AN OPEN-LABEL EXTENSION STUDY TO EVALUATE THE LONG-TERM SAFETY AND TOLERABILITY OF DAXDILIMAB (HZN-7734) IN SUBJECTS WITH SYSTEMIC LUPUS ERYTHEMATOSUS

SHORT TITLE: RECAST SLE OLE

Investigational Product	daxdilimab (also known as HZN-7734 and VIB7734); an anti-ILT7 monoclonal antibody for depletion of plasmacytoid dendritic cells
Protocol Number	HZNP-DAX-204
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PROTOCOL VERSION HISTORY

Version/Date	Rationale for amendment	Main changes to the protocol
1.0/17Mar2022	Initial version	N/A

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[redacted]

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STATEMENT OF COMPLIANCE

The study will be conducted in compliance with this clinical study protocol, Good Clinical Practice (GCP) as outlined by International Council for Harmonisation (ICH) E6(R2), and all applicable local and national regulatory requirements. Enrollment at any clinical study site may not begin prior to that site receiving approval from the ethics committee of record for the protocol and all materials provided to potential participants.

Any amendments to the protocol or changes to the consent document will be approved before implementation of that amendment. Reconsent of previously enrolled participants may be necessary depending on the nature of the amendment.

The Principal Investigator will ensure that changes to the study plan as defined by this protocol will not be made without prior agreement from the Sponsor and documented approval from the ethics committee of record, unless such a change is necessary to eliminate an immediate hazard to the study participants.

All personnel involved in the conduct of this study have completed Human Subjects Protection and GCP Training.

SIGNATURE PAGE

The signatures below constitute the approval of this protocol and provide the necessary assurances that this clinical study will be conducted according to this protocol, applicable local regulations, and ICH GCP guidelines.

Name	Title	Signature and Date (DD-MMM-YYYY)
[redacted], MD	Executive Medical Director Horizon Therapeutics	DocuSigned by: [redacted] Signer Name: [redacted] Signing Reason: I approve this document Signing Time: 17-Mar-2022 | 17:29 CDT [redacted]B48A8AE7BF3AC7D639383
[redacted], PhD	Sr. Director, Biostatistics, Biometrics Horizon Therapeutics	[redacted] Signer Name: [redacted] Signing Reason: I approve this document Signing Time: 17-Mar-2022 | 17:51 CDT 94348E43E05145848D3DCFDE0A20F5C3

PRINCIPAL/QUALIFIED INVESTIGATOR SIGNATURE PAGE

Investigator Name: _____

Signature: _____ **Date:** _____
(DD-MMM-YYYY)

Institution Name: _____

By my signature, I agree to personally supervise the conduct of this study at my study site and to ensure its conduct in accordance with the ethical principles that have their origin in the Declaration of Helsinki and in compliance with the protocol, informed consent, institutional review board/independent ethics committee procedures, instructions from Sponsor's representatives, ICH GCP guidelines, and applicable local regulations governing the conduct of clinical studies.

LIST OF ABBREVIATIONS

Abbreviation	Definition
21 CFR	Title 21 of the Code of Federal Regulations
ACTH	adrenocorticotropic hormone
ADA	Anti-drug antibodies
AE(s)	adverse event(s)
AESI	adverse event of special interest
ALT	alanine aminotransferase
ANA	antinuclear antibodies
AST	aspartate aminotransferase
AZA	azathioprine
BICLA	BILAG-based Composite Lupus Assessment
BILAG	British Isles Lupus Assessment Group
CD	cluster of differentiation
CDM	Clinical Data Management
[redacted]	
CLE	cutaneous lupus erythematosus
CNS	central nervous system
COVID-19	coronavirus disease 2019
CRF(s)	case report form(s)
CRO	clinical research organization
CTCAE	Common Terminology for Adverse Events
DC(s)	dendritic cell(s)
DMP	Data Management Plan
dsDNA	double-stranded DNA
ECG(s)	electrocardiogram(s)
eCRF(s)	electronic case report form(s)
ET	early termination
FDA	Food and Drug Administration
FSH	follicle-stimulating hormone
GCs	glucocorticoids
GCP	Good Clinical Practice(s)
GLP	Good Laboratory Practice

Abbreviation	Definition
HL	Hy's Law
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Council for Harmonisation
IEC(s)	Independent Ethics Committee(s)
IFN	interferon
Ig	immunoglobulin
IP	investigational product
IRB(s)	Institutional Review Board(s)
IV	intravenous(ly)
LN	lupus nephritis
mAb(s)	monoclonal antibody(ies)
MAD	multiple-ascending dose
MCP	metacarpophalangeal
MMF	mycophenolate mofetil
MPA	mycophenolic acid
[redacted]	
mTOR	mammalian target of rapamycin
MTX	methotrexate
NSAID(s)	nonsteroidal anti-inflammatory drug(s)
NK	natural killer
OGC(s)	oral glucocorticoid(s)
OLE	open-label extension
OTC	over the counter
PD	pharmacodynamic(s)
pDC(s)	plasmacytoid dendritic cell(s)
PEF	peak expiratory function
[redacted]	
PHL	Potential Hy's Law
PI	Principal Investigator
PIP	proximal interphalangeal
PK	pharmacokinetic(s)
PRN	as needed
PT	preferred term

Abbreviation	Definition
PtGA	Patient Global Assessment
Q4W	every 4 weeks
Q12W	every 12 weeks
SAD	single-ascending dose
SAE(s)	serious adverse event(s)
SAP	statistical analysis plan
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SC	subcutaneous(ly)
[redacted]	[redacted]
SDMC	Safety Data Monitoring Committee
SELENA	Safety of Estrogens in Lupus Erythematosus National Assessment
SFU	safety follow-up
SID	subject identifier
SLE	systemic lupus erythematosus
[redacted]	[redacted]
[redacted]	[redacted]
SoA	schedule of assessments
SOC	system organ class
TBL	total bilirubin
TEAE	treatment-emergent adverse event
TLR(s)	toll-like receptor(s)
ULN	upper limit of normal
US	United States

1 PROTOCOL SUMMARY

1.1 Synopsis

Protocol Title:

An Open-label Extension Study to Evaluate the Long-term Safety and Tolerability of Daxdilimab (HZN-7734) in Subjects with Systemic Lupus Erythematosus

Short Title:

RECAST SLE OLE

Rationale:

Daxdilimab (previously known as HZN-7734 or VIB7734) is being developed for the treatment of multiple autoimmune disorders in which plasmacytoid dendritic cells (pDCs) are believed to contribute to the pathogenesis including alopecia areata, dermatomyositis, discoid lupus erythematosus, lupus nephritis, and systemic lupus erythematosus (SLE). This is a Phase 2, multicenter, open-label extension (OLE) study to evaluate the long-term safety and tolerability of daxdilimab in subjects completing the treatment period of the RECAST SLE clinical study. Based on its mechanism of action, daxdilimab has the potential to decrease SLE disease activity. In addition, based on data currently available, daxdilimab presents an acceptable safety profile; therefore, it is justified to evaluate its long-term safety, pharmacokinetics (PK), and immunogenicity in subjects with active SLE, prior to advancing daxdilimab into larger clinical studies.

Objectives and Endpoints:

The primary and secondary objectives and associated endpoints are detailed below. For tertiary/exploratory objectives and endpoints, see Section 3 of this protocol.

Table S1 Primary and Secondary Objectives

Objectives	Endpoints
Primary Objective	
To evaluate the long-term safety and tolerability of 200 mg Q12W daxdilimab	Incidence of AEs, SAEs, and AESIs
Secondary Objectives	
To characterize the PK, PD, and immunogenicity of daxdilimab	Daxdilimab concentration, change in pDCs, and ADA rate

ADA = anti-drug antibody; AEs = adverse events; AESIs = adverse events of special interest; PD = pharmacodynamics; pDCs = plasmacytoid dendritic cells; PK = pharmacokinetics; Q12W = every 12 weeks; SAEs = serious adverse events

Overall Design:

This is a Phase 2, multicenter, OLE study to evaluate the long-term safety and tolerability of daxdilimab in subjects completing the treatment period of the RECAST SLE clinical study.

Once a subject has completed the treatment period (through Week 48) of the RECAST SLE study, signed the informed consent form, and met all study eligibility criteria, he/she may be enrolled in this OLE study. To allow for the continuous dosing of the subjects, the start of this OLE study should occur immediately after the completion of the RECAST SLE treatment period (ie, first OLE dosing [Day 1] coinciding with Week 48/Visit 14 of the RECAST SLE study). Any exceptions to this enrollment date must be reviewed and approved by the Medical Monitor before any subject is allowed to enroll after the Week 48/Visit 14 of the RECAST SLE study.

Subjects will be treated with open-label daxdilimab 200 mg at the study site every 12 weeks (Q12W) subcutaneously (SC) for 48 weeks. During the treatment period, a telehealth visit (eg, phone or video call) will also be performed every 4 weeks between in-clinic visits to assess the subject's current disease status, the OGC tapering schedule, safety, and concomitant medications. After the treatment period (Week 0 to Week 48), the study subjects will enter an 8-week safety follow-up period (Week 48 to Week 56).

The primary objective of this study is to evaluate the long-term safety and tolerability of 200 mg daxdilimab Q12W in adult subjects with moderately-to-severely active SLE. This will be assessed by summarizing adverse events (AEs), serious adverse events (SAEs), and AEs of special interest (AESIs). Local injection site tolerability, vital signs, physical examinations, electrocardiograms, and clinical laboratory tests will also be performed to support safety findings.

The study will be conducted on an outpatient basis. For all administrations, daxdilimab will be administered by study-site staff in the clinic, and the subject will be observed for at least 60 minutes after the first and second doses (Day 1 and Week 12) are administered to each subject.

Blood samples will be collected from all subjects to characterize the PK, pharmacodynamics, and immunogenicity of daxdilimab.

Number of Subjects:

Approximately 195 subjects have been randomized in the RECAST SLE study. Assuming that 20% of subjects will prematurely discontinue treatment, there will be a total of approximately 156 subjects who will be eligible for this long-term safety study.

Note: *Enrolled* means subjects, 'or their legally acceptable representatives', agreement to participate in a clinical study following completion of the informed consent process and eligibility review. Potential subjects who are screened for the purpose of determining eligibility for the study, but do not participate in the study, are not considered enrolled, unless otherwise specified by the protocol. A subject will be considered enrolled if the informed consent is not withdrawn prior to participating in any study activity after eligibility review.

Intervention Groups and Duration

Subjects will receive 200 mg daxdilimab Q12W for 48 weeks (Weeks 0 [Day 1], 12, 24, 36, and 48). Following the final dose administration at Week 48, subjects will be followed up for an additional 8 weeks for a total study duration of approximately 56 weeks.

Investigational Product: Dosage and Mode of Administration

The investigational product (IP) is daxdilimab. Daxdilimab will be provided as a sterile liquid in a 2R glass vial with a nominal 1.0 mL of 100 mg/mL daxdilimab. Daxdilimab drug product is stored at 2°C to 8°C in a refrigerator with adequate temperature monitoring in a location with limited access.

Daxdilimab is to be administered as two 1.0-mL SC injections.

Visit Frequency

The study will be conducted on an outpatient basis. For scheduled study visits, subjects will come to the study sites on 7 occasions: Weeks 0 [Day 1], 12, 24, 36, 48, 52, and 56. For all IP administrations, daxdilimab will be administered by study-site staff at the study site. Subjects will also attend telehealth visits (phone or video call) on 8 occasions: Weeks 4, 8, 16, 20, 28, 32, 40, and 44.

- Study duration: approximately 56 weeks
- Treatment duration and frequency: 48 weeks with in-clinic visits Q12W and telehealth visits Q4W between in-clinic visits
- Follow-up duration and frequency: 8 weeks with 2 visits 4 weeks apart

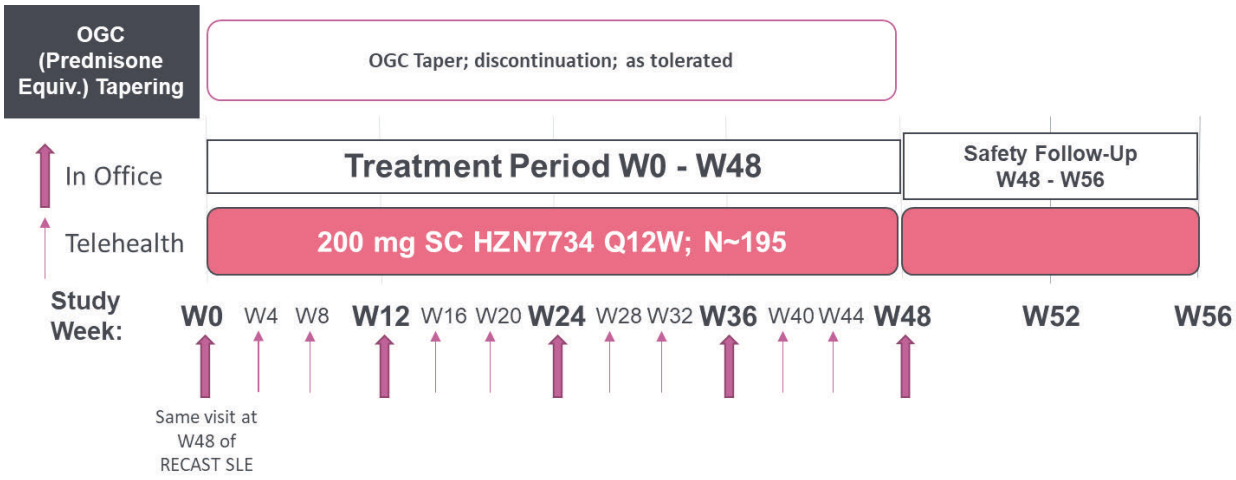
Data Monitoring/Other Committee:

An external, independent Safety Data Monitoring Committee (SDMC) is responsible for safeguarding the interests of study subjects via review of accumulating safety data and for supporting study integrity and interpretability based on their review of ongoing study conduct. The SDMC will provide the Sponsor with recommendations for actions with respect to study conduct and the management of subjects treated under the study protocol. The SDMC members are independent of the Sponsor and any clinical research organization or organization collaborating with the Sponsor on the study.

The SDMC will not be charged with any formal interim analysis, will not conduct a futility analysis, and will not be asked to consider early study completion for efficacy. For additional details, refer to the SDMC Charter.

1.2 Schema

Figure 1 Clinical Study Diagram



equiv. = equivalent; HZN7734 = also known as daxdilimab (previously VIB7734 or HZN-7734); N = number of subjects; OGC = oral glucocorticoid; Q12W = every 12 weeks; RECAST SLE = Phase 2 **R**andomized, Double-Blind, Placebo-Controlled **E**ffi**ca**cy and **S**afety Study of Daxdilimab for the **T**reatment of Moderate to Severely Active **S**ystemic **L**upus **E**rythematosus; SC = subcutaneous(ly); W = week.

1.3 Schedule of Activities

The tests and assessments to be conducted during the study and the timing for such tests/assessments are provided in Table 1.

Table 1 Schedule of Activities

	Treatment									Follow-Up	
Study Day	**1**	**29/57**	**85**	**113/141**	**169**	**197/225**	**253**	**281/309**	**337**	**365**	**393**
Week (window)	**0**	**4/8 (± 3 d)**	**12 (± 7 d)**	**16/20 (± 3 d)**	**24 (± 7 d)**	**28/32 (± 3 d)**	**36 (± 7 d)**	**40/44 (± 3 d)**	**48/ET (± 7 d)**	**52 (± 7 d)**	**56 (± 7 d)**
Procedure/Visit Number	**V1** [a]	**V2/V3** [b]	**V4**	**V5/V6** [b]	**V7**	**V8/V9** [b]	**V10**	**V11/V12** [b]	**V13**	**V14**	**V15**
General Assessments/Procedures											
ICF	X										
Eligibility review	X										
Review medical history and add any AEs/SAEs/AESIs from RECAST SLE (if appropriate)	X										
12-lead ECG (after 10 minutes rest in supine position) [c]	X				X				X		X
Vital signs and weight [d]	X		X		X		X		X	X	X
Physical examination [e]	X		X		X		X		X	X	X
[redacted]											
Laboratory Assessments											
Urine pregnancy test (in women of childbearing potential)	X		X		X		X		X	X	X
FSH [g]	X										
Hepatitis B DNA testing [h]	X		X		X		X		X		X
Routine hematology and chemistry	X		X		X		X		X	X	X
HbAlc	X				X				X		X

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Study Day	**1**	**29/57**	**85**	**113/141**	**169**	**197/225**	**253**	**281/309**	**337**	**365**	**393**
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Procedure/Visit Number	**V1** [a]	**V2/V3** [b]	**V4**	**V5/V6** [b]	**V7**	**V8/V9** [b]	**V10**	**V11/V12** [b]	**V13**	**V14**	**V15**
Lipids (after an 8-hour fast; water allowed) [i]	X				X				X		
Urinalysis and spot UPCr [j]	X		X		X		X		X	X	X
Confirmatory tests for hemolytic anemia [k]	X		X		X		X		X	X	X
C3 and C4	X		X		X		X		X	X	X
Anti-dsDNA antibodies	X		X		X		X		X	X	X
Anti-Smith antibodies	X								X		
ANA, anti-RNP, anti-SSA, anti-SSB, rheumatoid factor	X [l]								X		
PT/INR and PTT	X		X		X		X		X		X
Serum IgG, IgA, IgM	X		X		X		X		X		X
Serum IFNα	X		X		X		X		X		X
hs-CRP	X		X		X		X		X	X	X
pDC FACS	X		X		X		X		X		X
[redacted]											
Blood MxA	X				X				X		X
Daxdilimab PK (serum)	X		X		X		X		X		X
Daxdilimab ADA	X		X		X		X		X		X

Table 1 Schedule of Activities

	Treatment									Follow-Up	
Study Day	**1**	**29/57**	**85**	**113/141**	**169**	**197/225**	**253**	**281/309**	**337**	**365**	**393**
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Procedure/Visit Number	**V1 [a]**	**V2/V3 [b]**	**V4**	**V5/V6 [b]**	**V7**	**V8/V9 [b]**	**V10**	**V11/V12 [b]**	**V13**	**V14**	**V15**
Questionnaires [m]											
PtGA	X		X		X		X		X		X
PGIC	X		X		X		X		X		X
[redacted]	[redacted]		[redacted]		[redacted]		[redacted]		[redacted]		[redacted]
Investigational Product Administration											
IP administration	X		X		X		X		X		
Safety											
Steroid Taper Discussion	X	X	X	X	X	X	X	X			
Local injection tolerability	X		X		X		X		X		
Concomitant medications	X	X	X	X	X	X	X	X	X	X	X
AEs, SAEs, and/or AESIs	X	X	X	X	X	X	X	X	X	X	X

ADA = anti-drug antibody(ies); AEs = adverse events; AESI = adverse events of special interest; ANA = antinuclear antibodies; C = complement; [redacted] d = days; dsDNA = double-stranded DNA; ECG = electrocardiogram; ET = early termination; FACS = fluorescence-activated cell sorting; FSH = follicle-stimulating hormone; HbA1c = glycated hemoglobin A1c; HBV = hepatitis B virus; hs-CRP = high-sensitivity C reactive protein; ICF = informed consent form; IFNα = interferon alfa; Ig = immunoglobulin; INR = international normalized ratio; IP = investigational product; LLOQ = lower limit of quantitation; [redacted]; MxA = myxovirus resistance protein; [redacted]; pDC = plasmacytoid dendritic cell; [redacted] PK = pharmacokinetics; PT = prothrombin time; PtGA = Patient Global Assessment; PTT = partial thromboplastin time; RECAST SLE = Phase 2 **R**andomized, Double-Blind, Placebo-Controlled **Effi**cacy and **S**afety Study of Daxdilimab for the **T**reatment of Moderate to Severely Active **S**ystemic **L**upus **E**rythematosus; RNP = ribonucleoprotein; SAEs = serious adverse events; [redacted] SLE = systemic lupus erythematosus; [redacted] SSB = Sjögren's syndrome-related antibody B; UPCr = urine protein:creatinine ratio; V = visit

a Any procedure that is also completed on RECAST SLE V14 (if performed on the same day as V1 for this study should be utilized for this study and not repeated (Section 5.5).

b Visits 2, 3, 5, 6, 8, 9, 11, and 12 are telehealth visits (eg, phone or video call) (Section 8.1).

c ECGs should be performed after vital signs are collected (Section 8.3.3).
d Vital signs include systolic and diastolic blood pressure obtained after at least 5 minutes at rest in a seated position, heart rate, respiratory rate (breaths/min), and body temperature (Section 8.3.2).
e A full physical examination should be performed at Visit 1 and Visit 13. A focused physical examination will be performed at all other in-clinic visits, and these should always include assessment of head, ears, eyes, nose, throat, lungs, heart, abdomen, skin, and extremities (Section 8.3.1).
f Additional assessments, (eg, ECG or chest X-ray) should be performed as needed to fully obtain information needed for the [redacted]
g This test is conditional and can be performed at any in-clinic visit throughout the study if a female subject becomes postmenopausal during the OLE study (ie, 12 months with no menses without an alternative medical cause, unless on postmenopausal hormone replacement therapy) (Section 5.1).
h Reflex DNA testing if isolated hepatitis B core positive in RECAST SLE (Section 8.3.5.1). Investigational product will be discontinued if the subject's HBV DNA levels are confirmed to exceed the LLOQ as per the central laboratory.
i This visit is recommended to occur in the morning.
j Aim to collect urine at the same time of day, if possible. Urine collection can be postponed for up to 14 days in women with menstrual bleeding or a urinary tract infection at the scheduled visit.
k Serum aliquots will be used if needed to confirm suspected hemolytic anemia.
l ANA only
m Questionnaires are strongly recommended to be completed before any other procedures are performed (Section 8.10).

2 INTRODUCTION

2.1 Study Rationale

In the absence of exogenous triggers, dendritic cells (DCs) contribute to the clearance of dying cells and the maintenance of tolerance (Klarquist et al, 2016; Huang et al, 2015). However, during infection or in the context of autoimmunity, DCs play a key role in activating cluster of differentiation (CD)4 and CD8 T cells. Plasmacytoid DCs (pDCs) are also known for their capacity to produce vast amounts of interferon alpha (IFNα) via engagement of toll-like receptors (TLRs) in response to viruses, including virus-derived nucleic acids, and in response to lupus-related, nucleic acid-containing immune complexes (Siegal et al, 1999). While pDCs from healthy donors have been shown to induce suppressive T-regulatory cell features (Foxp3 expression) in vitro, systemic lupus erythematosus (SLE) pDCs failed to do so (Jin et al, 2010). In mouse models, constitutive depletion of pDCs in lupus-prone mice resulted in markedly reduced type I IFN production, a reduced IFN signature, reduced autoantibody production, and reduction in the severity of kidney pathology glomerulonephritis (Rowland et al, 2014). Importantly, transient pDC depletion during the early stages of disease was sufficient to significantly alter the course of the disease, suggesting a more prominent role for pDCs in the induction of the disease than in disease pathogenesis at later stages of disease (Rowland et al, 2014). Recent data from Phase 2 and Phase 3 studies with IFNα pathway-blocking agents (sifalimumab and anifrolumab) as well as another pDC antagonist (BIIB059) demonstrated improvement in SLE or cutaneous lupus disease activity, further supporting the rationale for blocking the IFN pathway and pDCs in patients with SLE (Furie et al, 2017; Furie et al, March 2019; Furie et al, November 2019; Khamashta et al, 2016; Morand et al, 2020; Werth et al, 2020).

Altogether, given the lack of highly efficacious and safe treatments for active SLE and the significant impact of this disease on health-related quality of life, in part from SLE-associated fatigue, cognitive dysfunction, and mood disorders, there is currently a significant unmet need for new targeted therapies.

Based on its mechanism of action (Section 2.2.3), daxdilimab has the potential to decrease SLE disease activity. In addition, based on data currently available, daxdilimab presents an acceptable safety profile; therefore, it is justified to evaluate its long-term safety, pharmacokinetics (PK), and immunogenicity in subjects with active SLE, prior to advancing daxdilimab into larger clinical studies.

The RECAST SLE study (VIB7734.P2.S1) is a Phase 2 randomized, double-blind, placebo-controlled efficacy and safety study of daxdilimab for the treatment of moderately-to-severely active systemic SLE. The study is enrolling approximately up 195 subjects. The SLE open-label extension (OLE) study (HZN-DAX-204) is a long-term OLE study of daxdilimab plus standard of care in subjects who complete the treatment period of the RECAST SLE protocol. Irrespective of their assigned treatment in the RECAST SLE study, all subjects participating in the OLE will be treated with daxdilimab subcutaneously (SC) every 12 weeks (Q12W) in addition to their standard-of-care SLE therapy.

2.2 Background

2.2.1 Systemic Lupus Erythematosus

Clinical Presentation

Systemic lupus erythematosus is an autoimmune disease that affects multiple organ systems and is unpredictable in disease severity, with periods of illness or flares alternating with periods of remission. The diverse presentation of lupus can range from rash and arthritis; anemia and thrombocytopenia; to serositis, nephritis, seizures, and psychosis. At its onset, SLE may involve one or more organ systems, including the musculoskeletal, cutaneous, vascular, renal, pulmonary, hematological, and nervous systems. Additional manifestations may occur over time. Disease prevalence is approximately one in 1000 individuals overall but varies with race and ethnicity. Systemic lupus erythematosus is more common in women than in men (9:1 ratio), and is more common in African American, African Caribbean, Hispanic, and Asian populations than Caucasians (Helmick et al 2008; Feldman et al, 2013). Onset in women typically occurs during their childbearing years. Patients with SLE rate their health-related quality of life as significantly worse than patients with common chronic diseases, such as hypertension and diabetes (Jolly, 2005), and they are chronically exposed to medication with significant side effects, such as, glucocorticoids (GCs) (typically prednisone or prednisolone) and immunosuppressive agents (King and Hahn, 2007). Fatigue, cognitive dysfunction, and depressed mood and anxiety are frequent debilitating comorbidities in patients with SLE and are associated with decreased health-related quality of life (Yurkovich et al, 2014; Saphnelo® USPI, 2021; Holloway et al, 2014; Lateef and Petri, 2012; Palagini et al, 2013).

Pathogenesis and Pathology

The pathogenesis of SLE is based on mechanisms that lead to loss of tolerance against nuclear autoantigens (Liu and Anders, 2014). Systemic lupus erythematosus develops when autoimmunization occurs against nuclear autoantigens (eg, by impairing lymphocyte depletion via apoptosis, opsonization, and rapid phagocytic clearance). Subsequently, endogenous nucleic acids directly activate TLRs on DCs or B cells that in turn drive IFNα-driven immunity, antigen presentation, and the activation of autoreactive lymphocyte subsets. Activation of B cells and their maturation to plasma cells promotes autoantibody production. Complement activation and proinflammatory cytokines drive the inflammatory process that can cause organ injury, scarring, and chronic disease.

The production of autoantibodies to a variety of nuclear antigens is a hallmark of SLE that accounts for some of the pathological findings (Rahman and Isenberg, 2008; Jimenez et al, 2003; Petri et al, 2009). Serologically, a series of these autoantibodies are used routinely in clinical practice to further characterize the disease and risk for potential manifestations. These include antinuclear antibodies (ANA), as well as anti-double-stranded DNA (dsDNA), anti-Ro (anti-Sjögren's syndrome-related antibody A), anti–La (anti-Sjögren's syndrome-related antibody B), anti-Smith, anti-ribonucleoprotein, and anti-ribosomal P antibodies. Histological results have shown association between the presence of autoantibodies and tissue damage. Levels of anti-dsDNA antibodies have been shown to be highly specific for SLE, correlate with disease activity, and may be correlated with renal involvement.

2.2.2 Unmet Need

Glucocorticoids remain a therapeutic mainstay for short- and long-term control of disease activity in SLE and lupus nephritis (LN) and are often administered in combination with chloroquine derivatives (ie, antimalarials, including hydroxychloroquine sulfate) and immunosuppressants (eg, mycophenolate mofetil [MMF], methotrexate [MTX], azathioprine [AZA], cyclophosphamide, and cyclosporine) (King and Hahn, 2007; Petri, 2006). The chloroquine derivatives are of moderate effectiveness and may prevent flares, though breakthrough flares occur frequently, while the toxicity of the more aggressive drug regimens for SLE contributes significantly to morbidity and mortality (King and Hahn, 2007; Petri, 2006; Ruiz-Arruza et al, 2014; Doria et al, 2014).

Recently, more targeted therapies (ie, monoclonal antibodies [mAbs]), have been used in the treatment of SLE. Inhibition of B-lymphocyte stimulator (also known as B-cell activating factor of the tumor necrosis factor family) with belimumab (Benlysta®) was shown to be safe and effective for SLE treatment (Furie et al, 2011; Navarra et al, 2011). Belimumab was approved in United States (US) by the Food and Drug Administration (FDA) in 2011 and in Canada and Europe for treatment of SLE. Belimumab with standard of care demonstrated an increased rate of treatment response in SLE subjects compared to those receiving placebo and standard of care. In addition, results suggested that there was a reduced likelihood of severe flares and reduction in GC doses. However, approximately 50% of the subjects did not respond with a decrease in SLE activity when treated with belimumab. Another mAb, anifrolumab-fnia (Saphnelo®), which binds to subunit 1 of the type I IFN receptor, was approved in US by the FDA in 2021 for the treatment of adult patients with moderate to severe SLE who are receiving standard-of-care therapy (Saphnelo® USPI, 2021). In the first Phase 3 study with anifrolumab (TULIP-1), a reduction in oral corticosteroid dose and Cutaneous Lupus Erythematosus Disease Area and Severity Index (CLASI) activity scores and the achievement of British Isles Lupus Assessment Group (BILAG)-based Composite Lupus Assessment (BICLA) responses suggested a clinical benefit for subjects treated with anifrolumab (Furie et al, November 2019). The second Phase 3 study with anifrolumab (TULIP-2) also showed a difference in BICLA response between anifrolumab and placebo groups (Morand et al, 2020). However, the percentage of anifrolumab-treated subjects who had a BICLA response or a reduction in CLASI activity score of at least 50% in either study was below 50% (Furie et al, November 2019; Morand et al, 2020).

Therefore, there is a very high unmet medical need for novel, targeted therapies with improved efficacy and benefit-risk ratio.

2.2.3 Daxdilimab

Daxdilimab is a human immunoglobulin (Ig)G1κ afucosylated mAb specific for human ILT7, a cell surface protein expressed by pDCs (Cho et al, 2008; Karnell et al, 2021; Rissoan et al, 2002). Daxdilimab binding to ILT7 on the surface of pDCs leads to recruitment of macrophages and natural killer (NK) cells, thus inducing apoptosis and reducing the number of pDCs. The afucosylation of daxdilimab is designed to improve the in-life potency of the molecule and to enhance the capacity for antibody-dependent cellular toxicity against pDCs.

2.2.4 Supportive Nonclinical Data

ILT7 is expressed only on the pDCs of humans and nonhuman primates; therefore, the cynomolgus monkey was selected as the relevant species for safety evaluation of daxdilimab.

Study 8311616 was a Good Laboratory Practice (GLP)-compliant, repeat-dose study in cynomolgus monkeys administered daxdilimab at 200 mg/kg intravenously (IV), 200 mg/kg SC, and 400 mg/kg SC once weekly for 4 weeks (5 doses). No daxdilimab-related clinical observations, body weight changes, ophthalmic observations, physical examination observations, macroscopic observations, or changes in blood pressure or electrocardiograms (ECGs) were observed. Daxdilimab administration had no clear or consistent group effects on clinical pathology parameters. Daxdilimab-related mild to moderate decreases of the group mean, absolute, and relative values of NK cells were observed in males given 200 or 400 mg/kg SC and in females given 200 mg/kg IV or SC and 400 mg/kg SC on Day 15 and Day 29 of the dosing phase. Daxdilimab-related pDC depletion was observed at all dose groups starting on Day 2 of the dosing phase. Plasmacytoid DC values were maintained at < 10% of mean baseline values in the majority of animals on Day 29. By Day 209, mean pDC values returned to baseline or approximately 50% of baseline in animals administered 200 mg/kg IV and 200 or 400 mg/kg SC, respectively. No other daxdilimab-related changes in peripheral blood immunophenotyping cells (total T cells, helper T cells, cytotoxic T cells, B cells, monocytes, and myeloid DCs) were observed in the blood, lymph nodes, and spleens of animals given ≥ 200 mg/kg IV or SC. Daxdilimab had no effect on the ability to mount a T-cell–dependent antibody response to primary or secondary administration of antigen, indicating intact humoral immunity during daxdilimab administration.

Study 8338846 was a GLP-compliant, 6-month, repeat-dose study in cynomolgus monkeys. Daxdilimab was administered once weekly via SC injection for 6 months (a total of 28 doses) at doses of 200 and 400 mg/kg/week. There were no daxdilimab-related clinical, ophthalmic, body weight, or physical observations; no changes were observed in cardiac measurements or observations, or clinical or anatomic pathology. In addition, there were no daxdilimab-related effects on reproductive organs or assessments. No daxdilimab-related changes were noted for IgG, IgM, IgA, IgE, or peripheral blood immunophenotyping, except pDCs as expected by pharmacology. Daxdilimab-related depletion of mean absolute and relative values for pDCs was noted on Day 2 of the dosing phase in animals administered 200 or 400 mg/kg/week. The only daxdilimab-related observation was a minor increase in mononuclear cell and macrophage infiltrates at the injection sites of animals administered daxdilimab compared with controls. These increases were not dose dependent, and partial reversibility was noted in recovery animals.

Based on these results, the no-observed-adverse-effect-level is 200 mg/kg when given via IV infusion and 400 mg/kg/week when given by SC injection. Additional details of these and other nonclinical studies are included in the Investigator's Brochure (IB).

2.2.5 Supportive Clinical Data

Daxdilimab has been investigated in Phase 1 single-ascending dose (SAD) and Phase 1b multiple-ascending dose (MAD) clinical studies in subjects with autoimmune diseases (Studies D6080C00001 and VIB7734.P1b.S1, respectively). Study D6080C00001 has been completed. Study VIB7734.P1b.S1 has a locked database, and all study-site visits have been completed.

2.2.5.1 Phase 1 Single-Ascending Dose Study in Subjects with Autoimmune Diseases

A Phase 1 SAD study (Study D6080C00001) of daxdilimab enrolled subjects with any of 5 autoimmune diseases: dermatomyositis, polymyositis, SLE, Sjögren's syndrome, and systemic sclerosis. Single SC doses of daxdilimab (1, 5, 15, 50, or 150 mg) or placebo were administered to 36 subjects (Karnell et al, 2021). No safety, tolerability, or immunogenicity issues were identified. Pharmacodynamic (PD) analysis showed a dose-dependent reduction in pDC levels, which was observable on Day 2 (one day after dosing on baseline [Day 1]) and maximal on Day 15 (Karnell et al, 2021). The duration of pDC reduction was largely dose dependent and was reversible in all cases. Median pDC levels returned to above 50% of baseline at the following time points for each cohort: 1 mg: Day 29; 5 mg: Day 57; 15 mg: Day 57; and 50 mg: Day 85. The time to return to above 50% of baseline could not be determined for 150 mg, since subjects met protocol-defined minimum absolute pDC number repletion criteria and exited the study before this occurred.

2.2.5.2 Phase 1b Multiple-Ascending Dose Study in Subjects with Autoimmune Diseases

In a single-blind (subjects and site blinded, Sponsor unblinded), Phase 1b MAD study (Study VIB7734.P1b.S1), daxdilimab or placebo was administered SC every 4 weeks (Q4W) for 3 doses to a total of 31 subjects in 3 cohorts (Karnell et al, 2021). In the first cohort, 8 subjects with any of 6 autoimmune diseases (dermatomyositis, polymyositis, SLE, cutaneous lupus erythematosus (CLE), Sjögren's syndrome, or systemic sclerosis) were randomized to daxdilimab (5 mg SC) or placebo in a 3:1 ratio. The second and third cohorts enrolled subjects with active cutaneous lupus, defined as a Cutaneous Lupus Erythematosus Disease Area and Severity Index-Activity (CLASI-A) score ≥ 8. In the second cohort, 12 subjects were randomized to daxdilimab 50 mg SC or placebo in a 2:1 ratio. In Cohort 3, 11 subjects were randomized to daxdilimab 150 mg SC or placebo in a 2:1 ratio.

A reduction in blood pDC level was observed at the first time point after dosing (Week 1) and persisted through the 3-month treatment period. A high type I IFN signature was present at baseline in 18 of 23 subjects (78%) in Cohorts 2 and 3. The median change in IFN signature at Month 3 was -54% in the daxdilimab 50 mg group, -83% in the daxdilimab 150 mg group, and +8% in the placebo group. On the skin biopsy at Month 3, the median change in pDC density was -87% for the 50 mg group, -99% for the 150 mg group, and -14% for the placebo group. The median change in CLASI-A from baseline to Month 3 was -5 in the 50 mg group, -9.5 in the 150 mg group, and -5 in the placebo group (Karnell et al, 2021). At Month 3, a $\geq 50\%$ improvement in CLASI-A was observed in 38% of subjects who received 50 mg daxdilimab, 75% of subjects who received 150 mg daxdilimab, and 29% of subjects who received placebo. The proportion of subjects with an adverse event (AE) was similar in the daxdilimab and placebo groups (73% versus 67%, respectively). No serious AEs (SAEs) or other clinically important AEs occurred in daxdilimab-treated study subjects (Karnell et al, 2021).

2.3 Benefit/Risk Assessment

More detailed information about the known and expected benefits and risks and reasonably expected AEs of daxdilimab may be found in the IB.

2.3.1 Risk Assessment

There are no important identified risks for daxdilimab. Important potential risks for daxdilimab may include viral infection and viral reactivation, opportunistic infection, malignancy, and hypersensitivity reactions, including anaphylaxis. More detailed descriptions of these potential risks are included in the IB.

Hypersensitivity reactions, including anaphylaxis, are a risk associated with administration of biologic drugs. Definitions for these reactions can be found in Appendix 5, Section 10.5. Appropriate drugs and medical equipment to treat acute anaphylactic and serious hypersensitivity reaction must be immediately available at study sites, and study personnel must be competent to recognize and treat anaphylaxis. In addition, subjects will be monitored after investigational product (IP) administration for immediate drug reactions. Hypersensitivity reactions and anaphylaxis have not been observed in Phase 1 SAD and Phase 1b MAD studies.

2.3.1.1 COVID-19 Risk Assessment

An additional risk of study participation includes potential exposure of the subject to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the virus that causes coronavirus disease 2019 (COVID-19), by visiting the study site. Sites must have a plan in place to minimize this risk. Although testing for COVID-19 prior to Dose 1 is not required, the Investigator may choose to have this test performed locally in accordance with his/her judgment based on subject risk. This test is not provided through the study's central laboratory, because the result of a test at Visit 1 would not be appropriately timed to be relevant to Dose 1. Such testing is not required.

To minimize risk to study subjects, study sites will be activated to initiate subject enrollment only after review of local COVID-19 disease incidence, prevalence, containment measures, availability of healthcare resources, ability to monitor site activities, and the presence of a site plan to minimize subject exposure to SARS-CoV-2 during site visits have been confirmed.

There are no data on the effect of daxdilimab on the risk for infection with SARS-CoV-2 or on the severity of COVID-19 illness.

The current available evidence does not suggest a difference in COVID-19 infection risk in persons with SLE compared to the general population except for what is known about the increased risk that may be associated with comorbid disease and use of immunosuppressive treatment.

The Investigator will assess the benefit-risk for each individual subject for determination of suitability for enrollment based on known risk factors for COVID-19 severity and possible or known exposure to SARS-CoV-2.

Because of the evolving spread and containment measures of COVID-19, ongoing risk assessment will be required of participating study sites and Investigators.

2.3.2 Benefit Assessment

Daxdilimab is being developed for the treatment of multiple autoimmune disorders in which pDCs are believed to contribute to their pathogenesis, including alopecia areata, dermatomyositis, discoid lupus erythematosus, LN, and SLE. The available nonclinical safety profile for daxdilimab is supportive of administration in subjects with SLE at exposures that do

not exceed those considered to be non-adverse to animals in toxicity studies performed per GLP guidelines (Section 2.2.4). In addition, the emerging clinical data available from two Phase 1 studies (Study D6080C00001 [Section 2.2.5.1] and Study VIB7734.P1b.S1 [Section 2.2.5.2]) demonstrates an acceptable safety profile, and no adverse drug reactions have been identified.

Given the daxdilimab mechanism of action (Section 2.2.3), the unmet need for patients with SLE (Section 2.2.2), and the favorable emerging data from the Phase 1 studies (Section 2.2.5), it is hypothesized that treatment with daxdilimab in study subjects with moderately-to-severely active SLE may result in maintenance or improvement in their condition as a result of participating in this study. Since all subjects in the study will receive unblinded, open-label daxdilimab irrespective of their assigned treatment in the RECAST SLE study, all study subjects have the potential to benefit from participating in this OLE study.

2.3.3 Overall Benefit-Risk Conclusion

To date, a relatively small number of subjects have been exposed to daxdilimab across the ongoing clinical studies, so a full evaluation of risk/benefit is limited at present. However, no clinically important safety issues have emerged that preclude further evaluation of daxdilimab in the relevant clinical study populations at the doses chosen for this study, and the benefit-risk evaluation remains favorable.

Considering the measures taken to minimize risk to subjects participating in this study, the potential risks identified in association with daxdilimab are justified by the anticipated benefits that may be afforded to study subjects with SLE.

3 OBJECTIVES AND ENDPOINTS

The objectives and endpoints to be evaluated in this study are provided in Table 2.

Table 2 Primary, Secondary, and Exploratory Objectives

Objectives	Endpoints
Primary Objective	
To evaluate the long-term safety and tolerability of 200 mg Q12W daxdilimab	• Incidence of AEs, SAEs, and AESIs
Secondary Objectives	
To characterize the PK, PD, and immunogenicity of daxdilimab	• Daxdilimab concentrations, change in pDCs, and ADA rate
Exploratory Objectives	
[redacted]	

Table 2 Primary, Secondary, and Exploratory Objectives

Objectives	Endpoints
[redacted]	

ADA = anti-drug antibodies; AE = adverse event; AESI = AE of special interest; [redacted]
PD = pharmacodynamic(s); pDC = plasmacytoid dendritic cell; [redacted];
PK, pharmacokinetic(s); Q12W = every 12 weeks; RECAST SLE = Phase 2 **R**andomized, Double-Blind, Placebo-Controlled **E**ffi**ca**cy and **S**afety Study of daxdilimab for the **T**reatment of Moderate to Severely Active **S**ystemic **L**upus **E**rythematosus; [redacted] SAE = serious AE; SLE = systemic lupus erythematosus; [redacted]

4 STUDY DESIGN

4.1 Overall Design

Protocol HZN-DAX-204 is an open-label study designed to evaluate the long-term safety and tolerability of 200 mg daxdilimab Q12W in subjects with SLE. The study design is provided in Section 1.2 (Figure 1).

Irrespective of their assigned treatment in the RECAST SLE study, all subjects participating in the SLE OLE will be treated with daxdilimab 200 mg SC Q12W in addition to their standard-of-care SLE therapy.

Once a subject has completed the treatment period (through Week 48) of the RECAST SLE study, signed the informed consent form (ICF), and met all study eligibility criteria, he/she may be enrolled in the OLE study. To allow for the continuous dosing of the subjects, the start of this OLE study should occur immediately after the completion of the RECAST SLE treatment period (ie, first OLE dosing [Day 1] coinciding with Week 48/Visit 14 of the RECAST SLE study). Any exceptions to this enrollment date must be reviewed and approved by the Medical Monitor before any subject is allowed to enroll after the Week 48/Visit 14 of the RECAST SLE study. (Section 5.5). Subjects will be treated with open-label daxdilimab 200 mg Q12W SC for 48 weeks. After the treatment period (Week 0 to Week 48), the subjects will enter an 8-week safety follow-up (SFU) period (Week 48 to Week 56).

Subjects who permanently discontinue IP at any point but who **do not** withdraw consent of study participation will complete the Study Week 48/early termination (ET) visit as soon as possible after IP discontinuation and then enter the SFU period as indicated in the schedule of assessments (SoA) (Table 1). Participants will not automatically be removed from the study if any administration of IP is missed.

The study will be conducted on an outpatient basis. For scheduled study visits, subjects will come to the study sites on 7 occasions: Weeks 0 [Day 1], 12, 24, 36, 48, 52, and 56. In addition, telehealth visits (phone or video call) will be performed on 8 occasions (Weeks 4, 8, 16, 20, 28, 32, 40, and 44) to assess the subject's current disease status, the OGC tapering schedule, safety, and concomitant medications (Section 8.1). For all IP administrations, daxdilimab will be

administered by study-site staff at the study site, and the subject will be observed for at least 60 minutes after the first and second doses (Day 1 and Week 12) are administered to each subject. Blood collection and study assessments will be performed at the times specified in the SoA (Table 1).

An external, independent Safety Data Monitoring Committee (SDMC) will be responsible for safeguarding the interests of study subjects via review of accumulating safety data and for supporting study integrity and interpretability based on their review of ongoing study conduct (Appendix 1, Section 10.1.5).

The primary objective of this OLE study is to evaluate the long-term safety and tolerability of 200 mg daxdilimab Q12W in adult subjects with moderately-to-severely active SLE. This will be assessed by summarizing AEs, SAEs, and AEs of special interest (AESI).

4.2 Scientific Rationale for the Study Design

4.2.1 Rationale for Study Population

HZNP-DAX-204 is a Phase 2 OLE study to evaluate the long-term safety and tolerability of daxdilimab in subjects with SLE. Subjects who complete the 48-week treatment period of the RECAST SLE study will be eligible to enroll in the SLE OLE study; therefore, the baseline characteristics of the study population in the SLE OLE study will be similar to that of the RECAST SLE study.

To evaluate the long-term safety and tolerability of daxdilimab in the SLE OLE study, only subjects who complete the 48-week treatment period of the RECAST SLE study and meet the eligibility criteria for the OLE will be eligible to participate in the clinical study. The selection criteria will allow for the assessment of long-term safety and tolerability of daxdilimab in subjects with SLE, while addressing safety concerns. This approach is justified by the favorable safety and tolerability profile observed in nonclinical (Section 2.2.4) and emerging clinical (Section 2.2.5) safety data from completed and ongoing clinical studies with daxdilimab .

The study population in the SLE OLE study reflects a subpopulation of patients who would be considered suitable for the therapy if daxdilimab is shown to be safe and effective.

4.2.2 Rationale for the Primary Outcome Measure

The safety endpoints are incidence of AEs, SAEs, and AESIs, which are standard assessments to evaluate safety and tolerability.

4.2.3 Rationale for the Secondary Outcome Measure

Pharmacokinetic sampling is included to evaluate subjects' exposure to multiple doses of daxdilimab administered SC. Pharmacodynamic assessments, [redacted]

General risks of biologic therapies include development of anti-drug antibodies (ADAs). Because ADAs to daxdilimab could result in altered daxdilimab levels or activity, ADA rate and the effect of ADA in the PK profile of daxdilimab will also be evaluated.

4.3 Rationale for Dose

A 200 mg daxdilimab dose administered Q12W has been selected to evaluate whether this decreased frequency of daxdilimab dosing can maintain clinical efficacy and to reduce the risk of safety and tolerability findings in the long term.

Treatment with daxdilimab in a single-blind, Phase 1b MAD study, resulted in a favorable safety profile and rapid and durable depletion of blood pDCs in all subjects receiving a 150 mg Q4W dose. Depletion of blood pDCs remained decreased until 3 months after the final dose when 90% of subjects recovered to within at least 50% of baseline. The 200 mg Q12W dosing strategy will allow for the evaluation of whether blood pDC depletion and recovery reaches a steady state and can be maintained by less frequent dosing.

A treatment period of 48 weeks is considered sufficient to evaluate long-term safety of daxdilimab and the secondary PK/PD outcome measures selected for this OLE study, and current nonclinical (Section 2.2.4) safety data supports this treatment duration.

4.4 End-of-Study Definition

An individual subject will be considered to have completed the study if the subject was followed up through the last protocol-specified visit, regardless of the number of doses of IP that was received.

Subjects will be considered not to have completed the study if consent was withdrawn (Section 7.2) or the subject was lost to follow-up (Section 7.3).

The end of the study ("study completion") is defined as the date of the last protocol-specified visit/assessment for the last subject in the study.

Information regarding site/study termination or suspension is found in Appendix 1, Section 10.1.12.

5 STUDY POPULATION

5.1 Inclusion Criteria

All subjects must meet all of the following criteria to be eligible for study participation:

1. Willing and able to understand and provide written informed consent (as described in Appendix 1, Section 10.1.3) prior to any study-related procedures and to comply with all study requirements and complete study assessments.
2. Must have qualified for and received IP (daxdilimab or placebo) and complete the treatment period (through Day 337) in the RECAST SLE study. Subjects who discontinued early from IP in RECAST SLE are not eligible for this study.
3. Women of childbearing potential must have a negative urine pregnancy test on Day 1. Women of childbearing potential are defined as those who are not surgically sterile (ie, surgical sterilization includes bilateral salpingectomy, bilateral oophorectomy, or hysterectomy) or those who are not postmenopausal (defined as 12 months with no menses without an alternative medical cause and a follicle-stimulating hormone [FSH] within the postmenopausal range as established by the central laboratory during the

screening period of the RECAST SLE study, unless on postmenopausal hormone replacement therapy).

If a female subject becomes postmenopausal during the study (ie, 12 months with no menses without an alternative medical cause, unless on postmenopausal hormone replacement therapy), a FSH test will be performed at the central laboratory. If the FSH level is within the postmenopausal range, the female subject will not be required to use contraception after that.

Women of childbearing potential who are sexually active with a nonsterilized male partner must agree to use a highly effective method of contraception from signing of the ICF and must agree to continue using such precautions through the end of the study follow-up or 3 months (approximately 5 half-lives) following the last dose of IP in the case of early withdrawal from the study, and refrain from egg retrieval/egg donation during this period. After this point, a decision about contraception should be made by the subject and her regular healthcare providers. Female subjects who participate in the SLE OLE are expected to maintain the same form of contraception they used during the RECAST SLE study. Effective methods of contraception are listed in Appendix 3, Section 10.3.

Sustained abstinence is an acceptable practice; however, periodic abstinence, the rhythm method, and the withdrawal method are not acceptable methods of contraception.

Note that because mycophenolate affects the metabolism of hormonal contraceptives and may reduce their effectiveness in women receiving MMF or mycophenolic acid (MPA) who are using hormonal contraceptives for birth control, the subject must employ an additional contraceptive method (eg, barrier method).

4. Nonsterilized male subjects who are sexually active with a woman partner of childbearing potential must agree to use a condom with spermicide from Day 1 and until 3 months (approximately 5 half-lives) after receipt of the last dose. Because a male condom with spermicide is not a highly effective contraception method, it is strongly recommended that male subjects advise their women partners of childbearing potential to use a highly effective method of contraception throughout this period. Effective methods of contraception are listed in Appendix 3, Section 10.3.

5.2 Exclusion Criteria

If an individual meets any of the following criteria, he or she is ineligible for this study:

General Criteria:

1. Any condition or change during the RECAST SLE study that in the opinion of the Investigator or the Sponsor would interfere with evaluation and interpretation of subject safety or alter the risk-benefit associated with IP administration.
2. Participation in another clinical study with an IP during the RECAST SLE study period.
3. Planned elective surgeries that in the opinion of the Investigator or the Sponsor would interfere with evaluation and interpretation of subject safety.
4. Any herpes zoster, cytomegalovirus, or Epstein-Barr virus infection that was not completely resolved prior to Visit 1.

5. Clinically significant active infection at Visit 1, in the opinion of the Investigator, including ongoing and chronic infection requiring antibiotics or antiviral medication (chronic nail infections are allowed).
6. Pregnant or lactating females.

Prior and Concomitant Therapy Criteria:

7. Receipt of any prohibited medication during the RECAST SLE study period. Receipt of any restricted medications during the RECAST SLE study period must be discussed with the Sponsor's Medical Monitor and agreed upon prior to enrollment into this study.

5.3 Lifestyle Considerations

Subjects must be instructed not to take any medications, including over-the-counter (OTC) or herbal products or ayurvedic medications without first consulting the Investigator. Prohibited and permitted medications are discussed in Section 6.9.

5.4 Screen Failures

A screen failure occurs when a subject who has consented to participate in the clinical study is not subsequently entered/enrolled in the study. A minimal set of screen failure information is required to ensure transparent reporting of screen failure subjects, to meet the Consolidated Standards of Reporting Trials publishing requirements, and to respond to queries from regulatory authorities. Minimal information includes screen failure details, eligibility criteria, and any SAEs.

Individuals who do not meet the criteria for participation in this study (screen failure) may not be rescreened. These subjects will remain in and complete the SFU period of the RECAST SLE study.

5.5 Criteria for Temporarily Delaying Enrollment or Administration of Investigational Product

To allow for the continuous dosing of the subjects, the start of this OLE study should occur immediately after the completion of the RECAST SLE treatment period (ie, first OLE dosing [Day 1] coinciding with Week 48/Visit 14 of the RECAST SLE study). Any exceptions to this enrollment date must be reviewed and approved by the Medical Monitor before any subject is allowed to enroll after the Week 48/Visit 14 of the RECAST SLE study.

6 INVESTIGATIONAL PRODUCT AND CONCOMITANT THERAPY

6.1 Investigational Product Administered

The IP will be administered by study-site staff in the study site. On Day 1 and Week 12, subjects will remain under observation for at least one hour after IP administration. The IP will be provided by the Sponsor. Further details regarding the IP can be found in Table 3.

Table 3 Description of Investigational Product and Dosing

Key Information	Investigational Product
Product name	Daxdilimab
[redacted]	
Source of procurement	Horizon Therapeutics
Unit dose strength(s)/Dosage level(s)	200 mg dose, administered as 2 × 1.0 mL SC injections
Route of Administration and frequency	SC, Q12W for 48 weeks (Weeks 0 [Day 1], 12, 24, 36, and 48)
Physical description	The drug product will be provided as a sterile liquid in a 2R glass vial with a nominal fill volume of 1.0 mL of 100 mg/mL.
Dosing instructions	Daxdilimab will be administered by clinic staff trained in best practices for SC administration of treatments. More details on the administration method are described in the study manual.

Q12W = once every 12 weeks; SC = subcutaneous; w/v = weight/volume

The contents of the label will be in accordance with all applicable regulatory requirements.

6.2 Preparation, Handling, Storage, and Accountability

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

Only subjects enrolled in the study may receive IP, and only authorized site staff may supply, prepare, or administer the IP.

All IP must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the Investigator and authorized site staff.

The Investigator or authorized site staff is responsible for IP accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records).

Further guidance and information for the final disposition of unused IP are provided in the Pharmacy Manual and Section 6.2.1.4.

6.2.1 Preparation/Storage/Handling

6.2.1.1 Inspection and Storage

Each daxdilimab vial selected for dose preparation should be inspected. Any defects with the IP must be reported immediately to the Sponsor's Quality Assurance Department and the site monitor. The Sponsor's Quality Assurance contact information for reporting product complaints is: clinicalproductcomplaints@horizontherapeutics.com. During the investigation of the product complaint, all IP must be stored at labeled conditions unless otherwise instructed.

Daxdilimab should be stored at 2°C to 8°C (36°F to 46°F). Labels will be prepared in accordance with Good Manufacturing Practice (GMP) and local regulatory guidelines.

Each kit has a unique number that is printed on all labels within the kit (ie, the outer carton label and the label on the vial within the carton).

6.2.1.2 Investigational Product Dose Preparation

Preparation of daxdilimab and preparation of the syringe for SC administration are to be performed by an unblinded pharmacist/IP manager using aseptic technique. The same unblinded pharmacist/IP manager in the RECAST SLE study will perform IP and syringe preparation in this OLE study.

Daxdilimab is supplied as a sterile liquid in a 2R glass vial at a nominal fill volume of 1.0 mL, stoppered with a 13-mm elastomeric stopper, and sealed with flip-off cap overseal. Allow the kits to equilibrate to room temperature about 30 minutes prior to dose preparation.

No incompatibilities between daxdilimab and plastic syringes (ie, polypropylene and polycarbonate) have been observed.

Daxdilimab does not contain preservatives and any unused portion must be discarded. Total in-use storage time from needle puncture of the IP vial to start of administration should not exceed 4 hours at room temperature or 24 hours at 2°C to 8°C (36°F to 46°F). If storage time exceeds these limits, a new dose must be prepared from new vials.

If syringes containing IP have been stored at 2°C to 8°C (36°F to 46°F) for any length of time, they must equilibrate to room temperature for one hour prior to administration to the subject. This one-hour equilibrium period is included in the total room temperature hold time for prepared syringes, which must not exceed 4 hours. DO NOT FREEZE.

A SC dose of 200 mg daxdilimab will be administered over 2 injections. To prepare each injection, withdraw one mL of IP into a 1 mL syringe using a 1½-inch needle. For SC dose administration, a 27G ½-inch needle should be used.

6.2.1.3 Investigational Product Dosing, Administration, and Monitoring

The first day of dosing is considered Day 1. This is an open-label study; therefore, study-site staff, and subject will be unblinded.

The same unblinded pharmacist/IP manager in the RECAST SLE study will perform IP and syringe preparation in this OLE study. The skin surface of the anterolateral thigh, upper outer triceps area, upper buttocks, or abdomen (avoiding a 2-inch [5 cm] radius around the umbilicus) should be prepared with an alcohol wipe and allowed to air dry. The skin will be pinched to isolate SC tissue from the muscle. The needle will be inserted at a 90-degree angle to the skin surface approximately halfway into the SC tissue. The prepared IP will be slowly injected (at least a 5-second duration is recommended per 1 mL syringe) into the SC tissue using gentle pressure. The area should not be massaged after injection. The SC injection site can be changed during the study as per subject preference.

The IP should **not** be administered if it has been at room temperature for more than 4 hours, or if it has been at 2°C to 8°C (36°F to 46°F) for more than 24 hours.

Subjects should be monitored under direct observation for at least 60 minutes after the first and second doses of IP administration or until the subject is stable, whichever is longer. Vital signs should be measured as indicated in Section 8.3.2.

As with any antibody, allergic reactions to dose administration are possible. Therefore, appropriate drugs and medical equipment to treat acute anaphylactic reactions must be immediately available, and study personnel must be trained to recognize and treat anaphylaxis. Guidance for anaphylaxis diagnosis is provided in Appendix 5, Section 10.5.

6.2.1.4 Handling and Disposal

It is preferred that unused IP be destroyed at the study site after accountability and approval to destroy, regardless of whether the study was completed or terminated prematurely, with agreement from the Sponsor.

The Investigator may return any unused vials of daxdilimab to the Sponsor or designee. At the time of return, the Investigator must verify, and the Study Monitor must confirm that unused or partially used study products have been returned and that no study products remain at the site.

6.2.2 Accountability

Study-site staff will maintain a record of the IP received, dispensed, administered, and destroyed (if done at the site). All records will be maintained with controlled access to site, Sponsor, and contract research organization (CRO) staff only. A Study Monitor will perform IP accountability and compliance monitoring during the study. A qualified study-site staff member will only administer the study product to subjects included in this study and according to procedures established in this study protocol. Each administration of study product will be documented and transferred to the electronic case report form (eCRF).

6.3 Assignment to Investigational Product

At the study site, each screened subject in the RECAST SLE study is assigned a subject identifier (SID) during screening that will be used on all subject documentation. Subjects enrolled in the SLE OLE study will retain their SID number from the RECAST SLE study.

No randomization scheme will be used, as all subjects will receive daxdilimab 200 mg Q12W.

6.4 Blinding

This is an open-label study. Subjects and Investigators are aware that the IP is daxdilimab 200 mg Q12W.

6.5 Investigational Product Compliance

Site staff will administer the IP SC at the study site. The dose and date of administration of IP must be recorded in the subject's medical/study record and eCRF. Treatment compliance will be assessed based on this information.

6.6 Dose Modification

Dose adjustment of daxdilimab is not allowed in this study.

6.7 Continued Access to Investigational Product After the End of the Study

After the end of the study, each subject will be treated according to standard clinical practice and local practice, at the discretion of the Investigator.

6.8 Treatment of Overdose or Misuse

Any instance of overdose of IP (suspected or confirmed) must be communicated to the Sponsor (Section 8.4.10). Any associated AEs or SAEs must also be reported, and their management should be recorded.

6.9 Prior and Concomitant Therapy

Any medication or vaccine (including OTC or prescription medicines, recreational drugs, vitamins, and/or herbal supplements) that the subject is receiving at the time of enrollment or receives during the study must be recorded along with:

- Name and indication
- Reason for use
- Dates of administration including start and end dates
- Dosage information including dose and frequency

Any change to concomitant drugs must also be recorded in the corresponding section of the eCRF.

The Medical Monitor should be contacted if there are any questions regarding concomitant or prior therapy.

6.9.1 Permitted Concomitant Therapy

6.9.1.1 Concomitant Medications and Treatments

All concomitant medications (from Visit 1) taken while the subject is participating in the study will be recorded on the eCRF. Subjects must be instructed not to take any medications, including OTC or herbal products or ayurvedic medications without first consulting the Investigator.

Permitted medications ([redacted]) are any medications required per the medical history and not specifically prohibited by the protocol during the clinical study (ie, from Visit 1 to the end of the SFU period). Any such medications prescribed or used should be recorded in the eCRF.

6.9.1.2 Concomitant Medications for Systemic Lupus Erythematosus Standard of Care During the Study

Concomitant standard-of-care medications used during the study are part of the subject's previous SLE treatment and, thus, will not be provided by the Sponsor.

6.9.1.2.1 Immunosuppressants

These medications, if given during the RECAST SLE study, must remain stable during the treatment period except for oral glucocorticoid (OGC) and nonsteroidal anti-inflammatory drugs (NSAIDs), which can be adjusted as long as doses are consistent with the parameters as indicated in Sections 6.9.1.2.2 and 6.9.1.2.3, respectively. Background therapy may only be changed for documented safety issues. The toxicity/event must be confirmed as a documented AE. The dose can be returned to the OLE baseline (Day 1) level if the toxicity/event resolves and if clinically indicated. Initiation of any new immunosuppressant or immunomodulator therapy or increase in

dose above the level used on Day 1 of the OLE may result in withdrawal of the subject from the IP (per Sponsor's Medical Monitor discretion).

6.9.1.2.2 Glucocorticoids

Oral GCs are permitted but not required for participation in the study. Oral GCs other than prednisone may be used orally (PO) at equivalent doses (refer to Appendix 7, Section 10.7). It is strongly encouraged that Investigators taper the OGC dose as much as tolerated after a subject enrolls into the study, as a goal of this OLE is to determine the lowest clinically appropriate level of steroids, including steroid discontinuation, by Week 36 that can be provided while maintaining responses. Guidance for taper and bursts is outlined below. During the study, Investigators may reach out to discuss any taper or burst scenario with the Medical Monitor as needed.

Oral Glucocorticoid Tapering Guidance

Oral GC tapering must be started by Week 4 of the clinical study.

An example of a suggested OGC tapering regimen is provided in Appendix 8, Section 10.8 as guidance for Investigators. However, due to variability in subject responses to OGC treatment and tolerability of taper, Investigators will have flexibility in how the OGC dose is reduced at each visit, however, it is encouraged that Investigators taper each month by at least 1 mg/day.

OGC tapering must be attempted unless at least one of the following criteria are met:

1. There are new or worsening organ system(s) affected by SLE.
2. There is an increase in skin involvement.
3. There is new or worsening joint involvement.

If there are scenarios outside these listed criteria in which the Investigator deems tapering not appropriate, then the Medical Monitor must be notified and the reason for not tapering will be discussed. All reasons for not tapering **must be** well documented within the EDC.

Glucocorticoid Burst Guidance

We encourage Investigators to limit the use of GC bursts throughout the clinical study as clinically feasible. GC bursts are allowed at the Investigators discretion. The reason for a GC burst and regimen prescribed **must be** well documented in the EDC.

Increase in Oral Glucocorticoids for Surgery and Prevention of Adrenal Insufficiency

Increases in OGCs for surgery and prevention of adrenal insufficiency are allowed as clinically indicated.

6.9.1.2.3 Other Permitted Medications

For all enrolled subjects, additional treatments given to subjects with SLE are permitted during the study as follows:

- Angiotensin-converting enzyme inhibitors and angiotensin receptor blockers:
  - If used during the RECAST SLE study, it is recommended that they be maintained at a stable dose during the OLE study, unless dose change, discontinuation, or initiation is required for documented safety reasons.

- Anti-COVID therapeutic antibodies
  - If used during the study, the Medical Monitor must be notified immediately, and continuation of IP will be determined on a case-by-case basis.
- Aspirin
  - Low-dose aspirin (≤ 350 mg/day) may be used for cardiovascular prophylaxis; this is permitted in addition to use of NSAID as specified below.
- Osteoporosis prophylaxis and treatment
  - Vitamin D and calcium supplementation, and if necessary, treatment of osteoporosis is allowed according to local standard-of-care guidelines. These medications will not be supplied by the Sponsor.
- Herbal supplements
  - May be continued during the study. It is strongly recommended that the dosages and preparations remain stable unless discontinued all together. It is recommended that no herbal supplements be initiated or reinitiated once discontinued during the study.
- Medications for the treatment of injection site reactions:
  - These are allowed and may include topical or systemic antihistamines, topical GCs, paracetamol, or NSAIDs.
- NSAIDs
  - NSAIDs can be used as needed (PRN) during the OLE (not exceeding local guidelines).
  - Subjects taking a NSAID (including cyclooxygenase 2 inhibitors; topical, prescription, or OTC) on a regular schedule for SLE symptoms at the OLE baseline (Day 1) can continue to do so throughout the study at a stable dose.
  - NSAIDs should not be taken on visit days until all assessments are complete. Subjects may have the dose adjusted during the study for documented toxicity/safety reasons.
  - Any NSAIDs (whether prescription, OTC, or topical) should not be used above the maximum allowable doses per local guidelines, and site should perform regular AE monitoring of these concomitant medications.
- Opioids
  - Up to 40 mg/day morphine-equivalent are permitted at a stable dose if present at the OLE baseline (Day 1). Initiation of opioids and/or PRN dosing of opioids after Day 1 of the OLE for SLE is discouraged and should not exceed 40 mg/day or equivalent if prescribed. These may be titrated off as tolerated during the study. Analgesics, including opiates, may be used at stable doses or PRN for temporary relief of symptoms not due to SLE, but then are strongly recommended to be avoided 24 hours prior to each study visit.
- Acetaminophen (paracetamol)

  - Short acting acetaminophen (paracetamol) may be initiated or continued for pain control during the study at approved doses. Pain medications should not be used within a minimum of 6 to 12 hours (based on known duration of effect) of a scheduled visit.

- Topical therapy for CLE
  - Concurrent use of topical therapy for CLE (eg, GCs, pimecrolimus) is permitted. Topical therapy must be the same being used in the 2 weeks prior to the OLE baseline (Day 1), and the dose and frequency of application must be stable. During the study, topical therapy may be reduced or discontinued based on clinical manifestations and Investigator discretion. Should cutaneous skin manifestations reoccur, the same topical therapy may be resumed up to the dose used at the OLE baseline (Day 1). New dermatologic preparations may be used for the duration of the study if needed. It is also recommended that subjects use sunscreen (list as concomitant medication for SLE) and avoid sun exposure during the study. Topical moisturizers are also permitted.

Any medications (other than those prohibited by the protocol) that are considered necessary for the subjects' welfare and will not interfere with the study medication may be given at the Investigator's discretion.

6.9.2 Prohibited Concomitant Medications

The treatments and therapies listed in Section 6.9.3 will not be permitted from Day 1 of the OLE until the end of the study (with exceptions as noted for those therapies that are potentially permitted per Section 6.9.1).

6.9.3 Medications and Therapies That Lead to Immediate Discontinuation of Investigational Product

The following therapies are prohibited from Day 1 of the OLE through end of the study. These medications are also excluded as per the inclusion and exclusion criteria (Section 5) and during the study:

- Biologic immunomodulators (including but not limited to belimumab, abatacept, or rituximab)
- Bone marrow, stem cell (eg, mesenchymal stem cells), or solid organ transplant
- Cyclophosphamide
- GCs
  - Intralesional
  - Intradermal for alopecia
  - Adrenocorticotropic hormone (ACTH) analogs (eg, Acthar®, Synacthen®)
  - dehydroepiandrosterone
  - Topical use (may be allowed per the permitted medications; see Section 6.9.1.2.3) if they are used in accordance with inclusion and exclusion criteria (Section 5).
- Ig therapy (for anti-COVID therapeutic antibodies, see Section 6.9.1.2.3).
- Investigational agents

- IPP-201101 (Lupuzor™)
- IV corticosteroids > 1 g methylprednisolone or equivalent
- Janus kinase inhibitors (eg, tofacitinib [Xeljanz®], baricitinib [Olumiant®], upadacitinib [Rinvoq™], filgotinib, peficitinib)
- Live or attenuated vaccines, including Bacille-Calmette-Guerin (the Sponsor recommends that Investigators ensure all subjects are up to date with required vaccinations prior to entry into the study)
- Minocycline
- Plasmapheresis, plasma exchange, or Therakos® photopheresis
- Thalidomide and thalidomide derivatives (eg, lenalidomide [Thalomid®, Revlimid®])
- Topical calcineurin or mammalian target of rapamycin (mTOR) inhibitors (eg, pimecrolimus [eg, Elidel®], sirolimus)
- Sulfasalazine
- Systemic mTOR inhibitors (eg, sirolimus [Rapamune®])

6.9.4 Restricted Medications

As daxdilimab is an investigative immunomodulatory agent, non-protocol–permitted changes to immune modifiers or immunosuppressants on study are strongly discouraged.

If a subject starts any of the following during the treatment period or increases the dose above the OLE baseline (Day 1) dose, the Investigator must notify the Sponsor's Medical Monitor immediately. The Medical Monitor will determine if the subject may continue to receive IP.

- Antimalarials:
  - Chloroquine
  - Hydroxychloroquine
  - Quinacrine
- AZA
- Cyclosporine
  - Cyclosporine eye drops are permitted for use while on study.
  - Lifitegrast ophthalmic solution (Xiidra eye drops) are permitted for use while on study.
- Danazol
- Dapsone
- GCs
  - Intramuscular > 80 mg/day methylprednisolone or equivalent.
  - Intra-articular/tendon sheath/bursal injections of total methylprednisolone > 80 mg or equivalent.
  - IV > 40 mg/day but ≤ 1 g/day methylprednisolone or equivalent.
  - OGC
    - > 40 mg/day prednisone or equivalent.
    - Treatment above the OLE baseline (Day 1) dose for a dosing period of > 14 days.
  - Long biologic half-life (eg, dexamethasone, betamethasone).

  - SC or intramuscular precursors (eg, ACTH).

- Intra-articular medications other than GCs
- Leflunomide
- 6-Mecaptopurine (6-MP)
- MPA
- MMF
- MTX or any change in the route of administration of PO, SC, or intramuscular MTX
- Sulfasalazine
- Tacrolimus
- Voclosporin

[redacted]

7 DISCONTINUATION OF INVESTIGATIONAL PRODUCT AND SUBJECT DISCONTINUATION/WITHDRAWAL

Discontinuation of specific sites or of the study as a whole are detailed in Appendix 1, Section 10.1.12.

7.1 Discontinuation of Investigational Product

An individual subject will not receive any further IP if any of the following occur in the subject:

- Receipt of any medications or therapies in Section 6.9.3.
- A Grade 3 or higher allergic reaction to the IP.
- A Grade 3 or higher infection considered related to the IP.
- Other AE that contraindicates further dosing in the opinion of the Investigator and/or the Sponsor, Medical Monitor, and/or the SDMC.
- Withdrawal of consent from further treatment with IP.
- Subject is determined to have met one or more of the exclusion criteria or failed to meet all the inclusion criteria for study participation and there is a potential safety risk associated with continuation identified upon consultation with the Medical Monitor.
- Pregnancy or a decision to become pregnant.
- Any of the following liver function abnormalities:
  - Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) ≥ 8× upper limit of normal (ULN).
  - ALT or AST ≥ 5 × ULN for more than 2 weeks.
  - ALT or AST ≥ 3 × ULN and total bilirubin ≥ 2 × ULN or international normalized ratio ≥ 1.5 without alternative explanation.
  - ALT or AST ≥ 3× ULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (≥ 5%).

Subjects who permanently discontinue IP at any point but who **do not** withdraw consent of study participation will complete the Study Week 48/ET visit as soon as possible after IP discontinuation and then enter SFU period unless the subject withdraws consent of study participation (as described in Section 7.2) or the subject is lost to follow-up (Section 7.3).

Appendix 4, Section 10.4 describes the process to be followed to identify and appropriately report potential Hy's Law cases and Hy's Law cases.

Follow the SoA (Table 1) for data to be collected at the time of discontinuation of IP and follow-up and for any further evaluations that need to be completed.

7.2 Subject Discontinuation/Withdrawal from the Study

Subjects are free at any time to withdraw from the study (IP and assessments) for any reason, without prejudice to further treatment (withdrawal of consent). Such subjects will always be asked about the reason(s) for withdrawal and the presence of any AEs. Adverse events will be followed-up. If a participant withdraws participation in the study, then no further study visits or data collection should take place.

Subjects who permanently discontinue IP at any point in the study but who **do not** withdraw consent of study participation will complete the Study Week 48/ET visit as soon as possible after IP discontinuation and then enter SFU period. Subjects who permanently discontinue IP at any point in the study **and** withdraw consent of study participation will only complete the Week 48/ET assessments (if they agree to do so before withdrawing consent). Subjects will **not** be automatically removed from the study if any administration of IP is missed.

Further details concerning use of samples collected during the study from a subject that withdraws consent are provided in Appendix 1, Section 10.1.7.

7.3 Lost to Follow-up

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

Subjects will be considered lost to follow-up only if no contact has been established by the time the study is completed such that there is insufficient information to determine the participant's status on Day 393 (Visit 15).

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

- The site must attempt to contact the subject and reschedule the missed visit as soon as possible, counsel the subject on the importance of maintaining the assigned visit schedule and ascertain whether the subject wishes to and/or should continue in the study.
- Before a subject is deemed lost to follow-up, the Investigator or designee must make every effort to regain contact with the subject with 3 documented attempts at contact (with one documented attempt being a registered letter/certified mail):
  - Registered letter/certified mail
  - Phone calls, text messages, or emails
  - Consulting publicly available sources, if allowed by local regulations, to determine the status of the subject.

These contact attempts should be documented in the subject's medical record.

- Should the subject continue to be unreachable, the subject will be considered to have withdrawn from the study.

"Lost to follow-up" as a reason for study discontinuation must be documented by time and date of telephone calls, emails, text messages, numbers called, individuals spoken to if not the subject, documentation that a certified/registered letter was sent, and documentation of publicly available sources that were consulted.

8 STUDY ASSESSMENTS AND PROCEDURES

Study procedures and their timing are summarized in the SoA (Table 1).

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

Thorough review of eligibility requirements must be completed by the Investigator to confirm that potential subjects meet all eligibility criteria. The Investigator will maintain a screening log to record details of all subjects screened and to confirm eligibility or record reasons for screening failure, as applicable.

In the event of a significant study-continuity issue (eg, caused by a pandemic), alternate strategies for subject visits, assessments, medication distribution, and monitoring may be implemented by the Sponsor or the Investigator, as per local health authority/ethics requirements.

Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples.

8.1 Administrative and General Procedures

Once a subject has completed the treatment period (through Week 48) of the RECAST SLE study, signed the ICF, and met all study eligibility criteria, he/she may be enrolled in this OLE study. Informed consent must be obtained by the Principal Investigator (PI) or a designee such as an appropriately qualified sub-Investigator at the beginning of the study visit. The informed consent process should be documented.

Subjects who complete the treatment period (through Week 48) of the RECAST SLE study and wish to enroll in the OLE study will undergo a review of eligibility requirements and enrollment on Day 1, a treatment and assessment period of 48 weeks, and a SFU period of 8 weeks (through Week 56) as indicated in the SoA (Table 1).

A laboratory manual will be provided to the study sites that specifies the procedures for collection, processing, storage, and shipment of samples, as well as laboratory contact information, specific to this clinical research study.

Treatment Period

To allow for the continuous dosing of the subjects, the start of this OLE study should occur immediately after the completion of the RECAST SLE treatment period (ie, first OLE dosing [Day 1] coinciding with Week 48/Visit 14 of the RECAST SLE study). Any exceptions to this enrollment date must be reviewed and approved by the Medical Monitor before any subject is allowed to enroll after the Week 48/Visit 14 of the RECAST SLE study.

On Day 1 (Visit 1), all assessments are to be performed prior to IP treatment; any procedure that was also completed for RECAST SLE Visit 14 (if performed on the same day as Visit 1 for this study) should be used for this study and not repeated.

On dosing days, all assessments are to be performed prior to IP treatment unless noted otherwise.

Telehealth Visits

Telehealth visits will be performed at Weeks 4, 8, 16, 20, 28, 32, 40, and 44 of the treatment period. Telephone or video calls may be utilized. Telehealth visits should be performed by a qualified healthcare provider. These telehealth visits will be used to assess the subject's current disease status, OGC tapering schedule and assess safety and concomitant medications. If there is any situation (including, but not limited to worsening of SLE symptoms or potential change in the expected steroid taper) that in the opinion of the Investigator requires evaluation, an in-clinic unscheduled visit should be arranged and all relevant assessments should be performed.

Early Termination/Follow-up Visits

The Week 48 visit (Visit 13) is the end-of-treatment visit for subjects who complete the treatment period. After the treatment period (Week 0 to Week 48), the subjects will enter an 8-week safety follow-up period (Week 48 to Week 56), which consists of 2 study-site visits (Week 52 and Week 56).

Subjects who discontinue IP early will follow the procedures for early discontinuation of IP (Section 7.1).

The full list of procedures and timing of assessments to be performed during the ET and SFU visits are provided in the SoA (Table 1).

Unscheduled Visits

An unscheduled visit should be performed if a subject complains of worsening SLE symptoms, if a subject use OGCs outside of study-permitted doses, if a blood test/evaluation needs to be repeated, if an AE needs to be evaluated, or any situation, which in the opinion of the Investigator, requires an evaluation. Clinically indicated relevant and necessary assessments should be performed during unscheduled visits, including assessment of concomitant medications and AEs, as appropriate.

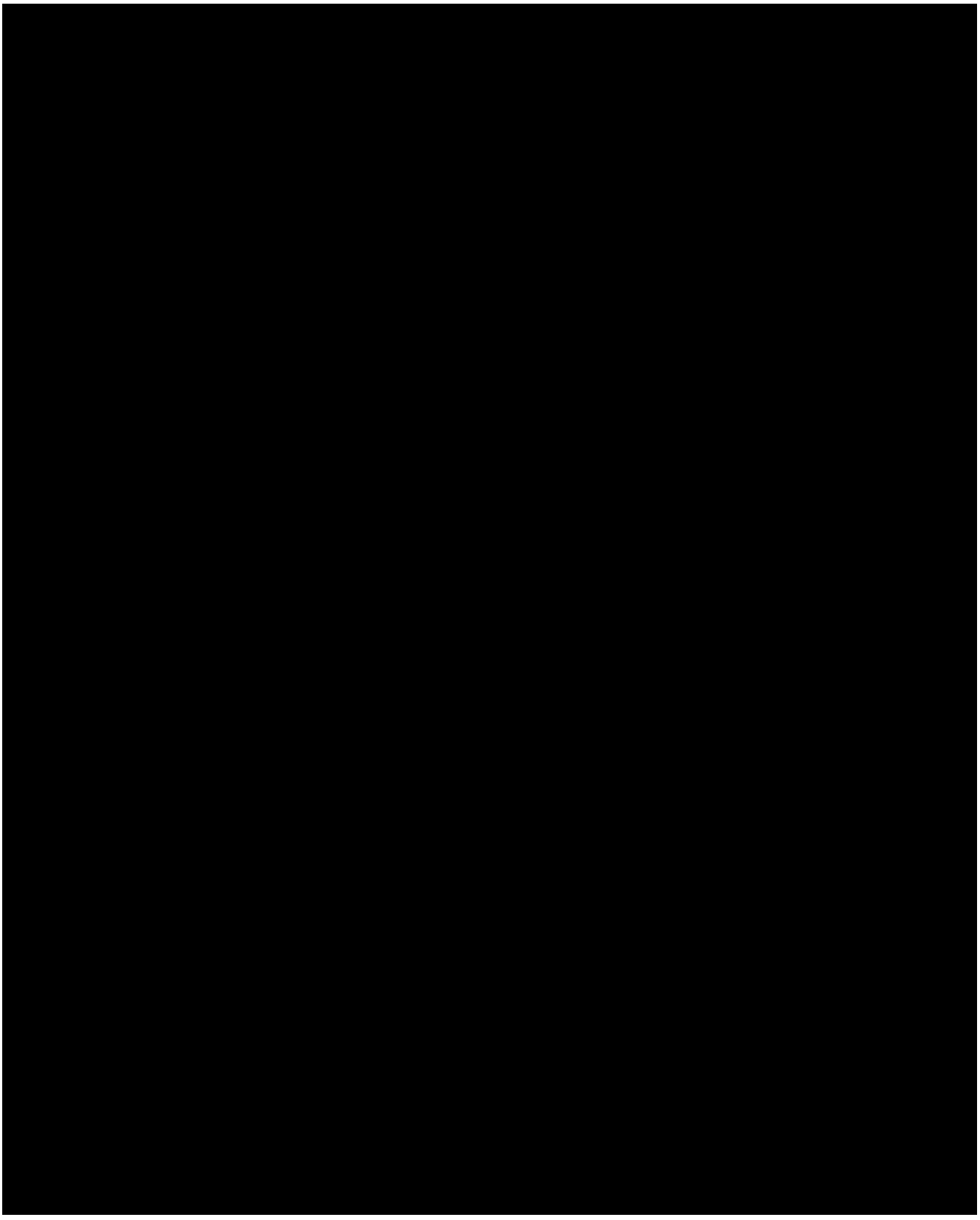
8.2 Exploratory Efficacy Assessments

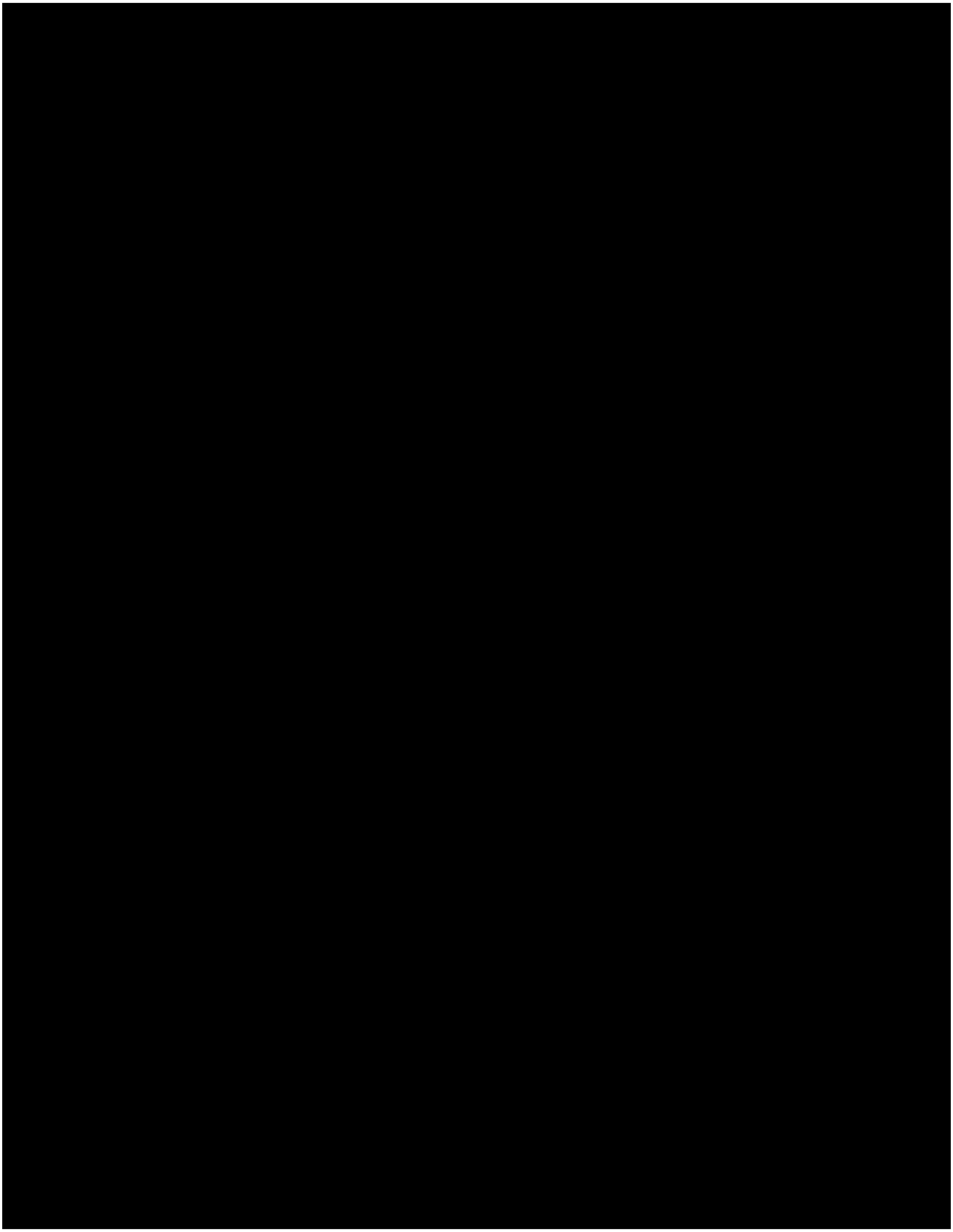
Planned time points for all exploratory efficacy assessments are provided in the SoA (Table 1).

8.2.1 Training Provision and Requirements

The Sponsor or designee will provide necessary training to instruct the Investigators, study coordinators, and other applicable site staff to ensure appropriate study conduct. This training will include information on the protocol, study procedures including completion of the lupus assessments, the completion of the case report forms (CRFs), and other identified training topics. Training will include printed training materials, online videos, and formal presentations, as well as web-based training modules. Required trainings will be documented in the site training plan. All assessments and certifications must be renewed prior to expiration. If there is a change in site personnel over the course of the study, new Investigators or physicians must complete all the

required training prior to performing study procedures. Documentation of completed training will be filed in the Investigator site file and the trial master file.





[redacted]

8.2.7 Oral Glucocorticoid Reduction

Refer to Section 6.9.1.2.2 for all information regarding OGC tapering.

[redacted]

[redacted]

8.3 Safety Assessments

Planned time points for all safety assessments are provided in the SoA (Table 1) and are described below.

8.3.1 Physical Examinations

A full physical examination will be performed at the Week 0 [Day 1] and Week 48 visits. A focused physical examination should be performed at all other visits. A focused physical examination should always include assessment of head, ears, eyes, nose, throat, lungs, heart, abdomen, skin, and extremities.

Medically significant changes from the screening physical examination will be recorded as AEs, unless they are considered a manifestation of SLE and [redacted].

8.3.2 Vital Signs

Vital signs, blood pressure (mmHg), pulse rate (beats/min), respiratory rate (breaths/min), and body temperature (ºC), and body weight (kg) will be obtained as outlined in Table 1 using clinically acceptable methods and devices as defined in the SoA. Vital signs should be measured in a seated position having rested in this position for at least 5 minutes before each reading and, when possible, should be taken before any blood draws. Prior to and after IP administration, vital signs should be checked as follows:

- Within 15 minutes prior to administration of IP but within 30 minutes on days when an ECG is to be performed.
- Every 30 minutes (± 5 minutes) for 60 minutes after administration or until stable, whichever is later (for the first 2 study visits only).

If anaphylaxis or a hypersensitivity reaction occurs after the SC administration of IP, vital signs will be taken more frequently, based on Investigator's judgment and as warranted by the severity of the reaction (Appendix 5, Section 10.5)

8.3.3 Electrocardiograms

A computerized 12-lead ECG will be performed at the visits specified in the SoA (Table 1). The Investigator or a qualified designee will review and indicate if the ECG is normal, abnormal but not clinically significant, or abnormal and potentially clinically significant.

The ECG should be performed after vital signs are examined and after 10 minutes at rest in a supine position.

8.3.4 Local Injection Tolerability Assessments

Daxdilimab will be administered by study-site staff in the clinic, and each subject will be assessed for local injection tolerability 60 minutes after the first and second doses (Day 1 and Week 12) are administered. The Investigator, or designee, will evaluate the injection sites at these visits, and will document the presence or absence of local intolerance/injection site reactions and will open an AE in case of local injection site intolerance. Additional local injection tolerability assessments will be conducted at additional time points as specified in the SoA (Table 1). Additional follow-up after Week 48 can be performed for any ongoing injection site reactions.

8.3.5 Clinical Safety Laboratory Tests

All protocol-required laboratory tests, as defined in Table 4, must be conducted in accordance with the laboratory manual and at a central laboratory at the visits specified in the SoA (Table 1).

The Investigator must review and sign the laboratory results, document this review, and record any clinically significant changes occurring during the study as an AE if applicable (see Section 8.4.2). The laboratory results must be retained with source documents.

Abnormal laboratory findings associated with the underlying disease are not considered clinically significant unless judged by the Investigator to be more severe than expected for the subject's condition.

All laboratory tests with values considered clinically significantly abnormal during participation in the study should be repeated as soon as possible (preferably within 24 to 48 hours) until the values return to normal or baseline or are no longer considered clinically significant by the Investigator or Medical Monitor.

Urgent safety labs should be performed at the central laboratory, if possible. If urgent results are needed, testing can be sent to a local laboratory, but blood for the same tests should be obtained at the same time for central laboratory analysis, if possible.

Additional safety samples may be collected as clinically indicated at the discretion of the Investigator or as required by local regulations.

Every attempt should be made to redraw any missing safety laboratory tests, even if the subject has received the IP.

The laboratory results should be signed and dated and retained at the site as source data for laboratory variables.

Table 4 Clinical Laboratory Tests

Immunology	
ANA	Anti-SSA
Anti- dsDNA	Anti-SSB
Anti-Smith	C3 and C4
Anti-RNP	Rheumatoid factor
Hematology and coagulation	
Hemoglobin	PT/INR and PTT
Hematocrit	RBC count
Mean corpuscular hemoglobin concentration	Reticulocyte count
Mean corpuscular volume	WBC with differential
Platelet count	
Pregnancy tests	
Urine dipstick β-hCG	FSH [a]
Other laboratory tests	
HbA1c	pDC
Hs-CRP	Serum IgG, IgA, and IgM
Lipids (TC, TG, HDL-C, and LDL-C)	
Serum chemistry	
Albumin	Creatinine
ALT	eGFR
ALP	GGT
AST	Glucose
Bicarbonate	Potassium
Blood urea nitrogen	Sodium
Calcium	Total bilirubin
Chloride	Total protein
Creatine kinase	
Serum virology	
HBcAb (reflex DNA testing if isolated hepatitis B core positive)	
Urinalysis	
Dipstick	Leukocyte esterase
Appearance	pH
Bilirubin	Protein
Blood	Specific gravity
Color	Microscopy, including WBC/HPF, RBC/HPF, and casts
Epithelial cells	Urine creatinine and protein; spot UPCr
Glucose	
Ketones	

ALP = alkaline phosphatase; ALT = alanine aminotransferase; ANA = antinuclear antibodies; AST = aspartate aminotransferase; β-hCG = beta-human chorionic gonadotropin; C = complement; dsDNA = double-stranded DNA; eGFR = estimated glomerular filtration rate; FSH = follicle-stimulating hormone; GGT = gamma glutamyl transferase; HbA1c = glycosylated hemoglobin; HBcAb = hepatitis B core antibody; HDL-C = high-density lipoprotein-cholesterol; HIV = human immunodeficiency virus; HPF = high-power field; hs-

Table 4 Clinical Laboratory Tests

CRP = high-sensitivity C-reactive protein; Ig = immunoglobulin; INR = international normalized ratio; LDL-C = low-density lipoprotein-cholesterol; pDC = plasmacytoid dendritic cell; PT = prothrombin time; PTT = partial thromboplastin time; RBC = red blood cell; RNP = ribonucleoprotein; SSA = Sjögren's syndrome-related antibody A; SSB = Sjögren's syndrome-related antibody B; TC = total cholesterol; TG = triglycerides; UPCr = urine protein:creatinine ratio; WBC = white blood cell

a See Section 5.1 (inclusion criterion 3) for procedures to be followed if a female subject becomes postmenopausal during the study.

8.3.5.1 Hepatitis B Assessments

Hepatitis B DNA testing (Reflex DNA testing) will continue to be performed Q12W if the subject had an isolated hepatitis B core positive result in the RECAST SLE study. The IP will be discontinued if the subject's hepatitis B virus DNA levels are confirmed to exceed the lower limit of quantitation as per the central laboratory.

8.3.6 Pregnancy Testing

Urine pregnancy tests will be performed in women of childbearing potential during treatment and follow-up at the study site using a dipstick, as indicated in the SoA (Table 1). See Section 5.1 (inclusion criterion 3) for procedures to be followed if a female subject becomes postmenopausal during the study.

8.4 Adverse Events, Serious Adverse Events, and Other Safety Reporting

An external, independent SDMC will perform evaluations of safety data at specified regular intervals throughout the study and make recommendations to the Sponsor regarding further conduct of the study. See Section 10.1.5 for details on SDMC activities.

8.4.1 Definitions

- **Adverse event:** An AE is any untoward medical occurrence in a subject administered a pharmaceutical product and 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 (new or exacerbated) temporally associated with the use of an IP, whether or not considered related to the IP. Events that meet and do **not** meet the AE definition are provided in Appendix 2, Section 10.2.1.
- **Serious adverse event**: An event is considered "serious" if, in the view of either the Investigator or Sponsor, it results in any of the following outcomes:
  - Death
  - A life-threatening AE (An event is considered ″life-threatening″ if, in the view of either the Investigator or Sponsor, its occurrence places the subject(s) at immediate risk of death. It does not include an AE or suspected adverse reaction that, had it occurred in a more severe form, might have caused death.)
  - Inpatient hospitalization or prolongation of existing hospitalization
  - A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
  - A congenital anomaly/birth defect

  - Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the subject(s) or may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

  Additional information is provided in Appendix 2, Section 10.2.2.

- **Adverse reaction**: An adverse reaction is any AE caused by a drug.
- **Adverse event of special interest**: An AESI is an AE of scientific and medical interest specific to understanding of the IP and may require close monitoring and collection of additional information by the Investigator. An AESI may be serious or nonserious. The rapid reporting of AESIs allows ongoing surveillance of these events in order to characterize and understand them in association with the use of this IP.

  The following AESIs will be particularly monitored in this study:

  - Hypersensitivity reaction, including anaphylaxis
  - Severe (Grade 3 or higher) viral infections/reactivations
  - Opportunistic infection as listed in Appendix 6, Section 10.6 (all cases)
  - Malignancy (except nonmelanoma skin cancer)

8.4.2 Adverse Event Reporting

The Investigator and any qualified designees are responsible for detecting, documenting, and recording events that meet the definition of an AE or SAE and remain responsible for following up all AEs. This includes events reported by the subject (or, when appropriate, by a caregiver, surrogate, or the subject's legally authorized representative).

Report initiation for all AEs and SAEs will begin from the time of signing ICF and continue up until the final study visit. All events will be followed to resolution or until they are considered as a non-clinically significant event.

Adverse events reported by the subject, spontaneously or in response to an open question from the study personnel, and AEs revealed by observation will be recorded during the study at the investigational site.

Clinically significant abnormalities in vital signs, body weight, physical examination, laboratory parameters, and ECGs will be recorded as separate AEs or SAEs if they are not considered as part of pre-existing medical conditions or have already been recorded due to other AEs or SAEs. Worsening or new manifestations of SLE (eg, [redacted] do not have to be reported as AEs, unless they meet the criteria for a SAE. All AEs meeting criteria must be reported immediately.

For each AE, the Investigator will evaluate and report the onset (date and time), resolution (date and time), severity, causality, action taken, serious outcome (if applicable), and whether it caused the subject to discontinue the study. The AE term should be reported in standard medical terminology when possible.

Additional information is provided in Appendix 2, Section 10.2.3.

8.4.3 Classification of an Adverse Event

8.4.3.1 Causality or Relatedness

The Investigator is required to provide an assessment of the relationship of AEs and SAEs to the IP. The Investigator will use clinical judgment to determine the relationship.

An event will be considered "not related" to use of IP if any of the following are met:

- An unreasonable temporal relationship between administration of the IP and the onset of the event (eg, the event occurred either before, or too long after, administration of the IP for it to be considered IP related).
- A causal relationship between the IP and the event is biologically implausible (eg, death as a passenger in an automobile accident).
- A clearly more likely alternative explanation for the event is present (eg, typical adverse reaction to a concomitant drug and/or typical disease-related event).

Individual AE/SAE reports will be considered "related" to use of the IP if the "not related" criteria are not met.

"Related" implies that the event is considered to be "associated with the use of the drug" meaning that there is "a reasonable possibility" that the event may have been caused by the IP (ie, there are facts, evidence, or arguments to suggest possible causation).

Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to IP administration, will be considered and investigated.

For causality assessment, the Investigator will also consult the IB.

The Investigator must review and provide an assessment of causality for each AE/SAE and document this in the medical notes. There may be situations in which an SAE has occurred, and the Investigator has minimal information to include in the initial report to the Sponsor. However, it is very important that the Investigator always make an assessment of causality for every event before the initial transmission of the SAE data to the Sponsor.

The Investigator may change their opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.

The causality assessment is one of the criteria used when determining regulatory reporting requirements.

8.4.3.2 Severity or Intensity

The guidelines outlined in Common Terminology for Adverse Events (CTCAE) v5.0 will be used for assessing the severity or intensity of the event. The general guidelines for assessing the AE grade are provided in Table 5.

Table 5 CTCAE v5.0 General Guidelines

Grade	Description
Grade 1	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
Grade 2	Moderate; minimal, local, or noninvasive intervention indicated; limiting age-appropriate instrumental ADL [a].
Grade 3	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL [b].
Grade 4	Life-threatening consequences, urgent intervention indicated.
Grade 5	Death related to AE.

ADL = activities of daily living; AE = adverse event; CTCAE = Common Terminology for Adverse Events.
The CTCAE v5.0 is dated to 27 NOV 2017.

a Instrumental ADL refers to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.

b Self-care ADL refers to bathing, dressing, and undressing, feeding self, using the toilet, taking medications, and not bedridden.

8.4.4 Time Period and Frequency for Collecting AE and SAE Information

All AEs and SAE reporting will begin from the time of signing ICF and continue up until the final study visit at the time points specified in the SoA (Table 1). All events will be followed to resolution or until they are considered a non-clinically significant event.

Investigators are not obligated to actively seek information on AEs or SAEs after conclusion of the study participation. However, if the Investigator learns of any SAE, including a death, at any time after a subject has been discharged from the study, and the Investigator considers the event to be reasonably related to the IP or study participation, the Investigator must promptly notify the Sponsor.

8.4.5 Method of Detecting AEs and SAEs

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

8.4.6 Follow-up of AEs and SAEs

The Investigator is responsible for appropriate medical care of subjects during the study. After the initial AE/SAE report, the Investigator is required to proactively follow each subject at subsequent visits/contacts. All events will be followed to resolution or until they are considered a non-clinically significant event, or the event is otherwise explained, or the participant is lost to follow-up (as defined in Section 7.3).

Additional information regarding follow-up procedures is provided in Appendix 2, Section 10.2.3.

8.4.7 Regulatory Reporting Requirements for SAEs

Any death, life-threatening event, or other SAE and any pregnancy, overdose, and AESI experienced by a subject during the course of the study, whether or not judged related to the

investigational product, must be reported within 24 hours of knowledge of the event by entering the information into the eCRF. If unable to access the eCRF, the event must be reported by submitting the completed SAE form via email or fax to the contact numbers provided below.

- Email: clinicalsafety@horizontherapeutics.com
- Fax: (800) 860-7836

The event must be documented in source documentation and the eCRF. The following steps will be taken to report promptly and document accurately any SAE, whether or not it appears to be related to IP:

1. Report the SAE to the Sponsor by entering the information into the eCRF within 24 hours after becoming aware that a subject has experienced an SAE. If unable to access the eCRF, the event must be reported by submitting the completed SAE form by email to clinicalsafety@horizontherapeutics.com or fax within 24 hours after becoming aware that a subject has experienced an SAE.
2. Perform appropriate diagnostic tests and therapeutic measures, and submit all follow-up substantiating data, such as diagnostic test reports, hospital discharge summaries, and autopsy report to the Sponsor's representative.
3. Respond in a timely manner to any queries from Sponsor regarding the SAE.
4. Conduct appropriate consultation and follow-up evaluation until the SAE is resolved, stabilized, or otherwise explained by the Investigator.
5. Review each SAE report and evaluate the relationship of the IP.
6. Each Investigator must report all AEs or SAEs to its Institutional Review Board (IRB) or Independent Ethics Committee (IEC) in accordance with IRB or IEC requirements.

After receipt of the initial report, the information will be reviewed, and the Investigator may be contacted with requests for additional information or for data clarification.

Follow-up will be obtained via the eCRF, fax, or email, as necessary, until the event resolves or attains a stable outcome. Sponsor or designee is responsible for the preparation of MedWatch 3500 A/Council for International Organizations of Medical Sciences I forms and analysis of similar events for individual occurrences (to be submitted as Investigational New Drug [IND] safety letters to the FDA and Investigators according to Title 21 of the Code of Federal Regulations [21 CFR 312.32] by the Sponsor).

Additional information regarding SAE reporting via an electronic or paper data collection tool is provided in Appendix 2, Section 10.2.4.

8.4.8 Pregnancy

Pregnancy in a woman who has received IP must be reported to the Sponsor from time of signed ICF until end-of-study follow-up or 3 months (approximately 5 half-lives) following the last dose of IP in case of early withdrawal. The Investigator must report the pregnancy to the Sponsor or representative as if it were an SAE (ie, within 24 hours of learning of the pregnancy) Refer to Section 8.4.7 for additional information.

Subjects who become pregnant during the study period must not receive additional doses of IP. These subjects will discontinue IP and follow the IP discontinuation procedures (Section 7.1). While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy for medical reasons will be reported as an AE or SAE.

Abnormal pregnancy outcomes (eg, spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs and will be reported as such.

The subject will be followed to determine the outcome of the pregnancy. The Investigator will collect follow-up information on the subject and the neonate, and the information will be forwarded to the Sponsor after the outcome.

Should the Investigator become aware of a pregnancy in the partner of a male study subject who has received IP, this should be reported to the Sponsor within 24 hours of knowledge of the event (refer to Section 8.4.7 for additional information). The Sponsor will endeavor to collect follow-up information on such pregnancies, provided the partner of the study subject provides consent for disclosure of their information.

Any poststudy pregnancy-related SAE considered reasonably related to the IP by the Investigator will be reported to the Sponsor as described in Section 8.4.7. While the Investigator is not obligated to actively seek this information in former study subjects or pregnant female partner, he or she may learn of an SAE through spontaneous reporting.

8.4.9 Adverse Events of Special Interest

The Investigator must report AESIs to the Sponsor as if it were an SAE (ie, within 24 hours of learning of the AESI). Refer to Section 8.4.7 for contact information.

Definition of an AESI and AESIs that will be monitored in the study are provided in Section 8.4.1.

8.4.10 Overdose or Misuse

Any instance of overdose of IP (suspected or confirmed) must be communicated to the Sponsor as if it were an SAE (ie, within 24 hours of learning of overdose or misuse). Refer to Section 8.4.7 for additional information. Any associated AEs or SAEs must also be reported, and their management should be recorded as described in Section 8.4.7.

8.5 Pharmacokinetics

Serum for PK analysis will be collected at the visits specified in Table 1 and analyzed using a validated bioanalytical method.

Samples will be collected, labeled, stored, and shipped as detailed in the laboratory manual. The time of PK sample collection must be recorded.

The timing of sampling may be altered during the course of the study based on newly available data (eg, to obtain data closer to the time of peak plasma concentrations) to ensure appropriate monitoring.

Samples will be used to evaluate the PK of daxdilimab. Samples collected for analyses of daxdilimab serum concentration may also be used to evaluate safety or efficacy aspects related to concerns arising during or after the study.

Genetic analyses will not be performed on these samples.

8.6 Pharmacodynamics

Whole blood will be collected for the assessment of pDC levels by flow cytometry at the visits specified in the SoA (Table 1). Daxdilimab binds to ILT7 on the surface of pDCs leading to recruitment of macrophages and NK cells, thus inducing apoptosis and reduction in the number of pDCs.

Samples will be analyzed using a validated analytical method in compliance with the Sponsor's standard operating procedures and analytical requirements. Instructions for sample collection, processing, storage, and shipment are provided in the study-site manual.

8.7 Genetics

Genetics will not be evaluated in this study.

[redacted]

8.9 Immunogenicity Assessments

Serum for immunogenicity ADA analysis will be collected at the visits specified in Table 1 and assessed using a validated immunoassay. Additionally, serum samples should also be collected at the final visit from subjects who discontinued IP or were withdrawn from the study. These samples will be tested by the Sponsor or Sponsor's designee.

The ADA samples will be collected at the same time as the PK samples and the time of sample collection must be recorded.

Serum samples will be screened for antibodies binding to daxdilimab and the titer of confirmed positive samples will be reported. Other analyses may be performed to further characterize the immunogenicity of daxdilimab.

Antibodies may be further characterized and/or evaluated for their ability to neutralize the activity of daxdilimab. Samples may be stored for a maximum of 25 years (or according to local

regulations) following the last subject's last visit for the study at a facility selected by the Sponsor to enable further analysis of immune responses to daxdilimab.

Samples will be collected, labeled, stored, and shipped as detailed in the study-site manual.

[redacted]

9 STATISTICAL CONSIDERATIONS

9.1 Primary Hypothesis

No formal statistical hypothesis will be evaluated in the SLE OLE study.

9.2 Analysis Sets

Safety analysis set: The safety analysis set is defined as subjects who received any dose of daxdilimab in this OLE study. The safety, PD, immunogenicity, and exploratory efficacy analyses will be based on the safety analysis set.

Pharmacokinetic analysis set: The PK analysis set is defined as subjects who received any dose of daxdilimab in this OLE study and have at least one measurable PK concentration post dose. The PK analyses will be based on PK analysis set.

9.3 Statistical Analyses

9.3.1 General Considerations

For continuous data, number of observations, mean, standard deviation, median, minimum, and maximum will be reported. For categorical data, percent and frequency will be reported. Data listings will be sorted by treatment group and subject number. Details of the statistical analysis will be specified in a separate SAP.

9.3.2 Primary Endpoint(s) Analysis

9.3.2.1 Safety Analysis

Adverse events will be coded using the Medical Dictionary for Regulatory Activities by system organ class (SOC) and preferred term (PT). In general, if an AE onset is on or after the first OLE dose date, the AE will be considered as a treatment-emergent AE (TEAE) for OLE. All TEAEs will be summarized overall and by SOC and PT, as well as by severity and by relationship to daxdilimab.

For the summary of TEAEs by severity, each participant will be counted only once within a SOC or a PT by using the AEs with the highest intensity within each category. For the summary of TEAEs by relationship to IP, each participant will be counted only once within a SOC or a PT by using the AEs with the greatest reported relationship within each category. TEAE leading to discontinuation of daxdilimab will be summarized by SOC and PT. Treatment-emergent SAEs and treatment-emergent AESIs will also be summarized.

Clinically significant abnormalities in laboratory parameters, vital signs, ECGs, and physical examinations will be recorded as AEs or SAEs. Laboratory assessments, vital signs, and ECGs, as well as their changes from baseline at each visit will also be summarized descriptively.

9.3.3 Secondary Endpoint(s) Analysis

9.3.3.1 Pharmacokinetics Analysis

The PK analysis will be based on the PK analysis set. Descriptive statistics of the serum daxdilimab concentration will be tabulated by visit.

9.3.3.2 Immunogenicity Analysis

Number and percentage of subjects who develop positive ADA will be summarized descriptively.

9.3.3.3 Pharmacodynamics Analysis

The observed count along with the change and percent change from baseline in pDCs will be summarized descriptively.

9.3.4 Exploratory Endpoint(s)Analyses

The exploratory efficacy analyses will be detailed in the SAP.

9.4 Interim Analysis

An interim analysis will not be performed.

9.5 Sample Size Determination

Sample size determination is based on the number of subjects who have completed the treatment period of Study VIB7734.P2.S1 (RECAST SLE). A total of 195 subjects have been randomized in the RECAST SLE study. Assuming that 20% of subjects will prematurely discontinue treatment, there will be a total of approximately 156 subjects who will be eligible for this long-term safety study.

10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1 Appendix 1: Regulatory, Ethical, and Study Oversight Considerations

10.1.1 Regulatory and Ethical Considerations

- This study will be conducted in accordance with the protocol and with the following:
  - Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and the Council for International Organizations of Medical Sciences international ethical guidelines
  - Applicable International Council for Harmonisation (ICH) Good Clinical Practice (GCP) guidelines
  - Applicable laws and regulations
- The protocol, protocol amendments, informed consent form, Investigator's brochure, and other relevant documents (eg, advertisements) must be submitted to an Institutional IRB/IEC by the Investigator and reviewed and approved by the IRB/IEC before the study is initiated.
- Any amendments to the protocol will require IRB/IEC approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study subjects.
- Protocols and any substantial amendments to the protocol will require health authority approval prior to initiation except for changes necessary to eliminate an immediate hazard to study subjects.
- The Investigator will be responsible for the following, as applicable:
  - Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC
  - Notifying the IRB/IEC of SAEs or other significant safety findings as required by IRB/IEC procedures
  - Providing oversight of the conduct of the study at the site and adherence to requirements of 21 CFR, ICH guidelines, the IRB/IEC, European regulation 536/2014 for clinical studies, European Medical Device Regulation 2017/745 for clinical device research, and all other applicable local regulations

10.1.2 Financial Disclosure

Investigators and sub-Investigators will provide the Sponsor with sufficient, accurate financial information as requested to allow the Sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the course of the study and for one year after completion of the study.

10.1.3 Informed Consent Process

The Investigator or the Investigator's representative will explain the nature of the study, including the risks and benefits, to the potential subject (or their legally authorized representative) and answer all questions regarding the study.

Potential subjects must be informed that their participation is voluntary. They (or their legally authorized representatives) will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, privacy and data protection requirements, where applicable, and the IRB/IEC or study site.

It is the responsibility of the Investigator (or their designee, where allowed by local requirements) to obtain written informed consent from all study subjects. The Investigator or their designee must provide the Sponsor/designee with a copy of the IRB/IEC-approved informed consent document(s) prior to the start of the study at the site. The informed consent must allow for access to the records for at least 25 years to allow for possible future inspections.

The medical record must include a statement that written informed consent was obtained before the subject was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.

Subjects must be reconsented to the most current version of the ICF(s) during their participation in the study.

The original, appropriately signed and dated ICF must be retained by the Investigator/study site as part of that subject's record. A copy of the signed ICF must be given to the subject.

The ICF must be fully approved by an IRB or an IEC prior to its use with study subjects.

The Sponsor reserves the right to delay initiation of the study at a site where the informed consent document(s) do not meet the standards of this section, applicable regulations, and/or ICH E6(R2).

The ICF will contain a separate section that addresses the use of leftover samples for future research. The investigator or authorized designee will explain to each subject the objectives of the future research. Subjects will be told that they are free to refuse to participate and may withdraw their consent at any time and for any reason during the storage period. A separate signature will be required to document a subject's agreement to allow any leftover samples to be used for future research. Subjects who decline to participate in this future research will not provide this separate signature.

10.1.4 Data Protection and Privacy

All information generated in this study is considered highly confidential and must not be disclosed to any person or entity not directly involved with the study unless prior written consent is obtained from the Sponsor. The subject must be informed that their medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the Sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

Subjects will be assigned a unique identifier by the Sponsor. Any subject records or datasets that are transferred to the Sponsor will contain the identifier only; subject names or any information which would make the subject identifiable will not be transferred.

The subject must be informed that their personal study-related data will be used by the Sponsor in accordance with local data protection law. The level of disclosure must also be explained to the subject who will be required to give consent for their data to be used as described in the informed consent

The contract between Sponsor and study sites specifies responsibilities of the parties related data protection, including handling of data security breaches and respective communication and cooperation of the parties.

Information technology systems used to collect, process, and store study-related data are secured by technical and organizational security measures designed to protect such data against accidental or unlawful loss, alteration, or unauthorized disclosure or access.

10.1.5 Committees Structure

10.1.5.1 Safety Data Monitoring Committee

The external, independent Safety Data Monitoring Committee (SDMC) is responsible for safeguarding the interests of study subjects via review of accumulating safety data and for supporting study integrity and interpretability based on their review of ongoing study conduct. The SDMC will provide the Sponsor with recommendations for actions with respect to study conduct and the management of subjects treated under the study protocol. The SDMC members are independent of the Sponsor and any CRO/organization collaborating with the Sponsor on the study.

The SDMC will not be charged with any formal interim analysis, will not conduct a futility analysis, and will not be asked to consider early study completion for efficacy. For additional details, refer to the SDMC Charter.

10.1.6 Dissemination of Clinical Study Data

The Sponsor is responsible for preparing and providing the appropriate regulatory authorities with clinical study reports, according to the applicable regulatory requirements.

A description of this clinical study will be available on http://www.clinicaltrials.gov, as will the summary of the main study results when they are available.

10.1.7 Biological Specimens and Data

Study data are protected by using a subject identification number, which is a number specific to the subject. The Investigator is in control of the information that is needed to connect a study sample to a subject; a subject may withdraw consent at any time by notifying the Investigator. If consent is withdrawn, any samples collected prior to that time may still be given to and used by the Sponsor, but no new data or samples will be collected unless specifically required to monitor the safety of the subject.

Leftover samples stored for future research with subject consent will be labeled with a sample identification number. If the subject consents to have his/her samples used for future research, this additional research may not start immediately and may start at any time during the storage period. The subject's sample(s) will be stored by the Sponsor with similar samples in a secure laboratory. The subject's samples will not be kept for more than 25 years after the end of the

study in which they were collected. If the subject chooses not to allow his/her study samples to be used for future research, the samples will be destroyed by the Sponsor once they are no longer required for the main study. If future use consent is withdrawn, the Sponsor and the Investigator will ensure that the subject's sample(s) are destroyed unless the identification number has been removed and the subject can no longer be linked to any samples. However, if the subject's sample has already been used for research, the Sponsor is not required to destroy the results of this research. In this case, only the remaining sample(s) will be destroyed.

10.1.8 Data Quality Assurance

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

Guidance on completion of CRFs will be provided in eCRF completion guidelines.

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

Monitoring details describing strategy, including definition of study critical data items and processes (eg, risk-based initiatives in operations and quality such as risk management and mitigation strategies and analytical risk-based monitoring), methods, responsibilities, and requirements, including handling of noncompliance issues and monitoring techniques (central, remote, or on-site monitoring) are provided in the monitoring plan and centralized monitoring plan.

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

The Sponsor assumes accountability for actions delegated to other individuals (eg, contract research organizations).

See Section 10.1.8.1 for details regarding study monitoring and Section 10.1.8.2 for details regarding the audit process.

10.1.8.1 Monitoring

The Sponsor and any third party to whom aspects of study management or monitoring have been delegated, will undertake their roles in accordance with all applicable regulations and ICH E6(R2).

A representative of the Sponsor and/or its designee will perform periodic monitoring of the study to ensure compliance with ICH GCP guidelines and regulatory requirements. The Sponsor's designated representatives (the Study Monitors) will inspect the site's study documentation (including qualification and training of site personnel, IRB communications, etc), study data, subjects' original medical records, and completed eCRFs. The Investigator agrees to allow unblinded Study Monitors to inspect the drug storage area, IP stocks, drug accountability records, subject charts, original study source documents (regardless of media), and other records relative to study conduct. The Study Monitors will maintain frequent contact with the

investigational site and meet with the Investigator and site staff throughout the course of the study.

The Investigator will facilitate monitoring activities and the Study Monitors' access to required records.

During scheduled monitoring visits, the Investigator and the investigational site staff must be available to meet with the Study Monitor in order to discuss the progress of the study, make necessary corrections to eCRF entries, respond to data clarification requests, and respond to any other study-related inquiries from the Study Monitor.

10.1.8.2 Audits/Inspections

To ensure compliance with GCP and all applicable regulatory requirements, the Sponsor or its authorized representatives may conduct a quality assurance audit. Local or foreign regulatory authorities may conduct regulatory inspections. Regulatory inspections may be in response to a marketing application, and this may occur years after completion of the clinical study.

Authorized representatives of the Sponsor, a regulatory authority, an IEC, and/or an IRB may visit the site to perform audits or inspections, including review of original medical records. The purpose of a Sponsor audit or regulatory inspection is to systematically and independently examine all study-related activities and documents to determine whether these activities were conducted, and data were recorded, analyzed, and accurately reported according to the protocol, ICH GCP guidelines, and any applicable regulatory requirements.

Initial IRB/IEC approval, and all materials approved by the IRB/IEC for this study, including the ICF and recruitment materials, must be maintained by the Investigator and made available for inspection.

In addition to the above, representatives of the Sponsor auditing staff or government inspectors may review the conduct/results of the study at the investigational site. The Investigator should contact the Sponsor immediately if contacted by a regulatory agency about an inspection. The Investigator cooperates with the auditor(s), makes available to the auditor all requested documentation, and ensures that issues detected during these audits are satisfactorily resolved. The Investigator supplies the Sponsor with copies of all documentation and correspondence related to regulatory agency audits as outlined in the Clinical Trial Agreement. If the results of the audit result in a Form FDA 483 (or similar document from another regulatory agency), the Investigator promptly provides a copy to a Sponsor representative and a draft response to the Sponsor prior to submission to the regulatory agency.

10.1.9 Data Capture and Management

Clinical Data Management (CDM) will be performed according to the Data Management Plan (DMP). The DMP will document procedures and roles and responsibilities related to CDM activities, including data validation, data transfer and reconciliation, CDM communications, medical coding and dictionaries, CDM reports, and data formats. An electronic data capture system compliant with 21 CFR Part 11 will be used for data collection and query handling. The Investigator will ensure that data are recorded in the eCRFs as specified in the study protocol and in accordance with the eCRF completion guidelines provided. The Investigator ensures the accuracy, completeness, and timeliness of the data recorded and of the provision of answers to

data queries. The Investigator will sign the completed eCRFs electronically. Upon completion of the study, a copy of the completed eCRFs will be provided to the study site for archival purposes.

10.1.10 Source Documents

Source documents provide evidence for the existence of the subject and substantiate the integrity of the data collected. Source documents are filed at the Investigator's site.

Data reported on the CRF or entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The Investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.

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

The Sponsor or designee will perform monitoring to confirm that data entered into the CRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of subjects are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.

10.1.11 Records Retention

Essential documents should be retained 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 IP. These documents should be retained for a longer period, however, if required by applicable regulatory requirement.

The Investigator may not destroy any study records without written permission from the Sponsor.

10.1.12 Study and Site Start and Closure

First Act of Recruitment

The study start date is the date on which the clinical study will be open for recruitment of subjects.

The first act of recruitment is the first subject enrolled.

Study/Site Termination

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

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

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

For site termination:

- Failure of the Investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the Sponsor's procedures, or GCP guidelines
- Inadequate or no recruitment (evaluated after a reasonable amount of time) of subjects by the Investigator
- Total number of subjects included earlier than expected

The reasons for suspending or terminating the study may include, but are not limited to, the following:

- The incidence or severity of AEs in this or other studies indicates a potential health hazard to participants.
- Participant enrollment is unsatisfactory.
- Noncompliance that might significantly jeopardize the validity or integrity of the study.
- Sponsor decision to terminate development.

If the Sponsor determines that temporary suspension or termination of the study is required, the Sponsor will discuss the reasons for taking such action with all participating Investigators. When feasible, the Sponsor will provide advance notice to all participating Investigators of the impending action.

If the study is suspended or terminated for safety reasons, the Sponsor will promptly inform all Investigators and/or institutions conducting the study. The Sponsor will also promptly inform the relevant regulatory authorities of the suspension/termination along with the reasons for such action. Where required by applicable regulations, the Investigator must inform the IRB or IEC promptly and provide the reason(s) for the suspension/termination. If the study is suspended for safety reasons and it is deemed appropriate by the Sponsor to resume the study, approval from the relevant regulatory authorities (and IRBs/IECs when applicable) will be obtained prior to resuming the study.

10.1.13 Publication Policy

The Sponsor is responsible for preparing and providing the appropriate regulatory authorities with clinical study reports, according to the applicable regulatory requirements.

10.2 Appendix 2: Adverse Events and Serious Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

10.2.1 Definition of AE

AE Definition

- An AE is any untoward medical occurrence in a subject administered a pharmaceutical product and 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 (new or exacerbated) temporally associated with the use of an IP, whether or not considered related to the IP.

Events Meeting the AE Definition

- Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (eg, ECG, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the Investigator (ie, not related to progression of underlying disease, or more severe than expected for the subject's condition)
- Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition
- New condition detected or diagnosed after IP administration even though it may have been present before the start of the study
- Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction
- Signs, symptoms, or the clinical sequelae of a suspected overdose of either IP or a concomitant medication. Overdose per se will not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae.

Events <u>not</u> Meeting the AE Definition

- Any abnormal laboratory findings or other abnormal safety assessments that are associated with the underlying disease, unless judged by the Investigator to be more severe than expected for the subject's condition
- The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the subject's condition
- Medical or surgical procedure (eg, endoscopy, appendectomy): the condition that leads to the procedure is the AE
- Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital)
- Anticipated day-to-day fluctuations of preexisting disease(s) or condition(s) present or detected at the start of the study that do not worsen

10.2.2 Definition of SAE

An SAE is defined as any untoward medical occurrence that, at any dose, meets one or more of the criteria listed:

- Results in death
- Is life-threatening

The term *life-threatening* in the definition of *serious* refers to an event in which the subject was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.

- Requires inpatient hospitalization or prolongation of existing hospitalization
  - In general, hospitalization signifies that the subject has been admitted (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether hospitalization occurred or was necessary, the AE should be considered serious.
  - Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.
- Results in persistent or significant disability/incapacity
  - The term disability means a substantial disruption of a person's ability to conduct normal life functions.
  - This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (eg, sprained ankle) that may interfere with or prevent everyday life functions but do not constitute a substantial disruption.
- Is a congenital anomaly/birth defect
- Other situations:
  - Medical or scientific judgment should be exercised by the Investigator in deciding whether SAE reporting is appropriate in other situations such as important medical events that that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the subject or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious.
    - Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias, convulsions not resulting in hospitalization, or development of intervention dependency or intervention abuse.

10.2.3 Recording and Follow-Up of AEs and/or SAEs

AE and SAE Recording

When an AE/SAE occurs, it is the responsibility of the Investigator to review all documentation (eg, hospital progress notes, laboratory reports, and diagnostics reports) related to the event.

The Investigator will then record all relevant AE/SAE information.

It is not acceptable for the Investigator to send photocopies of the subject's medical records to the Sponsor in lieu of completion of the required form.

There may be instances when copies of medical records for certain cases are requested. In this case, all subject identifiers, with the exception of the subject number, will be redacted on the copies of the medical records before submission.

The Investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

Follow-up of Adverse Events and Serious Adverse Events

The Investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by the Sponsor to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.

[If a subject dies during participation in the study or during a recognized follow-up period, the Investigator will provide the Sponsor with a copy of any postmortem findings including histopathology.]

New or updated information will be recorded in the originally submitted documents.

The Investigator will submit any updated SAE data to the Sponsor within 24 hours of receipt of the information.

10.2.4 Reporting of SAEs

SAE Reporting via an Electronic Data Collection Tool

The primary mechanism for reporting an SAE will be the electronic data collection tool.

If the electronic system is unavailable, then the site will use the paper SAE data collection tool (see next section) to report the event within 24 hours. The site will enter the SAE data into the electronic system as soon as it becomes available.

After the study is completed at a given site, the electronic data collection tool will be taken offline to prevent the entry of new data or changes to existing data.

If a site receives a report of a new SAE from a study subject or receives updated data on a previously reported SAE after the electronic data collection tool has been taken offline, then the site can report this information on a paper SAE form (see next section).

Contacts for SAE reporting can be found in Section 8.4.7.

Note that AESIs, pregnancies, overdose, or misuse experienced by a subject during the study, whether or not judged related to investigational product, must also be reported within 24 hours of knowledge of the event.

SAE Reporting via Paper Data Collection Tool

Note that SAE reporting via paper forms will only serve as backup if the electronic system were to be temporarily unavailable due to unforeseen reasons. This will ensure safety events are still reported within 24 hours of knowledge of the event. Initial reporting via email or fax does not replace the need for the Investigator to complete and sign the SAE data collection tool within the electronic system. In such cases, the electronic SAE form will be completed within the electronic system when it becomes available.

The paper SAE report forms are available in the Investigator site file and must be completed by the PI by signing and dating the SAE report form, verifying the accuracy of the information recorded in the form with the source documents, and sending the SAE form to the Sponsor.

Contacts for SAE reporting can be found in Section 8.4.7.

10.3 Appendix 3: Contraceptive Guidance

Highly effective methods of contraception are provided in Table 6.

Table 6 Highly Effective Methods of Contraception

Physical Methods	Hormonal Methods [a]
Intrauterine device Intrauterine hormone-releasing system [b] Bilateral tubal occlusion Vasectomized partner [c] Sexual abstinence [d]	Combined (estrogen and progestogen-containing hormonal contraception) PO (combined pill) Injectable Transdermal (patch) Progestogen-only hormonal contraception associated with inhibition of ovulation [e] Injectable Implantable Intravaginal

PO = oral(ly).

a A change in birth control method is allowed during the study. If a change occurs, unless the subject is changing the method to complete abstinence, the subject must employ a barrier method in addition to the highly effective method of contraception for at least 2 months.

b This is also considered to be a hormonal method.

c A vasectomized partner is a highly effective method of birth control provided that partner is the sole sexual partner of the woman of childbearing potential study subject and that the vasectomized partner has received medical assessment of the surgical success.

d Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of the study and if it is the preferred and usual lifestyle of the subject.

e Progestogen-only hormonal contraception where inhibition of ovulation is not the primary mode of action (minipill) is not accepted as a highly effective method.

10.4 Appendix 4: Liver Safety: Suggested Actions and Follow-up Assessments

This Appendix describes the process to be followed to identify and appropriately report potential Hy's Law (PHL) cases and Hy's Law (HL) cases. It is not intended to be a comprehensive guide to the management of elevated liver biochemistries.

During this study, the Investigator will remain vigilant for increases in liver biochemistry. The Investigator is responsible for determining whether a subject meets potential PHL criteria at any point during the study.

All sources of laboratory data are appropriate for the determination of PHL and HL events; this includes samples taken at scheduled study visits and other visits including central and all local laboratory evaluations even if collected outside of the study visits; for example, PHL criteria could be met by an elevated alanine aminotransferase (ALT) from a central laboratory and/or elevated total bilirubin (TBL) from a local laboratory.

The Investigator will also review AE data (for example, for AEs that may indicate elevations in liver biochemistry) for possible PHL events.

The Investigator participates, together with the Sponsor's clinical project representatives, in review and assessment of cases meeting PHL criteria to agree whether HL criteria are met. Hy's Law criteria are met if there is no alternative explanation for the elevations in liver biochemistry other than drug-induced liver injury caused by the IP.

The Investigator is responsible for recording data pertaining to PHL/HL cases and for reporting SAEs and AEs according to the outcome of the review and assessment in line with standard safety reporting processes.

Definitions

PHL is defined as:

- Aspartate aminotransferase (AST) or ALT ≥ 3 × upper limit of normal (ULN) together with TBL ≥ 2 × ULN at any point during the study following the start of IP irrespective of an increase in alkaline phosphatase (ALP).

HL is defined as:

- AST or ALT ≥ 3 × ULN together with TBL ≥ 2 × ULN, where no other reason, other than the IP, can be found to explain the combination of increases, eg, elevated ALP indicating cholestasis, viral hepatitis, or another drug.

For PHL and HL, the elevation in transaminases must precede or be coincident with (ie, on the same day) the elevation in TBL, but there is no specified timeframe within which the elevations in transaminases and TBL must occur.

To identify cases of PHL, it is important to perform a comprehensive review of laboratory data for any subject who meets any of the following identification criteria in isolation or in combination:

- ALT ≥ 3 × ULN
- AST ≥ 3 × ULN
- TBL ≥ 2 × ULN

10.5 Appendix 5: National Institute of Allergy and Infectious Disease and Food and Allergy Anaphylaxis Network Guidance for Anaphylaxis Diagnosis

National Institute of Allergy and Infectious Disease (NIAID) and Food and Allergy Anaphylaxis Network (FAAN) define anaphylaxis as a serious allergic reaction that is rapid in onset and may cause death (Sampson et al, 2006). They recognize 3 categories of anaphylaxis, with criteria designated to capture from 80% of cases (Category 1) to > 95% of all cases of anaphylaxis (for all 3 categories).

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 ONE OF THE FOLLOWING:
    a. Respiratory compromise (eg, dyspnea, wheeze-bronchospasm, stridor, reduced peak expiratory function [PEF], hypoxemia).
    b. 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 patient (minutes to several hours):
    a. Involvement of the skin-mucosal tissue (eg, generalized hives, itch-flush, swollen lips-tongue-uvula).
    b. Respiratory compromise (eg, dyspnea, wheeze-bronchospasm, stridor, reduced PEF, hypoxemia).
    c. Reduced blood pressure or associated symptoms (eg, hypotonia [collapse], syncope, incontinence).
    d. Persistent gastrointestinal symptoms (eg, crampy abdominal pain, vomiting).
3. Reduced blood pressure after exposure to known allergen for that subject (minutes to several hours):
    a. Infants and children ─ low systolic blood pressure (age specific) or greater than 30% decrease in systolic blood pressure.
    b. Adults ─ systolic blood pressure of less than 90 mmHg or greater than 30% decrease from that patient's baseline.

10.6 Appendix 6: Study-Specified Opportunistic Infections

The study-specified opportunistic infections that will monitored in this study are provided in Table 7.

Table 7 Study-Specified Opportunistic Infections

Definite [a,b] Opportunistic Infection	Probable [c] Opportunistic Infection
Pneumocystis jirovecii BK virus disease, including polyomavirus-associated nephropathy CMV disease Post-transplant lymphoproliferative disorder (EBV) Progressive multifocal leukoencephalopathy Bartonellosis (disseminated disease only) Blastomycosis Toxoplasmosis Coccidioidomycosis Histoplasmosis Aspergillosis (invasive disease only) Candidiasis (invasive disease or pharyngeal) Cryptococcosis Other invasive fungi: Mucormycosis (zygomycosis) (*Rhizopus*, *Mucor*, and *Lichtheimia*), *Scedosporium/Pseudallescheria boydii, Fusarium*) Legionellosis *Listeria monocytogenes* (invasive disease only) TB Nocardiosis Non-tuberculous mycobacterium disease Salmonellosis (invasive disease only) HBV reactivation Herpes simplex (invasive disease only) Herpes zoster (any form) Strongyloides (hyperinfection syndrome and disseminated forms only)	Paracoccidioides infections *Penicillium marneffei* (talaromyces) Sporothrix schenckii Cryptosporidium species (chronic disease only) Microsporidiosis Leishmaniasis (visceral only) *Trypanosoma cruzi* infection (Chagas's disease) (disseminated disease only) Campylobacteriosis (invasive disease only) Shigellosis (invasive disease only) Vibriosis (invasive disease due to *Vibrio vulnificus*) HCV progression

CMV = cytomegalovirus; EBV = Epstein-Barr virus; HBV = hepatitis B virus; HCV = hepatitis C virus; TB = tuberculosis

a Generally does not occur in the absence of immunosuppression, but whose presence indicates a potential or likely alteration in host immunity.

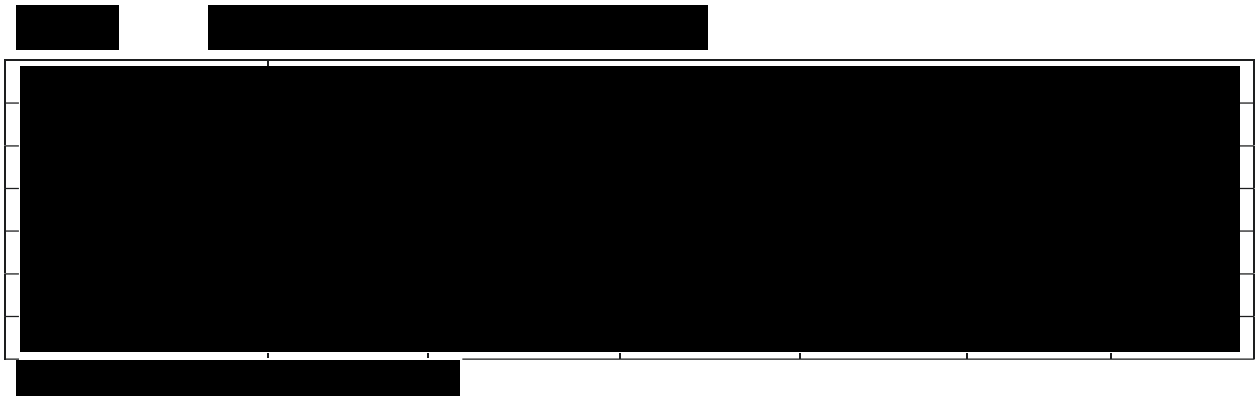
b Can occur in subjects without recognized forms of immunosuppression, but whose presence indicates a potential or likely alteration in host immunity.

c Published data are currently lacking, but expert opinion believes that risk is likely elevated in the setting of biologic therapy.

Source: Winthrop et al, 2015

10.7 Appendix 7: Prednisone Equivalent of Oral Glucocorticoid Dose

Oral GCs other than prednisone may be used PO at the equivalent doses shown in Table 8.



10.8 Appendix 8: Recommended Oral Glucocorticoid Tapering Schedule

To provide guidance to Investigators, a recommended OGC tapering regimen is provided in Table 9.

Table 9 Recommended Oral Glucocorticoid Tapering Schedule

Visit	Dose of Oral Prednisone or Equivalent at Start of Study [a]				
Week 0	40 mg	30 mg	20 mg	10 mg	7.5 mg [b]
Week 4	30 mg	22.5 mg	15 mg	7.5 mg	5 mg
Week 8	20 mg	15 mg	10 mg	5 mg	4 mg
Week 12	12.5 mg	10 mg	7.5 mg	4 mg	3 mg
Week 16	7.5 mg	7.5 mg	5 mg	3 mg	2 mg
Week 20	5 mg	5 mg	4 mg	2 mg	1 mg
Week 24	4 mg	4 mg	3 mg	1 mg	Discontinue
Week 28	3 mg	3 mg	2 mg	Discontinue	Discontinue
Week 32	2 mg	2 mg	1 mg	Discontinue	Discontinue
Week 36	1 mg	1 mg	Discontinue	Discontinue	Discontinue
Week 40	Discontinue	Discontinue	Discontinue	Discontinue	Discontinue
Week 44	Discontinue	Discontinue	Discontinue	Discontinue	Discontinue
Week 48	Discontinue	Discontinue	Discontinue	Discontinue	Discontinue

OGC = oral glucocorticoid

The OGC tapering schedule represents an example of a tapering regimen to provide guidance to Investigators in the approach to steroid taper throughout the study with the aim to lower the daily dose OGC to total discontinuation if clinically possible throughout the study.

a Specified prednisone dose is dose at the beginning of the week.

b Subjects entering study at < 7.5 mg/day dose of OGC must taper until full discontinuation if clinically possible. It is encouraged that Investigators taper each month by at least 1 mg/day.

11 REFERENCES

Aringer et al, 2019

Aringer M, Costenbader K, Daikh D, Brinks R, Mosca M, Ramsey-Goldman R, et al. 2019 European League Against Rheumatism/American College of Rheumatology Classification Criteria for Systemic Lupus Erythematosus. Arthritis Rheumatol. 2019;71(9):1400-12.

Arora et al, 2020

Arora S, Isenberg DA, Castrejon I. Measures of Adult Systemic Lupus Erythematosus: Disease Activity and Damage. Arthritis Care Res (Hoboken). 2020 Oct;72 Suppl 10:27-46.

Cho et al, 2008

Cho M, Ishida K, Chen J, Ohkawa J, Chen W, Namiki S, et al. SAGE library screening reveals ILT7 as a specific plasmacytoid dendritic cell marker that regulates type I IFN production. Int Immunol. 2008;20(1):155-64.

Doria et al, 2014

Doria A, Gatto M, Zen M, Iaccarino L, Punzi L. Optimizing outcome in SLE: treating-to-target and definition of treatment goals. Autoimmun Rev. 2014;13(7):770-7.

Feldman et al, 2013

Feldman CH, Hiraki LT, Liu J, Fischer MA, Solomon DH, Alarcón GS, et al. Epidemiology and sociodemographics of systemic lupus erythematosus and lupus nephritis among US adults with Medicaid coverage, 2000-2004. Arthritis Rheum. 2013;65(3):753-63.

Franklyn et al, 2016

Franklyn K, Lau CS, Navarra SV, Louthrenoo W, Lateef A, Hamijoyo L, et al. Definition and initial validation of a Lupus Low Disease Activity State (LLDAS). Ann Rheum Dis. 2016;75(9):1615-21.

Furie et al, 2011

Furie R, Petri M, Zamani O, Cervera R, Wallace DJ, Tegzová D, et al. A phase III, randomized, placebo-controlled study of belimumab, a monoclonal antibody that inhibits B lymphocyte stimulator, in patients with systemic lupus erythematosus. Arthritis Rheum. 2011;63(12):3918-30.

Furie et al, 2017

Furie R, Khamashta M, Merrill JT, Werth VP, Kalunian K, Brohawn P, et al. Anifrolumab, an anti-interferon-α receptor monoclonal antibody, in moderate-to-severe systemic lupus erythematosus. Arthritis Rheumatol. 2017;69(2):376-86.

Furie et al, March 2019

Furie R, Werth VP, Merola JF, Stevenson L, Reynolds TL, Naik H, et al. Monoclonal antibody targeting BDCA2 ameliorates skin lesions in systemic lupus erythematosus. J Clin Invest. 2019;129(3):1359-71.

Furie et al, November 2019

Furie RA, Morand EF, Bruce IN, Manzi S, Kalunian KC, Vital EM, et al. Type I interferon inhibitor anifrolumab in active systemic lupus erythematosus (TULIP-1): a randomised, controlled, phase 3 trial. Lancet Rheumatol. 2019;1(4):e208-19.

Helmick et al 2008

Helmick CG, Felson DT, Lawrence RC, Gabriel S, Hirsch R, Kwoh CK, et al. Estimates of the prevalence of arthritis and other rheumatic conditions in the United States. Part I. Arthritis Rheum. 2008;58(1):15-25.

Holloway et al, 2014

Holloway L, Humphrey L, Heron L, Pilling C, Kitchen H, Højbjerre L, et al. Patient-reported outcome measures for systemic lupus erythematosus clinical trials: a review of content validity, face validity and psychometric performance. Health Qual Life Outcomes. 2014;12:116.

Huang et al, 2015

Huang X, Dorta-Estremera S, Yao Y, Shen N, Cao W. Predominant role of plasmacytoid dendritic cells in stimulating systemic autoimmunity. Front Immunol. 2015;6:526.

Jimenez et al, 2003

Jimenez S, Cervera R, Font J, Ingelmo M. The epidemiology of systemic lupus erythematosus. Clin Rev Allergy Immunol. 2003;25(1):3-12.

Jin et al, 2010

Jin O, Kavikondala S, Mok MY, Sun L, Gu J, Fu R, et al. Abnormalities in circulating plasmacytoid dendritic cells in patients with systemic lupus erythematosus. Arthritis Res Ther. 2010;12(4):R137.

Jolly, 2005

Jolly M. How does quality of life of patients with systemic lupus erythematosus compare with that of other common chronic illnesses? J Rheumatol. 2005;32(9):1706-8.

Jolly et al, 2010

Jolly M, Pickard AS, Wilke C, Mikolaitis RA, Teh LS, McElhone K, et al. Lupus-specific health outcome measure for US patients: the LupusQoL-US version. Ann Rheum Dis. 2010;69(1):29-33.

Karnell et al, 2021

Karnell JL, Wu Y, Mittereder N, Smith MA, Gunsior M, Yan L, VIB7734 Trial Investigators, et al. Depleting plasmacytoid dendritic cells reduces local type I interferon responses and disease activity in patients with cutaneous lupus. Sci Transl Med. 2021;13(595):eabf8442.

Khamashta et al, 2016

Khamashta M, Merrill JT, Werth VP, Furie R, Klaunian K, Illei GG, et al. Sifalimumab, an anti-interferon-α monoclonal antibody, in moderate to severe systemic lupus erythematosus: a randomised, double-blind, placebo-controlled study. Ann Rheum Dis. 2016;75(11):1909-16.

King and Hahn, 2007

King JK, Hahn BH. Systemic lupus erythematosus: modern strategies for management: a moving target. Best Pract Res Clin Rheumatol. 2007;21(6):971-87.

Klarquist et al, 2016

Klarquist J, Zhou Z, Shen N, Janssen EM. Dendritic cells in systemic lupus erythematosus: From pathogenic players to therapeutic tools. Mediators Inflamm. 2016;2016:5045248.

Lateef and Petri, 2012

Lateef A, Petri M. Unmet medical needs in systemic lupus erythematosus. Arthritis Res Ther. 2012;14 Suppl 4(Suppl 4):S4.

Liu and Anders, 2014

Liu Y, Anders HJ. Lupus nephritis: from pathogenesis to targets for biologic treatment. Nephron Clin Pract. 2014;128(3-4):224-31.

McElhone et al, 2007

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(6):972-9.

Morand et al, 2020

Morand EF, Furie R, Tanaka Y, Bruce IN, Askanase AD, Richez C, et al. Trial of anifrolumab in active systemic lupus erythematosus. N Engl J Med. 2020;382(3):211-21.

Navarra et al, 2011

Navarra SV, Guzmán RM, Gallacher AE, Hall S, Levy RA, Jimenez RE, et al. Efficacy and safety of belimumab in patients with active systemic lupus erythematosus: a randomised, placebo-controlled, phase 3 trial. Lancet. 2011;377(9767):721-31.

Palagini et al, 2013

Palagini L, Mosca M, Tani C, Gemingnani A, Mauri M, Bombardieri S. Depression and systemic lupus erythematosus: a systematic review. Lupus. 2013:22(5):409-16.

Petri et al, 2005

Petri M, Kim MY, Kalunian KC, Grossman J, Hahn BH, Sammaritano LR, et al; OC-SELENA Trial. Combined oral contraceptives in women with systemic lupus erythematosus. N Engl J Med. 2005 Dec 15;353(24):2550-8.

Petri, 2006

Petri M. Systemic lupus erythematosus: 2006 update. J Clin Rheumatol. 2006;12(1):37-40.

Petri et al, 2009

Petri M, Singh S, Tesfasyone H, Malik A. Prevalence of flare and influence of demographic and serologic factors on flare risk in systemic lupus erythematosus: a prospective study. J Rheumatol. 2009;36(11):2476-80.

Rahman and Isenberg, 2008

Rahman A. Isenberg DA. Systemic lupus erythematosus. N Engl J Med. 2008;358(9):929-39.

Rissoan et al, 2002

Rissoan MC, Duhen T, Bridon JM, Bendriss-Vermare N, Péronne C, de Saint vis B, et al. Subtractive hybridization reveals the expression of immunoglobulin-like transcript 7, Eph-b1, granzyme B, and 3 novel transcripts in human plasmacytoid dendritic cells. Blood. 2002;100(9):3295-303.

Rowland et al, 2014

Rowland SL, Riggs JM, Gilfillan S, Bugatti M, Vermi W, Kolbeck R, et al. Early, transient depletion of plasmacytoid dendritic cells ameliorates autoimmunity in a lupus model. J Exp Med. 2014;211(10):1977-91.

Ruiz-Arruza et al, 2014

Ruiz-Arruza I, Ugarte A, Cabezas-Rodriguez I, Medina JA, Moran MA, Ruiz-Irastorza G. Glucocorticoids and irreversible damage in patients with systemic lupus erythematosus. Rheumatology (Oxford). 2014;53(8):1470-6.

Sampson et al, 2006

Sampson HA, Munoz-Furlong A, Campbell RL, Adkinson Jr NF, 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.

Saphnelo® USPI, 2021

SAPHNELO (anifrolumab-fnia injection, for intravenous use). US Prescribing information. AstraZeneca Pharmaceuticals LP, Wilmington, DE, USA; Approval 2021. Available at: https://www.saphnelo.com/hcp.html

Schwartz et al, 2009

Schwartz N, Rubinstein T, Burkly LC, Collins CE, Blanco I, Su L, et al. Urinary TWEAK as a biomarker of lupus nephritis: a multicenter cohort study. Arthritis Res Ther. 2009;11(5):R143.

Siegal et al, 1999

Siegal FP, Kadowaki N, Shodell M, Fitzgerald-Bocarsly PA, Shah K, Ho S, et al. The nature of the principal type 1 interferon-producing cells in human blood. Science. 1999;284(5421):1835-7.

Thanou et al, 2014

Thanou A, Chakravarty E, James JA, Merrill JT. How should lupus flares be measured? Deconstruction of the safety of estrogen in lupus erythematosus national assessment-systemic lupus erythematosus disease activity index flare index. Rheumatology (Oxford). 2014 Dec;53(12):2175-81.

Thanou et al, 2018

Thanou A, Askanase A, Arriens C, Aberle T, Kamp S, Chakravarty E, et al. Systemic Lupus Flares Based on BILAG and Sledai Rules Are Inconsistent, but May be Better Understood Using Visual Analogue Scales [abstract]. Arthritis Rheumatol. 2018;70(suppl9). https://acrabstracts.org/abstract/systemic-lupus-flares-based-on-bilag-and-sledai-rules-are-inconsistent-but-may-be-better-understood-using-visual-analogue-scales/. Accessed January 21, 2022.

Touma et al, 2010

Touma Z, Urowitz MB, Gladman DD. SLEDAI-2K for a 30-day window. Lupus. 2010;19(1):49-51.

Werth et al, 2020

Werth V, Furie R, Romero-Diaz J, Navarra SV, Kalunian KC, van Vollenhoven R. et al. OP0193 BIIB059, a humanized monoclonal antibody targeting BDCA2 on plasmacytoid dendritic cells (pDC), shows dose-related efficacy in the phase 2 LILAC study in patients (pts) with active cutaneous lupus erythematosus (CLE). Ann Rheum Dis. 2020;79:120-1.

Winthrop et al, 2015

Winthrop KL, Novosad SA, Baddley JW, Calabrese L, Chiller T, Polgreen P, et al. Opportunistic infections and biologic therapies in immune-mediated inflammatory diseases: consensus recommendations for infection reporting during clinical trials and postmarketing surveillance. Ann Rheum Dis. 2015;74(12):2107-16.

Yurkovich et al, 2014

Yurkovich M, Vostretsova K, Chen W, Aviña-Zubieta JA. Overall and cause-specific mortality in patients with systemic lupus erythematosus: a meta-analysis of observational studies. Arthritis Care Res (Hoboken). 2014;66(4):608-16.