PROTOCOL SL0023 AMENDMENT 1

A MULTI-CENTER, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED, PARALLEL-GROUP, DOSE-RANGING STUDY FOLLOWED BY AN OBSERVATIONAL PERIOD TO EVALUATE THE EFFICACY AND SAFETY OF DAPIROLIZUMAB PEGOL IN SUBJECTS WITH MODERATELY TO SEVERELY ACTIVE SYSTEMIC LUPUS ERYTHEMATOSUS

PHASE 2B

EudraCT Number: 2015-004457-40

IND Number: 100807

Sponsor:

UCB Biopharma SPRL

Allée de la Recherche 60, 1070

Brussels, Belgium

Protocol/Amendment Number	Date	Type of amendment
Final Protocol	12 Apr 2016	Not applicable
Protocol Amendment 1	14 Dec 2016	Nonsubstantial

STUDY CONTACT INFORMATION

Sponsor

UCB Biopharma SPRL
Allée de la Recherche 60, 1070
Brussels, Belgium

Sponsor Study Physician

Name:	[redacted], MD
Address:	UCB BIOSCIENCES GmbH Alfred-Nobel-Str. 10 40789 Monheim GERMANY
Phone:	[redacted]

Clinical Project Manager

Name:	[redacted]
Address:	UCB Biosciences Inc. 8010 Arco Corporate Drive, Ste 100 Raleigh, NC 27617 USA
Phone:	[redacted]

Clinical Trial Biostatistician

Name:	[redacted]
Address:	UCB Biosciences Inc. 8010 Arco Corporate Drive, Ste 100 Raleigh, NC 27617 USA
Phone:	[redacted]

Clinical Monitoring Contract Research Organization

Name:	INC Research
Address:	3201 Beechleaf Ct #600 Raleigh, NC 27604 USA
Phone:	+1 919 876 9300

SERIOUS ADVERSE EVENT REPORTING

Serious adverse event reporting (24h)	
Fax	**Europe and Rest of the World:** +32 2 386 6563 **USA:** +1 770 970 2494 **Canada:** +1 877 582 8842
Email	**Global:** safetyreportingCDP7657@ucb.com

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF ABBREVIATIONS

ACR	American College of Rheumatology
ACE	angiotensin converting enzyme
ADL	activities of daily living
AE	adverse event
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ANA	antinuclear antibody
anti-dsDNA	anti-double-stranded deoxyribonucleic acid
anti-ENA	extractable nuclear antigen antibody
anti-RNP	anti-ribonucleoprotein antibody
anti-SM	anti-Smith antibody
anti-SSA	Sjögren's syndrome antibody A
anti-SSB	Sjögren's syndrome antibody B
aPL	antiphospholipid
APS	antiphospholipid syndrome
aPTT	activated partial thromboplastin time
AST	aspartate aminotransferase
BICLA	BILAG 2004-based Composite Lupus Assessment
BILAG 2004	British Isles Lupus Assessment Group Disease Activity Index 2004
BST	BILAG 2004 Systems Tally
C3	complement 3
C4	complement 4
CD40L	CD40 ligand
CDMS	clinical data management system
CI	confidence interval
CLASI	Cutaneous Lupus Erythematosus Disease Area and Severity Index
CPM	Clinical Project Manager
CRO	contract research organization
CS	Completer Set
CSR	Clinical Study Report
C-SSRS	Columbia Suicide Severity Rating Scale

CTSO	Clinical Trial Supply Operations
DMC	Data Monitoring Committee
DNA	deoxyribonucleic acid
DZP	dapirolizumab pegol
ECG	electrocardiogram
eCRF	electronic Case Report Form
EDC	electronic data capture
eGFR	estimated glomerular filtration rate
EHR	Electronic Healthcare Record
ES	Enrolled Set
EWV	Early Withdrawal Visit
Fab′	fragment antigen-binding
FAS	Full Analysis Set
Fc	fragment crystallizable
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HIV	human immunodeficiency virus
HMG-CoA	3-hydroxy-3-methyl-glutaryl-coenzyme A
HRQoL	health-related quality of life
hsCRP	high sensitivity C-reactive protein
IB	Investigator's Brochure
ICH	International Council for Harmonisation
IEC	Independent Ethics Committee
Ig	immunoglobulin
IGRA	interferon-γ release assay
im	intramuscular(ly)
IMP	investigational medicinal product
IP	interphalangeal
IRB	Institutional Review Board
ITP	idiopathic thrombocytopenic purpura
iv	intravenous(ly)
IVRS	interactive voice response system

IWRS	interactive web response system
LupusQoL	Lupus Quality of Life questionnaire
LTB	latent tuberculosis
MCID	minimal clinically important difference
MCP	metacarpophalangeal
MCP-Mod	Multiple Comparison Procedure–Modelling
MILES	Michigan Lupus and Epidemiology Surveillance Program
mRNA	messenger ribonucleic acid
NHP	nonhuman primate
NSAID	nonsteroidal anti-inflammatory drug
NTMB	non-tuberculosis mycobacterium
PBO	placebo
PD	pharmacodynamics(s)
PDILI	potential drug-induced liver injury
PEF	peak expiratory flow
PEG	polyethylene glycol
PGA	Physician's Global Assessment of Disease
PIP	proximal interphalangeal
PK	pharmacokinetic(s)
PK-PPS	Pharmacokinetic Per Protocol Set
PPS	Per Protocol Set
PRO	patient-reported outcome
PS	Patient Safety
PtGA	Patient's Global Assessment of Disease
QFT-GIT	Quanti-FERON®-TB GOLD in-Tube test
RF	rheumatoid factor
RS	Randomized Set
SAE	serious adverse event
SAP	Statistical Analysis Plan
SFU	Safety Follow-up
SJC	swollen joint count
SLE	systemic lupus erythematosus

SLEDAI-2K	Systemic Lupus Erythematosus Disease Activity Index 2000
SLE-E	Systemic Lupus Erythematosus-Emotional States Instrument
SLE-F	Systemic Lupus Erythematosus-Fatigue Instrument
SLE-M	Systemic Lupus Erythematosus-Mobility Instrument
SLE-P	Systemic Lupus Erythematosus-Pain Instrument
SLE-S	Systemic Lupus Erythematosus-Symptom Inventory Instrument
SLICC	Systemic Lupus International Collaborating Clinics
SOP	Standard Operating Procedure
SRI-4, -5, and -6	Systemic Lupus Erythematosus Responder Index-4, -5, and -6
SRI-50	Systemic Lupus Erythematosus Disease Activity Index-2K Responder Index-50
SS	Safety Set
TB	tuberculosis
TJC	tender joint count
TT	tetanus toxoid
ULN	upper limit of normal
VAS	visual analog scale

1 SUMMARY

SL0023 is a 2-part study consisting of a randomized, double-blind, placebo (PBO)-controlled, parallel-group, dose-ranging period (24-week Double-Blind Treatment Period; Part 1) followed by a 24-week Observational Period (Part 2) in adult subjects with moderately to severely active systemic lupus erythematosus (SLE) who are receiving stable standard-of-care medications (ie, corticosteroids, immunosuppressants, and/or antimalarials) at study entry.

The primary objective of SL0023 is to assess the dose-response for the efficacy of intravenous (iv) dapirolizumab pegol (DZP; 3 dose groups) at Week 24 of the Double-Blind Treatment Period (Part 1). Secondary objectives are to assess the efficacy of the individual dose regimens of iv DZP at Week 24 and to assess the safety and tolerability of iv DZP. Other objectives are to assess the efficacy of iv DZP at additional time points; to assess the corticosteroid-sparing effect of iv DZP; to assess the pharmacokinetics (PK) of iv DZP and polyethylene glycol (PEG); to assess the pharmacodynamics (PD) of iv DZP; to assess the immunogenicity of iv DZP and PEG; to assess the effects of iv DZP on health-related quality of life (HRQoL), symptoms, fatigue, mobility, and pain; to perform exploratory analyses of the effects of iv DZP with transcriptomic and proteomic biomarkers; to assess durability of the clinical response after withdrawal of iv DZP; and to assess PD after withdrawal of iv DZP (including gene transcription signature).

The primary efficacy variable is the British Isle Lupus Assessment Group Disease Activity Index 2004 (BILAG 2004)-based Composite Lupus Assessment (BICLA) responder rate across 3 doses of DZP and PBO at Week 24. The secondary efficacy variable is the BICLA responder rate in the individual dose groups at Week 24. Several other efficacy variables assessing disease activity, corticosteroid-sparing effects, HRQoL, symptoms, fatigue, mobility, and pain are also included.

Safety variables include adverse events (AEs) and serious AEs (SAEs), subject withdrawals due to AEs, vital sign parameters, electrocardiograms (ECGs), and safety laboratory tests. Several variables evaluating PK, PD, biomarkers, and immunogenicity will also be assessed.

The study consists of a Screening Period of up to 4 weeks, a 24-week Double-Blind Treatment Period (Part 1), and a 24-week Observational Period (Part 2). At the start of the 24-week Double-Blind Treatment Period (Part 1), eligible subjects will be randomized (1:1:1:1) to 1 of 4 treatment arms (DZP 6mg/kg, 24mg/kg, or 45mg/kg, or PBO) and stratified in accordance with corticosteroid dose (≤10mg/day or >10mg/day prednisone equivalent) determined at Screening. Study drug will be administered by iv infusion every 4 weeks during Part 1 of the study. Subjects who withdraw early from the 24-week Double-Blind Treatment Period (Part 1) will enter an 8-week Safety Follow-up (SFU) Period (which ends 12 weeks after the final dose of study drug).

Subjects who complete the 24-week Double-Blind Treatment Period (Part 1) will continue into a 24-week Observational Period (Part 2), during which subjects will not receive study drug but will be able to receive standard-of-care treatment, as indicated. The subjects, Investigators, and study site staff will remain blinded to the treatment administered during Part 1 of the study until the end of the study. The maximum duration of the entire study (Parts 1 and 2) per subject will be approximately 52 weeks.

Eligible subjects will have active SLE at Baseline despite stable standard-of-care treatment with at least 1 of the following, either alone or in combination: corticosteroids (at doses of ≤40mg/day prednisone or equivalent), and/or antimalarials, and/or immunosuppressants. In subjects receiving concomitant corticosteroids, doses must have been stable for at least 2 weeks prior to Screening, must remain stable until Baseline (Visit 2), and should remain stable until 4 weeks after the first study drug infusion (until Day 28). Subjects 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 subjects receiving concomitant corticosteroid doses between 10mg/day and 40mg/day prednisone or equivalent at Screening, a mandatory corticosteroid taper must be initiated no later than 4 weeks after the first study drug infusion (on Day 29). The tapering regimen will aim to reduce the daily prednisone equivalent dose to 7.5mg/day or lower by Week 12 (Day 84) of the study. Treatment with antimalarials and immunosuppressants must have been started or stopped at least 12 weeks prior to dosing with study drug and doses must remain stable for at least 4 weeks for antimalarials and at least 8 weeks for immunosuppressants prior to the first study drug infusion (Visit 2). In subjects receiving concomitant antimalarials or immunosuppressants, doses must not exceed the specified maximum permitted doses (as outlined in Table 6-1 and Table 6-2).

The study is planned to enroll at least 267 subjects in order to randomize approximately 160 subjects (40 subjects per treatment group). Subjects eligible to enroll in this study are males or females, ≥18 years of age, diagnosed with SLE according to the Systemic Lupus International Collaborating Clinics (SLICC) Classification Criteria and having moderately to severely active disease, defined as having BILAG Grade A level disease activity in ≥1 body/organ system or BILAG Grade B in ≥2 body/organ systems if no BILAG Grade A level disease is present and Systemic Lupus Erythematosus Disease Activity Index-2000 (SLEDAI-2K) score ≥6 at Screening. Subjects must have 1 of the following 3 criteria confirmed by the central laboratory at Screening: (a) anti-double stranded deoxyribonucleic acid (anti-dsDNA) antibodies by Farr assay, or (b) low complement (ie, either low complement 3 [C3], low complement 4 [C4], or both), or (c) antinuclear antibody (ANA) titer of ≥1:80. In subjects meeting the latter ANA criterion "c," this must be in combination with at least 1 of the following: (1) historical positivity for anti-dsDNA at least twice in the past, or (2) positivity for extractable nuclear antigen antibodies (anti-ENA) (anti-Smith antibody [anti-SM], Sjögren's syndrome antibody A [anti-SSA], Sjögren's syndrome antibody B [anti-SSB], or anti-ribonucleoprotein antibody [anti-RNP]).

A Data Monitoring Committee (DMC) will monitor the safety of subjects in SL0023 on an ongoing basis, with a particular emphasis on occurrence of thromboembolic events.

An initial biomarker analysis may be performed on all evaluable biomarker data from Part 1 of the study when 25% to 35% of the randomized subjects have completed Visit 7 (Week 12) of the Double-Blind Treatment Period. Data from subjects who have prematurely withdrawn from the study prior to Visit 7 will be included. The initial biomarker analysis will focus on transcriptomic biomarker variables (eg, messenger ribonucleic acid [mRNA]), prespecified in a Biomarker Plan, in order to provide guidance for the DZP development program, and will not affect the conduct of the study.

After the last subject completes Part 1 of the study, the data for those subjects will be secured and an interim Clinical Study Report (CSR) will be written for the Double-Blind Treatment Period (Part 1) of the study; this interim CSR will not include any data from the Observational Period (Part 2). A biomarker analysis on the full Double-Blind Treatment Period (Part 1) dataset will be included in the interim CSR. Subsequently, a complete final CSR will be written for the entire study following completion of the Observational Period (Part 2) of the study.

2 INTRODUCTION

Systemic lupus erythematosus is a chronic autoimmune disease that can target nearly all major organ systems in the body (Tsokos et al, 2007). In Europe, the incidence rate of SLE varies from 1.0 per 100,000 person-years in Denmark to 4.7 per 100,000 person-years in the UK (Borchers et al, 2010). Studies in the US, Australia, and Canada report a similar incidence, with a range of 2 to 5 per 100,000 person-years (Borchers et al, 2010). These areas also have nonhomogeneous prevalence rates varying from 28.3 in Denmark to an estimated 149.5 per 100,000 adults in the US (Borchers et al, 2010). In the Asia Pacific countries, crude incidence rates of SLE are reported to be 0.9 to 3.1 per 100,000 patient-years and the crude prevalence is reported to be 4.3 to 45.3 per 100,000 people (Jakes et al, 2012). The disease is rarely diagnosed in Africa.

The observed regional variation can be partially explained by the racial and ethnic differences in SLE occurrence. The prevalence in the US per 100,000 people is estimated to be between 406 and 694 in blacks, 139 and 244 in Hispanics, 93 and 103 in Asian/Pacific Islanders, and 164 and 203 in whites (Borchers et al, 2010). Two recent studies were designed to minimize many of the limitations in previous US SLE studies (Somers et al, 2014; Lim et al, 2014). These studies used Centers for Disease Control funded registries including the Michigan Lupus and Epidemiology Surveillance Program (MILES) and the Georgia Lupus Registry. In the MILES study, the source population was 2.4 million people (in 2 counties in Michigan). The age-adjusted incidence of SLE was 5.5 per 100,000 (95% confidence interval [CI]: 5.0, 6.1) person-years, and the prevalence was 72.8 per 100,000 people (95% CI: 70.8, 74.8) (Somers et al, 2014). These rates are higher than previously reported but are also calculated from more robust data. The study in Georgia found crude and adjusted incidence rates for SLE were both 5.6 per 100,000 person-years and the prevalence was 74 and 73 (crude and adjusted) per 100,000 people (Lim et al, 2014). The more complete case ascertainment in both of these studies resulted in the highest incidence and prevalence statistics recorded in the US.

Manifestations of SLE are highly heterogeneous, with the most common organ manifestations being musculoskeletal, mucocutaneous, and renal (Nightingale et al, 2006; Cervera et al, 2003). There is a large degree of variability in disease activity and organ system involvement seen across patients; thus, the instruments to measure disease activity should encompass this range of organ systems. The disease often oscillates between periods of active disease (flare), low disease activity, and remission, but can also remain chronically active. All disease periods need individualized treatments; ie, if a patient flares, the patient needs a treatment intervention with high dose immunosuppressant therapy (ie, high dose corticosteroid therapy, potent immunosuppressants such as cyclophosphamide) to induce disease control; if a patient achieves a low disease activity, the treatment is adapted to lower dose immunomodulatory therapy (ie, low dose steroids, antimalarials) and/or symptomatic treatment to maintain disease control. The

highest unmet need remains in patients with frequent flares or persistently active disease in spite of the use of the currently available treatments.

Corticosteroids are the cornerstone of treatment of SLE, but they are associated with an extensive number of side effects most frequently seen during long-term use but also seen during short-term high dose induction therapy. Much of the organ damage in SLE is either directly or indirectly related to prednisone (Gladman et al, 2003). As the dose of prednisone increases in SLE patients, the likelihood of organ damage increases and the pattern of organ damage observed may differ depending on how the prednisone is administered (Thamer et al, 2009). For example, long-term, low dose prednisone may result in coronary artery disease, cataracts, or osteoporotic fractures; whereas high dose iv methylprednisone may additionally result in acute psychotic events or avascular necrosis of bone.

High dose corticosteroids (eg, short-term 0.5 to 1.0mg/kg/day oral prednisone [or equivalent] or 500mg to 1g daily pulse iv methylprednisolone) are used to manage acute SLE flares such as newly presenting grade III or IV lupus nephritis in combination with immunosuppressants as an induction therapy to gain disease control. Immunosuppressants are also generally used in both moderate and severe cases when other treatments are ineffective or to limit or prevent long-term major organ damage from the disease or corticosteroid use ("steroid-sparing") (Muangchan et al, 2015; Al Sawah et al, 2015). Antimalarials (eg, chloroquine or hydroxychloroquine) are generally recommended as standard-of-care maintenance treatment in SLE, if tolerated.

Other common drugs are initially used in the setting of lower-level disease activity, but their use continues as the disease progresses; they include analgesics, nonsteroidal anti-inflammatory drugs (NSAIDs), and local steroids, with common supportive medications, including vasodilators (calcium channel blockers, angiotensin-converting enzyme inhibitors) for systemic hypertension or Raynaud's syndrome, local treatments for rashes or sicca syndromes, transfusions, anticonvulsants, antimigraine medications, narcotic pain medications, anticoagulants for recurrent thromboses, and antidepressants (Muangchan et al, 2015).

The CD40 ligand (CD40L) (also known as CD154) is expressed on various types of cells, including activated T cells, and can also be found as a soluble protein. Through interactions with its receptor, CD40, CD40L plays an important role in regulating interactions between T cells and other immune cells, notably B cells and antigen presenting cells, and thus affects several important functional events thought to be involved in autoimmune disease. There is considerable pharmacological evidence in the literature (for reviews see Burkly, 2001; van Kooten and Banchereau, 2000) showing that blockade of CD40L is efficacious in inflammatory and autoimmune conditions. CD40L blockade could, therefore, be an innovative approach for the treatment of SLE, specifically to induce disease control in patients experiencing flare or persisted disease activity in spite of standard-of-care medication.

The monoclonal anti-CD40L antibodies hu5c8 (also known as BG9588 or ruplizumab [Antova®]) and IDEC-131 were developed and previously evaluated by Biogen and IDEC, respectively. Both products were humanized immunoglobulin (Ig) G1 antibodies that blocked humoral immune responses in nonhuman primate (NHP) models and showed evidence of potential efficacy in early clinical studies in idiopathic thrombocytopenic purpura (ITP) and SLE (Patel et al, 2008; Kuwana et al, 2004; Boumpas et al, 2003; Kalunian et al, 2002; Davis et al, 2001). Administration of hu5c8 was associated with an unusually high incidence of

thromboembolic events (approximately 10% of subjects exposed) and further clinical development of hu5c8 was discontinued. In over 150 subjects treated with IDEC-131, there was 1 report in the literature of a thromboembolism; this subject (who had chronic refractory ITP, and who was diabetic, overweight, and hypertensive) had a myocardial infarction when their platelet count increased to >100x10^9/L. Coronary angiography revealed longstanding atherosclerotic changes in the subject's coronary arteries (Patel et al, 2008).

The underlying mechanism for the induction of thromboembolic events by hu5c8 in humans has been investigated. It has been known for some time that human platelets carry both CD40 and fragment crystallizable (Fc) γIIA (CD32a) receptors, and that they secrete CD40L and express cell surface CD40L after activation. Hypothetically, therefore, administration of anti-CD40L antibody may cause platelet activation via CD32a receptor cross-linking by simultaneously binding both to CD40/CD40L and to the Fc receptor. Indeed, in a transgenic mouse model, administration of anti-CD40L antibodies caused platelet aggregation and thrombosis in an Fc-dependent manner (Robles-Carrillo et al, 2010). Thus, it can be hypothesized that removal of the Fc receptor binding site might alleviate this risk of thromboembolism and enable further assessment of this therapeutic strategy in patients with SLE.

Dapirolizumab pegol (previously referred to as CDP7657) is a purified recombinant, humanized fragment antigen-binding (Fab´) antibody fragment covalently bound to PEG that targets CD40L and represents a novel approach to the treatment of SLE in patients experiencing flare or persistent disease activity in spite of standard-of-care medication. In particular, DZP lacks the Fc portion of whole antibody, and instead has a PEG moiety to achieve the PK characteristics to enable adequate exposure (Fab´ PEG). Both hu5c8 and DZP display cross-reactivity against NHP CD40L with comparable affinity and potency in in vitro studies, and both are active in mechanistic studies. Extensive in vivo data from studies in NHPs together with data from in vitro functional experiments with human and Rhesus macaque platelets suggest that, for thromboembolism induction with an anti-CD40L antibody, 2 interactions are required: idiotypic binding of CD40L and interaction with the CD32a receptor via the Fc portion. In NHP studies, hu5c8 induced significant thromboembolic event-like lesions (thrombi, organized thrombi, and intimal hyperplasia) in the lungs of rhesus macaques after repeat dosing. In contrast, DZP does not result in any increase in pulmonary thrombi or vascular intimal hyperplasia above the background incidence level in rhesus macaques. There are no NHP disease models resembling SLE. Dapirolizumab pegol displays no cross-reactivity against murine CD40L; however, an anti-murine CD40L Fab´ PEG antibody suppresses nephritis and improves renal function (proteinuria) in the New Zealand Black/New Zealand White murine lupus model (see the DZP Investigator's Brochure [IB] for further details). The nonclinical efficacy and safety data support further development of DZP as a potential therapy for patients with SLE.

Two clinical studies have been conducted with DZP. SL0013 was the first-in-human single-dose study of DZP. In Part 1 of SL0013, 28 healthy volunteers received either PBO or DZP at doses of 0.004mg/kg to 5mg/kg, and in Part 2, 17 subjects with SLE received PBO or DZP at doses of 5mg/kg to 60mg/kg. Dapirolizumab pegol was well tolerated both in healthy subjects and in subjects with SLE in this study and no thromboembolic events were reported. The DZP IB contains additional information pertaining to data obtained in SL0013.

SL0014 was a Phase 1 study evaluating the safety, tolerability, PK, immunogenicity, and effects on disease activity of repeat-dose iv administration of DZP in subjects with active SLE, defined

as having a SLEDAI-2K score ≥4. A total of 24 subjects with SLE were randomized (2:1) to receive a loading dose of DZP 30mg/kg followed by DZP 15mg/kg every 2 weeks for a total of 6 doses of DZP or matching PBO on the same dosing schedule. DZP was well tolerated in this study, with a safety profile similar to subjects administered PBO, with the exception of a slightly higher incidence of nonserious infection in the DZP group. There were no AEs of thromboembolism and no laboratory findings suggestive of thromboembolic events. In exploratory analyses, numerically greater improvements from Baseline were observed in the DZP group compared with the PBO group for the BILAG 2004 total score, SLEDAI-2K, Patient's Global Assessment of Disease, SLEDAI-2K Responder Index-50 (SRI-50) score, and BICLA and SLE Responder Index-4 (SRI-4) responders. The BICLA response represents a clinically relevant improvement of moderate to severe disease activity, as it represents the change from a disease activity with an indication for systemic treatment intervention to a disease activity with no or limited indication to change the preexisting therapy; the SRI-4 represents a relevant decrease in disease activity. At Week 12, there were more BICLA and SRI-4 responders in the DZP group (45.5% and 41.7%, respectively) compared with the PBO group (14.3% for both BICLA and SRI-4). There was a small but statistically significant reduction in IgG concentrations at Week 12 (p=0.0436) in the DZP group compared with the PBO group. Messenger ribonucleic acid analysis demonstrated changes in the expression of genes associated with B cell and plasma cell function, as well as reductions in the expression of interferon-responsive genes (see the DZP IB for further details).

The current study, SL0023, is a Phase 2b, randomized, double-blind, PBO-controlled, parallel-group dose-ranging study followed by an observational period that will evaluate the efficacy in inducing disease control and safety of DZP in subjects with moderately to severely active SLE. Dapirolizumab pegol or PBO will be added to stable standard-of-care medication and randomization will be stratified by Screening corticosteroid dose (≤10mg/day or >10mg/day prednisone equivalent). Following completion of the 24-week Double-Blind Treatment Period (Part 1) of the study, subjects will continue into a 24-week Observational Period (Part 2), during which subjects will not receive study drug but will be able to receive standard-of-care treatment, as indicated.

3 STUDY OBJECTIVES

3.1 Primary objective

The primary objective of SL0023 is to assess the dose-response for the efficacy of iv DZP (3 dose groups) at Week 24 of the Double-Blind Treatment Period (Part 1) in adult subjects with moderately to severely active SLE receiving stable standard-of-care treatment.

3.2 Secondary objectives

The secondary objectives of SL0023 are:

- To assess the efficacy of the individual dose regimens of iv DZP at Week 24
- To assess the safety and tolerability of iv DZP

3.3 Other objectives

The other objectives of SL0023 are:

- To assess the efficacy of the individual dose regimens of iv DZP at additional time points

- To assess the corticosteroid-sparing effect of iv DZP
- To assess the PK of iv DZP and PEG
- To assess the PD of iv DZP
- To assess the immunogenicity of iv DZP and PEG
- To assess the effects of iv DZP on HRQoL, symptoms, fatigue, mobility, and pain
- To perform exploratory analyses of the effects of iv DZP with transcriptomic and proteomic biomarkers
- To assess durability of the clinical response after withdrawal of study drug
- To assess PD after withdrawal of study drug (including gene transcription signature)

4 STUDY VARIABLES

4.1 Efficacy variables

The Baseline value for efficacy variables is defined as the last value obtained prior to the first infusion of study drug (Visit 2), unless otherwise noted.

4.1.1 Primary efficacy variable

The primary efficacy variable is the BICLA responder rate across 3 doses of DZP and PBO at Week 24 (see Section 9.1.9.1 for a detailed description of this variable).

4.1.2 Secondary efficacy variable

The secondary efficacy variable is the BICLA responder rate in the individual dose groups at Week 24.

4.1.3 Other efficacy variables

Other efficacy variables being evaluated by visit will include all scheduled visits for that particular variable and will exclude the time points at which the primary and secondary variables are assessed, as specified in Section 4.1.1 and Section 4.1.2.

4.1.3.1 Clinical assessments of disease activity

- BICLA responder rates by visit
- Time to first maintained BICLA response (defined as BICLA response at 2 consecutive study visits)
- Percentage of subjects with maintained BICLA response from Week 12 to Week 24
- Percentage of subjects with maintained BICLA response from Week 24 to Week 48
- Number and percent of subjects with BILAG 2004 improvement (all BILAG 2004 Grade A improved to B, C, or D and all BILAG 2004 Grade B improved to C or D) by visit
- Absolute and change from Baseline in total BILAG 2004 score by visit
- BILAG 2004 Systems Tally (BST)
- Absolute and change from Baseline in SRI-50 score by visit

- Absolute and change from Baseline in SLEDAI-2K score by visit
- Change from Baseline in Physician's Global Assessment of Disease (PGA) and Patient's Global Assessment of Disease (PtGA) scores by visit
- SRI-4 responder rates by visit
- SLE Responder Index-5 (SRI-5) responder rates by visit
- SLE Responder Index-6 (SRI-6) responder rates by visit
- Percentage of subjects in each category in the Systemic Lupus International Collaborating Clinics/American College of Rheumatology (SLICC/ACR) Damage Index score at Week 24
- Percent change from Baseline in tender joint count (TJC) by visit
- Percent change from Baseline in swollen joint count (SJC) by visit
- Absolute and change from Baseline in Cutaneous Lupus Erythematosus Disease Area and Severity Index (CLASI) by visit
- Time to flare (with the occurrence of a flare determined by the Investigator)
- Time to flare after Week 24 (with the occurrence of a flare determined by the Investigator)
- Time to flare after Week 24 (with the occurrence of a flare defined as: a new sustained BILAG 2004 Grade A/B [present at ≥2 consecutive visits] after withdrawal of study drug or start of new induction therapy [either corticosteroid dose increase to ≥0.5 mg/kg/day prednisone equivalent or initiation of cyclophosphamide, rituximab, iv Ig, or plasma exchange] after withdrawal of study drug)

4.1.3.2 Variables assessing corticosteroid-sparing effects

- Absolute daily corticosteroid dose (in prednisone equivalent)
- Percentage of subjects with a daily corticosteroid dose of 7.5mg prednisone equivalent or less and BICLA response at Week 24
- Percentage of subjects with a daily corticosteroid dose of 7.5mg prednisone equivalent or less and a maintained BICLA response from Week 12 to Week 24
- Percentage of subjects with a daily corticosteroid dose of 7.5mg prednisone equivalent or less and SRI-4 response at Week 24
- Time-weighted area under the curve in corticosteroid dose for the period covering Baseline to Week 24
- Percentage of subjects with a daily corticosteroid dose of 7.5mg or less prednisone equivalents by visit
- Percentage of subjects with no concomitant corticosteroid treatment by visit

4.1.3.3 Patient-reported outcome variables

- Change from Baseline in Lupus Quality of Life (LupusQoL) questionnaire scores by visit
- The following exploratory patient-reported outcome (PRO) variables being developed by UCB will be assessed at sites in English- and Spanish-speaking countries (approximately 45% to 50% of the projected study population):
  - Change from Baseline in the SLE-Symptom Inventory Instrument (SLE-S) scores by visit
  - Change from Baseline in the SLE-Fatigue Instrument (SLE-F) scores by visit
  - Change from Baseline in the SLE-Mobility Instrument (SLE-M) scores by visit
  - Change from Baseline in the SLE-Pain Instrument (SLE-P) scores by visit
  - Change from Baseline in the SLE-Emotional States Instrument (SLE-E) scores by visit

4.2 Safety variables

- Incidence of AEs, SAEs, and AEs of interest including and not limited to infections, infusion-related reactions, thromboembolic events, neurological events, and malignancies
- Subject withdrawals due to AEs
- Changes from Baseline in vital sign parameters by visit
- ECGs (normal/abnormal) by visit
- Changes from Baseline in safety laboratory tests (hematology [including lymphocyte subsets], blood chemistry, urinalysis) by visit

4.3 Pharmacokinetic variables

- Plasma concentrations of DZP and PEG
- Urine concentrations of PEG

4.4 Pharmacodynamic variables

- Whole blood mRNA signature profiling to characterize potential changes in gene expression relevant to the inflammatory and immune response to DZP in SLE

4.4.1 Immunological variables

- Lupus Autoantibody Profile: anti-dsDNA antibodies, ANAs, anti-ENA (anti-SM, anti-SSA, anti-SSB, and anti-RNP), rheumatoid factor (RF), and antiphospholipid (aPL) antibodies
- Ig (total Ig, IgG, IgM, IgA, and IgE)
- High sensitivity C-reactive protein (hsCRP)
- C3 and C4 levels

4.5 Immunogenicity variables

- Anti-DZP and anti-PEG antibodies

4.6 Biomarkers

In addition to the PD variables (Section 4.4), the following samples will also be taken:

- Serum will be taken and stored for protein and lipid analysis to characterize potential changes relevant to inflammatory and immune responses and cardiovascular risk in SLE.
- Whole blood will be taken and stored to isolate deoxyribonucleic acid (DNA) which may be used to examine genetic and epigenetic changes. If samples are not used immediately, they will be stored at -80°C for later analysis until the completion of the DZP development program. They will be stored at BioStorage Technologies GmbH (Germany) and they will only be used in the context of understanding the molecular taxonomy of SLE and/or response to treatment with DZP.

5 STUDY DESIGN

5.1 Study description

SL0023 is a 2-part study consisting of a randomized, double-blind, PBO-controlled, parallel-group, dose-ranging period (24-week Double-Blind Treatment Period; Part 1) followed by a 24-week Observational Period (Part 2) in adult subjects with moderately to severely active SLE who are receiving stable standard-of-care medications (ie, corticosteroids, immunosuppressants, and/or antimalarials) at study entry.

The study consists of a Screening Period of up to 4 weeks, a 24-week Double-Blind Treatment Period (Part 1), and a 24-week Observational Period (Part 2) (see Figure 5-1). At the start of the 24-week Double-Blind Treatment Period (Part 1), eligible subjects will be randomized (1:1:1:1) to 1 of 4 treatment arms (DZP 6mg/kg, 24mg/kg, or 45mg/kg, or PBO) and stratified in accordance with Screening corticosteroid dose (≤10mg/day or >10mg/day prednisone equivalent). Study drug will be administered by iv infusion every 4 weeks during Part 1 of the study. Subjects who withdraw early from the 24-week Double-Blind Treatment Period (Part 1) will enter an 8-week SFU Period (which ends 12 weeks after the final dose of study drug).

Subjects who complete the 24-week Double-Blind Treatment Period (Part 1) will continue into a 24-week Observational Period (Part 2), during which subjects will not receive study drug but will be able to receive standard-of-care treatment, as indicated. The subjects, Investigators, and study site staff will remain blinded to the treatment administered during Part 1 of the study until the end of the study.

Eligible subjects will have active SLE at Baseline despite stable standard-of-care treatment with at least 1 of the following, either alone or in combination: corticosteroids (at doses of ≤40mg/day prednisone or equivalent), and/or antimalarials, and/or immunosuppressants. In subjects receiving concomitant corticosteroids, doses must have been stable for at least 2 weeks prior to Screening, must remain stable until Baseline (Visit 2), and should remain stable until 4 weeks after the first study drug infusion (until Day 28). Subjects 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). Treatment with antimalarials and immunosuppressants must have been started or stopped at least 12 weeks prior to dosing with study drug and doses must remain stable for at least 4 weeks for antimalarials and at least 8 weeks for immunosuppressants prior to the first study drug infusion (Visit 2). In subjects receiving concomitant antimalarials or

immunosuppressants, doses must not exceed the specified maximum permitted doses (as outlined in Table 6-1 and Table 6-2).

In subjects receiving concomitant corticosteroid doses between 10mg/day and 40mg/day prednisone or equivalent at Screening, a mandatory corticosteroid taper must be initiated no later than 4 weeks after the first study drug infusion (on Day 29). The tapering regimen, as recommended in Table 5-1, will aim to reduce the daily prednisone equivalent dose to 7.5mg/day or lower by Week 12 (Day 84) of the study. If such a rapid tapering is not considered by the Investigator to be appropriate for the individual subject, a slower tapering regimen can be used. Subjects achieving a dose of 7.5mg/day or lower may remain on this dose or continue to taper at the discretion of the Investigator. Subjects who cannot fulfill the taper based on the Investigator's judgment should remain in the study and receive corticosteroids at an appropriate dose as determined by the Investigator. Subjects will be considered nonresponders for the primary endpoint if the corticosteroid dose exceeds the prednisone equivalent dose at Baseline. Subjects will be issued a daily diary in which to record corticosteroid doses taken on a daily basis at home in between visits. Use of oral or parenteral steroids for non-SLE related conditions should be discussed in advance with the Sponsor on an individual basis.

Table 5-1: Corticosteroid tapering schedule

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**
Day 1 to Day 7	40	35	30	25	20	15	10	7.5	5	2.5	0
Day 8 to Day 14	40	35	30	25	20	15	10	7.5	5	2.5	0
Day 15 to Day 21	40	35	30	25	20	15	10	7.5	5	2.5	0
Day 22 to Day 28	40	35	30	25	20	15	10	7.5	5	2.5	0
Day 29 to Day 35	30	30	20	20	15	10	7.5	NA[b]	NA[b]	NA[b]	NA[b]
Day 36 to Day 42	30	20	20	15	15	10	NA[b]	NA[b]	NA[b]	NA[b]	NA[b]
Day 43 to Day 49	20	20	15	15	10	7.5	NA[b]	NA[b]	NA[b]	NA[b]	NA[b]
Day 50 to Day 56	20	15	15	10	7.5	NA[b]	NA[b]	NA[b]	NA[b]	NA[b]	NA[b]
Day 57 to Day 63	15	15	10	7.5	NA[b]	NA[b]	NA[b]	NA[b]	NA[b]	NA[b]	NA[b]
Day 64 to Day 70	15	10	7.5	NA[b]	NA[b]	NA[b]	NA[b]	NA[b]	NA[b]	NA[b]	NA[b]
Day 71 to Day 77	10	7.5	NA[b]	NA[b]	NA[b]	NA[b]	NA[b]	NA[b]	NA[b]	NA[b]	NA[b]
Day 78 to Day 84	7.5	NA[b]	NA[b]	NA[b]	NA[b]	NA[b]	NA[b]	NA[b]	NA[b]	NA[b]	NA[b]

[a] Corticosteroid tapering is only required in those subjects receiving continuous corticosteroids at doses ≥10mg/day at the time of enrollment into the study.
[b] Subjects 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.

Eligible subjects who are receiving a corticosteroid dose at Screening that is in between the specified starting doses of the corticosteroid tapering schedule (Table 5-1; eg, 12.5mg/day or 17.5mg/day) should transition to the lowest nearest prespecified starting dose over the first 2 weeks of Screening and will enter the study on this dose; the dose will be considered stable in

this case. This dose should then remain stable until 4 weeks after the first study drug infusion (until Day 28).

An initial biomarker analysis may be performed on all evaluable biomarker data from Part 1 of the study when 25% to 35% of the randomized subjects have completed Visit 7 (Week 12) of the Double-Blind Treatment Period. Data from subjects who have prematurely withdrawn from the study prior to Visit 7 will be included. The initial biomarker analysis will focus on transcriptomic biomarker variables (eg, mRNA), prespecified in a Biomarker Plan, in order to provide guidance for the DZP development program, and will not affect the conduct of the study.

After the last subject completes Part 1 of the study, the data for those subjects will be secured and an interim CSR will be written for the Double-Blind Treatment Period (Part 1) of the study. A complete final CSR will be written for the entire study following completion of the Observational Period (Part 2) of the study. See Section 15.7 for further details regarding these analyses.

5.1.1 Study duration per subject

The maximum duration of the entire study (Parts 1 and 2) per subject will be approximately 52 weeks, including a Screening Period of up to 4 weeks, a 24-week Double-Blind Treatment Period (Part 1), and a 24-week Observational Period (Part 2).

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

5.1.2 Planned number of subjects and sites

The study is planned to enroll at least 267 subjects in order to randomize approximately 160 subjects (40 subjects per treatment group). The study will be conducted at approximately 70 sites.

5.1.3 Anticipated regions and countries

This study is anticipated to be conducted in Western Europe, Eastern Europe, Latin America, and North America, with possible extension to other regions and countries, as needed. Capping rules for regions and sites will be described in detail in the interactive voice response system (IVRS)/interactive web response system (IWRS) specifications.

5.1.4 Data Monitoring Committee

A DMC will be formed to monitor the ongoing safety of the study. The DMC will consist of at least 3 individuals. These are clinicians knowledgeable about the disease or the treatment and 1 member may be a statistician. All members will have experience and expertise in clinical trials. The DMC members may not participate in the study as principal or coinvestigators, or as study subject care physicians. The duration of membership for the DMC will be inclusive of planned analyses for SL0023. The DMC will periodically review study data and evaluate the treatments for excess adverse effects and other potential safety issues. The DMC may also be asked to provide a review of final study results, as deemed appropriate. The detailed role, scope, composition, responsibilities, and operation of the DMC, as well as the identity of the DMC members, will be defined in a separate DMC Charter.

Safety and tolerability data will be made available to the DMC at each meeting as described in the DMC Statistical Analysis Plan (SAP). The data will be provided in a semi unblinded fashion (data will be visualized by real treatment groups, but the treatment/dose assigned to each group

will remain blinded) and the full unblinding can be requested by the DMC members, if appropriate. Pharmacokinetic data may be provided to the DMC at their request. These safety, tolerability, and PK data will be presented by individuals not otherwise involved in the conduct of the study. The deliberations and decisions of the DMC will be formally minuted/documented.

Ad hoc DMC meetings can be held for other reasons if deemed appropriate by the Sponsor or the DMC members.

In addition to ongoing review of safety data and safety signal detection within UCB (see Section 13.1.12), the occurrence of AEs of interest including thromboembolic events, in particular, will be monitored by the DMC to provide an assessment of the risk of occurrence of these events in the study. Statistical modeling will be used to provide estimates for quantification of the level of risk in the study based on the risk in the SLE population and in the intended patient population in the study (see Inclusion and Exclusion Criteria in Section 6). This analysis will inform any decisions regarding changes in study conduct and/or study termination.

The DMC procedures will ensure that the data remain blinded to the study team and investigators at all times throughout the conduct of the study until the data for Part 1 of the study have been unblinded.

5.2 Schedule of study assessments

A schedule of study assessments is provided in Table 5–2.

Table 5–2: Schedule of study assessments

Period	Screening	Double-Blind Treatment Period (Part 1)									Observational Period (Part 2)					
Visit	**V1**	**V2**	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9**	**V10/ EWV**	**V11/ SFU [b]**	**V12/ SFU [b]**	**V13**	**V14**	**V15**	**V16/ EWV**
Week [a]	**W-4 to -1**	**1[a]**	**W2**	**W4**	**W6**	**W8**	**W12**	**W16**	**W20**	**W24**	**W28[b]**	**W32[b]**	**W36**	**W40**	**W44**	**W48**
Day [a] (±3 days for Visits 3 to 16)	**D-28 to -1**	**D1[a]**	**D14**	**D28**	**D42**	**D56**	**D84**	**D112**	**D140**	**D168**	**D196[b]**	**D224[b]**	**D252**	**D280**	**D308**	**D336**
Written informed consent	X															
Demographic information	X															
Lifestyle	X															
History: general medical/procedures	X															
TB Signs & Symptoms questionnaire	X	X [c]					X [c]			X						
Chest x-ray [d]	X															
Verification of eligibility	X	X [c,e]														
C-SSRS	X									X		X [f]				X
Physical exam/interim medical history	X	X [c]		X [c]		X [c]	X [c]	X [c]	X [c]	X		X		X		X
12-lead ECG	X			X [c]						X						X
Randomization		X [c]														
Recording of concomitant medications	X	X [c]	X	X [c]	X	X [c]	X [c]	X [c]	X [c]	X	X	X	X	X	X	X
Recording of medical procedures		X [c]	X	X [c]	X	X [c]	X [c]	X [c]	X [c]	X	X	X	X	X	X	X
Adverse events	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Withdrawal criteria check		X [c]	X	X [c]	X	X [c]	X [c]	X [c]	X [c]	X	X [g]	X [g]	X	X	X	
Overnight fast (prior to visit) [h]		X [h]			X [h]		X [h]			X [h]						X [h]
Contact IVRS/IWRS	X	X	X	X	X	X	X	X	X	X						
Study drug administration		X		X		X	X	X	X							
Dispense daily diary	X	X	X	X	X	X	X	X	X	X	X	X [g]	X	X	X	
Collect/review daily diary/corticosteroid taper		X [c]	X	X [c]	X	X [c]	X [c]	X [c]	X [c]	X	X	X	X	X	X	X
Dispense urine collection container [i]	X							X	X	X	X	X [g]	X		X	

Table 5–2: Schedule of study assessments

Period	Screening	Double-Blind Treatment Period (Part 1)									Observational Period (Part 2)					
Visit	**V1**	**V2**	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9**	**V10/ EWV**	**V11/ SFU [b]**	**V12/ SFU [b]**	**V13**	**V14**	**V15**	**V16/ EWV**
Week [a]	**W-4 to -1**	**1[a]**	**W2**	**W4**	**W6**	**W8**	**W12**	**W16**	**W20**	**W24**	**W28[b]**	**W32[b]**	**W36**	**W40**	**W44**	**W48**
Day [a] (±3 days for Visits 3 to 16)	**D-28 to -1**	**D1[a]**	**D14**	**D28**	**D42**	**D56**	**D84**	**D112**	**D140**	**D168**	**D196[b]**	**D224[b]**	**D252**	**D280**	**D308**	**D336**
Vital signs [j]:																
Unspecified time during visit	X		X		X					X	X	X	X	X	X	X
Predose; every 15min post start of infusion; every 30min until 2h post end of infusion		X		X		X	X	X	X							
Collection of blood samples for:																
TB test [k]	X															
HIV and hepatitis screening	X															
Serum pregnancy testing (β-hCG) (subjects of childbearing potential)	X															
Hematology [l]	X	X [c]	X	X [c]		X [c]	X [c]	X [c]	X [c]	X	X	X		X		X
Clinical chemistry [l]	X	X [c]	X	X [c]		X [c]	X [c]	X [c]	X [c]	X	X	X		X		X
Additional laboratory assessments:																
Anti-dsDNA antibodies	X	X [c]		X [c]		X [c]	X [c]	X [c]	X [c]	X		X		X		X
ANAs, anti-ENAs (anti-SM, anti-SSA, anti-SSB, anti-RNP), and RF	X									X						X
aPL antibodies (anticardiolipin antibodies, lupus anticoagulant, and anti-β2 glycoprotein-1)	X									X						X
Anti-DZP, anti-PEG antibodies		X [c]		X [c]		X [c]	X [c]	X [c]	X [c]	X	X	X				X
Coagulation and hemostasis tests [m]	X						X [c]			X		X				X
Total Ig, IgG, IgM, IgA, and IgE		X [c]	X	X [c]		X [c]	X [c]	X [c]	X [c]	X		X				X

Table 5–2: Schedule of study assessments

Period	Screening	Double-Blind Treatment Period (Part 1)									Observational Period (Part 2)					
Visit	**V1**	**V2**	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9**	**V10/ EWV**	**V11/ SFU [b]**	**V12/ SFU [b]**	**V13**	**V14**	**V15**	**V16/ EWV**
Week [a]	**W-4 to -1**	**1[a]**	**W2**	**W4**	**W6**	**W8**	**W12**	**W16**	**W20**	**W24**	**W28[b]**	**W32[b]**	**W36**	**W40**	**W44**	**W48**
Day [a] (±3 days for Visits 3 to 16)	**D-28 to -1**	**D1[a]**	**D14**	**D28**	**D42**	**D56**	**D84**	**D112**	**D140**	**D168**	**D196[b]**	**D224[b]**	**D252**	**D280**	**D308**	**D336**
Serum complement (C3, C4)	X	X [c]	X	X [c]		X [c]	X [c]	X [c]	X [c]	X		X		X		X
hsCRP	X	X [c]	X	X [c]		X [c]	X [c]	X [c]	X [c]	X	X	X		X		X
Whole blood mRNA		X [c]	X	X [c]			X [c]	X [c]		X		X				X
Proteomic signature profile	X		X	X [c]		X [c]	X [c]	X [c]		X		X				X
Cardiovascular proteins, lipids, lipid particles [h]		X [c,h]			X [h]		X [c,h]			X [h]						X [h]
DNA (PGx analysis)		X [c]								X						X
Plasma PK sampling [n]:																
Unspecified time during visit			X		X					X	X	X	X	X		X
Predose; end of infusion; 30min, 1h, 2h post end of infusion		X		X					X							
Predose; end of infusion						X	X	X								
Collection of urine for:																
Urine pregnancy testing (β-hCG) (subjects of childbearing potential)		X [c]	X	X [c]	X	X [c]	X [c]	X [c]	X [c]	X	X	X	X	X	X	X
Urinalysis, chemistry, microscopy [l]	X	X [c]	X	X [c]		X [c]	X [c]	X [c]	X [c]	X	X	X		X		X
Urine PK sampling (to be collected at home) [i]		X							X	X	X	X	X	X		X
Clinical assessments of disease activity:																
BILAG 2004	X	X [c]		X [c]		X [c]	X [c]	X [c]	X [c]	X		X		X		X
SLEDAI-2K	X	X [c]		X [c]		X [c]	X [c]	X [c]	X [c]	X		X		X		X
SRI-50				X [c]		X [c]	X [c]	X [c]	X [c]	X		X		X		X
PGA		X [c]		X [c]		X [c]	X [c]	X [c]	X [c]	X		X		X		X

Table 5–2: Schedule of study assessments

Period	Screening	Double-Blind Treatment Period (Part 1)									Observational Period (Part 2)					
Visit	**V1**	**V2**	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9**	**V10/ EWV**	**V11/ SFU [b]**	**V12/ SFU [b]**	**V13**	**V14**	**V15**	**V16/ EWV**
Week [a]	**W-4 to -1**	**1 [a]**	**W2**	**W4**	**W6**	**W8**	**W12**	**W16**	**W20**	**W24**	**W28 [b]**	**W32 [b]**	**W36**	**W40**	**W44**	**W48**
Day [a] (±3 days for Visits 3 to 16)	**D-28 to -1**	**D1 [a]**	**D14**	**D28**	**D42**	**D56**	**D84**	**D112**	**D140**	**D168**	**D196 [b]**	**D224 [b]**	**D252**	**D280**	**D308**	**D336**
PtGA		X [c]					X [c]			X						X
SLICC/ACR Damage Index	X									X						X
TJC, SJC	X	X [c]		X [c]		X [c]	X [c]	X [c]	X [c]	X		X		X		X
CLASI	X	X [c]		X [c]		X [c]	X [c]	X [c]	X [c]	X		X		X		X
Investigator Assessment of Flare			X	X [c]	X	X [c]	X [c]	X [c]	X [c]	X	X	X	X	X	X	X
Patient-reported outcomes:																
LupusQoL		X [c]		X [c]		X [c]	X [c]	X [c]	X [c]	X		X		X		X
SLE-S [o]		X [c,o]		X [c,o]		X [c,o]	X [c,o]	X [c,o]	X [c,o]	X [o]		X [o]		X [o]		X [o]
SLE-F [o]		X [c,o]		X [c,o]		X [c,o]	X [c,o]	X [c]	X [c,o]	X [o]		X [o]		X [o]		X [o]
SLE-M [o]		X [c,o]		X [c,o]		X [c,o]	X [c,o]	X [c]	X [c,o]	X [o]		X [o]		X [o]		X [o]
SLE-P [o]		X [c,o]		X [c,o]		X [c,o]	X [c,o]	X [c]	X [c,o]	X [o]		X [o]		X [o]		X [o]
SLE-E [o]		X [c,o]		X [c,o]		X [c,o]	X [c,o]	X [c]	X [c,o]	X [o]		X [o]		X [o]		X [o]
Subject Experience Interview [o]				X [c,o]						X [o]						

ANA=antinuclear antibody; anti-dsDNA=anti-double-stranded deoxyribonucleic acid; anti-ENA=extractable nuclear antigen antibody; anti-RNP=anti-ribonucleoprotein antibody; anti-SSA=Sjögren's syndrome antibody A; anti-SSB=Sjögren's syndrome antibody B; anti-SM=Smith antibody; aPL=antiphospholipid; β-hCG=β-human chorionic gonadotropin; BILAG 2004=British Isles Lupus Assessment Group Disease Activity Index 2004; C3=complement 3; C4=complement 4; CLASI=Cutaneous Lupus Erythematosus Disease Area and Severity Index; C-SSRS=Columbia Suicide Severity Rating Scale; D=Day; DZP=dapirolizumab pegol; ECG=electrocardiogram; EWV=Early Withdrawal Visit; HIV=human immunodeficiency virus; hsCRP=high sensitivity C-reactive protein; Ig=immunoglobulin; IGRA=interferon-γ release assay; IVRS/IWRS=interactive voice/web response system; LupusQoL=Lupus Quality of Life questionnaire; mRNA=messenger ribonucleic acid; PEG=polyethylene glycol; PGA=Physician's Global Assessment of Disease; PGx=pharmacogenomics; PK=pharmacokinetic; PtGA=Patient's Global Assessment of Disease; QFT-GIT=Quanti-FERON®-TB GOLD in-Tube test; RF=rheumatoid factor; SFU=Safety Follow-up; SJC=swollen joint count; SLEDAI-2K=Systemic Lupus Erythematosus Disease Activity Index 2000; SLE-E=Systemic Lupus Erythematosus-Emotional States Instrument; SLE-F=Systemic Lupus Erythematosus-Fatigue Instrument; SLE-M=Systemic Lupus Erythematosus-Mobility Instrument; SLE-P=Systemic Lupus Erythematosus-Pain Instrument; SLE-S=Systemic Lupus Erythematosus-Symptom Inventory Instrument; SLICC/ACR=Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage Index; SRI-50=Systemic Lupus Erythematosus Disease Activity Index-2K Responder Index-50; TB=tuberculosis; TJC=tender joint count; V=Visit; W=Week

Note: Unscheduled visits are described in Section 8.11.

Table 5–2: Schedule of study assessments

Period	Screening	Double-Blind Treatment Period (Part 1)									Observational Period (Part 2)					
Visit	**V1**	**V2**	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9**	**V10/ EWV**	**V11/ SFU [b]**	**V12/ SFU [b]**	**V13**	**V14**	**V15**	**V16/ EWV**
Week [a]	**W-4 to -1**	**1[a]**	**W2**	**W4**	**W6**	**W8**	**W12**	**W16**	**W20**	**W24**	**W28[b]**	**W32[b]**	**W36**	**W40**	**W44**	**W48**
Day [a] (±3 days for Visits 3 to 16)	**D-28 to -1**	**D1[a]**	**D14**	**D28**	**D42**	**D56**	**D84**	**D112**	**D140**	**D168**	**D196[b]**	**D224[b]**	**D252**	**D280**	**D308**	**D336**

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

[b] Subjects who withdraw prior to Week 32 (Visit 12) will complete an EWV (Visit 10 assessments if withdrawn prior to Visit 10; Visit 16 assessments if withdrawn after Visit 10) as well as Visits 11 and 12 for SFU assessments at 8 and 12 weeks after their final dose of study drug (as applicable). Subjects who withdraw after Week 32 (Visit 12) do not require additional SFU visits and will complete the Visit 16/EWV assessments only.

[c] To be performed before study drug dosing is started.

[d] A chest x-ray should be performed if one is not available within 3 months prior to Visit 1 (Screening).

[e] Subject must have a SLEDAI-2K score without any laboratory values of ≥4 at Visit 2 in order to be eligible to be randomized.

[f] Performed only in subjects who have withdrawn from the study prior to Week 32 (Visit 12) and are undergoing SFU assessments.

[g] Performed only in subjects who are continuing into Part 2.

[h] Subjects should undergo an overnight fast (at least 8 hours) prior to coming to the site for Visits 2, 5, 7, 10, and 16 for the collection of fasting blood samples for cardiovascular proteins, lipids, and lipid particles. Subjects may then eat breakfast after serum samples have been obtained for these assessments and before study drug administration (if applicable).

[i] For urine PK assessments, a urine collection container will be dispensed to the subject at the designated visits for urine collection at home prior to their next visit. Prior to Visits 9 and 10 only, the subject will collect overnight urine samples, which includes the first void after the subject goes to sleep the night before the visit through the first morning void the morning of the visit. The subject should note the times for the first and last urine collection. For all other noted visits (Visits 2, 11, 12, 13, 14, and 16), the subject will only collect their first morning void.

[j] Height will only be measured at Screening. With the exception of weight, which should be measured predose, all other vital signs (pulse rate, blood pressure, and body temperature) should be measured at the times indicated. Weight should only be measured at Screening and on dosing visits. Vitals signs should be measured within ±5min of the scheduled time point for the every 15min assessments and within ±10min of the scheduled time point for the every 30min assessments. There are no time window requirements for vital signs assessments when measured pre-dose or at unspecified times during the visit.

[k] Tuberculosis testing should be done using IGRA. The QFT-GIT is the preferred IGRA test (see Section 13.6). It is recommended that the QFT-GIT be the first test performed at Screening to reduce the number of screening procedures conducted for any QFT-GIT-positive subjects that may need to be withdrawn from the study.

[l] Hematology, clinical chemistry, and urinalysis parameters to be assessed are defined in Section 13.9.

[m] As defined in the Laboratory Manual.

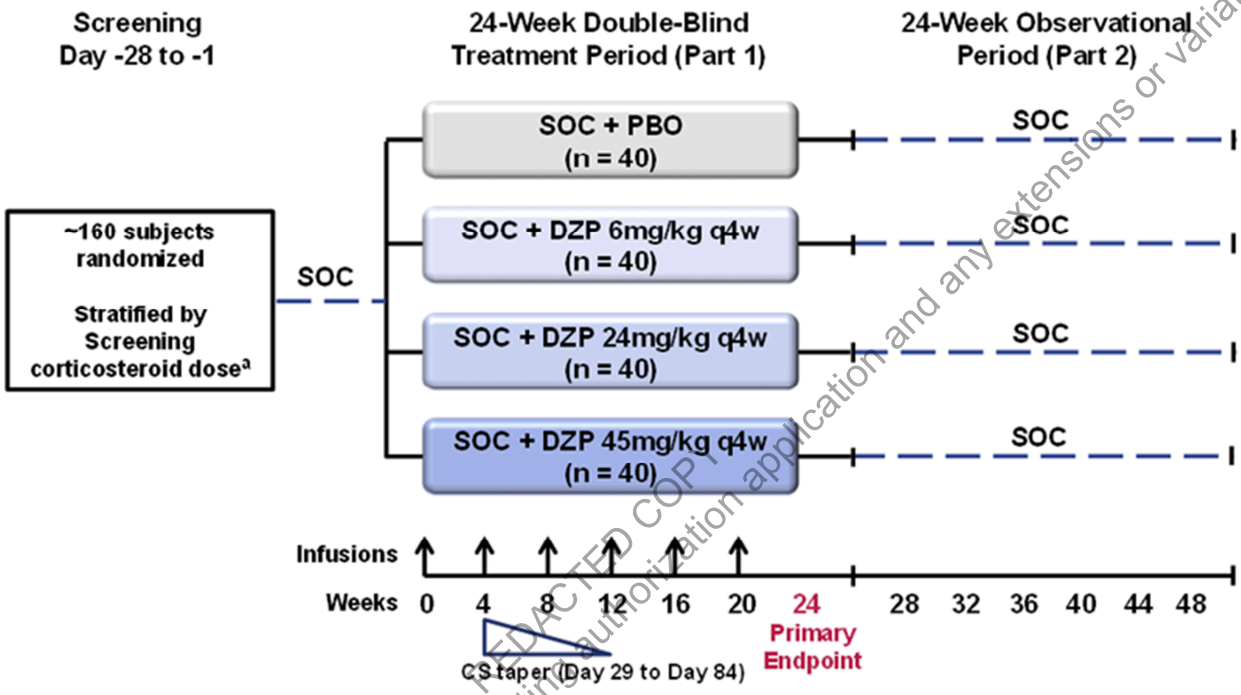
[n] Blood samples for PK measurements should be drawn within ±10min of the scheduled time point for each post-infusion time point or within 10min after the infusions ends for end of infusion time points (ie, not prior to the end of the infusion; further details are provided in the Laboratory Manual). There are no time window requirements for blood samples for PK measurements when measured pre-dose or at unspecified times during the visit.

[o] The exploratory SLE-S, SLE-F, SLE-M, SLE-P, and SLE-E Instruments and Subject Interview will be assessed at sites in English- and Spanish-speaking countries only.

5.3 Schematic diagram

A schematic diagram of the study design is provided in Figure 5-1.

Figure 5-1: Schematic diagram of SL0023



CS=corticosteroids; DZP=dapirolizumab pegol; PBO=placebo; q4w=every 4 weeks; SOC=standard-of-care
[a] Stratified in accordance with Screening corticosteroid dose (≤10mg/day or >10mg/day prednisone or equivalent).

5.4 Rationale for study design and selection of dose

Moderately to severely active SLE is a disease area with high unmet need, as, in many patients, disease remains uncontrolled and poorly managed with current standard-of-care immunosuppressants and corticosteroids at tolerable doses. Dapirolizumab pegol has been evaluated in 2 small Phase 1 studies: 1 single dose study at doses up to 5mg/kg in healthy subjects (SL0013, Part 1) and up to 60mg/kg in subjects with SLE (SL0013, Part 2), and 1 repeat dose study utilizing a loading dose of 30mg/kg followed by 5 doses of 15mg/kg every 2 weeks in subjects with SLE (SL0014). No treatment-limiting safety findings were observed in either study, and the results of SL0014 showed a trend for clinical efficacy in subjects with SLE. SL0023 is a dose-ranging study in subjects with moderately to severely active SLE (including neurological and renal involvement), where a spectrum of DZP doses will be administered over a Double-Blind Treatment Period of 24 weeks (Part 1) in subjects who have active disease despite stable standard-of-care treatment. Subjects completing the Double-Blind Treatment Period (Part 1) will enter a 24-week Observational Period (Part 2).

SL0023 is intended to evaluate 3 dose levels of DZP, 6mg/kg, 24mg/kg, and 45mg/kg, administered every 4 weeks for 24 weeks. These doses have been selected to explore a dose-response curve for DZP in SLE. The clinical data generated thus far for DZP have not allowed an exposure-response relationship to be defined in order to aid in the selection of doses to be tested in SL0023. Therefore, several target C_{trough} values were defined based on qualitative evidence from nonclinical and clinical data and dose levels were selected to maintain the DZP plasma concentration above the target C_{trough} values in more than 90% of subjects for the majority of the dosing interval.

The DZP dosing regimen in SL0014 (30 mg/kg loading followed by 15mg/kg every 2 weeks) was chosen in order to maintain DZP plasma concentrations above 100µg/mL, and in fact, the majority of subjects in SL0014 had $C_{trough} \geq 100$µg/mL. The 100µg/mL target was determined based on clinical data observed in clinical studies for hu5c8, a full length anti-CD40L monoclonal antibody. Study C99-1021 was an open-label, multiple dose study to evaluate the efficacy, safety, and PK of hu5c8 in subjects with proliferative lupus glomerulonephritis. Pharmacological activity was observed for hu5c8 in terms of meaningful changes in anti-dsDNA. Hu5c8 at 20mg/kg was planned to be administered every 2 weeks for 3 doses, and then every 28 days for 4 doses. Data from subjects who received at least 3 doses were evaluated. Following hu5c8 administration, there was a significant treatment-related decline in anti-dsDNA antibody titers, with mean reductions of 25.1% on Day 29 and 23.9% and 18.9%, respectively, 1 month and 2 months after the last treatment (Boumpas et al, 2003). A limited PK/PD relationship (log-linear model) was determined, and it highlighted that to achieve the 25% reduction in anti-dsDNA antibody titers, an hu5c8 plasma concentration >100µg/mL was required. Therefore, 100µg/mL was set as the target C_{trough} to be maintained in SL0014 and this study demonstrated greater improvement in clinical measures of disease activity in the DZP group compared with the PBO group. For SL0023, the dosing frequency is being reduced to every 4 weeks as a more patient-oriented regimen and no loading dose is proposed. A dose level of 45mg/kg administered every 4 weeks is predicted to maintain the C_{trough} >100µg/mL for the majority of the dosing interval.

In order to explore the dose response curve, 2 DZP dose levels below 45mg/kg have been selected (24mg/kg and 6mg/kg). The 24mg/kg dose has been selected in consideration of results

from the hu5c8 anti-dsDNA antibody PK/PD model demonstrating that minimum changes in anti-dsDNA antibody titers could be achieved with an hu5c8 plasma concentration of 40µg/mL. The dose of 24mg/kg every 4 weeks was selected to maintain a C_{trough} >40µg/mL for the majority of the dosing interval.

The lowest DZP dose level in SL0023 (6mg/kg) has been selected based on nonclinical pharmacology data. Nonclinical data from a NHP tetanus toxoid (TT) model showed that a minimal reduction of anti-TT IgG/IgM titers was observed at a dose of DZP 5mg/kg with a plasma concentration range of 15 to 31µg/mL. Based on these data, a target DZP C_{trough} of 10µg/mL for minimum pharmacological effect in nonclinical models has been defined and corresponds to a dose level of 6mg/kg every 4 weeks in SL0023.

A summary of the target C_{trough} values and corresponding proposed doses in SL0023 is provided in Table 5–3.

Table 5–3: Summary of qualitative evidence leading the selected target DZP C_{trough} and corresponding dose levels for SL0023

Evidence	Target DZP C_{trough} (µg/mL)	SL0023 Dose Level (mg/kg every 4 weeks)
DZP plasma concentration for minimum pharmacological effect in preclinical models	10	6
Hu5c8 plasma concentration to produce minimum observed change from baseline in anti-dsDNA antibodies	40	24
C_{trough} in SL0014 that showed evidence of clinical efficacy Hu5c8 plasma concentration to produce 25% reduction from baseline in anti-dsDNA antibodies	100	45

anti-dsDNA=anti-double-stranded deoxyribonucleic acid; C_{trough}=trough concentration; DZP=dapirolizumab pegol

The expected C_{max}, AUCτ (over the last dosing interval of 28 days), and C_{trough} at the proposed dose levels in SL0023 are presented in Table 5–4.

Table 5–4: Pharmacokinetic parameters expected at the dose levels proposed in SL0023 (median [5th-95th percentile])

DZP dose level (mg/kg) every 4 weeks	C_{max} (µg/mL)	AUCτ (µg.day/mL)	C_{trough} (µg/mL)
6	145 (93, 241)	1357 (974, 1384)	20 (10, 36)
24	582 (373, 966)	5429 (3895, 7937)	33 (17, 59)
45	1091 (698, 1811)	10179 (7305, 14882)	149 (75, 267)

AUCτ=area under the curve over the dosing interval; C_{max}=maximum concentration; C_{trough}=trough concentration; DZP=dapirolizumab pegol

At the highest DZP dose level proposed of 45mg/kg every 4 weeks, the expected DZP C_{max} is 1091µg/mL (698-1811µg/mL) and the expected AUCτ over the 28-day dosing interval is

10179µg.day/mL (7305-14882µg.day/mL) (median [5th-95th percentiles]). When comparing the mean AUCτ with the mean toxicokinetic data at the no-observed-adverse-effect level (NOAEL) of 50mg/kg obtained in the 26-week toxicology study in Cynomolgus monkeys, there is an exposure margin of 4-fold for AUC and 2-fold for C_{max}.

6 SELECTION AND WITHDRAWAL OF SUBJECTS

Subjects who initially fail to meet eligibility criteria or for whom eligibility assessments could not be completed as planned may be rescreened once on a case-by-case basis after discussion with the Medical Monitor (see Section 8.1).

6.1 Inclusion criteria

To be eligible to participate in this study, all of the following criteria must be met:

General

1a. An Institutional Review Board (IRB)/Independent Ethics Committee (IEC) approved written Informed Consent form is signed and dated by the subject prior to the initiation of any study-specific assessment at Screening (Visit 1).

2. Subject is considered reliable and capable of adhering to the protocol (eg, able to understand and complete diaries), visit schedule, and medication intake according to the judgment of the Investigator.

3. Subject (male or female) is ≥18 years of age at Screening (Visit 1).

4. Subject has a bodyweight of ≥50kg and ≤160kg.

5. Adequate reading and writing abilities (in native language) such that the subject can comprehend and answer the questions on the subject completed assessments.

Disease-specific

6. The subject has SLE diagnosed by a physician, confirmed by the SLICC Classification Criteria for SLE (see Appendix 19.1; Petri et al, 2012).

7. The subject has at least 1 of the following:

   – Anti-dsDNA antibodies by Farr assay confirmed by the central laboratory at Screening (Visit 1)

     OR

   – Low complement (ie, either low C3, or low C4, or both) confirmed by the central laboratory at Screening (Visit 1)

     OR

   – ANA titer of ≥1:80 confirmed by the central laboratory at Screening (Visit 1) in combination with at least 1 of the following:

     ◦ Historical positivity for anti-dsDNA (as defined for the SLICC criteria, at least twice in the past)

       or

- Positivity for anti-ENA (anti-SM, anti-SSA, anti-SSB, or anti-RNP) confirmed by the central laboratory at Screening (Visit 1)

8. The subject has moderate to severe SLE disease activity as demonstrated by BILAG 2004 Grade A level disease activity in at least 1 body/organ system at Screening (Visit 1) or BILAG 2004 Grade B level disease activity in at least 2 body/organ systems if no BILAG 2004 Grade A level disease is present.
9. The subject has moderate to severe SLE disease activity as demonstrated by a SLEDAI-2K total score of ≥6 at Screening (Visit 1) and a SLEDAI-2K score without any laboratory values of ≥4 at Baseline (Visit 2).
10. The subject is receiving stable standard-of-care medication, defined as at least 1 of the following, either alone or in combination: corticosteroids, and/or antimalarials, and/or immunosuppressants.
    - If the subject is receiving concomitant corticosteroids on a continuous regimen, the dose must be ≤40mg/day prednisone or equivalent dependent on the Investigator's assessment of disease activity (refer to the list of prednisone equivalents in Appendix 19.2). Doses of corticosteroids must have been stable for at least 2 weeks prior to Screening (Visit 1), must remain stable until Baseline (Visit 2), and should remain stable until 4 weeks after the first study drug infusion (until Day 28). Subjects 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).
        - Subjects who are receiving a corticosteroid dose at Screening (Visit 1) that is in between the specified starting doses of the corticosteroid tapering schedule (Table 5-1; eg, 12.5mg/day or 17.5mg/day prednisone or equivalent) should transition to the lowest nearest prespecified starting dose over the first 2 weeks of Screening and will enter the study on this dose; the dose will be considered stable in this case. This dose should then remain stable until 4 weeks after the first study drug infusion (until Day 28).
        - If iv steroids have been administered for treatment of acute disease flare, this must have occurred at least 6 weeks prior to the first study drug infusion (Visit 2).
    - Treatment with antimalarials must have been started or stopped at least 12 weeks prior to dosing with study drug. If the subject is receiving concomitant antimalarials at Screening, doses must remain stable for at least 4weeks prior to the first study drug infusion (Visit 2). The maximum doses for allowed antimalarials are specified in Table 6-1.

Table 6-1: 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

– Treatment with immunosuppressants must have been started or stopped at least 12 weeks prior to dosing with study drug. If the subject is receiving concomitant immunosuppressants at Screening, doses must remain stable for at least 8 weeks prior to the first study drug infusion (Visit 2). The maximum doses for allowed immunosuppressants are specified in Table 6-2.

Table 6-2: Maximum doses of permitted concomitant immunosuppressants

Immunosuppressant (generic name)	Maximum dose allowed
Azathioprine	300mg/day oral
Mycophenolate mofetil	3000mg/day oral
Leflunomide	40mg/day oral
Methotrexate	25mg/week any route

11. Subjects receiving memantine, bromocriptine (parlodel), danazol, dapsone, dehydroepiandrosterone, or retinoids must be on a stable dose for at least 4 weeks prior to the first study drug infusion (Visit 2) and the doses should remain stable throughout the Treatment Period.

12. Female subjects of childbearing potential must have a negative serum pregnancy test at the Screening Visit, which is confirmed to be negative by urine testing prior to the first dose of study drug at Week 1 (Visit 2) and prior to further dosing at each study visit thereafter.

13a. Female subjects of childbearing potential must agree to use a highly effective method of birth control during the study and for a period of 12 weeks after their final dose of study drug (ie, through completion of the SFU Period). Highly effective forms of birth control are methods which achieve a failure rate of less than 1% per year when used consistently and correctly. Highly effective methods of birth control include, but are not limited to:

– Combined (estrogen- and progesterone-containing) hormonal contraception (oral, implant, or injectable) associated with inhibition of ovulation (which must be stable for at least 1 full month prior to Screening [Visit 1], and should remain stable during the study)

– Progesterone-only hormonal contraceptives (oral, implant, or injectable) associated with inhibition of ovulation (which must be stable for at least 1 full month prior to Screening [Visit 1], and should remain stable during the study)

– Progesterone-releasing intrauterine systems or the TCu380A intrauterine device

- Vasectomized partner (provided sole partner and partner has medical proof of surgical success)
- True heterosexual sexual abstinence is an acceptable form of contraception when this is in line with the preferred and usual lifestyle of the person. Periodic abstinence (eg, calendar, ovulation, symptothermal, postovulation methods), declaration of abstinence for the duration of the study, and withdrawal are not acceptable methods of contraception.

Women not agreeing to use birth control must be of nonchildbearing potential, defined as being:

- Postmenopausal (for at least 2 years before the Screening Visit), verified by serum follicle-stimulating hormone level >40mIU/mL at the Screening Visit, or
- Permanently sterilized (eg, bilateral tubal occlusion, hysterectomy, bilateral salpingectomy), or
- Congenitally sterile

14. Contraception methods for male subjects and their female partners:
    - Male subjects with a partner of childbearing potential must be willing to use a condom when sexually active during the study and for 12 weeks after the final administration of study drug (ie, through completion of the SFU Period; approximately 5 half-lives).
    - In addition, the female partner of childbearing potential of a male subject must be willing to use a highly effective method of contraception (per Inclusion Criterion #13) during the study period and for 12 weeks after the final administration of study drug.

6.2 Exclusion criteria

Subjects are not permitted to enroll in the study if any of the following criteria is met:

General

1. Subject has previously been randomized in this study or has previously participated in a DZP clinical study.
2. Subject has any medical or psychiatric condition that, in the opinion of the Investigator, could jeopardize or would compromise the subject's ability to participate in this study.
3. Female subjects who are breastfeeding, pregnant, or plan to become pregnant during the study or within 3 months following their final dose of study drug.
4. Subject has a history of malignancy, except the following treated cancers: cervical carcinoma in situ, basal cell carcinoma, or dermatological squamous cell carcinoma.

5a. Subject has a mixed connective tissue disease, scleroderma, and/or overlap syndromes of SLE.

- Subjects with SLE and secondary Sjögren's syndrome are permitted provided they meet the eligibility criteria.

- Clarification: Subjects with rheumatoid arthritis in their medical history are not considered as having an overlap syndrome and are thereby eligible, except when erosive arthritis is the only symptom at Screening.

Disease specific

6. Subjects with severe neuropsychiatric SLE or other neurological symptoms that in the opinion of the Investigator, would prevent the subject from completing protocol required procedures and assessments.
7. Subject has active lupus that, in the opinion of the Investigator, requires an increase in standard-of-care therapy outside of that permitted in Table 6-1 and Table 6-2.
8. Subject has new or worsening Class III or IV lupus nephritis.
9. Subject has chronic kidney failure stage 3b, manifested by estimated glomerular filtration rate (eGFR) <45mL/min/1.73m^2, or serum creatinine >2.5mg/dL, or proteinuria >2g/day, or protein:creatinine ratio >226mg/mmol.
10. Subjects requiring plasma exchange or immunoabsorption in the 4 months prior to Visit 2 or during the study.

Infection-related risks

11. Subject has evidence of human immunodeficiency virus (HIV) infection, agammaglobulinemias, T-cell deficiencies, or human T-cell lymphotropic virus-1 infection at any time prior to or during the study.
12. Subject has clinically significant active or latent infection, for example, but not limited to, chronic viral hepatitis B or C.
13. Subject has a history of a serious infection within the last 60 days prior to the first study drug infusion (Visit 2) that required iv/intramuscular (im) antibiotics or required hospitalization/prolonged hospitalization. Subjects must have completed any prior anti-infective therapy for serious infections prior to the first study drug infusion.
14. Subject had an opportunistic infection (for example, but not limited to, pneumocystis, cytomegalovirus, herpes simplex virus, or herpes zoster) within 12 weeks prior to the first study drug infusion (Visit 2), or is currently receiving suppressive therapy for an opportunistic infection.
15. Subject has a clinically relevant recurrent (more than 3 times a year) infection.
16. Subjects with known tuberculosis (TB) infection, at high risk of acquiring TB infection, or latent TB (LTB) infection are excluded.
    a. Known TB infection whether present or past is defined as:
        - Active TB infection or clinical signs and symptoms suggestive of TB (pulmonary or extrapulmonary).
        - History of active TB infection involving any organ system or findings in other organ systems consistent with TB infection.

- Any evidence by radiography or other imaging modalities consistent with previously active TB infection that is not reported in the subject's medical history.

b. High risk of acquiring TB infection is defined as:

- Known exposure to another person with active TB infection within the 3 months prior to Screening (Visit 1).
- 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. LTB infection (refer to Section 13.6 for further details and instructions).

17. Subjects who have received live/live attenuated vaccines within 6 weeks prior to the first study drug infusion (Visit 2) or who plan to receive these vaccines during the study or 12 weeks after the final dose of study drug 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 drug.

Other safety risks

18. Subjects with a history of thromboembolic events within 12 months 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: Subjects 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 12 months prior to Screening (Visit 1).

    *Obstetric morbidity is defined as 1 or more unexplained deaths of a morphologically normal fetus at or beyond the 10th week of gestation with the latest incidence within 12 months 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 12 months prior Screening (Visit 1).

19. Subjects with a history of catastrophic APS or saddle pulmonary embolism.
20. Subject has blood laboratory values as follows: significant hematologic abnormalities of hemoglobin <7.0g/dL, or lymphocytes <500/mm^3, or absolute neutrophil count <500/mm^3, or platelets <25,000/mm^3 at Screening (Visit 1). Subjects with a higher platelet count should also be excluded if they have a clinical risk of bleeding for reasons other than SLE.
    Note: Subjects 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 subject may be randomized at the Baseline Visit, provided they meet all other eligibility criteria.
21. Subject has a vascular graft, valvular heart disease, or atrial fibrillation.
22. Subject has a known hypersensitivity to any components of the investigational medicinal product (IMP), including PEG.

23. Subject has a history of an anaphylactic reaction to parenteral administration of contrast agents, human or murine proteins, or monoclonal antibodies.

24. Subject has 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.

25. Subject has ≥3x the upper limit of normal (ULN) alanine aminotransferase (ALT), aspartate aminotransferase (AST), or alkaline phosphatase (ALP), or >ULN bilirubin (≥1.5xULN bilirubin if known Gilbert's syndrome). If subject only has >1.5xULN bilirubin, fractionate bilirubin to identify possible undiagnosed Gilbert's syndrome (ie, direct bilirubin <35%), 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.

    For subjects with a baseline result >ULN, a baseline diagnosis and/or the cause of any clinically meaningful elevation must be understood and recorded in the eCRF.

    If subject has >ULN that does not meet the exclusion limit for ALT, AST, or ALP at Screening, repeat, if possible, prior to dosing to ensure there is no further ongoing clinically relevant increase. In case of a clinically relevant increase, inclusion of the subject must be discussed with the Medical Monitor.

    An ALT and/or AST result up to 25% above the exclusion limit may be repeated once for confirmation. This includes rescreening.

Prior and concomitant medications

26. Subject has used the prohibited medications listed in Table 7-1, 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). Subject has used investigational agents not included in Table 7-1, including other investigational or recently approved biologics or device products, within 3 months 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.

    – 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.

27. Subject should 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, NSAIDs, 3-hydroxy-3-methyl-glutaryl-coenzyme A (HMG-CoA) reductase inhibitors (statins), angiotensin converting enzyme (ACE) inhibitors, and other anti-hypertensive drugs.

6.3 Withdrawal criteria

Subjects are free to withdraw from the study at any time, without prejudice to their continued care.

Subjects **must** be withdrawn from the study if any of the following occurs at any time during the study:

- Subject withdraws his/her consent.
- The Sponsor or a regulatory agency requests withdrawal of the subject.

Subjects **must** be discontinued from study drug (but not from the study) if any of the following occurs during Part 1 of the study (ie, through Visit 10 [Week 24] of the Double-Blind Treatment Period):

- There is confirmation of an ongoing pregnancy during the study, as evidenced by a positive pregnancy test.
- Subject experiences a thromboembolic event.
- Subject has a TB test that is confirmed positive or any further evidence suggestive of potential TB infection (eg, exposure) and further examinations result in a diagnosis of active TB or LTB. Refer to Section 13.6 (Assessment and management of TB and TB risk factors) for further details and instructions.
- Subject receives a live/live attenuated vaccine.
- Subject requires an induction therapy with cyclophosphamide for management of acute flare of lupus nephritis or other severe manifestation of SLE, in the opinion of the Investigator.

Subjects **may** be withdrawn from the study, at the Investigator's discretion, if any of the following occurs:

- Subject develops a clinically meaningful illness that would interfere with his/her continued participation, and/or render safety and efficacy data to be unreliable in the opinion of the Investigator.
- Subject is noncompliant with the study procedures or medications, in the opinion of the Investigator, in a manner that impacts the subject's safety.

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

Investigators should attempt to obtain information on subjects in the case of withdrawal. For subjects considered as lost to follow up, the Investigator should make an effort (at least 1 phone call and 1 written message to the subject), 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 subject, must be recorded in the source documents. The electronic Case Report Form (eCRF) must document the primary reason for withdrawal or discontinuation.

6.3.1 Potential drug-induced liver injury IMP discontinuation criteria

Subjects with potential drug-induced liver injury (PDILI) must be assessed to determine if IMP must be discontinued. In addition, all concomitant medications and herbal supplements that are not medically necessary should also be discontinued.

The following PDILI criteria require immediate and **permanent** discontinuation of IMP:

- Subjects with any of the following:
  - ALT or aspartate aminotransferase (AST) ≥8xULN
  - ALT or AST ≥3xULN and co-existing total bilirubin ≥2xULN

The following PDILI criterion requires immediate discontinuation of IMP:

- Subjects with ALT and/or AST ≥3xULN who exhibit temporally associated symptoms of hepatitis (excluding SLE-related hepatitis) or hypersensitivity. Hepatitis symptoms include fatigue, nausea, vomiting, right upper quadrant pain or tenderness. Hypersensitivity symptoms include fever (without clear alternative cause), rash, or eosinophilia (ie, >5%).

If a non-drug related cause for the symptoms can be confirmed, these subjects may resume IMP administration after discussion with the responsible UCB physician, but only when the requirements for rechallenge with IMP as provided in Section 13.7.2.1 are followed.

The following PDILI criteria allows for subjects to continue on IMP at the discretion of the Investigator:

- ALT or AST ≥3xULN (and ≥2x baseline) and <8xULN, total bilirubin <2xULN, and no eosinophilia (ie, ≤5%), with no fever, rash or symptoms of hepatitis (eg, fatigue, nausea, vomiting, right upper quadrant pain or tenderness)

Evaluation of PDILI must be initiated as described in Section 13.7. If subjects are unable to comply with the applicable monitoring schedule, IMP must be discontinued immediately (see Section 8.10).

Investigators should attempt to obtain information on subjects in the case of IMP discontinuation to complete the final evaluation. Subjects with PDILI should not be withdrawn from the study until investigation and monitoring are complete. All results of these evaluations and observations, together with a narrative description of the reason(s) for IMP discontinuation and subject withdrawal (if applicable), must be recorded in the source documents. The eCRF must document the primary reason for IMP discontinuation.

7 STUDY TREATMENTS

7.1 Description of IMPs

The DZP IMP will be supplied by UCB Clinical Trial Supply Operations (CTSO) or designee, as follows:

- DZP 20mL vial lyophilized drug product. Each DZP vial will be labeled.

The PBO IMP will not be supplied by UCB CTSO. The sites will use commercial 0.9% sodium chloride aqueous solution (physiological saline, preservative free) of pharmacopoeia (US Pharmacopeia/European Pharmacopoeia) quality.

7.2 Treatments to be administered

During the 24-week Double-Blind Treatment Period (Part 1), eligible subjects will be randomly allocated in a 1:1:1:1 ratio to receive an iv infusion of DZP (6mg/kg, 24mg/kg, or 45mg/kg) or PBO every 4 weeks, for a total of 6 doses (on Day 1 and at Weeks 4, 8, 12, 16, and 20). The

subject's body weight at Baseline (Visit 2) will be used to calculate the individual dose throughout the study.

Following completion of the 24-week Double-Blind Treatment Period (Part 1), subjects will enter a 24-week Observational Period, during which subjects will not receive study drug but will be able to receive standard-of-care treatment, as indicated. The subjects, Investigators, and study site staff will remain blinded to the treatment administered during Part 1 of the study until the end of the study.

Refer to Table 5–2 for details regarding the visits at which IMP should be administered.

7.2.1 Treatment preparation and administration

7.2.1.1 Preparation

Only DZP lyophilized drug product will be supplied by UCB CTSO. The lyophilized drug product provided in a 20mL vial will be reconstituted by adding 10mL water for injection and then diluted with saline to prepare for administration. Complete preparation instructions will be outlined in the Pharmacy Manual.

For PBO, commercial 0.9% sodium chloride aqueous solution will be used. Thus, in order to maintain blinding, an unblinded pharmacist or other suitably qualified site personnel will prepare each dose of IMP and provide it to the blinded site personnel for administration.

All the preparation steps, including the reconstitution of DZP and preparation for infusion, PBO material requirements, and dispensing material requirements will be described in full detail in the Pharmacy Manual.

7.2.1.2 Administration

The IMP will be administered as an iv infusion through a cannula placed in an easily accessible vein of the arm (eg, cephalic vein or median cubital vein); an iv infusion pump will be used for IMP administration.

For all subjects, the infusion volume will be 150mL and the infusion time will be approximately 120min. These timings are provided to allow a slow rise in plasma concentration and for the possibility of interrupting the infusion in case of an acute AE. Further instructions on administration will be provided in the Pharmacy Manual.

The infusion rate may be reduced at any time at the discretion of the Investigator. If an infusion is interrupted, it can be restarted if the Investigator considers it appropriate to do so. In such instances, the total infusion time may exceed 120min in order to administer the entire planned dose. The chronology of these events should be recorded accurately in the source data and eCRF.

After the infusion is completed, the subject will remain in the clinic for observation and assessments for at least 2 hours, or longer at the discretion of the Investigator.

Data from clinical studies SL0013 and SL0014 are limited, and because DZP is an iv administered protein, an increased risk for infusion-related reactions, including anaphylaxis, cannot be excluded at this time. A mandatory premedication for prophylaxis of infusion-related reactions is not planned in this study; however, premedication (with acetaminophen or antihistamines) is permitted at the discretion of the Investigator considering the individual risk profile of the subject (for example, but not limited to, medical history, comorbidities, and

concomitant medication) and current knowledge on the risk of DZP to induce anaphylactic reactions. Corticosteroids should be avoided as an antiallergic premedication given the protocol requirements for stable corticosteroid use and planned tapering (refer to Section 5.1 and Section 7.8.1).

7.3 Packaging

Dapirolizumab pegol lyophilized drug product is supplied in 20mL vials. Each vial and each box will be labeled and will be for individual use.

The site carton will be suitably packaged in such a way as to protect the product from deterioration during transport and storage. Further information regarding storage and transport conditions will be provided in the Pharmacy Manual.

The diluent and materials such as syringes and needles, perfusor syringes, and administration sets required for reconstitution, dilution, and final administration will be provided in the original packaging to the sites by the contract research organization (CRO) or will be sourced by the sites based on the material specifications noted in the Pharmacy Manual and provided by UCB.

7.4 Labeling

Clinical drug supplies will be labeled in accordance with the current International Council for Harmonisation (ICH) guidelines on Good Clinical Practice (GCP) and Good Manufacturing Practice and will include any locally required statements. If necessary, labels will be translated into the local language and adapted to the size of the IMP package.

7.5 Handling and storage requirements

The Investigator (or designee) is responsible for the safe and proper storage of IMP at the site. Investigational medicinal product stored by the Investigator is to be kept in a secured area with limited access according to the storage conditions mentioned in the IMP Handling Manual.

Appropriate storage condition must be ensured by controlled refrigerator temperature either using an automated temperature monitoring and recording system or by using a minimum/maximum thermometer and completing daily a temperature log in accordance with local requirements. Temperature data for IMP should be recorded on each working day with the actual and minimum/maximum temperatures reached during this period.

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

The physiological saline [0/9% sodium chloride] used for administration should be handled per specific site requirements and stored according to label requirements.

7.6 Drug accountability

A Drug Accountability form will be used to record IMP dispensing and return information on a by-subject basis and will serve as source documentation during the course of the study. Details of any IMP 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 only to the designated unblinded monitor (or designee) for review. In addition, the site will document all materials used for each subject dosing, including water for injection used for reconstitution,

saline for PBO, and infusion and other materials. The site will keep a log with the names of those individuals with access to IMP, including the names of those who are involved in preparation of doses for IMP administration.

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

The Investigator must assign duties for drug accountability at the study site to an appropriate unblinded pharmacist (or designee).

The Investigator must ensure that the IMP 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 IMP must be reconciled and either destroyed at the site according to local laws, regulations, and UCB SOPs 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.

7.7 Procedures for monitoring subject 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 subject's identifiers and visit schedule to assure that the subject 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.

Subjects are expected to receive all doses of IMP as detailed in the schedule of assessments. Any subject who deviates from the dosing schedule or misses any scheduled treatment should be reported to the Medical Monitor in a blinded fashion for determination of possible schedule adjustments and continued eligibility. These instances will be handled on a case-by-case basis.

7.8 Concomitant medications/treatments

7.8.1 Permitted concomitant treatments (medications and therapies) for SLE

The following concomitant medications are permitted for the treatment of SLE and SLE associated signs and symptoms under certain conditions:

- Corticosteroids (≤40mg/day prednisone or equivalent; see Inclusion Criterion #10)
- Antimalarials (eg, hydroxychloroquine, chloroquine, and quinacrine) (see Inclusion Criterion #10 and maximum dose restrictions in Table 6-1)
- Other immunosuppressant or immunomodulatory agents including (see Inclusion Criterion #10 and maximum dose restrictions in Table 6-2)
  - Methotrexate
  - Azathioprine

  - Mycophenolate (including mycophenolate mofetil, mycophenolate mofetil hydrochloride, and mycophenolate sodium)
  - Leflunomide
- Analgesics, NSAIDs, HMG-CoA reductase inhibitors (statins), ACE inhibitors, and other anti-hypertensive drugs

In subjects receiving concomitant corticosteroids, doses must have been stable for at least 2 weeks prior to Screening, must remain stable until Baseline (Visit 2), and should remain stable until 4 weeks after the first study drug infusion (until Day 28). Subjects 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 subjects receiving concomitant corticosteroid doses between 10mg/day and 40mg/day prednisone or equivalent, a mandatory corticosteroid taper must be initiated no later than 4 weeks after the first study drug infusion (on Day 29) The tapering regimen, as recommended in Section 5.1 and Table 5-1, will aim to reduce the daily prednisone equivalent dose to 7.5mg/day or lower by Week 12 (Day 84) of the study. If such a rapid tapering is not considered by the Investigator to be appropriate for the individual subject, a slower tapering regimen can be used. Subjects achieving a dose of 7.5mg/day or lower may remain on this dose or continue to taper at the discretion of the Investigator. Subjects who 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 (see Section 7.8.4). Subjects will be considered nonresponders for the primary endpoint if the corticosteroid dose exceeds the prednisone equivalent dose at Baseline. Subjects will be issued a daily diary in which to record corticosteroid doses taken on a daily basis at home in between visits (Section 7.8.5). Use of oral or parenteral steroids for non-SLE related conditions should be discussed in advance with the Sponsor on an individual basis.

Treatment with antimalarials or immunosuppressants must have been started or stopped at least 12 weeks prior to dosing with study drug. In subjects receiving concomitant antimalarials used for the treatment of SLE, doses must have been stable for at least 4 weeks prior to the first study drug infusion (Visit 2). In subjects receiving concomitant immunosuppressants for the treatment of SLE, doses must have been stable for at least 8 weeks prior to the first study drug infusion (Visit 2). Increases in doses of antimalarials and immunosuppressant or immunomodulatory agents above Baseline are not permitted until Visit 10 (Week 24) of the study, unless absolutely clinically indicated (dose reductions are allowed, if medically indicated [eg, due to toxicity], per the Investigator's discretion; refer to Section 7.8.4 for further details).

Subjects should stay on stable doses of the following other concomitant medications for the treatment of SLE during Part 1 (Double-Blind Treatment Period) of the study, unless changes in these treatments are clinically indicated: analgesics, NSAIDs, HMG-CoA reductase inhibitors (statins), ACE inhibitors, and other anti-hypertensive drugs.

7.8.2 Permitted concomitant treatments (medications and therapies) other than those for SLE

Concomitant medications for comorbidities are permitted as long as they comply with the restrictions imposed in the inclusion criteria (Section 6.1), exclusion criteria (Section 6.2), and are not explicitly prohibited (Section 7.8.3). Both ACE inhibitors and angiotensin receptor blockers are permitted.

Subjects will record their concomitant corticosteroid doses in the subject diary (Section 7.8.5).

7.8.3 Prohibited concomitant treatments (medications and therapies)

Table 7-1 provides a list of concomitant medications prohibited during the study until Visit 12 (Week 32) or until 10 weeks after permanent study drug discontinuation. Also included in this table are the wash-out periods (and, if applicable, additional requirements) as apply to inclusion (Section 6.1) and exclusion (Section 6.2) criteria.

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

Generic (trade) names	Wash-out period prior to Screening	Generic (trade) names	Wash-out period prior to Screening
Biologics (Mabs and Fusion Proteins)		**Immunosuppressants**	
Abatacept (CTLA4-Ig) (Orencia®)	6 months	Cyclophosphamide (Cytoxan®)	6 months
Belimumab (Benlysta™)	6 months	Cyclosporine (Sandimmune®, Neoral®, Gengraf®) (except cyclosporine eye drops)	4 weeks
Blisibimod	8 weeks	Pimecrolimus (Elidel®)	4 weeks
Eculizumab (Soliris®)	3 months	Sirolimus (Rapamune®)	4 weeks
ETI – 201 (Elusys Heteropolymer Product)	3 months	Tacrolimus (FK506) (Prograf®)	4 weeks (oral and topical)
Rituximab (Rituxan®), Ofatumumab (Arzerra®), Obinutuzimab (Gazyva®), Ocrelizumab, Veltuzumab	12 months	**Others**	
		Intravenous immunoglobulin	4 weeks
		IPP-201101 (Lupuzor™)	3 months
Natalizumab (Tysabri®)	12 weeks	Anifrolumab (MEDI 546) Sifalimumab (MEDI 545)	3 months
Vedolizumab (Entyvio®)	24 weeks		
Tabalumab	12 weeks	Minocycline	4 weeks
TACI-Ig (atacicept)	3 months	Thalidomide or lenalidomide (Thalomid®, Revlimid®)	2 months
Tocilizumab (Actemra®, MRA)	3 months		

Note: Topical formulations (eg, eye drops) are permitted without wash-out, unless otherwise indicated.

7.8.4 Rescue medication for SLE disease flares

Rescue treatment of SLE disease flares with corticosteroids (oral or iv) or with changes to dosing of the immunosuppressant medications listed in Section 7.8.1 are allowed at the discretion of the Investigator, if clinically indicated. Investigators should carefully evaluate their treatment decision, as an increase above the baseline dose between Visit 2 (Baseline) and Visit 10 (Week 24) will define a subject as a nonresponder with respect to the primary endpoint.

Subjects who receive rescue therapy should continue in the study (at the Investigator's discretion), unless they require one of the prohibited medications listed in Table 7-1 prior to Visit 12 (Week 32).

7.8.5 Subject diary

Subjects will be issued daily diaries at each visit to record concomitant corticosteroid doses taken on a daily basis at home in between visits. Subjects will be instructed to bring the diary to the clinic at each visit. Site personnel will collect and review the diary at each visit to ensure that subjects are adhering to their prescribed corticosteroid tapering regimen (where applicable), and will issue a new diary for the subject to use until their next visit.

7.9 Blinding

7.9.1 Procedures for maintaining and breaking the treatment blind

7.9.1.1 Maintenance of study treatment blind

All subject treatment details will be allocated and maintained by the IVRS/IWRS.

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

- Sponsor and designated CRO bioanalytical staff analyzing PK samples.
- Sponsor clinical trial supply staff
- IVRS/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 subjects via the IVRS/IWRS. The unblinded pharmacy monitors from the CRO, the Clinical Supply Manager, and the unblinded 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 Patient Safety (PS) staff as needed for reporting SAEs to regulatory authorities.
- On request, members of the DMC who participate in unblinded (closed) sessions will be given information about the IMP allocation for those subjects 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 DMC review.
- A Quantitative Clinical Pharmacologist/Modeling & Simulation Scientist may have access to the randomization code if PK data are requested for review by the DMC.

The following individuals may receive access to the randomization code and the first initial biomarker analysis:

- Quantitative Clinical Pharmacologist/Modeling & Simulation Scientist

If necessary, the results of the initial biomarker analysis during the Double-Blind Treatment Period (Part 1) may be shared with key UCB and Biogen personnel in order to facilitate additional Clinical Planning or Portfolio Management decisions. Only unblinded summary results will be provided, and individual subject data will be kept blinded. Those individuals who are not involved in the study conduct, but seeing unblinded summary data, will be documented in the Trial Master File. The DMC will also have access to any initial biomarker analysis data, if needed.

With the exception of emergency unblinding on a case-by-case basis as described in Section 7.9.1.2, the following individuals will remain blinded to the treatment assignment in Part 1 until the end of the study:

- Investigators
- Study site staff
- Subjects
- CRO staff, with the exception of the unblinded pharmacy monitors and any CRO staff supporting preparation of the analyses
- Personnel working on the study at the BILAG 2004 central independent efficacy reader

Under normal circumstances, the blinded treatment must not be revealed. It will be possible to break the blind, if medically indicated (Section 7.9.1.2). This should be discussed in advance with the Medical Monitor or the Sponsor's Study Physician whenever possible.

7.9.1.2 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 drug determines decisions on further diagnostic procedures or treatment), it will be possible to determine to which treatment arm and dose the subject has been allocated during the Double-Blind Treatment Period by contacting the IVRS/IWRS. All sites will be provided with details of how to contact the system for code breaking at the start of the study. The Medical Monitor or the Sponsor's Study Physician should be consulted prior to unblinding, whenever possible.

The CPM will be informed immediately via the IVRS/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.

7.10 Randomization and numbering of subjects

An IVRS/IWRS will be used for assigning eligible subjects to a treatment regimen based on predetermined randomization schedules generated by the CRO. The IVRS/IWRS is responsible for issuing treatment kit numbers, as appropriate, according to the visit schedule.

To enroll a subject (Visit 1), the Investigator or designee will contact the IVRS/IWRS and provide brief details about the subject to be enrolled. Each subject will receive a unique 5-digit subject number assigned at Screening that serves as the subject identifier throughout the study. The subject number will be required in all communication between the Investigator or designee and the IVRS/IWRS regarding a particular subject. Enrolled subjects who withdraw from the study prior to randomization will retain their subject number without receiving a randomization number (ie, subject numbers will not be reassigned).

To randomize a subject (Visit 2), the Investigator or designee will contact the IVRS/IWRS and provide brief details about the subject to be randomized. The IVRS/IWRS will automatically inform the Investigator or designee of the subject's unique 5-digit randomization number. The IVRS/IWRS will allocate treatment kit numbers to the subject based on the subject number during the course of the study. Randomization numbers and treatment kit numbers will be tracked via the IVRS and also will be required to be entered into the eCRF.

The study is planned to enroll at least 267 subjects in order to randomize approximately 160 subjects (40 subjects per treatment group). During the 24-week Double-Blind Treatment Period (Part 1), subjects will be randomized in a 1:1:1:1 ratio to receive DZP (6mg/kg, 24mg/kg, or 45mg/kg) or PBO. The randomization will be stratified by Screening corticosteroid dose (≤10mg/day or >10mg/day prednisone equivalent).

During the Observational Period (Part 2), subjects will not receive study drug but will be able to receive standard-of-care treatment, as indicated. The subjects, Investigators, and study site staff will remain blinded to the treatment administered during Part 1 of the study until the end of the study.

8 STUDY PROCEDURES BY VISIT

Table 5–2 provides a general overview of study assessments to be conducted at each visit. A detailed listing of procedures to be undertaken at each visit is presented in the sections that follow.

Visit windows of ±3 days on either side of the scheduled date are permitted for Visits 3 to 16 only; however, the Investigator should try to keep the subjects on the original dosing schedule. The window of ±3 days is relative to Baseline and applicable for all subsequent visits. Changes to the dosing schedule outside of the 3-day window must be discussed with the Medical Monitor and may result in subject withdrawal.

8.1 Visit 1 (Week -4 to -1/Day -28 to -1); Screening Visit

The Screening Period lasts a maximum of 28 days (Day -28 to -1). Prior to any study activities, subjects will be asked to read and sign an Informed Consent form that has been approved by an IEC/IRB and the Sponsor, and which complies with regulatory requirements. Subjects will be given adequate time to consider any information concerning the study given to them by the Investigator or designee. As part of the informed consent procedure, subjects will be given the opportunity to ask the Investigator any questions regarding potential risks and benefits of participation in the study.

It is recommended that the Quanti FERON®-TB GOLD in-Tube test (QFT-GIT) be the first test performed at Screening to reduce the number of screening procedures conducted for any QFT-GIT positive subjects that may need to be withdrawn from the study.

Subjects who initially fail to meet eligibility criteria or for whom eligibility assessments could not be completed as planned may be rescreened once after discussion with the Medical Monitor. In addition, subjects with an isolated laboratory parameter outside of the normal range (or negative in the case of auto-antibody assessments) at the Screening Visit may have a repeat test. If the repeat laboratory parameter meets the entry criteria, the subject may be randomized at the Baseline Visit, provided they meet all other eligibility criteria.

Assessments at Visit 1 (Screening) include:

- Obtain written informed consent(s)
- Demographic data (includes date of birth, gender, and race/ethnicity)
- Lifestyle (includes alcohol, tobacco, and drug use)
- Medical and procedure history and concomitant disease, including SLE disease history
- Prior and concomitant medications
- TB assessments:
  - TB test (QFT-GIT)
  - TB Signs and Symptoms questionnaire
  - Chest x-ray (if one is not available within 3 months prior to Screening)
- Verification of eligibility (inclusion/exclusion criteria)
- C-SSRS
- Physical examination
- HIV and hepatitis screening
- Vital signs: systolic and diastolic blood pressure, pulse rate, temperature, body weight, and height
- 12-lead ECG
- Serum pregnancy test for women of childbearing potential
- Safety laboratories: hematology, clinical chemistry, and urinalysis
- Additional laboratories:
  - ANAs, anti-ENAs (anti-SM, anti-SSA, anti-SSB, anti-RNP), and RF
  - anti-dsDNA antibodies
  - aPL antibodies
  - coagulation and hemostasis tests
  - serum complement (C3, C4)
  - hsCRP
  - proteomic signature profile

- BILAG 2004
- SLEDAI-2K assessing the past 10 days
- SLICC/ACR Damage Index
- TJC/SJC
- CLASI
- AEs
- Dispense subject daily diary
- Dispense urine collection container (for first morning urine collection at home on the morning of their next visit)
- Contact the IVRS/IWRS to indicate the subject has been enrolled

8.2 Visit 2 (Day 1); Randomization Visit

Visit 2 can occur at any time after the laboratory results from the Screening Visit are available, but no later than 28 days after the Screening Visit. Prior to Visit 2, the site must have received confirmation from the central independent efficacy reader for BILAG 2004 data that the subject has met BILAG 2004 eligibility for randomization. The site must confirm whether or not the subject is eligible to be randomized prior to contacting the IVRS/IWRS.

Subjects should undergo an overnight fast (at least 8 hours) prior to coming to the site for Visit 2. Subjects may then eat breakfast after serum samples have been obtained for the assessment of cardiovascular proteins, lipids, and lipid particles, and before study drug administration.

The PRO questionnaires should then be completed in a quiet place by the subjects themselves at the start of the study visit and prior to the remaining visit assessments.

All assessments should be performed prior to study drug dosing, unless otherwise indicated.

Assessments at Visit 2 (Randomization) include:

- LupusQoL
- PROs at sites in English- and Spanish-speaking countries only:
  - SLE-S
  - SLE-F
  - SLE-M
  - SLE-P
  - SLE-E
- Verification of continued eligibility (inclusion/exclusion criteria; including verification that the SLEDAI-2K score without any laboratory values is ≥4 prior to Randomization; see below)
- TB Signs and Symptoms questionnaire
- Concomitant medications

- Medical procedures
- Collect/review subject daily diary
- Collect PK urine sample obtained at home (first morning urine collection on the morning of the visit)
- Physical examination/interim medical history
- Urine pregnancy test for women of childbearing potential
- Withdrawal criteria check
- Vital signs:
  - systolic and diastolic blood pressure, pulse rate, and temperature: predose; every 15mins post start of infusion; every 30mins until 2h post end of infusion
  - body weight: predose

Note: Blood samples must not be drawn through the infusion cannula.

- Safety laboratories: hematology, clinical chemistry, and urinalysis
- Additional laboratories:
  - anti-dsDNA antibodies
  - anti-DZP and anti-PEG antibodies
  - total Ig, IgG, IgM, IgA, and IgE
  - serum complement (C3, C4)
  - hsCRP
  - whole blood mRNA
  - cardiovascular proteins, lipids, and lipid particles (blood samples should be collected under fasting conditions [at least 8 hours])
  - DNA
- PK plasma sampling (predose; end of infusion; and 30min, 1h, and 2h post end of infusion)
- BILAG 2004
- SLEDAI-2K assessing the past 10 days (including the SLEDAI-2K score without laboratory values assessment [defined as any SLEDAI-2K defined features excluding all laboratory parameters in the past **10 days** prior to Baseline] of ≥4 prior to Randomization)
- PGA
- PtGA
- TJC/SJC
- CLASI
- Contact the IVRS/IWRS for randomization or to note screen failure

- Study drug preparation (predose), administration, and accountability (postdose)
- AEs (pre and postdose)
- Dispense subject daily diary (postdose)

8.3 Visit 3 (Week 2/Day 14 [±3 days])

Assessments at Visit 3 (Week 2) include:

- Concomitant medications
- Medical procedures
- Collect/review subject daily diary
- Urine pregnancy test for women of childbearing potential
- Withdrawal criteria check
- Vital signs (systolic and diastolic blood pressure, pulse rate, and temperature)
- Safety laboratories: hematology, clinical chemistry, and urinalysis
- Additional laboratories:
  - total Ig, IgG, IgM, IgA, and IgE
  - serum complement (C3, C4)
  - hsCRP
  - whole blood mRNA
  - proteomic signature profile
- PK plasma sample
- Investigator assessment of flare
- AEs
- Dispense subject daily diary
- Contact the IVRS/IWRS

8.4 Visit 4 (Week 4/Day 28 [±3 days]) and Visit 6 (Week 8/Day 56 [±3 days])

The PRO questionnaires should be completed at the start of the study visit in a quiet place and by the subjects themselves.

All assessments should be performed prior to study drug dosing, unless otherwise indicated.

Assessments at Visit 4 (Week 4) and Visit 6 (Week 8) include:

- LupusQoL
- PROs at sites in English- and Spanish-speaking countries only:
  - SLE-S

  - SLE-F
  - SLE-M
  - SLE-P
  - SLE-E
  - Subject Experience Interview (Visit 4 only)
- Concomitant medications
- Medical procedures
- Collect/review subject daily diary
- Physical examination/interim medical history
- Urine pregnancy test for women of childbearing potential
- Withdrawal criteria check
- Vital signs:
  - systolic and diastolic blood pressure, pulse rate, and temperature: predose; every 15mins post start of infusion; every 30mins until 2h post end of infusion
  - body weight: predose
- 12-lead ECG (Visit 4 only)

<u>Note:</u> Blood samples must not be drawn through the infusion cannula.

- Safety laboratories: hematology, clinical chemistry, and urinalysis
- Additional laboratories:
  - anti-dsDNA antibodies
  - anti-DZP and anti-PEG antibodies
  - total Ig, IgG, IgM, IgA, and IgE
  - serum complement (C3, C4)
  - hsCRP
  - whole blood mRNA (Visit 4 only)
  - proteomic signature profile
- PK plasma sampling:
  - Visit 4: predose; end of infusion; and 30min, 1h, and 2h post end of infusion
  - Visit 6: predose; end of infusion
- BILAG 2004
- SLEDAI-2K assessing the past 30 days
- SRI-50

- PGA
- TJC/SJC
- CLASI
- Investigator assessment of flare
- Contact IVRS/IWRS
- Study drug preparation (predose), administration, and accountability (postdose)
- AEs (pre and postdose)
- Dispense subject daily diary (postdose)

8.5 Visit 5 (Week 6/Day 42 [±3 days])

Subjects should undergo an overnight fast (at least 8 hours) prior to coming to the clinic for Visit 5. Subjects may then eat breakfast after serum samples have been obtained for the assessment of cardiovascular proteins, lipids, and lipid particles, and prior to any other assessments.

Assessments at Visit 5 (Week 6) include:

- Concomitant medications
- Medical procedures
- Collect/review subject daily diary
- Urine pregnancy test for women of childbearing potential
- Withdrawal criteria check
- Vital signs (systolic and diastolic blood pressure, pulse rate, and temperature)
- Additional laboratories:
  - cardiovascular proteins, lipids, and lipid particles (blood samples should be collected under fasting conditions [at least 8 hours])
- PK plasma sample
- Investigator assessment of flare
- AEs
- Dispense subject daily diary
- Contact the IVRS/IWRS

8.6 Visit 7 (Week 12/Day 84 [±3 days]), Visit 8 (Week 16/Day 112 [±3 days]), and Visit 9 (Week 20/Day 140 [±3 days])

Subjects should undergo an overnight fast (at least 8 hours) prior to coming to the site for Visit 7 only. Subjects may then eat breakfast after serum samples have been obtained for the assessment of cardiovascular proteins, lipids, and lipid particles, and before study drug administration.

The PRO questionnaires should then be completed in a quiet place by the subjects themselves at the start of the study visit and prior to the remaining visit assessments.

All assessments should be performed prior to study drug dosing, unless otherwise indicated.

Assessments at Visit 7 (Week 12), Visit 8 (Week 16), and Visit 9 (Week 20) include:

- LupusQoL
- PROs at sites in English- and Spanish-speaking countries only:
  - SLE-S
  - SLE-F
  - SLE-M
  - SLE-P
  - SLE-E
- TB Signs and Symptoms questionnaire (Visit 7 only)
- Concomitant medications
- Medical procedures
- Collect/review subject daily diary
- Collect PK urine sample obtained at home (Visit 9 only; overnight void collection at home the night before the visit through the first morning void the morning of the visit)
- Physical examination/interim medical history
- Urine pregnancy test for women of childbearing potential
- Withdrawal criteria check
- Vital signs:
  - systolic and diastolic blood pressure, pulse rate, and temperature: predose; every 15mins post start of infusion; every 30mins until 2h post end of infusion
  - body weight: predose

<u>Note:</u> Blood samples must not be drawn through the infusion cannula.

- Safety laboratories: hematology, clinical chemistry, and urinalysis
- Additional laboratories:
  - anti-dsDNA antibodies
  - anti-DZP and anti-PEG antibodies
  - coagulation and hemostasis tests (Visit 7 only)
  - total Ig, IgG, IgM, IgA, and IgE
  - serum complement (C3, C4)

  - hsCRP
  - whole blood mRNA (Visits 7 and 8 only)
  - proteomic signature profile (Visits 7 and 8 only)
  - cardiovascular proteins, lipids, and lipid particles (Visit 7 only; blood samples should be collected under fasting conditions [at least 8 hours])
- PK plasma sampling:
  - Visits 7 and 8: predose; end of infusion
  - Visit 9: predose; end of infusion; and 30min, 1h, and 2h post end of infusion
- BILAG 2004
- SLEDAI-2K assessing the past 30 days
- SRI-50
- PGA
- PtGA (Visit 7 only)
- TJC/SJC
- CLASI
- Investigator assessment of flare
- Contact IVRS/IWRS
- Study drug preparation (predose), administration, and accountability (postdose)
- AEs (pre and postdose)
- Dispense subject daily diary (postdose)
- Dispense urine collection container (postdose; Visits 8 and 9 only; for overnight void collection at home the night before their next visit through the first morning void the morning of the visit)

8.7 Visit 10 (Week 24/Day 168 [±3 days]); Double-Blind Treatment Period End of Treatment/Early Withdrawal Visit

Subjects who withdraw prior to Week 32 (Visit 12) will complete an Early Withdrawal Visit (EWV; Visit 10 assessments if withdrawn prior to Visit 10; Visit 16 assessments if withdrawn after Visit 10) as well as Visits 11 and 12 for SFU assessments at 8 and 12 weeks after their final dose of study drug (as applicable). Subjects who withdraw after Week 32 (Visit 12) do not require additional SFU visits and will complete the Visit 16/EWV assessments only.

Subjects should undergo an overnight fast (at least 8 hours) prior to coming to the site for Visit 10. Subjects may then eat breakfast after serum samples have been obtained for the assessment of cardiovascular proteins, lipids, and lipid particles, and prior to any other assessments.

The PRO questionnaires should then be completed in a quiet place by the subjects themselves at the start of the study visit and prior to the remaining visit assessments.

Assessments at Visit 10 (Week 24) include:

- LupusQoL
- PROs at sites in English- and Spanish-speaking countries only:
  - SLE-S
  - SLE-F
  - SLE-M
  - SLE-P
  - SLE-E
  - Subject Experience Interview
- TB Signs and Symptoms questionnaire
- Concomitant medications
- Medical procedures
- Collect/review subject daily diary
- Collect PK urine sample obtained at home (overnight void collection at home the night before the visit through the first morning void the morning of the visit)
- C-SSRS
- Physical examination/interim medical history
- Urine pregnancy test for women of childbearing potential
- Withdrawal criteria check
- Vital signs (systolic and diastolic blood pressure, pulse rate, and temperature)
- 12-lead ECG
- Safety laboratories: hematology, clinical chemistry, and urinalysis
- Additional laboratories:
  - ANAs, anti-ENAs (anti-SM, anti-SSA, anti-SSB, anti-RNP), and RF
  - anti-dsDNA antibodies
  - anti-DZP and anti-PEG antibodies
  - aPL antibodies
  - coagulation and hemostasis tests
  - total Ig, IgG, IgM, IgA, and IgE
  - serum complement (C3, C4)

  - hsCRP
  - whole blood mRNA
  - proteomic signature profile
  - cardiovascular proteins, lipids, and lipid particles (blood samples should be collected under fasting conditions [at least 8 hours])
  - DNA
- PK plasma sampling
- BILAG 2004
- SLEDAI-2K assessing the past 30 days
- SRI-50
- PGA
- PtGA
- SLICC/ACR Damage Index
- TJC/SJC
- CLASI
- Investigator assessment of flare
- Contact IVRS/IWRS
- AEs
- Dispense subject daily diary
- Dispense urine collection container (for first morning urine collection at home on the morning of their next visit)

8.8 Visit 11/SFU (Week 28/Day 196 [±3 days]), Visit 13 (Week 36/Day 252 [±3 days]), and Visit 15 (Week 44/Day 308 [±3 days])

Subjects who withdraw prior to Week 32 (Visit 12) will complete an EWV (Visit 10 assessments if withdrawn prior to Visit 10; Visit 16 assessments if withdrawn after Visit 10) as well as Visits 11 and 12 for SFU assessments at 8 and 12 weeks after their final dose of study drug (as applicable). Subjects who withdraw after Week 32 (Visit 12) do not require additional SFU visits and will complete the Visit 16/EWV assessments only.

Assessments at Visit 11 (Week 28), Visit 13 (Week 36), and Visit 15 (Week 44) include:

- Concomitant medications
- Medical procedures
- Collect/review subject daily diary

- Collect PK urine sample obtained at home (first morning urine collection at home on the morning of visit; Visits 11 and 13 only)
- Urine pregnancy test for women of childbearing potential
- Withdrawal criteria check (only performed in subjects who are continuing in the study)
- Vital signs (systolic and diastolic blood pressure, pulse rate, and temperature)
- Safety laboratories (Visit 11 only): hematology, clinical chemistry, and urinalysis
- Additional laboratories:
  - anti-DZP and anti-PEG antibodies (Visit 11 only)
  - hsCRP (Visit 11 only)
- PK plasma sampling (Visits 11 and 13 only)
- Investigator assessment of flare
- AEs
- Dispense subject daily diary
- Dispense urine collection container (for first morning urine collection at home on the morning of their next visit)

8.9 Visit 12/SFU (Week 32/Day 224 [±3 days]) and Visit 14 (Week 40/Day 280 [±3 days])

Subjects who withdraw prior to Week 32 (Visit 12) will complete an EWV (Visit 10 assessments if withdrawn prior to Visit 10; Visit 16 assessments if withdrawn after Visit 10) as well as Visits 11 and 12 for SFU assessments at 8 and 12 weeks after their final dose of study drug (as applicable). Subjects who withdraw after Week 32 (Visit 12) do not require additional SFU visits and will complete the Visit 16/EWV assessments only.

The PRO questionnaires should be completed at the start of the study visit in a quiet place and by the subjects themselves.

Assessments at Visit 12 (Week 32) and Visit 14 (Week 40) include:

- LupusQoL
- PROs at sites in English- and Spanish-speaking countries only:
  - SLE-S
  - SLE-F
  - SLE-M
  - SLE-P
  - SLE-E
- Concomitant medications
- Medical procedures

- Collect/review subject daily diary
- Collect PK urine sample obtained at home (first morning urine collection at home on the morning of visit)
- C-SSRS (Visit 12; only performed in subjects who have withdrawn from the study and are undergoing SFU assessments)
- Physical examination/interim medical history
- Urine pregnancy test for women of childbearing potential
- Withdrawal criteria check (only performed in subjects who are continuing in the study)
- Vital signs (systolic and diastolic blood pressure, pulse rate, and temperature)
- Safety laboratories: hematology, clinical chemistry, and urinalysis
- Additional laboratories:
  - anti-dsDNA antibodies
  - anti-DZP and anti-PEG antibodies (Visit 12 only)
  - coagulation and hemostasis tests (Visit 12 only)
  - total Ig, IgG, IgM, IgA, and IgE (Visit 12 only)
  - serum complement (C3, C4)
  - hsCRP
  - whole blood mRNA (Visit 12 only)
  - proteomic signature profile (Visit 12 only)
- PK plasma sampling
- BILAG 2004
- SLEDAI-2K assessing the past 30 days
- SRI-50
- PGA
- TJC/SJC
- CLASI
- Investigator assessment of flare
- AEs
- Dispense subject daily diary (only performed in subjects who are continuing in the study)
- Dispense urine collection container (for first morning urine collection at home on the morning of their next visit; only performed at Visit 12 in subjects who are continuing in the study; not done at Visit 14)

8.10 Visit 16 (Week 48/Day 336 [± 3days]); Observation Period Final/Early Withdrawal Visit

Subjects who withdraw prior to Week 32 (Visit 12) will complete an EWV (Visit 10 assessments if withdrawn prior to Visit 10; Visit 16 assessments if withdrawn after Visit 10) as well as Visits 11 and 12 for SFU assessments at 8 and 12 weeks after their final dose of study drug (as applicable). Subjects who withdraw after Week 32 (Visit 12) do not require additional SFU visits and will complete the Visit 16/EWV assessments only.

Subjects should undergo an overnight fast (at least 8 hours) prior to coming to the site for Visit 16. Subjects may then eat breakfast after serum samples have been obtained for the assessment of cardiovascular proteins, lipids, and lipid particles, and prior to any other assessments.

The PRO questionnaires should then be completed in a quiet place by the subjects themselves at the start of the study visit and prior to the remaining visit assessments.

Assessments at Visit 16 (Week 48) include:

- LupusQoL
- PROs at sites in English- and Spanish-speaking countries only:
  - SLE-S
  - SLE-F
  - SLE-M
  - SLE-P
  - SLE-E
- Concomitant medications
- Medical procedures
- Collect/review subject daily diary
- Collect PK urine sample obtained at home (first morning urine collection at home on morning of visit)
- C-SSRS
- Physical examination/interim medical history
- Urine pregnancy test for women of childbearing potential
- Vital signs (systolic and diastolic blood pressure, pulse rate, and temperature)
- 12-lead ECG
- Safety laboratories: hematology, clinical chemistry, and urinalysis
- Additional laboratories:
  - ANAs, anti-ENAs (anti-SM, anti-SSA, anti-SSB, anti-RNP), and RF

  - anti-dsDNA antibodies
  - anti-DZP and anti-PEG antibodies
  - aPL antibodies
  - coagulation and hemostasis tests
  - total Ig, IgG, IgM, IgA, and IgE
  - serum complement (C3, C4)
  - hsCRP
  - whole blood mRNA
  - proteomic signature profile
  - cardiovascular proteins, lipids, and lipid particles (blood samples should be collected under fasting conditions [at least 8 hours])
  - DNA
- PK plasma sample
- BILAG 2004
- SLEDAI-2K assessing the past 30 days
- SRI-50
- PGA
- PtGA
- SLICC/ACR Damage Index
- TJC/SJC
- CLASI
- Investigator assessment of flare
- AEs

8.11 Unscheduled Visit

If at any point during the study the Investigator determines that a subject requires additional safety evaluations, the subject can return to the site and the Investigator may perform additional assessments, as clinically indicated, such as, but not limited to, the following assessments:

- Concomitant medications
- Medical procedures
- Vital signs (systolic and diastolic blood pressure, pulse rate, and temperature)
- 12-lead ECG
- Standard safety laboratories: hematology, serum chemistry, and urinalysis

- hsCRP
- Urine pregnancy test for women of childbearing potential
- AEs
- Contact the IVRS/IWRS

9 ASSESSMENT OF EFFICACY

9.1 Clinical assessments of disease activity

9.1.1 BILAG 2004

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

The Investigators will assess 97 BILAG 2004 components and record the assessments in the eCRF. Only clinical features attributable to SLE are to be recorded and based on the subject'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 separately:

- Constitutional (fatigue, fever, anorexia, weight loss, etc)
- Mucocutaneous (rash, alopecia, mucosal ulcers, etc)
- Neuropsychiatric (headache, seizure, psychosis, etc)
- Musculoskeletal (arthritis, myalgia, 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 document (chart, worksheet, clinic notes, and labs) capable of withstanding audit:

- For each entry indicating activity (and first time prior entry is no longer present)
- Indicating why feature new, improving, same, or worse
- Sufficient descriptive detail to support future changes (improved, worsening); eg, number/location of arthritic joints, size/location of rashes, etc
- Information indicating that all other features were not active at the time point of the visit

The Sponsor will provide centralized grading (A, B, C, D, and E) based on BILAG 2004 eCRF pages completed by the Investigator. Prior to Visit 2, the site must have received confirmation

from the central independent efficacy reader for BILAG 2004 data that the subject 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

Refer to Appendix 19.5 for protocol-specific clarification and extension of BILAG 2004 definitions.

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.

In addition, the BST is a new method of representing the BILAG 2004 scores longitudinally, which combines the flexibility and simplicity of numerical scoring with the clinical intuitiveness and meaningfulness of the BILAG 2004 categorical score. It was devised using a data-driven methodology and is based on counts of the number of systems with active/worsening disease and improving disease between 2 assessments. Further details will be provided in the SAP.

Only Investigators that complete BILAG 2004 training will be allowed to perform the BILAG 2004 assessments. Preferably, the same Investigator should evaluate the subject at each BILAG 2004 assessment from Screening to study completion.

9.1.2 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 and laboratory variables that are weighted by the type of manifestation, but not by severity. The SLEDAI-2K includes scoring for antibodies (anti-dsDNA 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 subject groups (Gladman et al, 2002).

To confirm subject 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. For both Visits 1 and 2, the SLEDAI-2K will assess disease activity in the past 10 days only.

9.1.3 PGA

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

"Please mark a vertical line on the scale below to assess the overall status of the subject's Systemic Lupus Erythematosus signs and symptoms and the functional capacity of the subject. Zero is 'very good, asymptomatic and no limitation of normal activities'; 100 indicates 'severe disease' and is at the very end of the scale. 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 PGA, the assessor should always look back at the score from the previous visit. This assessment by the Investigator must be made blinded to the PtGA performed at the same visit.

9.1.4 PtGA

Subjects will rate their global assessment of their SLE disease activity for the day of the visit in response to the statement "Considering all the ways your SLE affects you, please mark a vertical line on the scale below for how you are feeling today" using a 100mm visual analog scale (VAS) where 0 is "very good, no symptoms" and 100 is "very poor, very severe symptoms."

9.1.5 SLICC/ACR Damage Index

The 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 9–1), 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 9–1: SLICC/ACR Damage Index organ system scoring

Organ system	Range of possible scores
Ocular	0–2
Neuropsychiatric	0–6
Renal	0–3
Pulmonary	0–5
Cardiovascular	0–6
Peripheral vascular	0–5
Gastrointestinal	0–5
Musculoskeletal	0–6
Skin	0–3
Diabetes	0–1
Premature gonadal failure	0–1
Malignancy	0–2

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

9.1.6 Tender and Swollen Joint Counts (28 joints)

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 (IP) joint, proximal interphalangeal (PIP) joints (PIP 2, 3, 4, and 5), and the knees.

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

Subjects taking maintenance NSAIDs/analgesics, medical marijuana, or narcotics should not take a dose of these medications within 12 hours prior to the 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 9–2.

Table 9–2: 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 subject on examination (tender, winced, and withdrew)

Every effort should be made to ensure each subject is evaluated by the same Investigator (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.

9.1.7 CLASI

The 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 9–3) (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. Subjects are asked whether dyspigmentation due to cutaneous lupus erythematosus lesions usually remains visible for more than 12 months, which is taken to be permanent. 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. Associated symptoms, including itch, pain, and fatigue are recorded separately on a 1 to 10 VAS by the subjects.

Table 9–3: CLASI 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.

9.1.8 Assessment of flare

The reduction in lupus flares and increase in time to lupus flare is considered an appropriate measure to evaluate the efficacy of potential new lupus treatments. However, there is a lack of a universally accepted definition of a lupus flare. A recent international initiative involving multiple SLE experts led to a proposal for a consensus definition of disease flare in lupus (Ruperto et al, 2011):

> *A flare is a measurable increase in disease activity in 1 or more organ systems involving new or worse clinical signs and symptoms and/or laboratory measurements. It must be considered clinically significant by the assessor and usually there would be at least consideration of a change or an increase in treatment.*

Flare will be assessed by the Investigator and by the Sponsor, as follows.

Investigator Assessment of Flare:

To determine if the definition of flare is fulfilled in the opinion of the Investigator, the following question will be answered by the Investigator at each visit after Visit 2:

> "Do you consider that the SLE disease activity of the patient in 1 or more organ systems (involving new or worse clinical signs and symptoms and/or laboratory measurements) increased clinically significantly since the last visit and that you considered a change or increase the treatment for SLE of your patient?"

Sponsor Assessment of Flare:

The definition of flare according to the Sponsor is: a new sustained BILAG 2004 Grade A/B (present at ≥2 consecutive visits) after withdrawal of study drug or start of new induction therapy (either corticosteroid dose increase to ≥0.5 mg/kg/day prednisone equivalent or initiation of cyclophosphamide, rituximab, iv Ig, or plasma exchange] after withdrawal of study drug.

9.1.9 Responders based on clinical assessments of disease activity

9.1.9.1 BICLA

The primary efficacy variable, the BICLA responder rate across 3 doses of DZP and PBO at Week 24, is a categorical response variable (yes/no) incorporating the following criteria for achievement of responder status (ie, all criteria must be met to achieve responder status):

1. BILAG 2004 improvement, defined as BILAG 2004 Grade As at study entry improved to B/C/D, and BILAG 2004 Grade Bs at study entry improved to C/D, and no BILAG 2004 2004 worsening in other BILAG 2004 organ systems such that there are no new BILAG 2004 Grade As or greater than 1 new BILAG 2004 Grade B(s); and
2. No worsening in the SLEDAI-2K total score compared to study entry (defined as no increase in SLEDAI-2K total score); and
3. No worsening in the Physician's Global Assessment of Disease Activity compared to study entry ("no worsening" is defined as <10% worsening, equivalent to a 10mm increase on a 100mm VAS); and

4. No changes in concomitant medications according to the following criteria (all criteria must be met):
   - No increase of (or addition of a new) immunosuppressant nor antimalarial doses over Baseline (Visit 2) levels, nor initiation of any medication listed in Table 7-1
   - No increase in oral corticosteroid dose over Baseline (Visit 2) levels for an SLE-related indication
   - No iv, im, nor intra-articular injections of corticosteroids which are SLE related

In addition, subjects who discontinue study drug prematurely are primarily categorized as nonresponders.

The BICLA responder rate is based primarily on the BILAG 2004 disease activity measurement instrument. The BILAG 2004 was selected as the primary tool for measurement of disease activity on the basis of its comprehensiveness, ability to capture incremental changes in disease activity, and the clinical relevance of its grading system. The BILAG 2004 grading is anchored in the physician's intention to treat. 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 2004 grades mirror the decision points for treatment interventions. Consequently it represents the induction of disease control.

It is important to note that for the BILAG 2004 improvement, all As and Bs at entry need to improve. If an A improves to a B but a single B remains from entry, then the subject has not improved in their BILAG 2004.

9.1.9.2 SRI-4, -5, and -6

The SRI-4, SRI-5, and SRI-6 define responders as (ie, all criteria must be met):

- Reduction in SLEDAI-2K score of ≥4, ≥5, and ≥6 points, respectively
- 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, or from B to A, post-Baseline
- Increase in Physician's Global Assessment of Disease from Baseline of <10% (<10mm)

Assessments of SRI-4, -5, and -6 will include an assessment of nonresponders based on concomitant medication rules.

9.1.9.3 SRI-50

The SRI-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 SRI-50 reflects disease activity over the 30 days prior to the assessment (Touma et al, 2011). The total score of SLEDAI-2K falls between 0 and 105, with higher scores representing increased disease activity.

The SRI-50 score corresponds to the sum of each of the 24 descriptor scores on the SRI-50 data retrieval form. The method of scoring is simple, cumulative, and intuitive and similar to the SLEDAI-2K. One of 3 situations can result when a descriptor is present at the initial visit:

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 SRI-50 definition) but has not achieved complete remission, in which case the score is evaluated as one-half the score that would be assigned for SLEDAI-2K.

If a descriptor was not present at the initial visit, the value for the SRI-50 will be the same as that for SLEDAI-2K. This process is repeated for each of the 24 descriptors.

Finally, the SRI-50 score is evaluated as the sum of the scores of the 24 individual descriptors.

9.2 Patient-reported outcomes

The administration of the questionnaires for PRO assessments should be performed by study personnel other than the treating physician. The questionnaires should be filled in at the start of the study visit in a quiet place and by the subjects themselves.

The LupusQoL will be collected for all subjects at all sites participating in the study. In addition, the following exploratory PRO variables being developed by UCB will be assessed at sites in English- and Spanish-speaking countries (approximately 45% to 50% of the projected study population): SLE-S, SLE-F, SLE-M, SLE-P, and SLE-E. These newly developed instruments are being piloted in the current study and the data generated from this study will aid in refining the instruments for use in future studies. The Subject Experience Interview will also be assessed at sites in English- and Spanish-speaking countries.

The PRO questionnaires should be completed in the following order: LupusQoL, SLE-S, SLE-F, SLE-M, SLE-P, SLE-E, and Subject Experience Interview. The questionnaires should only be checked for completeness.

The visits at which PRO assessments are to be performed are described in Table 5–2.

9.2.1 LupusQoL

The LupusQoL (version 2007) is a disease-specific 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 (MCID) 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).

9.2.2 SLE-S

The SLE-S consists of 26 symptom items. The subject is asked to score each symptom item based on the severity experienced during the past 7 days using the following scale: 1=none; 2=mild; 3=moderate; 4=severe.

9.2.3 SLE-F

The SLE-F consists of 55 fatigue items across 3 scales: 16 physical domain items, 18 mental domain items, and 21 fatigability domain items. The subject is asked to score each fatigue item

based on how frequently they experienced the item during the past 7 days using the following scale: 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.

9.2.4 SLE-M

The SLE-M consists of 12 mobility items. The subject is asked to score each mobility item based on how frequently they experienced the item during the past 7 days using the following scale: 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.

9.2.5 SLE-P

The SLE-P consists of 3 Numeric Rating Scales and 29 items across a Pain and Physical Sensations Scale and a Pain Checklist. The subject is asked to indicate on Numeric Rating Scales the level of pain experienced in the past 7 days at its LEAST, at its WORST, ON AVERAGE, and also RIGHT NOW. The subject is then asked to score each of 12 pain and physical sensations items based on the severity experienced during the past 7 days using the following scale: 1=none; 2=very mild; 3=mild; 4=moderate; 5=severe; 6=very severe. Finally, the subject is asked to indicate the locations of the pain experienced in the past 7 days using a checklist consisting of 17 body locations.

9.2.6 SLE-E

The SLE-E consists of seven feelings and mood items. The subject is asked to score each item based on how frequently they experienced the item during the past 7 days using the following scale: 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.

9.2.7 Subject Experience Interview

Qualitative subject interviews will be conducted by an external third party vendor. The third party vendor will call the subject at home to collect the subject's experience with lupus in terms of symptoms and impact on daily activities, and the perceived changes during the course of the study. The extent to which the exploratory PRO items and scales used fully captured their experience will also be assessed.

10 ASSESSMENT OF PK AND PD VARIABLES

Subjects 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 and be drawn at the time points and sampling windows designated in Table 5–2 **Blood samples must not be drawn through the infusion cannula.**

10.1 Assessment of PK variables

The following PK variables will be evaluated:

- For plasma samples:
  - Plasma concentrations of DZP and PEG
- For urine samples:
  - Urine concentration of PEG

The DZP concentrations in the plasma will be determined by a validated electrochemiluminescence-based immunoassay. Concentrations of total PEG (both Fab' PEG and PEG) in plasma and of PEG in urine (following ultrafiltration) will be determined by a validated assay using ^{1}H nuclear magnetic resonance spectroscopy. Concentrations of DZP in urine may be measured depending on the availability of a bioanalytical method.

There are no time window requirements for blood samples for PK measurements when measured pre-dose or at unspecified times during the visit. Blood samples for PK measurements should be drawn within ±10min of the scheduled time point for each post-infusion time point or within 10min after the infusions ends for end of infusion time points.

For urine PK assessments, urine collection containers will be dispensed to the subjects at the designated visits for urine collection at home prior to the next visit. As outlined in Table 5–2, prior to Visits 9 and 10 only, the subject will collect overnight urine samples, which includes the first void after the subject goes to sleep the night before the visit through the first morning void the morning of the visit. The subject should note the times for the first and last urine collection. For all other visits requiring urine PK sample collection (Visits 2, 11, 12, 13, 14, and 16), the subject will collect only their first morning void.

10.2 Assessment of PD variables

The following PD assessments will be performed. Additional assessments may also be performed, as deemed appropriate.

- Whole blood mRNA signature profiling to characterize potential changes in gene expression relevant to the inflammatory and immune response in SLE
- Immunological variables:
  - Lupus Autoantibody Profile: anti-dsDNA, ANAs, anti-ENA (anti-SM, anti-SSA, anti-SSB, and anti-RNP), RF, and aPL antibodies
  - Ig (total Ig, IgG, IgM, IgA, and IgE)
  - hsCRP
  - C3 and C4 levels

10.3 Handling and shipment of blood and urine samples for PK and PD assessments

Sample work-up as well as the handling and shipment of samples should be performed as detailed in the Laboratory Manual.

11 ASSESSMENT OF IMMUNOGENICITY VARIABLES

The determination of the following immunogenicity variables will be performed from plasma samples (as noted in the Laboratory Manual):

- Anti-DZP and anti-PEG antibodies

Table 5–2 provides the timings for immunogenicity assessments.

Blood samples must not be drawn through the infusion cannula. Sample work-up as well as the handling and shipment of samples should be performed as detailed in the Laboratory Manual.

The detection of anti-DZP antibodies and anti-PEG antibodies will be done using validated methods. The details of analytical methods (including validation status) and results will be presented in the bioanalytical report.

12 ASSESSMENT OF BIOMARKERS

In addition to the PD variables (Section 10.2), the following samples will also be taken:

- Serum will be taken and stored for protein and lipid analysis to characterize potential changes relevant to inflammatory and immune responses and cardiovascular risk in SLE.
- Whole blood will be taken and stored to isolate DNA which may be used to examine genetic and epigenetic changes. If samples are not used immediately, they will be stored at -80°C for later analysis until the completion of the DZP development program. They will be stored at BioStorage Technologies GmbH (Germany) and they will only be used in the context of understanding the molecular taxonomy of SLE and/or response to treatment with DZP.

Table 5–2 provides the timings for biomarker assessments.

Blood samples must not be drawn through the infusion cannula. Sample work-up as well as the handling and shipment of samples should be performed as detailed in the Laboratory Manual.

13 ASSESSMENT OF SAFETY

13.1 Adverse events

13.1.1 Definition of adverse event

An AE is any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product that does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product. All AEs that occur during the study should be considered related unless clearly unrelated.

In order to ensure complete safety data collection, all AEs occurring during the study (ie, after the signing of the Informed Consent form), including any pretreatment and posttreatment periods required by the protocol, must be reported in the eCRF even if no IMP 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.

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

13.1.2 Procedures for reporting and recording adverse events

The subject 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.

13.1.3 Description of adverse events

When recording an AE, the Investigator should use the overall diagnosis of the underlying disease, condition, or syndrome using standard medical terminology, rather than recording individual symptoms or signs. The eCRF and source documents should be consistent. Any discrepancies between the subject's own words on his/her own records (eg, diary card) and the corresponding medical terminology should be clarified in the source documentation.

Details for completion of the Adverse Event eCRF (including judgment of relationship to IMP) are described in the eCRF Completion Guidelines.

13.1.4 Follow up of adverse events

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 subject is lost to follow up. This follow-up requirement applies to AEs, SAEs, and AEs of special interest; further details regarding follow-up of PDILI events are provided in Section 13.7.

If an AE is ongoing at the end of the study for a subject, follow up should be provided until resolution/stable level of sequelae is achieved, or until the Investigator no longer deems that it is clinically significant, or until the subject is lost to follow up. If no follow up is provided, the Investigator must provide a justification. For subjects withdrawn from the study prior to Visit 12 (Week 32), the follow up will be continued throughout the SFU Period (which ends 12 weeks after the final dose of study drug).

Information on SAEs obtained after clinical database lock will be captured through the PS database without limitation of time.

13.1.5 Rule for repetition of an adverse event

An increase in the intensity of an AE should lead to the repetition of the AE being reported with:

- The outcome date of the first AE that is not related to the natural course of the disease being the same as the start date of the repeated AE, and the outcome of "worsening"
- The AE verbatim term being the same for the first and repeated AE, so that the repeated AE can be easily identified as the worsening of the first one

13.1.6 Hypersensitivity and adverse drug reactions

In the event of a serious hypersensitivity reaction, the subject must permanently discontinue IMP and be progressed as described in Section 6.3.

In case of occurrence of a hypersensitivity reaction (not determined by the Investigator to be a minor local reaction at the infusion site, such as minimal itching) and depending upon its severity, appropriate countermeasures will immediately be taken by the Investigator.

In the event of an anaphylactic reaction, the infusion must be discontinued immediately and emergency resuscitation measures implemented. If the Investigator does not initially choose to discontinue the infusion of IMP and symptoms persist or escalate during continued infusion, the infusion should be stopped. In case of any severe infusion reaction(s), the infusion of IMP must be stopped immediately and appropriate treatment initiated, as necessary, at the discretion of the Investigator and in accordance with the standard-of-care.

Suggested guidelines for the management of infusion reactions are provided in Appendix 19.3. Refer to Section 7.2.1.2 for details regarding premedication for prophylaxis of infusion-related reactions.

Suspected anaphylactic reactions should be classified using Sampson's Criteria (Sampson et al, 2006) as described in Appendix 19.4.

13.1.7 Thromboembolic events

If the Investigator suspects a subject has a thromboembolic event, the Investigator should manage the subject in accordance with the standard-of-care and should discuss the event with the Medical Monitor. The IMP should be withheld while the suspected thromboembolic event is being investigated. After investigation, IMP administration will be addressed as follows:

- Suspected thromboembolic event is not confirmed: IMP may be continued
- Thromboembolic event is confirmed: IMP should be discontinued permanently

In the unexpected situation in which the study needs to be terminated due to the incidence of thromboembolic events, the following will occur:

- All Investigators will be informed of the details of the thromboembolic events
- All Investigators will be asked to evaluate each subject who received study drug within the past 12 weeks, to assess the potential increased risk of thromboembolic event, and to consider appropriate management that may include prophylactic anticoagulant therapy in case an increased risk cannot be excluded. Before a prophylactic anticoagulant treatment is started, the Investigator should break the blind in order to assure that the subject at risk was treated with DZP. Based on the half-life of DZP, the Sponsor recommends that the duration of anticoagulant therapy be for 18 weeks after the final dose of IMP.
- All subjects who are in the Double-Blind Treatment Period (Part 1) will enter and complete the SFU Period
- All subjects who are in in the SFU Period will complete the period as planned

13.1.8 Infections

Subjects who have the signs or symptoms of any infection should be managed according to local guidelines. This may include tests for possible infection with Epstein Barr virus and cytomegalovirus, if clinically indicated. The tests for Epstein Barr virus and cytomegalovirus will be performed at the central laboratory using blood provided by the site in accordance with the directions provided in the Laboratory Manual.

If a subject has an infection that requires parenteral (iv or im) antimicrobial treatment or that requires hospitalization, the subject's continuation in the study should be discussed with the Medical Monitor.

13.1.8.1 Suspected transmission of an infectious 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 13.2); 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.

13.1.9 Neurological events

Subjects who develop new neurological signs or symptoms or significantly worsening preexisting neurological signs or symptoms should be managed appropriately to evaluate the underlying disease or condition. This may include involvement of a neurologist, imaging, and other diagnostic activities as indicated. In case of severe and/or serious headache, positional headache, cranial nerve dysfunction, or signs and symptoms of meningitis, the Medical Monitor should be contacted immediately and the neurological event must be reported as an AE of interest to UCB within 24 hours.

13.1.10 Pregnancy

If an Investigator is notified that a subject has become pregnant after the first intake of any IMP, the Investigator must immediately notify UCB's PS department by providing the completed Pregnancy Report and Outcome form (for contact details see Serious Adverse Event Reporting information at the beginning of this protocol). The subject should be discontinued from the study drug as soon as pregnancy is known (by positive pregnancy test), and the following should be completed:

- The IMP should be immediately discontinued.
- The subject should complete the study per protocol.

If the Investigator becomes aware of a pregnancy only after an abortion, the withdrawal should be discussed with a Medical Monitor upfront. The Investigator must inform the subject of information currently known about potential risks and about available treatment alternatives.

The pregnancy will be documented on the Pregnancy Report and Outcome form provided to the Investigator. The progression of the pregnancy and the eventual birth (if applicable) must be followed up using the Pregnancy Report and Outcome form in which the Investigator has to report on the health of the mother and of the child. Every reasonable attempt should be made to follow the health of the child for 30 days after birth for any significant medical issues. In certain circumstances, UCB may request that follow up is continued for a period longer than 30 days. If the subject is lost to follow up and/or refuses to give information, written documentation of attempts to contact the subject needs to be provided by the Investigator and filed at the site. UCB's PS department is the primary contact for any questions related to the data collection for the pregnancy, eventual birth, and follow up.

In cases where the partner of a male subject enrolled in a clinical study becomes pregnant, the Investigator or designee is asked to contact the subject to request consent of the partner via the Partner Pregnancy Consent form that has been approved by the responsible IRB/IEC and should be available in the Investigator site file. In case of questions about the consent process, the Investigator may contact the UCB/CRO contract monitor for the study. The Investigator will complete the Pregnancy Report and Outcome form and send it to UCB's PS department (for contact details see Serious Adverse Event Reporting information at the beginning of this protocol) only after the partner has agreed that additional information can be captured and has provided the signed Partner Pregnancy Consent form. UCB's PS department is also the primary

contact for any questions related to the data collection for the partner pregnancy, eventual birth, and follow up.

A pregnancy becomes an SAE in the following circumstances: miscarriage, abortion (elective or spontaneous), unintended pregnancy after hormonal contraceptive failure (if the hormonal contraceptive was correctly used), ectopic pregnancy, fetal demise, or any congenital anomaly/birth defect of the baby. Those SAEs must be additionally reported using the Investigator SAE Report Form.

13.1.11 Overdose of IMP

Any SAE or nonserious AE associated with excessive dosing must be followed as any other SAE or nonserious AE. These events are only considered AEs or SAEs if there are associated clinical signs and symptoms or if the act of taking the excess medicine itself is an AE or SAE (eg, suicide attempt).

13.1.12 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 IMP so that Investigators, clinical study subjects, 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 PS representative.

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

In addition, a DMC will also monitor the ongoing safety of the study (see Section 5.1.4).

13.2 Serious adverse events

13.2.1 Definition of serious adverse event

Once it is determined that a subject experienced an AE, the seriousness of the AE must be determined. An SAE must meet 1 or more of the following criteria:

- Death
- Life-threatening

  (Life-threatening does not include a reaction that might have caused death had it occurred in a more severe form.)
- Significant or persistent disability/incapacity
- Congenital anomaly/birth defect (including that occurring in a fetus)
- Important medical event that, based upon appropriate medical judgment, may jeopardize the patient or subject and may require medical or surgical intervention to prevent 1 of the other outcomes listed in the definition of serious

  (Important medical events may include, but are not limited to, potential Hy's Law [see Section 13.3], allergic bronchospasm requiring intensive treatment in an emergency room or

at home, blood dyscrasias that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.)

- Initial inpatient hospitalization or prolongation of hospitalization

  (A patient admitted to a hospital, even if he/she is released on the same day, meets the criteria for the initial inpatient hospitalization. An emergency room visit that results in admission to the hospital would also qualify for the initial inpatient hospitalization criteria. However, emergency room visits that do not result in admission to the hospital would not qualify for this criteria and, instead, should be evaluated for 1 of the other criteria in the definition of serious [eg, life-threatening adverse experience, important medical event].

  Hospitalizations for reasons not associated with the occurrence of an AE [eg, preplanned surgery or elective surgery for a pre-existing condition that has not worsened or manifested in an unusual or uncharacteristic manner] do not qualify for reporting. For example, if a subject has a condition recorded on his/her medical history and later has a preplanned surgery for this condition, it is not appropriate to record the surgery or hospitalization as an SAE, since there is no AE upon which to assess the serious criteria. Please note that, if the pre-existing condition has worsened or manifested in an unusual or uncharacteristic manner, this would then qualify as an AE and, if necessary, the seriousness of the event would need to be determined.)

13.2.2 Procedures for reporting serious adverse events

If an SAE is reported, UCB must be informed within 24 hours of receipt of this information by the site (see contact information for SAE reporting listed in the Serious Adverse Event Reporting section at the front of the protocol). The Investigator must forward to UCB (or its representative) a duly completed "Investigator SAE Report Form for Development Drug" (SAE Report Form) provided by UCB, even if the data are incomplete, or if it is obvious that more data will be needed in order to draw any conclusions. Information recorded on this form will be entered into the global safety database.

An Investigator SAE report form will be provided to the Investigator. The Investigator SAE Report Form must be completed in English.

It is important for the Investigator, when completing the SAE Report Form, to include the assessment as to a causal relationship between the SAE and the IMP administration. This insight from the Investigator is very important for UCB to consider in assessing the safety of the IMP and in determining whether the SAE requires reporting to the regulatory authorities in an expedited manner.

Additional information (eg, autopsy or laboratory reports) received by the Investigator must be provided within 24 hours. All documents in the local language must be accompanied by a translation in English, or the relevant information included in the same document must be summarized in the Investigator SAE Report Form.

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 IMP), up to 30 days from the end of the study for each subject, and to also inform participating subjects of the need to inform the Investigator of any SAE within this period. Serious AEs that the

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

Upon receipt of the SAE Report Form, UCB will perform an assessment of expectedness of the reported SAE. The assessment of the expectedness of the SAE is based on the list of Anticipated SAEs provided in Section 13.5.

13.2.3 Follow up of serious adverse events

An SAE should be followed until it has resolved, has a stable sequelae, the Investigator determines that it is no longer clinically significant, or the subject is lost to follow up.

Information on SAEs obtained after clinical database lock will be captured through the PS database without limitation of time.

13.3 Adverse events 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. There are currently no AEs of special interest identified for DZP; however, in accordance with the Sponsor's internal guidelines for all drugs in development, Potential Hy's Law is to be reported as an AE of special interest as follows:

Potential Hy's law, defined as ≥3xULN ALT or AST with coexisting ≥2xULN bilirubin in the absence of ≥2xULN ALP, with no alternative explanation for the biochemical abnormality, must ALWAYS be reported to UCB as an AE of special interest (ie, without waiting for any additional etiologic investigations to have been concluded). Follow-up information should then be reported if an alternative etiology is identified during investigation and monitoring of the subject. Refer to Section 13.7 for details on investigation and monitoring of PDILI.

13.4 Immediate reporting of adverse events

The following AEs must be reported immediately to UCB (or its representative):

- SAEs: AEs that the Investigator classifies as serious by the above definitions regardless of causality
- Suspected transmission of an infectious agent via a medicinal product (see Section 13.1.8.1)
- AEs of special interest (see Section 13.3)
- AEs of interest (regardless of seriousness):
  - Moderate to severe infections, including opportunistic infections and TB
  - Infusion reactions (including hypersensitivity and anaphylaxis)
  - Thromboembolic events (including but not limited to cardiovascular events, stroke, myocardial infarction, pulmonary embolism, and deep vein thrombosis)
  - Prespecified neurological events: Severe and/or serious headache, positional headache, cranial nerve dysfunction, or signs and symptoms of meningitis (photophobia, neck stiffness)
  - Malignancies

13.5 Anticipated serious adverse events

Table 13–1 lists anticipated SAEs that have been identified as these events are anticipated to occur in the population studied in this protocol at some frequency that is independent of drug exposure. This original list will remain in effect for the duration of the protocol.

This list does not change the Investigator's obligation to report all SAEs (including Anticipated SAEs) as detailed in Section 13.2.2.

Table 13–1: Anticipated serious adverse events for subjects with SLE

Thromboembolism
Serious infection
Renal dysfunction
Neuropsychiatric episode
Leucopenia
Anemia
Thrombocytopenia
SLE

SLE=systemic lupus erythematosus

13.6 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 6.2 [Exclusion Criterion #16]) and Section 6.3 [Withdrawal Criteria]). Any presumptive diagnosis or diagnosis of a TB infection is a reportable event. Confirmed active TB must be reported as an SAE (Section 13.2.2). The Investigator is to complete and submit the TB follow-up form provided.

Signs and symptoms

The Investigator should consider all potential sites of infection when assessing for TB during the physical examination, and other evaluations, and based on the subject's history. Sites commonly infected by TB include: the lungs, larynx, lymph glands, pleura, gastrointestinal system, genitourinary tract (including renal), bones and joints, meninges, peritoneum, pericardium, and skin. This is not an exhaustive list and unusual presentations and areas of involvement should always be considered.

Common symptoms with which the subject may present with include cough, blood in sputum, night sweats, lymphadenitis, joint pain/swelling, spinal deformity, headache/confusion, abdominal pain mimicking inflammatory bowel disease, frequent or painful urination, scrotal mass in men and pelvic inflammatory disease in women as well as other symptoms, or nonspecific symptoms. This is not an exhaustive list and unusual presentations should always be considered.

If active TB is identified, the subject must undergo appropriate study specified withdrawal procedures.

Latent TB infection is defined as the absence of signs, symptoms (eg, evidence of organ-specific involvement), or physical findings suggestive of TB infection with a positive interferon-γ release assay (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 subject may not be randomized to study drug and, if already randomized, must undergo appropriate study specified withdrawal procedures. 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 (Centers for Disease Control, 2015).

Test conversion

Tuberculosis test conversion is defined as a positive result (IGRA) for the current test but previous test results were negative (IGRA). All subjects with TB test conversion must immediately stop study drug administration. In case of a TB test conversion, the subject 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. If test conversion indicates LTB infection, active TB, or non-mycobacterial TB infection then, per UCB TB working instructions, TB test conversion (confirmed) should be classified as due to LTB, active TB infection, or non-TB mycobacterial infection. Additional assessments (eg, blood tests or IGRA test, chest x-rays, or other imaging) should be performed as medically indicated.

Latent TB: In case the evaluation by the appropriate specialist indicates a new LTB, the subject must be withdrawn from the study.

Active TB/non-tuberculosis mycobacterium: Subjects who develop active TB or non-tuberculosis mycobacterium (NTMB) infection during the study (conversion demonstrated by IGRA) must be withdrawn from the study. The subject must be immediately discontinued from study drug and an EWV must be scheduled as soon as possible, but no later than the next scheduled visit. The subject should be encouraged to keep the SFU Visits as specified by the protocol. The TB must be documented as an SAE. Treatment should be immediately started.

Note that subjects with history of or active NTMB infection are excluded from the study regardless of prior or current therapy.

Confirmed active TB is an SAE and must be captured on an SAE Report Form and provided to the Sponsor in accordance with SAE reporting requirements. As with all SAEs, periodic follow-up reports should be completed as per protocol requirement until such time as the TB infection resolves.

Once withdrawn from study treatment, subjects should return for the End of Treatment/EWV, complete all early withdrawal assessments, and complete the SFU Visits.

13.6.1 TB assessments

During conduct of the study, the TB assessment by IGRA (QFT-GIT or Elispot, if QFT-GIT is not available locally), should be repeated at Week 48 or early withdrawal for all subjects. The test results will be reported as positive, negative, or indeterminate and must be reviewed by an experienced TB specialist, radiologist, or a pulmonologist. If the assessment by IGRA is positive

or indeterminate on retest for subjects who were previously negative at Screening, the subject must undergo appropriate study-specified withdrawal procedures. The retest during Screening must be done during the protocol-defined Screening window.

13.6.2 Chest x-ray

A plain posteroanterior chest x-ray (or, if done, computed axial tomography of the chest) should be performed during Screening unless one has been done within 3 months prior to the Screening Visit. The chest x-ray must be clear of signs of TB infection (previous or current) before first study drug administration. The chest x-ray should be repeated only if the TB test was confirmed positive or any further evidence is suggestive of potential TB infection (eg, exposure). Radiographic findings suggestive of inactive TB or active TB may include but are not limited to: apical fibrosis, pleural thickening, pulmonary nodules, fibrotic scars, calcified granulomas, upper lobe infiltrates, cavitations and pleural effusions, calcified lung nodules, calcified hilar lymph nodes, and pericardial calcification.

The chest x-ray (or, if done, computed axial tomography of the chest) must be negative for TB infection as determined by a qualified radiologist and/or pulmonary physician. Any new clinically significant findings post-Baseline during physical examination or on chest x-ray must be documented in the source documents and eCRF as an AE.

13.6.3 TB signs and symptoms 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 subjects who may require therapy for TB. A subject who answers "Yes" to the question [redacted] 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 subject has latent or active TB (see Section 6.2, Exclusion Criterion #16). A "Yes" response to any of the questions during the study should trigger further assessments to determine if the subject has either LTB or active TB infection.

Subjects with a LTB or active TB infection must be withdrawn from the study and will have further assessments.

13.6.4 TB management

For inclusion in the study, see Section 6.2, Exclusion Criterion #16.

LTB infection and active TB identified during study

During the study, subjects who develop evidence of LTB infection or active TB must immediately stop further administration of study drug and will be referred to an appropriate TB specialist (pulmonologist or infectious disease specialist) for further evaluation. Evidence of LTB infection is defined as the subject's IGRA test converting to positive or indeterminate (and confirmed indeterminate on repeat), or the subject's questionnaire history or physical examination indicating that TB infection or exposure may have occurred. Evidence of active TB includes, in addition to the aforementioned tests, signs and symptoms of organ involvement. In either situation, the subject should be carefully assessed by a TB specialist for active TB. Subjects diagnosed with active TB or LTB infection should receive appropriate TB or prophylaxis therapy and must be withdrawn from the study.

Confirmed active TB must be reported as a SAE. The Investigator is to complete and submit the TB follow-up form provided.

The subject should be transferred to the care of their physician and managed according to the standard-of-care. Subjects identified as having converted to active TB during the study must be withdrawn and scheduled to return for the EWV as soon as possible but no later than the next scheduled study visit and complete all EWV assessments. The subject should be encouraged to complete the SFU Visits after the final dose of study drug.

If infection with NTMB is identified during the study, the same procedure as for active TB acquired during the study must be followed.

Follow-Up information of suspected and confirmed TB cases should be provided to UCB at least after 3, 9, and 12 months of the start date of anti-TB treatment, including hematological and biochemical safety parameters, x-ray evolution data, and TB diagnostic procedures used to follow-up and confirm recovery of TB.

13.7 Evaluation of PDILI

The PDILI IMP discontinuation criteria for this study are provided in Section 6.3.1, with the accompanying required follow-up investigation and monitoring detailed below. All PDILI events must be reported as an AE and reported to the study site and Sponsor within 24 hours of learning of their occurrence. Any PDILI event that meets the criterion for potential Hy's Law must be reported as an AE of special interest (see Section 13.3), and, if applicable, also reported as an SAE (see Section 13.2.2).

Evaluation of PDILI consists of the diagnostic testing and continued monitoring included in Table 13–2 (specific tests dependent on lab results and corresponding symptoms) and consult with a local hepatologist (if applicable, discussed in Section 13.7.1). The local hepatologist is the expert usually consulted by the treating physician for assessment and management of potential hepatic disease. This would usually be a hepatologist, but may be a gastroenterologist. Additional investigation and monitoring may be required and adapted based on the diagnosis after the cause of the liver injury/abnormality is confirmed (details in Section 13.7.3).

The results of all monitoring, including labs and other testing, should be made available to the study site and Sponsor.

All initial abnormal hepatic lab values need to be repeated, but appropriate medical action must not be delayed waiting for the repeat result.

If tests are done locally for more rapid results, a concurrent sample should also be sent to the central laboratory whenever possible. Medical care decisions are to be made initially using the most rapidly available results and a conservative approach must be taken if the results from the 2 laboratory tests are significantly different. Data from the local and central laboratory are to be recorded on the applicable eCRF pages.

When IMP is discontinued, all concomitant medications and herbal supplements that are not medically necessary should also be discontinued. In these cases, the Investigator should also consider dose reduction for medically necessary concomitant medication and consider changing any medically required concomitant medication known to be hepatotoxic to a suitable alternative.

When IMP is stopped due to PDILI (as described in Section 6.3.1), IMP must be permanently discontinued unless a subsequent alternative diagnosis fully explains the hepatic findings. If a subsequent alternative diagnosis fully explains the hepatic findings, and the requirements provided in Section 13.7.2.1 are met, rechallenge with IMP may be appropriate.

Rechallenge with a substance potentially causing drug-induced liver injury is dangerous, may be fatal, and must not occur.

The table below summarizes the approach to investigate PDILI.

Table 13–2: Required investigations and follow up for PDILI

Laboratory value			Immediate		Follow up	
ALT or AST	**Total bilirubin**	**Symptoms[a] of hepatitis or hypersensitivity**	**Consultation requirements**	**Actions**	**Testing**	**Evaluation**
≥3xULN	≥2xULN[b]	NA	Hepatology consult.[c] Medical Monitor must be notified within 24 hours (eg, by laboratory alert) and subject discussed with Medical Monitor ASAP.	Immediate, permanent IMP discontinuation.	Essential: Must have repeat liver chemistry values and additional testing completed ASAP (see Section 13.7.3); recommended to occur at the site with HCP.	Monitoring of liver chemistry values at least twice per week until values normalize, stabilize, or return to within baseline values.[d]
≥8xULN	NA	NA				
≥3xULN	NA	Yes		Immediate, temporary or permanent, IMP discontinuation.		
≥3xULN (and ≥2x baseline) and <5xULN	<2xULN	No	Discussion with Medical Monitor required if the criterion that allows for IMP continuation is met.	Further investigation – immediate IMP discontinuation not required (see Section 13.7.2).	Not required unless otherwise medically indicated (at discretion of Investigator).	

Table 13–2: Required investigations and follow up for PDILI

Laboratory value			Immediate		Follow up	
ALT or AST	**Total bilirubin**	**Symptoms[a] of hepatitis or hypersensitivity**	**Consultation requirements**	**Actions**	**Testing**	**Evaluation**
≥5xULN (and ≥2x baseline) and <8xULN	<2xULN	No	Hepatology consult if there is no evidence of resolution (see Follow up requirements).[c] Discussion with Medical Monitor required.	IMP discontinuation required if any of the following occur: Subject cannot comply with monitoring schedule. Liver chemistry values continue to increase during 2 week monitoring period. Liver chemistry values remain ≥5xULN (and ≥2x baseline) after 2 week monitoring period.	Essential: Every attempt must be made to have repeat liver chemistry values and additional testing completed within 48 hours at the site with HCP (see Section 13.7.3).	Monitoring of liver chemistry values at least twice per week for 2 weeks.[d] Immediate IMP discontinuation required if liver chemistry values continue to increase. After 2 weeks of monitoring liver chemistry values: Discontinue IMP if levels remain ≥5xULN (and ≥2x baseline); monitor until values normalize, stabilize, or return to within baseline values.[d] Continue IMP if levels are no longer ≥5xULN (and ≥2x baseline); continue to monitor at least twice per week until values normalize, stabilize, or return to within baseline values.[d]

ALP=alkaline phosphatase; ALT=alanine aminotransferase; ASAP=as soon as possible; AST=aspartate aminotransferase; HCP=healthcare practitioner; IMP=investigational medicinal product; NA=not applicable; PDILI=potential drug-induced liver injury; ULN=upper limit of normal

[a] Hepatitis symptoms include fatigue, nausea, vomiting, and right upper quadrant pain or tenderness; hypersensitivity symptoms include eosinophilia (>5%), rash, and fever (without clear alternative cause).

[b] If the subject also has ≥2xULN ALP, the possibility of an indication of biliary obstruction should be discussed with the Medical Monitor.

[c] Details provided in Section 13.7.1. The local hepatologist is the expert usually consulted by the treating physician for assessment and management of potential hepatic disease. This would usually be a hepatologist, but may be a gastroenterologist.

[d] Unless an alternative monitoring schedule is agreed by the Investigator and UCB responsible physician. Determination of stabilization is at the discretion of the Investigator in consultation with the hepatologist (as applicable) and UCB responsible physician, as needed.

13.7.1 Consultation with Medical Monitor and local hepatologist

Potential drug-induced liver injury events require notification of the Medical Monitor, within 24 hours (eg by laboratory alert), and the subject must be discussed with the Medical Monitor as soon as possible. If required, the subject must also be discussed with the local hepatologist. The local hepatologist is the expert usually consulted by the treating physician for assessment and management of potential hepatic disease. This would usually be a hepatologist, but may be a gastroenterologist. If determined necessary, this discussion should be followed by a full hepatology assessment (see Section 13.7.3) and SAE report (if applicable).

13.7.2 Immediate action: determination of IMP discontinuation

All PDILI events require immediate action, testing, and monitoring.

The immediate action is dependent on the laboratory values and symptoms of hepatitis or hypersensitivity and ranges from continuation of IMP (followed by immediate investigation) to immediate and permanent discontinuation (see Section 6.3.1 and Table 13–2 for details).

When IMP is discontinued, all concomitant medications and herbal supplements that are not medically necessary should also be discontinued. The Investigator should also consider dose reduction for medically necessary concomitant medication and consider changing any medically required concomitant medication known to be hepatotoxic to a suitable alternative.

13.7.2.1 IMP restart/rechallenge (if applicable)

Rechallenge with a substance potentially causing drug-induced liver injury is dangerous, may be fatal, and must not occur.

Subjects who are immediately discontinued from IMP due to having met certain criteria for PDILI (as described in Section 6.3.1 and Table 13–2), but for whom an alternative diagnosis is confirmed, can rarely restart IMP. Rechallenge with IMP can occur only if ALL of the following requirements are met:

- The results of additional testing and monitoring described in Section 13.7.3 and Section 13.7.4 confirm a nondrug-related cause for the abnormal hepatic laboratory parameters and any associated symptoms (ie, a subsequent alternative diagnosis fully explains the hepatic findings).
- No alternative treatment options are available to the subject.
- The subject has shown clear therapeutic benefit from the IMP.
- Subject's ALT or AST elevations do not exceed ≥3xULN.
- Subject's total bilirubin is <1.5xULN.
- Subject has no signs or symptoms of hypersensitivity.

- The rechallenge is approved by the UCB responsible physician, DMC, and a hepatologist. The hepatologist must be external to UCB but may be a member of the DMC. It is recommended that the hepatologist be a local hepatology expert or the hepatologist treating the subject.
- Subject agrees to the Investigator-recommended monitoring plan.

13.7.3 Testing: identification/exclusion of alternative etiology

The measurements and additional information required for the assessment of PDILI events when there is a reasonable possibility that it may have been caused by the IMP are detailed in Table 13–3 (laboratory measurements) and Table 13–4 (additional information). Results of the laboratory measurements and information collected are to be submitted to the Sponsor on the corresponding eCRF. If medical history of the subject indicates a requirement for other assessments not included below, these additional assessments should be completed and submitted, as applicable.

All blood samples should be stored, if possible. If tests are done locally for more rapid results, a concurrent sample must also be sent to the central laboratory.

Table 13–3: PDILI laboratory measurements

Virology-related	**Hematology**
Hepatitis A immunoglobulin M (IgM) antibody	Prothombin time[a] International Normalized Ratio (INR)
Hepatitis B surface antigen (HBsAg)	Eosinophil count
Hepatitis E IgM antibody	**Urinalysis**
Hepatitis B core antibody-IgM (HBcAb-IgM)	Urine toxicology screen
Hepatitis C ribonucleic acid (RNA)	**Chemistry**
Cytomegalovirus IgM antibody	If bilirubin ≥1.5xULN, obtain fractionated bilirubin to obtain % direct bilirubin
Epstein Barr viral capsid antigen IgM antibody (if unavailable, obtain heterophile antibody or monospot testing)	Serum creatine phosphokinase (CPK) and lactate dehydrogenase (LDH) to evaluate possible muscle injury causing transaminase elevation
Immunology	Amylase
Anti-nuclear antibody (qualitative and quantitative)	**Additional**
Anti-smooth muscle antibody (qualitative and quantitative)	Serum pregnancy test
Type 1 anti-liver kidney microsomal antibodies (qualitative and quantitative)	PK sample

ALT=alanine aminotransferase; PDILI=potential drug-induced liver injury; PK=pharmacokinetic; ULN=upper limit of normal

[a] Measured only for subjects with ALT >8xULN, elevations in total bilirubin, and symptoms of hepatitis or hypersensitivity. Hepatitis symptoms include fatigue, nausea, vomiting, and right upper quadrant pain or tenderness; hypersensitivity symptoms include eosinophilia (>5%), rash, and fever (without clear alternative cause).

The following additional information is to be collected:

Table 13–4: PDILI information to be collected

New or updated information
Concomitant prescription and over the counter medications (eg, acetaminophen, herbal remedies, vitamins); dosages and dates should be included.
Pertinent medical history, including the following: • history of liver disease (eg, autoimmune hepatitis, nonalcoholic steatohepatitis or other "fatty liver disease") • adverse reactions to drugs • allergies • relevant family history or inheritable disorders (eg, Gilbert's disease, alpha 1 antitrypsin deficiency) • recent travel and/or progression of malignancy involving the liver (note that metastatic disease to the liver, by itself, should not be used as an explanation for significant AST and/or ALT elevations)
The appearance or worsening of clinical symptoms of hepatitis or hypersensitivity (eg, fatigue, nausea, vomiting, right upper quadrant pain or tenderness, decreased appetite, abdominal pain, jaundice, fever, or rash)
Recent clinically significant hypotension or hypoxemia with compromised cardiopulmonary function
Alcohol and illicit drug use; include dates where available
Results of liver imaging or liver biopsy, if done
Results of any specialist or hepatology consult, if done
Any postmortem/pathology reports

ALT=alanine aminotransferase; AST=aspartate aminotransferase

13.7.4 Follow-up evaluation

All PDILI events require follow-up monitoring as described in Table 13–2. Monitoring should continue until liver chemistry values normalize, stabilize, or return to baseline. Determination of stabilization is at the discretion of the Investigator in consultation with the hepatologist (as applicable) and UCB responsible physician, as needed.

13.8 Physical examination and interim medical history

The physical examination and the interim medical history is 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.

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. The outcome of physical examinations and the interim medical history must be documented in source documentation. The following body systems will be examined:

- General Appearance
- Ear, Nose and Throat
- Eyes
- Hair and Skin
- Respiratory
- Cardiovascular
- Gastrointestinal
- Musculoskeletal
- Hepatic
- Neurological (including focused assessment of reflexes, sensitivity, muscle strength)
- Mental Status

13.9 Laboratory measurements

A central laboratory will perform all blood- and urine-based laboratory assessments except urine pregnancy tests, which will be performed at the site.

Subjects 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.**

Certain coagulation tests (in particular, activated partial thromboplastin time [aPTT]) should only be performed using the central laboratory while subjects are receiving study drug as PEG may interfere with some aPTT assays leading to false results indicating prolongation of aPTT.

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.

Laboratory parameters that will be measured are listed in Table 13-5.

Table 13-5: Laboratory measurements

Category	Parameters to be assessed
Clinical chemistry	Liver function tests: bilirubin, AST, ALT, ALP, GGT, and LDH Creatinine Urea nitrogen Electrolytes (sodium, potassium, calcium, and phosphate) Total cholesterol and triglycerides Total protein and albumin Glucose Lipase Creatine phosphokinase
Hematology	Hemoglobin Hematocrit Mean corpuscular volume RBC count Erythrocyte sedimentation rate Mean corpuscular hemoglobin concentration Mean corpuscular hemoglobin WBC count with differential (basophils, eosinophils, lymphocytes, monocytes, and neutrophils) Platelet count T cells (CD3+) B cells (CD19+)
Additional assessments	HIV test Hepatitis screening Tuberculosis test (QFT-GIT) Anti-dsDNA antibodies ANAs, anti-ENAs (anti-SM, anti-SSA, anti-SSB, and anti-RNP) and RF aPL antibodies including anticardiolipin antibodies, lupus anticoagulant [a], and anti-β2 glycoprotein antibodies Total Ig, IgG, IgM, IgA, and IgE High sensitivity C-reactive protein Serum complement (C3, C4) Whole blood mRNA signature profiling Proteomic signature profile Cardiovascular proteins, lipids, lipid particles Coagulation and hemostasis [a] Coombs' test (reflex testing to be performed by the central laboratory as indicated if signs of anemia are observed) [a]
Pregnancy testing	Serum test (β-hCG) (subjects of childbearing potential) at Screening (Visit 1) Urine test (β-hCG) (subjects of childbearing potential) at all other visits
Urinalysis	pH Protein Glucose Ketone Urobilinogen Bilirubin Blood Nitrite Leukocytes

Table 13-5: Laboratory measurements

Category	Parameters to be assessed
Urine chemistry and microscopy	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 Proteins and metabolites relevant to SLE

ANA=antinuclear antibody; anti-ENA=extractable nuclear antigen antibody; anti-RNP=anti-ribonucleoprotein antibody; anti-SSA=Sjögren's syndrome antibody A; anti-SSB=Sjögren's syndrome antibody B; anti-SM=Smith antibody; aPL=antiphospholipid; ALP=alkaline phosphatase; ALT=alanine aminotransferase; AST=aspartate aminotransferase; β-hCG=beta human chorionic gonadotropin; dsDNA=double-stranded deoxyribonucleic acid; GGT=gamma-glutamyltransferase; HIV=human immunodeficiency virus; Ig=immunoglobulin; LDH=lactate dehydrogenase; mRNA=messenger ribonucleic acid; RBC=red blood cell; RF=rheumatoid factor; SLE=systemic lupus erythematosus; WBC=white blood cell

[a] As defined in the Laboratory Manual.

13.10 Vital signs

Vital sign measurements for all subjects will include height, weight, blood pressure (systolic and diastolic), pulse rate, and body temperature.

Subjects will rest in the position used for dosing for at least 10min before and continue to rest in that position while pulse rate and blood pressure are measured.

Table 5–2 indicates the timings for vital sign assessments. Vitals signs should be measured within ±5min of the scheduled time point for the every 15min assessments and within ±10min of the scheduled time point for the every 30min assessments.

13.11 12-lead ECGs

Twelve-lead ECG assessments should be performed prior to dosing (if applicable) and prior to obtaining PK or other laboratory samples. Electrocardiograms will be recorded digitally and read by the Investigator for recording in the eCRF.

Care should be taken to assure proper lead placement and quality ECG recording. Subjects should rest in a supine position in a controlled, calm environment for at least 15min 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.

Table 5–2 indicates the visits at which 12-lead ECG assessments will be performed.

13.12 Assessment of suicidal ideation and behavior

Suicidal ideation and behavior will be assessed by trained study personnel 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. Table 5–2 indicates the visits at which the C-SSRS assessments will be performed.

14 STUDY MANAGEMENT AND ADMINISTRATION

14.1 Adherence to protocol

The Investigator should not deviate from the protocol. However, the Investigator should take any measure necessary in deviation from or not defined by the protocol in order to protect clinical study subjects from any immediate hazard to their health and safety. In this case, this action should be taken immediately, without prior notification of the regulatory authority, IRB/IEC, or Sponsor.

After implementation of such measure, the Investigator must notify the CPM of the Sponsor within 24 hours and follow any local regulatory requirements.

14.2 Monitoring

UCB (or designee) will monitor the study to meet the Sponsor's monitoring Standard Operating Procedures (SOPs), ICH-GCP guideline, and applicable regulatory requirements, and to ensure that study initiation, conduct, and closure are adequate. Monitoring of the study may be delegated by UCB to a CRO or a contract monitor.

The Investigator and his/her staff are expected to cooperate with UCB (or designee) and to be available during the monitoring visits to answer questions sufficiently and to provide any missing information. The Investigator(s)/institution(s) will permit direct access to source data/documents for study-related monitoring, audits, IRB/IEC review, and regulatory inspection(s).

The Investigator will allow UCB (or designee) to periodically review all eCRFs and corresponding source documents (eg, hospital and laboratory records for each study participant). Monitoring visits will provide UCB (or designee) with the opportunity to evaluate the progress of the study, verify the accuracy and completeness of eCRFs, ensure that all protocol requirements, applicable authorities regulations, and Investigator's obligations are being fulfilled, and resolve any inconsistencies in the study records.

14.2.1 Definition of source data

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, ECGs or other printouts, completed scales, or electronic questionnaires, 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 subject'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).

UCB expects to select approximately 4 to 6 US sites to participate in an Electronic Healthcare Record (EHR) pilot, which will test data extraction from the subjects' EHR into the eCRF to populate fields in the Demography, Medical History, Concomitant Medications, and Vital Signs eCRFs. UCB stated the intention to pilot the use of EHR data in their response to FDA's Federal Register Notice, Source Data Capture from Electronic Health Records: Using Standardized Clinical Research Data. For the purposes of the pilot, the EHR is considered the source for these fields. The sites participating in the EHR pilot are not expected to print the subjects' EHRs.

14.2.2 Source data verification

Source data verification ensures accuracy and credibility of the data obtained. During monitoring visits, reported data are reviewed with regard to being accurate, complete, and verifiable from source documents (eg, subject files, recordings from automated instruments, tracings [ECG], x-ray films, laboratory notes). All data reported on the eCRF should be supported by source documents, unless otherwise specified in Section 14.2.1.

14.3 Data handling

14.3.1 Case Report Form completion

The study is performed using electronic data capture (EDC). The Investigator is responsible for prompt reporting of accurate, complete, and legible data in the eCRFs and in all required reports.

Any change or correction to the eCRF 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.

Detailed instructions will be provided in the eCRF Completion Guidelines.

14.3.2 Database entry and reconciliation

Case Report Forms/external electronic data will be entered/loaded into a validated electronic database using a clinical data management system (CDMS). Computerized data cleaning checks will be used in addition to manual review to check for discrepancies and to ensure completeness, consistency, and plausibility of the data.

An electronic audit trail system will be maintained within the CDMS to track all data changes in the database once the data have been saved initially into the system or electronically loaded. Regular backups of the electronic data will be performed.

14.3.3 Subject Screening and Enrollment Log/Subject Identification Code list

The subject's screening and enrollment will be recorded in the Subject Screening and Enrollment Log.

The Investigator will keep a Subject Identification Code list. This list remains with the Investigator and is used for unambiguous identification of each subject.

The subject's consent and enrollment in the study must be recorded in the subject's medical record. These data should identify the study and document the dates of the subject's participation.

14.4 Termination of the study

UCB reserves the right to temporarily suspend or prematurely discontinue this study either at a single site, multiple sites, or at all sites at any time for reasons including, but not limited to, safety or ethical issues, inaccurate or incomplete data recording, noncompliance, or unsatisfactory enrollment with respect to quality or quantity.

If the study is prematurely terminated or suspended, UCB (or its representative) will inform the Investigators/institutions and the regulatory authority(ies) of the termination or suspension and the reason(s) for the termination or suspension, in accordance with applicable regulatory requirement(s). The IRB/IEC should also be informed and provided with reason(s) for the termination or suspension by the Sponsor or by the Investigator/institution, as specified by the applicable regulatory requirement(s). In addition, arrangements will be made for the return of all unused IMP and other material in accordance with UCB procedures for the study.

14.5 Archiving and data retention

The Investigator will maintain adequate records for the study, including eCRFs, medical records, laboratory results, Informed Consent documents, drug dispensing and disposition records, safety reports, information regarding participants who discontinued, and other pertinent data.

All essential documents are to be retained by the Investigator until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region, or at least 2 years have elapsed since the formal discontinuation of clinical development of the IMP. These documents should be retained for a longer period, however, if required by the applicable regulatory requirement(s) or by an agreement with UCB (CPMP/ICH/135/95, 2002 [Section 4.9.5]). 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 study master file.

14.6 Audit and inspection

The Investigator will permit study-related audits mandated by UCB, after reasonable notice, and inspections by domestic or foreign regulatory authorities.

The main purposes of an audit or inspection are to confirm that the rights and well-being of the subjects enrolled have been protected, that enrolled subjects (ie, signing consent and undergoing study procedures) are appropriate for the study, and that all data relevant for the evaluation of the IMP have been processed and reported in compliance with the planned arrangements, the protocol, investigational site, and IRB/IEC SOPs, ICH GCP, and applicable regulatory requirements.

The Investigator will provide direct access to all study documents, source records, and source data. If an inspection by a regulatory authority is announced, the Investigator will immediately inform UCB (or designee).

14.7 Good Clinical Practice

Noncompliance with the protocol, ICH-GCP, or local regulatory requirements by the Investigator, institution, institution staff, or designees of the Sponsor will lead to prompt action by UCB to secure compliance. Continued noncompliance may result in the termination of the site's involvement in the study.

15 STATISTICS

A brief description of the planned statistical methods is provided in the sections that follow. Full details will be provided in the SAP. An additional interim SAP will describe the complete analysis of the Double-Blind Treatment Period (Part 1) of the study.

15.1 Definition of analysis sets

Seven analysis sets will be defined for this study: the Enrolled Set (ES), the Randomized Set (RS), the Safety Set (SS), the Full Analysis Set (FAS), the Per Protocol Set (PPS), the Pharmacokinetic Per Protocol Set (PK-PPS), and the Completer Set (CS).

15.1.1 Enrolled Set

The ES will consist of all subjects who have given informed consent.

15.1.2 Randomized Set

The RS will consist of all subjects randomized into the study.

15.1.3 Safety Set

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

It is expected that subjects will receive treatment as randomized; hence, safety analyses will be based on the randomized treatment group. However, if it is determined that a subject has consistently received treatment other than what they were randomized to, then for safety analyses, the subject will be allocated to the actual treatment they received.

15.1.4 Full Analysis Set

The FAS will consist of all subjects who have received at least 1 full dose of study drug and have at least 1 post-Baseline efficacy measurement during the Double-Blind Treatment Period. The FAS is the primary analysis set for efficacy analyses.

In case of mistreatment, subjects will be analyzed as randomized for the FAS. The FAS will only be used for subjects in Part 1 of the study (until the end of Double-Blind Treatment Period of the study).

15.1.5 Per Protocol Set

The PPS will consist of subjects in the FAS who have received at least 1 full dose of study drug and have no important protocol deviations during the Double-Blind Treatment Period that may influence the validity of the data for the primary efficacy variable, the BICLA.

Analyses of the primary efficacy variable will be repeated using the PPS.

15.1.6 Pharmacokinetic Set

The PK-PPS will consist of all subjects in the SS who have provided at least 1 PK sample and for whom no important protocol deviations affecting the PK variables have been documented. This analysis set will be used for all PK analyses.

15.1.7 Completer Set

The CS will consist of all subjects who did not permanently discontinue study drug during the Double-Blind Treatment Period (Part 1), completed Week 24 of Part 1, and continued into the Observational Period (Part 2) of the study.

15.2 General statistical considerations

For continuous data in general, summary statistics (n [number of available measurements], arithmetic mean, standard deviation, median, minimum, and maximum) will be presented by treatment group.

For descriptive statistics of continuous variables, change from Baseline and the value at the time point itself will be displayed.

Frequency tables (frequency counts and percentages) will be presented for categorical data. If there are missing values, either a missing category will be included in the display or the number of nonmissing results will be used for calculations.

In general, percentages will be calculated based on the utilized analysis set; however, in case any analysis subsets are affected then the N of the subset will be used as denominator. Subsets of analysis sets will be described more in detail in SAPs.

Unless otherwise specified in the SAPs, the last measurement before study drug infusion will be used as the Baseline value. For almost all variables, this will be the Baseline assessment. However, for some variables, assessments may be scheduled for Screening only and not for Baseline. In this case the Screening value will be utilized as Baseline value. If a Baseline measurement is missing, and a Screening value available, the Screening value will be utilized as Baseline instead.

In general (if not otherwise specified in the SAPs), tables and figures will be presented by randomized treatment during the Double-Blind Treatment Period for the entire study.

The end of the Double-Blind Treatment Period (Part 1) of the study is defined as the date of the last Week 24 visit of the last subject in the study or the date of the last SFU Visit of the last early terminating subject (before Week 24) in the study, whichever is later. The end of the study is defined as the date of the last visit of the last subject in the study.

For the calculation of the SLEDAI-2K, the central laboratory information will be used for anti-dsDNA and complement, not the eCRF-derived information.

Assessments of SRI-4, -5, and -6 will include an assessment of nonresponders based on concomitant medication rules.

Data from EWVs will be recoded to the closest scheduled treatment period visit (after the last nonmissing visit value).

Handling of any mistreatments will be described in more detail in the SAPs.

Analyses of the primary and secondary efficacy variables will be repeated for the PPS.

15.3 Planned efficacy analyses

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 level disease if no value can be imputed from the Screening Visit. For post-Baseline assessments, if the BILAG 2004 is scored, but the grade for 1 or more individual system(s) is missing or scored as "Not applicable," then the grade for that system will be set to the grade at the previous visit.

The underlying assumption supporting imputation of missing post-Baseline BILAG 2004 grades with results from the prior visit is that the value at the preceding visit is the most accurate estimate of the value at the current visit. The underlying assumption supporting imputation of missing BILAG 2004 grades at Baseline with a grade of BILAG 2004 D level disease is that this is a conservative reasonable approach, since no improvement can occur following a Baseline grade of BILAG 2004 D level disease.

Missing values for Physician's Global Assessment of Disease will be imputed via last observation carried forward (LOCF).

15.3.1 Analysis of the primary efficacy variable

The primary efficacy variable is the BICLA responder at Week 24 across 3 doses of DZP and PBO. The BICLA is a binary efficacy response variable, which is a composite endpoint derived from the efficacy components: BILAG 2004, SLEDAI-2K, and the Physician's Global Assessment of Disease Activity. The BILAG 2004 and SLEDAI-2K are themselves composite endpoints comprising of multiple assessments of several organ systems affected by SLE. In addition, usage of specified concomitant medication as escape treatment is also a factor in determining BICLA responder status. See Section 9.1.9.1 for a complete description of the BICLA composite variable. Modified nonresponder imputation will be used to impute missing data, after applying additional rules within each component, which are further detailed as follows:

If 1 of the 3 efficacy components (BILAG 2004, SLEDAI-2K, or Physician's Global Assessment of Disease) is missing, but the visit was performed and all other assessments were completed, the missing component will be imputed from the subject's previous post-baseline assessment, prior to computing the treatment response variable, following the last observation carried forward principle.

Furthermore, for BILAG 2004 and SLEDAI-2K, if the assessment was done, but individual system or item scores are missing, the respective individual score will be imputed from the respective previous post-baseline score, in order to obtain a score for the current visit, prior to computing the system or score. If the value at the previous visit is also missing, or if the subject has 2 or more missing components at Week 24, then the treatment response value is considered to be unknown (ie, left as missing and therefore considered a nonresponder).

In addition, subjects who discontinue treatment prematurely (while still remaining in the study) are primarily categorized as nonresponder from that visit and all subsequent visits.

The Week 24 BICLA dose-response relationship across 3 doses of DZP and PBO will be evaluated using the Multiple Comparison Procedure–Modelling (MCP-Mod) methodology (Bretz et al, 2005). Monotonic dose-response trends will be tested using the appropriate contrasts as determined by the MCP-Mod methodology such that the overall Type 1 error rate is controlled at 0.05 (one-sided testing).

The SAP will describe additional features and detail around the MCP-Mod methodology as well as handling of missing data.

15.3.2 Other efficacy analyses

The analysis of the secondary and other efficacy responder rates will use a similar approach for handling of dropouts as previously described for the primary efficacy variable of treatment response at Week 24 (ie, dropouts are included as nonresponders).

The number and percent of responders in each treatment group will be presented. The crude difference in proportions of responders between each DZP treatment group and PBO will also be presented along with 95% CIs for the difference in proportions (Fleiss, 1981). Treatment group differences between each DZP group and PBO will be computed along with odds ratio and 95% CI.

Additionally, an estimate of the treatment differences at Week 24 will be obtained from a longitudinal generalized estimating equation model for binary outcome, and with a treatment by week interaction term. An unstructured covariance matrix will be used for this analysis. Missing values are not explicitly imputed, and remain missing in the model. All available scheduled post-Baseline assessments are utilized for deriving Week 24 treatment differences.

Analyses of continuous efficacy variables will be performed using mixed effects models for repeat measurement. These models will use all available post-Baseline data at all visits up to and including Week 24, and will be incorporated as repeated measures within each subject. Data from EWVs (prior to Week 24) will be recoded to the closest scheduled treatment period visit (after the last nonmissing visit value). Multiple visits for each subject will be incorporated as repeated measures within each subject. An unstructured covariance matrix will be utilized and least squares means for changes from Baseline and 95% CIs for each treatment group will be presented. Estimated treatment differences for each DZP dose group versus PBO and corresponding 95% CIs and p-values will be presented for each scheduled time point. This will apply to the following variables: Physician's Global Assessment of Disease Activity scores and SLEDAI-2K scores.

Supportive models of the continuous efficacy variables will involve analysis of covariance models with treatment group as a factor and Baseline score as a covariate. Least squares means for changes from Baseline at each visit and 95% CIs for treatment groups and treatment difference will be presented. These supportive analyses will be performed using as observed case models using all available data at each visit.

Analyses of the secondary efficacy variable will be repeated for the PPS for the Double-Blind Treatment Period (Part 1).

Patient-reported outcomes variables will be analyzed as continuous efficacy variables. For PRO variables that cannot be considered continuous (if any), analysis methods for longitudinal ordinal data may be used. Analyses of PRO variables will be performed for the Double-Blind Treatment

Period (Part 1) and for the Observational Period (Part 2) of the study. Analysis of the PRO data in the Observational Period (Part 2) will aim to explore the maintenance of patient-perceived treatment benefits after end of treatment. Analyses to support the interpretation of change in PRO variables will be performed (cumulative distribution functions, responder analysis). In addition, psychometric analyses of the newly developed measures (SLE-S, SLE-F, SLE-M, SLE-P, and SLE-E) will be performed blinded from treatment arms. The association between PROs and clinical variables will also be explored, as well as the association between the various PROs.

For all efficacy variables, DZP treatment arms, when statistically compared with PBO, will use a two-sided α=0.05 level of significance, without any adjustment for multiple comparisons. As such, these results are considered exploratory in nature and caution should be exercised in interpreting these results. Pairwise treatment comparisons for efficacy variables will be performed for the Double-Blind Treatment Period (Part 1) only.

An observed case analysis will be also performed as another sensitivity analysis for responder efficacy variables (BICLA, SRI).

15.4 Planned safety and other analyses

All safety summaries will be performed using the SS.

15.4.1 Safety analyses

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 (Medical Dictionary for Regulatory Activities). The data will be displayed as number of subjects experiencing the AEs, percentage of subjects, and number of AEs. Data will also be corrected for exposure and reported by 100 patient-years.

The incidence of subjects with AEs will be presented by treatment group and total treatment. Additional tables will summarize AEs leading to permanent discontinuation of study drug (for Part 1 only), AEs by maximum intensity, AEs by intensity, and AEs by relationship to study drug 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 subjects who experienced the respective AE.

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.

15.4.2 PK analyses

Individual subject 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).

For DZP and PEG, the C_{max} and C_{trough} per visit will be obtained directly from the plasma concentration time profiles. The AUCτ will be derived via a population approach using nonlinear mixed effects modeling. Dapirolizumab pegol PK data from SL0023 may be combined with other studies in the population PK approach and the analysis will be described in a separate Data Analysis Plan. The AUCτ following the last treatment visit in SL0023 will be derived, listed, and summarized together with the C_{max} and C_{trough} values.

The concentration of PEG in urine will also be summarized.

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

Data Analysis Plans for PK/PD will be created separately for the Double-Blind Treatment Period (Part 1) alone, and for the complete study including the Observational Period (Part 2).

15.4.3 Immunogenicity analyses

Anti-DZP and anti-PEG antibodies will be tabulated. More detailed specifications will be presented in the SAP.

15.5 Handling of protocol deviations

Important protocol deviations are deviations from the protocol which potentially could have a meaningful impact on study conduct or on the primary efficacy, key safety, or PK outcomes for an individual subject. 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.

Important protocol deviations for the primary efficacy variable will be identified through Week 24.

Further details on the handling of protocol deviations will be described in the SAPs.

15.6 Handling of dropouts or missing data

Handling of missing endpoint data for the primary efficacy analysis is described in Section 15.3 and the analysis of the secondary and other efficacy responder rates will use a similar approach for handling of dropouts or missing data.

In the case where laboratory results are missing at a non-Baseline visit, the laboratory result from the central laboratory at the prior visit will be used in determining the BILAG 2004 body/organ system score at the visit at which the laboratory value is missing. In the case where the laboratory result is missing at the Baseline Visit, the BILAG 2004 body/organ system score for the body system requiring the missing laboratory result will be set to a score of BILAG 2004 D level disease.

In addition, for purposes of computing a SLEDAI-2K total score, in the case where the SLEDAI-2K assessment has been done yet individual items have been left blank (ie, a “Yes” or “No” response for the item was not provided), these individual items will be imputed from the previous visit value prior to computing the total score. As an additional sensitivity analysis,

rather than imputing missing component values from previous visit values, when a total score cannot be computed due to 1 or more missing individual items, the total score will be imputed by extrapolating from the score based on the nonmissing items at the visit. In this scenario, provided that at least 75% of the individual items have a nonmissing response, the total of nonmissing items will be computed. This total will then be extrapolated to the equivalent value based on the total maximum value of the SLEDAI-2K instrument. Additional sensitivity analyses based on alternate approaches for handling of dropouts or missing data may be performed to support the robustness of the study results and will be described in the SAPs.

15.7 Planned interim analysis and data monitoring

An initial biomarker analysis may be performed on all evaluable biomarker data from Part 1 of the study when 25%-35% of the randomized subjects have completed Visit 7 (Week 12) of the Double-Blind Treatment Period. Data from subjects who have prematurely withdrawn from the study prior to Visit 7 will be included. The initial biomarker analysis will focus on transcriptomic biomarker variables (eg, mRNA), prespecified in a Biomarker Plan, in order to provide guidance for the DZP development program, and will not affect the conduct of the study. This initial biomarker analysis will not affect the conduct of the study and no adjustment to the final analysis is planned.

The tabulations for the initial biomarker analysis will be provided by individuals not otherwise involved in the conduct of the study. Blinding aspects of the initial biomarker analysis are described in Section 7.9.1.

After the last subject completes Part 1 of the study (including the SFU Period for early withdrawals from Part 1 or subjects not continuing into Part 2, if applicable), the data for those subjects will be secured and an interim CSR will be written for the Double-Blind Treatment Period (Part 1) of the study; this interim CSR will not include any data from the Observational Period (Part 2). A biomarker analysis on the full Double-Blind Treatment Period (Part 1) dataset will be included in the interim CSR. A complete final CSR will be written for the entire study following completion of the Observational Period (Part 2) of the study.

15.8 Determination of sample size

The size of this study is governed by determining whether there is a dose-response relationship across the 3 doses of DZP and PBO using the MCP-Mod methodology, as described in Section 15.3.1. The primary endpoint of the study is a binary indicator of whether the subject responds to treatment. Four different dose-response models ("candidate models") were identified: a linear model, a logistic model, and 2 Emax models, and the MCP-Mod methodology controls for multiplicity.

The sample size assessment was estimated using the "DoseFinding" library in the R statistical package (Bretz et al, 2005). This library implements design and analysis aspects of the MCP-Mod method. The sample size requirement was obtained for each candidate model in turn and the maximum value was taken, thus maintaining the power requirement.

Since the Dose Finding library assumes Normal data with constant variance, and the primary endpoint (responder rate) is binary, the Normal approximation was used. This entailed calculating the predicted response probabilities at each dose, for each of the candidate models, computing the binomial variances and then using these variances in the sample-size calculations.

Based upon prior experience in SLE, a placebo responder rate for this study of 25% is postulated. The desired clinical effect is 29% above PBO, resulting in a responder rate of 54%. With power of 80%, a (multiple-comparison corrected) one-sided type-1 error of 5% and all dose groups of the same size, 112 subjects are required to complete Part 1 of the study.

Adjusting for an expected dropout rate of 30% results in the need to randomize 160 subjects (40 subjects per treatment group). Assuming a screening failure rate of approximately 40%, it is anticipated to enroll around 267 subjects in this study.

16 ETHICS AND REGULATORY REQUIREMENTS

16.1 Informed consent

Subject's informed consent 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 subject in both oral and written form by the Investigator (or designee). Each subject will have the opportunity to discuss the study and its alternatives with the Investigator.

Prior to participation in the study, the written Informed Consent form should be signed and personally dated by the subject, and by the person who conducted the informed consent discussion (Investigator or designee). The subject must receive a copy of the signed and dated Informed Consent form. As part of the consent process, each subject must consent to direct access to his/her medical records for study-related monitoring, auditing, IRB/IEC review, and regulatory inspection.

If the Informed Consent form 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 US must include the use of a Health Insurance Portability and Accountability Act Authorization form.

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

16.2 Subject identification cards

Upon signing the Informed Consent and Assent form (as applicable), the subject will be provided with a subject identification card in the language of the subject. The Investigator will fill in the subject identifying information and medical emergency contact information. The Investigator will instruct the subject to keep the card with him/her at all times.

16.3 Institutional Review Boards and Independent Ethics Committees

The study will be conducted under the auspices of an IRB/IEC, as defined in local regulations, 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, Informed Consent form, Investigator's Brochure, Investigator's curriculum vitae (if applicable), advertisement (if applicable), and all other subject-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 human subjects or others, and any protocol deviations, to eliminate immediate hazards to subjects.

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 subjects. 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 subject 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.

16.4 Subject privacy

UCB staff (or designee) will affirm and uphold the subject's confidentiality. Throughout this study, all data forwarded to UCB (or designee) will be identified only by the subject 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 subject'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 subject's study participation, and autopsy reports for deaths occurring during the study).

16.5 Protocol amendments

Protocol changes may affect the legal and ethical status of the study and may also affect the statistical evaluations of sample size and the likelihood of the study fulfilling its primary objective.

Significant changes to the protocol will only be made as an amendment to the protocol and must be approved by UCB, the IRB/IEC, and the regulatory authorities (if required), prior to being implemented.

17 FINANCE, INSURANCE, AND PUBLICATION

Insurance coverage will be handled according to local requirements.

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

18 REFERENCES

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.

Al Sawah S, Zhang X, Zhu B, Magder LS, Foster SA, Iikuni N, et al. Effect of corticosteroid use by dose on the risk of developing organ damage over time in systemic lupus erythematosus—the Hopkins Lupus Cohort. Lupus Sci Med. 2015;2:e000066.

Borchers AT, Naguwa SM, Shoenfeld Y, Gershwin ME. The geoepidemiology of systemic lupus erythematosus. Autoimmun Rev. 2010;9:A277-87.

Boumpas DT, Furie R, Manzi S, Illei GG, Wallace DJ, Balow JE, et al. A short course of BG9588 (anti-CD40 ligand antibody) improves serologic activity and decreases hematuria in patients with proliferative lupus glomerulonephritis. Arthritis Rheum. 2003;48:719-27.

Bretz F, Pinheiro JC, Branson M. Combining multiple comparisons and modeling techniques in dose-response studies. Biometrics. 2005;61:738-48.

Burkly LC. CD40L pathway blockade as an approach to immunotherapy. Adv Exp Med Biol. 2001;489:135-52.

Centers for Disease Control. Tuberculosis: Testing and Diagnosis. http://www.cdc.gov/TB/topic/testing/default.htm. Accessed 23 Jul 2015.

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.

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

Davis JC, Tortoritis MC, Rosenberg J, Sklenar TA, Wofsy D. Phase I clinical trial of a monoclonal antibody against CD40 ligand (IDEC-131) in patients with systemic lupus erythematosus. J Rheumatol. 2001;28:95-101.

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.

Fleiss J. Statistical methods for rates and proportions. 2nd ed. New York: John Wiley & Sons, Inc; 1981 p.101.

Food and Drug Administration. Guidance for Industry, Drug Induced Liver Injury: Premarketing Clinical Evaluation. July 2009.

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.

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

Jakes RW, Bae SC, Louthrenoo W, Mok CC, Navarra SV, Kwon N. Systematic review of the epidemiology of systemic lupus erythematosus in the Asia Pacific region: prevalence, incidence, clinical features, and mortality. Arthrit Care Res. 2012;64:159-68.

Kalunian KC, Davis JC, Merrill JT, Totoritis MC, Wofsy D, IDEC-131 Study Group. Treatment of systemic lupus erythematosus by inhibition of T cell costimulation with anti-CD154: a randomized, double-blind, placebo-controlled trial. Arthritis Rheum. 2002;46:3251-8.

Kuwana M, Nomura S, Fujimura K, Nagasawa T, Muto Y, Kurata Y, et al. Effect of a single injection of humanized anti-CD154 monoclonal antibody on the platelet-specific autoimmune response in patients with immune thrombocytopenic purpura. Blood. 2004;103:1229-36.

Lim SS, Bayakly AR, Helmick CG, Gordon C, Easley KA, Drenkard C. The inicidence and prevalence of systemic lupus erythematosus, 2002-2004: The Georgia Lupus Registry. Arthritis Rheum. 2014;66:357-68.

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.

Muangchan C, van Vollenhoven RF, Bernatsky SR, Smith CD, Hudson M, Inanç M, et al. Treatment algorithms in systemic lupus erythematosus. Arthritis Care Res (Hoboken). 2015;67(9):1237–45.

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.

Patel VL, Schwatz J, Bussel JB. The effect of anti CD40 ligand in immune thrombocytopenic purpura. Brit J Haematol. 2008;141:545-8.

Petri M, Orbai AM, Alarcón GS, Gordon C, Merrill JT, Fortin PR, et al. Derivation and Validation of the Systemic Lupus International Collaborating Clinics Classification Criteria for Systemic Lupus Erythematosus. Arthritis Rheum. 2012;64(8):2677–86.

Robles-Carrillo L, Meyer T, Hatfield M, Desai H, Dávila M, Langer F, et al. Anti-CD40L immune complexes potently activate platelets in vitro and cause thrombosis in FCGR2A transgenic mice. J Immunol. 2010;185:1577-83.

Ruperto N, Hanrahan LM, Alarcón GS, Belmont HM, Brey RL, Brunetta P, et al, International consensus for a definition of disease flare in lupus. Lupus. 2011;20(5):453-462.

Sampson HA, Muñoz-Furlong A, Campbell RL, Adkinson NF Jr, Bock SA, Branum A, et al. Second symposium on the definition and management of anaphylaxis: summary report--Second National Institute of Allergy and Infectious Disease/Food Allergy and Anaphylaxis Network symposium. J Allergy Clin Immunol. 2006;117(2):391-7.

Somers EC, Marder W, Cagnoli P, Lewis EE, DeGuire P, Gordon C, et al. Population based incidence and prevalence of systemic lupus erythematosus: The Michigan Lupus Epidemiology and Surveillance Program. Arthritis Rheum. 2014;66:369-78.

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 200 Responder Index-50 enhances the ability of SLE Responder Index to identify responders in clinical trials. J Rheumatol. 2011:38:2395-9.

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

Van Kooten C, Banchereau J. CD40-CD40 ligand. J Leukocyte Biol. 2000;67:2-17.

19 APPENDICES

19.1 SLICC classification criteria for SLE

A subject is classified as having SLE if he or she satisfies 4 of the clinical and immunologic criteria used in the SLICC classification criteria, including at least 1 clinical criterion and 1 immunologic criterion, OR if he or she has biopsy-proven nephritis compatible with SLE in the presence of ANAs or anti-dsDNA antibodies.

The criteria do not need to be present concurrently. A criterion should only be judged as fulfilled if better explained by other causal relationships (eg, other disease, drug-site effects).

2012 SLICC SLE Criteria		
Clinical Criteria		
Has the subject ever experienced any of the following clinical criteria?		
1. Acute Cutaneous Lupus		
Lupus malar rash (do not count if malar discoid)	☐ Yes	☐ No
Bullous lupus	☐ Yes	☐ No
Toxic epidermal necrolysis variant of SL	☐ Yes	☐ No
Maculopapular lupus rash	☐ Yes	☐ No
Photosensitive lupus rash in the absence of dermatomyosit	☐ Yes	☐ No
Subacute cutaneous lupus (nonindurated psoriaform and/or annular polycyclic lesions that resolve without scarring, although occasionally with postinflammatory dyspigmentation or telangiectasias)	☐ Yes	☐ No
2. Chronic Cutaneous Lupus		
Localized classical discoid rash (above the neck)	☐ Yes	☐ No
Generalized classical discoid rash (above and below the neck)	☐ Yes	☐ No
Hypertrophic (verrucous) lupus	☐ Yes	☐ No
Lupus panniculitis (profundus)	☐ Yes	☐ No
Mucosal lupus	☐ Yes	☐ No
Lupus erythematosus tumidus	☐ Yes	☐ No
Chillblains lupus	☐ Yes	☐ No
Discoid lupus/lichen planus overlap	☐ Yes	☐ No
3. Oral or nasal ulcers in the absence of other causes, such as vasculitis, Behcets disease, infection (herpes), inflammatory bowel disease, reactive arthritis, and acidic foods		
Palate	☐ Yes	☐ No
Buccal	☐ Yes	☐ No
Tongue	☐ Yes	☐ No
Nasal	☐ Yes	☐ No
4. Non-scarring alopecia in the absence of other causes such as alopecia areata, drugs that cause alopecia, iron deficiency and androgenic alopecia (diffuse thinning or hair fragility with visible broken hairs)	☐ Yes	☐ No

5. Synovitis involving 2 or more joints, characterized by swelling or effusion OR tenderness in 2 or more joints and thirty minutes or more of morning stiffness	☐ Yes	☐ No
6. Serositis		
Typical pleurisy for more than 1 day	☐ Yes	☐ No
Pleural effusions	☐ Yes	☐ No
Pleural rub	☐ Yes	☐ No
Typical pericardial pain (pain with recumbency improved by sitting forward) for more than 1 day	☐ Yes	☐ No
Pericardial effusion	☐ Yes	☐ No
Pericardial rub	☐ Yes	☐ No
Pericarditis by ECG in the absence of other causes, such as infection, uremia, and Dressler's pericarditis	☐ Yes	☐ No
7. Renal		
Urine protein/creatinine ratio (or 24hr urine protein) representing 500mg of protein/24hr	☐ Yes	☐ No
Red blood cell casts	☐ Yes	☐ No
8. Neurologic		
Seizures	☐ Yes	☐ No
Psychosis	☐ Yes	☐ No
Mononeuritis multiplex in the absence of other known causes such as primary vasculitis	☐ Yes	☐ No
Myelitis	☐ Yes	☐ No
Peripheral or cranial neuropathy in the absence of other known causes such as primary vasculitis, infection, and diabetes mellitus	☐ Yes	☐ No
Acute confusional state in the absence of other causes, including toxic-metabolic, uremia, drugs	☐ Yes	☐ No
9. Hemolytic anemia	☐ Yes	☐ No
10. Leukopenia		
Leucocytes <4000/mm^3 at least once in the absence of other known causes such as Felty's syndrome, drugs, and portal hypertension	☐ Yes	☐ No
Lymphocytes <1000/mm^3 at least once in the absence of other known causes such as corticosteroids, drugs and infection	☐ Yes	☐ No
11. Thrombocytopenia (<100000/mm^3) in the absence of other known causes such as drugs, portal hypertension, and thrombotic thrombocytopenic purpura (TTP)	☐ Yes	☐ No

Immunological criteria

1. ANA above laboratory reference range in the absence of drugs known to cause ANA increase	☐ Yes	☐ No
2. Anti-dsDNA antibody above laboratory reference range, except enzyme-linked immunosorbent assay (ELISA): twice above laboratory reference range	☐ Yes	☐ No
3. Anti-Sm antibod	☐ Yes	☐ No

4. Antiphospholipid antibody		
Positive lupus anticoagulant test	☐ Yes	☐ No
False-positive rapid plasma reagin	☐ Yes	☐ No
Medium or high titer anticardiolipin antibody level (IgA, IgG, or IgM)	☐ Yes	☐ No
Positive test result for anti-β_2 glycoprotein I (IgA, IgG, or IgM)	☐ Yes	☐ No
5. Low complement (C3, C4, CH50)		
Low C3	☐ Yes	☐ No
Low C4	☐ Yes	☐ No
Low CH50	☐ Yes	☐ No
6. Direct Coombs' test (in the absence of hemolytic anemia)	☐ Yes	☐ No

Pathohistological Findings

Biopsy proven Nephritis compatible with SLE:		
Class I	☐ Yes	☐ No
Class II	☐ Yes	☐ No
Class III	☐ Yes	☐ No
Class IV	☐ Yes	☐ No
Class V	☐ Yes	☐ No
Class VI	☐ Yes	☐ No

19.2 Equivalent doses of oral steroids

Oral Steroids	Equivalent Dose (mg/day)
Cortisone, oral	25
Hydrocortisone, oral	20
Deflacort, oral	6
Prednisolone, oral	5
Prednisone, oral	5
Methylprednisolone	4
Triamcinolone, oral	4
Dexamethasone, oral	0.75
Betamethasone, oral	0.6

Note: For topically applied corticosteroids and intra-articular, subcutaneous, or ocular steroids, equivalent dose=0.

Cortisol (hydrocortisone) is the standard of comparison for glucocorticoid potency.

Hydrocortisone is the name used for pharmaceutical preparations of cortisol.

19.3 Suggested management guidelines for 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

19.4 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 subject (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 subject (minutes to several hours): systolic blood pressure of <90mmHg or >30% decrease from the subject's Baseline.

19.5 Protocol-specific clarification and extension of BILAG 2004 definitions

A quick 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. Please refer to this guide when completing disease activity assessments. Important extensions of selected BILAG 2004 glossary definitions are included as follows:

Protocol specific extensions of BILAG 2004 and SLEDAI-2K clinical parameter definitions:

a. BILAG 2004 A or B score in the musculoskeletal organ system due to active polyarthritis, defined as follows:

   – "BILAG 2004 A": severe arthritis (BILAG 2004 #41) manifested by observed active synovitis in ≥2 joints with marked loss of functional range of movements and significant impairment of basic activities of daily living (ADL), that has been present on several days cumulatively over the past 4 weeks, including at the time of the Screening Visit. Basic ADL are defined as the following activities which require assistance or assistive devices (at least 1 must be present and documented in source): ambulation, toileting, grooming including bathing, dressing, feeding oneself (not responsive to steroids up to 10mg/day, antimalarials, NSAIDs).

   – "BILAG 2004 B": moderate arthritis or tendonitis or tenosynovitis (BILAG 2004 #42) defined as tendonitis/tenosynovitis or active synovitis in ≥1 joint (observed or through history) with some loss of functional range of movements which leads to some loss of functional range of motion as manifested by effects on instrumental ADLs (such as cooking, driving, using the telephone or computer, shopping, cleaning, etc), which has been present on several days over the last 4 weeks and is present at the time of the Screening Visit.

b. BILAG 2004 and SLEDAI-2K "lupus headache": lupus headache is rare; migraine, tension or cluster headaches should not be recorded. Lupus headache should only be recorded if it is disabling, lasts at least 3 days, and does not respond to narcotics. It is expected that its severity would prompt formal testing (lumbar puncture, magnetic resonance imaging, computed tomography, etc) and require corticosteroids and/or immunosuppressants and potentially hospitalization for treatment. Lupus headache is considered a manifestation of lupus cerebritis.

19.6 Protocol Amendment 1

Rationale for the amendment

The primary objective for this amendment is to allow for qualitative subject interviews to be conducted by an experienced, external third party vendor and to allow for assessments of hsCRP at 4-week intervals and serum complement (C3 and C4) at Visit 14. Anti-DZP and anti-PEG antibody assessments have been removed from Visits 13 and 14 and additional text has been added. The inclusion of subjects who lack capacity to consent mentally or physically has been removed since some protocol assessments require mental and physical abilities. The eligibility of subjects with an overlap syndrome has been clarified. The protocol has also been updated according to the new UCB protocol template (for example, with the update of text regarding

PDILI); these changes were strictly template-driven. They do not reflect a change in the liver safety signal for DZP and are included only for alignment with updated standard Sponsor text across programs.

Modifications and changes

Global changes

"Drug Safety" was changed to "Patient Safety" to reflect the renaming of that functional group at UCB.

"International Conference on Harmonisation" was changed to "International Council for Harmonisation."

Minor stylistic and typographical changes were made for consistency within the document (eg, "the investigator" was changed to "the Investigator" at all occurrences).

Specific changes

The following table presents specific changes made with Amendment 1. This table does not include global changes unless they occur in other changed text.

Specific changes with SL0023 Amendment 1

Protocol section(s) impacted	Key components of previous text	Key components of amended text	Rationale
Study contact information	Sponsor UCB Biosciences Inc. 8010 Arco Corporate Drive, Ste 100 Raleigh, NC 27617 USA **Clinical Project Manager** [redacted] **Clinical Trial Biostatistician** [redacted] UCB BIOSCIENCES GmbH Alfred-Nobel-Str. 10 40789 Monheim GERMANY [redacted]	Sponsor UCB Biopharma SPRL Allée de la Recherche 60, 1070 Brussels, Belgium **Clinical Project Manager** [redacted] **Clinical Trail Biostatistician** [redacted] UCB Biosciences Inc. 8010 Arco Corporate Drive, Ste 100 Raleigh, NC 27617 USA [redacted]	Update to match title page. Update to reflect current contact information.
SAE reporting	**Email** **Global:** safetyreportingCDP7657@ucb.com (for interventional clinical studies)	**Email** **Global:** safetyreportingCDP7657@ucb.com	Removal of unnecessary information about interventional studies.
List of Abbre-viations	DS: Drug Safety ICH: International Conference on Harmonisation	PS: Patient Safety ICH: International Council for Harmonisation	Administrative update.
Table 5-2 and Sections 8.8 and 8.9	Assessment of anti-DZP and anti-PEG antibodies included at Visits 13 and 14.	Assessment of anti-DZP and anti-PEG antibodies removed/excluded from Visits 13 and 14.	Removal since extensive testing during the observation period no longer considered necessary.

Specific changes with SL0023 Amendment 1

Protocol section(s) impacted	Key components of previous text	Key components of amended text	Rationale
Table 5-2 and Section 8.9	No assessment of serum complement (C3, C4) included at V14.	Assessment of serum complement (C3, C4) added to V14.	Correction of omitted serum complement measurement needed for SLEDAI-2K calculation.
Table 5-2 and Sections 8.1, 8.3, 8.4, 8.6, 8.8, 8.9, and 8.11	No assessment of hsCRP included at V1, V3, V4, V6, V8, V9, V11, V14, or the Unscheduled Visit.	Assessment of hsCRP added to V1, V3, V4, V6, V8, V9, V11, V14, and the Unscheduled Visit (Section 8.11).	Alignment with other laboratory assessments of safety.
Section 6.1	1. An Institutional Review Board (IRB)/Independent Ethics Committee (IEC) approved written Informed Consent form is signed and dated by the subject or legal representative prior to the initiation of any study-specific assessment at Screening (Visit 1). 13. Female subjects of childbearing potential must agree to use a highly effective method of birth control during the study and for a period of 12 weeks after their final dose of study drug (ie, through completion of the SFU Period). Highly effective forms of birth control are methods which achieve a failure rate of less than 1% per year when used consistently and correctly. Highly effective methods of birth control include:	1a. An Institutional Review Board (IRB)/Independent Ethics Committee (IEC) approved written Informed Consent form is signed and dated by the subject prior to the initiation of any study-specific assessment at Screening (Visit 1). 13a. Female subjects of childbearing potential must agree to use a highly effective method of birth control during the study and for a period of 12 weeks after their final dose of study drug (ie, through completion of the SFU Period). Highly effective forms of birth control are methods which achieve a failure rate of less than 1% per year when used consistently and correctly. Highly effective methods of birth control include, but are not limited to:	Revision to not include subjects who lack capacity to consent mentally or physically since some protocol assessments require mental and physical abilities. Revision to provide clarity that the birth control methods are examples only.

Specific changes with SL0023 Amendment 1

Protocol section(s) impacted	Key components of previous text	Key components of amended text	Rationale
Section 6.2	5. Subject has a mixed connective tissue disease, scleroderma, and/or overlap syndromes of SLE. – Subjects with SLE and secondary Sjögren's syndrome are permitted provided they meet the eligibility criteria.	5a. Subject has a mixed connective tissue disease, scleroderma, and/or overlap syndromes of SLE. – Subjects with SLE and secondary Sjögren's syndrome are permitted provided they meet the eligibility criteria. – Clarification: Subjects with rheumatoid arthritis in their medical history are not considered as having an overlap syndrome and are thereby eligible, except when erosive arthritis is the only symptom at Screening.	Clarification provided for the eligibility of subjects with a medical history of rheumatoid arthritis.
Section 6.3	• Subject has potential drug-induced liver injury (PDILI), as described in Section 6.3.1.	Removed.	Update to UCB protocol template text.
Section 6.3	Investigators should attempt to obtain information on subjects in the case of withdrawal or discontinuation.	Investigators should attempt to obtain information on subjects in the case of withdrawal.	Update to UCB protocol template text.
Section 6.3.1	Header: PDILI-related withdrawal criteria To enable the effective management and assessment of any PDILI as outlined in the Food and Drug Administration (FDA) Guidance for Industry, Drug Induced Liver Injury: Premarketing Clinical Evaluation	Header: Potential drug-induced liver injury IMP discontinuation criteria Subjects with potential drug-induced liver injury (PDILI) must be assessed to determine if IMP must be discontinued. In addition, all concomitant medications and herbal	Update to UCB protocol template text. Sponsor language for monitoring of PDILI events added to increase clarity for the sites and to align across

Specific changes with SL0023 Amendment 1

Protocol section(s) impacted	Key components of previous text	Key components of amended text	Rationale
	(2009), UCB has developed prespecified criteria for managing any PDILI events and discontinuing IMP. Subjects with PDILI must have IMP discontinued. In addition, all concomitant medications and herbal supplements that are not medically necessary should also be discontinued. The following PDILI criteria require immediate and **permanent** discontinuation of IMP: Subjects with any of the following: • ALT and/or aspartate aminotransferase (AST) ≥8xULN • ALT and/or AST ≥3xULN and co-existing total bilirubin ≥2xULN The following PDILI criterion requires immediate discontinuation of IMP: • Subjects with ALT and/or AST ≥3xULN who exhibit a temporally associated fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever (without clear alternative cause), rash, or eosinophilia (ie, >5%) must be immediately discontinued from IMP. If a non-drug related cause for the symptoms	supplements that are not medically necessary should also be discontinued. The following PDILI criteria require immediate and **permanent** discontinuation of IMP: • Subjects with any of the following: – ALT or aspartate aminotransferase (AST) ≥8xULN – ALT or AST ≥3xULN and co-existing total bilirubin ≥2xULN The following PDILI criterion requires immediate discontinuation of IMP: • Subjects with ALT and/or AST ≥3xULN who exhibit temporally associated symptoms of hepatitis (excluding SLE-related hepatitis) or hypersensitivity. Hepatitis symptoms include fatigue, nausea, vomiting, right upper quadrant pain or tenderness. Hypersensitivity symptoms include fever (without clear alternative cause), rash, or eosinophilia (ie, >5%). If a non-drug related cause for the symptoms can be confirmed, these subjects may resume IMP administration after discussion with the	programs. (Exception: program-specific exclusion of lupus hepatitis from hepatitis symptoms requiring immediate discontinuation of IMP). The addition of PDILI language is to align with FDA guidance regarding monitoring of PDILI events and does not reflect a change in the liver safety signal for DZP.

Specific changes with SL0023 Amendment 1

Protocol section(s) impacted	Key components of previous text	Key components of amended text	Rationale
	can be confirmed, these subjects may resume IMP administration after discussion with the Medical Monitor. The following PDILI criteria allows for subjects to continue on IMP at the discretion of the investigator: • ALT and/or AST ≥3xULN (and ≥2x baseline) and <8xULN, total bilirubin <2XULN, and no eosinophilia (ie, ≤5%), with no fever, rash or symptoms of hepatitis (eg, fatigue, nausea, vomiting, right upper quadrant pain or tenderness) Monitoring and investigation of PDILI must be initiated as described in Section 13.7. If subjects are unable to comply with the applicable monitoring schedule, IMP must be discontinued immediately.	responsible UCB physician, but only when the requirements for rechallenge with IMP as provided in Section 13.7.2.1 are followed. The following PDILI criteria allows for subjects to continue on IMP at the discretion of the Investigator: • ALT or AST ≥3xULN (and ≥2x baseline) and <8xULN, total bilirubin <2xULN, and no eosinophilia (ie, ≤5%), with no fever, rash or symptoms of hepatitis (eg, fatigue, nausea, vomiting, right upper quadrant pain or tenderness) Evaluation of PDILI must be initiated as described in Section 13.7. If subjects are unable to comply with the applicable monitoring schedule, IMP must be discontinued immediately (see Section 8.10).	
Section 7.5	The Investigator (or designee) is responsible for the safe and proper storage of IMP at the site. Investigational medicinal product stored by the Investigator is to be kept in a secured area with limited access. Appropriate storage conditions will be specified on the label and in the Pharmacy Manual. A temperature log will be completed in accordance with local requirements on a regular basis (eg, once a week), showing	The Investigator (or designee) is responsible for the safe and proper storage of IMP at the site. Investigational medicinal product stored by the Investigator is to be kept in a secured area with limited access according to the storage conditions mentioned in the IMP Handling Manual. Appropriate storage condition must be ensured by controlled refrigerator temperature either	Update to UCB protocol template text and IMP Handling Manual.

Specific changes with SL0023 Amendment 1

Protocol section(s) impacted	Key components of previous text	Key components of amended text	Rationale
	minimum and maximum temperatures reached over the period of IMP storage in order to document that appropriate storage was maintained. In case an out-of-range temperature is noted, it must be immediately communicated to the unblinded Clinical Project Manager (CPM) (or designee) before further use of the IMP. The unblinded CPM (or designee) will transmit the out-of-range temperature (copy of the temperature log and duration of the out-of-range temperature, if available) to the Clinical Supply Manager. Based on discussion with a UCB Quality Assurance representative, the Clinical Supply Manager will then provide the unblinded CPM (or designee) with instructions for the site regarding use of the IMP. The PBO and other materials used during drug administration will be stored and handled per specific requirements of each material and site requirements.	using an automated temperature monitoring and recording system or by using a minimum/maximum thermometer and completing daily a temperature log in accordance with local requirements. Temperature data for IMP should be recorded on each working day with the actual and minimum/maximum temperatures reached during this period. In case an out-of-range temperature is noted, it must be immediately reported as per instructions contained in the IMP Handling Manual. The physiological saline [0/9% sodium chloride] used for administration should be handled per specific site requirements and stored according to label requirements.	

Specific changes with SL0023 Amendment 1

Protocol section(s) impacted	Key components of previous text	Key components of amended text	Rationale
Section 7.6	A Drug Accountability form will be used to record IMP dispensing and return information on a by-subject basis and will serve as source documentation during the course of the study. Details of any IMP lost (due to breakage or wastage), not used, disposed of at the study site, or returned to the Sponsor or designee must also be recorded on the appropriate forms. Periodically, and/or after completion of the clinical phase of the study, all used (including empty containers) and unused IMP vials must be reconciled and returned to UCB (or designee), preferably in their original package or destroyed at the site following local procedures.	A Drug Accountability form will be used to record IMP dispensing and return information on a by-subject basis and will serve as source documentation during the course of the study. Details of any IMP 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. Periodically, and/or after completion of the clinical phase of the study, all used (including empty containers)/partially used, unused, damaged, and/or expired IMP must be reconciled and either destroyed at the site according to local laws, regulations, and UCB SOPs or returned to UCB (or designee).	Update to UCB protocol template text.
Section 9.2.7	Qualitative subject interviews will be conducted by a study nurse/study personnel to collect the subject's experience with lupus in terms of symptoms and impact on daily activities, and the perceived changes during the course of the study. The extent to which the exploratory PRO items and scales used fully captured their experience will also be assessed.	Qualitative subject interviews will be conducted by an external third party vendor. The third party vendor will call the subject at home to collect the subject's experience with lupus in terms of symptoms and impact on daily activities, and the perceived changes during the course of the study. The extent to which the exploratory PRO items and scales used fully captured their experience will also be assessed.	Provision for collection of subject interviews by an external third party vendor with experience in such interviews.

Specific changes with SL0023 Amendment 1

Protocol section(s) impacted	Key components of previous text	Key components of amended text	Rationale
Section 11	Not applicable.	The detection of anti-DZP antibodies and anti-PEG antibodies will be done using validated methods. The details of analytical methods (including validation status) and results will be presented in the bioanalytical report.	Provide information about methodology and reporting.
Section 13.1.4	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 subject is lost to follow up.	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 subject is lost to follow up. This follow-up requirement applies to AEs, SAEs, and AEs of special interest; further details regarding follow-up of PDILI events are provided in Section 13.7. Information on SAEs obtained after clinical database lock will be captured through the PS database without limitation of time.	Update to UCB protocol template text.

Specific changes with SL0023 Amendment 1

Protocol section(s) impacted	Key components of previous text	Key components of amended text	Rationale
Section 13.1.8.1	Not applicable.	Header: Suspected transmission of an infectious 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 13.2); 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.	Update to UCB protocol template requirements.
Section 13.1.10	The subject should be withdrawn from the study as soon as pregnancy is known (by positive pregnancy test), and the following should be completed: • The IMP should be immediately discontinued. • The subject should return for an EWV. • The subject should complete the SFU Period per protocol.	The subject should be discontinued from the study drug as soon as pregnancy is known (by positive pregnancy test), and the following should be completed: • The IMP should be immediately discontinued. • The subject should complete the study per protocol.	Update to UCB protocol template text.

Specific changes with SL0023 Amendment 1

Protocol section(s) impacted	Key components of previous text	Key components of amended text	Rationale
Section 13.2.1	(Important medical events may include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.)	(Important medical events may include, but are not limited to, potential Hy's Law [see Section 13.3], allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.)	Update to UCB protocol template text.
Section 13.3	There are currently no AEs of special interest identified for DZP. Potential Hy's law, defined as ≥3xULN ALT and/or AST with coexisting ≥2xULN bilirubin in the absence of ≥2xULN ALP, with no alternative explanation for the biochemical abnormality, must ALWAYS be reported to UCB as an AE of special interest and a serious unexpected AE (ie, without waiting for any additional etiologic investigations to have been concluded).	There are currently no AEs of special interest identified for DZP; however, in accordance with the Sponsor's internal guidelines for all drugs in development, Potential Hy's Law is to be reported as an AE of special interest as follows: • Potential Hy's law, defined as ≥3xULN ALT or AST with coexisting ≥2xULN bilirubin in the absence of ≥2xULN ALP, with no alternative explanation for the biochemical abnormality, must ALWAYS be reported to UCB as an AE of special interest (ie, without waiting for any additional etiologic investigations to have been concluded).	Update to UCB protocol template text with clarification regarding reporting of Hy's law.
Section 13.4	• Suspected transmission of an infectious agent via a medicinal product	• Suspected transmission of an infectious agent via a medicinal product (see Section 13.1.8.1)	Provision of assistance in document navigation.

Specific changes with SL0023 Amendment 1

Protocol section(s) impacted	Key components of previous text	Key components of amended text	Rationale
Section 13.6	Not applicable.	Any presumptive diagnosis or diagnosis of a TB infection is a reportable event. Confirmed active TB must be reported as an SAE (Section 13.2.2). The Investigator is to complete and submit the TB follow-up form provided.	Restatement of requirements for reporting for additional emphasis.
Section 13.7	Section header: Investigation and monitoring of PDILI UCB has developed prespecified procedures for managing PDILI events that are consistent with the FDA Guidance for Industry, Drug Induced Liver Injury: Premarketing Clinical Evaluation (2009). All PDILI events must be reported as SAEs and reported to the Sponsor within 24 hours of learning of its occurrence. If a PDILI event meets the criteria for Hy's law (ie, ≥3xULN ALT and/or AST with coexisting ≥2xULN bilirubin in the absence of ≥2xULN ALP, with no alternative explanation for the biochemical abnormality), it must also be reported as an AE of special interest and a serious unexpected AE (ie, without waiting for any additional etiologic investigations to have been concluded) (see Section 13.3 on AEs of Special Interest, Hy's law). Table 13-2 summarizes the approach to investigate PDILI. Table 13-2: Required testing and follow up for	Section header: Evaluation of PDILI The PDILI IMP discontinuation criteria for this study are provided in Section 6.3.1, with the accompanying required follow-up investigation and monitoring detailed below. All PDILI events must be reported as an AE and reported to the study site and Sponsor within 24 hours of learning of their occurrence. Any PDILI event that meets the criterion for potential Hy's Law must be reported as an AE of special interest (see Section 13.3), and, if applicable, also reported as an SAE (see Section 13.2.2). If tests are done locally for more rapid results, a concurrent sample should also be sent to the central laboratory whenever possible. Medical care decisions are to be made initially using the most rapidly available results and a conservative approach must be taken if the results from the 2 laboratory tests are significantly different. Data from the local and central laboratory are to be recorded on the	Update to UCB protocol template text and table.

Specific changes with SL0023 Amendment 1

Protocol section(s) impacted	Key components of previous text	Key components of amended text	Rationale
	PDLI. Replaced. The table that was replaced is provided below.	applicable eCRF pages. When IMP is discontinued, all concomitant medications and herbal supplements that are not medically necessary should also be discontinued. In these cases, the Investigator should also consider dose reduction for medically necessary concomitant medication and consider changing any medically required concomitant medication known to be hepatotoxic to a suitable alternative. When IMP is stopped due to PDILI (as described in Section 6.3.1), IMP must be permanently discontinued unless a subsequent alternative diagnosis fully explains the hepatic findings. If a subsequent alternative diagnosis fully explains the hepatic findings, and the requirements provided in Section 13.7.2.1 are met, rechallenge with IMP may be appropriate. Rechallenge with a substance potentially causing drug-induced liver injury is dangerous, may be fatal, and must not occur. The table below summarizes the approach to investigate PDILI. Table 13-2: Required investigations and follow up for PDILI. Replacement added.	
Section 13.7.1	Section header: Consultation with local hepatologist and/or Sponsor Study Physician	Section header: Consultation with Medical Monitor and local hepatologist	Update to UCB protocol template.

Specific changes with SL0023 Amendment 1

Protocol section(s) impacted	Key components of previous text	Key components of amended text	Rationale
	All PDILI events, as detailed in Table 13-2, require the Investigator to consult with a local hepatologist and/or Sponsor Study Physician, as applicable, within 24 hours. The local hepatologist is the expert usually consulted by the treating physician for assessment and management of potential hepatic disease. This would usually be a hepatologist, but may be a gastroenterologist. If deemed necessary, this discussion should be followed by a full hepatology assessment (see Section 13.7.2) and updated SAE report.	Potential drug-induced liver injury events require notification of the Medical Monitor, within 24 hours (eg by laboratory alert), and the subject must be discussed with the Medical Monitor as soon as possible. If required, the subject must also be discussed with the local hepatologist. The local hepatologist is the expert usually consulted by the treating physician for assessment and management of potential hepatic disease. This would usually be a hepatologist, but may be a gastroenterologist. If determined necessary, this discussion should be followed by a full hepatology assessment (see Section 13.7.3) and SAE report (if applicable).	

Specific changes with SL0023 Amendment 1

Protocol section(s) impacted	Key components of previous text	Key components of amended text	Rationale
Section 13.7.2	Not applicable.	Header: Immediate action: determination of IMP discontinuation All PDILI events require immediate action, testing, and monitoring. The immediate action is dependent on the laboratory values and symptoms of hepatitis or hypersensitivity and ranges from continuation of IMP (followed by immediate investigation) to immediate and permanent discontinuation (see Section 6.3.1 and Table 13-2 for details). When IMP is discontinued, all concomitant medications and herbal supplements that are not medically necessary should also be discontinued. The Investigator should also consider dose reduction for medically necessary concomitant medication and consider changing any medically required concomitant medication known to be hepatotoxic to a suitable alternative.	Update to UCB protocol template.
Section 13.7.2.1	Not applicable.	Header: IMP restart/rechallenge (if applicable) Rechallenge with a substance potentially causing drug-induced liver injury is dangerous, may be fatal, and must not occur. Subjects who are immediately discontinued from IMP due to having met certain criteria for PDILI (as described in Section 6.3.1 and Table 13-2), but for whom an alternative diagnosis is confirmed, can rarely restart IMP. Rechallenge	Update to UCB protocol template.

Specific changes with SL0023 Amendment 1

Protocol section(s) impacted	Key components of previous text	Key components of amended text	Rationale
		with IMP can occur only if ALL of the following requirements are met: • The results of additional testing and monitoring described in Section 13.7.3 and Section 13.7.4 confirm a nondrug-related cause for the abnormal hepatic laboratory parameters and any associated symptoms (ie, a subsequent alternative diagnosis fully explains the hepatic findings). • No alternative treatment options are available to the subject. • The subject has shown clear therapeutic benefit from the IMP. • Subject's ALT or AST elevations do not exceed ≥3xULN. • Subject's total bilirubin is <1.5xULN. • Subject has no signs or symptoms of hypersensitivity. • The rechallenge is approved by the UCB responsible physician, DMC, and a hepatologist. The hepatologist must be external to UCB but may be a member of the DMC. It is recommended that the hepatologist be a local hepatology expert	

Specific changes with SL0023 Amendment 1

Protocol section(s) impacted	Key components of previous text	Key components of amended text	Rationale
		or the hepatologist treating the subject. • Subject agrees to the Investigator-recommended monitoring plan.	
Section 13.7.3 (original protocol Section 13.7.2)	Header: Immediate testing: identification/exclusion of alternative etiology The measurements and additional information required for the assessment of PDILI events when there is a reasonable possibility that it may have been caused by the study drug are detailed in Table 13-3 (laboratory measurements) and Table 13-4 (additional information). Results of the laboratory measurements and collection of information is to be collected and submitted to the Sponsor on the corresponding eCRF. If medical history of the subject indicates a requirement for other assessments not included below, these should be completed and submitted, as applicable. Table 13-3: Pancreatic amylase specified.	Header: Testing: identification/exclusion of alternative etiology The measurements and additional information required for the assessment of PDILI events when there is a reasonable possibility that it may have been caused by the IMP are detailed in Table 13-3 (laboratory measurements) and Table 13-4 (additional information). Results of the laboratory measurements and information collected are to be submitted to the Sponsor on the corresponding eCRF. If medical history of the subject indicates a requirement for other assessments not included below, these additional assessments should be completed and submitted, as applicable. All blood samples should be stored, if possible. If tests are done locally for more rapid results, a concurrent sample must also be sent to the central laboratory. Table 13-3: Prothombin time added to hematology assessments. Table 13-3: Pancreatic amylase changed to amylase. Table 13-3: The following added to the	Update to UCB protocol template.

Specific changes with SL0023 Amendment 1

Protocol section(s) impacted	Key components of previous text	Key components of amended text	Rationale
		abbreviation list: ALT=alanine aminotransferase Table 13-3: The following footnote ("a") added to prothrombin time: Measured only for subjects with ALT >8xULN, elevations in total bilirubin, and symptoms of hepatitis or hypersensitivity. Hepatitis symptoms include fatigue, nausea, vomiting, and right upper quadrant pain or tenderness; hypersensitivity symptoms include eosinophilia (>5%), rash, and fever (without clear alternative cause). Table 13-4: The following lead-in text added: "The following additional information is to be collected:"	
Section 13.7.4 (original protocol Section 13.7.3)	Header: Follow-up monitoring All PDILI events require follow-up monitoring as described in Table 13-3 Monitoring should continue until liver chemistry values normalize, stabilize, or return to baseline. Determination of stabilization is at the discretion of the Investigator in consultation with the hepatologist and study team.	Header: Follow-up evaluation All PDILI events require follow-up monitoring as described in Table 13-2. Monitoring should continue until liver chemistry values normalize, stabilize, or return to baseline. Determination of stabilization is at the discretion of the Investigator in consultation with the hepatologist (as applicable) and UCB responsible physician, as needed.	Update to UCB protocol template.

Specific changes with SL0023 Amendment 1

Protocol section(s) impacted	Key components of previous text	Key components of amended text	Rationale
Section 14.2.1	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 of eCRFs are not considered acceptable 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.	Update to UCB protocol template.
Section 15.1.6	The PK-PPS will consist of all subjects in the SS who are randomized to 1 of the DZP treatment arms, have provided at least 1 PK sample, and for whom no important protocol deviations affecting the PK variables have been documented.	The PK-PPS will consist of all subjects in the SS who have provided at least 1 PK sample and for whom no important protocol deviations affecting the PK variables have been documented.	Clarification regarding composition of the PK-PPS.
Section 15.3	For purposes of computing a SLEDAI-2K total score, in the case where the SLEDAI-2K assessment has been done yet individual items have been left blank, these individual items will be imputed from the previous visit value prior to computing the total score.	Deleted.	Remove repetition of information provided in Section 15.3.1.
Section 15.3.1	The primary efficacy variable is the responder rate at Week 24 across 3 doses of DZP and PBO according to a combined response index (BICLA); the analysis will use a modified nonresponder imputation (mNRI) for missing data.	The primary efficacy variable is the BICLA responder at Week 24 across 3 doses of DZP and PBO. The BICLA is a binary efficacy response variable, which is a composite endpoint derived from the efficacy components: BILAG 2004, SLEDAI-2K, and	Update to provide additional information about methodology.

Specific changes with SL0023 Amendment 1

Protocol section(s) impacted	Key components of previous text	Key components of amended text	Rationale
	If Visit 24 was done but the value for a single component (BILAG 2004, SLEDAI-2K, or Physician's Global Assessment of Disease) is not available, then the missing component value will be imputed from the previous visit value prior to computing the treatment response variable. In the case where a subject has a missing component, but already is known to have failed to achieve responder status on the basis of the nonmissing components (eg, SLEDAI-2K is missing but the nonmissing BILAG 2004 may not have demonstrated sufficient improvement), the missing value does not need to be imputed to know the subject's treatment response classification. Thus, imputation only has a role for those subjects who have data at Visit 24 with all observed components meeting their respective criterion for treatment response, and hence the imputed missing component will ultimately dictate whether or not the subject is classified as a responder. If the value at the previous visit is also missing, or if the subject has 2 or more missing components at the visit, then the treatment response value is considered to be unknown (ie, left as missing and subject to the missing data approach specific to the given analysis). In addition, subjects who discontinue treatment prematurely are primarily categorized as	the Physician's Global Assessment of Disease Activity. The BILAG 2004 and SLEDAI-2K are themselves composite endpoints comprising of multiple assessments of several organ systems affected by SLE. In addition, usage of specified concomitant medication as escape treatment is also a factor in determining BICLA responder status. See Section 9.1.9.1 for a complete description of the BICLA composite variable. Modified nonresponder imputation will be used to impute missing data, after applying additional rules within each component, which are further detailed as follows: If 1 of the 3 efficacy components (BILAG 2004, SLEDAI-2K, or Physician's Global Assessment of Disease) is missing, but the visit was performed and all other assessments were completed, the missing component will be imputed from the subject's previous post-baseline assessment, prior to computing the treatment response variable, following the last observation carried forward principle. Furthermore, for BILAG 2004 and SLEDAI-2K, if the assessment was done, but individual system or item scores are missing, the respective individual score will be imputed from the respective previous post-baseline score, in order to obtain a score for the current visit, prior to computing the system or score. If	

Specific changes with SL0023 Amendment 1

Protocol section(s) impacted	Key components of previous text	Key components of amended text	Rationale
	nonresponders. In any situation where a subject is known to be a nonresponder based on available data, imputation will not be performed for missing data required to determine treatment response status, since the subject is known to be a nonresponder regardless of the result of the missing assessment(s). The primary efficacy analysis will be tested across 3 doses of DZP and PBO using the Multiple Comparison Procedure–Modelling (MCP-Mod) methodology (Bretz et al, 2005). Monotonic dose-response trends will be tested using the appropriate contrasts as determined by the MCP-Mod methodology such that the overall Type 1 error rate is controlled at 0.05 (one-sided testing).	the value at the previous visit is also missing, or if the subject has 2 or more missing components at Week 24, then the treatment response value is considered to be unknown (ie, left as missing and therefore considered a nonresponder). In addition, subjects who discontinue treatment prematurely (while still remaining in the study) are primarily categorized as a nonresponder from that visit and all subsequent visits. The Week 24 BICLA dose-response relationship across 3 doses of DZP and PBO will be evaluated using the Multiple Comparison Procedure–Modelling (MCP-Mod) methodology (Bretz et al, 2005). Monotonic dose-response trends will be tested using the appropriate contrasts as determined by the MCP-Mod methodology such that the overall Type 1 error rate is controlled at 0.05 (one-sided testing). The SAP will describe additional features and detail around the MCP-Mod methodology as well as handling of missing data.	

Specific changes with SL0023 Amendment 1

Protocol section(s) impacted	Key components of previous text	Key components of amended text	Rationale
Section 16.1	Prior to participation in the study, the written Informed Consent form should be signed and personally dated by the subject, or his/her legal representative, and by the person who conducted the informed consent discussion (Investigator or designee). The subject or his/her legal representative must receive a copy of the signed and dated Informed Consent form. As part of the consent process, each subject must consent to direct access to his/her medical records for study-related monitoring, auditing, IRB/IEC review, and regulatory inspection.	Prior to participation in the study, the written Informed Consent form should be signed and personally dated by the subject, and by the person who conducted the informed consent discussion (Investigator or designee). The subject must receive a copy of the signed and dated Informed Consent form. As part of the consent process, each subject must consent to direct access to his/her medical records for study-related monitoring, auditing, IRB/IEC review, and regulatory inspection.	Update to UCB protocol template.
Section 16.2	Upon signing the Informed Consent and Assent form (as applicable), the subject or legal representative will be provided with a subject identification card in the language of the subject.	Upon signing the Informed Consent and Assent form (as applicable), the subject will be provided with a subject identification card in the language of the subject.	Update to UCB protocol template.

The following table from the original protocol has been replaced by Table 13-2 of Amendment 1 as noted in the specific changes for Section 13.7 above:

Original protocol Table 13-2: Required testing and follow up for PDILI

Lab value		Symptoms [a] of hepatitis or hypersensitivity	Consultation requirements	Additional immediate testing	Continued monitoring
ALT and/or AST	Bilirubin				
≥3xULN	NA	No	Subject must be discussed with the Sponsor Study Physician within 24h	Must have repeat liver chemistries and additional testing completed as soon as possible (see Section 13.7.2); recommended to occur within 24hrs at site or with HCP	Monitoring of liver chemistries required at least 2 times weekly until liver chemistries normalize, stabilize, or return to within baseline values. [d]
≥3xULN	NA	Yes	Hepatology [b] consult Subject must be discussed with the Sponsor Study Physician within 24h		
≥3xULN	≥2xULN [c]	N/A	Hepatology [b] consult Subject must be discussed with the Sponsor Study Physician within 24h		

ALP=alkaline phosphatase; ALT=alanine aminotransferase; AST= aspartate aminotransferase ; HCP=health care practitioner; NA=not applicable; PDILI=potential drug-induced liver injury; ULN=upper limit of normal

[a] Hepatitis symptoms include fatigue, nausea, vomiting, and right upper quadrant pain or tenderness; hypersensitivity symptoms include eosinophilia (>5%), rash, fever (without clear alternative cause).

[b] Details provided in Section 13.7.1. The local hepatologist is the expert usually consulted by the treating physician for assessment and management of potential hepatic disease. This would usually be a hepatologist, but may be a gastroenterologist.

[c] If the subject also has ≥2xULN ALP, the possibility of an indication of biliary obstruction should be discussed with the Sponsor Study Physician.

[d] Unless an alternative monitoring schedule is agreed by the Investigator and Sponsor Study Physician. Determination of stabilization is at the discretion of the Investigator in consultation with the hepatologist and study team.

20 DECLARATION AND SIGNATURE OF INVESTIGATOR

I confirm that I have carefully read and understood this protocol and agree to conduct this clinical study as outlined in this protocol, according to current Good Clinical Practice and local laws and requirements.

I will ensure that all subinvestigators and other staff members read and understand all aspects of this protocol.

I have received and read all study-related information provided to me.

The objectives and content of this protocol as well as the results deriving from it will be treated confidentially, and will not be made available to third parties without prior authorization by UCB.

All rights of publication of the results reside with UCB, unless other agreements were made in a separate contract.

Investigator:

Printed name Date/Signature

21 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.

SL0023 Protocol Amendment 1

ELECTRONIC SIGNATURES

Signed by	Meaning of Signature	Server Approval Date (dd-mon-yyyy (HH:mm))
[redacted]	Clinical Approval	15-Dec-2016 13:40 GMT+01
[redacted]	Clinical Approval	16-Dec-2016 23:17 GMT+01