P1-54

# "bestPWS EU": A Phase 3 Study in Adolescent and Adult Patients With PWS in Europe

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## ABSTRACT

**Background:** Prader-Willi Syndrome (PWS) is a complex genetic disease; one hallmark of the disease is failure to regulate hunger and metabolism. Hyperphagia and severe obesity contribute significantly to the morbidity and mortality of this disease. Methionine aminopeptidase2 (MetAP2) inhibition reduces fat biosynthesis and stimulates fat oxidation and lipolysis. Beloranib is a selective and potent MetAP2 inhibitor. In a 4-week phase 2, placebo-controlled, proof-of-concept study in obese, adult PWS patients, beloranib resulted in dose-dependent decrease in body mass and reduction in total fat mass (DXA) despite 50% increase in total daily calorie intake. There was meaningful reduction in food related problem behaviors typical of PWS. Beloranib appeared safe and well tolerated in this patient population. Objective and hypotheses: To provide the study design of a phase 3 study being conducted in Europe in adolescent and adult PWS. Primary objectives include assessment of changes in hyperphagia-related behaviors and total body weight, and safety and tolerability of beloranib over 52 weeks.

**Method:**

*Study Design:*

- Randomized, double-blind, placebo controlled
- 150 obese subjects with PWS 12-50 years old
- Placebo vs. 2.4 mg beloranib (2:3 ratio)
- A 26-week open-label extension will be offered to patients at the end of the 52-week blinded study period with all patients receiving beloranib.

**Results:**

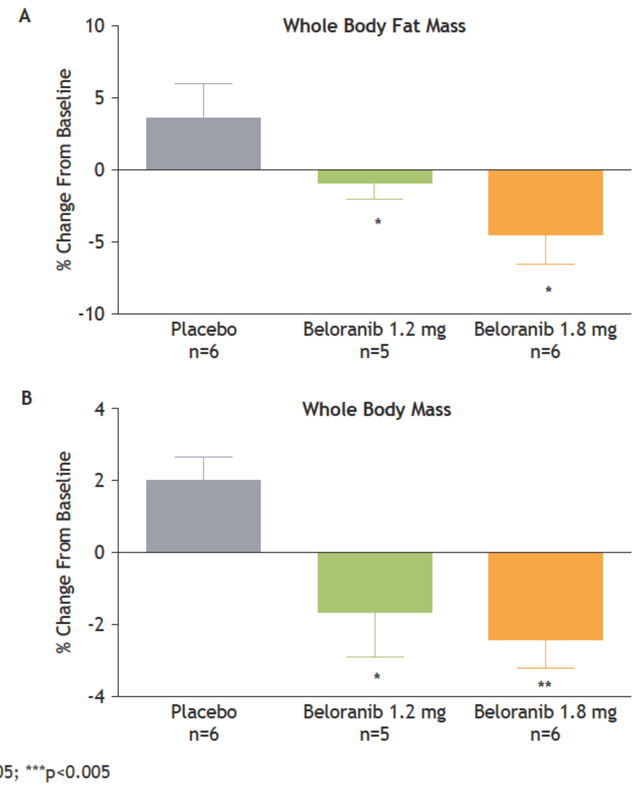
- Co-primary efficacy endpoints include:
  - Change in hyperphagia-related behavior based upon the Hyperphagia Questionnaire for Clinical Trials (HQ-CT) total score
  - Percent change from baseline in total body weight
- Key secondary endpoints will be reported including total body fat mass (DXA), LDL, and HDL cholesterol
- Safety and tolerability will be assessed

**Conclusion:** Beloranib shows promise for further development in the treatment of obesity and hyperphagia-related behaviors in PWS. A phase 3 study is underway in Europe in adolescent and adult PWS patients.

## INTRODUCTION

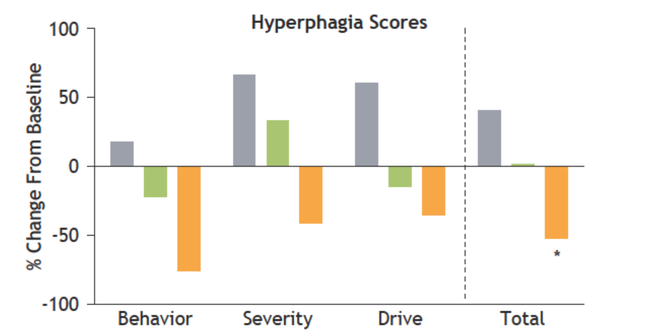
- Prader-Willi Syndrome (PWS) is a complex genetic disease that affects children and adults
- PWS is characterized by insatiable hunger and appetite
- In addition, severe obesity and associated problem behaviors occur
- Methionine aminopeptidase 2 (MetAP2) inhibition produces persistent weight loss in animal models of obesity, diabetes, and hypothalamic obesity with associated improvements in metabolic and inflammatory parameters[2]
- Beloranib is a selective and potent MetAP2 inhibitor that has been extensively studied in animal models and in patients with PWS, hypothalamic obesity and severe obesity
- In a Phase 2a study, exogenously obese subjects using twice weekly subcutaneous (SC) beloranib experienced ~11% body weight loss and ~60% reduction in sense of hunger over 12 weeks[3]
- In a 4-week phase 2, placebo-controlled, proof-of-concept study in obese, adult PWS patients, dose-dependent decreases in body mass and total fat mass (DXA) occurred[4] (**Figure 1a** and **1b**)
  - All subjects completed the study and received all planned doses of study medication
  - Beloranib was safe and well tolerated with injection site bruising as the most frequently reported adverse event (3 subjects [27%] with beloranib; 2 subjects [33%] with placebo)
- In addition, a meaningful reduction in food-related problem behaviors typical of PWS was observed (**Figure 2**)

### Figures 1a and 1b. Beloranib Reduced Whole Body Fat Mass and Whole Body Mass as Assessed by DXA




*p<0.05; ***p<0.005

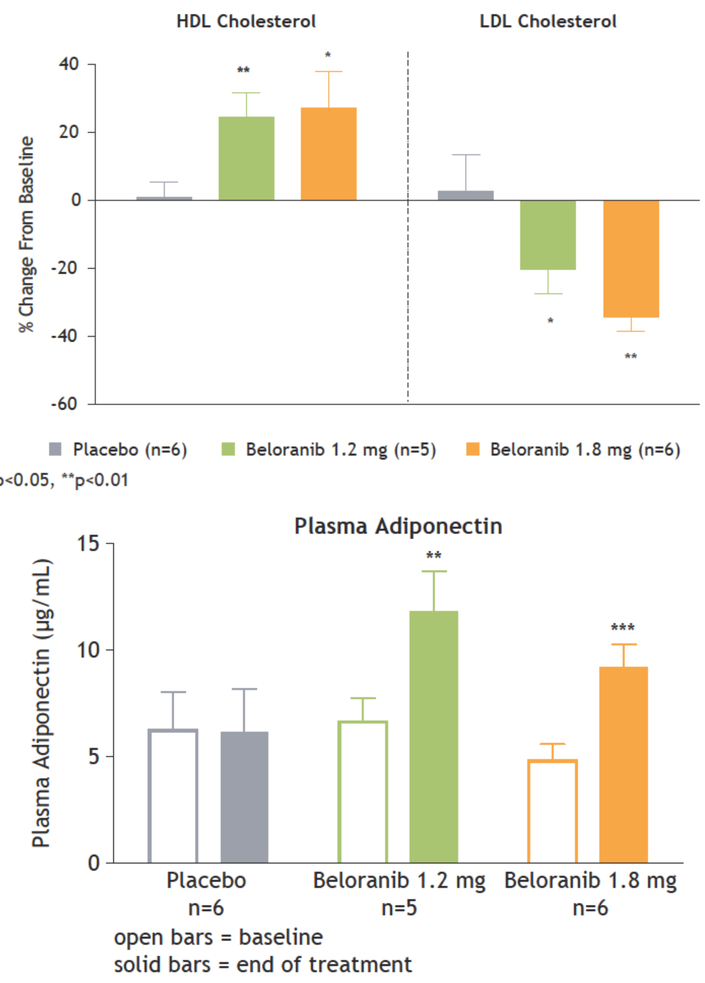
### Figure 2. Beloranib Improved Hyperphagia




p<0.05 for beloranib 2.4 mg vs. placebo on the total score

- Improvements in body mass and hyperphagia-related behaviors occurred even though food intake increased by 50%
- Subjects were on stringent caloric restriction prior to study entry (mean 917-1142 cal/day); 50% increase in calorie intake was allowed for all subjects for the entire trial duration
- Beloranib also results in improvements in HDL and LDL cholesterol and adiponectin (**Figure 3**)

### Figure 3. Beloranib Improved Plasma Lipids and Plasma Adiponectin




*p<0.05, **p<0.01, ***p<0.005 vs. baseline

**p<0.01, ***p<0.005 vs. baseline

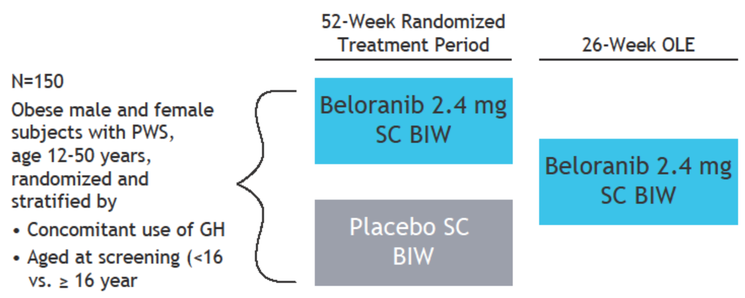
- The ongoing PWS phase 3 study (bestPWS), a 6-month, double-blind, randomized, placebo-controlled study, is fully recruited (n=108) and study conduct is ongoing in the U.S.
- This presentation describes the study design of the bestPWS EU phase 3 study, the second Phase 3 study with beloranib in this population

## STUDY DESIGN AND METHODS

### The bestPWS/EU study design includes the following:

- Randomized, double-blind, 52-week placebo-controlled
- 150 overweight or obese subjects 12-50 years of age with PWS
- A 26-week open-label extension will be offered to subjects at the end of the 52-week blinded study period with all patients receiving beloranib (**Figure 4**)

### Figure 4. Study Flow Chart




### Patient Selection

- Male and female patients aged 12-50 years with a confirmed diagnosis of PWS
- Hyperphagia Questionnaire for Clinical Trials (HQ-CT) score ≥11 on a scale of 0-36
- For age 12-17 years: BMI ≥90th percentile for age and gender
- For age 18-50 years: BMI ≥27 to ≤70 kg/m$^2$
- For those with type 2 diabetes: HbA1c <10%, fasting glucose <13.3 mmol/L (240 mg/dL), no history of ketoacidosis or hyperosmolar coma
- Patients must have at least one consistent and reliable primary caregiver

### Study Assessments

- Comprehensive study assessments to assess the effect of treatment on PWS will be performed during both study phases (**Table 1**)

### Table 1. Study Assessments

| Assessment | Double-blind Phase | Open-label Extension |
|---|---|---|
| Body Weight | X | X |
| DXA scan | X | X |
| Hyperphagia Questionnaire for Clinical Trials (HQ-CT) | X | X |
| Hyperphagia-related Behaviors Checklist | X | X |
| Caregiver Global Impression of Change | X | |
| Qualitative Interviews | X | X |
| Lipid profile, hs-CRP | X | X |
| HbA1c, insulin, C-peptide (subjects with type 2 diabetes) | X | X |
| Safety measurements (AEs, vital signs, ECG, physical exam, safety labs, patient-reported outcomes) | X | X |

- Food-related problem behaviors will be measured at baseline and at regular intervals in the double-blind and open-label extension phases using the HQ-CT, which is the PWS Hyperphagia Questionnaire (**Table 2**) modified for clinical trials[1]

### Table 2. Hyperphagia Questionnaire for Clinical Trials (HQ-CT)

Each item is scored on a scale of 0 to 4 for each question; total score range of 0 to 36

| Item | Question |
|---|---|
| 1 | During the past 2 weeks, how upset did the person generally become when denied a desired food? |
| 2 | During the past 2 weeks, how often did the person try to bargain or manipulate to get more food at meals? |
| 3 | During the past 2 weeks, how often did the person forage through trash for food? |
| 4 | During the past 2 weeks, how often did the person get up at night to food seek? |
| 5 | During the past 2 weeks, how persistent was the person in asking or looking for food after being told "no" or "no more"? |
| 6 | During the past 2 weeks, outside of normal meal times, how much time did the person generally spend asking or talking about food? |
| 7 | During the past 2 weeks, how often did the person try to sneak or steal food (that you are aware of)? |
| 8 | During the past 2 weeks, when others tried to stop the person from asking about food, how distressed did he or she generally appear? |
| 9 | During the past 2 weeks, how often did food-related behavior interfere with the person's normal daily activities, such as self-care, recreation, school, or work? |

NOTE: HQ-CT may not be used without permission from Zafgen, Inc.

- The Hyperphagia-related Behaviors Checklist will be completed by the same primary caregiver during the 7 days prior to each study visit. The primary caregiver will note the number of times the following occurred during the last 24 hours (**Table 3**)

### Table 3. Hyperphagia-related Behaviors Checklist

| | Description of Event | Answer |
|---|---|---|
| 1. | Sought food without permission (e.g., stealing food, asking non-caregivers for food) | |
| 2. | Attempted to eat inappropriate food (e.g., non-food items, uncooked foods, food that has passed its 'use by' date, pet food) | |
| 3. | Asked about or requested food during non-meal times (e.g., outside of scheduled meal or snack times) | |
| 4. | Did not consume all of the accessible food (food that was either provided/served or inappropriately obtained) | |
| 5. | Arrived late to a meal/snack (e.g., showed up for meal/snack time after it was served) | |
| 6. | Ran away to seek food | |
| 7. | Acted out as it related to food (e.g., temper tantrum, threatening, throwing objects) | |

### Study Endpoints

- Co-primary efficacy endpoints include:
  - Change in hyperphagia-related behavior based on the HQ-CT total score
  - Percent change from baseline to Week 52 in total body weight
- Key secondary endpoints include:
  - % HQ-CT responders
  - DXA assessments of:
    - Total body fat mass
    - Total lean body mass
    - Total body mass
  - Total, LDL, and HDL cholesterol and triglycerides
  - hs-CRP
- Safety and tolerability

## SUMMARY

- Beloranib is a selective and potent MetAP2 inhibitor
- A critical unmet need in PWS is for effective treatments that control hyperphagia
- Beloranib has demonstrated significant effects on hyperphagia, body composition, and body weight in phase 2 studies of patients with PWS, hypothalamic injury-associated obesity, and severe and complicated obesity
- Based on results from a phase 2a, proof-of-concept study, beloranib shows promise for the treatment of obesity and hyperphagia-related behaviors in patients with PWS
- The phase 3, bestPWS EU study will soon be recruiting participants in Europe in adolescent and adult PWS patients

## REFERENCES

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