



Clinical trial results:

A Phase 3 Trial of Setmelanotide (RM-493), a Melanocortin-4 Receptor (MC4R) Agonist, in Bardet-Biedl Syndrome (BBS) and Alstrom Syndrome (AS) Patients with Moderate to Severe Obesity

Summary

| | |
|--------------------------|----------------|
| EudraCT number | 2018-004058-11 |
| Trial protocol | FR ES GB |
| Global end of trial date | 08 March 2021 |

Results information

| | |
|--------------------------------|---------------|
| Result version number | v1 (current) |
| This version publication date | 08 March 2022 |
| First version publication date | 08 March 2022 |

Trial information

Trial identification

| | |
|-----------------------|------------|
| Sponsor protocol code | RM-493-023 |
|-----------------------|------------|

Additional study identifiers

| | |
|------------------------------------|-------------|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT03746522 |
| WHO universal trial number (UTN) | - |

Notes:

Sponsors

| | |
|------------------------------|---|
| Sponsor organisation name | Rhythm Pharmaceuticals, Inc. |
| Sponsor organisation address | 222 Berkeley Street, Boston, United States, MA 02116 |
| Public contact | Chief Medical Officer, Rhythm Pharmaceuticals, Inc., +1 857-264-4280, EU_medinfo@rhythmtx.com |
| Scientific contact | Chief Medical Officer, Rhythm Pharmaceuticals, Inc., +1 857-264-4280, EU_medinfo@rhythmtx.com |

Notes:

Paediatric regulatory details

| | |
|--|-----|
| Is trial part of an agreed paediatric investigation plan (PIP) | No |
| Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial? | No |
| Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial? | Yes |

Notes:

Results analysis stage

| | |
|--|---------------|
| Analysis stage | Final |
| Date of interim/final analysis | 24 May 2021 |
| Is this the analysis of the primary completion data? | Yes |
| Primary completion date | 08 March 2021 |
| Global end of trial reached? | Yes |
| Global end of trial date | 08 March 2021 |
| Was the trial ended prematurely? | No |

Notes:

General information about the trial

Main objective of the trial:

This was a trial with 2 parts: a randomised, double-blind, placebo-controlled, 14-week, double-blind treatment period followed by a 52-week open-label treatment period (total treatment period up to 66 weeks).

The main objective was to assess the effect of setmelanotide on the proportion of patients (≥ 12 years of age at baseline) treated with setmelanotide for approximately (\sim) 52 weeks who achieve a clinically meaningful reduction from baseline (ie, $\geq 10\%$) in body weight.

Protection of trial subjects:

The IRB/IEC reviewed all appropriate study documentation in order to safeguard the rights, safety, and well-being of the patients. The study was only conducted at sites where IRB/IEC approval had been obtained. This study was conducted in accordance with:

- Consensus ethics principles derived from international ethics guidelines, including the Declaration of Helsinki and Council for International Organizations of Medical Sciences International Ethical Guidelines
- The International Council for Harmonisation (ICH) Good Clinical Practices (GCP) Guideline [E6]
- Applicable laws and regulatory requirements.

After the study had been fully explained, written informed consent was obtained from either the patient or his/her guardian or legal representative prior to study participation. The method of obtaining and documenting the informed consent and the contents of the consent complied with ICH-GCP and all applicable regulatory requirement(s).

Background therapy:

Medications approved to treat obesity (e.g., orlistat, lorcaserin, phentermine-topiramate, naltrexone-bupropion) were not allowed within 3 months of randomization and were prohibited during the study.

Glucagon-like peptide-1 (GLP-1) receptor agonists were permitted up to the dose approved for the treatment of diabetes mellitus (e.g., liraglutide up to a daily dose of 1.8 mg) as long as (1) it was not prescribed for the treatment of obesity, (2) the dose had been stable for at least 3 months prior to randomization, (3) the patient had not experienced weight loss during the previous 3 months, and (4) the patient intended to keep the dose stable throughout the course of the study.

Other medications that could theoretically cause weight loss (e.g., stimulants) were allowed so long as the patient (1) had used them at a stable dose for at least 3 months prior to randomization, (2) had not lost weight during the previous 3 months, and (3) intended to keep the dose stable through the course of the study.

All concomitant medications were to be kept at a stable dose throughout the course of the study, unless a dose change was necessary to treat an adverse event (AE).

Evidence for comparator:

This was a placebo controlled trial for the first 14 weeks only. Thereafter, subjects were treated open-label with setmelanotide only, with no comparator group.

| | |
|---|-----------------------------|
| Actual start date of recruitment | 23 November 2018 |
| Long term follow-up planned | Yes |
| Long term follow-up rationale | Safety, Scientific research |
| Long term follow-up duration | 5 Years |
| Independent data monitoring committee (IDMC) involvement? | Yes |

Notes:

Population of trial subjects

Subjects enrolled per country

| | |
|--------------------------------------|-------------------|
| Country: Number of subjects enrolled | Canada: 7 |
| Country: Number of subjects enrolled | United States: 33 |
| Country: Number of subjects enrolled | Spain: 5 |
| Country: Number of subjects enrolled | United Kingdom: 2 |
| Country: Number of subjects enrolled | France: 5 |
| Worldwide total number of subjects | 52 |
| EEA total number of subjects | 10 |

Notes:

Subjects enrolled per age group

| | |
|---|----|
| In utero | 0 |
| Preterm newborn - gestational age < 37 wk | 0 |
| Newborns (0-27 days) | 0 |
| Infants and toddlers (28 days-23 months) | 0 |
| Children (2-11 years) | 11 |
| Adolescents (12-17 years) | 16 |
| Adults (18-64 years) | 25 |
| From 65 to 84 years | 0 |
| 85 years and over | 0 |

Subject disposition

Recruitment

Recruitment details:

The recruitment period started on 23 November 2018. The last patient last visit was on 08 March 2021. Patients were recruited in the United States, Canada, France, Spain, and the United Kingdom.

Pre-assignment

Screening details:

After obtaining informed consent, potential patients were screened to determine study eligibility. The screening period lasted up to 3 weeks prior to randomisation.

Period 1

| | |
|------------------------------|---|
| Period 1 title | Baseline (overall period) |
| Is this the baseline period? | Yes |
| Allocation method | Randomised - controlled |
| Blinding used | Double blind |
| Roles blinded | Subject, Investigator, Monitor, Data analyst, Carer, Assessor |

Blinding implementation details:

Eligible patients were randomised via an interactive website response system. Patients were randomised patients in a 1:1 ratio, stratified by age group (≥ 12 years or < 12 years) and disease (BBS or AS), to receive setmelanotide or placebo for the first 14 weeks of the study. For the double-blind period, placebo and setmelanotide were identical in appearance and were supplied in identical packaging. Thereafter, all patients were treated with open-label setmelanotide.

Arms

| | |
|------------------------------|----------------------|
| Are arms mutually exclusive? | No |
| Arm title | All treated patients |

Arm description:

All patients were treated with setmelanotide in this study.

The first 14 weeks of the study was a double-blind treatment period with patients randomised to setmelanotide or placebo. Thereafter, setmelanotide was administered open-label in all patients.

Patients randomised to setmelanotide were treated for up to 66 weeks with setmelanotide (14 weeks double-blind, followed by 52 weeks open-label).

Patients randomised to placebo were treated with placebo (matching setmelanotide) for 14 weeks followed by open-label setmelanotide for up to 52 weeks.

Dose escalations at the start of the double-blind and open-label treatment periods are described below.

A total of 38 patients (32 BBS patients and 6 AS patients) comprised the pivotal cohort.

| | |
|--|---|
| Arm type | All treated patients |
| Investigational medicinal product name | Setmelanotide (with or without placebo) |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Solution for injection |
| Routes of administration | Subcutaneous use |

Dosage and administration details:

Dosage by age group was as follows, including a dose escalation planned for the start of double-blind treatment (Weeks 1 and 2) and again at the start of open-label treatment to maintain the blind (Weeks 15 and 16).

Setmelanotide

Patients aged ≥ 16 years:

Week 1, 2.0mg setmelanotide; Week 2, 2.0mg setmelanotide; Weeks 3-14, 3.0 mg setmelanotide

Week 15, 2.0mg setmelanotide; Week 16 2.0mg setmelanotide; Weeks 17-66, 3.0 mg setmelanotide

Patients aged < 16 years:

Week 1, 1.0mg setmelanotide; Week 2, 2.0mg setmelanotide; Weeks 3-14, 3.0 mg setmelanotide

Week 15, 1.0mg setmelanotide; Week 16 2.0mg setmelanotide; Weeks 17-66, 3.0 mg setmelanotide

Placebo

All patients randomised to placebo (regardless of age group) were treated with placebo for Weeks 1-14. Thereafter, setmelanotide dosing was open-label, as detailed above by age group, for Weeks 15 to 66.

| | |
|------------------|------------------------------------|
| Arm title | Setmelanotide; double-blind period |
|------------------|------------------------------------|

Arm description:

All patients in the first 14 weeks of the study (ie, the randomised double-blind treatment period) who were treated with setmelanotide.

| | |
|--|---|
| Arm type | Experimental |
| Investigational medicinal product name | Setmelanotide (with or without placebo) |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Solution for injection |
| Routes of administration | Subcutaneous use |

Dosage and administration details:

Dosage by age group was as follows, including a dose escalation planned for the start of double-blind treatment (Weeks 1 and 2) and again at the start of open-label treatment to maintain the blind (Weeks 15 and 16).

Setmelanotide

Patients aged ≥ 16 years:

Week 1, 2.0mg setmelanotide; Week 2, 2.0mg setmelanotide; Weeks 3-14, 3.0 mg setmelanotide

Week 15, 2.0mg setmelanotide; Week 16 2.0mg setmelanotide; Weeks 17-66, 3.0 mg setmelanotide

Patients aged < 16 years:

Week 1, 1.0mg setmelanotide; Week 2, 2.0mg setmelanotide; Weeks 3-14, 3.0 mg setmelanotide

Week 15, 1.0mg setmelanotide; Week 16 2.0mg setmelanotide; Weeks 17-66, 3.0 mg setmelanotide

Placebo

All patients randomised to placebo (regardless of age group) were treated with placebo for Weeks 1-14. Thereafter, setmelanotide dosing was open-label, as detailed above by age group, for Weeks 15 to 66.

| | |
|------------------|------------------------------|
| Arm title | Placebo; double-blind period |
|------------------|------------------------------|

Arm description:

All patients in the first 14 weeks of the study (ie, the randomised double-blind treatment period) who were treated with placebo. At the end of the double-blind period these patients continued treatment with setmelanotide.

Patients aged ≥ 16 years:

Week 1-14, placebo

Week 15, 2.0 mg setmelanotide; Week 16 2.0 mg setmelanotide; Weeks 17-66, 3.0 mg setmelanotide

Patients aged < 16 years:

Week 1-14, placebo

Week 15, 1.0 mg setmelanotide; Week 16, 2.0 mg setmelanotide; Weeks 17-66, 3.0 mg setmelanotide

| | |
|--|------------------------|
| Arm type | Placebo |
| Investigational medicinal product name | Placebo |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Solution for injection |
| Routes of administration | Subcutaneous use |

Dosage and administration details:

Patients randomised to placebo received placebo under double-blind conditions for 14 weeks followed by active treatment with setmelanotide (open-label) until the end of the study. Dose escalation occurred over the first 2 weeks of the double-blind period and again at the start of the open-label period to maintain the blind.

Patients aged ≥ 16 years:

Week 1-14, placebo

Week 15, 2.0mg setmelanotide; Week 16 2.0mg setmelanotide; Weeks 17-66, 3.0 mg setmelanotide

Patients aged < 16 years:

Week 1-14, placebo

Week 15, 1.0mg setmelanotide; Week 16 2.0mg setmelanotide; Weeks 17-66, 3.0 mg setmelanotide

| Number of subjects in period 1 | All treated patients | Setmelanotide; double-blind period | Placebo; double- blind period |
|--|----------------------|---------------------------------------|----------------------------------|
| Started | 52 | 27 | 25 |
| Completed | 39 | 22 | 17 |
| Not completed | 13 | 5 | 8 |
| Transfer to extension study | 2 | - | - |
| Consent withdrawn by subject | 3 | 3 | 2 |
| Adverse event, non-fatal | 6 | 2 | 3 |
| Lost to follow-up | 2 | - | 1 |
| Discontinued during double-blind period | - | - | 2 |

Baseline characteristics

Reporting groups

| | |
|-----------------------|----------|
| Reporting group title | Baseline |
|-----------------------|----------|

Reporting group description:

All treated patients, including patients treated with placebo during the double-blind placebo-controlled period (first 14 weeks of study).

| Reporting group values | Baseline | Total | |
|--|----------|-------|--|
| Number of subjects | 52 | 52 | |
| Age categorical | | | |
| Units: Subjects | | | |
| Children (2-11 years) | 11 | 11 | |
| Adolescents (12-17 years) | 16 | 16 | |
| Adults (18-64 years) | 25 | 25 | |
| Age continuous | | | |
| Units: years | | | |
| arithmetic mean | 19.5 | | |
| standard deviation | ± 10.96 | - | |
| Gender categorical | | | |
| Units: Subjects | | | |
| Female | 31 | 31 | |
| Male | 21 | 21 | |
| Underlying condition | | | |
| Patients with Bardet-Biedl Syndrome (BBS) or Alström Syndrome (AS) condition were eligible to participate. | | | |
| Units: Subjects | | | |
| BBS | 44 | 44 | |
| AS | 8 | 8 | |
| Body Mass Index (kg/m2) | | | |
| Units: kg/m2 | | | |
| arithmetic mean | 41.78 | | |
| standard deviation | ± 11.116 | - | |
| Weight | | | |
| Units: kg | | | |
| arithmetic mean | 107.78 | | |
| standard deviation | ± 34.582 | - | |

End points

End points reporting groups

| | |
|-----------------------|----------------------|
| Reporting group title | All treated patients |
|-----------------------|----------------------|

Reporting group description:

All patients were treated with setmelanotide in this study.

The first 14 weeks of the study was a double-blind treatment period with patients randomised to setmelanotide or placebo. Thereafter, setmelanotide was administered open-label in all patients.

Patients randomised to setmelanotide were treated for up to 66 weeks with setmelanotide (14 weeks double-blind, followed by 52 weeks open-label).

Patients randomised to placebo were treated with placebo (matching setmelanotide) for 14 weeks followed by open-label setmelanotide for up to 52 weeks.

Dose escalations at the start of the double-blind and open-label treatment periods are described below.

A total of 38 patients (32 BBS patients and 6 AS patients) comprised the pivotal cohort.

| | |
|-----------------------|------------------------------------|
| Reporting group title | Setmelanotide; double-blind period |
|-----------------------|------------------------------------|

Reporting group description:

All patients in the first 14 weeks of the study (ie, the randomised double-blind treatment period) who were treated with setmelanotide.

| | |
|-----------------------|------------------------------|
| Reporting group title | Placebo; double-blind period |
|-----------------------|------------------------------|

Reporting group description:

All patients in the first 14 weeks of the study (ie, the randomised double-blind treatment period) who were treated with placebo. At the end of the double-blind period these patients continued treatment with setmelanotide.

Patients aged ≥ 16 years:

Week 1-14, placebo

Week 15, 2.0 mg setmelanotide; Week 16 2.0 mg setmelanotide; Weeks 17-66, 3.0 mg setmelanotide

Patients aged < 16 years:

Week 1-14, placebo

Week 15, 1.0 mg setmelanotide; Week 16, 2.0 mg setmelanotide; Weeks 17-66, 3.0 mg setmelanotide

Primary: Body weight change

| | |
|-----------------|--------------------------------------|
| End point title | Body weight change ^{[1][2]} |
|-----------------|--------------------------------------|

End point description:

The primary endpoint was the proportion of pivotal patients ≥ 12 years old who met the $\geq 10\%$ weight loss threshold from baseline (i.e., responders) after approximately 1 year of treatment with setmelanotide. This analysis was performed on the FAS population, with patients who received any study drug and at least one baseline assessment. Weight was measured in triplicate at each visit and mean values analysed. The estimated proportion of pivotal patients ≥ 12 years of age who achieved a $\geq 10\%$ reduction in body weight was compared to a historical control rate of 10%.

This was not a comparative analysis. Binomial proportions for 100 imputed datasets and outcomes were combined using Rubin's Rule to provide an overall estimate. A 1-sided 0.025 significance level was used based on the small sample size (due to rarity of the disease).

Results of statistical analysis: point estimate: 32.3% (95% CI 16.7, 51.4), $p=0.0006$, indicating primary efficacy endpoint was met.

| | |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

End point timeframe:

Baseline to 1 year on active treatment

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: The statistical analysis of the primary endpoint was based upon comparison with historical

data at the end of the open-label treatment period. Details of the statistical analysis are included with the endpoint description.

[2] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: No comparisons of efficacy for the setmelanotide and placebo groups at the end of the double-blind treatment period were planned or performed.

| End point values | All treated patients | | | |
|-----------------------------|----------------------|--|--|--|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 31 | | | |
| Units: Subjects | 10 | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage change in body weight

| | |
|-----------------|---|
| End point title | Percentage change in body weight ^[3] |
|-----------------|---|

End point description:

Mean percentage of body weight change (kg) from baseline in pivotal patients ≥ 12 years old after 1 year of treatment with setmelanotide within a single group of patients based on the FAS.

Analyses were based on a one-sample t-test for each of the 100 imputed datasets and assuming a mean percent change from baseline in body weight of zero. The outcomes from the 100 imputed datasets were combined using Rubin's Rule to provide a p-value and corresponding CIs. This was evaluated at a 1-sided, 0.025 significance level.

Results of statistical analysis: mean change after 52 weeks of treatment: -5.21% (95% CI -9.17, -3.77), $p=0.0005$, indicating this key secondary efficacy endpoint was met.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Change from baseline to Week 52

Notes:

[3] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: The statistical analysis of this secondary endpoint was based upon data at the end of the open-label treatment period. No comparisons of the setmelanotide and placebo groups at the end of the double-blind treatment period were planned or performed.

| End point values | All treated patients | | | |
|--------------------------------------|----------------------|--|--|--|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 31 | | | |
| Units: percent | | | | |
| arithmetic mean (standard deviation) | -5.21 (\pm 7.895) | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Change in hunger score

| | |
|-----------------|---------------------------------------|
| End point title | Change in hunger score ^[4] |
|-----------------|---------------------------------------|

End point description:

Evaluation of the mean percent change in hunger scores (weekly average hunger score of the daily most/worst hunger score over 24 hours) in pivotal patients ≥ 12 years of age at the end of approximately 1 year of treatment within a single group of patients.

Analyses were based on a one-sample t-test for each of the 100 imputed datasets with an assumed mean percent change from baseline in weekly average of daily hunger scores of zero. The outcomes from the 100 imputed datasets were combined using Rubin's Rule to provide a p-value and corresponding CIs. This was evaluated at a 1-sided, 0.025 significance level.

Results of statistical analysis: mean change after 52 weeks: -30.91% (95% CI -44.09, -17.73), $p < 0.0001$, indicating this key secondary efficacy endpoint was met.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

From baseline to Week 52

Notes:

[4] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: The statistical analysis of this secondary endpoint was based upon data at the end of the open-label treatment period. No comparisons of the setmelanotide and placebo groups at the end of the double-blind treatment period were planned or performed.

| End point values | All treated patients | | | |
|--------------------------------------|------------------------|--|--|--|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 16 | | | |
| Units: percent | | | | |
| arithmetic mean (standard deviation) | -30.91 (\pm 24.733) | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Improvement in daily hunger score

| | |
|-----------------|--|
| End point title | Improvement in daily hunger score ^[5] |
|-----------------|--|

End point description:

The proportion of pivotal patients ≥ 12 years of age in the FAS population who achieve a $\geq 25\%$ improvement from baseline in the weekly average of the daily hunger score after ~ 52 weeks of treatment was analyzed similarly to the primary efficacy endpoint (described above). Prior to analysis, daily hunger scores for each of the 3 hunger assessments (worst/most) were averaged separately by week.

Results of statistical analysis: point estimate: 62.5% (95% CI 35.4, 84.8); $p < 0.0001$.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

From baseline to Week 52.

Notes:

[5] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: The statistical analysis of this secondary endpoint was based upon data at the end of the open-label treatment period. No comparisons of the setmelanotide and placebo groups at the end of the double-blind treatment period were planned or performed.

| | | | | |
|-----------------------------|----------------------|--|--|--|
| End point values | All treated patients | | | |
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 16 | | | |
| Units: Subjects | 10 | | | |

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events after the start of study drug administration were treatment-emergent (TEAEs).

Total duration of treatment (randomised to setmelanotide/placebo): 66 weeks setmelanotide /14 weeks placebo plus 52 weeks setmelanotide.

Adverse event reporting additional description:

TEAEs are presented for all patients who received at least 1 study drug dose. Note, 25 of the 52 treated patients were treated with placebo in the 14-week double-blind period before starting setmelanotide.

NOTE: TEAEs in the 14-week double-blind period include ONLY those TEAEs with an onset during that 14-week period.

| | |
|-----------------|------------|
| Assessment type | Systematic |
|-----------------|------------|

Dictionary used

| | |
|--------------------|--------|
| Dictionary name | MedDRA |
| Dictionary version | 23.0 |

Reporting groups

| | |
|-----------------------|--|
| Reporting group title | All treated patients to end of follow-up |
|-----------------------|--|

Reporting group description:

All patients treated with study drug. Total duration of treatment (randomised to setmelanotide/placebo): up to 66 weeks setmelanotide /14 weeks placebo plus up to 52 weeks setmelanotide.

| | |
|-----------------------|---|
| Reporting group title | Setmelanotide during 14-week double-blind period only |
|-----------------------|---|

Reporting group description:

Patients randomised to setmelanotide for the 14-week double-blind period.

| | |
|-----------------------|---|
| Reporting group title | Placebo during 14-week double-blind period only |
|-----------------------|---|

Reporting group description:

Patients randomised to placebo for the 14-week double-blind period.

| Serious adverse events | All treated patients to end of follow-up | Setmelanotide during 14-week double-blind period only | Placebo during 14-week double-blind period only |
|---|--|---|---|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 3 / 52 (5.77%) | 1 / 27 (3.70%) | 2 / 25 (8.00%) |
| number of deaths (all causes) | 0 | 0 | 0 |
| number of deaths resulting from adverse events | 0 | 0 | 0 |
| Blood and lymphatic system disorders | | | |
| Anaemia | | | |
| subjects affected / exposed | 1 / 52 (1.92%) | 1 / 27 (3.70%) | 0 / 25 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Immune system disorders | | | |
| Anaphylactic reaction | | | |

| | | | |
|---|----------------|----------------|----------------|
| subjects affected / exposed | 1 / 52 (1.92%) | 0 / 27 (0.00%) | 1 / 25 (4.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Eye disorders | | | |
| Blindness | | | |
| subjects affected / exposed | 1 / 52 (1.92%) | 0 / 27 (0.00%) | 1 / 25 (4.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Psychiatric disorders | | | |
| Suicidal ideation | | | |
| subjects affected / exposed | 1 / 52 (1.92%) | 0 / 27 (0.00%) | 0 / 25 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

Frequency threshold for reporting non-serious adverse events: 5 %

| Non-serious adverse events | All treated patients to end of follow-up | Setmelanotide during 14-week double-blind period only | Placebo during 14-week double-blind period only |
|---|--|---|---|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 52 / 52 (100.00%) | 26 / 27 (96.30%) | 24 / 25 (96.00%) |
| Investigations | | | |
| High density lipoprotein decreased | | | |
| subjects affected / exposed | 4 / 52 (7.69%) | 4 / 27 (14.81%) | 0 / 25 (0.00%) |
| occurrences (all) | 4 | 4 | 0 |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Melanocytic naevus | | | |
| subjects affected / exposed | 6 / 52 (11.54%) | 1 / 27 (3.70%) | 0 / 25 (0.00%) |
| occurrences (all) | 7 | 2 | 0 |
| Nervous system disorders | | | |
| Headache | | | |
| subjects affected / exposed | 12 / 52 (23.08%) | 1 / 27 (3.70%) | 6 / 25 (24.00%) |
| occurrences (all) | 51 | 20 | 7 |
| Dizziness | | | |
| subjects affected / exposed | 4 / 52 (7.69%) | 1 / 27 (3.70%) | 2 / 25 (8.00%) |
| occurrences (all) | 4 | 1 | 2 |
| General disorders and administration | | | |

| | | | |
|-----------------------------|------------------|------------------|------------------|
| site conditions | | | |
| Injection site erythema | | | |
| subjects affected / exposed | 26 / 52 (50.00%) | 12 / 27 (44.44%) | 11 / 25 (44.00%) |
| occurrences (all) | 35 | 17 | 12 |
| Injection site pruritus | | | |
| subjects affected / exposed | 20 / 52 (38.46%) | 8 / 27 (29.63%) | 9 / 25 (36.00%) |
| occurrences (all) | 26 | 11 | 9 |
| Injection site pain | | | |
| subjects affected / exposed | 14 / 52 (26.92%) | 3 / 27 (11.11%) | 8 / 25 (32.00%) |
| occurrences (all) | 19 | 4 | 10 |
| Injection site bruising | | | |
| subjects affected / exposed | 18 / 52 (34.62%) | 6 / 27 (22.22%) | 9 / 25 (36.00%) |
| occurrences (all) | 18 | 6 | 9 |
| Injection site induration | | | |
| subjects affected / exposed | 14 / 52 (26.92%) | 6 / 27 (22.22%) | 4 / 25 (16.00%) |
| occurrences (all) | 17 | 6 | 4 |
| Fatigue | | | |
| subjects affected / exposed | 6 / 52 (11.54%) | 1 / 27 (3.70%) | 2 / 25 (8.00%) |
| occurrences (all) | 6 | 1 | 2 |
| Injection site haemorrhage | | | |
| subjects affected / exposed | 6 / 52 (11.54%) | 3 / 27 (11.11%) | 2 / 25 (8.00%) |
| occurrences (all) | 6 | 3 | 2 |
| Injection site oedema | | | |
| subjects affected / exposed | 6 / 52 (11.54%) | 2 / 27 (7.41%) | 1 / 25 (4.00%) |
| occurrences (all) | 6 | 2 | 1 |
| Injection site reaction | | | |
| subjects affected / exposed | 3 / 52 (5.77%) | 1 / 27 (3.70%) | 2 / 25 (8.00%) |
| occurrences (all) | 4 | 2 | 2 |
| Gastrointestinal disorders | | | |
| Nausea | | | |
| subjects affected / exposed | 19 / 52 (36.54%) | 7 / 27 (25.93%) | 6 / 25 (24.00%) |
| occurrences (all) | 25 | 7 | 7 |
| Vomiting | | | |
| subjects affected / exposed | 14 / 52 (26.92%) | 7 / 27 (25.93%) | 0 / 25 (0.00%) |
| occurrences (all) | 18 | 9 | 0 |
| Diarrhoea | | | |

| | | | |
|---|------------------------|------------------------|---------------------|
| subjects affected / exposed occurrences (all) | 10 / 52 (19.23%) 12 | 2 / 27 (7.41%) 3 | 1 / 25 (4.00%) 1 |
| Abdominal pain upper subjects affected / exposed occurrences (all) | 4 / 52 (7.69%) 6 | 0 / 27 (0.00%) 0 | 1 / 25 (4.00%) 1 |
| Abdominal pain subjects affected / exposed occurrences (all) | 4 / 52 (7.69%) 4 | 0 / 27 (0.00%) 0 | 1 / 25 (4.00%) 1 |
| Reproductive system and breast disorders Spontaneous penile erection subjects affected / exposed occurrences (all) | 5 / 52 (9.62%) 5 | 1 / 27 (3.70%) 1 | 0 / 25 (0.00%) 0 |
| Menorrhagia subjects affected / exposed occurrences (all) | 3 / 52 (5.77%) 3 | 0 / 27 (0.00%) 0 | 1 / 25 (4.00%) 1 |
| Respiratory, thoracic and mediastinal disorders Cough subjects affected / exposed occurrences (all) | 5 / 52 (9.62%) 5 | 0 / 27 (0.00%) 0 | 2 / 25 (8.00%) 2 |
| Nasal congestion subjects affected / exposed occurrences (all) | 3 / 52 (5.77%) 3 | 3 / 27 (11.11%) 3 | 0 / 25 (0.00%) 0 |
| Rhinorrhoea subjects affected / exposed occurrences (all) | 3 / 52 (5.77%) 3 | 0 / 27 (0.00%) 0 | 2 / 25 (8.00%) 2 |
| Skin and subcutaneous tissue disorders Skin hyperpigmentation subjects affected / exposed occurrences (all) | 33 / 52 (63.46%) 53 | 17 / 27 (62.96%) 24 | 0 / 25 (0.00%) 0 |
| Acne subjects affected / exposed occurrences (all) | 3 / 52 (5.77%) 3 | 1 / 27 (3.70%) 1 | 1 / 25 (4.00%) 1 |
| Dermatitis atopic subjects affected / exposed occurrences (all) | 3 / 52 (5.77%) 3 | 2 / 27 (7.41%) 2 | 0 / 25 (0.00%) 0 |
| Dry skin | | | |

| | | | |
|--|---------------------|---------------------|---------------------|
| subjects affected / exposed occurrences (all) | 3 / 52 (5.77%) 3 | 0 / 27 (0.00%) 0 | 2 / 25 (8.00%) 2 |
| Skin striae subjects affected / exposed occurrences (all) | 3 / 52 (5.77%) 3 | 1 / 27 (3.70%) 1 | 0 / 25 (0.00%) 0 |
| Psychiatric disorders Aggression subjects affected / exposed occurrences (all) | 3 / 52 (5.77%) 3 | 1 / 27 (3.70%) 1 | 1 / 25 (4.00%) 1 |
| Musculoskeletal and connective tissue disorders Back pain subjects affected / exposed occurrences (all) | 5 / 52 (9.62%) 5 | 0 / 27 (0.00%) 0 | 1 / 25 (4.00%) 1 |
| Arthralgia subjects affected / exposed occurrences (all) | 3 / 52 (5.77%) 3 | 0 / 27 (0.00%) 0 | 0 / 25 (0.00%) 0 |
| Infections and infestations Nasopharyngitis subjects affected / exposed occurrences (all) | 4 / 52 (7.69%) 4 | 2 / 27 (7.41%) 2 | 1 / 25 (4.00%) 1 |
| Upper respiratory tract infection subjects affected / exposed occurrences (all) | 3 / 52 (5.77%) 4 | 1 / 27 (3.70%) 1 | 0 / 25 (0.00%) 0 |
| Urinary tract infection subjects affected / exposed occurrences (all) | 4 / 52 (7.69%) 4 | 1 / 27 (3.70%) 1 | 1 / 25 (4.00%) 1 |
| Ear infection subjects affected / exposed occurrences (all) | 3 / 52 (5.77%) 3 | 0 / 27 (0.00%) 0 | 1 / 25 (4.00%) 1 |
| Pharyngitis streptococcal subjects affected / exposed occurrences (all) | 3 / 52 (5.77%) 3 | 0 / 27 (0.00%) 0 | 2 / 25 (8.00%) 2 |
| Metabolism and nutrition disorders Dyslipidaemia subjects affected / exposed occurrences (all) | 3 / 52 (5.77%) 3 | 1 / 27 (3.70%) 1 | 0 / 25 (0.00%) 0 |

| | | | |
|--|---------------------|---------------------|---------------------|
| Glucose tolerance impaired subjects affected / exposed occurrences (all) | 3 / 52 (5.77%) 3 | 0 / 27 (0.00%) 0 | 2 / 25 (8.00%) 2 |
|--|---------------------|---------------------|---------------------|

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|------------------|---|
| 10 October 2018 | <p>The following substantive changes were introduced:</p> <ul style="list-style-type: none">• Updated the packaging description.• Optional sleep study timepoint was added to V6.• Removed the requirement for electronic storage of ECGs, recording of ECGs in triplicate, and for use of equipment capable of transmitting to a central reader.• Clarified that the optional sleep study would be performed as a standard overnight sleep study. |
| 04 February 2019 | <ul style="list-style-type: none">•Synopsis updated to clarify ages of enrolment•Inclusion #2 updated to clarify the ages of enrolment•Clarification of Exclusion #2 allowable medications and timeframe•Exclusion #4 re-written to remove only DSM-V disorders•Exclusion # 7 added to exclude patients with HbA1c >9.0 at screening•Added glomerular filtration rate•Exclusion #14 added to exclude patients previously treated with setmelanotide•Exclusion #17 added to exclude patients with first degree relatives enrolled within the past 4 months•Clarification that the Investigator had direct access to the system to unblind the treatment in case of emergency•The prohibited medication section was revised•The Screening Period updated to a minimum of 1 week with at least 4 days completed in the electronic hunger diary•Schedule of Assessments updated to add the HbA1c testing noted above•The list of biomarkers to be tested for was revised (some were removed)•Extended the screening period•Table 2 footnote 8 updated to describe a minimum of 1 week of screening and to require hunger diary completion on 4 out of 7 days prior to randomization•Text removed to clarify genetic testing samples would not be used for any other purpose•Clarified that Global Hunger to be completed during visits and the Daily Hunger to be completed electronically each day•Text added to state the PWS-SEQ was to be used in place of the Global Hunger questions in patients with impaired cognitive function•Text added to state the neurocognition tests WAIS-IV or WISC-V could be waived after discussion with the sponsor•Clarified the collection of samples for ACTH and 24-hour urine•Added that archive samples would be discarded at the end of the study•Text added to further define unlikely AE relationship•Text added to describe analysis options of incomplete data•Cockcroft Gault Equation changed to the Modification of Diet in Renal Disease Study equation for patients ≥ 18 or the Bedside Schwartz for patients < 18 |

| | |
|-------------------|---|
| 16 August 2020 | <p>The following changes were introduced:</p> <ul style="list-style-type: none"> • Key secondary objectives updated to reflect a mean percent change from baseline in the weekly average of the daily hunger score. Key Secondary Objectives #1 and #4 were moved to Exploratory. Key Secondary Objective #2 was re-written to specify baseline body weight. Other Secondary Objective #2 was moved to Exploratory. • Key Secondary Endpoints # 1 and #3 were removed (moved to Exploratory). Added Exploratory Endpoint describing the proportion of patients who achieve an improvement in daily hunger score. • Updated to clarify the number of patients enrolled in the Pivotal and Supplemental cohorts. • Updated Inclusion Criteria #2 to specify age at time of first dose. • The Statistical Considerations section of the Synopsis and Section 8, Data Analysis/Statistical Procedures were revised. • The Clinical Overview section was updated with current exposure numbers and entire Clinical Safety section replaced providing updated TEAEs and SAE incidence to align with the annual Investigator Brochure update. • Text was added to allow Supplemental patients to roll into the extension study starting at Visit 8 or later. • Flexibility added to visit schedule windows upon sponsor approval to accommodate difficulty in scheduling due to COVID-19, holidays, and other logistical issue. • Schedule of Assessments was updated to make WISC-V/WAIS-IV optional based on investigator discretion. • Schedule of Assessments – removed Nutritional counselling and monitoring from V 2, 4, 6, 8, 10, and 12. • Schedule of Assessments bullet 11 was removed and 6.5.8 Measures of Insulin Sensitivity/Resistance OGTT was removed. • Updated PK profile blood draw time point preferences to pre-dose 4, 6, and 8 hours. Tubes provided in lab kits collect ~6 mL alloallowing for 2 aliquots. • Clarified that study medication should be taken after obtaining vital signs. |
| 09 September 2020 | <p>The following changes were introduced:</p> <ul style="list-style-type: none"> • Change and percent change in OGTT was removed from the Exploratory Endpoints (Already done for Ver 2.1 Marshfield Clinic only). • Additional clarity was added regarding the timing of dose escalation, the associated visit or phone call, and the visit windows for these days. |

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported