# Clinical Benefit of Setmelanotide in Patients With Alström Syndrome



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## Summary

- **In Phase 2 and 3 clinical trials, setmelanotide therapy was associated with meaningful improvements in age-appropriate weight-related measures, hunger, and quality of life (QOL) in most patients with ≥6 months of treatment**
- **Further research into the full extent of clinical benefit and specific characteristics of responders is needed**

## Introduction

- Alström syndrome is a rare autosomal recessive disorder characterized by multisystem dysfunction, including early-onset obesity[1-3]
- Hyperphagia and impairment in the melanocortin-4 receptor (MC4R) pathway due to cilia dysfunction are hypothesized to contribute to obesity in Alström syndrome[1,4]
- Setmelanotide, a targeted MC4R agonist, has demonstrated weight loss and hunger benefits in multiple rare MC4R pathway–associated diseases, including syndromic obesity (ie, Bardet-Biedl syndrome)[5,6]

## Objective

- To evaluate the efficacy and safety of setmelanotide in patients with Alström syndrome enrolled in Phase 2 and 3 trials

## Methods

### Phase 2 and 3 trial design

- Patients with Alström syndrome aged ≥6 years were enrolled in Phase 2 and 3 trials of setmelanotide (NCT03013543, NCT03746522)
  - In the Phase 2 study, patients received open-label setmelanotide for 3 months; patients tolerating treatment with ≥5.0-kg body weight reduction could continue to receive open-label setmelanotide in an extension phase
    - The primary endpoint was the proportion of patients achieving ≥5% weight loss at Month 3
  - In the Phase 3 study, patients were randomized 1:1 to receive setmelanotide or placebo for 14 weeks, followed by an open-label period where all patients received setmelanotide, for total setmelanotide treatment of ≥52 weeks
    - The primary endpoint was the proportion of patients achieving ≥10% weight loss at Week 52

### Efficacy and safety assessments

- Changes in weight, hunger, and QOL were evaluated across the aggregate population in the Phase 2 and 3 trials of patients who received ≥6 months of setmelanotide
  - The 6-month treatment requirement was selected to ensure adequate treatment time to evaluate response
- Meaningful changes were based on
  - ≥5% body weight[7] and/or body mass index (BMI) reduction in adults
  - ≥0.25-point reduction in BMI Z score[8,9] and/or decrease of ≥5 percentage points in the percentage of the 95th percentile[10] for BMI in pediatric patients
    - BMI Z scores were calculated on the basis of World Health Organization 2007 standards[11]
  - ≥25% decrease in hunger score
  - Increase in Impact of Weight on Quality of Life-Lite score of >7.7 in adult patients[12]
  - Increase in Pediatric Quality of Life Inventory score of >4.4 in pediatric patients[13]
- Safety was assessed based on adverse event (AE) frequency

## Results

### Patient population characteristics

- Across the 2 trials, 12 patients with Alström syndrome were enrolled (Table 1)

**Table 1.** Baseline Demographics of Patients With Alström Syndrome

| | Patients (N=12) |
|---|---|
| Age, mean (SD) [range], y | 16.6 (8) [10-39] |
| <18 years, n (%) | 8 (66.7) |
| ≥18 years, n (%) | 4 (33.3) |
| Sex, n (%) | |
| Female | 10 (83.3) |
| Male | 2 (16.7) |
| Race, n (%) | |
| White | 6 (50.0) |
| Black or African American | 3 (25.0) |
| Asian | 2 (16.7) |
| Other | 1 (8.3) |
| Ethnicity | |
| Hispanic or Latino | 0 |
| Not Hispanic or Latino | 11 (91.7) |
| Not reported | 1 (8.3) |
| Weight,[a] mean (SD) [range], kg | 96.6 (36.5) [59.3-191.8] |
| BMI,[a] mean (SD) [range], kg/m$^2$ | 40 (15.2) [27.8-83.0] |
| BMI Z score,[b] mean (SD) | 3.0 (0.4) |

[a]At active treatment baseline. One patient excluded from baseline characteristics because of unreported measurement at time of active treatment baseline. [b]In patients <18 years old. BMI, body mass index; SD, standard deviation.

### Efficacy outcomes

- Of 12 patients enrolled, 8 received ≥6 months of setmelanotide treatment and were included in this analysis
  - Reasons for patients having <6 months of treatment were withdrawal by patient (n=2) and withdrawal because of AEs (n=2)
- After 1 year of treatment, no adult patients with Alström syndrome achieved ≥10% reduction in body weight
- Among the 2 adult patients, percent change in weight from baseline ranged from +2.2% to +5.7%
- Most pediatric patients receiving ≥6 months of setmelanotide (n=6) demonstrated a ≥0.25-point reduction in BMI Z score (5 of 6 patients [83.3%]) (Figure)
  - A ≥0.3-point reduction was achieved by 3 of 6 patients (50.0%)

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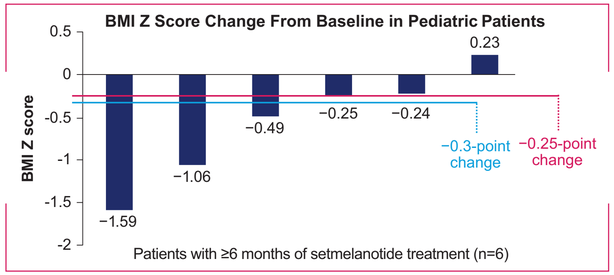
**Figure.** Change in BMI Z score from baseline in pediatric patients with ≥6 months of setmelanotide treatment.




Bars represent individual patients. BMI, body mass index.

- Of patients ≥12 years old self-reporting hunger (n=6), 66.7% demonstrated a ≥25% reduction in most/worst hunger score after 1 year of setmelanotide
- Of the patients receiving ≥6 months of setmelanotide (n=8), 7 (87.5%) achieved clinically meaningful improvement (ie, outcome stabilization) in ≥1 measure (Table 2)
  - Five of 6 pediatric patients demonstrated meaningful reductions in BMI Z score and/or percentage of the 95th percentile for BMI
  - One pediatric patient and 1 adult patient who did not demonstrate meaningful weight-related reductions demonstrated a substantial reduction in hunger score

### Safety

- Setmelanotide tolerability was consistent with previous clinical data, and AEs were generally mild and transient (Table 3)
  - Skin hyperpigmentation was the most frequent AE reported with setmelanotide; this AE infrequently led to withdrawals, and skin darkening plateaued within the initial months of treatment

**Table 3.** Safety of Setmelanotide in Patients With Alström Syndrome

| | Patients, n (%) (N=12) |
|---|---|
| Treatment-related AEs[a] | 10 (83.3) |
| Serious AEs | 2 (16.7) |
| Serious treatment-related AEs | 0 |
| AEs leading to study drug discontinuation[b] | 3 (25) |
| AEs leading to death | 0 |
| Treatment-emergent AEs occurring in ≥20% of the population | 2 (16.7) |
| Skin hyperpigmentation | 10 (83.3) |
| Cough | 4 (33.3) |
| Injection site pruritus | 4 (33.3) |
| Nausea | 4 (33.3) |
| Abdominal pain | 3 (25.0) |
| Back pain | 3 (25.0) |
| Dysmenorrhea | 3 (25.0) |
| Ear infection | 3 (25.0) |
| Glucose intolerance impaired | 3 (25.0) |
| Injection site erythema | 3 (25.0) |
| Irregular menstruation | 3 (25.0) |
| Viral upper respiratory tract infection | 3 (25.0) |

[a]AE noted as related or possibly related to the study drug. [b]Nausea, vomiting, eye redness (all mild and not treatment related); acne, hidradenitis (both moderate AEs and not treatment related); facial edema (moderate, treatment related). AE, adverse event.

## Conclusions

- In Phase 2 and 3 trials, 87.5% of patients with Alström syndrome had some form of clinical improvement across various weight-, hunger-, and QOL-related measures following ≥6 months of setmelanotide treatment
- The safety profile of setmelanotide was consistent with established clinical data
- Additional research into the impact of setmelanotide in Alström syndrome is needed to better understand the extent of clinical benefit and characteristics associated with response

**Table 2.** Clinical Benefit of Setmelanotide in Patients Receiving ≥6 Months of Setmelanotide

| Age at entry, years | Weeks on setmelanotide | Weight change,[a] % (baseline weight, kg) | BMI change,[a] % (baseline BMI, kg/m$^2$) | BMI Z score,[b] absolute change (baseline BMI Z score) | Percentage of the 95th percentile for BMI,[b] absolute change | Most/Worst hunger score change,[c] % | Quality of life improved? |
|---|---|---|---|---|---|---|---|
| 10 | 52 | -4.3 | | −0.49 (3.15) | −14.7 | | Yes |
| 10 | 54 | -7.4 | | −1.06 (3.57) | −29.6 | | NA |
| 12 | 64 | 15.1 | | 0.23 (3.89) | 1.1 | −58.8 | Yes |
| 19 | 42 | 2.2 (91.4) | 2.2 (36.1) | | | NA | NA |
| 39 | 51 | 5.7 (191.8) | NA | | | −28.6 | No change |
| 12 | 71 | -21.2 | | −1.59 (2.65) | −25.6 | −40.0 | NA |
| 15 | 72 | -1.7 | | −0.24 (2.49) | −6.5 | −85.7 | NA |
| 16 | 79 | -2.1 | | −0.25 (2.89) | −8.3 | 0 | NA |

Blue shading represents clinically meaningful improvement. Gray shading denotes parameters not appropriate based on patient age. [a]For patients ≥18 years old. [b]For patients <18 years old. [c]For patients ≥12 years old. BMI, body mass index; NA, data not available.

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