RHYTHM PHARMACEUTICALS, INC.

PROTOCOL #: LG-MCCL005

A RANDOMIZED, PLACEBO-CONTROLLED, DOUBLE-BLIND PHASE 2 STUDY TO ASSESS EFFICACY AND SAFETY OF LB54640 IN PATIENTS WITH HYPOTHALAMIC OBESITY, WITH AN OPEN-LABEL EXTENSION

STATISTICAL ANALYSIS PLAN

VERSION 2.0

Document last saved: 29-May-2025 7:34 PM

[redacted]

Rhythm Pharmaceuticals, Inc.

[redacted]

[redacted]

[redacted]

TABLE OF CONTENTS

1. INTRODUCTION 6

1.1. Protocol and Amendment History 6

1.2. Changes to Planned Analyses from Protocol 6

1.3. Revision History of the Statistical Analysis Plan 6

2. PROTOCOL OBJECTIVES 6

2.1. Primary Objective 6

2.2. Secondary Objectives 7

2.3. [redacted] 7

3. STUDY ENDPOINTS 7

3.1. Primary Endpoint 7

3.2. Secondary Endpoints 7

3.3. [redacted] 8

4. STUDY DESIGN 9

4.1. Design Overview 9

4.2. Sample Size 10

5. GENERAL ANALYTICAL CONSIDERATIONS 10

5.1. Data Sources 10

5.2. Definition of Baseline 10

5.3. Precision 11

5.4. Analysis Visit Windows 11

5.5. Missing Data 14
5.5.1. Partial and Missing Dates in AE and CM 14
5.5.2. Missing Safety Data 15
5.5.3. Missing Efficacy Data 15
5.5.4. Partial Dates in Height/Weight Histories 16

5.6. Multiple Study Centers 16

5.7. Covariate Adjustment in Primary Analysis 16

5.8. Planned Analyses 16
5.8.1. Independent Data Monitoring Committee (IDMC) 16
5.8.2. Interim Analysis 16
5.8.3. Final Analysis 17

5.9. Test Sizes 17

5.10. Multiple Comparisons 17

5.11. Analysis Populations 17
5.11.1. Modified Intent to Treat (mITT) Set 18
5.11.2. Per Protocol (PP) Set 18
5.11.3. Safety Analysis Set 18
5.11.4. OLE Analysis Set 18
5.11.5. Pharmacokinetic (PK) Analysis set 18

5.12. Definition of Subgroups 18

5.13. Data Display Characteristics 18

5.14. Software Version 20

6. PARTICIPANT ACCOUNTABILITY 20

6.1. Participant Characteristics 20
6.1.1. Demographics and Baseline Characteristics 20
6.1.2. Disease History 20
6.1.3. Medical History 21

6.2. Disposition 21

6.3. Protocol Deviations 22

7. EFFICACY ANALYSES 22

7.1. Efficacy Outcomes 22
7.1.1. Primary Efficacy Endpoint 22
7.1.2. Secondary Efficacy Endpoint 23
7.1.3. Participant's Overall Experience 24

7.2. Primary Efficacy Outcome Analysis 25
7.2.1. Primary Analysis 25
7.2.2. Sensitivity Analysis 26
7.2.3. Supplementary Analysis 26

7.3. Secondary Efficacy Endpoint Analyses 26
7.3.1. Continuous Secondary endpoints 26
7.3.2. Categorical Secondary Endpoints 27

7.4. Summary of Primary and Secondary Efficacy Analysis 27

7.5. [redacted] 30

7.6. Other endpoints 31

7.7. Long-term Efficacy Analysis 31

8. SAFETY ANALYSES 31

8.1. Exposure 31

8.2. Compliance 32

8.3. Adverse Events 32

8.4. Clinical Laboratory Results 34

8.5. Vital Signs 34

8.6. Electrocardiogram (ECG) 34

8.7. Physical Examination 34

8.8. Concomitant Medications 35

8.9. Concomitant Procedures 35

8.10. Other Safety Assessments 36

8.10.1. Pubertal Development Assessment 36

8.10.2. Columbia-Suicide Severity Rating Scale (C-SSRS) 36

8.10.3. Patient Health Questionnaire-9 (PHQ-9) or PHQ-A 37

8.10.4. Spectrophotometric assessment 37

9. PHARMACOKINETIC ANALYSIS 38

9.1. Pharmacokinetic Concentration 38

9.2. Pharmacokinetic Parameters 39

10. PHARMACODYNAMIC ANALYSIS 41

11. REFERENCES 42

12. APPENDIX 42

13. SAS PROCEDURES 42

ABBREVIATIONS

Abbreviation	Term
ACMG	American College of Medical Genetics and Genomics
ANCOVA	Analysis of Covariance
AE	Adverse Event
AESI	Adverse event of special interest
AUC_{0-t}	Area under the concentration-time curve from 0 to last quantifiable concentration
BLQ	Below the Limit of Quantification
BMI	Body Mass Index
C_{max}	Maximum observed concentration in plasma
C_{trough}	Trough plasma concentration
C-SSRS	Columbia Suicide Severity Rating Scale
[redacted]	[redacted]
ICF	Informed Consent Form
ICH	International Council for Harmonisation
IDMC	Independent data monitoring committee
[redacted]	[redacted]
[redacted]	[redacted]
LOCF	Last Observation Carried Forward
MedDRA	Medical Dictionary for Regulatory Activities
MI	Multiple Imputation
mITT	Modified Intent to Treat
MMRM	Mixed-effects Model of Repeated Measures
PD	Pharmacodynamics
PP	Per Protocol
PGI-C	Patient Global Impression of Change
PGI-S	Patient Global Impression of Severity
PHQ-9	Patient Health Questionnaire-9
PK	Pharmacokinetic
QTc	QT interval corrected
QTcF	QT corrected for heart rate by Fridericia's formula
SAE	Serious Adverse Event
SAP	Statistical analysis plan
SoA	Schedule of activities

T_{max}	Time to C_{max}
TEAE	Treatment-emergent adverse event
TFL	Tables, Figures and Listings
WHO	World Health Organization

1. INTRODUCTION

1.1. Protocol and Amendment History

This Statistical Analysis Plan (SAP) is based on version 3.0 of Protocol.

Version	Approval Date	Salient Changes, if any[1]
Protocol V3.0	08 March 2024	
Protocol V4.0	14 April 2025	

[1] Changes expected to require accommodation in analysis plan.

The study protocol describes the general approach to analysis of data from the study. This SAP describes additional detail needed to complete such an analysis and will govern the analysis of data from this study. The plan may be modified until the time of first Interim Analysis. Any deviations from the analysis plan, including any after the time of first Interim Analysis, will be documented as such in the study report.

1.2. Changes to Planned Analyses from Protocol

No changes to the planned analyses in the protocol are noted.

1.3. Revision History of the Statistical Analysis Plan

Version	Approval Date	Changes from Previous Version
1.0	09Oct2024	n/a

2. PROTOCOL OBJECTIVES

2.1. Primary Objective

The protocol (Section 3.0) lists the following primary objective:

- To assess the efficacy of LB54640

2.2. Secondary Objectives

The protocol (Section 3.0) lists the following secondary objectives:

- To assess the magnitude of the efficacy of LB54640
- To assess the efficacy of LB54640 on hunger
- To assess the long-term efficacy of LB54640
- To assess the safety and tolerability of treatment with LB54640
- To assess the pharmacokinetics (PK) of LB54640

2.3. [redacted]

[redacted]

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

3. STUDY ENDPOINTS

3.1. Primary Endpoint

The primary endpoint is:

- Mean percentage change in Body Mass Index (BMI) (Baseline to Week 14)

3.2. Secondary Endpoints

The protocol describes secondary efficacy endpoints as the following:

- Mean percentage change in BMI (Baseline to Weeks 6 and 10)
- Mean change in BMI (Baseline to Weeks 6, 10, and 14)
- Mean change in the (gender- and age-specific) BMI Z-score (Baseline to Weeks 6, 10and 14 for participants <18 years of age)
- Mean change in percentage of the (gender- and age-specific) 95th percentile of BMI (Baseline to Weeks 6, 10 and 14 for participants <18 years of age)
- Mean change and mean percentage change in body weight (Baseline to Weeks 6, 10 and 14)
- Percentage of participants who achieve ≥5% reduction in body weight (Baseline to Week 14)
- Percentage of participants who achieve ≥10% reduction in body weight (Baseline to Week 14)
- Percentage of participants who achieve ≥5% reduction in BMI (Baseline to Week 14)
- Percentage of participants who achieve ≥10% reduction in BMI (Baseline to Week 14)
- Mean change and mean percentage change in waist circumference (Baseline to Weeks 6, 10 and 14)

- Mean change and mean percentage change in waist-to-hip circumference ratio (Baseline to Weeks 6, 10 and 14)
- Mean change and mean percentage change in body composition (fat mass, lean mass) assessed by dual energy x-ray absorptiometry (DEXA) (Baseline to Week 14)
- Mean change in the weekly average of the daily most hunger score (Baseline to Week 14)
- Mean change in the weekly average of the Symptoms of Hyperphagia composite score (Baseline to Week 14)

Long term efficacy endpoints:

- Mean change and mean percentage change from baseline in BMI by visit during the open-label extension phase
- Mean change and mean percentage change from baseline by visit during the open-label extension phase
- Mean change and mean percentage change from baseline in waist circumference by visit during the open-label extension phase
- Mean change and mean percentage change from baseline in waist-to-hip circumference ratio by visit during the open-label extension phase
- Mean change and mean percentage change in body composition (fat mass, lean mass) assessed by DEXA (Baseline to Week 52)

Safety Endpoints:

- Frequency and severity of adverse events (AE)
- Frequency and severity of adverse events of special interest (AESI)
- Change from baseline in vital sign measurements (blood pressure, temperature, respiratory rate, and heart rate)
- Change from baseline in laboratory results
- Change from baseline in electrocardiogram (ECG) parameters
- Patient Health Questionnaire 9 (PHQ-9 or PHQ-A) total score
- Columbia-Suicide Severity Rating Scale (C-SSRS)
- Pubertal development for participants who have yet to reach Tanner Staging V

PK Endpoints:

- Maximum observed concentration in plasma (C_{max}) at Week 0 and Week 10
- Time to C_{max} (T_{max}) at Week 0 and Week 10
- Area under the concentration-time curve from 0 to last quantifiable concentration (AUC_{0-t}) at Week 0 and Week 10
- Trough plasma concentration (C_{trough}) at Weeks 1, 2, 6, 10, and 14

3.3. [redacted]

[redacted]

4. STUDY DESIGN

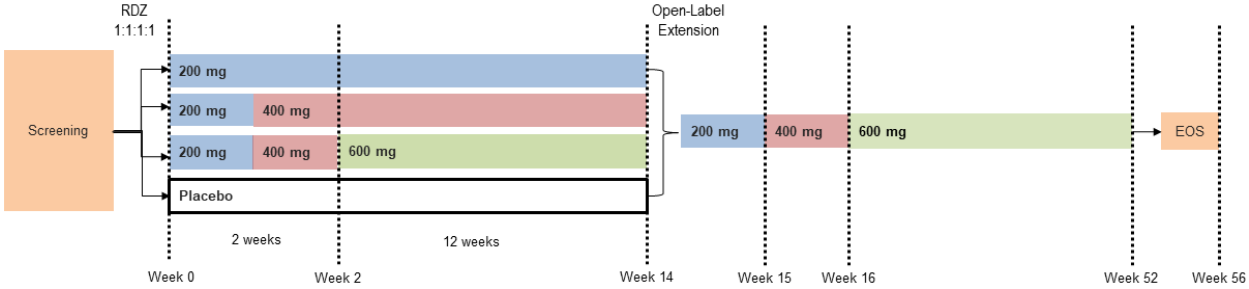
4.1. Design Overview

This study will begin with a 14-week randomized, double-blind, placebo-controlled treatment phase. The participants will be randomized and stratified by age group (≥18 years old , <18 years old) to receive 200 mg, 400 mg, or 600 mg of LB54640 or placebo in a 1:1:1:1 ratio.

- For the 200 mg cohort, participants will take 200 mg of LB54640 orally, once daily (QD) for 14 weeks.
- For the 400 mg cohort, participants will be orally administered with 200 mg LB54640 QD for 1 week then receive 400 mg QD for 13 weeks.
- For the 600 mg cohort, participants will be orally administered with 200 mg LB54640 QD for 1 week, then 400 mg QD for 1 week, followed by 600 mg QD for 12 weeks.

After the initial 14-week double-blinded randomized phase, the study will continue with an open-label extension (OLE) phase to evaluate the safety, tolerability and efficacy of LB54640 for up to 1 year. Participants who agree to continue into the open-label extension phase will be confirmed for eligibility. To prevent potential unblinding which can impact data integrity of previous double-blind treatment phase, participants, regardless of active or placebo assignment in the previous part of the study, will be titrated from 200 mg QD for 1 week, to 400 mg QD for 1 week, to 600 mg QD for 36 weeks, as tolerability allows. The dose may be modified at any time as required for safety or efficacy at the discretion of the Investigator. A schematic of the study design is shown in Figure 1.

Figure 1: Study Schema



Abbreviations: EOS = End of Study

All participants will be required to attend the study visits as described in the Schedule of Activities (SoA) in Protocol Section 1.3.

4.2. Sample Size

A total for 28 participants (7 participants per cohort) will be enrolled. Given the exploratory nature of the early efficacy signals in this Phase 2, proof-of-concept study in participants with hypothalamic obesity, as well as the rarity of this disorder, the sample size is not primarily driven by the statistical testing considerations, but rather by the clinical considerations.

5. General Analytical Considerations

5.1. Data Sources

Data are recorded on electronic case report forms (eCRFs). Central laboratory data, eCOA – Hunger score data, and PK data will be provided via electronic data transfers. Protocol Section 10 and the study Data Management Plan provide additional details regarding data recording and handling.

5.2. Definition of Baseline

For efficacy, unless otherwise specified below, baseline is defined as the last observed value of the parameter of interest prior to the randomization date. For pharmacodynamic and safety analyses, unless otherwise specified below, baseline is defined as the last observed value of the parameter of interest prior to the first administration date. For those who enter the open-label extension phase (Yes for the question “Will the subject continue to Long-term Extension” in the End of Treatment page), an additional baseline will be defined as the last measurement prior to receiving study treatment in the open-label extension phase.

The baseline weekly most hunger score will be calculated as the average of 7 daily scores prior to the randomization. If there are less than 7 daily scores available prior to the randomization, the baseline weekly score will be calculated using all available days. If the subject don’t have any available scores in the 7 days prior to

randomization, another 7days before one week prior to the randomization will be considered. If the subject did not complete Hunger questionnaire for any of the days during screening period, Hunger questionnaire completed on Day 1 will be used as baseline weekly daily most hunger score. The Week 14 visit weekly hunger scores will be calculated by taking the average of the consecutive 7 days before the date of week 14 visit and will be considered as the baseline of OLE. The baseline weekly hyperphagia composite score will be calculated using the similar method above.

Change from baseline is calculated as post-baseline value minus baseline values.
Percentage change from baseline is calculated as:
(post-baseline result – baseline result) / baseline result*100%.
Percentage change from baseline will be undefined if baseline value is 0.

The following rules specify the determination of baseline by both date/time information:
If recorded, both the measurement's time and date will be compared to those of the index date in order to establish a baseline (for example, safety lab). Otherwise, the baseline will only be established by comparing the measurement date to the index date. The last observed value on the same day of the index date will be considered as baseline.

5.3. Precision

All PK concentration will be reported and analyzed with the same precision as the source data provided by the bioanalytical laboratory regardless of how many significant figures or decimal the data carry.

PK parameters will be rounded for the reporting purpose in by-subject listings. For most derived PK parameters, 3 significant digits will be used as standard rounding procedure, with the following exceptions:

- PK parameters directly derived from source data (e.g., C_{max} and C_{trough}) will be reported and analyzed with the same precision as the source data.
- PK parameters directly derived from actual sample collection time (e.g., T_{max}) will be reported with 2 decimal places with unit of hours.

For the calculation of descriptive statistics and inferential analysis of the derived PK parameters, the unrounded value exported from Phoenix WinNonlin into SDTM will be used.
For reporting mean (arithmetic or geometric), SD, confidence interval (Cis) will be presented on digit more precision than source data. The median, minimum and maximum will be presented same precision as the source data. The CV% and GCV% will always be reported to 1 decimal place. Ratio of mean of PK parameters will be presented to two decimal places (as percentage) to meet regulatory requirement.

5.4. Analysis Visit Windows

For each collection date, study days are calculated relative to the date of the first dose of study drug (If the dosing date is missing, the randomization date will be used), and defined as the number of days between the date of the first

dose of study drug and the collection date. Study day = event/assessment date - date of first administration of study drug +1 (if event/assessment date is >= first dosing)
Study day = event/assessment date - date of first administration of study drug (if event/assessment date < first dosing). The day of the first dose of study drug is defined as Study Day 1. All efficacy and safety endpoints will be analyzed according to the nominal visits (i.e., assigned visit) except for assessments collected on early discontinuation visit and unscheduled visit. Early discontinuation visit and unscheduled visit will be mapped to analysis visits based on their actual study day according to the following table only if the scheduled visit is missing:

Visit	Target Day	Analysis Window
Baseline	1	On or prior to Day 1
Week 1	7	Post first dose – Day 10
Week 2	14	Day 11 – Day 28
Week 6	42	Day 29 – Day 56
Week 10	70	Day 57 – Day 84
Week 14/EOT	98	Day 85 – Day 105
Week 16	112	Day 106 – Day 154
Week 28	196	Day 155 – Day 238
Week 40	280	Day 239 – Day 322
Week 52	364	Day 323 – Day 378
Week 56/EOS	392	On or After Day 379

For spectrophotometric assessment, body composition by DEXA, metabolic assays and fasting lipoproteins, pubertal development, [redacted] endpoints, the following analysis window will be used:

Visit	Target Day	Analysis Window
Baseline	1	On or prior to Day 1
Week 14/EOT	98	Day 71 – Day 119
Week 52	364	Day 309 – Day 382

For PGI-S, PGI-C endpoints, the following analysis window will be used:

Visit	Target Day	Analysis Window
Baseline	1	On or prior to Day 1
Week 1	7	Post first dose – Day 10
Week 2	14	Day 11 – Day 42
Week 14/EOT	98	Day 71 – Day 105

Visit	Target Day	Analysis Window
Week 16	112	Day 106 – Day 168
Week 52	364	Day 309 – Day 378
Week 56/EOS	392	On or After Day 379

[redacted]

For PHQ-9 and C-SSRS endpoints, the following analysis window will be used:

Visit	Target Day	Analysis Window
Baseline	1	On or prior to Day 1
Week 1	7	Post first dose – Day 10
Week 6	42	Day 15 – Day 56
Week 10	70	Day 57 – Day 84
Week 14/EOT	98	Day 85 – Day 119
Week 28	196	Day 141 – Day 238
Week 40	280	Day 239 – Day 322
Week 52	364	Day 323 – Day 382

If the subject did not enter the long-term the open-label extension treatment period, the upper limit for the Week 14 in-clinic visit will be Day 120. There is also no upper limit for the Week 56 in-clinic visit. All visits even if done very late will be mapped in the last visit. If more than one visit or assessment occurs within a single visit window, then the analysis will take the one closest to the target day. If the 2 visits are equidistant from the target day, then the visit with later date and time will be used.

Unscheduled visits will be presented as they are in the data listings.

5.5. Missing Data

5.5.1. Partial and Missing Dates in AE and CM

Partial dates may be entered on the eCRF for adverse events (AEs) and prior and concomitant medications (CMs). Dates from these forms will be reported in listings as collected without any imputation. However, reported partial information will be utilized in classification of Treatment-emergent adverse events (TEAEs) and prior and concomitant medications according to the rules described below.

TEAEs are AEs with onset or worsening after the start of first administration of study intervention. Additional classification of TEAE by study phase is covered in Section 8.3 below.
In general, rules listed in the table below will be used for TEAE and non-TEAE determination. For adverse events occurred on the same date as first administration of study intervention, the TEAE classification will first be determined by the response to the eCRF question "Is this a Pre-dose event?" on the AE page. If the answer to the question is missing, the TEAE classification will then be determined using the table below.

Start Date	**End Date**	**Rule**
Known	Known	If start date < study intervention start date, then non-TEAE; If start date ≥ study intervention start date, then TEAE
	Partial	
	Missing	
Partial, known parts indicating AE cannot be on or after study intervention start date	Known	Non-TEAE
	Partial	
	Missing	
Partial, known parts indicating AE can be on or after study intervention start date OR Missing	Known	If end date < study intervention start date, then non-TEAE; If end date ≥ study intervention start date, then TEAE
	Partial	Assume end date as latest possible date (i.e., last day of month if day unknown or 31st December if day and month are unknown), then: If end date < study intervention start date, then non-TEAE; If end date ≥ study intervention start date, then TEAE
	Missing	TEAE

Prior medication is defined as any medication taken and stopped prior to the date of first study intervetion administration. Concomitant medication is defined as any medication that started prior to the date of first study intervention administration and continued to be taken after that day or any medication that started on or after the date of first study intervention administration. Additional classification of concomitant medications by study phase

is covered in Section 8.8 below. Rules for prior and concomitant medication determination:

Start Date	End Date	Rule
Known/Partial/ Missing	Known	If end date < study intervention start date, then prior; If end date ≥ study intervention start date, then concomitant
	Partial	Assume end date as latest possible date (i.e., last day of month if day unknown or 31st December if day and month are unknown), then: If end date < study intervention start date, then prior; If end date ≥ study intervention start date, then concomitant
	Missing	Concomitant

5.5.2. Missing Safety Data

Missing safety data will not be replaced with imputed values, except for the missing severity or relationship to study intervention for AE:

- Missing relationship to study intervention will be conservatively treated as "related" to study intervention.
- Missing severity will be conservatively treated as the Severe (Grade 3).

5.5.3. Missing Efficacy Data

During double-blind period, missing weight will be imputed using a multiple imputation method. Missing height will be imputed using last observation carried forward (LOCF) method considering the nature of the variable. For missing BMI values, the imputed height and weight will be used where either one is missing.

Under the assumption of missing at random (MAR), multiple imputation (MI) will be used to impute the missing data for the continuous measurement weights. The missing weight will be imputed using the predicted value from an imputation model using the monotone regression method if appropriate missing pattern (monotone missingness). If monotone is not appropriate due to missingness structure, Full Conditional Specification (FCS) will be applied here. The explanatory variables in the imputation model will include treatment group, baseline values, all other post-baseline values on and before Week 14, and randomization stratification factor (if any), and 50 imputed data sets will be obtained. The seed to be used in all MI models is 20240306. Change and percent change from baseline will be derived from the imputed values. Example SAS codes are provided in the Appendix of this document.

For OLE period, the missing efficacy date will not be imputed. The observed cases (OC) analysis will be used.

5.5.4. Partial Dates in Height/Weight Histories

Partial dates may be entered on the eCRF for height/weight histories. The informed consent date will be used to impute for only year known and 15th will be used to impute for only year and month known. Dates imputed will be used in figures only. Dates will be reported in listings as collected without any imputation.

5.6. Multiple Study Centers

No adjustment for study center is planned.

5.7. Covariate Adjustment in Primary Analysis

The primary efficacy analyses will adjust for baseline BMI and the randomization stratification factor if applicable.

5.8. Planned Analyses

The following analyses will be performed for this study:

- Analyses for Independent Data Monitoring Committee (IDMC) Meetings
- An interim analysis (Primary analysis) when all subjects have completed the 14-week double-blind treatment period or discontinued prior to Week 14
- Final analysis at end of the open-label extension period

5.8.1. Independent Data Monitoring Committee (IDMC)

An independent data monitoring committee (IDMC) will perform safety review of the clinical study data.

The detail and display content will be determined in the IDMC Tables, Figures and Listings (TFL) shell.

5.8.2. Interim Analysis

Data obtained from all subjects will be locked and analyzed separately once all participants have completed Visit 6 (Week 14) or prematurely withdrawn from the study before Visit 6 (Week 14).

The interim analysis (primary analysis) will include all analyses planned for the treatment phase as described in subsequent sections. The date of the last record in the Blinded drug administration page at Week 14 visit will be used as the data cutoff date. If the date is missing, the Week 14 in-clinic visit date of each individual will be used. Any event/assessment date on or prior to the cutoff date will be included. For subjects who discontinue the study before Week 14 or do not enter the open-label extension phase, all the data collected will be included. An interim Clinical Study Report (CSR) will be prepared after the interim analysis is performed.

5.8.3. Final Analysis

The final analysis will be conducted at the end of the open-label extension phase after the final database lock.

5.9. Test Sizes

Not applicable.

5.10. Multiple Comparisons

Not applicable.

5.11. Analysis Populations

The following analysis populations will be defined for use with various analyses. The following table illustrates the relationship between each population and the analyses for which the data from the population will be used.

Analysis Population	Type of Analysis						
	Baseline Characteristic / Participant Disposition	**Exposure/ Compliance**	**Efficacy**	**Long-term Efficacy**	**Safety**	[redacted]	**PK Endpoints**
Modified Intent to Treat (mITT) Set	X		X				
Per Protocol (PP) Set			X				
Safety Analysis Set		X			X		
Open Label Extension (OLE) Analysis Set				X	X		
Pharmacokinetic (PK) Analysis set							X

5.11.1. Modified Intent to Treat (mITT) Set

The mITT set will include all randomized participants who are exposed to at least 1 dose of study treatment (LB54640 or placebo). Participants will be analyzed according to the treatment to which they were randomized.

5.11.2. Per Protocol (PP) Set

The PP set will include all participants in the mITT population who do not have a significant protocol deviation having a major effect on the primary efficacy evaluation. Subject to be excluded from this analysis set will be identified prior to Week-14 database lock and unblinding.

5.11.3. Safety Analysis Set

All participants who enrolled into the study and received at least 1 dose of study treatment. This analysis set will be used for all safety analyses.

5.11.4. OLE Analysis Set

All participants who enrolled into the OLE period and received at least 1 dose of study treatment in OLE. This analysis set will be used for all long-term efficacy analyses.

5.11.5. Pharmacokinetic (PK) Analysis set

The PK set will include all participants who receive active study drug and have at least 1 quantifiable concentration at a scheduled PK time point after start of dosing for LB54640 without protocol violations or events with potential to affect the PK concentrations. Participants in this population will be used for all PK parameter analyses. Subjects who have compliance <80% or >120% will have their PK concentration-time profiles evaluated to determine inclusion in the PK analysis set. Participants will be excluded based on evaluation by pharmacokineticist.

5.12. Definition of Subgroups

Subgroup analyses will be performed for primary endpoints for the following subgroup:

- Age group: ≥18 years old , <18 years old

5.13. Data Display Characteristics

Data displays produced for this study will include three types—summary tables, data listings, and figures. Unless stated otherwise, data listings will be produced for all recorded data. Summary tables will be produced as specified in following sections. Additional data listings will be produced for outcome measures that involve extensive

procedures to derive the analyzed outcomes. Figures will be produced when specified in sections to follow.

Data listings will simply list the data recorded on the CRF, external sources (e.g. Q2lab, eCOA) or derived for each participant. They will be ordered by treatment groups, participant number, and time of assessment. Additional levels of ordering hierarchy will be specified in the programming note in the TFL shell . Summary tables will display summary statistics calculated for each of the treatment groups and the overall, unless described otherwise in following sections. In addition to conducting by-treatment analyses, the active dose cohorts will also be combined for an assessment of the long-term efficacy of LB54640. The summary statistics displayed will be a function of the type of data associated with the summarized assessment. All open label extension data will be summarized by the randomized treatments received in the double-blind treatment phase.

The exposure analysis and AE will be summarized separated by treatment phase and the open-label extension phase. The efficacy analysis and other safety analysis will be summarized separated by treatment phase and the open-label extension phase using different baseline defined in section 5.2. For the open-label extension phase analysis, the OLE analysis set will be used.

In general, the following rules will be used in programming to facilitate the classification of events by study phase. Additional rules may be utilized in programming based on actual data.

- Per protocol, only participants completed the 14-week treatment phase will be eligible to enter the open-label extension phase.
- For participants who discontinued from treatment phase early and did not enter the open-label extension phase, all data reported will be included in the treatment phase analyses/summaries.
- A participant will be considered enrolled into the long-term the open-label extension phase if the response to the question “Will the subject continue to Long-term Extension?” on the end of treatment (EOT) page at Week 14 is “Yes”.
- For participants who completed the treatment phase, the last dose date during treatment phase will be documented on the EOT at Week 14 page. Any administrations of study intervention after the documented last dose in treatment phase will be considered as exposure in the open-label extension phase.
- For participants who completed the treatment phase, any event/assessment date on or prior to the Week 14 in-clinic visit will be classified under treatment phase and event/assessment date after Week 14 visit will be classified under the open-label extension phase.

Unless stated otherwise in relevant sections to follow, continuous data will be summarized with the number of non-missing values, mean, standard deviation (SD), minimum, median, and maximum. Categorical data will be summarized with the number of non-missing values and the numbers of values equal to each of the possible values. Percentages of participants with each of the possible values will be calculated from the number of participants in the corresponding analysis population, unless stated otherwise. Some continuous variables may also be grouped into categorical levels and evaluated in frequency tables. For longitudinal efficacy endpoints, individual participant scatter and line plot will be utilized to present observations in time. Imputed data will not be included in the figure.

5.14. Software Version

All analyses will be conducted using SAS version 9.4 or higher. All PK parameters will be calculated by non-compartmental analysis methods using Phoenix® WinNonlin® version 8.5 or higher (Pharsight Corporation, Mountain View, California, USA).

6. PARTICIPANT ACCOUNTABILITY

6.1. Participant Characteristics

6.1.1. Demographics and Baseline Characteristics

Data collected about the following participant characteristics at the screening visit will be summarized and listed for mITT set only:

- Age (years): If the age is missing and the year of birth is non-missing then age will be calculated as the number of years elapsed between birth date and the date of the screening visit, adjusted for whether the birthday (assuming July 1st) has passed as of the day of the screening visit.
- Sex: Male and Female
- Ethnicity: Hispanic or Latino, Not Hispanic or Latino, Not Reported.
- Race: American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or Other Pacific Islander, White, Not Reported
- Baseline height (cm)
- Baseline weight (kg)
- Baseline BMI (kg/m^2)
- Baseline BMI Z-score for <18 years old participants
- Baseline percentage of the (gender- and age-specific) 95th percentile of BMI
- Baseline waist circumference (cm)
- Baseline waist/hip circumference ratio
- Baseline weekly score for most hunger
- Pubertal development at screening: overall tanner stage

6.1.2. Disease History

Data collected about the following participant characteristics and disease history at the screening visit will be summarized and listed for mITT set only:

- Tumor type: Craniopharyngioma, Hypothalamic hamartoma, Astrocytoma, Germinoma, Glioma, Meningioma, Pinealoma, Endothelioma, Colloid Cysts, Pituitary Macroadenoma, Other.

- Hypothalamic involvement: Bilateral, Unilateral, Unknown.
- Gastrointestinal Symptom: Nausea, Diarrhea, Vomiting, Other.
- Was there any cognitive impairment: Yes, No
- History of hyperphagia: Yes, No
- Age with first noticed symptom of uncontrolled hunger (years, convert the years and months to years with one decimal)
- Tumor treatment: Surgery, Radiotherapy, Chemotherapy, Other
- Time of confirmed hypothalamic injury: (Date of enrolled – Date of confirmed hypothalamic injury +1) in years
- Prior attempts at weight loss: Medication, Program, Surgical intervention

The height and weight histories from chart review will be listed also. The Gastrointestinal symptoms details collected in the CRF will be provided in the listing. The detail of prior weight loss programs, medication and surgery will be listed. The detail of prior tumor treatment will be listed.

6.1.3. Medical History

Medical History will be coded using MedDRA dictionary version 26.1 or later. The specific version will be identified in footnotes of applicable listings and summaries. The number and percentage of subjects in each medical history category (by MedDRA system organ class and preferred term) will be summarized overall and by treatment group. The table will be sorted by decreasing frequency of SOC followed by PT based on the overall incidence across treatment groups. Subjects reporting more than one condition/diagnosis will be counted only once in each row (SOC or preferred term). The medical history will also be presented in a by-participant data listing for mITT participants.

6.2. Disposition

Participant disposition will be summarized and tabulated by different treatment groups, with the number and percentage (as applicable) of participants who were screened, randomized, treated, completed treatment phase, discontinued the study during treatment phase (along with the reason for discontinuation), continue into the open-label extension phase, completed the open-label extension phase, discontinued the study during the open-label extension phase treatment, included in each analysis set.

Study eligibility with inclusion/exclusion criteria responses for all screened participants will be presented in listings. Screen failure will be presented in listing also. Dates of treatment or study completion or early withdrawal and the reason for early discontinuation will also be listed.

6.3. Protocol Deviations

Protocol deviations will be identified by the clinical team; there will be no additional deviations included using programmatic methods. Number and percentage of subjects with protocol deviations will be summarized by severity (overall, major, and minor) for each treatment group. A listing of protocol deviations will be presented for all Safety participants.

7. EFFICACY ANALYSES

Efficacy analyses will use data from the mITT set and PP set if needed. Long-term efficacy analysis will use data from the OLE analysis set.

7.1. Efficacy Outcomes

7.1.1. Primary Efficacy Endpoint

The primary efficacy endpoint is defined as the mean percentage change from baseline in BMI at Week 14. BMI (kg/m^2) will be calculated from height and weight according to the following formula:

$$BMI = \frac{\text{Weight (kg)}}{[\text{height (m)}]2}$$ (weight in kilograms divided by height in meters squared)

Height will be only measured at Screening for adults and at every visit for those <18 years old. During each measurement, the height will be measured twice without shoes and the average value of the two measurements will be used in analysis. If only a single height value is collected at a visit, that value will be used in analysis.

The following table will be used to define the BMI classification:

BMI classification	Pediatric (<18 years old)	Adult (≥18 years old)
Underweight	< 5th percentile for age and sex	< 18.5 kg/m^2
Normal	5th to < 85th percentile for age and sex	18.5 to < 25.0 kg/m^2
Overweight	85th to < 95th percentile for age and sex	25.0 to < 30.0 kg/m^2
Obesity Class Ⅰ	≥ 95th percentile and < 120% of the 95th percentile for age and sex	30.0 to < 35.0 kg/m^2
Obesity Class Ⅱ	120% to < 140% of the 95th percentile for age and sex or 35.0 to < 40.0 kg/m^2	35.0 to < 40.0 kg/m^2
Obesity Class Ⅲ	≥ 140% of the 95th percentile for age and sex or ≥ 40.0 kg/m^2	≥ 40.0 kg/m^2

7.1.2. Secondary Efficacy Endpoint

The secondary efficacy endpoints are described in Section 3.2. Key definitions for secondary endpoints are described as following:

BMI Z-score and Percentage of 95th Percentile of BMI

The BMI Z-score, also called BMI standard deviation scores, are measures of relative weight adjusted for child age and sex.

- The BMI Z-score will be calculated based on the Lambda Mu and Sigma method (LMS) method following the 2007 WHO reference[1]. The SAS Macro provided by WHO listed in the Appendix will be used to do the calculation.

The BMI values will be expressed as a percentage of the (gender- and age-specific) 95th percentile. The SAS Macro provided by CDC listed in the Appendix will be used to do the calculation.

Waist Circumference and Waist-to-Hip Circumference Ratio

The waist and hip circumference should be measured twice and rounded to the nearest 0.5 cm or 0.2 inches. The hip circumference is defined as the widest circumference around the buttocks. The waist circumference is defined as the minimal abdominal circumference located midway between the lower rib margin and the iliac crest. The average waist and average hip circumference at each time point will be used for analysis purpose. If only single assessment has been performed, the available measurement will be used for analysis.

Waist to hip ratio will be calculated as average waist circumference divided by average hip circumference.

Body Composition

Assessment of body composition by dual energy X-ray absorptiometry (DEXA) will be performed. Total body mass, fat mass and lean mass will be assessed.

Weekly Daily Hunger Scores

Patients ≥12 years of age who are able to validly and reliably self-report will be administered “Hunger Questions for Patients ≥12 Years of Age”. This questionnaire comprises 2 items (average and most hunger) that are designed to be evaluated separately (rather than as a composite score). Each item asks patients to rate their hunger on an 11-point numeric rating scale ranging from 0 to 10 (0 = not hungry at all and 10 = hungriest possible) with a recall period of 24 hours.

Hunger Questionnaires will be completed for 7 consecutive days before each scheduled date. The Hunger Questions should be completed before dosing and before the morning meal (fasted). The visit weekly hunger scores will be calculated by taking the average of the consecutive 7 days before the date of visit and will be used for the summary of the secondary endpoint. The visit weekly Daily Eats scores can be calculated even there is only one day of hunger score for a consecutive seven-day interval. If in the 7 days prior to the visit, no questionnaires are completed but a questionnaire is completed on the day of the visit prior to dosing, that data will be taken for the analysis. The timeframes to calculate the visit weekly hunger scores will be defined in the ADaM programming specification.

For the open-label extension phase, the weekly daily hunger score will be calculated using the similar timeframes

stated above.

Patient Global Impression of Severity and Change

For participants without cognitive impairment, Patient Global Impression of Severity and Change will be completed. The Patient Global Impression of Severity (PGI-S) is a global index used to rate the severity of a specific condition on a 4-point scale: No hunger (0), Mild hunger (1), Moderate hunger (2), Severe hunger (3). The Patient Global Impression of Change (PGI-C) is a single question that reflects a patient's belief about the efficacy of treatment on a 5-point scale: Much less hungry (1), Somewhat less hungry (2), No change in hunger (3), Somewhat hungrier (4), Much hungrier (5).

If the Caregiver reported Global Hunger Severity have been used, the following 4-point scale will be used: Not hungry at all (0), A little hungry (1), Moderate hunger (2), Extremely hunger (3). The Caregiver reported Global Hunger Change is a 5-point scale: Much less hungry (1), Somewhat less hungry (2), No change in hunger-related behavior (3), Somewhat more hungry (4), Much more hungry (5).

Symptoms of Hyperphagia

Patients ≥12 years of age who are able to self-report will be administered the Symptoms of Hyperphagia:Patient © Version 1.0. The questionnaire consists of 4 items related to the frequency of a patient's hunger symptoms on a scale (Never (score=0), 1 or 2 times (score=1), 3 or more times (score=2)) over the past 24 hours. The composite score of Patient version is derived by adding up all item scores divided by total number of items answered. Caregivers of patients who cannot self-report will be administered the Symptoms of Hyperphagia: Caregiver© Version 2.0. This questionnaire consists of 5 items that include caregivers assessing the frequency of hunger symptoms on a scale (Never (score=0), 1 or 2 times (score=1), or 3 or more times (score=2)) over the past 24 hours for their child/person in their care. The composite score of Caregiver Version is derived by adding up all item scores divided by total number of items answered. The Symptoms of Hyperphagia Questionnaire should be completed for 7 consecutive days before each scheduled and before dosing, and before the morning meal. The weekly symptoms of Hyperphagia composite score will be calculated using similar method as the hunger scores stated above.

[redacted]

7.1.3. Participant's Overall Experience

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

7.2. Primary Efficacy Outcome Analysis

7.2.1. Primary Analysis

The primary analysis of the primary efficacy endpoint will be based on the mITT set.

The primary endpoint will quantify the average treatment effect of LB54640 relative to placebo after 14 weeks in participants with hypothalamic obesity regardless of adherence to the study treatment and use of prohibited medication or therapy.

The MI method will be applied to impute the missing value of weights and LOCF will be used to impute the missing value of height. For missing BMI values, the imputed height and weight will be used where either one is missing. Percent change from baseline in BMI will then be derived using the imputed values. The mean and standard error of the percent change from baseline in BMI across all 50 imputed datasets will be reported.

In addition, the analysis for the mean percentage change in BMI at Week 14 will be conducted using an analysis of covariance (ANCOVA) with treatment cohort, randomization stratification factor (≥18 years old vs <18 years old) as factors and baseline BMI as covariate. The treatment difference between each LB54640 treatment versus placebo (LB54640 – Placebo) will be tested and the point estimates along with the standard error will be calculated for each imputation dataset. The analysis results across all imputation datasets will be combined following Rubin's method using SAS procedure PROC MIANALYZE. The treatment difference in the mean percentage change from baseline is estimated by the average of the treatment differences over the MI datasets. The estimate of the variance of the treatment difference in the mean percentage change from baseline is the weighted sum of the average within-imputation variance and the between-imputation variance. The combined estimated mean difference in percent change from baseline and associated 90% confidence interval (CI) along with the p-value will be reported. Sample SAS syntax are included in Section 13.

Individual patient with the mean from each treatment group scatter and line plot will be used to present the percentage change from baseline in BMI at all timepoints.
The change and percentage change from baseline in BMI, also for the BMI classification will be listed for the observed cases.

7.2.2. Sensitivity Analysis

For sensitivity analysis, the LOCF imputation method will be used to impute both the missing weights and heights at Week 14. The same ANCOVA model described above will be used. The least square mean and standard error of each treatment, least square mean treatment difference and its standard error between each LB54640 treatment and placebo, p-value will be reported.
For another sensitivity analysis, the observed cases (OC) will be used. The same ANCOVA model described above will be used.

7.2.3. Supplementary Analysis

In addition, as supplementary, the primary endpoint will be analyzed with mixed-effects model of repeated measures (MMRM) analysis that includes treatment cohort, baseline BMI in the model, visit, randomization stratification factor (≥18 years old vs <18 years old) and the interactions of treatment by-visit as fixed factors. An unstructured (UN) covariance matrix will be used to fit each MMRM model. If the model does not converge using an unstructured covariance matrix, other covariance structures will be tested, in the following order: 1) heterogeneous toeplitz (TOEPH), 2) heterogeneous autoregressive of order 1 (ARH1), 3) heterogeneous compound symmetry (CSH) and 4) compound symmetry (CS). The first covariance structure converging to the best fit will be used as the primary analysis. Imputed data will not be included in the model. Type III sums of squares for the least squares means will be used for the statistical comparison.

Another supplementary analysis will be performed based on the PP set using OC with the similar method with primary analysis.

7.3. Secondary Efficacy Endpoint Analyses

7.3.1. Continuous Secondary endpoints

The following are considered continuous secondary endpoints:

- Key secondary endpoints: Mean change and percent change from baseline in BMI, body weight, waist circumference, waist-to-hip circumference ratio, body composition (fat mass, lean mass) at each visit; Mean change from baseline in BMI Z-score, percentage of the (gender-and-age-specific) 95^{th} percentile of BMI at each visit; Mean change from baseline in weekly daily hunger score (most hunger).
- Other secondary endpoints: weekly daily hunger score (average hunger), weekly hyperphagia symptom (patient

version or caregiver version)

The key continuous secondary efficacy endpoints will be analyzed using ANCOVA model with the similar method stated in the primary analysis for primary endpoint. For BMI and body weight endpoints, missing data will be imputed using the multiple imputation. For all other endpoints, observed cases (OC) will be used for analysis.

The MMRM analysis will also be performed for all continuous secondary endpoints using observed cases as described in the primary analysis section.

In addition, the key efficacy endpoints will be further presented by individual participant scatter and line plot including all time points using the same way for primary endpoint.

7.3.2. Categorical Secondary Endpoints

The following are considered categorical secondary endpoints:

- Percentage of participants who achieve ≥5% reduction from baseline in body weight at Week 14
- Percentage of participants who achieve ≥10% reduction from baseline in body weight at Week 14
- Percentage of participants who achieve ≥5% reduction from baseline in BMI at Week 14
- Percentage of participants who achieve ≥10% reduction from baseline in BMI at Week 14

All categorical endpoints will be summarized using frequency counts and percentages by dose groups using the dataset imputed as the primary endpoints.

7.4. Summary of Primary and Secondary Efficacy Analysis

Efficacy Endpoint	**Primary Analysis: Population/ imputation method/Statistical Methods**	**Other Analysis: Population/ imputation method/Statistical Methods**	**Key points Summary**
Primary Endpoint			
• Mean Percentage Change from Baseline in Body Mass Index (BMI) at Week 14	• mITT/MI/ ANCOVA	Sensitivity analysis: • mITT/LOCF/ ANCOVA • mITT/OC/ ANCOVA Supplementary analysis • mITT/OC/MMRM • PP/OC/ANCOVA	• ANCOVA or MMRM
Continuous Secondary Endpoints			

Efficacy Endpoint	Primary Analysis: Population/ imputation method/Statistical Methods	Other Analysis: Population/ imputation method/Statistical Methods	Key points Summary
• Mean Percentage Change from Baseline in Body Mass Index (BMI) at Week 6, Week 10	• mITT/MI/ ANCOVA	• mITT/OC/MMRM • mITT/OC/ANCOVA	• ANCOVA or MMRM • Summary Statistics for other timepoints (Week 1, Week 2)
• Mean Percentage Change from Baseline in Body Weight at Week 6, Week 10 and Week 14	• mITT/MI/ ANCOVA	• mITT/OC/MMRM • mITT/OC/ANCOVA	• ANCOVA or MMRM • Summary Statistics for other timepoints (Week 1, Week 2)
• Mean Change from Baseline in Body Mass Index (BMI) at Week 6, Week 10 and Week 14	• mITT/MI/ ANCOVA	• mITT/OC/MMRM • mITT/OC/ANCOVA	• ANCOVA or MMRM • Summary Statistics for other timepoints (Week 1, Week 2)
• Mean Change from Baseline in Body Weight at Week 6, Week 10 and Week 14	• mITT/MI/ ANCOVA	• mITT/OC/MMRM • mITT/OC/ANCOVA	• ANCOVA or MMRM • Summary Statistics for other timepoints (Week 1, Week 2)
• Mean Change from Baseline in Body Mass Index (BMI) Z- scores at Week 6, Week 10 and Week 14	• mITT (Participants < 18 Years of Age)/OC/ANCOVA	• mITT(Participants < 18 Years of Age)/OC/MMRM	• ANCOVA or MMRM • Summary Statistics for other timepoints (Week 1, Week 2)
• Mean Change from Baseline in Percentage of the 95th Percentile of Body Mass Index (BMI) at Week 6, Week 10 and Week 14	• mITT (Participants < 18 Years of Age)/ OC/ANCOVA	• mITT(Participants < 18 Years of Age •)/OC/MMRM	• ANCOVA or MMRM • Summary Statistics for other timepoints (Week 1, Week 2)
• Mean Percentage Change from Baseline in Waist Circumference at Week 6, Week 10 and Week 14	• mITT/OC/ ANCOVA	• mITT/OC/MMRM	• ANCOVA or MMRM • Summary Statistics for other timepoints (Week 1, Week 2)
• Mean Change from Baseline in Waist Circumference at Week 6, Week 10 and Week 14	• mITT/OC/ ANCOVA	• mITT/OC/MMRM	• ANCOVA or MMRM • Summary Statistics for other timepoints (Week 1, Week 2)

Efficacy Endpoint	Primary Analysis: Population/ imputation method/Statistical Methods	Other Analysis: Population/ imputation method/Statistical Methods	Key points Summary
• Mean Percentage Change from Baseline in waist-to-hip circumference ratio at Week 6, Week 10 and Week 14	• mITT/OC/ ANCOVA	• mITT/OC/MMRM	• ANCOVA or MMRM • Summary Statistics for other timepoints (Week 1, Week 2)
• Mean Change from Baseline in waist-to-hip circumference ratio at Week 6, Week 10 and Week 14	• mITT/OC/ ANCOVA	• mITT/OC/MMRM	• ANCOVA or MMRM • Summary Statistics for other timepoints (Week 1, Week 2)
• Mean Percentage Change from Baseline in body composition at Week 14 • Fat mass • Lean mass	• mITT/OC/ ANCOVA		• ANCOVA
• Mean Change from Baseline in body composition at Week 14 • Fat mass • Lean mass	• mITT/OC/ ANCOVA		• ANCOVA
• Mean Change from Baseline in Weekly Daily Most Hunger Score at Week 14	• mITT/OC/ ANCOVA	• mITT/OC/MMRM	• ANCOVA or MMRM • Summary Statistics for other timepoints (Week 1, Week 2)
• Mean Change from Baseline in Weekly Daily Average Hunger Score	• mITT/OC	N/A	Summary Statistics in all timepoints
• Mean Change from Baseline in the composite score of the Weekly Hyperphagia Symptom • Patient Version • Caregiver Version	• mITT/OC	N/A	Summary Statistics in all timepoints
Categorical Secondary Endpoints			

Efficacy Endpoint	Primary Analysis: Population/ imputation method/Statistical Methods	Other Analysis: Population/ imputation method/Statistical Methods	Key points Summary

• Percentage of Participants Who Achieved Predefined Reduction from Baseline in Body Weight and Body Mass Index (BMI) at Week 14:
  • Achieved ⩾5% reduction from baseline for Body Weight
  • Achieved ⩾10% reduction from baseline for Body Weight
  • Achieved ⩾5% reduction from baseline for BMI
  • Achieved ⩾10% reduction from baseline for BMI
	• mITT/ MI	N/A	

7.5. [redacted]

[redacted]

[redacted]

7.6. Other endpoints

The following endpoints will be summarized using frequency counts and percentages by dose groups using observed cases. Fisher's exact test will be used to examine the treatment difference in categorical outcomes if applicable.

- Percentage of participants with a ≥ 2-point reduction from baseline in the weekly daily most hunger score at Week 14
- Observed values in PGI-S
- Shift summary in PGI-S
- Observed values in PGI-C

7.7. Long-term Efficacy Analysis

For long-term efficacy analysis, data from the OLE analysis set will be used. The change from baseline and change from OLE baseline will be provided separately for the following endpoints:

- BMI, body weight, waist circumference, waist-to-hip circumference ratio, body composition (fat mass, lean mass), weekly daily hunger score (most hunger), [redacted], weekly daily hunger score (average hunger), weekly hyperphagia symptom, PGI-S, PGI-C

8. SAFETY ANALYSES

Safety analyses will use data from the Safety analysis set for double-blind phase and the OLE analysis set for OLE phase.

8.1. Exposure

The following exposure parameters will be summarized descriptively for each dose cohort and study phase (treatment phase, open-label extension phase).

Duration of Exposure (Days)

The duration of exposure is defined as following:

Duration of exposure (days) = (last date of study intervention dosing) – (first date of study intervention dosing) + 1

For the treatment phase, the first date of study intervention will be the administration date in the drug administration page at Week 0 Visit. The last date of study intervention dosing will be the last date of study intervention dosing per the Week 14/EOT page (The last record in the Blinded drug administration page). If the last dosing day is missing, the date before drug administration date in the drug administration page at Week 14 Visit will be used.
For the open-label extension phase, the date after the last record in the Blinded drug administration page will be used as the first date of study intervention dosing for the open-label extension phase. The last dosing date per the Week 52 EOT page will be used as the last date of study intervention dosing. If the last dosing day is missing, the Week 52 visit date will be used. For early discontinued subject, the last dosing date per the ED page will be used.

The duration above includes the periods of temporary study drug interruption.

The study drug events information collected in the corresponding page will be listed, including administered dose during the event, start date, end date, reason for the event.

8.2. Compliance

% Compliance will be calculated as total compliance and compliance by different phase (treatment phase, open-label extension phase):

(duration of exposure in that phase– days of dose interrupted) / (end date in each phase– start date of each phase +1) × 100%

where the duration of exposure in that phase have been defined above.

The percentage of compliance with study drug will be summarized descriptively. The number and Percentage of participant with compliance <80%, 80%-120%, >120% will be provided.

8.3. Adverse Events

Adverse Events (AEs) will be coded using MedDRA dictionary version 26.1 or later. The specific version will be identified in footnotes of applicable listings and summaries.

Treatment-emergent adverse events (TEAEs) are AEs with onset or worsening after the start of study intervention. For data analysis purposes, a TEAE will be identified as an AE with start date on or after the start of study intervention. A non-TEAE will be defined as an AE with start date prior to the start of study intervention.

TEAEs will be further classified and analyzed separately by study phase (Treatment phase, Open-label extension phase) and overall:

- TEAE during double-blind treatment phase: defined as TEAEs with start date that on or after the date of first study intervention administration in treatment phase and on or before the date of the first study intervention in the open-label extension phase (the date after the last record in the Blinded drug administration page). For

participants who do not enter the open-label extension phase, all reported TEAEs will be considered within the treatment phase.

- TEAE during open-label extension phase: defined as TEAEs with start date after the date of first study drug administration in the open-label extension phase (the date after the last record in the Blinded drug administration page). For the TEAE during the open-label extension phase summary, only those subjects in OLE analysis set will be included.

If the first study intervention in the open-label extension phase is missing, the Week 14 visit date will be used as the cutoff date.

If relationship to study intervention is missing, the event will be conservatively treated as related to study intervention. Missing severity will be imputed as 'Grade 3 - Severe'.

Adverse events of special interest are events of scientific and medical interest specific to the further understanding of the safety profile of the study intervention. For this study, AESI's are:

- Skin pigmentation.
- Adrenal adverse events.

An overall AE summary will be presented by dose cohorts and active doses overall, using the number and percentages of participants with the following:

- Any AEs
- TEAEs
- Treatment-related TEAEs. This subset will include TEAEs with a drug relationship of Related.
- SAEs
- Serious TEAEs
- Treatment-related SAEs
- Grade ≥3 TEAE (Severe TEAE)
- TEAEs leading to study intervention discontinuation
- AEs of special interest (AESI) (overall and separately for skin pigmentation and adrenal AEs)

In addition, the following summaries of AE by system organ class (SOC) in alphabetical order and preferred term (PT) in descending order (of the overall frequency) will be produced. The tables will display counts and percentages of participants who reported at least one AE in each SOC and PT. At each level of summarization, a participant reporting more than one event will be counted only once. The severity grade and relationship to study drug will be summarized in a similar manner.

- All TEAEs
- Treatment-related TEAEs
- SAEs

- Serious TEAEs
- Grade ≥3 TEAE (Severe TEAE)
- TEAEs leading to study intervention discontinuation
- AEs of special interest (AESI)
- TEAEs by maximum severity

All AEs will be presented in a by-participant listing, detailing the verbatim term, the preferred term, system organ class, treatment-emergent (yes/no), study phase, onset date, end date, severity, outcome, relationship to study intervention, action taken with study intervention, other action taken, seriousness and criteria for seriousness. Serious AEs, AESIs, AEs leading to study intervention discontinuation and TEAEs leading to death will be presented in separate listings.

8.4. Clinical Laboratory Results

Absolute values and changes from Baseline of clinical laboratory data (hematology, chemistry, continuous urinalysis parameter) will be summarized with descriptive statistics through Week 14 for IA only, and through Week 52 and Week 56 for the final analysis. For the laboratory values which have the normal range (e.g., below/within/above the normal range) or categorical result (e.g., −/±/+), a shift table will display the cross tabulation of the Baseline result category versus the result of the post-treatment period at visit according to the study phase being reported.
Central and local laboratory test results (including hematology, coagulation, serum chemistry, and urinalysis), change from baseline and abnormal laboratory values at each visit will be presented in data listings. Values outside the normal ranges will be flagged. Flags will describe direction relative to normal range in relevant parameters.

8.5. Vital Signs

Vital sign results (pulse rate, respiratory rate, temperature, systolic blood pressure, and diastolic blood pressure) and change from baseline at each visit will be summarized and presented in data listings.

8.6. Electrocardiogram (ECG)

ECG parameters (heart rate [HR], PR interval, RR interval, QRS duration, QTinterval, QTcF), change from baseline and the overall ECG evaluation at each visit will be summarized and presented in the listing.

8.7. Physical Examination

Clinically significant abnormal physical examination results will be recorded as MH or AEs and analyzed accordingly. Full physical examination results at Screening will be presented in a listing.

The following findings will be present in a separate listing also:

- Were there any nevi or pigmentary lesions?
- Were there any newly developed or darkening of pre-existing nevi or pigmentary lesions?
- Is the participants referred to the dermatologist?

Additionally, results collected on the Comprehensive Skin Assessment CRF page at each visit will be provided in the listing.

8.8. Concomitant Medications

All medications will be coded using WHODrug Global March 1, 2023 or later. The specific version will be identified in footnotes of applicable listings and summaries. Prior medications include medications used to treat the disease conditions and any other medications taken prior to enrollment and stopped prior to first dose of study intervention. Concomitant medications during the study are defined as any medications that are ongoing or with stop dates on or after date of first study intervention. Concomitant medications will be further categorized by study phase as following:

- Double-blind treatment phase: includes all concomitant medications that are ongoing or with stop dates on or after date of first study medication in double-blind treatment period, but do not start on or after Week 14 dosing
- Open-label extension phase: includes all concomitant medications that start on or after Week 14 dosing

The number and percentage of subjects taking prior medications or concomitant medications (overall and by study phases) will be summarized by anatomical therapeutic chemical (ATC) level 2 and preferred term (PT) for the safety analysis set. Although a subject may have taken two or more medications, the subject is counted only once within an ATC classification. The same subject may contribute to two or more PNs in the same classification. All prior and concomitant medications will be listed by subject.

8.9. Concomitant Procedures

All procedures will be coded using MedDRA dictionary version 26.0 or later. The specific version will be identified in footnotes of applicable listings.

Prior (with end dates prior to first dose of study intervention) and concomitant (ongoing or with end dates on or after first dose of study intervention) procedures will be presented in a by-participant data listing. Concomitant procedures will be further categorized by study phase using similar definition as above.

8.10. Other Safety Assessments

8.10.1. Pubertal Development Assessment

Pubertal development will be assessed by the overall Tanner staging in accordance with stages 1 to 5. The above information at each visit will be presented in the listing.

8.10.2. Columbia-Suicide Severity Rating Scale (C-SSRS)

The C-SSRS measures 4 elements: The first is the severity of ideation, which is rated on a 5-point ordinal scale in which 1 = wish to be dead, 2 = nonspecific active suicidal thoughts, 3 = suicidal thoughts with methods, 4 = suicidal intent, and 5 = suicidal intent with plan. The second is the intensity of ideation subscale, which comprises 5 items, each rated on a 5-point ordinal scale: frequency, duration, controllability, deterrents, and reason for ideation. The third is the behavior subscale, which is rated on a nominal scale that includes actual, aborted, and interrupted attempts; preparatory behavior; and non-suicidal self-injurious behavior. And the fourth is the lethality subscale, which assesses actual attempts; actual lethality is rated on a 6-point ordinal scale, and if actual lethality is zero, potential lethality of attempts is rated on a 3-point ordinal scale.[4]

The following outcomes are C-SSRS categories and have binary responses (yes/no). The categories listed below have been re-ordered from the actual scale in an increasing order of severity from 1 to 10 to facilitate the definitions of the comparative endpoints.

Categories
Suicidal Ideation (1-5)
1 – Wish to be dead
2 – Non-specific active suicidal thoughts
3 – Active suicidal ideation with any methods (not plan) without intent to act
4 – Active suicidal ideation with some intent to act, without specific plan
5 – Active suicidal ideation with specific plan and intent
Suicidal behavior (6-10)
6 – Preparatory acts or behavior
7 – Aborted attempt
8 – Interrupted attempt
Suicidal acts (9-10)
9 – Non-fatal suicide attempt
10 – Completed suicide

- Suicidal ideation: A “yes” answer at any time during treatment to any one of the five suicidal ideation

questions (Categories 1-5) on the C-SSRS.

- Suicidal behavior: A "yes" answer at any time during treatment to any one of the five suicidal behavior questions (Categories 6-10) on the C-SSRS.
- Suicidal ideation or behavior: A "yes" answer at any time during treatment to any one of the ten suicidal ideation and behavior questions (Categories 1-10) on the C-SSRS.
- Suicidal Ideation Score: The maximum suicidal ideation category (1-5 on the C-SSRS) present at the assessment. Assign a score of 0 if no ideation is present.
- Suicidal Behavior Score: The maximum suicidal behavior category (6-10 on the C SSRS) present at the assessment. Assign a score of 0 if no behavior is present.
- Suicidal Ideation or Behavior Score: The maximum suicidal ideation or behavior category (1-10 on the C-SSRS) present at the assessment. Assign a score of 0 if no ideation or behavior is present.

The percentage and number of above suicidal ideation, suicidal behavior and Suicidal ideation or behavior will be summarized in the table and presented in the listing. The results of each categories, suicidal ideation score, suicidal behavior score and suicidal behavior or behavior score will be presented in the listing. The intensity of ideation (frequency, duration, controllability, deterrents and reason for ideation) and the actual/potential lethality of most recent attempt, most lethal attempt and initial attempt will also be presented in the listing.

8.10.3. Patient Health Questionnaire-9 (PHQ-9) or PHQ-A

The PHQ-9 is used to assess the severity of depression. It includes 9 items with response categories of 0 = not at all, 1 = several days, 2 = more than half the days, and 3 = nearly every day. The total score for the nine items ranges from 0 to 27. Higher score indicates more severe depression. The total score will not be calculated if one of the items is missing. The total score will be categorized as 0-4 Minimal, 5-9 Mild, 10-14 Moderate, 15-19 Moderately Severe, 20-27 Severe. The PHQ-A is a modification of the PHQ-9 for adolescents. The PHQ-A will be administered to patients 12 to <18 years of age and the PHQ-9 will be administered to patients ≥18 years of age. After the patient has completed the PHQ-9 or PHQ-A questionnaire, it is scored by the trial staff.

The individual questions, total score and change from baseline in total score and the total score categories will be summarized descriptively and presented in the listing.

8.10.4. Spectrophotometric assessment

The following information will be summarized in different location (Dorsum of hand, forehead, gluteal region or hip or buttock, axilla):

- Melanin Index
- Erythema Index

The spectrophotometric assessment results will be presented in the listing, including the assessment date, area, location, side, melanin index, erythema index.

9. PHARMACOKINETIC ANALYSIS

All PK analyses will be performed on the PK Analysis Set. Summaries of LB54640 plasma concentrations and derived PK parameters will be based on the PK Analysis Set. Moreover, listing of LB54640 plasma concentrations will done be for all participants in the Safety Analysis Set.

9.1. Pharmacokinetic Concentration

PK samples will be collected as per the Protocol Table 1.
Plasma LB54640 concentrations will be summarized using descriptive statistics (sample size (n), mean, median, minimum, maximum, standard deviation (SD), coefficient of variation (CV) by treatment cohort and nominal PK sampling time points).

All plasma LB54640 concentrations that are below the limit of quantification (BLQ) will be labeled as such in the concentration data listing. Concentration data in listing will be presented in the same number of significant figures as provided by the analytical laboratory.

The concentration data will be handled as follows for calculation of PK parameters:

- The time of collection of pre-dose samples will be set to zero.
- If the pre-dose sample prior to first dose is collected following study drug administration or is missing, pre-dose concentration will be set to zero.
- Concentrations below the lower limit of quantification (BLQ) in pre-dose samples and in time-points before first quantifiable concentration will be set to zero.
- BLQ concentrations appearing in terminal phase (after Cmax) of the concentration-time profile will be set to missing.
- BLQ concentrations in the middle of the curve that are flanked by measurable concentrations will be assigned a value of missing.
- Any PK samples collected outside of predetermined sample window as specified in Protocol Table 1 will be listed only and excluded from PK concentration table summary. Furthermore, they are included in the individual concentration-time profile and in calculation of PK parameters using the actual time point. The PK parameters will be listed as well as summarized.

Plasma LB54640 concentration data will be presented graphically (linear and semi-logarithm scales). Individual plasma concentration-time profiles and arithmetic mean (± SD) plasma concentration-time profiles for each cohort will be presented. Actual sampling time will be used to plot individual concentration-time profiles and nominal sampling time will be used for mean (± SD) plasma concentration-time profiles.

9.2. Pharmacokinetic Parameters

PK parameters will be calculated by non-compartmental analysis methods using Phoenix® WinNonlin® version 8.5 or higher (Certara, LP Princeton, New Jersey, USA).
Plasma PK parameters that are calculated for Plasma LB54640 are presented in protocol Section 8.4.3. The list of Plasma PK parameters is provided below. Additional plasma PK parameters may be calculated if data permit and deemed appropriate.

Plasma PK parameters	Unit	Definition
C_{max}	ng/mL	Maximum concentration, obtained directly from the observed concentration versus time data.
T_{max}	h	Time to Cmax.
AUC_{0-t}	h*ng/mL	Area under the plasma concentration-time curve from time zero to the time of last quantifiable concentration, calculated by linear up/log down trapezoidal summation.
C_{trough}	ng/mL	Concentration immediately prior to next dose

Abbreviation: h = hours.

The above-mentioned plasma PK parameters will be calculated and listed for each subject in PK Analysis Set. The PK parameters will be summarized using descriptive statistics (sample size (n), mean, median, minimum, maximum, SD, CV%) by treatment cohort.

The following guidelines will be followed to calculate PK parameters:

- Actual sampling times relative to dosing rather than nominal times will be used in the calculation of all derived PK parameters.
- Actual dosing interval will be used for calculation of PK parameters when applicable. Actual dosing interval is calculated using formula: Date/Time of pre-dose PK sample prior to next dose – Date/Time of last Study drug administration.
- If a pre-dose sample is collected at time greater than ± 20% of tau following the last dose i.e., 24 ± 4.8 h then, PK concentration will be listed only and excluded from summary statistics. Similarly, the C_{trough} (and related PK parameters) will be listed and excluded from summary statistics.
- There will be no imputation of missing data.
- Any anomalous concentration values observed at pre-dose prior to administration of first dose will be

identified in the study report. If the anomalous concentration is less than 5% of the observed maximum concentration (C_{max}), the PK parameters for the given subject will be calculated and reported in the listing and statistical summaries. If the anomalous concentration is greater than 5% of C_{max}, the PK parameters for the given subject will be calculated and reported in the listing but excluded from statistical summaries.

- When no date and/or time of study drug administration are recorded as per Protocol and eCRF, administration is deemed not to have been performed appropriately. Therefore, the PK concentration values collected at timepoints relative to the administration which has the missing date/time information will not be included in the derivation of PK parameters and will not be included in any PK concentration summaries or figures.
- If the pre-dose samples are collected following administration of study drug on Week 0 and Week 10, the PK concentrations will be included in the listing but excluded from summary statistics. Furthermore, the PK parameters will be listed only.
- If the pre-dose samples are collected following administration of study drug on Week 1, Week 2, Week 6 and Week 14, the PK concentrations will be included in the listing but excluded from summary statistics. The PK parameters will not be calculated.
- If the subjects are 100 % complaint to study drug administration, then PK concentrations and PK parameters will be summarized if the PK samples are collected within the visit window as defined by the Protocol section 1.3 Table 1 Schedule of Activities.
- If a subject missed their first dose, the subject will be flagged, and their PK profile will be assessed. The PK concentrations and parameters for the subject will be listed only but excluded from summary statistics.
- If a subject missed one or more doses following the first dose, the subject will be flagged, and their PK profile will be assessed. The PK concentrations and parameters for the subject will be listed only but excluded from summary statistics.
- For subject with vomiting recorded as AE, their PK profile will be assessed, and following rules will be applied:

    - For “Dose not changed”, PK data may be included in the NCA analysis if deemed appropriate. Concentrations and PK parameters will be listed and summarized.
    - For “Dose interrupted”, PK data may be included in the NCA analysis if deemed appropriate. Concentrations and PK parameters will be listed but excluded from summary statistics.

- A minimum requirement is to have 3 observations for calculating elimination rate constant (λz). If this is not possible or R square adj is less than 0.8, λz will be deemed as not reportable. Consequently, parameters dependent on λz (e.g., $t_{½}$, $AUC_{0\text{-inf}}$, CL/F, Vz/F) will be listed only but excluded from summary statistics.
- If %AUCex $\geqslant$ 20%, AUC(0-inf) and AUC(0-inf) dependent PK parameters will be listed but excluded in the summary statistics.
- Descriptive statistics will be determined regardless of the number of available individual PK parameters.
- PK parameters will be summarized by dose levels or cohorts.
- For T_{max} only sample size, median, minimum, and maximum values will be presented.

Note: These guidelines are considered as tentative. The analysis team will make decision case-by-case during the analysis phase.

10. PHARMACODYNAMIC ANALYSIS

[redacted]

11. REFERENCES

1. https://cdn.who.int/media/docs/default-source/child-growth/growth-reference-5-19-years/computation.pdf?sfvrsn=c2ff6a95_4.
2. https://www.who.int/tools/growth-reference-data-for-5to19-years/indicators/bmi-for-age
3. Fehnel S, Brown MT, Nelson L, et al. Development of the Hyperphagia Questionnaire for Use in Prader-Willi Syndrome Clinical Trial. Poster presented at: ISPOR 20th Annual International Meeting. 2015. Available from: https://www.rtihs.org/sites/default/files/Brown_ISPOR.2015_Poster.pdf. [Accessed 13 Jun 2023].
4. Posner K, Brown GK, Stanley B, et al. The Columbia-Suicide Severity Rating Scale: initial validity and internal consistency findings from three multisite studies with adolescents and adults. Am J Psychiatry. 2011;168(12):1266-77.

12. APPENDIX

SAS Macro to calculate the BMI-Z can be found in the following link:

Application tools (who.int)

SAS Macro to calculate the percentage of 95th percentiles:
SAS Program (ages 0 to < 20 years) | Resources | Growth Chart Training | Nutrition | DNPAO | CDC

13. SAS PROCEDURES

This section provides sample SAS® code to illustrate statistical tests specified in the statistical methods section. All computer output from SAS® statistical procedures serving as a basis for extracted results (e.g., GLM, MIXED, FREQ, MI) will be retained for quality control procedures and will be included in CSR appendices.

1) MI procedures for weights at Week 14 (primary endpoint is BMI, should be calculated based on the imputed weights):

   Monotone missing pattern:

   PROC MI DATA = MI1 OUT = MI3 SEED = **&seed.** NIMPUTE = **50** NOPRINT;

CLASS TRT01P STRATA;
MONOTONE REG(Weight1 Weight2 Weight6 Weight10 Weight14/details);
VAR TRT01P STRATA baseweight Weight1 Weight2 Weight6 Weight10 Weight14;
RUN;

Any other missing pattern:
PROC MI DATA = MI1 OUT = MI3 SEED = **&seed.** NIMPUTE = **50** NOPRINT;

CLASS TRT01P STRATA;
FCS REG(Weight1 Weight2 Weight6 Weight10 Weight14/details);
VAR TRT01P STRATA baseweight Weight1 Weight2 Weight6 Weight10 Weight14;
RUN;

2) MIANALYZE procedures will be used when each of the imputed dataset have been performed by using the corresponding analysis procedure, the value represents the lsmeans and lsmeansdifference. The STDERR represents the corresponding standard error:

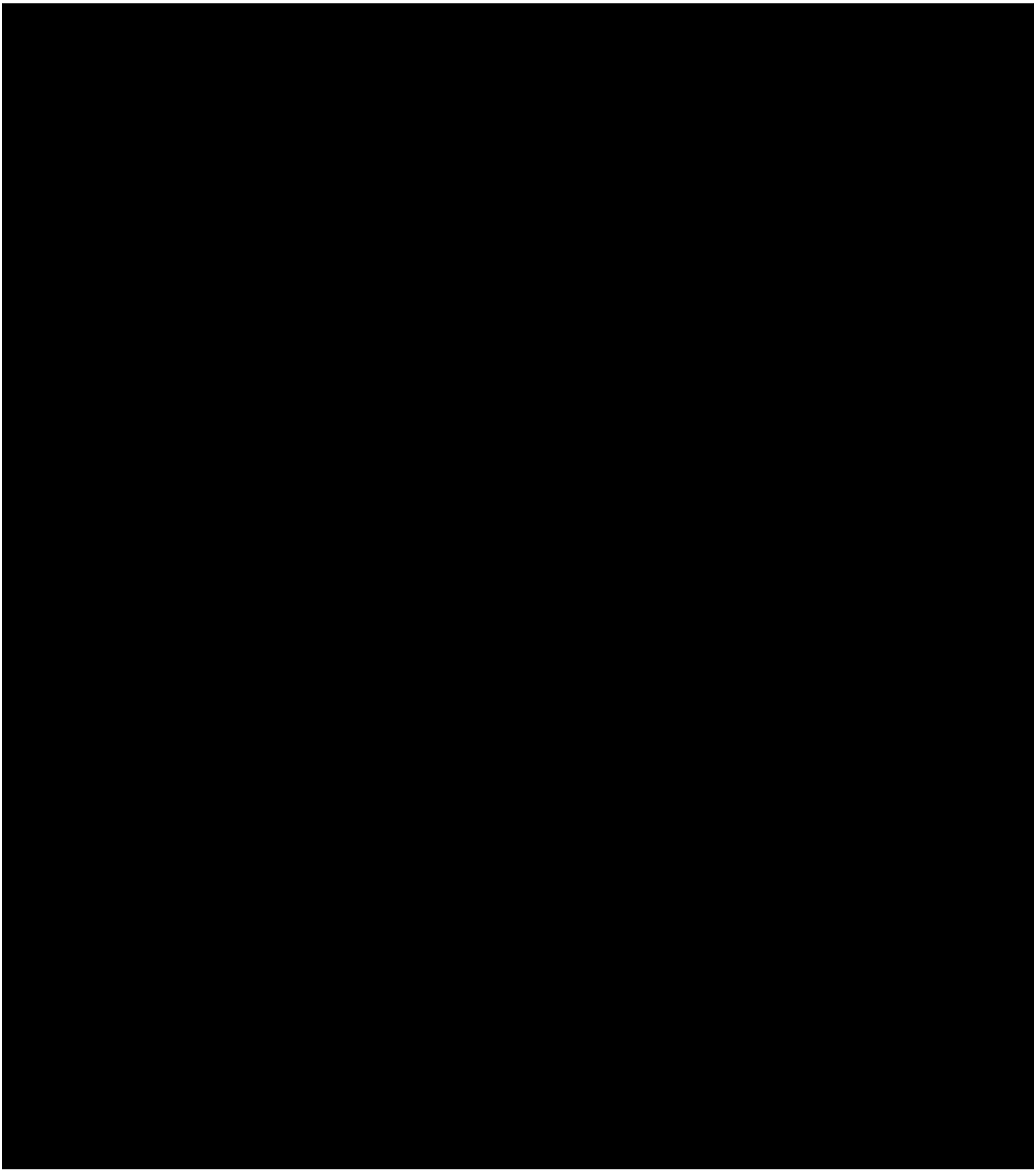
ods output ParameterEstimates=alldiff;
PROC MIANALYZE DATA = rrdiff;
MODELEFFECT VALUE;
STDERR STDERR;
RUN;

3) ANCOVA

```
PROC GLM DATA=BMI;
   WHERE CHG NE .;
   CLASS trt01p STRATA;
   MODEL CHG= trt01p BASE STRATA/solution;
   lsmeans trt01p/cl stderr tdiff diff pdiff cov
out=lsmeans_out;
run;
```

4) Repeated measures analysis

```
PROC Mixed DATA=BMI;
   CLASS usubjid trt01pn avisitn STRATA;
   MODEL CHG= trt01pn avisitn trt01pn*avisitn BASE
STRATA/noint;
   repeated avisitn / type = UN  subject = usubjid;
   lsmeans trt01pn*avisitn/cL diff pdiff;
run;
```



[redacted]

Electronic Record and Signature Disclosure created on: 5/16/2025 12:27:41 PM
Parties agreed to: [redacted]

ELECTRONIC RECORD AND SIGNATURE DISCLOSURE

From time to time, DSSM - Part11 (we, us or Company) may be required by law to provide to you certain written notices or disclosures. Described below are the terms and conditions for providing to you such notices and disclosures electronically through the DocuSign system. Please read the information below carefully and thoroughly, and if you can access this information electronically to your satisfaction and agree to this Electronic Record and Signature Disclosure (ERSD), please confirm your agreement by selecting the check-box next to 'I agree to use electronic records and signatures' before clicking 'CONTINUE' within the DocuSign system.

Getting paper copies

At any time, you may request from us a paper copy of any record provided or made available electronically to you by us. You will have the ability to download and print documents we send to you through the DocuSign system during and immediately after the signing session and, if you elect to create a DocuSign account, you may access the documents for a limited period of time (usually 30 days) after such documents are first sent to you. After such time, if you wish for us to send you paper copies of any such documents from our office to you, you will be charged a $0.00 per-page fee. You may request delivery of such paper copies from us by following the procedure described below.

Withdrawing your consent

If you decide to receive notices and disclosures from us electronically, you may at any time change your mind and tell us that thereafter you want to receive required notices and disclosures only in paper format. How you must inform us of your decision to receive future notices and disclosure in paper format and withdraw your consent to receive notices and disclosures electronically is described below.

Consequences of changing your mind

If you elect to receive required notices and disclosures only in paper format, it will slow the speed at which we can complete certain steps in transactions with you and delivering services to you because we will need first to send the required notices or disclosures to you in paper format, and then wait until we receive back from you your acknowledgment of your receipt of such paper notices or disclosures. Further, you will no longer be able to use the DocuSign system to receive required notices and consents electronically from us or to sign electronically documents from us.

All notices and disclosures will be sent to you electronically

Unless you tell us otherwise in accordance with the procedures described herein, we will provide electronically to you through the DocuSign system all required notices, disclosures, authorizations, acknowledgements, and other documents that are required to be provided or made available to you during the course of our relationship with you. To reduce the chance of you inadvertently not receiving any notice or disclosure, we prefer to provide all of the required notices and disclosures to you by the same method and to the same address that you have given us. Thus, you can receive all the disclosures and notices electronically or in paper format through the paper mail delivery system. If you do not agree with this process, please let us know as described below. Please also see the paragraph immediately above that describes the consequences of your electing not to receive delivery of the notices and disclosures electronically from us.

How to contact DSSM - Part11:

You may contact us to let us know of your changes as to how we may contact you electronically, to request paper copies of certain information from us, and to withdraw your prior consent to receive notices and disclosures electronically as follows:
To contact us by email send messages to: [redacted]

To advise DSSM - Part11 of your new email address

To let us know of a change in your email address where we should send notices and disclosures electronically to you, you must send an email message to us at [redacted] and in the body of such request you must state: your

previous email address, your new email address. We do not require any other information from you to change your email address

If you created a DocuSign account, you may update it with your new email address through your account preferences.

To request paper copies from DSSM - Part11

To request delivery from us of paper copies of the notices and disclosures previously provided by us to you electronically, you must send us an email to [redacted] and in the body of such request you must state your email address, full name, mailing address, and telephone number. We will bill you for any fees at that time, if any.

To withdraw your consent with DSSM - Part11

To inform us that you no longer wish to receive future notices and disclosures in electronic format you may:

i. decline to sign a document from within your signing session, and on the subsequent page, select the check-box indicating you wish to withdraw your consent, or you may;

ii. send us an email to [redacted] and in the body of such request you must state your email, full name, mailing address, and telephone number. We do not need any other information from you to withdraw consent. The consequences of your withdrawing consent for online documents will be that transactions may take a longer time to process.

Required hardware and software

The minimum system requirements for using the DocuSign system may change over time. The current system requirements are found here: https://support.docusign.com/guides/signer-guide-signing-system-requirements.

Acknowledging your access and consent to receive and sign documents electronically

To confirm to us that you can access this information electronically, which will be similar to other electronic notices and disclosures that we will provide to you, please confirm that you have read this ERSD, and (i) that you are able to print on paper or electronically save this ERSD for your future reference and access; or (ii) that you are able to email this ERSD to an email address where you will be able to print on paper or save it for your future reference and access. Further, if you consent to receiving notices and disclosures exclusively in electronic format as described herein, then select the check-box next to ‘I agree to use electronic records and signatures’ before clicking ‘CONTINUE’ within the DocuSign system.

By selecting the check-box next to ‘I agree to use electronic records and signatures’, you confirm that:

- You can access and read this Electronic Record and Signature Disclosure; and
- You can print on paper this Electronic Record and Signature Disclosure, or save or send this Electronic Record and Disclosure to a location where you can print it, for future reference and access; and
- Until or unless you notify DSSM - Part11 as described above, you consent to receive exclusively through electronic means all notices, disclosures, authorizations, acknowledgements, and other documents that are required to be provided or made available to you by DSSM - Part11 during the course of your relationship with DSSM - Part11.