Clinical Safety Summary of Setmelanotide in Healthy Volunteers With Obesity and Patients With Rare Genetic Diseases of Obesity

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Summary

- **Setmelanotide demonstrated an acceptable and consistent safety profile across 561 patients treated in multiple clinical trials**
- **The safety profile was generally consistent between the overall clinical trial population and the subgroup of patients with rare genetic diseases of obesity and was similar to that observed in patients with proopiomelanocortin (POMC), proprotein convertase subtilisin/kexin type 1 (PCSK1), or leptin receptor (LEPR) deficiency, for which setmelanotide is approved in the United States, Great Britain, and European Union**

Introduction

- Rare genetic diseases of obesity are often driven by gene variants in the melanocortin-4 receptor (MC4R) pathway[1]
- Treatment with the MC4R agonist setmelanotide demonstrated significant reductions in body weight and hunger after 1 year in Phase 3 trials of patients with obesity due to POMC, PCSK1, or LEPR deficiency[2]
  - These results led to US Food and Drug Administration, European Medicines Association, and Medicines and Healthcare products Regulatory Agency approval of setmelanotide for the treatment of obesity in patients with POMC, PCSK1, or LEPR deficiency[3,4]
  - Additionally, treatment with setmelanotide was associated with weight loss after 4 weeks in a Phase 1 trial of otherwise healthy volunteers with obesity[5]
- The efficacy and safety of setmelanotide are being investigated across multiple other rare genetic diseases of obesity, including Bardet-Biedl syndrome, and in patients with *NCOA1* and *SH2B1* variants[6-8]

Objective

- To evaluate the safety profile of setmelanotide from Phase 1, 2, and 3 clinical trials in the overall clinical trial population and the subgroup with rare genetic diseases of obesity

Methods

- Safety data were collected in 16 Phase 1, 2, or 3 clinical trials of setmelanotide in patients with various rare genetic diseases of obesity and otherwise healthy volunteers with obesity
  - The rare genetic diseases of obesity subgroup included patients with Bardet-Biedl syndrome; Alström syndrome; Prader-Willi syndrome; Smith-Magenis syndrome; and *POMC*, *PCSK1*, *LEPR*, *MC4R*, *NCOA1*, and *SH2B1* variants
- Treatment-emergent adverse events (TEAEs) were evaluated in the overall clinical trial population treated with study drug (either setmelanotide or placebo) and the subgroup with rare genetic diseases of obesity
  - Safety was evaluated in all patients who received ≥1 dose of setmelanotide or placebo
  - TEAEs of special interest were defined as TEAEs commonly occurring during treatment with setmelanotide (ie, hyperpigmentation disorders, injection site reactions, nausea, vomiting, disturbances in sexual arousal), mechanistic-related events (ie, hypertension), or comorbidities (ie, depression, suicidal ideation)
  - Incidences of skin hyperpigmentation included only events that were reported as a TEAE
- Incidence of TEAEs by age, sex, race, and ethnicity was also assessed

Results

Patient Population

- As of March 8, 2021, 561 patients (228 otherwise healthy volunteers with general obesity, 308 patients with rare genetic diseases of obesity, and 25 patients exposed to setmelanotide but not in any subpopulation) had received ≥1 dose of setmelanotide and 112 patients received placebo (Table 1)
  - Median time on treatment was 66 days (range, 1-2249 days) in setmelanotide-treated patients and 84 days (range, 2-105 days) in placebo-treated patients
  - 132 patients (24%) received ≥6 months of setmelanotide
  - 94 patients (17%) received ≥1 year of setmelanotide
  - All placebo-treated patients received placebo for <6 months

Table 1. Demographics and Baseline Characteristics for Patients Receiving Setmelanotide or Placebo Across the Clinical Trials

	Setmelanotide		Placebo
	Overall population (n=561)	Subgroup with rare genetic diseases of obesity (n=308)	Overall population (n=112)
Age, n (%)			
<12 years	26 (4.6)	26 (8.4)	0
12 to <18 years	86 (15.3)	86 (27.9)	1 (0.9)
18 to <65 years	430 (76.6)	190 (61.7)	110 (98.2)
≥65 years	19 (3.4)	6 (1.9)	1 (0.9)
Sex, n (%)			
Male	226 (40.3)	108 (35.1)	37 (33.0)
Female	335 (59.7)	200 (64.9)	75 (67.0)
Race, n (%)			
American Indian or Alaska Native	3 (0.5)	1 (0.3)	0
Asian	8 (1.4)	8 (2.6)	0
Black or African American	152 (27.1)	42 (13.6)	42 (37.5)
Native Hawaiian or other Pacific Islander	1 (0.2)	0	1 (0.9)
White	361 (64.3)	228 (74.0)	67 (59.8)
Other	35 (6.2)	28 (9.1)	2 (1.8)
Missing	1 (0.2)	1 (0.3)	0
Ethnic group, n (%)			
Hispanic or Latino	80 (14.3)	26 (8.4)	29 (25.9)
Not Hispanic or Latino	459 (81.8)	260 (84.4)	82 (73.2)
Not reported	7 (1.2)	7 (2.3)	0
Unknown	15 (2.7)	15 (4.9)	1 (0.9)
Baseline characteristics, mean (standard deviation)			
Weight, kg	112.5 (29.91)	119.7 (35.25)	103.5 (13.75)
Body mass index, kg/m^2	40.7 (10.40)	44.6 (11.59)	36.9 (4.78)

Common TEAEs

- TEAEs occurred in 515 patients overall (92%), 298 patients with rare genetic diseases of obesity (97%) who received setmelanotide, and 70 placebo-treated patients (62%) (Table 2)
  - Common TEAEs were generally consistent between the overall setmelanotide-treated population and the subgroup with rare genetic diseases of obesity; skin hyperpigmentation, injection site erythema, and injection site pruritis occurred at higher rates (>10% difference) in the latter
    - One and 2 patients experienced serious depression and suicidal ideation, respectively; the events were considered unrelated to setmelanotide in all patients
    - Skin hyperpigmentation is likely due to activation of the melanocortin-1 receptor by setmelanotide[9]
    - Median duration of nausea and vomiting in patients with a rare genetic disease of obesity was 4 days and 1 day, respectively
  - Most TEAEs were mild or moderate

Table 2. TEAEs in Patients Receiving Setmelanotide in the Overall Population and Patients With Rare Genetic Diseases of Obesity Compared With Those Receiving Placebo

	Setmelanotide		Placebo[a]
	Overall population (n=561)	Subgroup with rare genetic diseases of obesity (n=308)	Overall population (n=112)
TEAEs, n (%)	515 (91.8)	298 (96.8)	70 (62.5)
Treatment-related TEAEs, n (%)	474 (84.5)	283 (91.9)	38 (33.9)
Treatment-related TEAEs occurring in ≥15% of patients in either group, n (%)			
Skin hyperpigmentation	274 (48.8)	188 (61.0)	4 (3.6)
Injection site erythema	152 (27.1)	125 (40.6)	11 (9.8)
Injection site pruritus	117 (20.9)	98 (31.8)	1 (0.9)
Injection site induration	70 (12.5)	66 (21.4)	4 (3.6)
Nausea	171 (30.5)	87 (28.2)	2 (1.8)
Headache	112 (20.0)	57 (18.5)	6 (5.4)
TEAEs of special interest, n (%)	466 (83.1)	286 (92.9)	28 (25.0)
Hyperpigmentation disorders[b]	322 (57.4)	210 (68.2)	6 (5.4)
Injection site reactions[b]	260 (46.3)	204 (66.2)	12 (10.7)
Nausea	198 (35.3)	105 (34.1)	9 (8.0)
Vomiting	86 (15.3)	49 (15.9)	5 (4.5)
Disturbances in sexual arousal[b]	86 (15.3)	40 (13.0)	2 (1.8)
Depression[b]	22 (3.9)	18 (5.8)	0
Hypertension[b]	12 (2.1)	9 (2.9)	1 (0.9)
Suicidal ideation	5 (0.9)	5 (1.6)	0
Serious TEAEs, n (%)	30 (5.3)	NR	4 (3.6)
Treatment-related serious TEAEs, n (%)	2 (0.4)	NR	2 (1.8)
TEAEs leading to discontinuation, n (%)	60 (10.7)	NR	6 (5.4)
TEAEs leading to death, n (%)	2 (0.4)	2 (0.6)	0

NR, not reported; TEAE, treatment-emergent AE. [a]For patients who were randomized to placebo and subsequently received setmelanotide, TEAEs that occurred during placebo treatment were captured as having occurred on placebo and TEAEs that occurred during setmelanotide treatment were captured as having occurred on setmelanotide. [b]Grouped term.

Serious TEAEs and Discontinuations

- Serious TEAEs occurred in 30 of 561 setmelanotide-treated patients (5%) and 4 of 112 placebo-treated patients (4%); serious TEAEs occurring in >1 patient included suicidal ideation, pancreatitis, hypoglycemia, gastric banding reversal, and acute myocardial infarction (2 setmelanotide-treated patients each; <1%)
  - Most serious TEAEs were considered unrelated to the study drug; treatment-related serious AEs were reported in 2 setmelanotide-treated patients (chest pain in 1 patient and stage 1 endometrial cancer in 1 patient) and 2 placebo-treated patients (biliary dyskinesia in 1 patient and anaphylactic reaction in 1 patient)
- Across the clinical trials, 2 deaths occurred (acute myocardial infarction and automobile accident); neither were considered to be related to the study drug
- Overall, 60 of 561 setmelanotide-treated patients (11%) and 6 of 112 placebo-treated patients (5%) discontinued study drug because of TEAEs
  - The most common, albeit infrequently occurring, TEAEs leading to setmelanotide discontinuation were nausea (3%), skin hyperpigmentation (3%), vomiting (2%), headache (1%), and abdominal pain (1%)
- No cases of melanoma have been reported in connection with the administration of setmelanotide in any clinical trial

Safety Profile Across Age, Sex, Race, and Ethnicity

- The safety profile of setmelanotide was generally consistent across age, but rates of injection site reactions–related events were higher in patients <12 years old (Table 3)

Table 3. Most Common TEAEs (Occurring in ≥15% of Patients in Any Group) in the Overall Clinical Trial Population, by Age Group

	<12 years old (n=26)	12 to <18 years old (n=86)	18 to <65 years old (n=430)	≥65 years old (n=19)
Patients with ≥1 TEAE, n (%)	25 (96.2)	86 (100.0)	386 (89.8)	18 (94.7)
Skin hyperpigmentation	17 (65.4)	62 (72.1)	194 (45.1)	4 (21.1)
Injection site erythema	13 (50.0)	36 (41.9)	105 (24.4)	7 (36.8)
Injection site pruritus	11 (42.3)	26 (30.2)	80 (18.6)	3 (15.8)
Injection site bruising	9 (34.6)	12 (14.0)	41 (9.5)	2 (10.5)
Injection site pain	8 (30.8)	18 (20.9)	42 (9.8)	3 (15.8)
Nausea	7 (26.9)	28 (32.6)	152 (35.3)	11 (57.9)
Headache	7 (26.9)	31 (36.0)	112 (26.0)	4 (21.1)
Vomiting	7 (26.9)	15 (17.4)	55 (12.8)	9 (47.4)
Injection site induration	6 (23.1)	23 (26.7)	43 (10.0)	1 (5.3)
Injection site hemorrhage	6 (23.1)	1 (1.2)	3 (0.7)	1 (5.3)
Diarrhea	5 (19.2)	17 (19.8)	44 (10.2)	1 (5.3)
Injection site edema	5 (19.2)	17 (19.8)	31 (7.2)	0
Rhinorrhea	5 (19.2)	2 (2.3)	6 (1.4)	0
Spontaneous penile erection	4 (15.4)	2 (2.3)	36 (8.4)	2 (10.5)
Abdominal pain	3 (11.5)	20 (23.3)	41 (9.5)	0
Melanocytic naevus	2 (7.7)	18 (20.9)	31 (7.2)	0
Insomnia	1 (3.8)	6 (7.0)	15 (3.5)	3 (15.8)

TEAE, treatment-emergent adverse event.

- TEAEs were generally consistent by sex, with overall higher rates (>10% difference) in female versus male setmelanotide-treated patients for skin hyperpigmentation (57% vs 39%), nausea (42% vs 26%), and injection site pruritus (27% vs 14%)
- TEAEs were generally consistent across race, but there was a lower overall incidence of TEAEs in patients of Black race compared with patients of White race and those of other race categories
- TEAEs were generally consistent in populations of Hispanic or Latino ethnicity versus populations of non-Hispanic or Latino ethnicity, with injection site pruritis more common (>10% difference) in the latter (10% vs 22%) and skin discoloration more common in the former (18% vs 5%)

Conclusions

- Setmelanotide demonstrated an acceptable safety profile across 561 patients treated across the clinical trials
- The safety profile was generally consistent between the overall setmelanotide-treated population and the subgroup of patients with rare genetic diseases of obesity
- The safety profile across 561 patients was similar to that observed in patients with POMC, PCSK1, or LEPR deficiency, for which setmelanotide is approved in the United States, Great Britain, and European Union

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