STATISTICAL ANALYSIS PLAN

Protocol Title:	A Phase 3, Randomized, Double-Blind, Placebo-Controlled Study of the Safety and Efficacy of Losmapimod in Adult Subjects with COVID-19 (LOSVID STUDY)
Protocol Number:	FIS-001-2020
Protocol Version/Date:	Version 1/ 29MAY2020 Version 2/ 29JUN2020 Version 2.1/ 10JUL2020 Version 3.0/ 21Oct2020
Investigational Product:	Losmapimod
Sponsor:	Fulcrum Therapeutics 26 Landsdowne St., 5th floor Cambridge, MA 02139, USA
SAP Version/Date:	SAP 1.0/27APR2021

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SIGNATURE PAGE

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We, the undersigned, have reviewed and approved this Statistical Analysis Plan:

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VERSION HISTORY

Version	Version Date	Description
1.0	27APR2021	Original signed version

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LIST OF ABBREVIATIONS

Abbreviation	Definition
ADaM	Analysis Data Model
AE	Adverse event
AESI	Adverse event of special interest
ALT	Alanine aminotransferase/serum glutamic pyruvic transaminase (SGPT)
ANCOVA	Analysis of Covariance
[redacted]	[redacted]
AR(1)	First-order autoregressive
ARDS	Acute respiratory distress syndrome
AST	Aspartate aminotransferase/serum glutamic oxaloacetic transaminase (SGOT)
BID	Bis in diem / twice per day
BMI	Body mass index
CDISC	Clinical Data Interchange Standards Consortium
CoV	Coronavirus
COVID-19	Coronavirus disease 2019
CRP	C-reactive protein
DMC	Data Monitoring Committee
ECG	Electrocardiogram
ECMO	Extracorporeal membrane oxygenation
eGFR	Estimated glomerular filtration rate
FAS	Full Analysis Set
FCS	Fully conditional specification
FDA	Food and Drug Administration
[redacted]	[redacted]
IA	Interim analysis
ICU	Intensive care unit
IL-6	Interleukin-6
IxRS	Interactive/web voice response system
LDH	Lactate dehydrogenase
LLQ	Lower limit of quantitation
MAR	Missing at random
MCAR	Missing-completely-at-random
MedDRA	Medical Dictionary for Regulatory Activities
MI	Multiple imputation
MMRM	Mixed-Model-Repeated Measures
PD	Pharmacodynamic(s)
PK	Pharmacokinetics
PO	Per os / orally
PPS	Per protocol set
RNA	Ribonucleic acid
SAE	Serious adverse event
SAP	Statistical analysis plan
SARS-CoV-1	Severe acute respiratory syndrome coronavirus 1
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
SAS	Statistical Analysis Software

Abbreviation	Definition
SDTM	Study Data Tabulation Model
SOC	Standard of care
TEAE	Treatment-emergent adverse event
TFL	Tables Figures and Listings
WHO	World Health Organization

1 INTRODUCTION

The purpose of this Statistical Analysis Plan (SAP) is to provide a description of the statistical methods to be implemented for the analysis of data from the study with protocol number FIS-001-2020. The SAP will be finalized prior to the planned Interim Analysis (IA). Any deviations from the SAP after IA will be documented in the final Clinical Study Report (CSR).

2 STUDY OVERVIEW

2.1 Objectives and Endpoints

Objectives	Endpoints
Primary	
To assess the efficacy of losmapimod compared with placebo for treatment of COVID-19 when administered concurrently with standard of care	Proportion of progressors to death or respiratory failure by Day 28
Secondary	
To evaluate the effect of losmapimod compared with placebo on clinical outcomes	Clinical status by Days 7 and 14 as measured on the 9-point WHO ordinal scale: • (8) death • (7) ventilation plus additional organ support (vasopressors, renal replacement therapy, ECMO) • (6) Intubation and mechanical ventilation • (5) noninvasive ventilation or high-flow oxygen therapy • (4) oxygen therapy but not requiring high-flow or non-invasive ventilation • (3) hospitalized but not requiring oxygen therapy • (2) Discharged from the hospital but with limitation of activities

	• (1) Discharged from the hospital and without any limitation • (0) No clinical evidence of the disease
To assess the effect on clinical status of treatment with losmapimod compared with placebo	Total number of study days free of oxygen supplementation by Day 28 Total number of study days in ICU by Day 28 Total number of study days hospitalized by Day 28 Total number of respiratory failure-free study days by Day 28 Percentage of subjects discharged from the hospital by Day 28
To assess the effect on survival following treatment with losmapimod compared with placebo	All-cause mortality at Day 28 Number of study days alive by Day 28
To assess the safety and tolerability of losmapimod compared with placebo	Incidence of AEs and SAEs Incidence of clinically significant changes in laboratory parameters and vital sign measurements
To characterize changes in SARS-CoV-2 infection following treatment with losmapimod compared with placebo	Quantifiable viral RNA on Day 7
[redacted]	

2.2 Study Design

2.2.1 Overview

This Phase 3 multicenter, randomized, double-blind, placebo-controlled study will evaluate the safety and efficacy of losmapimod versus placebo on a background of standard of care in subjects with COVID-19 disease.

This study will be performed in hospitalized subjects ≥40 years old who have a CRP >15 mg/L, who have been diagnosed with COVID-19, and who can undergo randomization within 7 days of collection of the sample found positive for the SARS-CoV-2 virus and before progressing into critical disease. Critical disease is defined as cardiac failure, septic shock, or ARDS or immediate need for intubation or mechanical ventilation per the judgment of the investigator.

Subjects who sign informed consent and meet all entry criteria may be enrolled.

Up to 410 subjects will participate for a maximum of 34 days, divided as follows:

- Screening: Day -3 until Day -1 before the first study drug administration.
- Treatment period of 14 days:
  - Subjects randomized (1:1) to either:
    - losmapimod tablets 15 mg orally (PO) twice daily (BID); OR
    - matching placebo tablets PO BID
  - Randomization will be stratified by age (<65 or ≥65) and requirement for oxygen at randomization (yes/no)
- Follow-up: 7 (± 3) days after last dose and 14 (± 3) days after last dose.

The first 10 enrolled subjects will be dosed and followed for at least 72 hours after their first dose for a "sentinel" safety review before any additional subjects are dosed. Dosing of additional subjects will continue if there are no drug-related safety concerns from the initial subjects dosed as assessed by an independent Data Monitoring Committee (DMC). The DMC will review safety data for the sentinel subjects and all subjects at regular intervals throughout the study as outlined in the charter.

The Sponsor will monitor individual adverse events (AEs) and toxicities on an ongoing basis throughout the study.

All study visits during the first week of treatment are anticipated to be conducted in the inpatient setting. If the clinical status of the subject improves such that the clinician discharges the subject from the hospital before the end of the study, the follow-up assessments will be conducted on an outpatient basis by alternative methods, including the use of local laboratories/facilities or home visits for blood draws, telemedicine, and/or outpatient follow-up clinic visits as deemed clinically appropriate per COVID-19 follow-up standard of care (SOC) at each site.

2.2.2 Randomization and Blinding

A total of up to 410 subjects will be recruited into this study and will be randomized in a 1:1 ratio to 15 mg losmapimod (BID) or placebo using an interactive/web voice response system (IxRS) for randomization. The randomization will be stratified by age (<65 or ≥65) and requirement for oxygen at randomization (yes/no) at enrollment.

Only subjects who have completed screening assessments and are eligible for participation in the study will be randomized to receive study drug. Randomized subjects will be sequentially assigned a unique subject number from the randomization list per the IxRS. From the time of randomization and throughout the duration of the study, subjects will be identified by their unique randomization number.

The authorized site personnel will prepare the appropriate study drug for each subject based on the randomization schedule. Treatment codes should not be broken except in emergency situations, i.e., when knowledge of the treatment is essential for the immediate further management of the subject.

This study will be performed in a double-blind fashion. The investigator, study staff, subjects, sponsor, and monitor will remain blinded to subject-level treatment assignment until study closure. The investigational drug and its matching placebo are indistinguishable and will be packaged in the same way.

All doses will be administered either in the hospital (anticipated during the first week of study treatment) or taken by the study participants on an outpatient basis. The subject will bring the study treatment bottle to each visit (clinic or home assessment) for review by the site staff. The study treatment bottles will be collected at the Day 14 visit whether in the hospital or outpatient or at the ET visit if prior to Day 14.

2.2.3 Study Drug

Losmapimod will be provided in tablets of 7.5 mg for oral administration.

Matching placebo tablets will be provided for oral administration.

The tablets are plain white, round, biconvex, film-coated tablets. The proposed dosing regimen is as a twice daily dose of 15 mg (2 × 7.5 mg tablets/dose BID). The proposed duration of treatment is for up to 14 days.

Subjects should take their dose of losmapimod or placebo with food whenever possible and with 240 mL of room temperature water.

2.2.4 Sample Size Determination

The primary efficacy endpoint of this study is the proportion of subjects who progress to death or respiratory failure by the end of study (Day 28). It is estimated that approximately 30% of enrolled subjects receiving SOC plus placebo will attain this endpoint. It is assumed that losmapimod will improve the primary endpoint by 40% over placebo. On the basis of these assumptions, a total of up to 410 subjects randomized to the losmapimod arm or the placebo arm in a 1:1 ratio (205 subjects in the losmapimod arm and 205 subjects in the placebo arm) will yield approximately 80% power in a 1-sided test at the 2.5% significance level.

The sample size estimate assumes an IA will be conducted after approximately 206 subjects (103 in the losmapimod arm, and 103 in the placebo arm) have completed the Day 28 visit, to assess early futility, using the rules specified in Section 5.1.

3 STATISTICAL METHODOLOGY

3.1 General Considerations

3.1.1 Analysis Day

Analysis day will be calculated from the date of first dose of study drug. The day of the first dose of study drug will be Day 1, and the day immediately before Day 1 will be Day -1. There will be no Day 0.

3.1.2 Definition of Baseline

Baseline is defined as the last measurement prior to the first dose of study drug.

3.1.3 Summary Statistics

Categorical data will generally be summarized with counts and percentages of subjects. The denominator used for the percentage calculation will be clearly stated. Continuous data will generally be summarized with descriptive statistics including n (number of non-missing values), mean (with its standard error), first quartile, median, third quartile, standard deviation, minimum, and maximum.

[redacted]

Where appropriate, descriptive statistics may be presented with 95% CI.

3.1.4 Hypothesis Testing

All statistical comparisons will be made using one-sided tests at $\alpha = 0.025$. All null hypotheses will be of no treatment difference, and all alternative hypotheses will be one-sided. Confidence intervals will be 2-sided with $\alpha = 0.05$ and reported to the same precision as the applicable summary statistic (e.g., mean), and standard error will be reported to one additional decimal place. P-values will be reported to four decimal places, with p-values less than 0.0001 reported as “<0.0001”.

3.1.5 Type I Error for Testing Key Study Endpoints

The overall Type I error of the study will be controlled at 0.025 for 1-sided tests of hypotheses for the following key study endpoints, using a closed test procedure. The key endpoints will be tested in the fixed sequence procedure as the same sequence they are listed below. Assuming the analysis of the prior endpoint yields statistically significant treatment effect, the next key endpoint will be tested.

1. Proportion of progressors to death or respiratory failure by Day 28
2. Change in clinical status using the 9-point WHO scale at Day 14
3. Change in clinical status using the 9-point WHO scale at Day 7
4. Oxygen-free days by Day 28

3.1.6 Evaluation of Site Effect

Low enrolling sites will be pooled for analysis. For sites with less than 10 subjects in total, they will be pooled. Pooled sites will be only used for descriptive summary of biomarker endpoints of CRP and IL-6.

3.1.7 Adjustment of Covariates

In the event that the analysis models do not converge (e.g., due to sparse data), sex will be removed from the model, followed by the stratification factors until the model converges.

For mixed-model-repeated measures (MMRM) model, covariance structure will be updated to first-order autoregressive (AR(1)) prior to the removal of any covariate.

3.1.8 Handling of Dropouts and Missing Data

All missing or incomplete safety and PD data, including dates and times, will be treated as such. Missing test results or assessments will not be imputed, and as such, are assumed missing completely-at-random (MCAR).

For laboratory data, values below the limit of quantitation (recorded as "< LLQ") will be set to half that limit.

For the analysis of hospital-free and ICU-free days, subjects who die prior to the analysis time point will have post-death days considered to be not hospital-free and not ICU-free.

Adverse events with missing start dates will be considered as treatment-emergent unless the partial date excludes that possibility, e.g., the adverse event month is prior to the first dose of study drug. Otherwise, the first day of the month will be used to impute missing start days and January will be used to impute missing start months. For example, if the first dose of study drug was on January 8, 2021 and an adverse event started in January 2021 with missing day, the start date will be imputed as the first dose date (January 8, 2021) and this adverse event will be considered as treatment-emergent. In the same example, if another adverse event has start month of December 2020 with missing day (before the first dose date of January 8, 2021), its start date will be imputed as December 1, 2020 and will not be considered as treatment-emergent.

Subjects who terminate the study prior to the analysis time point, not due to death, will be considered as missing for the analysis of key efficacy endpoints. Missing data in each treatment arm will be imputed using the observed data in their respective arm under the missing at random (MAR) assumption. Multiple imputation (MI) will be performed using the fully conditional specification (FCS) model. The imputation model will include the stratification factors, sex, and baseline CRP.

The handling of missing data for the key efficacy endpoints are outlined as the following:

1. Primary endpoint: patients whose status could not be ascertained (lost-to-follow up, etc.) will be imputed using multiple imputation approach.
2. Change in Clinical Status at Days 7 and 14: missing clinical status at the post-baseline timepoint will be imputed using multiple imputation approach.
3. Oxygen-free, ICU, hospitalized, respiratory failure-free days: subjects who die prior to the analysis time point will have post-death days considered not event free. For example, if a subject died on Day 6, Day 6 and after will not be counted toward oxygen-

free, ICU, hospitalized, respiratory failure-free days. Subjects who terminate the study for other reasons prior to the analysis time point will be imputed using multiple imputation approach.

3.2 Analysis Populations

3.2.1 Full Analysis Set (FAS)

The FAS will consist of all subjects who are randomized and receive any study drug. All analyses using the FAS will group subjects according to randomized treatment. The primary endpoint, clinical outcomes/status, survival, and pharmacodynamic endpoints will be analyzed using the FAS. The IA will be based on FAS.

3.2.2 Safety Analysis Set

The Safety Analysis Set is defined as all subjects who receive any study drug. All analyses using the Safety Analysis Set will group subjects according to treatment actually received. The Safety Analysis Set will be used for all safety and tolerability analyses.

3.2.3 Pharmacokinetic (PK)/Pharmacodynamic (PD) Analysis Set

The PK/PD Analysis Set will consist of all the sentinel subjects who receive any study drug.

3.3 Subject Data and Study Conduct

3.3.1 Subject Disposition

Subject disposition will be listed by subject.

The number and percentage of subjects in each of the following categories will be presented by the treatment group and overall for all screened subjects:

- screened,
- randomized,
- treated,
- randomized but not treated,
- completed the Treatment Period, and
- completed the study.

Primary reasons for discontinuation of study treatment and primary reasons for discontinued study will be tabulated.

3.3.2 Protocol Deviations

Any major protocol deviation will be documented as described in the protocol deviation plan, and its impact on inclusion in each analysis population for any subject will be specified. The final list of protocol deviations impacting the analysis populations will be reviewed prior to database lock. Counts and percentages of subjects with major protocol deviations by deviation category will be summarized for all randomized subjects.

3.3.3 Analysis Populations

The numbers and percentages of subjects randomized and included in each analysis population will be tabulated.

3.3.4 Demographic and Baseline Characteristics

The following demographic and baseline characteristics will be summarized:

- Age (years) and age categories (<65 years, ≥65 years)
- Sex
- Race
- Ethnicity
- Height (cm)
- Weight (kg)
- Body mass index (BMI) (kg/m^2) and BMI categories (<30 kg/m^2, ≥30 kg/m^2)
- Requirement for oxygen at randomization (yes, no)
- Chest imaging
- COVID-19 diagnosis
- Baseline CRP by central lab (Day 1) and categories
- Baseline IL-6 by central lab (Day 1)
- Viral load by central lab PCR (Day 1 and Day 7, unless sentinel group or ET)
- Region (US, Ex-US)

Demographic and other baseline characteristics will be summarized using descriptive statistics for the treatment group and overall for all randomized subjects.

3.3.5 Medical History

Medical history terms will be coded using the Medical Dictionary for Regulatory Activities (MedDRA, Version 23.0). Medical history will be summarized by treatment group and overall using coded system organ class and preferred term. In addition, COVID-19 associated medical history which may include diabetes, obesity, chronic kidney disease, hypertension, cancer, cardiac disease, immunocompromised state post-transplant, Chronic obstructive pulmonary disease, and asthma will be summarized separately. Medical history will also be listed.

3.3.6 Prior and Concomitant Medications

Prior medications will include medications which started prior to the first dose of study drug.

Concomitant medications will include medications or non-medication therapeutic agents (convalescent plasma therapy for example) taken on and after the first dose of study drug.

Medications that started prior to the first dose of study drug but continued into treatment are considered as both prior and concomitant.

All medications will be coded using the World Health Organization Drug Dictionary (WHO Drug Global B3, March 2020). A frequency table of the number and percentage of subjects will be provided for concomitant medications by therapeutic class and preferred name for the Safety Analysis Set. Prior and concomitant medications will be summarized separately.

Prior and concomitant medications will be also listed by international nonproprietary names, dose, regimen, route and for which indication it was prescribed.

3.3.7 Concomitant Procedures/Non-Drug Therapies

Concomitant procedures and non-drug therapies will be listed.

3.3.8 Study Drug Exposure and Compliance

Exposure to study treatment will be described in terms of duration of treatment. Exposure in days is defined as the date of last dose of study drug minus the date of first dose of study drug plus 1. Exposure in days will be summarized. In addition, a contingency table will be provided to display the number and percentage of subjects with exposure in the following categories:

- <1 week (<7 days),
- >=1 - <=2 weeks (7 - 14 days),
- >2 weeks (>14 days).

Treatment compliance will be calculated as (the number of tablets dispensed - the number of tablets returned) divided by (the number of tablets expected to be taken during the Treatment Period, calculated as four tablets daily times 14 days). Percent compliance will be summarized. In addition, the number and percentage of subjects within each treatment group with overall compliance in the following categories: <80%, 80% to 120%, and >120%, will be provided for the Safety Analysis Set.

3.4 Efficacy Assessment

3.4.1 Primary Efficacy Endpoint

3.4.1.1 Primary Analysis

The primary efficacy endpoint is the proportion of subjects who progress to death or respiratory failure by Day 28.

Respiratory failure is defined as either need for mechanical ventilation (invasive or non-invasive) or high flow oxygen (defined by greater than 15 LPM flow of oxygen to maintain oxygen saturation between 90% and 95%), sustained for at least 48 hours, at any time during the study.

The fitted logistic regression model is used to predict the response rate for every subject in the study as if they had received the treatment or the control intervention.

Assuming p_t is probability of outcome in the losmapimod arm; p_c is the probability of outcome in the control arm

Study hypothesis: H_0: $p_t - p_c = 0$

H_1: $p_t - p_c < 0$

Assuming p_t=0.18, p_c=0.30, we can restate the hypothesis as

H_0: $\theta = \theta_0 = 0$

H_1: $\theta = \theta_1 = -0.12$

where θ is calculated as $p_t - p_c$. For the final analysis, the proportion of subjects achieving the primary endpoint in the treatment arms will be compared using an adjusted risk difference obtained from the logistic regression model, adjusted for stratification factors, sex, and baseline CRP. Sample SAS codes are provided in Appendix A. More details can be found in Guo et al. (2012) and Ge et al. (2011).

An interim analysis to assess futility analysis—and potential sample size re-estimation— will be conducted, as discussed in Section 5.1.

All results will be summarized descriptively by treatment arm and expressed as proportions, along with corresponding unadjusted/adjusted 95% CI of the difference between response rates, and p-values.

In the first step of multiple imputation, data will be multiple imputed using the FCS discriminant function separately by treatment arm to 20 imputed datasets. This analysis assumes data are missing at random. The imputation model will include the stratification factors, sex, baseline CRP, and a two-level binary factor (discharge from the hospital prior to discontinuing the study; Yes, No)

[redacted]

For each imputed dataset, the proportion of subjects achieving the primary endpoint in the treatment arms will be compared using an adjusted risk difference obtained from the logistic regression model, adjusted for stratification factors, sex, and baseline CRP for each imputed dataset.

The estimated treatment effect and associated standard errors from each imputation from the 20 logistic regression model will be combined using Rubin's rules to provide an overall treatment effect, associated 95% confidence interval (CI), and 2-sided p-value. Sample codes are listed below.

[redacted]

3.4.2 Secondary Efficacy Endpoints

Clinical status at Day 7 and Day 14:

Change in clinical status between baseline and at Days 7 and 14 will be modeled using ordinal logistic regression models, adjusting for stratification factors, sex and baseline CRP. If the subject progresses to death and the value of WHO 9-point scale is missing, the missing value of WHO 9-point will be imputed as (8) death.

Percentages for each category of the ranking scale will be tabulated by treatment arm, along with differences between treatment arms at each time point. The proportion of subjects for each of the items in the scale will be compared using an adjusted risk difference obtained from an ordinal logistic regression model, adjusting for stratification factors, sex and baseline CRP.

Total number of study days by Day 28:

(a) Free of oxygen supplementation; (b) in ICU; (c) of hospitalization; (d) free of respiratory failure; (e) alive; For each endpoint (a) – (e), a Poisson regression model will be used to assess

the relationship with treatment, adjusting for stratification factors, sex, baseline CRP and number of days on study. The key study endpoint of "oxygen free days by Day 28" will be tested at 1-sided significance level of 0.025 as outlined in Section 3.1.5.

If a patient died, the number of days of (a)-(e) are considered as having the events on and after the patient died. For example, if a patient died on Day 6. The days from Day 6 and after are considered not free of oxygen supplementation, hospitalization, ICU, and respiratory failure.

Percentage of subjects discharged from the hospital by Day 28:

Percentages of subjects discharged from the hospital will be tabulated by treatment arm, along with differences between treatment arms. The proportion of subjects will be compared using an adjusted risk difference obtained from a logistic regression model, adjusting for stratification factors, sex, and baseline CRP.

The percentage of subjects discharged from the hospital is defined as the number of subjects discharged from the hospital divided by the sum of the number of subjects who completed the study and the number of subjects who died during the study period.

A sensitivity analysis will be performed by excluding the subjects who died after being discharged from the hospital from the numerator of the above percentage calculation.

Missing data will be imputed similarly as primary endpoint for the above endpoints.

All-cause mortality at Day 28:

Percentages of subjects will be tabulated by treatment arm, along with differences between treatment arms, at each time point. The proportion of subjects will be compared using an adjusted risk difference obtained from a logistic regression model, adjusting for stratification factors, sex, and baseline CRP.

Standard survival analysis methods will be used as sensitivity analyses to compare the time to each of these clinical events of interest (death and respiratory failure) as well as the composite thereof. Specifically, the cumulative incidence rates between two groups at Day 28 will be compared, accounting for potential differential follow-up.

Incidence of AEs/SAEs by Day 28: will be summarized by system organ class and preferred term and by treatment arm using percentages.

Incidence of AEs/SAEs is calculated by the number of subjects who developed AEs/SAEs during the study divided by the sum of the number of subjects who completed the study and the number of subjects who died during the study period. (see above edit)

Incidence of clinically significant changes by Day 28: Percentage of subjects with clinically significant changes in laboratory parameters, ECG, and vital sign measurements will be computed for each treatment arm along with associated 2-sided 95% Clopper-Pearson CI.

Changes in the assessments will be considered as clinically significant if the Baseline assessment is not clinically significantly abnormal and there has been at least one occurrence of post-Baseline assessments with a clinically significant abnormal result by Day 28.

Death is not considered a form of missing data or censoring. The incidence of clinically significant changes is calculated by the number of subjects with clinically significant changes during the study divided by the sum of the number of subjects who completed the study and the number of subjects who died during the study period.

Clearance of quantifiable viral RNA by Day 7: percentages of subjects with clearance of quantifiable viral RNA will be tabulated by treatment arm, along with differences between treatment arms, at each time point. The proportion of subjects will be compared using an adjusted risk difference obtained from a logistic regression model, adjusting for stratification factors, sex, and baseline CRP.

Change from baseline in viral RNA will be summarized by treatment arm and also analyzed using an analysis of covariance (ANCOVA) model with fixed effects of treatment, and stratification factors, sex and baseline CRP as covariates.

Death is not considered a form of missing data or censoring. The proportion of subjects with clearance of quantifiable viral RNA by Day 7 is calculated by the number of subjects with clearance of quantifiable viral RNA by Day 7 divided by the sum of the number of subjects who is in study by Day 7 and the number of subjects died by Day 7.

The endpoint of comparing percentage of subjects discharged from the hospital, all-cause mortality by Day 28, incidence of AEs/SAEs, incidence of clinically significant changes, and percentage of subjects with clearance of quantifiable viral RNA by Day 7 between treatment groups will be analyzed similarly as the primary endpoint.

[redacted]

3.4.4 Subgroups

The key study endpoints will be analyzed over time, including Forest plots, for the following subgroups of the FAS:

- Age (<65 years, ≥65 years),

- Requirement for oxygen (Yes, No),
- Region (US, Ex-US),
- Baseline CRP (15-49, 50-100, >100 mg/L),
- Use of antivirals (Yes, No),
- Country.

3.5 Safety Assessment

3.5.1 Adverse Events (AEs)

The latest version of Medical Dictionary for Regulatory Activities (MedDRA) will be used for the coding of AEs.

Treatment-emergent AEs will be defined as an event that occurs on or after the first dose of study drug or the worsening of a preexisting condition on or after the first dose of study drug. If a subject does experience an event both prior to and after starting administration of a treatment, the event will be considered a TEAE (of the treatment) only if it has worsened (i.e., it is reported with a new start date and the event is worsened in severity or becomes serious) after starting administration of the specific treatment, and prior to the start of another treatment, if any. All TEAEs collected during the investigational period will be summarized.

A summary overview of TEAEs will be provided, which presents the number of events and the number and percentage of subjects in each treatment group from the Safety Analysis Set for each of the following categories:

- TEAEs (overall, by maximum severity, and by maximum drug relatedness)
- Study drug-related TEAEs (overall and by maximum severity)
- All treatment-emergent adverse events of special interest (AESI)
- All treatment-emergent serious AEs (TESAEs)
- All study drug-related TESAEs
- TEAEs leading to death
- TEAEs leading to study drug discontinuation
- Study drug-related TEAEs leading to study drug discontinuation
- TEAEs leading to study drug interruption
- Study drug-related TEAEs leading to study drug interruption

The number of TEAEs and the number of subjects with at least 1 TEAE will be summarized by treatment group for each of the categories in the overview.

All AEs will be displayed in listings. In addition, SAEs and TEAEs leading to study drug discontinuation will be listed.

3.5.2 Clinical Laboratory Tests

Reported values and change from baseline values of clinical laboratory variables will be summarized using descriptive statistics by treatment group and time point. The number of

available observations and out-of-range values (absolute and in percentage) will also be presented by treatment group. For out-of-range values summaries, all post-baseline values, including those from unscheduled visits will be evaluated.

3.5.3 Vital Signs

Reported values and change from baseline values of supine blood pressure and pulse rate and temperature will be summarized using descriptive statistics by treatment group and time point. The number of available observations and out-of-range values (absolute and in percentage) will be presented by treatment group. Vital sign variables will be listed. Values outside the reference range (see Table 1) will be flagged in the listing.

Table 1: Normal vital sign ranges for the average healthy adult while resting

Variable	Normal Range
Systolic Blood Pressure	90 to 120 mm Hg
Diastolic Blood Pressure	60 to 80 mm Hg
Breathing	12 to 19 breaths per minute
Pulse	60 to 100 beats per minute
Temperature	97.8 to 99.1°F (36.5°C to 37.3°C)

Extended vital signs, including oxygen saturation and fraction of inspired oxygen will also be summarized using descriptive statistics and listed in similar manners as other the vital signs.

3.5.4 ECG

Other than the summary table of ECG for one of the secondary endpoints, ECG values will be listed.

3.5.5 Other Safety Assessments

Other safety assessments such as hospitalizations and physical examinations will be listed.

4 DATA MONITORING COMMITTEE

An independent DMC composed of experts external to the sponsor and investigators will monitor the safety of trial participants and the conduct of the trial on an ongoing basis and will be responsible for the IA and recommendations regarding sample size re-estimation. Consistent with US Food and Drug Administration (FDA) recommendations (FDA Guidance for Industry, Establishment and Operation of Clinical Trial Data Monitoring Committees, 2006), the DMC will include at least 2 external clinicians with expertise relevant to the evaluation of COVID-19, such as Critical Care, Pulmonology, or Infectious Disease, as well as at least 1 independent biostatistician with expertise in clinical trial design and statistical methods for clinical research and analysis of research data including interim analysis. Details on the composition of the DMC and the schedule and format of DMC meetings and data outputs are provided in the DMC charter. The DMC will review, at a minimum, data for the sentinel subjects prior to continued

study drug dosing and cumulative safety data at regular intervals based on subject enrollment. The safety evaluations will be detailed in the DMC charter and will include review of conventional safety variables, such as serious adverse events. Any safety event that requires unblinding will be immediately reported to the DMC and to the FDA. The DMC may request and review any additional reports outside of the planned analyses at any time if deemed necessary to ensure the safety of subjects. The DMC will also review the efficacy data at the IA and make recommendations based on the futility criteria and for sample size re-estimation if needed (see Section 8.9). After reviewing study data, the DMC will make recommendations regarding continuation, termination, or modification of the study. The DMC may also perform ad hoc review of PK of subjects who require dialysis.

5 ANALYSIS TIMING

5.1 Interim Analysis

An IA will be conducted after 206 subjects have been enrolled (approximately 103 in each of the losmapimod and placebo arms) and have been treated for 14 days with 28 days of follow-up. Only futility—and potential sample size-estimation—will be assessed by the DMC at the IA. The O'Brien-Fleming group sequential method will be used to adjust alpha and beta for interim testing. Table 2, Figure 1, Figure 2, and Figure 3 contain sample size requirements, boundary information, and stopping probabilities for testing futility on the primary endpoint at both the IA and final analysis. P -values are single-sided. Sample size estimation was done using SAS® (Proc SeqDesign, Version 4.0). The study will not be stopped for efficacy at the IA.

5.1.1 Futility Testing

The process is as follows:

1. Futility at IA: If standardized z-value (MLE: maximum likelihood estimate) of $p_t - p_c$ is ≥ -0.67873 (-0.04017), or p-value ≥0.24865, then stop for futility. Probability of stopping for futility under null hypothesis is ~0.75.
2. At Final Analysis: The final p-value is tested at an adjusted alpha of 0.02784.

5.1.2 Sample Size Re-estimation

The Chen-DeMets-Lan method (Chen et al 2004) will be used for unblinded sample size re-estimation, with IA futility stopping boundaries created using O'Brien-Fleming method, as described above. Wald conditional probabilities will be calculated using the actual observed proportion from both treatment arms.

The maximum sample size allowed is 820 subjects. Sample size will be increased only if the observed data at the IA are promising; that is, if the conditional power is ≥50% and <80%. Sample size will be increased to ensure a target conditional power of at least 80%. See appendix A for sample SAS codes for the conditional power calculation.

There is only one IA, and conditional power at IA must lie between 50% and 80% for sample size re-estimation to be implemented. These 2 conditions ensure that the target Type I error of 2.5% is not exceeded by increasing sample size to meet the original target power (Chen et al 2004).

Sample size re-estimation will not be done in the following 2 instances:

- If conditional power is <50%, then sample size re-estimation will not be done, and decision on futility will be made based on boundary values from the O'Brien-Fleming method.
- If conditional power is ≥80%, then a sample size re-estimation will not be done, as the study will be considered sufficiently powered to detect the effect of interest at the final analysis.

A Wald Test statistic will be calculated and compared with the boundary value for futility (see Table 2). If the Wald Test statistic lies in the acceptance region then the study will stop for futility.

All calculations for the IA and the unblinded sample size re-estimation will be conducted by an external, unblinded statistician. The DMC will review the results in a closed session and make appropriate recommendations to the Sponsor afterwards.

Table 2: Boundary Values for Interim Analysis Futility Assessment

Analysis Stage	**Sample Size**		**Beta: Futility**			**Alpha: Efficacy**		
	Losmapimod	**Control**	**Standardized-Z (p-value)**	**MLE**	**Stopping Probability (accept null under null hypothesis)**	**Standardized-Z (p-value)**	**MLE**	**Stopping Probability (accept null under alternative hypothesis)**
Interim Analysis	103	103	-0.67873 (0.24865)	-0.04017	0.75135	Not applicable	--	0.08871
Final Analysis	205	205	-1.91358 (0.02784)	-0.08009	0.97500	--	--	0.20000

Overall alpha=0.025 (1-sided); overall power=80%.
Abbreviations: MLE: maximum likelihood estimate.

Figure 1 Acceptance Region (Standardized-Z Scale)

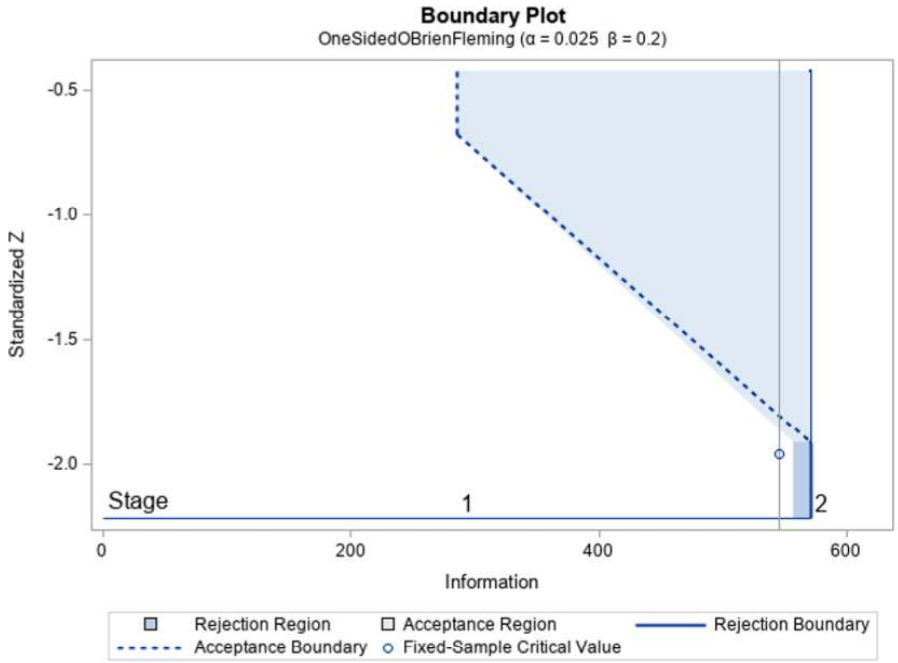


Figure 2 Acceptance Region (P-value)

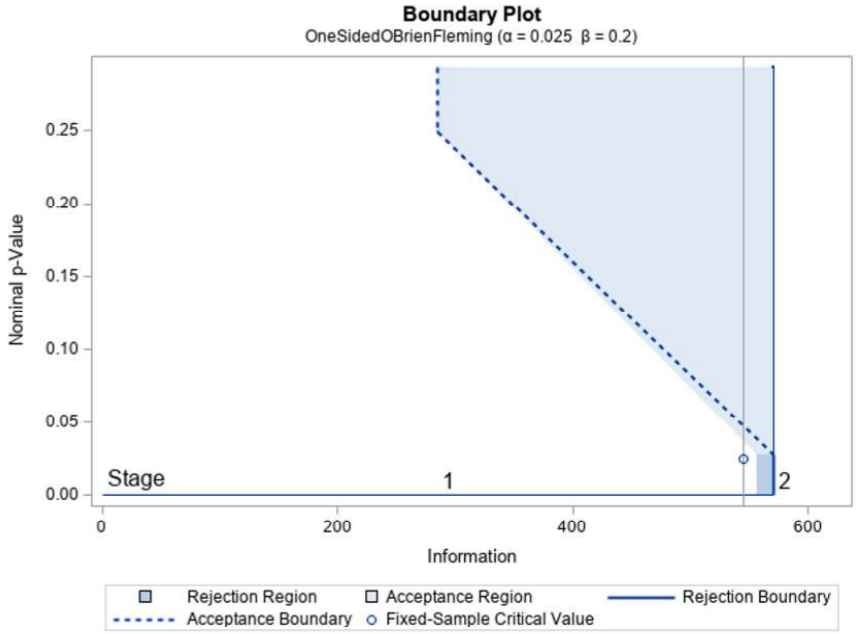
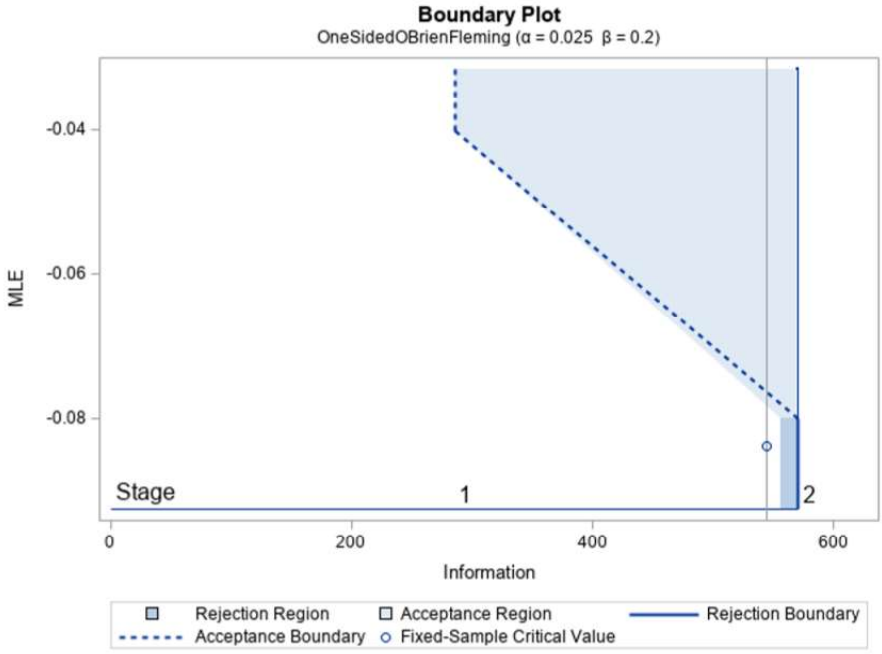


Figure 3 Acceptance Region (Maximum Likelihood Estimate)



5.1.3 Possible Recommendations by the DMC

After reviewing the results of the IA, the DMC may select 3 or more possible recommendations, based on the test statistics obtained at the IA:

1. Stop for Futility - Stop trial early due to strong evidence for futility due to test statistic being in the futility region.
2. Continue without change - Continue until next look with no changes due to test statistic not being in the futility region or the conditional power being <50% or ≥80%.
3. Add required additional sample size, n, without exceeding the maximum sample size of 820 and continue the trial.

At the final analysis, 2 recommendations can be made:

1. Efficacy is demonstrated.
2. Efficacy is NOT demonstrated.

5.1.4 Operating Characteristics of the Fixed Sample and Adaptive Designs, Conditional on Interim Outcome

The additional sample size resources are requested only if the interim results are promising, which means conditional power at IA lie between 50% and 80%. If the interim results are either unfavorable or favorable, there is no sample size adjustment. Table 3 shows the simulation results for the operating characteristics of the fixed sample and adaptive designs, conditional on interim outcome based on 10000 replications. The adaptive sample size was determined by ensuring a target conditional power of at least 80%. Under different simulation scenarios, the

gain in conditional power is substantial when there is an increase in sample size. The expected sample sizes after sample size adjustment are between 528 and 548.

Table 3: Operating Characteristics of the Fixed Sample and Adaptive Designs, Conditional on Interim Outcome

Pt	Pc	Interim Outcome	Probability of Interim Outcome	Power Conditional on Interim Outcome		Expected Sample Size		Unconditional Power
				Fixed	Adaptive	Fixed	Adaptive	
0.14	0.3	Unfavorable	8%	24%	24%	410	410	98%
		Promising	9%	67%	79%	410	530	99%
		Favorable	83%	98%	98%	410	410	100%
0.16	0.3	Unfavorable	15%	22%	22%	410	410	94%
		Promising	12%	68%	79%	410	528	97%
		Favorable	73%	97%	97%	410	410	99%
0.18	0.3	Unfavorable	26%	20%	20%	410	410	86%
		Promising	16%	67%	79%	410	537	92%
		Favorable	58%	96%	96%	410	410	96%
0.2	0.3	Unfavorable	38%	17%	17%	410	410	74%
		Promising	17%	66%	79%	410	543	84%
		Favorable	44%	95%	95%	410	410	91%
0.22	0.3	Unfavorable	53%	14%	14%	410	410	58%
		Promising	17%	66%	79%	410	548	72%
		Favorable	30%	95%	95%	410	410	82%

Note: The simulation result is based on 10000 replications using SAS. See Appendix B for codes.

5.2 Final Analysis

Topline TFLs (Tables Figures and Listings) will be provided approximately 1 week after the study database is declared final. Final TFLs will be provided approximately 3 weeks after the study database is declared final. In addition to TFLs, SDTM (Study Data Tabulation Model) data and ADaM (Analysis Data Model) data along with associated files will be provided. Associated files may include annotated case report forms (CRFs), SDTM specifications, SDTM programs, ADaM specifications, ADaM programs, TFL programs, and Clinical Data Interchange Standards Consortium (CDISC) Define packages for both SDTM and ADaM data.

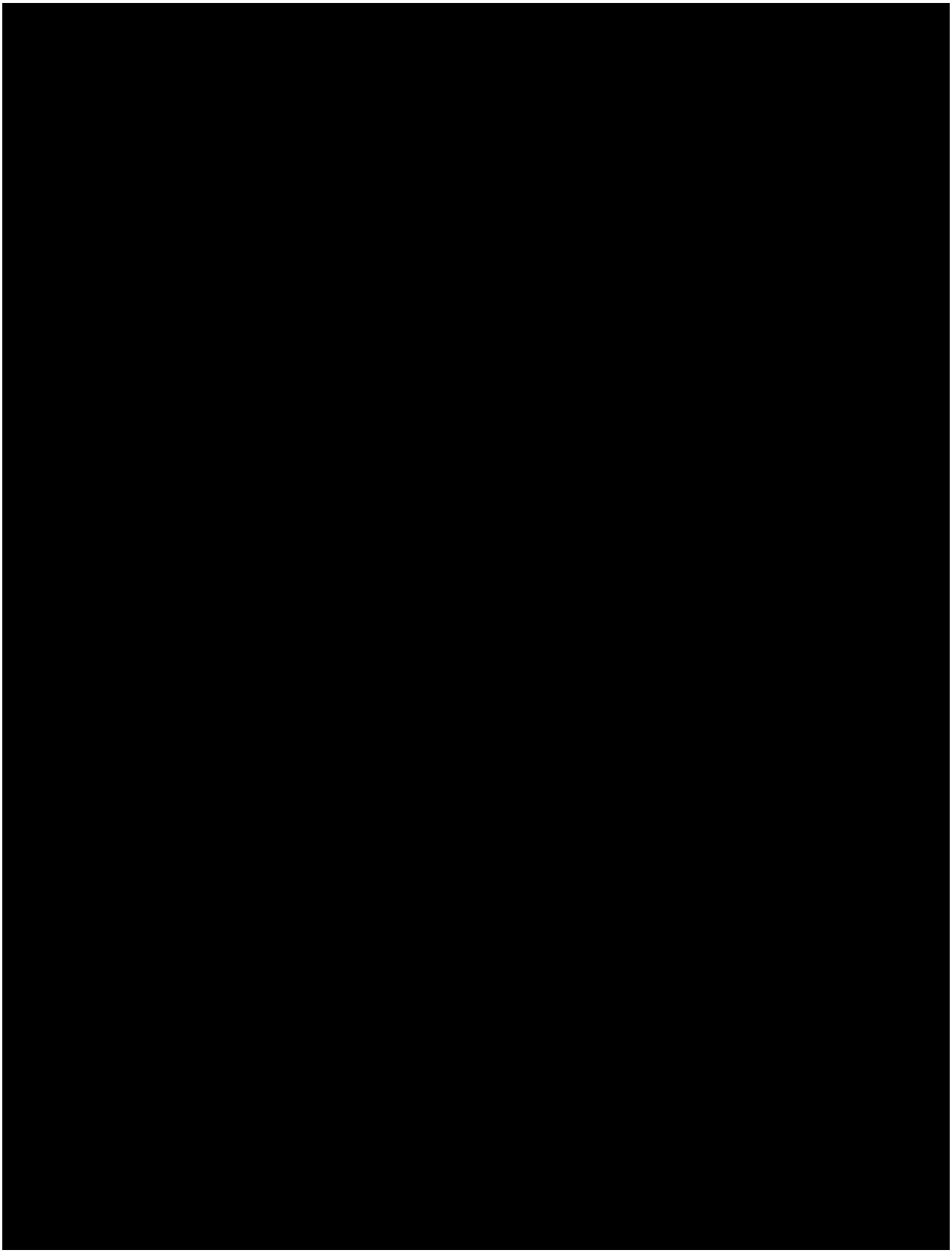
6 CHANGES FROM PROTOCOL-SPECIFIED STATISTICAL ANALYSES

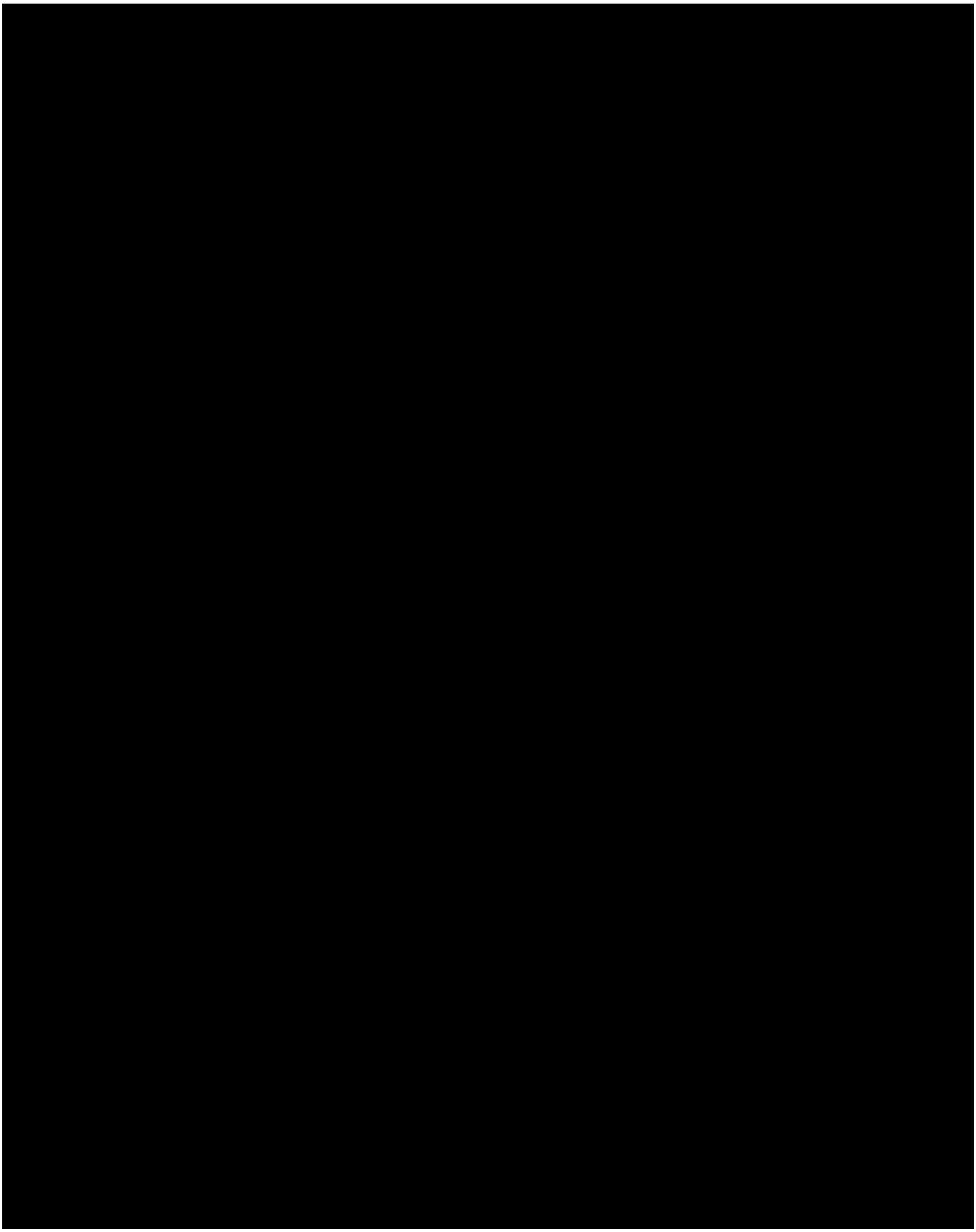
The statistical analysis plan introduced the following modifications to the analyses planned in the protocol:

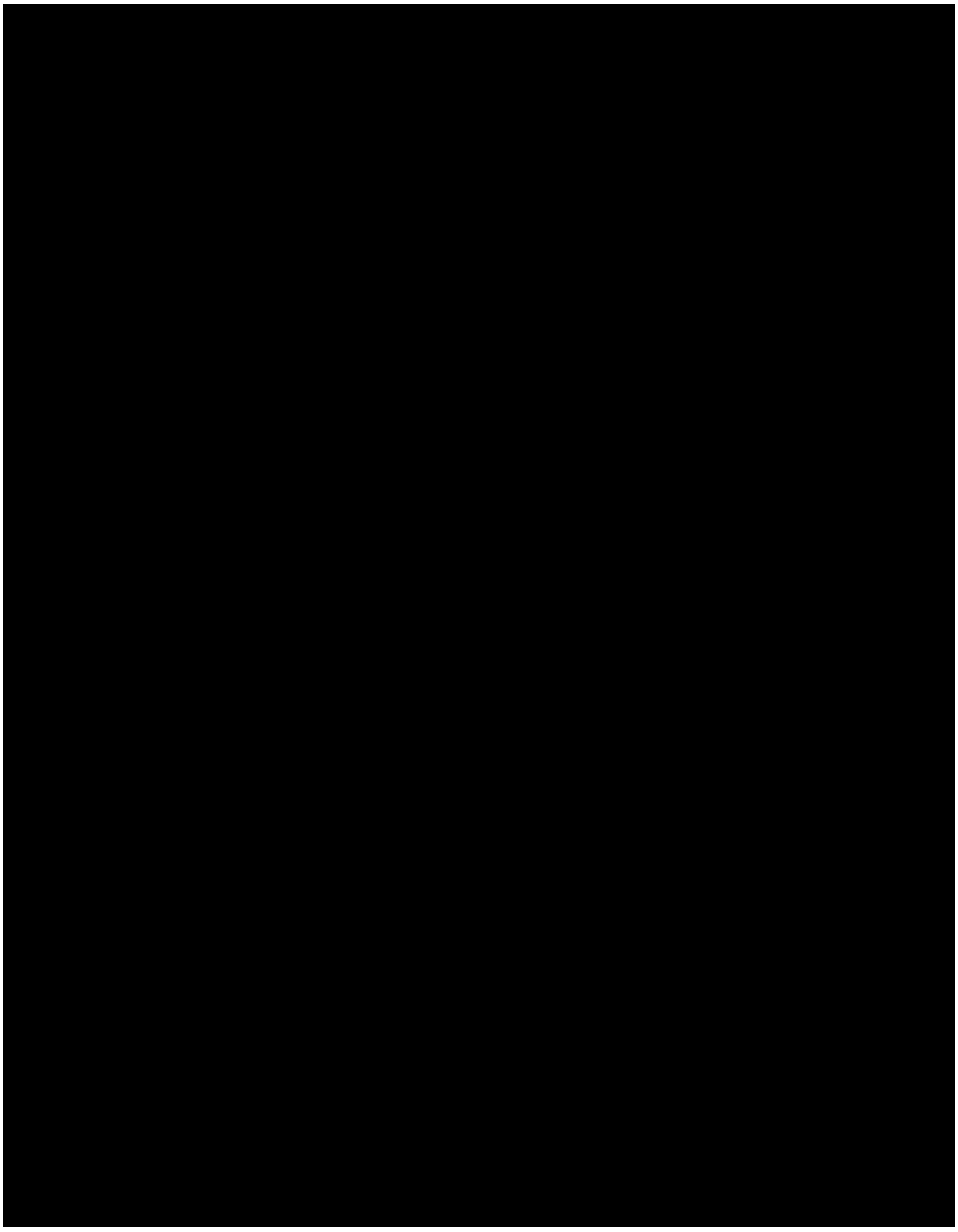
1. Per Protocol, the FAS will consist of all subjects who are randomly assigned to receive double-blind study drug. Due to limited data, the FAS is updated to consist of all subjects who are randomized and receive any study drug.
2. Due to limited data, considerations on adjusting the model covariates have been added in the SAP.

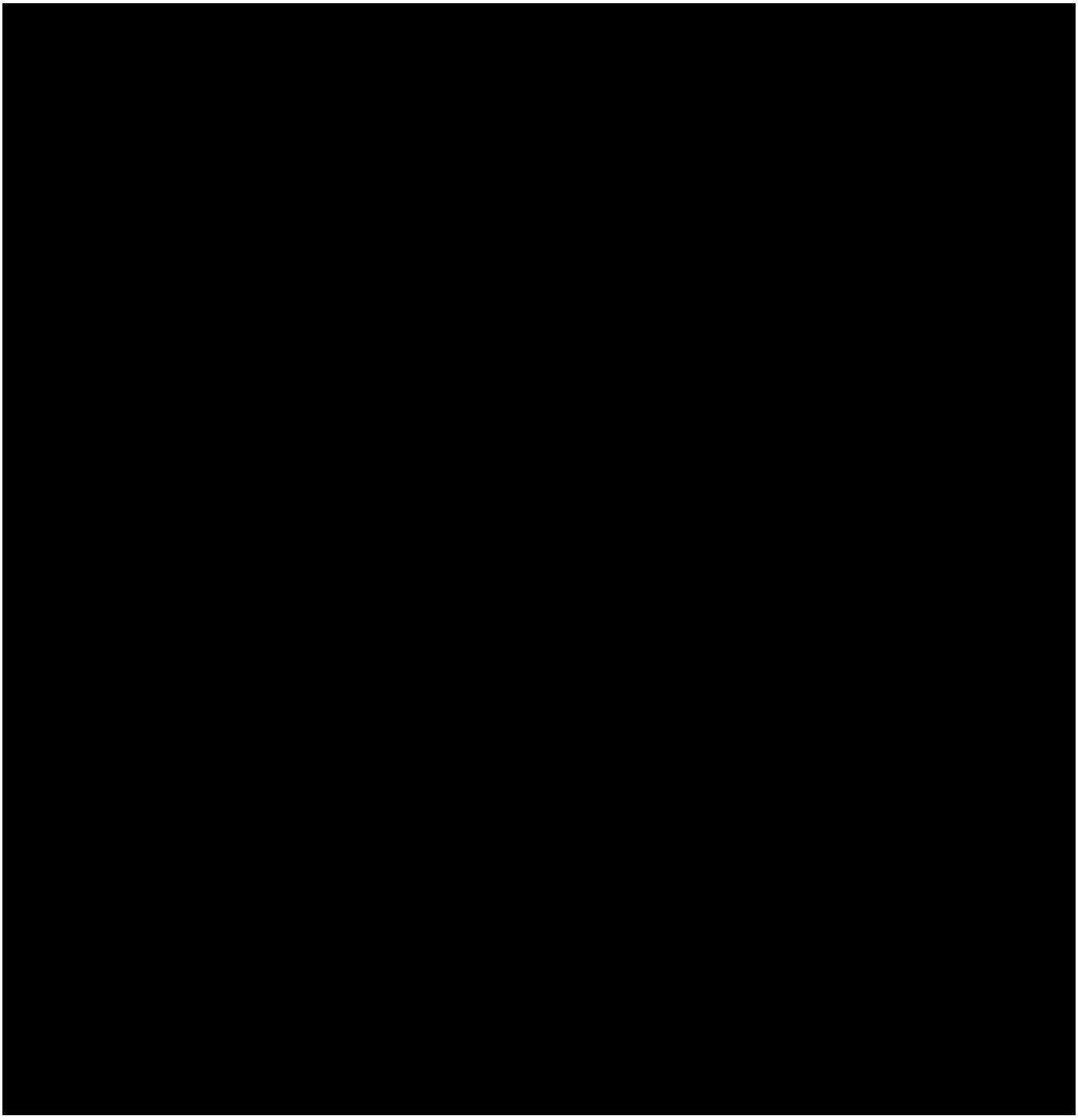
7 PROGRAMMING SPECIFICATIONS

Analyses will be performed using SAS® version 9.4 or higher. All available data will be presented in subject data listings which will be sorted by subject and visit date as applicable. Detailed Programming Specifications will be provided in a separate document.









APPENDIX C: REFERENCES

Chen YH, DeMets DL, Gordon Lan KK. Increasing the sample size when the unblinded interim result is promising. *Stat Med. 2004;23(7):*1023-38.

Guo, Y., Wu, V., Li, X., Xu, X., & Cheng, C. An Illustration of Rate Difference Estimation with SAS in Logistic Regression.

Ge, M., Durham, L. K., Meyer, R. D., Xie, W., & Thomas, N. (2011). Covariate-adjusted difference in proportions from clinical trials using logistic regression and weighted risk differences. *Drug information journal: DIJ/Drug Information Association*, *45*(4), 481-493.