VIELA BIO, INC.

STATISTICAL ANALYSIS PLAN

Investigational Product: **VIB4920**

Protocol Number: **VIB4920.P2.S2**

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

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF ABBREVIATIONS

Abbreviation or Specialized Term	Definition
ACR	American College of Rheumatology
ADA	anti-drug antibodies
ATC	Anatomical Therapeutic Chemical
AUC	area under the curve
AZA	azathioprine
CI	confidence interval
cDMARD	conventional disease-modifying anti-rheumatic drug
COA	clinical outcome assessment
CTCAE	common terminology criteria for adverse event
eCDF	empirical cumulative distribution function
ECG	electrocardiogram
ESSDAI	EULAR Sjögren's Syndrome Disease Activity Index
ESSPRI	EULAR Sjögren's Syndrome Patient Reported Index
EULAR	European League Against Rheumatism
FACIT-Fatigue	Functional Assessment of Chronic Illness Therapy -Fatigue
IP	Investigational product
IV	Intravenously
[redacted]	[redacted]
MedDRA	Medical Dictionary for Regulatory Activities
MMF	mycophenolate mofetil
MMRM	mixed-effect model for repeated measures
MTX	methotrexate
OSDI	Ocular Surface Disease Index
PDF	probability density function
[redacted]	[redacted]
PGIS	Patient's Global Impression of Severity
PK	Pharmacokinetic(s)
[redacted]	[redacted]
PT	preferred term
Q4W	once every 4 weeks
Q-Q	quartile-quartile
QTc	corrected QT interval
RF	rheumatoid factor
ROC	receiver operating characteristic
SE	standard error

Abbreviation or Specialized Term	Definition
[redacted]	[redacted]
SOC	system organ class
SPP	statistical programming plan
SS	Sjögren's Syndrome
TEAE	treatment-emergent adverse event
TEAESI	treatment-emergent adverse event of special interest
TESAE	treatment-emergent serious adverse event
[redacted]	[redacted]
WHO	world health organization

1 INTRODUCTION

This document describes the statistical analysis for protocol VIB4920.P2.S2, a Phase 2 randomized, double-blind, placebo controlled, proof of concept study to evaluate the efficacy and safety of VIB4920 in subjects with Sjögren's Syndrome (SS). The study will enroll 2 SS populations. Population #1 will be composed of subjects with moderate to severe systemic disease activity defined by European League Against Rheumatism (EULAR) Sjögren's Syndrome Disease Activity Index (ESSDAI) ≥ 5. Population #2 will be composed of subjects with moderate to severe subjective symptoms defined by EULAR Sjögren's Syndrome Patient Reported Index (ESSPRI) score ≥ 5 and residual stimulated salivary flow but with mild systemic disease activity defined by ESSDAI score < 5.

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**
• Population #1: To evaluate the clinical efficacy of multiple doses of VIB4920 in glandular and extraglandular manifestations of SS patients with moderate to high systemic disease activity	• Population #1: Change from baseline in ESSDAI at Day 169
• Population #2: To evaluate the clinical efficacy of multiple doses of VIB4920 in the key subjective complaints of SS (dryness, fatigue, pain)	• Population #2: Change from baseline in ESSPRI at Day 169
Secondary objectives	**Endpoints/variables**
• Population #1: To evaluate the effect of VIB4920 on systemic activity and patient-reported outcomes in subjects with SS	• ESSPRI • ESSDAI[3] and ESSDAI[4] response • Functional Assessment of Chronic Illness Therapy (FACIT)-Fatigue • Ocular Surface Disease Index (OSDI) • Patient's Global Impression of Severity (PGIS)
• Population #2: To evaluate the effect of VIB4920 on patient-reported outcomes in subjects with SS	• ESSPRI response • FACIT-Fatigue • OSDI • PGIS
• Population #1 & #2: To evaluate the safety and tolerability of multiple doses of VIB4920 in subjects with SS	• Incidence of treatment emergent adverse events (TEAEs), TE serious adverse events (TESAEs), TE adverse events of special interest (TEAESIs), and laboratory, vital sign, and electrocardiogram (ECG) abnormalities

Table 1 Study Objectives and Endpoints

• Population #1 & #2: To characterize the pharmacokinetics (PK) of VIB4920 in subjects with SS	• Drug concentration and PK parameters
• Population #1 & #2: To assess the immunogenicity of VIB4920 in subjects with SS	• Anti-drug antibodies (ADA)
Exploratory objectives (Population #1 & #2)	**Endpoints/variables**
[redacted]	

2.2 Study Design

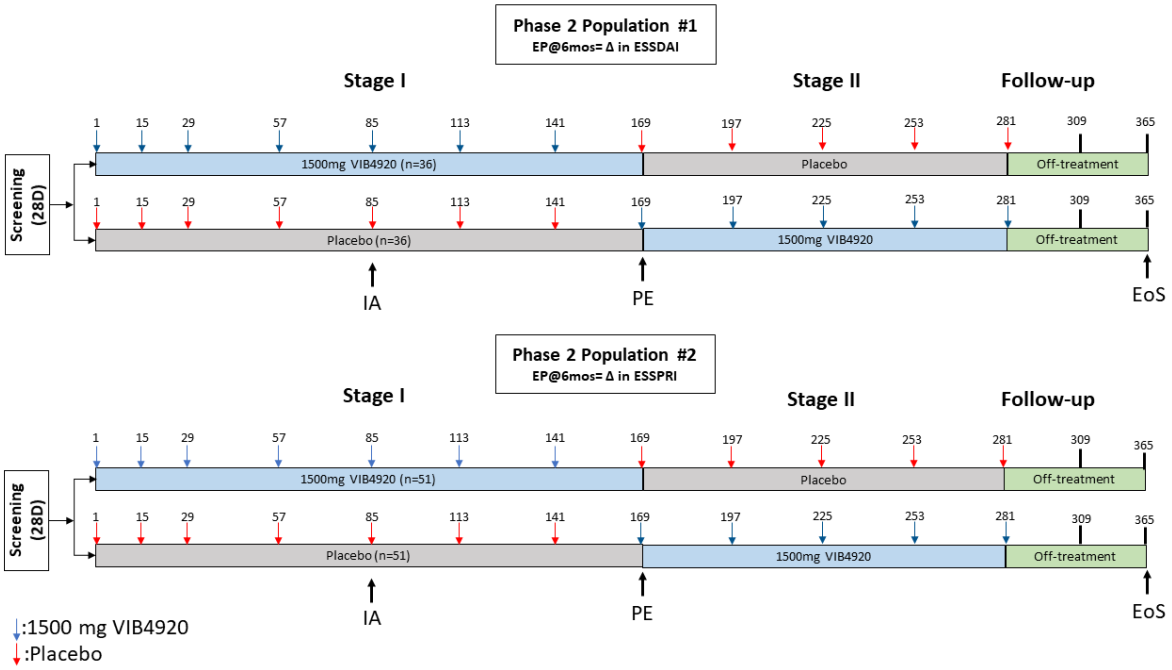
2.2.1 Overview

This is a randomized, double-blind, placebo-controlled, parallel-arm study to evaluate the efficacy, safety, and tolerability of VIB4920 in adult subjects with SS, diagnosed according to the 2016 American College of Rheumatology (ACR)/EULAR Criteria. The study will enroll 2 SS populations as defined in section 1 INTRODUCTION. Within each population,

eligible subjects will be randomized to receive VIB4920 1500 mg or placebo intravenously (IV) once every 2 weeks x 3 doses, then once every 4 weeks (Q4W) for 4 additional doses (Stage I). Randomization will be stratified by ESSDAI score at screening (< 10 points vs ≥ 10 points) for Population #1 and by ESSPRI score at screening (< 7.5 points vs ≥ 7.5 points) for Population #2. Starting on Day 169, subjects randomized to VIB4920 will receive placebo Q4W for 5 doses and subjects randomized to placebo will receive VIB4920 Q4W for 5 doses (Stage II). Subjects who had investigational product (IP) discontinuation will not be eligible for treatment during Stage II. All subjects will be followed for at least 12 weeks after their last dose of IP administration.

A study schematic is presented in Figure **1**.

Figure 1 **Study Flow Diagram**



2.3 Sample Size

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

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

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

Unless otherwise specified, baseline will be defined as the last non-missing valid observation prior to the first administration of IP. In cases where baseline measurements are taken on the same day as IP and no times are reported, it will be assumed that these measurements are taken prior to IP being administered.

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 except for the first post-treatment visit and Day 169 visit. The first post-treatment visit will start at Day 2. When slotting visits to the Day 169 window, this should only occur for assessments on or before the date of the nominal Day 169 dose. Assessments after this date should be slotted to the following visit window. The detailed analysis visit windows 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.
- Blindness of treatment assignment was broken by site investigator before Day 169
- Received prohibited concomitant medication
- Serious breach of good clinical practice

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

3.3 Analysis Sets

3.3.1 Full analysis set

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

3.3.2 Safety analysis set

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

If subjects who are randomized to placebo receive any dose of VIB4920 in Stage I of the study, the treatment actually received will be VIB4920 for the subjects.

3.3.3 Pharmacokinetics analysis set

The PK analysis set includes all subjects who received 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. PK analyses will be based on the PK analysis set.

3.3.4 Cross-over analysis set

The cross-over analysis set includes all subjects who received any dose of IP during Stage II of the study.

3.3.5 Any VIB4920 analysis set

The any VIB4920 analysis set includes all subjects who received at least one dose of VIB4920 during the study.

3.4 Study Subjects

3.4.1 Subject Disposition

A summary of subject disposition will be presented using the categories presented below.

- Screened

- Screen failed with reasons
- Randomized
- Randomized but not treated
- Randomized and treated
- Completed Stage I treatment
- Completed treatment
- Discontinued treatment with reasons
- Completed Stage I
- Completed study
- Discontinued study with reasons

3.4.2 Demographics, Baseline Characteristics, and Medical History

The demographics (age, gender, race, ethnicity, height, weight, and body mass index) will be summarized by treatment group and overall for the full analysis set.

A summary of baseline disease characteristics, by treatment group and overall for the full analysis set will include

- Baseline ESSDAI total score - descriptive statistics
- Baseline ESSDAI total score (< 10 points vs ≥ 10 points) - n (%)
- Baseline ESSPRI total and component score - descriptive statistics
- Baseline ESSPRI total score (< 7.5 points vs ≥ 7.5 points) - n (%)
- Baseline OSDI - descriptive statistics - descriptive statistics
- Schirmer's test ≤5 mm in at least 1 eye - n (%)
- Time (years) from initial diagnosis to randomization - descriptive statistics
- Positive SS-A/SS-B at baseline - n (%)
- Baseline RF auto-antibody levels: - descriptive statistics
- Stimulated salivary flow at baseline - descriptive statistics
- Concomitant RA or SLE - n (%)

Significant medical history finding will be summarized by MedDRA system organ class (SOC) and preferred term (PT) by treatment group and overall for the full analysis set.

3.4.3 Investigational Product Exposure

The number of doses received, amount (mg) of the IP received, durations of the IP exposure, and total subject years exposure will be summarized by treatment. This summary will be produced for the Stage I and Stage II separately using the safety analysis set and cross-over analysis set respectively, and for the overall study using any VIB4920 analysis set.

- Duration of the IP exposure is defined as follows
  - Stage I: minimum of (date of last dose before Day 169 + 28 – first dose date) and (Day 169 date - first dose date)
  - Stage II: last dose date + 28 – Day 169 date + 1
  - Overall study using any VIB4920 analysis set: duration of exposure to VIB4920 in the study

- The amount (mg) of IP: if a subject received partial dose at a dosing visit, then the amount of IP 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%.

3.4.4 Prior and Concomitant Medications

Number (%) of subjects who receive prior medications and concomitant medications during Stage I and during Stage II + Off-treatment follow-up period will be summarized by world health organization (WHO) Drug dictionary Anatomical Therapeutic Chemical (ATC) category and PT. At each level of summarization, a subject is counted once if he/she reported one or more medications at that level. The summary of prior medications and concomitant medications during Stage I will be based on the safety analysis set. The summary of concomitant medications during Stage II + Off-treatment follow-up period will be based on the cross-over analysis set.

The prior and concomitant medications are defined as below.

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

- Concomitant medications during Stage I are defined as follows:
  - Medications with a start date before the Day 169 IP administration date and stop date on or after the first IP administration date for subjects entering Stage II.
  - Medications with a stop date on or after the first IP administration date for subjects not entering Stage II.

- Concomitant medications during Stage II + Off-treatment follow-up period are defined as medications with a stop date on or after the Day 169 IP administration date.

Use of disease-related medications at baseline, defined as all disease-related medications with an intake at the date of first dose of IP (ie, start date on or before the date of first dose and end date on or after date of first dose or ongoing) will be summarized for the full analysis set. The number and percentage of subjects who receive rescue medication during Stage I and during Stage II + Off-treatment follow-up period will also be summarized for the full analysis set and cross-over analysis set respectively.

Rescue medications for population #1 are listed below:

- Azathioprine (AZA) > 150 mg/day, methotrexate (MTX) > 20 mg/week, leflunomide >20 mg/day, mycophenolate mofetil (MMF) > 2gm/day OR any increase from baseline (including initiation of treatment)

- Any increase from baseline in anti-malarial (including initiation of treatment)

- Initiation of any new conventional disease-modifying anti-rheumatic drug (cDMARD)

- Oral prednisone > 10 mg/day OR any increase from baseline (including initiation of treatment)

- Intramuscular, IV, or intraarticular corticosteroids

- Corticosteroids with a long biologic half-life (eg, dexamethasone, betamethasone)

Rescue medications for population #2 are listed below:

- Oral, intramuscular, IV, or intraarticular corticosteroids

- MTX, AZA, leflunomide, MMF, and other cDMARD or immunosuppressive or antiproliferative medications

- Any increase from baseline in anti-malarial (including initiation of treatment)

- Any increase or initiation of new doses of cevimeline or pilocarpine and cyclosporine eye drops (Restasis)

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

3.5 Efficacy Analyses

3.5.1 Primary Efficacy Endpoint(s) and Analyses

3.5.1.1 Primary efficacy endpoint

Population #1: The primary efficacy endpoint is change from baseline in ESSDAI at Day 169.

Population #2: The primary efficacy endpoint is change from baseline in ESSPRI at Day 169.

ESSDAI:

The ESSDAI is a validated consensus disease activity index that is able to capture changes in the severity of systemic manifestations of SS, with 12 domains, with associated weights as shown in Table 2.

Table 2 ESSDAI Domains, Weights and Activity Levels

Domain	Weight	Activity Levels
Constitutional	3	0-2
Lymphadenopathy	4	0-3
Glandular	2	0-2
Articular	2	0-3
Cutaneous	3	0-3
Pulmonary	5	0-3
Renal	5	0-3
Muscular	6	0-3
Peripheral Nervous System	5	0-3
Central Nervous System	5	0,2,3
Hematological	2	0-3
Biological	1	0-2

The final score is calculated as follows:

Total Score = Sum of all 12 domain scores

Domain score = Activity level × Domain weight

The theoretical range of values for the ESSDAI is 0 to 123, with higher ESSDAI scores indicate more severe disease.

ESSPRI:

The ESSPRI is a 3-item, subject-completed assessment of SS symptoms. The instrument captures subject-rated severity of dryness, fatigue, and pain using 0-10 numeric rating scales anchored as no symptom (0) and maximal imaginable symptom (10). The recall period is stated in each question as “the last 2 weeks.” The ESSPRI total score is the mean of the 3 items and is calculated as follows:

ESSPRI Total Score = (Dryness + Fatigue + Pain) / 3

3.5.1.2 Primary efficacy analysis

Population #1: The primary efficacy endpoint will be analyzed using the mixed-effect model for repeated measures (MMRM) approach based on Stage I data for the full analysis set. The

model will include fixed effects for treatment, visit, visit by treatment interaction, and baseline ESSDAI score.

Population #2: The primary efficacy endpoint will be analyzed using the MMRM approach based on Stage I data for the full analysis set. The model will include fixed effects for treatment, visit, visit by treatment interaction, and baseline ESSPRI score.

From the model, the estimated treatment effect (ie the difference (VIB4920 – placebo) in LSMeans) at Day 169 will be obtained, together with a two-sided 90% confidence interval (CI), standard error (SE) and p-value. The significance of treatment effect will be tested by using a two-sided test at significance level α of 0.1. Additionally, estimates of the LSMeans for each treatment group will be obtained, together with the associated SE.

Longitudinal presentations of results over time up to Day 169 based on the same analysis will be created.

Model assumptions for MMRM will be checked with graphical displays (residual plots and a quartile-quartile (Q-Q) plot). If the model assumptions are not met, appropriate data transformations or the non-parametric approaches will be used.

3.5.1.3 Handling plan for Intercurrent Events

Rescue medication use:

For subjects who take rescue medications defined in section 3.4.4 before Day 169, the data collected after administration of the rescue medications will not be included in the primary analysis. This approach attempts to reduce the confounding effects of rescue medications.

Treatment discontinuation:

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

3.5.1.4 Handling plan for missing data

Missing data will be handled using the MMRM approach.

3.5.1.5 Sensitivity analysis of primary efficacy endpoint

The sensitivity analysis will be performed for the primary efficacy endpoint using the same model as the primary analysis with the following handling plan for the rescue medication use and treatment discontinuation.

- Impute result after rescue medications using the worst score on or before Day 169 including baseline. Include data collected after discontinuation of study treatment.

- Include data collected after rescue medications and data collected after discontinuation of study treatment.

In addition, the primary efficacy endpoint will be analyzed based on the time adjusted area under the curve (AUC) of change from baseline. First, the AUC of the ESSDAI and ESSPRI score from baseline to Day 169 will be calculated using the trapezoidal rule. Second, the time adjusted AUC will be obtained by dividing the AUC by the total time for baseline. Third, time adjusted AUC of change from baseline will be calculated by subtracting the baseline score from the time adjusted AUC. All observed data including data collected after rescue medications will be used to calculate the time adjusted AUC. The time adjusted AUC of change from baseline will be analyzed using MMRM approach including fixed effects for treatment, visit, visit by treatment interaction, and corresponding baseline score.

3.5.1.6 Subgroup analyses of primary endpoint

3.5.1.7 Multiplicity adjustment

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

3.5.1.8 Additional analysis

The change from baseline in ESSDAI for population #1 and change from baseline in ESSPRI for population #2 will be analyzed for Stage II + Off-treatment follow-up period based on the cross-over analysis set using the same MMRM model as the primary analysis. Data collected after rescue medications and after discontinuation of study treatment will be included.

The change from baseline in modified ESSDAI excluding peripheral nervous system, central nervous system, and pulmonary domains for population #1 will be analyzed using MMRM approach for Stage I and Stage II + Off-treatment follow-up period based on the full analysis set and cross-over analysis set respectively. The model will include fixed effects for treatment, visit, visit by treatment interaction, and baseline modified ESSDAI score. The handling plan for rescue medication use and treatment discontinuation for Stage I analysis is the same as those for the primary (section 3.5.1.3) and sensitivity (section 3.5.1.5) analyses of the primary efficacy endpoint. Data collected after rescue medications and after discontinuation of study treatment will be included for the Stage II + Off-treatment follow-up period analysis.

3.5.2 Secondary Efficacy Endpoints and Analyses

3.5.2.1 Secondary efficacy endpoints

The secondary efficacy endpoints are as follows:

- Change from baseline in ESSPRI at Day 169 (population #1)
- Proportion of subjects achieving ESSDAI[3] and ESSDAI[4] response, defined as a decrease of at least 3[4] points from baseline in the ESSDAI at Day 169 without premature discontinuation from the study and without receiving rescue medications (population #1)
- Proportion of subjects achieving ESSPRI response, defined as ≥ 1 point or 15% reduction from baseline in ESSPRI score at Day 169 without premature discontinuation from the study and without receiving rescue medications (population #2)
- Change from baseline in FACIT-Fatigue score at Day 169 (population #1 and #2)
- Change from baseline in OSDI at Day 169 (population #1 and #2)
- Change from baseline in PGIS at Day 169 (population #1 and #2)

FACIT-Fatigue:

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

OSDI:

OSDI is a valid and reliable instrument for assessing effect on vision-related function and dry eye disease severity (normal, mild, moderate, and severe). Its recall period is 1 week. It is composed of 12 questions that the physician asks the subject and circles the number that best represents each question. The responses for each question range from 0 (None of the time) to 4 (All of the time). The OSDI score is calculated as follows:

OSDI score = (sum of scores for questions answered) / (number of questions answered) × 25

The OSDI score ranges from 0 to 100 with higher scores signifying greater disability.

PGIS:

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

3.5.2.2 Secondary efficacy analysis

The continuous secondary efficacy endpoints of population #1 and population #2 will be analyzed based on Stage I data for the full analysis set using the MMRM approach, with treatment, visit, visit by treatment interaction, randomization stratification factor, and corresponding baseline value. Handling plan for the rescue medication use and treatment discontinuation will be the same as those described for the primary endpoints in sections 3.5.1.3 and 3.5.1.5.

The details of these analyses and presentations of results will be the same as those described for the primary endpoints in section 3.5.1.2.

The analysis for Stage II + Off-treatment follow-up period will be performed using the same MMRM approach based on the cross-over analysis set. Data collected after rescue medications and after discontinuation of study treatment will be included.

The binary secondary efficacy endpoints of population #1 and population #2 will be analyzed for the full analysis set using a logistic regression model, with treatment and corresponding baseline score included in the model.

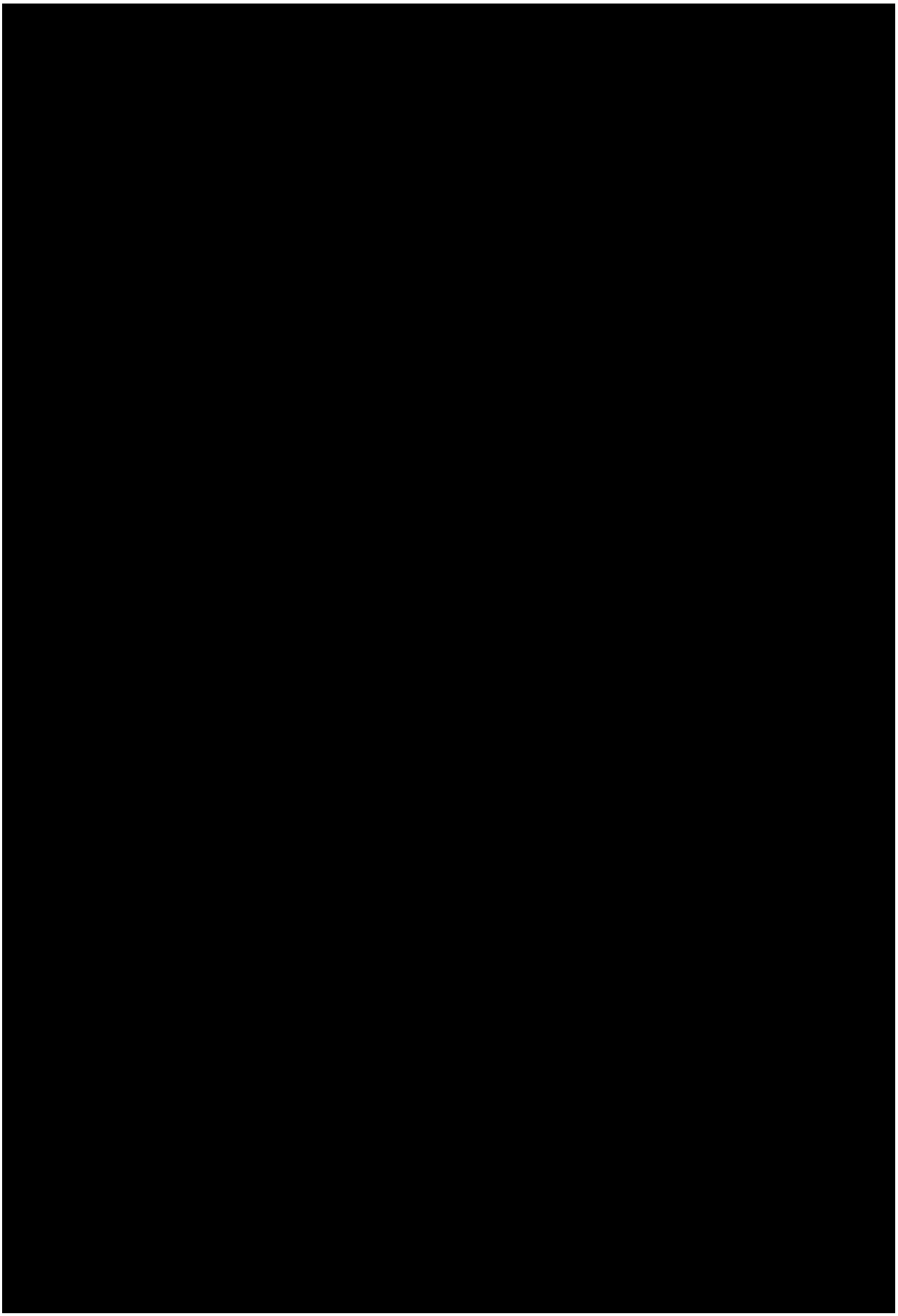
The estimated treatment effect (ie, the odds ratio for VIB4920 versus placebo), corresponding 90% CI, and 2-sided p-value will be presented. In addition, the response rate and the corresponding 90% CI within each treatment group will be presented. Longitudinal presentations of results over time up to Day 169 will be created using full analysis set. In addition, the analysis will be produced for Stage II + Off-treatment follow-up period separately using the cross-over analysis set.

3.5.3 Exploratory Efficacy Endpoints and Analyses

3.5.3.1 Exploratory efficacy endpoints

The exploratory efficacy endpoints are as follows:

[redacted]



3.5.4 Handling missing items of clinical outcome assessments (COAs)

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

3.5.4.1 ESSDAI and ESSPRI

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

3.5.4.2 FACIT-Fatigue

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

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

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

[redacted]

3.5.5 Explore clinically meaningful within-subject change score of COAs

The anchor-based methods supplemented with both empirical cumulative distribution function (eCDF) and probability density function (PDF) will be used to explore the clinically meaningful within-subject change score of COAs. The eCDFs display a continuous view of the score change (both positive and negative) in the COA endpoint from baseline to the proposed time point on the X-axis (horizontal axis), with the Y-axis (vertical axis) representing the cumulative proportion of subjects experiencing up to that level of score change.

The receiver operating characteristic (ROC) curve analysis will be used as supportive approach to explore the clinically meaningful within-subject change score.

Spearman's correlation analyses will be used to examine the strength and magnitude of relationship between the COA measures and potential anchors. The threshold for consideration as an anchor will be a correlation coefficient > 0.30.

3.5.5.1 ESSDAI

The clinically meaningful within-subject change score of ESSDAI will be explored for population #1 based on the pooled data across treatment groups. The anchor measures for ESSDAI are PGIS, [redacted]. The eCDF curve of change from baseline to Day 169 in ESSDAI will be plotted for each distinct anchor category as defined and identified by the anchor measures. A potential range for the meaningful change can be derived from eCDF plots (e.g., using median change, 25th percentile change, 75th percentile change).

- [redacted]
- PGIS and [redacted] ≥2 category decrease, 1 category decrease, no change, 1 category increase, and ≥2 category increase

The PDF curves of change from baseline to Day 169 in ESSDAI will also be plotted for each distinct anchor category to aid the interpretation of eCDF curves.

The eCDF curve of change from baseline to Day 169 in ESSDAI will also be plotted by each treatment group without separating into distinct anchor category.

The ROC curve analysis will be performed using logistic regression model with anchor as binary outcome and change from baseline to Day 169 in ESSDAI score as quantitative predictor. The score that best distinguishes levels of the anchor as listed below (based on sensitivity and specificity) will be identified.

- [redacted]
- PGIS and [redacted] ≥2 category decrease, ≥1 category decrease

3.5.5.2 ESSPRI

The clinically meaningful within-subject change score of ESSPRI will be explored for population #1 and population #2 based on the pooled data across treatment groups within each population. The anchor measures for ESSPRI are PGIS and [redacted] The eCDF and PDF curves of change from baseline to Day 169 in ESSPRI will be plotted the same way as that for ESSDAI. The ROC curve analysis will be performed as well.

3.6 Safety Analysis

3.6.1 Adverse Events

In general, if an AE onset is on or after the first dose of IP administration, the AE will be considered as a TEAE. Otherwise, the AE will be considered as a non-treatment emergent AE.

The AEs will be summarized for different study periods as defined in the Table 3.

Table 3 TEAEs for different study periods

Study Period	Inclusion of AEs for Summary
Stage I (Safety analysis set)	Include AEs with an onset on or after the first dose of IP in Stage I up to the time prior to the first dose of IP in Stage II (Day 169) for subjects entering Stage II, and AEs with an onset on or after the first dose of IP in Stage I for subjects not entering Stage II.
Stage II + Off-treatment follow-up (Cross-over analysis set)	Include AEs with an onset on or after the first dose of IP in Stage II (Day 169).
Any VIB4920 exposure (Any VIB4920 analysis set)	Include AEs with onset on or after the first VIB4920 dose (either Stage I or Stage II)

An overall summary table will be showing the number and percentage of subjects with at least 1 event in any of the following categories: TEAE, TESAE, TEAE with outcome of death, TEAE leading to discontinuation of IP, grade 3 or higher TEAE, serious and/or grade 3 or higher TEAE, IP related TEAE, IP related TESAE.

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.

The TEAEs, TESAEs, TEAEs resulting in death, TEAEs leading to discontinuation of IP, Grade 3 or higher TEAEs, IP related TEAEs, and IP related TESAEs will be summarized by SOC and PT. TESAEs will be summarized by SAE criteria as well. In addition, a summary of TEAEs sorted by frequency will be presented by PT.

An 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 (Grade 3 or higher) hypersensitivity reactions
- Severe Infusion-related reactions (common terminology criteria for adverse event (CTCAE) Grade 3 or higher)
- Malignant neoplasm
- Immune complex disease
- Infections:
  - Clinically significant (Grade 3 or higher)
  - Opportunistic infections including but not limited to reactivation of latent viral infection, invasive fungal infections, and TB

TEAESIs 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 hematology, coagulation, serum chemistry, urinalysis, and immunoglobulins parameters, as well as changes from baseline, will be summarized with descriptive statistics at each visit. Shift from the baseline relative to the normal range will also be summarized. Additionally, worst toxicity grade, ≥grade 3 toxicity post-baseline, and shift from baseline to worst toxicity grade in hematology, coagulation and serum chemistry parameter will be produced. The summary of clinical laboratory data will be generated for Stage I and Stage II + Off-treatment follow-up period separately based on the safety analysis set and cross-over analysis set respectively.

3.6.3 Other Safety Evaluations

3.6.3.1 Overdose

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

3.6.3.2 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. In addition, a summary of subjects with clinically significant vital signs values (meeting any of following criteria) will 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

The summary of vital sign data will be generated for Stage I and Stage II + Off-treatment follow-up period separately based on the safety analysis set and cross-over analysis set respectively.

3.6.3.3 Electrocardiogram

The observed values along with the changes from baseline will be summarized for heart rate, RR interval, PR Interval, QRS duration, QT interval and the corrected QT interval (QTc) using Bazett's and Fridericia's corrections. 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 ECG results (normal, abnormal, not clinically significant abnormal, clinically significant abnormal) will also be summarized.

The summary of ECG data will be generated for Stage I and Stage II + Off-treatment follow-up period separately based on the safety analysis set and cross-over analysis set respectively.

3.6.3.4 Weight

The observed values and the changes from baseline in the weight will be summarized for Stage I and Stage II + Off-treatment follow-up period separately based on the safety analysis set and cross-over analysis set respectively.

3.7 Pharmacokinetics

VIB4920 plasma concentration will be summarized descriptively by visits for PK analysis set. 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 in a clinical PK report (an addendum to the clinical study report) by PK group.

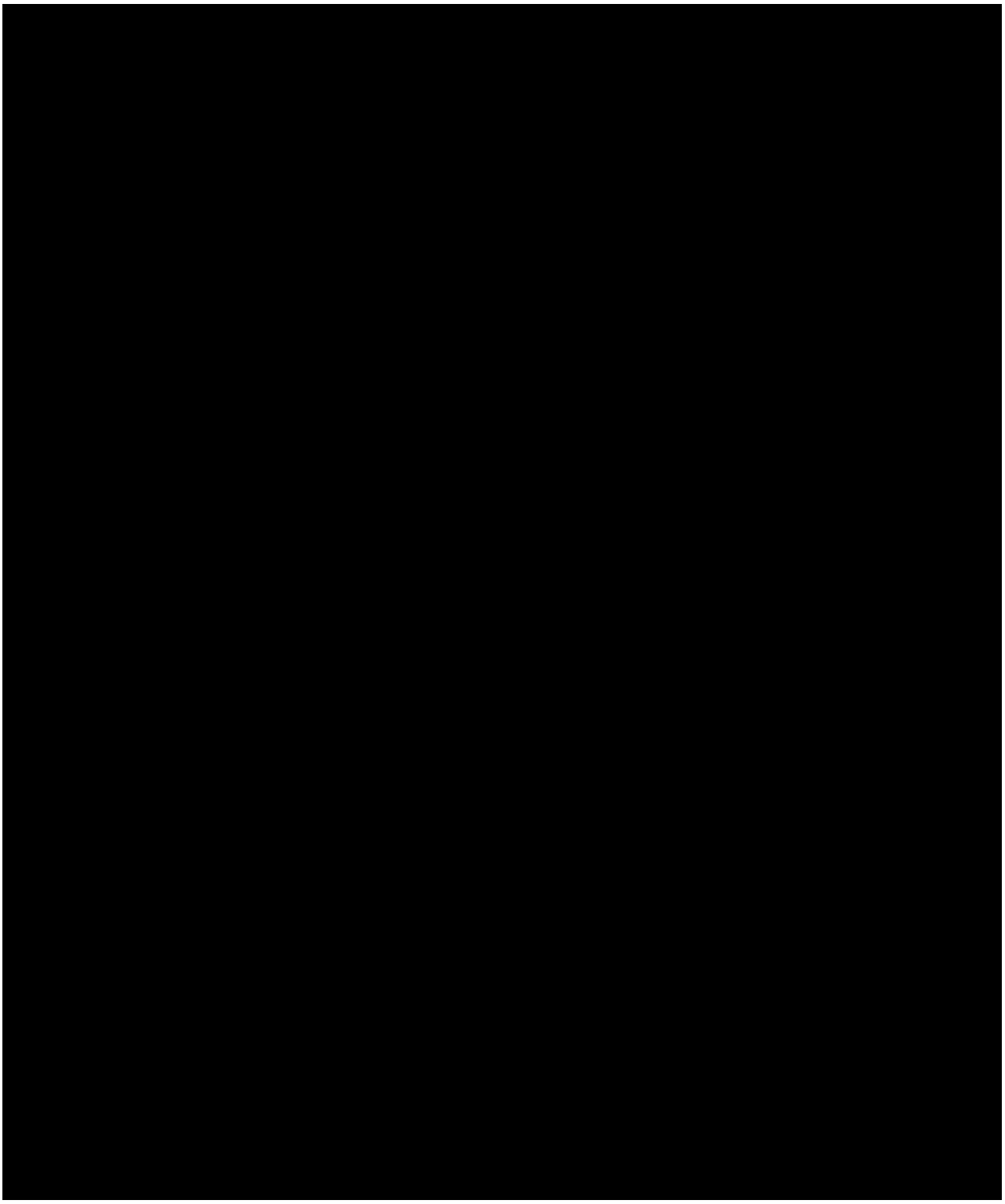
3.8 Immunogenicity

The ADA status will be summarized by the categories defined in Table 4. 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 determined before the database lock for the interim analysis. If data allow, the ADA titer for the ADA positive subjects will be summarized and the impact of ADA on efficacy and safety will be evaluated.

The ADA summary will be produced for Stage I using safety analysis set and for the whole study period using any VIB4920 analysis set. For the summary for the whole study period using any VIB4920 analysis set, the baseline positive is defined as any positive ADA prior to the first administration of VIB4920.

[redacted]

3.9 Exploratory Analyses



4 PLANNED ANALYSIS

4.1 Interim Analysis

An interim analysis will be conducted for each population after all subjects have completed the Day 85 visit or withdrawn prior to Day 85 for that population. The efficacy and safety data prior to the data cut-off for the interim analysis will be analyzed. No multiplicity

adjustment is planned for the interim analysis because there is no provision to stop the trial early at the interim analysis to claim efficacy. The final assessment of efficacy will be determined at the primary analysis. Details of the interim analysis will be specified in the interim unblinding analysis plan prior to unblinding.

4.2 Primary Efficacy Analysis

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

4.3 Final Analysis

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

5 REFERENCES

Fisher et al, 2017

Fisher B, Zeher M, Ng WF, Bombardieri M, Posch M, Farag AM, et al. The Novel Anti-CD40 Monoclonal Antibody CFZ533 Shows Beneficial Effects in Patients with Primary Sjögren's Syndrome: A Phase IIa Double-Blind, Placebo-Controlled Randomized Trial [abstract]. Arthritis Rheumatol. 2017; 69. Available at: https://acrabstracts.org/abstract/the-novel-anti-cd40-monoclonal-antibody-cfz533-shows-beneficial-effects-in-patients-with-primary-sjogrens-syndrome-a-phase-iia-double-blind-placebo-controlled-randomized-trial/.

Mariette et al, 2015

Mariette X, Seror R, Quartuccio L, Baron G, Salvin S, Fabris M, et al. Efficacy and safety of belimumab in primary Sjögren's syndrome: results of the BELISS open-label phase II study. Ann Rheum Dis. 2015; 74(3):526-31.

Revision History:

Version #	Description of Change
2	1. Change IgA, IgG and IgM RF to total RF 2. Added "If subjects who are randomized to placebo receive any dose of VIB4920 in Stage I of the study, the treatment actually received will be VIB4920 for the subjects." to section 3.3.2 [redacted]