VIELA BIO, INC.

STATISTICAL ANALYSIS PLAN

Investigational Product: **VIB4920**

Protocol Number: **VIB4920.P2.S1**

A PHASE 2A SINGLE-ARM, PROSPECTIVE, OPEN-LABEL PILOT STUDY TO EVALUATE THE SAFETY AND EFFICACY OF DUAL COSTIMULATION BLOCKADE WITH VIB4920 AND BELATACEPT FOR PROPHYLAXIS OF ALLOGRAFT REJECTION IN ADULTS RECEIVING A KIDNEY TRANSPLANT

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LIST OF ABBREVIATIONS

Abbreviation or Specialized Term	Definition
ADA	anti-drug antibodies
AE	adverse event
AESI	adverse event of special interest
BPAR	biopsy-proven acute rejection
CMV	cytomegalovirus
CSR	clinical study report
CTCAE	common terminology criteria for adverse events
DGF	delayed graft function
CCI	[redacted]
HLA	human leukocyte antigen
IP	investigational product
IV	intravenous
PK	pharmacokinetics
PRA	Panel Reactive Antibody test
PT	preferred term
QTc	corrected QT interval
SAE	serious adverse event
SOC	system organ class
SPP	statistical programming plan
tBPAR	treated biopsy-proven acute rejection
TEAE	treatment-emergent adverse event
TESAE	treatment-emergent serious adverse event

1 INTRODUCTION

This document describes the statistical analysis for protocol VIB4920.P2.S1, a Phase 2a, prospective single-arm, open-label pilot study to evaluate the efficacy, safety, and tolerability of dual costimulation blockade with VIB4920 + belatacept in adult male or female recipients of a renal allograft from a deceased, living unrelated, or human leukocyte antigen (HLA) non-identical living related donor.

2 STUDY OVERVIEW

2.1 Study Objectives and Endpoints

The objectives and corresponding endpoints are listed in Table 1 below:

Table 1 Study Objectives and Endpoints

Primary objective	**Endpoints/variables**
• To demonstrate that, when added to standard-of-care induction regimen that includes Thymoglobulin® (anti-thymocyte globulin [rabbit]) and corticosteroids, dual costimulation blockade with multiple doses of VIB4920 + belatacept, started at the time of kidney transplant surgery and repeated every 2-4 weeks post-transplantation, prevents composite efficacy failure (tBPAR of grade 1A or higher, graft loss, or death) at Week 24 post-transplantation in the majority of subjects (≥ 17/20)	• Incidence of efficacy failure, defined as treated biopsy-proven acute rejection (tBPAR) of grade 1A or higher, graft loss, or death, at Week 24 post-transplantation
Secondary objectives	**Endpoints/variables**
• To evaluate individual components (and combinations of the individual components) of the composite efficacy endpoint at Weeks 12, 24, and 48 post-transplantation.	• Incidence of efficacy failure, defined as treated biopsy-proven acute rejection (tBPAR) of grade 1A or higher, graft loss, or death, at Weeks 12 and 48 post-transplantation • Incidence of tBPAR, graft loss, death, or loss to follow-up at Weeks 12, 24, and 48 post-transplantation • Incidence of antibody-mediated rejection at Weeks 12, 24, and 48 post-transplantation • Incidence of tBPAR at Weeks 12, 24, and 48 post-transplantation • Incidence of BPAR at Weeks 12, 24, and 48 post-transplantation • Incidence of treated acute rejections at Weeks 12, 24, and 48 post-transplantation • Proportion of subjects with de novo donor-specific antibodies (dnDSA) at Weeks 12, 24, and 48 post-transplantation
• To evaluate safety and tolerability of dual costimulation blockade with VIB4920 +	• Treatment-emergent adverse events and treatment-emergent serious adverse events (TEAE and TESAE)

Table 1 Study Objectives and Endpoints

belatacept in subjects receiving a kidney transplant	• Treatment-emergent adverse events of special interest (TEAESI) • Laboratory data by visit • Vital signs data by visit • ECG data by visit
• To evaluate the pharmacokinetics (PK) and immunogenicity (anti-drug antibodies [ADA]) of VIB4920	• VIB4920 plasma concentration over visits • PK parameters • Proportion of subjects who develop detectable ADA
Exploratory objectives	**Endpoints/variables**
• Evaluate CCI at Weeks 4, 12, 24, and CCI in subjects receiving a kidney transplant	• Proportion of subjects with CCI at Weeks 12, 24, and 48 • Changes in CCI between Week 4 and Week 24; Week 4 and Week 48; and Week 24 and Week 48
• To understand CCI in CCI and CCI in blood related to pharmacology of VIB4920	• Changes over time in CCI related to VIB4920 pharmacology
• To evaluate the CCI of CCI CCI on CCI	• Changes over time in the CCI and CCI

ADA = anti-drug antibodies; dnDSA = de novo donor-specific antibodies; ECG = electrocardiogram; CCI MDRD = modification of diet in renal disease; PK = pharmacokinetics; tBPAR = treated biopsy-proven acute rejection; TEAE = treatment-emergent adverse event; TEAESI = treatment-emergent adverse event of special interest; TESAE = treatment-emergent serious adverse event

2.2 Study Design

2.2.1 Overview

This is a single-arm, open-label exploratory study. The study will be conducted at 2 centers in the United States in a total of approximately 20 subjects. All eligible subjects will undergo the scheduled kidney transplant on Day 0 and be treated with VIB4920 + belatacept (with Thymoglobulin and corticosteroids) according to the following regimen:

- Thymoglobulin 1.5 mg/kg by intravenous (IV) infusion prior to reperfusion of the allograft on the day of transplantation surgery (Day 0), prior to VIB4920+belatacept infusion on post-op Day 1, on post-op Day 2, and prior to VIB4920+belatacept infusion on post-op Day 3 or 4

- Methylprednisolone by IV infusion (500, 250, 125 and 60 mg on Days 0, 1, 2 and 3, respectively) followed by oral administration of prednisone 30 mg per day on Days 4, 5, 6 and 7. Subjects may be tapered to at least 20 mg per day on Day 8, to at least 10 mg per

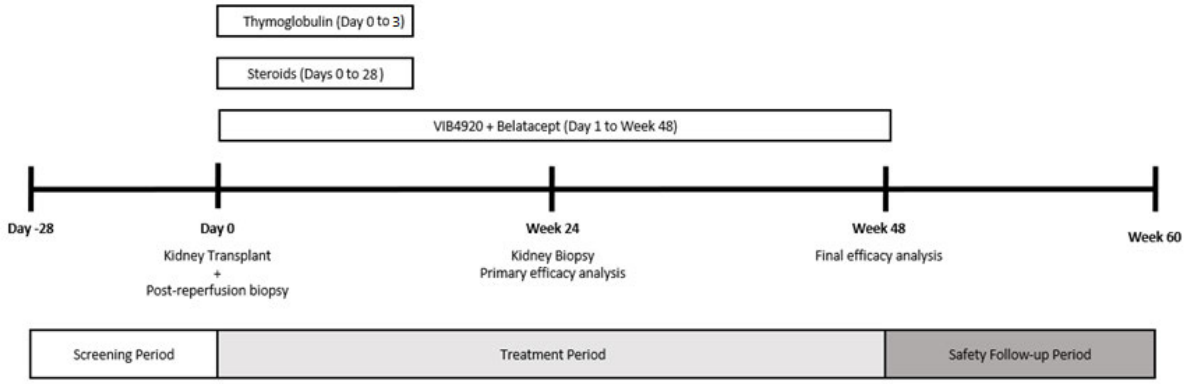
day on Day 15, and to at least 5 mg per day on Day 22. Discontinuation of prednisone should occur following the post-op Day 28 visit.

- VIB4920 1500 mg by IV infusion on post-op Days 1, repeated on post-op Day 3 or 4 (timing is at investigator's discretion), Week 2, and at the end of Weeks 4, 6, 8, and 10; then 1500 mg every 4 weeks from Week 12 to Week 48.

- Belatacept 10 mg/kg by IV infusion on post-op Day 1 (first dose ≥ 12 hours after Thymoglobulin infusion ends), repeated on post-op Day 3 or 4 (timing is at investigator's discretion), and at the end of Weeks 2, 4, 8, and 12; then 5 mg/kg IV every 4 weeks from Week 16 to Week 48.

VIB4920 should be administered prior to belatacept. The basic study flow diagram is presented in Figure 1Figure **1.**

Figure 1 **Study Flow Diagram**



2.3 Sample Size

The protocol was amended after 3 subjects were enrolled under the protocol v2.0. Approximately 20 subjects will be enrolled under protocol v3.0.

Belatacept added to standard induction therapy (basiliximab, mycophenolate mofetil, corticosteroids) resulted in efficacy failure in 21.7% of recipients of living- and standard criteria deceased-donor kidneys by 1 year (Nulojix® USPI). With 20 subjects, if 3 or fewer subjects are observed with efficacy failure (ie, response rate ≥ 85%) at week 24, there is > 89% confidence that the response rate is at least 70%.

3 STATISTICAL METHODS

3.1 General Considerations

All statistical calculations will be primarily performed using SAS® System Version 9.4 or higher. Categorical data will be summarized by the frequency counts and percentage of subjects in each category. Continuous variables will be summarized by descriptive statistics, including number of observations, mean, standard deviation, median, first quartile, third quartile, minimum, and maximum.

3.1.1 Definition of Baseline

In general, baseline will be defined as the last non-missing valid observation prior to the first administration of VIB4920 or belatacept, whichever occurs first. In cases where baseline measurements are taken on the same day as investigational product (IP) and no times are reported, it will be assumed that these measurements are taken prior to IP being administered.

For CCI [redacted] the baseline will be defined as Week 4 measurement.

3.1.2 Analysis Windows

Analysis visit windows will be used for all visit-based assessments to map longitudinal observations to scheduled visits and, thereby, allow for by-visit analyses, since not all assessments are performed on the scheduled day. Unless otherwise specified, all longitudinal efficacy and safety data analyses will be based on the analysis visit windows. The analysis visit windows will be calculated by bisecting the interval between adjacent scheduled visit days and will be specified in the statistical programming plan (SPP).

The actual assessment day will be mapped to the windows defined for each scheduled study visit with following rules:

- If more than one assessment falls within a visit window, the closest non-missing assessment to the scheduled day will be used in the analysis.
- If 2 non-missing assessment actual dates are equidistant from the target day, the later visit will be used in the analysis.
- For retest values of laboratory data, the retest value (the last valid observation assessed on the same visit day) will be chosen.

3.2 Protocol Deviations

All protocol deviations will be classified as either major protocol deviations or minor protocol deviations. The major protocol deviations are considered as the important protocol deviations, which may significantly impact the completeness, accuracy, and/or reliability of the study data, and may significantly affect a subject's rights, safety, or well-being. All the protocol deviations will be listed, and the major protocol deviation will be summarized. Some classifications of major protocol deviations are listed below.

- Did not meet inclusion criteria or met exclusion criteria.
- Received prohibited concomitant medication.
- Met IP discontinuation criteria but was not discontinued from the IP.
- Serious breach of good clinical practice.

The list may be updated and will be finalized and documented prior to the database lock.

3.3 Analysis Sets

3.3.1 Safety analysis set

The safety analysis set includes all subjects who received any dose of IP. The safety, pharmacodynamics, and anti-drug antibodies (ADA) analyses will be based on the safety analysis set.

3.3.2 Efficacy evaluable set

Efficacy evaluable set includes all subjects who received the revised regimen of Thymoglobulin and steroids, and any dose of IP. The efficacy analysis will be based on the efficacy evaluable set.

3.3.3 Pharmacokinetics analysis set

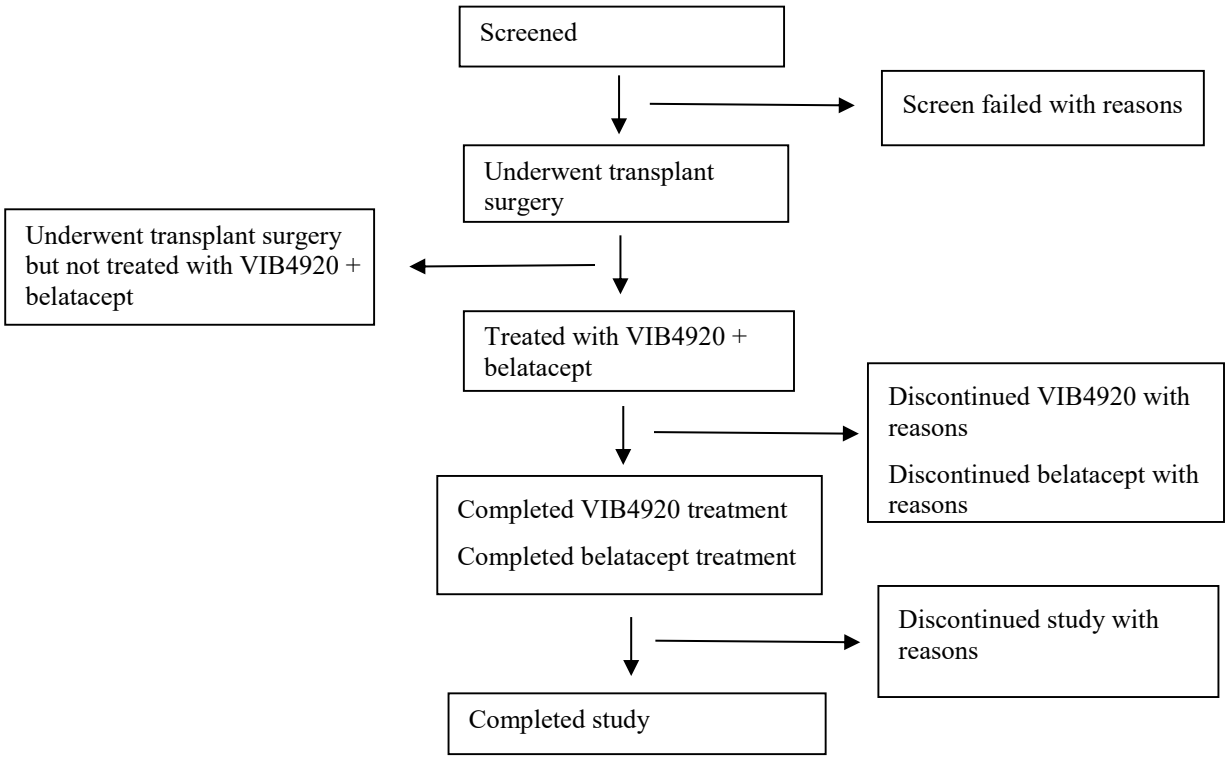
The pharmacokinetics (PK) analysis set includes all subjects who receive IP and have at least one quantifiable serum PK observation post-first dose. PK analyses will be based on the PK analysis set.

3.4 Study Subjects

3.4.1 Subject Disposition

A summary of subject disposition will be presented using the categories presented in Figure 2.

Figure 2 Subject Disposition



3.4.2 Demographics, Baseline Characteristics, and Medical History

The demographics (age, gender, race, ethnicity, height, weight, and body mass index) will be summarized.

Subject background information, including end-stage renal disease leading to transplantation, current dialysis (none, hemodialysis, peritoneal dialysis), highest Panel Reactive Antibody (PRA) test, most recent PRA, and HLA type, will be summarized. Donor background information, including sex, race, ethnicity, transplant donor type (living related, living unrelated, deceased heart beating, deceased non-heart beating), will be summarized as well.

Significant medical history finding will be summarized by MedDRA system organ class (SOC) and preferred term (PT).

3.4.3 Study Drug Exposure

VIB4920 and belatacept

The number of doses received, amount of the study drug received, durations of the study drug exposure, and treatment compliance will be summarized for VIB4920 and belatacept separately.

- Durations of the study drug exposure = last dose date + 28 – first dose date + 1.

- The amount of study drug exposure: if a subject received partial dose at a dosing visit, then the amount of study drug at that dosing visit will be estimated based on the actual volume administered.

- Treatment compliance for an individual subject = [Total number of doses received]/ [Total number of doses planned per protocol] ×100%.

Thymoglobulin and corticosteroids

Subjects will receive IV thymoglobulin1.5 mg/kg prior to reperfusion of the allograft on the day of transplantation surgery (Day 0), prior to VIB4920+belatacept infusion on post-op Day 1, on post-op Day 2, and prior to VIB4920+belatacept infusion on post-op Day 3 or 4. Number (%) of subjects who received thymoglobulin will be summarized by Day.

Subjects will receive methylprednisolone by IV infusion (500, 250, 125, and 60 mg on Days 0, 1, 2, and 3, respectively) followed by oral administration of prednisone 30 mg per day on Days 4, 5, 6 and 7. Subjects may be tapered to at least 20 mg per day on Day 8, to at least 10 mg per day on Day 15, and to at least 5 mg per day on Day 22. Discontinuation of prednisone should occur following the post-op Day 28 visit. The methylprednisolone and oral prednisone dose in mg/day will be summarized by Day (Days 0, 1, 2, 3, Day 4 - Day 7, Day 8 - Day14, Day 15 - Day 21, Day 22 - Day 28). The total corticosteroid dose in mg will also be summarized.

3.4.4 Prior and Concomitant Medications

Number (%) of subjects who received prior medications and concomitant medications will be summarized by WHO Drug dictionary. At each level of summarization, a subject is counted

once if the subject reported one or more medications at that level. The prior and concomitant medications are defined as below.

- Prior medications are defined as medications with a stop date occurring before the IP administration date.

- Concomitant medications are defined as medications with a start date on or after the IP administration date or stop date occurring on or after the IP administration date.

The missing start/stop date will be imputed as appropriate and the details of the imputation will be included in the SPP.

Number (%) of subjects who received the following medications will be summarized.

- Medications used for the treatment of suspected or confirmed acute rejections.

- Prophylaxis medications for each of cytomegalovirus (CMV), Pneumocystis jirovecii pneumonia, and oral Candida.

3.5 Efficacy Analyses

3.5.1 Primary Efficacy Endpoint(s) and Analyses

3.5.1.1 Primary efficacy endpoint

The primary efficacy endpoint is the incidence of efficacy failure, defined as treated biopsy-proven acute rejection (tBPAR) of grade 1A or higher, graft loss, or death at Week 24 post-transplantation.

3.5.1.2 Primary efficacy analysis

For the primary efficacy analysis, the acute rejection rating will be based on the consensus of the pathologists at the 2 participating sites.

The primary efficacy endpoint will be analyzed descriptively. The incidence of efficacy failure, defined as tBPAR of grade 1A or higher, graft loss, or death at Week 24 post-transplantation, and the corresponding 80% 2-sided exact confidence interval will be calculated. Missing data will not be imputed.

3.5.2 Secondary Efficacy Endpoints and Analyses

3.5.2.1 Secondary efficacy endpoints

The secondary efficacy endpoints are as follows:

- Incidence of efficacy failure defined as tBPAR of grade 1A or higher, graft loss, or death at Weeks 12 and 48

- Incidence of tBPAR, graft loss, death, or loss to follow-up at Weeks 12, 24, and 48

- Incidence of antibody-mediated rejection at Weeks 12, 24, and 48

- Incidence of tBPAR at Weeks 12, 24, and 48
- Incidence of BPAR at Weeks 12, 24, and 48
- Incidence of treated acute rejections at Weeks 12, 24, and 48
- Proportion of subjects with de novo donor-specific antibodies at Weeks 12, 24, and 48

3.5.2.2 Secondary efficacy analysis

The secondary efficacy endpoints will be analyzed in the same way as the primary efficacy endpoint.

3.5.3 Exploratory Efficacy Endpoints and Analyses

3.5.3.1 Exploratory efficacy endpoints

The exploratory efficacy endpoints are as follows:

- Proportion of subjects with CCI [redacted] at 12, 24, and 48 weeks
- Changes in CCI [redacted] between Week 4 and Week 24; Week 4 and Weeks 48; and Week 24 and Week 48

3.5.3.2 Exploratory efficacy analyses

Proportion of subjects with CCI [redacted] and the CCI [redacted] 2-sided exact confidence interval will be calculated. The CCI [redacted] will be summarized by visit. The missing CCI [redacted] will not be imputed.

3.6 Safety Analysis

3.6.1 Adverse Events

In general, if an adverse event (AE) onset is on or after the first dose of VIB4920 or belatacept, whichever occurs first, the AE will be considered as a treatment-emergent adverse event (TEAE). Otherwise, the AE will be considered as a non-TEAE.

AEs will be coded using the most recent version of MedDRA. All TEAEs will be summarized overall and by MedDRA SOC and PT, by severity and by relationship to IP. Specific AEs will be counted once for each subject for calculating rates, but all events will be presented in subject listings. In addition, if the same AE occurs multiple times within a particular subject, the highest severity and level of causality will be reported.

An overall summary table will be showing the number and percentage of subjects with at least one event in any of the following categories: TEAE, treatment-emergent serious adverse event (TESAE), TEAE with outcome of death, Grade 3 or higher TEAE, TEAE leading to discontinuation of VIB4920, TEAE leading to discontinuation of belatacept, VIB4920 related TEAE, belatacept related TEAE, VIB4920 related TESAE, and belatacept related TESAE.

The TEAEs, TESAEs, TEAEs resulting in death, Grade 3 or higher TEAEs, TEAE leading to discontinuation of VIB4920, TEAE leading to discontinuation of belatacept, VIB4920 related TEAE, belatacept related TEAE, VIB4920 related TESAE, and belatacept related TESAE will be summarized by SOC and PT. TESAEs will be summarized by serious adverse event (SAE) criteria as well. In addition, a summary of TEAEs sorted by frequency will be presented by PT. The treatment emergent non-SAE will also be summarized by SOC and PT.

An adverse event of special interest (AESI) is one of scientific and medical interest specific to understanding of the IP. AESIs for this protocol include:

- Thrombotic and embolic events
- Hepatic function abnormality (meeting the definition of Hy's Law)
- Anaphylaxis and clinically significant (common terminology criteria for adverse events [CTCAE] Grade 3 or higher) hypersensitivity reactions
- Immune complex disease
- Severe infusion-related reactions (CTCAE Grade 3 or higher)
- Malignant neoplasm
- Infections:
  - Clinically significant (CTCAE Grade 3 or higher)
  - Opportunistic infections associated with immunosuppression, including (but not limited to): reactivation of latent viral infection (varicella zoster virus, herpes simplex virus, Epstein-Barr virus, JC virus, CMV, BK polyoma virus), fungal infections, and tuberculosis.

Treatment-emergent adverse events of special interest will be summarized by SOC and PT.

Listings will be provided for all TEAEs and non-treatment emergent AEs.

3.6.2 Clinical Laboratory Evaluation

The analysis for the laboratory results are listed in Table 2.

Table 2 Laboratory Results Analysis

Laboratory dataset	Planned Analysis
Hematology, Chemistry, and Coagulation	• Summary of the toxicity grade defined using the national cancer institute's common terminology criteria for adverse events (NCI CTCAE) • Summary of at least 2-grade shift from the baseline to the worst post-baseline toxicity grade • Summary of shift from the baseline relative to the normal range • Summary of observed values and changes from the baseline

Table 2 Laboratory Results Analysis

Laboratory dataset	Planned Analysis
	• Summary of potential Hy's law cases
Urinalysis	• Summary of observed values and changes from the baseline • Summary of shift from the baseline relative to the normal range
Spot Urine Protein Creatinine Ratio	• Summary of observed values and changes from the baseline • Proportion of subjects with urine protein/creatinine ratio CR < 0.5
Immunoglobulins	• Summary of observed values and changes from the baseline

3.6.3 Other Safety Evaluations

Overdose

The incidence of TEAEs associated with overdose will be summarized by MedDRA SOC and PT, if applicable.

Delayed Graft Function

Subjects are considered to have delayed graft function (DGF) when:

- A dialysis is performed, where DGF is the reported reason, and/or
- DGF is reported as an AE

The proportion of subjects experienced DGF will be summarized.

Vital Signs

The observed values, along with the changes from baseline, will be summarized for systolic blood pressure, diastolic blood pressure, body temperature, heart rate, and respiratory rate. In addition, a summary of subjects with clinically significant vital signs values (meeting any of following criteria) will also be provided.

Systolic blood pressure: < 90 mmHg, > 160 mmHg

Diastolic blood pressure: < 60 mmHg, > 100 mmHg

Heart rate: < 50 beats/min, > 100 beats/min

Respiratory rate: < 12 breaths/min, > 23 breaths/min

Temperature: < 36°C, >38°C

Electrocardiogram

The observed values, along with the changes from baseline, will be summarized for ventricular heart rate, PR interval, QRS duration, QT interval, and the corrected QT interval (QTc). The number (%) of subjects meeting the following criteria will be summarized:

- QTc > 450 msec
- QTc > 480 msec
- QTc > 500 msec
- QTc increases from baseline > 30 msec
- QTc increases from baseline > 60 msec

In addition, the overall clinical evaluation of electrocardiogram results (normal, abnormal, not clinically significant abnormal, clinically significant abnormal) will also be summarized.

Physical Examination and Weight

The clinically important abnormal findings from the physical examinations will be recorded as AEs. The observed values and the changes from baseline in the weight will be summarized.

3.7 Pharmacokinetics

The PK components of the clinical study report (CSR) will be generated and reported by the PK group.

VIB4920 plasma concentration will be summarized descriptively by visits. VIB4920 concentration-time profiles will be generated. Noncompartmental analysis will be performed for VIB4920-treated subject. Descriptive statistics for PK parameters will be provided.

Plasma concentration of VIB4920, summary statistics, PK profile, and the additional PK-related analyses will be reported either in the CSR or in a clinical PK report as an addendum to the CSR.

The potential PK exposure-response relationship for efficacy and safety outcomes with VIB4920 when combined with belatacept, and as a monotherapy if feasible, will be evaluated in an exploratory manner.

3.8 Immunogenicity

The ADA status in Table 3 will be summarized by the categories included in the table and the ADA titer may be summarized for ADA positive subjects. The impact of ADA on safety may be evaluated if needed. The ADA incidence rate may also be summarized, where the incidence is the proportion of the subjects with ADA positive post-baseline only or boosted their pre-existing ADA during the study period. The cutoff for the boosted ADA will be finalized and documented before the database lock.

Table 3 Definition of ADA Status

ADA Status	Definition
Prevalence (Positive during the study)	ADA positive observed at least once during the study (baseline included)
Negative during the study	ADA positive not observed at any visit during the study (baseline included)
Baseline positive	ADA positive observed at baseline regardless of the post-baseline ADA status
Post-baseline positive	ADA positive observed at least once during post-baseline regardless of the baseline ADA status
Only baseline positive	ADA positive observed at baseline but not observed at any time post-baseline
Only post-baseline positive (treatment-induced)	ADA positive not observed at baseline but observed at least once post-baseline
Both baseline and post-baseline positive	ADA positive observed at baseline and observed at least once post-baseline
Persistent positive	Treatment-induced ADA positive at ≥ 2 post-baseline assessments (with ≥ 16 weeks between first and last positive) or positive at last post-baseline assessment
Transient positive	Treatment-induced ADA post-baseline positive but does not fulfil the criteria of persistent positive

ADA = anti-drug antibodies.

3.9 Exploratory Analyses

The following exploratory endpoints may be summarized descriptively.

- Changes over time in CCI related to VIB4920 pharmacology.
- Changes over time in the CCI , and CCI

4 PLANNED ANALYSIS

4.1 Primary Efficacy Analysis

The primary efficacy analysis will be performed when all subjects have completed Week 24 or withdrawn prior to Week 24 visit. All available data at the time of the data cut-off will be included in the analysis.

4.2 Final Efficacy Analysis

The final efficacy analysis will be performed when all subjects have completed Week 48 or withdrawn prior to Week 48 visit. All available data at the time of the data cut-off will be included in the analysis.

4.3 Final Analysis

The final analysis will be performed when all subjects have completed the study.

Revision History:

Version #	Description of Change
Version 2	1. Modified study design according to protocol v3.0 2. Added "Efficacy evaluable set" for the efficacy analysis.

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