Effect of Setmelanotide, an MC4R Agonist, on Obesity in Bardet-Biedl Syndrome

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Author contributions:
The study sponsor, RH, and JY were responsible for conception and design of the study. RH, SB, ED, KF, and JY acquired data for the study. RH, GY, and MS were responsible for analysis of the data. RH, GY, GG, MS, and JY were responsible for interpretation of the data. All authors were involved in drafting and critically revising the manuscript for important intellectual content or specific study site information and gave final approval of the manuscript for publication.

Competing interests
RH is a consultant for Rhythm Pharmaceuticals, Inc., and Trinity Life Sciences. He receives grant funding from the Bardet-Biedl Syndrome Foundation.
JY receives grant support for clinical investigations from the NICHD, NIH, Soleno Pharmaceuticals Inc, and Rhythm Pharmaceuticals, Inc.
GY, GG, and MS are employed by and may own stock in Rhythm Pharmaceuticals, Inc.
KF, ED, and SB have no conflicts of interest to disclose.
ABSTRACT

**Aims:** Bardet-Biedl syndrome (BBS) is characterized by early-onset obesity and hyperphagia. Setmelanotide decreases weight and hunger in individuals with rare genetic disorders of obesity. We report results of an open-label single-arm phase 2 study of setmelanotide in BBS (ClinicalTrials.gov identifier: NCT03013543).

**Materials and Methods:** Individuals aged ≥12 years with BBS received once-daily setmelanotide. The dose was titrated every 2 weeks to establish the individual therapeutic dose (≤3 mg); treatment continued for an additional 10 weeks. Participants who lost ≥5 kg (or ≥5% of body weight if <100 kg at baseline) continued into the 52-week extension phase. The primary outcome was mean percent change from baseline in body weight at 3 months. Hunger scores and safety were secondary outcomes.

**Results:** Between February 2017 and February 2018, ten individuals were screened; eight completed the 3-month treatment phase and seven completed the extension phase. Mean percent change in body weight from baseline to 3 months was −5.5% (90% CI, −9.3% to −1.6%; n=8); change from baseline was −11.3% (90% CI, −15.5% to −7.0%; n=8) at 6 months and −16.3% (90% CI, −19.9% to −12.8%; n=7) at 12 months. All participants reported ≥1 treatment-emergent adverse event (AE), most commonly injection-site reaction. No AEs led to study withdrawal or death. Most, morning, and average hunger scores were reduced across time points.

**Conclusions:** Setmelanotide reduced body weight and hunger in individuals with BBS and had a safety profile consistent with previous reports. Setmelanotide may be a treatment option in individuals with BBS-associated obesity and hyperphagia.
INTRODUCTION

Bardet-Biedl syndrome (BBS) is a rare, genetically heterogeneous syndrome associated with function-altering variants in ≥24 possible causative genes, including BBS1-21, NPHP1, FBN3, and CEP19, that each play a role in primary cilia function.1-4 In Europe and North America, function-altering variants in BBS1 (23.2%) and BBS10 (20.0%) are most commonly found among individuals with BBS.2 In addition to early-onset obesity and hyperphagia,5 BBS is also characterized by retinal degeneration, cognitive disability, polydactyly, renal abnormalities, and hypogonadism.1,2,6 The hypothalamic melanocortin-4 receptor (MC4R) neuronal pathway regulates energy balance and body weight.1,7 Rare function-diminishing variants in genes involved in this pathway have been associated with hyperphagia, or insatiable hunger, which leads to increased food intake, and development of obesity in early childhood.7-9 No specific pharmacotherapies exist for obesity and hyperphagia in most rare genetic disorders of obesity. Although the pathophysiology of BBS is not completely established, it is hypothesized that the associated obesity is at least in part a result of hypothalamic dysfunction.1 Data from rodents demonstrate that a dysfunctional BBS protein can impair trafficking of leptin receptor (LEPR) in hypothalamic proopiomelanocortin (POMC) neurons,10,11 thus reducing activation of MC4R. Further, serum leptin concentrations in people with BBS are higher than expected when compared with body mass index (BMI)–matched controls.12 This finding suggests that, in BBS, leptin resistance could be associated with diminished leptin signalling in the hypothalamus,12 which, in turn, would reduce downstream activation of MC4R and contribute to development of severe obesity and hyperphagia.1 Indeed, targeted deletion of BBS1 from LEPR-expressing cells in mice
causes hyperphagia and obesity, but, when \textit{BBS}1 is ablated from adipocytes, obesity does not occur.\textsuperscript{13} Finally, administration of the MCR agonist melanotan II reduces food intake and weight in \textit{BBS} knockout mice, implying that the downstream appetite-regulating melanocortin signalling pathway is intact.\textsuperscript{10}

Setmelanotide is an 8-amino-acid cyclic peptide that preferentially binds to MC4R and acts as a substitute for melanocyte-stimulating hormone for MC4R-expressing neurons.\textsuperscript{14,15} The unique mechanism of action of setmelanotide activates MC4R and can overcome many of the effects of genetic deficiencies that occur upstream in the pathway in some individuals with rare genetic disorders of obesity. In previous phase 2 studies, setmelanotide treatment led to reductions in body weight and hunger in individuals with POMC and LEPR deficiency obesities.\textsuperscript{14,15} Setmelanotide was well tolerated, and participants did not experience clinically substantial increases in blood pressure or heart rate, which had been observed with first-generation MC4R agonists.\textsuperscript{16} However, it remains unclear whether activation of MC4R by setmelanotide can reduce hunger and improve weight loss in individuals with syndromic forms of obesity that may be associated with impaired activity in the MC4R pathway, including BBS. We report an analysis of ~1 year of setmelanotide treatment for severe obesity and hunger, as well as metabolic and cardiac outcomes, in individuals with BBS.
MATERIALS AND METHODS

Study Design and Participants

These data were collected in an ongoing phase 2, open-label, single-arm, basket-design pilot study composed of several distinct cohorts of individuals aged ≥12 years diagnosed with one of several rare genetic disorders of obesity, including BBS, POMC deficiency, LEPR deficiency, Alström syndrome, Smith-Magenis syndrome, SRC1 deficiency, and SH2B1 deficiency (ClinicalTrials.gov identifier: NCT03013543). This analysis reports data from participants with a genetic or clinical diagnosis of BBS (according to Beales’ criteria6). All participants (or guardians/legal representatives) signed written informed consent forms, and child participants provided assent before any study-specific procedures were performed. This study was conducted in accordance with the International Council on Harmonisation for Good Clinical Practice, Declaration of Helsinki, and appropriate regulatory requirements. To safeguard the rights, safety, and well-being of all participants, all study documentation was reviewed and approved by the institutional review boards of the Eunice Kennedy Shriver National Institute of Child Health and Human Development, National Institutes of Health (Bethesda, MD) and Marshfield Clinic Health System (Marshfield, WI).

Eligible participants for the current analysis were adults (age ≥18 years) with BMI ≥30 kg/m² and adolescents (age 12 to <18 years) with body weight >97th percentile (adjusted for age and sex) who had a diagnosis of BBS. Participants could not have achieved >2% weight loss from intensive diet or exercise regimens within 2 months of enrolment or >10% weight loss durably maintained after gastric bypass surgery. Other exclusion criteria included diagnosis of a mental disorder that could substantially interfere with study adherence; any suicidal ideation or history
of suicide attempt; clinically significant pulmonary, cardiac, or oncologic disease (including dermatologic findings related to melanoma); history of liver disease other than nonalcoholic fatty liver disease; impaired glomerular filtration rate (≤30 mL/min/1.73 m²); family history of skin cancer, melanoma, or oculocutaneous albinism; and inability to adhere to a once-daily injection.

**Procedures**

Adults and adolescents received subcutaneous injections of 1.0 and 0.5 mg/day, respectively, with dose titration of 0.5-mg increments every 2 weeks up to a maximum of 3.0 mg.

Individualized therapeutic doses were determined primarily on weight loss (~2 to 3 kg lost per week for adults; ~1 to 2 kg lost per week for adolescents) as well as hunger (target score of 0 to 2 for adults; score reduction that remained >0 for adolescents). The dose-titration phase varied in duration from 2 to 12 weeks depending on number of titrations needed to establish the therapeutic dose. The last 2 weeks of the dose-titration phase that established the therapeutic dose were considered the first 2 weeks of the treatment phase. Participants received an additional 10 weeks of treatment for a total of 12 weeks (3 months) of the treatment phase at the therapeutic dose (Supplementary Figure). A 52-week treatment extension phase followed the treatment phase to evaluate the efficacy and safety of setmelanotide at 6 and 12 months in participants who achieved weight reduction from baseline of ≥5 kg (or ≥5% if baseline body weight was <100 kg) without evidence of severe or clinically relevant adverse events (AEs) or changes in vital signs, safety laboratory measurements, or electrocardiographic findings. Because of the variable length of the titration phase, each participant’s 3-, 6-, and 12-month time point occurred at different weeks of overall follow-up.
Body weight and safety assessments, including blood pressure and heart rate, were recorded at each visit. Body composition (as assessed by Tanita Scale SC-240 [TANITA Corporation, Tokyo, Japan] at the Marshfield Clinic or iDXA [Lunar Corporation, Madison, WI] at the National Institutes of Health) was assessed and physical examinations, plus metabolic, endocrine, hematologic, and pharmacokinetic testing, were also conducted at regular intervals. Depression and suicidality were assessed using the Columbia Suicide Severity Rating Scale and Patient Health Questionnaire-9 and were monitored over the entire course of the trial.

Participants self-assessed their hunger levels daily by answering the following questions: “In the last 24 hours, how hungry did you feel when you were the most hungry?”; “This morning when you woke up for the day, how hungry did you feel?”; and “In the last 24 hours, on average, how hungry did you feel?” The assessments used a Likert-type scale, where 0 = no hunger at all and 10 = most hunger, to generate a hunger score.

Exploratory observer-related questionnaires included a food problem diary (FPD) and significant event questionnaire (SEQ), which were completed by caregivers of individuals with cognitive impairment and intended to capture common and rare food-related behaviours, respectively.17,18 The FPD is a 10-item observer-reported outcome measure derived from an instrument used for individuals with Prader-Willi syndrome designed to capture common food-related behaviours as recorded daily by caregivers.19 Total scores range from 0 to 30, with higher scores suggestive of more severe hyperphagia/food-related behaviours. The SEQ is a novel instrument composed of an eight-item observer-reported outcome measure designed to capture rare food-related behaviours (ie, behaviours expected to occur only with reduction in hyperphagia in response to
treatment) as recorded weekly by caregivers. Total scores range from 0 to 24, with higher scores suggestive of more significant appetite suppression.

Outcomes
The primary outcome was percent change in body weight after 3 months of treatment at the therapeutic dose in participants completing the treatment phase. Percent change in body weight was also assessed after 6 and 12 months of treatment at the therapeutic dose as additional exploratory efficacy outcomes. Other key secondary or exploratory outcomes included daily hunger scores; BMI; body fat mass; glucose-related parameters; waist circumference; safety and tolerability (as assessed by frequency and severity of AEs and serious AEs); changes in physical examinations, electrocardiography, vital signs (including resting blood pressure and heart rate), and clinical laboratory evaluations; and injection-site reactions (ISRs) over 12 months.

Statistical Analysis
Given the exploratory nature of the early efficacy signals in the phase 2 proof-of-concept study in individuals with rare genetic disorders of obesity, as well as the rarity of this disorder, the sample size for each genetic disorder is not primarily driven by statistical testing considerations but rather clinical considerations. For all outcomes, the statistical analysis considered baseline as the last value obtained before the first dose of active treatment. Some patients may have completed their clinic visit outside of the protocol-specified window. To include as many data points as possible in the present analysis, a ±1-month window was applied on the 3-month time
point, and a ±2-month window was applied on the 6- and 12-month time points. Outcomes of participants completing each study phase (per-protocol population) were summarized using descriptive statistics. Weight outcomes were also summarized for the intent-to-treat (ITT) population using a last observation carried forward analysis. Unless otherwise stated, $P$ values (via a 1-sample $t$ test at a 1-sided 0.05 significance level) and corresponding 90% two-sided confidence intervals (CIs) were given as appropriate; however, the $P$ values and associated CIs should be considered exploratory for clinical scrutiny and estimation purposes rather than for formal statistical hypothesis testing. No adjustments for multiplicity were conducted.

**Role of Funding Source**

The funder of the study had a role in the study design, data collection, data analysis, data interpretation, and writing the report. All authors had full access to the data and are responsible for the accuracy and completeness of this report. The corresponding author had final responsibility for the decision to submit the report for publication.
RESULTS

Ten participants with BBS were screened for eligibility between February 2017 and February 2018, and all were enrolled. Eight participants had genetic confirmation of BBS with variants in a single BBS gene prior to enrolment; two were screened and enrolled in the study with clinical diagnoses of BBS. Of these two participants, genetic tests confirmed one participant to be composite heterozygous for BBS1/BBS10. The other participant was clinically diagnosed with BBS per Beales’ criteria without genetic confirmation. In each of the latter cases, symptoms and progression of the disorder were consistent with BBS. Study investigators enrolled these participants because known disease-causing biallelic variants are identified in only 80% of individuals with BBS. Eight participants completed the 3-month treatment period and entered the 52-week extension phase; of those, seven completed the 52-week extension phase (Figure 1). Demographics and baseline characteristics of the ITT population are shown in Table 1. The average age of the participants was 22.5 years. Mean baseline weight and BMI were 128.1 kg and 44.8 kg/m², respectively. Baseline hunger scores had mean values of 8 for most hunger, 6 for average hunger, and 5 for morning hunger.

Participants completing the initial treatment phase achieved a significant mean percent change in body weight from baseline at 3 months (−5.5% [90% CI, −9.3% to −1.6%]; n=8; P=0.02). In the long-term extension phase, mean percent change in body weight was also significant at 6 months (−11.3% [90% CI, −15.5% to −7.0%]; n=8; P<0.001) and 12 months (−16.3% [90% CI, −19.9% to −12.8%]; n=7; P<0.0001; Figure 2, panels A and B). A last observation carried forward analysis also showed significant mean percent change in body weight from baseline in the ITT population at 3 months (−4.6% [90% CI, −8.3% to −1.0%]; n=10; P=0.02), 6 months...
Participants also experienced a significant mean percent change in BMI from baseline at 3 months (−5.5%; n=8; \( P=0.01 \)), 6 months (−11.1%; n=8; \( P<0.001 \)), and 12 months (−16.2%; n=7; \( P<0.0001 \); Table 2).

In addition, participants reported significant reductions in most hunger score at 3, 6, and 12 months (\( P<0.05 \); Figure 2, panels C and D; Table 2). Participants also reported significant reductions in morning and average hunger scores at 3, 6, and 12 months (\( P<0.05 \); Table 2).

Three participants were unable to complete the self-reported hunger questionnaire because of cognitive impairment characterized by neuropsychologists as extremely low level of intelligence (n=2) and autism with mild cognitive impairment (n=1). For these participants, hunger was evaluated by caregivers using the FPD and SEQ. Among these participants, FPD scores improved from 23 to 6 at 12 weeks, 6 to 0 at 70 weeks, and 18 to 12 at 19 weeks. Two participants experienced improvements in SEQ scores at the last evaluated time point from baseline, from 3 to 24 at 12 weeks, and from 3 to 24 at 58 weeks. The third participant experienced no change from baseline to week 4.

At 3 months, participants experienced significant percent change from baseline in body fat mass (−9.3%; n=9; \( P=0.01 \)) and total body mass (−5.3%; n=9; \( P=0.01 \)). Similarly, at 12 months, participants experienced significant percent change from baseline in body fat mass (−24.0%; n=7; \( P<0.01 \)) and total body mass (−15.8%; n=7; \( P<0.0001 \)). A nonsignificant change at 3 months from baseline was observed in waist circumference (−4.9%; n=8; \( P=0.06 \)). Participants achieved significant percent change from baseline in waist circumference at both 6 (−10.8%; n=8; \( P<0.01 \)) and 12 months (−17.0%; n=7; \( P<0.001 \)).
At baseline, individuals had normal to mild elevation in mean (standard deviation [SD]) levels of high-density lipoprotein cholesterol (HDL-C) and low-density lipoprotein cholesterol (LDL-C) (44.2 [10.3] and 106.6 [18.8] mg/dL, respectively). Slight improvements but no meaningful changes in lipid profiles were observed with setmelanotide. At 3, 6, and 12 months, mean percent changes in HDL-C from baseline were \(-5.8\%\) (n=9; 90% CI: \(-14.3\%\) to \(2.7\%\)), \(-1.1\%\) (n=8; 90% CI: \(-13.3\%\) to \(11.2\%\)), and \(13.0\%\) (n=6; 90% CI: \(-2.5\%\) to \(28.5\%\)), respectively. Mean percent changes in LDL-C from baseline at 3, 6, and 12 months were \(-10.1\%\) (n=9; 90% CI: \(-20.8\%\) to \(0.7\%\)), \(-9.0\%\) (n=8; 90% CI: \(-24.6\%\) to \(6.6\%\)), and \(-1.9\%\) (n=7; 90% CI: \(-17.6\%\) to \(13.8\%\)), respectively. Mean (SD) baseline triglyceride value was 166.6 (85.8) mg/dL; mean percent changes in triglyceride values from baseline were \(-15.0\%\) (n=9; 90% CI: \(-31.1\%\) to \(1.1\%\)), \(-30.5\%\) (n=8; 90% CI: \(-46.7\%\) to \(-14.3\%\)), and \(-28.8\%\) (n=7; 90% CI: \(-40.1\%\) to \(-17.5\%\)), respectively.

Baseline mean (SD) glucose concentrations were normal to mildly elevated (103.7 [32.5] mg/dL). Setmelanotide was not associated with meaningful changes in glucose parameters. Mean percent change in fasting glucose from baseline at 3, 6, and 12 months was \(-0.6\%\) (n=9; 90% CI: \(-9.7\%\) to \(8.5\%\)), \(-4.8\%\) (n=8; 90% CI: \(-14.8\%\) to \(5.2\%\)), and \(-0.4\%\) (n=7; 90% CI: \(-7.4\%\) to \(6.5\%)\), respectively. Baseline mean (SD) glycated haemoglobin value was 5.8 (1.5%); setmelanotide was not associated with significant percent change from baseline in glycated haemoglobin at any time point.

At baseline, mean (SD) diastolic and systolic blood pressure values were normal (75.7 [14.5] mm Hg and 109.5 [13.9] mm Hg, respectively). Mean percent change in diastolic blood pressure values from baseline at 3 and 12 months were \(-3.2\%\) (n=8; 90% CI: \(-12.5\%\) to \(6.0\%\)) and
−5.3% (n=7; 90% CI: −20.9% to 10.4%), respectively. Mean percent change in systolic blood pressure values from baseline at 3 and 12 months were 8.9% (n=8; 90% CI: −0.2% to 17.9%) and 8.9% (n=7; 90% CI: −1.0% to 18.8%), respectively. Baseline mean (SD) heart rate was 68.0 (12.3) beats per minute; mean percent changes in heart rate from baseline at 3 and 12 months were −1.4% (n=8; 90% CI: −14.7% to 12.0%) and 5.2% (n=7; 90% CI: −5.7% to 14.4%), respectively. None of the changes in blood pressure or heart rate were statistically significant. Setmelanotide was generally well tolerated. All participants reported at least one treatment-emergent AE and at least one drug-related AE (Table 3). The most common treatment-emergent AEs were ISRs (100%) and hyperpigmentation (80%). The one serious treatment-emergent AE was a case of rotavirus in one participant, which was not related to setmelanotide treatment. There were no treatment-emergent AEs leading to study withdrawal or death.
DISCUSSION

We report the first clinical study to investigate the efficacy of an MC4R agonist for treatment of BBS, a condition that reduces LEPR signalling and therefore leads to insufficient melanocortin action at hypothalamic centres involved in appetite.1,10,11 This open-label, phase 2 trial investigated the efficacy of setmelanotide for BBS-associated obesity and hyperphagia as well as laboratory parameters and safety. Setmelanotide was associated with substantial reduction in body weight after 3 months of treatment. Significant weight loss was observed at all time points both in the per-protocol population as well as the ITT population. Because of the proportion of study withdrawals, the per-protocol population analysis may have overestimated the efficacy of setmelanotide. Conversely, the ITT population analysis may have underestimated weight loss because weight outcomes were assessed using a last observation carried forward analysis. Together, these analyses provide support for setmelanotide efficacy for weight loss in individuals with BBS.

Setmelanotide had previously demonstrated long-term efficacy in weight loss in individuals with other rare genetic disorders of obesity due to variants in the MC4R pathway, including POMC and LEPR deficiency obesities.14,15 The efficacy of setmelanotide in the current study suggests that BBS-related obesity may also be mediated by the MC4R pathway. Although the mechanism of obesity in BBS is not fully understood, evidence from rodent models suggests that variants in BBS affect the MC4R signalling pathway.10,11,22,23 BBS proteins appear to be involved in primary cilia generation and maintenance, and rodent models lacking cilia on POMC neurons had significant increases in weight and hyperphagia.9,11 Mice with BBS variants have leptin resistance due to attenuated LEPR signalling, leading to improper cellular response by POMC.

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neurons.\textsuperscript{10} In addition, depletion of BBS protein leads to LEPR mistrafficking.\textsuperscript{10} Selective disruption of the BBS protein complex in POMC neurons leads to weight gain and increased fat mass in mice driven by hyperphagia.\textsuperscript{23} The clinical efficacy of MC4R agonism in individuals with BBS provides evidence that, despite the clinical complexity of BBS, the observed hyperphagia and obesity are at least in part due to insufficient MC4R action.

The safety profile of setmelanotide was consistent with that observed in previous clinical studies in individuals with POMC or LEPR deficiency obesity.\textsuperscript{14,15} In participants with BBS, setmelanotide was well tolerated with no discontinuations due to AEs, and the most common treatment-emergent AE being ISRs. In the current study, setmelanotide was not associated with statistically significant changes in blood pressure or heart rate. In previous studies of setmelanotide, blood pressure and heart rate did not substantially change or were decreased.\textsuperscript{14,15} Because baseline blood pressure levels were normal, the effect of setmelanotide in individuals with high baseline blood pressure could not be evaluated. The impact of setmelanotide on blood pressure and heart rate should be evaluated in future trials and closely monitored in individuals receiving setmelanotide.

Currently, no approved targeted pharmacotherapies exist for the treatment of obesity and hyperphagia in individuals with BBS. Current treatments focus on management of symptoms associated with the disorder and may include bariatric surgery, antiobesity medications developed for the general population, and lifestyle or dietary management for treatment of obesity.\textsuperscript{14,24} However, effective and durable treatments, specifically those addressing hyperphagia in individuals with rare genetic disorders of obesity, are lacking.\textsuperscript{24,25} The efficacy of setmelanotide in reducing body weight and hunger scores suggests it is a useful treatment
option for obesity and hyperphagia in individuals with BBS. Uncontrolled obesity can lead to comorbidities, including cardiovascular issues, metabolic syndrome, diabetes, and reduced quality of life.26-28 Because obesity management can control these comorbidities, weight reduction through hyperphagia management with setmelanotide could potentially effectively manage or alleviate obesity-related comorbidities in individuals with BBS.29,30

Our study has some limitations. The study design is open-label, uncontrolled, and noncomparative. In addition, the participants did not undergo follow-up after a study medication withdrawal period. Therefore, it is possible that a placebo effect of setmelanotide could have affected outcomes. The open-label, nonrandomized design of the current study is supported by the substantial clinical response of setmelanotide demonstrated in previous open-label studies.14,15 However, randomized trials to evaluate setmelanotide compared with placebo are needed. Finally, the minimum age for enrolled participants was 12 years, which may have limited the generalizability of these findings for younger individuals. An ongoing phase 3 study of setmelanotide in individuals with BBS includes a double-blind randomized treatment period and will enrol participants aged ≥6 years, thereby addressing several of these limitations (NCT03746522).

Setmelanotide reduced body weight and hunger in participants with BBS during 1 year of treatment. Setmelanotide was well tolerated, and no new safety signals emerged over the course of treatment. The results of this study suggest that setmelanotide may be a useful pharmacotherapy for treatment of obesity and hyperphagia in individuals with BBS. The efficacy and safety of setmelanotide in individuals with BBS is being further evaluated in an ongoing phase 3 study (ClinicalTrials.gov identifier: NCT03746522).
ACKNOWLEDGMENTS

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Data sharing

Anonymized individual participant data and study documents can be requested for further research.
REFERENCES

syndrome. Poster presented at 57th Annual Meeting of the European Society of Paediatric Endocrinology; September 27–29, 2018; Athens, Greece.


### Table 1. Baseline Participant and Disease Characteristics (ITT)†

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<th>Participants</th>
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<tr>
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<tr>
<td>Waist circumference, cm</td>
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<td>Glucose concentration, mg/dL</td>
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<td>HbA₁c, %</td>
<td>5.8 (1.5)</td>
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Data are mean (SD) or n (%). BMI, body mass index; HbA₁c, glycated haemoglobin; ITT, intent to treat; SD, standard deviation. †N=10 unless otherwise noted. ‡n=6. §Most hunger score was determined on a 0 to 10 Likert scale based on the question, “In the last 24 hours, how hungry did you feel when you were the most hungry?” ¶n=9.
Table 2. Changes in BMI and Hunger Scores From Baseline Through 12 Months of Treatment (Per-Protocol Population)

<table>
<thead>
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<th></th>
<th>BMI, kg/m²</th>
<th>Most hunger score†</th>
<th>Average hunger score†</th>
<th>Morning hunger score†</th>
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<td>Mean (SD)</td>
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<td>Baseline</td>
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<td>P=0.01</td>
<td>n=8</td>
<td></td>
<td></td>
<td>P=0.01</td>
</tr>
<tr>
<td>6 months</td>
<td>38.9 (5.2)</td>
<td>−11.1 (6.3)</td>
<td>3.2 (1.5)</td>
<td>−64.0 (12.7) §</td>
</tr>
<tr>
<td>n=8</td>
<td></td>
<td></td>
<td></td>
<td>P&lt;0.001</td>
</tr>
<tr>
<td>12 months</td>
<td>36.0 (4.0)</td>
<td>−16.2 (5.3)</td>
<td>3.0 (2.1)</td>
<td>−70.2 (17.2) §</td>
</tr>
<tr>
<td>n=7</td>
<td></td>
<td></td>
<td></td>
<td>P&lt;0.001</td>
</tr>
</tbody>
</table>

BMI, body mass index; SD, standard deviation. †n=6 unless otherwise noted; 3 participants with cognitive impairment were given different assessments, and further fluctuation of n was caused by missing values at given time points. ‡n=7. §n=5.
<table>
<thead>
<tr>
<th>Table 3. Treatment-Emergent AEs (ITT)</th>
<th>n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment-emergent AE</td>
<td>10 (100)</td>
</tr>
<tr>
<td>Drug related</td>
<td>10 (100)</td>
</tr>
<tr>
<td>Leading to permanent discontinuation</td>
<td>0</td>
</tr>
<tr>
<td>Serious treatment-emergent AE</td>
<td>1 (10)</td>
</tr>
<tr>
<td>Drug related</td>
<td>0</td>
</tr>
<tr>
<td>Treatment-emergent AE of special interest</td>
<td></td>
</tr>
<tr>
<td>Injection-site reaction</td>
<td>10 (100)</td>
</tr>
<tr>
<td>Hyperpigmentation</td>
<td>8 (80)</td>
</tr>
<tr>
<td>Nausea</td>
<td>3 (30)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>2 (20)</td>
</tr>
<tr>
<td>Deaths</td>
<td>0</td>
</tr>
</tbody>
</table>

AE, adverse event; ITT, intent to treat.
FIGURE LEGENDS

**Figure 1.** Participant enrolment and disposition. ITT, intent to treat.

**Figure 2.** Mean weight and hunger changes with setmelanotide treatment in the per-protocol population. (A) Mean change from baseline in body weight at each visit over 1 year of setmelanotide treatment. (B) Percent change from baseline in mean body weight over 1 year of setmelanotide treatment. (C) Mean change from baseline in most hunger score at each visit over 1 year of setmelanotide treatment. (D) Percent change in mean most hunger score over 1 year of setmelanotide treatment. Panels A and B: N=8; panels C and D: N=5. Error bars are the 90% confidence interval. †Clinically meaningful change defined as weight loss of ≥5 kg (or ≥5% in patients with baseline body weight <100 kg). ‡n=6.
ITT population
10 participants enrolled and entered
dose-titration phase

ITT population
10 participants entered first open-label
treatment phase at therapeutic dose

2 participants discontinued
- 1 withdrawn by parent/guardian
- 1 for failure to meet inclusion
criteria for extension phase
  (loss of 5 kg)

3-month per-protocol population
8 participants entered
52-week extension phase

1 participant withdrawn by
parent/guardian

12-month per-protocol population
7 participants completed
52-week extension phase
Adult starting dose: 1.0 mg QD
Adolescent starting dose: 0.5 mg QD

Variable duration = 2-12 weeks†

Establish therapeutic dose†

Open-label dose titration†

Open-label treatment at therapeutic dose

Week 0
Week 2
Week 12

Last dose
End of study

Early termination or follow-up for participants with reduction of at least 5 kg, or 5% of body weight if weight <100 kg, without evidence of severe adverse events

End of extension phase