A Phase 2 Randomized, Double-Blind, Placebo-Controlled Efficacy and Safety Study of VIB7734 for the Treatment of Moderate to Severely Active Systemic Lupus Erythematosus

SHORT TITLE: RECAST SLE

(A Phase 2 Randomized, Double-Blind, Placebo-Controlled Efficacy and Safety Study of VIB7734 for the Treatment of Moderate to Severely Active Systemic Lupus Erythematosus)

Investigational Product	VIB7734 (anti-ILT7 mAb for depletion of pDCs)
Protocol Number	VIB7734.P2.S1
Clinical Trial Registry Identifiers	clinicaltrials.gov: NCT04925934 EudraCT: 2020-005528-12
Amendment	1
Version Date	10 February 2022
IND Number	IND 127898
Lead Principal Investigator	Dr. [redacted]
Sponsor	Viela Bio, Inc. One MedImmune Way, Gaithersburg, MD 20878 USA
Responsible Medical Officer	[redacted], MD Executive Medical Director Viela Bio [redacted] One MedImmune Way Gaithersburg, MD 20878 USA

NCT Number: NCT04925934
This NCT number has been applied to the document
for purposes of posting on Clinicaltrials.gov

SPONSORS SIGNATURE PAGE

The signatures below constitute the approval of this protocol and provide the necessary assurances that this trial 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 Viela Bio	DocuSigned by: [redacted] Signer Name: [redacted] Signing Reason: I approve this document Signing Time: 15-Feb-2022 | 09:05 CST BE79887EED2B48A8AE7BF3AC7D639383
[redacted], PhD	Sr. Director, Biostatistics, Biometrics Viela Bio	DocuSigned by: [redacted] Signer Name: [redacted] Signing Reason: I approve this document Signing Time: 14-Feb-2022 | 09:35 CST 94348E43E05145848D3DCFDE0A20F5C3

SUMMARY OF CHANGES

The major changes incorporated into this protocol (Version 2.0/Amendment 1) relative to the prior approved version (Version 1.0/Original) are summarized in the table below. Editorial and formatting changes are not included in this summary.

<table>
<tr><th>Text
Version 1.0, Original Protocol
21 December 2020</th><th>Amended Text
Version 2.0, Amendment 1
10 February 2022</th><th>Rationale for Change</th></tr>
<tr><td>Section 5.1 – Inclusion Criteria

8. Women of childbearing potential must have a negative urine pregnancy test at Randomization.
…
Women of childbearing potential who are sexually active with a non-sterilized male partner must agree to use a highly effective method of contraception (Table 1) from signing of the informed consent, 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.</td><td>Section 5.1 – Inclusion Criteria

8. Women of childbearing potential must have a negative serum pregnancy test at Screening and a negative urine pregnancy test at Randomization.
…
Women of childbearing potential who are sexually active with a non-sterilized male partner must agree to use a highly effective method of contraception (Table 1) from signing of the informed consent, 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.</td><td>Updated to clarify that both visits need to have negative serum/urine pregnancy tests and that women of childbearing potential must refrain from egg retrevial and donation while receiving IP..</td></tr>
<tr><td>Section 5.1 – Inclusion Criteria, Table 1

Table 1 Highly Effective Methods of Contraception
<table><tr><th>Physical Methods</th><th>Hormonal Methods</th></tr><tr><td>• Intrauterine device
• Intrauterine hormone-releasing system [a]
• Bilateral tubal occlusion
• Vasectomized partner [b]
• Sexual abstinence [c]</td><td>Combined (estrogen and progestogen-containing hormonal contraception)
• PO (combined pill)
• Injectable
• Transdermal (patch)
• Progestogen-only hormonal contraception associated with inhibition of ovulation [d]
• Injectable
• Implantable
• Intravaginal</td></tr></table>PO: oral(ly).</td><td>Section 5.1 – Inclusion Criteria; Table 1

Table 1 Highly Effective Methods of Contraception
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• PO (combined pill)
• Injectable
• Transdermal (patch)
• Progestogen-only hormonal contraception associated with inhibition of ovulation [e]
• Injectable
• Implantable
• Intravaginal</td></tr></table>PO: oral(ly).
[a] A change in birth control method is allowed during the study. If a change occurs, unless the patient is changing the method to complete abstinence, the patient must employ a barrier method in addition to the highly effective method of contraception for at least two months.</td><td>Updated to clarify what should occur when changing hormonal birth control methods.</td></tr>
<tr><td>Section 5.2.1 – General Exclusion Criteria</td><td>Section 5.2.1 – General Exclusion Criteria

2. Any condition that, in the opinion of the Investigator or the Sponsor/Central Review Committee, would interfere with</td><td>Updated to clarify that the Sponsor and Central Review Committee may also review a participant’s</td></tr>
</table>

2. Any condition that, in the opinion of the Investigator, would interfere with evaluation of the IP or interpretation of participant safety or study results.	evaluation of the IP or interpretation of participant safety or study results (including borderline disease activity).	*screening data and find reason to not allow participation in the study.*
Section 5.2.1 – General Exclusion Criteria 5. Breastfeeding or pregnant women or women who intend to become pregnant anytime from signing the ICF through 6 months after receiving the last dose of IP.	**Section 5.2.1 – General Exclusion Criteria** 5. Breastfeeding or pregnant women or women who intend to become pregnant anytime from signing the ICF through 3 months after receiving the last dose of IP.	*Updated to standardize the amount of time that breastfeeding or pregnant women are followed after receiving the last dose of IP throughout the protocol.*
Section 5.2.1 – General Exclusion Criteria 10. At Screening, any of the following per central laboratory (tests may be repeated once within the same Screening period to confirm results prior to Randomization): • Spot UPCr > 3 mg/mg	**Section 5.2.1 – General Exclusion Criteria** 10. At Screening, any of the following per central laboratory (tests may be repeated once within the same Screening period to confirm results prior to Randomization): • Spot UPCr > 3 mg/mg (> 339 mg/mmol)	*Updated to add the mg/mmol exclusionary value as it is generally used at ex-US sites.*
Section 5.2.1 – General Exclusion Criteria 13. Active TB, or positive IFN-gamma release assay (IGRA) test at Screening, unless documented history of appropriate treatment for active or latent TB. Participants with an indeterminated IGRA test result can repeat the test, but if the repeat test is also indeterminate, they are excluded.	**Section 5.2.1 – General Exclusion Criteria** 13. Active TB, or positive IFN-gamma release assay (IGRA) test at Screening, unless documented history of appropriate treatment for active or latent TB. Note that participants with an indeterminated IGRA test result with well-documented previous treatment do not need to repeat testing and are eligible for randomization. Participants with an indeterminate IGRA test result without previous treatment can repeat the test, but if the repeat test is also indeterminate, they are excluded.	*Updated to clarify actions for indeterminate IGRA test results.*
Section 5.2.1 – General Exclusion Criteria 18. Any acute illness or evidence of clinically significant active infection, such as fever ≥ 38.0° C (≥ 100.5° F) on Day 1.	**Section 5.2.1 – General Exclusion Criteria** 18. Any acute illness or evidence of clinically significant active infection.	*Removed fever example as it can be a manifestation of lupus and thus possibly confusing.*
Section 5.2.1 – General Exclusion Criteria	**Section 5.2.1 – General Exclusion Criteria**	*Updated to clarify the definition of clinically*

<table>
<tr>
<td>19. History of clinically significant cardiac disease including unstable angina; myocardial infarction within 6 months prior to Randomization; congestive heart failure; arrhythmia requiring active therapy, except for clinically insignificant extra systoles, or minor conduction abnormalities; or presence of clinically significant abnormality on ECG if, in the opinion of the Investigator, it would increase the risk of study participation.</td>
<td>19. Clinically significant cardiac disease including unstable angina and/or myocardial infarction and/or congestive heart failure within 6 months prior to Randomization. Or any cardiac condition including, but not limited to the following, if in the opinion of the Investigator or Medical Monitor, would increase the risk of study participation:
• Inadequately controlled arrhythmia.
• Presence of clinically significant abnormality on ECG.</td>
<td>significant cardiac disease.</td>
</tr>
<tr>
<td>Section 5.2.1 – General Exclusion Criteria

23. Active LN OR active severe or unstable neuropsychiatric SLE (eg, aseptic meningitis, cerebral vasculitis, myelopathy, demyelination syndromes [ascending, transverse, acute inflammatory demyelinating polyradiculopathy], acute confusional state, impaired level of consciousness, psychosis, acute stroke or stroke syndrome, cranial neuropathy, status epilepticus, cerebellar ataxia, and mononeuritis multiplex) where, in the opinion of the Investigator or Medical Monitor, protocol-specified SoC is insufficient and utilization of a more aggressive therapeutic approach, such as IV cyclophosphamide, high-dose IV pulse GC therapy, MMF of > 2 gm/day (MPA of > 1.44 gm/day), and/or other treatments not permitted in the protocol, may be indicated.</td>
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<td>Updated to include conventional anti-rheumatic doses for treatment of SLE that should not be excluded for in the protocol.</td>
</tr>
<tr>
<td>Section 6.2 – Tables 2, 3, 4; Section 6.3.4 – Clinical Laboratory Assessments

Table 2 Screening Procedures
<table><tr><td>Study Day</td><td>-28 to -1</td></tr><tr><td>Visit Number</td><td>1</td></tr><tr><td>Coombs Test</td><td>X</td></tr></table>
Table 3 Schedule of Assessments During the Treatment Period</td>
<td>Section 6.2 – Tables 2, 3, 4; Section 6.3.4 – Clinical Laboratory Assessments

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Table 3 Schedule of Assessments During the Treatment Period</td>
<td>Removed the direct coombs testing throughout the protocol as the specimen has limited stability which often does not allow testing to be performed by the central laboratory within the stability period due to courier transit time and is not needed on a routine basis.</td>
</tr>
</table>

Study Day	1	29	57	85	113	141	169	197	225	253	281	309	337
Visit Window (± days)	-	3	3	3	3	3	3	3	3	3	3	3	3
Study Week	0	4	8	12	16	20	24	28	32	36	40	44	48
Visit Number	2	3	4	5	6	7	8	9	10	11	12	13	14
Coombs test and confirmatory tests for hemolytic anemia and active APS [k]	X	X	X	X	X	X	X	X	X	X	X	X	X

Table 4 Schedule of Assessments During the Safety Follow-Up Period

Study Day	365	393
Visit Window (± Days)	7	7
Study Week	52	56
Visit Number	15	16
Coombs test and confirmatory tests of hemolytic anemia and active APS [j]	X	X

Table 5 Clinical Laboratory Tests

Immunology	• Anticardiolipin antibodies (IgG, IgA and IgM) • Anti-β2GP1 antibody • C3 and C4 • Direct Coombs • Lupus anticoagulant • Rheumatoid factor

Section 6.2 – Table 3, Table 4; Section 6.4.3 – Withdrawal From Study

Table 3 Schedule of Assessments During the Treatment Period

Study Day	1	29	57	85	113	141	169	197	225	253	281	309	337
Visit Window (± days)	-	3	3	3	3	3	3	3	3	3	3	3	3
Study Week	0	4	8	12	16	20	24	28	32	36	40	44	48
Visit Number	2	3	4	5	6	7	8	9	10	11	12	13	14

Table 4, Footnote – Safety Follow-Up visits will be conducted at 4 and 8 weeks after the last dose of investigational product (IP)

Study Day	1	29	57	85	113	141	169	197	225	253	281	309	337
Visit Window (± days)	-	3	3	3	3	3	3	3	3	3	3	3	3
Study Week	0	4	8	12	16	20	24	28	32	36	40	44	48/ET
Visit Number	2	3	4	5	6	7	8	9	10	11	12	13	14
Confirmatory tests for hemolytic anemia and active APS [k]	X	X	X	X	X	X	X	X	X	X	X	X	X

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Study Week	0	4	8	12	16	20	24	28	32	36	40	44	48/ET
Visit Number	2	3	4	5	6	7	8	9	10	11	12	13	14

ET: Early Termination

Updated to clarify that the Week 48 visit is also considered an early termination (ET) visit as it was not previously defined and to clarify that the safety follow up period as is only for subjects that have completed the 48-week treatment period

for participants who have been discontinued from IP or have completed the 48-week Treatment period. These assessments, however, will not be performed on participants who enter the long-term extension study. Section 6.4.3 – Participants are free at any time to withdraw from the study (IP and assessments), without prejudice to further treatment (withdrawal of consent). Such participants will always be asked about the reason(s) for withdrawal and the presence of any AEs. If possible, they will be seen and assessed by an Investigator. AEs will be followed-up. If a participant withdraws participation in the study, then no further study visits or data collection should take place. Further details concerning use of samples collected during the study from a participant that withdraws consent are provided in Section 10.6.	Table 4, Footnote – Safety Follow-Up visits will be conducted at 4 and 8 weeks after the last dose of investigational product (IP) for participants who have completed the 48-week Treatment period. These assessments, however, will not be performed on participants who enter the long-term extension study. Participants who permanently discontinue IP at any point in the study but who do not withdraw consent of study participation will complete all study visits through Study Week 48/ET and at least 12 weeks follow up after the last dose of IP. Participants who permanently discontinue IP at any point in the study and who do withdraw consent of study participation will only complete the Study Week 48/ET assessments (if they agree to do so before withdrawing consent). Section 6.4.3 – Participants are free at any time to withdraw from the study (IP and assessments), without prejudice to further treatment (withdrawal of consent). Such participants will always be asked about the reason(s) for withdrawal and the presence of any AEs. AEs will be followed-up. Participants who permanently discontinue IP at any point in the study but who do not withdraw consent of study participation will complete all study visits through Study Week 48/ET and at least 12 weeks follow up after the last dose of IP. Participants who permanently discontinue IP at any point in the study and who do withdraw consent of study participation will only complete the Study Week 48/ET assessments (if they agree to do so before withdrawing consent). If a participant withdraws consent to participation in the study, then no further study visits or data collection should take place. Further details concerning use of samples collected during the study from a participant that withdraws consent are provided in Section 10.6.	*and how participants who permantently discontinue IP should be followed after final IP administration.*
Section 6.2 – Table 3, Table 4; Section 6.3.4 – Clinical Laboratory Assessments Table 3, Footnote [f] – Women of childbearing potential or women who are postmenopausal for less than 2 years.	**Section 6.2 – Table 3, Table 4; Section 6.3.4 – Clinical Laboratory Assessments** Table 3, Footnote [f] – Women of childbearing potential as defined in Inclusion Criteria #8.	*Updated to align the definition of women of childbearing potential throughout the protocol.*

Table 4, Footnote [e] – Women of childbearing potential or women who are postmenopausal for less than 2 years. Section 6.3.4 – A serum pregnancy test in postmenopausal women will be performed at Screening at the central laboratory. Urine pregnancy tests will be performed at Screening, during treatment, and during follow-up at the site using a dipstick.	Table 4, Footnote [e] – Women of childbearing potential as defined in Inclusion Criteria #8. Section 6.3.4 – A serum pregnancy test (in women of childbearing potential as defined in Inclusion Criteria #8) will be performed at Screening at the central laboratory. Urine pregnancy tests will be performed in women of childbearing potential during treatment and follow-up at the site using a dipstick.	
[redacted]		
Section 6.2 – Table 3 Table 3, Footnote [g] – Reflex DNA testing if isolated hepatitis B core positive at Baseline.	**Section 6.2 – Table 3** Table 3, Footnote [g] – Reflex DNA testing if isolated hepatitis B core positive at Screening.	*Updated to reference the correct study visit.*
[redacted]		
Section 6.3.3.2 – Vital Signs Prior to and after IP administration, vital signs should be checked as follows: • Within 15 minutes prior to administration of IP.	**Section 6.3.3.2 – Vital Signs** Prior to and after IP administration, vital signs should be checked as follows: • Within 15 minutes prior to administration of IP (within 30 minutes for Week 24 due to ECG requirements).	*Updated to allow for additional time at Week 24 to ensure enough time to collect the vitals, labs, and ECG prior to dosing.*

• Every 30 minutes (± 5 minutes) for 60 minutes after administration or until stable, whichever is later (for the first 2 study visits only).	• Every 30 minutes (± 5 minutes) for 60 minutes after administration or until stable, whichever is later (for the first 2 study visits only).	
Section 6.3.3.6 – Tuberculosis Assessment A blood test for TB will be performed at Screening using the IGRA test (ie, QuantiFERON-TB Gold Plus or T-SPOT). Evaluation of all participants by IGRA test will be performed by either the local or central clinical laboratory. Results of an IGRA test performed within 12 weeks of the Screening visit (if available) are acceptable, provided there is no reason to suspect any re-exposure.	**Section 6.3.3.6 – Tuberculosis Assessment** A blood test for TB will be performed at Screening using the IGRA test (ie, QuantiFERON-TB Gold Plus or T-SPOT). Evaluation of all participants by IGRA test will be performed by the central clinical laboratory. Results of an IGRA test performed at a local laboratory within 12 weeks of the Screening visit (if available) are acceptable, provided there is no reason to suspect any re-exposure.	*Updated to clarify that TB assessments at Screening should occur only at the central laboratory.*
[redacted]		
Section 7.1.1.1 – Investigational Product Inspection The Sponsor's Quality Assurance contact information for reporting product complaints is: [redacted]	**Section 7.1.1.1 – Investigational Product Inspection** The Sponsor's Quality Assurance contact information for reporting product complaints is:	*Update to contact information*

Section 7.1.1.3 – Investigational Product Dose Preparation A SC dose of 200 mg VIB7734 will be administered over 2 injections. To prepare each injection, withdraw 1 mL of IP into a 1-mL syringe using an 18-19.5G 1½-inch needle. For SC dose administration, a 27G ½-inch needle should be used. Normal saline will be used as placebo. The number and volume of placebo injections will match that of active drug. Saline (1 mL) should be drawn into each of two 1-mL syringes using an 18-19.5G 1½-inch needle. For SC dose administration, a 27G ½-inch needle should be used.	**Section 7.1.1.3 – Investigational Product Dose Preparation** A SC dose of 200 mg VIB7734 will be administered over 2 injections. To prepare each injection, withdraw 1 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. Normal saline will be used as placebo. The number and volume of placebo injections will match that of active drug. Saline (1 mL) should be drawn into each of two 1-mL syringes using a 1½-inch needle. For SC dose administration, a 27G ½-inch needle should be used.	*Updated to remove the specific gauge size from the protocol, as these specific needles cannot be supplied at certain study sites where the study will be performed.*
Section 7.4.2.1 – Medications and Therapies That Lead to Immediate Discontinuation of Investigational Product Section 7.4.2.1 – Ig therapy (any).	**Section 7.4.2.1 – Medications and Therapies That Lead to Immediate Discontinuation of Investigational Product; Section 7.4.3.2.2.6 – Other** Section 7.4.2.1 – Ig therapy (For Anti-COVID therapeutic antibodies see Permitted Medications Section 7.4.3.2.2.6). Section 7.4.3.2.2.6 – 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.	*Updated to clarify how anti-COVID therapeutic antibody treatment should be handled within the study.*
Section 7.4.3.2.2.6 – Other Non-prescription NSAIDs for analgesic purposes not exceeding label-approved doses are permitted for pain as required based on Investigator judgment for up to 10 days at a time.	**Section 7.4.3.2.2.6 – Other** PRN NSAIDs not exceeding label-approved doses are permitted for SLE or non-SLE pain as required based on Investigator judgment for up to 10 consecutive days at a time. Duration exceeding 10 consecutive days is considered chronic use.	*Updated to clarify the limitations for the permitted use of PRN NSAIDs.*
Section 8.1 – Definitions – The following AESIs will be particularly monitored in this study: • Hypersensitivity reaction, including anaphylaxis. • Viral infection/reactivation. • Opportunistic infection. • Malignancy (except non-melanoma skin cancer).	**Section 8.1 – Definitions** – The following AESIs will be particularly monitored in this study: • Hypersensitivity reaction, including anaphylaxis. • Severe (Grade 3 or higher) viral infections/reactivations. • Opportunistic infection listed in Appendix 3 (all cases).	*Updated to clarify that AESI for viral infection and reactivation only includes those that are Grade 3 or higher and all cases of opportunistic infections listed in Appendix 3*

	• Malignancy (except non-melanoma skin cancer).	*(which includes herpes zoster).*
8.3 – Events Requiring Immediate Reporting All SAEs, AESIs, pregnancies, overdose, or misuse must be reported to the Sponsor's designated representative, ICON, within 24 hours of site staff awareness by submitting a SAE/AESI/Pregnancy/Overdose Report Form by email to: **ICON Patient Safety** **Email: icon-mads@iconplc.com** Alternatively, the Report Form can be submitted by fax to: **ICON Patient Safety** **Fax: 1-215-616-3096**	**8.3 – Events Requiring Immediate Reporting** All SAEs, AESIs (only after Randomization), pregnancies, overdose, or misuse must be reported to the Sponsor within 24 hours of site staff awareness by submitting a SAE/AESI/Pregnancy/Overdose Report Form by email to: **Sponsor (Horizon Therapeutics/Viela Bio)** **Email:** [redacted] Alternatively, the Report Form can be submitted by fax to: **Sponsor (Horizon Therapeutics/Viela Bio)** **Fax: 1-800-860-7836** *All other references to ICON Patient Safety or ICON have been updated to indicated Sponsor throughout protocol	*Updated to clarify that AESIs only need to be immediately reported after Randomization and contact information for immediate reporting.*

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 (PI) 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.

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[redacted]

[redacted]

[redacted]

[redacted]

LIST OF TABLES

LIST OF FIGURES

LIST OF APPENDICES

LIST OF ABBREVIATIONS

Abbreviation or special term	Definition
ACTH	adrenocorticotropic hormone
[redacted]	
AE	adverse event
AESI	adverse event of special interest
ALT	alanine aminotransferase
ANA	antinuclear antibodies
APS	antiphospholipid syndrome
AST	aspartate aminotransferase
AZA	azathioprine
BCG	Bacille-Calmette-Guerin
BICLA	BILAG 2004 Index-Based Combined Lupus Assessment
BILAG	British Isles Lupus Assessment Group
[redacted]	
CD	cluster of differentiation
CDM	Clinical Data Management
CLASI	Cutaneous Lupus Erythematosus Disease Area and Severity Index
CLASI-A	Cutaneous Lupus Erythematosus Disease Area and Severity Index-Activity
CLE	cutaneous lupus erythematosus
CMV	cytomegalovirus
CNS	central nervous system
CoV	coronavirus
COVID-19	coronavirus disease 2019
CRF	case report form
CRO	contract research organization
DC	dendritic cell
DMARD	disease-modifying antirheumatic drug
DMP	Data Management Plan
dsDNA	double-stranded DNA
ECG	electrocardiogram
eCRF	electronic case report form
FDA	Food and Drug Administration
FSH	follicle-stimulating hormone
[redacted]	
GC	glucocorticoid
GCP	Good Clinical Practice(s)
GLP	Good Laboratory Practice(s)
[redacted]	
HBcAb	hepatitis B core antibody

Abbreviation or special term	Definition
HBV	hepatitis B virus
HIV	human immunodeficiency virus
ICF	informed consent form
ICH	International Council for Harmonisation
IEC	Independent Ethics Committee
IFN	interferon
Ig	immunoglobulin
IGRA	IFN-gamma release assay
IL	interleukin
ILT	Ig-like transcript
IP	investigational product
IRB	Institutional Review Board
IV	intravenous(ly)
IXRS	interactive voice/web response system
LLDAS	Lupus Low Disease Activity State
LLOQ	lower limit of quantitation
LN	lupus nephritis
LTE	long-term extension
[redacted]	
mAb	monoclonal antibody
MAD	multiple-ascending dose
MCP	metacarpophalangeal
MMF	mycophenolate mofetil
6-MP	6-mercaptopurine
MPA	mycophenolic acid
MTX	methotrexate
NK	natural killer
NSAID	nonsteroidal anti-inflammatory drug
OGC	oral glucocorticoid
PD	pharmacodynamics(s)
pDC	plasmacytoid DC
PEF	peak expiratory function
PGA	Physician Global Assessment
PI	Principal Investigator
PIP	proximal interphalangeal
PK	pharmacokinetic(s)
PO	oral(ly)
[redacted]	
Q4W	every 4 weeks

Abbreviation or special term	Definition
Q12W	every 12 weeks
SAD	single-ascending dose
SAE	serious adverse event
SAP	statistical analysis plan
SARS	severe acute respiratory syndrome
SC	subcutaneous(ly)
SDMC	Safety Data Monitoring Committee
SFU	Safety Follow-Up
SID	subject identification number
SLE	systemic lupus erythematosus
SLEDAI-2K	SLE Disease Activity Index 2000
SoC	standard of care
SRI	SLE Responder Index
TB	tuberculosis
TLR	toll-like receptor
TNF	tumor necrosis factor
ULN	upper limit of normal
UPCr	urine protein:creatinine ratio
VAS	visual analog scale

1 SYNOPSIS

Title	A Phase 2 Randomized, Double-Blind, Placebo-Controlled Efficacy and Safety Study of VIB7734 for the Treatment of Moderate to Severely Active Systemic Lupus Erythematosus
Short Title	RECAST SLE (A Phase 2 Randomized, Double-Blind, Placebo-Controlled Efficacy and Safety Study of VIB7734 for the Treatment of Moderate to Severe Systemic Lupus Erythematosus)
Phase	2
Study Design	Randomized, double-blind, placebo-controlled, parallel-group study
Rationale	Data from Phase 2 and 3 studies with interferon (IFN) α-blocking agents and a plasmacytoid dendritic cell (pDC) antagonists have demonstrated improvement in systemic lupus erythematosus (SLE) or cutaneous lupus disease activity, supporting the rationale for blocking the IFN pathways and pDCs in patients with SLE. 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, there is currently a significant unmet need for new targeted therapies. Based on its mechanism of action (binding to immunoglobulin-like transcript 7 (ILT7) on the surface of pDCs, thus inducing apoptosis and reduction in the number of pDCs), VIB7734 has the potential to decrease SLE disease activity. In addition, based on data currently available, VIB7734 presents an acceptable safety profile, and hence it is justified to evaluate its potential efficacy in patients with active SLE.
Target Population	Adults aged ≥ 18 to ≤ 70 years who have moderate to severely active (recent flares or chronic active disease) SLE as defined by the SLE Disease Activity Index 2000 (SLEDAI-2K), British Isles Lupus Assessment Group (BILAG) 2004 Index, and Physician Global Assessment (PGA).
Number of Participants	Approximately 195 participants will be randomized to 3 treatment groups; approximately 65 participants to each treatment group.
Length of Participation	On treatment: 48 weeks On study (including Screening and Safety Follow-Up periods): up to 60 weeks
Interventions	**Group 1:** VIB7734 200 mg subcutaneous(ly) (SC) every 4 weeks (Q4W) **Group 2:** VIB7734 200 mg SC every 12 weeks, with an additional 200 mg SC dose at Week 4 **Group 3:** Placebo SC Q4W
Primary Objective	**Outcome Measure**
To evaluate the effect of VIB7734 compared to placebo in reducing SLE disease activity at Week 48 in participants treated with standard of care therapy.	Proportion of participants achieving a BILAG 2004 Index-based Combined Lupus Assessment (BICLA) response and an oral glucocorticoid (OGC) dose ≤ 7.5 mg/day and ≤ Baseline (Day 1) dose of prednisone or equivalent at Week 48.

Secondary Objectives	
Efficacy Objectives	**Outcome Measures**
To evaluate the effect of VIB7734 compared with placebo to reduce cutaneous disease activity at Week 12.	Proportion of participants with Cutaneous Lupus Erythematosus Disease Area and Severity Index (CLASI)-Activity (CLASI-A) score ≥ 10 at Baseline (Day 1) who achieve ≥ 50% reduction from Baseline (Day 1) in CLASI-A score at Week 12.
To evaluate the effect of VIB7734 compared with placebo to reduce SLE disease activity at Week 48.	Proportion of participants achieving a Systemic Lupus Responder Index (SRI)-4 response and an OGC dose ≤ 7.5 mg/day and ≤ Baseline (Day 1) dose of prednisone or equivalent at Week 48.
To evaluate the effect of VIB7734 compared with placebo on sustained OGC reduction from Week 36 to Week 48.	Proportion of participants at OGC dose ≥ 10 mg prednisone or equivalent at Baseline (Day 1) who achieve OGC dose ≤ 7.5 mg/day prednisone or equivalent at Week 36 and maintained through Week 48.
To evaluate the effect of VIB7734 compared with placebo to achieve low disease activity at Week 48.	Proportion of participants achieving Lupus Low Disease Activity State at Week 48.
Pharmacokinetic/Pharmacodynamic/ Immunogenicity Objectives	**Outcome Measures**
To characterize the pharmacokinetics, pharmacodynamics, and immunogenicity of VIB7734.	VIB7734 concentrations, change in pDCs, and [redacted]
Safety Objectives	**Outcome Measures**
To evaluate the safety and tolerability of VIB7734.	Incidence of adverse events (AEs), serious AEs, and AEs of special interest.
Exploratory Objectives	**Outcome Measures**
[redacted]	

Number of Sites	Approximately 88 sites
Study Duration	Estimated total study duration is approximately 60 weeks, including a Screening period of approximately 4 weeks (Days -28 to -1), treatment and assessments through Week 48, and a Safety Follow-Up period of 8 weeks (through Week 56).
Data Monitoring Committee	An external, independent Safety Data Monitoring Committee (SDMC) will evaluate safety data at regular intervals throughout the study and make recommendations to the Sponsor as needed. The SDMC will not perform a futility analysis or consider early study completion for efficacy.

2 INTRODUCTION

2.1 Background

2.1.1 Systemic Lupus Erythematosus

Clinical Presentation

Systemic lupus erythematosus (SLE) 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, to 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. SLE 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, Schmeding and Schneider, 2013, Holloway et al, 2014, Lateef and Petri, 2014, 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). SLE 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 toll-like receptors (TLRs) on dendritic cells (DCs) or B cells that in turn drive interferon (IFN)α-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

[redacted]

[redacted]

Unmet Need

GCs 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 utilized in the treatment of SLE. Inhibition of B lymphocyte stimulator (also known as B cell activating factor of the tumor necrosis factor [TNF] 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 by the US Food and Drug Administration (FDA) in 2011 and in Canada and Europe for treatment of SLE. As the only targeted therapy approved for the treatment of SLE, belimumab with standard of care (SoC) demonstrated an increased rate of treatment response in SLE patients compared to those receiving placebo and SoC. In addition, results suggested that there was a reduced likelihood of severe flares and reduction in glucocorticoid (GC) doses. However, approximately 50% of the patients did not respond with a decrease in SLE activity when treated with belimumab. Therefore, there is a very high unmet medical need for novel, targeted therapies with improved efficacy and benefit-risk ratio.

2.1.2 VIB7734

VIB7734 is a human immunoglobulin (Ig)G1κ afucosylated mAb specific for human ILT7, a cell surface protein expressed by plasmacytoid DCs (pDCs) (Cho et al, 2008; Rissoan et al, 2002). VIB7734 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 VIB7734 is designed to improve the in-life potency of the molecule and to enhance the capacity for antibody-dependent cellular toxicity against pDCs.

2.1.3 Supportive Nonclinical Data

ILT7 is expressed only on the pDCs of humans and non-human primates; therefore, the cynomolgus monkey was selected as the relevant species for safety evaluation of VIB7734.

Study 8311616 was a Good Laboratory Practice (GLP)-compliant, repeat-dose study in cynomolgus monkeys administered VIB7734 at 200 mg/kg intravenously (IV), 200 mg/kg subcutaneously (SC), and 400 mg/kg SC once weekly for 4 weeks (5 doses). No VIB7734-related clinical observations, body weight changes, ophthalmic observations, physical examination observations, macroscopic observations, or changes in blood pressure or electrocardiograms (ECGs) were observed. VIB7734 administration had no clear or consistent group effects on clinical pathology parameters. VIB7734-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 Days 15 and 29 of the dosing phase. VIB7734-related pDC depletion was observed at all dose groups starting on Day 2 of the dosing phase. pDC 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 VIB7734-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. VIB7734 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 VIB7734 administration.

Study 8338846 was a GLP-compliant, 6-month, repeat-dose study in cynomolgus monkeys. VIB7734 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 VIB7734-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 VIB7734-related effects on reproductive organs or assessments. No VIB7734-related changes were noted for IgG, IgM, IgA, IgE, or peripheral blood immunophenotyping, except pDCs as expected by pharmacology. VIB7734-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 VIB7734-related observation was a minor increase in mononuclear cell and macrophage infiltrates at the injection sites of animals administered VIB7734, 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.

2.1.4 Risk Assessment for VIB7734

There are no important identified risks for VIB7734. Important potential risks for VIB7734 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 Investigator's Brochure.

Hypersensitivity reactions, including anaphylaxis, are a risk associated with administration of biologic drugs. Definitions for these reactions can be found in Appendix 1. 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, participants will be monitored after investigational product (IP) administration for immediate drug reactions. Hypersensitivity reactions and anaphylaxis have not been observed in Phase 1 single-ascending dose (SAD) and 1b multiple ascending dose (MAD) studies.

2.1.4.1 COVID-19 Risk Assessment

An additional risk of study participation includes potential exposure of the participant to severe acute respiratory syndrome (SARS)-coronavirus (CoV)-2, the virus that causes CoV 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 participant risk. This test is not provided through the study's central laboratory, because the result of a test at Screening would not be appropriately timed to be relevant to Dose 1. Such testing is not required.

To minimize risk to participants, study sites will be activated to initiate participant 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 participant exposure to SARS-CoV-2 during site visits have been confirmed.

There are no data on the effect of VIB7734 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 participant 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.

2.1.5 Supportive Clinical Data

VIB7734 has been investigated in Phase 1 SAD and Phase 1b MAD clinical studies in patients 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 clinic visits have been completed.

2.1.5.1 Phase 1 Single-Ascending Dose Study in Patients With Autoimmune Diseases

A Phase 1 SAD study (Study D6080C00001) of VIB7734 enrolled participants with any of 5 autoimmune diseases: dermatomyositis, polymyositis, SLE, Sjögren's syndrome, and systemic sclerosis. Single SC doses of VIB7734 (1, 5, 15, 50, or 150 mg) or placebo were administered to 36 participants. 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. 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 participants met protocol-defined minimum absolute pDC number repletion criteria and exited the study before this occurred.

2.1.5.2 Phase 1b Multiple-Ascending Dose Study in Patients With Autoimmune Diseases

In a single-blind (participants and site blinded, Sponsor unblinded), Phase 1b MAD study (Study VIB7734.P1b.S1), VIB7734 or placebo was administered SC every 4 weeks (Q4W) for 3 doses to a total of 31 participants in 3 cohorts. In the first cohort, 8 participants with any of 6 autoimmune diseases (dermatomyositis, polymyositis, SLE, cutaneous lupus erythematosus (CLE), Sjögren's syndrome, or systemic sclerosis) were randomized to VIB7734 (5 mg SC) or placebo in a 3:1 ratio. The second and third cohorts enrolled participants with active cutaneous lupus, defined as a Cutaneous Lupus Erythematosus Disease Area and Severity Index (CLASI)-Activity (CLASI-A) score ≥ 8. In the second cohort, 12 participants were randomized to VIB7734 50 mg SC or placebo in a 2:1 ratio. In Cohort 3, 11 participants were randomized to VIB7734 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 participants (78%) in Cohorts 2 and 3. The median change in IFN signature at Month 3 was -54% in the VIB7734 50 mg group, -83% in the VIB7734 150 mg group, and +8% in the placebo group. On the Month 3 skin biopsy, 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. At Month 3, a ≥ 50% improvement in CLASI-A was observed in 38% of participants who received 50 mg VIB7734, 75% of participants who received 150 mg VIB7734, and 29% of participants who received placebo. The proportion of participants with an adverse event (AE) was similar in the VIB7734 and placebo groups (73% versus 67%, respectively). No serious AEs (SAEs) or other clinically important AEs occurred in VIB7734-treated study participants.

2.2 Study Rationale

In the absence of exogenous triggers, 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. pDCs are also known for their capacity to produce vast amounts of IFNα via engagement of 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, 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, VIB7734 has the potential to decrease SLE disease activity. In addition, based on data currently available, VIB7734 presents an acceptable safety profile, and hence, it is therefore justified to evaluate its potential efficacy in patients with active SLE.

2.3 Study Hypotheses

Primary Hypothesis

VIB7734 is efficacious in reducing disease activity in participants with moderate to severely active SLE.

Secondary Hypothesis

VIB7734 has an acceptable safety, tolerability, and immunogenicity profile in participants with moderate to severely active SLE.

3 OBJECTIVES AND OUTCOME MEASURES

3.1 Primary Objective and Outcome Measure

Objective	Outcome Measure
To evaluate the effect of VIB7734 compared to placebo in reducing SLE disease activity at Week 48 in participants treated with SoC therapy.	Proportion of participants achieving a BICLA response and an OGC dose ≤ 7.5 mg/day and ≤ Baseline (Day 1) dose of prednisone or equivalent at Week 48. The BICLA response is defined as meeting all the following conditions as compared to Baseline (Day 1): • BILAG 2004 Index improvement (all Baseline [Day 1] BILAG A improving to B/C/D, all Baseline [Day 1] BILAG B to C/D, and ≤ 1 new BILAG B and no new BILAG A). • No deterioration in SLEDAI-2K total score. • No significant worsening in PGA score (< 10% increase). • No use of restricted medications beyond the protocol-allowed threshold before assessment. • No discontinuation of IP.

BICLA: BILAG 2004 Index-based Combined Lupus Assessment; BILAG: British Isles Lupus Assessment Group; IP: investigational product; OGC: oral glucocorticoid; PGA: Physician Global Assessment; SLE: systemic lupus erythematosus; SLEDAI-2K: SLE Disease Activity Index 2000; SoC: standard of care.

3.2 Secondary Objectives and Outcome Measures

Efficacy Objectives	Outcome Measures
To evaluate the effect of VIB7734 compared with placebo to reduce cutaneous disease activity at Week 12.	Proportion of participants with CLASI-A score ≥ 10 at Baseline (Day 1) who achieve ≥ 50% reduction from Baseline (Day 1) in CLASI-A score at Week 12. Reduction of 50% in CLASI-A score is defined by meeting all the following conditions: • A ≥ 50% reduction of CLASI-A score at Week 12 as compared to Baseline (Day 1). • No use of restricted medications beyond the protocol-allowed threshold before assessment. • No discontinuation of IP.
To evaluate the effect of VIB7734 compared with placebo to reduce SLE disease activity at Week 48.	Proportion of participants achieving an SRI-4 response and an OGC dose ≤ 7.5 mg/day and ≤ Baseline (Day 1) dose of prednisone or equivalent at Week 48. The SRI-4 response is defined as meeting all of the following conditions compared to Baseline (Day 1): • Reduction from Baseline (Day 1) of ≥ 4 points in the SLEDAI-2K. • No new organ system affected as defined by one or more BILAG A or 2 or more BILAG B items. • No significant worsening in PGA score (< 10% increase). • No use of restricted medications beyond the protocol-allowed threshold before assessment. • No discontinuation of IP.

Efficacy Objectives	**Outcome Measures**
To evaluate the effect of VIB7734 compared with placebo on sustained OGC reduction from Week 36 to Week 48.	Proportion of participants at OGC dose ≥ 10 mg prednisone or equivalent at Baseline (Day 1) who: • Achieve OGC dose ≤ 7.5 mg/day prednisone or equivalent at Week 36. • Maintain OGC dose ≤ 7.5 mg/day from Week 36 through Week 48. • No use of restricted medications beyond the protocol-allowed threshold before assessment. • No discontinuation of IP.
To evaluate the effect of VIB7734 compared with placebo to achieve low disease activity at Week 48.	Proportion of participants achieving LLDAS at Week 48. LLDAS is defined as meeting all the following conditions: • SLEDAI-2K ≤ 4, with no activity in major organ system (renal, CNS, cardiopulmonary, vasculitis, fever) and hemolytic anemia or gastrointestinal activity. • No new lupus disease activity as compared to the previous assessment. • PGA ≤ 1 (on a scale of 0 to 3). • Current prednisone or equivalent dose of ≤ 7.5 mg/day. • Well-tolerated standard maintenance doses of immunosuppressive drugs and approved treatments as allowed and specified in the Clinical Study Protocol. • No use of restricted medications beyond the protocol-allowed threshold. • No discontinuation of IP.
PK/PD/Immunogenicity Objectives	**Outcome Measures**
To characterize the PK, PD, and immunogenicity of VIB7734.	VIB7734 concentrations, change in pDCs, [redacted].
Safety Objectives	**Outcome Measures**
To evaluate the safety and tolerability of VIB7734.	Incidence of AEs, SAEs, and AESIs.

[redacted] AE: adverse event; AESI: AE of special interest; BILAG: British Isles Lupus Assessment Group; CLASI-A: Cutaneous Lupus Erythematosus Disease Area and Severity Index-Activity; CNS: central nervous system; IP: investigational product; LLDAS: Lupus Low Disease Activity State; OGC: oral glucocorticoid; PD: pharmacodynamic(s); pDC: plasmacytoid dendritic cell; PGA: Physician Global Assessment; PK: pharmacokinetic(s); SAE: serious AE; SLEDAI-2K: Systemic Lupus Erythematosus Disease Activity Index 2000; SRI: Systemic Lupus Erythematosus Responder Index.

3.3 Exploratory Objectives and Outcome Measures

Objectives	**Outcome Measures**
[redacted]	

Objectives	Outcome Measures
[redacted]	

4 STUDY PLAN

4.1 Study Design

This study is a Phase 2, multicenter, international, double-blind, randomized, placebo-controlled, parallel-group trial to assess the efficacy and safety of VIB7734 in participants with moderate to severely active SLE.

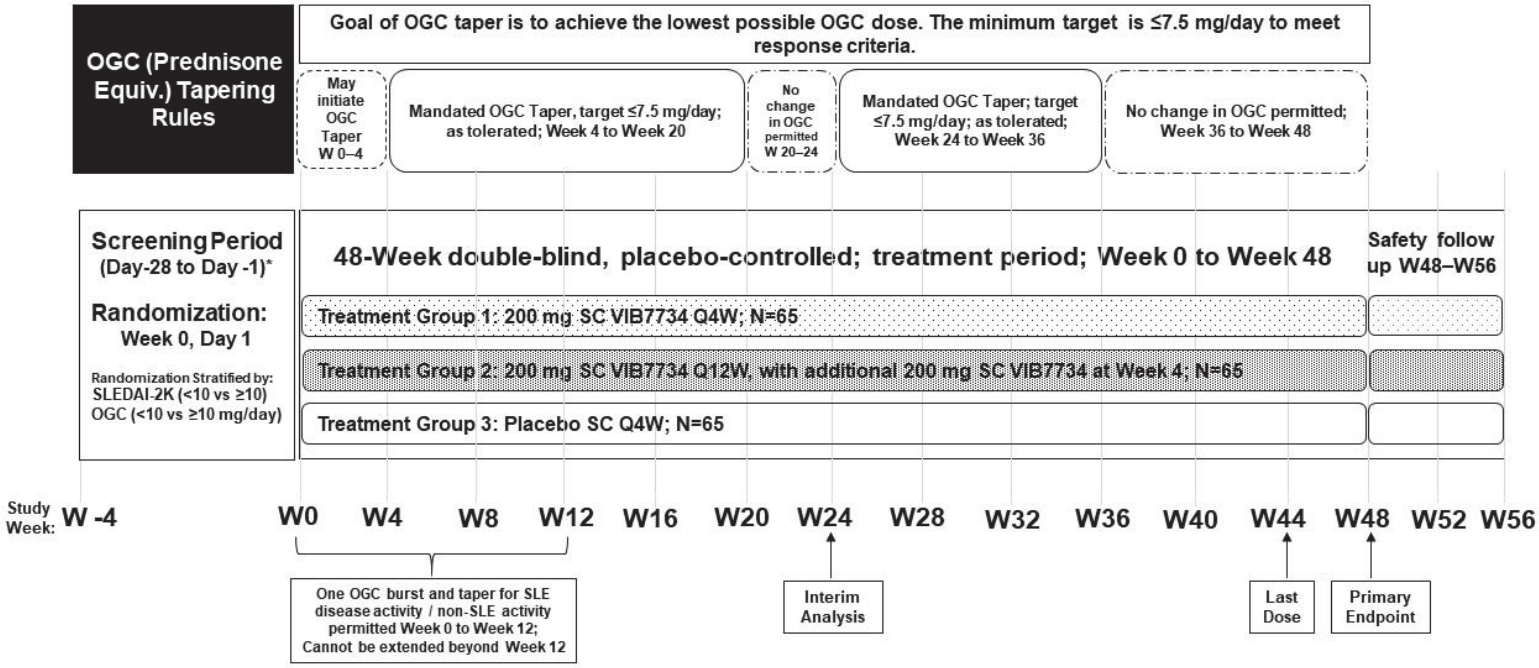
In this study, approximately 195 participants will be randomized in a ratio of 1:1:1 (65 participants per group) to receive VIB7734 200 mg Q4W SC, VIB7734 200 mg every 12 weeks (Q12W) SC, with an additional 200 mg SC dose at Week 4, or placebo. To maintain blinding, participants randomized to the VIB7734 200 mg Q12W SC dosing regimen will receive SC placebo injections on dosing visits outside the Q12W schedule. Randomization will be stratified by SLE Disease Activity Index 2000 (SLEDAI-2K) total score at Screening (≥ 10 or < 10) and prednisone or equivalent oral GC (OGC) dose at Baseline (Day 1) (≥ 10 mg or < 10 mg).

The study will comprise a Screening period of approximately 4 weeks (Days -28 to -1), Randomization on Day 1, treatment and assessments through Week 48, and a Safety Follow-Up (SFU) period of 8 weeks (through Week 56). Under exceptional circumstances such as delayed laboratory results, drug washout, or the impact of COVID-19, the Screening period may be increased by 2 weeks, upon approval by the Medical Monitor. The study will be conducted on an outpatient basis. For all administrations, IP will be administered by site staff in the clinic and the participant will be observed for at least 60 minutes after the first and second doses. Participants who prematurely stop dosing prior to Week 44 will be followed through Week 56. Participants will not automatically be removed from the study if any administration of IP is missed.

A long-term extension (LTE) study for safety and efficacy may be offered as part of a separate protocol, to participants who complete the Week 48 visit. Participants who enter the LTE study directly after completion of the Week 48 visit will not complete the visits of the SFU period.

The study design is summarized in Figure 1.

Figure 1 Study Design



*Two Week extension under exceptional consideration (delayed labs, drug wash out, COVID-19-related delays) with Medical Monitor approval.

COVID-19: coronavirus disease 2019; OGC: oral glucocorticoid; Q4W: every 4 weeks; Q12W: every 12 weeks; SC: subcutaneous(ly); SLE: systemic lupus erythematosus; SLEDAI-2K: SLE Disease Activity Index 2000; W: week.

4.2 Dose and Treatment Rationale

The VIB7734 SAD study demonstrated that the safety profile for single SC doses of 1 to 150 mg is acceptable (Section 2.1.5.1). Pharmacokinetic (PK) exposure increased in an approximately dose-proportional manner. Increasing doses were associated with an increase in maximal pDC reductions and a longer duration of pDC reduction. In the VIB7734 MAD study (Section 2.1.5.2), up to 150 mg Q4W was demonstrated to have an acceptable safety profile in patients with SLE, CLE, Sjögren's syndrome, systemic sclerosis, polymyositis, and dermatomyositis. Treatment with VIB7734 resulted in rapid and durable depletion of blood pDCs in all patients receiving a 150 mg Q4W dose. In addition, at Day 85, the median percent change from Baseline in CLASI-A was -59% for patients receiving the 150 mg Q4W dose and -33% for the 50 mg Q4W dose, compared with -38% in the placebo-dosed group.

In this Phase 2 study, 2 dose regimens, 200 mg Q4W and 200 mg Q12W, have been selected to establish an exposure-response relationship. A nonclinical safety study of VIB7734 in cynomolgus monkeys provided sufficient PK exposure coverage (over 300-fold) for the proposed clinical dose regimens to be evaluated in this study. The high dose selected to be evaluated in participants with moderate to severely active SLE is 200 mg Q4W. Furthermore, given the prolonged pDC suppression observed after completion of treatment in the MAD study (Section 2.1.5.2), a second dose regimen of 200 mg Q12W has been selected to evaluate pDC response and efficacy of less frequent dosing of VIB7734.

A 48-week treatment duration is considered sufficient to demonstrate an effect on the primary and secondary outcome measures selected for this study and current nonclinical safety data (Section 2.1.3) supports this treatment duration.

4.3 Rationale for Study Population

This study is designed to assess the efficacy of VIB7734 in reducing SLE disease activity. At Screening, participants will be required to have moderate to severely active disease as defined by the SLEDAI-2K, British Isles Lupus Assessment Group (BILAG) 2004 Index, and Physician Global Assessment (PGA) (Bombardier et al, 1992; Gladman et al, 2000). This active disease can either be a recent flare or chronic active disease. Failure of the Phase 2 trial of belimumab in SLE patients was attributed in part to the relative lack of responsiveness in the approximately 25% of patients with a negative ANA or anti-dsDNA at Screening compared to those with a positive serology (Wallace et al, 2009). The responsiveness of seropositive patients was corroborated by the positive efficacy results observed in the BLISS-52 and BLISS-76 belimumab trials that included only seropositive patients (Furie et al, 2011; Navarra et al, 2011). Hence, the presence of a positive ANA and/or autoantibodies with high specificity for SLE are a mandatory criterion for enrollment in this study.

Stabilization of the SLE treatment regimen in SLE participants prior to Baseline (Day 1) decreases the confounding of the study results by the SoC (ie, changes in disease activity post-Baseline [Day 1] are more likely to be attributable to the introduction of VIB7734, rather than a change in background therapy).

Severe central nervous system (CNS) lupus and LN may be less responsive to therapy than other manifestations or may require different treatment regimens (eg, cyclophosphamide, IV Ig, high-dose mycophenolate) than typically used in extrarenal SLE. Therefore, these individuals will be

excluded from participating in this study. Also, individuals with significantly impaired renal function are excluded since they may have advanced, fixed disease that will not be responsive to therapy, and furthermore, these individuals are at higher risk for AEs.

A urine protein:creatinine ratio (UPCr) of up to 3 mg/mg is allowed. This limit is applied because higher levels of proteinuria increase the risk of AEs.

The recent or ongoing use of systemic GCs for any comorbidities other than SLE is excluded. Such use would confound the analysis of the effect of VIB7734 on SLE activity. In addition, it would confound the analysis of the potential GC-sparing effects of VIB7734, which is a component of the primary objective of the study. Individuals with active or significant recent infection are excluded to avoid possible recurrence or worsening. Individuals with active or untreated latent tuberculosis (TB) infection or hepatitis B or C infection are excluded to avoid the risk of reactivation. A number of abnormalities or interventions known to interfere with the immune system are excluded to avoid possible confounding of the VIB7734 efficacy and safety profile. In terms of cardiac risk, individuals with an increased risk of recurrent cardiovascular events (those with a recent event) and/or significant arrhythmia will be excluded to decrease potential confounding of study outcomes. Randomization of a screened participant will require review to confirm that all relevant inclusion and exclusion criteria have been applied in consideration of the participant's eligibility. The protocol contains specific inclusion and exclusion criteria; however, not every possible clinical scenario can be addressed in the protocol. The impetus for this requirement has been the observance in other studies that some participants enrolled in trials are not considered appropriate participants by those reviewing the study. The most common reasons for exclusion in trials are the presence of certain comorbidities as well as the absence of sufficient SLE activity. Participants failing to be randomized (ie, screen failures) may be rescreened once for participation with Medical Monitor approval.

4.4 Rationale for the Primary Outcome Measure

The primary outcome measure is the proportion of participants achieving a BILAG 2004 Index-based Combined Lupus Assessment (BICLA) response and an oral (PO) prednisone (or equivalent) dose of ≤ 7.5 mg/day and ≤ Baseline (Day 1) dose at Week 48. The BICLA is driven by improvement in the BILAG 2004 Index score, which measures organ-specific activity (Wallace et al, 2011). The BILAG 2004 Index incorporates a comprehensive, organ-specific, 97-question assessment, which requires the Investigator to score organ manifestations as improving, same, worse, or new over the previous 4 weeks. The scores (A, B, C, D) derived from the assessments (improving, same, worse, or new, respectively) will determine whether further treatment is needed to resolve disease activity. The change in treatment does not determine the scoring (Yee et al, 2009).

The BICLA was used as the primary endpoint in a Phase 2b trial of epratuzumab (Wallace et al, 2014) and in a Phase 3 trial of anifrolumab (Morand et al, 2020). Given the clinical relevance for the use of BICLA and its ability to discern effect as suggested in the anifrolumab Phase 3 study, the BICLA was selected as the clinical disease activity assessment for the primary outcome measure. In addition, there is a requirement to achieve and maintain an PO prednisone or equivalent dose of ≤ 7.5 mg/day and ≤ Baseline (Day 1) dose for at least 12 weeks. A major potential benefit of any new therapeutic in SLE is to be GC sparing. Further, as placebo-treated participants on stable SoC therapy may be less likely to have their GCs tapered, but with higher

doses of OGC relative to the active treatment group still achieve/maintain lower levels of disease activity, the ability to have OGC tapered is included as a component of the primary outcome measure.

5 POPULATION

5.1 Inclusion Criteria

To be included in this study, each participant must satisfy all the following criteria:

1. Age ≥ 18 years to ≤ 70 years at the time of signing the informed consent form (ICF).
2. Willing and able to understand and provide written informed consent prior to any study-related procedures and to comply with all study requirements and complete study assessments.
3. Fulfill the 2019 European League Against Rheumatism/American College of Rheumatology Classification Criteria for SLE (Appendix 2) (Aringer et al, 2019).
4. Disease duration of at least 6 months from the time of diagnosis at the time of signing the ICF.
5. Active SLE as indicated by presence of all the following:

- SLEDAI-2K total score ≥ 6 at Screening, excluding fever, SLE headache, or organic brain syndrome.
- SLEDAI-2K total score ≥ 4, excluding points attributable to any urine or laboratory results, immunologic measures, fever, SLE headache, or organic brain syndrome at Screening and Baseline (Day 1).
- At least one of the following BILAG 2004 Index levels of disease at Screening:
  - BILAG A disease in ≥ 1 organ system.
  - BILAG B disease in ≥ 2 organ systems.
- PGA score ≥ 1 on a 0 to 3 visual analog scale (VAS) at Screening.

6. Have at least one of the following at Screening per central lab:

[redacted]

7. Ongoing treatment for SLE defined as (a) or (b):
   a. Treatment with one or more disease-modifying anti-rheumatic drug (DMARD) or immunosuppressive medication: Any of the following medications each administered at conventional anti-rheumatic doses for treatment of SLE for at least 12 weeks before Screening (unless discontinued or dose adjusted for documented drug-related toxicity or size/weight), and at a stable dose (including route of administration) for a minimum of 8 weeks prior to Screening and maintained through Baseline (Day 1):
      i. Antimalarial
         - Chloroquine
         - Hydroxychloroquine
         - Quinacrine
      ii. Azathioprine (AZA) or 6-mercaptopurine (6-MP)
      iii. Leflunomide
      iv. Mycophenolate mofetil (MMF) or mycophenolic acid (MPA)

v. Methotrexate (MTX) (participants must be on concomitant folic or folinic acid supplementation if using MTX)
vi. Voclosporin (if approved for treatment)
vii. GCs are permitted but not required if a participant is receiving at least one other medication listed above. If GCs are used in combination with allowed DMARDs or immunosuppressants, they must be at an average daily dose of PO prednisone ≤ 40 mg (or prednisone equivalent) for a minimum of 2 weeks prior to Screening and at a stable dose for a minimum of 2 weeks prior to Screening. In addition, the dose of OGC must be kept stable for a minimum of 2 weeks prior to Randomization. Daily dosing or alternate day dosing of PO prednisone (or prednisone equivalent) is allowed.

b. Treatment with OGC monotherapy (without the concomitant use of DMARDs or immunosuppressants):
   i. Average daily dose of PO prednisone ≥ 10 mg but ≤ 40 mg (or prednisone equivalent) for a minimum of 4 weeks prior to Screening and at a stable dose for a minimum of 2 weeks prior to Screening. In addition, the dose of OGC must be kept stable for a minimum of 2 weeks prior to Randomization. Daily dosing or alternate day dosing of PO prednisone (or prednisone equivalent) is allowed.

8. Women of childbearing potential must have a negative serum pregnancy test at Screening and a negative urine pregnancy test at Randomization. Women of childbearing potential are defined as those who are not surgically sterile (ie, surgical sterilization includes bilateral tubal ligation, 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, unless on postmenopausal hormone replacement therapy).

   Women of childbearing potential who are sexually active with a non-sterilized male partner must agree to use a highly effective method of contraception (Table 1) from signing of the informed consent, 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. A decision about contraception after this point should be made by the participant and her regular healthcare providers.

   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 MPA who are using hormonal contraceptives for birth control, the participant must employ an additional contraceptive method (eg, barrier method).

Table 1 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 patient is changing the method to complete abstinence, the patient must employ a barrier method in addition to the highly effective method of contraception for at least two 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 participant and that the vasectomized partner has received medical assessment of the surgical success.

[d] Sexual abstinence is considered to be 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 participant.

[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.

9. Non-sterilized male participants who are sexually active with a woman partner of childbearing potential must agree to use a condom with spermicide from Randomization 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 participants advise their women partners of childbearing potential to use a highly effective method of contraception throughout this period (refer to Table 1).

5.2 Exclusion Criteria

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

5.2.1 General Exclusion Criteria

1. Individuals involved in the conduct of the study, their employees, or immediate family members of such individuals.
2. Any condition that, in the opinion of the Investigator or the Sponsor/Central Review Committee, would interfere with evaluation of the IP or interpretation of participant safety or study results (including borderline disease activity).
3. History of allergy, hypersensitivity reaction, or anaphylaxis to any component of the IP or to a previous mAb or human Ig therapy.
4. Participation in another clinical study with an investigational drug within 4 weeks prior to Day 1 or within 5 published half-lives, whichever is longer (also refer to Section 5.2.3).
5. Breastfeeding or pregnant women or women who intend to become pregnant anytime from signing the ICF through 3 months after receiving the last dose of IP.

6. History of drug or alcohol abuse that, in the opinion of the Investigator, might affect participant safety or compliance with visits, or interfere with other study assessments.
7. Major surgery within 8 weeks prior to Screening or elective surgery planned from Screening through Day 393.
8. Spontaneous or induced abortion, still or live birth, or pregnancy ≤ 4 weeks prior to Screening.
9. Known history of a primary immunodeficiency or an underlying condition such as known human immunodeficiency virus (HIV) infection, a positive result for HIV infection per central laboratory, splenectomy, or any underlying condition that in the opinion of the Investigator significantly predisposes the participant to infection.
10. At Screening, any of the following per central laboratory (tests may be repeated once within the same Screening period to confirm results prior to Randomization):

- Aspartate aminotransferase (AST) > 2.5× upper limit of normal (ULN)
- Alanine aminotransferase (ALT) > 2.5× ULN
- Total bilirubin > 1.5× ULN (unless due to Gilbert's syndrome)
- Serum IgG < 600 mg/dL (or < 6 g/L)
- Neutrophil count < 1000/µL (or < 1.0×10^9/L) or < 500/µL (< 0.5×10^9/L) if due to active SLE
- Platelet count < 50,000/µL (or < 50×10^9/L) or < 25,000/µL (< 25×10^9/L) if due to active SLE
- Hemoglobin < 8 g/dL (or < 80 g/L) or < 7 g/dL (< 70 g/L) if due to active SLE
- Glycosylated hemoglobin > 8% (or > 0.08)
- Total lymphocyte count < 200 cells/mm^3
- Glomerular filtration rate < 30 mL/min/1.73 m^2
- Spot UPCr > 3 mg/mg (> 339 mg/mmol)

11. Confirmed positive test for hepatitis B serology defined as:

- Hepatitis B surface antigen (HBsAg), or
- Hepatitis B core antibody (HBcAb) AND hepatitis B virus (HBV) DNA detected above the lower limit of quantitation (LLOQ) by reflex testing by the central laboratory at Screening.

  Note that participants who are HBcAb positive at Screening will be tested every 3 months for HBV DNA. Study drug will be discontinued if the participant's HBV DNA levels are confirmed to exceed the LLOQ as per the central laboratory.

12. Positive test for hepatitis C virus antibody.
13. Active TB, or a positive IFN-gamma release assay (IGRA) test at Screening, unless documented history of appropriate treatment for active or latent TB.

    Note that participants with an indeterminate IGRA test result with well-documented previous treatment do not need to repeat testing and are eligible for randomization. Participants with an indeterminate IGRA test result without previous treatment can repeat the test, but if the repeat test is also indeterminate, they are excluded.
14. Any severe herpes virus family infection (including Epstein-Barr virus, cytomegalovirus [CMV]) at any time prior to Randomization, including, but not limited to, disseminated

herpes, herpes encephalitis, recent recurrent herpes zoster (defined as 2 episodes within the last 2 years), or ophthalmic herpes.

15. Any herpes zoster, CMV, or Epstein-Barr virus infection that was not completely resolved 12 weeks prior to Randomization.
16. Any of the following within 30 days prior to signing the ICF and though Randomization:

- Clinically significant active infection in the opinion of the Investigator, including ongoing, and chronic infection requiring antibiotics or antiviral medication (chronic nail infections are allowed).
- Any infection requiring hospitalization or treatment with IV anti-infectives.
- A participant with a documented positive SARS-CoV-2 test may be rescreened at least 2 weeks after a positive test if the participant is asymptomatic and at least 3 weeks after symptomatic COVID-19 illness.

17. Opportunistic infection requiring hospitalization or parenteral antimicrobial treatment within 2 years prior to Randomization (Appendix 3).
18. Any acute illness or evidence of clinically significant active infection,
19. Clinically significant cardiac disease including unstable angina and/or myocardial infarction and/or congestive heart failure within 6 months prior to Randomization. Any cardiac condition including, but not limited to the following, if in the opinion of the Investigator or Medical Monitor, would increase the risk of study participation:

- Inadequately controlled arrhythmia.
- Presence of clinically significant abnormality on ECG.

20. History of cancer within the past 5 years, except as follows:

- In situ carcinoma of the cervix treated with apparent success with curative therapy > 12 months prior to Screening, or
- Cutaneous basal cell or squamous cell carcinoma treated with apparent success with curative therapy.

21. Receipt of a live-attenuated vaccine within 4 weeks prior to Day 1. Administration of inactivated (killed) vaccines is acceptable.
22. Participant should be assessed for epidemiologic risk of COVID-19 (ie, recent exposure, high-risk housing) and for health-related risk of COVID-19 severity based on current understanding of risk factors for severe disease when making a decision regarding the individual's risk of participation. Participants who have COVID-19 or other significant infection, or in the judgment of the Investigator, may be at a high risk of COVID-19 or its complications should not be randomized.

5.2.2 Disease-Related Criteria

23. Active LN OR active severe or unstable neuropsychiatric SLE (eg, aseptic meningitis, cerebral vasculitis, myelopathy, demyelination syndromes [ascending, transverse, acute inflammatory demyelinating polyradiculopathy], acute confusional state, impaired level of consciousness, psychosis, acute stroke or stroke syndrome, cranial neuropathy, status epilepticus, cerebellar ataxia, and mononeuritis multiplex) where, in the opinion of the Investigator or Medical Monitor, protocol-specified SoC is insufficient and utilization of a more aggressive therapeutic approach, such as IV cyclophosphamide, high-dose IV pulse GC therapy, MMF of > 3 gm/day (MPA of > 2.16 gm/day), or an increase from

baseline dose of MMF/MPA and/or other treatments not permitted in the protocol, may be indicated.

24. Current diagnosis of non-SLE vasculitis syndrome, mixed connective tissue disease, or rheumatic (overlap) syndrome that may confound clinical assessments in the study (eg, scleroderma/systemic sclerosis). Secondary sicca or Sjögren's syndrome, antiphospholipid antibody syndrome, and overlap with myositis or rheumatoid arthritis without erosive joint disease ("rhupus") are allowed provided the participant also meets the criteria for classification as SLE. A history of mixed connective tissue disease that over time has developed into a diagnosis of SLE is permitted provided diagnosis of SLE has been present for at least 6 months.
25. History of antiphospholipid syndrome (APS) with thromboembolic event within 6 months of Screening or not on an adequate anticoagulation regimen in the 6 weeks prior to or at Screening in the opinion of the Investigator. However, presence of antiphospholipid antibodies alone (without a history of thromboembolic event) is not exclusionary.
26. Current inflammatory joint or skin disease other than SLE that, in the opinion of the Investigator, could interfere with the inflammatory arthritis or skin assessments and confound the disease activity assessments.

5.2.3 Prior and Concomitant Therapy Criteria

27. Unstable dosing or initiation of a regularly used nonsteroidal anti-inflammatory drug (NSAID) within 2 weeks prior to Baseline (Day 1) other than low-dose [≤ 350 mg] aspirin for cardiovascular prophylaxis or for APS, which is permitted. Non-regular use of NSAID for pain control is permitted.
28. Receipt of any of the following treatments within the following timeframes. Refer to Section 7.4.1 for more details:

- 2 Weeks prior to Screening and through Randomization:
  - Initiation of or unstable dosing of topical therapy (eg, GCs, calcineurin inhibitors) for cutaneous lupus (cyclosporine eye drops are permitted).
  - Opioid use above 40 mg/day morphine-equivalent, unstable dosing, or initiation of regular dosing.
- 4 Weeks prior to Screening and through Randomization:
  - Intra-articular therapies, such as GCs.
  - Systemic GC doses of ≥ 100 mg prednisone or equivalent or intramuscular, IV or intralesional GCs.
  - Intradermal GC for alopecia.
  - IV, intramuscular, or SC Ig.
  - Other non-biologic immunosuppressive agents (eg, dapsone, danazol, calcineurin inhibitors, sulfasalazine, mizoribine, mechanistic target of rapamycin inhibitors, retinoids, thalidomide, lenalidomide, adrenocorticotropic hormone [ACTH] analogs, dehydroepiandrosterone), or Janus kinase inhibitors.
  - Transfusion with blood, packed red blood cells, platelets or treatment with plasmapheresis, plasma exchange, or Therakos® photopheresis.

- 12 Weeks (or 5 half-lives, whichever is longer) prior to Randomization:
  - Cyclophosphamide or alkylating agents (eg, chlorambucil).
  - Cytokine or cytokine receptor antagonists, including but not limited to interleukin (IL)-1, IL-6, IL-17, IL-12/23, IL-23, IFN, integrin, or TNFα antagonists (except for IFNα kinoid, for which receipt at any time is exclusionary).
  - Belimumab, abatacept, or eculizumab.
  - Other biologics used for immunosuppression or immunomodulation (eg, IFN therapy, IL-2).
  - Investigational drugs.
  - IPP-201101 (Lupuzor™).
- 24 Weeks prior to Randomization:
  - B cell-depleting therapies (eg, rituximab, ocrelizumab, ofatumumab, inebilizumab, telitacicept) other than atacicept or obinutuzumab.
  - Receipt of systemic GCs for more than a total of 2 weeks for any concurrent illness, including asthma, inflammatory bowel disease, or drug-induced SLE.
    - Systemic is defined as PO, rectal, or any injectable route of administration.
- 40 Weeks prior to Randomization:
  - Atacicept.
- 1 Year prior to Randomization:
  - Bacille-Calmette-Guerin (BCG) vaccination.
- 1.5 Years prior to Randomization:
  - Obinutuzumab.

5.3 Rescreening Procedures

Participants may be rescreened once after a screen failure for inadequate disease activity or other reason which, in the opinion of the Investigator, may change to make the participant eligible. A participant who rescreens will be required to re-sign the ICF. A screen failure is a consented participant who has been deemed ineligible on the basis of one or more eligibility criteria or who has withdrawn consent prior to treatment assignment. Participants who rescreen within 8 weeks of signing the ICF do not have to repeat serum virology, TB assessment, or chest X-ray if performed within 12 weeks, or, if relevant, FSH testing.

5.4 Replacement of Participants

Participants who have been randomized but not dosed will not be followed to completion of the study and may be replaced at the discretion of the Sponsor.

6 STUDY CONDUCT

6.1 General Instructions

Participants will undergo a Screening period of approximately 4 weeks (Days -28 to -1), Randomization on Day 1, treatment and assessments through Week 48, and a SFU period of 8 weeks (through Week 56).

6.2 Schedule of Study Assessments

Table 2, Table 3, and Table 4 summarize the Screening, treatment, and follow-up assessments and procedures.

Table 2 Screening Procedures

Study Day	**-28 to -1**
Visit Number	**1**
General Assessments	
Informed consent	X
Eligibility review	X
Demographic data	X
Review of SLE and other medical history, medications, and surgery/procedures	X
Documentation of SLE classification criteria	X
Chest X-ray [a]	X
TB assessment [b]	X
12-lead ECG (after 10 minutes rest in supine position) [c]	X
Vital signs, height, and weight [d]	X
Physical examination [e]	X
BILAG 2004 assessments, SLEDAI-2K, CLASI, PGA, [redacted] [f]	X
Laboratory Assessments	
Pregnancy (serum βhCG) test (in women of childbearing potential)	X
FSH (to confirm postmenopausal status, as appropriate) [g]	X
Serum virology [h]	X
Routine hematology and chemistry [i]	X
HbA1c	X
Urinalysis and spot UPCr (aim to collect urine sample at same time of day, if possible) [j]	X
Anticardiolipin antibodies (IgG, IgA, and IgM)	X
Anti-β2GP1 antibody	X
Lupus anticoagulant	X
Haptoglobin [k]	X
C3 and C4	X
[redacted]	
PT/INR and PTT	X

Table 2 Screening Procedures

Study Day	**-28 to -1**
Visit Number	**1**
Serum IgG, IgA, IgM	X
[redacted]	
Questionnaires [l]	
[redacted]	
Safety	
Concomitant medications	X
AEs, SAEs, and/or AESIs	X

AE: adverse event; AESI: AE of special interest; [redacted] β2GP1: β2-glycoprotein 1; BILAG: British Isles Lupus Assessment Group; C: complement; [redacted] CLASI: Cutaneous Lupus Erythematosus Disease Area and Severity Index: [redacted] ECG: electrocardiogram; FSH: follicle-stimulating hormone; HbA1c: glycosylated hemoglobin; [redacted] Ig: immunoglobulin; INR: international normalized ratio; [redacted] PT: prothrombin time; [redacted] PTT: partial thromboplastin time; SAE: serious AE; SLE: systemic lupus erythematosus; SLEDAI-2K: SLE Disease Activity Index 2000; TB: tuberculosis; UPCr: urine protein:creatinine ratio; X: to be performed.

[a] The results of a chest X-ray (posterior-anterior, anterior-posterior, and lateral views) performed within 12 weeks of the Screening visit (if available) are acceptable, provided there is no reason to suspect any clinical changes. The chest X-ray may be completed anytime during the Screening period as long as all results have been reviewed by the Investigator prior to Randomization. If the chest X-ray is performed at Screening, posterior-anterior and lateral views should be evaluated, unless where prohibited by local health authority. Magnetic resonance imaging or computed tomography scans of the chest performed within 12 weeks of the Screening visit are acceptable.

[b] The results of an IFN-gamma release assay (ie, QuantiFERON-TB Gold Plus or T-SPOT) performed within 12 weeks of the Screening visit (if available) are acceptable, provided there is no reason to suspect any re-exposure.

[c] Should be performed after vital signs are collected.

[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. Height will be measured at Screening only.

[e] A focused physical examination should be performed. A focused physical examination should always include assessment of head, ears, eyes, nose, throat, lungs, heart, abdomen, skin, and extremities.

[f] Additional assessments, (eg, ECG or chest radiograph) should be performed as needed to fully obtain information needed for the BILAG 2004 Index and and/or SLEDAI-2K assessments. Assessments at Screening should be compared to previous lupus disease and medical history, as appropriate.

[g] FSH testing does not have to be repeated if performed within 12 weeks prior to Screening (eg, re-Screening).

[h] Includes human immunodeficiency virus testing, hepatitis B testing (hepatitis B surface antigen and hepatitis core antibody [HBcAb] with reflex DNA testing), and hepatitis C virus antibody testing. Participants who are HBcAb positive with a negative hepatitis B virus (HBV) DNA at Screening will be tested every 3 months for HBV DNA. To remain eligible for the study, the participant's HBV DNA levels must be confirmed to remain below the lower limit of quantitation as per the central laboratory. Serum virology does not have to be repeated if performed within 12 weeks prior to Screening (eg, re-Screening).

[i] Refer to Table 5 for a list of routine laboratory assessments.

[j] 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] Haptoglobin will be collected during Screening but will only be tested if needed to confirm suspected hemolytic anemia.

[l] Questionnaires are strongly recommended to be completed before any other procedures are performed.

Table 3 Schedule of Assessments During the Treatment Period

Study Day	**1**	**29**	**57**	**85**	**113**	**141**	**169**	**197**	**225**	**253**	**281**	**309**	**337**
Visit Window (± days)	**-**	**3**	**3**	**3**	**3**	**3**	**3**	**3**	**3**	**3**	**3**	**3**	**3**
Study Week	**0**	**4**	**8**	**12**	**16**	**20**	**24**	**28**	**32**	**36**	**40**	**44**	**48/ET**
Visit Number	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**
General Assessments/Procedures													
12-lead ECG (after 10 minutes rest in supine position) [a]							X						X
Vital signs and weight [b]	X	X	X	X	X	X	X	X	X	X	X	X	X
Physical examination [c]	X	X	X	X	X	X	X	X	X	X	X	X	X
[redacted]													
BILAG 2004 assessments, SLEDAI-2K, CLASI, PGA, and Joint Count [d]	X	X	X	X	X	X	X	X	X	X	X	X	X
Eligibility review [e]	X												
Randomization	X												
Laboratory Assessments													
Pregnancy (urine) test [f]	X	X	X	X	X	X	X	X	X	X	X	X	X
Hepatitis B DNA testing [g]	X			X			X			X			X
Routine hematology and chemistry [h]	X	X	X	X	X	X	X	X	X	X	X	X	X
HbA1c							X						X
Lipids (after an 8-hour fast; water allowed) [i]	X						X						X
Urinalysis and spot UPCr (aim to collect urine sample at same time of day, if possible) [j]	X	X	X	X	X	X	X	X	X	X	X	X	X
Confirmatory tests for hemolytic anemia and active APS [k]	X	X	X	X	X	X	X	X	X	X	X	X	X
Anticardiolipin antibodies (IgG, IgA, IgM)	X			X			X			X			X
Anti-β2GP1 antibody	X			X			X			X			X
Lupus anticoagulant [l]							X						X
C3 and C4	X	X	X	X	X	X	X	X	X	X	X	X	X
[redacted]													

Table 3 Schedule of Assessments During the Treatment Period

Study Day	**1**	**29**	**57**	**85**	**113**	**141**	**169**	**197**	**225**	**253**	**281**	**309**	**337**
Visit Window (± days)	**-**	**3**	**3**	**3**	**3**	**3**	**3**	**3**	**3**	**3**	**3**	**3**	**3**
Study Week	**0**	**4**	**8**	**12**	**16**	**20**	**24**	**28**	**32**	**36**	**40**	**44**	**48/ET**
Visit Number	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**
[redacted]													
PT/INR and PTT	X			X			X			X			X
Serum IgA, IgG, and IgM	X			X			X			X			X
[redacted]													
hs-CRP	X			X			X			X			X
pDC FACS	X	X	X	X		X	X		X	X		X	X
[redacted]													
Whole blood transcriptomics	X	X		X			X			X			X
PBMC cytometry	X						X						X
VIB7734 PK (serum)	X	X	X	X	X	X	X	X	X	X	X	X	X
[redacted]													
Questionnaires [m]													
[redacted]													

Table 3 Schedule of Assessments During the Treatment Period

Study Day	**1**	**29**	**57**	**85**	**113**	**141**	**169**	**197**	**225**	**253**	**281**	**309**	**337**
Visit Window (± days)	**-**	**3**	**3**	**3**	**3**	**3**	**3**	**3**	**3**	**3**	**3**	**3**	**3**
Study Week	**0**	**4**	**8**	**12**	**16**	**20**	**24**	**28**	**32**	**36**	**40**	**44**	**48/ET**
Visit Number	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**
Investigational Product Administration													
IP administration	X	X	X	X	X	X	X	X	X	X	X	X	
Safety													
Local injection tolerability	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant medications	X	X	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	X	X

[redacted] AE: adverse event; AESI: AE of special interest [redacted] APS: antiphospholipid syndrome; β2GP1: β2-glycoprotein 1; BILAG: British Isles Lupus Assessment Group; C: complement; [redacted] CLASI: Cutaneous Lupus Erythematosus Disease Area and Severity Index: ECG: electrocardiogram; ET: Early Termination; FACS: fluorescence-activated cell sorting; [redacted] HbA1c: glycosylated hemoglobin; hs-CRP: high-sensitivity C-reactive protein; Ig: immunoglobulin; [redacted] INR: international normalized ratio; IP: investigational product; [redacted] PBMC: peripheral blood mononuclear cells; pDC: plasmacytoid dendritic cell; PGA: Physician Global Assessment; [redacted] PK: pharmacokinetic(s); PT: prothrombin time; [redacted] PTT: partial thromboplastin time; [redacted] SAE: serious AE; [redacted] SLEDAI-2K: Systemic Lupus Erythematosus Disease Activity Index 2000; [redacted] UPCr: urine protein:creatinine ratio; X: to be performed.

All collections and assessments should be performed predose on days when IP is administered, unless otherwise specified.

[a] Should be performed after vital signs are collected.

[b] 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.

[c] A focused physical examination should be performed at all visits, except during the Baseline (Day 1), Week 48, or Early Termination visits. A focused physical examination should always include assessment of head, ears, eyes, nose, throat, lungs, heart, abdomen, skin, and extremities.

[d] Additional assessments, (eg, ECG or chest X-ray) should be performed as needed to fully obtain information needed for the BILAG and and/or SLEDAI-2K assessments.

[e] Participant eligibility (based on Screening assessments, including non–laboratory-based assessments at Baseline [Day 1] as per the inclusion and exclusion criteria [Section 5]) must be checked again on Day 1 prior to Randomization.

[f] Women of childbearing potential as defined in Inclusion Criteria #8.

[g] Reflex DNA testing if isolated hepatitis B core positive at Screening.

Table 3 Schedule of Assessments During the Treatment Period

Study Day	**1**	**29**	**57**	**85**	**113**	**141**	**169**	**197**	**225**	**253**	**281**	**309**	**337**
Visit Window (± days)	**-**	**3**	**3**	**3**	**3**	**3**	**3**	**3**	**3**	**3**	**3**	**3**	**3**
Study Week	**0**	**4**	**8**	**12**	**16**	**20**	**24**	**28**	**32**	**36**	**40**	**44**	**48/ET**
Visit Number	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**

[h] Refer to Table 5 for a list of routine laboratory assessments.
[i] This visit recommended to occur in the morning.
[j] 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 for the BILAG confirmatory tests, including haptoglobin if needed to confirm suspected hemolytic anemia, and anticardiolipin antibodies (IgG, IgA, and IgM) and anti-β2GP1 antibody if needed to confirm suspected APS.
[l] If an active manifestation of APS is suspected, the lupus anticoagulant should be collected and tested at all relevant study days, in addition to those already indicated in the schedule of assessments during the Treatment period.
[m] Questionnaires are strongly recommended to be completed before any other procedures are performed.

Table 4 Schedule of Assessments During the Safety Follow-Up Period

Study Day	**365**	**393**
Visit Window (± Days)	**7**	**7**
Study Week	**52**	**56**
Visit Number	**15**	**16**
General Assessments		
12-lead ECG (after 10 minutes rest in supine position) [a]		X
Vital signs and weight [b]	X	X
Physical examination [c]	X	X
BILAG 2004 Index assessments, SLEDAI-2K, CLASI, PGA, [redacted] [d]	X	X
Laboratory Assessments		
Pregnancy (urine) test [e]	X	X
Hepatitis B DNA testing [f]		X
Routine hematology and chemistry [g]	X	X
HbA1c		X
Lipids (after an 8-hour fast; water allowed) [h]		X
Urinalysis and spot UPCr (aim to collect urine sample at same time of day, if possible) [i]	X	X
Confirmatory tests for hemolytic anemia and active APS [j]	X	X
Anticardiolipin antibodies (IgG, IgA, and IgM)		X
Anti-β2GP1 antibody		X
Lupus anticoagulant [k]		X
C3 and C4	X	X
[redacted]		
PT/INR and PTT		X
Serum IgA, IgG, and IgM		X
[redacted]		
hs-CRP	X	X
pDC FACS	X	X
[redacted]		
PBMC cytometry		X
VIB7734 PK (serum)	X	X
[redacted]		
Questionnaires [l]		
[redacted]		

Table 4 Schedule of Assessments During the Safety Follow-Up Period

Study Day	**365**	**393**
Visit Window (± Days)	**7**	**7**
Study Week	**52**	**56**
Visit Number	**15**	**16**
[redacted]		
Safety		
Concomitant medications	X	X
AEs, SAEs, and/or AESIs	X	X

[redacted] AE: adverse event; AESI: AE of special interest; [redacted] APS: antiphospholipid syndrome; β2GP1: β2-glycoprotein 1; BILAG: British Isles Lupus Assessment Group; C: complement; CLASI: Cutaneous Lupus Erythematosus Disease Area and Severity Index; [redacted] ECG: electrocardiogram; FACS: fluorescence-activated cell sorting; [redacted] HbA1c: glycosylated hemoglobin; hs-CRP: high-sensitivity C-reactive protein; [redacted] Ig: immunoglobulin; INR: international normalized ratio; [redacted] PBMC: peripheral blood mononuclear cells; pDC: plasmacytoid dendritic cell; PGA: Physician Global Assessment; [redacted] PK: pharmacokinetic(s); PT: prothrombin time; [redacted] PTT: partial thromboplastin time; SAE: serious AE; SLEDAI-2K: Systemic Lupus Erythematosus Disease Activity Index 2000; UPCr: urine protein:creatinine ratio; X: to be performed., Safety Follow-Up visits will be conducted at 4 and 8 weeks after the last dose of investigational product (IP) for participants who have completed the 48-week Treatment period. These assessments, however, will not be performed on participants who enter the long-term extension study.

Participants who permanently discontinue IP at any point in the study but who **do not** withdraw consent of study participation will complete all study visits through Study Week 48/ET and at least 12 weeks follow up after the last dose of IP. Participants who permanently discontinue IP at any point in the study and who **do** withdraw consent of study participation will only complete the Study Week 48/ET assessments (if they agree to do so before withdrawing consent).

[a] Should be performed after vital signs are collected.

[b] 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.

[c] A focused physical examination should be performed. A focused physical examination should always include assessment of head, ears, eyes, nose, throat, lungs, heart, abdomen, skin, and extremities.

[d] Additional assessments, (eg, ECG, or chest radiograph) should be performed as needed to fully obtain information needed for the BILAG 2004 Index and and/or SLEDAI-2K assessments.

[e] Women of childbearing potential as defined in Inclusion Critertia #8.

[f] Reflex DNA testing if isolated hepatitis B core positive.

[g] Refer to Table 5 for a list of routine laboratory assessments.

[h] This visit recommended to occur in the morning.

[i] Urine collection can be postponed for up to 14 days in women with menstrual bleeding or a urinary tract infection at the scheduled visit.

[j] Serum aliquots will be used for the BILAG confirmatory tests, including haptoglobin if needed to confirm suspected hemolytic anemia, and anticardiolipin antibodies (IgG, IgA, and IgM) and anti-β2GP1 antibody if needed to confirm suspected APS.

[k] If an active manifestation of APS is suspected, the lupus anticoagulant should be collected and tested at both Study Days 365 and 393.

[l] Questionnaires are strongly recommended to be completed before any other procedures are performed.

6.3 Description of Study Assessments and Procedures

A laboratory manual will be provided to the 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.

6.3.1 Screening and Randomization Procedures

All candidates for enrollment will sign an ICF prior to any protocol-related procedures, including Screening activities. Informed consent must be obtained by the PI or a designee, such as an appropriately qualified sub-Investigator. The informed consent process should be documented. Storage and future testing of blood samples will be conducted for participants who sign an additional optional consent.

All Screening procedures listed in Table 2 will be performed within 28 days prior to IP treatment. The Screening period may be increased by 2 weeks, under exceptional circumstances such as delayed laboratory results or the impact of COVID-19, and upon approval by the Medical Monitor. Once Screening assessments are complete, all necessary laboratory results required to confirm eligibility are reported, and Medical Monitor eligibility review is complete, a participant may be randomized.

After signing the ICF, each participant will be assigned a subject identification number (SID) that will be used on all participant documentation. SIDs will be assigned in ascending sequential order. Rescreened participants will receive a new SID.

On Day 1, the Investigator will confirm that all eligibility criteria still are fulfilled prior to Randomization, including that the SLEDAI-2K eligibility criteria (Section 5.1; Item 5), OGC dose, and dose and route of other permitted immunosuppressants have been stable during the Screening period as defined in the eligibility criteria [Section 5]).

Randomization will be stratified by SLEDAI-2K score at Screening (≥ 10 or < 10) and prednisone or equivalent OGC dose at Baseline (Day 1) (≥ 10 mg or < 10 mg). Stratification is implemented in order to minimize risk for Baseline imbalances across treatment groups on disease activity and OGC dose/use. Baseline imbalances of disease activity and OGC dose/use impact efficacy and/or safety assessments of VIB7734 versus placebo.

6.3.2 Efficacy Assessments

Efficacy measurements will be made at the times indicated in Section 6.2; refer to Table 2, Table 3, and Table 4 for Screening, treatment, and follow-up assessments and procedures.

6.3.2.1 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.

6.3.2.1.1 Collection of Efficacy Assessments and Lupus Assessment Completion and Review Process

Appropriately trained and qualified Investigators will complete the lupus assessments, including but not limited to, the BILAG 2004 Index, SLEDAI-2K, CLASI, [redacted] The SLEDAI-2K, BILAG 2004 Index, PGA, and CLASI must be administered by the Investigator or appropriately qualified physician, unless prior Sponsor approval has been obtained for any other clinically trained site personnel with documentation of adequate assessment experience. [redacted] The PI retains overall responsibility for the accuracy of the collected data. The lupus assessments will be reviewed centrally by a team designated by the Sponsor to ensure appropriate disease activity level at study entry and accurate completion and consistency in scoring throughout the study Treatment period.

Assessment scores will be programmatically derived and reviewed centrally. Additional information regarding programmatic calculation including any data imputation considerations will be detailed in the statistical analysis plan (SAP).

Prior to Randomization, the Sponsor or designee Medical Monitor will confirm the Investigator's assessment of participant eligibility based on specified data to be reviewed centrally. This confirmation must be obtained prior to Randomization. If the central review team does not agree on participant disease activity level for eligibility, the Sponsor and/or an external unbiased consultant may be consulted for input. The PI retains responsibility for final confirmation of participant eligibility based on all specified study entry criteria.

6.3.2.2 Systemic Lupus Erythematosus Efficacy Assessments

6.3.2.2.1 Systemic Lupus Erythematosus Disease Activity Index 2000

The SLEDAI-2K index consists of a list of organ manifestations, each with a definition. A certified Investigator or designated physician will complete the SLEDAI-2K assessment and decide whether each manifestation is "present" or "absent" within the last 4 weeks. The assessment also includes the collection of blood and urine for assessment of the laboratory categories of the SLEDAI-2K.

The SLEDAI-2K assessment consists of 24 lupus-related items. It is a weighted instrument, in which descriptors are multiplied by an organ's "weight". For example, renal descriptors are multiplied by 4 and CNS descriptors by 8; these weighted organ manifestations are totaled into the final score. The SLEDAI-2K scores are valid, reliable, and sensitive clinical assessments of lupus disease activity. The SLEDAI-2K, calculated using a timeframe of 30 days prior to a visit for clinical and laboratory values, has been shown to be like the SLEDAI-2K with a 10-day window (Touma et al, 2010). A timeframe of 28 days (± allowed visit window) will be used in this study.

6.3.2.2.2 British Isles Lupus Assessment Group 2004 Index

The BILAG 2004 Index is a translational index with 9 systems (General, Mucocutaneous, Neuropsychiatric, Musculoskeletal, Cardiorespiratory, Gastrointestinal, Ophthalmic, Renal, and Hematology) that can capture the changing severity of clinical manifestations. It has ordinal scales by design and does not have a global score; rather it captures disease activity across the different systems at a glance by comparing the immediate past 4 weeks to the 4 weeks preceding them. It is based on the principle of physicians' intention to treat and categorizes disease activity into 5 different levels, from A to E:

- Grade A represents very active disease requiring immunosuppressive drugs and/or a prednisone dose of > 20 mg/day or equivalent.
- Grade B represents moderate disease activity requiring a lower dose of GCs, topical GCs, topical immunosuppressives, antimalarials, or NSAIDs.
- Grade C indicates mild stable disease.
- Grade D implies no disease activity, but the system has previously been affected.
- Grade E indicates no current or previous disease activity.

Although the BILAG 2004 Index was developed based on the principle of intent to treat, the treatment has no bearing on the scoring index. Only the presence of active manifestations influences the scoring.

6.3.2.2.3 Physician Global Assessment

A trained and certified Investigator will complete the PGA after all laboratory tests have been reviewed. The PGA represents the physician's overall assessment of average SLE disease severity on a VAS with 0 (no disease) to 3 (severe) disease activity over the previous 4 weeks. The PGA for a given participant should be completed by the same physician whenever possible.

The PGA is a modification of the classic analog scale in that it is anchored with numbers from 0 to 3 demarcating no, mild, moderate, and severe disease. The number 3 indicates severe disease and is at the end of the scale. This refers to the most severe disease possible; it does not reflect the most severe disease observed in a particular participant, but the most severe disease ever observed in all SLE participants. Therefore, the line made along this scale by the physician should virtually never approach this edge. Any disease rated greater than 2.5 is very severe. The range of moderate disease covers approximately 1.5 to 2.4. Mild disease falls below 1.5. The instrument is like a logarithmic scale, with greater distances or demarcations possible among more mild-moderate symptoms.

When scoring the PGA, the score from the previous visit should be reviewed and the mark should be moved relative to the score from the previous visit. This is a global assessment, factoring in all aspects of the participant's lupus disease activity. It should not reflect non-lupus medical conditions.

6.3.2.2.4 Lupus Low Disease Activity State

The Lupus Low Disease Activity State (LLDAS) is a composite measure of SLE disease activity that has been utilized in clinical trials (Franklyn et al, 2016). LLDAS is defined and measured by attaining all the following 5 criteria:

1. SLEDAI-2K ≤ 4, with no activity in major organ systems (renal, CNS, cardiopulmonary, vasculitis, fever) and no hemolytic anemia or gastrointestinal activity,
2. No new lupus disease activity compared with the previous assessment (SLEDAI-2K),
3. PGA ≤ 1 (scale 0 to 3),
4. A current prednisone (or equivalent) dose ≤ 7.5 mg daily, and
5. Well-tolerated standard maintenance doses of immunosuppressive drugs and approved biological agents (Franklyn et al, 2016).

6.3.2.2.5 Oral Glucocorticoid Reduction

Refer to Section 7.4.3.2.2 for all information regarding OGC tapering.

[redacted]

6.3.2.2.7 Cutaneous Lupus Erythematosus Disease Area and Severity Index

The CLASI is a validated index used for assessing the cutaneous lesions of SLE and consists of 2 separate scores: the first summarizes the inflammatory activity of the disease; the second is a measure of the damage done by the disease. The activity score considers erythema, scale/hypertrophy, mucus membrane lesions, recent hair loss, and non-scarring alopecia. The damage score represents dyspigmentation, scarring/atrophy/panniculitis, and scarring of the scalp. Participants are asked if their dyspigmentation lasted 12 months or longer, in which case the dyspigmentation score is doubled. Each of the above parameters is measured in 13 different anatomical locations, included specifically because they are the most often involved in CLE. The most severe lesion in each area is measured.

[redacted]

[redacted]

6.3.3 Safety Assessments

Key safety assessments are AEs, AEs of special interest (AESIs), vital signs, physical examinations, safety laboratory tests, and ECGs. Safety assessments will be performed at the visits specified in Section 6.2; refer to Table 2, Table 3, and Table 4 for Screening, treatment, and follow-up assessments and procedures.

6.3.3.1 Adverse Events

AEs, SAEs, and AESIs are defined in Section 8.1. Recording of AEs is described in Section 8.2 and reporting of SAEs and AESIs is described in Section 8.3.

6.3.3.2 Vital Signs

Vital signs, blood pressure (mmHg), pulse rate (beats/min), respiratory rate (breaths/min), body temperature (ºC), and body weight (kg) will be obtained at Screening, treatment, and follow-up as outlined in Table 2, Table 3, and Table 4 using clinically acceptable methods and devices as defined in the schedule of assessments. 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 (within 30 minutes for Week 24 due to the ECG requirements).
- 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 judgment and as warranted by the severity of the reaction (Appendix 1).

6.3.3.3 Physical Examination

Body height will be collected at Screening only. Participants will be weighed at each study visit. Medically significant changes from the Screening physical examination will be recorded as AEs, unless they are considered a manifestation of SLE and captured on the BILAG 2004 Index, SLEDAI-2K, or CLASI.

A focused physical examination should be performed at all visits, except for Baseline (Day 1) and Week 48 (Day 337)/Early Termination visits, where a complete physical examination should be performed.

A focused physical examination should always include assessment of head, ears, eyes, nose, throat, lungs, heart, abdomen, skin, and extremities. A complete physical examination should include all organ systems; a genital, rectal, and breast examination can be omitted from the complete physical examination unless clinically indicated.

6.3.3.4 Electrocardiogram

A computerized 12-lead ECG will be performed at the visits specified in Section 6.2; refer to Table 2, Table 3, and Table 4 for Screening, treatment, and follow-up assessments and procedures. 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.

6.3.3.5 Chest X-Ray

A chest X-ray will be performed at Screening. Results of a chest X-ray (posterior-anterior, anterior-posterior, and lateral views) performed within 12 weeks of the Screening visit (if available) are acceptable, provided there is no reason to suspect any clinical changes. If performed at Screening, posterior-anterior and lateral views should be evaluated, unless where prohibited by local health authority. Magnetic resonance imaging or computed tomography scans of the chest performed within 12 weeks of the Screening visit are acceptable.

6.3.3.6 Tuberculosis Assessment

A blood test for TB will be performed at Screening using the IGRA test (ie, QuantiFERON-TB Gold Plus or T-SPOT). Evaluation of all participants by IGRA test will be performed by the central clinical laboratory. Results of an IGRA test performed at a local laboratory within 12 weeks of the Screening visit (if available) are acceptable, provided there is no reason to suspect any re-exposure.

6.3.4 Clinical Laboratory Assessments

All clinical laboratory tests will be performed at a central laboratory at the visits specified in Section 6.2; refer to Table 2, Table 3, and Table 4 for Screening, treatment, and follow-up assessments and procedures. 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 sent to the central laboratory as well, if possible.

A serum pregnancy test (in women of childbearing potential as defined in Inclusion Criteria #8) will be performed at Screening at the central laboratory. Urine pregnancy tests will be performed in women of childbearing potential during treatment and follow-up at the site using a dipstick.

Abnormal safety laboratory results should be repeated as clinically indicated, as soon as possible (preferably within 24 to 48 hours).

Additional safety samples may be collected as clinically indicated at the discretion of the Investigator.

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

The Investigator should assess the available results with regards to clinically relevant abnormalities.

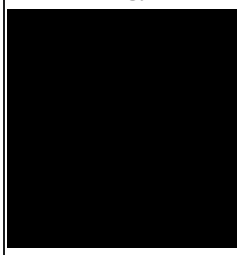
For suspected hemolytic anemia, a haptoglobin level should be tested, if needed, for confirmation. For suspected APS, anticardiolipin antibodies (IgG, IgA, IgM), anti-β2-glycoprotein 1 antibody, and lupus anticoagulant should be tested.

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

Clinical laboratory tests are presented in Table 5.

Table 5 Clinical Laboratory Tests

Immunology



- Anticardiolipin antibodies (IgG, IgA and IgM)
- Anti-β2GP1 antibody
- C3 and C4
- Lupus anticoagulant
- Rheumatoid factor

Hematology and Coagulation

- Hemoglobin
- Hematocrit
- Mean corpuscular hemoglobin concentration
- Mean corpuscular volume
- Platelet count
- PT/INR and PTT
- RBC count
- Reticulocyte count
- WBC with differential

Pregnancy Tests

- Serum β-hCG [a]
- Serum FSH [a]
- Urine dipstick β-hCG [b]

Other Laboratory Tests

- Haptoglobin
- HbA1c
- Hs-CRP
- Lipids (TC, TG, HDL-C, and LDL-C)
- pDC
- Serum IgG, IgA, and IgM

Serum Chemistry

- Albumin
- ALT
- ALP
- AST
- Bicarbonate
- Blood urea nitrogen
- Calcium
- Creatinine
- eGFR
- GGT
- Glucose
- Potassium
- Sodium
- Total bilirubin

Table 5 Clinical Laboratory Tests

• Chloride • Creatine kinase	• Total protein
Serum Virology	
• HBcAb (reflex DNA testing if isolated hepatitis B core positive) • Hepatitis B surface antigen	• Hepatitis C antibody • HIV
Urinalysis	
• Dipstick – Appearance – Bilirubin – Blood – Color – Epithelial cells – Glucose – Ketones – Leukocyte esterase – pH – Protein – Specific gravity	• Microscopy, including WBC/HPF, RBC/HPF, and casts • Urine creatinine and protein; spot UPCr

ALP: alkaline phosphatase; ALT: alanine aminotransferase; [redacted] AST: aspartate aminotransferase; β2GP1: β2-glycoprotein 1; β-hCG: beta-human chorionic gonadotropin; C: complement; [redacted] 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-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; [redacted] TC: total cholesterol; TG: triglycerides; UPCr: urine protein:creatinine ratio; WBC: white blood cell.

[a] At Screening only.

[b] At every visit post-Screening.

6.3.5 Pharmacokinetic Assessments

Serum for PK analysis will be collected at the visits specified in Table 3 and Table 4 and analyzed using a validated bioanalytical method.

6.3.6 Immunogenicity Assessments

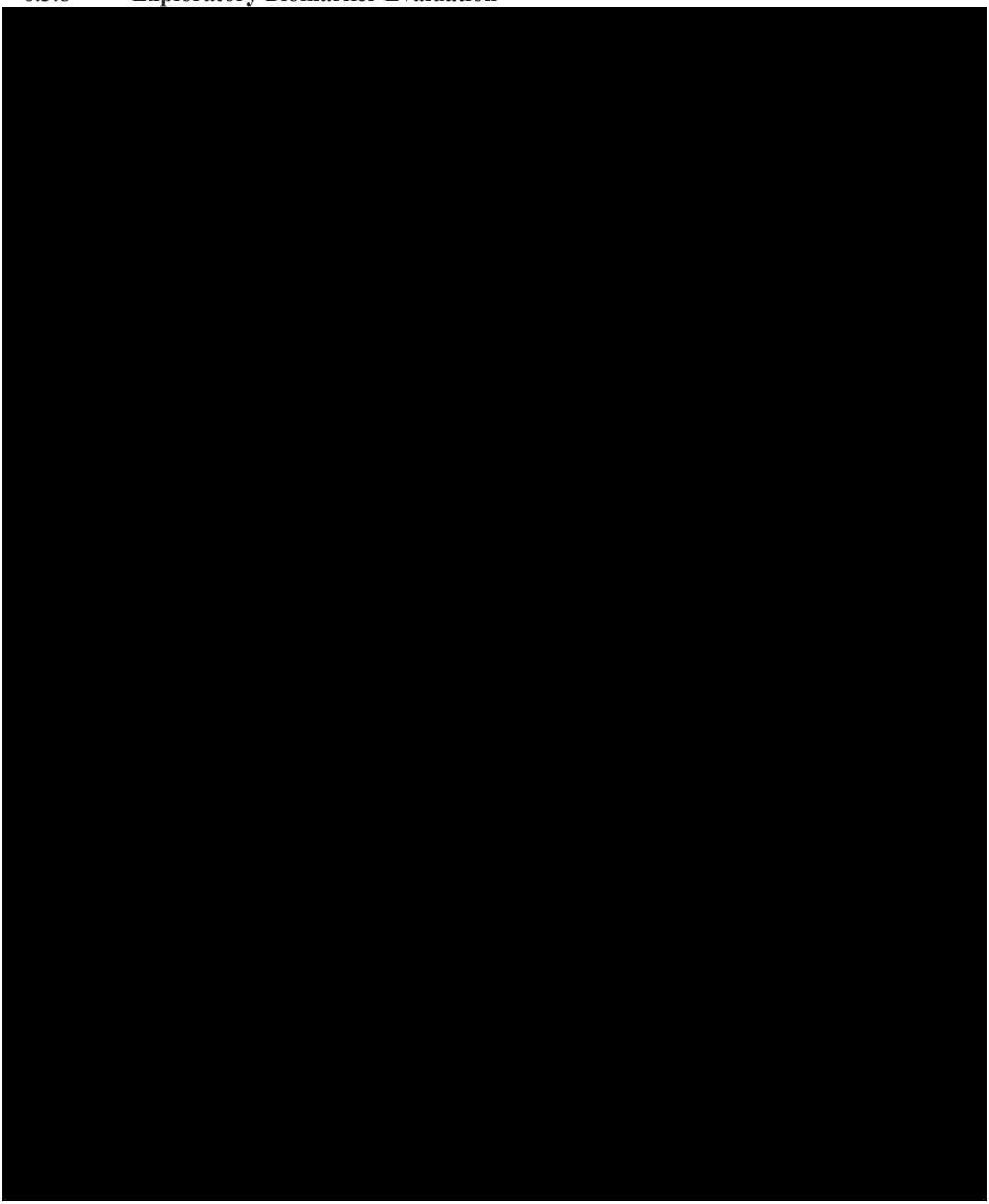
[redacted]

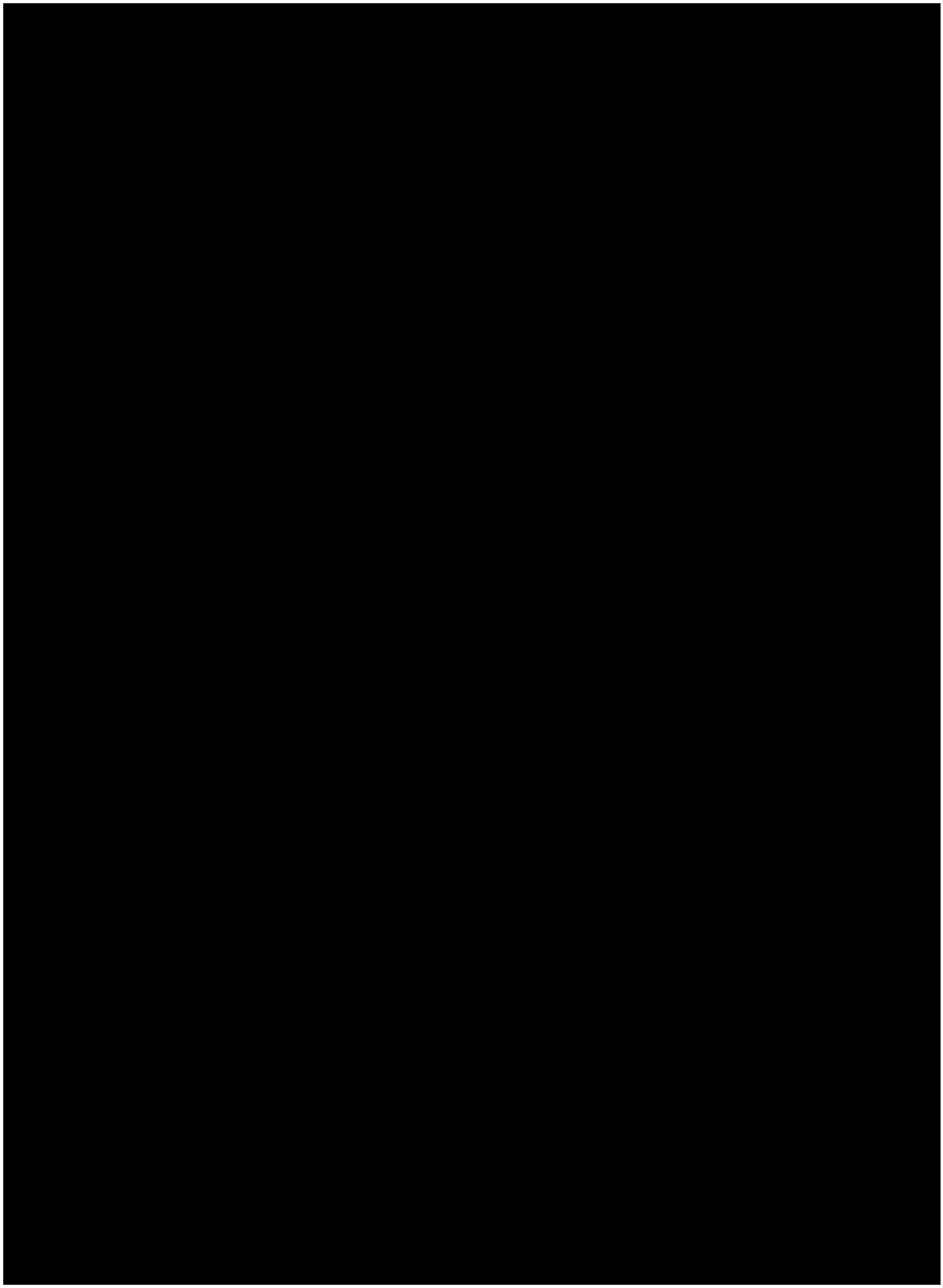
6.3.7 Pharmacodynamic Assessments

Whole blood will be collected for the assessment of pDC levels by flow cytometry at the visits specified in Table 3 and Table 4. VIB7734 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.

6.3.8 Exploratory Biomarker Evaluation





6.4 Discontinuation of Investigational Product, Unscheduled Visits, Withdrawal From Study, and Loss to Follow-up

6.4.1 Discontinuation of Investigational Product

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

- Receipt of any medications in Section 7.4.2.1.
- 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 Safety Data Monitoring Committee (SDMC).
- Withdrawal of consent from further treatment with IP.
- Participant 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:
  - ALT or AST ≥ 8× 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%).

Participants who are permanently discontinued from receiving IP will be followed for protocol-specified assessments including follow-up of any AEs unless consent is withdrawn specifically from further study participation (as defined in Section 6.4.3), or the participant is lost to follow-up (Section 6.4.4).

6.4.2 Unscheduled Visits

An Unscheduled Visit should be performed if a participant complains of worsening SLE symptoms, use of OGC outside of study-permitted doses, necessity to repeat a blood test/evaluation, evaluation of an AE, 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.

6.4.3 Withdrawal From Study

Participants are free at any time to withdraw from the study (IP and assessments), without prejudice to further treatment (withdrawal of consent). Such participants will always be asked about the reason(s) for withdrawal and the presence of any AEs. AEs will be followed-up.

Participants who permanently discontinue IP at any point in the study but who **do not** withdraw consent of study participation will complete all study visits through Study Week 48/ET and at least 12 weeks follow up after the last dose of IP. Participants who permanently discontinue IP at any point in the study and who **do** withdraw consent of study participation will only complete the Study Week 48/ET assessments (if they agree to do so before withdrawing consent).

If a participant withdraws consent to participation in the study, then no further study visits or data collection should take place. Further details concerning use of samples collected during the study from a participant that withdraws consent are provided in Section 10.6.

6.4.4 Participants Lost to Follow-up

Participants will be considered lost to follow-up only if no contact has been established by the time the study is completed and such that there is insufficient information to determine the participant's status at Day 393/Visit 16. A participant is considered lost to follow-up when 3 documented attempts at contact (with one documented attempt being registered letter/certified mail) are unsuccessful:

- 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 participant.

"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 participant, documentation that a certified/registered letter was sent, and documentation of publicly available sources that were consulted.

6.5 Study Suspension or Termination

The Sponsor reserves the right to suspend or terminate this study at any time. 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 Institutional Review Board (IRB) or Independent Ethics Committee (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.

6.6 End of Study

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

Participants will be considered not to have completed the study if consent was withdrawn (Section 6.4.3) or the participant was lost to follow-up (Section 6.4.4).

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

7 STUDY INTERVENTIONS

7.1 Description of Investigational Products

Table 6 provides a description of the IP to be used in the study.

Table 6 Description of Investigational Products and Dosing

Product	Concentration and Formulation as Supplied	Manufacturer
VIB7734	Supplied as a 2R vial with nominal 1 mL of 100 mg/mL VIB7734 containing [redacted]mM L-histidine/L-histidine HCl, [redacted]mM sucrose,[redacted]% (w/v) PS 80, pH[redacted]	Berkshire Sterile Manufacturing, Inc.
Placebo	Normal saline	Commercially available

PS: polysorbate; w/v: weight per volume.

7.1.1 VIB7734 or Placebo

7.1.1.1 Investigational Product Inspection

Each VIB7734 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: [redacted] During the investigation of the product complaint, all IP must be stored at labeled conditions unless otherwise instructed.

7.1.1.2 Investigational Product Storage

VIB7734 should be stored at [redacted]. 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).

7.1.1.3 Investigational Product Dose Preparation

Preparation of VIB7734 and preparation of the syringe for SC administration are to be performed by an unblinded pharmacist/IP manager using aseptic technique.

VIB7734 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 VIB7734 and plastic syringes (ie, polypropylene and polycarbonate) have been observed.

VIB7734 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 [redacted] If storage time exceeds these limits, a new dose must be prepared from new vials.

If syringes containing IP have been stored at [redacted] for any length of time, they must equilibrate to room temperature for one hour prior to administration to the participant.

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 VIB7734 will be administered over 2 injections. To prepare each injection, withdraw 1 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.

Normal saline will be used as placebo. The number and volume of placebo injections will match that of active drug. Saline (1 mL) should be drawn into each of two 1-mL syringes using a 1½-inch needle. For SC dose administration, a 27G ½-inch needle should be used.

7.1.1.4 Investigational Product Dosing and Administration

The first day of dosing is considered Day 1. To reduce the risk of unblinding the study personnel who will be evaluating the participant, IP will be administered by an unblinded pharmacist/IP Manager or a study site staff member who is not otherwise involved in the participant's participation in the study. The IP administrator should be experienced in performing SC injections. 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 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 participant 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 [redacted] for more than 24 hours.

7.1.1.5 Monitoring of Dose Administration

Participants should be monitored under direct observation for at least 60 minutes after the first and second doses of IP administration or until the participant is stable, whichever is longer. Vital signs should be measured as indicated in Section 6.3.3.2.

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.

7.1.2 Investigational Product Accountability

Study site staff will maintain a record of the IP received, dispensed, administered, and destroyed. All records will be maintained with controlled access to unblinded Site, Sponsor, and contract research organization (CRO) Staff only. An unblinded 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 participants included in this study and according to procedures established in this study protocol. There is potential of unblinding of staff members who administer the study product, however, they will not be involved in any other parts of the study. Each administration of study product will be documented and transferred to the electronic CRF (eCRF).

7.1.3 Investigational Product Handling and Disposal

It is preferred that unused IP be destroyed at the 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 VIB7734 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.

7.2 Assessment and Verification of Compliance

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

7.3 Treatment Assignment and Bias Minimization

7.3.1 Randomization Strategy and Procedure

An interactive voice/web response system (IXRS) will be used for Randomization to a treatment group and assignment of IP kit numbers. A participant is considered randomized into the study when the Investigator or appropriate designee notifies the IXRS that the participant meets eligibility criteria and the IXRS provides the assignment of treatment group.

Additional details are provided in the IXRS manual.

7.3.2 Extent and Maintenance of Blinding

This is a double-blind study. IP handling and administration is managed to ensure proper blinding for the Sponsor and investigational site staff. Since VIB7734 and the placebo can be distinguished at the preparation step with potential for unblinding during administration, the IP will be prepared by an unblinded pharmacist/IP manager at the site. Because VIB7734 and placebo could be distinguished during administration, the IP will be administered by either the unblinded pharmacist/IP manager or site personnel who will not be involved in management of the study participants. To maintain blinding, participants randomized to VIB7734 Q12W SC dosing regimen will receive SC placebo injections on study visits outside the Q12W schedule.

Neither the participant nor any of the Investigator or Sponsor staff who are involved in the treatment or clinical evaluation and monitoring of the participants will be aware of the treatment received. If treatment allocation for a participant becomes known to the Investigator or other study staff in the management of study participants, the Sponsor must be notified immediately.

7.3.3 Unblinding Procedures

7.3.3.1 Unblinding in the Event of a Medical Emergency

In the event of a medical emergency, the Investigator may unblind an individual participant's IP allocation. Instructions for unblinding an individual participant's IP allocation are contained in the IXRS manual. In general, unblinding should only occur if management of the medical emergency would be different based on the participant having received VIB7734. In most cases,

the management of a medical emergency would be the same whether or not VIB7734 was received by the participant. If this was the case, the IP allocation should not be unblinded.

7.3.3.2 Unblinding for the Interim Analysis

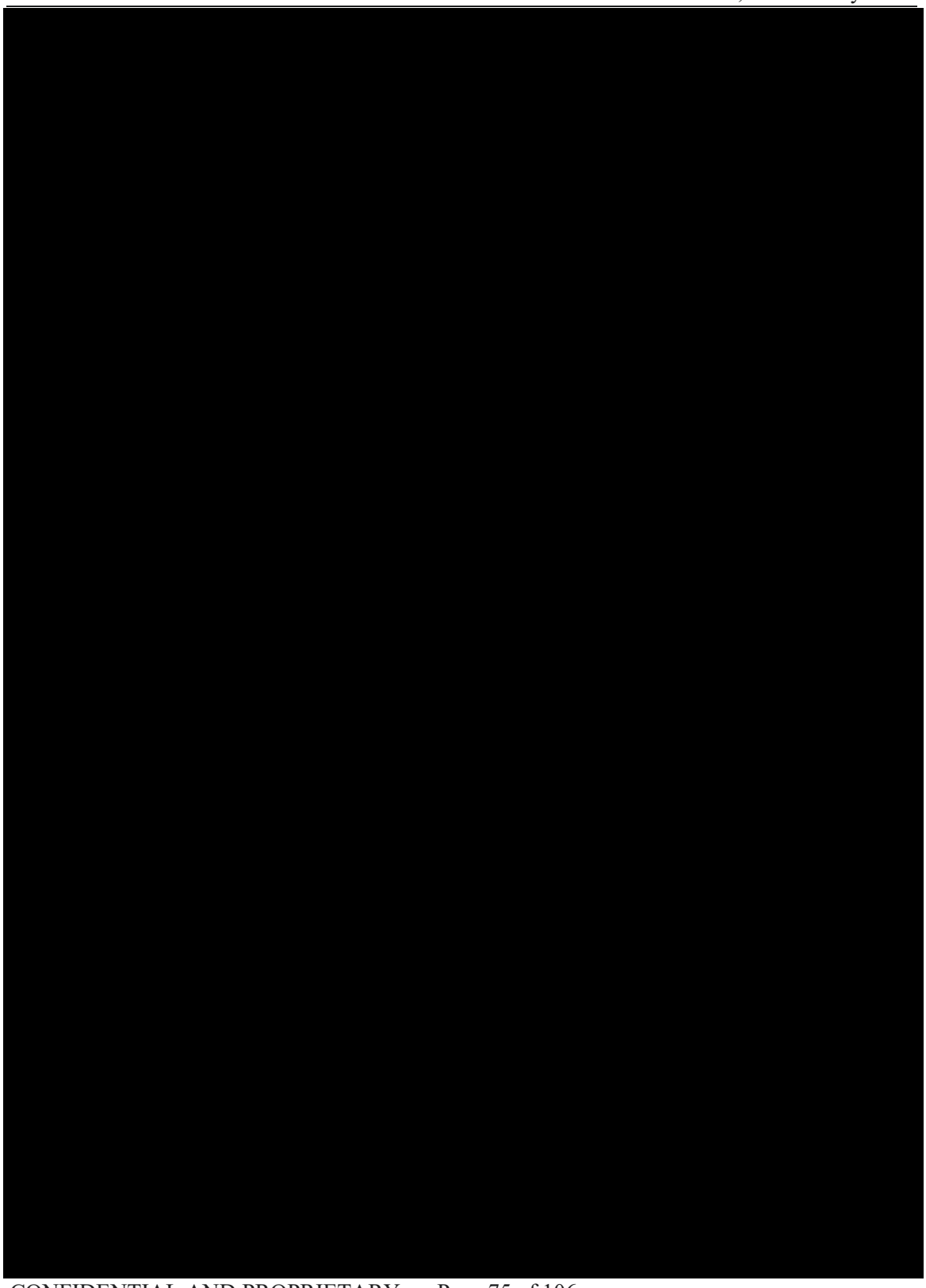
The interim analysis will be conducted after all participants have completed the Week 24 visit or discontinued early from the study. A small pre-specified number of Sponsor staff who are not directly involved in the conduct of the study will be unblinded for decision making purposes. Study site personnel, participants, and CRO and Sponsor personnel directly associated with the conduct of the study will remain blinded to the treatment assignment for individual participants and the results of the interim analysis until the completion of the study.

7.4 Restricted and Concomitant Medications and Treatments

Any additional concomitant therapy that becomes necessary during the trial and any change to concomitant drugs must be recorded in the corresponding section of the eCRF, noting the name, dose, duration, and indication of each drug.

7.4.1 Medications Prohibited Prior to Screening or Randomization

The treatments and therapies listed in Table 7 are not permitted prior to Screening or Randomization with specific usage washout periods provided for each treatment. Additionally, these treatments should not be used during the trial (with exceptions as noted for those therapies that are potentially permitted per Section 7.4.3.2).



7.4.3 Permitted Medications

7.4.3.1 Concomitant Medications and Treatments

All concomitant medications, from the time of the Screening visit, taken while the participant is participating in the study will be recorded on the eCRF. Participants must be instructed not to take any medications, including over-the-counter or herbal products or ayurvedic medications without first consulting the Investigator.

Permitted medications (including rescue medications) are any medications required per the medical history and not specifically prohibited by the protocol during the trial (ie, from Screening to the end of the SFU period). Any such medications prescribed or used should be recorded in the eCRF.

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

The SoC medications are part of the participant's previous SLE treatment and, thus, will not be provided by the Sponsor.

7.4.3.2.1 Immunosuppressants

All immunomodulator therapy for SLE given prior to Screening must have been kept stable or discontinued according to the specifications in the inclusion and exclusion criteria (Section 5) for a participant to be eligible for the study. These medications must remain stable during the Screening and Treatment periods except for OGC and NSAIDs, which can be adjusted as long as doses are consistent with the parameters as indicated in Sections 7.4.3.2.2 and 7.4.3.2.2.6, 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 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 Baseline (Day 1) level would be considered a treatment failure and may result in withdrawal of the participant from the IP (per Sponsor Medical Monitor discretion).

7.4.3.2.2 Glucocorticoids

OGCs are permitted but not required for participation in the study as outlined in the inclusion criteria [Section 5.1]). OGCs other than prednisone may be used at equivalent PO doses (refer to Appendix 4). Investigators are required to decrease the OGC dose as much as tolerated by the participant starting at Week 4 up until Week 36 of the Treatment period, within the rules for dose changes outlined below.

7.4.3.2.2.1 Oral Glucocorticoid Tapering Guidance

OGC tapering may be started at any time prior to Week 4 but must be started within 14 days after the Week 4 visit. On treatment days, tapering will start after all assessments have been completed and IP has been administered. Tapering can be started on the scheduled study visit day (eg, Week 4 Visit) based on clinical manifestations and the laboratory values from the previous visit. If laboratory values of the current visit show SLE activity consistent with Exception Rule 1 or 2 below, the tapering can be reversed. OGC tapering should be attempted until Week 36 to achieve the lowest possible OGC dose, including discontinuation of the OGC, if clinically feasible. Note that there is no change in OGC dose permitted between Week 20 and Week 24. Beginning at Week 4 and continuing through Week 36, tapering to an OGC dose of ≤ 7.5 mg/day MUST be attempted at all visits in all participants with OGC dose of > 7.5 mg/day, unless at least one of the following criteria (Exception Rules) is met:

1. SLEDAI-2K activity which is worsened compared to Baseline (Day 1) in major organ systems (renal, CNS, cardiopulmonary, vasculitis, fever, thrombocytopenia), hemolytic anemia, or increased gastrointestinal activity.
2. Newly affected organ system(s) based on the SLEDAI-2K, excluding serological abnormalities (dsDNA antibodies, hypocomplementemia).
3. Moderate to severe skin disease as reflected by a CLASI-A score ≥ 10.
4. Moderate to severe arthritis as reflected by ≥ 8 tender and/or swollen joints.

If OGC tapering is not attempted in an eligible participant, the Sponsor or Sponsor's designee must be contacted immediately. An example of suggested OGC tapering regimen is provided in Appendix 5 as guidance for Investigators. However, due to variability in participant responses to OGC treatment and tolerability of taper, Investigators will have flexibility in how the OGC dose is reduced at each visit.

Investigators will not be required to, but are encouraged to, taper OGC dose beyond the target of 7.5 mg/day including discontinuation of OGC up to Week 36, if clinically feasible. Tapering will not be permitted after Week 36. A participant experiencing an increase in disease activity secondary to OGC tapering may increase the OGC dose up to a maximum of the Baseline (Day 1) OGC therapy dose between Week 4 up to Week 36. Participants who require an OGC dose above their Baseline (Day 1) level may continue in the study but could be considered nonresponders for subsequent assessments of disease activity.

7.4.3.2.2.2 Steroid Burst and Taper – Week 0 (Day 1) to Week 12

In order to allow adequate time for the IP to achieve significant clinical benefit, Investigators may administer one burst and taper of OGCs between and including Baseline (Day 1) and prior to Week 12 for increased SLE disease activity/non-SLE activity as outlined below.

A GC burst is defined as receipt of only one of the following:

- An OGC increase above Baseline (Day 1) up to a maximum daily dose of 40 mg/day prednisone (or equivalent) for up to a total of 14 days which must be fully administered and tapered to less than or equal to the Baseline (Day 1) dose by the end of the 14th day. Any course of OGC above the Baseline (Day 1) dose must not extend beyond Week 12, regardless of when the course was started.
- Intramuscular methylprednisolone (≤ 80 mg) or equivalent administered as a single dose between Baseline (Day 1) and Week 10.
- A maximum of 2 intra-articular/tendon sheath/bursal injections (for a total methylprednisolone dose of ≤ 80 mg or equivalent) can be given between Baseline (Day 1) and Week 10.

Participants who receive more than one OGC burst and taper between Baseline (Day 1) and prior to Week 12, or who violate any of the criteria above, may continue in the study, but will be considered nonresponders for subsequent assessments of disease activity, regardless of whether the OGC burst was administered for increased SLE activity or non-SLE causes.

7.4.3.2.2.3 Increase in OGC from Week 12 to Week 36

Between Week 12 and Week 36, an increase in OGC dose above Baseline (Day 1) dose for increased SLE activity is NOT allowed. A participant receiving an OGC dose above his or her Baseline (Day 1) dose after Week 12 for SLE may continue in the study but will be considered a nonresponder for subsequent assessments of disease activity.

An increase in OGC above current dose for non-SLE causes (eg, asthma or chronic obstructive pulmonary disease exacerbation) is allowed ONCE either between Week 12 and Week 20 ahead of planned interim analysis time point at Week 24 OR between Week 24 (after all assessments complete) and Week 36. This might include a non-SLE OGC dose up to ≤ 20 mg/day of prednisone or equivalent for up to a total of 10 days. This will be captured as burst and taper not attributable to SLE. The non-SLE indication must be clearly indicated in the source documents. The increase must be fully administered and tapered to less than or equal to the dose used prior to the implementation of the increase by the end of the 10th day after initiating the OGC burst and by the Week 20 Visit day (if the increase is implemented between Week 12 and Week 20) or by the Week 36 Visit day (if the increase is implemented between Week 24 and Week 36).

Participants who receive an increase in OGC for non-SLE causes at a dose of > 20 mg/day prednisone (or equivalent) OR above Baseline (Day 1) dose for > 10 days will be considered nonresponders for subsequent assessments of disease activity. If a participant receives > 40 mg prednisone or equivalent or a dose above Baseline (Day 1) level for more than 10 days, it must be reported to the Medical Monitor. The Medical Monitor will determine with the Sponsor if the participant may continue to receive IP based on the assessment of potential risk.

7.4.3.2.2.4 Oral Glucocorticoids After Week 36

No change in OGC is allowed after Week 36. Participants who receive an increase in their OGC dose above 7.5 mg/day or Baseline (Day 1) dose after Week 36 will be considered nonresponders for the primary and secondary outcome measures at Week 48.

7.4.3.2.2.5 Increase in Oral Glucocorticoids for Surgery and Prevention of Adrenal Insufficiency

In addition to the burst and tapers described above, participants who are taking ≤ 7.5 mg/day prednisone or equivalent will be allowed to receive up to an additional 7.5 mg/day to a total of 15 mg/day prednisone or equivalent for a total of up to 14 days or a single course of IV hydrocortisone (≤ 100 mg hydrocortisone followed by half that dose for 2 days before returning to their usual dose of OGC) for surgery or symptoms of adrenal insufficiency or GC withdrawal if clinically warranted from Baseline (Day 1) to Week 36. The non-SLE indication must be clearly indicated in the source documents.

7.4.3.2.2.6 Other

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

- Angiotensin-converting enzyme inhibitors and angiotensin receptor blockers
  - If used at Screening, it is recommended that they be maintained at a stable dose during the trial, 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 SoC 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

  – Regularly prescribed NSAIDs may not be initiated during the 48-week Treatment period.
  – Participants taking a NSAID (including cyclooxygenase 2 inhibitors; topical, prescription, or over-the-counter) on a regular schedule for SLE symptoms at Randomization can continue to do so throughout the trial at a stable dose.
  – NSAIDs should not be taken on visit days until all assessments are complete. Participants may have the dose adjusted during the trial for documented toxicity/safety reasons.
  – Any NSAIDs (whether prescription, over-the-counter, or topical) should not be used above the maximum allowable doses per local labeling, and site should perform regular AE monitoring of these concomitant medications.
  – PRN NSAIDs not exceeding label-approved doses are permitted for SLE or non-SLE pain as required based on Investigator judgment for up to 10 consecutive days Duration exceeding 10 consecutive days is considered chronic use.

- Opioids

  – Up to 40 mg/day morphine-equivalent are permitted at stable dose if present at Screening. Initiation of opioids and/or prn (as needed) dosing of opioids after Screening for SLE is not permitted. These may be titrated off as tolerated during the study. Analgesics, including opiates, may be used at stable doses or prn (as needed) for temporary relief of symptoms not due to SLE, but then are strongly recommended to be avoided 24 hours prior to each trial 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 Screening and the dose and frequency of application must be stable during Screening. 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 Baseline (Day 1) dose. It is encouraged that no new dermatologic preparations be used for the duration of the study. It is also recommended that participants 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 participants' welfare and will not interfere with the trial medication may be given at the Investigator's discretion.

8 SAFETY DATA COLLECTION AND REPORTING

The Investigator is responsible for the detection and documentation of events meeting the criteria and definition of an AE or SAE, as provided in the protocol. During the study when there is a safety evaluation, the Investigator or site staff will be responsible for detecting, documenting, and reporting AEs and SAEs as detailed in this section of the protocol.

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 11.1 for details on SDMC activities.

8.1 Definitions

- **Adverse event (AE)** – An AE is any untoward medical occurrence associated with the use of an intervention in humans whether or not it is considered intervention-related.
- **Serious adverse event (SAE)** – 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 participant or participant 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 participant or participant and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

- **Adverse reaction** – An adverse reaction is any AE caused by a drug.
- **Adverse event of special interest (AESI)** – 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 listed in Appendix 3 (all cases).
- Malignancy (except non-melanoma skin cancer).

8.2 Documenting Adverse Events

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.

AEs reported by the participant, 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, those captured by SLEDAI-2K, BILAG 2004 Index, or CLASI) 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 participant to discontinue the study. The AE term should be reported in standard medical terminology when possible.

8.2.1 Causality or Relatedness

The Investigator is required to provide an assessment of the relationship of AEs and SAEs to the IP. An event will be considered "not related" to use of IP if any of the following tests 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).

8.2.2 Severity or Intensity

The guidelines outlined in 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 8.

Table 8 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 27Nov2017.
[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.

8.2.3 Pregnancy

Pregnancy in a woman who has received IP must be reported to 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 (Section 8.3).

Participants who become pregnant during the study period must not receive additional doses of IP but will not be withdrawn from the study. If the participant requests to know which treatment she received, this information will be provided to her. The pregnancy will be followed for outcome of the mother and child (including any premature terminations) and should be reported to the Sponsor after outcome.

Should the Investigator become aware of a pregnancy in the partner of a male study participant who has received IP, this should be reported to Sponsor within 24 hours of knowledge of the event, by fax or email using the Pregnancy Report Form (refer to Section 8.3 for contact information). The Sponsor will endeavor to collect follow-up information on such pregnancies, provided the partner of the study participant provides consent for disclosure of their information.

8.2.4 Overdose or Misuse

Any instance of overdose of IP (suspected or confirmed) must be communicated to Sponsor (Section 8.3). Any associated AEs or SAEs must also be reported and their management should be recorded.

8.3 Events Requiring Immediate Reporting

All AEs will be recorded from written ICF signature up to exit from the study, whether related to the study.

All SAEs, AESIs (only after Randomization), pregnancies, overdose, or misuse must be reported to the Sponsor within 24 hours of site staff awareness by submitting a SAE/AESI/Pregnancy/Overdose Report Form by email to:

Sponsor (Horizon Therapeutics/Viela Bio)
Email: [redacted]

Alternatively, the Report Form can be submitted by fax to:

Sponsor (Horizon Therapeutics/Viela Bio)
Fax: 1-800-860-7836

Additional follow-up information, if required or available, should all be reported within one business day of receipt, should be completed on a follow-up report form, placed with the original SAE information, and kept with the appropriate section of the study file.

Sponsor will work with the Investigator to ensure that all the necessary information is provided within 1 calendar day of initial receipt for fatal and life-threatening events and within 5 calendar days of initial receipt for all other SAEs.

Sponsor is responsible for notifying the relevant regulatory authorities of certain events. Notification of the IRB or IEC of all SAEs that occur at the Investigator's site are the responsibility of the Investigator. Investigators will be notified of all unexpected, serious, drug-related events (7-- and 15--Calendar Day Safety Reports) that occur at other investigative sites during the clinical trial. Each Investigator is responsible for notifying its IRB or IEC of these additional SAEs in accordance with IRB or IEC requirements.

9 STATISTICAL CONSIDERATIONS

9.1 General Considerations

Tabular summaries will be presented by treatment group. 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 participant number. Details of the statistical analysis will be specified in a separate SAP.

9.2 Statistical Hypothesis

The following are the statistical hypotheses associated with the primary efficacy outcome measure (proportion of participants achieving BICLA response + OGC ≤ 7.5 mg/day and ≤ Baseline (Day 1) prednisone or equivalent dose at Week 48).

- Null hypothesis (H0): Difference in proportion of responders (VIB7734 versus placebo) = 0.
- Alternative hypothesis (Ha): Difference in proportion of responders (VIB7734 versus placebo) ≠ 0.

9.3 Determination of Sample Size

The sample size was calculated based on the primary efficacy outcome measure. Assuming a placebo response rate of 20%, 65 participants per treatment group will provide at least 80% power to detect an increase in response of 20% in a VIB7734 group as compared to the placebo group at the 2-sided alpha level of 0.10 using a Chi-square test. The minimum detectable difference is 13% between the 2 treatment groups. The assumption of a 20% responder rate for placebo is based upon published results (Furie et al, 2017).

9.4 Analysis Sets

Full Analysis Set: The Full Analysis Set will include all randomized participants who receive any dose of IP in the study. Participants will be analyzed according to the treatment randomized. The efficacy analysis will be based on the Full Analysis Set.

Safety Analysis Set: The Safety Analysis Set will include all participants who received any dose of IP in the study. Participants will be analyzed according to the treatment that they received. Safety, PD, and [redacted] analyses will be based on the Safety Analysis Set.

PK Analysis Set: The PK Analysis Set will include all participants who receive any dose of VIB7734 in the study and have at least one quantifiable serum PK observation post-first dose. Participants will be analyzed according to the treatment that they received. The PK analysis will be based on the PK Analysis Set.

9.5 Methods for Statistical Analyses

9.5.1 Analysis of the Primary Efficacy Outcome Measure

The estimand of primary interest is defined as follows, using composite variable strategy to address intercurrent events.

- Population: Participants in the Full Analysis Set with active SLE despite receiving one or more SoC treatments as defined by the inclusion-exclusion criteria of the study.
- Variable (outcome measure): Response in BICLA + OGC ≤ 7.5 mg/day and ≤ Baseline (Day 1) dose at Week 48, where BICLA is defined by meeting the following criteria compared to Baseline:
  - BILAG 2004 Index improvement (all Baseline BILAG A improving to B/C/D, all Baseline BILAG B to C/D, and ≤ 1 new BILAG B and no new BILAG A).
  - No deterioration in SLEDAI-2K total score.
  - No significant worsening in PGA score (< 10% increase).
  - No use of restricted medications beyond the protocol-allowed threshold before assessment.
  - No discontinuation of IP.
- Intercurrent event:
  - Rescue medications: Captured in the primary variable definition.
  - Treatment discontinuation: Captured in the primary variable definition.
- Population-level summary: Difference in proportion of responders between the VIB7734 group and placebo group.

The proportion of participants achieving BICLA response + OGC ≤ 7.5 mg/day and ≤ Baseline (Day 1) dose prednisone or equivalent at Week 48 in the VIB7734 treatment group will be compared to that of the placebo group using a logistic regression model with treatment, Randomization stratification factors, and Baseline IFN inducible gene signature level included in the model. The difference in proportion of responders of VIB7734 versus placebo will be estimated together with its associated 90% CI.

A sensitivity analysis with the same model will be performed using a treatment policy strategy to address intercurrent events defined above. All observed values will be used regardless of occurrence of an intercurrent event.

9.5.2 Analysis of Secondary Efficacy Outcome Measures

All secondary outcome measures will be analyzed similarly to the primary outcome measure using composite variable strategy to address intercurrent events. The estimands are defined as follows:

- Population:
  - CLASI: Participants in the Full Analysis Set with active SLE and CLASI-A score ≥ 10 at Baseline despite receiving one or more SoC treatments as defined by the inclusion-exclusion criteria of the study.
  - OGC reduction: Participants in the Full Analysis Set with active SLE taking an OGC of ≥ 10 mg/day of prednisone or equivalent at Baseline despite receiving one or more SoC treatments as defined by the inclusion-exclusion criteria of the study.
  - SRI-4 + OGC ≤ 7.5 mg/day and ≤ Baseline (Day 1) dose and LLDAS: Participants in the Full Analysis Set with active SLE despite receiving one or more SoC treatments as defined by the inclusion-exclusion criteria of the study.

- Variable (outcome measure):
  - CLASI: ≥ 50% reduction in CLASI-A score at Week 12 defined by meeting the following criteria:
    - A ≥ 50% reduction of CLASI-A score at Week 12 as compared to Baseline.
    - No use of restricted medications beyond the protocol-allowed threshold before assessment.
    - No discontinuation of IP before assessment.
  - SRI-4 + OGC ≤ 7.5 mg/day and ≤ Baseline (Day 1) dose: Response in SRI-4 + OGC ≤ 7.5 mg/day and ≤ Baseline (Day 1) dose at Week 48, where SRI-4 is defined by meeting the following criteria compared to Baseline:
    - Reduction from Baseline of ≥ 4 points in the SLEDAI-2K.
    - No new organ system affected as defined by one or more BILAG A or 2 or more BILAG B items.
    - No significant worsening in PGA score (< 10% increase).
    - No use of restricted medications beyond the protocol-allowed threshold before assessment.
    - No discontinuation of IP.
  - OGC reduction: Maintained OGC reduction from Week 36 to Week 48 defined by meeting the following criteria:
    - An OGC dose of ≤ 7.5 mg/day prednisone or equivalent at Week 36 that is maintained through Week 48.
    - No use of restricted medications beyond the protocol-allowed threshold before assessment.
    - No discontinuation of IP before assessment.
  - LLDAS: Response in LLDAS at Week 48, where LLDAS is defined by meeting the following criteria:
    - A SLEDAI-2K ≤ 4, with no activity in major organ systems (renal, CNS, cardiopulmonary, vasculitis, fever) and no hemolytic anemia or gastrointestinal activity.
    - No new lupus disease activity compared with the previous assessment measured by SLEDAI-2K.
    - A PGA ≤ 1 (on a scale of 0 to 3).
    - Current prednisone or equivalent dose of ≤ 7.5 mg/day.
    - Well-tolerated standard maintenance doses of immunosuppressive drugs and approved medications as allowed and specified in the Clinical Study Protocol.
    - No use of restricted medications beyond the protocol-allowed threshold before assessment.
    - No discontinuation of IP.
- Intercurrent event:
  - Rescue medications: Captured in the variable definition.
  - Treatment discontinuation: Captured in the variable definition.
- Population-level summary for all secondary outcome measures: Difference in proportions of responders between VIB7734 and placebo.

Similar sensitivity analysis to the primary outcome measure analysis will be performed using a treatment policy strategy to address intercurrent events defined above. All observed values will be used regardless of occurrence of an intercurrent event.

9.5.3 Missing Data Handling Plan

Intermittent missing data will be imputed using last observation carried forward approach. Participants with missing primary or secondary outcome measures due to early discontinuation of study will be considered nonresponders.

9.5.4 Control of Type I Error

No multiplicity adjustment will be planned to control Type I error.

9.5.5 Safety Analysis

AEs will be coded using the Medical Dictionary for Regulatory Activities by System Organ Class and Preferred Term. The number and percentage of participants reporting treatment-emergent AEs with onset on or after the start of the first administration of IP will be summarized for each treatment group by System Organ Class and Preferred Term, by severity, and by relationship to the IP. The number and percentage of participants reporting 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.

9.5.6 Pharmacokinetics Analysis

The PK analysis will be based on the PK Analysis Set. Descriptive statistics of the serum VIB7734 concentration will be tabulated by visit and by treatment group. Individual and mean serum concentration-time profiles of VIB7734 by treatment group will be generated. Population modeling will be performed to better characterize the PK of VIB7734 given by SC injection in SLE participants.

9.5.7 Immunogenicity Analysis

[redacted]

9.5.8 Pharmacodynamics Analysis

Absolute values and change from baseline in pDCs will be summarized descriptively by visit for each treatment group.

9.5.9 Exploratory Analysis

The exploratory analyses will be detailed in the SAP.

9.6 Planned Interim Analysis

An interim analysis will be conducted after all participants have completed the Week 24 visit or are discontinued early from the study. A small prespecified number of Sponsor staff who are not directly involved in the conduct of the study will be unblinded to make a go/no-go decision for future studies.

Sponsor personnel directly associated with the conduct of the study, study site personnel, participants, and CRO will remain blinded to the treatment assignment for individual participants and the results of the interim analysis until the completion of the study. The efficacy and safety data prior to the data cut-off for the interim analysis will be analyzed. No multiplicity adjustment is planned for the interim analysis because there is no provision to stop the trial early at the interim analysis to claim efficacy. Details of the interim analysis (go/no-go criteria, unblinding plan, and communication plan) will be specified in an interim unblinding analysis plan prior to unblinding.

9.7 Planned Primary Analysis

The primary analysis will be conducted after the last participant has completed the Week 48 visit or discontinued from study early. For the primary analysis, all the efficacy and safety data collected prior to the data cut-off for the primary analysis will be analyzed.

9.8 Planned Final Analysis

The final analysis will be conducted after all participants have completed or discontinued early from the study.

10 ETHICAL CONSIDERATIONS

10.1 Good Clinical Practice

The study will be performed in accordance with ICH/GCP, applicable regulatory requirements, and the Viela Bio policy on Ethical Interactions.

10.2 Ethics Review

The final study protocol, including the final version of the ICF, must be approved or given a favorable opinion in writing by an IRB or IEC, as appropriate. The Investigator must submit written approval to the Sponsor or representative before he or she can enroll any participant into the study.

The PI is responsible for informing the IRB or IEC of any amendment to the protocol in accordance with local requirements, and obtaining their approval prior to its implementation, except to avoid an immediate hazard to participants. In addition, the IRB or IEC must approve all advertising used to recruit participants for the study. The protocol must be re-approved by the IRB or IEC upon receipt of amendments and annually, as local regulations require. The PI is also responsible to adhere to requirements stipulated by the respective IRB/IEC and for providing the IRB/IEC with reports, including those of any reportable serious adverse drug reactions from any other study conducted with the IP. The Sponsor will provide this information to the PI.

10.3 Informed Consent

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. It is the responsibility of the Investigator (or their designee, where allowed by local requirements) to obtain written informed consent from all study participants. All consent documentation must be in accordance with applicable regulations and ICH E6(R2). The participants will be informed that their study record and medical records/documents that identify them, that pertain directly to the study, will be reviewed by the Sponsor or its designee, and or a local or foreign governmental agency (such as FDA), and that every effort will be made to maintain participant confidentiality. The informed consent must allow for access to the records for at least 25 years to allow for possible future inspections. The participant should be given the opportunity to ask questions and allowed time to consider the information provided.

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

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

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).

10.4 Data 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. However, authorized regulatory officials, IRB/IEC personnel, the

Sponsor and its authorized representatives must be allowed full access to the original source records.

10.5 Disclosure

The Sponsor is responsible for preparing and providing the appropriate regulatory authorities with Clinical Study Reports, according to the applicable regulatory requirements.

10.6 Biological Specimens and Data

Study data are protected by the use of a SID number, which is a number specific to the participant. The Investigator is in control of the information that is needed to connect a study sample to a participant; a participant 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 participant.

Leftover samples stored for future research with participant consent will be labeled with a sample identification number. If the participant 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 participant's sample(s) will be stored by the Sponsor with similar samples in a secure laboratory. The participant's samples will not be kept for more than 25 years after the end of the study in which they were collected. If the participant 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 participant's sample(s) are destroyed unless the identification number has been removed and the participant can no longer be linked to any samples. However, if the participant'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.

11 OVERSIGHT

11.1 Safety Data Monitoring Committee

The external, independent SDMC is responsible for safeguarding the interests of study participants 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 Viela Bio with recommendations for actions with respect to study conduct and the management of participants treated under the study protocol. The SDMC members are independent of Viela Bio and any CRO/organization collaborating with Viela Bio 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.

11.2 Quality Control and Assurance

To ensure compliance with GCP and all applicable regulatory requirements, the Sponsor may conduct a quality assurance audit. See Section 11.4 for details regarding the audit process.

11.3 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, participants' 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.

11.4 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.

11.4.1 Records

11.4.2 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 Code of Federal Regulations 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.

11.4.3 Source Documentation

The Investigator is responsible for maintaining adequate and accurate medical records from which the Investigator/designee will transcribe information in the eCRFs.

11.4.4 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.

12 PUBLICATION POLICY

The publication policy of the Sponsor is discussed in the Investigator's Clinical Research Agreement.

13 FINANCING AND INSURANCE

Financing and insurance for this study will be addressed in the Clinical Trial Agreement with the study site(s).

14 REFERENCES

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15 APPENDICES

APPENDIX 1 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 patient (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 participant's baseline.

APPENDIX 2 2019 EUROPEAN LEAGUE AGAINST RHEUMATISM/AMERICAN COLLEGE OF RHEUMATOLOGY CLASSIFICATION SYSTEM FOR SYSTEMIC LUPUS ERYTHEMATOSUS

Entry criterion
Antinuclear antibodies (ANA) at a titer of ≥1:80 on HEp-2 cells or an equivalent positive test (ever)

↓

If absent, do not classify as SLE
If present, apply additive criteria

↓

Additive criteria
Do not count a criterion if there is a more likely explanation than SLE.
Occurrence of a criterion on at least one occasion is sufficient.
SLE classification requires at least one clinical criterion and ≥10 points.
Criteria need not occur simultaneously.
Within each domain, only the highest weighted criterion is counted toward the total score§.

Clinical domains and criteria	Weight	Immunology domains and criteria	Weight
Constitutional		***Antiphospholipid antibodies***	
Fever	2	Anti-cardiolipin antibodies OR	
Hematologic		Anti-β2GP1 antibodies OR	
Leukopenia	3	Lupus anticoagulant	2
Thrombocytopenia	4	***Complement proteins***	
Autoimmune hemolysis	4	Low C3 OR low C4	3
Neuropsychiatric		Low C3 AND low C4	4
Delirium	2	***SLE-specific antibodies***	
Psychosis	3	Anti-dsDNA antibody* OR	
Seizure	5	Anti-Smith antibody	6
Mucocutaneous			
Non-scarring alopecia	2		
Oral ulcers	2		
Subacute cutaneous OR discoid lupus	4		
Acute cutaneous lupus	6		
Serosal			
Pleural or pericardial effusion	5		
Acute pericarditis	6		
Musculoskeletal			
Joint involvement	6		
Renal			
Proteinuria >0.5g/24h	4		
Renal biopsy Class II or V lupus nephritis	8		
Renal biopsy Class III or IV lupus nephritis	10		

Total score:

↓

Classify as Systemic Lupus Erythematosus with a score of 10 or more if entry criterion fulfilled.

Source: Aringer et al, 2019.
β2GP1: β2-glycoprotein 1; C: complement; dsDNA: double-stranded DNA; Hep-2: human epithelial type 2 cells; SLE: systemic lupus erythematosus.

APPENDIX 3 STUDY-SPECIFIED OPPORTUNISTIC INFECTIONS THAT MEET EXCLUSION CRITERIA

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.

Source: Winthrop et al, 2015.

[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 patients 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.

APPENDIX 4 PREDISONE EQUIVALENT OF ORAL GLUCOCORTICOID DOSE

Glucocorticoid	**Prednisone Equivalent Dose**					
PO prednisone	5 mg	7.5 mg	10 mg	20 mg	30 mg	40 mg
Prednisolone	5 mg	7.5 mg	10 mg	20 mg	30 mg	40 mg
Methylprednisolone	4 mg	6 mg	8 mg	16 mg	24 mg	32 mg
Hydrocortisone	20 mg	30 mg	40 mg	80 mg	120 mg	160 mg
Cortisone	25 mg	37.5 mg	50 mg	100 mg	150 mg	200 mg
Triamcinolone	4 mg	6 mg	8 mg	16 mg	24 mg	32 mg

PO: oral(ly).

APPENDIX 5 ORAL GLUCOCORTICOID TAPERING SCHEDULE

Visit	Dose of Oral Prednisone or Equivalent at Start of Specified Study Visit [a]				
Week 0	Investigators may initiate OGC taper as tolerated; target ≤ 7.5 mg/day to meet response criteria [b]				
Week 4	40 mg	30 mg	20 mg	10 mg	7.5 mg
Week 8	30 mg	22.5 mg	15 mg	7.5 mg	5 mg [c]
Week 12	20 mg	15 mg	10 mg	7.5 mg	5 mg [c]
Week 16	12.5 mg	10 mg	7.5 mg	5 mg [c]	≤ 5 mg [c]
Week 20	7.5 mg	7.5 mg	7.5 mg	≤ 5 mg [c]	≤ 5 mg [c]
No Change in OGC Permitted between Week 20 and Week 24					
Week 24 to Week 36	It is encouraged to taper OGC dose beyond the target for response criteria of 7.5 mg/day including discontinuation of OGC up to Week 36, if clinically feasible.				
No change in OGC is permitted between Week 36 and Week 48.					

OGC: oral glucocorticoid.
The doses in the table are shown for prednisone. Refer to Table 3 for equivalent doses of other OGCs.
The OGC tapering schedule represents an example of a tapering regimen to provide guidance to Investigators in the approach to mandatory steroid taper starting at Week 4 with a target OGC dose of ≤ 7.5mg/day prednisone (or equivalent) to meet the response criteria at Week 20 and to aim for a lower daily dose at Week 36.

[a] Specified prednisone dose is dose at the beginning of the week.
[b] Due to variability in participant responses to OGC treatment and tolerability of taper, Investigators have flexibility in how the OGC dose is reduced at each study visit.
[c] Investigators are encouraged to taper OGC dose beyond the target for response criteria of ≤ 7.5 mg/day including discontinuation of OGC, if clinically feasible.