VIELA BIO

A PHASE 2, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED, MECHANISTIC INSIGHT AND DOSAGE OPTIMIZATION STUDY OF THE EFFICACY AND SAFETY OF VIB4920 IN PATIENTS WITH RHEUMATOID ARTHRITIS (RA) (SHORT TITLE: MIDORA)

Investigational Product	VIB4920
Protocol Number	VIB4920.P2.S3
Clinical Trial Registry Identifiers	NCT04163991, EudraCT 2019-003697-70
Version Number	4.0
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Amendment	3
IND Number	IND 128905
Principal Investigator	[redacted]
Sponsor	Viela Bio **Responsible Medical Officer:** [redacted], Viela Bio [redacted]

SUMMARY OF CHANGES TO THE PROTOCOL

Protocol Amendment 1; 15 October 2019

Changes to the protocol in Amendment 1 included the following:

Protocol Section(s) Impacted by Change	Change	Reason for Change
Section 6.1, Schedules of Study Assessments, Table 2	Removed RF isotypes from list of screening assessments. RF isotypes will be assessed during the study, but not at screening.	To eliminate unnecessary laboratory testing and assays.
Section 6.1, Schedules of Study Assessments Section 6.4.3.1, Autoantibody Panel	Removed ANA from list of assessments. ANA will not be assessed during the study.	To eliminate unnecessary laboratory testing and assays.
Section 6.1, Schedules of Study Assessments Section 6.4.3.1, Autoantibody Panel Section 6.4.3.6, Serum and Plasma Biomarkers	• In Sections 6.1 and 6.4.3.6: Removed ACPA from the autoantibody panel planned for the study assessments. ACPA will still be assessed at screening. • In Section 6.4.3.6: "ACPA will be assessed with a fit-for-purpose quantitative assay (in development)."	The available clinical assay is not appropriately quantitative. An alternative quantitative assay is in development and will be used to assess ACPA in samples collected on or after Day 1.
Section 6.1, Schedules of Study Assessments Section 6.4.3.3, Inflammatory Markers Section 8.5.2, Serum Chemistry	Removed IgE from list of plasma immunoglobulins that will be assessed.	To eliminate unnecessary laboratory testing and assays.
Section 6.1, Schedules of Study Assessments, Table 3	Removed "Flow cytometry (T regulatory panel" from list of study assessments and procedures.	The T regulatory assessment will be performed on the PBMC samples.

ACPA = anti-citrullinated protein antibodies; ANA = antinuclear antibody; IgE = immunoglobulin E; PBMC = peripheral blood mononuclear cells; RF = rheumatoid factor.

Protocol Amendment 2; 26 June 2020

Changes to the protocol in Amendment 2 included the following:

Protocol Section(s) Impacted by Change	Change	Reason for Change
Cover page	Inserted lead investigator's name and address and clinical trial registry identifiers	To provide the lead investigator's information and the registry information in the protocol
Synopsis, [redacted] Section 6.1, Schedules of Study Assessments,	• [redacted] • In Section 6.1, removed Vectra DA testing and replaced it with a blood sample for other biomarkers.	To eliminate unnecessary laboratory testing

Section 6.4.3.2, Multi-biomarker Disease Activity Panel (Vectra DA), References	• In References, removed the reference related to Vectra DA testing	
Section 7.1.1.2 Dose Preparation	In Section 7.1.1.2, added a sentence about the required filter	To ensure that the requirement for use of a filter, which is in the Pharmacy Manual, is easily noted
Section 5.2 Exclusion criteria (Exclusion 18)	In Exclusion criterion 18, added text to require investigators to • Consider the risks associated with SARS-CoV-2 circulation when assessing the suitability of a subject for enrollment, including both the subject's epidemiologic risk and health-related risks. • Ensure that the subject has a documented negative SARS-CoV-2 viral test within two weeks prior to randomization	To address risks associated with the COVID-19 pandemic, which had not begun at the time of study start.
Section 2.1.6, Risk Assessment--2.1.6.3 Infections, and Section 13 References.	• In Section 2.1.6.3, added potential risks of VIB4920 as they relate to COVID-19 or to COVID-19 vaccine response and individual subject risk factors for SARS-CoV-2 infection and for severe COVID-19 disease • In Section 13 added relevant references	To address infection risks associated with the COVID-19 pandemic, which had not begun at the time of study start.
Section 2.2 Study Rationale	In Section 2.2, added text addressing the benefit-risk of conducting this study during the potential circulation of SARS-CoV-2 and steps taken to minimize risk	To address the benefit-risk of conducting the study during the potential circulation of SARS-CoV-2, because of the onset of the COVID-19 pandemic.
Section 6.1 Schedules of Study Assessments Section 8.5 Clinical Laboratory Findings 8.5.5 Testing for SARS-CoV-2	• In Section 6.1, Table 2, Screening Assessments and Procedures, added a requirement for subject to have a documented negative SAR-CoV-2 viral test within 14 days of randomization. • In Sections 8.5 and 8.5.5, description of testing for SARS-CoV-2 is provided.	To establish testing for SARS-CoV-2 prior to Dose 1 as a safety measure

Protocol Amendment 3; 30 Sept 2020

Changes to the protocol in Amendment 3 included the following:

Protocol Section(s) Impacted by Change	Change	Reason for Change
Section 5.1 Inclusion Criteria	In Inclusion 6, the circumstance under which a subject can be enrolled if methotrexate (MTX) intolerant is expanded to clarify that this includes if MTX is contraindicated	Clarification in response to investigator query
Section 5.2 Exclusion Criteria	In Exclusion 21, blood tests at screening that exclude from enrollment were changed	A high rate of screen failure (>20%) due to abnormal

	from a prothrombin time (PT) or partial thromboplastin time (PTT) > upper limit of normal (ULN) to > 1.2 x ULN	coagulation values (primarily PTT values close to ULN) was unexpectedly observed. Tubes were not expired, and there were no instrumentation, maintenance or quality control issues in the laboratory. Sites were reinstructed in sample handling. The permissible limit for PT or PTT result was increased to eliminate unnecessary screen failures without affecting subject safety.
Section 5.2 Exclusion Criteria	At the end of Section 5.2, under Repeat of screening laboratory tests, guidance is provided to allow for some tests to be repeated within the initial screening period to assess for eligibility	The information was provided to sites in the administrative clarification letter dated 11Sep2020 and is now added to the protocol for clarity
Section 7.1.1.2 Dose preparation	In Section 7.1.1.2, the timing between vial puncture to start of IV bag administration may not exceed 4 hours at room temperature or 24 hours at 2-8°C	To clarify the information for investigators
Section 8.4 Adverse events of special interest	In Section 8.4, the process for reporting of adverse events of special interest (AESI) was clarified	To ensure that the process of reporting of AESIs was clear to investigators.

STATEMENT OF COMPLIANCE

The study will be conducted in compliance with this clinical study protocol, Good Clinical Practices (GCP) as outlined by International Council for Harmonisation 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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LIST OF ABBREVIATIONS

Abbreviation	Definition
ACPA	anti-citrullinated protein antibody(ies)
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
anti-HBc	hepatitis B core antibody
AST	aspartate aminotransferase
bDMARD	biologic disease-modifying anti-rheumatic drug
β-hCG	serum human chorionic gonadotropin
CD	cluster of differentiation
CD40L	CD40 ligand
CDAI	Clinical Disease Activity Index
CDM	Clinical Data Management
cDMARD	conventional disease-modifying anti-rheumatic drug
CI	confidence interval
CL	systemic clearance
CRO	contract research organization
CRP	C-reactive protein
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
EU	European Union
EULAR	European League Against Rheumatism
FACIT-Fatigue	Functional Assessment of Chronic Illness Therapy - Fatigue
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HAQ	Health Assessment Questionnaire
HBsAg	hepatitis B surface antigen
HPF	high power field
IB	Investigator’s Brochure
ICF	informed consent form

Abbreviation	Definition
ICH	International Council for Harmonisation
IEC	Independent Ethics Committee
Ig	immunoglobulin
IL	interleukin
IP	investigational product
IRB	Institutional Review Board
IV	intravenous(ly)
IXRS	interactive voice/web response system
JAK	Janus kinase
KLH	keyhole limpet hemocyanin
mAb	monoclonal antibody(ies)
MAD	multiple ascending dose
MBDA	multi-biomarker disease activity test
MDGA	physician global assessment of disease activity
MMRM	mixed-effect model for repeated measures
MTX	methotrexate
NOAEL	no-observed-adverse-effect level
PD	pharmacodynamic(s)
PGA	patient global assessment of disease activity
PK	pharmacokinetic(s)
PI	Principal Investigator
PRO	patient-reported outcome
PTT	partial thromboplastin time
RA	rheumatoid arthritis
RF	rheumatoid factor
SAE	serious adverse event
SAP	statistical analysis plan
SAR	suspected adverse reaction
SC	subcutaneous
sCD40L	soluble CD40 ligand
SDAI	Simplified Disease Activity Index
SDMC	Safety Data Monitoring Committee
SID	subject identification number
SJC	swollen joint count
$t_{1/2}$	terminal elimination half-life
TB	tuberculosis
TBL	total bilirubin
TDAR	T-cell dependent antibody response inhibition
TEAE	treatment-emergent adverse event

Abbreviation	Definition
TESAE	treatment-emergent serious adverse event
TJC	tender joint count
Tn3	an engineered form of the third fibronectin type III protein domain of human Tenascin C
TNF	tumor necrosis factor
ULN	upper limit of normal
VAS	visual analog scale
w/v	weight/volume
WBC	white blood cell count

1 SYNOPSIS

Title	A Phase 2, Randomized, Double-Blind, Placebo-Controlled, Mechanistic Insight and Dosage Optimization Study of the Efficacy and Safety of VIB4920 in Patients with Rheumatoid Arthritis (RA) (short title: MIDORA)
Phase	2
Study Design	Randomized, double-blind, placebo-controlled, parallel-cohort study
Rationale	The cluster of differentiation 40 (CD40)/CD40 ligand (CD40L) pathway has been extensively studied for its role in immunity and autoimmunity, especially its role in B and T cell activation and costimulation. Activation of CD40 has been shown to be critical for germinal center formation, immunoglobulin class switching, and expression of cytokines such as IFNα, tumor necrosis factor α (TNFα), and interleukin-6 (IL-6). It is generally accepted that B cells contribute to the pathophysiology of RA. Defective central and peripheral B-cell tolerance checkpoints in RA result in accumulation of autoreactive B cells. By blocking the CD40/CD40L interaction, VIB4920 may act as an immune modulator in RA. Genome-wide association studies have identified a common variant in the CD40 locus that increases the risk of RA, and the expression of CD40L on CD4+ T helper cells is increased in patients with active RA. These observations suggest that inhibition of the CD40L/CD40 pathway may be beneficial in RA. The potential for use of VIB4920 in RA was suggested in a phase 1b study, in a population similar to that in this current study, in which the 2 highest doses of VIB4920 demonstrated sustained clinical benefit and an acceptable safety profile.
Target Population	Adults with active, moderate-to-severe adult-onset RA (Disease Activity Score in 28 Joints Using C-reactive Protein [DAS28-CRP] > 3.2, ≥ 4 tender joints, and ≥ 4 swollen joints) who have: • Serum rheumatoid factor (RF) and/or anti-citrullinated protein antibodies (ACPAs) • A prior inadequate response to methotrexate, other conventional disease-modifying anti-rheumatic drugs, or an anti-TNFα agent • No prior treatment with rituximab or B-cell depletive agents
Number of Subjects	Approximately 75 subjects will be randomized in a 1:1:1:1:1 ratio among 5 treatment groups; approximately 15 subjects to each cohort.
Length of Participation	Screening period: Up to 28 days On-study period: approximately 309 (± 7) days
Interventions	Cohort 1: VIB4920 1500 mg on Days 1, 15, 29, and 57 Cohort 2: VIB4920 1500 mg on Days 1 and 57, placebo on Days 15 and 29 Cohort 3: VIB4920 3000 mg on Days 1 and 57, placebo on Days 15 and 29 Cohort 4: VIB4920 3000 mg on Day 1 and placebo on Days 15, 29, and 57 Cohort 5: Placebo on Days 1, 15, 29, and 57
Primary Objectives and Primary Endpoints	**Primary objectives**: • To evaluate the effect of VIB4920 on disease activity as assessed by a composite measure in subjects with adult-onset RA • To evaluate the safety and tolerability of VIB4920 in subjects with adult-onset RA **Primary endpoints**: • Change in DAS28-CRP from baseline to Day 113 • The incidence of treatment-emergent adverse events (TEAEs) and treatment-emergent serious adverse events and TEAEs of special interest during the study

Secondary Objectives and Corresponding Endpoints	**Secondary objectives**: • To characterize the pharmacokinetics (PK) of VIB4920 in subjects with adult-onset RA • To evaluate the pharmacodynamic effect of VIB4920 in subjects with adult-onset RA • To evaluate the immunogenicity of VIB4920 in subjects with adult-onset RA • To evaluate the effect of VIB4920 on autoantibodies in subjects with adult-onset RA • To assess the effect of VIB4920 on clinical remission as assessed by a composite measure in subjects with adult-onset RA • To evaluate the duration of clinical response to VIB4920 as assessed by time to institution of rescue therapy **Secondary endpoints**: • The PK profile of VIB4920 • The time-concentration profile of total soluble CD40L • The proportion of subjects with anti-drug antibodies to VIB4920 • Change in RF and ACPAs from baseline to Day 113 • The proportion of subjects with clinical remission defined as DAS28-CRP < 2.6 at Day 113 • Time to start of new treatment for RA (rescue medication)
[redacted]	[redacted]

Number of Sites	Approximately 30 sites in 2-4 countries
Study Duration	Estimated duration: 19 months
Data Monitoring Committee	An external, independent Safety Data Monitoring Committee will evaluate safety data at regular intervals throughout the study and make recommendations to the Sponsor as needed. The Committee will not perform a futility analysis or consider early study completion for efficacy.

2 INTRODUCTION

2.1 Background

2.1.1 Description of VIB4920

VIB4920 (formerly MEDI4920) is a cluster of differentiation 40 ligand (CD40L) antagonist that is a non-antibody biologic composed of 2 identical Tn3 modules fused to human serum albumin. Each Tn3 is an engineered form of the third fibronectin type III protein domain of human Tenascin C. Polyglycine linkers join the 2 Tn3 domains and the second Tn3 domain to the human serum albumin protein. Each Tn3 binds specifically to human CD40L and inhibits its interaction with human CD40. The CD40/CD40L interaction plays a critical role in T-cell dependent immunity, antigen presentation and 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 rheumatoid arthritis (RA).

In nonclinical studies, disruption of the CD40/CD40L interaction with antibodies against CD40L has been shown to be beneficial in autoimmune disease models (Choi et al, 2018; Kalled et al, 2001; Croft et al, 2013). In clinical studies of monoclonal antibodies (mAbs) targeting CD40L, expected changes in biomarkers were observed, but further development was terminated because of thromboembolic events considered to be related to interaction of the Fc region of the anti-CD40L mAbs with platelets (Boumpas et al, 2003; Robles-Carrillo et al, 2010; Visvanathan et al, 2019). VIB4920 is not an antibody, does not have an Fc receptor, and was not associated with platelet aggregation in nonclinical studies or with thrombotic events or coagulation abnormalities in phase 1 studies.

2.1.2 Rheumatoid Arthritis

RA is a chronic systemic inflammatory disease that is associated with significant morbidity and mortality. The disease is characterized by inflammation of the synovial joints that can result in pain, swelling, and joint damage with secondary deformity and progressive disability. Worldwide, the prevalence of RA is estimated to be between 0.6-1.1% with variations across geographical regions. The incidence is 2-3 times higher in women than in men with a peak age of onset between 35-55 years of age (Symmons, 2002). Uncontrolled active RA causes joint damage, disability, and decreased quality of life; comorbidities include cardiovascular disease and osteoporosis, and reduced life expectancy (Wong et al, 2001).

Rapidly acting anti-inflammatory medications, including nonsteroidal anti-inflammatory drugs and systemic and intraarticular corticosteroids, are often used to treat RA, generally in combination with disease-modifying anti-rheumatic drugs (DMARDs). Two main classes of DMARDs are available for the treatment of RA: conventional DMARDs (cDMARDs; such as methotrexate [MTX], sulfasalazine, leflunomide, and hydroxychloroquine) and biologic DMARDs (bDMARDs; such as tumor necrosis factor [TNF]-inhibitors). MTX is the most commonly used DMARD for the treatment of moderate and severe RA; however, many patients fail to achieve an adequate or sustained response to MTX alone (Smolen et al, 2017). To improve efficacy, MTX is being combined with newer biologic agents targeting various components of the immune system, including anti-TNFα agents (etanercept, infliximab, adalimumab, certolizumab, and golimumab) and agents targeting different compartments of the immune

system such as B cells (rituximab), cytotoxic T lymphocyte antigen 4 (abatacept), and interleukin-6 (IL-6) receptors (tocilizumab). Newer oral compounds such as inhibitors of Janus kinase (JAK; tofacitinib) are also used. Despite the availability and utility of multiple therapeutic agents for the treatment of RA, there is a need for new treatments to reduce disease activity, because only a minority of patients achieve clinical remission (Smolen et al, 2017; Bykerk and Massarotti, 2012).

2.1.3 Evidence for the CD40 Pathway in RA

It is generally accepted that B cells contribute to the pathophysiology of RA (van Baarsen et al, 2013). Defective central and peripheral B-cell tolerance checkpoints in RA result in accumulation of autoreactive B cells (Bugatti et al, 2014), and depletion of CD20-positive B cells with rituximab results in clinical improvement in a subset of patients. Approximately 80% of patients with RA have detectable levels of rheumatoid factors (RFs), which are antibodies of any isotype (immunoglobulin [Ig] M, IgG, IgA) against the Fc portion of IgG. The majority of patients with RA also have detectable levels of anti-citrullinated protein antibodies (ACPAs). Indeed, the presence of RF or ACPA is included in the American College of Rheumatology (ACR) 2010 diagnostic criteria for RA (Aletaha et al, 2010).

The CD40 receptor is a member of the TNF family of receptors expressed on the plasma membrane of antigen-stimulated B cells, macrophage, and dendritic cells (Croft et al, 2013). The CD40 receptor functions to provide a co-stimulatory signal for B cells that have bound antigen. The cognate ligand for CD40 is CD40L (also known as CD154), which is expressed on the plasma membrane of T cells and other cell types, including platelets. Cell contact-dependent interaction between CD40L and CD40 is critical for the development of a comprehensive immune response (Ford et al, 2014).

The CD40/CD40L pathway has been extensively studied for its role in immunity and autoimmunity, especially its role in B cell and T cell activation and B and T cell costimulation (Karnell et al, 2018). Specifically, activation of CD40 has been shown to be critical for germinal center formation, Ig-class switching, and expression of cytokines such as IFNα, TNFα, and IL-6.

Genome-wide association studies have identified a common variant in the CD40 locus that increases the risk of RA (Scheinman, 2013). The RA risk allele is a gain-of-function allele that increases the amount of CD40 on the surface of primary human B-lymphocyte cells and probably other cell types (Li et al, 2013). The expression of CD40L on CD4+ T helper cells is also increased in patients with active RA compared to those in clinical remission or healthy controls (Berner et al, 2000; Zhang et al, 2013). Taken together, these observations suggest that inhibition of the CD40L/CD40 pathway may be beneficial in RA.

In clinical studies of mAbs targeting CD40L, expected changes in biomarkers were observed, but further development was terminated because of thromboembolic events considered to be related to Fc region of the mAbs (Boumpas et al, 2003; Robles-Carrillo et al, 2010; Visvanathan et al, 2019).

Data from a phase 1b study of VIB4920 in patients with RA, in which higher doses of VIB4920 were shown to have activity against RA, provide additional support for the importance of the CD40/CD40L pathway in RA.

2.1.4 Summary of Nonclinical Experience

In nonclinical pharmacology studies, VIB4920 was shown to bind human CD40L specifically and with high affinity. Additionally, VIB4920/soluble CD40 ligand (sCD40L) immune complexes were used in human ex vivo platelet aggregation assays in various concentrations without inducing platelet aggregation. In single- and repeat-dose pharmacokinetic (PK), toxicokinetic, and pharmacodynamic (PD) studies of VIB4920 in cynomolgus monkeys, there were no VIB4920-related adverse findings, and the no-observed-adverse-effect levels (NOAELs) for repeat-dose studies were the highest doses tested for most of the studies: 150 mg/kg weekly intravenous (IV) and subcutaneous (SC) and 300 mg/kg weekly IV for the 5-week studies; 250 mg/kg weekly SC for the 6-month study. The NOAEL for the single dose study was 600 mg/kg IV. No NOAEL was established for IV dosing at 150 or 300 mg/kg weekly for 6 months because of early euthanasia of one animal on Day 92 for a potential systemic infection, and an opportunistic fungal infection detected in one animal at scheduled Day 192 necropsy. However, the NOAEL for the SC cohort in the 6-month study was 250 mg/kg weekly. There were no VIB4920-related effects on female or male reproductive endpoints, but embryo-fetal studies have not been conducted. See the Investigator's Brochure (IB) for details.

2.1.5 Summary of Clinical Experience

A phase 1a, randomized, blinded (Investigator and participants were blinded to treatment assignment, and Sponsor was unblinded to treatment assignment), placebo-controlled, first-time-in-human study (D5100C00001) to evaluate the safety and tolerability of single-ascending IV doses of VIB4920 was conducted in healthy volunteers (Karnell et al, 2019). Fifty-six healthy adult male subjects were IV administered a single dose of either placebo (N = 12) or VIB4920 (N = 44) at doses of 3, 10, 30, 100, 300, 1000, or 3000 mg. No deaths, thromboembolic events, severe or serious hypersensitivity reactions, severe or serious infections, or infusion-related reactions were observed. PK was linear with dose proportional increases in exposure, and the increase in total sCD40L after VIB4920 administration was dose-dependent, indicating binding of VIB4920 to sCD40L and target engagement. A dose-response model generated for T-cell dependent antibody response inhibition (TDAR) (based on antibody responses to keyhole limpet hemocyanin [KLH]) showed that the 1000 mg dose achieved ~78% inhibition of TDAR and the 3000 mg dose ~86% inhibition of TDAR compared with placebo, indicating adequate inhibition for the 2 highest doses tested.

In Study D5100C00001, there was a decrease in anti-drug antibody (ADA) incidence and titers observed with increasing doses of VIB4920 (incidence of 90% in subjects at doses ≤ 100 mg and 29% at doses ≥ 300 mg) consistent with the immunosuppressive mechanism of action of VIB4920. There was no association of ADA with any treatment-emergent adverse events (TEAEs) reported in this study. The PK and total sCD40L profiles were similar between ADA-positive subjects with low titer and ADA-negative subjects; however, subjects with high ADA titers (defined as > 480) had reduced VIB4920 and total sCD40L concentrations compared to subjects who were negative or had low ADA titers.

VIB4920 was assessed in a subsequent phase1b, randomized, double-blind, placebo-controlled, multiple ascending dose (MAD) study (D5100C00002) to evaluate the safety, tolerability, PK, immunogenicity, PD, and clinical response of VIB4920 in 57 subjects with moderate-to-severe adult-onset RA as defined by Disease Activity Score in 28 Joints Using C-reactive Protein

(DAS28-CRP) > 3.2 at screening and an inadequate response to MTX or other cDMARDs and/or a biologic anti-TNFα agent (Karnell et al, 2019). Subjects received VIB4920 (N = 42) at doses of 75, 500, 1000, or 1500 mg or placebo (N = 15) by IV infusion every other week for a total of 7 doses over 12 weeks followed by a 12-week follow-up period. The PK profile of VIB4920 following IV infusions suggested the absence of target-mediated clearance. Following the first IV infusion, the mean systemic clearance (CL) ranged from 405-654 mL/day in subjects with adult-onset RA. The mean terminal elimination half-life ($t_{1/2}$, last dose) was 7.8-9.7 days. The mean volume of distribution at steady state was 4.10-5.60 L, indicating limited extravascular distribution of VIB4920. Repeat administration of VIB4920 led to substantial and prolonged elevation of total sCD40L; this PD effect plateaued at doses ≥ 500 mg. ADA developed in 3/6 subjects in the 75 mg group, 3/10 subjects in the 500 mg group, 1/12 subjects in the 1000 mg group, and 0/12 subjects in the 1500 mg group. There was no apparent impact of ADA on PK, PD (total sCD40L), or safety.

VIB4920 significantly reduced disease activity as quantified by DAS28-CRP score at Day 85 in the 1000 mg and 1500 mg groups. Reductions in DAS28-CRP score were evident as early as Day 15, after a single dose of VIB4920. As compared with placebo, this reduction was both clinically and statistically meaningful in the groups receiving the 2 highest doses of VIB4920: the adjusted mean (standard error) difference compared to placebo at Week 12 for VIB4920 1000 mg and 1500 mg groups were -1.2 (0.4) and -1.4 (0.4) with p-values of 0.006 and 0.002, respectively. Low disease activity or DAS28-CRP remission (score of ≤ 3.2) was achieved in 50% of subjects at 1000 mg and 75% at 1500 mg compared to 13.4% in placebo at Day 85. 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. A statistically significant reduction in RF was observed over placebo for the 500 mg (34.9%; p = 0.010), 1000 mg (44.6%; p < 0.001), and 1500 mg (48.0%; p < 0.001) doses at Day 85. The adjusted mean difference vs placebo in Vectra DA® score from baseline to Day 85 was -10.3 (90% confidence interval [CI]: -17.4, -3.3; p = 0.018) and -14.4 (90% CI: -21.5, -7.2; p = 0.001) for the 1000 mg and 1500 mg doses, respectively. The safety profile of VIB4920 in subjects with adult-onset RA was acceptable for further development.

2.1.5.1 Summary of Safety Experience

VIB4920 has been shown to be well-tolerated and to have an acceptable safety profile in both animals and humans. Animal toxicology is described in the IB.

The safety of VIB4920 was evaluated in single-ascending dose (SAD) clinical study in healthy volunteers and in a MAD study in subjects with active RA. Overall, VIB4920 was well-tolerated with a balanced distribution of TEAEs observed between placebo and the active dose groups in both studies. There were no infusion-related reactions, severe infections or deaths (Karnell et al, 2019). One serious adverse event (SAE) of fractured tibia was reported in the placebo group in the SAD study. VIB4920 showed inhibition of the TDAR IgG response after the second administration of KLH on Day 15 at higher doses ≥ 300 mg.

In the MAD study in RA, VIB4920 was generally well-tolerated with a balanced distribution of TEAEs between placebo and the 4 active groups. There were few clinically significant laboratory abnormalities. One Grade 4 SAE of encephalitis occurred in the 1500 mg cohort that was

considered by the Investigator to be unrelated to investigational product (IP). After completion of follow-up in the study, the subject had a recurrence of similar symptoms and was diagnosed with metastatic melanoma of the brain.

In both studies, there was a decrease in ADA incidence and titers observed with increasing doses of VIB4920, consistent with the immunosuppressive mechanism of action of VIB4920. There was no identified association of ADA with any TEAEs reported in either study.

2.1.6 Risk Assessment

[redacted]

[redacted]

[redacted]

2.1.6.5 Exposure in Utero

No embryo-fetal studies have been conducted to date.

2.2 Study Rationale

VIB4920 is being developed for the treatment of B-cell dependent autoimmune disease, including RA. Based on the data in support of the role of both B cells and CD40L in the pathogenesis of RA, and the medical need for new treatments for RA, the efficacy and safety of VIB4920 are being explored in the current study.

Data from previous studies also provide a rationale for the current study. In the phase 1a SAD study (D5100C00001) in healthy volunteers, VIB4920 was shown to have an acceptable safety profile for further development and to result in a dose-dependent increase in total sCD40L, indicating binding of VIB4920 to sCD40L and target engagement. A phase 1b MAD study (D5100C00002) in subjects with adult-onset RA demonstrated an acceptable safety profile in subjects and provided preliminary clinical and [redacted] in support of the potential efficacy of VIB4920 for the treatment of RA.

The current study is designed to further characterize the safety and tolerability of single and multiple IV doses of VIB4920 in subjects with adult-onset RA and to obtain an assessment of efficacy and effects on biomarkers in these subjects. These data, along with PK and PD data, will be useful in the selection of dose and dosing interval for further development.

After this study was opened to enrollment in December 2019, the onset of the pandemic caused by SARS-CoV-2 resulted in temporary closure 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 RA on or off treatment (Favalli et al, 2020, Gianfrancesco et al, 2020), and there are no data on the effect of VIB4920 on this risk. A potential risk of VIB4920 is infection (See Section 2.1.6.3 Infections), based on its mechanism of action. The subjects in this study, however, have the health risk of active RA despite treatment

and the potential of the benefit, based on data from the Phase 1b study, of improvement in their RA in response to treatment with VIB4920. In addition, the standard of care for their treatment is likely to include a drug that can increase the risk of infection.

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

1. 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.
2. 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.
3. Ensuring that the subject has a documented negative SARS-CoV-2 viral test within two 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 supports re-opening the study.

2.3 Study Hypotheses

1. VIB4920 will reduce disease activity in subjects with adult-onset RA of moderate to high systemic activity.
2. VIB4920 will be well-tolerated and have an acceptable safety profile in subjects with adult-onset RA.
3. The duration of reduction in disease activity and PD parameters observed after dosing will inform dose selection for further study.

3 OBJECTIVES AND ENDPOINTS

3.1 Primary Objectives and Endpoints

3.1.1 Primary Objectives

- To evaluate the effect of VIB4920 on disease activity as assessed by a composite measure in subjects with adult-onset RA.
- To evaluate the safety and tolerability of VIB4920 in subjects with adult-onset RA.

3.1.2 Primary Endpoints

- Change in DAS28-CRP from baseline to Day 113.
- The incidence of TEAEs and treatment-emergent serious adverse events (TESAEs) and treatment-emergent AEs of special interest (AESIs) during the study. AESIs include:
  - Thrombotic and embolic events
  - Anaphylaxis and clinically significant (Grade 3 or higher) hypersensitivity reactions (see Appendix 1)

- Severe infusion-related reactions (Common Terminology Criteria for Adverse Events [CTCAE] Grade 3 or higher)
- Immune complex disease
- Severe (Grade 3 or higher) and/or opportunistic infections
- Hepatic function abnormality meeting the definition of Hy's Law (see Appendix 2)
- Malignant neoplasm

3.2 Secondary Objectives and Endpoints

3.2.1 Secondary Objectives

- To characterize the PK of VIB4920 in subjects with adult-onset RA
- To evaluate the PD effect of VIB4920 in subjects with adult-onset RA
- To evaluate the immunogenicity of VIB4920 in subjects with adult-onset RA
- To evaluate the effect of VIB4920 on autoantibodies in subjects with adult-onset RA
- To assess the effect of VIB4920 on clinical remission as assessed by a composite measure in subjects with adult-onset RA
- To evaluate the duration of clinical response to VIB4920 as assessed by time to institution of rescue therapy

3.2.2 Secondary Endpoints

- The PK profile of VIB4920
- The time-concentration profile of total sCD40L
- The proportion of subjects with ADAs to VIB4920
- Change in RF and ACPAs from baseline to Day 113
- The proportion of subjects with clinical remission defined as DAS28-CRP < 2.6 at Day 113
- Time to start of new treatment for RA (rescue medication)

3.3 [redacted]

3.3.1 [redacted]

- [redacted]
- [redacted]
- [redacted]
- [redacted]

3.3.2 [redacted]

- [redacted]
- [redacted]

[redacted]

4 STUDY PLAN

4.1 Study Design

This is a multicenter, randomized, double-blind (Investigator, subject, and Sponsor will be blinded to treatment assignment), placebo-controlled, parallel-cohort study to evaluate the safety, efficacy, and PK of VIB4920 in adults with active, moderate-to-severe adult-onset RA (DAS28-CRP > 3.2; [redacted] and presence of serum RF and/or ACPA who have had an inadequate response to MTX, cDMARD, or an anti-TNFα agent; who are not currently receiving an anti-TNFα agent; and who have had no prior treatment with rituximab or B-cell depletive agents. The study is planned to be conducted at approximately 30 sites in 2-4 countries.

After a screening period of up to 28 days, approximately 75 subjects will be randomized in a 1:1:1:1:1 ratio using an interactive voice/web response system (IXRS) into 5 cohorts:

Cohort 1: VIB4920 1500 mg on Days 1, 15, 29, and 57 (N = 15)

Cohort 2: VIB4920 1500 mg on Days 1 and 57, placebo on Days 15 and 29 (N = 15)

Cohort 3: VIB4920 3000 mg on Days 1 and 57, placebo on Days 15 and 29 (N = 15)

Cohort 4: VIB4920 3000 mg on Day 1 and placebo on Days 15, 29, and 57 (N = 15)

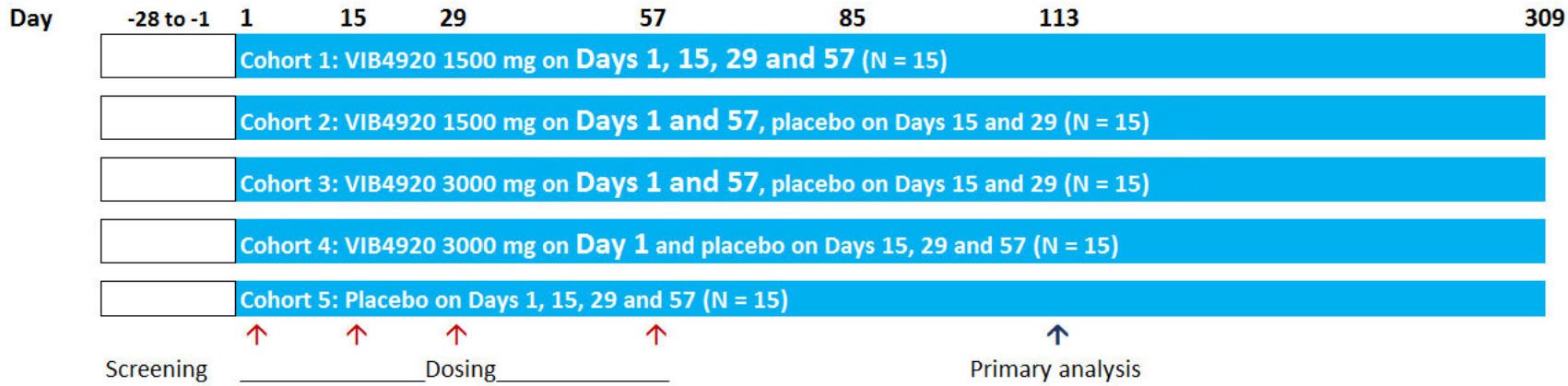
Cohort 5: Placebo on Days 1, 15, 29, and 57 (N = 15)

A study schematic is presented in Figure 1.

Subjects are to be followed on their stable background anti-RA therapy at least through 12 weeks (Day 85), at which time rescue therapy may be instituted. All subjects are followed at least through the primary (interim) analysis (Day 113), and those who have not instituted rescue therapy will be followed through Day 309 to determine the duration of clinical response.

The primary analysis will be after all subjects have completed Day 113, and the final analysis will be after all subjects have completed follow-up.

Figure 1 Study Flow Diagram



N = total number of subjects planned for each cohort.

4.2 Dose and Treatment Regimen Rationale

All subjects in this study receive the background therapy that was established for them by their personal physician. Although there is use of a placebo in this study, no subject is untreated, and both placebo and VIB4920 are add-on therapies to the subject's treatment. To accomplish the research aims of this study and to permit an assessment of the efficacy of VIB4920 in a pre-treated population, subjects are asked, but not required, to delay institution of any new treatment for RA for 12 weeks (Day 85), a limited period not expected to result in significant harm, to permit this assessment (FDA draft guidance, 2013).

The safety, tolerability, and PD effects of a single IV dose of up to 3000 mg of VIB4920 in healthy volunteers and multiple IV doses of up to 1500 mg in subjects with adult-onset RA have been assessed. No dose-limiting toxicities were identified in these human studies, and the observed safety profiles were acceptable for continued development. No thrombotic events were observed, and no infusion-related reactions were observed.

In subjects with RA in a MAD study, VIB4920 doses of 1000 mg and 1500 mg every 2 weeks for 3 months were efficacious in significantly decreasing disease activity, and this clinical efficacy persisted for at least 3 months after the last dose. Low disease activity or clinical remission at Day 85 was achieved in 50% and 75% of subjects in the 1000 mg and 1500 mg dose groups, respectively, per the DAS28-CRP score.

Four dosing regimens with varying dosage levels and dosing intervals were selected for the evaluation of the efficacy and safety of VIB4920 in adult subjects with RA in this phase 2 study.

The cohort 1 dosing regimen was selected to be similar to dosing in subjects with RA that was observed to be efficacious in the MAD study.

Cohorts 2 and 3 explore less frequent dosing that, based on the duration of clinical effect observed in the MAD study, might improve the patient experience without compromising clinical efficacy.

The cohort 4 dosing schedule was selected to determine the effect of a single induction dose on the duration of clinical response. Given the previously observed long duration of activity, a strategy of higher induction dose with a longer dosing interval may be effective.

Data generated on the clinical effect of VIB4920 in these dosing cohorts will aid in the selection of dosing strategies for future studies.

4.3 Rationale for Study Population

Subjects will be adults diagnosed with adult-onset RA according to the European League Against Rheumatism (EULAR)/ACR 2010 criteria (Aletaha et al, 2010) at least 6 months prior to screening. Subjects must, based on moderate-to-severe disease despite DMARD therapy, have failed a prior regimen. To avoid confounding interpretation of safety and efficacy data based on the use of prior biologics, especially B-cell depletive agents, patients with prior use of these drugs, other than prior but not current use of TNFα inhibitors, are excluded. Patients must have at least 4 tender and 4 swollen joints to permit assessment of joint response during the study.

This DMARD-experienced population represents one at high medical need, and it is the population in which VIB4920 was previously studied and in which the 2 highest doses of

VIB4920 demonstrated clinically meaningful, sustained clinical benefit with an acceptable safety profile. Use of a similar population will contribute to assessment of dosing strategies and expand the understanding of the safety of the combination of VIB4920 with MTX.

4.4 Rationale for Primary Endpoint Selection

The primary efficacy endpoint, the change in DAS28-CRP from baseline to Day 113, is a standardized measure that is widely used in clinical trials of RA and in the care of patients with RA (Prevoo et al, 1995).

The primary endpoints for the assessment of safety, which are the incidence of TEAEs, TESAEs, and AESIs, are widely used and accepted methods to assess safety in clinical trials. Other important safety parameters will be assessed, including vital signs, laboratory parameters, electrocardiograms (ECGs), and physical examinations; if clinically important, they will be recorded as adverse events (AEs) or SAEs.

5 POPULATION

5.1 Inclusion Criteria

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

1. Male or female adults, ≥ 18 years of age at time of informed consent.
2. 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 prior to performing any protocol-related procedures, including screening evaluations.
3. Diagnosed with RA according to the EULAR/ACR 2010 criteria (Aletaha et al, 2010) ≥ 6 months prior to screening.
4. DAS28-CRP > 3.2 at screening with [redacted] assessed for DAS28 present at screening and confirmed present at Visit 2 prior to randomization.
5. Positive for RF and/or ACPA at screening, in accordance with criteria at the central laboratory.
6. Treated with MTX given orally, SC, or intramuscularly at a dose of 7.5-25.0 mg/week, with or without a concomitant cDMARD other than leflunomide, with MTX and the cDMARD delivered by the same route for ≥ 12 weeks without change in dose for ≥ 6 weeks prior to screening,

   OR, if MTX intolerant or if MTX is contraindicated, treated with one or more cDMARD for ≥ 12 weeks without change in dose for ≥ 6 weeks prior to screening. (JAK inhibitors are not considered cDMARDs).
7. Willing and able to comply with the protocol, complete study assessments, and complete the study period.
8. Females of childbearing potential who are sexually active with a non-sterilized male partner must use a highly effective method of contraception (Table 1) from signing informed consent and must agree to continue using such precautions through the end of the follow-up of the study; cessation of contraception after this point should be discussed with a responsible physician. 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 will be made.

a. Females of childbearing potential are defined as those who are not surgically sterile (ie, surgical sterilization includes bilateral tubal ligation, bilateral oophorectomy, or hysterectomy) or those who are not postmenopausal (defined as 12 months with no menses without an alternative medical cause and a follicle-stimulating hormone within the postmenopausal range as established by the clinical laboratory).
b. Because some of the background medications used in RA and accepted in the current study (eg, MTX or leflunomide) are known to have potential deleterious effects on conception, pregnancy, and fetal health, the Investigator must inform the subjects about these risks and should manage every case of planned conception or pregnancy according to the local medical practice standards.

9. Non-sterilized 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.

Table 1 Highly Effective Methods of Contraception for Females of Childbearing Potential

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

a This is also considered to be a hormonal method.
b With appropriate post-vasectomy documentation of surgical success (absence of sperm in ejaculate).
c Sexual abstinence is considered to be a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of the study and if it is the preferred and usual lifestyle of the patient.
d Progestogen-only hormonal contraception, where inhibition of ovulation is not the primary mode of action (minipill) is not accepted as a highly effective method.

5.2 Exclusion Criteria

Any of the following excludes an individual from participation in the study:

1. Prior or current (1) inflammatory joint disease other than RA (eg, gout, reactive arthritis, psoriatic arthritis, seronegative spondyloarthropathy, Still's disease, or Lyme disease); (2) other systemic autoimmune disorder (eg, systemic lupus erythematosus, inflammatory bowel disease, scleroderma, inflammatory myopathy, mixed connective tissue disease, or

other overlapping syndrome) or polymyalgia rheumatica except that patients with RA and secondary Sjögren's syndrome may enroll.
2. Severe interstitial lung disease.
3. Prior receipt of any biologic B-cell-depleting therapy (eg, rituximab, ocrelizumab, ofatumumab).
4. Receipt of any anti-TNFα biologic agent < 8 weeks prior to screening (discontinuation could have been for any reason: lack of efficacy, safety/tolerability issues, or lack of access to drug).
5. Receipt of any bDMARD with a mechanism of action other than direct TNF blockade, including any JAK inhibitor, < 12 weeks or < 5 half-lives of the drug (whichever is longer) prior to screening.
6. Receipt of any experimental therapy < 12 weeks or < 5 half-lives of the drug (whichever is longer) prior to screening.
7. Injectable corticosteroids (including intraarticular) or treatment with > 10 mg/day dose of oral prednisolone or equivalent within 4 weeks prior to screening. Concomitant treatment with oral corticosteroids ≤ 10 mg/day prednisone or equivalent is permitted provided that the dose is stable for ≥ 4 weeks prior to screening and during the screening period 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.
8. Previous treatment with anti-CD40L compounds at any time before randomization.
9. History of confirmed deep venous thrombosis or arterial thromboembolism within 2 years of enrollment OR history of recurrent deep venous thrombosis or arterial thromboembolism OR 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, known congenital or inherited deficiency of antithrombin III, protein C, protein S, or confirmed diagnosis of catastrophic antiphospholipid syndrome).
10. Treatment with anticoagulant drugs (clopidogrel, prasugrel, warfarin, low molecular weight heparin, others). Low-dose aspirin treatment (up to 325 mg/day) is allowed.
11. History of solid organ or cell-based transplantation.
12. Active malignancy or history of malignancy that was active within the last 15 years, except as follows:
    a. In situ carcinoma of the cervix following apparently curative therapy > 12 months prior to screening; or
    b. Cutaneous basal cell or squamous cell carcinoma following apparently curative therapy.
13. Pregnancy, lactation, or planning to become pregnant during the duration of the study.
14. Positive test for, or prior treatment for, hepatitis B, hepatitis C, or HIV infection. A positive test for hepatitis B is detection of either (1) hepatitis B surface antigen (HBsAg); or (2) hepatitis B core antibody (anti-HBc).
15. Evidence of active tuberculosis (TB) or being at high risk for TB based on:

a. History of active TB or untreated/incompletely treated latent TB. Patients with latent TB who have documentation of completion of treatment according to local guidelines may be enrolled.
b. History of recent (≤ 12 weeks prior to screening) close contact with someone 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).
c. Signs or symptoms that could represent active TB by medical history or physical examination.
d. Positive, indeterminate or invalid interferon-gamma release assay test result at screening, unless previously adequately treated for latent TB. Patients with an indeterminate test result can repeat the test once, but if the repeat test is also indeterminate, the patient is excluded.
e. Chest radiograph that suggests a possible diagnosis of TB or suggests that a work-up for TB should be considered; all patients must have had a chest radiograph with an acceptable reading within 6 months prior to screening or at screening.

16. History of (a) more than one episode of herpes zoster in the 12 months prior to screening or (b) any opportunistic infection in the 12 months prior to screening, excluding localized mucocutaneous candidiasis.
17. Known history of severe allergy or reaction to any component of the IP formulation.
18. 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 patient at unacceptable risk of complications, interfere with evaluation of the IP, or confound the interpretation of patient safety or study results.

    Subjects should be assessed for 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.

    Ensure that the subject has a documented negative SARS-CoV-2 test within two 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.

19. Inflammatory osteoarthritis.
20. Receipt of live vaccine or live therapeutic infectious agent within the 4 weeks prior to screening.
21. Blood tests at screening that meet any of the following criteria:

    a. Aspartate aminotransferase (AST) > 2 × upper limit of normal (ULN) for the central laboratory
    b. Alanine aminotransferase (ALT) > 2 × ULN

c. Total bilirubin (TBL) > 2 × ULN unless AST, ALT, and hemoglobin are within central laboratory normal range and the patient has a known history of Gilbert syndrome
d. Hemoglobin < 85 g/L
e. Neutrophils < 1.5×10^9/L
f. Platelets < 100×10^9/L
g. Prothrombin time or partial thromboplastin time (PTT) > 1.2 x ULN

22. History of alcohol or drug abuse that, in the opinion of the Investigator, might affect patient safety or compliance with visits, or interfere with safety or other study assessments.

Repeat of screening laboratory tests

Repeat of study laboratory tests noted below is acceptable in the event that an initial screening safety laboratory result is outside of acceptable limits for the study. If the initial value is exclusionary, and the investigator considers the value to be a potential outlier not representative of the subject's true state of health, testing may be repeated once, using the central laboratory, at the investigator's discretion, in accordance with the following:

- This applies to serum hematology, coagulation and chemistry parameters only.
  - It does not apply to hepatitis B, hepatitis C, HIV, RF, ACCP, or CRP tests, which may not be repeated (unless for technical reasons there is no study result)
  - Repeat of inconclusive or positive Quantiferon test must be handled as in exclusion 15
  - A positive SARS-CoV-2 test must be handled as in exclusion 18.
- The subject must be within the initial 28-day screening period. If the 28-day screening period has elapsed, the subject must be fully rescreened in accordance with protocol requirements.
- The blood test is repeated in the central laboratory.
- The blood test is repeated only once.

Rescreening Procedures: Patients may be rescreened once if, in the Investigator's judgment, the reason for ineligibility is likely to have resolved at the time of rescreening.

6 STUDY CONDUCT

Subjects will undergo a screening period of up to 28 days followed by randomization on Day 1. Subjects will receive 4 doses of IP (VIB4920 or placebo) on Day 1, Day 15 (± 1 day), Day 29 (± 3 days), and Day 57 (± 3 days). Thereafter, subjects will be followed for safety and to assess duration of efficacy. The expected full duration of each subject's participation in this study is up to 337 days.

6.1 Schedules of Study Assessments

Table 2 summarizes the screening procedures for the study. In some cases, more than one screening visit may be required to complete all procedures.

Table 2 Screening Assessments and Procedures

Study Period	**Screening**
Visit Number	**V1**
Study Day **Procedure**	**Day -28 to Day -1**
Written informed consent and IXRS assignment of SID number	X
Medical history	X
Assessment of prior and concomitant medications	X
Vital signs (temperature, pulse, respiration rate, and blood pressure)	X
Assessment of AEs/SAEs [a]	X
Height and weight	X
Physical examination excluding pelvic and rectal exam	X
[redacted]	[redacted]
Physician Global Assessment of Disease Activity	X
12-lead ECG	X
Chest radiograph (posterior-anterior and lateral) if reading not available from x-ray within 6 months prior to screen	X
DAS28-CRP for RA [b]	X
Blood collection for: • Safety laboratory testing (serum chemistry, hematology, and coagulation) • Serum β-hCG pregnancy test (all females) • Follicle-stimulating hormone (potentially postmenopausal females) • Hepatitis B, hepatitis C, HIV-1, and HIV-2 testing • IGRA testing for TB • [redacted] • [redacted] • CRP, RF, and ACPA testing	X
Urine collection for urinalysis (dipstick and, for abnormal dipstick, microscopic)	X
Ensure that the subject has a documented negative SARS-CoV-2 viral test within two weeks prior to randomization	X
[redacted]	[redacted]
Verify eligibility criteria based on data from Screening Visit prior to scheduling Visit 2	X

ACPA = anti-citrullinated protein antibodies; AE = adverse event; β-hCG = serum human chorionic gonadotropin; CRP = C-reactive protein; DAS28-CRP = Disease Activity Score in 28 Joints Using C-reactive Protein; ECG = electrocardiogram; IGRA = interferon-gamma release assay; IXRS = interactive voice/web response system; [redacted]; RA = rheumatoid arthritis; RF = rheumatoid factor; SAE = serious adverse event; sCD40L = soluble CD40 ligand; SID = subject identification; [redacted]; TB = tuberculosis; [redacted]; V1 = visit 1.

a All AEs will be recorded from the date of informed consent through the end of the study.

b DAS28-CRP for RA will be calculated and the result provided to the Investigator as part of the determination of eligibility.

The schedules of study assessments for the treatment period are presented in Table 3.

Subjects should be asked to complete all PRO assessments prior to other procedures.

All laboratory sample collections and assessments that are scheduled for a dosing day must be performed prior to dosing, except for post-dose PK sampling. Safety laboratory results from the day of dosing will not be available prior to dosing because a central laboratory will perform those analyses. Any ECG performed on the day of dosing should be examined by the Investigator prior to dosing to assess the safety of dosing.

Whenever vital signs, 12-lead ECGs, and blood draws are scheduled for the same nominal time, blood draws should occur after ECGs and vital signs (temperature, pulse, respiratory rate, and blood pressure). If these investigations did not occur in this order, at least 15 minutes must elapse between blood draw and either ECG or vital signs.

Abnormal laboratory or ECG results that, in the Investigator's opinion, represent a clinically significant finding or clinically significant change from baseline should be repeated as soon as possible, preferably within 48 hours. If urgent results are needed, testing can be sent to a local laboratory, but blood for the same tests should be sent to the central laboratory as well.

The following results from Visit 2 to the end of study will not be made available to the study site personnel, subjects, or contract research organization (CRO) and Sponsor personnel directly associated with the conduct of the study, except as specified in Sections 7.2.3 and 7.2.4.2, to minimize bias and because results of some [redacted]

Table 3 Schedule of Study Assessments and Procedures

Visit number	**V2**	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9**	**V10**	**V11**	**V12**	**V13**	**V14 or EDV**
Study Day **Procedure**	**1** **Dose 1**	**15 ± 1d** **Dose 2**	**29 ± 3d** **Dose 3**	**57 ± 3d** **Dose 4**	**85 [g] ± 3d**	**113 ± 5d**	**141 ± 5d**	**169 ± 5d**	**197 ± 7d**	**225 ± 7d**	**253 ± 7d**	**281 ± 7d**	**309 ± 7d**
Assessment of AEs/SAEs/AESIs	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X	X
Patient global assessment of disease activity	X	X	X	X	X	X	X	X	X	X	X	X	X
[redacted]	■	■	■	■	■	■	■	■	■	■	■	■	■
ECG	X				X								X
Vital Signs	X [e]	X [e]	X [e]	X [e]	X	X	X	X	X	X	X	X	X
Weight	X				X								X
Full physical examination	X				X								X
Symptom-driven physical examination		X	X	X		X	X	X	X	X	X	X	
[redacted]	■	■	■	■	■	■	■	■	■	■	■	■	■
Physician global assessment of disease activity	X	X	X	X	X	X	X	X	X	X	X	X	X
DAS28-CRP for RA, [redacted]	X	X	X	X	X	X	X	X	X	X	X	X	X
Urine pregnancy test [a]	X	X	X	X	X	X	X	X	X	X	X	X	X
Urinalysis	X	X	X	X	X	X	X	X	X	X	X	X	X
Safety labs (chemistry, hematology, coagulation)	X	X	X	X	X	X	X	X	X	X	X	X	X
Total sCD40L (plasma)	X	X	X	X	X	X	X	X	X	X	X	X	X
Autoantibody panel (RF, RF isotypes)	X	X	X	X	X	X	X	X	X	X	X	X	X

Table 3 Schedule of Study Assessments and Procedures

Visit number	**V2**	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9**	**V10**	**V11**	**V12**	**V13**	**V14 or EDV**
Study Day Procedure	**1 Dose 1**	**15 ± 1d Dose 2**	**29 ± 3d Dose 3**	**57 ± 3d Dose 4**	**85 [g] ± 3d**	**113 ± 5d**	**141 ± 5d**	**169 ± 5d**	**197 ± 7d**	**225 ± 7d**	**253 ± 7d**	**281 ± 7d**	**309 ± 7d**
[redacted]	■	■	■	■	■	■	■	■	■	■	■	■	■
CRP	X	X	X	X	X	X	X	X	X	X	X	X	X
[redacted]	■	■	■	■	■	■	■	■	■	■	■	■	■
Flow cytometry sample	X	X	X	X	X	X	X	X	X	X			X
[redacted]	■				■			■					■
[redacted]	■	■	■	■	■	■	■	■			■		■
Plasma PK sample [b]	X [f]	X [f]	X [f]	X [f]	X	X	X	X	X	X			
ADA (plasma)	X	X	X		X			X			X		X
[redacted]	■	■	■	■	■	■	■	■	■	■	■	■	■
PBMC collection [c]	X	X			X			X					X
Verify eligibility criteria	X												
Randomization	X												
IP administration [d, e]	X	X	X	X									

ACPA = antibodies to citrullinated peptides; ADA = anti-drug antibody; AE = adverse event; AESI = adverse event of special interest; [redacted]; cDMARD = conventional disease-modifying anti-rheumatic drug; ECG =electrocardiogram; EDV = early discontinuation visit; [redacted]; Ig = immunoglobulin; IP = investigational product; [redacted] MTX = methotrexate; PBMC = peripheral blood mononuclear cells; PK = pharmacokinetics; RA = rheumatoid arthritis; RF = rheumatoid factor; SAE = serious adverse event; [redacted]; V = visit.

a In females of childbearing potential; result must be negative prior to dosing.
b On study days when IP is not administered, only one plasma sample for PK is required to be collected at a consistent time across the different study days.
c Whole blood will be collected on indicated days for processing to PBMCs.
d IP administration should, wherever possible, be at a consistent time of day for each dose. All procedures and blood sampling, except for postdose PK, must be performed before IP administration.

e Vital signs will be obtained prior to the start of each IP infusion, every 30 (± 5) minutes during the infusion, and at the end of the infusion (+ 5 minutes). Vital signs also will be checked every hour (± 10 minutes) during the 4-hour observation period after Dose 1 and at the end (+ 10 minutes) of the one-hour observation period after Doses 2, 3 and 4. If vital signs are abnormal, they should be repeated.

f Plasma samples for PK of VIB4920 will be collected predose (within 30 minutes prior to start of infusion), and within 10 minutes of the end of infusion.

g After the Day 85 visit, the dose of background cDMARDs and corticosteroids may be adjusted or a new cDMARD may be added (except that MTX and leflunomide may not be used concurrently and rituximab may not be added without discontinuation of VIB4920) if it is clinically indicated to improve disease management.

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.

6.2 Screening Period

All screening procedures listed in Table 2 will be performed within 28 days prior to randomization.

6.2.1 Informed Consent

Subjects officially enter the screening period following provision of informed consent.

All candidates for enrollment will sign an informed consent form (ICF) prior to any protocol -related procedures, including screening activities. Informed consent must be obtained by the Principal Investigator (PI) or a designee, such as an Investigator, with Institutional Review Board (IRB)/Independent Ethics Committee (IEC) approved qualifications. See Section 10.3 for additional details.

After signing the ICF, each subject will be assigned a subject identification (SID) number that will be used on all subject documentation.

Numbers will be assigned in ascending sequential order. This number will also correspond to the subject number entered on test materials. Rescreened patients will receive a new SID number. See Section 5.2 for limitations on rescreening.

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 (with the exception of rectal and pelvic examinations) will be conducted, including vital signs, height, and weight.

As part of the eligibility evaluation, the DAS28-CRP assessments will be performed at screening along with testing for RF and ACPA.

Subjects will also complete the PGA on an electronic tablet at a screening visit.

6.2.3 Safety Assessments at Screening

Safety-related screening assessments will include AEs, safety laboratory tests (serum chemistry, hematology, and urinalysis), coagulation parameters, chest X-ray (unless recent reading available [prior 6 months]), ECG, and serum human chorionic gonadotropin (β-hCG) pregnancy test for females. For details on safety assessments, see Section 6.4.2 and 8.

Safety tests only scheduled for screening include:

- Hepatitis B testing: HbsAg, anti-HBc
- Hepatitis C antibody
- HIV testing: HIV-1 antibody, HIV-2 antibody

- TB testing (eg, QuantiFERON®-TB Gold Test or other interferon-gamma release assay test) as per local standard of care guidelines

6.3 Randomization

[redacted]. The results of laboratory values from Visit 2 will not be available prior to randomization, which will be based on values from Visit 1.

Subjects who continue to meet all eligibility criteria 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. A randomized subject is one who has been deemed eligible and has been assigned to a treatment group.

6.4 Treatment Period

All assessments that will be conducted in the treatment period are summarized by study visit in Table 3. Efficacy assessments are described in Section 6.4.1 and safety assessments are described in Section 6.4.2.

6.4.1 Efficacy Assessments

Over the course of the study, Investigator assessments for a given subject should be completed by the same Investigator, designated physician, or qualified site personnel whenever possible.

6.4.1.1 Composite Disease Scores

DAS28-CRP: The DAS28-CRP is a composite score that includes the assessment of 28 specified joints for tenderness and swelling [redacted] the PGA, and CRP levels (mg/L) (Table 4). Calculation of the DAS28-CRP scores will use the equation in Section 9.5.1. The established definition of remission by DAS28-CRP score is DAS28-CRP < 2.6 (Anderson et al, 2012). Low disease activity is defined as DAS28-CRP ≤ 3.2, and an improvement of DAS28-CRP score > 0.6 defines a responder (Wells et al, 2009).

[redacted]

[redacted]

Table 4 summarizes the assessments that comprise each composite score. Details on the 28-joint count, MDGA, and PGA are given in Section 6.4.1.2 and details on CRP testing are provided in Section 6.4.3.2.

Table 4 Summary of Composite Disease Scores and Assessments

Assessment	Composite Disease Scores		
	DAS28-CRP	[redacted]	[redacted]
[redacted]	X	[redacted]	[redacted]
[redacted]	X	[redacted]	[redacted]
[redacted]		[redacted]	[redacted]
[redacted]	X	[redacted]	[redacted]
CRP (mg/dL)	X		X

[redacted] CRP = C-reactive protein; DAS28-CRP = Disease Activity Score in 28 Joints Using C-reactive Protein; [redacted]

6.4.1.2 Assessments for Composite Disease Scores

[redacted] in Table 3.

[redacted]

[redacted]

CRP: See Section 6.4.3.2.

6.4.1.3 Time to Start of Rescue Medication

Investigators will record on the electronic case report form (eCRF) when a subject starts rescue medication (see Section 7.4.2).

6.4.1.4 [redacted]

[redacted]

- [redacted].
- [redacted].

[redacted]

6.4.2 Safety Assessments

Safety assessments will be conducted during the active treatment period according to the assessments shown in Table 3 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: hematology, serum chemistry, coagulation parameters, and urinalysis (see Section 8.5 for details)
- Concomitant medications (see Section 7.4 for details)
- Vital signs, physical examination (full or symptom-driven depending on the visit), and body weight (see Section 8.6 for details)
- ECG (see Section 8.7 for details)
- Urine pregnancy test (for females of childbearing potential) (see Section 8.8 for details)

For definitions of safety terminology, see Section 8.1.

6.4.3 [redacted]

[redacted]

6.4.3.1 Autoantibody Panel

Serum will be collected to assess and quantify RF, RF isotypes (IgA, IgG, and IgM).

[redacted]

6.4.3.3 Flow Cytometry for B-Cell and T-Cell Subsets

Whole blood samples will be collected for the assessment of changes in the number, activation status, and frequency of B- and T-cell subsets.

6.4.3.4 Leukocyte Populations and Intracellular Cytokines

Whole blood samples will be collected for subsequent separation of peripheral blood mononuclear cells to assess change in leukocyte populations and intracellular cytokines after VIB4920 administration.

6.4.3.5 [redacted]

[redacted]

6.4.4 Immunogenicity Assessments

Plasma samples for immunogenicity (ADA to VIB4920) will be obtained prior to IP administration according to the visits specified in Table 3 and will be 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 3 and measured using a validated immunoassay.

6.4.6 [redacted]

[redacted].

6.5 Discontinuation or Withdrawal

6.5.1 [redacted]

[redacted]

The reason(s) for discontinuing IP must be recorded on the appropriate page of the eCRF.

6.5.2 Withdrawal from Study

Subjects who discontinue IP and have not received rescue therapy should remain in the study and complete all study visits and assessments with the exception of those directly related to dosing, unless they have withdrawn consent for study participation or withdrawn consent for specific assessments (if subjects will not agree to return for visits, safety data can be collected by telephone call if subjects agree). Subjects who discontinue IP following the initiation of rescue therapy will complete the study according to procedures in Section 7.4.2.

Subjects who choose to discontinue IP or withdraw from the study will be asked for the reason for discontinuation or withdrawal, such as an AE, lack of efficacy, or other reason, and the reason will be recorded in the eCRF.

Subjects who wish to withdraw from the study will be invited to return, if willing, for a single additional early discontinuation visit (EDV) unless all study procedures to be completed at the EDV visit had been completed within the past 30 days.

6.5.3 Replacement of Subjects

Subjects will not be replaced after randomization.

6.5.4 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 the steps taken to contact the subject, eg, dates of telephone calls, registered letters, etc.

Efforts to ensure complete subject follow-up include proactive site contact of subjects who have missed visits (at least 3 documented attempts to reach by telephone and at least 3 documented attempts to reach by letter) or through emergency/other contact if subjects have provided such contacts. Email can be used for contact and scheduling of visits as long as subjects have given permission for email contact.

6.6 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.

If Viela Bio determines that temporary suspension or termination of the study is required, Viela Bio will communicate the reasons for taking such action to all participating investigators (or head of the medical institution, where applicable). When feasible, Viela Bio 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, Viela Bio will promptly inform all investigators, heads of the medical institutions (where applicable), and/or institutions conducting the study. Viela Bio 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/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.

6.7 End of Study

The study will be completed once the last active subject has completed all assessments listed for Visit 14 (Day 309 ± 7 days). If the last active subject has received rescue therapy, the study will end when that subject completes participation according to the procedures described in Section 7.4.2.

7 STUDY INTERVENTIONS

7.1 Description of Products

Table 5 provides a description of IP to be used in the study. Details are presented in the following sections.

Table 5 Description of Investigational Products

IPs	Concentration and Formulation as Supplied	Manufacturer
[redacted])	[redacted]	[redacted]
Placebo	0.9% (w/v) saline	Provided by site

IP = investigational product; IV = intravenous; w/v = weight/volume.

7.1.1 VIB4920

7.1.1.1 Inspection, Storage, and Handling

Each vial selected for dose preparation should be inspected. VIB4920 is supplied as a clear to opalescent, colorless to yellow liquid; free from, or practically free from, visible particles. VIB4920 is a sterile liquid Drug Product (500 mg VIB4920 per vial, nominal) intended for IV infusion following dilution in normal saline.

If there are any defects noted with VIB4920, the Investigator and site monitor should be notified immediately.

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 2ºC to 8ºC (36ºF to 46ºF) in a 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.

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 IV infusion bags made of polyolefin or polyvinyl chloride 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.

The total allowable in-use storage time from the time of the first vial puncture of VIB4920 to start of IV bag administration should not exceed 4 hours at room temperature or 24 hours at 2°C to 8°C. However, 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.

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

The dose preparation steps for 1500 mg are as follows:

One kit (3 vials) of VIB4920, one 250 mL IV bag containing 0.9% (weight/volume [w/v]) saline, and one IV infusion pump are required for administration of each 1500 mg dose of VIB4920.

- 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 with an opaque cover to protect blinding.

The dose preparation steps for 3000 mg are as follows:

Two kits (6 vials) of VIB4920, one 250 mL IV bag containing 0.9% (w/v) saline, and one IV infusion pump are required for administration of each 3000 mg dose of VIB4920.

- 30.0 mL of 0.9% (w/v) saline should be removed from a prefilled 250 mL IV bag.
- 30.0 mL of VIB4920 will be obtained from six (6) 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 with an opaque cover to protect blinding.

IP must be infused through a low-protein binding 0.2 - 0.22 µm in-line filter.

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

IP administration should, wherever possible, be at a consistent time of day for each dose. Vital signs will be obtained prior to the start of each IP infusion, every 30 (± 5) minutes during the infusion, and at the end of the infusion (+ 5 minutes). Vital signs also will be checked every hour (± 10 minutes) during the 4-hour observation period after Dose 1 and at the end (+ 10 minutes) of the one-hour observation period after Doses 2, 3, and 4. If vital signs are abnormal, they should be rechecked.

IP will be infused using an IV infusion pump. An experienced and qualified staff member will place the IV access. Infusion times will be as per Table 6. For Doses 1 and 4, IP will be either VIB4920 1500 mg, VIB4920 3000 mg, or placebo (Table 7). For Doses 2 and 3, IP will be either VIB4920 1500 mg or placebo.

Table 6 Infusion Times

Dose 1, Day 1 Infusion Time (VIB4920 mg/min)[a, b]	**Dose 2, Day 15 Infusion Time (VIB4920 mg/min) [a, c, d]**	**Dose 3, Day 29 Infusion Time (VIB4920 mg/min)[a, d]**	**Dose 4, Day 57 Infusion Time (VIB4920 mg/min)[a, d,]**
120 min (~13-25 mg/min)	60 min (25 mg/min)	60 min (25 mg/min)	90 min (~17-33 mg/min)

SDMC = Safety Data Monitoring Committee.

a Or placebo matched to that dose of VIB4920.

b If, after dosing of at least 4 subjects with Dose 1, > 25% of the subjects dosed have a Grade 2 or higher infusion reaction, all subsequent doses that could include 3000 mg (ie, Dose 4) will be administered over 180 minutes(~8-17 mg/min) and Doses 2 and 3 will be administered over 120 minutes (~13 mg/min).

c If > 25% of the subjects dosed have a Grade 2 or higher infusion reaction, Dose 3 will be administered over 120 minutes and Dose 4 will be administered over 180 minutes.

d For other scenarios, dose reactions will be reviewed by the SDMC or SDMC Chair to recommend dose duration.

Table 7 Summary of Treatments by Cohort and Dose Day

Cohort	Dose 1, Day 1	Dose 2, Day 15	Dose 3, Day 29	Dose 4, Day 57
Cohort 1	VIB4920 1500 mg	VIB4920 1500 mg	VIB4920 1500 mg	VIB4920 1500 mg
Cohort 2	VIB4920 1500 mg	Placebo	Placebo	VIB4920 1500 mg
Cohort 3	VIB4920 3000 mg	Placebo	Placebo	VIB4920 3000 mg
Cohort 4	VIB4920 3000 mg	Placebo	Placebo	Placebo
Cohort 5	Placebo	Placebo	Placebo	Placebo

Subjects who have had an infusion-related reaction of Grade 1 or Grade 2 may be premedicated prior to subsequent dosing with antihistamines and/or acetaminophen in accordance with doses in the package instructions. For details on grading of infusion-related reactions, refer to Section 8.4.

The study SDMC will also monitor infusion-related reactions to suggest appropriate rate of infusion and use of pre-medications if infusion-related reactions are observed.

A physician must be present at the site or immediately available to respond to emergencies during administration of IP. Appropriate drugs and medical equipment to treat acute hypotensive, bronchoconstrictive, or anaphylactic reactions must be immediately available and study personnel must be trained to recognize and treat these reactions. Additionally, appropriate drugs and medical equipment to treat infusion-related reactions must be immediately available, and study personnel must be trained to recognize and treat infusion-related reactions. Fully functional resuscitation facilities should be available.

To monitor for infusion and/or hypersensitivity reactions, subjects will be closely monitored in a clinical study facility with personnel, drugs, and medical equipment nearby for at least 4 hours after the end of the infusion for the first dose. Subsequently, subjects must remain in the clinical study facility for at least 1 hour after each dose.

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

7.1.1.4 Investigational Product Accountability

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

7.1.1.5 VIB4920 Handling and Disposal

The Investigator or designee must return any unused vials of VIB4920 to Viela Bio 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 IPs have been returned and that no IPs remain at the site. As an alternative to returning unused IP at the end of the study, the Investigator may destroy unused IP on site with agreement from Viela Bio.

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 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 1:1:1:1:1 by IXRS to Cohorts 1 to 5 using a parallel-cohort design.

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 are 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, Investigators, site staff, Sponsor, CRO 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 with an opaque bag to maintain the blind.

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 the Primary (Interim) Analysis

The primary efficacy analysis will be conducted after all subjects have completed the Day 113 visit (Visit 7) or discontinued early from the study. As the primary analysis will be an interim analysis, a small prespecified number of Sponsor staff who are not directly involved in the conduct of the study will be unblinded for decision-making purposes. Study site personnel, subjects, and CRO and Sponsor personnel directly associated with the conduct of the study will remain blinded to the treatment assignment for individual subjects and the results of the primary (interim) analysis until the completion of the study.

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 Concomitant Medications and Treatments

Although subjects are asked to remain on their stable background medications until the Day 85 visit, subjects should receive all medications, including treatments for RA, that are considered by their physician to be necessary for their health.

The Sponsor recommends that Investigators ensure that all patients are up to date with required vaccinations prior to entry into the study.

7.4.1 Prohibited Medications

If a subject receives any of the listed prohibited medications after the screening visit and prior to Day 85, the Investigator must notify the Sponsor/designee Medical Monitor immediately. These changes in medications must be clearly recorded, with the reason for the change, in the eCRF. The prohibited medications are:

- Rescue medication prior to Day 85 (defined in Section 7.4.2)
- Investigational agents
- Live vaccines or live therapeutic infectious agents
- Plasmapheresis or plasma exchange

7.4.2 Rescue Therapy

Rescue therapy is any new or intensified immunosuppressive, conventional, or bDMARD treatment for RA, including:

- Initiation of or increase in dose of any cDMARD
- Initiation of a bDMARD therapy or JAK inhibitor therapy
- Increase in baseline corticosteroid dose
- Intraarticular steroid injection > 40 mg methylprednisolone (or its equivalent) OR more than one intraarticular steroid injection of any dose. One intraarticular steroid injection ≤ 40 mg methylprednisolone in one joint is permitted and not considered rescue therapy.

If a subject receives rescue therapy prior to the final dose of IP, IP will be discontinued (Section 6.5.1).

Subjects administered rescue therapy do not need to be followed until Day 309 but can complete the study at or after Day 113. Subjects must also complete a 3-month safety follow-up period after the final dose of IP and must return for at least one visit after initiating rescue therapy to complete remaining assessments (Table 8).

Table 8 Alternate Study Completion Schedules Following Rescue Therapy

Last Dose Prior to Rescue Therapy	Last Study Visit
≤ Dose 3 (Day 29 ± 3d)	Day 113 OR + 1 visit post-initiation of rescue therapy, whichever is later
≥ Dose 4 (Day 57 ± 3d)	Day 141 OR + 1 visit post-initiation of rescue therapy, whichever is later

Note: All actions include the required Day 113 visit, 3 months of follow-up, and one visit post-initiation of rescue therapy.

8 SAFETY ASSESSMENTS

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 11.1 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** – A 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 to a concomitant drug and/or typical disease-related event)

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

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

- **Adverse reaction** – An adverse reaction is any AE caused by a drug.
- **Suspected adverse reaction** – A SAR is any AE for which there is a reasonable possibility that the drug caused the AE. For the purposes of safety reporting to regulatory agencies, "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 an adverse reaction.
- **Unexpected** – An event is considered unexpected if it is not listed in the 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. 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 study, 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:

[redacted]

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

[redacted]

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 one calendar day of initial receipt for fatal and life-threatening events and within 5 calendar days of initial receipt for all other SAEs.

Viela Bio or designee is responsible for notifying the relevant regulatory authorities of certain events. It is the PI'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 an AE of scientific and medical interest specific to understanding of the IP and may require close monitoring and collection of additional information by the Investigator. An AESI may be serious or nonserious. The rapid reporting of AESIs allows ongoing surveillance of these events in order to characterize and understand them in association with the use of this IP.

The following AESIs will be particularly monitored in this study and should be reported to ICON Patient Safety within 24 hours of awareness as in Section 8.3.

- Thrombotic and embolic events
- Anaphylaxis and clinically significant (Grade 3 or higher) hypersensitivity reactions (see Appendix 1 for guidance on diagnosis of anaphylaxis reactions)
- Severe infusion-related reactions (CTCAE Grade 3 or higher; Table 9)

- Immune complex disease
- Severe (Grade 3 or higher) and/or opportunistic infections
- Hepatic function abnormality meeting the definition of Hy's Law (see Appendix 2)
- Malignant neoplasm

Table 9 CTCAE Grading of Infusion-related Reactions

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 hrs
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
Grade 5	Death

CTCAE = Common Terminology Criteria for Adverse Events; IV = intravenous; NSAID = nonsteroidal anti-inflammatory drug.
Note: These CTCAE grades are specific to infusion-related reactions.
Source: Common Terminology Criteria for Adverse Events v5.

8.5 Clinical Laboratory Findings

Blood, urine and respiratory (swab or saliva) samples will be collected for laboratory safety tests as specified in the Schedule of Assessments shown in Table 2 (screening) and Table 3 (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 white blood cell count (WBC) and differential (basophils, eosinophils, lymphocytes, monocytes, and neutrophils), hemoglobin, hematocrit, and platelet count.

8.5.2 Serum Chemistry

Serum chemistry assessments will include:

- Albumin
- Alkaline phosphatase (ALP)
- ALT
- AST
- Bicarbonate
- Blood urea nitrogen
- CRP
- Calcium
- Chloride
- Cholesterol
- Creatinine
- HbA1C
- Immunoglobulins: Total, IgA, IgG, and IgM
- Magnesium
- Phosphorus
- Potassium
- Sodium
- TBL (if > 1.5 ULN, indirect and direct bilirubin will be measured)
- Total protein
- Triglycerides (fasting not required unless abnormal at baseline, in which case an 8-hour fast is required)

- Gamma-glutamyl transferase
- Glucose (random)
- Uric acid

Tests for AST, ALT, ALP, and TBL must be conducted concurrently and assessed concurrently.

8.5.3 Coagulation Parameters

Coagulation parameters will include prothrombin time and PTT.

8.5.4 Urinalysis

Urinalysis will evaluate color, appearance, and specific gravity. Dipstick analysis will include pH, protein, glucose, blood, ketones, and bilirubin. Samples with abnormal dipstick will have microscopy performed. Microscopy will include WBC/HPF (high power field) and red blood cell count/HPF.

8.5.5 Testing for SARS-CoV-2

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

8.6 Vital Signs, Body Weight, and Physical Examinations

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 2 (screening), Table 3 (treatment period), and the IP Administration Manual.

Depending on the visit, physical examinations will be either a full examination (with the exception of rectal and pelvic examinations) or a symptom-driven examination.

8.7 Electrocardiogram

A 12-lead ECG will be performed according to the schedule of assessments in Table 2 (screening) and Table 3 (treatment period). All ECG recordings will be made with the subject in a supine position, having rested in this position for at least 5 minutes before the start of the ECG.

Each ECG will include ventricular heart rate and intervals (PR, QRS, QT, QTc). The Investigator will be responsible for providing an interpretation of the ECG. Clinically significant abnormalities will be recorded as AEs.

8.8 Pregnancy

Serum β-hCG pregnancy test(s) will be completed for all females during the screening period and urine pregnancy tests will be completed in females of childbearing potential at all subsequent study visits (Table 3). At Visits 2 through 5 (dosing visits), pregnancy testing must be completed prior to administration of IP. Urine pregnancy tests will be performed at the site.

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 Viela Bio or a specified designee within 24 hours and be fully documented as a SAE. Details of any signs or symptoms and their management should be recorded, including details of any antidote(s) administered.

9 STATISTICAL CONSIDERATIONS

9.1 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).

9.2 Statistical Hypotheses

Four primary hypotheses will be tested (each of the 4 VIB4920 cohorts vs placebo). The null and alternative hypothesis for each VIB4920 cohort compared with placebo are listed below.

Null hypothesis: The mean change from baseline to Day 113 in DAS28-CRP score for the VIB4920 group is equal to that for the placebo group.

Alternative hypothesis: The mean change from baseline to Day 113 in DAS28-CRP score for the VIB4920 group is not equal to that for the placebo group.

9.3 Determination of Sample Size

The planned sample size of 75 subjects (15 subjects per treatment group) will provide approximately 80% power to detect a difference of 1.2 in mean change from baseline to Day 113 in DAS28-CRP (assumed standard deviation of 1.25) between the VIB4920 and placebo treatment groups at a 2-sided alpha level of 0.10 using a 2-sample t-test.

9.4 Analysis Sets

Full analysis set: The full analysis set includes all subjects randomized and receiving any dose of IP in the study. Subjects will be analyzed according to the treatment randomized. The efficacy analysis will be based on the full analysis set.

Safety analysis set: The safety analysis set 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.

PK analysis set: The PK analysis set includes all subjects who receive IP and have at least one quantifiable plasma 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.

9.5 Methods for Statistical Analyses

9.5.1 Analysis of the Primary Efficacy Endpoint

Primary efficacy analyses:

The primary efficacy endpoint of change from baseline DAS28-CRP to Day 113 will be analyzed using a mixed-effect model for repeated measures (MMRM) approach.

DAS28-CRP values will be calculated as follows (Wells et al, 2009):

$$DAS28\text{-}CRP = 0.56 \times \sqrt{(TJC28)} + 0.28 \times \sqrt{(SJC28)} + 0.014 \times PGA + 0.36 \times \ln(CRP + 1) + 0.96,$$

where [redacted], and PGA is the patient global assessment on a scale 0-100 mm. The range of the DAS28-CRP score is 0.96-9.31.

Handling plan for rescue medication use:

For subjects who take rescue medications, 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 without receiving rescue medications will be asked to come to scheduled evaluations until the end of study. The data collected after discontinuation of IP will be included in the analysis.

Handling plan for missing data:

Missing data will be handled using the MMRM approach.

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:

The type I error rate will be controlled at 0.1 level (2-sided) for the primary efficacy analysis using the following sequential testing strategy.

1. The primary endpoint will be tested for Cohort 1 (VIB4920 1500 mg on Days 1, 15, 29, and 57) compared with placebo
2. If p-value is ≤ 0.1 in step 1, the primary endpoint will be tested for Cohort 3 (VIB4920 3000 mg on Days 1 and 57) compared with placebo
3. If p-value is ≤ 0.1 in both step 1 and step 2, the primary endpoint will be tested for Cohort 2 (VIB4920 1500 mg on Days 1 and 57) and Cohort 4 (VIB4920 3000 mg on Day 1) compared with placebo using the Hochberg method (Hochberg 1988)

9.5.2 Analysis of Secondary Efficacy Endpoints

The continuous secondary endpoints of change in RF and ACPA from baseline to Day 113 will be analyzed using a MMRM approach.

The binary secondary endpoint of the proportion of subjects with DAS28-CRP < 2.6 at Day 113 will be analyzed using a logistic regression model.

Time to start of new treatment for RA (rescue medication) will be analyzed using the Cox proportional hazards model.

9.5.3 Safety Analysis

Safety endpoints will be summarized descriptively.

The number and percentage of subjects reporting TEAEs will be summarized for each treatment group by system organ class and preferred terms, by severity, and by relationship to the IP. The number and percentage of subjects reporting SAEs and AESIs will also be summarized.

AESI identification will be based on MedDRA coding. The search criteria for the AESIs will be established prior to database lock for the primary analysis.

Clinically important abnormalities in vital signs, laboratory parameters, ECGs, and physical examinations will be recorded as AEs or SAEs.

9.5.4 Pharmacokinetics Analysis

Plasma VIB4920 concentration data will be tabulated by dose cohort together with descriptive statistics. Individual and mean plasma concentration-time profiles of VIB4920 by treatment will be generated.

Noncompartmental analysis will be performed for VIB4920-treated subjects. When possible, the following PK parameters will be accessed for VIB4920 plasma concentration: maximum observed concentration (C_{max}), area under the concentration-time curve (AUC), CL, and $t_{1/2}$. Additional PK parameters may be determined and reported as appropriate. Descriptive statistics for PK parameters will be provided.

The plasma concentration of VIB4920, summary statistics, PK profile, and the additional PK-related analyses will be reported in a clinical PK report.

9.5.5 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.

9.5.6 [redacted]

[redacted]

9.5.7 [redacted]

[redacted]

10 ETHICAL CONSIDERATIONS

10.1 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 Council for Harmonisation (ICH)/Good Clinical Practice (GCP), applicable regulatory requirements, and the Viela Bio policy on Ethical Interactions.

10.2 Ethics Review

The final study protocol, including the final version of the ICF, must be approved or given a favorable opinion in writing by an IRB or IEC as appropriate. The Investigator must submit written approval to Viela Bio 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. Viela Bio 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 Viela Bio's representative.

10.3 Informed Consent

The PI, or an Investigator or other study site designee with IRB/IEC-approved qualifications, will ensure that the patient is given full and adequate oral and written information about the nature, purpose, possible risk, and benefit of the study. Patients must also be notified that they are free to discontinue from the study at any time. The patients will be informed that their study record and medical records/documents that pertain directly to the study will be reviewed and possibly copied by Viela Bio or its designee, or a governmental agency (such as the Food and Drug Administration [FDA]), and that every effort will be made to maintain patient confidentiality. The patient 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 PI or his/her designee, and the original retained by the Investigator/study site as part of that subject's record.

The Investigator must maintain the original, signed ICF. A copy of the signed ICF must be given to the patient.

Patients 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.

10.4 Data Privacy

All information generated in this study is considered highly confidential and must not be disclosed to any person or entity not directly involved with the study unless prior written consent is obtained from Viela Bio. However, authorized regulatory officials, IRB/IEC personnel, Viela Bio and its authorized representatives are allowed full access to the records.

Identification of subjects and CRFs 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.

10.5 Disclosure

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

10.6 Biological Specimens and Data

Study data are protected by the use of a SID number, which is a number specific to the 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.

Leftover samples stored 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.

11 OVERSIGHT

11.1 Safety Data Monitoring Board

The external, independent SDMC is responsible for safeguarding the interests of study participants via review of accumulating safety data and for supporting study integrity and interpretability based on their review of ongoing study conduct. The SDMC will provide Viela Bio with recommendations for actions with respect to study conduct and the management of

subjects treated under the study protocol. The SDMC members are independent of Viela Bio and any CRO/organization collaborating with Viela Bio on the study.

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

11.2 Quality Control and Assurance

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

11.3 Monitoring

Before an investigational site can enter a subject into the study, a representative of Viela Bio or of the CRO 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 Viela Bio or its representatives. This will be documented in a Clinical Study Agreement between Viela Bio and the Investigator.

During the study, a representative from Viela Bio will have regular contact 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 CRFs 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 study-related records for each subject (eg, clinic charts).
- Record and report any protocol deviations not previously sent to Viela Bio.
- Confirm AEs and SAEs have been properly documented on eCRFs and confirm that any SAEs have been forwarded to Viela Bio or representative and those SAEs that met criteria for reporting have been forwarded to the IRB/IEC.
- 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 CRF entries, respond to data clarification requests, and respond to any other study-related inquiries from the monitor.

11.4 Audits

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

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

In addition to the above, representatives of Viela Bio auditing staff or government inspectors may review the conduct/results of the study at the investigational site. The Investigator should contact Viela Bio 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 Viela Bio 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 Viela Bio representative and a draft response to Viela Bio prior to submission to the regulatory agency.

11.5 Records

11.5.1 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 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.

11.5.2 Source Documentation

Viela Bio 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, IP stocks, drug accountability records, subject charts, study source documents, and other records relative to study conduct.

11.5.3 Records Retention

Investigators 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 Viela Bio or the regulatory authority to review any documentation relating to the study, the Investigator must permit access to such records.

12 PUBLICATION POLICY

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

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14 APPENDICES

APPENDIX 1 GUIDANCE FOR ANAPHYLAXIS DIAGNOSIS

The National Institute of Allergy and Infectious Disease (NIAID) and Food and Allergy Anaphylaxis Network (FAAN) define anaphylaxis as a serious allergic reaction that is rapid in onset and may cause death. 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). Their clinical criteria for diagnosing anaphylaxis are:

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 blood pressure (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.

Reference

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(2):391-7.

APPENDIX 2 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. 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 Viela Bio clinical project representatives, in review and assessment of cases meeting PHL criteria to agree whether Hy's Law (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 adverse events (AEs) and serious adverse events (SAEs) according to the outcome of the review and assessment in line with standard safety reporting processes.

Definitions

Potential Hy's Law

Aspartate aminotransferase (AST) or alanine aminotransferase (ALT) ≥ 3 × upper limit of normal (ULN) together with total bilirubin (TBL) ≥ 2 × ULN at any point during the study following the start of investigational product (IP) irrespective of an increase in alkaline phosphatase (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 electronic case report form (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

Reference

FDA. Guidance for Industry: Drug-induced liver injury: premarketing clinical evaluation. 2009. Available from: https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM174090.pdf

APPENDIX 3 INVESTIGATOR'S AGREEMENT

INVESTIGATOR'S AGREEMENT

I have read the protocol, appendices, and accessory materials related to Study VIB4920.P2.S3 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 International Council for Harmonisation 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**
Signature		**Date**

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Approval	[redacted] 05-Oct-2020 15:23:01 GMT+0000
Approval	[redacted]evelopment Lead 05-Oct-2020 15:39:14 GMT+0000
Approval	[redacted]onal Science Representative 05-Oct-2020 17:58:18 GMT+0000
Approval	[redacted] 05-Oct-2020 18:29:08 GMT+0000
Approval	[redacted] 06-Oct-2020 12:16:14 GMT+0000
Approval	[redacted] 06-Oct-2020 17:28:53 GMT+0000

Signature Page for VV-CLIN-001820 v1.0

Full Name and Role: _____

Signature & Date:

Full Name and Role: _____

Signature & Date: