HORIZON THERAPEUTICS IRELAND DAC (FORMERLY VIELA BIO, INC.)

A PHASE 2 RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED, PROOF OF CONCEPT STUDY TO EVALUATE THE EFFICACY AND SAFETY OF VIB4920 IN SUBJECTS WITH SJÖGREN'S SYNDROME (SS)

Investigational Product(s)	VIB4920
Protocol Number	VIB4920.P2.S2
Clinical Trial Registry Identifiers	ClinicalTrials.gov: NCT04129164 EudraCT: 2019-002713-19
Version Number	3.0
Version Date	8 Nov 2022
Amendment	2
Administrative Change	1
IND Number	IND 128905
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SUMMARY OF CHANGES TO THE PROTOCOL

Protocol Amendment 1; 21 July 2020

The Amendment 1changes to the protocol included the following:

Protocol Section(s) Impacted by Change (Section Title)	Change	Reason for Change
Title page (Clinical Trial Registry Identifiers)	Clinical Trial Registry Identifiers added.	Clarification.
Title page (Responsible Medical Officer)	Responsible Medical Officer changed from "[redacted]" to "[redacted]". (Corresponding details regarding qualifications, role, and contact details updated to align with change.)	Correction.
List of Abbreviations Synopsis Section 3.3.3 (Exploratory Endpoints for Population #1) Section 3.4.3 (Exploratory Endpoints for Population #2) Section 6.4.1.14 (ClinESSDAI)	[redacted]	Correction
List of Abbreviations	The term "serum human chorionic gonadotrophin" was changed to "beta-human chorionic gonadotrophin".	Correction.
List of Abbreviations Synopsis Section 6.7 (Study Suspension or Termination) Section 8 (Safety Assessment) Section 12.1 (Safety and Data Monitoring Committee)	The terms "Data and Safety Monitoring Board" and "DSMB" were changed to "Safety and Data Monitoring Committee" and "SDMC", respectively.	Clarification and consistency in nomenclature.
Section 1 (Synopsis) Section 3.3.3 (Exploratory Endpoints for Population #1) Section 3.4.3 (Exploratory Endpoints for Population #2) Section 6 (Study Conduct), Table 1 and Table 3 Section 6.2.4 ([redacted] (optional))	The term "(optional)" was added to end of items/statements/headings describing [redacted]	Clarification.
Section 1 (Synopsis) Section 4.1 (Study Design)	The number of sites was revised from approximately "50" to "70".	Correction.
Section 2.1.5.1 (Benefit-Risk Assessment)	Text describing the benefit-risk assessment of VIB4920 was inserted.	Clarification.

Section 2.1.5.2 (Anaphylaxis, Serious Allergic Reactions, and Infusion-Related Reactions)	Text inserted describing premedication options in the event of Grade ≥ 2 infusion-related reactions being observed was added.	Clarification.
Section 2.1.5.7 (Risks related to the COVID-19 pandemic)	Section providing update on how COVID-19 affected the study to date, and overview of COVID-19 risk factors associated with study participation was added.	Clarification.
Section 2.2 (Study Rationale), Table 1	Text addressing COVID-19 risk, and steps to minimize COVID-19 risk was added. This includes the requirement for a negative SARS-CoV-2 test within 2 weeks prior to randomization. SARS-CoV-2 testing added to screening procedures (Table 1).	Clarifies the benefit-risk assessment is reasonable for a phase 2 study.
Section 4.1 (Study Design), Figure 1	Figure replacing previous figure was added.	Correction. Day 309 arrows denoting administration of study treatment during safety follow-up period in Population #2 replaced by tick marks.
Section 5.1.1 (Inclusion Criteria for Population #1) Section 5.1.3 (Inclusion Criteria for Population #2)	The phrase "(the minimum age for adult participants can be higher than 18 years in countries with different regulations)" was added.	Clarifies potential country-specific differences in the study population.
Section 5.1.1 (Inclusion Criteria for Population #1)	Text inserted clarifying that, in subjects with ESSDAI score of ≥ 5 at screening, all ESSDAI domains will be scored; however, not all will contribute to the minimum ESSDAI score of 5 that is required for inclusion.	Clarification.
Section 5.1.1 (Inclusion Criteria for Population #1) Section 5.1.3 (Inclusion Criteria for Population #2)	Text providing additional details regarding appropriate contraception methods that must be adhered to in order to meet eligibility criteria was added.	Clarification.
Section 5.1.2 (Exclusion Criteria for Population #1) Section 5.1.4 (Exclusion Criteria for Population #2)	The term "enrollment" was revised to "signing the ICF".	Clarification of medical history timeframe applicable to patients' eligibility (confirmed deep venous thrombosis or arterial thromboembolism).
Section 5.1.2 (Exclusion Criteria for Population #1) Section 5.1.4 (Exclusion Criteria for Population #2)	Text clarifying additional exclusion criteria relating to infections (bacterial/viral/other), including COVID-19 risk was added.	Clarification.
Section 5.1.2 (Exclusion Criteria for Population #1)	The phrase "indications other than SS" was changed to "indications other than SS, RA, and SLE".	Clarification of additional autoimmune diseases excluded from systemic corticosteroid treatment timeframe applicable to patients' eligibility.

Section 5.1.2 (Exclusion Criteria for Population #1)	The term "ICF signature" was revised to "screening visit".	Clarification of systemic corticosteroid treatment timeframe applicable to patients' eligibility.
Section 5.1.2 (Exclusion Criteria for Population #1)	Text inserted providing timeframe applicable to use of "other DMARDs, immunosuppressant, or antiproliferative agents" and patients' eligibility.	Clarification.
Section 5.1.4 (Exclusion Criteria for Population #2)	Text inserted providing timeframe applicable to use of "MTX, AZA, leflunomide any other DMARDs, immunosuppressant, or antiproliferative agents" and patients' eligibility.	Clarification.
Section 6 (Study Conduct)	Sentence "More than one visit might be needed to complete screening" was added.	Clarification.
Section 6 (Study Conduct), Table 1 and Table 2. Section 6.4.3.1 (Autoantibody Panel).	The term "cryoglobulins" removed from autoantibody panel.	Correction.
Section 6 (Study Conduct), Table 1.	The term "cryoglobulins" added as part of ESSDAI-required blood tests.	Correction.
Section 6 (Study Conduct), Table 1.	[redacted]	Correction.
Section 6 (Study Conduct), Table 2 and Table 3.	Footnote "If no symptoms are present, the exam can be limited to assess ESSDAI" added as part of symptom-driven physical exam.	Clarification.
Section 6 (Study Conduct), Table 2.	Number of visits when an autoantibody panel needs to be conducted has been revised.	Clarification that autoantibody panel to be conducted at Visits 6 and 9 only.
Section 6 (Study Conduct), Table 2.	[redacted]	Correction.
Section 6 (Study Conduct), Table 2 and Table 3	[redacted]	Assessments no longer required.
Section 6 (Study Conduct), Table 2 and Table 3	[redacted]	Clarification.
Section 6 (Study Conduct), Table 3	Inserted requirement for additional urine pregnancy test(s) at Visit 15 and EDV.	Clarification.
Section 6 (Study Conduct), Table 3	The procedures "Autoantibody panel" and "Cryoglobulins" deleted.	Correction. These procedures are no longer required during the off-treatment period or at any unscheduled visits.
Section 6.2.1 (Informed Consent)	The phrase "by the interactive voice/web response system (IXRS)" was inserted.	Clarification on how the subject identification (SID) number will be assigned.

Section 6.4.1.10 [redacted])	[redacted].	Clarification.
Section 6.4.3.2 (Inflammatory Markers) Section 8.5.3 (Immunoglobulins)	[redacted]	
Section 6.4.3.3 (Exploratory [redacted]	[redacted]	Correction.
Section 6.6.1 (Discontinuation of Treatment)	Reason for study drug discontinuation (withdrawal of consent) expanded to incorporate additional text addressing "noncompliance with study procedures".	Clarification.
Section 6.6.1 (Discontinuation of Treatment)	Three additional reasons for study drug discontinuation provided (relating to receipt of restricted medication, receipt of rescue medication, and "any other reason" in the opinion of the Investigator).	Clarification.
Section 6.8 (End of Study)	Phrase "or if a subject withdraws and completes the EDV (Table 2)" deleted.	Correction.
Section 7.1.1.4 (Peri- and Post-Administration Observations)	Text describing the monitoring of vital signs on dosing days (from Section 8.6) was repositioned to here.	Clarification.
Section 7.1.1.5 (Investigational Product Accountability)	The sentences "The study IXRS system will be used by clinical sites to acknowledge receipt of study drug. Damaged shipments will be replaced" were inserted.	Clarification.
Section 7.4 (Prohibited and Restricted Therapies)	Text inserted explaining Investigator discretion to give "medications that are considered necessary for the safety and well-being of subjects".	Clarification.
Section 7.4.3 (Rescue Medications for Population #1)	New section stating, "The initiation or increase in dose of the restricted medications in Section 7.4.2 are also considered as rescue medications for Population #1" was inserted.	Clarification.
Section 7.4.5 (Rescue Medications for Population #2)	New section stating, "The initiation or increase in dose of the restricted medications in Section 7.4.4 are also considered as rescue medications for Population #2" was inserted.	Clarification.
Section 8.5.2 (Serum Chemistry)	The parameter "creatine kinase" was added to the components that will be measured as part of the Chemistry and Renal Profile.	Clarification.
Section 8.5.6 (Testing for SARS-CoV-2)	Section added explaining requirement for negative SARS-CoV-2 test.	Clarification.
Section 8.6 (Vital Signs)	Sentence regarding frequency of vital sign observations prior, during, and post infusion (including cross-reference to Section 7.1.1.4) was inserted.	Clarification.

Section 8.10 (Contacting Sponsor Regarding Urgent Protocol-related Medical Questions)	Section added providing 24-7 contact details in the event of a study-related health emergency.	Clarification.
Section 9 (Other Assessments), Section 9.1 (Qualitative Patient Interviews) and Table 2.	Section added describing qualitative patient interviews and corresponding details added to table of scheduled study assessments.	To gain insights into the overall study experience of participants and to generate patient-level qualitative evidence to support the suitability of currently utilized clinician-reported outcome and patient-reported outcome instruments.
Protocol Amendment 2: 7 Oct 2022		
The Amendment 2 changes to the protocol included the following:		
Protocol Section(s) Impacted by Change (Section Title)	Change	Reason for Change
Page 1	Updated company name from Viela Bio, Inc to Viela Bio, Inc.(acquired by Horizon Therapeutics)	Update
Section 6.1 Sjögren's Syndrome Data Medical Review Team	Text clarifying the MR team will remain blinded to the treatment assignment for individual subjects until the completion of the study.	Clarification
Section 7.2.4.2 Unblinding for Interim Analysis and Primary Analysis	Text clarifying any communication of unblinded results will be documented in an unblinding memo. Population-based treatment group level results may be released after completion of primary analysis.	Clarification
Administrative Change 1: 8 Nov 2022		
The administrative change to the protocol includes the following		
Protocol Section(s) Impacted by Change (Section Title)	Change	Reason for Change
Title Page	Updated company name from Viela Bio, Inc. (acquired by Horizon Therapeutics) to Horizon Therapeutics Ireland DAC (formerly known as Viela Bio, Inc.)	This administrative change includes Sponsor entity and company name change
All Sections	Viela Bio, Inc. name is removed throughout protocol and is replaced with Sponsor	

STATEMENT OF COMPLIANCE

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

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

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

All personnel involved in the conduct of this study have completed Human Subjects Protection and GCP Training as outlined by their governing institution.

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[redacted]

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LIST OF ABBREVIATIONS

Abbreviation	Definition
ACR	American College of Rheumatology
ADA	anti-drug antibody(ies)
AE	adverse event
AESI	adverse event of special interest
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AR	adverse reaction
AST	aspartate aminotransferase
AZA	azathioprine
β-hCG	beta-human chorionic gonadotrophin
HBc	hepatitis B core
HBsAg	hepatitis B surface antigen
CD	cluster of differentiation
CD40L	CD40 ligand
CDM	Clinical Data Management
cDMARD	conventional disease-modifying anti-rheumatic drug
CI	confidence interval
ClinESSDAI	Clinical EULAR Sjögren's Syndrome Disease Activity Index
COA	clinical outcome assessment
CRP	C-reactive protein
CSR	clinical study report
CTCAE	Common Terminology Criteria for Adverse Events
DAS28-CRP	Disease Activity Score in 28 Joints Using C-reactive Protein
DMARD	disease-modifying anti-rheumatic drug
DMP	Data Management Plan
ECG	electrocardiogram
eCRF	electronic Case Report Form
EDV	early discontinuation visit
E_{max}	maximum effect
ESSDAI	EULAR Sjögren's Syndrome Disease Activity Index
ESSPRI	EULAR Sjögren's Syndrome Patient Reported Index
EU	European Union
EULAR	European League Against Rheumatism
FACIT-Fatigue	Functional Assessment of Chronic Illness Therapy -Fatigue
FAS	full analysis set
FDA	Food and Drug Administration
Fn3	fibronectin type III

Abbreviation	Definition
GCP	Good Clinical Practice
HSA	human serum albumin
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
Ig	immunoglobulin
IGRA	Interferon Gamma Release Assay
IL	interleukin
IP	investigational product
IRB	Institutional Review Board
IV	intravenous(ly)
IXRS	interactive voice/web response system
KLH	keyhole limpet hemocyanin
mAb	monoclonal antibody
MAD	multiple-ascending dose
MCP	metacarpophalangeal
MMF	mycophenolate mofetil
MMRM	mixed-effect model for repeated measures
MR	Medical Review
MTX	methotrexate
NOAEL	no-observed-adverse-effect level
OSDI	Ocular Surface Disease Index
PD	pharmacodynamic(s)
[redacted]	
PGIS	Patient's Global Impression of Severity
PIP	proximal interphalangeal
PK	pharmacokinetic(s)
PRO	patient-reported outcome
[redacted]	
pSS	primary Sjögren's syndrome
PT	preferred term
PTT	partial thromboplastin time
Q2W	once every 2 weeks
Q4W	once every 4 weeks
QoL	quality of life
RA	rheumatoid arthritis
RF	rheumatoid factor

Abbreviation	Definition
SAE	serious adverse event
SAR	suspected adverse reaction
SAP	statistical analysis plan
SC	subcutaneous
sCD40L	soluble CD40 ligand
SDMC	Safety and Data Monitoring Committee
[redacted]	
SID	subject identification number
SLE	systemic lupus erythematosus
SNP	single nucleotide polymorphism
SOC	system organ class
SS	Sjögren's syndrome
sSS	secondary Sjögren's syndrome
TB	tuberculosis
TBL	total bilirubin
TDAR	T-cell dependent antibody response
TEAE	treatment-emergent adverse event
TESAE	treatment-emergent serious adverse event
TK	toxicokinetic(s)
TNF	tumor necrosis factor
ULN	upper limit of normal
[redacted]	
w/v	weight/volume

1 SYNOPSIS

Title	A Phase 2 Randomized, Double-Blind, Placebo-Controlled, Proof of Concept Study to Evaluate the Efficacy and Safety of VIB4920 in Subjects with Sjögren's Syndrome (SS)
Phase	2
Study Design	Randomized, double-blind, placebo-controlled, parallel-arm study
Rationale	Activation of cluster of differentiation (CD40) has been shown to be critical in germinal center formation, immunoglobulin (Ig)-class switching and expression of cytokines, such as interferon-α, tumor necrosis factor-α, and interleukin-6, all of which have been previously associated with the pathophysiology of SS. Dysregulation of the CD40/ CD40 ligand (CD40L) has been observed in patients with SS in both the circulating cells and in the epithelial salivary cells. Downregulation of T- and B-cell activation, inhibition of CD40-mediated epithelial activation, and reduction in the local inflammatory factors contributing to salivary gland inflammation would be expected to improve glandular function in SS.
Target Population	The study will enroll 2 SS populations: Population #1: subjects with moderate to high systemic disease activity defined by European League Against Rheumatism (EULAR) Sjögren's Syndrome Disease Activity Index (ESSDAI) ≥ 5. Population #2: subjects with moderate to severe subjective symptoms defined by EULAR Sjögren's Syndrome Patient Reported Index (ESSPRI) score ≥ 5 and residual [redacted] but with mild systemic disease activity defined by ESSDAI score < 5.
Number of Subjects	Total: Population #1: 72 subjects; Population #2: 102 subjects Per treatment: Population #1: n = 36 per treatment group Population #2: n = 51 per treatment group
Length of Participation	On treatment: 40 weeks. Subjects will receive randomized treatment (VIB4920 or placebo) 24 weeks (Stage I). After completion of Stage I, subjects initially randomized to VIB4920 will initiate placebo treatment and subjects initially randomized to placebo will initiate VIB4920 treatment for 16 weeks (Stage II). On study (including screening and follow-up): 56 weeks (393 days).
Intervention	Stage I: VIB4920, 1500 mg intravenously (IV) once every 2 weeks x 3, then once every 4 weeks (Q4W) or placebo Stage II: VIB4920 Q4W x 5 or placebo
Primary Objective and Primary Endpoint	**Objective**: Population #1: To evaluate the clinical efficacy of multiple doses of VIB4920 in glandular and extraglandular manifestations of SS patients with moderate to high systemic disease activity. Population #2: To evaluate the clinical efficacy of multiple doses of VIB4920 in the key subjective complaints of SS (dryness, fatigue, and pain). **Endpoint**: Population #1: Change from baseline in ESSDAI at Day 169. Population #2: Change from baseline in ESSPRI at Day 169.

Secondary Objective(s) and Corresponding Endpoint(s)	**Objectives:** Population #1: 1. To evaluate the effect of VIB4920 on systemic activity and patient-reported outcomes in subjects with SS 2. To evaluate the safety and tolerability of multiple doses of VIB4920 in subjects with SS 3. To characterize the pharmacokinetics (PK) of VIB4920 in subjects with SS 4. To assess the immunogenicity of VIB4920 in subjects with SS Population #2: 1. To evaluate the effect of VIB4920 on patient-reported outcomes in subjects with SS 2. To evaluate the safety and tolerability of multiple doses of VIB4920 in subjects with SS 3. To characterize the PK of VIB4920 in subjects with SS 4. To assess the immunogenicity of VIB4920 in subjects with SS **Endpoints:** Population #1: 1. Change from baseline in ESSPRI at Day 169. 2. Proportion of subjects achieving ESSDAI[3] and ESSDAI[4] response, defined as a decrease of at least 3[4] points from baseline in the ESSDAI at Day 169 without premature discontinuation from the study and without receiving rescue therapy 3. Change from baseline in Functional Assessment of Chronic Illness Therapy (FACIT)-Fatigue score at Day 169. 4. Change from baseline in Ocular Surface Disease Index (OSDI©) at Day 169. 5. Patient's Global Impression of Severity (PGIS) at Day 169 6. Safety and tolerability of multiple IV doses of VIB4920 as measured by the incidence of treatment-emergent adverse events (TEAEs), treatment-emergent serious adverse events (TESAEs), adverse events of special interest (AESIs), and laboratory, vital sign, and electrocardiogram (ECG) abnormalities. 7. PK during the study. 8. Proportion of subjects with positive immunogenic response measured by anti-VIB4920 antibodies until the completion of the study. Population #2: 1. Proportion of subjects achieving ESSPRI response, defined as ≥ 1 point or 15% reduction from baseline in ESSPRI score at Day 169 without premature discontinuation from the study and without receiving rescue therapy. 2. Change from baseline in FACIT-Fatigue at Day 169. 3. Change from baseline in OSDI at Day 169. 4. PGIS at Day 169 5. Safety and tolerability of multiple IV doses of VIB4920 as measured by the incidence of TEAEs, TESAEs, AESIs, and laboratory, vital sign, and ECG abnormalities. 6. PK during the study. 7. Proportion of subjects with positive immunogenic response measured by anti-VIB4920 antibodies until the completion of the study.

Exploratory Objective(s) and Corresponding Endpoint(s)	**Objectives:** [redacted] **Endpoints:** [redacted]

	[redacted]
Number of Sites	Approximately 70 international sites.
Study Duration	Estimated duration: 25 months
Safety and Data Monitoring Committee	An independent Safety and Data Monitoring Committee 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.

2 INTRODUCTION

2.1 Background

Sjögren's syndrome (SS) is a systemic autoimmune disease characterized by chronic lymphocytic inflammation of the exocrine glands, mainly the salivary and lacrimal glands, leading to loss of function manifesting as excessive dryness (Mavragani, 2017). Additionally, extraglandular manifestations are described as multi-organ involvement affecting musculoskeletal, pulmonary, renal, nervous, dermatological, gastrointestinal, hematological, hepatobiliary, or vascular systems, while fatigue is one of the most prominent comorbidities (Leone et al, 2017; Manuel et al, 2017; McCoy and Baer, 2017). The joints, lung, skin, and peripheral nerves are the most frequent organ systems involved, while cytopenia, hypocomplementemia, and cryoglobulinemia at diagnosis are strongly associated with greater systemic activity. SS may also present in association with other autoimmune diseases and historically it has been characterized as secondary Sjögren's syndrome (sSS) when co-existing with selected other autoimmune diseases such as rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), or scleroderma (Hernandez-Molina et al, 2010).

The subjective aspects of SS, which include the patient's perception of dryness, musculoskeletal pain, and fatigue can be debilitating and have been shown to have a substantial negative impact on quality of life (QoL) (Hammit et al, 2017). QoL is also affected by psychological and emotional challenges and impaired social life with dependency on relatives in daily life and difficulties at work, as well as with other tasks (Lackner et al, 2017).

Demographic data for SS vary largely. A meta-analysis of epidemiological studies in primary Sjögren's syndrome (pSS) published in 2014 estimated a worldwide prevalence of pSS of 60.82 per 100,000 inhabitants, or one person in 1644 (Qin et al, 2015). Even more recently, a French group estimated the prevalence of pSS in Europe of being lower, using exclusively studies with good methodology (population-based study, effective case-finding methods, ascertainment of cases using the initially developed diagnostic criteria, large background population) and that have been performed exclusively in European countries. Only 3 studies have been identified fulfilling all the above criteria and combining these results, the estimated prevalence of SS in Europe was calculated to be 38.95/100,000, or one person in 2567 (Cornec and Chiche 2015).

Until recently, the most commonly used classification criteria for SS were developed in 2002 (Vitali et al, 2002). As of 2016, an international set of classification criteria for pSS based on guidelines from the American College of Rheumatology (ACR) and the European League Against Rheumatism (EULAR) was developed and validated (Shiboski et al, 2017). Although these criteria were developed for classification of pSS and not for sSS, the International SS Criteria Working Group suggested that these criteria could also be applicable for sSS, and recommended confirmatory studies (Shiboski et al, 2017; Tsuboi et al, 2017).

Two disease activity indices suitable for use as SS endpoints have recently been developed by EULAR through an international collaborative project: the EULAR Sjögren's Syndrome Disease Activity Index (ESSDAI) to assess the systemic manifestations, and the EULAR Sjögren's Syndrome Patient Reported Index (ESSPRI) for patients' symptoms (Seror et al, 2010; Seror et al, 2011).

Standard of care for SS focuses on controlling sicca symptoms using pharmaceutical and nonpharmaceutical approaches and managing extraglandular manifestations with glucocorticoids and immunosuppressive drugs (Ramos-Casals et al, 2010). Sialogogues, such as pilocarpine or cevimeline, can be used to stimulate residual saliva production, but they have limited efficacy and systemic side effects. Cyclosporine eye drops are effective in improving dry eye symptoms in a subset of SS patients. Currently, there are no approved immunomodulating agents or evidence-based therapeutic guidelines available for treatment of the extraglandular manifestations of SS. Therefore, standard of care for extraglandular manifestations varies widely and is based on local practices, expert opinion, and personal experience of the treating physicians (Ramos-Casals et al, 2010). Disease-modifying anti-rheumatic drugs (DMARDs) approved for other rheumatic diseases are frequently used for the treatment of extraglandular manifestation based on clinical similarities but without direct evidence of efficacy in SS. Hydroxychloroquine is also used often for improvement of fatigue and joint pain despite a negative clinical trial (Gottenberg et al, 2014).

A number of biological treatments have been evaluated for efficacy in controlled and uncontrolled clinical studies. Tumor necrosis factor inhibitors were shown to be ineffective and are not recommended in SS (Ramos-Casals et al, 2010). Several studies evaluated B-cell depletion with rituximab with mixed results with the 2 larger trials failing to reach their primary endpoints (Dass et al, 2008; Meijer et al, 2010; Devauchelle-Pensec et al, 2014; Bowman et al, 2017). An open label study with abatacept showed encouraging results (Meiners et al, 2014) that need further exploration in controlled studies. In fact, abatacept recently completed enrollment in a large phase 3 trial (NCT02915159). A trial targeting the costimulatory molecule CD40 (NCT02291029) was recently completed and showed a statistically significant decrease in disease activity (ESSDAI score) in 12 weeks in pSS (Fisher et al, 2017).

2.1.1 Target Indication and Population

It is possible to use the ESSDAI and ESSPRI indices to define SS population subsets with distinct disease manifestations, both of which have significant unmet medical needs. For this clinical study, these have been termed Population #1 and Population #2.

Population #1, which includes SS patients with moderate to high systemic activity defined by ESSDAI ≥ 5, has been the focus of many recent SS trials. About 15-20% of SS patients present with systemic manifestations beyond the commonly affected exocrine glands (salivary and ocular). These manifestations most commonly include arthritis, lung disease, renal disease, vasculitis, neuropathies, and autonomic nervous system dysfunction, which accompany glandular involvement. Moderate to high disease activity is not only debilitating but can also lead to dysfunction of the affected organ(s), or to hematologic pathologies, including thrombocytopenia and lymphoma, that have been associated with increased risk of mortality (Brito-Zeron et al, 2016). Despite the increased number of trials, no biologics or DMARDs have been shown to be efficacious in significantly reducing SS systemic disease activity.

Population #2 includes SS patients with exocrine dysfunction, severe subjective symptoms defined by an ESSPRI score of ≥ 5, considered as the cut-off point for "unsatisfactory symptom state" (Seror et al, 2016a) but with lower systemic disease activity (with ESSDAI score < 5). This population represents a large subset of SS patients who have been excluded from recent trials despite the substantial disease burden and overall unacceptable health status.

Based on patient surveys and assessments supported by the SS Foundation, SS makes every day a challenge for 86% of patients, interfering with their everyday activities and also adding a significant emotional and financial burden. The major contributors to the decreased QoL are dryness and fatigue. When asked how important it would be to have a new systemic therapy created to address a list of symptoms, 82% of the "patients were most likely to say it is absolutely essential/extremely important to have a therapy created to address dryness" (Sjögren's Syndrome Foundation, 2017). The inclusion of Population #2 in the proposed study is intended to address this clear unmet clinical need.

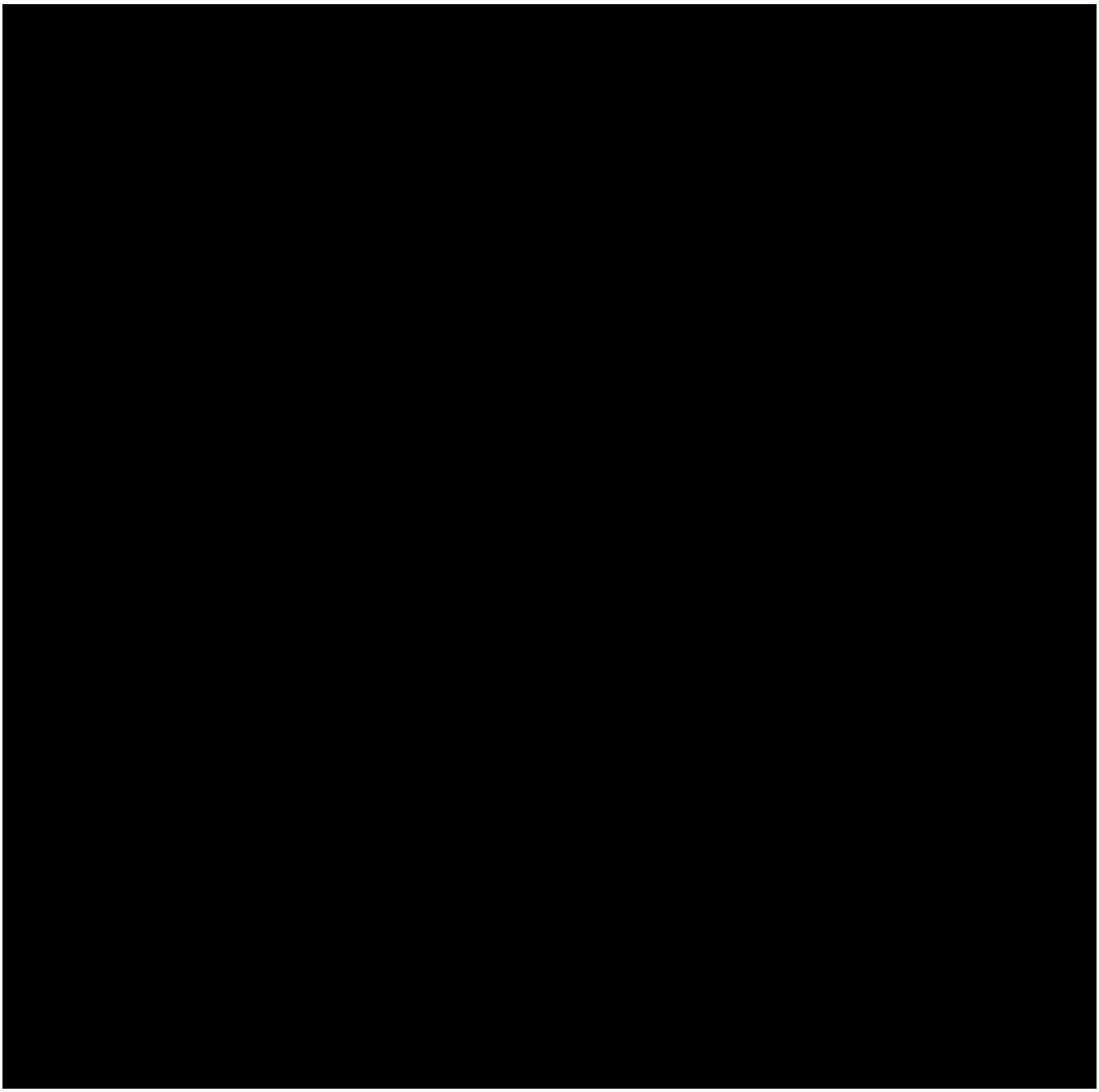
2.1.2 Description of VIB4920

VIB4920 (formerly known as MEDI4920) is a cluster of differentiation (CD) 40 ligand (CD40L) antagonist that comprises 2 identical Tn3 modules fused to human serum albumin (HSA). Each Tn3 is an engineered form of the third fibronectin type III (Fn3) protein domain of human Tenascin C. Polyglycine linkers join the 2 Tn3 domains, and the second Tn3 domain to the HSA protein. Each Tn3 binds specifically to human CD40L and inhibits its interaction with human CD40. The CD40/CD40L interaction plays a critical role in the activation of B cells, which produce autoantibodies and inflammatory mediators that contribute to autoimmune disease pathology. By blocking the CD40/CD40L interaction, VIB4920 may act as an immune modulator with potential therapeutic activity in a range of autoimmune diseases, including SS (Jobling and Ng, 2018; Karnell et al, 2018; Wieczorek et al, 2019).

2.1.3 Supportive Nonclinical Data

2.1.3.1 Pharmacology

Nonclinical pharmacology studies demonstrated that VIB4920 binds human CD40L specifically and with high affinity. In addition, in vitro and in vivo studies have demonstrated the mechanism of action of VIB4920. Lastly, VIB4920 demonstrated an acceptable safety profile in in vivo and in in vitro functional platelet assessment systems, compared with anti-CD40L monoclonal antibodies (mAbs), which have been tested in both nonclinical and clinical studies. These results highlight the potential for VIB4920 to be a key modulator in treating autoimmune disease.



2.1.4 Supportive Clinical Data

2.1.4.1 Phase 1 Single-ascending Dose Study in Healthy Volunteers

Study D5100C00001 was a single-center, first-time-in-human single-ascending dose study that evaluated the safety and tolerability of IV doses of VIB4920 in healthy adult male subjects and healthy adult female subjects of non-childbearing potential. The study also characterized the PK of VIB4920, assessed ADA to VIB4920, and evaluated the effect of VIB4920 on TDAR after administration of KLH antigen. VIB4920 was administered as a single IV infusion at dose levels of 3, 10, 30, 100, 300, 1000, and 3000 mg. A total of 59 male subjects were randomized, 56 subjects were treated, and 53 subjects completed the study. In this study, VIB4920 demonstrated

an acceptable safety and tolerability profile. There were no reports of thromboembolic events or clinically significant abnormalities related to hemostasis. The PK of VIB4920 was linear following a single IV dose ranging from 3 to 3000 mg. TDAR was inhibited in a dose-dependent manner, showing statistically significant differences with the higher VIB4920 doses (300, 1000, and 3000 mg) compared with placebo. There was a dose-dependent increase in total sCD40L after VIB4920 administration, indicating binding of VIB4920 to sCD40L and target engagement. There was a decrease in ADA incidence and titers observed with increasing doses of VIB4920 that is consistent with the immunosuppressive mechanism of action of VIB4920. There was no identified association of ADA with any treatment-emergent adverse events (TEAEs) reported in this study. A dose-response model was generated for TDAR inhibition and showed that the 1000 mg dose achieved approximately 78% inhibition and the 3000 mg approximately 86% inhibition compared with placebo, indicating adequate inhibition for the 2 highest doses tested.

2.1.4.2 Phase 1b Multiple-ascending Dose Study in Rheumatoid Arthritis

A phase1b, multiple-ascending dose (MAD) study (D5100C00002) recruited 57 subjects with RA. This multicenter, randomized, double-blind (Investigator, subject, and Sponsor blinded to treatment assignment), placebo-controlled study evaluated the safety and tolerability of MADs of VIB4920 in subjects with adult-onset RA (moderate to severe, as defined by Disease Activity Score in 28 Joints Using C-reactive Protein (DAS28-CRP) ≥ 3.2 at screening) with an inadequate response to methotrexate (MTX) or other conventional DMARDs (cDMARDs) or to a biologic anti-tumor necrosis factor (TNF)-α agent. Subjects were randomized and treated across 4 sequential cohorts; the VIB4920 doses used were 75, 500, 1000, and 1500 mg. Treatment with investigational product (IP) (VIB4920 or placebo) was administered by IV infusion once every 2 weeks (Q2W) up to Day 85/Week 12 for a total of 7 doses, followed by a 12-week follow-up period.

VIB4920 significantly reduced disease activity, quantified by DAS28-CRP score, in RA patients at higher doses at Day 85 (VIB4920 1500 mg and VIB4920 1000 mg). The effect of VIB4920 on DAS28-CRP was rapid, with reductions evident as early as Day 15, after only a single dose of drug. The reduction of disease activity as compared with placebo was both clinically and statistically meaningful in the groups receiving the highest 2 doses of VIB4920: the adjusted mean (standard error) difference compared to placebo at Week 12 for VIB4920 1500 mg and 1000 mg groups were -1.4 (0.4) and -1.2 (0.4) with p-values of 0.002 and 0.006, respectively.

The statistically significant response over placebo observed in DAS28-CRP at Day 85 with the VIB4920 1000 mg and VIB4920 1500 mg doses was maintained for 3 months after the last dose until the end of the study at Day 169.

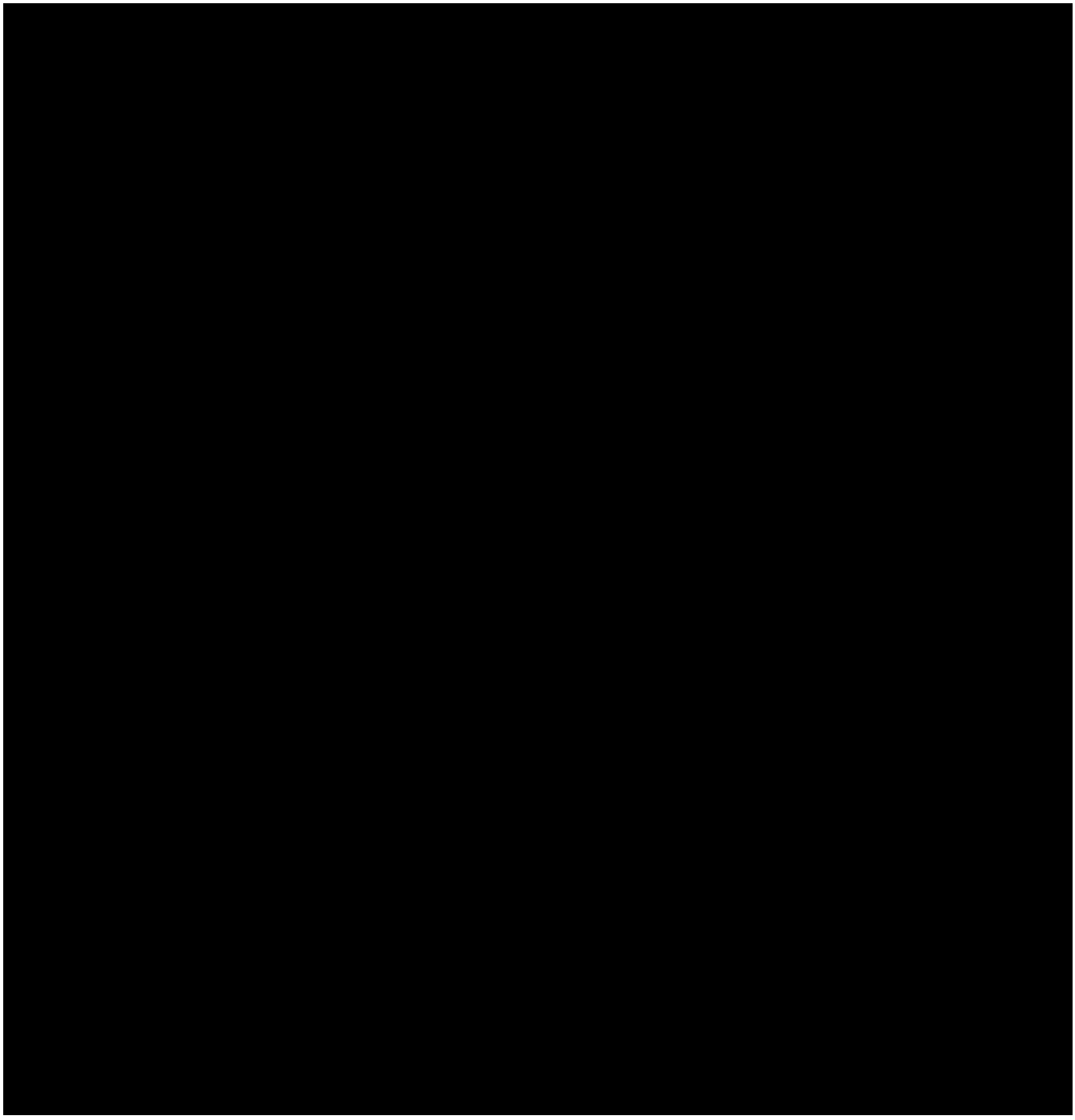
In terms of individual clinical response, 75% of subjects in the 1500 mg group and 50% of subjects in 1000 mg dose group achieved a DAS28-CRP score ≤ 3.2 at Day 85, indicating they were in low disease activity or clinical remission.

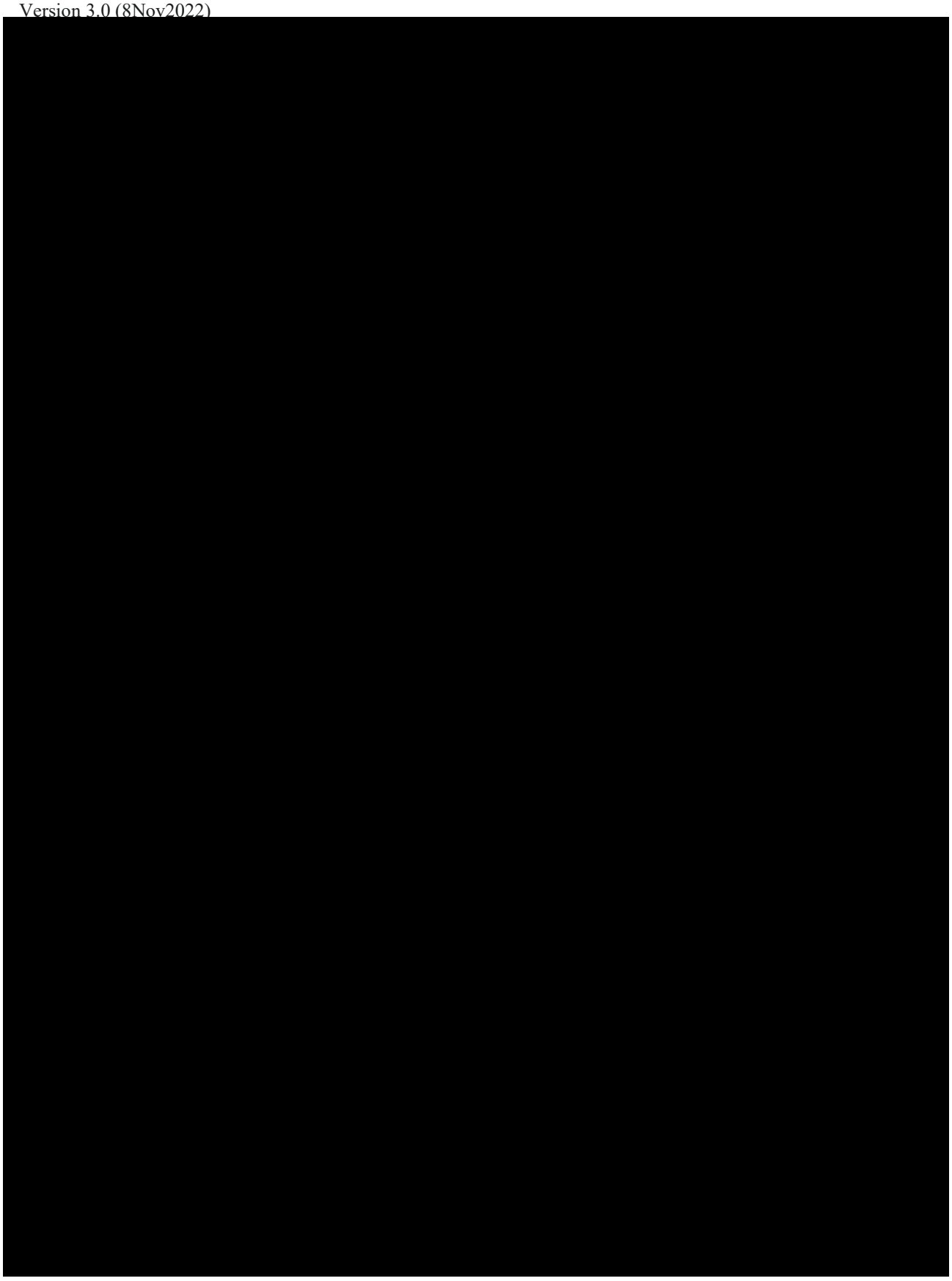
RF exhibited a statistically significant E_{max} dose response (E_{max} = maximum effect attributable to VIB4920) for change from baseline in RF at Day 85 ($p < 0.001$). The estimated percent reduction over placebo at Day 85 was 47% (90% confidence interval [CI]: 38%, 55%) for the 1000 mg dose, and 52% (90% CI: 43%, 60%) for the 1500 mg dose. Vectra® DA score was also reduced by VIB4920 1500 and 1000 mg dose levels. The adjusted mean difference vs placebo at Day 85 was -14.4 (90% CI: -21.5, -7.2), $p = 0.001$ and -10.3 (90% CI: -17.4, -3.3), $p = 0.018$ for the

1500 and 1000 mg dose, respectively. Other endpoints (eg, Clinical Disease Activity Index, tender joint count, swollen joint count, Patient's Global Assessment, Physician's Global Assessment, C-reactive protein [CRP], and erythrocyte sedimentation rate) generally supported the result for 1000 and 1500 mg not only at Day 85, but to the end of the study.

Based on clinical data from Study D5100C00001 and Study D5100C00002, there are no identified risks for humans associated with VIB4920.

2.1.5 Risk Assessment





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2.1.5.6 Exposure In Utero

No embryo-fetal studies have been conducted to date.

2.1.5.7 Risks related to the COVID-19 pandemic

After the start of this study, the COVID-19 pandemic resulted in temporary study closure after 6 subjects had been dosed. All 6 participants continued on the study after discussing with the site Investigators the potential risks from SARS-CoV-2. None of the 6 subjects is known to have had COVID-19. There are limited data on the excess risks from COVID-19 in patients with SS or receiving the protocol allowed concomitant treatments for SS, such as steroids (Gianfrancesco et al, 2020). There are no data on the effect of VIB4920 on the risk for infection with SARS-CoV-2 or on the severity of COVID-19 illness.

Risk factors for severe or life-threatening COVID-19 illness continue to be assessed; currently, risk factors are thought to include older age, male sex, obesity (especially body mass index > 40), comorbidities such as hypertension, diabetes, heart disease (especially heart failure), chronic kidney disease, lung disease, and malignancy (Docherty et al, 2020; Petrilli et al, 2020; Zhou et al, 2020). Subjects also have individual epidemiologic risk related to local rates of infection and infection transmission, and also to their individual exposure or potential exposure to infected individuals; for example, transmission risks have been very high in care facilities such as nursing homes.

It is possible that, based on its mechanism of action, VIB4920 will interfere with mounting an optimal vaccine response. It is possible that a vaccine may not provide optimal or even any protection if administered during the effect of VIB4920 on the immune system. For this reason, Investigators should ensure that all patients are up to date with required vaccinations prior to entry into the study. There is currently no vaccine against COVID-19, but there is a risk that VIB4920 could impair a response to any/all COVID-19 vaccines that might become available.

An additional risk of study participation includes exposure of the subject to SARS-CoV-2, the virus that causes COVID-19, by visiting the study site. Sites must have a plan in place to minimize this risk.

2.2 Study Rationale

The CD40/CD40L pathway has been extensively studied for its role in immunity and autoimmunity, especially in its role in B- and T-cell activation and B- and T-cell costimulation

(Jobling and Ng, 2018; Karnell et al, 2018). Specifically, activation of CD40 has been shown to be critical in germinal center formation, Ig-class switching and expression of cytokines such as interferon-α, TNF-α and interleukin (IL)-6, all of which have been previously associated with the pathophysiology of SS (Jobling and Ng, 2018; Wieczorek et al, 2019).

CD40L on circulating CD4+ T cells has also been shown to be increased in women with SS (Belkhir et al, 2014). Ectopic lymphoid follicles are commonly found in SS salivary glands and are believed to be involved in tissue destruction and the local production of autoantibodies (Karnell et al, 2018). Additionally, in SS salivary glands, 30-50% of the infiltrating lymphocytes have been shown to express CD40L (Dimitriou et al, 2002).

Importantly, the dysregulation of the CD40/CD40L is not only seen in the circulating cells but also in the epithelial salivary cells. Immunocytochemistry and flow cytometry have identified significantly higher, constitutively expressed CD40 on long term primary epithelial salivary cell cultures from SS patients compared to controls, suggesting pathologic intrinsic activation (Dimitriou et al, 2002). Epithelial activation, an important component of the pathophysiologic process in SS, results in the secretion of proinflammatory cytokines and other mediators, which in turn may contribute to the initiation and/or propagation of the chronic inflammatory response.

The importance of the CD40/CD40L pathway in SS is central to autoimmunity in general and this conceptual framework has led to a number of clinical trials of novel therapies targeting this pathway in autoimmune diseases such as lupus nephritis, psoriatic arthritis, SLE, and RA, among others. A phase 2a trial in SS with an anti-CD40 agent showed efficacy in decreasing ESSDAI in subjects with moderate to high disease activity (Fisher et al, 2017) which supports the rationale for the proposed study of VIB4920 in this disease.

Although they preferentially target different tissues, SS and RA share common underlying autoimmune pathologic mechanisms likely to involve activation of the CD40/CD40L pathway. For example, the target tissues, namely the salivary glands and synovium, respectively, are populated by hyperactivated B cells that often contain ectopic lymphoid organelles thought to contribute to the disease progression. The clinical and biomarker improvements observed in subjects with RA following treatment with VIB4920 in the phase 1b study provide further rationale for targeting the CD40-CD40L pathway in SS. Downregulation of T- and B-cell activation, inhibition of CD40-mediated epithelial activation, and reduction in the local inflammatory factors contributing to salivary gland inflammation would be expected to improve glandular function in SS (Dimitriou et al, 2002). Moreover, CD40-CD40L pathway blockade may also favorably impact the diverse systemic manifestations of SS that are dependent on this pathway, as observed in patients with RA showing improvement in joint inflammation and in other organ systems, such as the lung and kidney, where epithelial cells may play key roles in driving the inflammatory response.

After this study was opened to enrollment in November 2019, the onset of the pandemic caused by SARS-CoV-2 resulted in temporary halt of the study to enrollment. The decision to re-open the study was based on an overall assessment of potential benefit-risk for subjects in the study during what is likely to be continued circulation of COVID-19. There are no clear data on the possible potentiation of COVID-19 risk by active SS on- or off-treatment and there are no data on the effect of VIB4920 on this risk. A potential risk of VIB4920 is infection, based on its mechanism of action. The subjects in this study, however, have the health risk of active SS despite standard of care treatment.

The following are included in this study to minimize risk to subjects:

- Opening a site only after review of local COVID-19 epidemiology, availability of healthcare resources, ability to monitor site activities, and the presence of a site plan to minimize patient exposure to SARS-CoV-2 during site visits. Each of these factors is likely to differ over time in ways that are difficult to predict, so ongoing risk assessment is required and will be implemented.
- Assessment of the benefit-risk for each individual subject for determination of suitability for enrollment based on known risk factors for COVID-19 severity and possible or known exposure to SARS-CoV-2.
- Requiring a negative SARS-CoV-2 test within 2 weeks prior to randomization.

Considering the measures taken to minimize risk to subjects participating in this study and the benefit that may be afforded to study subjects, the benefit-risk assessment is reasonable for a phase 2 study.

2.3 Study Hypotheses

Primary Hypothesis for Population #1:

- VIB4920 reduces clinical activity in subjects with SS with moderate to high systemic disease activity

Primary Hypothesis for Population #2:

- VIB4920 reduces clinical activity in subjects with SS with moderate to severe subjective complaints

Secondary Hypothesis for Populations #1 and #2:

- VIB4920 has an acceptable safety profile and is well tolerated in subjects with SS

3 OBJECTIVES AND ENDPOINTS

This study will be conducted in 2 SS subpopulations, as discussed in Section 2.1.1, Population #1 and Population #2. There will be a different set of objectives and endpoints in each population.

3.1 Objectives in Population #1

3.1.1 Primary Objective in Population #1

To evaluate the clinical efficacy of multiple doses of VIB4920 in glandular and extraglandular manifestations of SS patients with moderate to high systemic disease activity.

3.1.2 Secondary Objectives in Population #1

1. To evaluate the effect of VIB4920 on systemic activity and patient-reported outcomes in subjects with SS.
2. To evaluate the safety and tolerability of multiple doses of VIB4920 in subjects with SS.
3. To characterize the PK of VIB4920 in subjects with SS.

4. To assess the immunogenicity of VIB4920 in subjects with SS.

3.1.3 Exploratory Objectives in Population #1

3.2 Objectives in Population #2

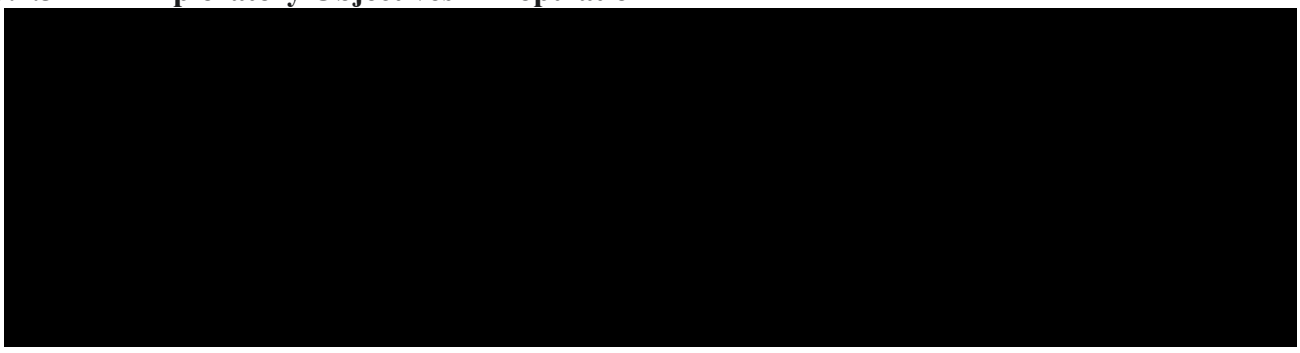
3.2.1 Primary Objective in Population #2

To evaluate the clinical efficacy of multiple doses of VIB4920 in the key subjective complaints of SS (dryness, fatigue, and pain).

3.2.2 Secondary Objectives in Population #2

1. To evaluate the effect of VIB4920 on patient-reported outcomes in subjects with SS.
2. To evaluate the safety and tolerability of multiple doses of VIB4920 in subjects with SS.
3. To characterize the PK of VIB4920 in subjects with SS.
4. To assess the immunogenicity of VIB4920 in subjects with SS.

3.2.3 Exploratory Objectives in Population #2



3.3 Endpoints for Population #1

3.3.1 Primary Endpoint for Population #1

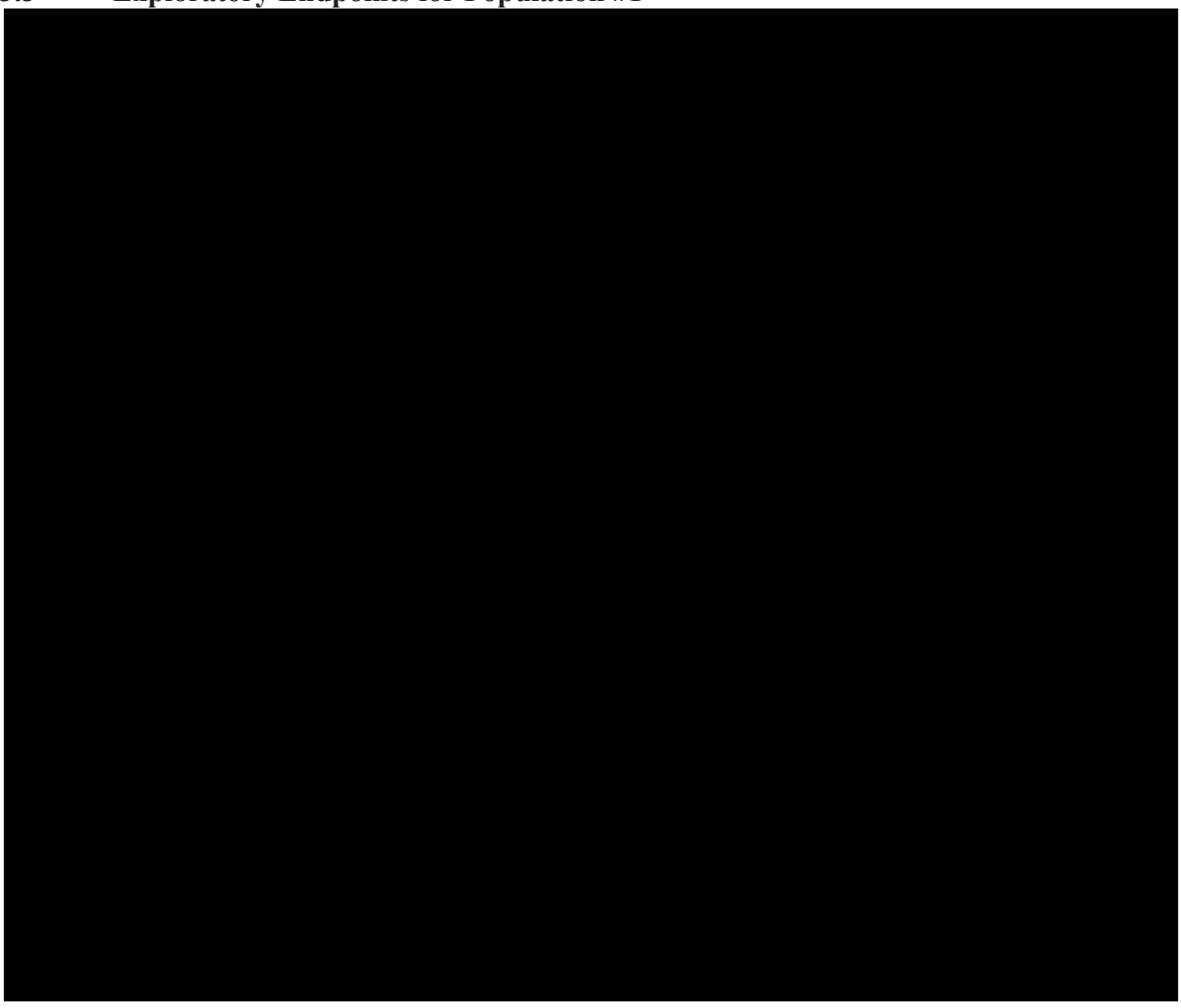
Change from baseline in ESSDAI at Day 169.

3.3.2 Secondary Endpoints for Population #1

1. Change from baseline in ESSPRI at Day 169.

2. Proportion of subjects achieving ESSDAI[3] and ESSDAI[4] response, defined as a decrease of at least 3[4] points from baseline in the ESSDAI at Day 169 without premature discontinuation from the study and without receiving rescue therapy.
3. Change from baseline in Functional Assessment of Chronic Illness Therapy (FACIT)-Fatigue score at Day 169.
4. Change from baseline in Ocular Surface Disease Index (OSDI©) at Day 169.
5. Patient's Global Impression of Severity (PGIS) at Day 169.
6. Safety and tolerability of multiple IV doses of VIB4920 as measured by the incidence of TEAEs, treatment-emergent serious adverse events (TESAEs), adverse events of special interest (AESIs), and laboratory, vital sign, and electrocardiogram (ECG) abnormalities.
7. PK during the study.
8. Proportion of subjects with positive immunogenic response measured by anti-VIB4920 antibodies until the completion of the study.

3.3.3 Exploratory Endpoints for Population #1



3.4 Endpoints for Population #2

3.4.1 Primary Endpoint for Population #2

Change from baseline in ESSPRI at Day 169.

3.4.2 Secondary Endpoints for Population #2

1. Proportion of subjects achieving ESSPRI response, defined as ≥ 1 point or 15% reduction from baseline in ESSPRI score at Day 169 without premature discontinuation from the study and without receiving rescue therapy.
2. Change from baseline in FACIT-Fatigue score at Day 169.
3. Change from baseline in OSDI at Day 169.
4. Patient's Global Impression of Severity at Day 169
5. Safety and tolerability of multiple IV doses of VIB4920 as measured by the incidence of TEAEs, TESAEs, AESIs, and laboratory, vital sign, and ECG abnormalities.
6. PK during the study.
7. Proportion of subjects with positive immunogenic response measured by anti-VIB4920 antibodies until the completion of the study.

3.4.3 Exploratory Endpoints for Population #2

4 STUDY PLAN

4.1 Study Design

This is a randomized, double-blind, placebo-controlled, parallel-arm study to evaluate the efficacy, safety, and tolerability of VIB4920 in adult subjects with SS diagnosed according to the 2016 ACR/EULAR Criteria (see Appendix 1). The study will enroll 2 SS populations. Population #1 will be composed of subjects with moderate to severe systemic disease activity defined by ESSDAI ≥ 5. Population #2 will be composed of subjects with mild systemic disease activity defined by ESSDAI score < 5 but with moderate to severe subjective symptoms defined by ESSPRI score ≥ 5 and residual stimulated salivary flow. Approximately 70 international sites may be involved in this study.

SS patients meeting the 2016 ACR/EULAR classification criteria and the rest of the inclusion/exclusion criteria will be accordingly assigned to Population #1 or Population #2. Each of the populations will then be randomized at 1:1 ratio to receive either placebo (n = 36 for Population #1, n = 51 for Population #2) or 1500 mg VIB4920 (n = 36 for Population #1, n = 51 for Population #2). Randomization will be stratified by ESSDAI score at screening (< 10 points vs ≥ 10 points) for Population #1 and by ESSPRI score at screening (< 7.5 points vs ≥ 7.5 points) for Population #2. To ensure balanced rates of enrollment of the 2 populations throughout the study, the Sponsor will implement a procedure where enrollment of subjects in Population #2 at each site is linked to enrollment of Population #1 subjects at the site with a progressively increasing ratio of Population #2:Population #1 subjects. At least 1 subject of the first 2 randomized at each site must be from Population #1.

The primary objective for Population #1 is to evaluate the clinical efficacy of multiple doses of VIB4920 in glandular and extraglandular manifestations of SS subjects with moderate to high systemic disease activity. The primary objective for Population #2 is to evaluate the clinical

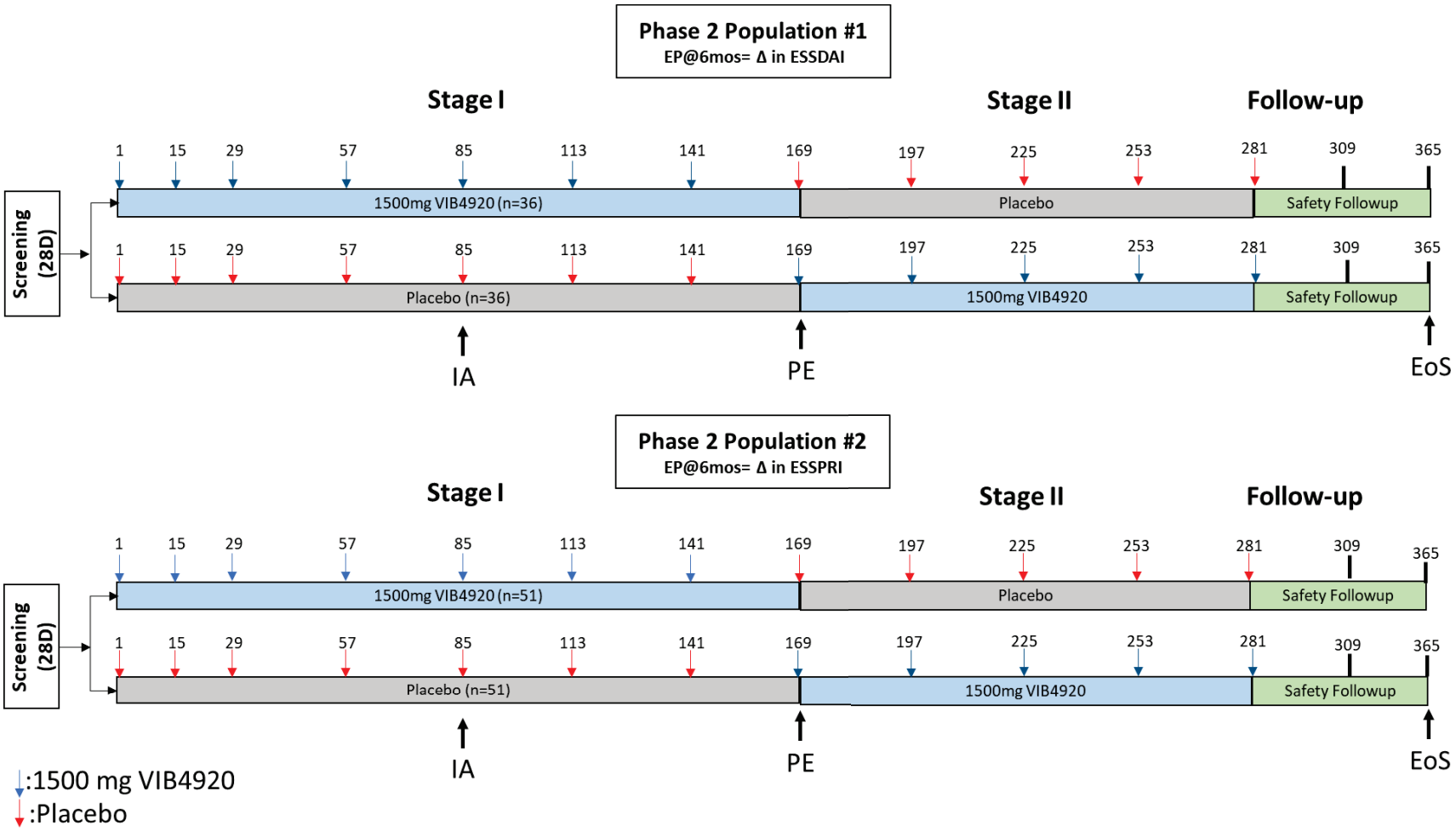
efficacy of VIB4920 in the key subjective complaints of SS. Full lists of the objectives for Populations #1 and #2 are presented in Sections 3.1 and 3.2, respectively.

The primary endpoint for Population #1 will be change from baseline in ESSDAI at Day 169. The primary endpoint for Population #2 will be change from baseline in ESSPRI at Day 169. Full lists of the endpoints for Populations #1 and #2 are presented in Section 3.3 and 3.4, respectively.

Within each population, eligible subjects will be randomized to receive VIB4920 1500 mg IV or placebo Q2W x 3 doses, then once every 4 weeks (Q4W) for 4 additional doses (Stage I). Starting on Day 169, subjects randomized to VIB4920 will receive placebo Q4W for 5 doses and subjects randomized to placebo will receive VIB4920 Q4W for 5 doses (Stage II). Subjects who had IP discontinuation will not be eligible for treatment during Stage II. All subjects will be followed for at least 12 weeks after their last dose of IP administration.

A study schematic is presented in Figure 1.

Figure 1 Study Flow Diagram



Δ = delta; D = days; EoS = End of Study; EP = endpoint; ESSDAI = European League Against Rheumatism Sjögren's Syndrome Disease Activity Index; ESSPRI = in EULAR Sjögren's Syndrome Patient Reported Index; IA = interim analysis; mos = months; PE = primary endpoint.

4.2 Dose and Treatment Regimen Rationale

The safety, tolerability, and PD effects of multiple IV doses of 1500 mg VIB4920 have been evaluated in RA patients with moderate to severe disease activity.

VIB4920 1500 mg Q2W proved to be efficacious in significantly decreasing disease activity, and clinical improvement lasted through the final visit at 12 weeks after the last dose. Based on PK/PD modeling and biomarker changes observed in the RA patients, the selected dose for this trial is 1500 mg IV Q2W for 3 doses as an induction dose, followed by 1500 mg IV administrations Q4W for an additional 4 doses. Starting at Day 169 of treatment, assignment of subjects will be crossed: subjects randomized to placebo will receive VIB4920 and subjects randomized to VIB4920 will receive placebo in a blinded fashion Q4W for 5 doses. This design has several advantages. First, it provides exposure to VIB4920 to all randomized subjects. Second, omitting the Day 15 induction dose in Stage II allows assessment of the effect of such an induction dose on the rate and magnitude of biologic response and may help optimize the dosing regimen. Third, the longer follow-up of the VIB4920 arms provides an opportunity to better assess the duration of clinical and biologic responses.

No dose-limiting toxicities were identified in the human trials.

4.3 Rationale for 2 Study Populations

The 2 SS populations, which distinguish patients with predominantly glandular dysfunction and those with both glandular dysfunction and systemic manifestations, represent subsets with significant unmet need that require different endpoints to assess efficacy. The ESSDAI is a validated instrument to assess systemic disease activity (Seror et al, 2010). The ESSPRI uses a 0-10 numerical analog scale, one for the assessment of each of the 3 domains of SS symptoms: dryness, fatigue, and pain (articular and/or muscular).

Population #1 with moderate to high systemic activity, defined by ESSDAI ≥ 5, has been the focus of many recent SS trials. About 15-20% of SS patients present with systemic manifestations beyond the commonly affected exocrine glands (salivary and ocular). These manifestations most commonly include arthritis, lung disease, renal disease, vasculitis, and peripheral neuropathies, as well as autonomic nervous system dysfunctions that accompany glandular involvement. Moderate to high disease activity may lead to physical dysfunction and poor QoL, as well as dysfunction of the affected organ(s). In addition, patients with pSS who have moderate to high disease activity are more prone to developing B-cell lymphoma, which in turn, has been associated with an increased risk of death (Brito-Zeron et al, 2016). Despite the increased number of trials, no biologics or DMARDs have been shown to be efficacious in significantly reducing SS systemic disease activity.

Population #2 comprises SS patients with exocrine dysfunction and severe subjective symptoms defined by an ESSPRI score of ≥ 5, considered as the cut-off point for "unsatisfactory symptom state" (Seror et al, 2016a) but lower systemic disease activity. This population represents a large subset of SS patients who have been excluded from recent trials despite the substantial disease burden and overall unacceptable health status.

The Eligibility Criteria related to the 2016 ACR/EULAR Classification Criteria for SS for both Population #1 and Population #2 and the disease activity data for the ESSDAI score for

Population #1 will be reviewed by the Sponsor/designee prior to enrollment to confirm subject eligibility.

4.4 Rationale for Primary Endpoint Selection

VIB4920 targets B cell-mediated autoimmune diseases and has been shown in the phase 1b RA trial to significantly decrease inflammatory markers and inflammatory cytokines (eg, CRP, IL-6) that are known to be associated with systemic, glandular, and subjective manifestations of SS, including pain, fatigue, and dryness. Thus, VIB4920 has the potential to improve inflammatory manifestations of SS and also to alleviate the most prominent features that lead to the unsatisfactory symptom state observed in SS.

The primary endpoints have been selected for each of the 2 SS Populations in this study: Change from baseline in ESSDAI for Population #1 and Change from baseline in ESSPRI for Population #2. Both are validated measures of objective (ESSDAI) and subjective (ESSPRI) disease activity in SS and have been used widely in SS clinical trials.

5 POPULATION

5.1 Inclusion and Exclusion Criteria

The study medical review (MR) team will review the Eligibility Criteria related to the 2016 ACR/EULAR Classification Criteria for SS and ESSDAI score to confirm patient eligibility for Population #1 and will review items related to the 2016 ACR/EULAR Classification Criteria for SS for Population #2 (see Section 6.1 for details).

5.1.1 Inclusion Criteria for Population #1

To be included in Population #1 of this study, each individual must satisfy all the following criteria:

1. Adults, 18 years or older at time of informed consent (the minimum age for adult participants can be higher than 18 years in countries with different regulations).
2. Diagnosed with SS by meeting the 2016 ACR/EULAR Classification Criteria.
3. Have an ESSDAI score of ≥ 5 at screening; the following domains will be scored but they will not contribute to the minimum ESSDAI score of 5 required for inclusion: Peripheral nervous system, Central nervous system, and Pulmonary.
4. Positive for either anti-Ro autoantibodies or RF, or both at screening, as per the definition of the standard central laboratory test.
5. Written informed consent and any locally required authorization (eg, Health Insurance Portability and Accountability Act in the United States, European Union [EU] Data Privacy Directive in the EU) obtained from the subject/legal representative prior to performing any protocol-related procedures, including screening evaluations.
6. Females of childbearing potential who are sexually active with a nonsterilized male partner must use a highly effective method of contraception from signing the informed consent form (ICF), and must agree to continue using such precautions through the end of

the study follow-up; cessation of contraception after this point should be discussed with a responsible physician. Highly effective methods of contraception include:

- combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation:
  - oral
  - intravaginal
  - transdermal
- progestogen-only hormonal contraception associated with inhibition of ovulation:
  - oral
  - injectable
  - implantable
- intrauterine device (IUD)
- intrauterine hormone-releasing system (IUS)
- bilateral tubal occlusion
- vasectomized partner
- sexual abstinence

Sexual abstinence is considered a highly effective method only if it is the preferred and usual lifestyle of the subject and the subject agrees to refrain from heterosexual intercourse from signing the ICF through the end of the study follow-up. Periodic abstinence, the rhythm method, and the withdrawal method are not acceptable methods of contraception. A recommendation that the female partners (of childbearing potential) of male study participants should use a highly effective method of contraception other than a barrier method is made.

- Females of childbearing potential are defined as those who are not surgically sterile (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).
- Vasectomized partner is a highly effective birth control method provided that partner is the sole sexual partner of the woman of childbearing potential trial participant and that the vasectomized partner has received medical assessment of the surgical success.

7. Nonsterilized male subjects who are sexually active with a female partner of childbearing potential must use a condom with spermicide from Day 1 through the end of the study.
8. Meets all of the following tuberculosis (TB) criteria:
   a. No history of latent or active TB prior to screening, with the exception of latent TB with documented completion of appropriate treatment.
   b. No signs or symptoms suggestive of active TB from medical history or physical examination.

c. No recent (≤ 12 weeks of screening) close contact with a person with active TB (close contact is defined as ≥ 4 hours/week OR living in the same household OR in a house where a person with active TB is a frequent visitor).

d. Negative Interferon Gamma Release Assay (IGRA) test result for TB obtained within 12 weeks prior to randomization. Subjects with an indeterminate test result can repeat the test, but if the repeat test is also indeterminate, they are excluded.

e. A chest radiograph (obtained during the screening period or any time within 12 weeks prior to signing of the ICF) with no evidence of current active TB or other infection, or old active TB, malignancy, or clinically significant abnormalities suggesting an active process (unless due to SS).

5.1.2 Exclusion Criteria for Population #1

If an individual for Population #1 meets any of the following criteria, he or she is ineligible for this study:

1. Patients with medical history of confirmed deep venous thrombosis or arterial thromboembolism within 2 years of signing the ICF.
2. Patients with risk factors for venous thromboembolism or arterial thrombosis (eg, immobilization or major surgery within 12 weeks before screening), prothrombotic status (including, but not limited to, congenital or inherited deficiency of antithrombin III, protein C, protein S, or confirmed diagnosis of catastrophic antiphospholipid syndrome).
3. Patients requiring treatment with anticoagulant drugs (clopidogrel, prasugrel, warfarin, low molecular weight heparin, others). Low-dose aspirin treatment (up to 325 mg/day) is allowed.
4. Concomitant polymyositis or dermatomyositis or systemic sclerosis.
5. Active malignancy or history of malignancy, except as follows:
   a. In situ carcinoma of the cervix treated with apparent success with curative therapy > 12 months prior to screening; or
   b. Cutaneous basal cell carcinoma following apparently curative therapy.
6. Subjects who are pregnant or lactating or planning to become pregnant during the duration of the study.
7. Subjects who have a positive test for, or have been treated for hepatitis B, hepatitis C, or HIV infection.

   Regarding hepatitis B, positive test for chronic hepatitis B infection at screening, defined as either (1) positive hepatitis B surface antigen (HBsAg) or (2) a positive hepatitis B core antibody (anti-HBc).
8. Subjects with:
   a. A history of more than one episode of herpes zoster and/or opportunistic infections in the last 12 months, with the exception of oral candidiasis, vaginal candidiasis, and cutaneous fungal infections.

b. Active viral, bacterial or other infections requiring systemic treatment at the time of screening or through randomization, or history of more than 2 infections requiring IV antibiotics within 12 months prior to signing the ICF.

c. Epidemiologic risk of COVID-19 (recent exposures, 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 subject's risk of participation. Subjects who have active COVID-19 infection or disease or other significant infection, or, in the judgment of the investigator, who may be at unacceptable risk of COVID-19 or its complications should not be randomized.

d. A documented positive SARS-CoV-2 test within 2 weeks prior to randomization. Subjects with a positive test for SARS-CoV-2 may be rescreened at least 2 weeks after a positive test if asymptomatic and at least 3 weeks after symptomatic COVID-19 illness.

9. Subjects with known history of severe allergy or reaction to any component of the IP formulation or to any other biologic therapy.
10. Subjects with any severe cardiovascular, respiratory, endocrine, gastrointestinal, hematological, neurological, psychiatric, or systemic disorder or any other condition that in the opinion of the Investigator, would place the subject at unacceptable risk of complications, interfere with evaluation of the IP or confound the interpretation of subject safety or study results.
11. Subjects who are unable or unwilling to comply with protocol requirements (eg, active drug or alcohol abuse).
12. Subjects who have received live (attenuated) vaccine within the 4 weeks prior to ICF signature.
13. Last administration of experimental biologic (other than those listed in Point 14) or oral agents < 3 months or 5 half-lives before randomization.
14. Subjects who have had previous treatment with any biologic B-cell-depleting therapy (eg, rituximab, ocrelizumab, or ofatumumab) within 12 months or other B-cell targeting therapy (eg, belimumab) < 3 months before randomization.
15. Injectable corticosteroids (including intra-articular) or treatment with > 10 mg/day dose oral prednisone or equivalent within 6 weeks prior to randomization. Concomitant treatment with oral corticosteroids ≤ 10 mg/day prednisone or equivalent is permitted provided that the dose is stable ≥ 2 weeks prior to screening through randomization (Day 1) and is expected to remain stable for the duration of the treatment period. Inhaled or topical corticosteroids given for asthma, chronic obstructive pulmonary disease or dermatological conditions are allowed provided doses are expected to be stable during the study.
16. Subjects treated with systemic corticosteroids for indications other than SS, RA, and SLE for more than a total of 2 weeks within 24 weeks prior to screening visit.
17. Use of the following medications:

a. Antimalarials (eg, chloroquine, hydroxychloroquine, quinacrine) if they have been initiated or if the dose has changed within 8 weeks prior to signing the ICF or during the screening period.

b. MTX, if the dose is > 20 mg/week; or if there is any change or initiation of new dose within 4 weeks prior to signing the ICF through randomization (Day 1), or if there has been any change in route of administration.

c. Azathioprine (AZA), if the dose is > 150 mg/day and there is any change or initiation of new dose within 4 weeks prior to signing the ICF through randomization (Day 1) and any change in route of administration.

d. Leflunomide, if the dose is >20 mg/day; or if there is any change or initiation of new dose within 4 weeks prior to signing the ICF through randomization (Day 1).

e. Mycophenolate mofetil (MMF), if the dose is >2g/day; or if there is any change or initiation of new dose within 4 weeks prior to signing the ICF through randomization (Day 1).

f. Any other DMARD, immunosuppressant, or antiproliferative agents, if last dose was taken within:

   – 4 weeks prior to signing ICF or

   – Drug-specific 5 half-lives elimination period (if longer than 4 weeks).

g. Any medication that, in the opinion of the Investigator, would interfere with evaluation of the IP or interpretation of subject safety or study results.

h. Any increase or initiation of new doses of cevimeline or pilocarpine and cyclosporine eye drops (Restasis®) within 2 weeks prior to signing the ICF through randomization (Day 1).

18. Subjects who have received previous treatment with anti-CD40L compounds at any time before screening.

19. Subjects with blood tests, at screening, of any of the following:

- Aspartate aminotransferase (AST) > 2 x upper limit of normal (ULN)
- Alanine aminotransferase (ALT) > 2 x ULN
- Total bilirubin (TBL) > 2 x ULN
- Hemoglobin < 75 g/L
- Neutrophils < 1.0 x 109/L
- Platelets < 100 x 109/L
- Prothrombin or partial thromboplastin time (PTT) > ULN

5.1.3 Inclusion Criteria for Population #2

To be included in Population #2 of this study, each individual must satisfy all the following criteria.

1. Adults, 18 years or older at time of informed consent (the minimum age for adult participants can be higher than 18 years in countries with different regulations).

2. Diagnosed with SS by meeting the 2016 ACR/EULAR Classification Criteria.
3. Have an ESSPRI score of ≥ 5 at screening.
4. Have an ESSDAI score of < 5 at screening.
5. Positive for either anti-Ro autoantibodies or RF, or both at screening, as per the definition of the standard central laboratory test available.
6. Residual salivary gland function as defined by whole stimulated salivary flow > 0.1 mL/min.
7. Written informed consent and any locally required authorization (eg, Health Insurance Portability and Accountability Act in the United States, EU Data Privacy Directive in the EU) obtained from the subject/legal representative prior to performing any protocol-related procedures, including screening evaluations.
8. Females of childbearing potential who are sexually active with a nonsterilized male partner must use a highly effective method of contraception from signing the ICF, and must agree to continue using such precautions through the end of the study follow-up; cessation of contraception after this point should be discussed with a responsible physician. Highly effective methods of contraception include:

    - combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation:

    – oral
    – intravaginal
    – transdermal

    - progestogen-only hormonal contraception associated with inhibition of ovulation:

    – oral
    – injectable
    – implantable

    - intrauterine device (IUD)
    - intrauterine hormone-releasing system (IUS)
    - bilateral tubal occlusion
    - vasectomized partner
    - sexual abstinence

    Sexual abstinence is considered a highly effective method only if it is the preferred and usual lifestyle of the subject and the subject agrees to refrain from heterosexual intercourse from signing the ICF through the end of the study follow-up. Periodic abstinence, the rhythm method, and the withdrawal method are not acceptable methods of contraception. A recommendation that the female partners (of childbearing potential) of male study participants should use a highly effective method of contraception other than a barrier method is made.

    – Females of childbearing potential are defined as those who are not surgically sterile (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).

- Vasectomized partner is a highly effective birth control method provided that partner is the sole sexual partner of the woman of childbearing potential trial participant and that the vasectomized partner has received medical assessment of the surgical success.

9. Nonsterilized male subjects who are sexually active with a female partner of childbearing potential must use a condom with spermicide from Day 1 through to the end of the study.
10. Meets all of the following TB criteria:
    a. No history of latent or active TB prior to screening, with the exception of latent TB with documented completion of appropriate treatment.
    b. No signs or symptoms suggestive of active TB from medical history or physical examination.
    c. No recent (≤ 12 weeks of screening) close contact with a person with active TB (close contact is defined as ≥ 4 hours/week OR living in the same household OR in a house where a person with active TB is a frequent visitor).
    d. Negative IGRA test result for TB obtained within 12 weeks prior to randomization. Subjects with an indeterminate test result can repeat the test, but if the repeat test is also indeterminate, they are excluded.
    e. A chest radiograph (obtained during the screening period or anytime within 12 weeks prior to signing of the ICF) with no evidence of current active TB or other infection, or old active TB, malignancy, or clinically significant abnormalities suggesting an active process (unless due to SS).

5.1.4 Exclusion Criteria for Population #2

If an individual for Population #2 meets any of the following criteria, he or she is ineligible for this study:

1. Patients with medical history of confirmed deep venous thrombosis or arterial thromboembolism within 2 years of signing the ICF.
2. Patients with risk factors for venous thromboembolism or arterial thrombosis (eg, immobilization or major surgery within 12 weeks before screening), prothrombotic status (including, but not limited to, congenital or inherited deficiency of antithrombin III, protein C, protein S, or confirmed diagnosis of catastrophic antiphospholipid syndrome).
3. Patients requiring treatment with anticoagulant drugs (clopidogrel, prasugrel, warfarin, low molecular weight heparin, etc). Low-dose aspirin treatment (up to 325 mg/day) is allowed.
4. Concomitant polymyositis or dermatomyositis or systemic sclerosis.
5. Active malignancy or history of malignancy, except as follows:

a. In situ carcinoma of the cervix treated with apparent success with curative therapy > 12 months prior to screening; or

b. Cutaneous basal cell carcinoma treated with apparent success with curative therapy

6. Subjects who are pregnant or lactating or planning to get pregnant during the duration of the study.

7. Subjects who have a positive test for, or have been treated for, hepatitis B, hepatitis C, or HIV infection.

   Regarding hepatitis B, a positive test for chronic hepatitis B infection at screening is defined as detection of either (1) hepatitis B surface antigen (HBsAg); or (2) hepatitis B core antibody (anti-HBc).

8. Subjects with:

   a. A history of more than one episode of herpes zoster and/or opportunistic infections in the last 12 months, with the exception of oral candidiasis, vaginal candidiasis, and cutaneous fungal infections.

   b. Active viral, bacterial or other infections requiring systemic treatment at the time of screening or through randomization, or history of more than 2 infections requiring IV antibiotics within 12 months prior to signing the ICF.

   c. Epidemiologic risk of COVID-19 (recent exposures, 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 subject's risk of participation. Subjects who have active COVID-19 infection or disease or other significant infection, or, in the judgment of the investigator, who may be at unacceptable risk of COVID-19 or its complications should not be randomized.

   d. A documented positive SARS-CoV-2 test within 2 weeks prior to randomization. Subjects with a positive test for SARS-CoV-2 may be rescreened at least 2 weeks after a positive test if asymptomatic and at least 3 weeks after symptomatic COVID-19 illness.

9. Subjects with known history of severe allergy or reaction to any component of the IP formulation or to any other biologic therapy.

10. Subjects with any severe cardiovascular, respiratory, endocrine, gastrointestinal, hematological, neurological, psychiatric, or systemic disorder or any other condition that, in the opinion of the Investigator would interfere with evaluation of the IP or interpretation of subject safety or study results.

11. Subjects who are unable or unwilling to comply with protocol requirements (eg, active drug or alcohol abuse).

12. Subjects who have received live (attenuated) vaccine within the 4 weeks before ICF signature.

13. Last administration of experimental biologic (other than those listed in Point 14) or oral agents < 3 months or 5 half-lives before randomization.

14. Subjects who have had previous treatment with any biologic B cell-depleting therapy (eg, rituximab, ocrelizumab, ofatumumab) within 12 months or other B-cell targeting therapy (eg, belimumab) < 3 months before randomization.
15. Use of the following medications:
    a. Antimalarials (eg, chloroquine, hydroxychloroquine, quinacrine) if they have been initiated or if the dose has changed within 8 weeks prior to signing the ICF or during the screening period.
    b. Oral, intramuscular, IV, or intra-articular corticosteroids within 4 weeks prior to signing the ICF through randomization (Day 1).
    c. MTX, AZA, leflunomide, other cDMARD, or immunosuppressive or antiproliferative medications, if last dose was taken within:
        – 4 weeks prior to signing ICF or
        – Drug-specific 5 half-lives elimination period (if longer than 4 weeks).
    d. Any medication that in the opinion of the Investigator would interfere with evaluation of the IP or interpretation of subject safety or study results
    e. Any increase or initiation of a new dose of regularly scheduled nonsteroidal anti-inflammatory drugs within 2 weeks prior to signing the ICF through randomization (Day 1).
    f. Any increase or initiation of new doses of cevimeline or pilocarpine and cyclosporine eye drops (Restasis) within 2 weeks prior to signing the ICF through randomization (Day 1).
16. Subjects who have received previous treatment with anti-CD40L compounds at any time before screening.
17. Subjects with blood tests, at screening, of any of the following:
    - AST > 2 x ULN
    - ALT > 2 x ULN
    - TBL > 2 x ULN
    - Hemoglobin < 75 g/L
    - Neutrophils < 1.0 x 109/L
    - Platelets < 100 x 109/L
    - Prothrombin or PTT > ULN

6 STUDY CONDUCT

Subjects will undergo a screening period of up to 4 weeks followed by randomization and treatment for 40 weeks (24 weeks [169 days] for Stage I and 16 weeks [112 days] for Stage II). Subjects will be followed for an additional 12 weeks [84 days] for safety and for assessment of duration of efficacy. The expected full duration of each subject's participation in this study is up to 393 days.

Table 1 summarizes the screening procedures for the study. More than one visit might be needed to complete screening.

The 2016 ACR/EULAR Criteria for Classification of SS are provided in Appendix 1.

Table 1 Screening Procedures

Study Period	**Screening**
Visit Number	**V1**
Procedure / Study Day	**Day -28 to Day -1**
Written informed consent	X
SID number assignment	X
Medical history	X
2016 ACR/EULAR Criteria for classification of SS	X
[redacted]	
ESSDAI	X
ESSPRI	X
Assessment of prior and concomitant medications	X
Verify eligibility criteria	X
Complete physical examination (including weight and height)	X
[redacted]	
ECG	X
Vital signs	X
Assessment of AEs/SAEs	X
Virology: Hepatitis B, C; HIV-1; HIV-2, SARS-CoV-2[b]	X
TB test (IGRA)[c]	X
Safety Lab Tests: Serum Chemistry, Hematology, Urinalysis	X
Baseline coagulation panel (prothrombin time, PTT)	X
Autoantibody panel (anti-SSA [Ro], anti-SSB [La], ANA)	X
[redacted]	
RF	X
[redacted]	
Chest X-ray[d]	X
Thyroid Function Tests (TSH, T3, T4, free T4)	X
Pregnancy test (serum β-hCG; females of childbearing potential only)	X
ActiGraph provided to subject (optional)	X

AE = adverse event; ANA = antinuclear antibodies; APL = antiphospholipid; β–hCG = beta-human chorionic gonadotropin; C = complement; ECG = electrocardiogram; ESSDAI = European League Against Rheumatism (EULAR) Sjögren's Syndrome Disease Activity Index; ESSPRI = EULAR Sjögren's Syndrome Patient Reported

Index; HIV = human immunodeficiency virus; IGRA = Interferon Gamma Release Assay; PTT = partial thromboplastin time; RF = rheumatoid factor; SAE = serious adverse event; SID = subject identification; SS = Sjögren's syndrome; TB = tuberculosis; TSH = thyroid stimulating hormone.

[redacted]

b To participate in study, subjects required a negative SARS-CoV-2 test within 2 weeks prior to randomization.
c IGRA not required during screening if performed within 12 weeks prior to screening visit with a documented negative result.
d Chest X-ray not required during screening if performed within 12 weeks prior to screening visit.

The schedules of study assessments for the active treatment period and for the off-treatment period are presented in Table 2 and Table 3, respectively.

Table 3 also summarizes all assessments that could be conducted at any unscheduled visit during the study.

Table 2 Schedule of Study Assessments During the Treatment Period

Visit number	**V2**	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9**	**V10**	**V11**	**V12**	**V13**
	Stage I							**Stage I/ Stage II[a]**	**Stage II**			
Study day Procedure	**1 Baseline**	**15 ± 1d**	**29 ± 3d**	**57 ± 3d**	**85 ± 3d**	**113 ± 3d**	**141 ± 3d**	**EP:169 ± 3d**	**197 ± 3d**	**225 ± 3d**	**253 ± 3d**	**281 ± 3d**
Verify eligibility criteria	X											
Randomization	X											
ESSPRI	X		X	X	X	X	X	X	X	X	X	X
[redacted]												
FACIT-Fatigue Questionnaire	X		X	X	X	X	X	X	X	X	X	X
[redacted]												
OSDI	X		X	X	X	X	X	X	X	X	X	X
[redacted]												
PGIS	X		X	X	X	X	X	X	X	X	X	X
[redacted]												
ESSDAI	X		X	X	X	X	X	X	X	X	X	X
Assessment of AEs/SAEs	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

Table 2 Schedule of Study Assessments During the Treatment Period

Visit number	**V2**	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9**	**V10**	**V11**	**V12**	**V13**
	Stage I							**Stage I/ Stage II[a]**	**Stage II**			
Study day Procedure	**1 Baseline**	**15 ± 1d**	**29 ± 3d**	**57 ± 3d**	**85 ± 3d**	**113 ± 3d**	**141 ± 3d**	**EP:169 ± 3d**	**197 ± 3d**	**225 ± 3d**	**253 ± 3d**	**281 ± 3d**
Full physical examination	X							X				X
Symptom-driven physical exam[b]		X	X	X	X	X	X		X	X	X	
Vital Signs (BP, HR, RR and temp)	X	X	X	X	X	X	X	X	X	X	X	X
ECG	X							X				
Weight	X							X				X
[redacted]												
Safety lab tests[c]	X	X	X	X	X	X	X	X	X	X	X	X
Urine pregnancy test in women of childbearing potential	X		X	X	X	X	X	X	X	X	X	X
Coagulation tests (prothrombin time, PTT)	X	X	X	X	X	X	X	X	X	X	X	X
Autoantibody panel[d]					X			X				
RF	X	X	X	X	X	X	X	X	X	X	X	X

Table 2 Schedule of Study Assessments During the Treatment Period

Visit number	**V2**	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9**	**V10**	**V11**	**V12**	**V13**
	Stage I							**Stage I/ Stage II[a]**	**Stage II**			
Study day Procedure	**1 Baseline**	**15 ± 1d**	**29 ± 3d**	**57 ± 3d**	**85 ± 3d**	**113 ± 3d**	**141 ± 3d**	**EP:169 ± 3d**	**197 ± 3d**	**225 ± 3d**	**253 ± 3d**	**281 ± 3d**
Inflammatory markers[e]	X	X	X	X	X	X	X	X	X	X	X	X
[redacted]												
ADA (plasma)	X		X		X			X	X		X	
[redacted]												
PK (plasma)	X[g]	X	X	X	X	X	X[g]	X[g]	X	X	X	X
[redacted]												

Table 2 Schedule of Study Assessments During the Treatment Period

Visit number	**V2**	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9**	**V10**	**V11**	**V12**	**V13**
	Stage I							**Stage I/ Stage II[a]**	**Stage II**			
Study day Procedure	**1 Baseline**	**15 ± 1d**	**29 ± 3d**	**57 ± 3d**	**85 ± 3d**	**113 ± 3d**	**141 ± 3d**	**EP:169 ± 3d**	**197 ± 3d**	**225 ± 3d**	**253 ± 3d**	**281 ± 3d**
[redacted]												
Qualitative Patient Interview (optional)[h]								X				
Administration of IP	X	X	X	X	X	X	X	X	X	X	X	X

ADA = anti-drug antibodies; AE = adverse event; ANA = antinuclear antibody; BP = blood pressure; C = complement; d = day(s); ECG = electrocardiogram; EP = endpoint; ESSDAI = EULAR Sjögren's Syndrome Disease Activity Index; ESSPRI = EULAR Sjögren's Syndrome Patient Reported Index; FACIT-Fatigue = Functional Assessment of Chronic Illness Therapy -Fatigue; HR = heart rate; IP = investigational product; OSDI = Ocular Surface Disease Index; [redacted]; PGIS = Patient Global Impression of Severity; PK = pharmacokinetic; [redacted] PTT = partial thromboplastin time; RF = rheumatoid factor; RR = respiratory rate; SAE = serious adverse event; [redacted]; V = Visit; [redacted].

Note: All laboratory sample collections and assessments on dosing day must be performed at pre-dose, unless specified otherwise.

a Day 169 is primary endpoint for Stage I and first day of IP administration for Stage II.

b If no symptoms are present, the exam can be limited to assess ESSDAI.

c Safety laboratory tests: Serum chemistry, hematology and urinalysis.

d Autoantibody panel: anti-SSA (Ro), anti-SSB (La), and ANA.

[redacted] 3

g Plasma sample for PK to be collected pre- and postdose (at the end of infusion).

h Telephone-based interview applicable to English-speaking subjects in the USA and UK only, and can be conducted anytime from Day 169 onwards.

Table 3 Schedule of Assessments During the Off-treatment Period and Any Unscheduled Visits

Visit number	**V14**	**V15 and EDV**	**Unscheduled Visit[a]**
	Off-treatment Period		
Study day Procedure	**D309 ± 7d**	**D365 ± 7d**	
ESSPRI	X	X	
[redacted]			
FACIT-Fatigue questionnaires	X	X	
[redacted]			
OSDI	X	X	
[redacted]			
PGIS	X	X	
[redacted]			
ESSDAI	X	X	
Assessment of AEs/SAEs	X	X	X
Concomitant medications	X	X	X
Full physical examination	X	X	
Symptom-driven physical exam[b]			X
Vital Signs (BP, HR, RR and temp)	X	X	X
ECG		X	
Weight	X	X	
[redacted]			
Safety lab tests	X	X	X
Urine pregnancy test	X	X	X

Table 3 Schedule of Assessments During the Off-treatment Period and Any Unscheduled Visits

Visit number	**V14**	**V15 and EDV**	**Unscheduled Visit[a]**
	Off-treatment Period		
Study day Procedure	**D309 ± 7d**	**D365 ± 7d**	
Coagulation tests	X	X	X
RF	X	X	
Inflammatory markers	X	X	
[redacted]			
ADA	X	X	
[redacted]			
PK (plasma)	X	X	
[redacted]			
ActiGraph collected from subject (optional)		X	

ADA = anti-drug antibodies; AE = adverse event; BP = blood pressure; C = complement; D = Day; d = days; ECG = electrocardiogram; EDV = early discontinuation visit; ESSDAI = EULAR Sjögren's Syndrome Disease Activity Index; ESSPRI = EULAR Sjögren's Syndrome Patient Reported Index; FACIT-Fatigue = Functional Assessment of Chronic Illness Therapy -Fatigue; HR = heart rate; OSDI = Ocular Surface Disease Index; [redacted]; PGIS = Patient Global Impression of Severity; PK = pharmacokinetic; RF = rheumatoid factor; RR = respiratory rate; SAE = serious adverse event; [redacted] V = Visit; [redacted]

a The assessments at any unscheduled visits may be adjusted as clinically indicated.
b If no symptoms are present, the exam can be limited to assess ESSDAI.
c Will not be collected in China.

The study assessments are described by study period in the following sections, with reference to the study schedules of assessment for details by study visit.

6.1 Sjögren's Syndrome Data Medical Review Team

The SS Data MR team members are medically qualified individuals who will review all SS data in conjunction with any other relevant data (including medical history, adverse event [AE], laboratory data, and concomitant medications as appropriate) that is necessary to characterize the subject's SS. The MR team members will have access to an expert on SS disease activity for unanticipated issues with regard to interpretation of these indices.

A separate procedure will outline the review and escalation details. The MR team will be utilized throughout the study to confirm classification of SS and ESSDAI scoring. The purpose of the review is to ensure medical plausibility, coherence, consistency, and clarity of data. The MR team will query any inconsistent scoring and follow for resolution of any discrepancy. The MR team will monitor trends in issues encountered during their review and liaise with the study team for additional training to be provided for the site staff or study monitoring team as appropriate. The MR team will remain blinded to the treatment assignment for individual subjects until the completion of the study.

6.2 Screening Procedures

6.2.1 Informed Consent

All screening procedures listed in Table 1 will be performed within 28 days prior to randomization.

Subjects officially enter the screening period following provision of informed consent either directly or via a legally authorized representative.

A screen failure is a consented subject who has been deemed ineligible on the basis of one or more eligibility criteria or who has withdrawn consent prior to treatment assignment. Screen failures may be rescreened with Medical Monitor approval.

A randomized subject is one who has been deemed eligible and has been assigned to a treatment group.

All candidates for enrollment or legally authorized representative will sign an ICF prior to any protocol-related procedures, including screening activities. Informed consent must be obtained by the Principal Investigator or a designee, such as an Investigator, with Institutional Review Board (IRB)-approved qualifications.

After signing the ICF, each subject will be assigned a subject identification (SID) number by the interactive voice/web response system (IXRS) that will be used on all subject documentation.

Numbers will be assigned in ascending sequential order. Rescreened patients will receive a new SID number. This number will also correspond to the subject number entered on test materials.

6.2.2 Demographics and Baseline Characteristics

Demographic information to be collected includes date of birth, sex, race and ethnicity. Medical history information to be collected includes all ongoing conditions and relevant/significant

medical history (including all major hospitalizations and surgeries), as determined by the Investigator. Prior and concomitant medications will be recorded. A complete physical examination, including weight, height, and [redacted] will be conducted.

The 2016 ACR/EULAR Criteria will be used for classification of SS for both Population #1 and Population #2, as confirmed by the MR team (Section 6.1). The classification of SS will apply to any individual who meets the inclusion criteria, does not have any condition listed as an exclusion criterion, and who has a score ≥ 4 when summing the weights from the items listed in Appendix 1. Eligibility related to ESSDAI scores for Population #1 will also be confirmed by the MR team.

Whole [redacted] will be conducted at screening to determine study eligibility. See Section 6.4.1 (Efficacy Assessments) for details on these assessments. ESSDAI-required blood tests will be conducted.

Additionally, an autoantibody panel, which includes RF will be collected. See Section 6.4.3.1 for details.

Safety-related screening assessments will include AEs, safety laboratory tests (serum chemistry, hematology, and urinalysis), coagulation parameters, chest X-ray, thyroid function tests, and serum beta-human chorionic gonadotropin (β-hCG) pregnancy test for females of childbearing potential. For details on safety assessments, see Section 6.4.2 and 8.

6.2.3 Re-screening Procedures

Abnormal laboratory values meeting exclusion criteria may be re-tested during the screening period without this being considered re-screening. Subjects may be rescreened once if, in the Investigator's judgment, the reason for ineligibility is likely to have resolved at the time of rescreen.

[redacted]

6.3 Randomization

Prior to randomization, subject eligibility must be confirmed by the MR team (see Section 6.1). Subjects who meet all eligibility criteria, including confirmation of eligibility by the study MR review team, will be randomized. A subject is considered randomized into the study when the Investigator notifies the IXRS that the subject meets eligibility criteria and the IXRS provides the assignment of treatment group and allocates treatment, including IP kit number (Day 1, Baseline [Table 2]). To ensure balanced rates of enrollment for the 2 populations, the Sponsor will implement a procedure where enrollment of subjects in Population #2 at each site is linked to enrollment of Population #1 subjects at the site with a progressively increasing ratio of

Population #2:Population #1 subjects. At least one subject of the first 2 randomized at each site must be from Population #1.

For details on the MR procedure, see Section 6.1.

6.4 Treatment Period

All assessments that will be conducted during Stage I and Stage II of the treatment period are summarized by study visit in Table 2. Efficacy assessments are described in Section 6.4.1 and safety assessments are described in Section 6.4.2.

The primary endpoint assessments will be conducted on Day 169 (Visit 9) of Stage I of the active treatment period.

6.4.1 Efficacy Assessments

Some of the efficacy assessments are patient-reported outcomes (PRO) instruments. PRO instruments will be administered electronically and will be completed at the site.

To ensure data integrity the following best practice guidelines should be followed:

- Always administer PRO instruments before other study procedures.
- Provide the subject with a quiet and private location to complete the instrument.
- Remind subjects that there are no right or wrong answers and the reason they are being asked to complete these questionnaires is because we are interested in hearing directly from them as to how they feel.

Assist subjects only with procedural questions, such as what it means to "tick a box" and do not clarify the meaning of questions to avoid bias. Subjects should be told to select the response that best answers the question as they understand it.

Subject should be given as much time as is needed to complete the questionnaires.

Promptly review the questionnaires for completeness and provide an opportunity for the subject to answer if an item is left blank.

6.4.1.1 ESSDAI

The ESSDAI is a systemic disease activity index that includes organ-by-organ definitions of disease activity (Seror et al, 2010). The ESSDAI grades disease activity in 12 domains (cutaneous, respiratory, renal, articular, muscular, peripheral nervous system, central nervous system, hematological, glandular, constitutional, lymphadenopathic, and biological). The weights of each domain were obtained by multiple regression modeling, using the Physician's Global Assessment of Activity as gold standard.

Each domain is weighted from 1 (Biologic domain) to 6 (Muscular domain) and has 3 or 4 levels of activity per domain, ranging from 0 (no activity) to 3 (high activity).

The theoretical range of values for the ESSDAI is 0 to 123, with the final score being calculated as follows:

Final Score = Sum of all 12 domain scores
Domain score = Activity level × Domain weight

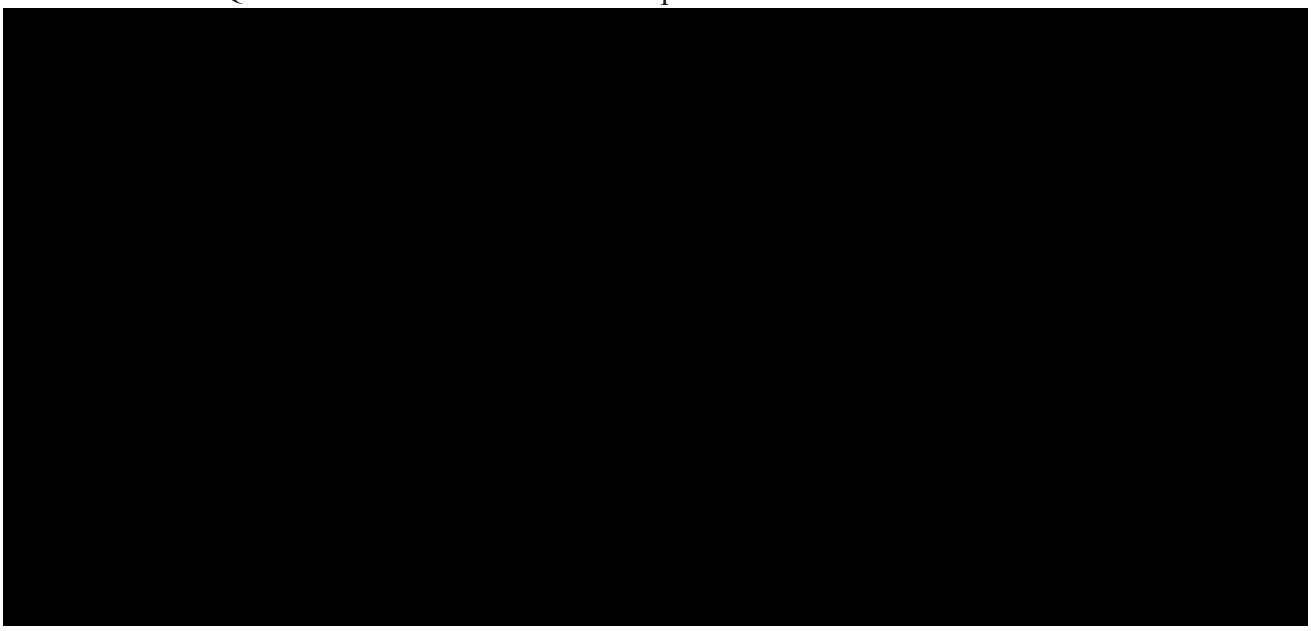
Low activity status is defined as ESSDAI < 5, moderate activity as 5 ≤ ESSDAI ≤ 13 and high activity as ESSDAI ≥ 14 (Seror et al, 2016a). The MR team described in Section 6.1 will confirm disease activity based on ESSDAI at key time points during the study.

6.4.1.2 ESSPRI

ESSPRI is a self-evaluation tool that was developed in a multicenter international cohort of 230 patients (Seror et al, 2011). The ESSPRI uses a 0 to 10 numerical analog scale (ranging from 0 [no symptoms] to 10 [maximal imaginable severity]), one for the assessment of each of the 3 domains: dryness, fatigue, and pain (articular and/or muscular). The weights of the domains are identical, and the mean of the scores of the 3 domains represents the final score. The recall period is stated in each question as "the last 2 weeks." The instrument can be completed in approximately 1 minute.

6.4.1.4 Functional Assessment of Chronic Illness Therapy (FACIT)-Fatigue

The FACIT-Fatigue is a 13-item questionnaire, subject-completed, used to assess the impact of fatigue. Its recall period is 7 days. The responses range from 0 (Not at all) to 4 (Very Much). To calculate the total score, the negatively stated items are reversed by subtracting the response from "4". Final scores are the sum of the responses and range from 0 to 52. Higher scores indicate better QoL. It takes 5-10 minutes to complete.



6.4.1.7 Ocular Surface Disease Index (OSDI)

OSDI is a valid and reliable instrument for assessing effect on vision-related function and dry eye disease severity (normal, mild, moderate, and severe). Its recall period is 1 week. It is composed of 12 questions that the physician asks the subject and circles the number that best represents each question. The responses for each question range from 0 (None of the time) to 4 (All of the time). The OSDI score is calculated as (sum of scores for questions answered)/(number of questions answered)×25, which ranges from 0 to 100 with higher scores signifying greater disability. The assessment can be completed in 5 minutes.

[redacted]

6.4.1.9 Patient Global Impression of Severity

The PGIS is a single item designed to capture the subject's perception of overall symptom severity over the past week on a 5-point categorical response scale (none, mild, moderate, severe, or very severe).

[redacted]

[redacted]

[redacted]

6.4.1.14 ClinESSDAI

ClinESSDAI is a validated SS disease activity index, based on ESSDAI that excludes the biological domain and assigns different weights assigned to each domain. ClinESSDAI was developed in an effort to diminish possible associations between the B-cell biomarkers measured by the ESSDAI biological domain and clinical activity measures (Seror et al, 2016b). The theoretical range of values for the ClinESSDAI is 0 to 135, and similar to ESSDAI, low-activity status is defined as < 5, moderate-activity as 5 ≤ ClinESSDAI ≤ 13 and high-activity as ≥ 14 (Seror et al, 2016a). ClinESSDAI has been validated and shown to correlate well with ESSDAI and is considered a useful tool to detect change independent of biological effect of the drug (Seror et al, 2016b; Dumusc et al, 2018; Quartuccio et al, 2017).

6.4.2 Safety Assessments

Safety assessments will be conducted during the active treatment period according to the assessments shown in Table 2 and will consist of:

- Monitoring and recording all AEs (including AESIs) and SAEs (see Section 8.1 through 8.4 for details)
- Safety laboratory tests (serum chemistry, hematology, and urinalysis [see Section 8.5 for details])
- Concomitant medications
- Vital signs, physical examination (full or symptom-driven depending on the visit), and weight
- ECG
- Urine pregnancy test (for females of childbearing potential)
- Coagulation tests

6.4.3 Additional Disease-related Assessments

The assessments related to SS described in the following sections will be conducted according to the schedules shown in Table 2 (treatment period) and Table 3 (off-treatment period).

6.4.3.1 Autoantibody Panel

Serum will be collected to assess the presence of anti-SSA (Ro), anti-SSB (La), antinuclear antibodies, and RF.

6.4.3.2 Inflammatory Markers

Whole blood, plasma, serum, and urine will be collected to assess levels of plasma immunoglobulins (IgM, IgG, and IgA), beta-2 microglobulin, high sensitivity CRP, C3, C4, serum free light chains, cryoglobulins, and serum and urine immunofixation.

[redacted]

6.4.4 Immunogenicity Assessments

Plasma samples for immunogenicity (ADA to VIB4920) will be taken prior to drug administration according to the visits specified in Table 2 (treatment period) and Table 3 (off-treatment period) and assessed using a validated immunoassay.

6.4.5 Pharmacokinetic Assessments

Plasma samples to determine the concentration of VIB4920 will be taken according to the visits specified in Table 2 (treatment period) and (Table 3) (off-treatment period) using a validated assay.

6.5 Off-treatment Period

The off-treatment period will comprise 12 weeks following the last dose of IP and includes Visit 14 and Visit 15 (or EDV in the event of premature discontinuation from the study). All procedures to be conducted at the Off-treatment visits are listed in Table 3.

Efficacy assessments to be conducted at the off-treatment visits will include: Patient Global Impression of Severity, Patient Global Impression of Change, ESSPRI, [redacted] FACIT-Fatigue, [redacted], OSDI, [redacted], and [redacted]. Details on these assessments are presented in Section 6.4.1.

Safety assessments will include: AEs/SAEs, concomitant medications, full or symptom-driven physical examination, vital signs, ECG, weight, and safety laboratory tests. For details of these assessments, see Section 8.

Additional disease-related assessments will be conducted as shown in Table 3 and are described in Section 6.4.3.

The [redacted] device will be collected at the last patient visit or the EDV, whichever is later (Table 3).

6.6 Discontinuation or Withdrawal

6.6.1 Discontinuation of Treatment

IP must be discontinued if the Investigator determines that continuing it would result in a significant safety risk for that subject. Reasons for study drug discontinuation are or can be:

1. Withdrawal from the study (due to withdrawal of consent or noncompliance with study procedures), as described in Section 6.6.2.

2. Withdrawal of consent from further treatment with IP.
3. Receipt of restricted medication, as described in Section 7.4.2 for Population #1 and Section 7.4.4 for Population #2.
4. Receipt of rescue medication for increased disease activity may lead to discontinuation of IP, as described in Section 7.4.3 for Population #1 and Section 7.4.5 for Population #2.
5. AE or significant laboratory abnormality that, in the opinion of the Investigator and/or the Sponsor, warrants discontinuation of further dosing.
6. Pregnancy or a decision to become pregnant.
7. Any Grade ≥ 3 TEAE that is considered to be related to IP by the Investigator, unless in the opinion of the Investigator, the event(s) are manifestations of SS (eg, within the definitions included in the ESSDAI). Isolated Grade ≥ 3 laboratory abnormalities without a clinical event meeting the above criteria will not automatically lead to discontinuation of IP.
8. Any of the following liver function abnormalities:
    a. ALT or AST > 8 × ULN;
    b. ALT or AST > 5 × ULN for more than 2 weeks;
    c. ALT or AST > 3 × ULN and bilirubin > 2 × ULN or international normalized ratio (INR) > 1.5; see Appendix 3 for additional details regarding reporting of subjects with ALT or AST > 3 × ULN and bilirubin > 2 × ULN with unknown etiology (ie, Hy's law [HL] cases).
9. Anaphylaxis or a serious hypersensitivity reaction attributed to VIB4920.
10. Any life-threatening or serious infection or opportunistic infection.
11. Malignancy.
12. Any other reason when the Investigator determines that continuing IP would result in a significant safety risk for that subject.

Subjects who prematurely discontinue IP before Day 169 will undergo scheduled evaluations until Day 169 visit and at least 3 months of off-treatment follow-up after the last IP administration, at which time they will undergo an EDV. They will not be eligible for treatment during Stage II.

Subjects who prematurely discontinue IP after Day 169, while in Stage II, will undergo scheduled evaluations until the end of the off-treatment period (Day 365) or complete at least 3 months of off-treatment follow-up after the last IP administration, at which time they will have an EDV. An IP discontinuation form should be completed, giving the date and primary reason for stopping study treatment.

6.6.2 Withdrawal from Study

For subjects who withdraw prematurely from the study (eg, due to withdrawal of consent or noncompliance with study procedures), the reason(s) for withdrawal must be recorded on the appropriate page of the electronic case report form (eCRF). If possible, any subject who is

withdrawn from the study will have, at the time of withdrawal, all exit procedures performed (ie, Day 365 safety and efficacy assessments). All clinically significant abnormalities will be followed-up, if possible, until resolved to the satisfaction of the Investigator.

6.6.3 Replacement of Subjects

Subjects will not be replaced after randomization.

6.6.4 Subjects Lost to Follow-up

For subjects who are lost to follow-up (ie, those subjects whose status is unclear because they fail to appear for study visits without stating an intention to withdraw), the Investigator should show "due diligence" by documenting in the source documents steps taken to contact the subject, eg, dates of telephone calls, registered letters, etc.

6.7 Study Suspension or Termination

The Sponsor reserves the right to temporarily suspend or terminate this study at any time. The reasons for temporarily suspending or terminating the study may include but are not limited to the following:

- The incidence or severity of AEs indicates a potential health hazard to subjects.
- Subject enrollment is unsatisfactory.
- Noncompliance that might significantly jeopardize the validity or integrity of the study.
- Sponsor decision to terminate development.

Additional guidance is provided in the Safety and Data Monitoring Committee (SDMC) Charter.

If Sponsor determines that temporary suspension or termination of the study is required, Sponsor will communicate the reasons for taking such action with all participating Investigators (or head of the medical institution, where applicable). When feasible, Sponsor will provide advance notice to all participating Investigators (or head of the medical institution, where applicable) of the impending action.

If the study is suspended or terminated for safety reasons, Sponsor will promptly inform all Investigators, heads of the medical institutions (where applicable), and/or institutions conducting the study. Sponsor or designee 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 or head of the medical institution must inform the IRB/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.

6.8 End of Study

Once a subject has completed all assessments listed for Visit 15 (Day 365 ± 7 days), the subject will be considered to have completed the study. The study will be completed once the last subject out has completed all Visit 15 or EDV assessments (Day 365 ±7 days; shown in Table 3).

7 STUDY INTERVENTIONS

7.1 Description of Products

Table 4 provides a description of IP to be used in the study. Details are presented in the following sections.

Table 4 Description of Investigational Products

Product	Dose	Frequency	Route	Duration	Manufacturer
VIB4920	1500 mg	Stage I: Q2W x 3 Q4W x 4 Stage II: Q4W x 5	IV	Up to 169 days	MedImmune, LLC
VIB4920 Placebo	0.9% (w/v) saline	Stage I: Q2W x 3 Q4W x 4 Stage II: Q4W x 5	IV	Up to 169 days	Provided by site

IV = intravenous; Q2W = once every 2 weeks; Q4W = once every 4 weeks; w/v = weight/volume.

7.1.1 VIB4920

7.1.1.1 Formulation, Storage, Preparation, and Handling

VIB4920 is formulated at 100 mg/mL VIB4920 in [redacted] mM sodium phosphate buffer, [redacted] mM sucrose, [redacted]% (weight/volume [w/v]) poloxamer 188, pH [redacted]. The nominal volume in each vial is 5.0 mL. VIB4920 is a sterile liquid Drug Product (500 mg VIB4920 per vial, nominal) intended for IV infusion following dilution in normal saline.

The IP will be appropriately labeled in accordance with national laws and regulations. VIB4920 is provided with 3 vials per kit.

VIB4920 should not be shaken and requires no special biohazard handling. It must be stored at [redacted] in refrigerator with adequate temperature monitoring. VIB4920 must not be frozen. It should be stored in the original outer package in a location with limited access.

Each vial selected for dose preparation should be inspected. If there are any defects noted with the VIB4920, the Investigator and site monitor should be notified immediately.

7.1.1.2 Dose Preparation

VIB4920 is supplied as a sterile liquid in a 6R glass vial at a nominal fill volume of 5.0 mL, stoppered with 20 mm Teflon-coated elastomeric stopper, and sealed with flip-off cap overseal.

No incompatibilities between VIB4920 and the components recommended for IV infusion (ie, polyolefin IV bags for IV infusion, non-diethylhexyl phthalate infusion lines, and syringes used for dose preparation) have been observed.

VIB4920 does not contain preservatives and any unused portions must be discarded. Preparation of IP and IV bags is to be performed aseptically.

Prepared VIB4920 IV Bags may be stored refrigerated at 2-8°C for up to 24 hours and/or at room temperature for up to 4 hours. The total allowable in-use storage time from the time of the first vial puncture of VIB4920 to IV bag administration is 24 hours.

DO NOT FREEZE. If storage time exceeds these limits, a new dose must be prepared from new vials.

Three vials, one 250 mL IV bag containing 0.9% (w/v) saline (weight/volume [w/v]), and one IV infusion pump is required for administration of each 1500 mg dose of VIB4920.

The dose preparation steps are as follows:

- For each 1500 mg IV dose, 15.0 mL of 0.9% (w/v) saline should be removed from a prefilled 250 mL IV bag.
- 15.0 mL of VIB4920 will be obtained from three (3) 500 mg vials by withdrawing 5.0 mL from each vial. Use a new needle for each withdrawal.
- IP should be added to the saline bag.
- Gently mix the contents of the IV bag. The saline bag should then be inspected to ensure the solution is clear.
- Prepared bags will be covered to protect blinding.

During preparation of the IP for infusion, the capacity of the tubing should be calculated in order to adjust the volume of IP solution needed to prime the IV tubing. This step is also necessary because the same volume of saline will be needed to flush the IV tubing at the completion of the infusion in order to deliver the complete volume of IP solution. Because the IV tubing contains IP solution, the saline flush must be infused using the same infusion rate as that used for the IP solution in the infusion bag.

For example, if the IV tubing capacity is 15 mL, the IV tubing should be primed with 15 mL of IP solution from the infusion bag before initiating the infusion. Once the infusion bag is empty, the IV tubing should be flushed with at least 15 mL of 0.9% (w/v) saline via the infusion pump at the same rate as dosing. The start time of the infusion will be the time when infusion of the IP solution from the infusion bag (with IV tubing primed with IP solution) is started. The stop time of the infusion will be the time when the IV tubing has been flushed with a volume of 0.9% (w/v) normal saline equivalent to IV tubing capacity (eg, 15 mL for the example above) to administer the residual IP solution.

7.1.1.3 Dosing and Administration

Both Populations #1 and #2 will receive the following treatment regimen:

- Treatment group 1 will receive 1500 mg VIB4920 as an IV infusion, Q2W x 3, then Q4W for 4 additional doses (Stage I). Starting on Day 169 subjects will receive placebo Q4W for 5 doses (Stage II).
- Treatment group 2 will receive placebo as an IV infusion Q2W x3, then Q4W for 4 additional doses (Stage I). Starting on Day 169 subjects will receive VIB4910 1500 mg Q4W for 5 doses (Stage II).

An experienced and qualified staff member will place the IV access.

IP will be infused using an IV infusion pump. During Stage I each subject must receive the entire volume of IP solution in the IV bag over at least 90 minutes (approximately 2.8 mL/min). IP must be infused through a low-protein binding 0.2- or 0.22-line filter. Vital signs will be obtained prior to the start of each IP infusion. For Stage II, infusions can be administered over at least 60 minutes (approximately 4.2 mL/min).

A physician must be present at the site or immediately available to respond to emergencies during administration of IP. Fully functional resuscitation facilities should be available.

Further information on IP preparation and administration is provided in the IP Manual.

7.1.1.4 Peri- and Post-Administration Observations

On the first 2 dosing days of both Stage I (Day 1 and Day 15) and Stage II (Day 169 and Day 197) vital signs will be measured within 30 minutes prior to the start of infusion, every 30 minutes (± 5 minutes) during the infusion, at the end of the infusion (+ 5 minutes), then at 1 hour and 2 hours after the end of infusion (± 10 minutes). On subsequent dosing days, vital signs will be measured within 30 minutes prior to the start of infusion, every 30 minutes (± 5 minutes), at the end of the infusion (+ 5 minutes) and 30 minutes after the end of the infusion (± 5 minutes). At the end of these observation periods, subjects can be discharged if they are stable.

7.1.1.5 Investigational Product Accountability

The study IXRS system will be used by clinical sites to acknowledge receipt of study drug. Damaged shipments will be replaced. Study site staff will maintain a record of the IP received, dispensed, administered, and destroyed. All records will be maintained with controlled access. An unblinded study monitor will perform drug accountability and compliance monitoring during the study. The Investigator will administer the study product only to subjects included in this study and according to the procedures established in this clinical study protocol. Each administration of study product will be documented and transferred to the eCRF.

7.1.1.6 VIB4920 Handling and Disposal

The Investigator or designee must return any unused vials of VIB4920 to Sponsor or designee regardless of whether the study was completed or terminated prematurely. At the time of return, the Investigator must verify that unused or partially used study products have been returned and that no study products remain at the site. As an alternative to returning unused study product at the end of the study, the Investigator may destroy unused study medication on site with agreement from Sponsor.

7.1.2 Placebo

7.1.2.1 Formulation, Storage, Preparation and Handling

Placebo will be 0.9% (w/v) saline provided by the site as 250 mL prefilled IV bags.

7.1.2.2 Dosing and Administration

For each dose of placebo, one 250 mL IV bag containing 0.9% (w/v) saline (weight/volume [w/v]) and one IV infusion pump is required for administration.

7.2 Treatment Assignment and Bias Minimization

7.2.1 Treatment Allocation

Subjects will be randomized in a 1:1 ratio to receive either VIB4920 or placebo.

IP (VIB4920 or placebo) must be administered the same day the IP is assigned. If there is a delay in the administration of IP such that it will not be administered within the specified timeframe, the study monitor must be notified immediately.

7.2.2 Randomization Strategy and Procedure

An IXRS will be used for randomization to a treatment group and assignment of IP kit numbers. A subject is considered randomized into the study when the Investigator notifies the IXRS that the subject meets eligibility criteria and the IXRS provides the assignment of treatment group.

Additional details will be provided in the IXRS Manual.

7.2.3 Extent and Maintenance of Blinding

This is a double-blind study in which VIB4920 and the saline placebo are not identical in appearance. For maintaining the blinding of the subjects, Investigator, site staff, Sponsor, Contract Research Organization and staff, a local unblinded pharmacy staff member will be nominated by each site and will have the responsibility of allocating, dispensing and preparing the IP, and covering the IV bags. In addition, a separate unblinded monitor will be used for the oversight of IP management. If treatment allocation for a subject becomes known to the Investigator or other study staff involved in the management of study subjects, the Sponsor must be notified immediately.

7.2.4 Unblinding Procedures

7.2.4.1 Unblinding in the Event of a Medical Emergency

In the event of a medical emergency, the Investigator may unblind an individual subject's IP allocation. Instructions for unblinding an individual subject'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 subject having received IP. In the majority of cases, the management of a medical emergency would be the same whether or not IP was received by the subject. If this was the case, the IP allocation should not be unblinded.

7.2.4.2 Unblinding for Interim Analysis and Primary Analysis

An interim analysis will be conducted for each population after all subjects have completed the Day 85 visit for that population, and the primary analysis will be conducted for each population after all subjects have completed the Day 169 visit for that population (see Section 10.6). To ensure the blinding of each subject's treatment assignment throughout the study, both the interim

analysis and the primary analysis will be performed by a limited number of Sponsor personnel who are not involved in the conduct of the study. Study site personnel, subjects, and Sponsor personnel directly associated with the conduct of the study will remain blinded to the treatment assignment for individual subjects until the completion of the study. Any communications of unblinded results will be documented in an unblinding memo. Population-based treatment group level results may be released after completion of primary analysis.

7.3 Assessment and Verification of Compliance

Site staff will administer all IPs IV at the study center. The dose and date of administration of IP must be recorded in the subject eCRF. Treatment compliance will be assessed based on this information.

7.4 Prohibited and Restricted Therapies

Medications that are considered necessary for the safety and well-being of subjects may be given at the discretion of the Investigator, and recorded in the appropriate section of the eCRF. Use of treatments listed below may lead to IP discontinuation. Subjects should not start taking any of the following without discussing with the Investigator:

1. Naturopathic, herbal, or ayurvedic remedies.
2. Nutritional or dietary supplements
3. Vitamins and/or minerals.

7.4.1 Medications Leading to Immediate Discontinuation of Investigational Product for Both Populations

Receipt of any of these medications leads to immediate discontinuation of IP:

- Investigational agents
- Immunosuppressants with the exceptions listed below
- Biologic immunomodulators (including belimumab, abatacept, rituximab)
- Live or attenuated vaccines (the Sponsor recommends that Investigators ensure all subjects are up-to-date with required vaccinations prior to entry into the study)
- Plasmapheresis/Plasma exchange
- Any Ig therapy
- Corticosteroids > 0.5 mg/kg/day or > 40 mg/day prednisone-equivalent

7.4.2 Restricted Medications in Population #1

If a subject receives any of the following after randomization, the Investigator must notify the Sponsor/Designee Medical Monitor immediately. The Medical Monitor will determine with the Sponsor if the subject may continue to receive IP, however, the subject would be considered a non-responder for binary assessments.

- AZA > 150 mg/day, MTX > 20 mg/week, leflunomide >40 mg/day, MMF > 2gm/day, hydroxychloroquine > 400 mg/day OR any increase from baseline (including initiation of treatment)
- Prednisone > 10 mg/day OR any increase from baseline (including initiation of treatment)

- Initiation of any new cDMARD
- Corticosteroids with a long biologic half-life (eg, dexamethasone, betamethasone)

7.4.3 Rescue Medications for Population #1

The initiation or increase in dose of the restricted medications in Section 7.4.2 are also considered as rescue medications for Population #1.

7.4.4 Restricted Medications in Population #2

If a subject receives any of the following after randomization, the Investigator must notify the Sponsor/Designee Medical Monitor immediately. The Medical Monitor will determine with the Sponsor if the subject may continue to receive IP, however, the subject would be considered a non-responder for binary assessments.

- Oral, intramuscular, IV, or intra-articular corticosteroids
- MTX, AZA, leflunomide MMF, and other cDMARD or immunosuppressive or antiproliferative medications.
- Any medication that in the opinion of the Investigator would interfere with evaluation of the IP or interpretation of subject safety or study results
- Any increase or initiation of new doses of cevimeline or pilocarpine and cyclosporine eye drops (Restasis).

7.4.5 Rescue Medications for Population #2

The initiation or increase in dose of the restricted medications in Section 7.4.4 are also considered as rescue medications for Population #2.

8 SAFETY ASSESSMENT

An 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 12.1 for details on SDMC activities.

8.1 Definitions

- **Adverse event** – 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** – An SAE 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 patient or subject at immediate risk of death. It does not include an AE or suspected adverse reaction (SAR) 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 patient or subject 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.

- **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 [AR] 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 product under investigation (ie, there are facts, evidence, or arguments to suggest possible causation).

- **Adverse reaction** – An AR is any AE caused by a drug.

- **Suspected adverse reaction (SAR)** – An SAR is any AE for which there is a reasonable possibility that the drug caused the AE. For the purposes of Investigational New Drug safety reporting, "reasonable possibility" means there is evidence to suggest a causal relationship between the drug and the AE. SAR implies a lesser degree of certainty about causality than AR.

- **Unexpected** – An event is considered unexpected if it is not listed in the Investigator's Brochure (IB), is not listed at the specificity or severity that has been observed, or, if an IB is not required or available, is not consistent with the risk information described in the General Investigational Plan or elsewhere in the IND. Unexpected also refers to events that are mentioned in the IB as occurring with a class of drugs or as anticipated from the pharmacological properties of the drug but are not specifically mentioned as occurring with the particular IP.

- **Severity or intensity**:

Severity will be assessed according to the following scale:

- Grade 1: An event of mild intensity that is usually transient and may require only minimal treatment or therapeutic intervention. The event does not generally interfere with usual activities of daily living.
- Grade 2: An event of moderate intensity that is usually alleviated with additional, specific therapeutic intervention. The event interferes with usual activities of daily living, causing discomfort but poses no significant or permanent risk of harm to the subject.
- Grade 3: A severe event that requires intensive therapeutic intervention. The event interrupts usual activities of daily living, or significantly affects the clinical status of the subject.
- Grade 4: An event, and/or its immediate sequelae, that is associated with an imminent risk of death or with physical or mental disabilities that affect or limit the ability of the subject to perform activities of daily living (eating, ambulation, toileting, etc).
- Grade 5: Death (loss of life) as a result of an event.

8.2 Documenting Adverse Events

AEs spontaneously reported by the subject and/or in response to an open question from the study personnel or revealed by observation will be recorded during the study at the investigational site. 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 or not it caused the subject to discontinue the study. The AE term should be reported in standard medical terminology when possible.

8.3 Reporting Adverse Events

All AEs (related and unrelated) will be recorded from written ICF signature up to the end of the off-treatment period, whether or not they are related to the study. Any SAEs considered related to the IP and discovered by the Investigator at any time after the study should be reported.

All SAEs must be reported within 24 hours by submitting a SAE Report Form by email to:

ICON Patient Safety
Email: icon-mads@iconplc.com

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

ICON Patient Safety
Fax: 1-215-616-3096

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 SAE form, placed with the original SAE information and kept with the appropriate section of the eCRF and/or study file.

The designated Sponsor representative (ICON) 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 or designee is responsible for notifying the relevant regulatory authorities of certain events. It is the Principal Investigator's responsibility to notify the IRB or IEC of all SAEs that

occur at his or her site. Investigators will also be notified of all unexpected, serious, drug-related events (7/15 Day Safety Reports) that occur during the clinical trial. Each site is responsible for notifying its IRB or IEC of these additional SAEs.

8.4 Adverse Events of Special Interest

An AESI is one 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 (see the Safety Handling Plan for instructions and timing on completing any additional information required for specific types of events related to the categories noted below):

- Thrombotic and embolic events
- Hepatic function abnormality (meeting the definition of HL) (see Appendix 3) for details)
- Anaphylaxis and clinically significant (Grade 3 or higher) hypersensitivity reactions (see Appendix 2 for guidance on diagnosis of anaphylaxis reactions)
- Severe Infusion-related reactions (Common Terminology Criteria for Adverse Events (CTCAE) Grade 3 or higher).

  Severity will be assessed according to CTCAE v5

  - Grade 1: Mild transient reaction; infusion interruption not indicated; intervention not indicated.
  - Grade 2: Therapy or infusion interruption indicated but responds promptly to symptomatic treatment (eg, antihistamines, NSAIDS, narcotics, IV fluids); prophylactic medications indicated for ≤ 24 hours
  - Grade 3: Prolonged (eg, not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for clinical sequelae
  - Grade 4: Life-threatening consequences; urgent intervention indicated

- Malignant neoplasm
- Immune complex disease
- Infections:

  - Clinically significant (Grade 3 or higher)
  - Opportunistic infections including but not limited to reactivation of latent viral infection, invasive fungal infections, and TB

8.5 Clinical Laboratory Findings

Blood and urine samples will be collected for laboratory safety tests as specified in the Schedule of Assessments shown in Table 1 (screening), Table 2 (during the treatment period [Stages I and II]), and Table 3 (off-treatment period). Laboratory testing is described below. For further details regarding laboratory assessments see the Study Laboratory Manual.

8.5.1 Hematology

The hematology panel will include a complete blood count, with differential (including basophils, eosinophils, lymphocytes, monocytes, and neutrophils), hemoglobin, hematocrit, platelets and white blood cell count.

8.5.2 Serum Chemistry

Chemistry and Renal Profile:

- Creatinine, blood urea nitrogen, fasting glucose, total protein, creatine kinase and electrolytes (including sodium, potassium, chloride, calcium, bicarbonate, and phosphorus)

Hepatic Profile:

- Albumin, TBL, indirect bilirubin, AST, ALT, alkaline phosphatase (ALP), and gamma-glutamyltransferase.

8.5.3 Immunoglobulins

- Total immunoglobulins, IgA, IgG, and IgM.

8.5.4 Coagulation Parameters

Subjects will be evaluated for prothrombin time and PTT during screening and at all study visits during the treatment and off-treatment periods (Table 2 and Table 3, respectively).

8.5.5 Urinalysis

The urinalysis will include protein, glucose, blood, ketones, leukocytes, and pH by dipstick analysis. Microscopy (crystals, casts, white blood cells, red blood cells) will also be performed if any abnormalities are observed.

8.5.6 Testing for SARS-CoV-2

The investigator must ensure that the subject has a documented negative SARS-CoV-2 viral test within 2 weeks prior to randomization. Testing for antibodies to SARS-CoV-2 will not meet the testing requirement.

8.6 Vital Signs

Vital signs including systolic and diastolic blood pressure (mmHg), pulse rate (beats/min), respiratory rate (breaths/min), body temperature (ºC) and body weight (kg) will be measured using clinically acceptable methods and devices as defined in the schedule of assessments in Table 1 (screening), Table 2 (treatment period), and Table 3 (off-treatment period) and the IP Administration manual.

Section 7.1.1.4 describes the frequency of vital sign observations prior, during and post infusion.

8.7 Electrocardiogram

A 12-lead ECG will be performed according to the schedule of assessments in Table 1 (screening), Table 2 (treatment period), and Table 3 (off-treatment period). Each ECG will

include ventricular heart rate and intervals (PR, QRS, QT, QTc). The Investigator will be responsible for providing an interpretation of the ECGs in terms of clinical significance to the subject (ie, normal, abnormal but not clinically significant, abnormal and clinically significant.). Any abnormalities and clinical significance will be entered on the eCRF.

8.8 Pregnancy

Serum β-hCG pregnancy test(s) will be completed for all females of childbearing potential during the screening period (before Day 0) and by urine pregnancy test at the visits in the Schedule of Assessments in Table 2 (treatment period) and Table 3 (off-treatment period).

8.9 Overdose or Misuse

Any instance of overdose (suspected or confirmed and irrespective of whether or not it involved VIB4920) must be communicated to Sponsor or a specified designee within 24 hours and be fully documented as an SAE. Details of any signs or symptoms and their management should be recorded including details of any antidote(s) administered.

8.10 Contacting Sponsor Regarding Urgent Protocol-related Medical Questions

In the event of a study-related health emergency (when assigned Medical Monitors for a study cannot be reached by a caller for discussion of urgent protocol-related medical questions), an on-call physician can be reached 24 hours per day, 7 days per week via an ICON Call-Center:

- Telephone: +1 857 957 5013 (global reachable number)
- https://icophone.iconplc.com/24-7-Medical.pdf

On this internet page, a list of country-specific contact numbers is provided. Countries not listed here need to dial the global reachable number as indicated above. Furthermore, there may be restrictions when dialing a country-specific number from a mobile phone.

9 OTHER ASSESSMENTS

9.1 Qualitative Patient Interviews (optional)

In the USA and UK, a subset of English-speaking patients will be asked to participate in a telephone-based qualitative interview after completing protocol Day 169. The overall objective of these interviews is to gather additional information about patients' experiences with SS and its treatment. Although not intended as a formal study assessment, the qualitative interviews aim to collect additional contextual information from the patient perspective that can further inform the formal efficacy and safety assessments detailed in Sections 6.4.1 and 6.4.2. Specific details regarding the methods used to conduct these qualitative patient interviews will be provided to the IRBs/IECs of the participating countries (USA and UK) as a separate appendix to the protocol.

Participation in the qualitative patient interview is optional and will only be conducted after obtaining specific consent from interested subjects.

10 STATISTICAL CONSIDERATIONS

10.1 General Considerations

Tabular summaries will be presented by treatment group. Categorical data will be summarized by the number and percentage of subjects in each category. Continuous variables will be summarized by descriptive statistics. Additional details of statistical analyses will be described in the statistical analysis plan (SAP).

10.2 Statistical Hypotheses

Population #1:

- Null hypothesis: the mean change from baseline in ESSDAI score at Day 169 for the VIB4920 group is equal to that for the placebo group.
- Alternative hypothesis: the mean change from baseline in ESSDAI score at Day 169 for the VIB4920 group is not equal to that for the placebo group.

Population #2:

- Null hypothesis: the mean change from baseline in ESSPRI score at Day 169 for the VIB4920 group is equal to that for the placebo group.
- Alternative hypothesis: the mean change from baseline in ESSPRI score at Day 169 for the VIB4920 group is not equal to that for the placebo group.

10.3 Determination of Sample Size

Population #1: The planned sample size of 72 subjects (36 subjects in the VIB4920 group and 36 subjects in the placebo group) will provide 80% power to detect a difference in mean change from baseline to Day 169 in ESSDAI of 3.0 (assumed standard deviation of 5) between the VIB4920 and placebo treatment groups at a 2-sided alpha level of 0.10 using 2-sample t-test. The minimum detectable difference is 2.0 between the 2 treatment groups. The estimated standard deviation of 5 is based on the published results (Mariette et al, 2015; Fisher et al, 2017) and internal data.

Population #2: The planned sample size of 102 subjects (51 subjects in the VIB4920 group and 51 subjects in the placebo group) will provide 80% power to detect a difference in mean change from baseline to Day 169 in ESSPRI of 1.0 (assumed standard deviation of 2) between the VIB4920 and placebo treatment groups at a two-sided alpha level of 0.10 using 2-sample t-test. The minimum detectable difference is 0.66 between the 2 treatment groups. The estimated standard deviation of 2 is based on the published results (Mariette et al, 2015; Fisher et al, 2017) and internal data.

10.4 Analysis Sets

10.4.1 Full Analysis Set

The full analysis set (FAS) includes all randomized subjects who received any dose of IP in the study. Subjects will be analyzed according to the treatment randomized. The efficacy analysis will be based on the FAS.

10.4.2 Safety Analysis Set

The safety analysis set includes all subjects who received any dose of IP. Subjects will be analyzed according to the treatment that they actually received. The safety and ADA analysis will be based on the safety analysis set.

10.4.3 Pharmacokinetic Analysis Set

The PK analysis set includes all subjects who receive IP and have at least 1 quantifiable serum PK observation post-first dose. Subjects will be analyzed according to the treatment that they actually received. The PK analysis will be based on the PK analysis set.

10.5 Methods for Statistical Analyses

10.5.1 Analysis of the Primary Efficacy Endpoint

Primary efficacy analyses:

Population #1: The primary efficacy endpoint of change from baseline to Day 169 in ESSDAI score will be analyzed using the mixed-effect model for repeated measures (MMRM) approach based on the FAS.

Population #2: The primary efficacy endpoint of change from baseline to Day 169 in ESSPRI score will be analyzed using the MMRM approach based on the FAS.

Handling plan for rescue medication use:

For subjects who take rescue medications before Day 169, the data collected after administration of the rescue medications will not be included in the primary analysis. This approach attempts to reduce the confounding effects of rescue medications.

Handling plan for treatment discontinuation:

Subjects who discontinue IP before Day 169 will be asked to come to scheduled evaluations until Day 169 visit and at least 3 months of off-treatment follow-up after the last IP administration. The data collected after discontinuation of study treatment will be included in the analysis.

Handling plan for missing data:

Missing data will be handled using the MMRM approach based on missing at random assumption.

Supplementary analysis with a different handling plan for rescue medication use and missing data due to dropouts will be detailed in the SAP.

Multiplicity adjustment:

There is no multiplicity issue for the primary endpoint analysis for each population because there is only one primary comparison (VIB4920 1500mg vs placebo) for each population.

10.5.2 Analysis of Secondary Efficacy Endpoints

The categorical secondary efficacy endpoints of Population #1 and Population #2 will be analyzed using a logistic regression model based on the FAS. The continuous secondary efficacy

endpoints of Population #1 and Population #2 will be analyzed using the MMRM approach based on the FAS.

10.5.3 Explore Clinically Meaningful Within-subject Change Score of Clinical Outcome Assessments (COAs)

The anchor-based methods supplemented with both empirical cumulative distribution function (eCDF) and probability density function will be used to explore the clinically meaningful within-subject change score of COAs. The detailed plan will be specified in the SAP.

10.5.4 Handling Missing Items of COAs

The ESSDAI is a clinician reported outcome. There will be very few missing items expected. All PROs will be administered by ePRO. Questions are mandatory so there will be no skipped items. But in case there are missing items, the following algorithms will be used to handle the missing items.

10.5.4.1 ESSDAI and ESSPRI

If less than 50% of items are missing, the missing individual items are imputed using last observation carry forward approach before calculation of total score. The total score will not be calculated and will be treated as missing if 50% or more of items are missing.

10.5.4.2 FACIT-Fatigue

The missing items will be handled according to FACIT scoring guidelines. If less than 50% of items are missing, the total scores will be calculated as follows:

Total score = (Sum of scores for items answered)/(N of items answered)×13

The total score will not be calculated and will be treated as missing if 50% or more of items are missing.

[redacted]

10.5.5 Safety Analysis

10.5.5.1 Adverse Events

The AEs will be summarized descriptively for each population. AEs will be coded using the Medical Dictionary for Regulatory Activities by system organ class (SOC) and preferred term (PT). The number and percentage of subjects reporting TEAEs with onset on or after the start of the first infusion of IP will be summarized for each treatment group by SOC and PTs, by severity, and by relationship to the IP. The number and percentage of subjects reporting TESAEs and AESIs will also be summarized.

10.5.5.2 Clinical Laboratory

Laboratory results, as well as changes from baseline, at each visit and shift from baseline, if applicable, will be summarized descriptively by treatment group for each population.

10.5.5.3 Vital Signs

Vital signs results, as well as changes from baseline, at each visit will be summarized descriptively by treatment group for each population.

10.5.5.4 Electrocardiogram

ECG results, as well as their changes from baseline, at each visit will be summarized descriptively by treatment group for each population. The overall clinical evaluation of ECG results (normal, abnormal, not clinically significant abnormal, clinically significant abnormal) will also be summarized.

10.5.6 Pharmacokinetics Analysis

Plasma VIB4920 concentration data at each time point will be tabulated by dose cohort together with descriptive statistics. Individual and mean plasma concentration-time profiles of VIB4920 by population and treatment will be generated. If the data allow, population PK analysis will be performed and reported separately from the clinical study report (CSR).

10.5.7 Immunogenicity Analysis

ADA will be summarized using descriptive statistics for each population. Number and percentage of subjects who developed positive ADA will be summarized by treatment group. The impact of ADA on PK endpoint will be assessed. The potential association of ADA with safety and efficacy may be explored if data allow.

[redacted]

10.5.9 Exploratory Analysis

[redacted]

10.6 Planned Analysis

An interim analysis will be conducted for each population after all subjects have completed the Day 85 visit for that population. 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. The final assessment of efficacy will be determined at the primary analysis. Details of the interim analysis will be specified in the interim unblinding analysis plan prior to unblinding.

The primary analysis will be conducted for each population after all subjects have completed the Day 169 visit for that population. The efficacy and safety data prior to the data cut-off for the interim analysis will be analyzed.

The final analysis will be conducted for each population after all subjects have completed study for that population.

11 ETHICAL CONSIDERATIONS

11.1 Good Clinical Practice

The study will be performed in accordance with ethical principles that have their origin in the Declaration of Helsinki and are consistent with International Conference on Harmonisation (ICH) / Good Clinical Practice (GCP), applicable regulatory requirements and the Sponsor policy on Ethical Interactions.

11.2 Ethics Review

The final clinical 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 Sponsor or representative before he or she can enroll any patient into the study.

The PI is responsible for informing the IRB or IEC of any amendment to the protocol in accordance with local requirements. In addition, the IRB or IEC must approve all advertising used to recruit subjects 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 of any reportable serious adverse drug reactions from any other study conducted with the IP. Sponsor will provide this information to the PI.

Progress reports and notifications of serious adverse drug reactions will be provided to the IRB or IEC according to local regulations and guidelines. Copies of all correspondence between the Investigator and the IRB/IEC is provided to Sponsor representative.

11.3 Informed Consent

The PI(s) or other members of the study site's treatment team will ensure that the subject or legally authorized representative is given full and adequate oral and written information about the nature, purpose, possible risk and benefit of the study. Subjects or legally authorized representative must also be notified that they are free to discontinue from the study at any time. The subjects or legally authorized representatives will be informed that their study record and medical records/documents that pertain directly to the study will be reviewed and possibly copied by Sponsor or its designee, or a governmental agency (such as the FDA), and that every effort will be made to maintain patient confidentiality. The patient or legally authorized representative should be given the opportunity to ask questions and allowed time to consider the information provided.

The ICF must be witnessed and dated by the Investigator or his/her designee, and the original retained by the Investigator/study site as part of that subject's record.

The PI(s) must maintain the original, signed ICF. A copy of the signed ICF must be given to the patient or legally authorized representative.

Subjects may be rescreened within 30 days under the current and signed ICF.

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

11.4 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 Sponsor. However, authorized regulatory officials, IRB/IEC personnel, Sponsor and its authorized representatives are allowed full access to the records.

Identification of subjects and eCRFs shall be by initials, screening, and treatment numbers only. If required, the subject's full name may be made known to an authorized regulatory agency or other authorized official.

11.5 Disclosure

Sponsor is responsible for preparing and providing the appropriate regulatory authorities with CSRs, according to the applicable regulatory requirements.

11.6 Biological Specimens and Data

Study data are protected by the use of a SID number, which is a number specific to the subject. The Investigator is in control of the information that is needed to connect a study sample to a subject. A subject's consent to the use of data does not have a specific expiration date, but the subject may withdraw consent at any time by notifying the Investigator. If consent is withdrawn, any samples collected prior to that time may still be given to and used by the Sponsor, but no new data or samples will be collected unless specifically required to monitor the safety of the subject.

Samples obtained for future research will be labeled with a sample identification number. If the subject withdraws consent for participating in future research, the Sponsor will locate the subject's sample and destroy it.

If the subject consents to have his/her samples used for future research, this additional research may not start immediately and may start at any time during the storage period. The subject's sample(s) will be stored by the Sponsor with similar samples in a secure central laboratory. The subject's samples will not be kept for more than 25 years after the end of the study in which they were collected. If the subject chooses not to allow his/her study samples to be used for future research, the samples will be destroyed by the Sponsor once they are no longer required for the main study.

If consent is withdrawn, the Sponsor and the Investigator will ensure that the subject's sample(s) are destroyed unless the identification number has been removed and the subject can no longer be linked to any samples. However, if the subject's sample has already been used for research, the Sponsor is not required to destroy the results of this research. In this case only, the remaining sample(s) will be destroyed.

12 OVERSIGHT

12.1 Safety and Data Monitoring Committee

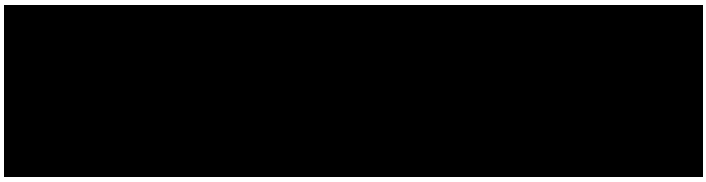
An independent SDMC will perform evaluations of safety data at specified regular intervals throughout the study and make recommendations to the Sponsor regarding further conduct of the study. The SDMC will not routinely review efficacy data (blinded or unblinded).

At any time during the study, as well as on an ad hoc basis, the SDMC will also review any safety data assessed by the Sponsor/Designee Medical Monitor as medically relevant. Additional information, including frequency of SDMC review, can be found in the SDMC charter.

If any event(s) occur that, in the opinion of the SDMC, contraindicates further dosing of additional subjects, the Sponsor will conduct a prompt cumulative review of safety data and the circumstances of the event in question to determine whether dosing and study randomization should be stopped, whether the protocol will be modified, or whether the study will be discontinued permanently. In the event that the study is interrupted, review by the SDMC and Sponsor decision to resume (with or without modifications) is required for resumption of the study. Where applicable, the regulatory authorities and IRBs/IECs will be notified of any actions taken with the study.

12.2 Training of Site Personnel

To maintain consistent evaluation of SS disease activity within and across study sites, Sponsor will provide training or access to training tools to Principal Investigators and any designated site personnel who will be completing the following disease evaluation assessments:



The ESSDAI and joint count must be administered by the Investigator or another qualified site personnel who, as per Investigator discretion, are qualified to perform the assessments. Training will include printed training materials and formal presentations, as well as web-based training modules.

Over the course of the study, Investigator assessments for a given subject should be completed by the same trained Investigator, designated physician, or qualified site personnel whenever possible. If there is a change in site personnel over the course of the study, new Principal Investigators or site physicians/personnel must be trained prior to performing the ESSDAI and joint count assessments.

It is expected that the Investigator will ensure their site personnel have adequate experience and training qualifications to perform disease assessments. Documentation of all training will be maintained in the site's study file.

12.3 Quality Control and Assurance

To ensure compliance with GCP and all applicable regulatory requirements, Sponsor may conduct a quality assurance audit. See Section 12.5 for details regarding the audit process.

12.4 Monitoring

Before an investigational site can enter a subject into the study, a representative of Sponsor or of the Contract Research Organization will visit the investigational study site to:

- Determine the adequacy of the facilities.
- Discuss with the Investigator(s) and other personnel their responsibilities with regard to protocol adherence, and the responsibilities of Sponsor or its representatives. This will be documented in a Clinical Study Agreement between Sponsor and the Investigator.

During the study, a representative from Sponsor will have regular contacts with the investigational site, for the following:

- Provide information and support to the Investigator(s).
- Confirm that facilities remain acceptable.
- Confirm compliance with the principles of GCP and regulatory requirements.
- Review of written ICFs for subjects screened/enrolled
- Confirm that the investigational team is adhering to the protocol, that data are being accurately recorded in the eCRFs, and that IP accountability checks are being performed.
- Perform source data verification. This includes a comparison of the data in the case report forms with the subject medical records at the hospital or practice, and other records relevant to the study for accuracy and completeness. This will require direct access to all original medical and other trial related records for each subject (eg, clinic charts).
- Record and report any protocol deviations not previously sent to Sponsor
- Confirm AEs and SAEs have been properly documented on eCRFs and confirm that any SAEs have been forwarded to Sponsor or representative and those SAEs that met criteria for reporting have been forwarded to the IRB.
- 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 monitor.

12.5 Audits

To ensure compliance with GCP and all applicable regulatory requirements, Sponsor may conduct a quality assurance audit.

Authorized representatives of Sponsor, a regulatory authority, an IEC and/or an IRB may visit the site to perform audits or inspections, including source data verification. The purpose of a Sponsor audit or 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, GCP guidelines of the ICH, and any applicable regulatory requirements.

Initial IRB approval, and all materials approved by the IRB 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 Sponsor auditing staff or government inspectors may review the conduct/results of the study at the investigational site. The Investigator should contact 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 the course of these audits are satisfactorily resolved. The Investigator supplies 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 Sponsor prior to submission to the regulatory agency.

12.6 Records

12.6.1 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.

A 21 CFR Part 11 compliant electronic data capture system will be used for data collection and query handling. The Investigator will ensure that data are recorded on the eCRFs as specified in the clinical 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 according to the Clinical Study Agreement. 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.

12.6.2 Source Documentation

Sponsor will be allowed to conduct site visits to the investigation facilities for the purpose of monitoring any aspect of the study. The Investigator agrees to allow the monitor to inspect the drug storage area, study drug stocks, drug accountability records, subject charts and study source documents, and other records relative to study conduct.

12.6.3 Records Retention

The PI must maintain all documentation relating to the study for a period of 2 years after the last marketing application approval, or if not approved 2 years following the discontinuance of the test article for investigation. If it becomes necessary for Sponsor or the regulatory authority to review any documentation relating to the study, the Investigator must permit access to such records.

13 PUBLICATION POLICY

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

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15 APPENDICES

APPENDIX 1 ACR-EULAR CLASSIFICATION CRITERIA FOR PRIMARY SJÖGREN'S SYNDROME

The classification of SS applies to any individual who meets the inclusion criteria,[1] does not have any condition listed as exclusion criteria,[2] and who has a score ≥ 4 when summing the weights from the following items:

Item	Weight / Score
Labial salivary gland with focal lymphocytic sialadenitis and focus score ≥ 1.[3]	3
Anti-SSA (Ro) +	3
Ocular staining score ≥ 5 (or van Bijsterveld score ≥ 4) on at least one eye[4]	1
Schirmer ≤ 5 mm/5min on at least one eye	1
Unstimulated whole saliva flow rate ≤ 0.1 ml/min[5]	1

1 Inclusion criteria: these criteria are applicable to any patient with at least one symptom of ocular or oral dryness (defined as a positive response to at least one of the following questions: 1) Have you had daily, persistent, troublesome dry eyes for more than 3 months? 2) Do you have a recurrent sensation of sand or gravel in the eyes? 3) Do you use tear substitutes more than 3 times a day? 4) Have you had a daily feeling of dry mouth for more than 3 months? 5) Do you frequently drink liquids to aid in swallowing dry food?); or suspicion of SS from ESSDAI questionnaire (at least one domain with positive item)

2 Exclusion criteria: Prior diagnosis of any of the following conditions would exclude diagnosis of SS and participation in SS studies or therapeutic trials because of overlapping clinical features or interference with criteria tests:

- History of head and neck radiation treatment
- Active Hepatitis C infection (with positive PCR)
- Acquired immunodeficiency syndrome
- Sarcoidosis
- Amyloidosis
- Graft versus host disease
- IgG4-related disease

Note: Patients who are normally taking anticholinergic drugs should be evaluated for objective signs of salivary hypofunction and ocular dryness after a sufficient interval off these medications for these components to be a valid measure of oral and ocular dryness

3 The histopathologic examination should be performed by a pathologist with expertise in the diagnosis of focal lymphocytic sialadenitis, and focus score count (based on number of foci per 4 mm^2) following a protocol described in Daniels et al, 2011.

4 Ocular staining score described in Whitcher et al, 2009; van Bijsterfeld score described in van Bijsterveld, 1969.

5 Unstimulated whole saliva described Navazesh and Kumar, 2008.

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APPENDIX 2 GUIDANCE FOR ANAPHYLAXIS DIAGNOSIS

National Institute of Allergy and Infectious Disease (NIAID) and Food and Allergy Anaphylaxis Network (FAAN) Guidance for Anaphylaxis Diagnosis

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

NIAID and FAAN define anaphylaxis as a serious allergic reaction that is rapid in onset and may cause death. 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 flow (PEF), hypoxemia)

   b. Reduced BP 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 BP or associated symptoms (eg, hypotonia [collapse], syncope, incontinence)

   d. Persistent gastrointestinal symptoms (eg, crampy abdominal pain, vomiting)

3. Reduced BP after exposure to known allergen for that patient (minutes to several hours):

   a. Infants and children: low systolic BP (age specific) or greater than 30% decrease in systolic BP

   b. Adults: systolic BP of less than 90 mm Hg or greater than 30% decrease from that person's baseline.

APPENDIX 3 ACTIONS REQUIRED IN CASES OF INCREASES IN LIVER BIOCHEMISTRY AND EVALUATION OF HY'S LAW

Introduction

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

During the course of the study the Investigator will remain vigilant for increases in liver biochemistry. The Investigator is responsible for determining whether a subject meets potential Hy's Law (PHL) criteria at any point during the study.

The Investigator participates, together with Sponsor clinical project representatives, in review and assessment of cases meeting PHL criteria to agree whether HL criteria are met. HL criteria are met if there is no alternative explanation for the elevations in liver biochemistry other than Drug-Induced Liver Injury (DILI) caused by the IP.

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

Definitions

Potential Hy's Law

AST or ALT ≥ 3 × ULN together with total bilirubin (TBL) ≥ 2 × ULN at any point during the study following the start of IP irrespective of an increase in ALP.

Hy's Law

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

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

Identification of Potential Hy's Law Cases

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

ALT ≥ 3 × ULN

AST ≥ 3 × ULN

TBL ≥ 2 × ULN

The Investigator will without delay review each new laboratory report and if the identification criteria are met will:

Notify the Sponsor study representative

Determine whether the subject meets PHL criteria by reviewing laboratory reports from all previous visits

Promptly enter the laboratory data into the laboratory eCRF.

Follow-up

Potential Hy's Law Criteria Are Not Met

If the subject does not meet PHL criteria the Investigator will:

Inform the Sponsor representative that the subject has not met PHL criteria

Perform follow-up on subsequent laboratory results according to the guidance provided in the clinical study protocol.

Potential Hy's Law Criteria Are Met

If the subject does meet PHL criteria the Investigator will notify the Sponsor study representative who will then inform the central study team. The Medical Monitor contacts the Investigator, to provide guidance, discuss and agree an approach for the study subject's follow-up and the continuous review of data. Subsequent to this contact the Investigator will:

Monitor the subject until liver biochemistry parameters and appropriate clinical symptoms and signs return to normal or baseline levels, or as long as medically indicated

Investigate the etiology of the event and perform diagnostic investigations as discussed with the Study Physician.

If at any time (in consultation with the Medical Monitor) the PHL case meets serious criteria, report it as an SAE using standard reporting procedures.

Review and Assessment of Potential Hy's Law Cases

The instructions in this section should be followed for all cases where PHL criteria are met.

No later than 3 weeks after the biochemistry abnormality was initially detected, the Medical Monitor will contact the Investigator in order to review available data and agree on whether there is an alternative explanation for meeting PHL criteria other than DILI caused by the IP. The Medical Monitor and safety physician will also be involved in this review together with other subject matter experts as appropriate.

According to the outcome of the review and assessment, the Investigator will follow the instructions below.

If there is an agreed alternative explanation for the ALT or AST and TBL elevations, a determination of whether the alternative explanation is an AE will be made and subsequently whether the AE meets the criteria for a SAE:

If the alternative explanation is not an AE, record the alternative explanation on the appropriate eCRF.

If the alternative explanation is an AE/SAE, record the AE/SAE in the eCRF accordingly and follow the sponsor standard processes.

If it is agreed that there is no explanation that would explain the ALT or AST and TBL elevations other than the IP:

Report an SAE (report term 'Hy's Law') according to Sponsor standard processes.

- The 'Medically Important' serious criterion should be used if no other serious criteria apply
- As there is no alternative explanation for the HL case, a causality assessment of 'related' should be assigned

If there is an unavoidable delay, of over 3 weeks, in obtaining the information necessary to assess whether or not the case meets the criteria for HL, then it is assumed that there is no alternative explanation until such time as an informed decision can be made:

Report an SAE (report term 'Potential Hy's Law') applying serious criteria and causality assessment as per above

Continue follow-up and review according to agreed plan. Once the necessary supplementary information is obtained, repeat the review and assessment to determine whether HL criteria are met. Update the SAE report according to the outcome of the review

FDA Guidance for Industry (issued July 2009) 'Drug-induced liver injury: premarketing clinical evaluation':

https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM174090.pdf

APPENDIX 4 INVESTIGATOR'S AGREEMENT

I have read the protocol, appendices, and accessory materials related to Study VIB4920.P2.S2 and agree to the following:

- To conduct this study as described by the protocol and any accessory materials
- To protect the rights, safety, and welfare of the participants under my care
- To provide oversight to all personnel to whom study activities have been delegated
- To control all investigational products provided by the Sponsor and maintain records of the disposition of those products
- To conduct the study in accordance with all applicable local and national regulations, the requirements of the ethics committee of record for my clinical site, and Good Clinical Practices as outlined by ICH E6(R2)
- To obtain approval for the protocol and all written materials provided to participants prior to initiating the study at my site
- To obtain informed consent – and updated consent in the event of new information or amendments – from all participants enrolled at my study site prior to initiating any study-specific procedures or administering investigational products to those participants
- To maintain records of each subject's participation and all data required by the protocol

Name	**Title**	**Institution**
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