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

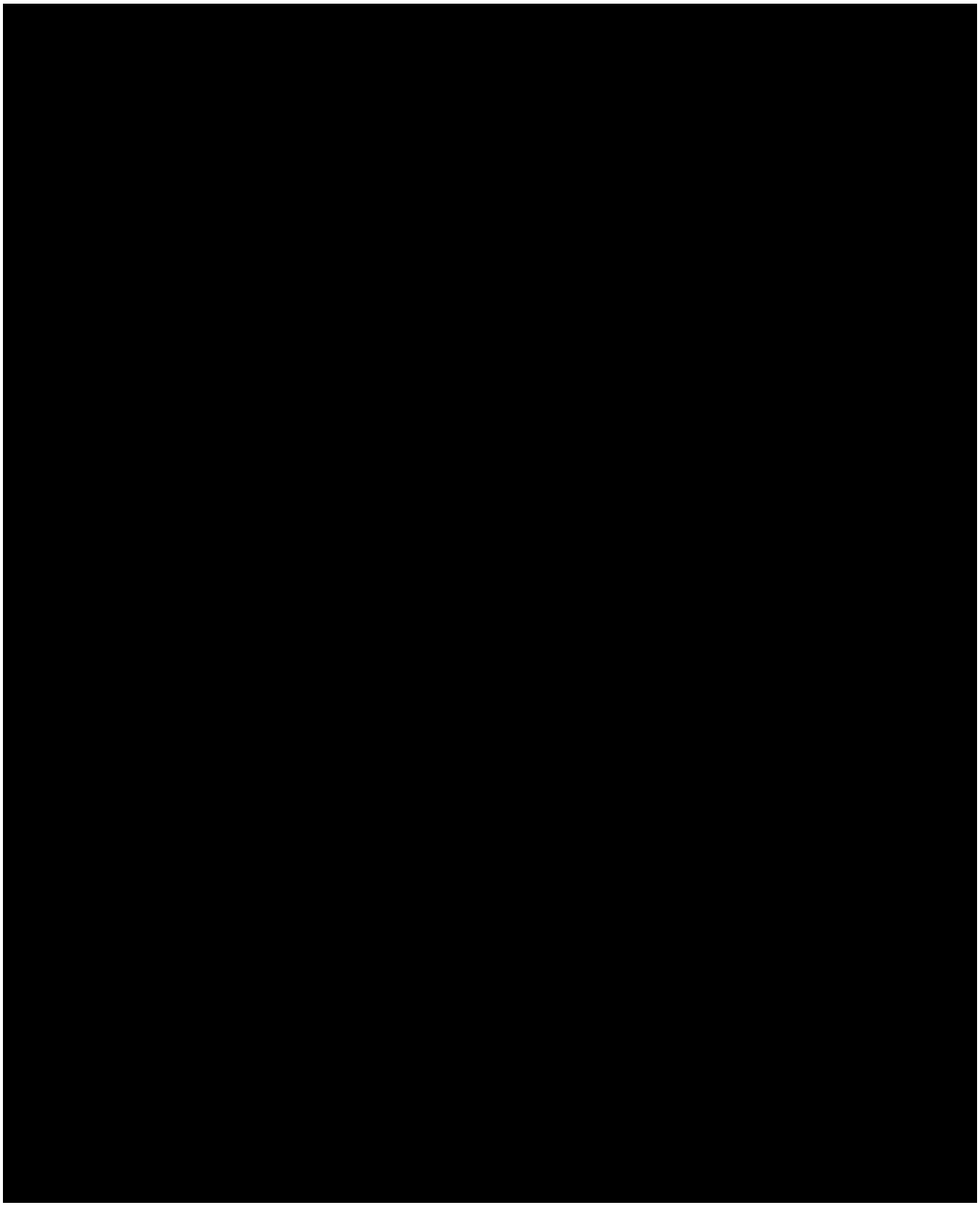
This trial will be conducted according to the protocol and in compliance with Good Clinical Practice, the ethical principles stated in the Declaration of Helsinki, and other applicable regulatory requirements.

[redacted]

Short Title:	Safety and Efficacy of LB54640 in Hypothalamic Obesity
Compound:	LB54640
Study Phase:	Phase 2
Trial Sponsor:	Rhythm Pharmaceuticals, Inc. 222 Berkeley Street 12th Floor Boston, MA 02116
Document Date (Version):	14 April 2025 (4.0)

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APPROVAL SIGNATURE PAGE

Protocol Title:	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
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Document Date:	14 April 2025

REVIEWED/APPROVED BY:

[redacted] [redacted] _____

Signature Date

[redacted]
Rhythm Pharmaceuticals, Inc.

INVESTIGATOR STATEMENT

Protocol Title:	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
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I understand that all documentation provided to me by Rhythm Pharmaceuticals, Inc. (Rhythm) or its designated representative(s) concerning this trial that has not been published previously will be kept in the strictest confidence. This documentation includes the trial protocol, Investigator's Brochure, case report forms, and other scientific data.

This trial will not commence without the prior written approval of a properly constituted Institutional Review Board. No changes will be made to the trial protocol without the prior written approval of Rhythm and the Institutional Review Board, except where necessary to eliminate an immediate hazard to the subject.

I have read, understood, and agree to abide by all the conditions and instructions contained in this protocol.

Investigator Name	Investigator Signature	Date

TABLE OF CONTENTS

SUMMARY OF CHANGES TO THE PROTOCOL 2
APPROVAL SIGNATURE PAGE 4
INVESTIGATOR STATEMENT 5
LIST OF TABLES 11
LIST OF FIGURES 11
1. PROTOCOL SUMMARY 12
1.1. Synopsis 12
1.2. Schema 16
1.3. Schedule of Activities 17
2. INTRODUCTION 23
2.1. Study Rationale 23
2.2. Background 24
2.2.1. Hypothalamic Obesity 24
2.2.2. Leptin-melanocortin signaling pathway 24
2.2.3. LB54640 25
2.2.4. [redacted] 25
2.2.4.1. [redacted] 25
2.3. Benefit/Risk Assessment 25
2.3.1. [redacted] 26
2.3.2. Benefit Assessment 28
2.3.3. Overall Benefit Risk Conclusion 29
3. OBJECTIVES, ENDPOINTS 30
4. STUDY DESIGN 33
4.1. Overall Design 33
4.2. Scientific Rationale for Study Design 33
4.3. [redacted] 34
4.4. End of Study Definition 34
4.5. Long-term Extension Study 34
5. STUDY POPULATION 35
5.1. Inclusion Criteria 35
5.2. Exclusion Criteria 36

5.3. Lifestyle Considerations 37
5.3.1. Meals and Dietary Restrictions 37
5.3.2. Caffeine, Alcohol, and Tobacco 38
5.3.3. Activity 38
5.4. Screen Failures 38
5.5. Criteria for Temporarily Delaying Enrollment/ Randomization/ Administration of Study Intervention 38
6. STUDY INTERVENTION(S) AND CONCOMITANT THERAPY 40
6.1. Study Drug(s) Administered 40
6.2. Preparation, Handling, Storage, and Accountability 41
6.3. Randomization and Blinding 42
6.3.1. Unblinding Procedure 42
6.4. Study Intervention Compliance 42
6.5. Dose Modification 43
6.6. Concomitant Therapy 44
6.6.1. Permitted Concomitant Therapy 44
6.6.2. Prohibited Concomitant Therapy 45
6.6.3. Rescue Medicine 45
6.7. Treatment of Overdose 46
7. DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/ WITHDRAWAL 47
7.1. Discontinuation of Study Intervention for Individual Participants 47
7.1.1. Liver Chemistry Stopping Criteria 48
7.1.2. Corrected QT Interval Stopping Criteria 48
7.1.3. Temporary Discontinuation 48
7.2. Participant Discontinuation/Withdrawal from the Study 49
7.3. Lost to Follow-up 50
8. STUDY ASSESSMENTS AND PROCEDURES 51
8.1. Efficacy Assessments 52
8.1.1. Assessment of Height, Body Weight and Body Mass Index 52
8.1.2. Assessment of Waist and Hip Circumference 52
8.1.3. Assessment of Body Composition by Dual Energy X-ray Absorptiometry 53
8.1.4. Hunger Questions 53

8.1.5. Patient Global Impression of Severity and Change (PGI-S, PGI-C) 54
8.1.6. Symptoms of Hyperphagia 54
8.1.7. [redacted] 54
8.1.8. [redacted] 55
8.1.9. Chart Review and Diagnostic History 55
8.1.10. [redacted] 55
8.2. Safety Assessments 56
8.2.1. Physical Examinations 56
8.2.1.1. Skin Assessment 56
8.2.2. Pubertal Development Assessment 56
8.2.3. Spectrophotometry 57
8.2.4. Comprehensive Skin Assessment 57
8.2.5. Vital Signs 57
8.2.6. Electrocardiograms 57
8.2.7. Clinical Laboratory Tests 58
8.2.8. Pregnancy and Contraception 58
8.2.9. Depression, Suicidal Ideation and Behavior Risk Monitoring 59
8.2.9.1. Suicide Depression Assessment Using C-SSRS 60
8.2.9.2. Suicide Depression Assessment Using PHQ-9 or PHQ-A 60
8.2.10. Telephone Visit 61
8.3. Adverse Events, Serious Adverse Events, and Other Safety Reporting 61
8.3.1. Time Period and Frequency for Collecting AE and SAE Information 61
8.3.2. Method of Detecting AEs and SAEs 62
8.3.3. Follow-up of AEs and SAEs 62
8.3.4. Regulatory Reporting Requirements for SAEs 62
8.3.5. Pregnancy 62
8.3.6. Adverse Events of Special Interest 63
8.4. Pharmacokinetics 63
8.4.1. Collection of Samples 63
8.4.2. Determination of Drug Concentration 64
8.4.3. Calculation of Derivation of Pharmacokinetic Variables 64
8.5. Pharmacodynamics 64
8.5.1. [redacted] 64

8.5.2. [redacted] 64
8.6. Genetics 65
8.7. Biomarkers 65
8.8. Immunogenicity Assessments 65
9. STATISTICAL CONSIDERATIONS 66
9.1. Statistical Hypotheses 66
9.1.1. Multiplicity Adjustment 66
9.2. Analysis Sets 66
9.3. Statistical Analyses 66
9.3.1. General Considerations 66
9.3.2. Primary Endpoint Analysis 67
9.3.3. Secondary Endpoints Analyses 67
9.3.4. [redacted] 68
9.3.5. Pharmacokinetic/Pharmacodynamic Analyses 68
9.3.6. Safety Analyses 68
9.3.7. Other Analyses 69
9.4. Interim Analysis 69
9.5. Sample Size Determination 69
10. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS 70
10.1. Appendix 1: Regulatory, Ethical, and Study Oversight Considerations 70
10.1.1. Regulatory and Ethical Considerations 70
10.1.2. Adequate Resources 70
10.1.3. Financial Disclosure 71
10.1.4. Insurance 71
10.1.5. Informed Consent Process 71
10.1.6. Data Protection 72
10.1.7. Committees Structure 72
10.1.7.1. Independent Data Monitoring Committee 72
10.1.8. Dissemination of Clinical Study Data 73
10.1.9. Data Quality Assurance 73
10.1.10. Source Documents 74
10.1.11. Study and Site Start and Closure 74

10.1.12. Publication Policy 75
10.2. Appendix 2: Clinical Laboratory Tests 76
10.3. Appendix 3: AEs and SAEs: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting for Study Intervention 78
10.3.1. Definition of AE 78
10.3.2. Definition of SAE 79
10.3.3. Recording and Follow-Up of AE and/or SAE 80
10.3.4. Reporting of SAEs and Pregnancies 81
10.4. Appendix 4: Collection of Pregnancy Information 83
10.5. Appendix 6: Abbreviations 84
11. REFERENCES 87

LIST OF TABLES

Table 3: [redacted] 26
Table 4: Study Drug(s) Administered 40
Table 5: Study Arms for Double-Blind Treatment Phase 41
Table 6: Study Arm for Open-label Extension Phase 41
Table 6: Pharmacokinetic Parameters 64
Table 7: Protocol-required Safety Laboratory Tests 76

LIST OF FIGURES

Figure 1: Study Schema 16

1. PROTOCOL SUMMARY

1.1. Synopsis

Protocol Title: 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

Rationale: Hypothalamic obesity is a complex neuroendocrine disorder caused by hypothalamic damage and is characterized by rapid weight gain, extreme obesity, hyperphagia, decreased resting energy expenditure, and reduced physical activity (Bereket 2012). Amongst suprasellar tumors, craniopharyngioma is the most common cause with about half of craniopharyngioma patients developing altered eating behavior and extreme obesity (Denzer 2019). These patients also typically suffer from panhypopituitarism and demonstrate significant hyperleptinemia due to anatomic leptin resistance, inadequate hyperinsulinemia, impaired incretin response, and reduced levels of α-MSH. There are currently no approved treatments for hypothalamic obesity and available interventions provide only modest and variable effects.

The melanocortin 4 receptor (MC4R) is a G protein-coupled receptor involved in the hypothalamic leptin-melanocortin signaling pathway (Tao 2010), and LB54640 is a selective oral MC4R agonist with a low molecular weight. The present trial is a 14-week, multicenter, randomized, double-blind, placebo-controlled study, followed by a 38-week open-label extension phase, designed to assess safety, tolerability and efficacy of LB54640 in participants with hypothalamic obesity.

Objectives and Endpoints:

Objectives	Endpoints
Primary	
To assess the efficacy of LB54640	• Mean percentage change in Body Mass Index (BMI) (Baseline to Week 14)
Secondary	
To assess the magnitude of efficacy of LB54640	• 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, 10 and 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 from baseline in waist-to-hip circumference ratio (at 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)
To assess the efficacy of LB54640 on hunger	• Mean change in the weekly average of the daily most hunger score in participants ≥12 years old from (Baseline to Week 14) • Mean change in the weekly average of the Symptoms of Hyperphagia composite score (Baseline to Week 14)

Objectives	Endpoints
To assess the long-term efficacy of LB54640	• 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 in body weight 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 extension phase • Mean change and mean percentage change in body composition (fat mass, lean mass) assessed by dual energy x-ray absorptiometry (DEXA) (Baseline to EOLTET/ED)
To assess the safety and tolerability of treatment with LB54640	• Frequency and severity of adverse events (AE) and adverse events of special interest (AESI)
To assess the pharmacokinetics (PK) of LB54640	• Maximum observed concentration in plasma (C_{max}) at Week 0 and 10 • Time to C_{max} (T_{max}) at Week 0 and 10 • Area under the concentration-time curve from 0 to last quantifiable concentration (AUC_{0-t}) at Week 0 and 10 • Trough plasma concentration (C_{trough}) at Weeks 1, 2, 6, 10 and 14
[redacted]	
[redacted]	

Objectives	Endpoints
[redacted]	

Overall Design:

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 vs <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 randomized phase, the study will continue with an open-label extension phase to evaluate the safety, tolerability and efficacy of LB54640 for a total study duration of 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 up to 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.

Number of Participants:

A total of 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. Inclusion and Exclusion criteria are outlined in Section 5.1 and Section 5.2.

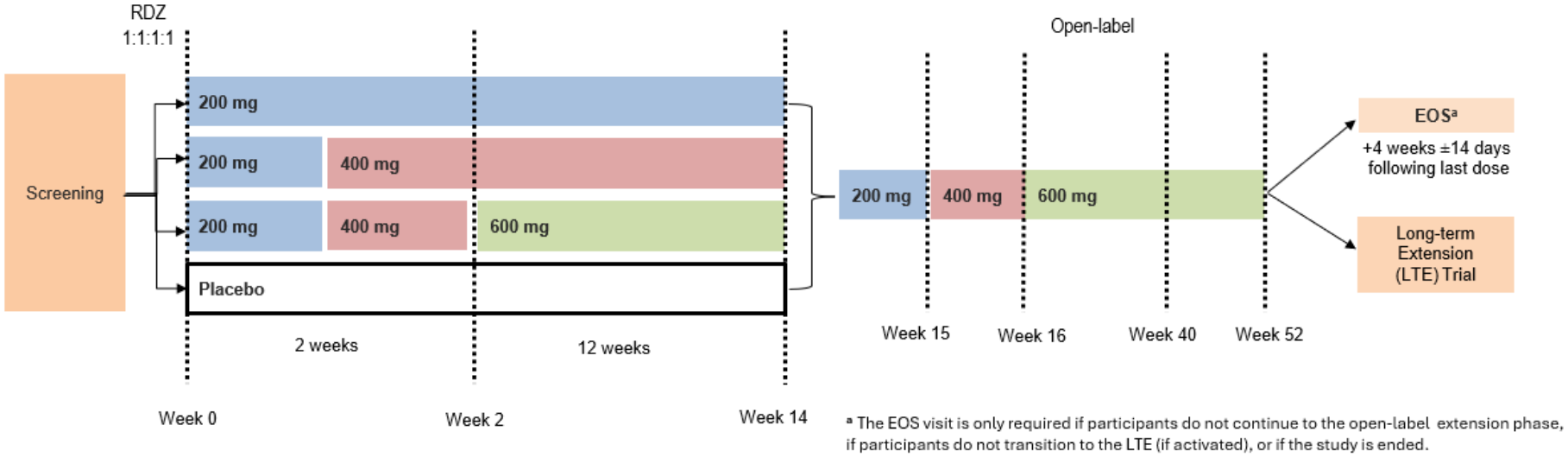
Intervention Groups and Duration:

This study will consist of 4 treatment cohorts during the randomized, double-blind, placebo-controlled phase: 200 mg LB54640, 400 mg LB54640, 600 mg LB54640, and placebo. All participants continuing on to the open-label extension phase will be titrated from 200 mg for 1 week, 400 mg for 1 week, to 600 mg LB54640 as tolerability allows. The total treatment duration of the study is up to 52 weeks.

Independent Data Monitoring Committee: An IDMC will perform periodic safety review of the clinical study data.

1.2. Schema

Figure 1: Study Schema



1.3. Schedule of Activities

Visit	Screening	Double-Blind Treatment Phase							Open-Label Extension Phase				EOS**
		1 *Baseline*	2	3	3-1	4	5	6	7	8	9	10	11
Week	**D-60 to D-1**	**W0**	**W1 (±2 days)**	**W2 (±2 days)**	**W3 Telephone visit (±2 days)**	**W6 (±5 days)**	**W10 (±5 days)**	**W14 EOT/ ED*[a] (±5 days)**	**W16 (±5 days)**	**W28 (±5 days)**	**W40 (±5 days)**	**W52 (±5 days) EOLTET/ ED [a]**	**W56 (±14 days)****
Written Informed Consent[b]	X							X					
Demographics	X												
Diagnostic and Medical History[c]	X	X											
Pregnancy Test[d]	X	X	X	X		X	X	X	X	X	X	X	X
Previous Medication (including any medications used for weight control)	X												
Concomitant Medications	Continuous from signing of the ICF through completion of study participation.												
Inclusion/Exclusion Criteria	X	X											
Randomization		X											
Study Intervention Dispensing[e]		X	X	X		X	X	X	X	X	X		
Medication Diary[f]		X	X	X		X	X	X	X	X	X	X	
Study Intervention Return			X	X		X	X	X	X	X	X	X	

Visit	Screening	Double-Blind Treatment Phase							Open-Label Extension Phase				EOS**
		1 *Baseline*	2	3	3-1	4	5	6	7	8	9	10	11
Week	**D-60 to D-1**	**W0**	**W1 (±2 days)**	**W2 (±2 days)**	**W3 Telephone visit (±2 days)**	**W6 (±5 days)**	**W10 (±5 days)**	**W14 EOT/ ED*[a] (±5 days)**	**W16 (±5 days)**	**W28 (±5 days)**	**W40 (±5 days)**	**W52 (±5 days) EOLTET/ ED [a]**	**W56 (±14 days)****
Physical Examination including Skin Assessment[g]	X	X	X	X		X	X	X	X	X	X[a]	X	X
Comprehensive Skin Assessment[h] (as needed)		As needed. Refer to Section 8.2.4.											
Spectrophotometric Assessment[i]		X						X				X	
Vital Signs[j]	X	X	X	X		X	X	X	X	X	X	X	X
Adverse Events	Continuous from signing from signing of ICF through completion of study participation.												
Clinical Laboratory Tests[k]	X	X	X	X		X	X	X	X	X	X	X	X
FSH[l]	X												
12-lead ECG[n]	X	X	X	X		X	X	X	X	X	X	X	X
Weight and Waist and Hip Circumference[o]	X	X	X	X		X	X	X	X	X	X	X	X
Height[o]	X	X	X	X		X	X	X	X	X	X	X	X

Visit	Screening	Double-Blind Treatment Phase							Open-Label Extension Phase				EOS**
		1 *Baseline*	2	3	3-1	4	5	6	7	8	9	10	11
Week	**D-60 to D-1**	**W0**	**W1 (±2 days)**	**W2 (±2 days)**	**W3 Telephone visit (±2 days)**	**W6 (±5 days)**	**W10 (±5 days)**	**W14 EOT/ ED*[a] (±5 days)**	**W16 (±5 days)**	**W28 (±5 days)**	**W40 (±5 days)**	**W52 (±5 days) EOLTET/ ED [a]**	**W56 (±14 days)****
Body Composition by DEXA		X						X				X	
Hunger questionnaire[p]	X	X	X	X		X	X	X	X	X	X	X	X
Symptoms of Hyperphagia[p]		X	X	X		X	X	X	X	X	X	X	X
PGI-S (or CGI-S) [p]		X	X	X				X	X			X	X
PGI-C (or CGI-C) [p]			X	X				X	X			X	X
[redacted]													
PHQ-9 (or PHQ-A for participants <18 years) and C-SSRS[q]	X	X				X	X	X		X	X	X	
[redacted]													

Visit	Screening	Double-Blind Treatment Phase							Open-Label Extension Phase				EOS**
		1 *Baseline*	2	3	3-1	4	5	6	7	8	9	10	11
Week	**D-60 to D-1**	**W0**	**W1 (±2 days)**	**W2 (±2 days)**	**W3 Telephone visit (±2 days)**	**W6 (±5 days)**	**W10 (±5 days)**	**W14 EOT/ ED*[a] (±5 days)**	**W16 (±5 days)**	**W28 (±5 days)**	**W40 (±5 days)**	**W52 (±5 days) EOLTET/ ED [a]**	**W56 (±14 days)****
Pubertal Development Assessment[r]	X							X				X	
PK Sampling[s]		X	X	X		X	X	X					

Abbreviations: AE = adverse event, CGI-C = Caregiver Global Impression of Change, CGI-S = Caregiver Global Impression of Severity, C-SSRS = Columbia Suicide Severity Rating Scale, DEXA= Dual-Energy X-ray Absorptiometry ECG = electrocardiogram, ED = Early Discontinuation, EOLTET = End of Long-term Extension Treatment, EOS = End of Study, EOT = End of Treatment (at Week 14), EOLTET = End of Long-term Extension Treatment, EOLTET ED = End of Long-term Extension Treatment Early Discontinuation, [redacted] FPG = fasting plasma glucose, [redacted] ICF = informed consent form, [redacted] LTE = Long-term Extension, PGI-S = Patient Global Impression of Severity, PGI-C = Patient Global Impression of Change, PHQ-9 = Patient Health Questionnaire-9, PHQ-A = Patient Health Questionnaire-Adolescents, PK = pharmacokinetics, W = Week, WOCBP = women of childbearing potential.

* Participants who withdraw or discontinue early will complete an Early Discontinuation Visit.

** The EOS Visit (approximately 4 weeks ±14 days after last dose) is only required if either: the participant does not continue in the open-label extension phase, or the participant does not transition to the LTE, or if no LTE is activated, or if the study is ended.

[a] Participants will be encouraged to continue all study assessments regardless of premature discontinuation of the study intervention. They will be asked to continue the remaining study visits even though the study intervention is permanently discontinued. If the participant refuses to continue all study procedures and/or withdraws consent, they will be asked to complete an ED visit. If the participant discontinues during the double-blind treatment phase, the ED visit will be performed as per Week 14 schedule (except ICF). If the participant discontinues during the open-label extension phase, an assessment of the ED visit will be performed as per the EOLTET/ED schedule. If eligible and if the LTE is activated at the participant's site, participants may transition to the LTE at the EOLTET Visit.

[b] For the participants below 18 years of age, the informed consent will be signed by participant's parent/guardian and the assent form will be signed by the participants (see Section 10.1.5).

[c] Refer to Section 8.1.9 for chart review and a detailed analysis and collection of the clinical and diagnostic history of participants.

[d] Pregnancy testing will be performed for WOCBP only: urine pregnancy test will be performed at all applicable visits, except Screening. At Screening, a serum pregnancy test will be performed. If the result of urine pregnancy test is positive, it must be confirmed with a serum pregnancy test. If post-menopausal status is confirmed by FSH at screening visit, no pregnancy test is needed throughout the study.

[e] On days when participants visit the site, the IP must be taken at the site.
[f] Medication diary will be dispensed at every in-person study visit except W52 and W56 and it will be returned to the site at every subsequent in-person visit to evaluate drug compliance. Participants will record administration information of study drugs including the reasons for departure from the expected dispensing regimen, information about AEs that occurred during the study, other medications the patient has taken using study medication diary (see Section 6.4).
[g] A complete physical examination will be conducted at Screening, Week 14, and either the EOLTET or the EOLTET ED Visit (see Section 8.2.1). At other visits, a brief/symptom-lead physical examination will be conducted. Clinical monitoring of adrenal hyper or hypofunction and skin assessment will be conducted during the physical examination at each visit. As part of the physical examination at each visit, the investigator will note any significant skin abnormalities and refer the participant to the dermatologist for comprehensive skin assessment if necessary. In cases where newly developed nevi or pigmentary lesions are identified, the investigator may refer the participant to a dermatologist to perform the comprehensive skin assessment, including dermoscopy. Photographs of any nevus or pigmented skin lesions that do not meet the exclusion criteria should be captured (see Section 8.2.2).
[h] At the investigator's discretion, if a participant needs to receive a comprehensive skin assessment, the participant can be referred to the dermatologist. In the event a patient experiences changes to skin or skin lesions that are unresolved at the EOLTET/ED visit, a referral for a comprehensive skin assessment should be performed.
[i] Skin pigmentation levels of all participants will be measured using spectrophotometry as per the SoA (see Section 8.2.3).
[j] Body temperature, pulse rate, respiratory rate, and blood pressure will be assessed (see Section 8.2.4).
[k] Clinical laboratories will include hematology panel, chemistry panel, urinalysis with microscopic analysis (if positive findings on dipsticks warrant further examination), thyroid panel, and coagulation parameters. Refer to Section 10.2 for the list of parameters included under each panel. Fasting samples (8-hour minimum) are required at all time points, where feasible.
[l] FSH tested at screening period can be used to exclude child-bearing potential of the participants who are suspected postmenopausal.
[m] [redacted]
[n] A standard 12-lead ECG will be recorded locally at the study sites after 5 minutes of rest in a supine position (see Section 8.2.6).
[o] Refer to Section 8.1.1 for guidelines regarding height and weight assessment and Section 8.1.2 for measurement of waist and hip circumference. For adult participants, height assessment is only required at Screening.
[p] Hunger Questionnaires and Symptoms of Hyperphagia Questionnaire will be recorded for at least 4 of 7 consecutive days during the Screening Period (before the enrollment visit) and for at least 4 of 7 consecutive days before the other scheduled trial visits. These questionnaires should be completed prior to the morning meal (fasted) before dosing and at home. Two versions of each of these questionnaires will be available; Participants who cannot self-report will use the Symptoms of Hyperphagia: Caregiver Version. Participants ≥12 years old and who can reliably and validly self-report will use the Hunger Questions for Participants ≥12 Years of Age and the Symptoms of Hyperphagia: Patient Version (see Section 8.1.4 and Section 8.1.6). For PGI-C/PGI-S (or CGI-C/CGI-S), see Section 8.1.5.
[q] The PHQ-A will be administered to participants 11to <18 years of age and the PHQ-9 will be administered to participants ≥18 years of age. See Section Section 8.2.9 for criteria and values related to C-SSRS and PHQ-9/PHQ-A.
[r] For participants who have yet to reach Tanner Staging V (see Section 8.2.2)
[s] PK sampling time for W0 and W10 will include pre-dose and 1, 2, 4, and 6 and 24-hr post-dose. For all other visits, pre-dose only. Pre-dose sampling will be taken within 30 minutes before dosing. The post-dose PK samples at Week 0 and Week 10 will be collected within a sampling window of ±15 minutes for 1 and 2-hour samples, and ±30 minutes for 4 and 6-hour samples.

Note: Refer to Section 8 (Study Assessments and Procedures) for complete guidance regarding assessment of efficacy, safety, and participant-reported outcome (questionnaire/scales) parameters.

Note: If a participant is not able to visit the study site for any reason (including coronavirus disease 2019) they should contact the study site by telephone. Adverse event and concomitant medication details may be collected during a telephone call. It may not be possible to collect all clinical laboratory samples or

conduct clinical assessments during this time, but any details should be recorded in the electronic case report form (eCRF). If alternative arrangements can be agreed for the sample collection or clinical assessments, the details should be documented in the eCRF. Further guidance regarding alternative arrangements will be included in the risk management tracker. See Section 5.5 for contingency measures in case of regional or national emergency declared by a governmental agency.

Note: At the investigator's discretion, participants may be allowed for an unscheduled visit apart from the SoA. During such unscheduled visits, certain or all assessments from visit 6 may be conducted, depending on the purpose of the unscheduled visit and the discretion of the investigator.

2. INTRODUCTION

2.1. Study Rationale

Obesity is defined as abnormal or excessive fat accumulation that presents a risk to health, with increased risk of various secondary diseases including cardiovascular disease, type 2 diabetes mellitus, certain types of cancer, hyperlipidemia, non-alcoholic fatty liver disease, and asthma. Therefore, obesity has a significant impact on mortality as well as quality of life.

The MC4R is a G protein-coupled receptor involved in the hypothalamic leptin-melanocortin signaling pathway. The central melanocortin pathway, driven by the peripheral adipocyte hormone leptin, has emerged as a critical signaling system regulating body weight and energy homeostasis.

Hypothalamic obesity is a condition caused by physical damage to the hypothalamus, resulting in disruption of the hypothalamic pathways including the leptin-melanocortin signaling pathway. The melanocortin 4 receptor (MC4R) is a G protein-coupled receptor involved in the hypothalamic leptin-melanocortin signaling pathway and MC4R agonists have shown a weight loss effect by reducing food intake through appetite regulation in animal models of obesity and obese patients. LB54640 is a selective oral MC4R agonist with a low molecular weight. This agent showed reduced food intake and weight loss effect after once daily oral administration in several rodent models of obesity as well as in otherwise healthy overweight or obese volunteers.



LB54640 is an MC4R agonist and has a similar mode of action to setmelanotide which is currently authorized for marketing and is under clinical investigation globally for its ability to impact body weight, hunger, and quality of life including in patients with HO (Abuzzahab 2023). LB54640 has the potential to deliver meaningful clinical benefit for the patients with hypothalamic obesity.

According to The International Registry of Hypothalamic Obesity Disorders, craniopharyngiomas accounted for 72% of brain tumor type in patients with HO and represented the most common type of non-glial tumor in children (Rose 2018). The age range peaks for craniopharyngiomas are adolescence (10-19 years of age) and older adults (65-74 years of age) with 30% to 50% of these cases occurring in childhood (Roth 2015). More than 40% of the patients in the registry were younger than 20 years old. Due to the acute hypothalamic injury and progressive symptoms of HO despite age of onset, there is a strong rationale to treat patients earlier in life.

Given the preclinical toxicology, safety pharmacology [redacted], LB54640 has an acceptable profile for entry to Phase 2 clinical study. The aim of this Phase 2 study is to investigate safety, tolerability and efficacy of LB54640 in participants with hypothalamic obesity.

2.2. Background

Detailed information on the chemistry, pharmacology, efficacy, and safety of LB54640 is provided in the current Investigator's Brochure (IB).

2.2.1. Hypothalamic Obesity

Hypothalamic obesity is a complex neuroendocrine disorder caused by hypothalamic damage and is characterized by rapid weight gain, extreme obesity, hyperphagia, decreased resting energy expenditure, and reduced physical activity (Bereket 2012). Leptin levels corrected for body mass index (BMI) are higher in patients with hypothalamic obesity than in general obesity, indicating more severe leptin resistance in hypothalamic obesity (Guran 2009). The most common cause of hypothalamic obesity is brain tumor or tumor therapies, including surgery and radiation (Rose 2018).

Patients with hypothalamic obesity often have difficulty losing weight through available interventions.

2.2.2. Leptin-melanocortin signaling pathway

The hypothalamus is a key regulator of food intake and energy expenditure and disruption of the central leptin-melanocortin signaling pathway in the hypothalamus by inherited gene mutations, as well as hypothalamic injury, can lead to severe obesity in humans. Leptin is a hormone produced by adipocytes and the levels of circulating leptin fluctuate based on changes in calorie intake (Baldini 2019). Circulating leptin is transported across the blood brain barrier where it binds to leptin receptor (LEPR) on both pro-opiomelanocortin (POMC) and agouti related neuropeptide (AgRP)/neuropeptide Y (NPY) neurons in the arcuate nucleus (ARC) of the hypothalamus.

Activation of LEPR on POMC and AgRP/NPY neurons have opposing downstream actions on melanocortin-4 receptor (MC4R) neurons. The binding of leptin to LEPR on POMC neurons initiates a signaling cascade that results in an increase in POMC transcription. POMC is a prohormone that undergoes posttranslational proteolytic cleavage by several peptidases, including proprotein convertase subtilisin/kexin type 1 (PCSK1) (Yeo 2021). Inside secretory granules, POMC is cleaved into several hormones, including alpha-melanocyte stimulating hormone (α-MSH) and beta (β)-MSH, which are then released at the axon terminals of POMC neurons (D'Agostino 2010). POMC neurons synapse on MC4R positive neurons in the hypothalamic paraventricular nucleus (PVN). α-MSH and β-MSH are agonists of MC4R and MC4R activation potentiates other excitatory signaling received by MC4R positive neurons, ultimately leading to decreased food intake and increased energy expenditure (Baldini 2019).

2.2.3. LB54640

LB54640 is a small molecule agonist of MC4R being developed for once daily (QD) oral administration. LB54640 showed high selectivity to MC4R compared to other MCR subtypes (MC1R, MC2R, MC3R, and MC5R) in radioligand binding assay.

2.2.4. [redacted]

[redacted]

2.2.4.1. [redacted]

[redacted]

2.3. Benefit/Risk Assessment

More detailed information about the known and expected benefits and risks and reasonably expected adverse events (AEs) of LB54640 may be found in the IB.

The Sponsor will immediately notify the investigator if any additional safety or toxicology information becomes available during the study.

This study will be performed in compliance with the protocol, International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) Good Clinical Practice (GCP), European Union Clinical Trial Regulation, and applicable regulatory requirements. Aspects of the study concerned with the investigational medicinal product(s) will meet the requirements of European Union – Good Manufacturing Practice.

The Sponsor and investigator may take appropriate safety measures in order to protect the participants of a clinical study against any immediate hazard to their health or safety. If such measures are taken, the Sponsor will notify the licensing authority and/or the relevant ethics committee of the measures taken and the circumstances giving rise to those measures according to local requirements.

2.3.1. [redacted]

[redacted]



[redacted]

2.3.2. Benefit Assessment

LB54640 may potentially benefit patients with hypothalamic obesity. LB54640 is an oral MC4R agonist and the MC4R pathway is well known to serve a critical role in controlling food intake and energy expenditure through brain periphery signaling networks. In preclinical study, LB54640 showed a high selectivity to MC4R compared to the other 4 melanocortin receptor subtypes. Additionally, it showed a dose-dependent weight loss effect in a mouse model of obesity induced by a high-fat diet, a rat model of obesity induced by a high-fat diet and the KK-A^y mouse model of obesity. [redacted]

2.3.3. Overall Benefit Risk Conclusion

Overall, considering the unmet medical need in participants with hypothalamic obesity for chronic weight management [redacted], the benefit risk profile of LB54640 in participants with hypothalamic obesity appears favorable.

Taking into account the measures taken to minimize risk to participants participating in this study, the potential risks identified in association with LB54640 are justified by the anticipated benefits that may be afforded to participants with hypothalamic obesity.

3. OBJECTIVES, ENDPOINTS

Objectives	Endpoints
Primary	
To assess the efficacy of LB54640	• Mean percentage change in Body Mass Index (BMI) (Baseline to Week 14)
Secondary	
To assess the magnitude of efficacy of LB54640	• 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, 10 and 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 from baseline in waist-to-hip circumference ratio at 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 Weeks 14)
To assess the efficacy of LB54640 on hunger	• Mean change in the weekly average of the daily most hunger score in participants ≥12 years old from Baseline to Week 14). • Mean change in the weekly average of the Symptoms of Hyperphagia composite score (Baseline to Week 14)

Objectives	Endpoints
To assess the long-term efficacy of LB54640	• 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 in body weight 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 extension phase • Mean change and mean percentage change in body composition (fat mass, lean mass) assessed by dual energy x-ray absorptiometry (DEXA) (Baseline to EOLTET/ED)
To assess the safety and tolerability of treatment with LB54640	• Frequency and severity of adverse events (AE) and adverse events of special interest (AESI)
To assess the pharmacokinetics (PK) of LB54640	• Maximum observed concentration in plasma (C_{max}) at Week 0 and 10 • Time to C_{max} (T_{max}) at Week 0 and 10 • Area under the concentration-time curve from 0 to last quantifiable concentration (AUC_{0-t}) at Week 0 and 10 • Trough plasma concentration (C_{trough}) at Weeks 1, 2, 6, 10 and 14
[redacted]	[redacted]

Objectives	Endpoints
[redacted]	

Abbreviations: AE = adverse event, AESI = adverse event of special interest, AUC_{0-t} = area under the concentration time curve from 0 to last quantifiable concentration, BMI = Body Mass Index, C_{max} = maximum observed concentration, C-SSRS = Columbia Suicide Severity Rating Scale, C_{trough} = trough plasma concentration, ECG = electrocardiogram, EOLTET = End of Long-Term Extension Treatment, EOLTET ED = End of Long-Term Extension Treatment Early Discontinuation, DEXA=Dual Energy X-ray Absorptiometry, [redacted], Hs-CRP = high sensitivity C-reactive protein, [redacted] PGI-C=Patient Global Impression of Change, PGI-S=Patient Global Impression of Severity, PHQ-9 = Patient Health Questionnaire 9, PK = pharmacokinetics, T_{max} = Time to C_{max}.

4. STUDY DESIGN

4.1. Overall Design

This study is a Phase 2, multicenter study, which consists of a 14-week randomized, double-blind, placebo-controlled phase, followed by a 38-week open-label extension phase, to assess the efficacy, safety and PK of LB54640 in participants with hypothalamic obesity. Participants will be randomized and stratified by age group (≥18 years old vs <18 years old), to receive LB54640 200 mg, 400 mg, or 600 mg, or placebo by oral administration in a 1:1:1:1 ratio. Participants assigned to the LB54640 200 mg cohort will receive 200 mg once daily (QD) for 14 weeks. Those assigned to the 400 mg cohort will be titrated from 200 mg QD after 1 week to 400 mg QD for an additional 13 weeks. For those assigned to the LB54640 600 mg cohort, participants will be titrated from 200 mg QD for 1 week, to 400 mg QD for 1 week, and to 600 mg QD for an additional 12 weeks.

Upon completion of the double-blind treatment phase at Week 14, if the participant agrees and there are no safety concerns as judged by the investigator, the participant will enter an open-label extension phase and receive treatment with LB54640 for up to an additional 38 weeks. To prevent potential unblinding which can impact data integrity, participants, regardless of active or placebo assignment in the treatment phase, will be titrated from 200 mg QD for 1 week, to 400 mg QD for 1 week, to 600 mg QD for up to 36 weeks, as tolerability allows. The dose may be modified at any time during the open-label extension phase as required for safety or efficacy at the discretion of the Investigator.

The duration of the entire trial will be up to 52 weeks. This includes the double-blind treatment phase and the open-label extension phase. An EOS Visit is scheduled within approximately 4 weeks ±14 days after the last dose of LB54640. The EOS Visit is only required if either the participant does not continue in the open-label extension phase, the participant does not transition to the LTE, if no LTE is activated, or if the study is ended. Participants who remain enrolled up through the Week 52 Visit may be eligible to participate in the LTE trial with open-label LB54640.

In total, 28 participants (7 in each cohort) will be enrolled across approximately 15 sites in the US and UK.

4.2. Scientific Rationale for Study Design

The study is comprised of a 14-week randomized, double-blind, placebo-controlled phase and an up to 38-week open-label extension phase, to assess the efficacy, safety and PK of LB54640 in participants with hypothalamic obesity. As there are currently no approved treatments for hypothalamic obesity, the main treatment phase will use a placebo-controlled design and to minimize potential bias, assignment will be conducted in a randomized and double-blind manner. [redacted]. To assess the long-term safety and efficacy of LB54640, an open-label extension phase will be included.

4.3. [redacted]

[redacted]

4.4. End of Study Definition

The end of the study is defined as the date of the last visit of the last participant in the study or last scheduled procedure shown in the SoA for the last participant in the study globally.

A participant is considered to have completed the study if he/she has completed all phases of the study, including the EOS (as required).

4.5. Long-term Extension Study

Participants who remain enrolled up through the Week 52 Visit may be eligible to participate in an LTE study with open-label LB54640.

5. STUDY POPULATION

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, is not permitted.

5.1. Inclusion Criteria

Participants are eligible to be included in the study only if all of the following criteria apply:

1. Age ≥12 years at the time of enrollment.
2. Obesity, defined as BMI ≥30 kg/m^2 for participants ≥18 years of age or BMI ≥95th percentile for age and gender for participants <18 years of age.
3. Participant has documented evidence of hypothalamic obesity, defined as:
   - Diagnosis of craniopharyngioma or other brain lesion affecting the hypothalamic region and has undergone surgery, or chemotherapy, or radiation therapy involving the hypothalamus at least 6 months before Screening, OR
   - Documented injury to the hypothalamus at least 6 months before Screening for which surgery/radiation is not indicated
4. Documented increase in BMI (change from pre-surgery baseline in BMI Z score ≥0.2 for participants <18 years of age or BMI >5% for participants ≥18 years of age) either during the first 6 months following surgery or within 1 year before surgery AND still present at Screening.
5. If the participant is receiving hormone replacement therapy (e.g., hydrocortisone for adrenal insufficiency, sex hormone for hypogonadism, thyroid hormone for hypothyroidism and growth hormone for growth hormone deficiency), the dose should have been stable for at least 2 months prior to Screening.
6. Body weight should have been stable (less than 5% weight gain or 2% loss for participants ≥18 years of age; BMI reduction >2% for participants <18 years of age) for at least 3 months prior to Screening.
7. A female participant is eligible to participate if she is not pregnant (see Section 10.4), not breastfeeding, not intending to become pregnant during the study and for at least 90 days after the last dose of study intervention and at least 1 of the following conditions applies:

   i. Not a woman of childbearing potential (WOCBP) as defined in Section 10.4.

   OR

   ii. A WOCBP who agrees to follow the contraceptive guidance provided in Section 10.4 during the study and for at least 90 days after the last dose of study intervention.
8. A male participant with a female partner of child-bearing potential must agree to use contraception as detailed in Section 10.4 of this protocol during the study and for 90 days after the last administration of study intervention and refrain from donating sperm during this period.
9. The study participant or their parent/guardian is capable of understanding all study procedures and giving signed informed consent/assent as described in Section 10.1 which

includes compliance with the requirements and restrictions listed in the informed consent form (ICF) and in this protocol.

5.2. Exclusion Criteria

Participants are excluded from the study if any of the following criteria apply:

1. Weight loss >2% in the previous 3 months for participants aged ≥18 years or >2% reduction in BMI for participants aged 12 to <18 years.

   NOTE: Dietary and/or exercise regimens, with or without the use of medications, supplements or herbal treatments associated with weight loss (e.g., orlistat, lorcaserin, phentermine, phentermine-topiramate, naltrexone-bupropion) or the treatment of diabetes mellitus are allowed if:

   - the regimen and/or dose has been stable for at least 3 months prior to randomization
   - the patient has not experienced weight loss >2% (for participants ≥18 years) or >2% BMI (for participants aged 12 to <18 years) during the previous 3 months, and
   - the patient intends to keep the regimen and/or dose stable throughout the course of the trial.

   NOTE: use of glucagon-like peptide-1 [GLP-1] receptor agonists are permitted only as a treatment for diabetes mellitus and are not permitted for weight loss (See Section 6.6.2).
2. Diagnosis of Prader-Willi syndrome (PWS) or Rapid-onset obesity with hypoventilation, hypothalamic, autonomic dysregulation, neuroendocrine tumor syndrome (ROHHADNET).
3. Previous use of MC4R agonists (e.g., setmelanotide, RM-718, or LB54640).
4. Weight loss surgery within the previous 6 months prior to Screening or any prior weight loss surgery resulting in >10% weight loss durably maintained from the baseline pre-operative weight with no evidence of weight regain.
5. History of major surgical procedure within 30 days prior to Screening.
6. Diagnosis of schizophrenia, bipolar disorder, personality disorder or other disorders that the investigator believes would interfere significantly with study compliance.
7. Patient Health Questionnaire-9 (PHQ-9)/PHQ-Adolescents (PHQ-A) score ≥15 at Screening, any suicidal ideation of type 4 or 5 on the Columbia-Suicide Severity Rating Scale (C-SSRS), any history of a suicide attempt, or any suicidal behavior in the last month prior to Screening.

   Note: Participants who are unable to complete the PHQ-9/PHQ-A or C-SSRS due to significant neurocognitive defects may be enrolled where no clinical signs or symptoms of suicidal behavior are present at the discretion of the Investigator.
8. Current, clinically significant pulmonary, cardiac, or oncologic disease considered severe enough to interfere with the study and/or confound the results.
9. [redacted].

10. Fasting glucose level >270 mg/dL at Screening.
11. History of significant liver disease or abnormal liver tests at Screening (i.e. >2 × upper limit of normal [ULN] for alanine transaminase [ALT], aspartate transaminase [AST]; >1.5 × ULN for alkaline phosphatase and serum bilirubin; cirrhosis Child Pugh class B or C with any etiology of liver disease).
12. History or presence of impaired renal function. Estimated glomerular filtration rate (eGFR) calculated by Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation <30 mL/min/1.73 m^2 at Screening (for participants aged ≥18 years old). eGFR calculated by updated Schwartz formula <30 mL/min/1.73 m^2 at Screening (for participants aged <18 years).
13. Personal history of melanoma or ocular cutaneous albinism. History of melanoma in immediate family members. Any persons with clinically dysplastic nevi or lesions suspicious for melanoma at comprehensive skin assessment during screening may be enrolled if confirmed benign through biopsy prior to enrollment.
14. Use of strong CYP3A4 inhibitors or strong CYP3A4 inducers within 14 days prior to enrollment or the need for ongoing treatment with concomitant oral or intravenous therapy with strong CYP3A4 inhibitors or strong CYP3A4 inducers during the study. (see Section 6.6.2)
15. Use of inhibitors or substrates of P-glycoprotein within 14 days prior to enrollment or the need for on-going treatment with concomitant inhibitors or substrates of P-glycoprotein during the study. (see Section 6.6.2).
16. Unwillingness to abstain from grapefruit (grapefruit containing food and beverages), star fruit (carambola), pomegranate, Seville orange and other food components that may interact with CYP3A4 within 14 days prior to enrollment and throughout the study.
17. Treatment with any IMPs in another study within 3 months or 5 half-lives (whichever is longer) of the previous investigational treatment prior to the first administration of study intervention.
18. Hypersensitivity to LB54640 or any excipient in the study intervention.
19. Not suitable to participate in the study, in the opinion of the investigator, including medical or psychiatric conditions, or participants potentially at risk of noncompliance to study procedures.

5.3. Lifestyle Considerations

5.3.1. Meals and Dietary Restrictions

Participants must abstain from grapefruit (grapefruit containing food and beverages), star fruit (carambola), pomegranate, Seville orange and other food components that may interact with CYP3A4 within 14 days prior to enrollment and throughout the entire course of the study.

There is no consensus on the recommended diet and exercise advice specifically for patients with hypothalamic obesity. If patients were already following a diet and exercise plan as part of the site's standard of care and have maintained a stable body weight, they will continue with the

same diet and exercise regimen. Introduction of newly prescribed diet and exercise advice will not be permitted.

5.3.2. Caffeine, Alcohol, and Tobacco

Participants should refrain from caffeine and smoking for 1 hour prior to study visits and during the study visits. Participants should restrict alcohol consumption for 24 hours prior to study visits.

5.3.3. Activity

Participants will be advised not to donate blood or plasma for at least 3 months after the last dose administration.

Participants must abstain from any activities that will intentionally cause their skin to tan (e.g., visit to ultraviolet tanning salons, use of spray tanners or self-tanning lotions, exposure to sunlight for a long period).

5.4. Screen Failures

A screen failure occurs when a participant who consents to participate in the clinical study is not subsequently randomly assigned to study intervention. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the Consolidated Standards of Reporting Trials publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any SAE.

Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened once. A second rescreening will be allowed in case of a delay due to the restrictions related to pandemic or similar emergency. Rescreened participants should not be assigned the same participant number as for the initial screening. Results of screening procedures can be used for rescreening if not older than 28 days, otherwise all screening procedures should be repeated.

5.5. Criteria for Temporarily Delaying Enrollment/ Randomization/ Administration of Study Intervention

During a regional or national emergency declared by a governmental agency, if the site is unable to adequately follow protocol mandated procedures, contingency measures are to be considered.

- Contingency procedures are suggested for an emergency that prevents access to the site, to ensure the safety of the participants, to consider continuity of the clinical study conduct, protect study integrity, and assist in maintaining compliance with GCP in Conduct of Clinical Trials Guidance. Sponsor agreement MUST be obtained prior to the implementation of these procedures for the duration of the emergency.
- During the emergency, if the site will be unable to adequately follow protocol mandated procedures, alternative treatment outside the clinical study should be proposed, and screening/enrollment/administration of study intervention may be temporarily delayed/halted.

- For a regional or national emergency declared by a governmental agency, contingency procedures may be implemented for the duration of the emergency. The participant or their legally authorized representative (LAR) should be verbally informed prior to initiating any changes that are to be implemented for the duration of the emergency (e.g., study visit delays/treatment extension, use of local laboratories).

Attempts should be made to perform all assessments in accordance with the approved protocol to the extent possible. In case this is not possible due to a temporary disruption caused by a regional or national emergency, focus should be given to assessments necessary to ensure the safety of participants and those assessments important to preserving the main scientific value of the study.

Procedures to be considered in the event of a regional or national emergency declared by a governmental agency for the duration of the emergency (after Sponsor agreement is obtained) may include:

- If onsite visits are not possible, remote visits (e.g., with home nurses, home health vendor) may be planned for the study intervention administration and collection of possible safety and/or efficacy data.
- If onsite visits are not possible, visit windows may be extended for assessment of safety and/or efficacy data that cannot be obtained remotely.
- Use of local clinic or laboratory locations may be allowed for hematology and clinical chemistry samples.

Further guidance will be included in the risk management tracker. Contingencies implemented due to a regional or national emergency must be documented.

6. STUDY INTERVENTION(S) AND CONCOMITANT THERAPY

Study intervention is defined as any investigational intervention or placebo intended to be administered to a study participant according to the study protocol.

6.1. Study Drug(s) Administered

Table 2: Study Drug(s) Administered

Study Drug Name	LB54640	Placebo
Intervention Description	LB54640 will be provided as oblong type film coated tablets (white to almost white color).	Placebo will be provided as oblong type film coated tablets (white to almost white color).
Type	Drug	Placebo
Dose Formulation	Tablet	Tablet
Unit Dose Strength(s)	200 mg	NA
Dosage Level(s)	200 mg, 400 mg, or 600 mg QD	QD
Route of Administration	Participants will self-administer study drug orally once daily in the morning in the fasting condition, if possible, at approximately the same time each day, with water. On the days of scheduled visits, participants should withhold administration until pre-dose sampling has been completed.	Participants will self-administer study drug orally once daily in the morning in the fasting condition, if possible, at approximately the same time each day, with water. On the days of scheduled visits, participants should withhold administration until pre-dose sampling has been completed.
Use	Experimental	Placebo
IMP and NIMP/AMP.	IMP	IMP
Sourcing	Provided centrally by the Sponsor	Provided centrally by the Sponsor
Packaging and Labeling	Study drug will be provided in a bottle of 35 tablets during the double-blind treatment phase. For open-label extension phase, study drug will be provided in a bottle of 100 tablets. Each bottle will be labeled as required per country requirement.	Study drug will be provided in a bottle of 35 tablets during the double-blind treatment phase. For open-label extension phase, study drug will be provided in a bottle of 100 tablets. Each bottle will be labeled as required per country requirement.

Abbreviations: AMP = auxiliary medicinal product, IMP = investigational medicinal product; NA = not applicable, NIMP = non-investigational medical product QD = once daily

Each bottle will contain a (randomized) dosage for 1 subject and will contain a sufficient quantity for dispensing. A total of 3 bottles will be dispensed per visit during the double-blind treatment phase and the subject must take 1 tablet of LB54640 200 mg strength or matching placebo from each bottle.

During the open-label extension phase, subjects will sequentially take the required number of tablets from each dispensed bottle. Detailed administration instructions will be provided in the pharmacy manual.

Details on the procedures for study intervention distribution, handling, storage, logistics, participant training, and accountability are provided in the Pharmacy Manual.

Table 3: Study Arms for Double-Blind Treatment Phase

Arm Title	LB54640 200 mg	LB54640 400 mg	LB54640 600 mg	Placebo
Arm Type	Experimental	Experimental	Experimental	Placebo
Arm Description	Participants will take LB54640 200 mg QD starting on Day 1. LB54640 200 mg will be taken QD for the next 14 weeks.	Participants will take LB54640 200 mg QD for 1 week starting on Day 1. Participants will then take LB54640 400 mg QD for the next 13 weeks.	Participants will take LB54640 200 mg QD for 1 week starting on Day 1. Participants will then take LB54640 400 mg QD for 1 week, followed by LB54640 600 mg QD for the next 12 weeks.	Participants will take placebo QD starting on Day 1. Placebo will be taken QD for the next 14 weeks.

Abbreviations: QD = once daily.

Table 4: Study Arm for Open-label Extension Phase

Arm Title	LB54640 600 mg
Arm Type	Experimental
Arm Description	Participants will take LB54640 200 mg QD for 1 week starting on Week 14. Participants will then take LB54640 400 mg QD for 1 week, followed by LB54640 600 mg QD through EOLTET/ED.

Abbreviations: QD = once daily.

6.2. Preparation, Handling, Storage, and Accountability

The investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study drug received, and any discrepancies are reported and resolved before use of the study drug.

Only participants enrolled in the study may receive study drug, and only authorized study site staff may supply or administer study drug. All study drug must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the investigator and authorized study site staff.

The investigator, institution, or the head of the medical institution (where applicable) is responsible for study drug accountability, reconciliation, and record maintenance (i.e. receipt, reconciliation, and final disposition records).

The investigator, a member of the study site staff, or a hospital pharmacist must maintain an adequate record of the receipt and distribution of all study drug using the Drug Accountability Form. These forms must be available for inspection at any time.

Study interventions will be dispensed at the study visits (see Section 1.3) and the participants will be requested to return the study drugs (unused and empty packets) at the study visits

specified in the SoA (see Section 1.3). Returned study drug should not be re-dispensed to participants.

Destruction of unused study intervention may be performed at the study site or returned to Sponsor. Further guidance and information for the final disposition of unused study interventions are provided in the Pharmacy Manual.

6.3. Randomization and Blinding

All participants will be centrally assigned to randomized study treatment using an Interactive Web Response System (IWRS). Before the study is initiated, the log-in information and directions for the IWRS will be provided to each study center. Participants who meet all inclusion and no exclusion criteria will be randomized in a 1:1:1:1 ratio to receive LB54640 200 mg, LB54640 400 mg, LB54640 600 mg, or placebo on Day 1 via block randomization.

To maintain blinding throughout the study while modifying the dose and dose titration , an Interactive Web Response System (IWRS) will be used in conjunction with a double-dummy technique to randomly assign subjects to different treatment groups and allow for dose adjustments at the Investigator's discretion. Employing the double-dummy technique, subjects will receive three tablets, containing either the active drug or a placebo during the double-blind period. Dose modifications and dose titration will be made by adjusting the number of tablets of each type. This approach ensures that both subjects and investigators remain blinded to the treatment group and any dose modifications.

The placebo and active drug will have identical packaging, labeling, appearance, taste, and weight.

The treatment that each subject will receive will not be disclosed to the Investigator, study center staff, subject, Sponsor (except for the those designated as un-blinded personnel). The IWRS will be programmed with blind breaking instructions.

Upon entering the open-label extension phase, all participants will be titrated from LB54640 200 mg, in order to maintain blinding of the double-blind treatment phase until study unblinding.

6.3.1. Unblinding Procedure

Each participant's treatment cohort assignment will not be broken until database lock of the double-blind treatment phase. In case of an emergency, the Investigator has the sole responsibility for determining if unblinding of a participant’s treatment assignment is warranted. Participant safety must always be the first consideration in making such a determination. If a participant’s treatment assignment is unblinded, the Sponsor must be notified within 24 hours after unblinding.

6.4. Study Intervention Compliance

The prescribed dosage, timing, and mode of administration may not be changed. Refer to Section 4.1 for details regarding the dosing schedule.

Any departures from the intended regimen must be recorded in the electronic case report form (eCRF).

Participants exhibiting poor compliance as assessed by tablet counts should be counseled on the importance of good compliance to the study dosing regimen.

Noncompliance is defined as taking less than 80% or more than 120% of study intervention during any evaluation period (visit to visit).

When participants self-administer study intervention at home, they should take their prescribed study intervention at the same time each day. Compliance will be assessed by direct questioning, counting returned tablets, review the medication diary, etc., during the study site visits and documented in the source documents and relevant form. Deviation(s) from the prescribed dosage regimen should be recorded.

Participants will record administration information of study drugs including the reasons for departure from the expected dispensing regimen, information about adverse events that occurred during the study, other medications the patient has taken using study medication diary.

A record of the quantity of LB54640 dispensed to and administered by each participant must be maintained and reconciled with study intervention and compliance records. Intervention start and stop dates, including dates for intervention delays and/or dose reductions will also be recorded.

6.5. Dose Modification

Study intervention dose modification during the treatment phase is only allowed, for management of intolerable GI symptoms. Participants who experience intolerable GI symptoms (e.g., nausea, vomiting, diarrhea, or loose stool) may be given symptomatic medication, at the discretion of the investigator. If intolerable GI symptoms (e.g., nausea, vomiting, diarrhea, or loose stool) persist despite medication/treatment, the study intervention dose may be lowered through sequential 200 mg decreases at the discretion of the investigator. For any dose reductions below 200 mg or for any study drug interruptions for safety or tolerability concerns, the Medical Monitor should be contacted. The Sponsor should be informed about any dose reductions (see Section 4.1). After the participant's GI symptoms have subsided, the dose will be returned to the original designated level. If the participants experience recurring GI symptoms, the dose will be reduced and there will be no re-challenge to the designated dose level. If intolerable GI symptoms persist despite measures, including symptomatic treatment and reduction to a lower dose of study intervention, the participant should be discontinued from the study intervention. All participants who discontinue study intervention should continue to attend the scheduled study visits (see Section 7.1).

Due to any AEs, the investigator may temporarily interrupt study intervention. The investigator should contact Sponsor to consider temporary interruption. A temporary interruption of daily dose of study intervention is limited to a maximum of 5 days (Exception: antiviral therapy due to COVID-19 infection. See Section 6.6.2). Every effort should be made by the investigator to maintain participants on the study intervention and to restart study intervention in case of any temporary interruption, after evaluating safety of the participants (see Section 7.1.3).

Upon entering the open-label extension phase, to prevent unblinding, all participants, regardless of their assignment in the treatment phase, will receive a starting dose of 200 mg once daily for 1 week, followed by 400 mg once daily for 1 week, then 600 mg once daily, as tolerability allows. Depending on the participant's safety/tolerability and/or efficacy profile, the dose level

may be adjusted (increased or decreased) at the discretion of the investigator during the open-label extension phase.

6.6. Concomitant Therapy

Any medication or vaccine (including over-the-counter or prescription medicines, recreational drugs, vitamins, and/or herbal supplements) that the participant is receiving at the time of enrollment or receives during the study must be recorded along with:

- Reason for use
- Dates of administration including start and end dates
- Dosage information including dose and frequency
- Route of administration
- For vaccines (if applicable) include brand name and manufacturer (plus lot number if available)

The medical monitor should be contacted if there are any questions regarding concomitant or prior therapy.

Any previous medications used for weight control (medications that were used off-label for this purpose) must be documented.

6.6.1. Permitted Concomitant Therapy

The following medications are permitted during the study:

- Growth hormone
- Contraceptives
- Hydrocortisone
- Desmopressin
- Sex hormone replacement therapy
- Antihypertensives
- GLP-1 receptor agonists alone or in combination may be used only for the treatment of diabetes mellitus per criteria outlined in Section 5.2 (not for weight loss).
- Statins and other lipid lowering therapies
- Thyroxine or other thyroid supplements
- Administration of live or inactivated vaccines (e.g., SARS-CoV-2 vaccines)
- Other medications commonly used in participants with obesity (e.g., anti-constipation medications, anti-allergic medications, estrogens, alendronic acid, hydrocortisone, carnitine, Coenzyme Q10, vitamins, calcium supplements, etc.).

- Other medications, except for those with narrow therapeutic index (e.g., warfarin, etc.), may be permitted after consultation with the Sponsor, if the participant is receiving a stable dose.

Background Therapy

Therapeutic lifestyle management for weight loss.

6.6.2. Prohibited Concomitant Therapy

The following medications are prohibited during the study (see Section 5.2 for eligibility criteria related to excluded medications):

- Medications that could impact the efficacy assessments during the study, such as anorectic agents or drugs with anorexia as a non-rare side effect.
- Strong inhibitors and strong inducers of CYP3A4 including grapefruit juice (e.g., carbamazepine, rifampin).*
- Inhibitors or substrates of P-glycoprotein (e.g., digoxin, fexofenadine, erithromycin, itraconazole).*
- GLP-1s except for the treatment of diabetes.

* Note: For a current list of strong inhibitors or inducers of CYP3A4 and inhibitors or substrates of P-glycoprotein, refer to the FDA guidance and website for Drug Development and Drug Interactions. Table of Substrates, Inhibitors and Inducers or FDA's Examples of Drugs that Interact with CYP Enzymes and Transporter Systems for Healthcare Professionals (FDA_2023a; FDA_2023b; WHO 2007a; WHO 2007b). (Exception: If any participant requires the administration of nirmatrelvir/ritonavir for COVID-19 infection according to the local treatment guidelines, it can be permitted. The study intervention will be temporarily discontinued until 3 days after the completion of nirmatrelvir/ritonavir. After 3 days of concluding the antiviral therapy, the previous treatment dose of the study intervention will be resumed.)



6.6.3. Rescue Medicine

Not applicable.

6.7. Treatment of Overdose

Any dose of study intervention >600 mg per day will be considered an overdose.

The Sponsor does not recommend specific treatment for an overdose.

In the event of an overdose or medication error, the investigator or designee should:

- Evaluate the participant to determine, in consultation with the medical monitor, whether study intervention should be interrupted.
- Closely monitor the participant for any AE/SAE and laboratory abnormalities (as medically appropriate).
- Document the quantity of the excess dose as well as the duration of the overdose in the eCRF.

7. DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/ WITHDRAWAL

Discontinuation of specific study sites or of the study as a whole are detailed in Section 10.1.11.

7.1. Discontinuation of Study Intervention for Individual Participants

It may be necessary for a participant to permanently discontinue study intervention. If study intervention is permanently discontinued, the participant will remain in the study to be evaluated for safety and efficacy. Refer to the SoA in Section 1.3 for data to be collected at the time of discontinuation of study intervention and follow-up and for any further evaluations that need to be completed.

If a participant who does not meet enrollment criteria is inadvertently enrolled, that participant must be discontinued from study intervention and the Sponsor, or Sponsor designee, must be contacted. An exception may be granted in rare circumstances for which there is a compelling safety reason to allow the participant to continue. In these rare cases, the investigator must obtain documented approval from the Sponsor, or Sponsor designee, to allow the participant to continue in the study.

In addition, participants must be permanently withdrawn from the study intervention for the following reasons:

- At their own request or at the request of their LAR.
- If, in the investigator's opinion, continuation in the study intervention would be detrimental to the participants well-being.
- Occurrence of any AE/SAE/AESI which in the opinion of the investigator would require study intervention discontinuation.
- Participant becomes pregnant or begins breastfeeding.
- Unexplainable elevations in liver enzymes. Participants should be monitored until all abnormal values return to normal or baseline values, and the outcomes must be recorded in the eCRF (for drug stopping criteria and guidance on monitoring, see Section 7.1.1).
- Participants with serum creatinine elevations at any visit >1.5 times baseline value will be closely monitored. If serum creatinine elevations are >2.0 times compared to baseline, and if this observation cannot be explained by concomitant disease or another alternative etiology, participants should discontinue the study intervention.
- If participants develop any skin lesion suspicious for melanoma or develop 1 or more dysplastic nevi, the participants will be referred to a dermatologist. If the malignant potential of the skin lesion cannot be ruled out, the participants must discontinue the study intervention and only continue to be monitored for safety during the remainder of the study period.
- In the event of a protocol deviation/violation, at the discretion of the investigator or the Sponsor.

- Lost to follow-up.
- Study discontinuation by the Sponsor.
- Participant requires treatment with a prohibited medication.
- Cardiac changes, QT interval corrected (QTc) stopping criteria (see Section 7.1.2)
- Participant conduct or any other events, which, in the clinical judgment of the investigator or after discussion with the Sponsor, may invalidate the study.

Participants who discontinue study intervention will not be replaced.

7.1.1. Liver Chemistry Stopping Criteria

Unexplainable elevations in liver enzymes: participants should be monitored until all abnormal values return to normal or baseline values, and the abnormal laboratory values must be reported as an AE/SAE as per the guidelines provided in Section 10.3.

- Participants should discontinue the study intervention immediately if ALT or AST elevations are ≥8 × ULN at any time during the clinical study.
- If ALT or AST elevations are ≥5 × ULN at any time during the study, laboratory tests should be repeated within 3 days. If elevations ≥5 × ULN are confirmed, participants should discontinue the study intervention.
- Participants should discontinue the study intervention if ALT or AST are elevated ≥3 × ULN in combination with laboratory findings of either total bilirubin is ≥2 × ULN or international normalized ratio of PT is ≥1.5 × ULN at any time during the study.
- Participants should discontinue the study intervention immediately if ALT or AST are elevated ≥3 × ULN and clinical symptoms (fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia [>5%]) are present at any time during the study.

7.1.2. Corrected QT Interval Stopping Criteria

If a clinically significant finding is identified including, but not limited to, changes from baseline in QTc using Fridericia's formula (QTcF) after enrollment, the investigator or qualified designee will determine if the participant can continue the study intervention and if any change in participant management is needed. This review of the ECG printed at the time of collection must be documented. Any new clinically relevant finding should be reported as an AE.

7.1.3. Temporary Discontinuation

Temporary intervention discontinuation may be considered by the investigator because of suspected AEs or disruption of the clinical study due to a regional or national emergency declared by a governmental agency. For all temporary intervention discontinuations, duration should be recorded by the investigator in the appropriate pages of the eCRF.

For any AEs, the investigator may need temporary interruption of study intervention. The investigator should contact Sponsor to consider temporary interruption of study intervention. A

temporary interruption of daily dose of study intervention is limited to a maximum of 5 days (Exception: COVID-19 infection which requires antiviral treatment, see Section 6.6.2). Every effort should be made by the investigator to maintain participants on the study intervention and to restart study intervention in case of any temporary interruption, after evaluating safety of the participants.

7.2. Participant Discontinuation/Withdrawal from the Study

A participant may withdraw from the study at any time at his/her own request or may be withdrawn at any time at the discretion of the investigator for safety, behavioral, or compliance, or administrative reasons. This is expected to be uncommon.

Participants must be permanently withdrawn from the study for the following reasons:

- Termination of the study by the investigator, Sponsor, IRB/IEC, or regulatory authority.
- In the event of a protocol deviation, at the discretion of the investigator or the Sponsor.
- Decision by the investigator that study discontinuation is in the participant's best medical interest.
- Pregnancy.
- Lost to follow-up.

In addition, the site/ study may be terminated/suspended by the Sponsor for the following reasons:

- New information or other evaluation regarding the safety or efficacy of the IMP or active comparator that indicates a change in the known risk/benefit profile for the compound, such that the risk/benefit is no longer acceptable for participants participating in the study.
- Significant violation of GCP that compromises the ability to achieve the primary study objectives or compromises participant safety or data integrity.
- The development of the study drug is paused or terminated;
- Any other reason at the Sponsor's discretion.

At the time of discontinuing from the study, if possible, an Early Discontinuation visit as well as EOS visit should be conducted, as shown in the SoA (Section 1.3). Refer to the SoA for data to be collected at the time of study discontinuation and follow-up and for any further evaluations that need to be completed.

The participant will be permanently discontinued from the study intervention and the study at that time.

If the participant withdraws consent for disclosure of future information, the Sponsor may retain and continue to use any data collected before such a withdrawal of consent.

If a participant withdraws from the study, he/she may request destruction of any samples taken and not tested, and the investigator must document this in the study site study records.

Should a participant request or decide to withdraw from the study, all efforts must be made to complete and report the observations as thoroughly as possible up to the date of withdrawal. Participants withdrawing due to an AE should be followed up according to the study discontinuation guidelines outlined in the SoA (see Section 1.3).

Participants who voluntarily withdraw are termed dropouts. If any participants dropout from the study before taking a single dose of study intervention, the participant will be replaced.

7.3. Lost to Follow-up

A participant will be considered lost to follow-up if he/she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site.

The following actions must be taken if a participant fails to return to the clinic for a required study visit:

- The study site must attempt to contact the participant and reschedule the missed visit as soon as possible, counsel the participant on the importance of maintaining the assigned visit schedule and ascertain whether the participant wishes to and/or should continue in the study.
- Before a participant is deemed lost to follow-up, the Investigator or designee must make every effort to regain contact with the participant. At least 3 unique documented contact attempts (e.g., phone calls or local equivalent outreach methods) to follow-up should be made and documented in the participant's medical record.
- Should the participant continue to be unreachable, he/she will be considered to have withdrawn from the study.

8. STUDY ASSESSMENTS AND PROCEDURES

Study procedures and their timing are summarized in the SoA (Section 1.3). Protocol waivers or exemptions are not allowed.

Immediate safety concerns should be discussed with the Sponsor immediately upon occurrence or awareness to determine if the participant should continue or discontinue study intervention.

Adherence to the study design requirements, including those specified in the SoA (Section 1.3), is essential and required for study conduct.

All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.

Procedures conducted as part of the participant's routine clinical management and obtained before signing of the ICF may be utilized for screening or baseline purposes provided the procedures met the protocol-specified criteria and were performed within the timeframe defined in the SoA (Section 1.3).

Any medical condition identified or other trial procedures performed prior to the first dose administration of study intervention can be considered and captured as a medical history in eCRF, not an adverse event.

To assure the safety of participants, maintain compliance with GCP, and minimize risks to study integrity during a regional/national emergency (e.g., Coronavirus Disease 2019 [COVID-19] pandemic), the clinical study conduct, and oversight may require implementation of temporary or alternative mechanisms. These may include, but will not be limited to, phone contact, virtual visits, telemedicine visits, online meetings, noninvasive remote monitoring devices, alternative location for assessment including local laboratories or imaging centers, home visits by skilled study personnel, and direct-to-participant study intervention shipment.

No waivers to deviate from protocol inclusion and exclusion criteria due to a regional/national emergency (e.g., COVID-19 pandemic) will be granted. All temporary mechanisms employed, and deviations performed from planned study procedures in response to a regional/national emergency are to be documented as being related to a regional/national emergency and will remain in effect only for the duration of the regional/national emergency. As far as possible, all scheduled study visits should be completed within the respective visit windows. If a participant is unable to visit the study site because of the regional/national emergency, a safety call to the participant should be made in place of the study site visit. The safety call should encompass all scheduled visit assessments that can be completed remotely, such as assessment for AEs, compliance, and concomitant medications. Home visits will be permitted if a participant cannot come to the study site because of the regional/national emergency. Home visits must be permitted by the site IRB and the participants via informed consent and have prior approval from the Sponsor (or designee).

If study visits are disrupted and cannot be completed within given window period because of a regional/national emergency, the visit window may be extended.

Suggested Order of Assessments: Vital signs and ECG must be taken before blood collection for laboratory tests including PK (see Section 8.4.1) and PD (see Section 8.5) sampling. Participant-reported outcome questionnaires and mental health questionnaires (C-SSRS and PHQ-9/PHQ-A) should be completed after the assessment for AEs.

Participant-reported Outcome Scales/Questionnaires: Specific trainings will be provided by the site staff to the participants/LAR/parent/guardian for completing the scales/questionnaires, as applicable. Participant's age at Screening should be used for selection of questionnaires and same scale should be used throughout the study.

8.1. Efficacy Assessments

8.1.1. Assessment of Height, Body Weight and Body Mass Index

Participant's height and weight will be recorded as per the SoA (see Section 1.3). For adult participants, height assessment is only required at Screening.

Height (cm or inches, 1 decimal) will be measured twice without shoes (2 individual measurements). Participant should be repositioned between the 2 measurements.

Body weight must be measured to the nearest 0.1 kg or 0.1 pounds. The same digital scale should be used throughout the trial and the scale should be calibrated on a regular basis. Weight should be measured when participants are in the fasting state and without shoes; participants should have an empty bladder and must wear light clothing for weight assessment.

Weight measured at screening is used for the calculation of BMI, whereas weight measured at enrolment is used as baseline for assessment of change in body weight. BMI is calculated in the eCRF.

Body Mass Index (kg/m^2) will be calculated from height and weight according to the following formula:

Weight (kg)/[height (m)]^2 (weight in kilograms divided by height in meters squared)

For participants <18 years of age, BMI Z-score and percentage of 95th percentile of BMI by age and gender will also be calculated. The BMI Z-scores, also called BMI standard deviation scores, are measures of relative weight adjusted for child age and sex. Given a child's age, sex, BMI, and an appropriate reference standard, a BMI Z-score (or its equivalent BMI for age percentile) can be determined. The BMI-Z scores and percentage of 95th percentile will be calculated using an external reference data from the World Health Organization (WHO) and the Centers for Disease Control (CDC). Refer to Section 9.3.3).

8.1.2. Assessment of Waist and Hip Circumference

Participant's waist and hip circumference will be assessed as per the SoA (see Section 1.3).

The waist and hip circumference should be measured twice and rounded to the nearest 0.5 cm or 0.2 inches. The measurements should be performed in the following order: hip, waist, hip, waist. Both measurements will be recorded in the eCRF. If the difference between the 2 measurements exceeds 1 cm or 0.4 inches, this set of measurements should be discarded and the 2 measurements should be repeated. Whenever possible, the same study staff member should perform the measurement for a given participant to minimize variability.

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.

Waist and hip circumference should be measured when participants are in the fasting state and approximately at the same time at each visit. Participants should wear light clothing and must empty their bladder prior to the assessment.

Waist and hip circumference (cm or inches, 1 decimal) will be measured with a tape measure in a standing position. The guidelines listed below should be followed for measuring the waist and hip circumference:

- Make sure tape is horizontal around the waist (and just above the hip bones)
- Keep the tape snug, but not compressing the skin
- Measure just after breathing out.

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

The waist circumference should be measured twice and rounded to the nearest 0.5 cm or 0.2 inches. The measuring tape should be removed between the 2 measurements. Both measurements will be recorded in the eCRF. If the difference between the 2 measurements exceeds 1 cm or 0.4 inches, this set of measurements should be discarded and the 2 measurements should be repeated. Whenever possible, the same study staff member should perform the measurement for a given participant to minimize variability. Waist circumference should be measured when participants are in the fasting state and approximately at the same time at each visit. Participants should wear light clothing and must empty their bladder prior to the assessment.

8.1.3. Assessment of Body Composition by Dual Energy X-ray Absorptiometry

Assessment of body composition by dual energy X-ray absorptiometry (DEXA) will be performed as per the SoA (see Section 1.3).

If particpants are extremely overweight and cannot undergo assessment in the available DEXA scanner due to their body size exceeding practical limits, the sponsor will be exempted from performing DEXA measurements for these participants. Once the patient's body size becomes suitable for measurement using the DEXA machine, DEXA assessments will be conducted for the relevant visit starting from that point.

8.1.4. Hunger Questions

Participants ≥12 years of age who are able to validly and reliably self-report will be administered "Hunger Questions for Participants ≥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 participants 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 at least 4 of 7 consecutive days during the Screening Period (before the enrollment visit) and for at least 4 of the 7 consecutive days before

each scheduled trial visit detailed in the SoA (Section 1.3). The Hunger Questions should be completed before dosing and before the morning meal (fasted).

8.1.5. Patient Global Impression of Severity and Change (PGI-S, PGI-C)

The global hunger questions are comprised of 2 parts: the Patient Global Impression of Severity (PGIS) and the Patient Global Impression of Change (PGIC). Both questions have a recall period of 7 days.

For participants who can self-report, the Global Hunger Questions for Patients ≥12 Years of Age will be used.

For participants who are unable to self-report, the Caregiver Reported Global Hunger Questions (comprised of the Caregiver Global Impression of Severity [CGIS] and Caregiver Global Impression of Change [CGIC]) will be used.

Only the PGIS/CGIS is administered at baseline and both parts (PGIS/PGIC and CGIS/CGIC) are administered thereafter per the SoA.

During the trial, these questions should be completed before dosing and at home.

8.1.6. Symptoms of Hyperphagia

Participants ≥12 years of age who are able to self-report will be administered the Symptoms of Hyperphagia: Patient© Version. The questionnaire consists of 4 items related to the frequency of a patient's hunger symptoms on a scale (Never, 1 or 2 times, 3 or more times) over the past 24 hours. The questionnaire is scored using a composite score across the 4 items.

Caregivers of participants who cannot self-report will be administered the Symptoms of Hyperphagia: Caregiver© Version. This questionnaire consists of 5 items that include caregivers assessing the frequency of hunger symptoms on a scale (Never, 1 or 2 times, or 3 or more times) over the past 24 hours for their child/person in their care. The questionnaire is scored using a composite score. This is derived by adding up all item scores and dividing by the total number of items answered.

The Symptoms of Hyperphagia Questionnaire should be completed for at least 4 of 7 consecutive (before the enrollment visit) and for at least 4 of the 7 consecutive days before each scheduled trial visit detailed in the SoA (Section 1.3). This is completed before dosing and before the morning meal.

8.1.7. [redacted]



[redacted]

8.1.8. [redacted]

[redacted]

8.1.9. Chart Review and Diagnostic History

Investigators will be asked by the Sponsor to perform a chart review and a detailed analysis and collection of the clinical history of participants (if available).

If available, the following parameters will be collected:

- Growth charts and/or weight records for age of onset of obesity and weight trajectory.
- Previous records of treatments or interventions for obesity or weight management (e.g., timing, duration, and efficacy; related to lifestyle, behavioral, herbal/supplements, pharmacological, and/or surgical/endoscopic interventions).
- Hunger/hyperphagia history. (Any information pertaining to hunger or hyperphagia that has been previously recorded by a healthcare provider in the medical records or any questionnaires on hunger or hyperphagia completed by the patient or a caregiver and documented in the medical records, will be captured as hunger or hyperphagia history).
- Documentation of hypothalamic injury on radiographic imaging, radiographic imaging reports, and/or other medical documentation, as confirmed by the clinical investigator, at least 6 months before Screening. Hypothalamic Lesion score (Roth 2015) will be noted and collected for each patient when possible.

8.1.10. [redacted]

[redacted]



8.2. Safety Assessments

8.2.1. Physical Examinations

Complete or brief physical examination will be performed as per the SoA (see Section 1.3).

A complete physical examination will include review of peripheral lymph nodes, head, eyes (including conjunctiva), ears, nose, mouth and oropharynx, neck, heart, lungs, abdomen, skin, musculoskeletal including back, extremities, and neurological systems. Height and weight will also be measured and recorded (see Section 8.1).

Significant new findings that begin or worsen after study intervention must be recorded as adverse events in the eCRF. However, an abnormal or clinically significant findings noted at the start of the trial (screening visit) or found as a result of a screening procedure or other trial procedures performed prior to the first dose administration of study intervention will be recorded as medical history, although the findings are identified after informed consent.

A brief physical examination will be a symptom-lead physical examination. Clinical monitoring of adrenal hyper or hypofunction and skin assessment will be conducted during the physical examination at each visit.

8.2.1.1. Skin Assessment

As part of the physical examination at each visit, the investigator will note any significant skin abnormalities and refer the participant to the dermatologist for comprehensive skin assessment, if necessary. Photographs of any nevus or pigmented skin lesions that do not meet the exclusion criteria should be captured. It is also recommended to capture the photographs of lesion progression using standard dermatological procedures or using a hand-held camera to record the changes in skin condition.

8.2.2. Pubertal Development Assessment

Pubertal development assessment will be done as per the SoA (see Section 1.3) for participants who have yet to reach Tanner Staging V.

Tanner staging is not required once the participant reaches Tanner Stage V, as judged by the investigator.

8.2.3. Spectrophotometry

Skin pigmentation levels of all participants will be measured using spectrophotometry as per the SoA (Section 1.3). Spectrophotometry with a narrowband reflectance spectrophotometer (Mexameter MX18) will be performed at 2 sun-exposed areas (forehead and dorsal hand where the left or right side can be used; however, it must be consistent) and 2 sun-protected areas (e.g., gluteus and axilla where the left or right side can be used; however, it must be consistent) by the investigators or the designated site staffs.

8.2.4. Comprehensive Skin Assessment

If an investigator decides at any time to refer a patient to a dermatologist for comprehensive skin assessment, this skin assessment can be done by a dermatologist.

8.2.5. Vital Signs

Body temperature (tympanic), pulse rate, respiratory rate, and blood pressure will be assessed.

Blood pressure and pulse measurements will be assessed in a seated position.

Blood pressure and pulse measurements should be preceded by at least 5 minutes of rest for the participant in a quiet setting without distractions (e.g., television, cell phones).

Vital signs (to be taken before blood collection for laboratory tests) will consist of 1 pulse and 3 blood pressure measurements (3 consecutive blood pressure readings will be recorded at intervals of at least 2 minutes). The average of the 3 blood pressure readings will be recorded.

Any abnormal clinically significant findings noted at the start of the trial (screening visit) or found as a result of a screening procedure or other trial procedures performed prior to the first dose administration of study intervention should be recorded as medical history. Significant new findings that begin or worsen after study intervention must be recorded as AEs in the eCRF.

8.2.6. Electrocardiograms

A standard 12-lead ECG will be recorded locally at the study sites after 5 minutes of rest in a supine position, as outlined in the SoA (see Section 1.3). The investigator (or designee) will interpret the ECGs using the following categories: within normal limits, abnormal but not clinically significant, or abnormal with clinical significance. The following parameters will be recorded from the participant's ECG trace as calculated by the machine algorithm: heart rate, QT interval, PR interval, QRS interval, RR interval, and QTc using the Fridericia correction (QTcF = QT ÷ cube root of the R-R interval [where R-R is the duration of the entire cardiac cycle]). Refer to Section 7.1.2 for QTc withdrawal criteria.

Any abnormal findings must be evaluated for clinical significance by the investigator. The investigator must report/record any clinically significant abnormal findings occurring during the study as an AE. An abnormal or clinically significant findings noted at the start of the trial (screening visit) or found as a result of a screening procedure or other trial procedures performed prior to the first dose administration of study intervention will be recorded as medical history. Significant new findings that begin or worsen after study intervention must be recorded as adverse events in the eCRF.

8.2.7. Clinical Laboratory Tests

See Section 10.2 for the list of clinical laboratory tests to be performed and the SoA (Section 1.3) for the timing and frequency. Clinical laboratory tests will be performed by the central laboratory. In case of unforeseen circumstances or regional/national emergency (e.g., COVID-19 pandemic), and upon Sponsor approval local laboratories may be considered for performing the tests.

The investigator must review the laboratory report, document this review, and report/record any clinically significant changes occurring during the study as an AE. The laboratory reports must be filed with the source documents.

Abnormal laboratory findings associated with the underlying disease are not considered clinically significant unless judged by the investigator to be more severe than expected for the participant's condition.

An abnormal or clinically significant findings noted at the start of the trial (screening visit) or found as a result of a screening procedure or other trial procedures performed prior to the first dose administration of study intervention will be recorded as medical history. Significant new findings that begin or worsen must be recorded as adverse events in the eCRF.

All protocol-required laboratory tests, as defined in Section 10.2, must be conducted in accordance with the laboratory manual and the SoA (Section 1.3).

If laboratory values from non-protocol-specified laboratory tests performed at the institution's local laboratory require a change in participant management or are considered clinically significant by the investigator (e.g., SAE or AE or dose modification), then the results must be recorded.

8.2.8. Pregnancy and Contraception

Women of childbearing potential (WOCBP) defined as fertile, following menarche and until becoming post-menopausal unless permanently sterile (hysterectomy, bilateral salpingectomy, or bilateral oophorectomy) should only be included after a confirmed menstrual period and a negative highly sensitive serum pregnancy test at Screening and urine pregnancy test at Visit 1 (prior to the first dose administration of study intervention).

Additional pregnancy testing should be performed as per the SoA (Section 1.3).

Urine pregnancy testing will be performed at site using the test kit provided by the central laboratory and in accordance with instructions provided in its package insert. Serum pregnancy testing will be performed by the central laboratory.

For WOBCP childbearing potential, a highly effective form of contraception (as defined in the Inclusion Criteria, (Section 5.1) must be used/practiced throughout the trial and for 90 days following the trial.

- Combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation (oral, intravaginal, or transdermal)
- Progestin-only hormonal contraception associated with inhibition of ovulation (oral, implantable, or injectable)

- IUD
- Intrauterine hormone-releasing system
- Bilateral tubal occlusion
- Vasectomy/vasectomized partner (provided that the vasectomized partner is the sole sexual partner of the female participant, and the vasectomized partner has received medical assessment of surgical success)
- Sexual abstinence, only if it is the preferred and usual lifestyle of the patient

Female participants of non-childbearing potential, defined as: permanently sterile (status post hysterectomy, bilateral oophorectomy, or bilateral salpingectomy), or postmenopausal for at least 12 months (and confirmed with a screening follicle-stimulating hormone level in the post-menopausal lab range) do not require contraception during the trial. Younger female participants who have not achieved sexual maturity at trial entry will be assessed for Tanner Staging and required to comply with contraception requirements at first menarche.

Females with tertiary and/or secondary hypogonadism on hormonal replacement therapy for this condition and not receiving fertility treatment (ovarian stimulation) do not meet the criteria of WOCBP, unless otherwise determined by the Investigator.

Male participants with female partners of childbearing potential must agree to use a highly effective method of contraception if they become sexually active during the trial or within 90 days following their participation in the trial. Male participants must also not donate sperm during and for 90 days following their participation in the trial.

If a pregnancy should occur while a male or female patient is on trial treatment, relevant pregnancies will be followed up on to determine birth and neonatal outcomes.

Males with tertiary and/or secondary hypogonadism on hormonal replacement therapy are not considered fertile and do not need to comply with contraception requirements, unless otherwise determined by the Investigator.

8.2.9. Depression, Suicidal Ideation and Behavior Risk Monitoring

Participants being treated with LB54640 should be monitored appropriately and observed closely for suicidal ideation and behavior (SIB), depression, or any other unusual changes in behavior.

Suicidal ideation and depression will be monitored during the study using PHQ-9/PHQ-A and C-SSRS questionnaires and by assessment of AEs. All factors contributing to SIB should be evaluated and consideration should be given to discontinuation of the study intervention at the discretion of the investigator.

When informed consent or assent has been given, families and parents/guardian of participants being treated with LB54640 should be alerted about the need to monitor participants for the emergence of unusual changes in behavior, as well as the emergence of SIB and to report such symptoms immediately to the study investigator.

Participants will be referred to a mental health provider (MHP) and an AE should be recorded, if in the opinion of the investigator, it is necessary for the safety of the participant, or if the participant reports any of the following:

- A PHQ-9/PHQ-A score ≥10 or
- Any suicidal behavior or
- Any suicidal ideation of type 4 or type 5 on any C-SSRS assessment.

In participants with cognitive impairment, mental health assessment may be limited. Self-reported measures may be administered by either a caregiver or study staff, if needed, and an instrument may be skipped if it is not appropriate or cannot be effectively administered to an individual. Any change from the intended mode of administration or any skipped instrument should be documented.

To be eligible for the trial, a patient cannot have:

- a suicidal ideation of type 4 or 5 at Screening, a suicide attempt during the patient's lifetime, or any suicidal behavior in the last month.
- A PHQ 9/PHQ A score >15 at Screening.

8.2.9.1. Suicide Depression Assessment Using C-SSRS

The C-SSRS is designed to: 1) provide definitions of SIB and nonsuicidal self-injurious behavior and corresponding probes, 2) quantify the full spectrum of suicidal ideation and suicidal behavior and gauge their severity over specified periods, 3) distinguish suicidal behavior and nonsuicidal self-injurious behavior, and 4) employ a user-friendly format that allows integration of information from multiple sources (e.g., direct patient interview, family and other interviews, and medical records) (Posner 2011).

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 nonsuicidal 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 (Posner 2011).

The Investigator or designee will complete the C-SSRS as per the SoA (see Section 1.3).

8.2.9.2. Suicide Depression Assessment Using PHQ-9 or PHQ-A

The PHQ-9 is a 9-item, multipurpose instrument for screening, diagnosing, monitoring, and measuring the severity of depression. The PHQ-9 is the depression module, which scores each of the 9 Diagnostic and Statistical Manual Fourth Edition (DSM-IV) criteria as "0" (not at all) to "3" (nearly every day). The PHQ-A is a modification of the PHQ-9 for adolescents.

The PHQ-A will be administered to participants 12 to <18 years of age and the PHQ-9 will be administered to participants ≥18 years of age as per the SoA (see Section 1.3). After the patient has completed the PHQ-9 or PHQ-A questionnaire, it is scored by the trial staff.

In order to be eligible for the trial, the patient must have a Screening PHQ-9/PHQ-A score <15. If at any time during the trial an individual patient's PHQ-A or PHQ-9 score is ≥10, an AE should be recorded, and the patient should be referred to an MHP.

8.2.10. Telephone Visit

The participant will perform a telephone visit in Week 3.

For the telephone visit, the site will need to contact the participant by phone.

The site should guide the participant through the adverse events and concomitant medication information obtained from the participant during the telephone call so that it can be recorded in the medication diary, and the participant should complete the medication diary with the adverse events and concomitant medication information experienced. If a participant experiences an adverse event, an unscheduled visit can be conducted if deemed appropriate by the Investigator.

8.3. Adverse Events, Serious Adverse Events, and Other Safety Reporting

The definitions of AEs and SAEs can be found in Section 10.3.

AEs will be reported by the participant (or, when appropriate, by a parents/guardian, surrogate, or the participant's LAR).

The investigator and any qualified designee are responsible for detecting, documenting, and recording events that meet the definition of an AE or SAE and remain responsible for following up all AEs.

The method of recording, evaluating, and assessing causality of AEs and SAEs and the procedures for completing and transmitting SAE reports are provided in Section 10.3.

8.3.1. Time Period and Frequency for Collecting AE and SAE Information

All AEs, including SAEs, will be collected from the signing of the ICF until the final study visit as specified in the SoA (Section 1.3).

All SAEs will be recorded and reported to the Sponsor or designee within 24 hours of the investigator's awareness of the event, as indicated in Section 10.3. The investigator will submit any updated SAE data within 24 hours of awareness of the updated information to the Sponsor or designee.

Investigators are not obligated to actively seek information on AEs or SAEs after conclusion of the study participation. However, if the investigator learns of any SAE, including a death, at any time after a participant has been discharged from the study, and he/she considers the event/cause of death to be reasonably related to the study intervention or study participation, the investigator must promptly notify the Sponsor or designee.

The method of recording, evaluating, and assessing causality of AE and SAE and the procedures for completing and transmitting safety reports are provided in Section 10.3.

8.3.2. Method of Detecting AEs and SAEs

Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and nonleading verbal questioning of the participant/LAR is the preferred method to inquire about AE occurrences.

8.3.3. Follow-up of AEs and SAEs

After the initial AE/SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts. All SAEs will be followed until resolution, stabilization, the event is otherwise explained, or the participant is lost to follow-up (as defined in Section 7.3). Further information on follow-up procedures is provided in Section 10.3.

8.3.4. Regulatory Reporting Requirements for SAEs

Prompt notification by the investigator to the Sponsor for applicable regulatory reporting of an SAE is essential so that legal obligations and ethical responsibilities toward the safety of participants and the safety of a study intervention under clinical investigation are met.

The Sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. The Sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, IRBs/IECs, and investigators.

An investigator who receives an IND safety report describing an SAE or other specific safety information (e.g., summary or listing of SAEs) from the Sponsor will review and then file it along with the IB and will notify the IRB/IEC, if appropriate according to local requirements.

IND safety reports must be prepared for suspected unexpected serious adverse reactions (SUSARs) according to local regulatory requirements, and Sponsor policy and forwarded to investigators as necessary.

8.3.5. Pregnancy

Details of all pregnancies in female participants and female partners of male participants will be collected after the start of study intervention and until 90 days after the last administration of study intervention (see Section 5.1).

If a pregnancy is reported, the investigator will record pregnancy information on the appropriate form and submit it to the Sponsor or designee within 24 hours of learning of the female participant or female partner of male participant (after obtaining the necessary signed informed consent from the female partner) pregnancy and should follow the procedures outlined in Section 10.4.

While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy for medical reasons will be reported as an AE or SAE.

If the outcome of the pregnancy meets the criteria for immediate classification as an SAE (i.e. spontaneous abortion, stillbirth, neonatal death, or congenital anomaly [including that in an aborted fetus, stillbirth, or neonatal death]), the investigator will report according to the SAE reporting procedures described in Section 10.3.

The participant/pregnant female partner will be followed to determine the outcome of the pregnancy (see Section 10.4). The investigator will collect follow-up information on the participant/pregnant female partner and the neonate and the information will be forwarded to the Sponsor or designee.

Any poststudy pregnancy-related SAE considered reasonably related to the study intervention by the investigator will be reported to the Sponsor as described in Section 8.3.4. While the investigator is not obligated to actively seek this information in former study participants/pregnant female partner, he or she may learn of an SAE through spontaneous reporting.

Any female participant who becomes pregnant while participating in the study will discontinue study intervention and will be followed up for safety.

8.3.6. Adverse Events of Special Interest

AESIs are events of scientific and medical interest specific to the further understanding of the safety profile of the study treatment. For this study, AESIs are:

- Skin pigmentation
- Adrenal adverse events

Skin pigmentation and adrenal related AEs will be monitored as AESIs. As part of the physical examination at each visit, the investigator will note any significant skin abnormalities and refer the participant to the dermatologist, as needed.

For adrenal AE, clinical monitoring of adrenal hyper- or hypofunction will be conducted through history evaluation and physical examination on a regular basis throughout the study. Participants who are currently on hydrocortisone or other medications, the doses will be closely monitored as concomitant medications. In the clinical laboratory test, serum potassium and sodium level will be continuously monitored which can be altered by adrenal hyper- or hypofunction.

All AESIs will be recorded in the eCRF. An AESI can be serious or non-serious and will be reported as detailed in Section 10.3.

8.4. Pharmacokinetics

8.4.1. Collection of Samples

Venous blood samples of approximately 4 mL will be collected for measurement of plasma concentrations of LB54640 as per the SoA (see Section 1.3). Blood samples will be taken either by direct venipuncture (any suitable vein) or an indwelling cannula inserted in a vein (depending on the time point). The actual date and time (24-hour clock time) of each sample, and the reason for any samples not collected, will be recorded in the eCRF. The date and time (24-hour clock time) of the last LB54640 administration prior to collecting the blood samples will be recorded in the eCRF as well.

Instructions for the collection and handling of biological samples, including details for sample collection, labeling, shipping and storage will be provided in a Laboratory Manual.

8.4.2. Determination of Drug Concentration

Samples for the determination of LB54640 concentrations in plasma will be analyzed at a central laboratory using appropriate validated bioanalytical methods. Full details of the bioanalytical methods will be described in a separate Bioanalytical Report.

8.4.3. Calculation of Derivation of Pharmacokinetic Variables

Pharmacokinetic parameters will be derived using noncompartmental methods with Phoenix® WinNonlin® Version 8.1 or higher (Certata, LP Princeton, New Jersey, USA) and/or SAS® Version 9.4 or higher (SAS Institute, Inc., Cary, North Carolina, USA). Actual elapsed time from dosing will be used for the final plasma PK parameter calculations.

Table 5: Pharmacokinetic Parameters

Pharmacokinetic Parameter	Definition
C_{max}	Maximum concentration, obtained directly from the observed concentration versus time data.
T_{max}	Time to C_{max}.
C_{trough}	Trough plasma concentration at Weeks 1, 2, 6, 10 and 14
AUC_{0-t}	Area under the plasma concentration-time curve from time zero to the time of the last quantifiable concentration, calculated by linear up/log down trapezoidal summation.

8.5. Pharmacodynamics

Blood samples for analyses of PD assessments [redacted] will be collected as per the SoA (see Section 1.3) and tested for the purpose of this study.

Instructions for sample collection, processing, shipment, and storage will be provided in the Laboratory Manual. All samples will be taken before dosing.

8.5.1. [redacted]

[redacted]

8.5.2. [redacted]

[redacted]

8.6. Genetics

Genetics are not evaluated in this study.

8.7. Biomarkers

Biomarkers are not evaluated in this study.

8.8. Immunogenicity Assessments

Immunogenicity assessments are not evaluated in this study.

9. STATISTICAL CONSIDERATIONS

The statistical analysis plan (SAP) will be finalized prior to the database lock of the double-blind treatment phase and will include a more technical and detailed description of the statistical analyses described in this section. This section is a summary of the planned statistical analyses of the most important endpoints including primary and key secondary endpoints. Additional analysis details on the other assessments will be described in the SAP.

9.1. Statistical Hypotheses

No formal statistical hypotheses will be established.

9.1.1. Multiplicity Adjustment

Not applicable.

9.2. Analysis Sets

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.

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.

Safety Analysis set: The Safety set will include all randomized participants who received at least 1 dose of study treatment.

Pharmacokinetics 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.

Unless specified otherwise, efficacy will be assessed using the mITT set and the PP set. The Safety set will be used for all safety analyses.

9.3. Statistical Analyses

9.3.1. General Considerations

Data collected in this study will be presented using summary tables, subject data listings and figures. For continuous variables this means calculation of the number of observations, mean, standard deviation, median, minimum, and maximum. Categorical variables will be summarized by subject counts and percentages. For longitudinal efficacy endpoints, individual participant scatter and line plot will be utilized to present observations in time.

For efficacy related endpoints, the last value obtained prior to randomization in the double-blind treatment phase will be considered the baseline value for statistical analyses unless otherwise stated.

For those who enter the open-label extension phase, an additional baseline will be defined as the last measurement prior to receiving study treatment in the open-label extension phase. The treatment arms based on the treatments assigned in the double-blind treatment phase will be used to perform efficacy analyses of the extended follow-up.

All statistical tests will be performed with two-sided 90% confidence interval (CI) and 10% of two-sided type I error.

Missing weight will be imputed using a multiple imputation method. Details of multiple imputation methods will be described in the SAP. 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.

9.3.2. Primary Endpoint Analysis

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 analysis for the mean percentage change in BMI obtained at the 14-week visit will be conducted using an analysis of covariance (ANCOVA) with treatment cohort as a factor and baseline BMI as covariate and adjusted by a stratification factor of age group (≥18 years old vs <18 years old) as appropriate. The p-value and two-sided 90% CI will be provided for pairwise comparisons between each dose cohort and placebo.

For sensitivity analysis, the LOCF method will be used for missing data imputation.

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, and the interactions of treatment by-visit as fixed factors. The covariance structure to model the within-subject errors will be unstructured. 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. Appropriate non-parametric tests may be conducted as additional sensitivity analysis if the assumptions of analysis model are not met.

9.3.3. Secondary Endpoints Analyses

The ANCOVA model will be used to analyze the continuous outcomes. Each model will include treatment cohort and corresponding baseline value for the dependent value. The MMRM analysis will also be performed where applicable. The mixed effect model will include treatment cohort, corresponding baseline value for the dependent variable, and the interactions of treatment by-visit as fixed factors. The covariance structure to model the within-subject errors will be unstructured.

Summary statistics for categorical measures (including categorized continuous measures) will include sample size, frequency, and percentages, if necessary. Fisher’s exact test will be used to examine the treatment difference in categorical outcomes.

For participants with age <18 years, the following 2 additional BMI values will be calculated:

- The BMI Z-scores will be calculated based on the Lambda Mu and Sigma method (LMS) method following the 2007 WHO reference (WHO 2007a; WHO 2007b).
- The BMI values will be expressed as a percentage of the (gender- and age-specific) 95th percentile following the 2000 CDC BMI-for-Age Growth Charts form.

In addition to conducting by-cohort analyses, the active dose cohorts will also be combined for an assessment of the long-term efficacy of LB54640.

For the PK and safety related endpoints, see Sections 9.3.5 and 9.3.6, respectively.

9.3.4. [redacted]

[redacted]

9.3.5. Pharmacokinetic/Pharmacodynamic Analyses

Plasma LB54640 concentrations will be listed for all participants in the PK Analysis Set. Summaries of plasma LB54640 concentrations and derived PK parameters will be based on the PK Analysis Set.

Plasma LB54640 concentrations will be listed and summarized using descriptive statistics by treatment cohort and nominal PK sampling time point. All plasma LB54640 concentrations that are below the limit of quantification will be labeled as such in the concentration data listings.

Individual and arithmetic mean (per treatment) plasma concentration-time profiles will also be presented graphically.

Pharmacokinetic parameters of plasma LB54640 will be listed and summarized by treatment cohort using descriptive statistics.

[redacted]

9.3.6. Safety Analyses

All safety analyses will be performed on the Safety Analysis Set. All TEAEs. Adverse Events

Adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA®). Treatment-emergent adverse events (TEAEs) are AEs with onset or worsening after the start of study intervention. The AE summaries will be primarily based on TEAEs. The number and percentage of participants with TEAEs will be summarized by system organ class, and preferred term for all TEAEs, treatment-related TEAEs, SAEs, serious TEAEs, severe TEAEs, TEAEs of special interest, and all TEAEs leading to study intervention discontinuation. All TEAEs will be further summarized by maximum severity.

All AEs will be presented in a by-participant listing. SAEs, AESIs, AEs leading to study intervention discontinuation and AEs leading to death will be presented in separate listings.

Clinical Laboratory Tests

All laboratory data will be presented in the listings. A by-participant listing will also be provided for participants with abnormal laboratory results.

12-Lead Electrocardiogram

All ECG data will be presented in listings.

Vital Signs

All vital signs data will be presented in listings.

The analysis of all other safety endpoints will be detailed in the SAP.

9.3.7. Other Analyses

All collected data that were not defined as endpoints will be summarized by descriptive statistics and listed.

Additional exploratory data analyses may be conducted as deemed appropriate.

9.4. Interim Analysis

The interim analysis will be the primary analysis for optimal dose selection for Phase 3. The interim analysis will be performed when all subjects have completed assessments for the 14-week double-blind treatment phase or discontinued prior to Week 14. All planned analysis using endpoints within Week 14 will be done at the interim analysis. The final analysis will be conducted at the end of the open-label extension phase and a clinical study report (CSR) will be written and submitted in accordance with local regulations per current ICH E3 Guidelines.

9.5. Sample Size Determination

A total of 28 participants (7 participants per treatment cohort) will be enrolled. The sample size is determined based on clinical considerations rather than statistical considerations.

10. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1. Appendix 1: Regulatory, Ethical, and Study Oversight Considerations

10.1.1. Regulatory and Ethical Considerations

This study will be conducted in accordance with the protocol and with the following:

- Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences international ethical guidelines
- Applicable ICH GCP guidelines
- Applicable laws and regulations.

The protocol, protocol amendments, ICF, IB, and other relevant documents (e.g., advertisements) must be submitted to an IRB/IEC by the investigator and reviewed and approved by the IRB/IEC before the study is initiated.

Any amendments to the protocol will require IRB/IEC approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.

Protocols and any substantial amendments to the protocol will require health authority approval prior to initiation except for changes necessary to eliminate an immediate hazard to study participants.

The investigator will be responsible for the following:

- Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC
- Notifying the IRB/IEC of SAEs, or other significant safety findings as required by IRB/IEC procedures
- Providing oversight of the conduct of the study at the study site and adherence to requirements of 21 Code of Federal Regulations (CFR), ICH guidelines, the IRB/IEC, European regulation 536/2014 for clinical studies (if applicable), European Medical Device Regulation 2017/745 for clinical device research (if applicable), and all other applicable local regulations.

After reading the protocol, each investigator will sign the protocol signature page and send a copy of the signed page to the Sponsor or representative. The study will not start at any study site at which the investigator has not signed the protocol.

10.1.2. Adequate Resources

The investigator is responsible for supervising any individual or party to whom the investigator delegates study-related duties and functions conducted at the study site.

If the investigator/institution retains the services of any individual or party to perform study-related duties and functions, the investigator/institution should ensure this individual or party is qualified to perform those study-related duties and functions and should implement procedures to ensure the integrity of the study-related duties and functions performed and any data generated.

10.1.3. Financial Disclosure

Investigators and sub-investigators will provide the Sponsor with sufficient, accurate financial information as requested to allow the Sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study.

10.1.4. Insurance

The Sponsor has obtained liability insurance, which covers this study as required by local law and/or national regulations and/or ICH guidelines, whichever is applicable. The terms of the insurance will be kept in the study files.

10.1.5. Informed Consent Process

It is the responsibility of the investigator or his/her representative to explain the nature of the study, including the risks and benefits, to the participant or their LAR (defined as an individual or juridical or other body authorized under applicable law to consent, on behalf of a prospective participant, to the participant's participation in the clinical study) and answer all questions regarding the study, by making use of the IRB/IEC approved informed consent document(s), including the objective and procedures of the study and the possible risks involved before inclusion in the study. In obtaining and documenting informed consent, the investigator or his/her designee must comply with applicable regulatory requirements and should adhere to ICH GCP. Prior to the beginning of the trial, the investigator or his/her designee should have the IRB's written approval for the protocol and the written ICFs and any other written information to be provided to the participants. Participants will be asked to read and review IRB-approved ICFs and other written information.

Participants must be informed that their participation is voluntary (including consent for the use and disclosure of research-related health information). Participants or their LARs will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, privacy, and data protection requirements, where applicable, and the IRB/IEC or study site. For the participants below 18 years of age, the informed consent will be signed by participant's parent/guardian and the assent form will be signed by the participants. The consent must be obtained prior to performing any study-related procedures that are not part of normal patient care, including screening and changes in medications as well as any washout of medications.

The medical record must include a statement that written informed consent was obtained before the participant was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.

Participants must be reconsented to the most current version of the ICF(s) during their participation in the study. The ICF should include detailed description of study procedures, risk

and benefits, directions, participant's rights, compensation if applicable, and contact of Human Patient Protection Services.

A copy of the ICF(s)/assent form must be provided to the participant or their LAR.

A participant who is rescreened is not required to sign another ICF if the rescreening occurs within 60 days from the previous ICF signature date.

10.1.6. Data Protection

- Participants will be assigned a unique identifier by the Sponsor. Any participant records or datasets that are transferred to the Sponsor will contain the identifier only; participant names or any information which would make the participant identifiable will not be transferred.
- The participant must be informed that his/her personal study-related data will be used by the Sponsor in accordance with local data protection law. The level of disclosure must also be explained to the participant who will be required to give consent for their data to be used as described in the informed consent.
- The participant must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the Sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.
- The ICF will incorporate (or, in some cases, be accompanied by a separate document incorporating) wording that complies with relevant data protection and privacy legislation.
- The Sponsor or its representative will not provide individual genotype results to participants, any insurance company, any employer, their family members, general physician, or any other third party, unless required to do so by law.
- Extra precautions are taken to preserve confidentiality and prevent data being linked to the identity of the participant. In exceptional circumstances, however, certain individuals might see the personal identifiers of a participant. For example, in the case of a medical emergency, the Sponsor or representative physician or an investigator might know a participant's identity and also have access to his or her data. Also, regulatory authorities may require access to the relevant files.
- Storage and use of biological samples (as applicable) will be in accordance with the General Data Protection Regulation.

10.1.7. Committees Structure

10.1.7.1. Independent Data Monitoring Committee

An independent data monitoring committee (IDMC) will perform a periodic safety review. The IDMC will include a pediatric endocrinologist who specializes in treating participants with obesity related to the MC4R pathway and a statistician. Further details will be described in the IDMC charter.

10.1.8. Dissemination of Clinical Study Data

All clinical trial information shall be recorded, processed, handled, and stored by the Sponsor or investigator, as applicable, in such a way that it can be accurately reported, interpreted, and verified while the confidentiality of records and the personal data of the participants remain protected in accordance with the applicable law on personal data protection.

The study may be registered on publicly accessible websites (e.g., ClinicalTrials.gov) according to applicable law, regulation and guidance, after discussion with the sponsor. It shall be accompanied by a summary written in a manner that is understandable to laypersons.

10.1.9. Data Quality Assurance

- All participant data relating to the study will be recorded on printed or electronic CRFs unless transmitted to the Sponsor or designee electronically (e.g., laboratory data). The investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.
- Guidance on completion of CRFs will be provided in the electronic Trial Master File.
- The investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.
- Quality tolerance limits will be predefined in the Risk Management Tracker to identify systematic issues that can impact participant safety and/or reliability of study results. These predefined parameters will be monitored during the study, and important deviations from the quality tolerance limits and remedial actions taken will be summarized in the clinical study report.
- Monitoring details describing strategy, including definition of study critical data items and processes (e.g., risk-based initiatives in operations and quality such as risk management and mitigation strategies and analytical risk-based monitoring), methods, responsibilities, and requirements, including handling of noncompliance issues and monitoring techniques (central, remote, or onsite monitoring) are provided in the monitoring plan.
- Details of study monitoring, including action required due to SARS-CoV-2 (COVID-19), will be included in a separate Study Monitoring Plan.
- The Sponsor or designee is responsible for the data management of this study, including quality checking of the data.
- The Sponsor assumes accountability for actions delegated to other individuals (e.g., contract research organizations).
- Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the investigator for 15 years after study completion unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the Sponsor. No records may be transferred to another location or party without written notification to the Sponsor.

10.1.10. Source Documents

The investigator/institution should maintain adequate and accurate source documents and study records that include all pertinent observations on each of the study site's participants.

Source data should be attributable, legible, contemporaneous, original, accurate, and complete. Changes to source data should be traceable, should not obscure the original entry, and should be explained if necessary (e.g., via an audit trail).

Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the investigator's site.

Data reported on the CRF or entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.

Definition of what constitutes source data, and its origin can be found in monitoring guidelines.

The investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.

Study monitors will perform ongoing source data verification to confirm that data entered into the CRF by authorized study site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.

10.1.11. Study and Site Start and Closure

First Act of Recruitment

The study start date is the date on which the clinical study will be open for recruitment of participants.

The first act of recruitment is the first study site open and will be the study start date.

Study/Site Termination

The Sponsor or designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the Sponsor. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study site closure visit has been performed.

The investigator may initiate study site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a study site by the Sponsor or investigator may include but are not limited to:

For study termination:

- Discontinuation of further study intervention development.

For study site termination:

- Failure of the investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the Sponsor's procedures, or GCP guidelines
- Inadequate or no recruitment (evaluated after a reasonable amount of time) of participants by the investigator

If the study is prematurely terminated or suspended, the Sponsor shall promptly inform the investigators, the IECs/IRBs, the regulatory authorities, and any contract research organization(s) used in the study of the reason for termination or suspension, as specified by the applicable regulatory requirements. The investigator shall promptly inform the participant and should assure appropriate participant therapy and/or follow-up.

In the event of a regional or national emergency (e.g., SARS-CoV-2 infection outbreak) that makes it not feasible for mandatory site visits to continue, the affected site(s) may be temporarily closed for visits, after the approval of the Sponsor. During the discontinuation period, remote checks (e.g., telephone calls) will take the place of site visits per the SoA (see Section 1.3). The Sponsor will also determine if treatment with study intervention can be resumed.

10.1.12. Publication Policy

The data generated by this study are confidential information of the Sponsor. The Sponsor will make the results of the study publicly available. The publication policy with respect to the investigator and study site will be set forth in the Clinical Trial Agreement.

The results of this study may be published or presented at scientific meetings. If this is foreseen, the investigator agrees to submit all manuscripts or abstracts to the Sponsor before submission. This allows the Sponsor to protect proprietary information and to provide comments.

The Sponsor will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the Sponsor will generally support publication of multicenter studies only in their entirety and not as individual study site data. In this case, a coordinating investigator will be designated by mutual agreement.

Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

10.2. Appendix 2: Clinical Laboratory Tests

The tests detailed in Table 7 will be performed by the central laboratory. Fasting samples (8-hour minimum) are required at all timepoints, where feasible.

In case of regional/national emergency (e.g., COVID-19 pandemic), local laboratories may be considered for performing the tests.

Protocol-specific requirements for inclusion or exclusion of participants are detailed in Section 4.5 of the protocol.

Additional tests may be performed at any time during the study as determined necessary by the investigator or required by local regulations.

Table 6: Protocol-required Safety Laboratory Tests

Laboratory Assessments	Parameters	
Hematology	Platelet count	White blood cell count with differential:
	Red blood cell count	Neutrophils
	Hemoglobin	Lymphocytes
	Hematocrit	Monocytes
	Red blood cell indices:	Eosinophils
	MCV	Basophils
	MCH	MCHC
	%Reticulocytes	
Clinical laboratory[a]	BUN	AST
	Creatinine	ALT
	Fasting plasma glucose	ALP
	GGT	Albumin
	Magnesium	Chloride
	Uric acid	Total protein
	Potassium	Phosphorus
	Sodium	Total and direct bilirubin
	Calcium	Creatine kinase
	LDH	
	Carbon dioxide (bicarbonate)	
[redacted]		

Table 6: Protocol-required Safety Laboratory Tests

Laboratory Assessments	Parameters	
Coagulation	INR	APTT
	PT	Thrombin time
	Fibrinogen	
FSH	FSH (Screening only)	
Urinalysis (microscopic analysis)	Leucocytes	Red blood cells
	Protein	pH
	Glucose	Nitrite
	Urobilinogen	Specific gravity
	Ketones	
Thyroid profile	TSH	Free T4
	Total T4	
Pregnancy test	Pregnancy testing will be performed for WOCBP only: urine pregnancy test will be performed using the test kit provided by the central laboratory at all applicable visits (as per SoA), except Screening. At Screening, a serum pregnancy test will be performed. If the result of urine pregnancy test is positive, it must be confirmed with a serum pregnancy test.	
[redacted]		

Abbreviations: ALT = alanine aminotransferase, ALP = alkaline phosphatase, APTT = activated partial thromboplastin time, AST = aspartate aminotransferase, BUN = blood urea nitrogen, CPK = creatine phosphokinase, FSH = follicle stimulating hormone, GGT = gamma glutamyl transferase, [redacted], INR = international normalized ratio, LDH = lactate dehydrogenase, [redacted] MCH = mean corpuscular hemoglobin, MCHC = mean cell hemoglobin concentration, MCV = mean corpuscular volume, PT = prothrombin time, TSH = thyroid stimulating hormone, T4 = thyroxine, WOCBP = women of childbearing potential

[a] Details of liver chemistry stopping criteria are given in Section 7.1.1.

Investigators must document their review of each laboratory safety report.

10.3. Appendix 3: AEs and SAEs: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting for Study Intervention

10.3.1. Definition of AE

AE Definition

- An AE is any undesirable and unintended medical event occurring to a participant in a clinical study and which does not necessarily have a causal relationship with that IMP.

  NOTE: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease (new or exacerbated), whether or not considered related to the study intervention/treatment. Any change in the nature, severity or frequency of a participant's pre-existing condition/symptoms/signs (ie, before signing of ICF) or change in the medical terminology of the pre-existing condition will also be considered as an AE.

Events Meeting the AE Definition

- Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (e.g., ECG, radiological scans, vital signs measurements), including those that worsen in severity and/or frequency from baseline, considered clinically significant in the medical and scientific judgment of the investigator (e.g., not related to progression of underlying disease).
- Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or severity of the condition.
- New condition detected or diagnosed after study intervention administration even though it may have been present before the start of the study.
- Signs, symptoms, or the clinical sequelae of a suspected intervention-intervention interaction.
- Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication. Overdose per se will not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae.
- Lack of efficacy or failure of expected pharmacological action per se will not be reported as an AE or SAE. Such instances will be captured in the efficacy assessments. However, the signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as AE or SAE if they fulfill the definition of an AE or SAE.

Events <u>NOT</u> Meeting the AE Definition

- Any clinically significant abnormal laboratory findings or other abnormal safety assessments that are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition. Medical occurrences at the start of the trial (screening visit) or found as a result of a screening procedure or other trial procedures performed will be recorded as Medical History form via the eCRF.
- The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the participant's condition.
- Medical or surgical procedure (e.g., endoscopy, appendectomy): the condition that leads to the procedure is the AE.
- An elective surgery/procedure scheduled to occur during a study will not be considered an AE if the surgery/procedure is being performed for a pre-existing condition and the surgery/procedure has been pre-planned prior to the first dose administration of study intervention. However, if the pre-existing condition deteriorates unexpectedly during the study (e.g., surgery performed earlier than planned), then the deterioration of the condition for which the elective surgery/procedure is being done will be considered an AE.
- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected prior to the first dose administration of study intervention that do not worsen in severity and/or frequency from baseline.

10.3.2. Definition of SAE

An SAE is defined as any untoward medical occurrence that, at any dose, meets one or more of the criteria listed:

a. Results in death

- For SAEs with the outcome of death, the date and cause of death will be recorded on the appropriate case report form.

b. Is life-threatening

- The term *life-threatening* in the definition of *serious* refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.

c. Requires inpatient hospitalization or prolongation of existing hospitalization

- In general, hospitalization signifies that the participant has been admitted (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether hospitalization occurred or was necessary, the AE should be considered serious.
- Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.

d. Results in persistent or significant disability/incapacity

- The term disability means a substantial disruption of a person's ability to conduct normal life functions.
- This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (e.g., sprained ankle) that may interfere with or prevent everyday life functions but do not constitute a substantial disruption.

e. Is a congenital anomaly/birth defect

- The term congenital anomaly/birth defect means there is suspect that exposure to an IMP prior to conception or during pregnancy may have resulted in an adverse outcome in the child.

f. Other important medical event:

- Medical or scientific judgment should be exercised by the investigator in deciding whether SAE reporting is appropriate in other situations such as significant medical events that may jeopardize the participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious.
  - Examples of such events include invasive or malignant cancers, intensive treatment for allergic bronchospasm, blood dyscrasias, convulsions or development of intervention dependency or intervention abuse.

10.3.3. Recording and Follow-Up of AE and/or SAE

AE and SAE Recording

- When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (eg, hospital progress notes, laboratory reports, and diagnostics reports) related to the event.
- The investigator will then record all relevant AE/SAE information in the eCRF. Each event must be recorded separately. Additionally, any AE which meets serious criteria (Section 10.3.2) must be reported on the paper SAE report form and submitted to the Sponsor or designee within 24 hours of the Investigator's awareness.
- It is **not** acceptable for the investigator to send photocopies of the participant's medical records to the Sponsor or designee in lieu of completion of the applicable/required report form.
- There may be instances when copies of medical records for certain cases are requested by the Sponsor or designee. In this case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission to the Sponsor or designee.
- The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

Assessment of Severity

AE severity will be evaluated by the investigator according to the definitions below using the following guidelines:

- Grade 1: Mild: Asymptomatic or mild symptoms; clinical or diagnostic observations only; no intervention indicated; no disruption to daily activity.
- Grade 2: Moderate: Discomfort sufficient to reduce or affect normal daily activity.
- Grade 3: Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; inability to work or perform normal daily activity.
- Grade 4: Life-threatening consequences; urgent intervention indicated.
- Grade 5: Fatal outcome.

The terms "severe" and "serious" are not synonymous. Severity refers to the severity of an AE; the event itself may be of relatively minor medical significance (such as severe headache without any further findings). Severity and seriousness need to be independently assessed for each AE recorded on the CRF.

Assessment of Causality

- The investigator is obligated to assess the relationship between study intervention and each occurrence of each AE/SAE. The investigator will use clinical judgment to determine the relationship. The following general guidance should be used:
  - **Related:** If the temporal relationship of the clinical event to study intervention makes a causal relationship likely and other drugs, therapeutic interventions or underlying conditions do not provide a sufficient explanation for the observed event
  - **Not related:** If the temporal relationship of the clinical event to study intervention makes a causal relationship unlikely, or other drugs, therapeutic interventions or underlying conditions provide a sufficient explanation for the observed event
- A *related causality assessment* conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.
- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study intervention administration, will be considered and investigated.
- For causality assessments, events assessed as having a reasonable possibility of being related to study intervention will be considered "Related." Events assessed as having no reasonable possibility of being related to study intervention will be considered "Not related."
- The investigator will also consult the IB and/or product information, for marketed products, in his/her assessment.
- For each AE/SAE, the investigator **must** document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.
- There may be situations in which an SAE has occurred and the investigator has minimal information to include in the initial report to the Sponsor or designee. However, it is very important that the investigator always makes an assessment of causality for every event before the initial transmission of the SAE data to the Sponsor or designee.
- The investigator may change his/her opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.

Follow-up of AEs and SAEs

- The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by the Sponsor or designee to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.
- If a participant dies during participation in the study or during a recognized follow-up period, the investigator will provide the Sponsor or designee with a copy of any postmortem findings including histopathology, if requested.
- New or updated information will be recorded in the originally submitted documents.
- The investigator will submit any updated SAE data to the Sponsor or designee within 24 hours of the investigator's awareness of the information.

10.3.4. Reporting of SAEs and Pregnancies

SAE and Pregnancy Reporting to the Sponsor or Designee via Paper SAE Report Form and/or Pregnancy Report Form

- Email transmission of the paper SAE report form and/or pregnancy report form is the preferred method of reporting.
  - In rare circumstances if email is not available, notification by telephone or fax is acceptable. Once email transmission is available, the completed SAE report form and/or pregnancy report form is still required.

SAE and Pregnancy Reporting to the Sponsor or Designee via Paper SAE Report Form and/or Pregnancy Report Form
– Initial notification via telephone does not replace the need for the investigator to complete and sign the SAE CRF pages within the designated reporting time frames. – Contacts for SAE and pregnancy reporting will be provided to sites and included in the Investigator Site File (ISF).

10.4. Appendix 4: Collection of Pregnancy Information

Male participants with partners who become pregnant

- The investigator will attempt to collect pregnancy information on any male participant's female partner who becomes pregnant while the male participant is in this study. This applies only to male participants who receive study intervention.
- After obtaining the necessary signed informed consent from the pregnant female partner directly, the investigator will record pregnancy information on the appropriate form and submit it to the Sponsor or designee within 24 hours of learning of the partner's pregnancy. The female partner will also be followed to determine the outcome of the pregnancy. Information on the status of the mother and child will be forwarded to the Sponsor. Generally, the follow-up will be no longer than 6 to 8 weeks following the estimated delivery date. Any termination of the pregnancy will be reported regardless of fetal status (presence or absence of anomalies) or indication for the procedure.

Female participants who become pregnant

- The investigator will collect pregnancy information on any female participant who becomes pregnant while participating in this study. Information will be recorded on the appropriate form and submitted to the Sponsor or designee within 24 hours of learning of a participant's pregnancy. The participant will be followed to determine the outcome of the pregnancy. The investigator will collect follow-up information on the participant and the neonate and the information will be forwarded to the Sponsor or designee. Generally, follow-up will not be required for longer than 6 to 8 weeks beyond the estimated delivery date. Any termination of pregnancy will be reported, regardless of fetal status (presence or absence of anomalies) or indication for the procedure.
- While pregnancy itself (during maternal or paternal exposure to the study intervention) is not considered to be an AE or SAE, any pregnancy complication will be reported as an AE or SAE. If the outcome of the pregnancy for both mother and fetus meets the criteria for immediate classification as an SAE (ie, spontaneous abortion, stillbirth, neonatal death, or congenital anomaly [including that in an aborted fetus, stillbirth, or neonatal death]), the investigator will report according to the SAE reporting procedures described in Section 10.3.
- Any post-study pregnancy-related SAE considered reasonably related to the study intervention by the investigator will be reported to the Sponsor or designee as described in Section 10.3. While the investigator is not obligated to actively seek this information in former participants, he or she may learn of an SAE through spontaneous reporting.
- Any female participant who becomes pregnant while participating in the study will discontinue study intervention.

10.5. Appendix 6: Abbreviations

Abbreviation	Definition
AE	Adverse event
AESI	Adverse event of special interest
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
AUC_{0-t}	Area under the concentration-time curve from 0 to last quantifiable concentration
BMI	Body Mass Index
CCR_{abw}	Creatine clearance for adjusted body weight
CDC	Centers for Disease Control and Prevention
CFR	Code of Federal Regulations
COVID-19	Coronavirus disease 2019
C_{max}	Maximum observed concentration in plasma
C_{trough}	Trough plasma concentration
CNS	Central nervous system
CRF	Case report form
C-SSRS	Columbia Suicide Severity Rating Scale
CYP	Cytochrome P450
DEXA	Dual energy X-ray absorptiometry
ECG	Electrocardiogram
eCRF	Electronic case report form
eGFR	Estimated glomerular filtration rate
EOLTET	End of long-term extension treatment period
EOT	End of treatment
EOS	End of Study
[redacted]	[redacted]
GCP	Good Clinical Practice
GLP-1	Glucagon-like peptide-1
GI	Gastrointestinal
[redacted]	[redacted]
HIV	Human immunodeficiency virus
HRT	Hormone replacement therapy

Abbreviation	Definition
IB	Investigator's Brochure
ICF	Informed consent form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IDMC	Independent data monitoring committee
IEC	Independent Ethics Committee
IMP	Investigational medicinal product
IRB	Institutional Review Board
IVRS/IWRS	Interactive Voice/Web Response System
[redacted]	[redacted]
LAR	Legally authorized representative
MAD	Multiple ascending dose
MC4R	Melanocortin 4 receptor
MedDRA	Medical Dictionary for Regulatory Activities
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
PD	Pharmacodynamics
[redacted]	[redacted]
PGI-C	Patient Global Impression change
PGI-S	Patient Global Impressions scale
PHQ-9	Patient Health Questionnaire-9
PHQ-A	Patient Health Questionnaire- Adoloescents
PK	Pharmacokinetic
POMC	Pro-opiomelanocortin
QTcF	QT corrected for heart rate by Fridericia's formula
SAD	Single ascending dose
SAE	Serious adverse event
SAP	Statistical analysis plan
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
SD	Standard deviation
SIB	Suicidal ideation and behavior
SoA	Schedule of activities
T_{max}	Time to C_{max}

Abbreviation	Definition
TEAE	Treatment-emergent adverse event
ULN	Upper limit of normal
WHO	World Health Organization
WOCBP	Women of childbearing potential

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