SETMELANOTIDE
RM-493-032

A Randomized, Double-Blind, 3-arm, Parallel Group, Placebo- and Positive-controlled Study to Investigate the Effects of Setmelanotide on QTc Interval in Healthy Subjects

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

[redacted]

Short Title:	Double-Blind Study of Setmelanotide Effects on QTc Interval in Healthy Subjects
Study Sponsor:	Rhythm Pharmaceuticals, Inc. [redacted]
Document Date (Version):	24 NOV 2021 (V2.0; Amendment 1)

APPROVAL SIGNATURE PAGE

Protocol Title: A Randomized, Double-Blind, 3-arm, Parallel Group, Placebo- and Positive-controlled Study to Investigate the Effects of Setmelanotide on QTc Interval in Healthy Subjects

Protocol Number: RM-493-032

Document Version: Version 2.0; Amendment 1

Document Date: 24 NOV 2021

Sponsor's Approval:

The protocol has been approved by Rhythm Pharmaceuticals, Inc.

Responsible Medical Officer:

[redacted]
Rhythm Pharmaceuticals, Inc.

Sponsor's Authorized Officer:

[redacted] Date

INVESTIGATOR STATEMENT

Protocol Title: A Randomized, Double-Blind, 3-arm, Parallel Group, Placebo- and Positive-controlled Study to Investigate the Effects of Setmelanotide on QTc Interval in Healthy Subjects

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

This study will not commence without the prior written approval of a properly constituted Institutional Review Board. No changes will be made to the study 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.

_____

Printed Name of Investigator

_____

Signature of Investigator

_____

Date

_____

_____

_____

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

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

The following abbreviations and specialist terms are used in this study protocol.

Abbreviation or Specialist Term	Explanation
Δ	Change from baseline
ΔΔ	Placebo-corrected change from baseline
ADR	Adverse drug reaction
AE	Adverse event
ALT	Alanine aminotransferase
aPTT	Activated partial thromboplastin time
AST	Aspartate aminotransferase
AUC	Area under the plasma concentration-time curve
AUClast	AUC from time zero to the time of last measurable concentration
AUCtau	AUC during the dosing interval
BMI	Body mass index
BP	Blood Pressure
BUN	Blood urea nitrogen
CI	Confidence interval
Cl/f	Apparent clearance
Cmax	Maximum observed concentration
CO_2	Carbon dioxide
CPK	Creatine phosphokinase
C-QTc	Concentration-QTc
CRA	Clinical Research Associate
CRU	Clinical Research Unit
C-SSRS	Columbia Suicide Severity Rating Scale
CTCAE	Common Terminology Criteria for Adverse Events
DBP	Diastolic blood pressure
EC_{50}	50% effective concentration
ECG	Electrocardiogram
eCRF	Electronic case report form
FSH	Follicle stimulating hormone
GCP	Good Clinical Practice

Abbreviation or Specialist Term	Explanation
GFR	Glomerular filtration rate
GGT	Gamma-glutamyltranspeptidase
HBsAG	Hepatitis B surface antigen
HCV	Hepatitis C virus
hERG	Human ether-à-go-go-related gene
HIV	Human immunodeficiency virus
HR	Heart rate
IB	Investigator's Brochure
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
INR	International normalized ratio
IRB	Institutional Review Board
IUD	Intrauterine device
K_i	Inhibitory constant
LDH	Lactate dehydrogenase
LEPR	Leptin receptor
MC4R	Melanocortin-4 receptor
MedDRA	Medical Dictionary for Regulatory Activities
MHP	Mental health professional
NCA	Noncompartmental analysis
PCSK1	proprotein convertase subtilisin/kexin type 1
PI	Principal Investigator
PK	Pharmacokinetics
POMC	Pro-opiomelanocortin
PT	Prothrombin time
PTT	Partial thromboplastin time
QD	Once daily dosing
QTcF	QTc interval corrected by the Fridericia method
RGDO	Rare genetic disorders of obesity
SAE	Serious adverse event
SBP	Systolic blood pressure
SC	Subcutaneous

Abbreviation or Specialist Term	Explanation
SD	Standard Deviation
SoA	Schedule of Assessments
TdP	Torsades de Pointes
TEAE	Treatment-emergent adverse events
Tmax	Time of the maximum observed plasma concentration
Vd	Apparent volume of distribution
VUS	Gene variants interpreted as pathogenic, likely pathogenic, or of uncertain significance
WHO	World Health Organization

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1. SYNOPSIS

Name of Sponsor/Company: Rhythm Pharmaceuticals, Inc.		
Name of Investigational Product: IMCIVREE™ (setmelanotide) injection		
Name of Active Ingredient: Setmelanotide (RM-493; Melanocortin-4 Receptor Agonist)		
Protocol Number: RM-493-032	**Phase:** 4	**Country:** USA
Title of Study: A Randomized, Double-Blind, 3-arm, Parallel Group, Placebo- and Positive -controlled Study to Investigate the Effects of Setmelanotide on QTc Interval in Healthy Subjects		
Study center(s): [redacted]		
Principal Investigator: [redacted]		
Studied period (years): Estimated date first subject enrolled: September, 2021 Estimated date last subject completed: March, 2022		
Objectives: ***Primary*:** • To evaluate the effects of therapeutic and supratherapeutic setmelanotide concentrations on QTc corrected by the Fridericia method (QTcF) interval in healthy subjects. ***Secondary*:** • To assess the effects of therapeutic and supratherapeutic setmelanotide concentrations on heart rate (HR), PR interval, QRS interval, T-wave morphology, and cardiac safety in healthy subjects. • To evaluate assay sensitivity and the effect of a positive control, a single 400 mg oral dose of moxifloxacin, on the QT/QTcF interval in healthy subjects. • To assess the pharmacokinetics (PK) of setmelanotide following administration of therapeutic and supratherapeutic doses of subcutaneous (SC) setmelanotide in healthy subjects.		

- To evaluate the safety and tolerability of therapeutic and supratherapeutic doses of SC setmelanotide in healthy subjects.

[redacted]

Methodology:

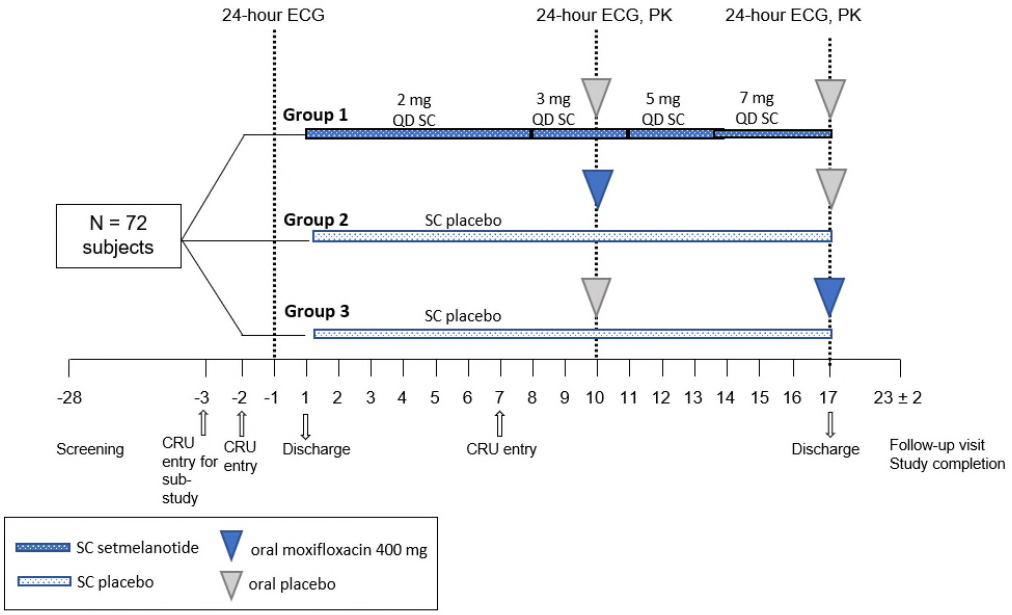
This is a double-blind, randomized, placebo- and positive-controlled, parallel group, 3-arm study to assess the potential for therapeutic and supratherapeutic concentrations of setmelanotide to affect the QTcF interval compared with placebo. SC setmelanotide doses will be titrated throughout the study (2 mg × 7 days, 3 mg × 3 days, 5 mg × 3 days, and 7 mg × 3 days) to reduce the potential of experiencing gastrointestinal effects previously observed at initiation of treatment and to titrate to higher doses. Oral moxifloxacin will be used as a positive control to establish the assay sensitivity of this study.

Approximately 72 healthy adult male and female subjects will be enrolled and randomized 1:1:1 to 1 of 3 groups:

- **Group 1:** SC setmelanotide; oral placebo on Days 10 and 16
- **Group 2:** SC placebo; oral moxifloxacin on Day 10 and oral placebo on Day 16
- **Group 3:** SC placebo; oral placebo on Day 10 and oral moxifloxacin on Day 16.

The following treatments will be administered according to the figure below:

- SC setmelanotide: SC injection: 2 mg × 7 days followed by 3, 5, and 7 mg × 3 days per dose level
- SC placebo (matched to active setmelanotide): SC placebo injection × 16 days
- Oral moxifloxacin: single oral dose of 400 mg moxifloxacin
- Oral placebo (matched to oral moxifloxacin): single oral placebo dose



[redacted]

After a 28-day Screening period, subjects will check-in to the Clinical Research Unit (CRU) on the morning of Day −2 and will begin an overnight fast in the evening of Day −2. On Day −1, subjects will receive a standard breakfast at approximately 7:00 AM, followed by 24-hour Holter monitor electrocardiogram (ECG) collection (to begin at 7:30 AM, the same time as the anticipated daily dosing), baseline assessments. On the morning of Day 1, subjects will receive their first SC dose (SC setmelanotide or SC placebo).

From Days 2 through 16, the assigned SC treatment (SC setmelanotide or SC placebo) will be administered to each group at approximately the same time every morning. On Days 10 and 16, subjects in Group 1 will receive an oral placebo with their SC setmelanotide dose. Subjects in Group 2 will receive oral moxifloxacin 400 mg on Day 10 and oral placebo on Day 16, while Subjects in Group 3 will receive oral placebo on Day 10 and oral moxifloxacin 400 mg on Day 16. Oral treatments on Days 10 and 16 (oral moxifloxacin or oral placebo) will be administered within 2 minutes after the SC placebo dose. All treatments (SC setmelanotide versus SC placebo and oral placebo versus oral moxifloxacin) will be administered in a double-blinded manner.

Subjects will remain in the CRU through the morning of Day 17 and will be discharged after completion of all study assessments if safety parameters are acceptable to the Investigator. Subjects will return to the CRU for a Follow-up visit 7 ± 2 days after receiving the last SC dose (Day 23 ± 2).

Subjects will be instructed to fast overnight (at least 10 hours) prior to all continuous Holter ECG dosing days (Days -1, 10, and 16). A standard breakfast will be provided to subjects at approximately 7:00 AM each day. Treatments will be administered 30 minutes after the start of the meal, between 5:30 AM to 9:30 AM. Lunch, dinner, and a snack will be provided at approximately 12:00 PM (after 4-hour assessments), 6:00 PM (after 10-hour assessments), and 9:00 PM, respectively. All meals should be administered at the same time every day throughout the treatment period.

Continuous Holter ECG monitoring and PK samples will be collected up to 24 hours post-dose on Days 10 and 16. Continuous Holter ECGs (obtained on Days -1, 10, and 16) will be read with manual adjudication at a central laboratory. The Holter ECG laboratory and cardiologist responsible for reading the Holter ECGs will be blinded to treatment, timepoint, and subject.

Safety will be assessed throughout the study via collection of adverse events (AEs), 12-lead safety ECGs, Columbia Suicide Severity Rating Scale (C-SSRS), clinical laboratory tests, vital signs, physical examinations, and concomitant medication monitoring.

[redacted]

Number of subjects (planned):

Approximately 72 subjects are planned to be enrolled to achieve study completion of 60 subjects, accounting for dropouts. Dropouts may be replaced, at the Sponsor's discretion.

[redacted]

Sample Size Justification:

Using a 2-sample t-test with a 1-sided 0.05 significance level, a sample size of 60 evaluable subjects who complete the study (20 subjects in Group 1 receiving SC setmelanotide and 20 subjects each in Groups 2 and 3 receiving SC placebo) will provide at least 85% power to exclude that setmelanotide causes more than a 10 msec QTc effect at clinically relevant plasma levels, as shown by the upper bound of the 2-sided 90% confidence interval (CI) of the model-predicted QTc effect (ΔΔQTcF) at the observed geometric mean Cmax of setmelanotide on Day 10 and Day 16 in the study individually.

To demonstrate assay sensitivity using moxifloxacin with a 1-sided 0.05 significance level, a sample size of 20 evaluable subjects receiving moxifloxacin and 20 evaluable subjects receiving placebo at each Holter ECG assessment day (Days 10 and 16) will provide at least 81% power to demonstrate assay sensitivity with a 1-sided 0.05 significant level. The power to detect the effect of moxifloxacin on QTc over the entire crossover period is at least 86%.

As such, a total of approximately 72 subjects are planned for enrollment to achieve 60 completers, accounting for dropouts.

Inclusion Criteria:

Subjects must meet all of the following criteria to be eligible for study participation:

1. Males or females between 18 and 50 years of age, inclusive.
2. Subject has body mass index (BMI) between 18.0 and 30.0 kg/m^2, inclusive.
3. Subject is in good health, as confirmed by no clinically significant findings from medical history, physical examination, 12-lead ECG, vital signs measurements, clinical laboratory evaluations, and liver function tests at Screening, Check-in (Day −2) and baseline (Day −1).
4. Female participants of childbearing potential must be confirmed non-pregnant and agree to use contraception. Female participants of non-childbearing potential, defined as: surgically sterile (status post hysterectomy, bilateral oophorectomy, or bilateral tubal ligation), post-menopausal for at least 12 months (and confirmed with a screening follicle stimulating hormone [FSH]) level in the post-menopausal lab range), do not require contraception during the study.
5. Male participants with female partners of childbearing potential must agree to use contraception (e.g., if not vasectomized, should either abstain from sexual intercourse or use a highly reliable method of contraception such as condom and diaphragm with spermicide during intercourse) if they become sexually active during the study or within 90 days following their participation in the study. Male subjects must also not donate sperm during and for 90 days following their participation in the study.
6. Subject is a nonsmoker (for at least 3 months) with negative urinary cotinine test at Screening and agrees to abstain from alcohol, recreational drugs (including marijuana), and tobacco- or nicotine-containing products for the duration of the study.
7. Subject is able to comprehend and is willing to sign an informed consent form and abide by the study restrictions.

Exclusion criteria:

Subjects meeting any of the following criteria are not eligible for study participation:

1. Subject has sustained systolic blood pressure (SBP) >150 mmHg or <90 mmHg or a diastolic blood pressure (DBP) >100 mmHg or <60 mmHg in the supine position at Screening.
2. Subject has supine pulse rate of <45 beats per minute (bpm) or >100 bpm.
3. Subject has abnormal screening ECG indicating a second- or third-degree atrioventricular block, or one or more of the following: QRS>110 msec, QTcF >450 msec for males and >470 msec for females, PR interval >200 msec.
4. Subject has a history of risk factors for Torsades de Pointes (TdP), including unexplained syncope, diagnosis or family history of Brugada syndrome or long QT syndrome, heart failure, myocardial infarction, angina, or clinically significant abnormal laboratory assessments including hypokalemia, hypercalcemia, or hypomagnesaemia.
5. Glomerular filtration rate (GFR) <60 mL/min at Screening.
6. Subject has significant dermatologic findings relating to melanoma or pre-melanoma skin lesions (excluding non-invasive basal or squamous cell lesion), determined as part of comprehensive skin evaluation performed by the Investigator during Screening. If any concerning lesions are identified during Screening, the subject should be referred to a dermatologist for evaluation prior to enrollment. If the pre-treatment evaluation results are of significant concern, the subject is not eligible for study participation.
7. Subject has history or close family history (parents or siblings) of melanoma or subject history of ocular-cutaneous albinism.
8. Subject has significant history or clinical manifestation of any metabolic, allergic, dermatological, hepatic, renal, hematological, pulmonary, cardiovascular, gastrointestinal, neurological, or psychiatric disorder (as determined by the Investigator).
9. Subject has suicidal ideation of type 4 or 5 on the C-SSRS at Screening, a history of a suicide attempt in their lifetime, or any suicidal behavior in the last month.
10. Subject has participated in any clinical study with an investigational drug/device within 30 days (or 5 half-lives) prior to the first day of dosing.
11. Subject was previously enrolled in a clinical study involving setmelanotide or any previous exposure to setmelanotide.
12. Subject has inability to comply with QD injection regimen.
13. Female subjects who are breastfeeding or nursing.
14. Subject has cognitive impairment that, in the Investigator's opinion, precludes participation to the study.
15. Subject is, in Investigator's opinion, otherwise not suitable to participate in the study.

Note: Exclusion criteria #1, 2, 3 and 5 can be repeated at the discretion of the Investigator. Vital signs will be limited to 3 repeats. Safety laboratory tests and ECGs will be limited to 1 repeat.

Investigational product, dosage, and mode of administration:

IMCIVREE (setmelanotide), 10 mg/mL solution in 1 mL multiple-dose vial for SC injection (2, 3, 5, and 7 mg doses)

Placebo for SC injection (vehicle only; identical in appearance to SC setmelanotide treatment)

Reference therapy, dosage and mode of administration:

Moxifloxacin 400 mg capsules for oral administration

Placebo capsules for oral administration (identical in appearance to oral moxifloxacin treatment)

Duration of treatment:

All subjects will receive study treatment for a total of 16 days. Total study participation will be between 23 and 53 days, based on the variable length of the Screening Period and the Follow-up visit.

Criteria for evaluation:

Primary cardiac endpoint:

- Setmelanotide concentration-related change from baseline (Δ) in QTc and placebo-adjusted change from baseline (ΔΔ) in QTc corrected for HR using QTcF (ΔQTcF and ΔΔQTcF)

Secondary cardiac endpoints:

- Change from baseline (Δ) and placebo-corrected change from baseline (ΔΔ) in HR, QTcF, PR, and QRS intervals after administration of SC setmelanotide or oral moxifloxacin
- Categorical outliers for QTcF, HR, PR, and QRS intervals after administration of SC setmelanotide
- Frequency of treatment-emergent changes of T-wave morphology and U-wave presence after administration of SC setmelanotide
- Relationship between moxifloxacin concentrations and ΔΔQTcF

Pharmacokinetic endpoints:

The following PK endpoints will be calculated for setmelanotide:

- Area under the plasma concentration-time curve during the dosing interval (AUCtau)
- AUC from time zero to the time of last measurable concentration (AUClast)
- Maximum observed concentration (Cmax)
- Time of the maximum observed plasma concentration (Tmax)
- Apparent clearance (Cl/F)
- Apparent volume of distribution (Vd/F)

The following PK endpoints will be calculated for moxifloxacin:

- AUCinf
- AUClast
- Tmax
- Cmax

Safety endpoints:

- Frequency and severity of AEs (assessed separately for relation to SC setmelanotide and/or oral moxifloxacin), clinical laboratory evaluations, safety ECGs, C-SSRS score, vital signs, and physical examinations

[redacted]

[redacted]

Statistical methods:

Cardiodynamic Holter ECG Assessment:

The primary analysis will be based on C-QTc modeling of the relationship between plasma concentrations of setmelanotide (or placebo) and ΔQTcF (using Day -1 time-matched Holter ECGs as baseline) with the intent to exclude an effect of ΔΔQTcF >10 msec at clinically relevant plasma levels, using the concepts presented in the "Scientific White Paper on C-QTc modeling" (Garnett 2018b, Garnett 2018a). After development of the C-QTc model and assessment of model performance through nonparametric bootstrapping, the ΔΔQTcF associated with the Cmax of therapeutic and supratherapeutic doses will be computed using bias-corrected 90% CI. An increase in QTc of 10 msec or greater can be ruled out if the upper 90% CI is <10 msec.

The change from baseline (Δ) and placebo-corrected change from baseline (ΔΔ) QTcF, HR, PR, and QRS will be summarized by nominal time and treatment using descriptive statistics. An analysis of categorical outliers will be performed for changes in QTcF, HR, PR, and QRS, and T-wave morphology, and U-wave presence and results will be summarized.

Assay sensitivity will be evaluated by C-QTc analysis of the effect on ΔΔQTcF of moxifloxacin using a similar model as for the primary analysis. Assay sensitivity will be deemed as met if the predicted QT effect (i.e., the lower bound of the 2-sided 90% CI of ΔΔQTcF) is above 5 msec at the observed geometric mean Cmax of 400 mg oral moxifloxacin.

Pharmacokinetics:

Setmelanotide and moxifloxacin concentration data will be summarized by nominal time point and treatment using descriptive statistics. PK parameters for setmelanotide and moxifloxacin (as listed in the PK endpoints section) will be calculated using noncompartmental methods (NCA) and summarized by treatment.

Safety:

All AEs will be listed and TEAEs will be summarized using descriptive methodology (setmelanotide and moxifloxacin AEs reported separately). Each AE will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). Observed values for clinical laboratory test data, 12-lead safety ECGs, C-SSRS score, vital signs measurements, and physical examination findings will be listed.

No formal statistical analysis of safety data is planned.

[redacted]

2. SCHEDULE OF ASSESSMENTS

The Schedule of Assessments (SoA) is presented in Table 1.

Table 1: Schedule of Assessments

Study Period	**Screening**	[redacted]	**Check-In**	**Baseline**	**Treatment**										**Follow-up**	**Treatment Discontinuation**
Study Day **Assessment**	**-28 to -2**		**-2**	**-1**	**1**	**2-6**	**7**	**8**	**9**	**10**	**11-14**	**15**	**16**	**17**	**23 ± 2**	**7 ± 4 days after last SC dose**
Informed consent	X															
Inclusion/exclusion review	X		X													
Medical history review	X															
Physical exam [a]	X			X										X	X	X
Comprehensive skin exam [b]	X															
Fitzpatrick classification scale	X															
Height and weight [c]	X			X										X	X	X
Vital signs [d]	X			X										X	X	X
Pregnancy test [e]	X		X												X	X
FSH test	X		X													
Urine drug screen	X		X													
CRU confinement			X	X	X	X	X	X	X	X	X	X	X			
CRU discharge														X		
Fasting [f]			X						X			X				

Study Period	**Screening**	[redacted]	**Check-In**	**Baseline**	**Treatment**										**Follow-up**	**Treatment Discontinuation**
Study Day **Assessment**	**-28 to -2**		**-2**	**-1**	**1**	**2-6**	**7**	**8**	**9**	**10**	**11-14**	**15**	**16**	**17**	**23 ± 2**	**7 ± 4 days after last SC dose**
Meal administration [g]				X				X	X	X	X	X	X			
Setmelanotide administration [h]					X	X	X	X	X	X	X	X	X			
Moxifloxacin administration [i]										X			X			
PK sampling [j]										X			X			
Continuous 12-lead ECGs (Holter monitor) [k, l]				X						X			X			
Safety 12-lead ECGs [l, m]	X			X			X							X	X	X
Clinical labs [n]	X			X			X							X	X	X
Adverse events	X		Continuous →													X
Concomitant medication review	X		Continuous →													X
C-SSRS [o]	X			X										X		X
[redacted]			[redacted]								[redacted]					

Study Period	Screening	[redacted]	Check-In	Baseline	Treatment										Follow-up	Treatment Discontinuation
Study Day Assessment	-28 to -2		-2	-1	1	2-6	7	8	9	10	11-14	15	16	17	23 ± 2	7 ± 4 days after last SC dose
[redacted]																

CRU = Clinical Research Unit; C-SSRS = Columbia Suicide Severity Rating Scale; ECG = electrocardiogram; FSH = follicle stimulating hormone; INR = international normalized ratio; PK = pharmacokinetic; PT = prothrombin time; PTT (or aPTT) = partial thromboplastin time.

[a] A full physical exam will be conducted at Screening. A brief physical exam will be conducted at each check-in, baseline, study discharge, and follow-up.

[b] A comprehensive skin evaluation will be performed by the Investigator at Screening. If any concerning lesions are identified during the screening period, the subject should be referred to a dermatologist for assessment and potential biopsy and results should be confirmed as to whether the lesion is benign prior to first dose of setmelanotide. If the pre-treatment biopsy results are of concern, the subject will be excluded from the study.

[c] Height will only be collected at Screening.

[d] Supine blood pressure, supine heart rate, pulse rate, and tympanic (ear) body temperature. Heart rate and blood pressure will be measured using the same arm for each reading after the subject has been resting in the supine position for at least 5 minutes. For timepoints at which vital signs, PK blood samples, and/or ECGs are all to be collected, ECGs should be collected first followed by vital signs then PK samples, with the timing of the PK sample to occur at the nominal time.

[e] Serum pregnancy test will be performed at Screening. Urine pregnancy test will be performed on all other designated days.

[f] On the evening before continuous Holter ECG sampling, subjects will undergo a 10-hour overnight fast.

[g] Breakfast is to be administered at approximately 7:00 AM every day in the CRU (30 minutes pre-dose). Lunch, dinner, and a snack will be administered at approximately 12:00 PM (after 4-hour assessments), 6:00 PM (after 10-hour assessments), and 9:00 PM, respectively.

[h] **Group 1** will receive SC setmelanotide QD (approximately 7:30 AM) at a dose of 2 mg from Days 1 to 7; 3 mg from Days 8 to 10; 5 mg from Days 11 to 13; and 7 mg from Days 14 to 16.
Groups 2 and 3 will receive SC placebo QD (approximately 7:30 AM) from Days 1 through 16.
All doses will be double-blinded.

[i] **Group 1** will receive oral placebo with their SC setmelanotide dose on Days 10 and 16.
Group 2 will receive oral moxifloxacin 400 mg on Day 10 and oral placebo on Day 16.
Group 3 will receive oral placebo on Day 10 and moxifloxacin 400 mg on Day 16.

All doses will be double-blinded. On Days 10 and 16, subjects should receive SC setmelanotide/placebo first. Oral moxifloxacin/placebo should then be administered within 2 minutes of the SC dose.

[j] Blood samples for quantification of setmelanotide and moxifloxacin concentrations will be collected at pre-dose and 0.5, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 7, 8, 9, 10, 12, 16, and 24 hours post-dose on Days 10 and 16. The PK samples collected at 0.5 hours post-dose will have a sampling window of ± 2 minutes, samples collected from 1 hour though 2.5 hours post-dose will have a sampling window of ± 5 minutes, samples collected from 3 hours through 10 hours post-dose will have a sampling window of ± 10 minutes, and samples collected from 12 through 24 hours postdose will have a sampling window of ± 20 minutes; however, collection of samples outside of the window will not be considered protocol deviations. The timing of all PK samples should be recorded to the nearest minute. For timepoints at which vital signs, PK blood samples, and/or ECGs are all to be collected, ECGs should be collected first followed by vital signs then PK samples, with the timing of the PK sample to occur at the nominal time.

[k] Holter ECGs will be extracted at Day -1 and on Days 10 and 16 at the following timepoints: pre-dose and 0.5, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 7, 8, 9, 10, 12, 16, and 24 hours post-dose. The Day -1 extractions will begin at 7:30 AM (the time of anticipated dosing on Days 10 and 16).

[l] For ECG collection, subjects will rest in the supine position for at least 10 minutes before and 5 minutes after each timepoint. For timepoints at which vital, PK blood samples, and/or ECGs are all to be collected, ECGs should be collected first followed by vital signs then PK samples, with the timing of the PK sample to occur at the nominal time.

[m] Safety ECGs will be collected at the Screening visit, CRU baseline (Day−1), final CRU discharge, and the Follow-up visit.

[n] Safety clinical laboratory tests will include: hematology with platelet count and standard indices, chemistry panel (includes sodium, potassium, chloride, CO_2, albumin, total protein, glucose, BUN, creatinine, uric acid, AST, ALT, GGT, CPK, alkaline phosphatase, total bilirubin, direct bilirubin, LDH, calcium, phosphorus, magnesium), and urinalysis with microscopic analysis if positive findings on dipsticks warrant further examination. Safety laboratories will also include a coagulation profile (PT or INR, and PTT also referred to as aPTT).

[o] In order to be eligible for the study, at Screening, a subject cannot have a suicidal ideation of type 4 or 5, a history of a suicide attempt in the past 20 years, or any suicidal behavior in the last month. If at any time during the study a subject has a suicidal ideation of type 4 or 5, or any suicidal behavior, the subject should be referred to a mental health professional.

[p] [redacted]

3. INTRODUCTION

3.1. Background

3.1.1. Rare Genetic Disorders of Obesity

Human genetics studies have identified several diseases that are the result of genetic defects affecting the melanocortin-4 receptor (MC4R) pathway, including, but not limited to, pro-opiomelanocortin (POMC) deficiency obesity due to mutations in the *POMC* gene; heterozygous proprotein convertase subtilisin/kexin type 1 (PCSK1) deficiency due to mutations in the *PCSK1* gene, leading to a hormone processing defect that also causes POMC deficiency obesity; and leptin receptor (LEPR) deficiency obesity due to mutations in the *LEPR* gene. These MC4R pathway mutations cause rare genetic disorders of obesity (RGDO) that start early in childhood, progress over time, and can become life-threatening in severity.

3.1.2. Setmelanotide

Setmelanotide (also known as RM-493) is a synthetic, cyclic octapeptide (8-amino acid-containing peptide) that functions as a potent MC4R agonist. Setmelanotide is an 8-amino acid, cyclic peptide that binds with high affinity (inhibitory constant [K_i] = 2.1 nM) to the human MC4R and is efficient in activating MC4R (50% effective concentration [EC_{50}] = 0.27 nM). Setmelanotide is indicated for chronic weight management in adult and pediatric patients 6 years of age and older with obesity due to POMC, PCSK1, or LEPR deficiency confirmed by genetic testing demonstrating variants in *POMC*, *PCSK1*, *or LEPR* genes that are interpreted as pathogenic, likely pathogenic, or of uncertain significance (IMCIVREE (setmelanotide) Prescribing Information 2020).

Setmelanotide was evaluated extensively in nonclinical studies for cardiovascular parameters, primarily because of the potential concern for effects on blood pressure (BP) and heart rate (HR). The IC_{50} for the effect of setmelanotide on human ether-à-go-go-related gene (hERG) potassium current was estimated to be greater than 300 µg/mL, the maximum concentration tested. In addition, an extensive, multi-day cardiovascular telemetry study with setmelanotide administered by subcutaneous (SC) continuous infusion was performed in cynomolgus monkeys. No setmelanotide-related effects were noted on the electrocardiogram (ECG) parameters (PR, QRS, QT, and QTc intervals) following the administration at doses of 2.5, 12, and 25 mg/kg/day. In both these studies, there were extremely large exposure/concentration margins to the approximate Cmax of the maximum therapeutic 3 mg SC injection dose (~40.0 ng/mL) and the anticipated Cmax of the supratherapeutic 7 mg SC injection dose (~93.3 ng/mL, assuming dose proportionality).

QTc evaluations were additionally conducted in 3 initial Phase 1 and Phase 2 clinical studies, as well as in 57 patients with monogenic obesity in 3 Phase 2 and Phase 3 studies. Mean and median data for QTcF demonstrate no effect of setmelanotide on QTc interval at doses up to 3 mg QD.

3.2. Study Rationale

This study is being conducted to fulfill Postmarketing Requirement [redacted] to assess the risk of QT interval prolongation by SC setmelanotide. Oral moxifloxacin will be used as a positive control to determine the assay sensitivity of this study, with an expected peak QTcF effect (ΔΔQTcF) of 10 to 15 msec. Continuous Holter ECG measurements will be collected at baseline, after administration of SC and oral placebo, after SC setmelanotide administration, and after oral moxifloxacin administration; these ECGs will be read with manual adjudication at a central laboratory. The effect of setmelanotide and moxifloxacin on placebo- and baseline-corrected (ΔΔ) QTcF will be determined.

[redacted]

3.3. Benefit/Risk Assessment

This study 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.

Healthy subjects in the current study will not receive any health benefit (beyond that of an assessment of their medical status) from participating in the study. The risks of participation are primarily those associated with adverse reactions to the study treatments, in addition to the possibility of mild discomfort due to blood sampling and other study procedures. Further information about the known and expected benefits, risks, and reasonably anticipated adverse events (AEs) associated with SC setmelanotide are found in the Investigator's Brochure (IB) and IMCIVREE (setmelanotide) Prescribing Information (2020).

4. TRIAL OBJECTIVES

4.1. Primary Objective

The primary objective of this study is:

- To evaluate the effects of therapeutic and supratherapeutic setmelanotide concentrations on QTc corrected by the Fridericia method (QTcF) interval in healthy subjects.

4.2. Secondary Objectives

The secondary objectives of this study are:

- To assess the effects of therapeutic and supratherapeutic setmelanotide concentrations on HR, PR interval, QRS interval, T-wave morphology, and cardiac safety in healthy subjects.
- To evaluate assay sensitivity and the effect of a positive control, a single 400 mg oral dose of moxifloxacin, on the QT/QTcF interval in healthy subjects.
- To assess the pharmacokinetics (PK) of setmelanotide following administration of therapeutic and supratherapeutic doses of SC setmelanotide in healthy subjects.
- To evaluate the safety and tolerability of therapeutic and supratherapeutic doses of SC setmelanotide in healthy subjects.

5. INVESTIGATIONAL PLAN

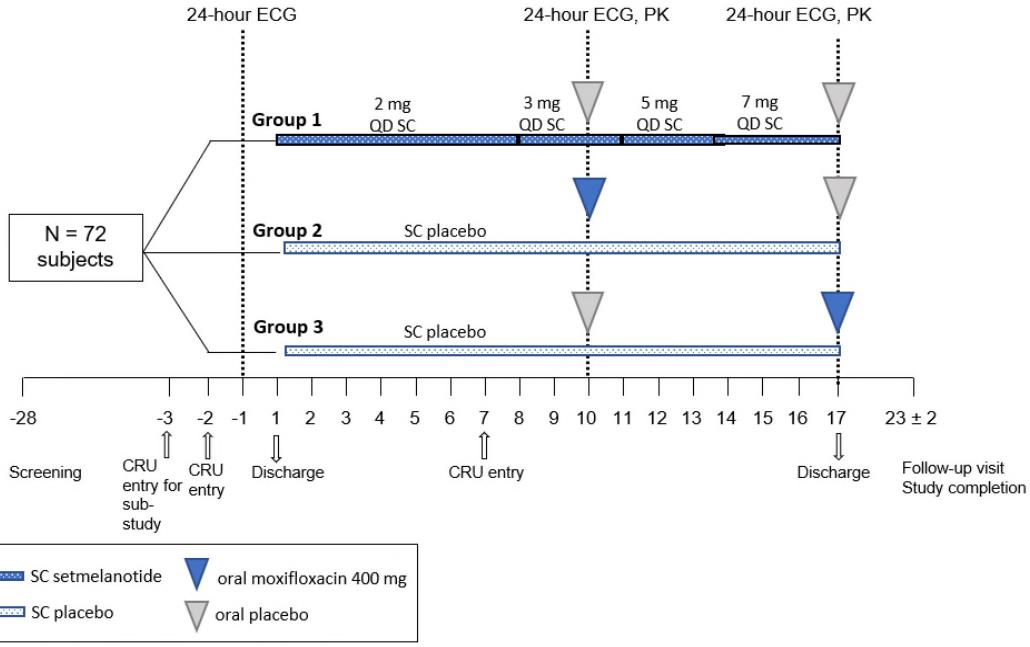
5.1. Overall Study Design

This is a double-blind, randomized, placebo- and positive-controlled, parallel group, 3-arm study to assess the potential for therapeutic and supratherapeutic concentrations of SC setmelanotide administered as IMCIVREE to affect the QTcF interval compared with placebo. Approximately 72 healthy subjects aged 18 to 50 years of age, inclusive, are planned to be enrolled in the United States. Subjects will be enrolled into 1 of 3 groups as follows:

- **Group 1:** SC setmelanotide; oral placebo on Days 10 and 16
- **Group 2:** SC placebo; oral moxifloxacin on Day 10 and oral placebo on Day 16
- **Group 3:** SC placebo; oral placebo on Day 10 and oral moxifloxacin on Day 16.

The study design is presented in Figure 1.

Figure 1: Study Design Schematic



[redacted]

Upon providing informed consent, subjects will enter a 28-day Screening period, during which they will be assessed for eligibility and complete all screening procedures as described in the Schedule of Assessments (SoA) (Table 1).

Following the Screening period, eligible subjects will check-in to the Clinical Research Unit (CRU) on the morning of Day −2. Subjects will be randomized 1:1:1 into Group 1, 2, or 3 and will be fasted overnight (for at least 10 hours). On the morning of Day -1 following a standard

breakfast, subjects will undergo 24-hour continuous ECG Holter monitoring beginning 30 minutes after the meal (at the time of anticipated dosing on Days 10 and 16). Baseline assessments (Table 1) will occur on Day -1.

On the morning of Day 1, subjects will receive SC setmelanotide 2 mg (Group 1) or SC placebo (Groups 2 and 3) in a double-blinded fashion.

From Days 2 to 16 following a standardized breakfast, subjects will continue receiving SC setmelanotide (3 mg QD from Days 8 to 10; 5 mg QD from Days 11 to 13; 7 mg QD from Days 14 to 16) or SC placebo according to their assigned group. On Days 10 and 16, oral placebo or oral moxifloxacin 400 mg will be administered with the SC dose according to the assigned dose group. Continuous Holter ECGs and PK sampling will be conducted on Days 10 and 16 pre-dose and for up to 24 hours post-dose according to the SoA (Table 1). All treatments administered in the CRU will be double-blinded and will be given at the same time every day (approximately 30 minutes after the start of breakfast).

Subjects will remain in the CRU through the morning of Day 17 and will be discharged after completion of all study assessments if safety parameters are acceptable to the Investigator. Subjects will return to the CRU for a Follow-up visit 7 ± 2 days after receiving the last SC dose (Day 23 ± 2).

Adverse events (AEs), 12-lead safety ECGs, Columbia Suicide Severity Rating Scale (C-SSRS) score, clinical laboratory tests, vital signs, and concomitant medication monitoring will be collected throughout the study for safety assessments as described in the SoA (Table 1).

[redacted]

5.2. Study Endpoints

5.2.1. Primary Cardiac Endpoint

The primary cardiac endpoint of the study is:

- Setmelanotide concentration-related change from baseline in QTc (Δ) and placebo-adjusted change from baseline in QTc (ΔΔ) corrected for HR using QTcF (ΔQTcF and ΔΔQTcF)

5.2.2. Secondary Cardiac Endpoints

The secondary cardiac endpoints of the study are:

- Change from baseline (Δ) and placebo-corrected change from baseline (ΔΔ) in HR, QTcF, PR, and QRS intervals after administration of SC setmelanotide or oral moxifloxacin
- Categorical outliers for QTcF, HR, PR, and QRS intervals after administration of SC setmelanotide
- Frequency of treatment-emergent changes of T-wave morphology and U-wave presence after administration of SC setmelanotide
- Relationship between moxifloxacin concentrations and ΔΔQTcF

5.2.3. Pharmacokinetic Endpoints

The following PK endpoints will be calculated for setmelanotide:

- Area under the plasma concentration-time curve during the dosing interval (AUCtau)
- AUC from time zero to the time of last measurable concentration (AUClast)
- Maximum observed concentration (Cmax)
- Time of the maximum observed plasma concentration (Tmax)
- Apparent clearance (Cl/F)
- Apparent volume of distribution (Vd/F)

The following PK endpoints will be calculated for moxifloxacin:

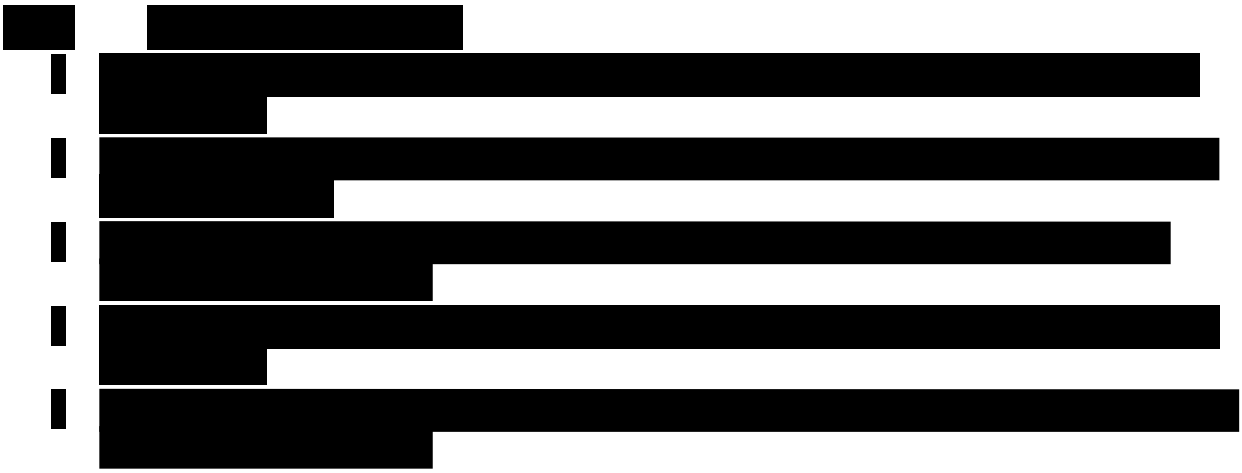
- AUCinf
- AUClast
- Tmax

- Cmax

5.2.4. Safety Endpoints

The safety endpoints are:

- Frequency and severity of AEs (assessed separately for relation to setmelanotide and/or moxifloxacin)
- Changes from baseline in clinical laboratory evaluations, vital signs, 12-lead safety ECGs, C-SSRS score, vital signs, and physical examinations



5.3. Justification of Study Design

This study will be randomized and double-blinded. Randomization eliminates confounding by baseline variables, while blinding eliminates confounding by concomitant interventions and biased safety findings. These measures therefore eliminate the possibility that the observed effects of intervention are due to differential use of other treatments or biased expectations regarding safety.

Subjects in Groups 2 and 3 will receive both oral placebo and oral moxifloxacin in order to serve as their own controls, thus reducing the variability between treatments.

Healthy subjects will be used for this study to eliminate variables that are known to have effects on ECG parameters, such as concomitant drugs and disease. Both male and female subjects will be included to eliminate similar known ECG variability effects.

As non-drug-related increases in HR and shortening of QT and QTcF within 4 hours of a meal (maximal effect at 2 hours post-meal) have been reported in the literature (Taubel 2012), meals will be administered at the same time each day during the study (Section 7.2) to control for the effect of food on QTc interval.

5.4. Dose Rationale

Setmelanotide effect on QTcF will be evaluated at doses of 3 mg (maximum therapeutic dose) and 7 mg (supratherapeutic dose). The dose of SC setmelanotide will be titrated to these doses in a manner similar to that used for therapeutic dosing to alleviate gastrointestinal symptoms

previously observed with SC setmelanotide dosing (IMCIVREE (setmelanotide) Prescribing Information 2020).

5.5. Number of Subjects and Study Completion

This study is planned to enroll 72 subjects to achieve a total of 60 completed subjects (Section 11.1).

A subject is considered to have completed the study after completion of the Follow-up visit on Day 23 ± 2.

Subjects who discontinue before completing the Follow-up visit are to attend a Treatment Discontinuation visit within 7 days (± 4 days) after the last SC dose for final study assessments. Subjects who discontinue the study early may be replaced, at the discretion of the Sponsor, in order to assure that the final sample size is large enough to maintain sufficient statistical power.

[redacted]

The end of the study is defined as the date of the last visit of the last subject under the auspices of the current study.

5.6. Dose Adjustment Criteria

If a subject experiences gastrointestinal side effects (e.g., nausea or vomiting), a dose may be delayed or decreased, or dose escalation may be postponed, at the discretion of the Principal Investigator. If a subject has not received at least 4 consecutive days of SC treatment by Day 7, the subject's enrollment should be discussed with the Sponsor prior to his/her continuation in the study.

In general, all subjects in this study are intended to complete the study at the highest dose of SC setmelanotide that they can tolerate. If >30% of the proposed patients cannot escalate SC setmelanotide up to a dose of at least 5 mg/day, additional subjects may be enrolled to ensure appropriate statistical power. If this occurs, a Note to File will be issued to explain the rationale for enrolling additional patients and the statistical justification for the change in sample size.

5.7. Criteria for Study Termination

This study or a clinical site may be prematurely terminated, if in the opinion of the Sponsor, there is sufficiently reasonable cause. The Sponsor will provide written notification documenting the reason for study or site termination.

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

- Determination of unexpected, significant, or unacceptable risk to subjects.
- Failure to enroll subjects into the study.
- Insufficient adherence to protocol requirements.
- Insufficient complete and/or evaluable data.
- Plans to modify, suspend, or discontinue the development of the study drug.

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

5.8. Replacement of Early Termination Subjects

If a subject is replaced in attempt to limit completer bias, the replaced subject should have a new unique subject ID, and a new randomization number with the same treatment group by the pre-specified randomization schedule, which will remain blinded until the study database is locked and unblinded. All the procedures of the replacement will be documented and kept in the study electronic trial master file (eTMF).

6. SELECTION AND WITHDRAWAL OF SUBJECTS

6.1. Subject Inclusion Criteria

Subjects must meet all of the following criteria to be eligible for study participation:

1. Males or females between 18 and 50 years of age, inclusive.
2. Subject has body mass index (BMI) between 18.0 and 30.0 kg/m^2, inclusive.
3. Subject is in good health, as confirmed by no clinically significant findings from medical history, physical examination, 12-lead ECG, vital signs measurements, clinical laboratory evaluations, and liver function tests at Screening, Check-in (Day −2) and baseline (Day −1).
4. Female participants of childbearing potential must be confirmed non-pregnant and agree to use contraception (Section 10.1.9.4). Female participants of non-childbearing potential, defined as: surgically sterile (status post hysterectomy, bilateral oophorectomy, or bilateral tubal ligation), post-menopausal for at least 12 months (and confirmed with a screening follicle stimulating hormone [FSH] level in the post-menopausal lab range), do not require contraception during the study.
5. Male participants with female partners of childbearing potential must agree to use contraception (e.g., if not vasectomized, should either abstain from sexual intercourse or use a highly reliable method of contraception such as condom and diaphragm with spermicide during intercourse) if they become sexually active during the study or within 90 days following their participation in the study. Male subjects must also not donate sperm during and for 90 days following their participation in the study.
6. Subject is a nonsmoker (for at least 3 months) with negative urinary cotinine test at Screening and agrees to abstain from alcohol, recreational drugs (including marijuana), and tobacco- and nicotine-containing products for the duration of the study.
7. Subject is able to comprehend and is willing to sign an informed consent form and abide by the study restrictions.

6.2. Subject Exclusion Criteria

Subjects meeting any of the following criteria are not eligible for study participation:

1. Subject has sustained systolic blood pressure (SBP) >150 mmHg or <90 mmHg or a diastolic blood pressure (DBP) >100 mmHg or <60 mmHg in the supine position at Screening.
2. Subject has supine pulse rate of <45 beats per minute (bpm) or >100 bpm.
3. Subject has abnormal screening ECG indicating a second- or third-degree atrioventricular block, or one or more of the following: QRS >110 msec, QTcF >450 msec for males and >470 msec for females, PR interval >200 msec.
4. Subject has a history of risk factors for Torsades de Pointes (TdP), including unexplained syncope, diagnosis or family history of Brugada syndrome or long QT syndrome, heart

failure, myocardial infarction, angina, or clinically significant abnormal laboratory assessments including hypokalemia, hypercalcemia, or hypomagnesaemia.

5. Glomerular filtration rate (GFR) <60 mL/min at Screening.
6. Subject has significant dermatologic findings relating to melanoma or pre-melanoma skin lesions (excluding non-invasive basal or squamous cell lesion), determined as part of comprehensive skin evaluation performed by the Investigator during Screening. If any concerning lesions are identified during Screening, the subject should be referred to a dermatologist for evaluation prior to enrollment. If the pre-treatment evaluation results are of significant concern, the subject is not eligible for study participation.
7. Subject has history or close family history (parents or siblings) of melanoma or subject history of ocular-cutaneous albinism.
8. Subject has significant history or clinical manifestation of any metabolic, allergic, dermatological, hepatic, renal, hematological, pulmonary, cardiovascular, gastrointestinal, neurological, or psychiatric disorder (as determined by the Investigator).
9. Subject has suicidal ideation of type 4 or 5 on the C-SSRS at Screening, a history of a suicide attempt in their lifetime, or any suicidal behavior in the last month.
10. Subject has participated in any clinical study with an investigational drug/device within 30 days (or 5 half-lives) prior to the first day of dosing.
11. Subject was previously enrolled in a clinical study involving setmelanotide or any previous exposure to setmelanotide.
12. Subject has inability to comply with QD injection regimen.
13. Female subjects who are breastfeeding or nursing.
14. Subject has cognitive impairment that, in the Investigator's opinion, precludes participation to the study.
15. Subject is, in Investigator's opinion, otherwise not suitable to participate in the study.

Note: Exclusion criteria #1, 2, 3 and 5 can be repeated at the discretion of the Investigator. Vital signs will be limited to 3 repeats. Safety laboratory tests and ECGs will be limited to 1 repeat.

6.3. Subject Withdrawal Criteria

Subjects will be informed that they have the right to withdraw their consent to participate in the study at any time for any reason, without prejudice to their medical care. The Investigator also has the right to withdraw subjects from the study, after discussion with the Sponsor, for any of the following reasons:

- Non-adherence to study drug regimen or protocol requirements.
- Non-compliance with instructions or failure to return for follow-up.
- Subject safety.

If a subject is withdrawn or discontinued from the study, the primary reason for withdrawal from the study is to be recorded in the source documents/electronic case report form (eCRF).

Any subject that discontinues treatment prior to completing the study should be strongly encouraged to attend a Treatment Discontinuation visit within 7 days (± 4 days) after the last SC dose to complete all remaining visits and procedures as outlined in the SoA (Table 1), even if they are no longer receiving study drug.

In case of discontinuation, all AEs should be followed as described in Section 10.2.5.

7. TREATMENT OF SUBJECTS

7.1. Administration of Treatments

Subjects will receive SC setmelanotide or SC placebo as an injection QD for the duration of the study. Doses will be administered in the CRU by study staff.

On Days 10 and 16, oral placebo or oral moxifloxacin will be administered within 2 minutes of SC setmelanotide or SC placebo based on the assigned dose group (Section 5.1). Subjects will be instructed to take oral doses with 240 mL of water at room temperature. Dosing will be conducted by study staff.

7.2. Administration of Food

Subjects will be instructed to fast overnight prior to all continuous Holter ECG sampling days (Days -1, 10, and 16), with water permitted [redacted]. A standard breakfast will be provided in the CRU every morning at approximately 7:00 AM, with study drug dosing to occur 30 minutes after the start of the meal (between 5:30 AM to 9:30 AM). Lunch, dinner, and a snack will be provided at approximately 12:00 PM, 6:00 PM, and 9:00 PM, respectively. On Days -1, 10, and 16, lunch and dinner should be provided after completion of the 4-hour and 10-hour assessments, respectively.

Prior to the [redacted] energy intake assessment periods, subjects will be provided a standardized evening meal on Day −3 and Day 12. [redacted].

7.3. Concomitant Medications and Prohibited Therapies

With the exception of contraceptives or the occasional use of acetaminophen, naproxen, and ibuprofen, subjects should not take any other prescription or non-prescription drugs, including individual vitamins, herbal and dietary supplements, within 7 days or 5 half-lives (whichever is longer) prior to CRU admission and for the duration of the study, unless in the opinion of the Investigator and Sponsor's Medical Monitor the medication is not expected to interfere with the study procedures or compromise subject safety.

7.4. Randomization

Upon entering the CRU on Day -2, subjects will be assigned a unique randomization number based on a randomization code that will be generated prior to the start of the study. The randomization number codes the subject's assignment to Group 1, 2, or 3 to receive the following treatments:

Group	SC Treatment Days 1 to 16	Oral Treatment Day 10	Oral Treatment Day 16
1	SC setmelanotide	oral placebo	oral placebo
2	SC placebo	oral moxifloxacin	oral placebo

3	SC placebo	oral placebo	oral moxifloxacin

The randomization scheme will assign subjects in a 1:1:1 ratio.

7.5. Study Blind and Breaking the Blind

The Investigator, study site staff, clinical research organization staff providing site management, and Medical Monitor will not have access to the actual treatment assignment administered during the study, except in the case of emergency. Every attempt will be made to maintain the blind through the study (i.e., until the database snapshot prior to completing the primary statistical analysis). Breaking the blind for a subject should be done only in the event of a medical emergency where the identity of study drug is necessary to appropriately treat the subject. The Principal Investigator will be provided with access to a system to unblind, but if possible, the decision to break the blind should first be discussed with the Medical Monitor. If the blind is broken, the reason, when, and how the blind was broken will be documented.

8. STUDY DRUG MATERIALS AND MANAGEMENT

8.1. Description of Study Drugs

SC setmelanotide, SC placebo, oral moxifloxacin, and oral placebo will be provided as detailed in Table 2.

Table 2: Description of Study Drugs

Product Name	SC Setmelanotide (IMCIVREE)	SC placebo	Moxifloxacin HCl	Oral placebo
Dosage Form	Solution for injection	Solution for injection	Tablets	Tablet
Unit Dose	10.0 mg/mL solution in a 1 mL multiple-dose vial	1 mL multiple-dose vial	400 mg	N/A
Route of Administration	SC	SC	Oral	Oral
Physical Description	Clear, colorless to slightly opalescent solution essentially free of visible particulates	Identical in appearance to active setmelanotide	Pink/beige hard tablet	Identical in appearance to oral moxifloxacin

SC setmelanotide and SC placebo will be manufactured by Recipharm (Monts, France).

8.2. Study Drug Packaging and Labeling

SC setmelanotide and SC placebo will be supplied by Rhythm (manufactured by Recipharm). Oral moxifloxacin and oral placebo will be supplied by the CRU.

Setmelanotide packaging and labeling will be prepared according to the IMCIVREE (setmelanotide) Prescribing Information (2020).

To ensure that the subject and site are blinded with respect to subject's randomized treatment assignment, SC placebo and SC setmelanotide are identical in appearance and are supplied in identical packaging. Each package and vial will contain a code that identifies the contents as either SC placebo or SC setmelanotide. For each dose the study pharmacist will select the correct study drug based on the package code and will provide the blinded study medication to the subject for administration.

8.3. Preparation, Handling, and Storage

All study 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.

SC setmelanotide and SC placebo should be stored at a temperature between 2°C to 8°C. Both SC setmelanotide and SC placebo are stable at room temperature for a short time period.

Oral moxifloxacin and oral placebo should be stored at 25°C, with excursions are permitted to 15-30°C.

8.4. Study Drug Accountability, Handling, and Disposal

Accountability for the study drug at the study site is the responsibility of the Investigator. The Investigator will ensure that the study drug 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 subject, and return to Rhythm (or disposal of the drug, if approved by Rhythm) 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.

All unused study drug supplies and equipment will either be returned to Rhythm or destroyed after the site close-out visit. The Sponsor, or designee, will verify study drug disposition at the site close-out visit. If the study drug is returned to Rhythm, documentation of the shipment will be provided. If the study drug is destroyed by the site, a Certificate of Destruction will be provided to Rhythm, or designee, by the site to document the disposal.

9. PHARMACOKINETIC ASSESSMENTS

Serial blood samples for determination of setmelanotide and moxifloxacin concentrations in plasma will be collected at the timepoints indicated in the SoA (Table 1). All efforts should be made to collect samples within the sampling windows specified in Table 1; however, collection of samples outside of the window will not be considered protocol deviations. For all PK blood samples, the actual (clock) time that the sample is collected will be recorded in source documents and the eCRF. For timepoints at which vital signs, PK blood samples, and/or ECGs are all to be collected, ECGs should be collected first followed by vital signs then PK samples, with the timing of the PK sample occurring at the nominal time.

Plasma will be harvested from PK samples and will be frozen, shipped to a bioanalytical laboratory designated by the Sponsor. Plasma samples will be analyzed for setmelanotide and moxifloxacin concentrations using validated analytical methods, as detailed in the laboratory manual. Samples collected after placebo dosing will not be analyzed.

10. ASSESSMENT OF SAFETY

10.1. Safety Parameters

Safety and tolerability of setmelanotide will be assessed by monitoring and recording of all AEs throughout the study (setmelanotide and moxifloxacin AEs reported separately). Regular monitoring of 12-lead safety ECGs, C-SSRS, clinical laboratory assessments, vital signs, physical examinations, and concomitant medications will be conducted as detailed in the SoA (Table 1) and below. Subjects will return to the CRU for a Follow-up visit 7 ± 2 days after receiving the last SC dose to assess for AEs and other safety parameters as described in the SoA (Table 1).

10.1.1. Demographic, Medical History, and Concomitant Medication Review

Medical history and demographic data including the subject's sex, race, date of birth, and concomitant medication use will be obtained for all subjects during the Screening period (Table 1).

The medical history should be updated on when the subject enters the CRU on Day -2 (prior to first dose of study drug on Day 1), to assess continued study 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 subject's recent medication use to assess whether any changes have occurred since the previous visit.

A review of concomitant medications will be conducted during the Screening Period and throughout the study. Any medications taken by study subjects will be reviewed by the Investigator or Sponsor's Medical Monitor to determine whether it is expected to interfere with study procedures or compromise subject safety and will be recorded in source documents and on the appropriate eCRF.

10.1.2. Physical Examination

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 assessments. 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 eCRF.

10.1.3. Comprehensive Skin Examination

Each subject will receive a complete, comprehensive skin exam as part of Screening, prior to any treatment. If any concerning lesions are identified, the subject will be referred to a dermatologist for assessment and potential biopsy prior to study start. If the pre-treatment biopsy results are of concern, the subject will be excluded from the study.

10.1.4. Fitzpatrick Scale

Each subject is to be categorized for skin type according to the Fitzpatrick scale (Fitzpatrick 1975). The Fitzpatrick Scale is depicted in Appendix 14.1.

10.1.5. Weight and Height

Weight and height will be recorded at the time points designated in the SoA (Table 1) for the calculation of body mass index (BMI) as follows:

$$BMI\ (kg/m^2) = \frac{weight\ (kg)}{height\ (m)^2}$$

10.1.6. Vital Signs

Vital signs include systolic and diastolic BP, HR, pulse rate, and tympanic (ear) body temperature (°C). BP and HR will be obtained in the supine position following at least 5 minutes of rest in the supine position at each timepoint designated in the SoA (Table 1). BP and HR will be measured using the same arm for each reading. Repeat measures and more frequent monitoring can be implemented for significant increases in BP or HR.

For timepoints at which vital signs, PK blood samples, and/or ECGs are all to be collected, ECGs should be collected first followed by vital signs then PK samples, with the timing of the PK sample occurring at the nominal time.

10.1.7. 12-Lead Electrocardiogram (ECG)

Continuous Holter 12-lead ECGs (for C-QTc analysis; collected by Holter monitors) and single 12-lead safety ECGs will be obtained at the timepoints detailed in the SoA (Table 1). The following guidelines will be applied for ECG measurements obtained using a Holter monitor:

- ECG technicians should be thoroughly trained in the administration of a 12-lead ECG, the institution's specific protocols and procedures for ECG tests and the requirements of the study protocol.
- ECG analysts will be blinded to the treatment, timepoint, and subject.
- The same make and model of ECG machine with the same style of leads should be used for all subjects. Such equipment should be recently serviced and calibrated. Machine calibration records and performance data should be maintained on file.
- Subjects should be in a supine position and have rested for 10 minutes before and 5 minutes after each timepoint.
- For Holter ECG extractions, the ECG will be captured for 5 minutes after the subject has been supine for 10 minutes. The subject will remain supine for additional 5 minutes after the end of Holter extraction.

Continuous Holter ECGs will be read with manual adjudication at a central laboratory.

For timepoints at which vital signs, PK blood samples, and/or ECGs are all to be collected, ECGs should be collected first followed by vital signs then PK samples, with the timing of the PK sample to occur at the nominal time.

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

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 (e.g., referral to a mental

health professional [MHP]). Two versions of the C-SSRS will be administered according to the SoA (Table 1):

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

To be eligible for the study, a subject cannot have a suicidal ideation of type 4 or 5 on the C-SSRS at Screening, a history of suicide attempt in the last 20 ears, or any suicidal behavior in the last month.

Any deviation from the intended use of the instrument should be documented by the Investigator, along with the reason for the deviation.

10.1.9. Laboratory Assessments

10.1.9.1. Clinical Laboratory Tests

Blood samples will be collected prior to dosing according to the SoA (Table 1).

All clinically significant laboratory abnormalities will be followed-up by repeat testing and further investigated per the judgment of the Investigator.

Specific tests are described below:

- **Hematology:** complete blood count with platelet count and standard indices will be obtained.
- **Chemistry:** sodium, potassium, chloride, carbon dioxide (CO_2), albumin, total protein, glucose, blood urea nitrogen (BUN), creatinine, uric acid, aspartate aminotransferase (AST), alanine aminotransferase (ALT), gamma-glutamyltranspeptidase (GGT), creatine phosphokinase (CPK), alkaline phosphatase, total bilirubin, direct bilirubin, lactate dehydrogenase (LDH), calcium, phosphorus and magnesium.
- **Coagulation Profile:** prothrombin time (PT) or international normalized ratio (INR), and partial thromboplastin time (PTT), also referred to as activated partial thromboplastin time (aPTT).
- **Urinalysis:** pH, glucose, protein, ketones, bilirubin, blood, urobilinogen, specific gravity, nitrite, and leukocytes by dipstick analysis or machine urinalysis. Urine microscopic examination will be performed if positive findings on dipsticks warrant further examination.

10.1.9.2. Virus Serology

At Screening approximately 8 mL of blood will be withdrawn into a plain vacutainer for standard serological tests for the presence of human immunodeficiency virus infection (HIV), hepatitis B virus infection (HBsAg), and hepatitis C virus infection (anti-HCV).

10.1.9.3. Urine Drug Screen

Urine screens will be conducted at Screening and at each CRU admission for drugs of abuse (at a minimum amphetamines, barbiturates, benzodiazepines, cannabinoids, cocaine, and opiates), alcohol, and cotinine. A positive result for drugs of abuse or alcohol, or cotinine levels indicative of active smoking at any time will result in subject exclusion from the study.

10.1.9.4. Pregnancy Testing and Contraception

Females of childbearing potential must not be pregnant and must have a negative serum pregnancy test result at the Screening Visit and negative urine pregnancy test on CRU admission days, with results known prior to initiating dosing; pregnancy testing will be monitored during the study.

Females of non-childbearing potential, defined as surgically sterile (status post hysterectomy, bilateral oophorectomy, or bilateral tubal ligation), or post-menopausal for at least 12 months (and confirmed with a screening FSH level in the post-menopausal range) do not require contraception during the study.

For females of childbearing potential, a highly reliable form of contraception must be used/practiced throughout the study and for 90 days following the study. Highly reliable acceptable forms of contraception include hormonal (i.e., oral, implantable, or injectable) and single-barrier method (i.e., condom), or an intrauterine device (IUD) and single-barrier method (i.e., condom) or vasectomized partner. True abstinence is acceptable only if it is the preferred and usual lifestyle of the subject.

It is not known if setmelanotide will affect spermatogenesis. Therefore, males with female partners of childbearing potential must agree to use contraception (e.g., if they have not had a vasectomy then should either (a) abstain from reproductive sexual intercourse or (b) use a highly reliable method such as condom and diaphragm with spermicide during intercourse) if they become sexually active during the study and for 90 days following the study. True abstinence is acceptable only if it is the preferred and usual lifestyle of the subject. Male subjects must not donate sperm for 90 days following their participation in the study.

In the event of pregnancy during setmelanotide treatment, setmelanotide is to be permanently discontinued.

If a pregnancy is reported, the Investigator should inform the Sponsor within 24 hours of learning of the pregnancy and should follow the procedures outlined in Section 10.2.4.

Details of all pregnancies in female subjects and female partners of male subjects will be collected after the start of study treatment through 30 days after the last SC setmelanotide dose.

Note that pregnancy itself is not considered a serious adverse event (SAE). However, abnormal pregnancy outcomes (e.g., spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs.

10.2. Adverse Events

10.2.1. Definition of Adverse Events and Serious Adverse Events

10.2.1.1. Adverse Event

An AE is any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related. An adverse event (also referred to as an adverse experience) can be any unfavorable and unintended sign (e.g., an abnormal laboratory finding), symptom, or disease temporally associated with the use of a drug, without any judgment about causality. An AE can arise from any use of the drug (e.g., off-label use, use in combination with another drug) and from any route of administration, formulation, or dose, including an overdose.

10.2.1.2. Serious Adverse Event

An AE or suspected adverse reaction is considered an SAE if, in the view of either the Investigator or Sponsor, it results in any of the following outcomes:

- Death.
- Life-threatening. Life-threatening means that the subject was at immediate risk of death from the reaction as it occurred, ie, it does not include a reaction which hypothetically might have caused death had it occurred in a more severe form.
- In-patient hospitalization or prolongation of existing hospitalization. Hospitalization admissions and/or surgical operations scheduled to occur during the study period but planned prior to study entry are not considered AEs if the illness or disease existed before the subject was enrolled in the study, provided that it did not deteriorate in an unexpected manner during the study (eg, surgery performed earlier than planned).
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions.
- Congenital anomaly/birth defect.
- Important medical event. An important medical event is an event that may not result in death, be life-threatening, or require hospitalization but may be considered an SAE when, based upon appropriate medical judgment, it may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed in the definitions for SAEs. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in in-patient hospitalization, or the development of drug dependency or drug abuse.

10.2.1.3. Unexpected Adverse Drug Reaction

An unexpected adverse drug reaction (ADR) is a reaction for which the nature or severity is not consistent with the product information (i.e., IMCIVREE (setmelanotide) Prescribing Information (2020)). Until product information is amended, expedited reporting is required for additional occurrences of the reaction. Reports that add significant information on specificity or severity of a known, already documented SAE constitute unexpected events. For example, an

event more specific or more severe than described in product label would be considered "unexpected".

10.2.2. Relationship to Study Drug

Relationship to study drug administration (setmelanotide or moxifloxacin, assessed separately) will be determined by the Investigator according to the following criteria.

- **None:** No relationship between the event and the administration of study drug. The event is related to other etiologies, such as concomitant medications or subject's clinical state.
- **Unlikely:** The current state of knowledge indicates that a relationship to study drug is unlikely, the temporal relationship is such that study drug would not have had any reasonable association with the observed event or another reasonable explanation for the event (e.g., a pre-existing clinical condition or other concomitant treatment) is more likely.
- **Possible:** A reaction that follows a plausible temporal sequence from administration of the study drug and follows a known response pattern to the suspected study drug. The reaction might have been produced by the subject's clinical state or other modes of therapy administered to the subject.
- **Probable:** A reaction that follows a plausible temporal sequence from administration of the study drug and follows a known response pattern to the suspected study drug. The reaction cannot be reasonably explained by the known characteristics of the subject's clinical state or other modes of therapy administered to the subject.

For the purpose of safety analyses, all AEs that are classified as possible or probable will be considered treatment-related events.

10.2.3. Severity of Adverse Events

For both serious and non-serious AEs, the Investigator must determine both the intensity of the event and the relationship of the event to study drug administration. Only those injection site reactions considered clinically significant by the Investigator will be recorded as AEs.

Intensity of all AEs including clinically significant treatment-emergent laboratory abnormalities, injection site reactions, and potential systemic reactions, where appropriate, will be guided per the Common Terminology Criteria for Adverse Events (CTCAE). 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).

AEs not listed by the CTCAE will be graded as follows:

- **Mild:** discomfort noticed but no disruption of normal daily activity.
- **Moderate:** discomfort sufficient to reduce or affect daily activity.
- **Severe:** inability to work or perform normal daily activity.
- **Life-threatening:** represents an immediate threat to life.

10.2.4. Procedures for AE and SAE Reporting

Each subject must be carefully monitored for the development of any AEs. This information should be obtained in the form of non-leading questions (e.g., "How are you feeling?") and from signs and symptoms detected during each examination, observations of study personnel, and spontaneous reports from subjects.

All AEs (serious and non-serious) spontaneously reported by the subject and/or in response to an open question from study personnel or revealed by observation, physical examination, or other diagnostic procedures will be recorded on the appropriate eCRF. Any clinically relevant deterioration in laboratory assessments or other clinical findings is considered an AE and must be recorded on the appropriate eCRF. When possible, signs and symptoms indicating a common underlying pathology should be noted as one comprehensive event.

All SAEs that occur during the study must be reported by the Investigator to the Medical Monitor within 24 hours from the point in time when the Investigator becomes aware of the SAE. All SAEs must be reported whether or not considered causally related to the study drug. SAE forms will be completed, and the information collected will include subject number, a narrative description of the event, and an assessment by the Investigator as to the severity of the event and relatedness to study drug. Follow-up information on the SAE may be requested by the Sponsor or its designee.

If there are serious, unexpected adverse drug reactions associated with the use of the study drug, the Sponsor or designee will notify the appropriate regulatory agency(ies), Independent Ethic Committees (IECs) and all participating investigators on an expedited basis. It is the responsibility of the Investigator to promptly notify the Institutional Review Board (IRB)/IEC where required by the IRB/IEC of all unexpected serious adverse drug reactions involving risk to human subjects.

10.2.5. Adverse Event Monitoring and Follow-up

Monitoring of AEs will be conducted throughout the study. AEs will be recorded in the eCRFs from Screening through the Follow-up visit. AEs that occur after the start of study drug administration will be considered treatment-emergent adverse events (TEAEs). SAEs will be recorded through the Follow-up visit. All AEs should be monitored until they are resolved.

After the initial AE/SAE report, the Investigator is required to proactively follow each subject at subsequent visits/contacts. All SAEs will be followed until resolution, stabilization, the event is otherwise explained, or the subject is lost to follow-up.

Any SAE that occurs at any time after completion of the study, which the Investigator considers to be related to study drug, must be reported to the Sponsor or designee.

In the event a subject is withdrawn from treatment due to an AE, the subject should be encouraged to complete the final study/early termination visit to monitor the event to resolution and obtain additional protocol defined safety assessments.

10.2.6. Depression or Suicidality

A subject should be referred to an MHP if he/she has:

- Any suicidal behavior.
- Any suicidal ideation of type 4 or 5 on the C-SSRS.

A referral to a MHP should also be made if in the opinion of the Investigator it is necessary for the safety of the subject. If a subject's psychiatric disorder can be adequately treated with psycho- and/or pharmacotherapy, then the subject, at the discretion of the MHP, should be continued in the study.

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11. STATISTICS

11.1. Sample Size Determination

11.1.1. Sample Size for Setmelanotide C-QTc Analysis

A sample size of 60 evaluable subjects who complete the study (20 subjects in Group 1 receiving SC setmelanotide and 20 subjects each in Groups 2 and 3 receiving SC placebo) will provide at least 85% power to exclude that setmelanotide causes more than 10 msec QTc effect at clinically relevant plasma levels, as shown by the upper bound of the 2-sided 90% confidence interval (CI) of the model-predicted QTc effect (ΔΔQTcF) at the observed geometric mean Cmax of setmelanotide on Day 10 and Day 16 in the study individually. This power is estimated approximately using a 2-sample t-test using nQuery 8 (www.statsols.com). The calculation assumes a 1-sided 0.05 significance level, a small underlying effect of setmelanotide of 3 msec and a standard deviation (SD) of the ΔQTcF of 8 msec for both SC setmelanotide and SC placebo. Note that this calculation is conservative, since it does not take into account any gain in precision due to the use of all data from each subject with the help of a linear mixed effects model. The concentration-QTc analysis method is supported by Darpo (2015) and Ferber (2015).

11.1.2. Sample Size for Assay Sensitivity of C-QTc Analysis

To demonstrate assay sensitivity with C-QTc analysis, it must be shown that the ΔΔQTcF of a single dose of 400 mg moxifloxacin exceeds 5 msec (i.e., the lower bound of the 2 sided 90% CI of the predicted QTcF effect [ΔΔQTcF] should exceed 5 msec) at the observed geometric mean Cmax of 400 mg moxifloxacin. Under the assumption that the predicted moxifloxacin QTc effect is 10 msec with a SD of ΔQTcF of 8 msec for both oral moxifloxacin and oral placebo, a sample size of 40 evaluable subjects in a crossover of moxifloxacin and placebo will provide at least 81% power to demonstrate assay sensitivity with a 1-sided 0.05 significant level. The power to detect the effect of moxifiloxicin on QTc over the entire crossover period is at least 86%. This power is estimated approximately using a 2-sample t-test in nQuery 8 (www.statsols.com). The number of 20 evaluable subjects in each sequence on moxifloxacin (40 over both Day 10 and 16) also agrees with recent recommendations of the FDA, which proposes at least 20 subjects (Huang 2019).

11.2. Analysis Populations

The following populations are defined for this study:

- **Safety Population:** all subjects who received at least one dose of study drug (SC setmelanotide, SC placebo, oral moxifloxacin, or oral placebo).
- **Pharmacokinetic Population:** all subjects who received at least 1 dose of setmelanotide or moxifloxacin and have at least one quantifiable concentration of setmelanotide or moxifloxacin. A subject may be excluded from the PK summary statistics and statistical analysis if the subject has an AE of vomiting that occurs at or before 2 times the median Tmax during moxifloxacin dosing.
- **QT/QTc Population:** all subjects in the Safety Population with measurements at baseline as well as on-treatment with at least one post-dose timepoint with a valid ΔQTcF value.

The QT/QTc population will be used for the by-timepoint and categorical analyses of the cardiodynamic ECG parameters.

- **PK/QTc Population:** all subjects who are in both the QT/QTc and PK populations with at least 1 pair of post-dose PK and QTcF data from the same timepoint as well as subjects in the QT/QTc population who received placebo. The PK/QTc population will be used for the C-QTc analysis. The PK/QTc population will be defined for setmelanotide and for moxifloxacin.

11.3. Planned Analysis

Separate statistical and PK analysis plans will be developed, which will include more technical and detailed descriptions of the statistical and PK analyses described in this section. This section is a summary of the planned statistical analyses of the most important endpoints, including primary and other endpoints.

11.3.1. Cardiodynamic ECG Assessment

The primary analysis will be based on C-QTc modeling of the relationship between plasma concentrations of setmelanotide (or placebo) and ΔQTcF (using Day -1 time-matched Holter ECGs as baseline) with the intent to exclude an effect of ΔΔQTcF >10 msec at clinically relevant plasma levels, using the concepts presented in the "Scientific White Paper on C-QTc modeling" (Garnett 2018b, Garnett 2018a). After development of the C-QTc model and assessment of model performance through nonparametric bootstrapping, the ΔΔQTcF associated with the Cmax of therapeutic and supratherapeutic doses will be computed using bias-corrected 90% CI. An increase in QTc of ≥10 msec can be ruled out if the upper 90% CI is <10 msec.

The change from baseline (Δ) and placebo-corrected change from baseline (ΔΔ) QTcF, HR, PR, and QRS will be summarized by nominal time and treatment using descriptive statistics. An analysis of categorical outliers will be performed for changes in QTcF, HR, PR, and QRS, and T-wave morphology, and U-wave presence and results will be summarized.

11.3.2. Assay Sensitivity

Assay sensitivity will be evaluated by C-QTc analysis of the effect on ΔΔQTcF of moxifloxacin using a similar model as for the primary analysis. Assay sensitivity will be deemed as met if the predicted QT effect (i.e., the lower bound of the 2-sided 90% CI of ΔΔQTcF) is above 5 msec at the observed geometric mean Cmax of 400 mg oral moxifloxacin.

11.3.3. Pharmacokinetic Analysis

Setmelanotide and moxifloxacin plasma concentration versus time data will be summarized by treatment and nominal time using descriptive statistics (number of observations [n], mean, median, CV%, SD, minimum, and maximum). Individual and mean concentration versus time plots will be presented.

PK parameters for setmelanotide will be calculated using noncompartmental methods and will include: Cmax, Tmax, AUClast, AUCtau, CL/F, and V/F. PK parameters from the PK populations will be summarized by treatment using descriptive statistics (including n, arithmetic and geometric mean, arithmetic and geometric CV%, SD, median, minimum, and maximum).

11.3.4. Safety Analysis

AEs will be coded by using the most current version of Medical Dictionary for Regulatory Activities (MedDRA) and summarized by system organ class, preferred term, and treatment group for the number and percent of AEs reported, the number of subjects reporting each AE, and the number of subjects with any AE.

A by-subject 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 12-lead safety ECGs, C-SSRS, clinical laboratory evaluations, vital signs, and concomitant medication monitoring will be summarized by time of collection and by treatment group. In addition, change from baseline to any post-dose values will be summarized for safety ECGs, C-SSRS, clinical laboratory results, and vital signs. Frequency of subjects with abnormal safety laboratory results will be tabulated by treatment.

No formal statistical analysis of safety data is planned.

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12. ADMINISTRATIVE REQUIREMENTS

12.1. Good Clinical Practice

The study will be conducted in accordance with the International Conference on Harmonization for Good Clinical Practice (ICH-GCP) and the appropriate regulatory requirement(s). The Investigator will be thoroughly familiar with the appropriate use of the study drug as described in the protocol, IB, and labeling documents. Essential clinical documents will be maintained to demonstrate the validity of the study and the integrity of the data collected. Master files should be established at the beginning of the study, maintained for the duration of the study, and retained according to the appropriate regulations.

12.2. Ethical Considerations

The study will be conducted in accordance with ethical principles founded in the Declaration of Helsinki. The IRB/IEC will review all appropriate study documentation in order to safeguard the rights, safety, and well-being of the subjects. The study will only be conducted at sites where IRB/IEC approval has been obtained. The protocol, IB, informed consent, advertisements (if applicable), written information given to the subjects, safety updates, annual progress reports, and any revisions to these documents will be provided to the IRB/IEC by the Investigator.

12.3. Subject Information and Informed Consent

After the study has been fully explained, written informed consent will be obtained from the subject prior to study participation. The method of obtaining and documenting the informed consent and the contents of the consent will comply with ICH-GCP and all applicable regulatory requirement(s).

12.4. Subject Confidentiality

In order to maintain subject privacy, all source documents/eCRFs, study drug accountability records, study reports, and communications will identify the subject by initials and the assigned subject number. The Investigator will grant monitor(s) and auditor(s) from the Sponsor or its designee and regulatory authority(ies) access to the subject's original medical records for verification of data gathered on the source documents/eCRFs and to audit the data collection process. The subject's confidentiality will be maintained and will not be made publicly available to the extent permitted by the applicable laws and regulations.

12.5. Protocol Compliance

The Investigator will conduct the study in compliance with the protocol provided by the Sponsor and given approval/favorable opinion by the IRB/IEC and the appropriate regulatory authority(ies). Modifications to the protocol should not be made without agreement of both the Investigator and the Sponsor. Changes to the protocol will require written IRB/IEC approval/favorable opinion prior to implementation, except when the modification is needed to eliminate an immediate hazard(s) to subjects. The IRB/IEC may provide, if applicable regulatory authority(ies) permit, expedited review and approval/favorable opinion for minor change(s) in ongoing studies that have the approval /favorable opinion of the IRB/IEC. The Sponsor or

designee will submit all protocol modifications to the regulatory authority(ies) in accordance with the governing regulations.

When immediate deviation from the protocol is required to eliminate an immediate hazard(s) to subjects, the Investigator will contact the Sponsor, if circumstances permit, to discuss the planned course of action. Any departures from the protocol must be fully documented in the source documents/eCRF.

12.6. Data Management

12.6.1. Data Handling

Data will be recorded at the site on source documents and reviewed by the Clinical Research Associate (CRA) during monitoring visits. The CRA will verify data recorded in the eCRF system with source documents. All corrections or changes made to any study data must be appropriately tracked in an audit trail in the eCRF system. eCRFs will be considered complete when all missing, incorrect, and/or inconsistent data have been accounted for.

12.6.2. Computer Systems

Data will be processed using a validated computer system conforming to regulatory requirements.

12.6.3. Data Entry

Data must be recorded using the eCRF system as the study is in progress. All study site personnel must log into the system using their secure username and password in order to enter, review, or correct study data. These procedures must comply with Title 21 of the Code of Federal Regulations (21 CFR Part 11). All passwords will be strictly confidential.

12.6.4. Medical Information Coding

For medical information the following thesauri will be used:

- Medical Dictionary for Regulatory Activities (MedDRA) for AEs
- World Health Organization (WHO) Drug for concomitant medications

12.6.5. Data Validation

Validation checks programmed within the eCRF system, as well as supplemental validation performed via review of the downloaded data, will be applied to the data in order to ensure accurate, consistent, and reliable data. Data identified as erroneous, or data that are missing, will be referred to the investigative site for resolution through data queries.

Electronic CRFs must be reviewed and electronically signed by an Investigator who signed the protocol.

12.7. Direct Access to Source Data

Monitoring and auditing procedures developed or reviewed and approved by the Sponsor will be followed, to comply with GCP guidelines.

The study will be monitored by the Sponsor or its designee. Monitoring will be done by personal on-site or remote visits from a representative of the Sponsor (site monitor) and will include review of the source documents/CRFs for completeness and clarity and cross-checking with source documents. Clarification of administrative matters will be performed, if necessary. The review of medical records will be performed in a manner to ensure that subject confidentiality is maintained.

The site monitor will ensure that the investigation is conducted according to protocol design and regulatory requirements by frequent communications (letter, telephone, and fax).

All unused study drug and other study materials are to be returned to the Sponsor or destroyed after the site close-out visit (see Section 8.4).

Regulatory authorities, the IRB/IEC, and/or the Sponsor's clinical quality assurance group or designee may request access to all source documents, CRFs, and other study documentation for on-site audit or inspection. Direct access to these documents must be guaranteed by the Investigator, who must provide support at all times for these activities.

12.8. Source Document/Case Report Form Completion

Source documents/CRFs will be completed for each study subject. It is the Investigator's responsibility to ensure the accuracy, completeness, and timeliness of the data reported in the subject's source document/CRF. The source document/CRF should indicate the subject's participation in the study and should document the dates and details of study procedures, AEs, and subject status.

The Investigator, or designated representative, should complete the source document/CRF as soon as possible after information is collected, preferably on the same day that a study subject is seen for an examination, treatment, or any other study procedure. Any outstanding entries must be completed immediately after the final examination. An explanation should be given for all missing data.

The Investigator must sign and date the Investigator's Statement at the end of the source document/CRF to endorse the recorded data.

The Sponsor will retain the originals of all CRFs. The Investigator will retain all completed source documents/CRFs.

12.9. Record Retention

The Investigator will maintain all study records according to ICH-GCP and applicable regulatory requirement(s). Records will be retained for at least two years after the last marketing application approval or two 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 study records, custody must be transferred to a person willing to accept the responsibility. The Sponsor must be notified in writing if a custodial change occurs.

12.10. Liability Insurance

The Sponsor has subscribed to an insurance policy covering, in its terms and provisions, its legal liability for injuries caused to participating persons and arising out of this research performed strictly in accordance with the scientific protocol as well as with applicable law and professional standards.

12.11. Publication of Study Findings and Use of Information

All information regarding setmelanotide supplied by the Sponsor to the Investigator is privileged and confidential information. The Investigator agrees to use this information to accomplish the study and will not use it for other purposes without consent from the Sponsor. It is understood that there is an obligation to provide the Sponsor with complete data obtained during the study.

The information obtained from the clinical study will be used towards the development of setmelanotide and may be disclosed to regulatory authority(ies), other investigators, corporate partners, or consultants as required.

It is the intention of the Sponsor and the academic investigators to publish the results of this study.

13. LIST OF REFERENCES

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14. APPENDICES

14.1. Appendix 1: Fitzpatrick Classification 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; Middle Eastern skin types	Very rarely burns, tans very easily
VI	Black	Never burns, tans very easily

Source: Fitzpatrick (1975)