STATISTICAL ANALYSIS PLAN

Protocol Title:	A phase 2 randomized, double-blind, placebo-controlled efficacy and safety study of VIB7734 for the treatment of moderate to severely active systemic lupus erythematosus (RECAST SLE)
Name of Test Drug:	Daxdilimab (HZN-7734)
Protocol Number:	VIB7734.P2.S1
Protocol Version (Date):	10-Feb-2022
Analysis Type:	All Planned Analyses
Analysis Plan Version:	v2.0
Analysis Plan Author(s):	[redacted]

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for purposes of posting on Clinicaltrials.gov

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF ABBREVIATIONS

Abbreviation or Specialized Term	Definition
[redacted]	
AE	adverse event
AESI	adverse event of special interest
[redacted]	
ANCOVA	Analysis of covariance
AUC	area under the concentration-time curve
BICLA	BILAG 2004 Index-Based Combined Lupus Assessment
BILAG	British Isles Lupus Assessment Group
[redacted]	
CI	confidence interval
CLASI	Cutaneous Lupus Erythematosus Disease Area and Severity Index
CLASI-A	Cutaneous Lupus Erythematosus Disease Area and Severity Index-Activity
[redacted]	
CNS	central nervous system
ECG	electrocardiogram
[redacted]	
GC	glucocorticoid
[redacted]	
HRQoL	health related quality of life
[redacted]	
IP	Investigational product
PGA	physician global assessment of disease activity
LLDAS	Lupus Low Disease Activity State
LLN	lower limit of normal
LOCF	last observation carried forward
[redacted]	
mCLASI-A	modified CLASI-A
MCP	metacarpophalangeal
MDA	minimal disease activity
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	mixed model for repeated measures
OGC	oral glucocorticoid

Abbreviation or Specialized Term	Definition
PD	pharmacodynamic(s)
pDC	plasmacytoid DC
[redacted]	
PK	Pharmacokinetic(s)
PIP	proximal interphalangeal
[redacted]	
PT	preferred term
[redacted]	
Q12W	every 12 weeks
QTc	corrected QT interval
RF	rheumatoid factor
SAE	serious adverse event
SC	subcutaneous(ly)
[redacted]	
SE	standard error
SLE	systemic lupus erythematosus
SLEDAI-2K	SLE Disease Activity Index 2000
SLEDAI-2KG	SLEDAI-2K GC
SOC	system organ class
SPP	statistical programming plan
SRI	SLE Responder Index
TEAE	treatment-emergent adverse event
TESAE	treatment-emergent serious adverse event
ULN	upper limit of normal
UPCR	urine protein:creatinine ratio
VAS	visual analog scale

1 INTRODUCTION

This document describes the statistical analysis for protocol VIB7734.P2.S1, a Phase 2, multicenter, international, randomized, double-blind, placebo-controlled, parallel-arm trial to assess the efficacy and safety of VIB7734 in participants with moderate to severely active systemic lupus erythematosus (SLE).

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 evaluate the effect of VIB7734 compared to placebo in reducing SLE disease activity at Week 48 in participants treated with standard of care therapy	Proportion of participants achieving a BILAG-2004 Index-based BICLA response and an OGC dose ≤ 7.5 mg/day and ≤ Baseline (Day 1) dose of prednisone or equivalent at Week 48. The BICLA response is defined as meeting all the following conditions as compared to Baseline: • BILAG-2004 Index improvement (all Baseline [Day 1] BILAG A improving to B/C/D, all Baseline [Day 1] BILAG B to C/D, and ≤ 1 new BILAG B and no new BILAG A. • No deterioration in SLEDAI-2K total score. • No significant worsening in PGA score (< 10% increase (< 0.3-point increase on a 3-point VAS)). • No use of restricted medications beyond the protocol-allowed threshold before assessment. • No discontinuation of IP.
Secondary objectives	**Endpoints/variables**
To evaluate the effect of VIB7734 compared with placebo to reduce cutaneous disease activity at Week 12.	Proportion of participants with CLASI-A score ≥ 10 at Baseline who achieve ≥ 50% reduction from Baseline in CLASI-A score at Week 12. Reduction of 50% in CLASI-A score is defined by meeting all the following conditions: • A ≥ 50% reduction of CLASI-A score at Week 12 as compared to Baseline. • No use of restricted medications beyond the protocol-allowed threshold before assessment. • No discontinuation of IP.
To evaluate the effect of VIB7734 compared with placebo to reduce SLE disease activity at Week 48.	Proportion of participants achieving a SRI-4 response and an OGC dose ≤ 7.5 mg/day and ≤ Baseline (Day 1) dose of prednisone or equivalent at Week 48. The SRI-4 response is defined as meeting all of the following conditions compared to Baseline:

Table 1 Study Objectives and Endpoints

	• Reduction from Baseline of ≥ 4 points in the SLEDAI-2K. • No new organ system affected as defined by 1 or more BILAG A or 2 or more BILAG B items. • No significant worsening in PGA score (< 10% increase (< 0.3 point increase on a 3-point VAS)). • No use of restricted medications beyond the protocol-allowed threshold before assessment. • No discontinuation of IP.
To evaluate the effect of VIB7734 compared with placebo on sustained OGC reduction from Week 36 to Week 48.	Proportion of participants with OGC dose ≥ 10 mg prednisone or equivalent at Baseline (Day 1) who: • Achieve OGC dose ≤ 7.5 mg/day prednisone or equivalent at Week 36. • Maintain OGC dose ≤ 7.5 mg/day from Week 36 through Week 48. • No use of restricted medications beyond the protocol-allowed threshold before assessment. • No discontinuation of IP.
To evaluate the effect of VIB7734 compared with placebo to achieve low disease activity at Week 48.	Proportion of participants achieving LLDAS at Week 48. LLDAS is defined as meeting all the following conditions: • SLEDAI-2K ≤ 4, with no activity in major organ system (renal, CNS, cardiopulmonary, vasculitis, fever) and hemolytic anemia or gastrointestinal activity. • No new lupus disease activity as compared to the previous assessment. • PGA ≤ 1 (on a 3-point VAS). • Current prednisone or equivalent dose of ≤ 7.5 mg/day. • Well-tolerated standard maintenance doses of immunosuppressive drugs and approved treatments as allowed and specified in the protocol. • No use of restricted medications beyond the protocol-allowed threshold. • No discontinuation of IP.
Safety objective	**Endpoints/variables**
To evaluate the safety and tolerability of VIB7734.	Incidence of adverse events, serious adverse events, and adverse events of special interest.
PK/PD/Immunogenicity Objectives	**Outcome Measures**
To characterize the PK, PD, and immunogenicity of VIB7734.	VIB7734 concentrations, change in pDC, [redacted]

Table 1 Study Objectives and Endpoints

Exploratory objectives	Endpoints/variables
[redacted]	

2.2 Study Design

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

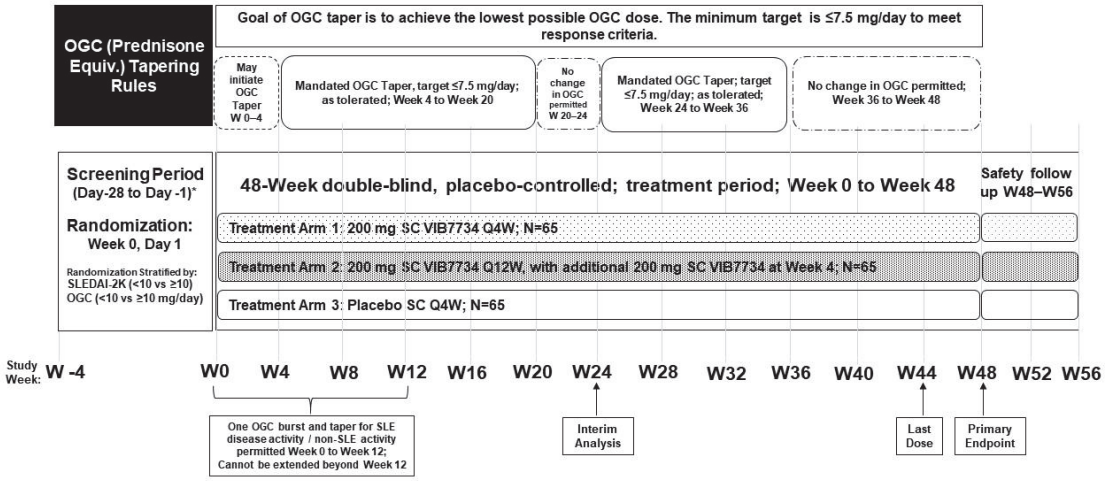
In this study, approximately 195 participants will be randomized in a ratio of 1:1:1 (65 participants per group) to receive VIB7734 200 mg every 4 weeks subcutaneously (SC), VIB7734 200 mg every 12 weeks (Q12W) SC, with an additional 200 mg SC dose at Week 4, or placebo. To maintain blinding, participants randomized to the VIB7734 200 mg Q12W SC dosing regimen will receive SC placebo injections on dosing visits outside the Q12W schedule. Randomization will be stratified by SLEDAI-2K total score at Screening

(≥ 10 or < 10) and prednisone or equivalent oral glucocorticoid (OGC) dose at Baseline (Day 1) (≥ 10 mg or < 10 mg).

The study will comprise a Screening period of approximately 4 weeks (Days -28 to -1), Randomization on Day 1, treatment and assessments through Week 48, and a Safety Follow-Up period of 8 weeks (through Week 56).

A study schematic is presented in Figure 1.

Figure 1 **Study Flow Diagram**



2.3 Sample Size

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

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 participants 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 investigational product (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, safety, and biomarker 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. The first post-treatment visit will start at Day 2. 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 value of laboratory data, the retest value will be chosen.

All observations will be included in data listings.

3.2 Protocol Deviations

All protocol deviations will be classified as critical protocol deviations, major protocol deviations, or minor protocol deviations. A critical protocol deviation is a significant departure from protocol requirements resulting in a life-threatening risk to an individual subject, or where the safety or well-being of trial subjects has been or has significant potential to be jeopardized, a significant portion of the clinical trial data might be unreliable, and/or a significant portion of critical data being jeopardized. All the protocol deviations will be listed, and the critical protocol deviation will be summarized. Some classifications of critical protocol deviations are listed below.

- Did not meet inclusion criteria or met exclusion criteria
- Blinding of treatment assignment was broken by site investigator
- 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 All participant analysis set

This analysis set includes all participants screened for the study and will be used for the reporting of participant disposition.

3.3.2 Full analysis set

The full analysis set includes all randomized participants who receive any dose of IP. Participants will be analyzed according to the treatment randomized. The efficacy analysis will be based on the full analysis set.

3.3.3 Safety analysis set

The safety analysis set includes all participants who receive any dose of IP. Participants will be analyzed according to the treatment that they received. The safety, pharmacodynamics (PD), [redacted] analyses will be based on the safety analysis set.

3.3.4 Pharmacokinetic analysis set

The pharmacokinetic (PK) analysis set includes all participants who receive any dose of VIB7734 in the study and have at least 1 quantifiable serum PK observation post-first dose. Participants will be analyzed according to the treatment that they received. The PK analysis will be based on the PK analysis set.

3.4 Study Participants

3.4.1 Participant Disposition

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

- Screened
- Screen failed with reasons
- Randomized
- Randomized but not treated
- Randomized and treated
- Completed treatment
- Discontinued treatment with reasons
- 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 characteristics, by treatment group and overall, for the full analysis set will include the following:

- Time from initial diagnosis to randomization
- SLE Disease Activity Index-2000 (SLEDAI-2K) total score
- SLEDAI-2K total score category (<10 vs ≥10)
- British Isles Lupus Assessment Group (BILAG)-2004 total score
- BILAG-2004 organ system involvement at baseline (yes vs no for each organ system domain). Involvement requires a baseline BILAG-2004 scale of A or B
- Physician global assessment (PGA) score
- Cutaneous Lupus Erythematosus Disease Area and Severity Index (CLASI) activity (CLASI-A) [redacted]
- CLASI-A score category (<10 vs ≥10)

[redacted]

- Low C3 (below lower limit of normal (<LLN) (yes vs no)
- Low C4 (<LLN) (yes vs no)
- Positive rheumatoid factor (RF) (yes vs no)
- Region (Europe, North America, Latin America, and Asia)

American College of Rheumatology criteria will be summarized by treatment group and overall for the full analysis set. Significant medical history findings will be summarized by Medical Dictionary for Regulatory Activities (MedDRA) system organ class (SOC) and preferred term (PT) by treatment group and overall for the full analysis set.

3.5 Investigational Product Exposure

The number of doses received, amount (mg) of the IP received, durations of the IP exposure, and total participant years exposure will be summarized by treatment using the full analysis set. The number and percentage of participants treated ≥4 weeks, ≥12 weeks, ≥24 weeks, ≥36 weeks, and ≥48 weeks will also be provided.

- Duration of the IP exposure is defined as (last dose date + 28 – first dose date + 1)
- The amount of IP received: if a participant 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. The amount of VIB7734 is 0 mg for dosing visits with placebo administered.

- Treatment compliance for an individual patient = (Total number of doses received)/ (Total number of doses planned per protocol) ×100%.

Furthermore, the time to discontinuation of IP will be presented as Kaplan-Meier plot including the number of participants at risk.

3.6 Prior and Concomitant Medications

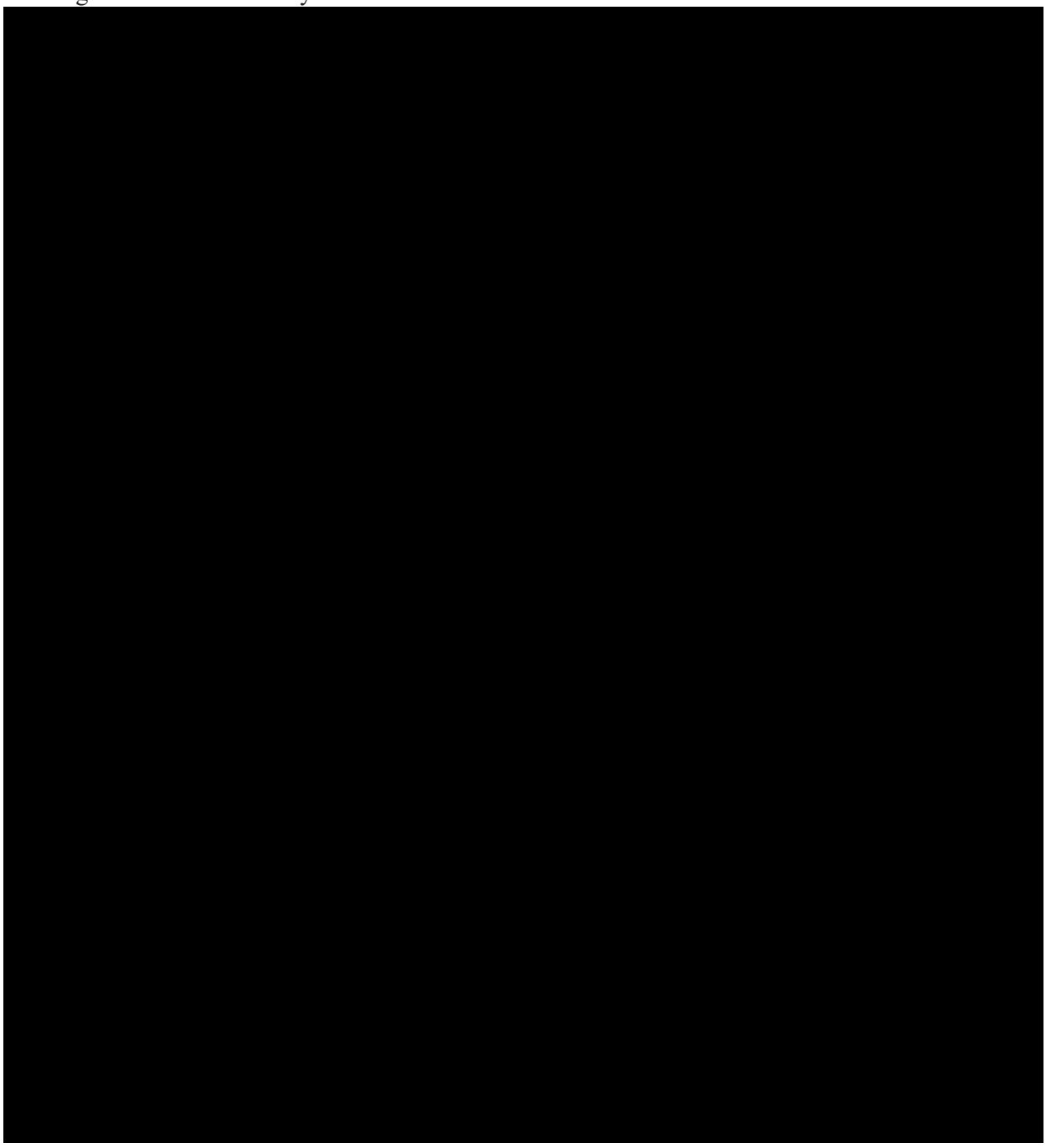
Number (%) of participants who receive prior medications and concomitant medications will be summarized by world health organization drug dictionary Anatomical Therapeutic Chemical category and PT based on the full analysis set and safety analysis set respectively. At each level of summarization, a participant is counted once if he/she reported one or more medications at that level. The concomitant medications will be summarized by category (immunomodulatory vs non- immunomodulatory medications). 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 are defined as medications with a stop date on or after the first IP administration date.

SLE disease related immunosuppressants including glucocorticoid (GC) at Baseline are defined as all immunosuppressants 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). Disease related immunosuppressants at Baseline will be summarized in the following categories for the full analysis set.

- Baseline oral glucocorticoid (OGC) dose (≥10 mg/day vs. <10 mg/day of prednisone or equivalent)
- Baseline OGC use (yes vs no)
- Baseline OGC dose of prednisone or equivalent for participants on OGC at Baseline
- Baseline antimalarial use (yes vs no)
- Other immunosuppressants (mycophenolate, methotrexate, azathioprine, etc.) use at Baseline (yes vs no)
- OGC only
- Antimalarials only
- Other immunosuppressants only
- OGC and antimalarials only
- OGC and other immunosuppressants only
- Antimalarials and other immunosuppressants only
- OGC, antimalarials, and other immunosuppressants

The number and percentage of participants who receive restricted medications beyond the protocol-allowed threshold during treatment period will also be summarized in the following categories for the full analysis set.



The selection of GC and non-GC immunosuppressants will be specified in the SPP. The missing start/stop date of medications will be imputed as appropriate, and the details of the imputation will be included in the SPP.

3.7 Efficacy Analyses

3.7.1 Primary Endpoint and Analyses

3.7.1.1 Primary endpoint and estimand

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

- Population: Participants in the full analysis set with active SLE despite receiving 1 or more standard of care treatments as defined by the inclusion-exclusion criteria of the study (excluding subjects from Russia and Ukraine sites)
- Variable (endpoint): Response in BICLA + OGC ≤ 7.5 mg/day and ≤ Day 1 dose at Week 48, where BICLA is defined by meeting the following criteria compared to Baseline:
  - BILAG-2004 Index improvement (all Baseline BILAG A improving to B/C/D, all Baseline BILAG B to C/D, and ≤ 1 new BILAG B and no new BILAG A).
  - No deterioration in SLEDAI-2K total score, where deterioration is defined as an increase from baseline of > 0 points in SLEDAI-2K.
  - No significant worsening in PGA score (< 0.3 point increase).
  - No use of restricted medications beyond the protocol-allowed threshold (see section 3.6) before assessment.
  - No discontinuation of IP.
- Intercurrent event:
  - Rescue medications: Captured in the primary variable definition.
  - Treatment discontinuation: Captured in the primary variable definition.
- Population-level summary: Difference in proportions of responders between the VIB7734 group and placebo group.

3.7.1.2 Primary efficacy analysis

Participants with no BILAG A or B at baseline and no worsening in any organ systems (≤ 1 new BILAG B and no new BILAG A), as well as participants with a baseline PGA score > 2.7 will be considered as having met the criteria for BILAG and PGA, respectively.

The proportion of participants achieving BICLA response + OGC ≤ 7.5 mg/day and ≤ Day 1 dose prednisone or equivalent at Week 48 in the VIB7734 treatment group will be compared to that of the placebo group for the full analysis set using a logistic regression model with treatment, and randomization stratification factors included in the model.

The difference in proportions of responders between each of VIB7734 groups and placebo group will be estimated together with its associated 2-sided 90% confidence interval (CI) and p-value. The significance of treatment effect will be tested by using a 2-sided test at significance level α of 0.1. Additionally, estimates of the response rate for each treatment group will be obtained, together with the associated standard error (SE).

Longitudinal presentations of results over time based on the same analysis will be created.

3.7.1.3 Supplementary analysis of primary endpoint

A supplementary analysis with the same model as primary analysis will be performed using a treatment policy strategy to address intercurrent events defined in section 3.7.1.1. All observed values will be used regardless of occurrence of an intercurrent event.

[redacted]

3.7.1.4 Handling plan for missing data

Intermittent missing data will be imputed using last observation carried forward approach (LOCF). Participants with missing primary outcome measures due to early discontinuation of study will be considered nonresponders. If any of the criteria cannot be evaluated at a visit, that criterion will be imputed using LOCF.

[redacted]

Missing items in SLEDAI-2K and BILAG-2004 will be imputed according to the specific rules described in Section 3.7.4.

3.7.1.5 Multiplicity adjustment

No multiplicity adjustment is planned since this is a phase 2 exploratory trial.

3.7.2 Secondary Efficacy Endpoints and Analyses

3.7.2.1 Secondary efficacy endpoints and estimands

The estimands are defined as follows, using composite variable strategy to address intercurrent events.

- Population:
  - CLASI: Participants in the full analysis set with active SLE and CLASI-A score ≥ 10 at Baseline despite receiving one or more standard of care treatments as defined by the inclusion-exclusion criteria of the study (excluding subjects from Russia and Ukraine sites).
  - OGC reduction: Participants in the full analysis set with active SLE taking an OGC of ≥ 10 mg/day of prednisone or equivalent at Baseline despite receiving one or more standard of care treatments as defined by the inclusion-exclusion criteria of the study (excluding subjects from Russia and Ukraine sites).
  - SRI-4 + OGC ≤ 7.5 mg/day and ≤ Baseline (Day 1) dose and LLDAS: Participants in the full analysis set with active SLE despite receiving one or more standard of care treatments as defined by the inclusion-exclusion criteria of the study (excluding subjects from Russia and Ukraine sites).
- Variable (endpoint):

- CLASI: ≥ 50% reduction in CLASI-A score at Week 12 defined by meeting the following criteria:
  - A ≥ 50% reduction of CLASI-A score at Week 12 as compared to Baseline.
  - No use of restricted medications beyond the protocol-allowed threshold (see section 3.6) before assessment.
  - No discontinuation of IP before assessment.
- SRI-4 + OGC ≤ 7.5 mg/day and ≤ Baseline (Day 1) dose: Response in SRI-4 + OGC ≤ 7.5 mg/day and ≤ Baseline (Day 1) dose at Week 48, where SRI-4 is defined by meeting the following criteria compared to Baseline:
  - Reduction from Baseline of ≥ 4 points in the SLEDAI-2K.
  - No new organ system affected as defined by one or more BILAG A or 2 or more BILAG B items.
  - No significant worsening in PGA score (< 0.3 point increase).
  - No use of restricted medications beyond the protocol-allowed threshold (see section 3.6) before assessment.
  - No discontinuation of IP.
- OGC reduction: Maintained OGC reduction from Week 36 to Week 48 defined by meeting the following criteria:
  - An OGC dose of ≤ 7.5 mg/day prednisone or equivalent at Week 36 that is maintained through Week 48.
  - No use of restricted medications beyond the protocol-allowed threshold (see section 3.6) before assessment.
  - No discontinuation of IP before assessment.
- LLDAS: Response in LLDAS at Week 48, where LLDAS is defined by meeting the following criteria:
  - A SLEDAI-2K ≤ 4, with no activity in major organ systems (renal, central nervous system (CNS), cardiopulmonary, vasculitis, fever) and no hemolytic anemia or gastrointestinal activity.
    - SLEDAI-2K organ system is define in section 3.7.3.1.8. Hemolytic anemia and gastrointestinal activity will be assessed by BILAG-2004 (present evidence of active hemolysis and gastrointestinal manifestation respectively).
  - No new lupus disease activity compared with the previous assessment measured by SLEDAI-2K.
    - New lupus disease activity is defined as present activity (item score >0) in at least one new SLEDAI-2K item compared with the previous visit.
  - A PGA ≤ 1 (on a scale of 0 to 3).
  - Current prednisone or equivalent dose of ≤ 7.5 mg/day.
  - Well-tolerated standard maintenance doses of immunosuppressive drugs and approved medications as allowed and specified in the protocol.

        - Any discontinuation of permitted non-GC immunosuppressants is assumed to be due to toxicity.
    - No use of restricted medications beyond the protocol-allowed threshold (see section 3.6) before assessment.
    - No discontinuation of IP.

- Intercurrent event:
  - Rescue medications: Captured in the variable definition.
  - Treatment discontinuation: Captured in the variable definition.
- Population-level summary for all secondary endpoints: Difference in proportions of responders between VIB7734 and placebo.

3.7.2.2 Secondary efficacy analysis

SRI-4 + OGC ≤ 7.5 mg/day and ≤ Baseline (Day 1) dose at Week 48 and LLDAS at Week 48 will be analyzed using the same logistic regression model as described in section 3.7.1.2 for the primary endpoint based on the full analysis set.

Maintained OGC reduction from Week 36 to Week 48 will be analyzed using a similar logistic regression model as described in section 3.7.1.2 replacing baseline OGC category (≥ 10 or < 10 mg/day) with Baseline OGC dose based on subgroup of participants with OGC of ≥ 10 mg/day of prednisone or equivalent at Baseline.

Achieving a ≥ 50% reduction in CLASI-A score at Week 12 will be analyzed using a similar logistic regression model as described in section 3.7.1.2 including Baseline CLASI-A score as an additional covariate based on subgroup of participants with CLASI-A score ≥ 10 at Baseline.

The difference in proportions of responders of VIB7734 versus placebo will be estimated for all secondary endpoints together with its associated 2-sided 90% CI and p-value. In addition, estimates of the response rate for each treatment group will be obtained, together with the associated SE.

Longitudinal presentations of results over time based on the same analysis will be created.

3.7.2.3 Supplementary analysis of secondary endpoints

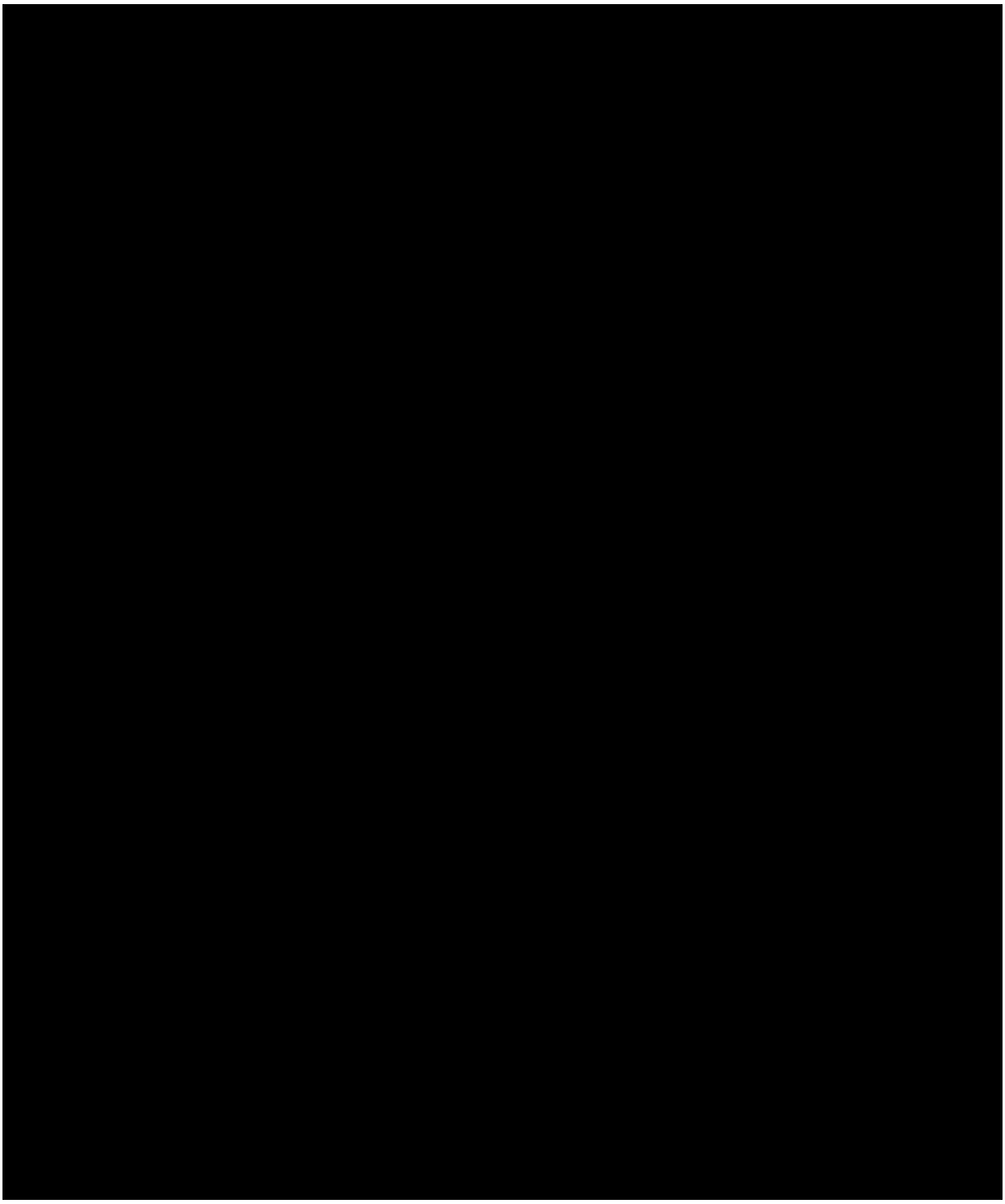
A supplementary analysis with the same model as described in section 3.7.2.2 for each secondary endpoint will be performed using a treatment policy strategy to address intercurrent events defined in section 3.7.2.1. All observed values will be used regardless of occurrence of an intercurrent event.

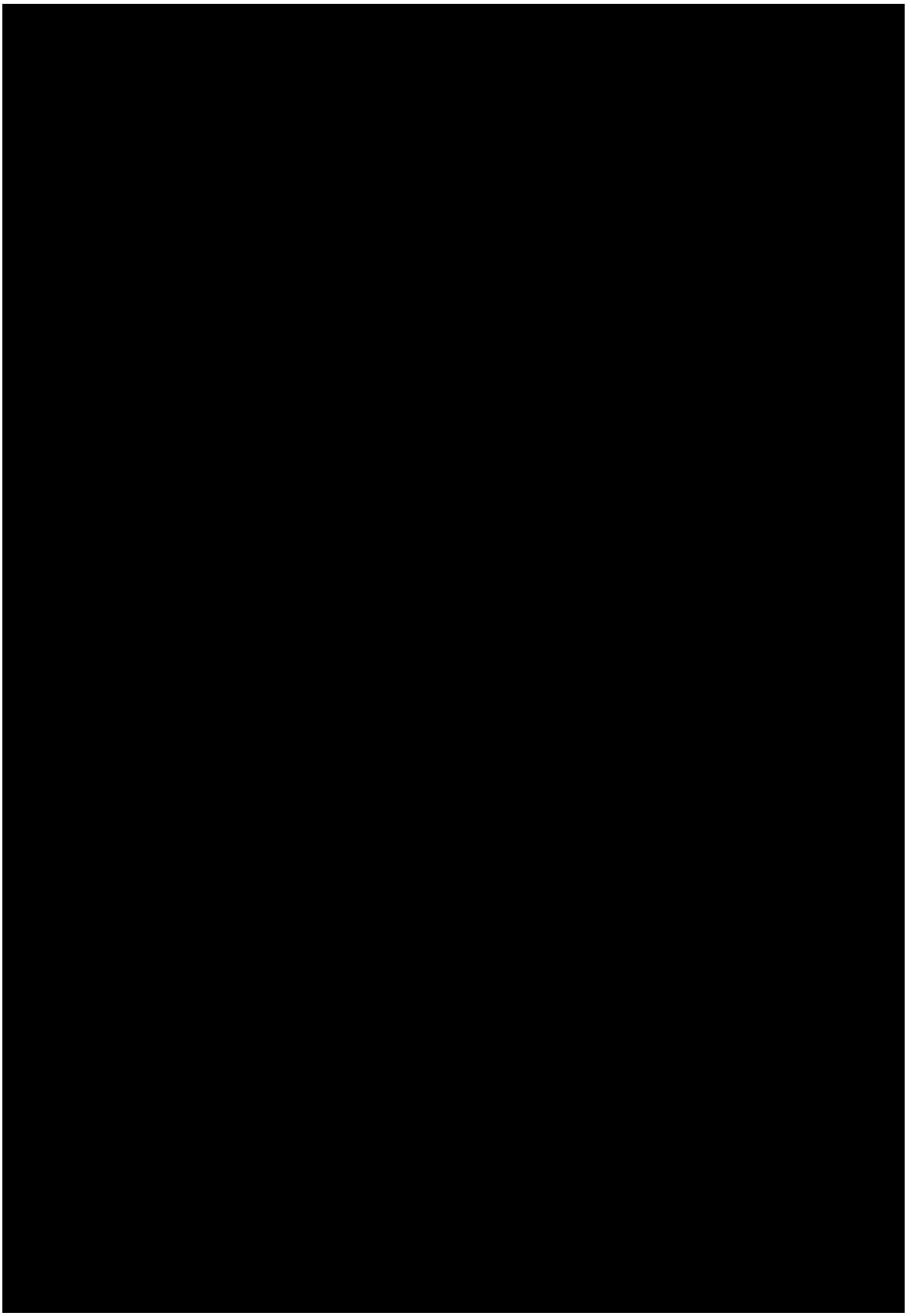
3.7.2.4 Handling plan for missing data

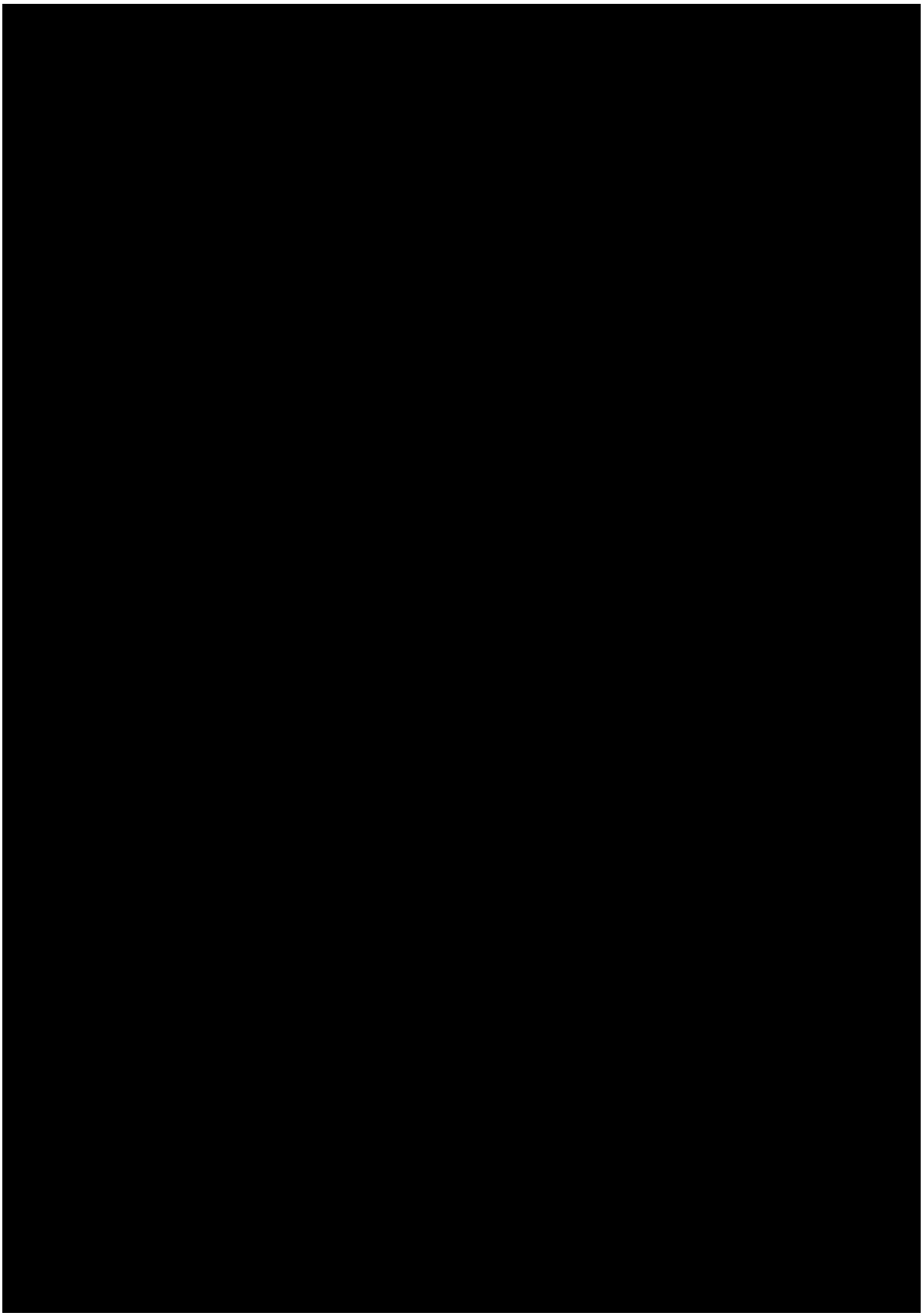
The missing data will be handled the same way as that for the primary endpoint analysis (see section 3.7.1.4).

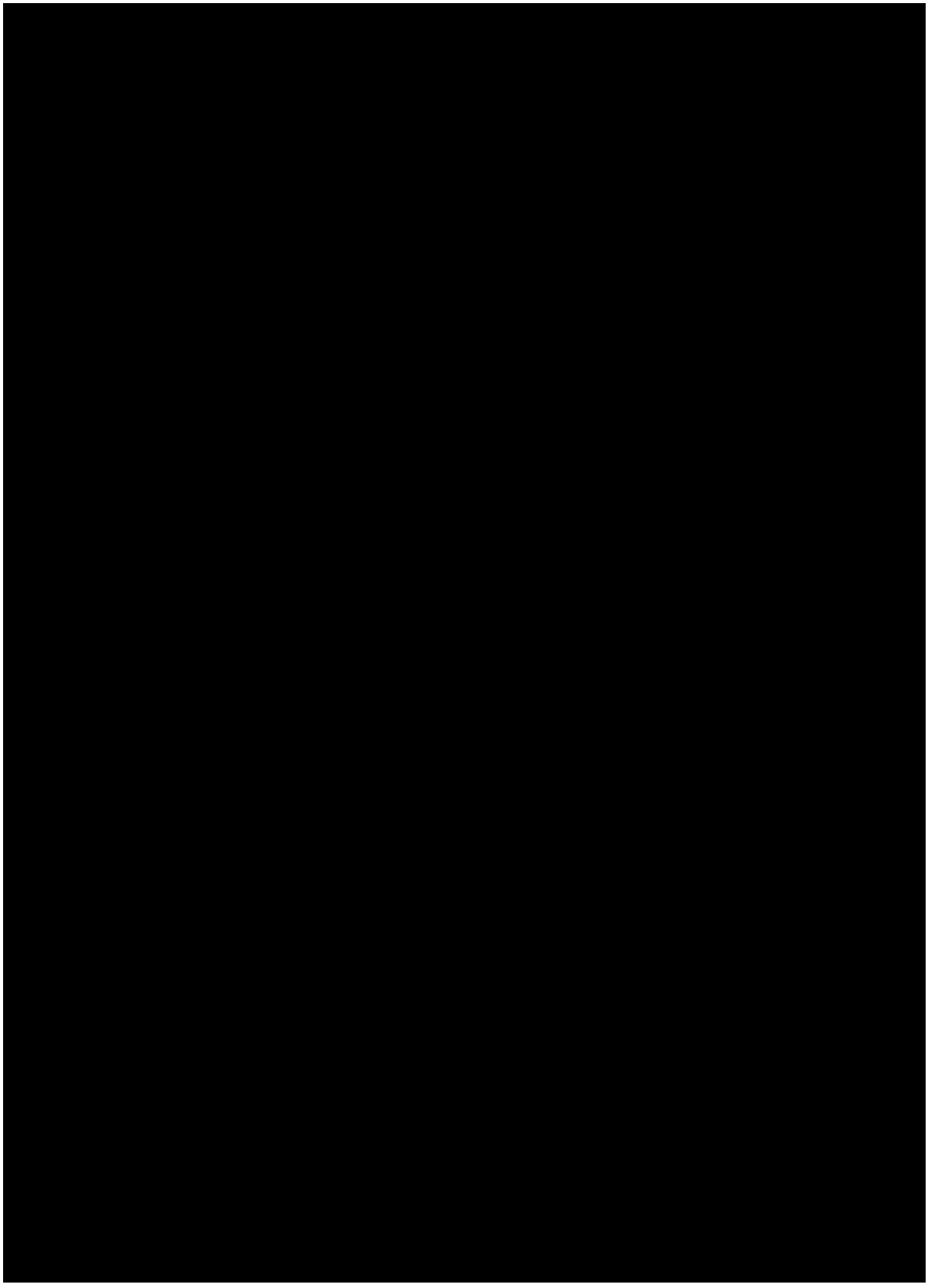
3.7.3 Exploratory Efficacy Endpoints and Analyses

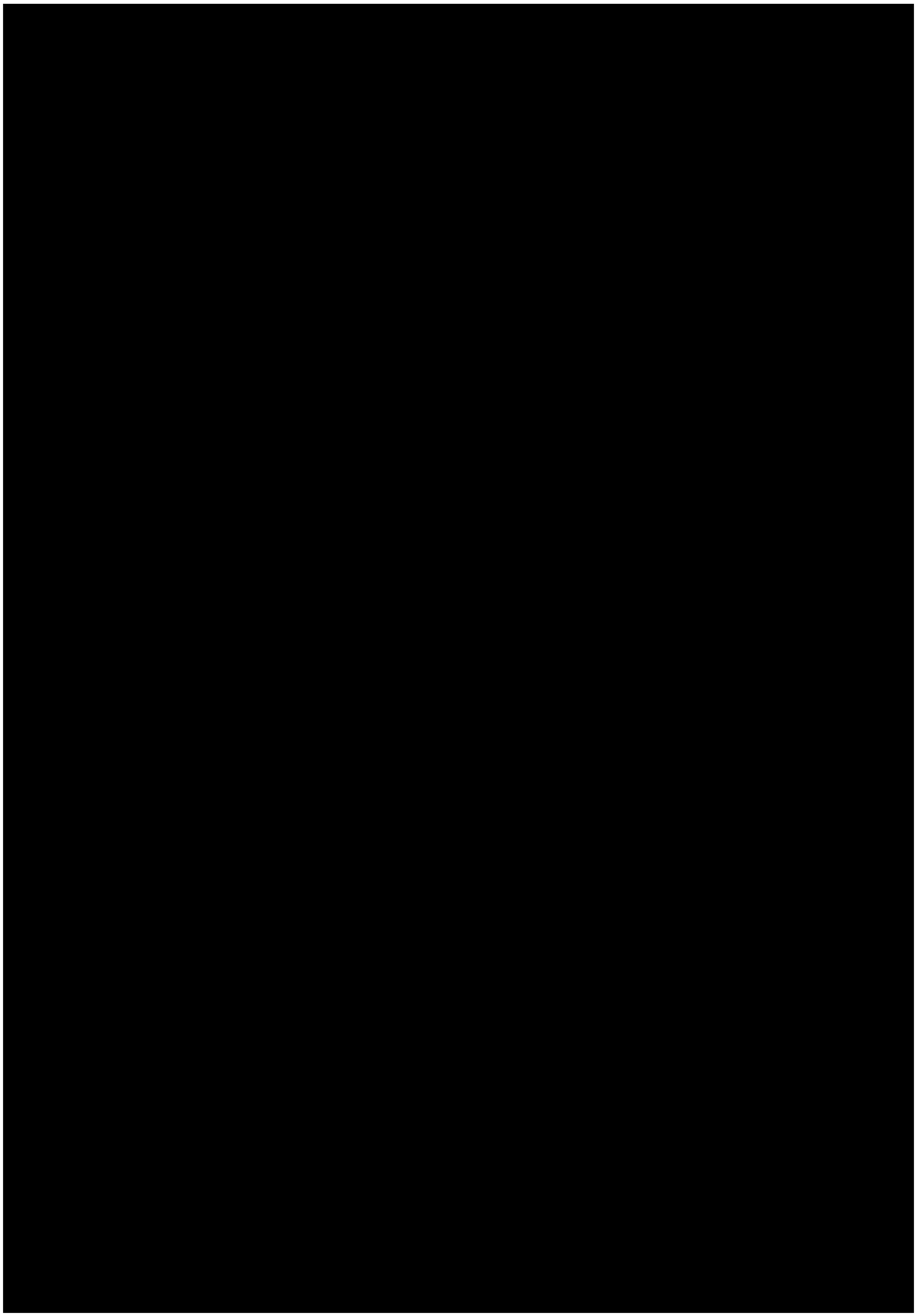
3.7.3.1 Exploratory efficacy endpoints

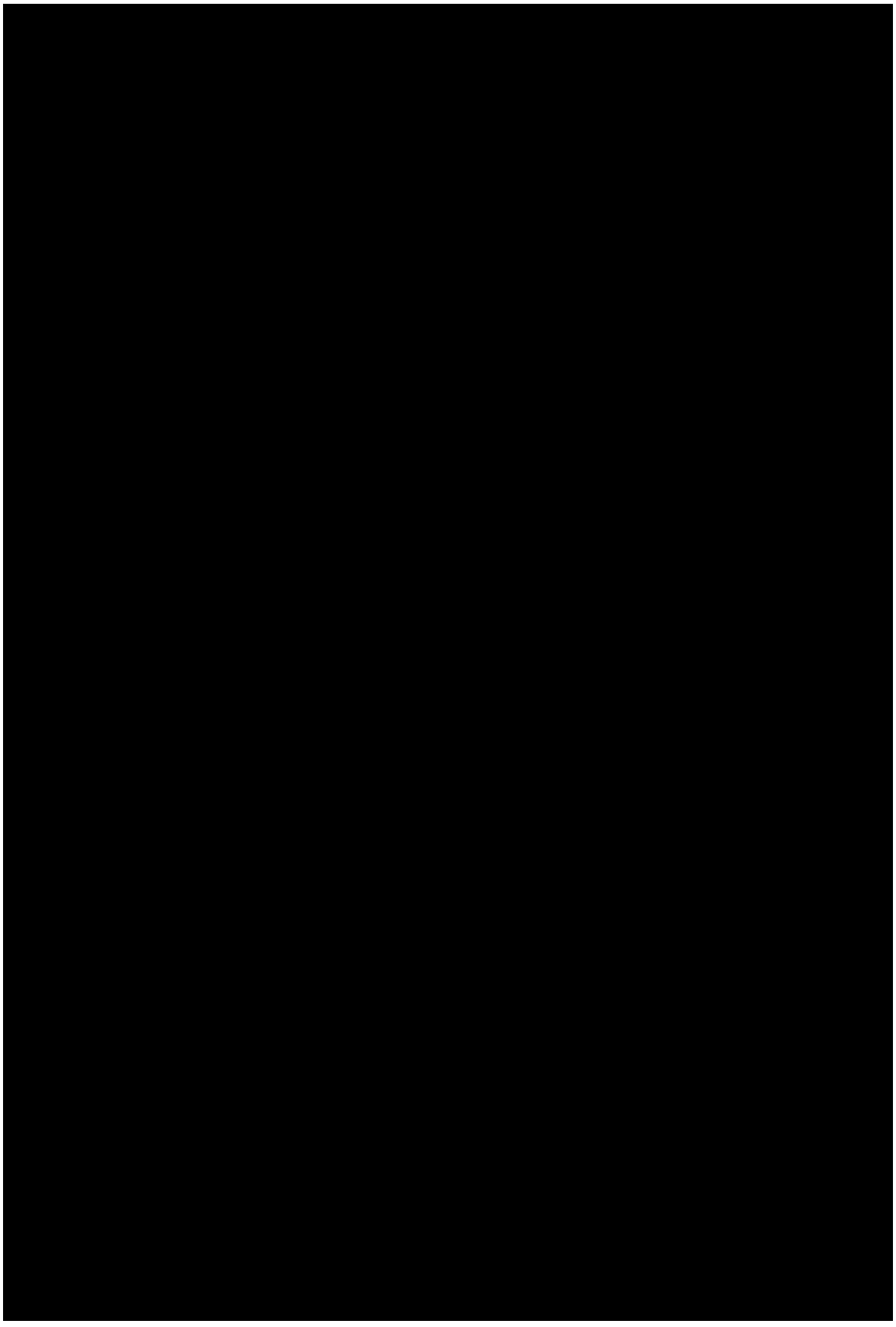












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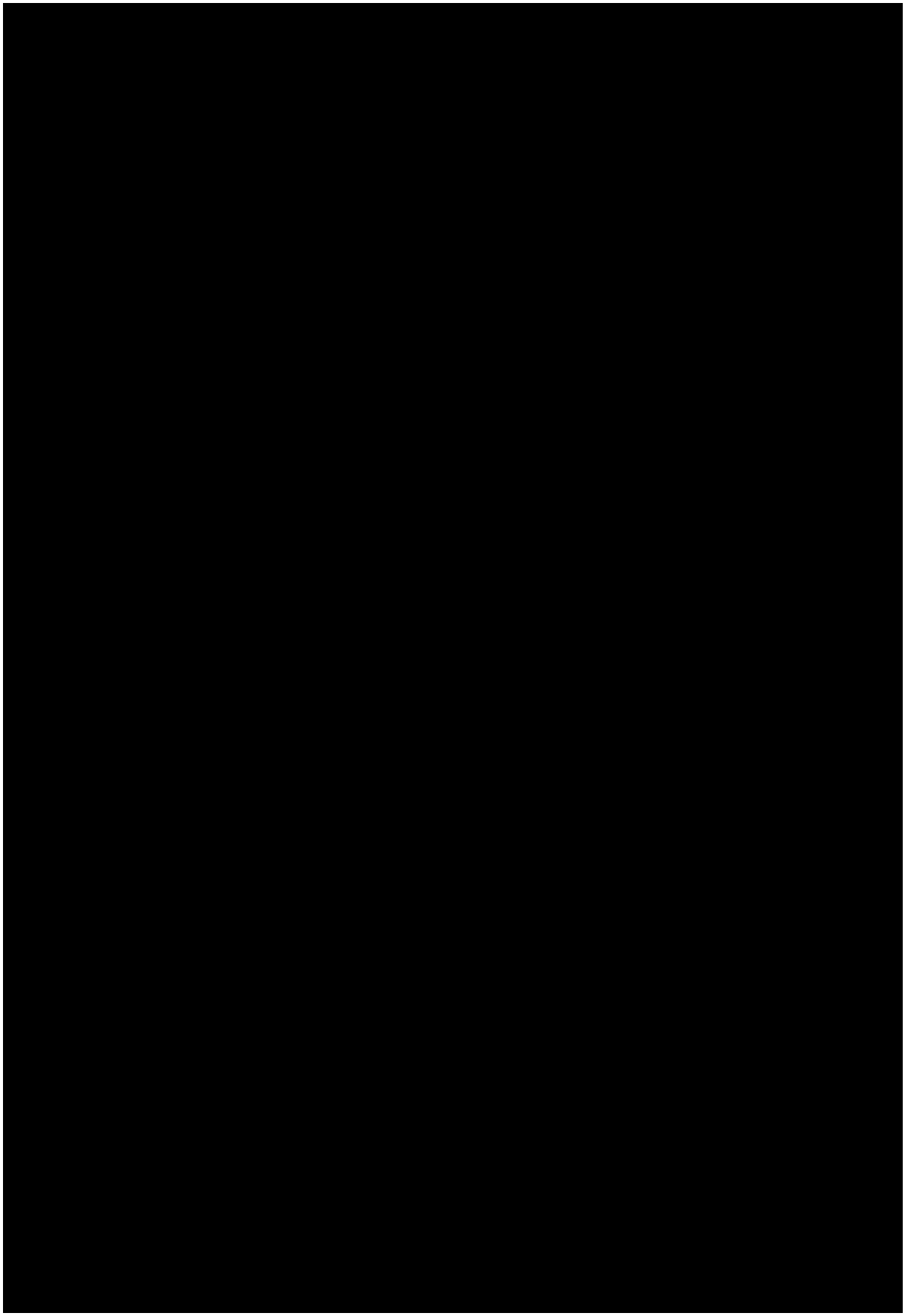

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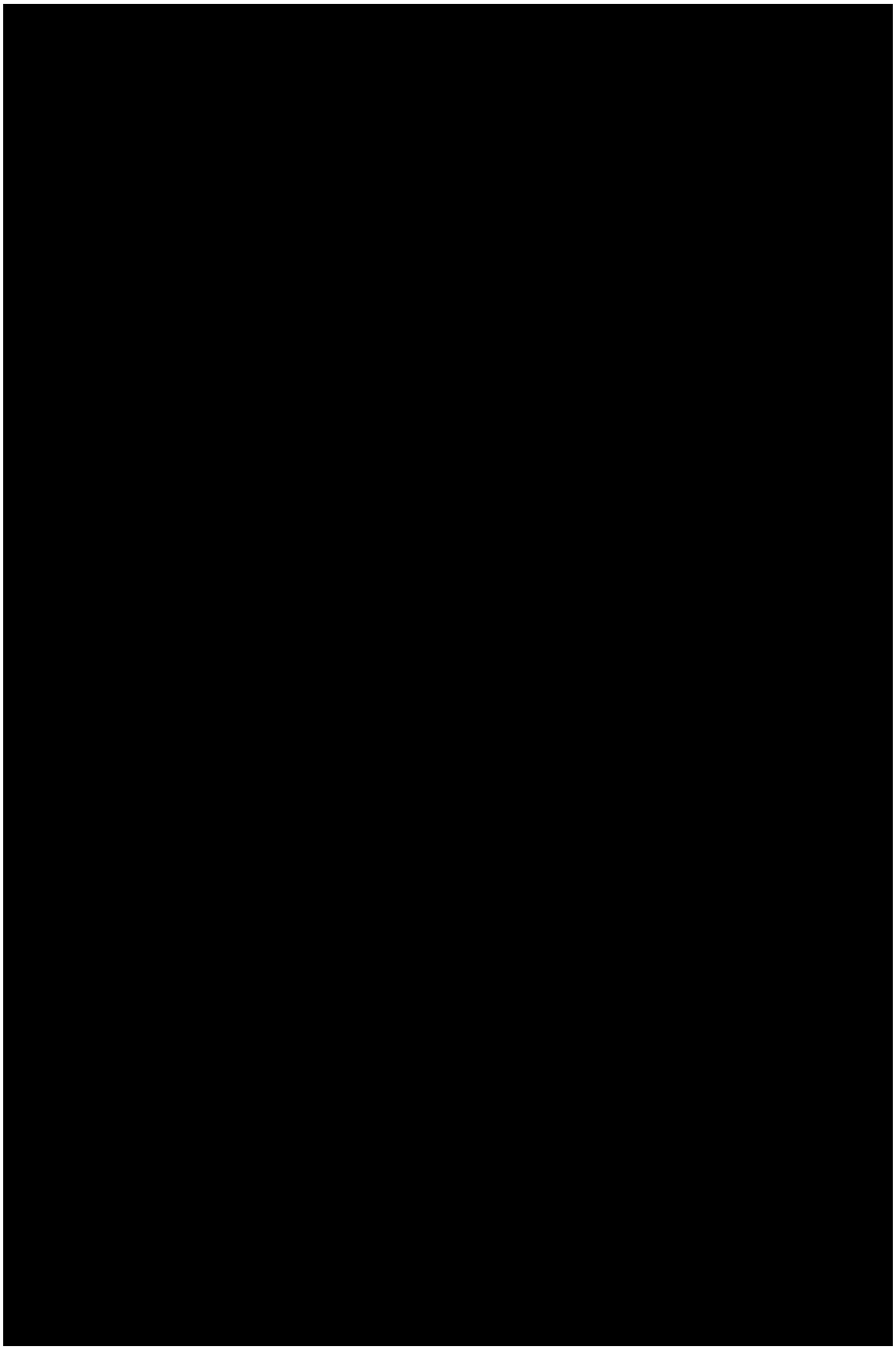
3.7.3.2 Exploratory efficacy analyses

[redacted]

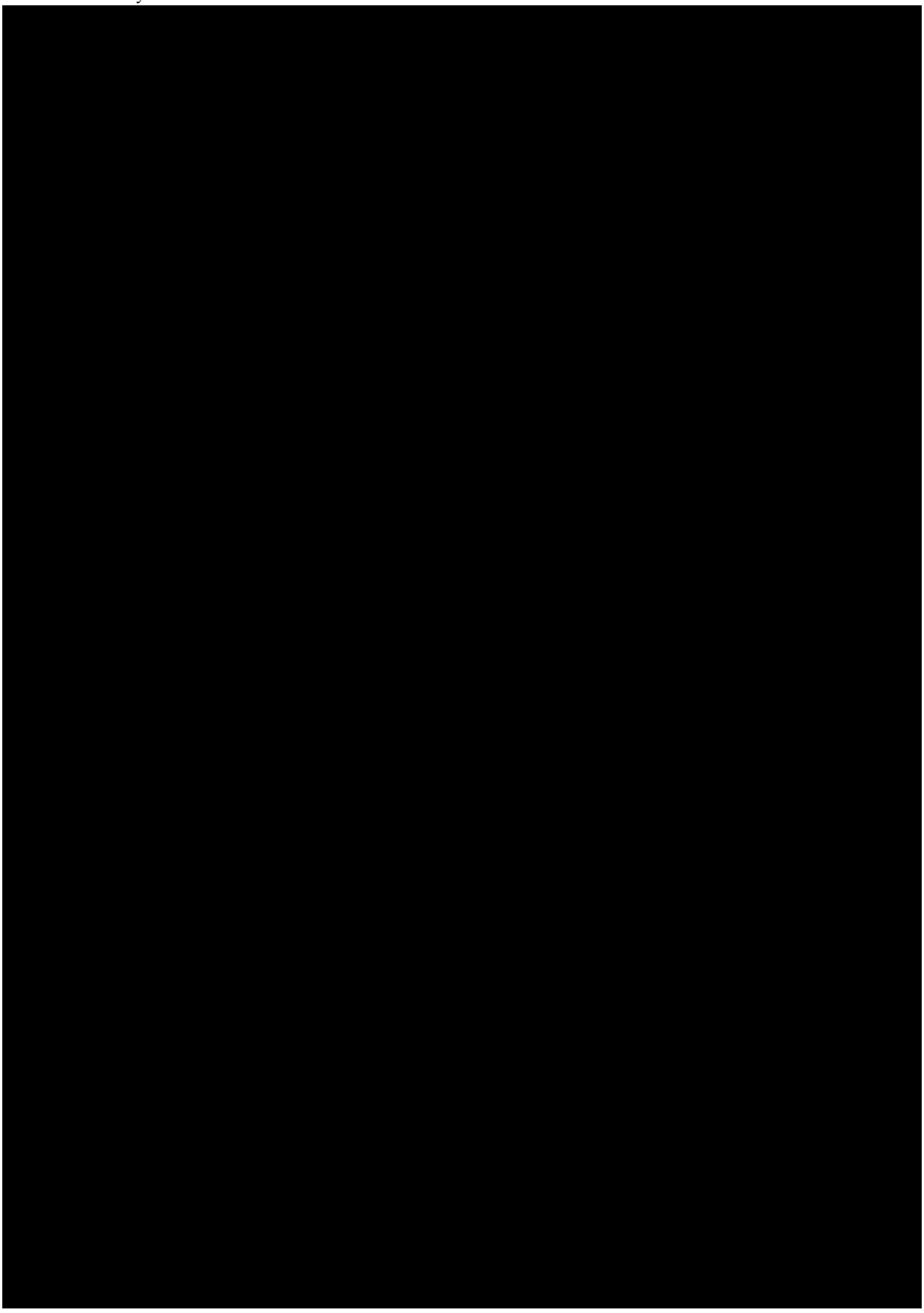


[redacted]

3.7.4 Handling Missing Items of Clinical Outcome Assessments

The BILAG-2004, SLEDAI-2K, CLASI, [redacted] are clinician reported outcomes and will be captured electronically. There will be very few missing items expected. All PROs will be administered electronically too. Questions are mandatory so there will be very few missing items expected. But in case there are missing items, the following algorithms will be used to handle the missing items.

[redacted]



[redacted]

3.7.5 Subgroup Analysis

To explore the uniformity of the detected overall treatment effect, subgroup analyses on the primary endpoint and secondary endpoints of SRI-4 + OGC ≤ 7.5 mg/day and ≤ Baseline dose and LLDAS will be performed for the following factors:

- SLEDAI-2K total score at screening (<10 points versus ≥10 points)
- OGC dose at baseline (<10 mg/day versus ≥10 mg/day prednisone or equivalent)

[redacted]

- Age (<55 versus ≥55 years)
- Onset of disease (adult versus pediatric onset)
- BMI (≤30 versus >30 kg/m^2)
- Race (white, black or African American, other)
- Ethnicity (Hispanic/Latino versus not Hispanic/Latino)
- Geographic region (Asia, Latin America, Europe, North America)

[redacted]

3.8 Safety Analysis

3.8.1 Adverse Events

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

An overall summary table will be showing the number and percentage of participants with at least 1 event in any of the following categories: TEAE, treatment emergent serious AE (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 participant for calculating rates, but all events will be presented in subject listings. In addition, if the same AE occurs multiple times within a particular participant, 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 AE of special interest (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. AESIs for this protocol include:

- Hypersensitivity reaction, including anaphylaxis
- Viral infection/reactivation
- Opportunistic infection
- Malignancy (except non-melanoma skin cancer)

Treatment emergent AESIs will be summarized by SOC and PT.

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

3.8.2 Clinical Laboratory Evaluation

The hematology, coagulation, serum chemistry, lipid profile, urinalysis, immunoglobulins parameters, and high-sensitivity C-reactive protein, 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, serum chemistry, and lipid profile parameter will be produced.

3.8.3 Other Safety Evaluations

3.8.3.1 Overdose

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

3.8.3.2 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 participants 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

3.8.3.3 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 participants 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.

3.8.3.4 Physical Examination and Weight

Significant physical examination findings will be summarized if data are available. The observed values and the changes from baseline in the weight and BMI will be summarized.

3.9 Pharmacokinetics

The PK analysis will be based on the PK analysis set. Descriptive statistics of the serum VIB7734 concentration will be tabulated by visit and by treatment group. Mean serum concentration-time profiles of VIB7734 by treatment group will be generated. Serum VIB7734 concentration data for individual participant will be presented in a listing.

Population modeling will be performed by vendor to better characterize the PK of VIB7734 given by SC injection in SLE participants.

3.10 Immunogenicity

3.11 Pharmacodynamics

Absolute values and change from baseline in pDCs will be summarized descriptively by visit for each treatment group based on safety analysis set.

3.12 Exploratory Analyses

4 PLANNED ANALYSIS

4.1 Planned Interim Analysis

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

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

4.2 Planned Primary Analysis

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

4.3 Planned Final Analysis

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

5 REFERENCES

Furie R, et al, 2017

Furie R, Khamashta M, Merrill JT et al. Anifrolumab, an anti-interferon-alpha receptor monoclonal antibody, in moderate-to-severe systemic lupus erythematosus. Arthritis Rheumatology 2017; 69(2): 376-386

Merrill JT, et al, 2018

Merrill JT, Furie R, Werth VP et al. Anifrolumab effects on rash and arthritis: impact of the type I interferon gene signature in the phase IIb MUSE study in patients with systemic lupus erythematosus. Lupus Science & Medicine 2018; 5: e000284. doi: 10.1136/lupus-2018-000284

Penner IK, et al 2009

Penner IK, Raselli C, Stöcklin M et al. The Fatigue Scale for Motor and Cognitive Functions (FSMC): Validation of a new instrument to assess multiple sclerosis-related fatigue. Multiple Sclerosis Journal 2009; 15(12): 1509–1517

Smarr KL and Keefer AL 2011

Smarr KL and Keefer AL. Measures of depression and depression symptoms: Beck Depression Inventory-II (BDI-II), Center for Epidemiologic Studies Depression Scale (CES-D), Geriatric Depression Scale (GDS), Hospital Anxiety and Depression Scale (HADS), and Patient Health Questionnaire-9 (PHQ-9). Arthritis Care Research 2011; 63(Suppl 11): S454-466

van Vollenhoven RF, et al, 2021

2021 DORIS definition of remission in SLE: final recommendations from an international task force. Lupus Science & Medicine 2021; 8:e000538. doi:10.1136/ lupus-2021-000538

Yee CS, et al, 2010

Yee CS, Cresswell L, Farewell V et al. Numerical scoring for the BILAG-2004 index. Rheumatology 2010; 49(9): 1665-1669

Revision History:

Version #	Description of Change
1.0	Initial version
2.0	[redacted]

6 APPENDIX

APPENDIX 1. Grading Algorithm for Each Domain of BILAG-2004

CONSTITUTIONAL

Category A:
Pyrexia recorded as 2 (same), 3 (worse) or 4 (new) **AND**

Any 2 or more of the following recorded as 2 (same), 3 (worse) or 4 (new):

Weight loss
Lymphadenopathy/sp
lenomegaly
Anorexia

Category B:
Pyrexia recorded as 2 (same), 3 (worse) or 4 (new) **OR**

Any 2 or more of the following recorded as 2 (same), 3 (worse) or 4 (new):

Weight loss
Lymphadenopathy/sp
lenomegaly
Anorexia

BUT do not fulfil criteria for Category A

Category C
Pyrexia recorded as 1 (improving) **OR**

One or more of the following recorded as > 0:

Weight loss
Lymphadenopathy/Splenomegaly
Anorexia

BUT does not fulfil criteria for category A or B

Category D
Previous involvement

Category E
No previous involvement

MUCOCUTANEOUS

Category A
Any of the following recorded as 2 (same), 3 (worse) or 4 (new):

Skin eruption -
severe Angio-
oedema -
severe Mucosal
ulceration -
severe
Panniculitis/Bullous lupus - severe
Major cutaneous vasculitis/thrombosis

Category B
Any Category A features recorded as 1 (improving) **OR**

Any of the following recorded as 2 (same), 3 (worse)

or 4 (new): Skin eruption - mild
Panniculitis/Bullous
lupus - mild Digital
infarcts or nodular
vasculitis Alopecia -
severe

Category C
Any Category B features recorded as 1 (improving) **OR**

Any of the following recorded as > 0:

Angio-oedema - mild
Mucosal ulceration - mild
Alopecia - mild
Periungual erythema/chilblains
Splinter haemorrhages

Category D
Previous involvement

Category E
No previous involvement

NEUROPSYCHIATRIC

Category A
Any of the following recorded as 2 (same), 3 (worse) or 4 (new):

Aseptic meningitis
Cerebral vasculitis
Demyelinating syndrome
Myelopathy
Acute confusional state
Psychosis
Acute inflammatory demyelinating polyradiculoneuropathy
Mononeuropathy (single/multiplex)
Cranial neuropathy
Plexopathy
Polyneuropathy
Status epilepticus
Cerebellar ataxia

Category B
Any Category A features recorded as 1 (improving) **OR**

Any of the following recorded as 2 (same), 3 (worse) or 4 (new):

Seizure disorder
Cerebrovascular disease (not due to vasculitis) Cognitive dysfunction
Movement disorder
Autonomic disorder
Lupus headache - severe unremitting
Headache due to raised intracranial hypertension

Category C
Any Category B features recorded as 1 (improving)

Category D
Previous involvement

Category E
No previous involvement

MUSCULOSKELETAL

Category A
Any of the following recorded as 2 (same), 3 (worse) or 4 (new):

Severe Myositis
Severe Arthritis

Category B
Any Category A features recorded as 1 (improving) **OR**

Any of the following recorded as 2 (same), 3 (worse) or 4 (new):

Mild Myositis
Moderate Arthritis/Tendonitis/Tenosynovitis

Category C
Any Category B features recorded as 1 (improving) **OR**

Any of the following recorded as > 0:

Mild Arthritis/Arthralgia/Myalgia

Category D
Previous involvement

Category E
No previous involvement

CARDIORESPIRATORY

Category A
Any of the following recorded as 2 (same), 3 (worse) or 4 (new):

Myocarditis/Endocarditis + Cardiac failure
Arrhythmia
New valvular dysfunction
Cardiac tamponade
Pleural effusion with dyspnoea
Pulmonary haemorrhage/vasculitis
Interstitial alveolitis/pneumonitis
Shrinking lung syndrome
Aortitis
Coronary vasculitis

Category B
Any Category A features recorded as 1 (improving) **OR**

Any of the following recorded as 2 (same), 3 (worse) or 4 (new):

Pleurisy/Pericarditis
Myocarditis - mild

Category C
Any Category B features recorded as 1 (improving)

Category D
Previous involvement

Category E
No previous involvement

GASTROINTESTINAL

Category A
Any of the following recorded as 2 (same), 3 (worse) or 4 (new):

Peritonitis
Lupus enteritis/colitis
Intestinal pseudo-obstruction
Acute lupus cholecystitis
Acute lupus pancreatitis

Category B
Any Category A feature recorded as 1 (improving) **OR**

Any of the following recorded as 2 (same), 3 (worse) or 4 (new):

Abdominal serositis and/or ascites
Malabsorption
Protein losing enteropathy
Lupus hepatitis

Category C
Any Category B features recorded as 1 (improving)

Category D
Previous involvement

Category E

No previous involvement

OPHTHALMIC

Category A
Any of the following recorded as 2 (same), 3 (worse) or 4 (new):

Orbital inflammation/myositis/proptosis
Keratitis - severe
Posterior uveitis/retinal vasculitis - severe
Scleritis - severe
Retinal/choroidal vaso-occlusive disease
Optic neuritis
Anterior ischaemic optic neuropathy

Category B
Any Category A features recorded as 1 (improving) **OR**

Any of the following recorded as 2 (same), 3 (worse) or 4 (new):

Keratitis - mild
Anterior uveitis
Posterior uveitis/retinal vasculitis - mild
Scleritis - mild

Category C
Any Category B features recorded as 1 (improving) **OR**

Any of the following recorded as > 0:

Episcleritis
Isolated cotton-wool spots (cytoid bodies)

Category D
Previous involvement

Category E
No previous involvement

RENAL

Category A
Two or more of the following **providing 1, 4 or 5 is included**:

1. Deteriorating proteinuria (severe) defined as

   (a) urine dipstick increased by ≥ 2 levels (used only if other methods of urine protein estimation not available); **or**
   (b) 24 hour urine protein > 1 g that has not decreased (improved) by ≥ 25%; **or**
   (c) urine protein-creatinine ratio > 100 mg/mmol that has not decreased (improved) by ≥25%; **or**
   (d) urine albumin-creatinine ratio > 100 mg/mmol that has not decreased (improved) by ≥25%

2. Accelerated hypertension
3. Deteriorating renal function (severe) defined as

   (a) plasma creatinine > 130 µmol/l and having risen to > 130% of previous value; **or**
   (b) GFR < 80 ml/min per 1.73 m^2 and having fallen to < 67% of previous value; **or**
   (c) GFR < 50 ml/min per 1.73 m^2, and last time was > 50 ml/min per 1.73 m^2 or was not measured.

4. Active urinary sediment
5. Histological evidence of active nephritis within last 3 months
6. Nephrotic syndrome

Category B
One of the following:

1. One of the Category A feature

2. Proteinuria (that has not fulfilled Category A criteria)
   (a) urine dipstick which has risen by 1 level to at least 2+ (used only if other methods of urine protein estimation not available); **or**
   (b) 24 hour urine protein ≥ 0.5 g that has not decreased (improved) by ≥ 25%; **or**
   (c) urine protein-creatinine ratio ≥ 50 mg/mmol that has not decreased (improved) by ≥25%; **or**
   (d) urine albumin-creatinine ratio ≥ 50 mg/mmol that has not decreased (improved) by ≥25%

3. Plasma creatinine > 130 µmol/l and having risen to ≥ 115% but ≤ 130% of previous value

Category C
One of the following:

1. Mild/Stable proteinuria defined as

(a) urine dipstick ≥ 1+ but has not fulfilled criteria for Category A & B (used only if other methods of urine protein estimation not available); **or**
(b) 24 hour urine protein > 0.25 g but has not fulfilled criteria for Category A & B ; **or**
(c) urine protein-creatinine ratio > 25 mg/mmol but has not fulfilled criteria for Category A & B; **or**
(d) urine albumin-creatinine ratio > 25 mg/mmol but has not fulfilled criteria for Category A & B

2. Rising blood pressure (providing the recorded values are > 140/90 mm Hg) which has not fulfilled criteria for Category A & B, defined as

(a) systolic rise of ≥ 30 mm Hg; and
(b) diastolic rise of ≥ 15mm Hg

Category D
Previous involvement

Category E
No previous involvement

Note: although albumin-creatinine ratio and protein-creatinine ratio are different, we use the same cut- off values for this index

HAEMATOLOGICAL

Category A
TTP recorded as 2 (same), 3 (worse) or 4 (new) **OR**

Any of the following:

Evidence of haemolysis and Haemoglobin < 8 g/dl
Platelet count < 25 x 10^9/l

Category B
TTP recorded as 1 (improving) **OR**

Any of the following:

Evidence of haemolysis and Haemoglobin 8 - 9.9 g/dl
Haemoglobin < 8 g/dl (without haemolysis)
White cell count < 1.0 x 10^9/l
Neutrophil count < 0.5 x 10^9/l
Platelet count 25 - 49 x 10^9/l

Category C
Any of the following:

Evidence of haemolysis and Haemoglobin ≥ 10g/dl
Haemoglobin 8 - 10.9 g/dl (without haemolysis)
White cell count 1 - 3.9 x 10^9/l
Neutrophil count 0.5 - 1.9 x 10^9/l
Lymphocyte count < 1.0 x 10^9/L
Platelet count 50 - 149 x 10^9/l
Isolated Coombs' test positive

Category D
Previous involvement

Category E
No previous involvement

APPENDIX 2. APPROVALS

Confirmation by the study biostatistician (or designee), biostatistics management (or designee), and the study clinical colleague or therapeutic lead (or designee) that the review of this statistical analysis plan is complete, and there is agreement on the content.

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[redacted]
Signer Name: [redacted]
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Signing Time: 01-Dec-2022 | 14:56 CST
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Sr Director, Biostatistics

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Signing Reason: I approve this document
Signing Time: 02-Dec-2022 | 08:17 CST
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[redacted]
Executive Medical Director, Clinical Development

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Title

Signature/Date

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