Weight Loss and Improvement in Hyperphagia-Related Behavior: Results from bestPWS, a Phase 3, Randomized, Placebo-Controlled, Clinical Trial of Beloranib in Prader-Willi Syndrome

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Disclosures

- Butler, McCandless, Roof, Dykens, Fu, Stafford, Angulo, Myers, Bird, Salehi, Barlow, Abuzzahab, Yanovski, Viskochil, Chan, Styne all received research support to participate as Principal Investigators or Study Coordinators for ZAF-311
- Malloy, Zhuang and Kim are employees of Zafgen

Beloranib - Methionine Aminopeptidase 2 (MetAP2) Inhibitor

Pre-clinical and clinical studies indicate beloranib has the potential to reduce body weight, improve body composition and decrease hyperphagia

Liver

- Reduces fat and cholesterol synthesis
- Reduces LDL cholesterol and C-reactive protein

Adipose Tissue

- Increases fat mobilization and use of stored fat as energy source

Hyperphagia

- Reduces hunger, food intake and hyperphagia-related behaviors
- Patients lose weight and feel less hungry

Prader-Willi Syndrome (PWS)

- Rare and complex metabolic disorder due to errors in genomic imprinting
  - Most common genetic cause of morbid obesity
  - Prevalence estimates 1:10,000-1:30,000
  - Multiple endocrine, behavioral, and cognitive abnormalities
- Life-threatening and life-limiting
  - Hyperphagia: unrelenting pathologic hunger leading to dangerous food seeking behavior
  - Obesity: Low metabolic rate and high fat mass; multiple associated comorbidities
  - Annual mortality rate 1-4%, life expectancy is shortened with majority not living into their late 40's
- QoL for patients and families is severely diminished as chronic vigilance is required to prevent individuals from obtaining food
- There are no treatment options for the intractable obesity and hyperphagia

Butler MG, Hanchett JM, Thompson T. Clinical findings and natural history of Prader-Willi syndrome. In: Butler MG, Lee PDK, Whitman BY, eds. Management of Prader-Willi Syndrome. 3rd ed. New York, NY: Springer; 2006:3-48

Butler MG, Lee PDK, Whitman B, eds. Management of Prader-Willi Syndrome, Springer, 2006.
Butler MG, Prader-Willi syndrome: Current understanding of cause and diagnosis. *Am J Med Genet.* 1990;35:319-332.
Cassidy SB, Schwartz S, Miller JL, Driscoll DJ. Prader-Willi syndrome. *Genet Med.* 2011;14(1):10-26.
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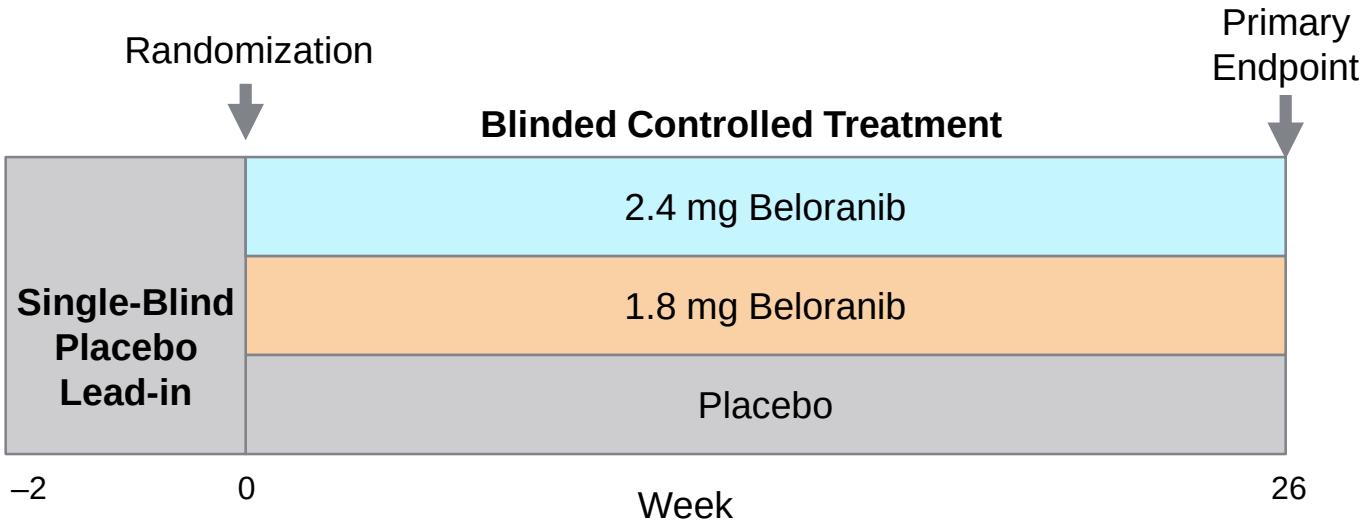
bestPWS Study Design

- Randomized, double-blind, parallel comparison of 2 doses of beloranib (sc injection twice weekly) vs. placebo for 26 weeks following a 2-week single-blind placebo lead-in
- Study included optional open-label, open-ended extension (OLE)
- Co-primary endpoints: change in % body weight and Hyperphagia Questionnaire for Clinical Trial (HQ-CT) total score



Placebo includes placebo low-volume and placebo high-volume. Subjects randomized to 2.4 mg beloranib and all subjects in the OLE received 1.8 mg beloranib for the first 4 weeks of treatment. All doses were administered twice-weekly by subcutaneous injection.

Subject Disposition
Intent to Treat (ITT) Population

n (%)	Placebo (N=34)	1.8 mg Beloranib (N=36)	2.4 mg Beloranib (N=37)
Completion of Randomized Treatment Prior to October 16, 2015	24 (70.6)	26 (72.2)	24 (64.9)
Randomized Treatment Discontinuation Prior to October 16, 2015			
Adverse Event	0 (0.0)	3 (8.3)	2 (5.4)
Death	0 (0.0)	1 (2.8)	0 (0.0)
Randomized Treatment Discontinuation On/After October 16, 2015 (all treatment halted)	10 (29.4)	6 (16.7)	11 (29.7)

Beloranib treatment within the randomized period was halted on October 16, 2015 due to the occurrence of venous thromboembolism events within the beloranib clinical development program.

Demographics and Baseline Characteristics ITT Population

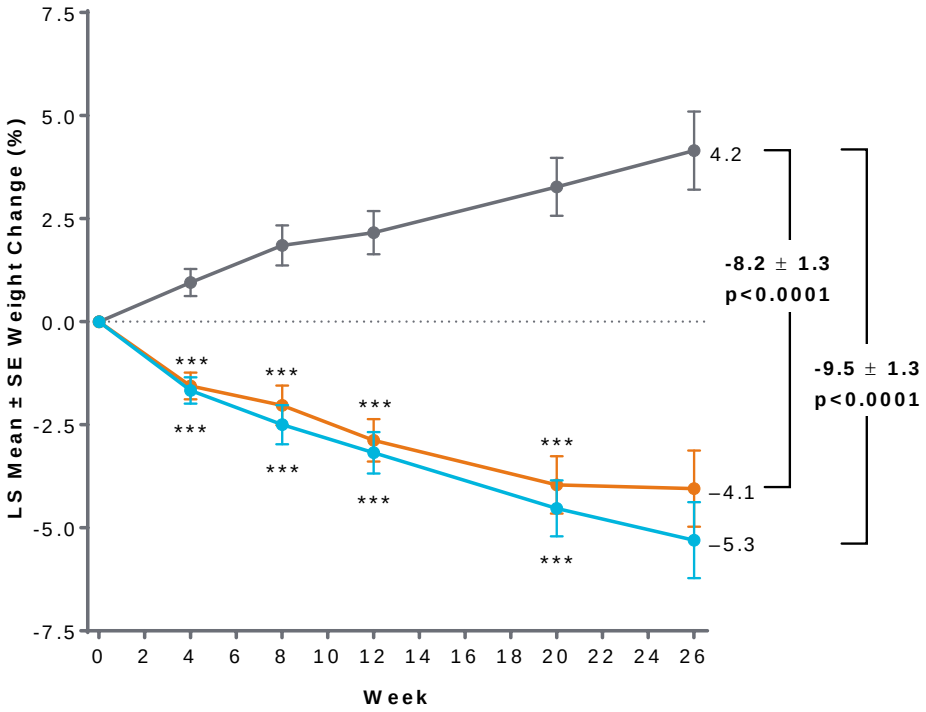
Mean ± SD N (%)	Placebo N=34	1.8 mg Beloranib N=36	2.4 mg Beloranib N=37
Age, years (inclusion 12-65 yo)	20.9 ± 7.8	19.2 ± 5.2	19.5 ± 5.8
Sex (% Male)	15 (44.1%)	19 (52.8%)	22 (59.5%)
Proportion <18 years	15 (44.1%)	15 (41.7%)	17 (45.9%)
Growth Hormone Use (% yes)	15 (44.1%)	15 (41.7%)	15 (40.5%)
Intelligence Quotient	71.6 ± 23.3	69.6 ± 23.1	67.1 ± 25.1
Race (% White/Black/Other)	91/6/3%	83/14/3%	95/3/3%
Weight, kg	100.9 ± 25.5	97.5 ± 24.1	105.7 ± 29.1
BMI, kg/m^2	40.3 ± 9.4	38.2 ± 8.9	41.4 ± 11.7
Body Fat Mass, kg	51.5 ± 15.5	47.6 ± 14.6	53.2 ± 19.4
HQ-CT Total Score	15.0 ± 5.8	17.4 ± 6.2	18.3 ± 7.3

PWS Medical Characteristics
ITT Population

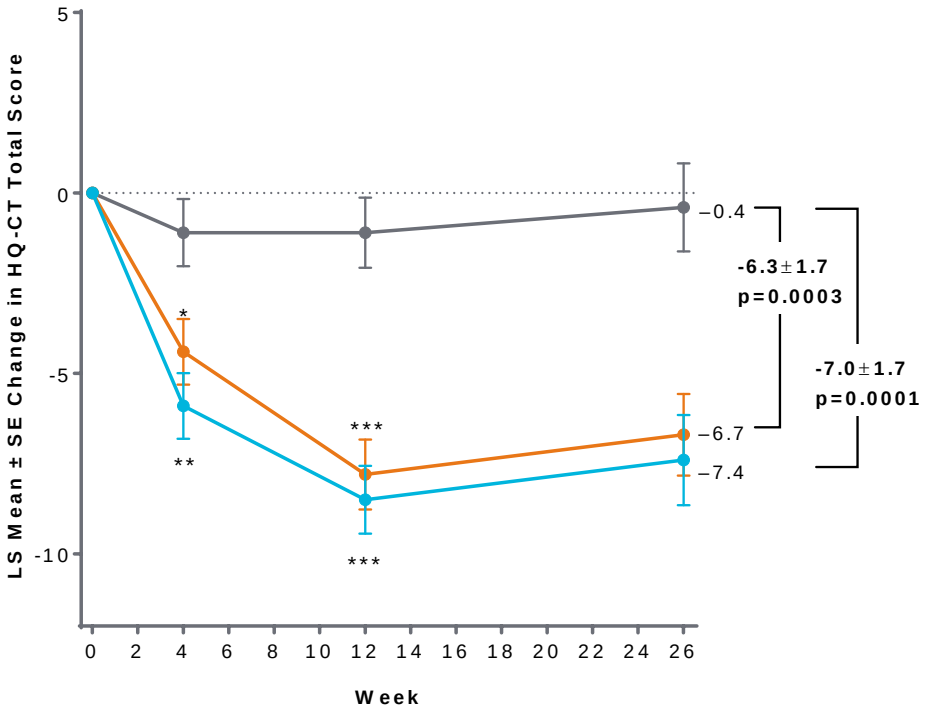
N (%)	Placebo N=34	1.8 mg Beloranib N=36	2.4 mg Beloranib N=37
Chromosome 15q Deletion	25 (73.5%)	24 (66.7%)	27 (73.0%)
Maternal Uniparental Disomy (mUPD)	7 (20.6%)	11 (30.6%)	9 (24.3%)
Imprinting Defect	2 (5.9%)	1 (2.8%)	1 (2.7%)
PWS Medical History			
Hyperphagia	29 (85.3%)	26 (72.2%)	28 (75.7%)
Skin Picking	27 (79.4%)	23 (63.9%)	29 (78.4%)
Aggression	23 (67.6%)	21 (58.3%)	23 (62.2%)
Scoliosis	12 (35.3%)	16 (44.4%)	9 (24.3%)
Vomiting	7 (20.6%)	12 (33.3%)	10 (27.0%)
Sleep Apnea Syndrome	8 (23.5%)	12 (33.3%)	6 (16.2%)
Self-Injurious Behavior	5 (14.7%)	9 (25.0%)	12 (32.4%)
Growth Hormone Deficiency	12 (35.3%)	4 (11.1%)	7 (18.9%)
Hypothyroidism	9 (26.5%)	4 (11.1%)	4 (10.8%)
Anxiety	4 (11.8%)	6 (16.7%)	6 (16.2%)

Beloranib Treatment Results in Improvements in Both Body Weight and Hyperphagia-Related Behaviors

Body Weight



HQ-CT Total Score



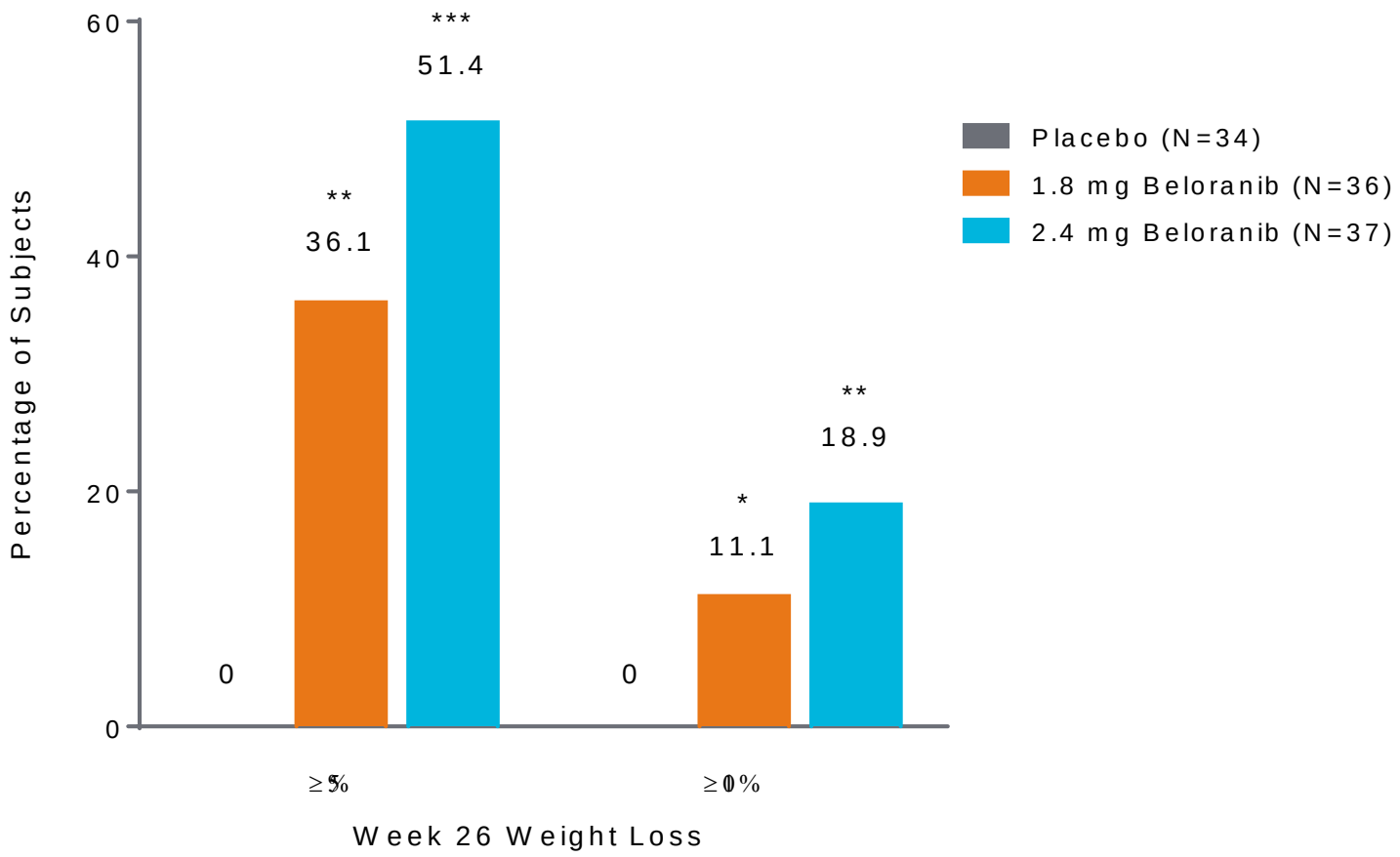
Placebo (N=34); BL Wt=100.9 kg; BL HQ-CT=15.0

1.8 mg Beloranib (N=36); BL Wt=97.5 kg; BL HQ-CT=17.4

2.4 mg Beloranib (N=37); BL Wt=105.7 kg; BL HQ-CT=18.3

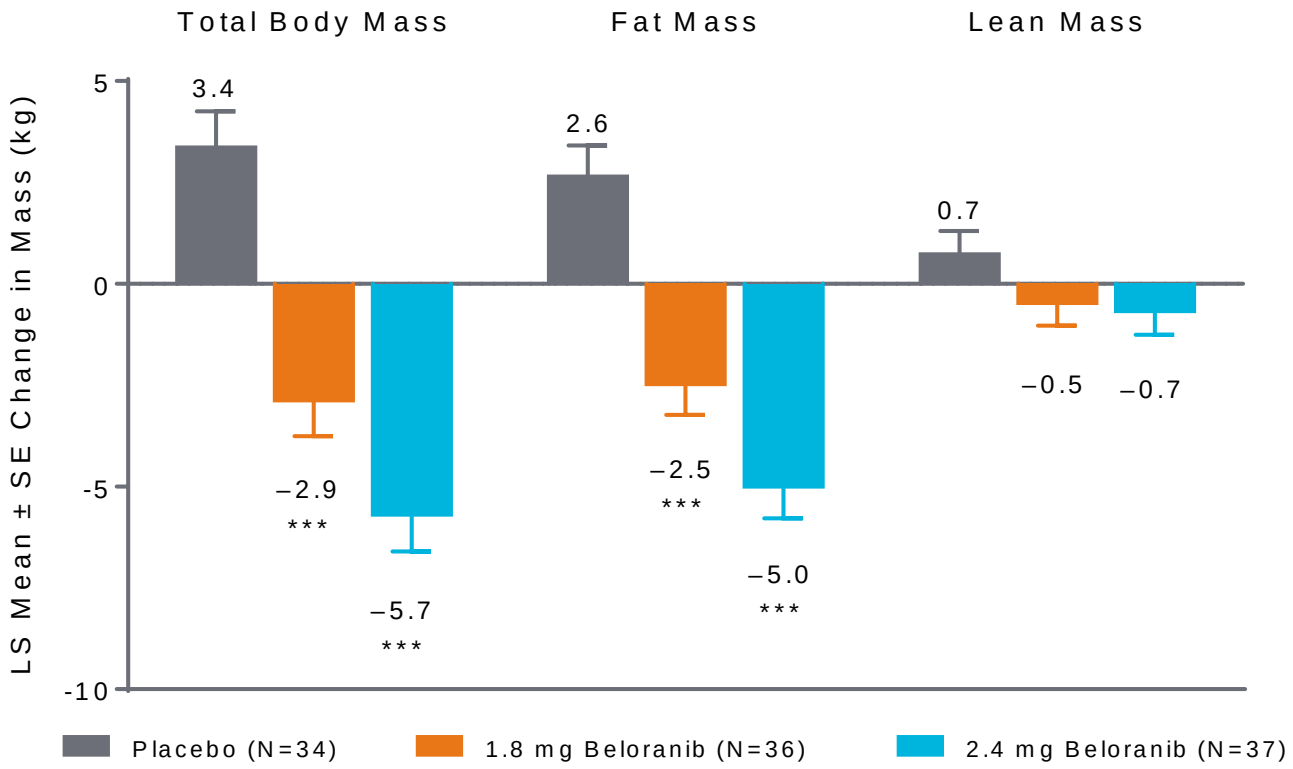
ITT Population: Analysis is implemented via a mixed model repeated measures (MMRM) model.
*p<0.05, **p<0.01, ***p<0.0001 for change from baseline (BL) with beloranib vs. placebo.

Beloranib Treatment Results in PWS Subjects Achieving ≥5% and ≥10% Weight Loss Targets



ITT Population: analysis implemented with last observation before 16Oct2015 carried forward
*p<0.05, **p<0.01, ***p<0.0001 for change from baseline with beloranib vs. placebo

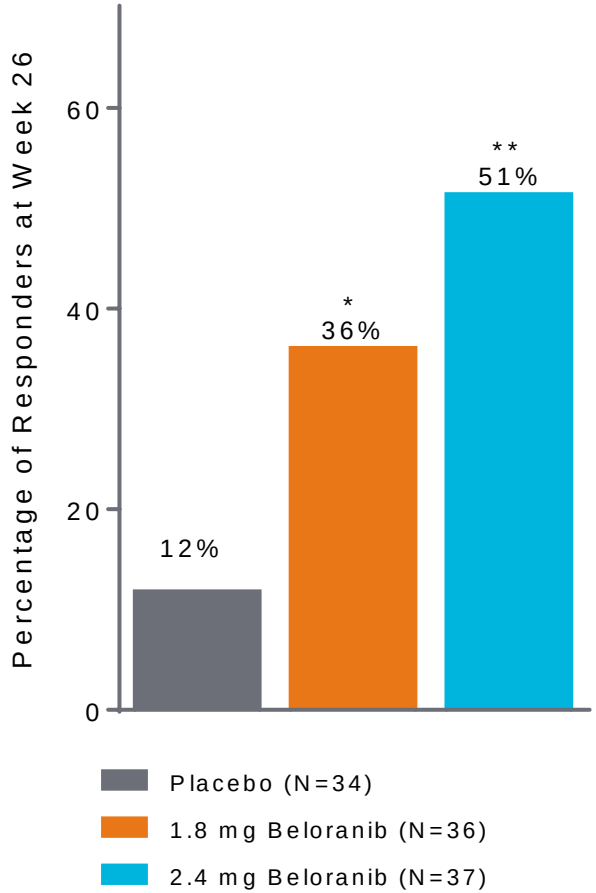
Beloranib Treatment Results in Significant Improvements in Body Composition in PWS as Assessed by DXA



- Reduction in fat mass accounted for 90% of total body mass reduction

ITT Population: Analysis is implemented via a mixed model repeated measures (MMRM) model.
*p<0.05, **p<0.01, ***p<0.0001 for change from baseline with beloranib vs. placebo

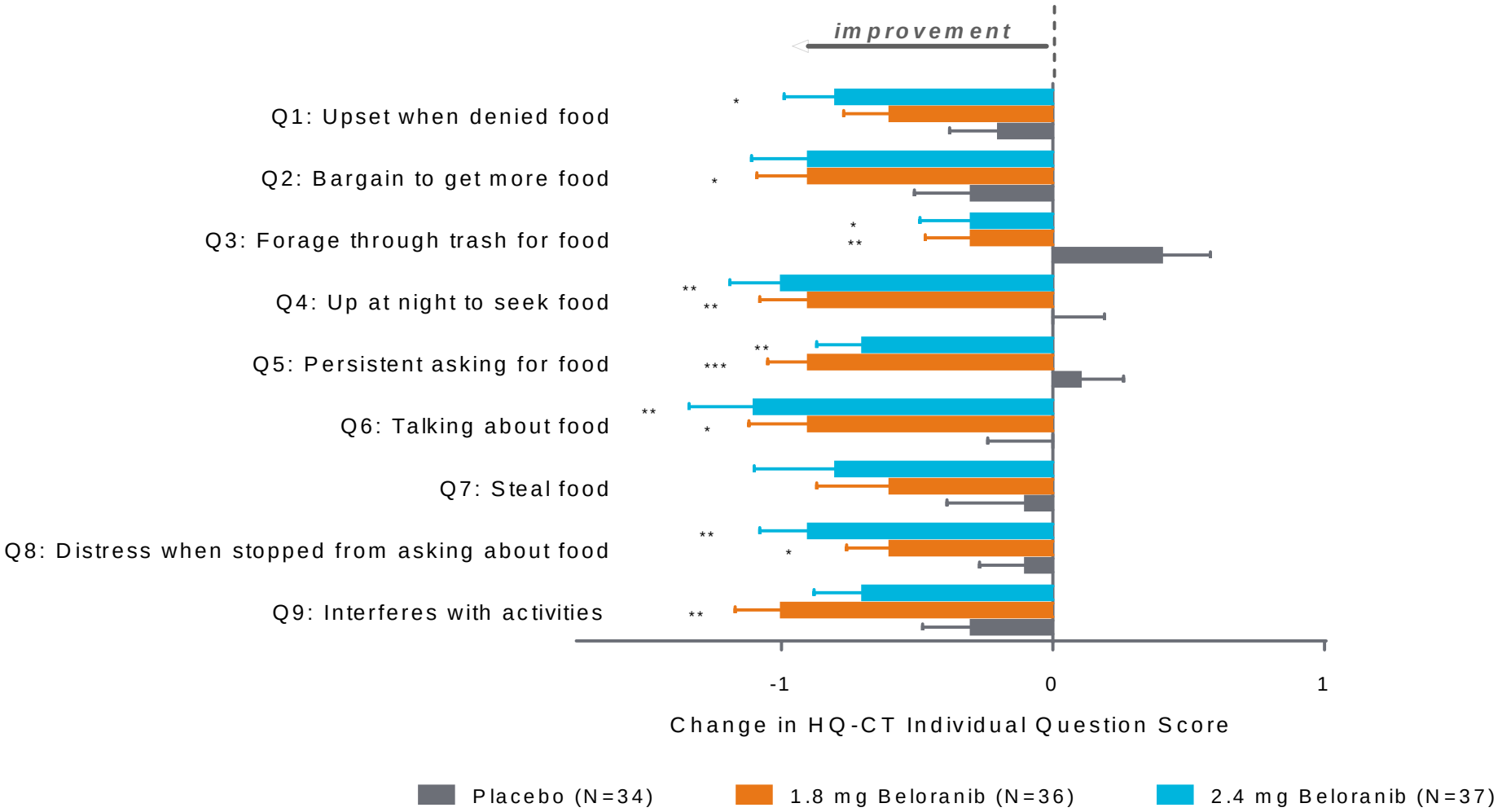
Beloranib Treatment Results in Majority of Subjects Achieving Improvements in HQ-CT Total Score



Responders were classified by an anchor-based method utilizing Caregiver Global Impression of Change item. All subjects achieving a reduction in HQ-CT of ≥ 7.7 were classified as responders

ITT Population: Analysis is implemented via a mixed model repeated measures (MMRM) model.
*p<0.05, **p<0.01, ***p<0.0001 for change from baseline with beloranib vs. placebo

Beloranib Treatment Results in Improvements Across Individual Questions in HQ-CT



ITT Population: Analysis is implemented via a mixed model repeated measures (MMRM) model.
*p<0.05, **p<0.01, ***p<0.0001 for change from baseline with beloranib vs. placebo

Summary of Safety and Tolerability of Beloranib Treatment in PWS

N (%) events	Placebo N=34	1.8 mg Beloranib N=36	2.4 mg Beloranib N=37
Any TEAE	22 (64.7%) 104	30 (83.3%) 130	29 (78.4%) 125
Severe TEAE	2 (5.9%) 2	4 (11.1%) 4	2 (5.4%) 2
TEAE leading to withdrawal of study drug prior to October 16, 2015	0	4 (11.1%) 4	2 (5.4%) 2
Serious TEAE	2 (5.9%) 2	2 (5.6%) 2	1 (2.7%) 1
TEAE Resulting in Death	0	1 (2.8%) 1	0

Safety Population (N=107): all subjects who received at least 1 dose of randomized study drug.
TEAE = Treatment-emergent adverse event

Summary of Safety and Tolerability of Beloranib Treatment in PWS

Frequent TEAE (>10% in any treatment group)

N (%)	Placebo N=34	1.8 mg Beloranib N=36	2.4 mg Beloranib N=37
Injection site bruising	1 (2.9%)	4 (11.1%)	6 (16.2%)
Aggression	5 (14.7%)	5 (13.9%)	4 (10.8%)
Hyperphagia	3 (8.8%)	6 (16.7%)	2 (5.4%)
Fatigue	0	5 (13.9%)	1 (2.7%)
Headache	5 (14.7%)	2 (5.6%)	2 (5.4%)

Safety Population (N=107): all subjects who received at least 1 dose of randomized study drug.
TEAE = Treatment-emergent adverse event

Summary of Safety and Tolerability of Beloranib Treatment in PWS

N (%)	Placebo N=34	1.8 mg Beloranib N=36	2.4 mg Beloranib N=37
Any Serious TEAE	2 (5.9%)	2 (5.6%)	1 (2.7%)
Ankle fracture	1 (2.9%)	0	0
Aggression	1 (2.9%)	0	1 (2.7%)
Mental status changes	0	1 (2.8%)	0
Pulmonary embolism	0	1 (2.8%)	0
Any TEAE leading to withdrawal of study drug prior to October 16, 2015	0	4 (11.1%)	2 (5.4%)
Abnormal behavior	0	1 (2.8%)	0
Anxiety	0	1 (2.8%)	0
Injection site pain	0	0	1 (2.7%)
Mental status changes	0	1 (2.8%)	0
Psychotic disorder	0	0	1 (2.7%)
Pulmonary embolism	0	1 (2.8%)	0

Safety Population (N=107): all subjects who received at least 1 dose of randomized study drug.
TEAE = Treatment-emergent adverse event

Overview of Venous Thrombotic Events in Beloranib Clinical Development Program

- ~ 400 patients have been exposed to beloranib, with more than 2.5 times the cumulative exposure with beloranib vs placebo
- Eleven venous thrombotic events (pulmonary embolism, deep vein thrombosis, superficial thrombophlebitis) (6AE, 5 SAE) in beloranib treated patients, none in placebo
- Experience with PWS:
  - no venous thrombotic events in ZAF-211 (phase 2)
  - 2 fatal pulmonary embolism events, 2 deep vein thrombosis events in ZAF-311 (phase 3)
- Beloranib is currently on clinical hold
- Zafgen is comprehensively evaluating non-clinical and clinical data to assess the potential for a pro-thrombotic effect of beloranib. In addition, the available information on patients with PWS is being inspected to understand any increased risk in this population

Summary of Beloranib Treatment in PWS

- bestPWS Study is the first Phase 3 clinical trial to show statistically and clinically significant weight-loss and improvement in hyperphagia-related behaviors in PWS patients
  - Both beloranib treatment groups had statistically and clinically significant weight loss that was progressive and sustained
  - The reduction in hyperphagia-related behaviors in the beloranib treated groups represents a clinically meaningful benefit to patients
- Further understanding of venous thrombosis in PWS and with beloranib treatment is required; extensive work is underway
- Along with the overall safety data, the efficacy results of this study continue to inform the benefit/risk profile of beloranib in PWS