A Randomized, Placebo-Controlled Trial of Beloranib for the Treatment of Hypothalamic Injury-Associated Obesity

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ABSTRACT

Aims: Hypothalamic injury-associated obesity (HIAO) results from damage to the hypothalamus that often occurs with surgical removal/radiation therapy of tumors in the hypothalamic region, such as craniopharyngioma. There is currently no rigorously studied pharmaceutical treatment for the intractable weight gain and cardiometabolic consequences that occur in patients with HIAO. We aimed to assess efficacy, safety, and tolerability of beloranib treatment for 4 to 8 weeks in patients with HIAO.

Materials and Methods: This Phase 2a, double-blind, placebo-controlled study included 14 patients with HIAO randomized to receive beloranib 1.8 mg or placebo subcutaneously twice weekly for 4 weeks with an optional 4-week open-label extension in which all patients received beloranib. The primary endpoint was change in weight from baseline to Week 4.

Results: Participants were 64% female, with mean (SD) age 32 (9) years, BMI 43 (7) kg/m^2, and weight 126 (22) kg. Compared with placebo (N=4), beloranib 1.8 mg (N=8) resulted in a mean (95% CI) difference in weight of -3.2 (-5.4, -0.9) kg after 4 weeks. Weight loss continued through the 8 weeks in patients randomized to beloranib (mean -6.2 [-8.2, -4.1] kg). Beloranib treatment was associated with improvements in high-sensitivity CRP. Adverse events were mild to moderate. No patients who received beloranib discontinued treatment.

Conclusion: Beloranib treatment resulted in progressive weight loss in patients with HIAO that was comparable to that observed with beloranib in patients with exogenous obesity. These findings indicate a novel mechanism for treating obesity in patients with HIAO.

INTRODUCTION

Hypothalamic injury-associated obesity (HIAO) is a life-altering complication resulting from damage to the hypothalamus. The most common etiology of HIAO is craniopharyngioma, but it is observed with other insults to the hypothalamus [1]. Despite craniopharyngioma having high survival rates, post-treatment pituitary hormone deficiencies and visual and neurological deficits are common [2], and at least 50% experience intractable weight gain resulting in severe obesity. Patients with HIAO are at increased risk for metabolic and cardiovascular disorders and have increased obesity-associated morbidity and mortality [2, 3].

Treatment options for patients with HIAO are limited. One potential barrier to treatment of HIAO is that most available pharmaceutical agents have putative actions mediated through the hypothalamus. Attempts at caloric restriction or pharmacotherapy have been met with little or only brief success [4, 5]. Even bariatric surgery has shown mixed success [6] and is controversial due to unproven efficacy and significant morbidity and mortality [7]. There are no rigorously studied, accepted pharmacological treatments for obesity in patients with HIAO [2].

Methionine aminopeptidase 2 (MetAP2) inhibitors are a novel class of compounds that lead to marked weight loss in animals and humans [8, 9]. Although not fully elucidated, the mechanism for weight loss associated with MetAP2 inhibitors is believed to be due to a reduction in fat biosynthesis and increased fat oxidation and lipolysis, resulting in reduced fat mass as well as a reduction in caloric intake [9-13]. As patients report a reduction in hunger [9], it is also possible that some MetAP2 inhibitory effects are centrally mediated, or occur through peripheral feedback to the brain, though a mechanism has not been elucidated.

In a Phase 2 clinical trial in patients with exogenous obesity, administration of the MetAP2 inhibitor, beloranib, for 12 weeks produced a dose-dependent reduction in body weight (up to approximately 11%), improvements in markers of cardiometabolic risk, and a reduction in hunger [9]. In obese mice with chemically-induced HIAO with gold-thioglucose, beloranib administration consistently

reduced food intake, body weight, and adipocyte mass. Thus, MetAP2 inhibition may induce weight loss in humans with compromised hypothalamic regulation of energy balance, such as patients with HIAO. Development of beloranib has ceased due to an imbalance in venous thromboembolic events in beloranib-treated patients with obesity and Prader-Willi syndrome (manuscript in preparation) or type 2 diabetes (T2D; manuscript in preparation). Investigation of other MetAP2 inhibitors with similar efficacy but an improved safety margin to mitigate risk of venous thrombotic events is underway.

The aim of this clinical trial was to investigate the efficacy, safety, and tolerability of beloranib suspension compared to placebo, administered subcutaneously twice weekly, for 4 weeks in 14 adult patients with HIAO. The clinical trial included an open-label extension (OLE) in which all patients received beloranib for an additional 4 weeks.

MATERIALS AND METHODS

Study design

This was a double-blind, randomized, placebo-controlled, parallel-group, 4-week study with an optional 4-week OLE. Eligible patients were enrolled at 2 sites in the United States and 2 sites in Australia, between June and September 2014. The Institutional Review Boards at all study sites approved the protocol prior to study initiation. All patients provided written informed consent. Study drug administration could be stopped at any time at the discretion of the Investigator.

Patients were randomized via Medidata Balance (New York, NY), a central Interactive Web Response System in a 4:3 ratio to beloranib (1.8 mg) or placebo for the 4-week randomized treatment period. Patients had the option to participate in a subsequent 4-week OLE during which all patients received beloranib 1.8 mg twice weekly.

Blinding was maintained by study Investigators, study staff, and patients throughout the study, except by select pharmacy and designated study drug administrators who did not take part in any other aspects of the study. Beloranib or placebo was administered twice weekly at the study site by a study drug administrator or at the patient's home/work by a home health nurse (study drug administrators were unblinded and were not otherwise involved in the care or evaluation of study subjects) via subcutaneous injection in the lateral abdominal region. Beloranib was prepared by adding diluent (placebo) containing carboxymethylcellose, mannitol, poloxamer 188, and phosphate buffer (pH 7.3) to a single-use vial of beloranib sterile powder. Due to slight differences in coloration (study drug is opaque and placebo is clear) patient blinding was maintained by shielding study drug from the patient's view during the administration process.

No diet or exercise regimens were administered. All patients were followed for at least 1 week after the last dose of beloranib or placebo.

Patients

The study included male and female patients aged 18–65 years with obesity as a consequence of acquired anatomical hypothalamic damage as evidenced by medical history and radiographic evidence of hypothalamic lesion on review of magnetic resonance imaging (MRI). All patients had a minimum of 10% self-reported weight gain within 2 years of diagnosis (considered by the Investigator to be secondary to hypothalamic injury), and body mass index (BMI) e30 and d60 kg/m^2. Additional inclusion criteria are detailed in Supplemental Table 1.

Study Outcomes

The primary outcomes were change in body weight from baseline to Week 4, safety and tolerability. Secondary outcomes included the change in fasting lipids, fasting glucose, self-reported sense of hunger and eating behavior, quality of life, and sleep quality. Exploratory analysis was conducted on biomarkers of lipid metabolism as well as on panels of biomarkers related to cardiometabolic health (Metabolic MAP and Cardiovascular MAP; Myriad RBM, Inc. Austin, TX).

Body weight was measured after an overnight fast using a designated calibrated scale. Patients wore a hospital gown and voided immediately prior to being weighted. Fasting hemoglobin A1c (HbA1c), glucose, and insulin levels were measured in patients with T2D. Sense of hunger and eating behavior over the 2 days prior to select study visits were assessed in the fasted state using an 8-Question visual analog scale (8Q-VAS) [14]. Quality of life was assessed using the Impact of Weight on Quality of Life Questionnaire-Lite Version (IWQOL-Lite) [15]. Sleep quality was evaluated using a 3-Question Sleep Quality Questionnaire which assesses sleep latency, duration of sleep, and overall sleep quality.

Safety evaluations included assessment of treatment-emergent events (AEs) and serious AEs, physical examination, electrocardiogram, vital signs, concomitant medications, and laboratory parameters.

Statistical Analysis

The sample size was selected to provide preliminary data and was not based on statistical considerations. The safety population included all participants who received at least 1 dose of blinded study drug. The per protocol (PP) population included all randomized patients who received at least 7 of 8 doses of blinded study drug with no major protocol deviations and no dosing errors during the randomized period. The modified intent-to-treat (mITT) population included all randomized patients who received at least 1 dose of blinded study drug and who had at least 1 post-baseline body weight measurement during the randomized treatment period.

The primary comparison was the least squares (LS) mean treatment effect between beloranib and placebo at Week 4 in the PP population. Unless otherwise noted, all efficacy data are presented for the PP population. The primary analysis was conducted using an analysis of covariance (ANCOVA) model with absolute or percent change in body weight as the dependent variable, treatment group as a factor, and baseline value as a covariate. Secondary outcomes were tested using an ANCOVA model with treatment group as factors and baseline values as covariates. A 2-sided test at the 5% level was used to determine statistical significance. AEs were summarized by treatment group, system organ class, and preferred term.

RESULTS

A total of 14 patients were randomized to beloranib (N=8) and placebo (N=6) with 13 patients (beloranib n=8; placebo n=5) completing the randomized treatment period and the OLE (Supplemental Figure 1). One patient in the beloranib group missed a single dose; there were no other issues with study drug compliance. During the randomized treatment period, 1 patient discontinued placebo treatment after 3 doses due to an AE of urticaria and 1 additional patient receiving placebo treatment was excluded from the PP population prior to data analysis due to receiving a dose of active drug.

Patient baseline demographics and characteristics were generally similar across treatment groups (Table 1). The majority of patients were white (78.6%) females (64.3%), with a mean age of 31.9 (range 18 to 48) years, mean BMI of 42.9 (range 30.3 to 54.8) kg/m^2 and mean body weight 126.4 kg (range 89.7 to 166.3). The study included 3 patients with T2D (2 beloranib, 1 placebo). No patients were treated with glucagon-like peptide-1 (GLP-1) receptor agonists.

Body Weight

Body weight decreased from baseline through the end of the randomized treatment period in patients randomized to beloranib but remained stable for patients randomized to placebo (Figure 1 and Supplemental Figure 2). At Week 4, the change in body weight in the PP population was statistically greater for patients randomized to beloranib compared with placebo (LS mean [95% Confidence Interval] difference from placebo: -3.2 kg [-5.4, -0.9; p=0.010]; -2.6% change from baseline [-4.5, -0.7; p=0.013]; Figure 1). The treatment effect on body weight was similar in the mITT population: -3.2 kg (-5.1, -1.2; p=0.005); -2.7% (-4.3, -1.0; p=0.006).

In the beloranib group, significant weight loss was observed at Week 4 and Week 8, while the placebo group exhibited weight loss only during the 4-week OLE period when they received beloranib (Figure 1). At Week 8, patients randomized to beloranib (PP population) exhibited LS mean (95% CI) weight loss of -6.2 kg [-8.2, -4.1] (-5.0% [-6.6, -3.3]). Patients originally randomized to placebo (placebo/beloranib) had weight loss of -3.0 kg [-5.9, -0.1] (-2.5% [-4.9, -0.1]) from the start of beloranib

treatment in the OLE, which was similar in magnitude to that observed during the first 4 weeks of treatment in patients randomized to beloranib.

The single subject with a disease history of pituitary macroadenoma was randomized to placebo, but exhibited a 1.8 kg (1.5%) mean weight loss during the OLE after starting beloranib treatment. The 1 placebo subject who completed the trial, but was not included in the PP analysis (dosing error) exhibited 0.0 kg difference from baseline at Week 4, and -3.3 kg weight change after 4 weeks of treatment with beloranib, which was similar to that observed in placebo patients included in the PP analysis.

Patients with diabetes

Two patients with T2D were randomized to beloranib and exhibited weight loss consistent with the overall cohort (-3.2 kg [-2.4%] and -3.9 kg [-2.8%] at the end of the randomized period), whereas the single placebo patient with T2D exhibited no weight change during the randomized period. One patient with T2D did not complete the baseline HbA1c assessment. The remaining patient with T2D in the beloranib group had an improvement in HbA1c from 8.5% (baseline) to 7.3% at 4 weeks and 6.6% at 8 weeks. The patient with T2D in the placebo group had a baseline HbA1c of 7% was 6.7% at 4 weeks (placebo) and 6.1% at 8 weeks (beloranib).

Markers of Cardiometabolic Status

There was no change from baseline in total cholesterol, low-density lipoprotein, high-density lipoprotein, and triglycerides at the end of this 4-week treatment period (Supplemental Table 2). High-sensitivity CRP (hsCRP) was highly elevated at baseline in these patients (mean [standard error]: 19.9 [3.9] mg/L for beloranib-randomized patients, 14.4 [6.1] for placebo-randomized patients; normal range 0-3 mg/L). hsCRP improved rapidly at the onset of beloranib treatment (Figure 2), and placebo patients experienced a similar magnitude of reduction following initiation of beloranib in the OLE. At the follow-up 7 days after cessation of study drug treatment, hsCRP concentrations returned to near baseline levels. An exploratory analysis of additional biomarkers related to cardiometabolic health was also conducted (Supplemental Table 2).

Markers of Adipocyte Function

Adiponectin and leptin, hormones related to metabolic dysregulation with obesity, were significantly improved compared to placebo after 4 weeks of treatment. At the end of randomized treatment, patients treated with beloranib exhibited significantly greater change from baseline in both adiponectin (LS mean difference, +1.2 mg/L; $p<0.05$) and leptin (-19.8 µg/L; $p<0.01$; Supplemental Table 2) compared with placebo. Beloranib-randomized patients appeared to maintain improvements through the end of the extension period; placebo-randomized patients exhibited improvements in mean adiponectin and leptin during the OLE that were similar in magnitude to those observed by beloranib-treated patients during the randomized period (data not shown).

Reported Eating Behavior

There were no significant differences in change from baseline to the end of the randomized treatment period between beloranib-treated vs. placebo-treated patients for any of the 8 items assessed using the VAS questionnaire in this small subject population over 4 weeks. In the OLE period, prospective food intake indicated favorable mean changes in both treatment arms: -37% (95% CI: -53%, -21%) for the beloranib group and -54% (-79%, -29%) following beloranib treatment of the placebo-randomized patients.

Safety

During the randomized treatment period, the most frequent AEs were dizziness, headache, and nasopharyngitis, Of these, dizziness was the only event reported with beloranib alone (Supplemental Table 3). One patient in the placebo group withdrew from the study due to a treatment-emergent AE of urticaria at the injection site that occurred following administration of study drug on study day 7; no patients randomized to beloranib discontinued treatment due to an AE in the randomized treatment period. The majority of events were mild in intensity (85% of all AEs) and transient, and there were no severe events in the randomized period.

During the OLE period, no AE was reported more than once. Similar to the randomized treatment period, AEs were primarily mild in intensity. One severe AE of back pain occurred during the OLE in a patient randomized to beloranib; the Investigator did not attribute this to the study drug. During the OLE, there were no AEs leading to discontinuation of study drug.

There were no serious AEs in the study, and there were no clinically meaningful or unexplained changes in vital signs, electrocardiogram measurements, or clinical chemistry measurements. One beloranib-treated subject experienced alanine aminotransferase (ALT) e 3 times the upper limit of normal (ULN) and aspartate aminotransferase (AST) e 5 times the ULN, concurrent with the AEs of viral gastroenteritis and fever. This patient was diagnosed with mild diarrhea/viral gastroenteritis that was subsequently treated with anti-motility medications. ALT and AST levels returned to normal and the patient continued in the study without any subsequent liver function test abnormalities. Two patients randomized to beloranib experienced reduced neutrophil counts during the randomized period; both events resolved during the OLE. One placebo-randomized patient experienced decreased neutrophil count on the last day of beloranib treatment in the OLE, which was mild in intensity and resolved at follow-up. None of these patients reported any AEs consistent with immunosuppression. Assessments of coagulation (activated partial thromboplastin time, prothrombin time, International Normalized Ratio) revealed no treatment differences, and there were no events related to venous thrombotic events.

There was a transient increase from baseline in sleep latency as measured by the 3Q Sleep Quality Questionnaire (median increase: +5.0 minutes) with beloranib at Week 2 that subsequently returned to baseline at the next visit approximately 2 weeks later. There was a similar trend for patients previously randomized to placebo (median increase: +5.0 minutes) in the second week of the OLE that was maintained through the end of the OLE.

DISCUSSION

In this randomized, double-blind, placebo-controlled Phase 2a study of beloranib in patients with HIAO, beloranib produced statistically and clinically significant weight loss comparable to that observed with beloranib in prior trials in neuroanatomically intact obese patients [9]. Beloranib was associated with greater than 6 kg weight loss from baseline after to 8 weeks in patients with HIAO. This was observed without diet and exercise counseling and without indication of a plateau in weight loss through 8 weeks. HIAO is one of the most recalcitrant forms of obesity, so it is notable that the weight loss observed with beloranib treatment in HIAO patients was comparable to that observed with beloranib in patients with exogenous obesity [9]. This suggests that beloranib has potent effects on body weight that occur via mechanisms that operate in the setting of compromised hypothalamic regulation of energy balance. The patients in this study had long-standing HIAO with average onset of disease occurring a decade prior to enrollment; typically a group considered refractory to treatment [16].

Mean weight change in HIAO after bariatric surgery peaks at ~20% in the first year after Roux-en-Y gastric bypass (RYGB) or sleeve gastrectomy [6], significantly less than the 35-40% weight loss typical for RYGB in patients with exogenous obesity [17]. Some effects of bariatric surgery are likely mediated through the hypothalamus, perhaps accounting for the decreased efficacy in HIAO. The similar weight loss observed in HIAO and exogenous obesity with beloranib treatment, albeit after 8 weeks, suggests that a primary mechanism of weight loss associated with beloranib is independent of a fully functioning hypothalamus. Additional studies in HIAO, including mechanistic studies and studies of longer duration are required to fully characterize the effect of MetAP2 inhibition in HIAO.

Rapid improvement was observed in other biomarkers of inflammation, fatty liver disease, insulin resistance, and other indicators of cardiovascular risk (Supplemental Table 2). In particular, hsCRP was extremely elevated at baseline in patients with HIAO (mean 19.9 mg/L), >3 times higher than that observed in patients with other chronic diseases such as exogenous obesity, T2D, and polycystic ovary syndrome [18-23]. Elevated hsCRP is associated with development of cardiovascular disease and

diabetes [24, 25]. hsCRP levels fell rapidly at the onset of beloranib treatment (Figure 2) followed by a rapid rise after cessation of treatment, suggesting that beloranib may exert salutary effects on hsCRP that are independent of weight loss.

The mechanisms for the weight-independent effects of MetAP2 inhibition are under investigation. One hypothesized mechanism for reduced hsCRP with MetAP2 inhibition is via suppression of extracellular signal regulated kinase (ERK) hyperphosphorylation [26]. Putative ERK-mediated effects of MetAP2 inhibition that influence inflammation, lipid biosynthesis, and insulin action include suppression of sterol regulatory element binding protein (SREBP) activity [11, 12] and activation of retinoic acid-related orphan receptor ± (ROR±) [27].

The weight reduction observed with beloranib in patients with exogenous obesity may be predominantly a result of reduced fat biosynthesis and increased fat oxidation and lipolysis, resulting in reduced adipocyte mass as well as a reduction in measures of hunger and prospective food intake [9-12]. Although the short duration of this study makes it difficult to elucidate the mechanisms responsible for weight loss in HIAO, the trend toward a reduction in prospective food intake observed in this study, in the context of the underlying structural abnormalities of the hypothalamus in these patients, suggest extrahypothalamic actions of appetite regulation mediated by beloranib treatment.

In patients with exogenous obesity treated with beloranib, the most commonly reported AEs were insomnia and sleep disorders, followed by gastrointestinal disorders [9]. In patients with HIAO, beloranib was not associated with a sustained increased incidence of insomnia and sleep disorders or gastrointestinal AEs. A possible explanation for the apparent difference in AE pattern is that the medial hypothalamus mediates the effects of beloranib on insomnia, sleep disorders, and gastrointestinal AEs. Thus, patients with HIAO may not experience these AEs to the same degree, if at all. Furthermore, beloranib may have simply attenuated the increased somnolence frequently observed in patients with HIAO [28]. After conclusion of this study, 2 ongoing studies (1 in patients with Prader-Willi syndrome and another in patients with exogenous obesity and T2D) were concluded early as a result of a complete

clinical hold due to an imbalance in venous thromboembolic events, including 2 patient deaths due to pulmonary embolism, in the beloranib development program. No venous thromboembolic events were reported in the current trial; investigation is underway to elucidate a mechanism for the observed imbalance in venous thromboembolic events.

This small proof of concept study was designed to provide initial data on the safety and efficacy of beloranib in patients with HIAO. A limitation is our inability to precisely define the extent of hypothalamic damage as patients were up to 25 years post-diagnosis and uniform MRI imaging was not available. However, weight loss was generally consistent, implying that the location of hypothalamic injury did not dramatically affect the response to treatment with a MetAP2 inhibitor. Improvements in lipids occurred with beloranib treatment in other clinical studies of beloranib in patients with obesity [9, 13]. In this study, the small number of subjects and short duration of treatment likely contributed to the lack of a statistically significant change in lipids. Additional studies of longer duration and larger sample size are needed to obtain a better understanding of the effects of beloranib treatment.

This is the first study to demonstrate rapid and significant weight loss with beloranib, a MetAP2 inhibitor, in patients with HIAO. These results support a novel extra-hypothalamic mode of action of beloranib to mediate improvements in weight and markers of adipocyte function and cardiovascular risk. Given the impact on the severe obesity observed in patients with HIAO, MetAP2 inhibitors represent a potential novel non-surgical treatment that warrants further investigation for not only HIAO, but as a potential therapy for other causes of obesity without adequate efficacious therapies. Development of second generation MetAP2 inhibitors is underway.

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AUTHOR CONTRIBUTIONS

JP, MJA, TM and AHS participated as trial Investigators, discussion and interpretation of results, and reviewed/edited manuscript. JM participated in conduct of the study, design and conduct of the statistical analyses, discussion and interpretation of results, and reviewed/edited manuscript. DK participated in design of study, conduct of study, discussion and interpretation of results, and reviewed/edited manuscript. All authors approved the final manuscript.

FINANCIAL DISCLOSURE

This study was funded by Zafgen, Inc.

CONFLICT OF INTEREST STATEMENT

JP, MJA and TM have nothing to declare. AHS is a consultant for Zafgen, Inc. and has received an Investigator initiated grant from AstraZeneca. JM and DK are employed by Zafgen, Inc.

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398 TABLES AND FIGURES

399 **Table 1. Patient Demographics and Characteristics at Screening**

	Placebo (N=6)	Beloranib (N=8)
Female, n (%)	4 (66.7%)	5 (62.5%)
Age, years	34.3 ± 8.8	30.0 ± 9.5
Body weight, kg	124.8 ± 23.0	127.6 ± 22.8
BMI, kg/m^2	42.1 ± 6.0	43.4 ± 8.0
White race, n (%)	4 (66.7%)	7 (87.5%)
Non-Hispanic/non-Latino, n (%)	5 (83.3%)	7 (87.5%)
Etiology of Hypothalamic Injury, n (%)		
Craniopharyngioma	5 (83.3%)	8 (100.0%)
Pituitary macroadenoma	1 (16.7%)	0
Time from confirmed hypothalamic injury, years	11.4 ± 9.4	9.0 ± 10.1
Hormone replacement		
Diabetes insipidus	5 (83.3%)	8 (100%)
Central hypothyroidism	6 (100%)	8 (100%)
Gonadotropin deficiency	5 (83.3%)	6 (75%)
Adrenal insufficiency	5 (83.3%)	7 (87.5%)

400

401 Safety Population. Data are mean ± SD except where indicated.

402

403 FIGURE LEGENDS

404 **Figure 1. Change in Body Weight**

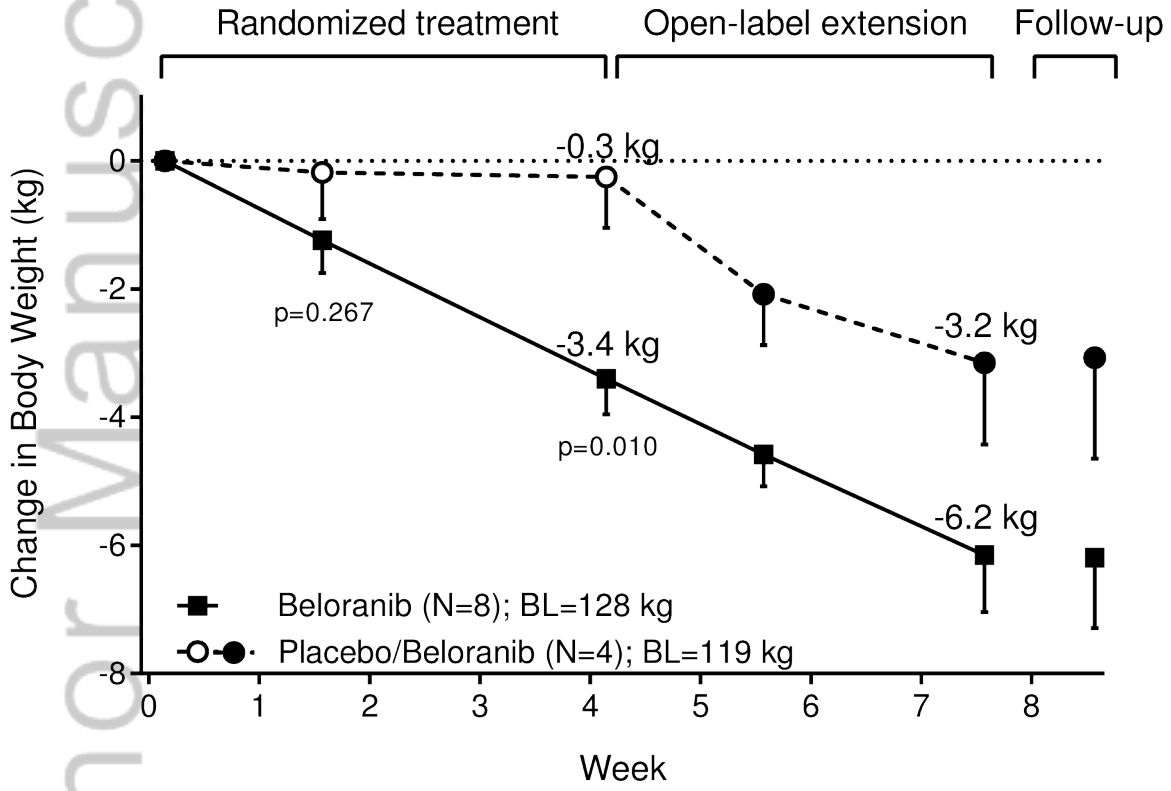
405 Data are least squares mean (SE) for the Per Protocol Population. The follow-up visit was 5-10 days after

406 the last dose of study drug. BL = baseline.

407 **Figure 2. Change in hsCRP**

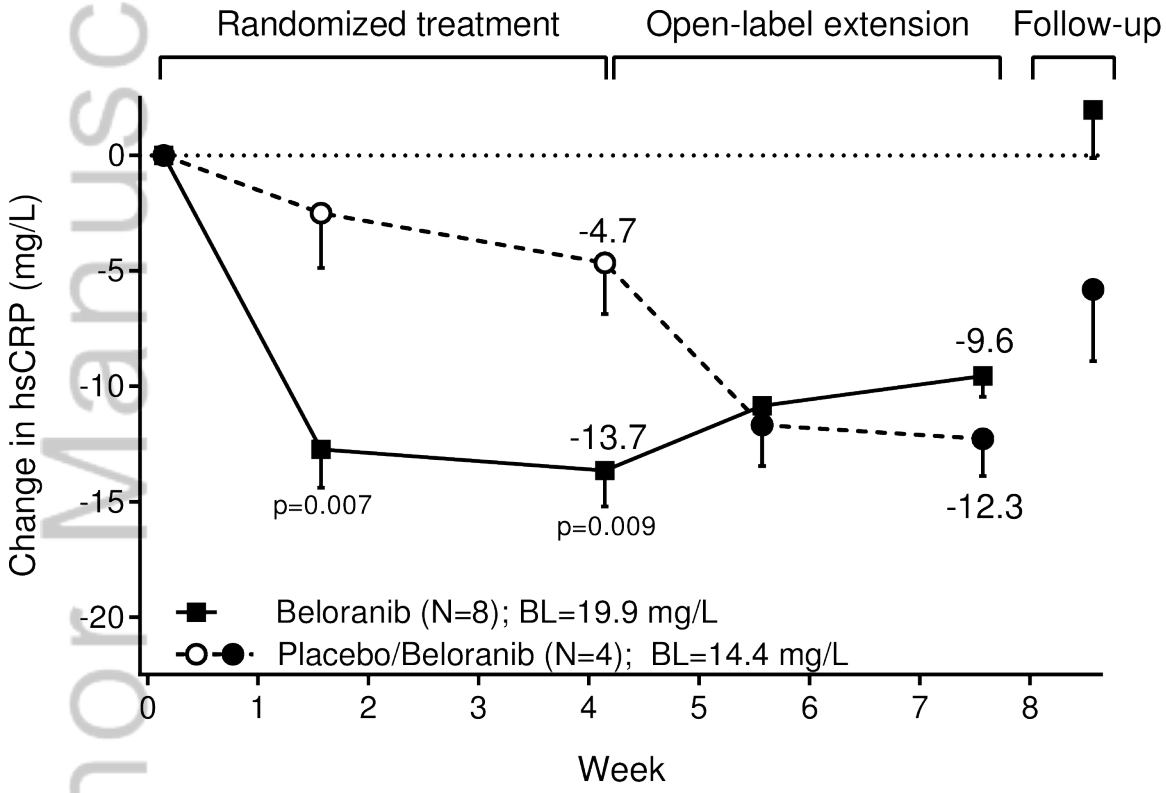
408 Data are least squares mean (SE) for the Per Protocol Population. The follow-up visit was 5-10 days after

409 the last dose of study drug. BL = baseline.



Data are LS mean (SE); BL = Baseline

dom-16-0848-op-file002.eps



Data are LS mean (SE); BL = Baseline

dom-16-0848-op-file003.eps

Author/s:
Shoemaker, A;Proietto, J;Abuzzahab, MJ;Markovic, T;Malloy, J;Kim, DD

Title:
A randomized, placebo-controlled trial of beloranib for the treatment of hypothalamic injury-associated obesity

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