SETMELANOTIDE

RM-493-040

A Phase 3, Double Blind, Randomized, Placebo-Controlled Trial to Evaluate the Efficacy and Safety of Setmelanotide in Patients with Acquired Hypothalamic Obesity

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.

CCI [redacted]

EU Clinical Trial Number. 2022-503116-16-00

Short Title: Phase 3 Trial of Setmelanotide in Acquired Hypothalamic Obesity

Trial Sponsor: Rhythm Pharmaceuticals, Inc.
222 Berkeley Street
12th Floor
Boston, MA 02116

Document Date (Version): 19 December 2024 (Version 6.0)

CONFIDENTIALITY NOTE

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CCI

[redacted]


CCI

APPROVAL SIGNATURE PAGE

Protocol Title:	A Phase 3, Double-Blind, Randomized, Placebo-Controlled Trial to Evaluate the Efficacy and Safety of Setmelanotide in Patients with Acquired Hypothalamic Obesity
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REVIEWED/APPROVED BY:

PPD

Electronically signed by: PPD
Reason: I have reviewed and approve this document.
Date: Dec 20, 2024 13:54 EST

PPD MD, PhD

PPD
Rhythm Pharmaceuticals, Inc.

Signature

Date

INVESTIGATOR STATEMENT

Protocol Title:	A Phase 3, Double-Blind, Randomized, Placebo-Controlled Trial to Evaluate the Efficacy and Safety of Setmelanotide in Patients with Acquired Hypothalamic Obesity
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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 (IB), 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

Investigational site (or name of institution) and location (printed)

1. PROTOCOL SUMMARY

1.1. Synopsis

Name of Sponsor/Company: Rhythm Pharmaceuticals, Inc.	
Name of Investigational Product: Setmelanotide	
Name of Active Ingredient: Setmelanotide (RM-493; Melanocortin-4 Receptor Agonist)	
Title of Trial: A Phase 3, Double-Blind, Randomized, Placebo-controlled Trial to Evaluate the Efficacy and Safety of Setmelanotide in Patients with Acquired Hypothalamic Obesity	
Trial center(s): Up to 35 clinical sites in North America, Europe, United Kingdom, and Japan	
Phase of development: 3	
Objective	**Endpoint**
Primary	
To evaluate the efficacy of setmelanotide on change in body mass index (BMI)	– Mean % change in BMI from Baseline after approximately 52 weeks on a therapeutic regimen of setmelanotide compared to placebo
Key Secondary	
To evaluate the efficacy of setmelanotide on proportion of patients with ≥5% reduction in BMI or ≥0.2-point reduction in BMI Z-score	– The proportion of patients with ≥5% reduction in BMI in adult patients (≥18 years of age), or BMI Z-score reduction of ≥0.2 points in pediatric patients (<18 years of age) from Baseline after approximately 52 weeks on a therapeutic regimen of setmelanotide compared to placebo – The proportion of all patients with ≥5% reduction in BMI from baseline after approximately 52 weeks on a therapeutic regimen of setmelanotide compared to placebo
To evaluate changes in hunger in response to setmelanotide	– Mean change in the weekly average of the daily most hunger score in patients ≥12 years old from Baseline after approximately 52 weeks on a therapeutic regimen of setmelanotide compared to placebo
Secondary	
To evaluate changes in hunger and in symptoms of hyperphagia in response to setmelanotide	– The proportion of patients with a ≥2-point reduction in the weekly average of the daily most hunger score from Baseline after approximately 52 weeks on a therapeutic regimen of setmelanotide compared to placebo

	– Mean change in the weekly average of the Symptoms of Hyperphagia composite score from Baseline after approximately 52 weeks on a therapeutic regimen of setmelanotide compared to placebo
To evaluate changes in additional parameters of body weight	– The proportion of patients with a ≥10% reduction in BMI from Baseline after approximately 52 weeks on a therapeutic regimen of setmelanotide compared to placebo – The proportion of patients with a ≥10% reduction in weight from Baseline after approximately 52 weeks on a therapeutic regimen of setmelanotide compared to placebo – Mean percent change in weight in patients ≥18 years from Baseline after approximately 52 weeks on a therapeutic regimen of setmelanotide compared to placebo – Mean BMI Z-score and BMI percentile reduction in patients <18 years of age from Baseline after approximately 52 weeks on a therapeutic regimen of setmelanotide compared to placebo – The proportion of patients aged ≥4 to <18 years with ≥0.2-point reduction of BMI Z-score from Baseline after approximately 52 weeks on a therapeutic regimen of setmelanotide compared to placebo – The proportion of patients with BMI <30 kg/m^2 (patients aged ≥18 years) or <95th percentile (patients aged <18 years) from Baseline after approximately 52 weeks on a therapeutic regimen of setmelanotide compared to placebo
To evaluate changes in quality of life in response to setmelanotide	– Mean change in physical functioning score and total score for the Impact of Weight on Quality of Life-Lite (IWQOL) (IWQOL-Lite-CT in patients ≥18 years and IWQOL-Kids in patients 11 to <18 years), from Baseline after approximately 52 weeks on a therapeutic regimen of setmelanotide compared to placebo
To evaluate changes in waist circumference following treatment with setmelanotide compared to placebo	– Change in waist circumference from Baseline after approximately 52 weeks on a therapeutic regimen of setmelanotide compared to placebo
To evaluate changes in cardiometabolic parameters following treatment with setmelanotide compared to placebo	– The difference in change in cardiometabolic parameters including BP, CCI [redacted], liver function and CCI [redacted] from Baseline after

	approximately 52 weeks on a therapeutic regimen of setmelanotide compared to placebo
Safety	
To evaluate the safety and tolerability of setmelanotide compared to placebo	– Safety and tolerability assessed by the frequency and severity of adverse events (AEs), AEs of special interest (AESIs), vital signs, and laboratory evaluations from Baseline after approximately 52 weeks on a therapeutic regimen of setmelanotide compared to placebo
To evaluate the effect of setmelanotide on blood pressure (BP)	– Change in ambulatory BP and heart rate (HR) from Baseline after approximately 52 weeks on a therapeutic regimen of setmelanotide compared to placebo

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[redacted]

CCI [redacted]

Design

This is a Phase 3, double-blind, multi-center, placebo-controlled, randomized 2:1 (active to placebo), registrational trial, designed to assess the efficacy and safety of setmelanotide on weight loss and hunger in patients ≥4 years of age with acquired hypothalamic obesity (HO). Approximately 120 patients (at least 12 from sites in Japan) aged 4 years and older are planned to be enrolled at up to 35 clinical sites in North America, Europe, and Japan.

The trial schema is in Figure 1.

CCI [redacted]

Screening

The Screening Period will last up to 8 weeks (from Day -56 to -1 with a minimum of 3 weeks to allow for the completion of all necessary tests and evaluations, including the collection of CCI [redacted] baseline data for 2-3 weeks prior to randomization). Upon providing informed consent, patients will complete all screening procedures as listed in the Schedule of Assessments (SoA) to determine if they meet the study criteria.

At the Screening Visit, all patients will be given and instructed on how to use:

- CCI [redacted]
- a hand-held device for recording daily diary information throughout the study; and
- an ambulatory blood pressure monitor (ABPM) (≥4 years of age, as applicable in North America and Europe. See Section 6.8.2 for patients <12 and regional applicability of assessment). CCI [redacted]

Patients who are determined not to be eligible will be asked to return their devices to the clinic. See Section 6 for instructions on how these data should be collected during the Screening Period.

Treatment Period

To enter the Treatment Period on Day 1 and prior to randomization, the trial center must confirm that patients have completed the Screening assessments, including the e-diary at least 4 of the 7 days prior to the baseline visit. If the e-diary is not appropriately completed before the baseline visit, patients may be asked to complete the e-diary collection and re-schedule randomization and the baseline visit if the remaining visit window allows. Throughout the trial, patients (or caregivers) will need to complete the e-diary entries.

The Treatment Period is intended to last until each patient has been dosed for 52 weeks on a therapeutic regimen (56 weeks to 60 weeks). Trial drug administration details are provided in Section 5.5.3 and

Table 6. During the Treatment Period, patients will attend in-clinic visits and may attend at home tele-health visits at Weeks 8, 16, 20, 28, 36, 44, 52 at the discretion of the investigator. Patients and caregivers will complete the assessments listed in the SoA (Table 1). Detailed assessment information is provided in Section 6.

CCI [redacted]

Assessments

Efficacy:

Height, weight, waist circumference, hunger, symptoms of hyperphagia

Safety:

Vital signs including ABPM (as applicable), physical examinations, complete skin exams, electrocardiograms, clinical laboratory assessments, pharmacokinetics (PK), anti-drug antibodies (ADA), injection site examination, suicidal ideation and depression monitoring, AEs (including changes in concomitant medications)

Other Outcome-Related:

Quality of life (IWQOL-Lite, IWQOL-Kids/Parent Proxy, CCI [redacted]), CCI [redacted], body composition (as applicable at participating US sites).

End of Treatment

The End of Treatment (EOT) visit is the final planned dosing visit. The EOT will occur as an in-person clinic visit after approximately 52 weeks on a therapeutic dose. At the EOT, patients who complete 52 weeks of treatment and complete assessments through the EOT may be eligible to enter an open-label Long-Term Extension (LTE) trial or attend Bridging visits with open-label setmelanotide if the LTE is not yet available. Patients must meet the LTE eligibility criteria and should discuss eligibility with the Investigator.

All patients who discontinue treatment prematurely should attend an Early Termination of Treatment (ETT) Visit as soon as possible after the last dose of trial treatment. Patients who discontinue treatment but remain enrolled in the trial should continue to complete assessments (as Retained Dropouts). These patients will be required to complete the Safety Follow-up Visit (SFV) as applicable, following the ETT (Section 5.1.4). Patients who discontinue treatment prematurely are not eligible to enroll in the optional LTE. Exceptions may be made in consultation with the Sponsor.

Patients who discontinue prematurely and withdraw from the trial will not be required to complete the SFV following the ETT.

If the ETT Visit occurs 4 weeks or later following the last dose of trial treatment, then the ETT Visit will replace the SFV if no AEs are being monitored.

CCI [redacted]

Safety Follow-up Visit

An SFV will occur as an in-person visit 14 days (±4 days) after the last dose of trial treatment. The SFV is not required for patients who complete the treatment period and either:

- enroll in the LTE study (or bridging visits if the LTE is not yet available) or transition to another qualified Rhythm study (e.g., managed access)
- transition to a commercially available Rhythm MC4R agonist regimen

Post-treatment Follow-up and Bridging Visits

Patients who complete 52 weeks of treatment on a therapeutic regimen and remain enrolled are eligible to participate in the LTE trial. If the LTE is not yet available and the patient continues to meet inclusion/exclusion criteria, patients may initiate open-label setmelanotide via Bridging visits that occur in clinic every 12 weeks and last until either the LTE or a post-trial access program is available, commercial drug is available in the region, or the trial ends. Additional visits may be scheduled at the discretion of the Investigator. Since the patient's initial assignment to either setmelanotide or placebo will continue to be blinded to all parties, open-label dosing in Bridging visits will follow the setmelanotide dosing schedule outlined in Section 5.5.3.

CCI [redacted]

Completion of Trial Participation

Completion of trial participation for an individual patient is defined as 1 of the following:

- For patients who receive the last planned dose of trial treatment at the EOT and enroll in the LTE (or Bridging visits) or transition to either commercial drug or a post-trial access program: the EOT Visit
- For patients in bridging visits or who have transitioned from bridging visits to commercial drug or a post-trial access program: the last Bridging visit
- For patients who complete trial treatment through the EOT and do not enroll in the LTE, bridging visits, or transition to either commercial drug or a post-trial access program: the SFV
- For patients who prematurely discontinue trial treatment and complete some trial assessments but do not withdraw consent (and assent, as applicable): the latest of the EOT, ETT Visit, or SFV (if required)
- For patients who withdraw consent or assent: date of withdrawal of consent or assent (ETT Visit)

CCI [redacted]

The end of the trial overall is defined in Section 5.3.

Number of patients (planned):

Approximately 120 patients (at least 12 from sites in Japan) are planned to be enrolled and randomized (2:1 ratio, active: placebo) with stratification by age group (≥18 years old, ≥12 and <18 years old, <12 years old) and subpopulation (Japanese vs non-Japanese).

CCI [redacted]

CCI [redacted]

Diagnosis and main criteria for inclusion and exclusion

Patients must meet all of the Inclusion and none of the Exclusion Criteria to be eligible for trial participation.

Inclusion criteria are detailed in Section 4.1 and Exclusion Criteria are detailed in Section 4.2.

CCI [redacted]

Investigational product, dosage, and mode of administration:

Investigational product: Setmelanotide, 10 mg/mL in a sterile solution for injection

Dosage: CCI [redacted] See Section 5.5.3.

Mode of administration: Subcutaneous injection (SC)

Reference therapy, dosage, and mode of administration:

Reference product: Placebo (vehicle) in a sterile solution for injection.

Dosage: Placebo QD (escalated in the same manner as active treatment)

Mode of administration: SC injection.

Duration of treatment:

Patients will receive trial treatment (setmelanotide or placebo, per randomization) for 52 weeks on a therapeutic regimen (up to approximately 60 weeks).

CCI [redacted]

Statistical methods:

The primary objective of this trial is to evaluate the percent change in BMI in response to setmelanotide administered SC daily in patients with acquired HO compared to placebo at the end of the placebo-controlled trial. To evaluate the primary objective, the primary statistical hypothesis is that the percent reduction of BMI from baseline after ~52 weeks of treatment on a therapeutic regimen in the setmelanotide group is greater than that in the placebo group in the modified Intention-to-treat set (mITT), which is defined as all randomized patients exposed to at least one dose of trial treatment.

The sample size is mainly driven by the primary hypothesis with the safety database taken into consideration. The planned sample size of ~120 patients includes the planned enrollment of 12 patients from sites in Japan (~80 patients in setmelanotide group vs ~40 patients in placebo group). The trial provides ~99.5% power to detect a treatment difference (treatment - placebo) of -10% in percent change of BMI from baseline after ~52 weeks of treatment on a therapeutic regimen at 2-sided alpha of 0.05. It assumes a common standard deviation of 10% (estimated from trial RM-493-030), a dropout rate of 20%, and 2:1 randomization.

An analysis of covariance (ANCOVA) model, with an unequal variance to account for possible unequal residual variances, will be used for the primary analysis on the primary endpoint, adjusted with stratification factors of age groups (≥18 years old, ≥12 and <18 years old, <12 years old) and subpopulation (Japanese vs non-Japanese). The primary analysis will be conducted based on the mITT population and sensitivity analysis based on Per-protocol (PP) may be conducted as appropriate.

A primary efficacy analysis cohort is defined as the first 120 patients who complete the EOT visit. The primary efficacy analysis will be based on all patients who have completed the trial and any patients who discontinued after receiving their first dose. For patients already enrolled who are still progressing in the study (in any region), missing values will be imputed using multiple imputation. Following ICH E9 (R1) guidance, the primary analysis will be based on treatment policy estimand approach.

The primary analysis model will adjust the stratification factors of age group (≥18 years old, ≥12 and <18 years old, <12 years old) and subpopulation (Japanese/non-Japanese). In order to ensure integrity of the study at the site level, investigators and patients will remain blinded after the unblinding of the sponsor for the primary analysis. Study site personnel will be instructed on the method for breaking the blind. The blinding/unblinding methods will be detailed in a separate Blinding/Unblinding Plan. A supplemental analysis will be performed after all patients have completed the study, as supportive information.

Adverse events/serious adverse events (SAEs) will be summarized with frequencies and percentages by treatment group and overall. A by-patient AE data listing including onset and resolution dates, verbatim term, preferred term, treatment, severity, relationship to treatment, action taken, and outcome will be provided. Safety data including laboratory evaluations and vital signs assessments will be summarized by time of collection. In addition, change from baseline to any post-dose values will be summarized for vital signs and clinical laboratory results. Frequency of patients with abnormal safety laboratory results will be tabulated. Safety analysis will be conducted based on a Safety Analysis Set.

CCI [redacted]

1.2. Schedule of Assessments

Table 1: Schedule of Assessments

Trial Period/ Procedure*	**Screening**	**Treatment Period**															**EOT†† (after 52 weeks on a therapeutic regimen)**		**ETT**	**SFV[2]**	**Bridging Visits****
Clinic Visit Number		**V1[1]**	**Call**	**V2**	**V3†**	**V4**	**V5†**	**V6†**	**V7**	**V8†**	**V9**	**V10†**	**V11**	**V12†**	**V13**	**V14†**	**V15††**	**V16††**			**Every 12 weeks**
Trial Day	**-56 to -1**	**1**	**8**	**22**	**50**	**78**	**106**	**134**	**162**	**190**	**218**	**246**	**274**	**302**	**330**	**358**	**386**	**414**			
Trial Week	**-8 to -1**	**1**	**2**	**4**	**8**	**12**	**16**	**20**	**24**	**28**	**32**	**36**	**40**	**44**	**48**	**52**	**56**	**60**			
Visit Window (days)	**-**	**-**	**±4**	**±4**	**±4**	**±4**	**±4**	**±4**	**±4**	**±4**	**±4**	**±4**	**±4**	**±4**	**±4**	**±4**	**±4**	**-4 weeks +4 days**		**±4**	**±2 weeks**
Informed consent/assent[3]	X																				
Inclusion/ exclusion criteria review	X	X																			X
Medical history	X	X																			
Diagnostic history[4]	X	X																			
Randomization		X																			
Physical examination[5]	X	X				X							X				*X*††	X	X	X	X
Comprehensive skin examination[6]	X			X													*X*††	X	X		X
Fitzpatrick scale		X																			

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Trial Day	**-56 to -1**	**1**	**8**	**22**	**50**	**78**	**106**	**134**	**162**	**190**	**218**	**246**	**274**	**302**	**330**	**358**	**386**	**414**			
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Visit Window (days)	**-**	**-**	**±4**	**±4**	**±4**	**±4**	**±4**	**±4**	**±4**	**±4**	**±4**	**±4**	**±4**	**±4**	**±4**	**±4**	**±4**	**-4 weeks +4 days**		**±4**	**±2 weeks**
Height[7]	X	X		X	X	X	X	X†	X	X†	X	X†	X	X†	X	X†	X	X	X	X	X
Weight[8]	X	X		X	X	X	X	X†	X	X†	X	X†	X	X†	X	X†	X	X	X	X	X
Waist circumference[9]	X	X		X		X			X			X†			X		*X*††	X	X		X
Vital signs[10]	X	X		X	X	X	X	X†	X	X†	X	X†	X	X†	X	X†	X	X	X	X	X
ECG (12-lead)[11]	X																				
Pregnancy test[12]	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
FSH[13]	X																				
T4, FT4, T3	X																				X[34]
IGF1[14]		X				X			X			X			X		*X*††	X	X		X[34]
Estradiol, Testosterone		X															*X*††	X	X		X[34]
CCI	X	X				X			X								*X*††	X	X		

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Clinic Visit Number		V1[1]	Call	V2	V3†	V4	V5†	V6†	V7	V8†	V9	V10†	V11	V12†	V13	V14†	V15††	V16††			Every 12 weeks
Trial Day	-56 to -1	1	8	22	50	78	106	134	162	190	218	246	274	302	330	358	386	414			
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Visit Window (days)	-	-	±4	±4	±4	±4	±4	±4	±4	±4	±4	±4	±4	±4	±4	±4	±4	-4 weeks +4 days		±4	±2 weeks
Safety laboratory tests[15]	X	X		X		X			X				X				X††	X	X	X	X
CCI	X	X							X								X††	X	X		
Hunger Questions[17]	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
CCI	X	X		X	X	X		X		X		X		X		X	X††	X	X		X
C-SSRS[18]	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
CDI-2[19]	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
PHQ-A **or** PHQ-9[19]	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
CGIS or PGIS[20] (Global Hunger)		X					X				X						X††	X			X
CGIC or PGIC[20] (Global Hunger)									X								X††	X	X		X

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Visit Window (days)	-	-	±4	±4	±4	±4	±4	±4	±4	±4	±4	±4	±4	±4	±4	±4	±4	-4 weeks +4 days		±4	±2 weeks
CCI [redacted]		X				X											X††	X	X		
IWQOL-Lite-CT or IWQOL-Kids (Parent Proxy)[21]		X				X											X††	X	X		X (Week 12, then every 24 weeks)
CCI [redacted]		X							X								X††	X	X		
CCI [redacted]		X							X								X††	X	X		X (Week 12, then every 24 weeks)
CCI [redacted]		X							X								X††	X			
CCI [redacted]		X															X††	X			
PK (trough)[23]		X				X			X								X††	X	X		

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Visit Window (days)	-	-	**±4**	**±4**	**±4**	**±4**	**±4**	**±4**	**±4**	**±4**	**±4**	**±4**	**±4**	**±4**	**±4**	**±4**	**±4**	**-4 weeks +4 days**		**±4**	**±2 weeks**
ADA[23]		X				X			X								X††	X	X	X	X
CCI	X[24]	CCI																			
Telephone call[25]			X																		X[25]
Dispense/ Return study drug[26]		X		X	X	X	X	X	X	X	X	X	X	X	X	X	X††	X	X		X
Study drug administration[27]		Daily																			Daily
Injection site inspection[28]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X††	X	X		X
Drug compliance assessment[29]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X††	X	X		X
Adverse event collection[30]	Continuous from signing of ICF through completion of trial participation																				

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Trial Week	**-8 to -1**	**1**	**2**	**4**	**8**	**12**	**16**	**20**	**24**	**28**	**32**	**36**	**40**	**44**	**48**	**52**	**56**	**60**			
Visit Window (days)	-	-	**±4**	**±4**	**±4**	**±4**	**±4**	**±4**	**±4**	**±4**	**±4**	**±4**	**±4**	**±4**	**±4**	**±4**	**±4**	**-4 weeks +4 days**		**±4**	**±2 weeks**
Concomitant medications review	Continuous from signing of ICF through completion of trial participation																				
ABPM sub-trial[31]	X[31]								X[31]								X[31]††				
CCI [redacted]		X															X††		X		
Informed Consent for CCI [redacted]																	X††				

Abbreviations: ABPM = Ambulatory Blood Pressure Monitoring; ADA = anti-drug antibody; CDI-2 = Children's Depression Inventory-2; C-SSRS = Columbia-Suicide Severity Rating Scale; D = Days; ECG = electrocardiogram; EOT = End of Treatment; CCI [redacted]; ETT = Early Termination of Treatment; CCI [redacted]; FSH = follicle-stimulating hormone; FT4 = free thyroxine; HbA1c = glycated hemoglobin; IGF1 = Insulin-like Growth Factor 1; IWQOL-Lite-CT = Impact of Weight on Quality of Life-Lite Clinical Trials version; LTE = Long-Term Extension; PHQ = Patient Health Questionnaire; PK = pharmacokinetic; SFV = Safety Follow-up Visit; V = Trial Visit Number.

CCI [redacted] See

Appendix 8 for a summary of the Patient and Safety Questionnaires, the timing relative to dosing, the location where the assessment should be conducted, and the method of data collection.

** Patients who complete the EOT Visit and remain enrolled may be eligible to participate in the LTE or open-label Bridging visits (if the LTE is not yet available). Bridging Visits occur at the clinic every 12 weeks (until either the LTE or a post-trial access program is available, commercial drug is available in the region, or the trial ends). Additional visits may be scheduled at the discretion of the Investigator.

† The Week 8, 16, 20, 28, 36, 44, and 52 visits may be scheduled in-clinic or as at home telehealth visits at the discretion of the Investigator. If these visits are conducted as telehealth visits, the following assessments are not required to be collected: height, weight, waist circumference (cm), vital signs. For patients on hormone replacement therapy, one or more of these visits may be required in-person. See Section 6.8.6.

†† The EOT visit occurs after 52 weeks on a therapeutic regimen. CCI [redacted].

1 All patients will initiate setmelanotide at 0.5 mg once daily (QD). The first dose will be administered in clinic. Dose titration will be made per Section 5.5.3.

2 The SFV visit will occur 14 days after the last dose of trial treatment (ETT) for patients who prematurely discontinue. The SFV is not required for patients who complete the EOT Visit and enroll in the optional LTE. For LTE eligibility, see Section 5.1.3.

3 Prior to the initiation of any trial procedures and assessments, signed informed consent and/or assent (as applicable) are required per protocol. A separate informed consent and/or assent (as applicable) will be required CCI [redacted]. Additional considerations for reducing pain in distress in patients younger than 18 years of age are included in Appendix 2.

4 CCI [redacted]

5 A complete physical examination will be conducted at Screening and at the EOT Visit (or at the ETT Visit, as applicable). At other time points, an abbreviated examination will be performed. The abbreviated examination should focus on heart, lungs, skin, and any areas of previous abnormal findings, noting any changes from baseline. In addition, Tanner Staging for assessment of pubertal development will be conducted for those patients who have yet to reach Tanner Stage V. Whenever possible, the same trained health care professional will conduct the exam and Tanner Staging.

6 A comprehensive skin examination will be performed by the Investigator. The skin examination should include a full body (head-to-toe skin examination). If any concerning lesions are identified during Screening, the patient should be referred to a dermatologist. Any concerning lesions will be biopsied by the dermatologist and results must be benign prior to the first dose of setmelanotide. If the pre-treatment biopsy results are of concern, the patient will be excluded from the trial. Additionally, any concerning lesion or change in an existing lesion during the course of the trial must be evaluated by the dermatologist and biopsied, if clinically indicated in the opinion of the dermatologist.

7 For patients ≥21 years of age, height is to be measured at screening only. For patients <21 years of age, height is to be measured at the time points listed in the Schedule of Activities (SoA). Height (cm) will be measured, without shoes, socks, or hats, using a wall-mounted stadiometer. For clinic visits, the stadiometer should be calibrated by site personnel on a daily basis prior to height assessment. All measurements will be done at each time point and recorded to the nearest half cm.

8 Weight (kg) is to be measured at the clinic using the same scale throughout the trial. Weight should be measured after patients have attempted to empty their bladders and after an overnight fasting. Patients are to wear light clothing or underwear and no shoes, with empty pockets, and will be weighed at approximately the same time of day. All measurements will be measured in triplicate and recorded to the nearest 10th of a kg if reported with a digital scale, or half kg with a mechanical scale, and will be measured in triplicate.

9 Waist circumference (cm) should be measured at approximately the same time at each visit. Patients should be standing and in light clothing and have emptied their bladder. Whenever possible, the same trial staff member should perform the measurement for a given patient to minimize variability.

10 All blood pressure (BP) and heart rate (HR) measurements are to be obtained with the patient in the sitting position following at least 5 minutes of rest. All measurements will be taken in triplicate, approximately 2 minutes apart. When possible, BP should be taken in the non-dominant arm throughout the trial, using the same methodology (automated or manual). Body temperature (°C) and respiration rate (breaths/minute) will be obtained in the sitting position following at least 5 minutes of rest. Repeat measures and more frequent monitoring can be implemented for significant increases in BP or HR.

[11] At Screening, a single 12-lead ECG will be performed in the supine position following a period of at least 10 minutes of rest. See Section 6.8.5.

[12] A urine pregnancy test may be performed to expedite availability of results prior to dosing on Day 1. All in-clinic pregnancy tests per SoA will be serum tests; dosing may continue with results pending. At telehealth visits, urine pregnancy tests will be performed using pregnancy test kits. Additional pregnancy tests may be required according to local regulations and/or requirements.

[13] See Section 6.8.6 for FSH screening requirements.

[14] IGF1 labs will be drawn at Baseline and approximately every 3 months for patients taking growth hormones.

[15] Safety laboratory tests will be performed per Section 6.8.6 before the morning meal (fasted).

[16] Blood samples will be collected prior to dose administration for CCI

[17] See Section 6.6.4. Hunger Questionnaires and Symptoms of Hyperphagia Questionnaire will be recorded during the trial using an at-home e-diary as follows: during the Screening Period for 7 consecutive days before the enrollment visit (Day 1) for 7 consecutive days before each scheduled trial visit, scheduled tele-health visit, or at the ETT visit as applicable. These questionnaires should be completed prior to the morning meal (fasted) before dosing and at home using the e-diary. CCI

[18] The Baseline/Screening version of the C-SSRS scale is the initial form of the instrument to assess suicidality in a patient's lifetime and is administered at Screening. In order to be eligible for the trial, a patient at Screening cannot have a suicidal ideation of type 4 or 5, a suicide attempt during the patient's lifetime, or any suicidal behavior in the last month, as per the C-SSRS. After Screening, the 'Since Last Visit' version of the scale will be used to assess suicidality since the patient's last visit. If at any time during the trial a patient has a suicidal ideation of type 4 or 5, or any suicidal behavior, the patient should be referred to a mental health professional (MHP). The C-SSRS should be completed before dosing either in clinic or in the presence of trained nursing or site staff during telehealth visits, as applicable.

[19] The PHQ-A will be administered to patients 11-17 years of age and the PHQ-9 will be administered to patients ≥18 years of age. The CDI-2 will be administered to patients 7 to <12 years of age (self-report short form) and to caregivers of patients 7 to <12 years of age (parent version).
To be eligible for the trial, an individual patient's PHQ-A or PHQ-9 score must be <15 at Screening or a CDI-2 T-score <70. If at any time during the trial an individual patient's PHQ-A or PHQ-9 score is ≥10 or has a CDI-2 T-score ≥65, the patient should be referred to a MHP. See Sections 6.8.10.2 and 6.8.10.3. The PHQ-9/PHQ-A and CDI-2 should be completed before dosing either in clinic or in the presence of trained nursing or site staff during telehealth visits, as applicable.

[20] The Global Hunger Questions for Patients ≥12 Years of Age and can self-report consist of two parts: the Patient Global Impression of Severity (PGIS) and the Patient Global Impression of Change (PGIC). The Caregiver Reported Global Hunger Questions consist of the Caregiver Global Impression of Severity (CGIS) and the Caregiver Global Impression of Change (CGIC) and will be administered to caregivers of patients <12 years of age or to caregivers of patients who are unable to self-report. PGIS/CGIS only is administered at baseline. 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 using the e-diary. For patients who continue to Bridging visits, these questions should be completed at the clinic before dosing and the morning meal. See Section 6.6.4.2.

[21] CCI

[23] Samples for ADA (anti-setmelanotide and anti-αMSH) and PK (trough) will be collected at timepoints per the SoA. All samples should be collected before study drug administration on the day of collection. Patients should be instructed to not administer study drug prior to the clinic visit. Any patient with a positive anti-setmelanotide ADA will be followed every 3 months after the ADA sample analysis until resolution of the ADA.

[24] CCI [redacted]. See Section 6.7.3.

[25] Site personnel will call the patient on Day 8 to confirm the proper dose escalation has occurred and to collect AEs and any changes in concomitant medications. For patients who continue to Bridging visits, a telephone call will be scheduled for the beginning of Week 2 to confirm proper dose escalation. Additional calls to patients may occur throughout dose escalation to a therapeutic regimen. See Section 5.5.3.

[26] Patients/caregivers will return all (the number recorded) used vials to the clinic when they visit, and both clinic-administered study drug as well as outpatient study drug administration will be recorded in a trial e-diary.

[27] Patients/caregivers will draw up and self-administer/administer the drug once daily in the morning beginning the morning of Day 1 and for the duration of dosing. On days with clinic visits, the patients/caregivers will administer the drug in the clinic in the presence of the clinical staff following blood draws, and to assure proper technique.

[28] Injection site evaluations and scoring (by the clinical staff) will include identification and measurement of areas of erythema, edema, and induration, as well as the presence of localized pain, tenderness, and itching. Additional evaluation data can be collected at any visit in which there are injection site reactions, even if not a time point for formal assessment.

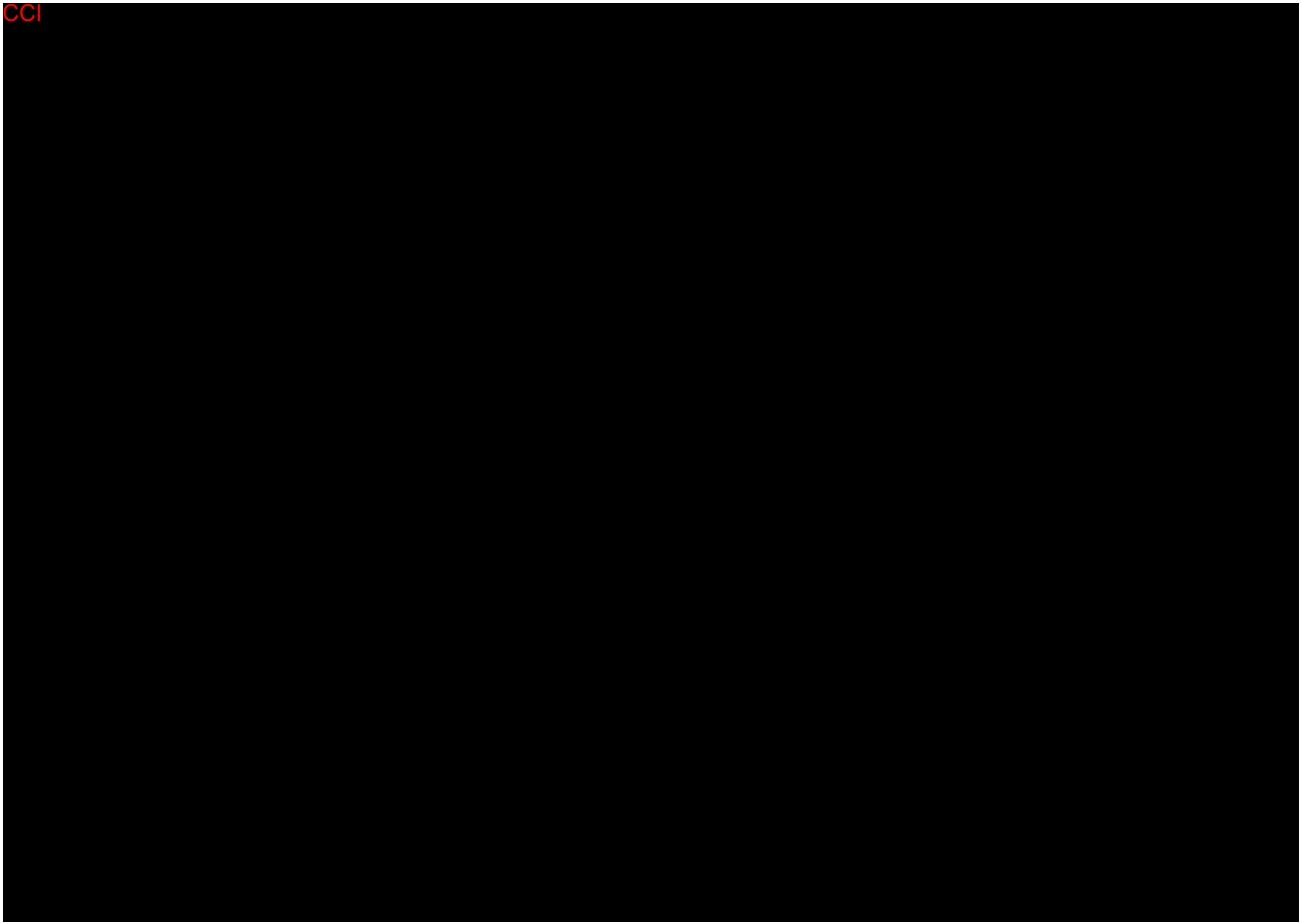
[29] A question querying whether the patient completed their daily injection will be asked via an e-diary. Patients in Bridging visits will record compliance on paper forms.

[30] AEs will be recorded from the time a patient provides informed consent. AEs reported after dosing on Day 1 will be considered TEAEs.

[31] At applicable sites measuring ABPM, this assessment will be conducted outside of the clinic setting in patients ≥4 years of age, (See Section 6.8.2 for patients <12 years of age and regional applicability. ABPM assessments will require wearing the device at each time point for any 24-hour period prior to: the Day 1 Visit (from last day in Screening window), the Week 24 Visit, and the EOT Visit (occurs after 52 weeks on a therapeutic dose). The ABPM device will measure BP (systolic and diastolic) and heart rate (HR) in 30-minute intervals for each 24-hour period. CCI [redacted] arate ICF/Assent for this assessment. A CCI will be taken at the Day 1 Visit. If CCI is not available at the clinic, this procedure may be skipped. If a patient discontinues before the EOT Visit, CCI should be performed at the ETT Visit. See Section 6.7.4.

[33] CCI [redacted]

[34] Lab tests to be conducted only as needed at the discretion of the Investigator.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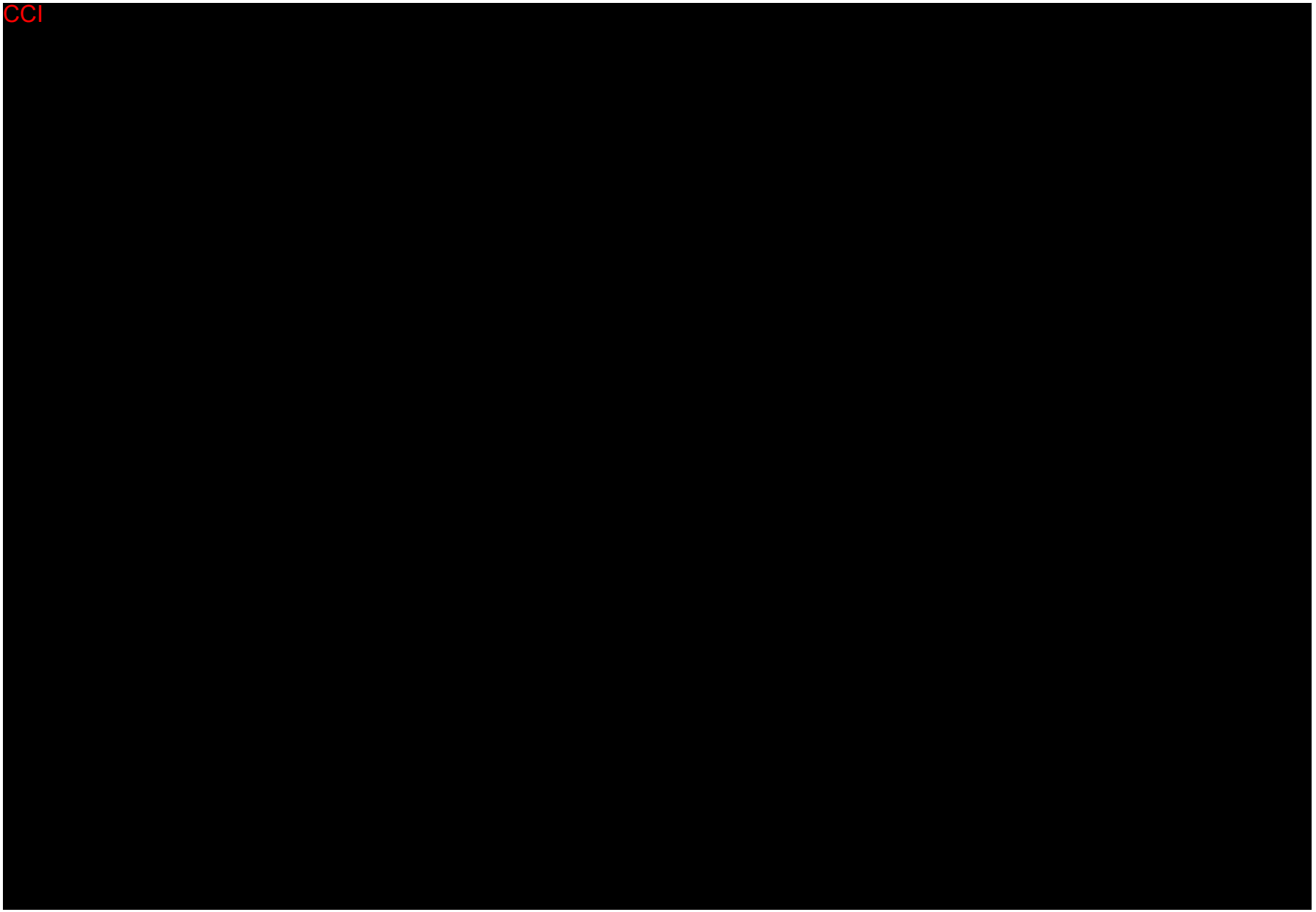
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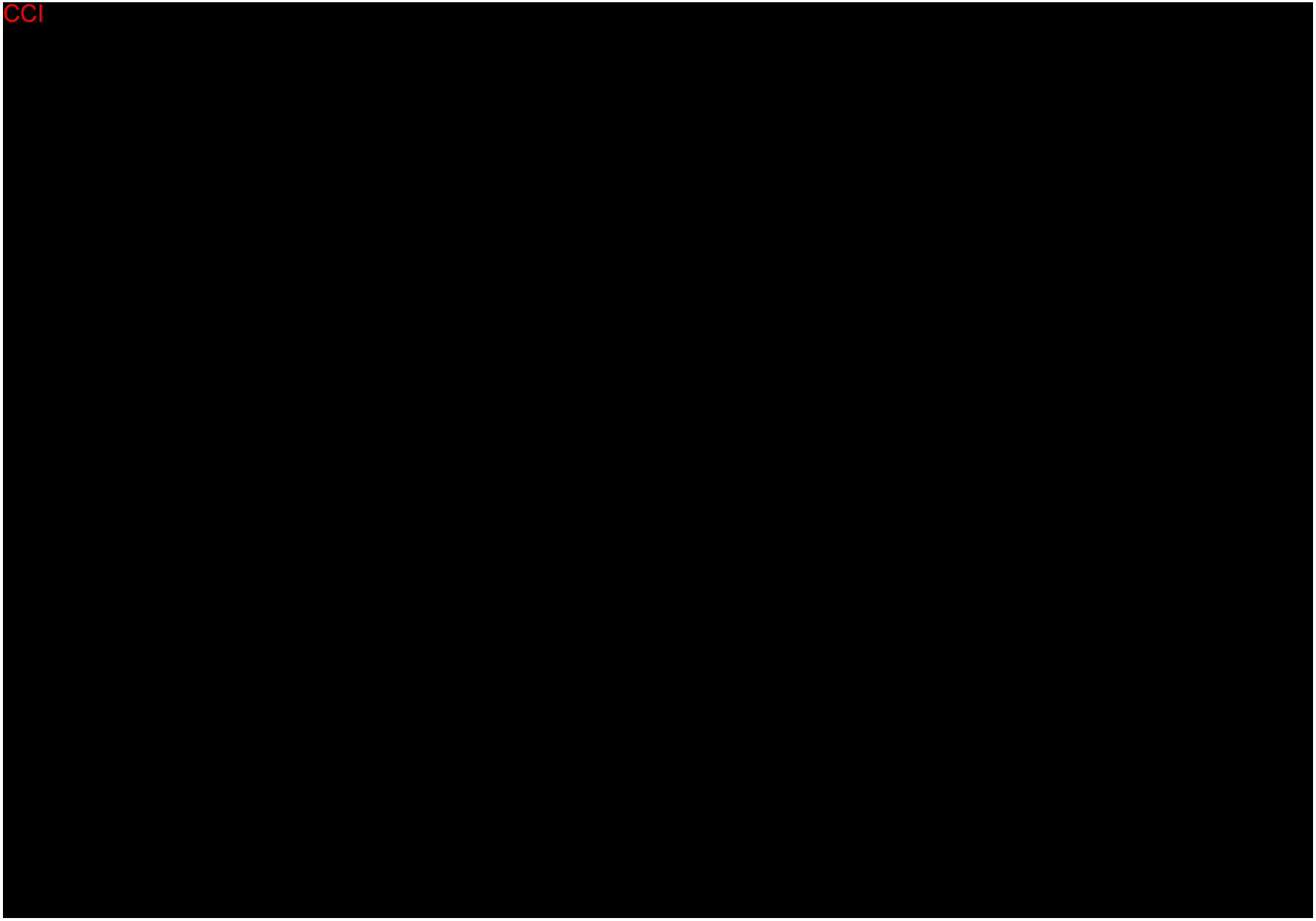
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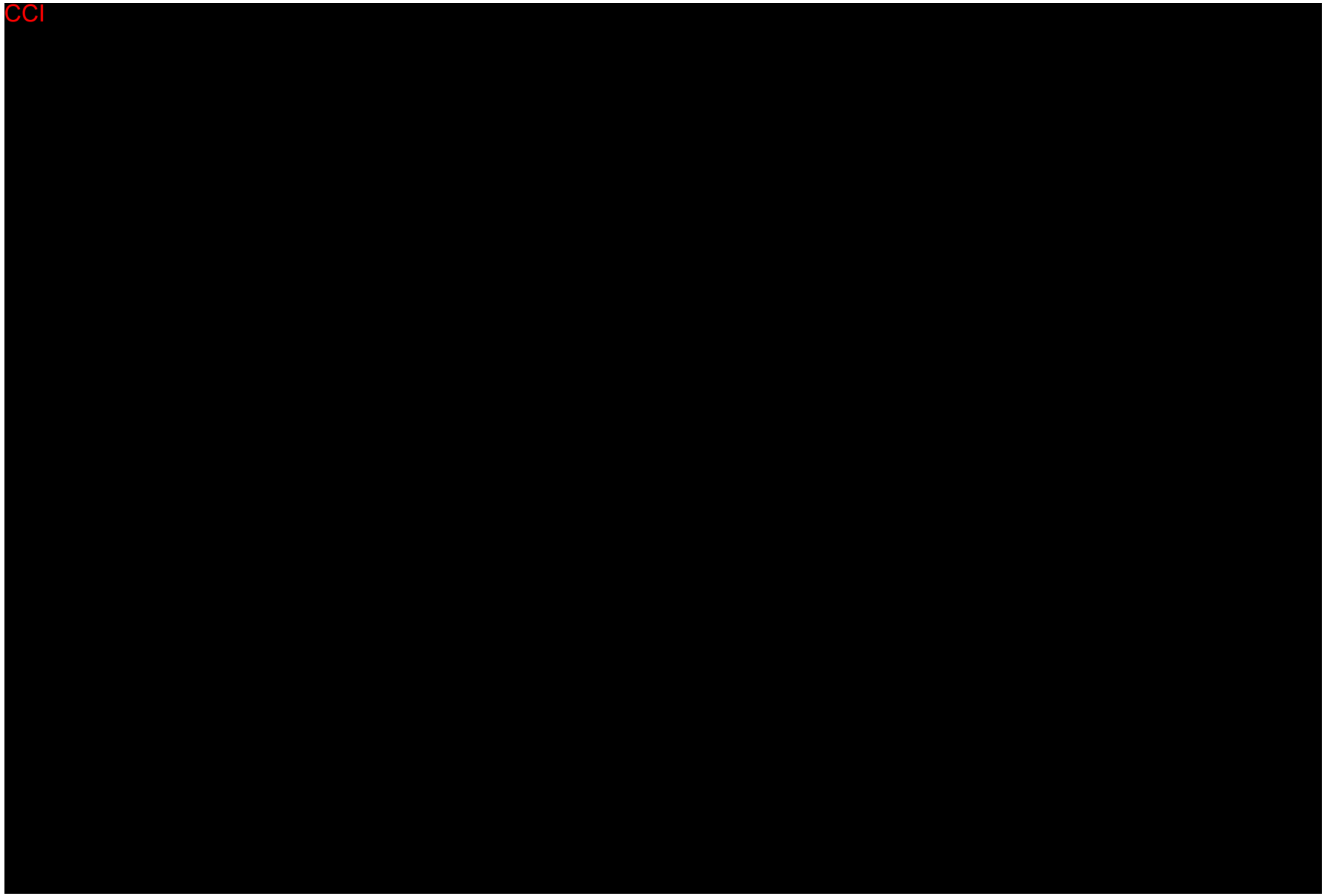
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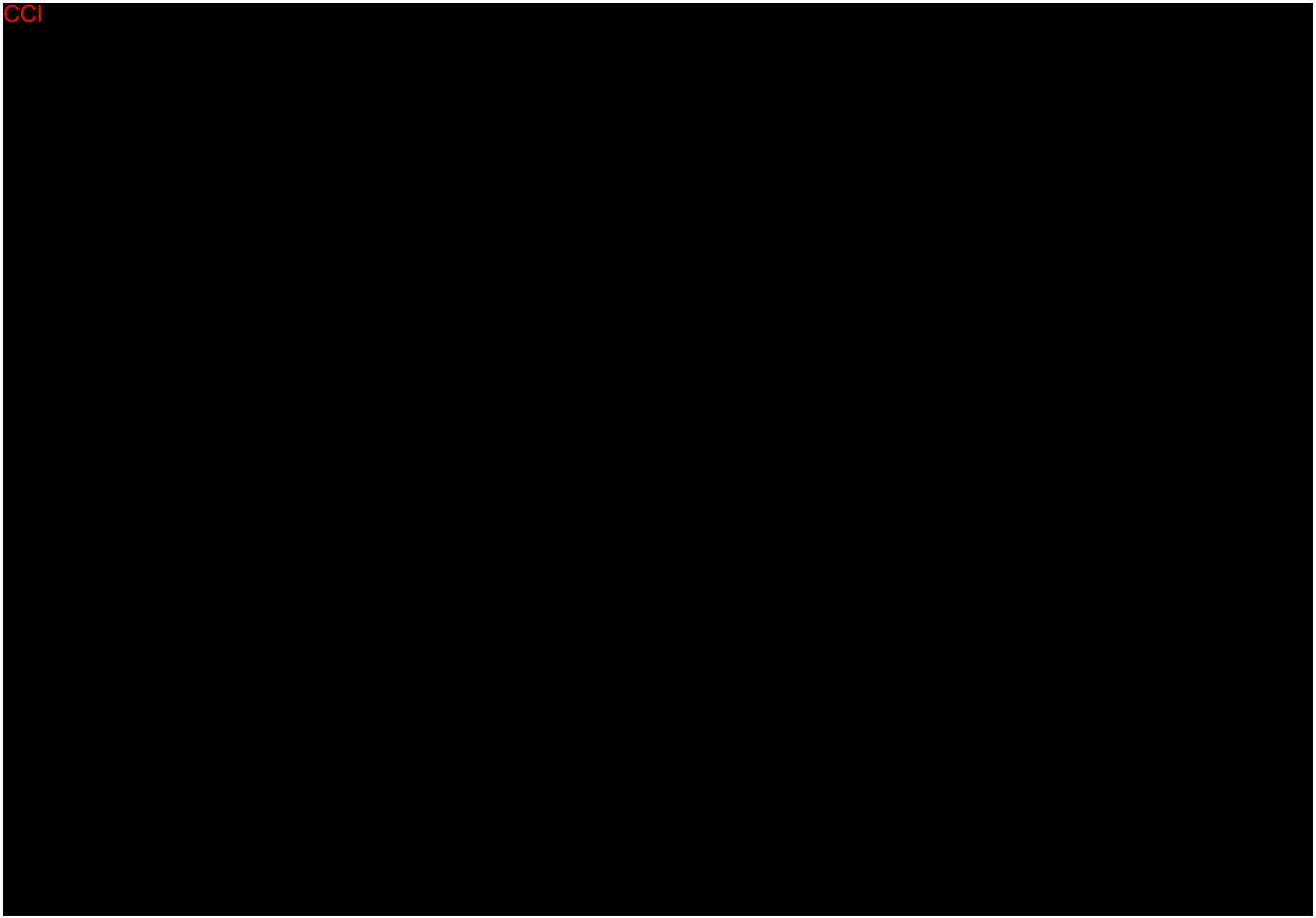
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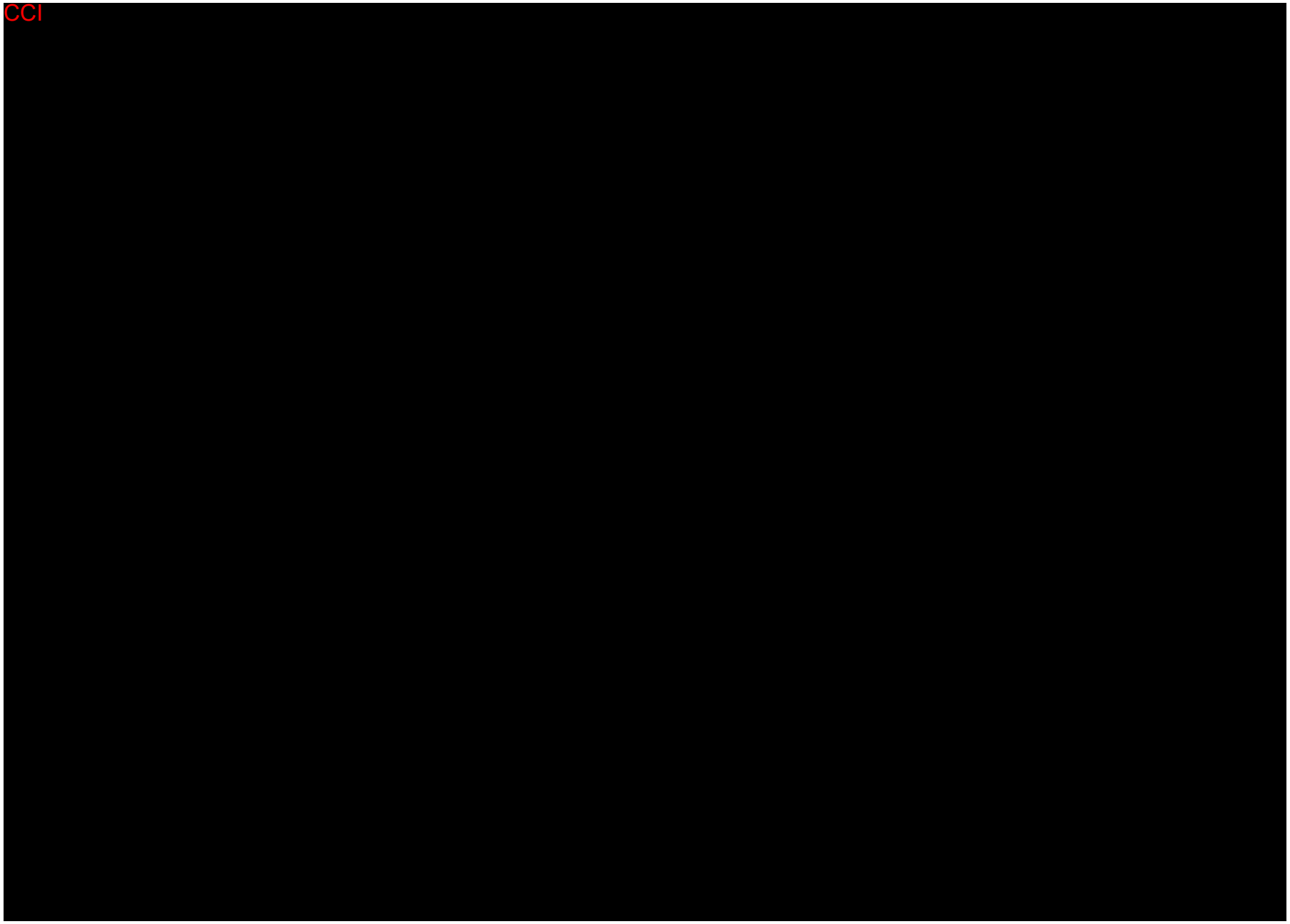

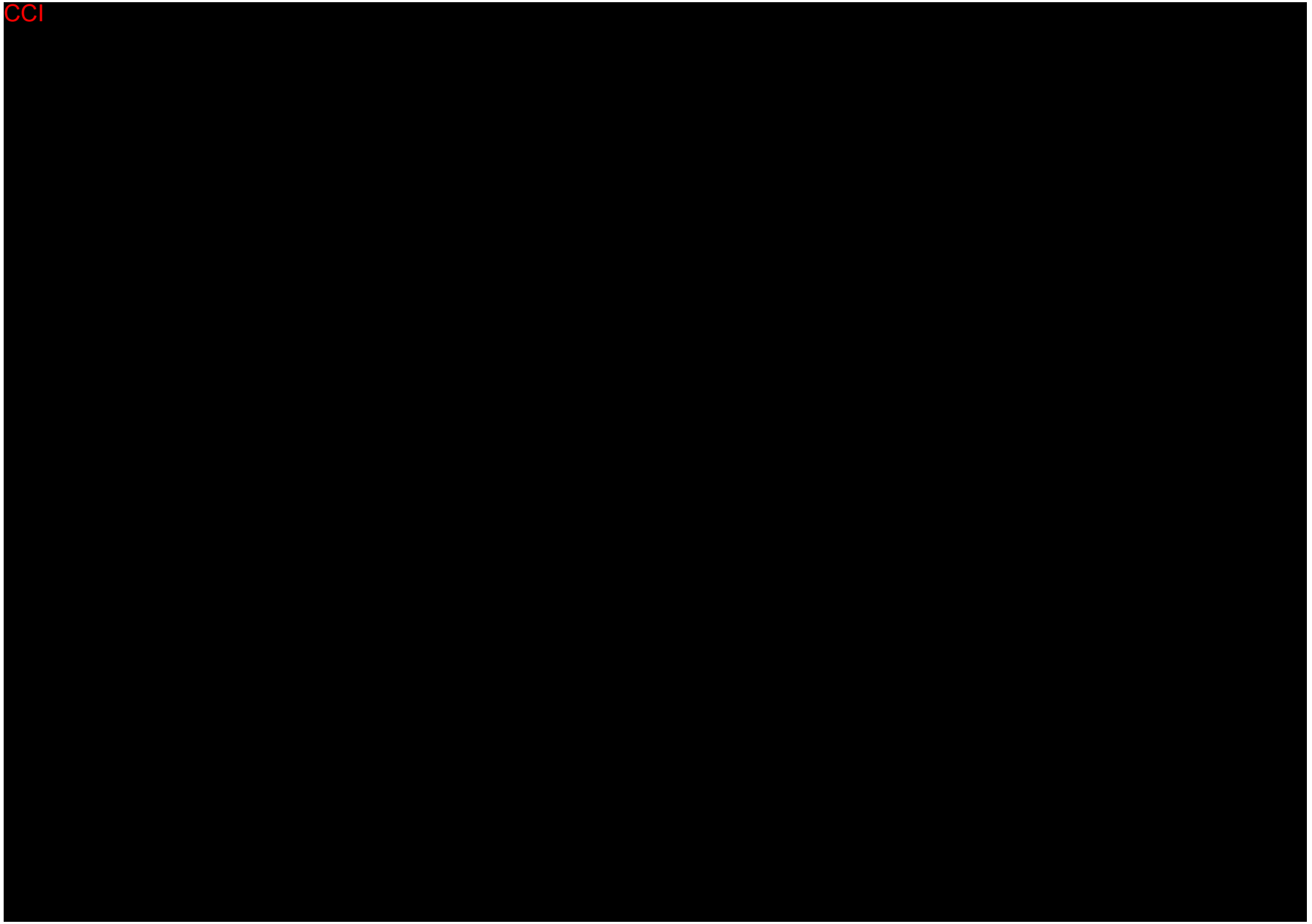
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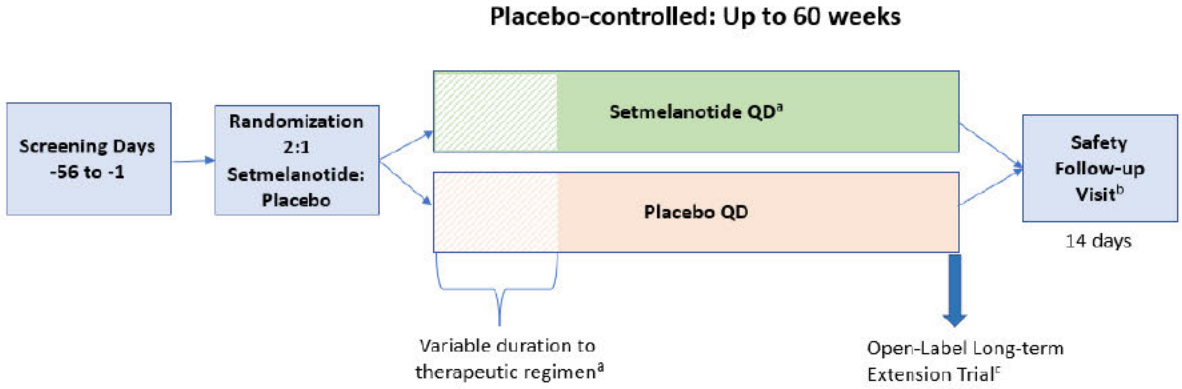
1.3. Schema

Figure 1: Trial Diagram



[redacted] See Section 5.5.3 for dose and escalation scheme [redacted].

[b] The Safety Follow-up Visit (SFV) is only required for patients who prematurely discontinue treatment or for patients who complete the trial and do not enroll in the Long-Term Extension (LTE) or Bridging Visits.

[c] Patients who complete the trial and trial assessments may be eligible to participate in the LTE (or receive open-label setmelanotide and attend Bridging Visits if the LTE is not yet available).

[redacted]

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2. INTRODUCTION

2.1. Background

Hypothalamic obesity (HO) is a severe, devastating disease of obesity that may be either acquired due to injury to the hypothalamus or be part congenital disorder (including early developmental disease) that involves the hypothalamus. Acquired HO affects approximately 5,000 to 10,000 patients in the United States (US) and is believed to have similar incidence and prevalence in the European Union and rest of world (EU; Teng 2021; Roth 2015).

Acquired HO develops after injury to the hypothalamus, most often as a result of a tumor (eg, craniopharyngiomas, gliomas, pituitary adenomas, hamartomas), and/or the surgery or radiation therapy used to treat the tumor (Hochberg 2010). Other much rarer causes of injury include inflammatory conditions involving the hypothalamus such as sarcoidosis or trauma. Craniopharyngiomas represent the most common tumor associated with the development of HO and account for 5% to 15% of pediatric intracranial tumors, and occur with 2 peaks of incidence, one during childhood (10 to 19 years of age [29%]) and the second in adulthood (30 to 49 years of age [25%]) (Muller 2022).

Patients with acquired HO develop an aggressive form of obesity characterized by a high degree of sudden, severe, and sustained weight gain that is generally unresponsive to lifestyle or medical intervention. The weight gain is most dramatic in the first 6-12 months after injury and then continues for the next 8 to 12 years before plateauing (Sterkenburg 2015). Hyperphagia may occur in approximately 50% of patients along with lethargy due to decreased energy expenditure, and psychosocial disorders spanning from depression to aggressive behavior (Muller 2011).

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Central melanocortin signaling has been extensively discussed as the primary element of energy homeostasis (Holland 2019). In patients with hypothalamic lesions or deficiencies, leptin signaling is often disturbed and results in reduced melanocortin signaling. This has been associated with hyperphagia and excessive weight gain. (Enriori 2016; Roth 2010; Roth 1998; Patel 2002; Shaikh 2008). In patients with craniopharyngioma or post-surgical treatment for it, for example, levels of alpha-melanocortin-stimulating hormone (α-MSH) were found to be significantly reduced (Roth 2010; Roth 2011). Reduced serum α-MSH levels suggest melanocortin pathway deficiency, which might explain lower energy expenditure in peripheral tissues due to reduced fat and muscle fatty acid oxidation (Roth 2010; Roth 2011; An 2007).

Setmelanotide, a potent melanocortin 4 receptor (MC4R) agonist, is a synthetic 8 amino acid, cyclic peptide that binds with high affinity to the human MC4R and is efficient in activating MC4R. While not an analog, it retains the specificity and functionality of the naturally occurring pro-opiomelanocortin (POMC)-derived neuropeptide, αMSH, which is the endogenous ligand for the MC4R.

Setmelanotide is authorized for marketing in several regions including the US, UK, Israel, the EU, and Canada. Additional information is available in the current Investigator's Brochure (IB).

Setmelanotide is under continued clinical investigation globally for the treatment of various rare diseases of obesity as well as acquired diseases resulting in obesity such as HO that are demonstrated or hypothesized to impact signaling in the hypothalamic MC4R pathway. There is currently no effective treatment for HO.

2.2. Trial Rationale

Data obtained to date in the setmelanotide clinical program demonstrate robust weight reduction and hunger suppression efficacy in obesity disorders that impact signaling in the leptin-melanocortin pathway, such as POMC deficiency, LEPR deficiency, and BBS, as well as obesity disorders caused by hypothalamic injury such as HO (Phase 2 Trial RM-493-030).

By restoring impaired signaling in this pathway, setmelanotide can serve as an indirect form of replacement therapy for patients with hypothalamic deficiencies (both acquired and congenital) that lead to extreme obesity, with the potential for improvements in body weight and appetite control.

2.3. Benefit/Risk Assessment

Data generated in the Phase 2 proof of concept trial RM-493-030 have indicated a favorable efficacy response profile, specifically in HO patients treated with setmelanotide. Given the observed clinical benefit of setmelanotide in adults and children with HO and a consistent well-understood adverse event (AE) profile, it is considered that setmelanotide will have a positive benefit-risk profile in patients with HO who currently have no other long-term successful therapeutic options. In patients with rare genetic forms of obesity, setmelanotide has been associated with clinically meaningful reductions in weight, improvement in hunger, as well as improvements in quality of life.

Setmelanotide has been well tolerated by patients in clinical studies. The AEs associated with setmelanotide are predictable, well understood, and do not present significant safety concerns. Safety data obtained to date show that AEs commonly associated with setmelanotide include injection site reactions, skin hyperpigmentation, nausea and headaches. Less commonly, vomiting was reported and, rarely, sexual events have been observed (this study will collect information on these known events related to the study drug in detailed case report forms to obtain as much information as possible in the HO population). Potential mechanistic-based events such as hypertension have not been observed throughout the setmelanotide clinical development program. Events associated with severe obesity such as depression and suicidal ideation occurred infrequently and were assessed as not related to setmelanotide.

More detailed information about the known and expected benefits and risks and reasonably expected AEs of setmelanotide may be found in the IB.

3. OBJECTIVES AND ENDPOINTS

The objectives and endpoints are summarized in Table 3.

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Table 3: Objectives and Endpoints

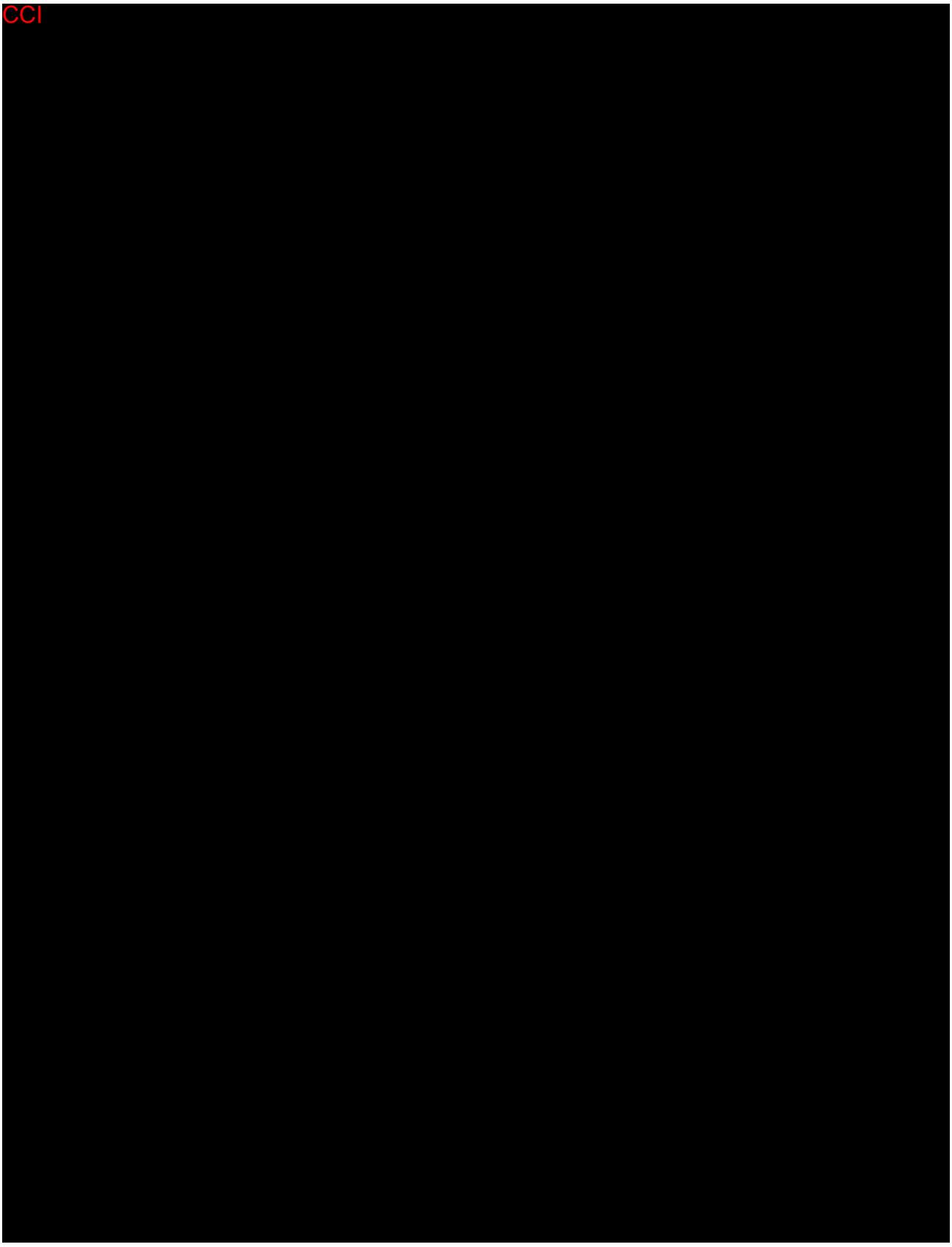
Objective	Endpoint
Primary	
To evaluate the efficacy of setmelanotide on change in body mass index (BMI)	– Mean % change in BMI from Baseline after approximately 52 weeks on a therapeutic regimen of setmelanotide compared to placebo
Key Secondary	
To evaluate the efficacy of setmelanotide on proportion of patients with ≥5% reduction in BMI or ≥0.2-point reduction in BMI Z-score	– The proportion of patients with ≥5% reduction in BMI in adult patients (≥18 years of age), or BMI Z-score reduction of ≥0.2 points in pediatric patients (<18 years of age) from Baseline after approximately 52 weeks on a therapeutic regimen of setmelanotide compared to placebo – The proportion of all patients with ≥5% reduction in BMI from baseline after approximately 52 weeks on a therapeutic regimen of setmelanotide compared to placebo
To evaluate changes in hunger in response to setmelanotide	– Mean change in the weekly average of the daily most hunger score in patients ≥12 years old from Baseline after approximately 52 weeks on a therapeutic regimen of setmelanotide compared to placebo
Secondary	
To evaluate changes in hunger and in symptoms of hyperphagia in response to setmelanotide	– The proportion of patients with a ≥2-point reduction in the weekly average of the daily most hunger score from Baseline after approximately 52 weeks on a therapeutic regimen of setmelanotide compared to placebo – Mean change in the weekly average of the Symptoms of Hyperphagia composite score from Baseline after approximately 52 weeks on a therapeutic regimen of setmelanotide compared to placebo
To evaluate changes in additional parameters of body weight	– The proportion of patients with a ≥10% reduction in BMI from Baseline after approximately 52 weeks on a therapeutic regimen of setmelanotide compared to placebo – The proportion of patients with a ≥10% reduction in weight from Baseline after approximately 52 weeks

Table 3: Objectives and Endpoints

Objective	Endpoint
	on a therapeutic regimen of setmelanotide compared to placebo – Mean percent change in weight in patients ≥18 years from Baseline after approximately 52 weeks on a therapeutic regimen of setmelanotide compared to placebo – Mean BMI Z-score and BMI percentile reduction in patients <18 years of age from Baseline after approximately 52 weeks on a therapeutic regimen of setmelanotide compared to placebo – The proportion of patients aged ≥4 to <18 years with ≥0.2-point reduction of BMI Z-score from Baseline after approximately 52 weeks on a therapeutic regimen of setmelanotide compared to placebo – The proportion of patients with BMI <30 kg/m^2 (patients aged ≥18 years) or <95th percentile (patients aged <18 years) from Baseline after approximately 52 weeks on a therapeutic regimen of setmelanotide compared to placebo
To evaluate changes in quality of life in response to setmelanotide treatment	– Mean change in physical functioning score and total score for the Impact of Weight on Quality of Life-Lite (IWQOL) (IWQOL-Lite-CT in patients ≥18 years and IWQOL-Kids in patients 11 to <18 years), from Baseline after approximately 52 weeks on a therapeutic regimen of setmelanotide compared to placebo
To evaluate changes in waist circumference following treatment with setmelanotide compared to placebo	– Change in waist circumference from Baseline after approximately 52 weeks on a therapeutic regimen of setmelanotide compared to placebo
To evaluate changes in cardiometabolic parameters following treatment with setmelanotide compared to placebo	– The difference in change in cardiometabolic parameters including BP, CCI [redacted], liver function and CCI [redacted] from Baseline after approximately 52 weeks on a therapeutic regimen of setmelanotide compared to placebo

Table 3: Objectives and Endpoints

Objective	Endpoint
Safety	
To evaluate the safety and tolerability of setmelanotide compared to placebo	– Safety and tolerability assessed by the frequency and severity of adverse events (AEs), AEs of special interest (AESIs), vital signs, and laboratory evaluations from Baseline after approximately 52 weeks on a therapeutic regimen of setmelanotide compared to placebo
To evaluate the effect of setmelanotide on blood pressure (BP)	– Change in ambulatory BP and heart rate (HR) from Baseline after approximately 52 weeks on a therapeutic regimen of setmelanotide compared to placebo (in patients ≥12 years)
CCI [redacted]	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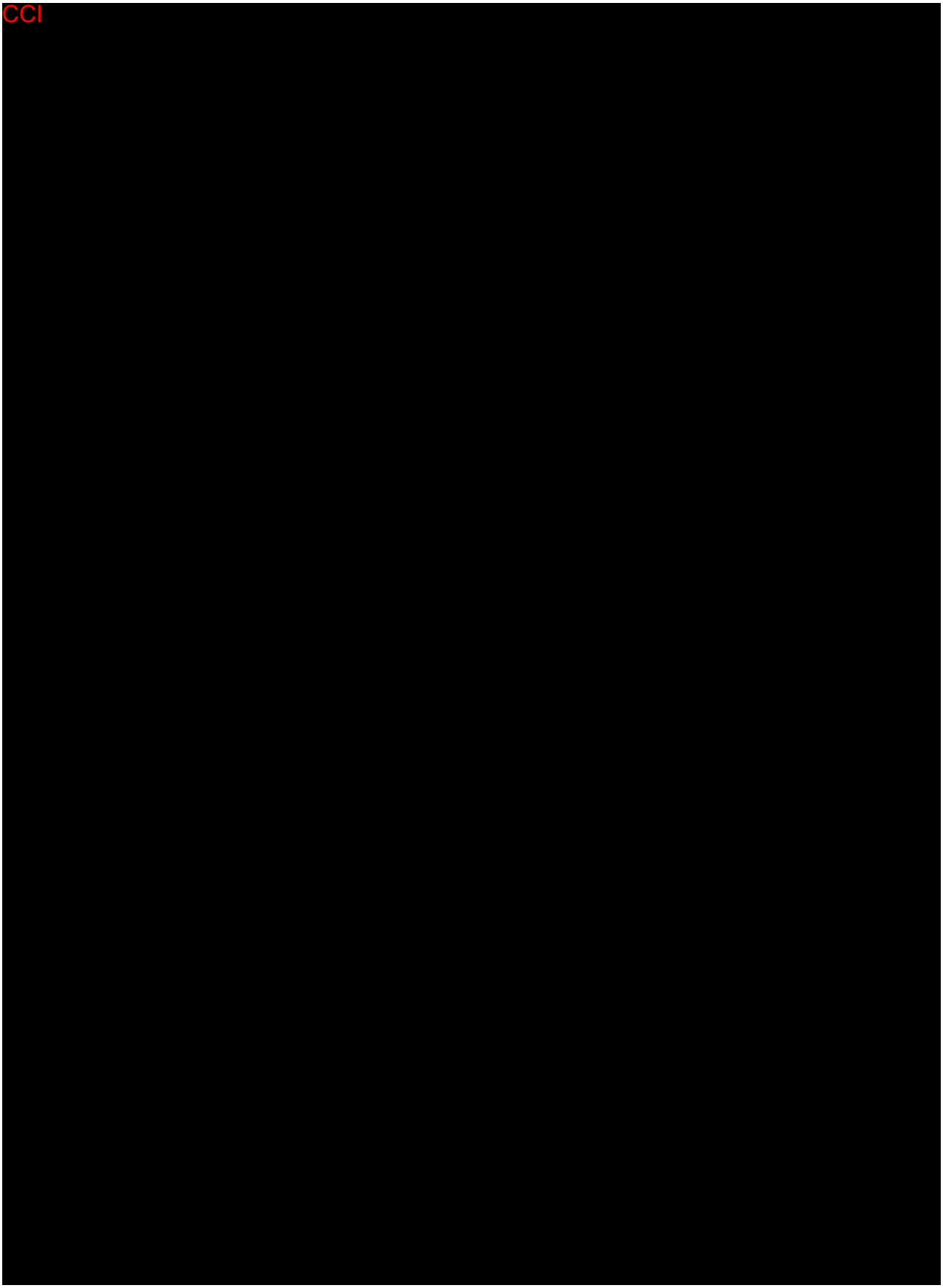
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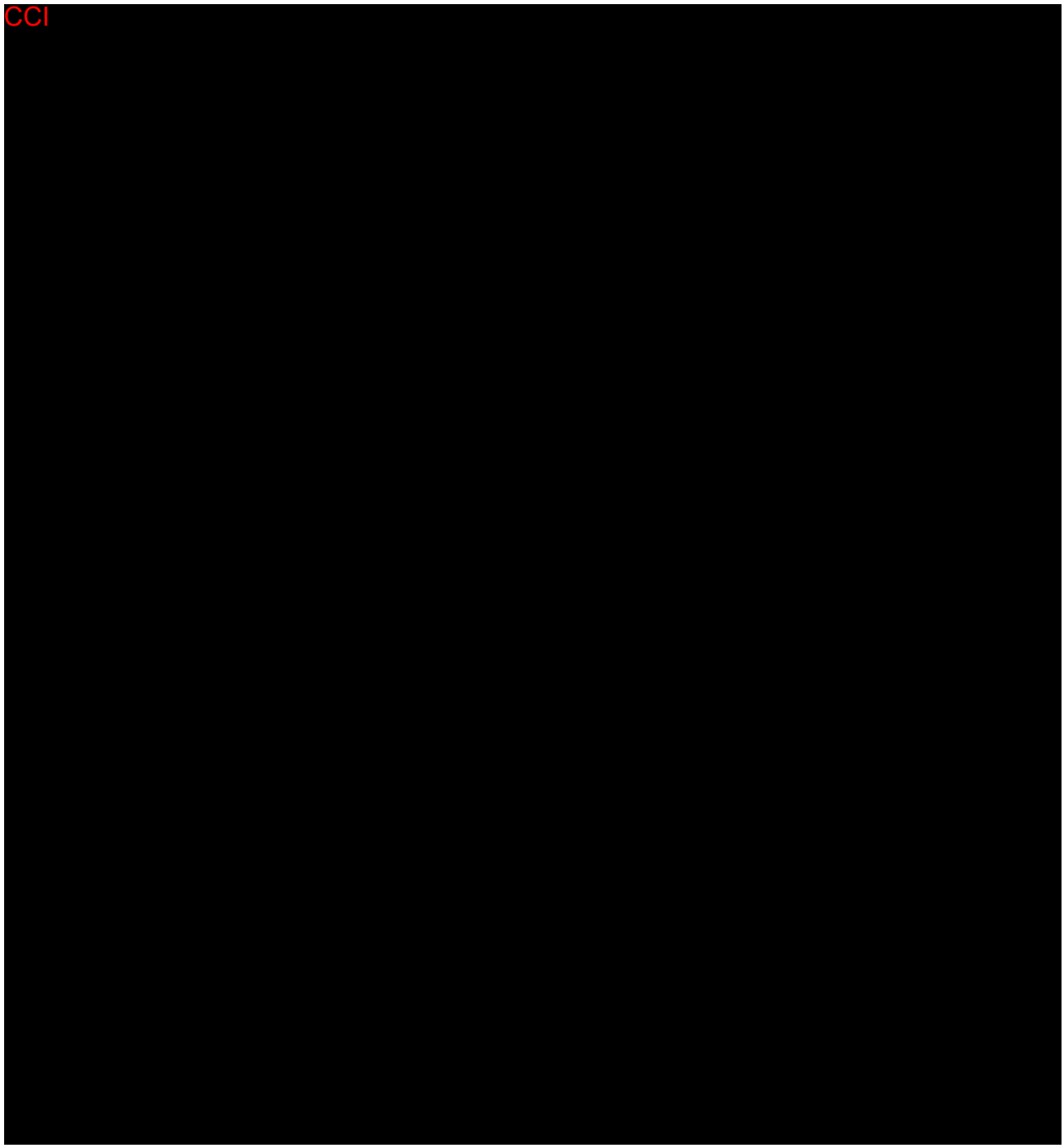
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4. SELECTION AND WITHDRAWAL OF PATIENTS

Prospective approval of protocol deviations to recruitment and enrollment criteria (ie, protocol waivers or exemptions) is not permitted.

4.1. Inclusion Criteria

Inclusion criteria are detailed below. CCI [redacted]

Patients must meet all of the following criteria to be eligible for trial participation:

1. Patient has documented evidence of acquired HO defined as:
   - CCI [redacted]
   [redacted]
2. Aged 4 years and older at time of enrollment
3. Documented weight gain associated with the hypothalamic injury either before therapy or following therapy (surgery and/or following chemotherapy or radiotherapy), and a body mass index (BMI) of ≥30 kg/m^2 for patients ≥18 years of age, or BMI ≥95th percentile for age and sex for patients 4 to <18 years of age based on the US Centers for Disease Control and Prevention criteria.
4. Patients must meet the contraception requirements outlined in Section 6.8.9 unless otherwise indicated.
5. Ability to communicate well with the Investigator, understand and comply with the requirements of the trial, and understand and sign the written informed consent and/or assent for patients aged <18 years, a parent/legal guardian that can sign.
6. If receiving hormone replacement therapy (ie, thyroid hormones, glucocorticoids, growth hormone or other medications known to affect metabolism or weight/body composition), the dose of such therapy has remained stable for at least 2 months prior to Screening.
   Note:
   - Changes in dose of ≤25% may be permissible, with the Sponsor's approval. If results of free thyroxine (FT4) warrant changes in therapy >50% or the addition of new medication the patient is screen failed and can be reassessed after 2 months.
   - This does not apply to patients experiencing adrenal crisis.

4.2. Exclusion Criteria

Patients meeting any of the following criteria are not eligible for trial participation:

1. Diagnosis of Prader-Willi syndrome (PWS) or Rapid-onset obesity with hypoventilation, hypothalamic, autonomic dysregulation, neuroendocrine tumor syndrome (ROHHADNET).
2. Weight loss >2% in the previous 3 months for patients aged ≥18 years or >2% reduction in BMI for patients aged 4 to <18 years.

   NOTE: Dietary and/or exercise regimens, with or without the use of medications, supplements or herbal treatments associated with weight loss (eg, orlistat, lorcaserin, phentermine, topiramate, naltrexone, bupropion, glucagon-like peptide-1 [GLP-1] receptor agonists, etc) 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 patients ≥18 years) or >2% BMI (for patients aged 4 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: This exclusion criterion applies only to initial study screening and is not applicable at the time of the inclusion/exclusion review for the LTE (or Bridging).

3. Bariatric surgery or procedure (eg, gastric bypass/band/sleeve, duodenal switch, gastric balloon, intestinal barrier, etc) within the last 2 years. All patients with a history of bariatric surgery or procedures must be discussed with and receive approval from the Sponsor prior to enrollment.
4. Diagnosis of severe psychiatric disorders (eg, schizophrenia, bipolar disorder, personality disorder), or Major Depressive Disorder (MDD) within the previous 2 years, or Screening Patient Health Questionnaire (PHQ)-9/PHQ-A score ≥15, or any suicidal ideation of type 4 or 5 on the Columbia-Suicide Severity Rating Scale (C-SSRS), or a Children's Depression Inventory-2 (CDI-2) T-score ≥70 during Screening, or lifetime history of suicide attempts, or any suicidal behavior in the last month.
5. Glycated hemoglobin (HbA1c) >11.0% at Screening.
6. Current, clinically significant pulmonary, cardiac, metabolic, or oncologic disease considered severe enough to interfere with the trial and/or confound the results. Any patient with a potentially clinically significant disease should be reviewed with the Sponsor or contract research organization (CRO) monitor to determine eligibility.
7. End stage renal disease (GFR <15 mL min/1.73 m^2) in any age or glomerular filtration rate (GFR) <30 mL/min/1.73 m^2 during Screening in patients <12 years of age (GFR calculated using the Bedside Schwartz Formula for patients <18 years of age).
8. Significant dermatologic findings relating to melanoma or pre-melanoma skin lesions (excluding non-invasive basal or squamous cell lesion), determined as part of a comprehensive skin evaluation performed by the Investigator during Screening. Any concerning lesions identified during Screening will be biopsied and results known to be benign prior to enrollment. If the pre-treatment biopsy results are of significant concern, the patient is not eligible for trial participation.
9. History or close family history (parents or siblings) of skin cancer or melanoma (not including noninvasive, infiltrative basal or squamous cell lesion), or patient history of ocular-cutaneous albinism.
10. Participation in any clinical trial with an investigational drug/device within 3 months or 5 half-lives, whichever is longer, prior to the first trial dose.
11. Previously enrolled in a clinical trial involving setmelanotide or any previous exposure to setmelanotide.
12. Inability to comply with once daily (QD) injection regimen.
13. Pregnant and/or breastfeeding or desiring to become pregnant during this trial.
14. Patients with obesity attributable to other genetic or syndromic conditions (eg, PPL [POMC, PCSK1, LEPR, collectively], BBS) prior to the hypothalamic injury.

15. Cognitive impairment that, in the Investigator's opinion, precludes participation in the trial and completion of trial procedures or questionnaires.
16. Patient is, in the Investigator's opinion, otherwise not suitable to participate in the trial.
17. Legally protected persons per local regulations (eg, those that fall under the L1121-6 article of the Public Health Code in France).
18. The patient or a relative of the patient is the Investigator or a sub-investigator, research assistant, pharmacist, study coordinator, or other staff directly involved with the conduct of the trial.
19. Hypersensitivity to setmelanotide and/or any excipients contained in the investigational drug.

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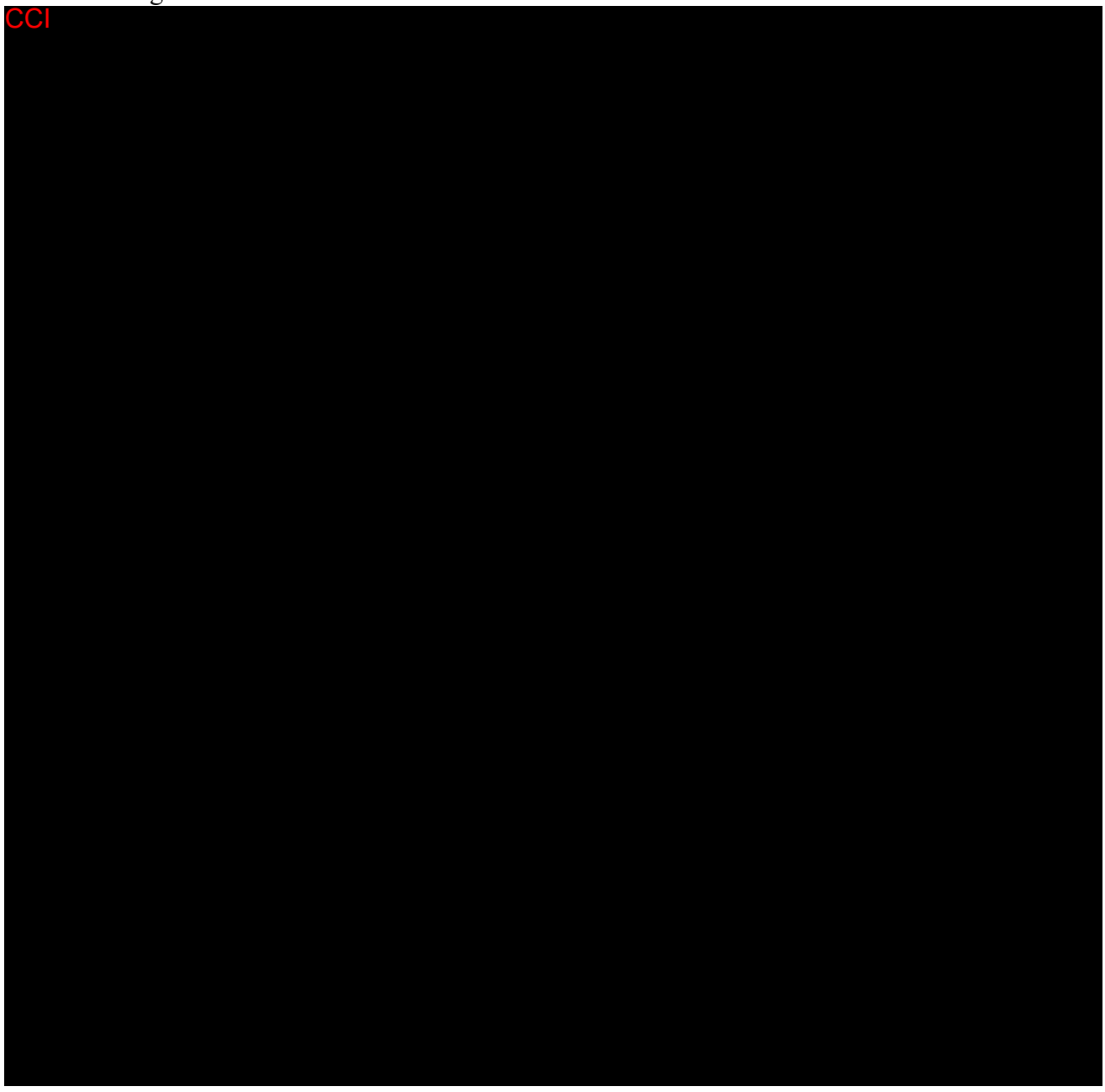

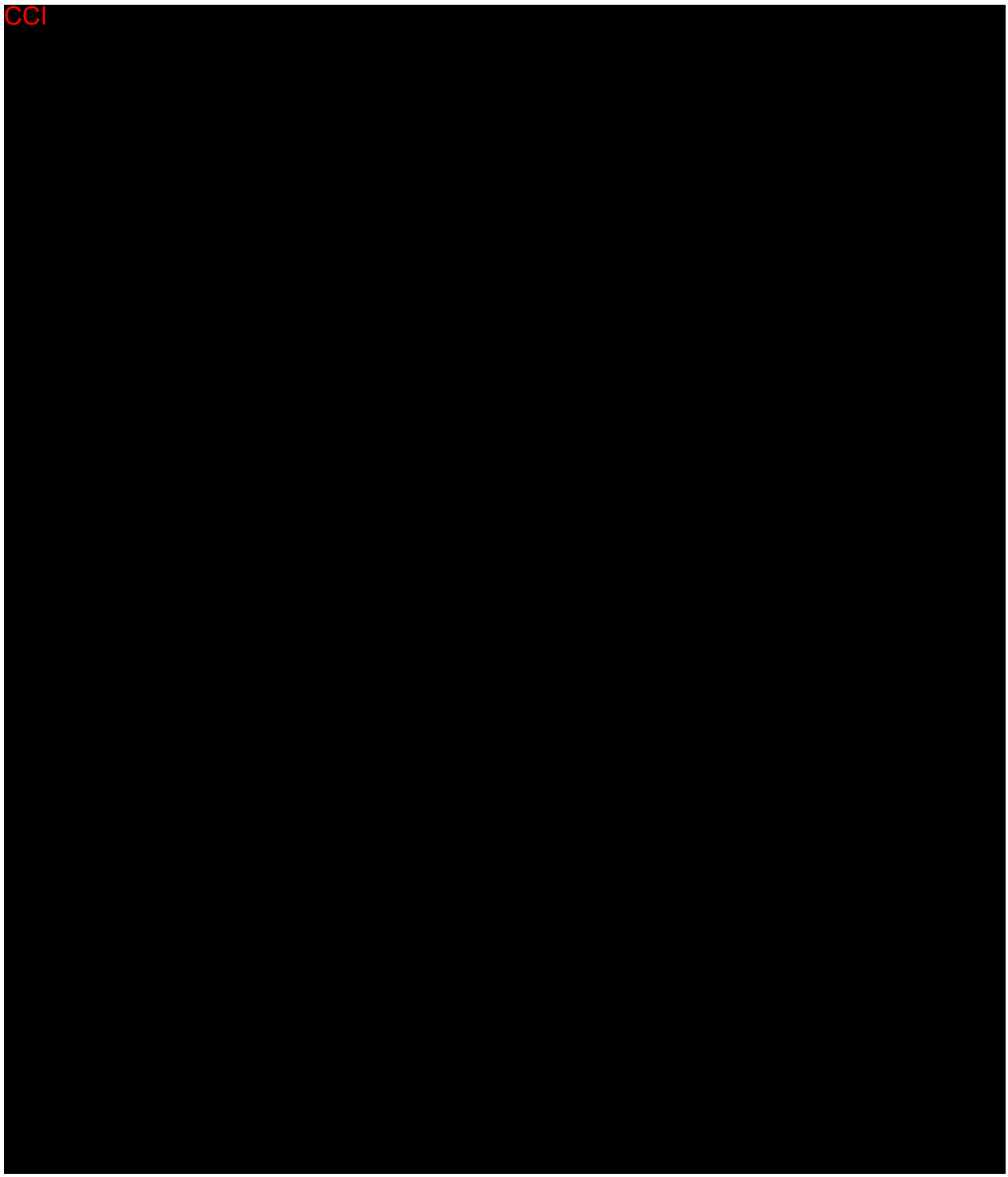

4.3. Treatment Discontinuation and Withdrawal from Trial

Given this rare patient population, every effort should be made to encourage and keep patients enrolled in the trial until completion, unless there are any safety concerns necessitating withdrawal of the trial treatment or the patient from the trial. If patients must discontinue

treatment, they should be encouraged to continue to participate in all regular trial visits and assessments (other than dosing and pharmacokinetic [PK] assessments), if possible, as a Retained Dropout.

The Sponsor will provide assistance for patient and caregiver travel and will provide other necessary logistical support to ease the burden on the patient in order to facilitate compliance and completion of trial participation.

Discontinuation of trial treatment or skipped visits/doses may be allowed without withdrawal from the trial upon consultation with the Sponsor and CRO Medical Monitor.

Patients who either discontinue treatment or withdraw from the trial before completing the trial are to attend an Early Termination of Treatment (ETT) Visit as soon as possible after the last dose of trial treatment. Patients who prematurely discontinue treatment may also be required to complete the Safety Follow-up Visit (SFV), if applicable (Section 5.1.4).

If the ETT Visit occurs 4 weeks or later following the last dose of trial treatment, then the ETT Visit will replace the SFV if no ongoing AEs are being monitored. Patients who prematurely discontinue study drug treatment will continue to complete all scheduled study visits for assessments following completion of the ETT.

Patients who complete the trial will have the opportunity to participate in the LTE with open-label setmelanotide (or Bridging visits if the LTE is not yet available). Patients must meet the LTE eligibility criteria and should discuss eligibility with the Investigator.

Patients who discontinue trial treatment but remain in the trial should be encouraged to attend all planned visits until the final Visit. See Section 5.1.3. Patients who discontinue treatment will be counted as non-responders, irrespective of treatment assignment. Patients who discontinue treatment prematurely are not eligible to enroll in the optional LTE. Exceptions may be made in consultation with the Sponsor.

Patients who withdraw from the trial will attend an ETT visit only.

If the patient 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 patient withdraws from the trial, he/she may request destruction of any samples taken and not tested, and the Investigator must document this in the site trial records and inform the Sponsor.

Patients will be informed that they have the right to withdraw from the trial at any time for any reason, without prejudice to their medical care. The Investigator also has the right to withdraw patients from the trial for reasons such as:

- AEs, which in the opinion of the Investigator justifies treatment or trial withdrawal. For specific predefined events, additional monitoring and guidance for the Investigator is provided in Appendix 5.
- Non-adherence to trial medication regimen or protocol requirements.
- Non-compliance with instructions or failure to return for follow-up.

All patients who withdraw prior to completing the treatment period should be strongly encouraged to complete the ETT visit as outlined in the SoAs (Table 1, CCI), even if they are no longer receiving trial medication.

4.4. Lost to Follow-up

Patients are considered as being lost to follow-up if they fail to return for scheduled evaluations and cannot be contacted by the site. The following actions must be taken if the patient fails to return to the clinic for a required trial evaluation:

- The trial site must attempt to contact the patient and reschedule the missed evaluation as soon as possible and counsel the patient on the importance of maintaining the assigned evaluation schedule.
- Before a patient is deemed lost to follow-up, the Investigator or designee must make every effort to regain contact with them or next of kin by, for example, repeat telephone calls, certified letter to the patient's last known mailing address, or local equivalent methods. At least 3 unique documented contact attempts to follow-up should be made and documented in the patient's records.

5. INVESTIGATIONAL PLAN

5.1. Overall Trial Design

This is a Phase 3, double-blind, randomized 2:1 (active to placebo), placebo-controlled, multi-center trial designed to assess the effect of setmelanotide on weight loss and hunger in patients with a diagnosis of acquired HO. Approximately 120 patients (at least 12 from sites in Japan) aged 4 years and older are planned to be enrolled at up to 35 clinical sites in North America, Europe, and Japan).

The trial design is depicted in Figure 1.

5.1.1. Screening Period

The Screening Period will last up to 8 weeks (from Day -56 to -1 with a minimum of 3 weeks to allow for the completion of all necessary tests and evaluations, including the collection of CCI baseline data for 2-3 weeks prior to randomization). Upon providing informed consent, patients will complete all screening procedures as listed in the SoAs to determine if they meet the study criteria.

At the Screening Visit, all patients will be given and instructed on how to use:

- a wearable actigraphy device to measure activity and sleep;
- a hand-held device for recording daily diary information throughout the study; and
- an ambulatory blood pressure monitor (ABPM) (patients ≥4 years of age, as applicable. See Section 6.8.2 for conduct in patients <12 and regional applicability of assessment). CCI

Patients who are determined not to be eligible will be asked to return their devices to the clinic.

See Section 6 for instructions on how these data should be collected during the Screening Period.

5.1.1.1. Rescreening

Screening assessments (labs) may be repeated once to establish trial eligibility within the screening period. If repeat values of the screening assessments meet eligibility criteria and are completed within the screening window, then the patient is eligible for the trial.

If a patient screen fails due to one of the following tests, screening can be repeated for: CCI [redacted] later and T4 up to 60 days later. If a patient is rescreened for out-of-range lab results those results will be re-tested and the updated values will be captured on a rescreen form in electronic data capture (EDC).

5.1.2. Treatment Period

To enter the Treatment Period on Day 1 and prior to randomization, the trial center must confirm that patients have completed the Screening assessments, including the e-diary at least 4 of the 7 days prior to the baseline visit. If the e-diary is not appropriately completed before the baseline visit, patients may be asked to complete the e-diary collection and re-schedule randomization and the baseline visit if the remaining visit window allows. Throughout the trial, patients (or caregivers) will need to complete the e-diary entries.

The Treatment Period will last up to 60 weeks. Trial drug administration details are provided in Section 5.5.3. During the Treatment Period, patients will attend the in-clinic visits and may attend at-home tele-health visits at Weeks 8, 16, 20, 28, 36, 44, 52 at the discretion of the investigator. Patients and caregivers will complete the assessments listed in the SoA (Table 1). Detailed assessment information is provided in Section 6.

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5.1.3. End of Treatment

The End of Treatment (EOT) visit will occur as an in-person clinic visit after 52 weeks on a therapeutic regimen, which is the final planned week of dosing with trial treatment. At the EOT, patients who complete 52 weeks on a therapeutic regimen and complete assessments through the EOT visit may be eligible to enter an open-label LTE trial or attend Bridging visits with open-label setmelanotide if the LTE is not yet available. Patients must meet the LTE eligibility criteria and should discuss eligibility with the Investigator.

CCI [redacted]

All patients who discontinue treatment prematurely should attend an ETT Visit as soon as possible after the last dose of trial treatment. Patients who discontinue treatment but remain enrolled in the trial should continue to complete assessments (as Retained Dropouts). These patients will be required to complete the SFV as applicable following the ETT (Section 5.1.4). Patients who discontinue treatment prematurely are not eligible to enroll in the optional LTE trial. Exceptions may be made in consultation with the Sponsor.

Patients who discontinue prematurely and withdraw from the trial will not be required to complete the SFV following the ETT.

If the ETT Visit occurs 4 weeks or later following the last dose of trial treatment, then the ETT Visit will replace the SFV if no AEs are being monitored.

5.1.4. Safety Follow-up Visit

An SFV will occur as an in-person visit 14 days (±4 days) after the last dose of trial treatment. The SFV is not required for patients who complete the treatment period and either:

- enroll in the LTE (or bridging visits if the LTE is not yet available) or transition to another qualified Rhythm study (e.g., managed access)
- transition to a commercially available Rhythm MC4R agonist regimen

5.1.5. Post-treatment Follow-up and Bridging visits

Patients who complete 52 weeks on a therapeutic regimen and remain enrolled are eligible to participate in the LTE trial. If the LTE is not yet available and the patient continues to meet inclusion/exclusion criteria, patients may initiate open-label setmelanotide via Bridging visits that occur in clinic every 12 weeks and last until either the LTE or a post-trial access program is available, commercial drug is available in the region, or the trial ends. Additional visits may be scheduled at the discretion of the Investigator. Since the patient's initial assignment to either setmelanotide or placebo will continue to be blinded to all parties, open-label dosing in Bridging visits will follow the dosing schedule outlined in Section 5.5.3.

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[redacted]

5.1.6. Completion of Trial Participation

Completion of trial participation for an individual patient is defined as 1 of the following:

- For patients who completed 52 weeks on a therapeutic regimen at the EOT and enroll in the LTE (or Bridging visits) or transition to either commercial drug or a post-trial access program: the EOT Visit

- For patients in bridging visits or who have transitioned from bridging visits to commercial drug or a post-trial access program: the last bridging visit.
- For patients who complete 52 weeks on a therapeutic regimen through the EOT Visit and do not enroll in the LTE, bridging visits, or transition to either commercial drug or a post-trial access program: the SFV
- For patients who prematurely discontinue trial treatment and complete some trial assessments but do not withdraw consent (and assent, as applicable): the latest of the EOT Visit, ETT Visit, or SFV (if required)
- For patients who withdraw consent or assent: date of withdrawal of consent or assent (ETT Visit)

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The end of the trial overall is defined in Section 5.3.

5.2. Trial or Site Termination or Suspension

This trial or any site may be suspended or terminated, if in the opinion of the Sponsor, there is sufficiently reasonable cause. The Sponsor will provide written notification documenting the reason for cohort/site/trial termination to the Investigator.

Circumstances that may warrant suspension or termination include, but are not limited to:

At the Trial level

- Determination of unexpected, significant, or unacceptable risk to patients
- Plans to modify, suspend or discontinue the development of the trial medication

At the Site level

- Failure to enroll patients at an acceptable rate

- Insufficient adherence to protocol requirements
- Insufficiently complete and/or evaluable data

If the study is prematurely terminated or suspended, the Sponsor shall promptly inform the Investigator, the Independent Ethics Committees (IECs)/Institutional Review Boards (IRBs), the regulatory authorities, and any CRO(s) used in the study about the reason for suspicion or termination, as specified by the applicable regulatory requirements. The Investigator shall promptly inform the trial patients and should ensure appropriate patient therapy and/or follow-up.

Should the trial be closed prematurely, all trial materials must be returned to the Sponsor or designee.

5.2.1. Trial Conduct During the COVID-19 (Coronavirus) Pandemic

The worldwide Coronavirus Disease 2019 (COVID-19) pandemic may impact the conduct of clinical studies due to the challenges from quarantines, site closures, travel limitations, and other considerations if site personnel or trial participants become potentially exposed to or infected with COVID-19. To assure the safety of trial participants, maintain compliance with Good Clinical Practice (GCP), and minimize risks to trial integrity, if necessary, in consultation with the Sponsor, the method of assessment may be changed). In addition, site visits may be replaced with telephone, internet-based video-conferencing applications, or home visits by qualified health care professionals. Normal procedures, as detailed in this protocol, will be resumed as soon as possible thereafter. More detailed guidance on trial conduct during the COVID-19 pandemic is provided in Appendix 7.

5.3. End of Trial

The End of Trial is defined as the date of the last scheduled visit (or contact) of the last patient.

The last visit or contact for each patient may be an unscheduled visit, the ET visit, the EOT visit, the SFV, or a scheduled Bridging Visit.

5.4. Rationale for Trial Elements

5.4.1. Trial Design

Setmelanotide is being evaluated as a potential treatment for obesity in populations with rare mechanistically induced acquired hypothalamic injury.

This Phase 3, double-blind, randomized (2:1 active to placebo), placebo-controlled, multi-center registrational trial is designed to assess the effect of setmelanotide on weight loss and hunger in patients with acquired HO ≥4 years of age. Placebo is considered the appropriate comparator since no treatment has been approved for use in patients with acquired HO.

The duration of this Phase 3 trial provides sufficient time to collect long-term controlled efficacy and safety data and demonstrate the efficacy of setmelanotide versus placebo.

CCI [redacted]

CCI [redacted]

5.4.2. Trial Population

This trial will enroll patients with acquired HO who are ≥4 years of age. Setmelanotide is expected to provide clinical benefit to these patients based on the results of a Phase 2 trial (RM-493-030), which demonstrated efficacy and safety of setmelanotide in patients ≥6 years of age with acquired HO. Due to the acute injury and progressive symptoms of HO, there is a strong rationale to treat patients earlier in life. Experience with setmelanotide in pediatric patients as young as 2 years of age suggests that the safety profile of setmelanotide will be similar for patients 4 to 6 years of age.

CCI [redacted]

5.4.3. Justification for Dose

The dose and titration scheme of setmelanotide in this trial is based on safety, tolerability, and efficacy observed in previous nonclinical and clinical trials.

CCI [redacted] ensure that exposure to excipients is well within the safe range (refer to IB). Table 3 lists the maximum therapeutic dose by patient CCI based on the associated excipient concentration.

Dose modifications are permitted as deemed necessary by the Investigator. It is recommended that the Investigator reach out to the Sponsor/Medical Monitor to discuss potential dosing changes where possible. See Section 5.5.3 for dose escalation scheme.

5.4.4. Rationale for Trial Assessments

A majority of the efficacy, safety, and PK assessments in this trial are generally recognized as standard parameters in the study of patients in clinical trials.

Hunger, CCI [redacted] are reliable assessments relevant to the

study of energy expenditure and quality of life in patients with rare diseases of obesity, including HO.

The suicidal ideation and depression monitoring questionnaires are recommended to detect any effect on central nervous system (CNS) safety at Screening or during the trial.

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5.5. Treatment of Patients

Trial treatment is defined as any investigational treatment(s), marketed product(s), placebo, or medical device(s) intended to be administered to a trial patient according to the trial protocol.

5.5.1. Description of Trial Treatment

All trial treatment is for investigational use only and is to be used only within the context of this protocol. All investigational trial treatment (setmelanotide and placebo) will be supplied by the Sponsor.

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The reference therapy for the double-blind period of this trial is a placebo vehicle. CCI

Setmelanotide and placebo are clear, colorless to slightly opalescent solutions essentially free of visible particulates and are suitable for a double-blind trial.

5.5.2. Randomization and Blinding

5.5.2.1. Randomization

Patients who are eligible to enter the trial will be randomized in a blinded manner on Day 1 in a 2:1 ratio, stratified by age group (≥18 years old, ≥12 and <18 years old, <12 years old) and subpopulation (Japanese vs non-Japanese), to receive either setmelanotide (2) or placebo (1). The randomization schedule will be generated by the Sponsor or its designee, and trial personnel will use a web-based interactive response technology (IRT) system to obtain the patient number for each eligible patient.

The patient, Investigator, and the Sponsor will be blinded to trial treatment assignment. Full details for the blinding and unblinding are provided in the separate Blinding and Unblinding Plan.

CCI [redacted]

5.5.2.2. Replacement of Patients

Patients who withdraw or are withdrawn from the trial after randomization will not be replaced. Randomization will not be revised once a patient is randomized.

5.5.2.3. Blinding and Unblinding

Blinded randomization will occur via an IRT system.

At the initiation of the study, study site personnel will be instructed on the method for breaking the blind. To conduct the primary analysis, the Sponsor will be unblinded when 120 patients have completed the study. To ensure the integrity of the study at the site level, investigators and patients will remain blinded after the unblinding of the sponsor.

Emergency unblinding for AEs may be performed through the IRT system. The IRT system will be programmed with blind-breaking instructions. In case of an emergency, the Investigator has the sole responsibility for determining if unblinding of a patient's intervention assignment is warranted. Patient safety must always be the first consideration in making such a determination. If the Investigator decides that unblinding is warranted, the Investigator should make every effort to contact the Sponsor or CRO Medical Monitor before unblinding a patient's intervention assignment unless this could delay emergency treatment for the patient. The date and reason for the unblinding by the Investigator must be recorded. If a patient's intervention assignment is unblinded, the Sponsor must be notified by the Investigator within 24 hours of occurrence. The Investigator should not reveal to the Sponsor the patient's treatment allocation unless the Sponsor requests this information for safety purposes.

For any unexpected serious adverse event (SAE) that is treatment-related (eg, possible or probable), the blind will be lifted by the Sponsor only for that specific patient. The blind will be maintained for persons responsible for the ongoing conduct of the trial (such as the monitors, investigators, etc) and those responsible for data analysis and interpretation of results at the conclusion of the trial (such as biometrics personnel). Unblinded information will only be accessible to those who need to be involved in the safety reporting to Health Authorities, IEC, and/or IRB. Investigators will receive only blinded information unless unblinded information is judged necessary for safety reasons.

5.5.3. Administration of Study Drug

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CCI [redacted]

To confirm the proper initial dose escalation has occurred and to collect AEs and any changes in concomitant medications, site personnel will call patients on Day 8. Additional calls to patients may occur throughout dose escalation to the maximum therapeutic dose.

Patients ≥6 years of age

CCI [redacted]

Patients <6 years of age

CCI [redacted]

CCI [redacted]

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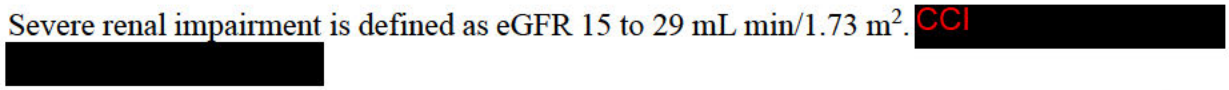
The dose may continue to be evaluated and adjusted for all patients based on tolerability, at the discretion of the Investigator.

Patients/caregivers will draw up and self-administer/administer the drug QD in the morning beginning the morning of Day 1 and for the duration of dosing. On days with clinic visits, the patients/caregivers will administer the drug in the clinic in the presence of the clinical staff following required pre-dose questionnaires and blood to assure proper technique.

There will be extensive training of patients and caregivers (as applicable) in trial treatment administration including educational materials. Trial-specific training materials will be provided to the Investigative staff and trial patients and caregivers.

5.5.3.1. Patients with Severe Renal Impairment

Severe renal impairment is defined as eGFR 15 to 29 mL min/1.73 m^2. CCI



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For trial treatment interruption and stopping rules, see Section 6.10.4.

5.5.3.2. Dose Adjustments

Dose modifications are permitted as deemed necessary by the Investigator. It is recommended that the Investigator contact the Sponsor/Medical Monitor to discuss potential dosing changes where possible outside of the planned escalations described above. This includes delaying a planned escalation per the protocol schedule.

5.5.4. Treatment Compliance and Trial Treatment Accountability

Accountability for the trial treatment at the trial site is the responsibility of the Investigator. The Investigator will ensure that the trial treatment is used only in accordance with this protocol. Where allowed, the Investigator may choose to assign drug accountability responsibilities to a pharmacist or other appropriate individual. Drug accountability records indicating the delivery date to the site, inventory at the site, use by each patient, return of all used trial treatment to the trial center, and return to the Sponsor (or disposal of the drug, if approved by the Sponsor) will be maintained by the clinical site. Reasons for departure from the expected dispensing regimen must also be recorded. The Sponsor or its designee will review drug accountability at the site during monitoring visits.

Compliance to dosing will be monitored throughout the trial by having the patient complete a dosing log in an e-diary (or paper forms for patients in Bridging visits) that records daily dosing information, including whether the dose was administered, and if not administered, the rationale for why it was not administered. If a patient is non-compliant with the dosing schedule, the Sponsor may implement steps to ensure compliance, eg, sending a nurse to the patient's home for retraining or having a nurse administer the trial treatment.

5.5.5. Preparation/Handling/Storage/Accountability

Only patients enrolled in the trial may receive trial treatment and only authorized site staff may supply or administer trial treatment. All trial treatments 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 site staff.

All trial treatment must be kept in a secure, limited-access storage area at a temperature between 2°C to 8°C. Trial drug is stable at room temperature for a short time period that will allow patients to transport trial treatment home; ice packs and cooler bags will be provided for patients and caregivers who will travel long distances from the clinic. Once home, the un-opened trial treatment must be stored in the patient's refrigerator. Open trial treatment may be stored at room temperature for up to 30 days.

Patients/caregivers will return all (the number recorded) used and unused vials to the clinic when they visit, and both clinic-administered trial treatment as well as outpatient trial treatment administration will be recorded in a trial diary.

6. PATIENT ASSESSMENTS

Trial procedures and their timing are summarized in the SoAs (Table 1, CCI). Adherence to the trial design requirements, including those specified in the SoA, is essential and required for trial conduct.

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

When scheduled at the same time point, the order of procedures should be as follows at Screening: vital signs, 12-lead electrocardiogram (ECG), blood draws.

When scheduled at the same time point, the order of procedures should be as follows during the Treatment Period: collection of ABPM reading (from previous 24 hours) e[redacted], vital signs, perform blood draws. Adjustments may be made depending upon specific circumstances and in consultation with the Sponsor.

Patients should come to each clinic visit (or each tele-health visit) in the morning in an overnight fasted state so that required assessments (ie, specific questionnaires, safety labs, PK draws, and weight) can be performed per the requirements of the protocol.

All assessments will be completed at timepoints listed in the SoAs (Table 1, [redacted]). A telephone call is also scheduled at Week 2 to remind patients about the planned initial dose escalation. Other phone calls may be scheduled during the weeks of dose escalation.

For all patient and safety questionnaires, training will be provided on the use of tablets and e-diaries for site and patient data collection. Table 9 (Appendix 8) summarizes the timing relative to dosing, the location where the assessment should be conducted, and the method of data collection.

Immediate safety concerns should be discussed with the Sponsor immediately upon occurrence or awareness to determine if the patient should continue or discontinue trial treatment.

6.1. Informed Consent/Assent

A complete description of the trial is to be presented to each potential patient and parent or legal guardian/representative and signed and dated informed consent and/or assent is to be obtained before any trial-specific procedures are performed. Patients must be informed of and provide consent/assent to the most current version of the informed consent form(s) (ICFs) during their participation in the trial, and a copy of the ICF(s) must be provided to the patient or their legally authorized representative. [redacted]

ee Section 6.3.

[redacted]

6.2. Inclusion/Exclusion Review

Inclusion and exclusion criteria are to be reviewed per the SoAs (Table 1, [redacted]) to ensure the patient is eligible for the trial. Patients must meet all inclusion and no exclusion criteria to be enrolled. All eligibility information must be adequately documented in the patient's medical records.

CCI [redacted]

6.4. Demographics, Medical and Diagnostic History Review, Concomitant Medications

Medical history (including diagnostic medical history related to hypothalamic injury/[or hypothalamic disease diagnoses for patients in the sub-study] and obesity and prior obesity management therapies), demographic data including age and year of birth at the time informed consent/assent is provided, historical height/weight, gastrointestinal (GI) history and current GI complaints (nausea, vomiting, diarrhea), type of hypothalamic lesion identified on radiographic imaging CCI [redacted] and concomitant medication use will be obtained for all patients during the Screening Period (Table 1, CCI [redacted]).

The medical history should be updated on Day 1 prior to the first dose of trial treatment, to assess continued trial eligibility and adherence to final inclusion/exclusion criteria. This medical history update includes a review for changes from Screening as well as a review of the patient's recent medication use to assess whether any changes or AEs (Section 6.10) have occurred since the previous visit.

6.4.1. Diagnostic History

All patients will be screened for documented evidence of prior hypothalamic injury and obesity occurring at least 6 months before Screening. This will include prior radiographic imaging, weight and BMI history and an assessment of GI health.

CCI [redacted]

6.4.1.1. Type of Lesion on Radiographic Imaging

Patients must have 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.

CCI [redacted]

6.4.2. Concomitant Medications

Medication that is considered necessary for the patient's safety and wellbeing may be given during the trial at the discretion of the treating physician after discussion with the Medical Monitor.

All concomitant medications should be kept at a stable dose throughout the course of the trial unless a dose change is necessary due to a change in the patient's condition. During the trial, any required increase in hormonal replacement therapy >25% should be discussed with the Sponsor.

As GLP-1 treatments may cause nausea and vomiting, they should not be started simultaneously with trial treatment. However, trial treatment can be started in patients who are on stable doses of GLP-1 treatments for at least 3 months prior to randomization.

At present, there is little evidence that setmelanotide will result in drug interactions, but data are limited.

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

- Reason for use
- Dates of administration including start and end dates
- Dosage information including dose and frequency

The Medical Monitor should be contacted if there are any questions regarding concomitant or prior therapy.

6.4.2.1. Concomitant Obesity Medications

Medications that are approved to treat obesity (eg, orlistat, phentermine-topiramate, naltrexone-bupropion, GLP-1, etc) are permitted if the patient has had <2% weight loss in the previous 3 months, the dose has been stable for at least 3 months prior to randomization, and the patient intends to continue the same dose throughout the trial.

6.5. Fitzpatrick Scale

Each patient is to be categorized for skin type according to the Fitzpatrick scale (Fitzpatrick1975). The Fitzpatrick Scale is presented in Appendix 3.

6.6. Efficacy Assessments

6.6.1. Height

For patients ≥21 years of age, height is to be measured at screening only. For patients aged <21 years, height is to be measured at the time points listed in the SoAs (Table 1, CCI). Height (cm) will be measured, without shoes, socks, or hats, using a wall-mounted stadiometer (or portable stadiometer, if available). In the clinic, the stadiometer should be calibrated by site personnel on a daily basis prior to height assessment.

All measurements will be done at each time point and recorded to the nearest half centimeter.

6.6.2. Weight

Weight (kg) will be recorded at the time points designated in the SoAs (Table 1, CCI . Weight (kg) is to be measured at the clinic using the same scale throughout the trial. Weight should be measured after patients have attempted to empty their bladders and after fasting for at least 8 hours. Patients are to wear light clothing or underwear and no shoes, with empty pockets, and will be weighed at approximately the same time of day. All measurements will be recorded to the nearest 10th of a kg if reported with a digital scale, or half kg with a mechanical scale.

The scale should be calibrated on a regular basis per the manufacturer's specifications.

6.6.3. Waist Circumference

Waist circumference (cm) will be measured in centimeters (cm) CCI during the trial at the time points designated in the SoAs (Table 1, CCI Waist circumference should be measured at approximately the same time at each visit. CCI

6.6.4. Hunger and Symptoms of Hyperphagia

Hunger will be assessed using the following measures: Hunger Questions and the Global Hunger Questions. Hyperphagia will be assessed using the Symptoms of Hyperphagia Questionnaires.

Hunger, Global Hunger, and the Symptoms of Hyperphagia questions should be completed in the morning prior to the morning meal and prior to dosing via the e-diary according to schedule in the SoAs (Table 1, CCI See Appendix 8 for a summary of the Patient and Safety Questionnaires, the timing relative to dosing, the location where the assessment should be conducted, and the method of data collection.

6.6.4.1. Hunger Questions

Patients ≥12 years of age who are able to validly and reliably self-report will be administered "CCI

Patients 6 to <12 years of age will be administered CCI .

Hunger Questionnaires will be recorded as follows:

- during the Screening Period for 7 consecutive days before the enrollment visit (Day 1). Patients should be contacted to remind them to complete all at-home assessments that are required prior to the Day 1 visit, including this questionnaire. During the

Screening Period, the patient should complete these questionnaires at least 4 of the 7 days prior to Day 1 Visit.

- for 7 consecutive days before each scheduled trial visit,
- at the ETT visit as applicable.

The Hunger Questions should be completed before dosing, before the morning meal (fasted), and at home using the e-diary.

6.6.4.2. Global Hunger Questions

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 patients ≥12 years of age who can self-report, t[CCI] will be used.

For patients <12 years of age or those who are unable to self-report, the [CCI] 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 (Table 1, [CCI]

During the trial, these questions should be completed before dosing and at home using the e-diary. For patients who continue to Bridging visits, these questions should be completed at the clinic before dosing and the morning meal.

6.6.4.3. Symptoms of Hyperphagia

Patients ≥12 years of age who are able to self-report will be administered the [CCI]

Caregivers of patients who cannot self-report will be administered the [CCI] The Symptoms of Hyperphagia Questionnaire will be recorded as follows:

- during the Screening Period for 7 consecutive days before the enrollment visit (Day 1). Patients should be contacted to remind them to complete all at-home assessments that are required prior to the Day 1 visit, including this questionnaire. During the Screening Period, the patient should complete these questionnaires at least 4 of the 7 days prior to Day 1 Visit.
- for 7 consecutive days before each scheduled trial visit,

- at the ETT visit as applicable.
- During Bridging visits (as applicable): for 7 consecutive days before each scheduled visit.

The Symptoms of Hyperphagia Questions should be completed before dosing, before the morning meal, and at home. During the trial, patients will use an e-diary to complete the questionnaire. Patients who transition to Bridging visits will use a paper diary.

6.7. Other Outcome-related Assessments

6.7.1. CCI [redacted]

Quality of life will be assessed using the Impact of Weight on Quality of Life-Lite-Clinical Trials questionnaires (IWQOL-Lite-CT or IWQOL-Kids) and CCI [redacted]). The impact of hyperphagia will be measured by the CCI [redacted].

The IWQOL-Lite-CT/IWQOL-Kids, CCI [redacted], and CCI [redacted] questionnaires do not need to be completed before dosing but should be completed at the clinic according to the SoA.

See Appendix 8 for a summary of the Patient and Safety Questionnaires, the timing relative to dosing, the location where the assessment should be conducted, and how the data will be collected.

6.7.1.1. Quality of Life

IWQOL Lite Clinical Trials Version© (IWQOL-Lite-CT)

The IWQOL-Lite-CT will be administered to patients ≥18 years of age. The IWQOL-Lite-CT is a validated 20-item self-report measure of obesity-specific quality of life questionnaire (Kolotkin 2019). The IWQOL-Lite-CT yields a Total score and 3 composite scores: Physical (7 items), including Physical Function (5 items), and Psychosocial (13 items). The questionnaire is appropriate for assessing weight-related physical and psychosocial functioning in populations commonly targeted for weight management clinical trials.

The IWQOL-Lite-CT questionnaire does not need to be completed before dosing but should be completed in clinic according to the SoA.

Impact of Weight on Quality of Life-Kids© (IWQOL-Kids)/Parent Proxy

The IWQOL-Kids will be administered to patients between the ages of 11 and <18.

The IWQOL –Kids Parent Proxy version will be used for patients 11 to <18 years of age who are unable to self-report.

The IWQOL-Kids is a validated 27-item self-report measure of weight-related quality of life for youth. It provides a total score inclusive of 4 domains: physical comfort, body esteem, social life, and family relations.

The IWQOL-Kids questionnaire does not need to be completed before dosing but should be completed in clinic according to the SoA.

CCI [redacted]

6.7.1.2. CCI [redacted]

[redacted]

CCI [redacted]

[redacted] e Scale or peds FACIT-F. The FACIT assessments will be conducted according to the SoA.

See Appendix 8 for a summary of the Patient and Safety Questionnaires, the timing relative to dosing, the location where the assessment should be conducted, and how the data will be collected.

The FACIT assessments do not need to be completed before dosing but should be completed in clinic.

CCI [redacted]

CCI [redacted]

CCI [redacted]

[redacted] as applicable (Section 6.8.2).

CCI [redacted]

CCI [redacted]

Refer to the Trial Manual for additional details.

6.7.4. CCI [redacted]

CCI [redacted] will be performed at select US trial sites for patients who agree to provide separate ICF/Assent for this assessment.

CCI [redacted] and will occur at the time points designated in the SoAs (Table 1, CCI [redacted]). If DXA is not available at the clinic, this procedure may be skipped, with prior approval of the Sponsor.

For CCI [redacted] methodology, CCI [redacted] The risk associated with exposure to ionizing radiation is minimal and further minimized through the exclusion of pregnant women and the requirement to collect an additional consent/assent for this assessment.

If patients have severe obesity and cannot be measured in the CCI [redacted] available due to practical limitations CCI [redacted], then this assessment can be skipped.

6.8. Safety Assessments

6.8.1. Vital Signs

Vital signs include systolic and diastolic blood pressure (BP), heart rate (HR), respiration rate (RR; breaths/minute), and body temperature (°C). Vital signs will be obtained in the sitting position following at least 5 minutes of rest each time point designated in the SoAs (Table 1, CCI [redacted]

All BP and HR measurements will be taken in triplicate, approximately 2 minutes apart. When possible, BP should be taken in the non-dominant arm throughout the trial, using the same methodology (automated or manual). Repeat measures and more frequent monitoring can be implemented for significant increases in BP or HR.

6.8.2. Ambulatory BP Monitoring (ABPM)

At select sites in North America and Europe, ABPM will be conducted outside of the clinic setting in all patients ≥4 years of age. For patients ≤12 years of age, both caregiver and Investigator will confirm feasibility of patient compliance in this assessment. The ABPM monitor will measure BP (systolic and diastolic) and HR in 30-minute intervals for each 24-hour period. ABPM assessments will require patients to wear the monitor at each time point (per SoA) below for any 24-hour period before each of the following visits:

- Day 1 (conducted during Screening)
- Week 24

- The EOT Visit

CCI [redacted]

[redacted]

6.8.3. Physical Examinations

A complete physical examination will be conducted at Screening, at the EOT Visit and at the ETT, as applicable. At other time points, as designated in the SoAs (Table 1 CCI), an abbreviated examination will be performed.

- A complete physical examination will include review of peripheral lymph nodes; head; eyes (including conjunctiva); ears; nose; mouth and oropharynx; neck; heart; lungs; abdomen; musculoskeletal including back and extremities; and neurologic examination.
- The abbreviated examination should focus on heart, lungs and skin, and any areas of previous abnormal findings, noting any changes from baseline.
- Tanner Staging for assessment of pubertal development will be conducted for those patients who have yet to reach Tanner Stage V (at V1, EOT or ETT, as applicable). If a female patient reaches menarche during the trial, the Tanner exam after V1 can be skipped.

Whenever possible, the same trained health care professional will conduct the examination and Tanner Staging.

All physical examinations are to be conducted in adequate light.

Changes from baseline in any physical examination findings identified by the Investigator as clinically significant must be recorded as an AE on the appropriate electronic case report form (eCRF).

6.8.4. Comprehensive Skin Examinations

A comprehensive skin examination will be performed by the Investigator at the time points designated in the SoA (Table 1, CCI The skin examination should include a full body (head-to-toe skin examination). If any concerning lesions are identified during Screening, the patient should be referred to a dermatologist. Any concerning lesions will be biopsied by the dermatologist and results must be benign prior to the first dose of setmelanotide. If the pre-treatment biopsy results are of concern, the patient will be excluded from the trial. Additionally, any concerning lesion or change in an existing lesion during the course of the trial must be evaluated by the dermatologist and biopsied, if clinically indicated in the opinion of the dermatologist.

6.8.5. Electrocardiograms

A single 12-lead ECG will be performed at the time points designated in the SoA (Table 1, CCI ECGs are to be performed with the patient in the supine position following a period of at least 10 minutes of rest. The ECG will be performed after vitals are collected and before any other procedures that may affect heart rate, such as blood draw. A printout of the ECG traces will

be made available for safety review by the investigator and maintained with source documentation. Clinically significant ECG abnormalities that occur during the study will be recorded as AEs.

6.8.6. Clinical Laboratory Tests

Blood and urine samples for clinical laboratory tests are to be collected at the time points designated in the SoAs (Table 1, CCI and analyzed at a central laboratory (with the exception of urine pregnancy tests, which may be performed at home, as applicable). For purposes of study conduct, only laboratory tests analyzed in the central laboratory may be used. Local laboratories may be used at the discretion of the investigator to monitor urgent medical issues. If a local laboratory value is abnormal and clinically significant, it will be verified by the central laboratory as soon as the investigator becomes aware of the abnormal result. If it is not possible to send a timely sample to the central laboratory, the investigator may base an AE on the value of the local laboratory test. Samples are to be collected prior to trial drug administration.

All clinically significant laboratory abnormalities will be followed-up by repeat testing and further investigated according to the judgment of the Investigator. The Investigators will adhere to the site-specific blood volume limits for safety laboratory and PK analyses both to ensure minimal distress and reduce the number of venipunctures in pediatric patients (Refer to Appendix 2).

The safety laboratory test panels are shown in Table 7.

Table 7. Safety Laboratory Test Panels

Serum Chemistry	Hematology	Urinalysis[b]
Glucose Blood urea nitrogen Uric acid Creatinine Creatine phosphokinase Sodium Potassium Chloride Bicarbonate Calcium Lactate dehydrogenase Magnesium Phosphate Total bilirubin Direct bilirubin Alkaline phosphatase Alanine transaminase Aspartate transaminase	Hematocrit Hemoglobin CCI Mean Corpuscular Hemoglobin Erythrocytes Mean Corpuscular Volume Platelets Leukocytes Differentials (absolute and percent): Basophils Eosinophils Neutrophils Lymphocytes Monocytes	Color Clarity Leukocyte esterase Nitrite Urobilinogen Urine protein pH Specific gravity Urine ketones Urine bilirubin Urine glucose Blood

Serum Chemistry	Hematology	Urinalysis[b]
Albumin Gamma-glutamyl transferase Total protein CCI [redacted]		

[redacted]

[c] If urinalysis results are positive on a urine dipstick for leukocyte esterase, nitrites, protein, or blood, microscopic examination of urine will be performed, and results will be provided.

Additional Tests at Screening:

The following tests will be performed during Screening to assess eligibility:

- Levels of serum follicle-stimulating hormone (FSH) for suspected postmenopausal women who have been post-menopausal >12 months and should be in post-menopausal range. FSH is not required at screening for females with tertiary and/or secondary hypogonadism who are on hormonal replacement therapy for this condition.
- Urine beta-human chorionic gonadotropin (β-hCG) for Women of Childbearing Potential (WOCBP). The pregnancy tests must be negative before the Day 1 dosing.

Thyroid Tests at Screening:

- T4, Free T4, and T3 will be measured at Screening.

Additional Tests Throughout Trial

1) Pregnancy Testing for WOCBP (as defined in Section 6.8.9):
   - A urine pregnancy test may be performed to expedite availability of results prior to dosing on Day 1. All in-clinic pregnancy tests per SoAs (Table 1, CCI will be serum tests and analyzed at the central laboratory; dosing may continue with results pending. At telehealth visits, urine pregnancy tests will be performed using pregnancy test kits. Additional pregnancy tests may be required according to local regulations and/or requirements.
   - Pregnancy testing is not required for females with tertiary and/or secondary hypogonadism who are on replacement therapy for this condition and are not on ovarian stimulation therapy Pregnancy testing may be conducted at the discretion of the investigator.
2) CCI [redacted]
3) Hormone Testing

- IGF1 labs will be drawn at Baseline and approximately every 3 months for patients taking growth hormones.
- Estradiol and testosterone labs will be drawn for all patients at Baseline (V1), EOT, and ETT (as applicable).

If the testing occurs during a permitted telehealth visit, that visit will be required in person.

4) Additional Evaluations

Additional clinical laboratory evaluations will be performed at other times if judged to be clinically appropriate.

Bridging Visits

For patients who transition to Bridging visits, specific labs will be collected as indicated in the SoA (Table 1, CCI

6.8.6.1. CCI

[redacted]

6.8.7. Pharmacokinetics and Anti-Drug Antibodies

6.8.7.1. Pharmacokinetics

Blood samples for determination of setmelanotide levels in plasma at trough will be collected as indicated in the SoAs (Table 1, CCI). Samples for PK (trough) and anti-drug antibodies (ADA) will be collected on the same schedule during the trial. All samples should be collected before trial treatment administration on the day of collection. For all blood samples for PK analysis, the actual (clock) time each PK blood sample and the time of the last dose will be recorded in the source documents and eCRF. Plasma will be harvested from each blood sample collected for PK analysis and the plasma will be frozen, shipped to a bioanalytical laboratory designated by the Sponsor, and analyzed for setmelanotide concentrations.

Setmelanotide plasma PK will be assessed in all patients by trough (pre-dose) concentrations measured prior to dose administration in the clinic as per the SoAs.

The trough concentration values will be reported descriptively as mean, standard deviation (SD), maximum (Max), minimum (Min), median, and percent coefficient of variation (%CV) based on dose and visit.

6.8.7.2. ADA

Blood samples for analysis of ADAs (anti-setmelanotide and anti-αMSH) will be collected at the time points specified in the SoA. Samples for ADA and PK (trough) will be collected on the same schedule during the trial. All samples should be collected before trial treatment administration on the day of collection. Any patient with a positive anti-setmelanotide ADA will

be followed every 3 months after the ADA sample analysis until resolution of the ADA (ie, no measurable ADA response).

6.8.8. Injection Site Examination

Injection sites will be carefully inspected, evaluated, and scored during the trial period. The injection site evaluation and scoring (by the clinical staff) will include identification and measurement of areas of erythema, edema, and induration, as well as the presence of localized pain, tenderness, and itching. Additional evaluation data can be collected at any visit in which there are injection site reactions, even if not a time point for formal assessment.

A sample injection site evaluation form is included in Appendix 4.

In addition, unscheduled evaluations may also be recorded as warranted by clinical conditions.

6.8.9. Pregnancy and Contraception

In animal reproduction studies, setmelanotide was not teratogenic at doses >10 times the maximum recommended human dose of 3 mg QD. No evidence of embryo-fetal toxicity was observed. Pre-and postnatal development studies in rats showed no adverse setmelanotide-related effects. Please refer to the IB for additional information.

WOCBP, defined as fertile, following menarche and until becoming post-menopausal unless permanently sterile (hysterectomy, bilateral salpingectomy, or bilateral oophorectomy) must not be pregnant and must have a negative serum pregnancy test result at the Screening Visit. A urine pregnancy test may be performed to expedite availability of results prior to dosing on Day 1. Serum pregnancy testing will also be performed during the trial at the time points specified in the SoA. At sites where pregnancy tests are required for tele-health visits, WOCBP will be given urine pregnancy tests for use at the following visits: Visits 2, 6, 8, 10, 12, and 14 CCI [redacted] (if these visits are conducted as remote visits with visiting nurses).

Furthermore, it is imperative that all trial patients adhere to the contraception requirements as outlined below.

For WOBCP childbearing potential, a highly effective form of contraception (as defined in the Inclusion Criteria, (Section 4.1) 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 patients 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 patients 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.

6.8.10. Suicidal Ideation and Depression Monitoring

All 3 questionnaires, the C-SSRS, the PHQ-9/PHQ-A, the CDI-2 should be completed prior to the morning dose at the clinicor in the presence of trained nursing or site staff during telehealth visits, as applicable (as scheduled per SoA).

A patient should be referred to a mental health professional (MHP) if he/she has:

- A PHQ-9/PHQ-A score ≥10.
- Any suicidal behavior.
- Any suicidal ideation of type 4 or 5 on the C-SSRS.
- A CDI-2 T-score ≥65

An AE should also be reported for PHQ-9/PHQ-A ≥10 or a CDI-2 T-score ≥65or a C-SSRS of type 4 or 5.

A referral to an MHP should be recorded as an AE and should also be made if in the opinion of the Investigator it is necessary for the safety of the patient. If a patient's psychiatric condition can be adequately treated with psychotherapy and/or pharmacotherapy, then the patient, at the discretion of the MHP, may be continued in the trial.

In patients with cognitive impairment or pediatric patients, the ability to complete the C-SSRS or PHQ-9 may be limited. If in the clinical opinion of the Investigator a specific patient cannot complete the instrument(s), the following strategies may be employed:

- Site staff may administer the questions directly to the patient or may ask for the information from a third party, such as a caregiver or family members, as appropriate.
- The Investigator may use his/her clinical judgment to skip any questionnaires that he/she feels are not appropriate for a specific patient.

Any deviation from the intended use of an instrument should be documented by the Investigator, along with the reason for the deviation. If the PHQ-9 and C-SSRS are not administered, the Investigator should document that the issues of depression and suicidality were assessed clinically (eg, discussion with caregivers).

See Appendix 8 for the pre-dose timing, location, and format of the Patient and Safety Questionnaires.

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

Patients ≥6 years of age

As required in the US by the Food and Drug Administration (FDA), for clinical trials of CNS-acting medications, changes in suicidality as assessed by the C-SSRS will be monitored over the course of the trial to ensure patient safety.

The C-SSRS is a tool used not only to predict suicide attempts but to assess the full range of evidence-based ideation and behavior items, with criteria for next steps (eg, referral to an MPH). There are 2 versions of the C-SSRS that will be administered according to the SoAs (Table 1, CCI).

- **The Baseline/Screening version** of the scale is the initial form of the instrument to assess suicidality in a patient's lifetime. This version can assess a patient's lifetime suicidality for data collection purposes as well as eligibility based on inclusion/exclusion criteria.
- **The Since Last Visit version** of the scale assesses suicidality since the patient's last visit. This version is meant to assess patients who have completed at least 1 initial C-SSRS assessment and should be used in subsequent visits. The 'Since Last Visit' version of the C-SSRS is asking about any suicidal thoughts or behaviors the patient/participant may have had since the last time the C-SSRS was administered.

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.

Any patient who reports suicidal behavior or suicidal ideation of type 4 or 5 on the C-SSRS during the trial will be captured as an AE and referred to an MHP.

The C-SSRS should be completed before dosing either in clinicor in the presence of trained nursing or site staff during telehealth visits, as applicable.

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

The PHQ-9 is a 9-item depression scale of the Patient Health Questionnaire. The PHQ-9 is a tool for assisting clinicians in diagnosing depression as well as selecting and monitoring treatment. The PHQ-A is a modification of the PHQ-9 for adolescents. After the patient has completed the PHQ-9 or PHQ-A questionnaire, it is scored by the trial staff.

The PHQ-A will be administered to patients 11 to 17 years of age and the PHQ-9 will be administered to patients ≥18 years of age.

The PHQ-9 or PHQ-A will be implemented at the time points designated in the SoAs (Table 1, CCI).

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.

The PHQ-9/PHQ-A questionnaires should be completed before dosing either in clinicor in the presence of trained nursing or site staff during telehealth visits, as applicable.

6.8.10.3. Children's Depression Inventory-2

The CDI-2 has both a self-report and a parent version. The CDI-2: Self-Report Short version is an efficient screening measure that contains 12 items. The self-report short version will be administered to patients 7 to <12 years of age according to the SoAs (Table 1, CCI

Items on the CDI-2 Parent form correspond to items on the self-report version and are suitably rephrased. Item selection for the parent forms was guided to maximize validity, and thus focused on observable manifestations of depression. The CDI-2 parent form consists of 17 items and the 4 choices provided for each item correspond to 4 levels of symptomatology: 0 (not at all), 1 (some of the time), 2 (often), or 3 (most of the time). The CDI2 parent version will be administered to caregivers of patients 7 to <12 years of age according to the SoAs (Table 1, CCI).

An AE will be recorded for any patient with a CDI-2 T-score ≥65 and the patient will be referred to an MHP.

The CDI-2 questionnaire should be completed before dosing either in clinicor in the presence of trained nursing or site staff during telehealth visits, as applicable.

6.9. Data Safety Monitoring

The Investigators will be responsible to review and evaluate safety data from their patients in a continuous manner. Cumulative safety data from the trial will be reviewed by the Sponsor on an ongoing basis for any safety signals or tolerability concerns. Additionally, this trial will be monitored by an independent Data Safety Monitoring Board (DSMB). The DSMB will operate under a separate charter and will meet periodically (ie, every 3 months) to review the cumulative safety data from the trial and will make a recommendation to continue or modify the trial, if needed. Details of the DSMB's composition and operations will be in the DSMB charter.

6.10. Adverse Events

The definitions of an AE or SAE can be found in Appendix 5. AEs will be recorded from the time a patient provides informed consent/assent. AEs reported after dosing on Day 1 will be considered treatment-emergent AEs (TEAEs).

AE will be reported by the patient (or, when appropriate, by a caregiver, surrogate, or the patient's legally authorized representative).

The Investigator and any designees are responsible for detecting, documenting, and recording events that meet the definition of an AE or SAE and remain responsible for following up AEs that are serious, considered related to the trial treatment or trial procedures, or that caused the patient to discontinue trial treatment (see Section 4.3).

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

All AEs, including SAEs, will be collected from the provision of informed consent/assent until the SFV at the time points designated in the SoAs (Table 1, CCI AEs reported after dosing on Day 1 will be considered TEAEs.

Medical occurrences that begin before the start of trial treatment will be recorded on the Medical History/Current Medical Conditions section of the eCRF (not the AE section).

All SAEs will be recorded and reported to the Sponsor or designee within 24 hours, as indicated in Appendix 5. The Investigator will submit any updated SAE data to the Sponsor within 24 hours of it being available.

Investigators are not obligated to actively seek AE or SAE in former trial patients. However, if the Investigator learns of any SAE, including a death, at any time after a patient has been discharged from the trial, and he/she considers the event to be reasonably related to the trial treatment or trial participation, the Investigator must promptly notify the Sponsor.

The method of recording, evaluating, and assessing causality of AE and SAE and the procedures for completing and transmitting SAE reports are provided in Appendix 5.

6.10.2. Method of Detecting AEs and SAEs

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

6.10.3. Follow-up of AEs and SAEs

After the initial AE/SAE report, the Investigator is required to proactively follow each patient at subsequent visits/contacts. All SAEs will be followed until resolution, stabilization, the event is otherwise explained, or the patient is lost to follow-up. Further information on follow-up procedures is given in Appendix 5.

6.10.4. Trial Treatment and Stopping Rules for Safety Considerations

Safety parameters will be monitored during the trial. Trial treatment administration will be interrupted if certain safety parameter criteria are met, and additional assessments may be implemented. The Monitoring Plan provides for detailed instructions.

6.10.4.1. Liver Function Tests

The central laboratory will notify the medical monitor of ALT or AST ≥2 x upper limit of normal (ULN) or total bilirubin >2 x ULN.

Patients with treatment-emergent ALT or AST elevations of ≥3 x ULN, with or without total bilirubin ≥2 x ULN, should interrupt treatment immediately and be followed closely with confirmatory follow-up testing performed by central laboratory within 48 to 72 hours of the initial finding. If a patient cannot come to the site for confirmatory testing, a local laboratory may be used. Local laboratory results may be reported immediately to the medical monitor as soon as possible. A detailed plan for monitoring transaminases, treatment interruption, discontinuation, and treatment resumptions will be provided in the Medical Monitoring plan.

6.10.5. Overdose

An overdose is a significant variation from the recommended/scheduled dosage for a product. For this study, an overdose of setmelanotide is considered a dose higher than:

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

In the event of an overdose, the Investigator should contact the Medical Monitor immediately. Appropriate supportive treatment should be initiated according to the patient's clinical signs and symptoms.

The quantity of the excess dose as well as the duration of the overdose are to be documented in the eCRF.

Decisions regarding dose interruptions or modifications will be made by the Investigator in consultation with the Medical Monitor based on the clinical evaluation of the patient.

6.10.6. Regulatory Reporting Requirements for SAEs

- Prompt notification by the Investigator to the Sponsor of a SAE is essential so that regulatory obligations and ethical responsibilities towards the safety of patients and the safety of a trial treatment 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 trial treatment under clinical investigation. The Sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, IRBs, IECs, and investigators.
- Investigator safety reports must be prepared for suspected unexpected serious adverse reactions (SUSAR) according to local regulatory requirements and Sponsor policy and forwarded to investigators as necessary.
- An investigator who receives an investigator safety report describing a SAE or other specific safety information (eg, 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.

7. STATISTICAL CONSIDERATIONS

This section describes the plans for analysis. Details of the statistical methodology for summaries and statistical analyses will be provided in a separate statistical analysis plan (SAP), which will be maintained by the Sponsor. The SAP may modify the plans outlined in the protocol; however, any major modifications of the primary endpoint definition and/or its analysis will also be reflected in a protocol amendment. If, after the trial has completed, changes are made to the SAP, then these deviations to the plan will be listed, along with an explanation as to why they occurred, in the clinical study report for the trial, as appropriate.

The primary analysis includes the first 120 patients with acquired HO dosed in any region who have completed the trial and any patients with acquired HO who discontinued after receiving their first dose.

A separate double-blind, multi-center, placebo-controlled, randomized sub-study (RM-493-040-A) will be conducted in the United States and the United Kingdom. The sub-study is designed to evaluate the efficacy and safety of setmelanotide on weight loss and hunger in a population of patients with congenital HO aged 4 years and older.

This sub-study in patients with congenital HO will be analyzed and reported separately. Sub-study analyses will be documented in the SAP and a CSR addendum with data from this sub-study will be submitted separately.

CCI [redacted]

7.1. Sample Size Determination

The primary objective of this trial is to evaluate the percent change in BMI in response to setmelanotide administered subcutaneously (SC) daily in patients with HO compared to placebo at the end of placebo-controlled trial. To evaluate the primary objective, the primary statistical hypothesis is that the percent reduction of BMI from baseline in the setmelanotide group is greater than that in the placebo group after approximately 52 weeks on a therapeutic regimen of setmelanotide in the Modified Intent-to-Treat (mITT) analysis set.

The sample size is mainly driven by the primary efficacy hypothesis with the safety database taken into consideration. With the planned sample size of ~120 patients (~80 patients in setmelanotide group vs ~40 patients in placebo group), the trial provides ~99.5% power to detect a treatment difference (treatment - placebo) of -10% in percent change of BMI from baseline after approximately 52 weeks on a therapeutic regimen of setmelanotide at 2-sided alpha of 0.05, assuming a common standard deviation of 10% (estimated from trial RM-493-030), a dropout rate of 20%, and 2:1 randomization. It is planned to enroll ~12 patients from Japan within the ~120 patients.

The primary safety hypothesis will be assessed by reviewing the accumulated safety data. The below table (Table 8) summarizes the approximate difference in percentage points (treatment – placebo) that can be ruled out with different power and 95% confidence if there are 80 patients in the treatment arm and 40 patients in the placebo arm.

Table 8: Difference in AE Proportions (Treatment – Placebo) That Can Be Ruled Out with 80 Patients in the Treatment Arm and 40 Patients in the Placebo Arm

Power (%)	Assumed True AE Incidence Rate				
	10%	20%	30%	40%	50%
80	22.4	25.4	26.5	26.6	25.6
85	24.0	27.2	28.4	28.3	27.2
90	26.1	29.4	30.6	30.5	29.2
95	29.2	32.6	33.8	33.5	32.0

If no particular AE/SAEs are observed from the 80 patients in the setmelanotide group, the trial provides 97.5% confidence that the true rate for the specific AE/SAE is <4.51%. If the incidence rate of an AE/SAE is 2.34%, then there is an 85% chance of observing at least one such AE/SAE among 80 patients in the setmelanotide group. If the incidence rate is 0.86%, then there is a 50% chance of observing at least one such AE/SAE.

7.2. Analysis Set

The following analysis populations will be used in the statistical analyses. A primary efficacy analysis cohort is defined as the first 120 patients dosed in any region who have completed the trial and any patients who discontinued after receiving their first dose.

Screening Analysis Set: is defined as all patients who signed the informed consent form.

Safety Analysis Set (SA): is defined as all patients who received at least 1 dose of study treatment (placebo or setmelanotide). Analyses performed on the safety set will be based on patients according to the treatment received.

Full Analysis Set (FAS): is defined as all randomized patients. Analyses performed on the FAS will be based on patients as randomized.

Modified Intention-to-Treat Analysis Set (mITT): is defined as all randomized patients who are exposed to at least 1 dose of study treatment.

Per-Protocol Set (PP): is defined as all patients in the FAS without any major protocol violations.

7.3. Definition of Baseline

Baseline is defined as the last available measurement prior to the randomization, for patients randomized into either the setmelanotide or placebo group.

7.4. Analysis of the Primary Efficacy Endpoint

The primary objective of this trial is to evaluate the mean percent change in BMI in response to setmelanotide administered SC daily in patients with HO compared to placebo at the end of placebo-controlled trial. To evaluate the primary objective, the primary efficacy endpoint of the trial is the mean percent change in BMI from Baseline after approximately 52 weeks on a therapeutic regimen of setmelanotide.

The statistical hypothesis for the primary efficacy endpoint is:

$$H_0: \mu_t - \mu_p \geq 0 \quad \text{vs} \quad H_1: \mu_t - \mu_p < 0$$

where μ_t is the mean percent change in BMI from baseline after approximately 52 weeks on a therapeutic regimen in setmelanotide group, and μ_p is the mean percent change in BMI from baseline after approximately 52 weeks on a therapeutic regimen in placebo group.

An analysis of covariance (ANCOVA) model, with an unequal variance to account for possible unequal residual variances, will be used for the primary analysis on the primary endpoint, adjusted with a stratification factor of age groups (≥18 years old, ≥12 and <18 years old, <12 years old) and subpopulations (Japanese and non-Japanese). The consistency of efficacy on the primary endpoint in the overall population and the Japanese population will be evaluated. A primary efficacy analysis cohort is defined as the first 120 patients dosed. The primary efficacy analysis will be based on all patients in any region who have completed the trial and any patients who discontinued after receiving their first dose. To ensure the integrity of the study at the site level, investigators and patients will remain blinded after the unblinding of the sponsor for the primary analysis. For patients already enrolled who are still progressing (in any region), missing values will be imputed using multiple imputation. The interaction of treatment effect and subpopulations will be explored and assessed in the statistical model. Descriptive summaries/analysis and graphical displays by subpopulations will be assessed and presented. The statistical hypothesis will be tested at a 2-sided 0.05 significance level. A 2-sided 95% confidence interval (CI) will be calculated and presented. The success criterion for the primary

hypothesis requires the rejection of the null hypothesis at the 2-sided 0.05 significance level. The statistical criterion corresponds to the 2-sided 95% CI for the mean difference (setmelanotide – placebo) excluding 0 (ie, upper bound of the CI <0).

The primary analysis will be conducted based on the mITT population and sensitivity analysis based on the PP may be conducted as appropriate. Multiple Imputation approach assuming missing not at random (MNAR) will be used as the primary approach for missing values and will model the missing measurements based on known measurements from retrieved dropouts in the same treatment group. Should there be insufficient retrieved dropouts to provide a reliable multiple imputation model, then the wash-out imputation method will be used where missing values for subjects on active drug will be imputed with observed baseline and data from the placebo group. No intermediate values from the active treatment group will be used in the imputation.

The primary efficacy analysis will be based on the treatment policy estimand approach, in which all patients, regardless of intercurrent events, continue to be measured at each prespecified clinical visit unless consent to collect such data is explicitly withdrawn, and in which all such measurements are included in the statistical analyses.

To assess the sensitivity of results to the primary missing data handling approach, a two-dimensional tipping point analysis will be conducted that will vary assumptions about the missing outcomes on the two treatment arms independently, including scenarios in which dropouts on treatment have worse outcomes than dropouts on placebo.

Other sensitivity analysis, based on data as observed (ie, no imputation on missing values) and Last Observation Carried Forward (LOCF), etc, may be explored and provided. Subgroup analyses by sex, age, and race may be explored and provided as appropriate. Details will be documented in the SAP.

7.5. Analysis of the Secondary Efficacy Endpoints

7.5.1. Key Secondary Efficacy Endpoints

Due to the rarity of the disease indication and small sample size, formal multiplicity adjustment procedures will not be enforced. However, to assist the comprehensive assessment and interpretation of the efficacy of setmelanotide, appropriate statistical testing will be performed on the key secondary efficacy endpoints according to the following hierarchical order to control the overall type I error rate. The p-values and the corresponding CIs will be provided.

- The proportion of patients with ≥5% reduction in BMI in adult patients (≥18 years of age), or BMI Z-score reduction of ≥0.2 points in pediatric patients (<18 years of age) from Baseline after approximately 52 weeks on a therapeutic regimen of setmelanotide compared to placebo.

  The between-group comparison on the proportion of patients with ≥5% reduction in BMI in adult patients (≥18 years of age), or BMI Z-score reduction of ≥0.2 in pediatric patients (<18 years of age) from Baseline after approximately 52 weeks on a therapeutic regimen will be conducted with a Cochran–Mantel–Haenszel (CMH) test with adjustment of stratification factors of age group and subpopulation (Japanese

and non-Japanese). The associated corresponding 2-sided 95% CI will be presented. The analysis will be based on the mITT.

- The proportion of all patients with ≥5% reduction in BMI from baseline after approximately 52 weeks on a therapeutic regimen of setmelanotide compared to placebo.

  The between-group comparison on the proportion of all patients with ≥5% reduction in BMI from baseline after approximately 52 weeks on a therapeutic regimen will be conducted Cochran–Mantel–Haenszel (CMH) test with adjustment of stratification factors of age group and subpopulation (Japanese and non-Japanese) at a 2-sided 0.05 significance level. The associated corresponding 2-sided 95% CI will be presented. The analysis will be based on the mITT.

- Mean change in the weekly average of the daily most hunger score in patients ≥12 years old from Baseline after approximately 52 weeks on a therapeutic regimen of setmelanotide compared to placebo.

An ANCOVA model, with unequal variance to account for possible unequal residual variances, will be used for the between-group comparison on this endpoint, adjusted with baseline daily most hunger score and a stratification factor of age groups (≥18 years old, ≥12 and <18 years old) and subpopulations (Japanese and non-Japanese populations). The consistency of efficacy on this endpoint in the overall population and the Japanese population will be evaluated. Descriptive summaries/analysis and graphical displays by subpopulations will be assessed and presented. The statistical hypothesis will be tested at a 2-sided 0.05 significance level. A 2-sided 95% CI will be calculated and presented. The success criterion for the hypothesis requires the rejection of the null hypothesis at the 2-sided 0.05 significance level. The statistical criterion corresponds to the 2-sided 95% CI for the mean difference (setmelanotide – placebo) excluding 0 (ie, upper bound of the CI <0).

7.5.2. Other Secondary Efficacy Endpoints

There are 11 other secondary efficacy endpoints in the trial:

1. The proportion of patients with a ≥2-point reduction in the weekly average of the daily most hunger score from Baseline after approximately 52 weeks on a therapeutic regimen of setmelanotide compared to placebo
2. The mean change in the weekly average of the symptoms of hyperphagia composite score from Baseline after approximately 52 weeks on a therapeutic regimen of setmelanotide compared to placebo
3. The proportion of patients with a ≥10% reduction in BMI from Baseline after approximately 52 weeks on a therapeutic regimen of setmelanotide compared to placebo
4. The proportion of patients with ≥10% reduction in weight from Baseline after approximately 52 weeks on a therapeutic regimen of setmelanotide compared to placebo.
5. Mean percent change in weight in patients ≥18 years from Baseline after approximately 52 weeks on a therapeutic regimen of setmelanotide compared to placebo

6. Mean BMI Z-score and BMI percentile reduction in patients <18 years of age from Baseline after approximately 52 weeks on a therapeutic regimen of setmelanotide compared to placebo
7. The proportion of patients aged ≥4 to <18 years with ≥0.2-point reduction of BMI Z-score from Baseline after approximately 52 weeks on a therapeutic regimen of setmelanotide compared to placebo
8. The proportion of patients with BMI <30 kg/m^2 (patients aged ≥18 years) or <95th percentile (patients aged <18 years) from Baseline after approximately 52 weeks on a therapeutic regimen of setmelanotide compared to placebo
9. Mean change in physical functioning score and total score for the IWQOL (IWQOL-Lite-CT in patients ≥18 years and IWQOL-Kids in patients 11 to <18 years), from Baseline after approximately 52 weeks on a therapeutic regimen of setmelanotide compared to placebo.
10. Change in waist circumference from Baseline after approximately 52 weeks on a therapeutic regimen of setmelanotide compared to placebo.
11. The difference in change in cardiometabolic parameters including blood pressure, CCI [redacted] liver function and CCI [redacted] from Baseline after approximately 52 weeks on a therapeutic regimen of setmelanotide compared to placebo.

The between-group comparison on the two-sample proportions in the above No. 1, 3, 4, 7, and 8 endpoints will be conducted with a Cochran–Mantel–Haenszel (CMH) test with adjustment of stratification factors of age group and subpopulation (Japanese and non-Japanese) at a 2-sided 0.05 significance level. The associated corresponding 2-sided 95% CI will be presented. The analysis will be based on the mITT population.

The between-group comparison on the two-sample means in the above number 2, 5, 6, 9, 10 and 11 endpoints will be conducted with ANCOVA models. The statistical hypothesis will be tested at a 2-sided 0.05 significance level. A 2-sided 95% CI will be calculated and presented.

7.5.3. Analysis of the Exploratory Efficacy Endpoints

CCI [redacted]

CCI [redacted]

CCI [redacted]

7.6. Safety Analyses

AEs/SAEs will be summarized descriptively with frequencies and percentages by treatment group and overall. A by-patient AE data listing including onset and resolution dates, verbatim term, preferred term, treatment, severity, relationship to treatment, action taken, and outcome will be provided.

Laboratory evaluations, vital signs, and other assessments (as appropriate) will be summarized by date and time of collection. In addition, change from baseline to any post-dose values may be summarized. Continuous outcomes (eg, vital signs, safety laboratory parameters) will be summarized using n, mean, median, SD, etc. Frequency of patients with abnormal safety laboratory results will be tabulated. Patient listings may also be produced for these safety assessments.

Nausea, vomiting, and diarrhea will be designated as AEs of Special Interest.

Safety analysis will be conducted based on the SA Set.

7.7. Interim Analyses

No formal interim analysis is currently planned for this trial.

7.8. Multiplicity

No multiplicity adjustments are required because this trial has only 1 primary endpoint. This controls the overall alpha at 0.05, 2-sided.

There are 3 key secondary efficacy endpoints planned in the trial. Based on the rarity of this disease, and the small number of patients to be enrolled in this trial, the ability to use extremely rigorous statistical approaches to address multiplicity for these key secondary endpoints is limited. Therefore, for publication, nominal-p-values will be used to interpret *each endpoint separately* in this small trial. The Sponsor acknowledges that this approach may increase the probability of potential Type 1 error for the *set* of 3 key secondary efficacy endpoints being analyzed. Therefore, if the primary endpoint is successfully met, then the Sponsor intends to apply a step-down procedure (i.e. sequential testing/fixed sequence testing) on the 3 key secondary endpoints to control the overall type 1 error based on the below order:

- The proportion of patients with ≥5% reduction from baseline in BMI in adult patients (≥18 years of age), and BMI Z-score reduction of ≥0.2 in pediatric patients from Baseline after approximately 52 weeks on a therapeutic regimen of setmelanotide treatment compared to placebo.
- The proportion of all patients with ≥5% reduction in BMI from Baseline after approximately 52 weeks on a therapeutic regimen of setmelanotide compared to placebo.
- Mean change in the weekly average of the daily most hunger score in patients ≥12 years old from Baseline after approximately 52 weeks on a therapeutic regimen of setmelanotide treatment compared to placebo.

8. REFERENCES

All literature references are available upon request.

Ahmad T, Garcia-Filion P, Borchert M, Kaufman F, Burkett L, Geffner M. Endocrinological and auxological abnormalities in young children with optic nerve hypoplasia: a prospective study. J Pediatr. 2006 Jan;148(1):78-84.

An JJ, Rhee Y, Kim SH, et al. Peripheral effect of alpha-melanocyte-stimulating hormone on fatty acid oxidation in skeletal muscle. J Biol Chem. 2007;282:2862-70.

CCI

Enriori PJ, Chen W, Garcia-Rudaz MC, et al. alpha-Melanocyte stimulating hormone promotes muscle glucose uptake via melanocortin 5 receptors. Mol Metab. 2016;5:807-22.

Fitzpatrick TB. Soleil et peau. J Med Esthet. 1975;2:33034.

CCI

Hochberg I, Hochberg Z. Hypothalamic obesity. Endocr Dev. 2010;17:185-196. doi: 10.1159/000262539. Epub 2009 Nov 24. PMID: 19955767.

Holland J, Sorrell J, Yates E, et al. A brain-melanocortin-vagus axis mediates adipose tissue expansion independently of energy intake. Cell Rep. 2019;27:2399-410 e6.

CCI

Kolotkin RL, Williams VSL, Ervin CM, et al. Validation of a new measure of quality of life in obesity trials: Impact of Weight on Quality of Life-Lite Clinical Trials Version. Clin Obes. 2019;9(3):e12310.

Müller HL. Consequences of craniopharyngioma surgery in children. J Clin Endocrinol Metab. 2011 Jul;96(7):1981-91. doi: 10.1210/jc.2011-0174. Epub 2011 Apr 20. PMID: 21508127.

Müller HL, Tauber M, Lawson EA, et al. Hypothalamic syndrome. Nat Rev Dis Primers. 2022 Apr 21;8(1):24.

CCI [redacted]

NHLBI. The Practical Guide Identification, Evaluation, and Treatment of Overweight and Obese in Adults. NIH Publication No. 00-4084, October 2000.

CCI [redacted]

Patel L, Cooper CD, Quinton ND, et al. Serum leptin and leptin binding activity in children and adolescents with hypothalamic dysfunction. J Pediatr Endocrinol Metab. 2002;15:963-71.

CCI [redacted]

Rhythm Pharmaceuticals. IMCIVREE (setmelanotide). Israel Ministry of Health. https://israeldrugs.health.gov.il/#!/byDrug. Accessed December 2024.

Rhythm Pharmaceuticals. IMCIVREE (setmelanotide) Package Insert. U.S. Food and Drug Administration. https://www.accessdata.fda.gov/drugsatfda_docs/label/2022/213793s001lbl.pdf. Revised June 2022. Accessed 18 December 2024.

Rhythm Pharmaceuticals. IMCIVREE Product Monograph. Health Canada. https://pdf.hres.ca/dpd_pm/00070511.PDF. Accessed 18 December 2024.

Rhythm Pharmaceuticals. IMCIVREE (setmelanotide) Summary of Product Characteristics. European Medicines Agency. https://www.ema.europa.eu/en/documents/product-information/imcivree-epar-product-information_en.pdf.. Accessed 18 December 2024.

Rhythm Pharmaceuticals. IMCIVREE (setmelanotide) Summary of Product Characteristics. Medicines and Healthcare Products Regulatory Agency. https://mhraproducts4853.blob.core.windows.net/docs/2adfa2315cbead1e03988f01ac07b8fdcbc5b8e7. Accessed 18 December 2024.

Roth C, Wilken B, Hanefeld F, et al. Hyperphagia in children with craniopharyngioma is associated with hyperleptinaemia and a failure in the downregulation of appetite. Eur J Endocrinol. 1998;138:89-91.

Roth CL, Enriori PJ, Gebhardt U, et al. Changes of peripheral alpha-melanocyte-stimulating hormone in childhood obesity. Metabolism. 2010;59:186-94.

Roth CL, Blevins JE, Ralston M, et al. A novel rodent model that mimics the metabolic sequelae of obese craniopharyngioma patients. Pediatr Res. 2011;69:230-6.

Roth CL, Gebhardt U, Muller HL. Appetite-regulating hormone changes in patients with craniopharyngioma. Obesity (Silver Spring). 2011;19:36-42.

Roth CL, Eslamy H, Werny D, et al. Semiquantitative analysis of hypothalamic damage on MRI predicts risk for hypothalamic obesity. Obesity. 2015;23(6):1226-1233.

Shaikh MG, Grundy RG, Kirk JM. Hyperleptinaemia rather than fasting hyperinsulinaemia is associated with obesity following hypothalamic damage in children. Eur J Endocrinol. 2008;159:791-7.

Sterkenburg AS, Hoffmann A, Gebhardt U, Warmuth-Metz M, Daubenbüchel AM, Müller HL. Survival, hypothalamic obesity, and neuropsychological/psychosocial status after childhood-onset craniopharyngioma: newly reported long-term outcomes. Neuro Oncol. 2015 Jul;17(7):1029-38. Epub 2015 Apr 2.

Teng H, Liu Z, Yan O, et al. Nomograms for predicting overall survival among patients with craniopharyngiomas at initial diagnosis: A SEER population-based analysis. Int J Gen Med. 2021;14:3517-3527.

9. APPENDICES

APPENDIX 1. LIST OF ABBREVIATIONS

Abbreviation	Definition
α-MSH	alpha-melanocyte-stimulating hormone
ABPM	Ambulatory blood pressure monitoring
ADA	Anti-drug antibody
AE	Adverse event
ALT	Alanine aminotransferase
ANCOVA	Analysis of covariance
AST	Aspartate aminotransferase
BBS	Bardet-Biedl syndrome
BMI	Body mass index
BP	Blood pressure
BUN	Blood urea nitrogen
CDI-2	Children's Depression Inventory-2
CFR	Code of Federal Regulations
CGIC	Caregivers Global Impression of Change
CGIS	Caregivers Global Impression of Severity
CI	Confidence interval
CIOMS	Council for International Organizations of Medical Sciences
CNS	Central nervous system
COVID-19	Coronavirus Disease 2019
CRO	Contract research organization
CPHD	Childhood-onset Combined Pituitary Hormone Deficiency
C-SSRS	Columbia-Suicide Severity Rating Scale
CTCAE	Common Terminology Criteria for Adverse Events
%CV	Percent coefficient of variation
DSMB	Data Safety Monitoring Board
CCI	[redacted]
ECG	Electrocardiogram
eCRF	Electronic case report form
EDC	Electronic data capture
CCI	[redacted]

Abbreviation	Definition
CCI	[redacted]
EOT	End of treatment
EU	European Union
ETT	Early Termination of Treatment
CCI	[redacted]
FAS	Full Analysis Set
FDA	Food and Drug Administration
FSH	Follicle-stimulating hormone
GCP	Good Clinical Practice
GFR	Glomerular filtration rate
GI	Gastrointestinal
GLP-1	Glucagon-like peptide-1
CCI	[redacted]
β-hCG	Beta-human chorionic gonadotropin
CCI	[redacted]
HO	Hypothalamic obesity
HR	Heart rate
IB	Investigator's Brochure
ICF	Informed consent form
ICH	International Council for Harmonization
IEC	Independent Ethics Committee
IGF1	Insulin-like Growth Factor 1
IRB	Institutional Review Board
IRT	Interactive response technology
IUD	Intrauterine device
IWQOL	Impact of Weight on Quality of Life
CCI	[redacted]
LEPR	Leptin receptor
LOCF	Last observation carried forward
LTE	Long-term extension
Max	Maximum
MC4R	Melanocortin 4 receptor

Abbreviation	Definition
MDD	Major Depressive Disorder
MHP	Mental health professional
Min	Minimum
mITT	Modified Intention-to-Treat
CCI [redacted]	[redacted]
CCI [redacted]	[redacted]
MSH	Melanocortin stimulating hormone
MVPA	Moderate to vigorous physical activity
NHLBI	National Heart, Lung, and Blood Institute
CCI [redacted]	[redacted]
PCSK1	Proprotein convertase subtilisin/kexin type 1
PGIC	Patient global impression of change
PGIS	Patient global impression of severity
PHQ	Patient Health Questionnaire
PK	Pharmacokinetic
POMC	Proopiomelanocortin
PP	Per protocol set
PPL	POMC, PCSK1, LEPR, collectively
PRO	Patient Reported Outcome
CCI [redacted]	[redacted]
PWS	Prader-Willi syndrome
QD	Once daily
q.s.	Quantity sufficient
RGDO	Rare genetic diseases of obesity
ROHHADNET	Rapid-onset obesity with hypoventilation, hypothalamic, autonomic dysregulation, neuroendocrine tumor syndrome
RR	Respiration rate
SA	Safety Analysis Set
SAE	Serious adverse event
SAP	Statistical analysis plan
SC	Subcutaneous(ly)
SD	Standard deviation

Abbreviation	Definition
SFV	Safety Follow-up Visit
SoA	Schedule of Assessments
CCI	[redacted]
SUSAR	Suspected unexpected serious adverse reaction
FT4	Free thyroxine
TEAE	Treatment-emergent adverse event
ULN	Upper limit of normal
UK	United Kingdom
US	United States
WOCBP	Woman of childbearing potential

APPENDIX 2. CONSIDERATIONS FOR REDUCING PAIN AND DISTRESS IN THE PEDIATRIC POPULATION

Although the trial procedures and assessments required per protocol are classified as "No or Minimal Risk" (with the exception of CCI at participating US sites which may be classified as "Minor Increase over Minimal Risk") according to the 2008 Guidance Document "*Ethical Considerations for Clinical Trials on Medicinal Products Conducted with the Paediatric Population*", considerations for reducing pain in distress in participants <18 years of age are suggested below.

- The clinical trial may only be conducted if it exposes the person concerned to as little burden and other foreseeable risks as possible.
- Physical and emotional pain should be prevented as much as possible, and effectively treated when unavoidable.
- In order to minimize pain, distress, and fear, facilities should be appropriate to childcare, and the personnel should be trained to look after children and supervised by experienced health care professionals. Staff should be trained to communicate with both parents (or legal representative) and children. Generally, this would assume non-adult patients are being studied at experienced pediatric centers.
- For most procedures, the child should always be accompanied by a trial-related staff member who could provide reassurance. At the sign of distress and/or dissent, the procedure should be stopped. A short pause to allow the child to feel in control, further explanation, and an assessment of the situation may be needed to reassure the child, or to decide to definitely abandon the procedure at the discretion of the Investigator.
- In all situations, investigations/interventions should be limited to the minimum required for obtaining valid data and performed using size-/age-appropriate material and devices, including limiting in advance the number of attempts for sampling.
- Trial treatment injections should only be performed by parents (or home health care professionals), unless the child is of suitable age and competency, and desires the ability to do so.
- Although almost all trial procedures are classified as low risk (with the exception of CCI, which may be classified as "minor increase over minimal risk"), risk should be continuously monitored and assessed by appropriate personnel.
- For assessments in which there is a psychological component, measures should be taken to minimize distress. For example, Tanner Staging assessments could utilize a diagram for the child to point to and indicate what stage they currently are, vs. having to have an exam without clothes.

A comment on benefit risk: Risk is very low, from procedures and/or known safety profile of the drug (both clinically and toxicologically, where large margins and preliminary data from juvenile toxicology studies have not identified any new or concerning safety concerns), and based on one representative example of rare genetic disease of obesity impacting the MC4 pathway, there is the possibility of major benefit.

APPENDIX 3. FITZPATRICK SCALE

Skin Type	Skin Color	Characteristics
I	White; very fair; red or blond hair; blue eyes; freckles	Always burns, never tans
II	White; fair; red or blond hair; blue, hazel, or green eyes	Usually burns, tans with difficulty
III	Cream white; fair with any eye or hair color; very common	Sometimes mild burn, gradually tans
IV	Brown; typical Mediterranean Caucasian skin	Rarely burns, tans with ease
V	Dark Brown; mid-eastern skin types	Very rarely burns, tans very easily
VI	Black	Never burns, tans very easily

Fitzpatrick 1975.

APPENDIX 4. INJECTION SITE EVALUATIONS

Injection sites will be assessed using a form similar to the depiction below at the time points outlined in the SoA and in the setting of any injection site reaction adverse experience.

Local Skin Tolerability Assessment

Reaction	NONE	Mild	Moderate	Severe	Measurement (if applicable)
Erythema*	□	□	□	□	
Edema*	□	□	□	□	
Induration*	□	□	□	□	
Itching	□	□	□	□	
Pain or Tenderness*	□	□	□	□	
Other: _____	□	□	□	□	

* If present, region will be measured, length and width as appropriate.

Initials: _____

APPENDIX 5. ADVERSE EVENTS: DEFINITIONS AND PROCEDURES FOR RECORDING, EVALUATING, FOLLOW-UP, AND REPORTING

Definition of Adverse Event (AE)

AE Definition
• An AE is any untoward medical occurrence in a patient or clinical trial patient, temporally associated with the use of trial treatment, whether or not considered related to the trial treatment. • NOTE: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of trial treatment.

Events Meeting the AE Definition
• Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (eg, ECG, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator (ie, not related to progression of underlying disease). • Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition. • New conditions detected or diagnosed after trial treatment administration even though it may have been present before the start of the trial. • Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction. • Signs, symptoms, or the clinical sequelae of a suspected overdose of either trial treatment 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 fulfil the definition of an AE or SAE.

Events NOT Meeting the AE Definition
• Any clinically significant abnormal laboratory findings or other abnormal safety assessments which are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the patient's condition. • The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the patient's condition. • Medical or surgical procedure (eg, endoscopy, appendectomy): the condition that leads to the procedure is the AE. • Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital). • Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the trial that do not worsen.

Definition of Serious Adverse Event (SAE)

If an event is not an AE per definition above, then it cannot be an SAE even if serious conditions are met (eg, hospitalization for signs/symptoms of the disease under trial, death due to progression of disease).

An SAE is defined as any untoward medical occurrence that, at any dose:
a. Results in death
b. Is life-threatening • The term 'life-threatening' in the definition of 'serious' refers to an event in which the patient 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 patient has been detained (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 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 (eg, sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.
e. Is a congenital anomaly/birth defect
f. Important medical event • Medical or scientific judgment should be exercised in deciding whether SAE reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the patient 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 in an emergency room or at home for allergic bronchospasm, blood dyscrasias, or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

Recording and 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.
- It is **not** acceptable for the investigator to send photocopies of the patient's medical records in lieu of completion of the AE/SAE CRF page.
- There may be instances when copies of medical records for certain cases are requested. In this case, all patient identifiers, with the exception of the patient number, will be redacted on the copies of the medical records before submission.
- 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 Intensity

Intensity of all AEs including clinically significant treatment-emergent laboratory abnormalities, injection site reactions and potential systemic reactions will be graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE), Version 5.0. The CTCAE grade refers to the severity of the AE and ranges from Grade 1 (mild AE), Grade 2 (moderate AE), Grade 3 (severe AE) and Grade 4 (life-threatening or disabling AE) to Grade 5 (death related to AE).

Adverse events not listed by the CTCAE will be graded as follows:

- Mild: An event that is easily tolerated by the patient, causing minimal discomfort and not interfering with everyday activities.
- Moderate: An event that causes sufficiently discomfort and interferes with normal everyday activities.
- Severe: An event that prevents normal everyday activities. An AE that is assessed as severe should not be confused with a SAE. Severe is a category utilized for rating the intensity of an event; and both AEs and SAEs can be assessed as severe.
- An event is defined as 'serious' when it meets at least 1 of the predefined outcomes as described in the definition of an SAE, NOT when it is rated as severe.

Assessment of Causality

- The investigator is obligated to assess the relationship between trial treatment and each occurrence of each AE/SAE.
- A "reasonable possibility" of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.
- The investigator will use clinical judgment to determine the relationship.
- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to trial treatment administration will be considered and investigated.
- The investigator will also consult the Investigator's Brochure (IB) and/or Product Information, for marketed products, in his/her assessment.

Assessment of Causality

- 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. However, **it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the SAE data**.
- The investigator may change his/her opinion of causality in light of follow-up information and send a SAE follow-up report with the updated causality assessment.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.

A medically qualified Investigator must assess the relationship of any AE (including SAEs) to the use of the trial treatment, as related or not related, based on clinical judgment and using all available information, and may include consideration of the following factors:

- Possible alternative causes of the AE, including the disease under treatment, pre-existing conditions, concomitant use of other drugs, and presence of environmental or genetic factors.
- The temporal association between trial treatment exposure and onset of the AE.
- Whether the manifestations of the AE are consistent with known actions or toxicity of the trial treatment.
- The AE resolved or improved with decreasing the dose or stopping use of the trial treatment (dechallenge). Judgment should be used if multiple products are discontinued at the same time.

The causal relationship between the trial treatment and the AE will be assessed using one of the following categories:

- **Not Related:** Factors consistent with an assessment of Not Related include:
  - Temporal relationship is lacking (eg, the event did not occur within a reasonable time frame following administration of the trial treatment); or
  - Other causative factors more likely explain the event (eg, a pre-existing condition, other concomitant treatments).
- **Related:** Factors consistent with an assessment of Related include:
  - There is a “reasonable possibility” of a relationship; ie, there are facts, evidence, and/or arguments to suggest a causal relationship (not just that “a relationship cannot be ruled out”);
  - There is a positive temporal relationship (eg, the event occurred within a reasonable time frame following administration of trial treatment);
  - The AE is more likely explained by the investigational product than by another cause (ie, the AE shows a pattern consistent with previous knowledge of the investigational product or the class of the trial treatment).

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 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 patient dies during participation in the trial or during a recognized follow-up period, the investigator will provide a copy of any post-mortem findings including histopathology. • New or updated information will be recorded in the originally completed CRF. • The investigator will submit any updated SAE data to the Sponsor within 24 hours of receipt of the information.

Reporting of SAEs

SAE Reporting via an Electronic Data Collection Tool
• The primary mechanism for reporting an SAE will be the electronic data collection tool. • If the electronic system is unavailable for more than 24 hours, then the site will use the paper SAE data collection tool (see next section). • The site will enter the SAE data into the electronic system as soon as it becomes available. • After the trial is completed at a given site, the electronic data collection tool will be taken off-line to prevent the entry of new data or changes to existing data. • If a site receives a report of a new SAE from a trial patient or receives updated data on a previously reported SAE after the electronic data collection tool has been taken off-line, then the site can report this information on a paper SAE form (see next section) or by telephone.

SAE Reporting to via Paper CRF
• Facsimile transmission of the SAE paper CRF is the preferred method to transmit this information • In rare circumstances and in the absence of facsimile equipment, notification by telephone is acceptable with a copy of the SAE data collection tool sent by overnight mail or courier service. • 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 reporting will be provided to sites.

APPENDIX 6. TRIAL GOVERNANCE CONSIDERATIONS

Regulatory and Ethical Considerations

- This trial 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 (CIOMS) International Ethical Guidelines
  - Applicable International Council for Harmonisation (ICH) Good Clinical Practice (GCP) Guidelines
  - Applicable laws and regulations
- The protocol, protocol amendments, Informed Consent form (ICF), Investigator Brochure, and other relevant documents (eg, advertisements) must be submitted to an IRB/IEC (Investigational Review Board/Independent Ethics Committee) by the investigator and reviewed and approved by the IRB before the trial is initiated.
- Any amendments to the protocol will require IRB/IEC approval before implementation of changes made to the trial design, except for changes necessary to eliminate an immediate hazard to trial patients.
- The investigator will be responsible for the following:
  - Providing written summaries of the status of the trial to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB
  - Notifying the IRB/IEC of SAEs or other significant safety findings as required by IRB/IEC procedures
  - Providing oversight of the conduct of the trial at the 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), and all other applicable local regulations

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 trial and for 1 year after completion of the trial.

Informed Consent Process

- The investigator or his/her representative will explain the nature of the trial to the patient or his/her legally authorized representative and answer all questions regarding the trial.
- Patients must be informed that their participation is voluntary. Patients or their legally authorized representative will be required to sign a statement of informed consent that

meets the requirements of 21 CFR 50, local regulations, ICH guidelines, Health Insurance Portability and Accountability Act requirements, where applicable, and the IRB or trial center.

- The medical record must include a statement that written informed consent/assent was obtained before the patient was enrolled in the trial and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.
- Patients must be re-consented to the most current version of the ICF(s) during their participation in the trial; patients must also be re-consented if they become of age, as applicable.
- A copy of the ICF(s) must be provided to the patient or the patient's legally authorized representative.

Patients who are rescreened are required to sign a new ICF.

Data Protection

- Patients will be assigned a unique identifier by the Sponsor. Any patient records or datasets that are transferred to the Sponsor will contain the identifier only; patient names or any information which would make the patient identifiable will not be transferred. Data systems will have control and requirements in accordance with local data protection law.
- The patient must be informed that his/her personal trial-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 patient who will be required to give consent for their data to be used as described in the informed consent.
- The patient 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.

Clinical Study Report

Per the current ICH E3 Guidelines, a clinical study report (CSR) will be written and submitted in accordance with local regulations. Analysis from the sub-study in patients with congenital HO (RM-493-040-A) will be submitted separately.

Data Quality Assurance

All patient data relating to the trial will be recorded on printed or eCRF unless transmitted to the Sponsor electronically (eg, electronic diary). The Investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the eCRF.

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

The Investigator must permit trial-related monitoring, audits, IRB/IEC review and regulatory agency inspections and provide direct access to source data documents.

Monitoring details describing strategy (eg, 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 on-site monitoring) are provided in the Monitoring Plan.

The Sponsor or designee is responsible for the data management of this trial including quality checking of the data.

The Sponsor assumes accountability for actions delegated to other individuals (eg, Contract Research Organizations).

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

Records and documents, including signed ICFs, pertaining to the conduct of this trial must be retained by the Investigator for at least 2 years after the last marketing application approval or 2 years after formal discontinuation of the clinical development of the investigational product or according to applicable regulatory requirement(s). If the Investigator withdraws from the responsibility of keeping the trial records, custody must be transferred to a person willing to accept the responsibility. The Sponsor must be notified immediately by telephone or e-mail and the notification confirmed in writing if a custodial change occurs.

Source Documents

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

Data 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 trial. Also, current medical records must be available.

Any electronic trial data are to be entered into a secure, validated data processing system and a backup maintained. Any changes to electronic trial data will be documented.

Trial or Site Closure

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

The Investigator may initiate trial-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 trial site by the Sponsor or Investigator may include but are not limited to:

For trial termination:

- Determination of unexpected, significant, or unacceptable risk to patients

- Discontinuation of further trial intervention development.

For 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.
- Total number of participants enrolled earlier than expected.
- Insufficiently complete and/or evaluable data

If the trial is prematurely terminated or suspended, the Sponsor shall promptly inform the Investigators, the IRBs/IECs, the regulatory authorities, and any contract research organization(s) involved in the trial 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.

Publication Policy

All information regarding setmelanotide supplied by the Sponsor to the Investigator or generated as a result of any clinical studies is privileged and confidential information belonging to the Sponsor. The Investigator agrees to use Sponsor’s confidential information solely to accomplish the trial and will not use such information for any other purposes without the prior written consent of Rhythm. It is understood that there is an obligation to provide the Sponsor with complete and accurate data obtained during the trial. The information obtained from the clinical trial will be used towards the development of setmelanotide and may be disclosed by Rhythm to regulatory authority(ies), other investigators, corporate partners, or consultants as required.

It is anticipated that the results of this trial may be presented at scientific meetings and/or published in a peer reviewed scientific or medical journal. The Sponsor generally supports publication of multicenter studies initially in their entirety and not as individual site data. A coordinating investigator will be designated.

Subsequently, individual Investigators may publish results from the trial in compliance with their agreement with the Sponsor.

A pre-publication manuscript is to be provided to Rhythm at least 30 days prior to the submission of the manuscript to a publisher. Similarly, the Sponsor will provide any company-prepared manuscript to the Investigators for review at least 30 days prior to submission to a publisher. All publications and presentations must be approved in writing by Rhythm before public disclosure.

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

APPENDIX 7. GUIDANCE ON TRIAL CONDUCT DURING THE COVID-19 (CORONAVIRUS) PANDEMIC

The Coronavirus Disease 2019 (COVID-19) pandemic could impact the conduct of this clinical trial for several reasons, including: self-isolation/quarantine by patients and trial-site personnel; travel restrictions/limited access to public places, including hospitals; and reassignment of site personnel to critical tasks.

In accordance with recent health authority guidance, the Sponsor is providing temporary considerations for trial conduct in the event of disruption of the trial. This guidance does not supersede any local or government requirements or the clinical judgment of the investigator. If at any time a patient's safety is considered to be at risk, trial intervention will be discontinued, and trial follow-up will be conducted.

If COVID restrictions are imposed on or by the trial site and the site cannot fully carry out normal operations, the following measures are recommended on a temporary basis during the COVID-19 pandemic:

- Where possible, every effort should be made to complete all protocol-required assessments. In place of a required site visit, a qualified healthcare provider could perform trial-related procedures as per the Schedule of Events via a home visit, including but not limited to collection of body weight, vital signs, physical examinations, electrocardiograms (ECGs), recording of adverse events (AEs), collection of blood and urine samples. Most efficacy assessments could potentially be done off site. Investigators should use their clinical judgment to determine whether a patient can continue trial treatment in the absence of on-site clinic visits or consider alternatives such as temporary treatment interruption or trial discontinuation.
- All protocol-required assessments missed due to COVID restrictions should be documented in detail within the patients' source documents and should be clearly designated as "COVID-19 RELATED". It must be documented if a site visit is instead conducted remotely. Source documentation should detail how each assessment was collected (eg, remote vs. on-site, central vs. local laboratory, vital signs taken at home by caregiver vs. delegated in-home nursing, etc).
- If applicable, discontinuations of trial interventions and withdrawal from the trial due to disruption of trial conduct by the pandemic should be documented with the prefix "COVID-19 RELATED" in the case report form (CRF).

COVID-19 Infection in Trial Patients:

There is currently no available data suggesting that patients treated with setmelanotide should have treatment interrupted during the COVID-19 pandemic. If a patient develops symptoms associated with coronavirus infection, it is recommended to confirm the diagnosis using locally approved laboratory kits and report it to the local health authorities, as required. Patients with positive test results for SARS-COV-2 should have this recorded as an AE, and if hospitalized, this should be reported as a serious adverse event (SAE).

APPENDIX 8. PRO AND SAFETY QUESTIONNAIRES

All assessments will be completed at timepoints listed in the SoA (Table 1). For all patient and safety questionnaires, training will be provided on the use of tablets and e-diaries for site and patient data collection. The table below summarizes the timing relative to dosing, the location where the assessment should be conducted, and how the data will be collected. In the sub-study (RM-493-040-A), paper may be used for the collection of PROs

Table 9: PROs and Safety Questionnaires: Timing and Format of Collection

PROs and Safety Questionnaires	Required Pre-dose	Location	Format During Trial	Format During Bridging Visits
C-SSRS	Yes	At clinic/telehealth	EDC	EDC
PHQ-9/PHQ-A	Yes	At clinic/telehealth	EDC	EDC
CDI-2	Yes	At clinic/telehealth	EDC	EDC
Hunger Questions	Yes	At home	E-diary	N/A
CCI [redacted] a	Yes	At home	E-diary	Paper diary (entered in EDC at clinic)
CCI [redacted] a	No	At clinic*	Tablet	N/A
CCI [redacted]	No	At clinic	Tablet	EDC
CCI [redacted]	No	At clinic	Tablet	N/A
IWQOL-Lite-CT **or** IWQoL-Kids	No	At clinic	Tablet	EDC
CGIS or PGIS (Global Hunger)	Yes	During trial: At home; During Bridging visits: At clinic	E-diary	EDC
CGIC or PGIC (Global Hunger)	Yes	During trial: At home; During Bridging visits: At clinic	E-diary	EDC

Abbreviations: CDI-2 = Children's Depression Inventory-2; CGIC = Caregiver Global Impression of Change; CGIS = Caregiver Global Impression of Severity; C-SSRS = Columbia-Suicide Severity Rating Scale; EQ-5D-5L = EuroQol-Five Dimension; FACIT = Functional Assessment of Chronic Illness Therapy; IWQOL-Lite-CT = Impact of Weight on Quality of Life-Lite-Clinical Trial; PGIC = Patient Global Impression of Change; PGIS = Patient Global Impression of Severity; PHQ = Patient Health Questionnaire; PRO = patient-reported outcome.

*For select visits that do not require planned or unplanned safety lab draws, the visit may be converted to a telehealth visit and this assessment would be conducted via telehealth visit.

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