name: [redacted] Capacity: Clinical Date of Signature: 16-Mar-2023 12:46:54 GMT+0000
Approval Verdict: Approved	Name: [redacted] Capacity: Subject Matter Expert Date of Signature: 16-Mar-2023 14:27:54 GMT+0000
Approval Verdict: Approved	Name: [redacted] Capacity: Clinical Date of Signature: 16-Mar-2023 17:53:55 GMT+0000