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ORIGINAL ARTICLE

Efficacy and safety of beloranib for weight loss in obese adults: a randomized controlled trial

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Aim: To assess the efficacy, safety and tolerability of beloranib treatment for obesity.

Methods: This phase II, double-blind, randomized study investigated the effects of beloranib suspension (0.6, 1.2 and 2.4 mg) or placebo, administered subcutaneously, for 12 weeks in 147 participants (primarily white women) with obesity. No diet or exercise advice was administered.

Results: At week 12, beloranib resulted in dose-dependent progressive weight loss of -5.5 ± 0.5, -6.9 ± 0.6 and -10.9 ± 1.1 kg for the 0.6, 1.2 and 2.4 mg beloranib doses, respectively, compared with -0.4 ± 0.4 kg with placebo (all $p < 0.0001$ vs placebo). Weight loss with beloranib was associated with corresponding reductions in waist circumference and body fat mass, as well as improvements in lipids, high-sensitivity C-reactive protein and blood pressure. Sleep disturbance and gastrointestinal adverse events were more common with beloranib than with placebo; these were generally mild to moderate, transient and dose-related, and led to more early study withdrawals in participants in the group with the highest dose of beloranib.

Conclusions: In this 12-week phase II study, beloranib produced clinically and statistically significant weight loss and corresponding improvements in cardiometabolic risk factors. Beloranib appeared safe, and the 0.6 and 1.2 mg doses were generally well tolerated. The 2.4 mg dose was associated with increased sleep latency and mild to moderate gastrointestinal adverse events over the first month of treatment. These findings represent a novel mechanism for producing clinically meaningful weight loss.

Keywords: clinical trial, drug development, obesity therapy, randomized trial, weight loss therapy

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Introduction

The rising prevalence of obesity is a global phenomenon that poses serious health risks [1]. Obesity is a leading risk factor for type 2 diabetes, metabolic syndrome, heart disease, cancer, infertility, liver and gallbladder disease and other conditions [2]. The most effective treatment for obesity and obesity-related conditions is bariatric surgery, which produces greater weight loss and higher remission rates of type 2 diabetes and metabolic syndrome than non-surgical treatments [3,4]. Because of significant risk of adverse events, including reoperation, hernia, thromboembolism, anaemia and death, as well as weight regain, bariatric surgery is often relegated to an option of last resort [2,5].

There are few non-surgical obesity treatments for patients who either do not meet the criteria for bariatric surgery or for whom surgical treatment is not an option. Obesity medications generally result in 30–60% of patients achieving at least 5% weight loss by 12 weeks and mean placebo-subtracted weight loss of 3–9% at 1 year [6], which falls short of patient expectations [7]. There is a need for additional non-surgical weight loss therapies that produce clinically significant weight loss and improvements in cardiometabolic risk factors that are similar to those produced by bariatric surgery but without its risks and limitations.

Methionine aminopeptidase 2 (MetAP2) inhibition reduces fat biosynthesis and stimulates fat oxidation and lipolysis [8]. MetAP2 inhibitors are a novel class of drugs that produce striking weight loss in animal and clinical studies [9–11]. Beloranib is a selective and potent MetAP2 inhibitor that significantly reduces food intake, body weight, fat content and adipocyte size in obese rodent models [9]. In an investigational 4-week trial in obese women, intravenous beloranib administration produced weight loss of up to 1 kg/week, as well as improvements in plasma lipids and reductions in hunger [10]. The aim of the present phase II study was to further investigate the efficacy, safety and tolerability of a beloranib

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suspension, administered subcutaneously, for 12 weeks in ~150 obese subjects.

Materials and Methods

Participants were enrolled at eight study sites in Australia beginning in August 2012, and the study was completed in May 2013. The institutional review boards at all study sites approved the protocol before study initiation. All participants provided written informed consent. The Safety Review Committee evaluated safety and tolerability periodically.

This was a double-blind study. Participants were randomized using Medidata Balance (New York, NY, USA), a central interactive web response system, in a 1 : 1 : 1 : 1 ratio to beloranib 0.6, 1.2 or 2.4 mg or placebo to achieve ~37 participants in each group. Randomization was stratified by study site, type 2 diabetes status and sex.

Blinding was maintained by study investigators, study staff and participants throughout the study, except by select pharmacy and study drug administrators who did not take part in any other aspects of the study and two Safety Review Committee members. Because of slight differences in coloration (the study drug was pale yellow and placebo was colourless) blinding was maintained by shielding the study drug from view during administration. Beloranib was prepared and administered twice weekly at the study site via subcutaneous injection. 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, which was mixed well before being administered.

Eligible participants were men and women aged 18–65 years, with a body weight of ≥50 kg, a body mass index of 30–50 kg/m^2, and were generally healthy. Female participants with type 2 diabetes (treated with diet/exercise and/or metformin) with glycated haemoglobin (HbA1c) 7–9% were included. Because of the mild and reversible spermatogenic suppression effects observed in rodents with high doses of beloranib *in vivo* (data on file at Zafgen Inc.), male participants were enrolled at a single designated site and were excluded from the 2.4 mg dose group. All participants (male and female) were surgically sterile, of non-childbearing potential, or agreed to use acceptable birth control during the study. Exclusion criteria included recent use of weight loss medications and any condition that would interfere with participation in the trial according to the investigator.

No dietary or exercise counselling was provided. All participants were followed for at least 5 days after the last dose of study drug and underwent study termination procedures (week 13).

Assessment of Study Outcomes

Safety and efficacy assessments were conducted on day 1 (baseline), and at weeks 1, 3, 7 and 12 (end of treatment) and the study exit visit. Sense of hunger and eating behaviour over the 2 days before selected study visits were assessed in the fasted state using an eight-question visual analogue scale (8Q-VAS) [12]. Sleep quality was recorded using the Pittsburgh Sleep Quality Index (PSQI), which assesses the duration of sleep, sleep disturbance, sleep latency, day dysfunction attributable to sleepiness, sleep deficiency, overall sleep quality and the need for medication to sleep, with scores ranging from 0 (best) to 3 (worst) [13]. Participants at selected sites underwent 24-h Holter and ambulatory blood pressure monitoring (ABPM) before the first dose of study drug and after week 12.

Bioimpedance measurements to assess body composition, as well as hip and waist circumference (measured directly), were taken at screening and end of treatment. Fasting blood samples were obtained before dosing at weeks 1, 2, 4, 8 and 13. HbA1c and insulin levels were measured in patients with type 2 diabetes.

Safety evaluations included assessment of treatment-emergent adverse events, physical examination, ECG, 24-h Holter and ABPM (at select study sites), vital signs, concomitant medications and laboratory variables.

Statistical Analysis

The primary efficacy measure was the change in weight from baseline to week 12. Secondary efficacy measures included the change in waist and hip circumference, body fat mass, laboratory measures [total cholesterol, HDL cholesterol, LDL cholesterol, triglycerides and high-sensitivity C-reactive protein (hsCRP)], and the 8Q-VAS questionnaire. Safety and tolerability data were also evaluated.

The sample size was selected to provide preliminary evaluation of subcutaneous administration of the selected doses of beloranib and was not powered for statistical comparisons. The change in weight from baseline to week 12 was analysed using an analysis of covariance (ANCOVA) model with treatment group and type 2 diabetes status as factors and baseline weight included as the covariate. The primary efficacy analysis compared the mean weight change in the 2.4 mg beloranib group and placebo using a two-sided test at the 5% significance level. Secondary analyses compared each of the beloranib treatment groups with placebo. Differences between each treatment group and placebo were estimated using least squares (LS) means and 95% confidence intervals (CIs) based on the mean square error from the ANCOVA.

The change from baseline to week 12 in efficacy laboratory variables, bioelectric impedance analysis, the 8Q-VAS, average heart rate (Holter and ABPM), and blood pressure (ABPM) were analysed using an ANCOVA model with treatment group as factors and baseline values as covariates. Adverse events were summarized by treatment group, system organ class and preferred term.

The safety population included all participants who received at least one dose of study drug or placebo (n = 147). The per protocol population included all participants who received at least 16 doses (67%) of study drug without any major protocol violations (n = 122).

The trial was registered with clinicaltrials.gov under the number NCT01666691.

Results

Of the 267 individuals screened, 147 were randomized to treatment or placebo (Figure S1). A total of 112 (70%) of participants completed the study. The primary reason for study

Table 1. Baseline characteristics.

	Placebo	Beloranib		
	n = 38	0.6 mg n = 37	1.2 mg n = 37	2.4 mg n = 35
Age, years	49.2 ± 10.5	47.9 ± 14.2	47.7 ± 12.2	48.2 ± 10.4
Female, n (%)	34 (89.5)	34 (91.9)	34 (91.9)	35 (100.0)
White race, n (%)	38 (100.0)	36 (97.3)	35 (94.6)	34 (97.1)
Weight, kg	101.7 ± 17.6	101.2 ± 15.2	100.1 ± 14.0	100.1 ± 14.4
Body mass index, kg/m^2	37.6 ± 4.4	37.7 ± 5.6	37.3 ± 4.5	38.3 ± 5.9
Type 2 diabetes, n (%)	2 (5.3)	1 (2.7)	2 (5.4)	2 (5.7)

Data are mean ± standard deviation unless otherwise specified.

discontinuation was adverse events, the most common of which were sleep-related, and these occurred most frequently in the beloranib 2.4 mg group.

Participant demographics and baseline characteristics were similar across treatment groups (Table 1). The majority of participants were white (98%) and female (94%), with a mean (range) age of 48.4 (18–65) years, weight of 100.9 (70.2–160.3) kg, and body mass index of 37.6 (29.8–53.7) kg/m^2.

The study included 7 (4.7%) patients with type 2 diabetes; 6 of whom were taking metformin, 1 was also taking another diabetes medication (dipeptidyl peptidase-4 inhibitor), and 1 was newly diagnosed (drug-naïve). All 7 patients with diabetes had elevated fasting glucose (mean 10.2 mmol/l) and HbA1c (mean 8.4%) concentrations at baseline.

There was a progressive decrease in mean body weight from baseline to the end of the study (weeks 12–13) in all beloranib treatment groups (Figure 1). The reduction in body weight at week 12 was statistically significant compared with placebo for all doses of beloranib ($p < 0.0001$; Table 2). The change in mean and percent body weight was dose-dependent and greatest with the highest dose of beloranib.

Consistent with weight loss in participants in the beloranib groups, there was a statistically significant reduction in waist and hip circumference, as well as body fat mass (Table 2). The greatest reductions occurred in the 2.4 mg beloranib treatment group. There was a limited reduction in lean body mass with 0.6 mg beloranib: mean [standard error (s.e.)] −0.8 (0.6) kg, 1.2 mg beloranib −0.5 (0.8) kg, and a slightly greater reduction with the highest dose of beloranib of −2.5 (0.6) kg versus no change with placebo [0.3 (0.4) kg].

Beloranib treatment was also associated with dose-related improvements in lipids. The highest dose, 2.4 mg beloranib, resulted in improvements in mean total cholesterol, LDL and HDL cholesterol and triglyceride levels, which were statistically significant compared with placebo (Table 2). Improvements in HDL cholesterol and triglycerides also occurred with 1.2 mg beloranib compared with placebo.

Compared with placebo, hsCRP level was significantly reduced in all beloranib treatment groups ($p < 0.001$ for all beloranib groups). Beloranib was also associated with reductions in leptin ($p < 0.001$ for all beloranib groups) and

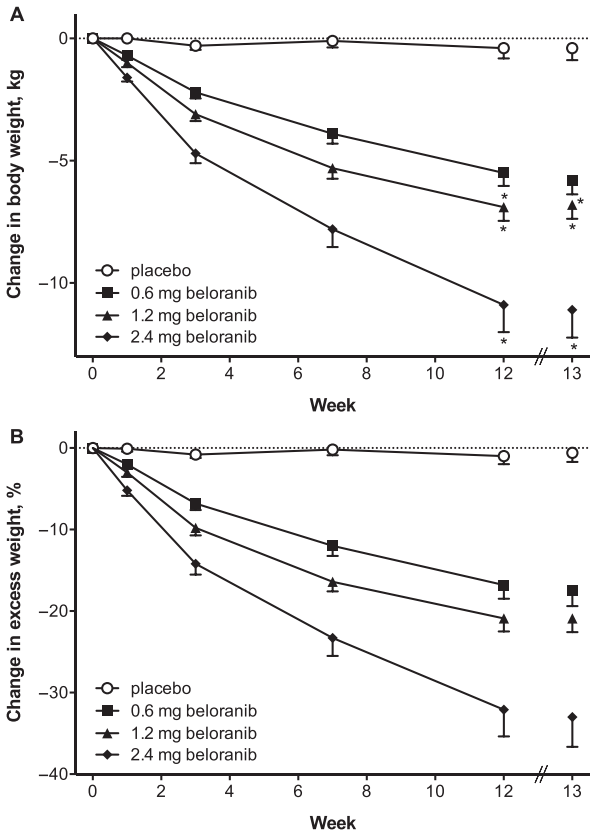

Figure 1. Change in body weight and excess weight. Change from baseline (week 0) in body weight (A) and excess weight (B). Data are mean (standard error of the mean) for observed values by visit for the per protocol population. *$p < 0.0001$ for change from baseline for beloranib vs. placebo at week 12 assessed by analysis of covariance.

increases in adiponectin ($p < 0.001$ for all beloranib groups) at week 12 compared with placebo. There was a trend for an increase in mean β-hydroxybutyrate from baseline to week 12 for beloranib [mean standard error (s.e.) for 0.6 mg beloranib: 0.04 (0.02) mmol/l; for 1.2 mg beloranib: 0.05 (0.4) mmol/l; and for 2.4 mg beloranib: 0.10 (0.05) mmol/l] compared with placebo [mean (s.d.) 0.00 (0.01) mmol/l]. There were no changes in glucose or free fatty acid levels.

Exploratory analyses indicate that beloranib was associated with significant improvements in 8Q-VAS measures, including participant-reported sensation of hunger and prospective food intake (Figure 2). There also was a trend for increased sensation of fullness and satiety.

The sample size was too small for a statistical analysis of beloranib effects on blood glucose in patients with type 2 diabetes (0.6 mg beloranib, n = 1; 1.2 mg beloranib, n = 2; 2.4 mg beloranib, n = 2; placebo, n = 2); however, exploratory analyses indicated a trend for reduced mean fasting blood glucose and HbA1c with beloranib. The mean (s.e.) changes in fasting blood glucose from baseline for all beloranib doses were −1.9 (1.4) mM (n = 4; p = 0.26) while placebo appeared unchanged 0.2 (0.2) mM (n = 2). Similarly, the mean (s.e.) change in HbA1c from baseline was −1.2 (0.3)% (n = 4; p = 0.017) with beloranib and no apparent change for placebo 0.1 (0.6)% (n = 2).

Table 2. Change in weight and cardiometabolic factors.

	Placebo	0.6 mg beloranib		1.2 mg beloranib		2.4 mg beloranib	
	n = 36	n = 35	p	n = 33	p	n = 18	p
Weight, kg							
Baseline	102.3 ± 17.9	102.6 ± 15.2		102.6 ± 14.2		102.2 ± 11.6	
Week 12 absolute change	−0.4 ± 0.4	−5.5 ± 0.5		−6.9 ± 0.6		−10.9 ± 1.1	
LS mean (95% CI) difference		−5.0 (−6.4, −3.6)	<0.001	−6.4 (−7.9, −5.0)	<0.001	−10.5 (−12.3, −8.6)	<0.001
Week 12% change	−0.3 ± 0.4	−5.3 ± 0.5		−6.7 ± 0.5		−10.6 ± 1.0	
LS mean (95% CI) difference		−5.0 (−6.3, −3.7)	<0.001	−6.3 (−7.6, −5.0)	<0.001	−10.3 (−12.0, −8.6)	<0.001
Waist circumference*, cm							
Baseline	113.5 ± 13.0	111.8 ± 13.3		109.0 ± 7.8		117.1 ± 11.6	
Week 12 absolute change	−0.5 ± 0.6	−4.9 ± 0.8		−3.8 ± 1.1		−10.7 ± 1.8	
LS mean (95% CI) difference		−4.5 (−6.8, −2.3)	<0.001	−4.0 (−6.4, −1.6)	<0.01	−9.3 (12.3, −6.3)	<0.001
Hip circumference*, cm							
Baseline	124.2 ± 12.4	125.5 ± 12.5		122.3 ± 12.3		128.4 ± 12.3	
Week 12 absolute change	−1.4 ± 0.8	−6.2 ± 1.1		−4.6 ± 1.3		−11.8 ± 1.9	
LS mean (95% CI) difference		−4.5 (−7.4, −1.7)	<0.01	−3.4 (−6.4, −0.4)	0.027	−10.0 (−13.8, −6.2)	<0.001
Body fat mass*, kg							
Baseline	48.0 ± 10.8	46.3 ± 11.7		45.8 ± 10.5		48.8 ± 8.1	
Week 12% change	−2.0 ± 1.2	−8.9 ± 1.7		−14.4 ± 2.3		−18.1 ± 2.0	
LS mean (95% CI) difference		−6.7 (−11.3, −2.1)	<0.01	−12.1 (−16.9, −7.4)	<0.001	−16.1 (−22.1, −10.1)	<0.001
Total cholesterol, mmol/l							
Baseline	5.7 ± 1.1	5.1 ± 1.0		5.5 ± 1.0		5.3 ± 1.2	
Week 12 absolute change	−0.4 ± 0.1	−0.3 ± 0.1		−0.5 ± 0.1		−1.0 ± 0.2	
LS mean (95% CI) difference		−0.1 (−0.4, 0.3)	0.687	−0.2 (−0.6, 0.1)	0.160	−0.8 (−1.2, −0.3)	<0.001
LDL cholesterol, mmol/l							
Baseline	3.5 ± 0.9	3.0 ± 0.9		3.4 ± 0.9		3.3 ± 1.1	
Week 12 absolute change	−0.3 ± 0.1	−0.3 ± 0.1		−0.5 ± 0.1		−1.0 ± 0.2	
LS mean (95% CI) difference		−0.2 (−0.5, 0.2)	0.318	−0.3 (−0.6, 0.0)	0.077	−0.8 (−1.2, −0.4)	<0.001
HDL cholesterol, mmol/l							
Baseline	1.4 ± 0.4	1.5 ± 0.4		1.4 ± 0.3		1.3 ± 0.3	
Week 12 absolute change	0.0 ± 0.0	0.1 ± 0.0		0.1 ± 0.0		0.2 ± 0.1	
LS mean (95% CI) difference		0.1 (0.0, 0.2)	0.081	0.1 (0.0, 0.2)	0.038	0.1 (0.0, 0.3)	0.045
Triglycerides, mmol/l							
Baseline	1.8 ± 1.0	1.4 ± 0.6		1.5 ± 0.8		1.4 ± 0.6	
Week 12 absolute change	−0.3 ± 0.1	−0.2 ± 0.1		−0.4 ± 0.1		−0.4 ± 0.2	
LS mean (95% CI) difference		−0.2 (−0.4, 0.0)	0.060	−0.3 (−0.4, −0.1)	0.012	−0.4 (−0.6, −0.1)	<0.01
hsCRP, mg/l							
Baseline	6.7 ± 7.1	5.8 ± 5.9		5.3 ± 6.2		6.6 ± 6.2	
Week 12 absolute change	1.0 ± 0.9	−2.5 ± 0.8		−2.3 ± 0.7		−1.9 ± 0.5	
LS mean (95% CI) difference		−4.0 (−5.6, −2.4)	<0.001	−4.1 (−5.7, −2.4)	<0.001	−3.7 (−5.8, −1.7)	<0.001
Systolic blood pressure*, mmHg							
Baseline	121.5 ± 7.4	124.6 ± 8.0		125.8 ± 8.6		128.4 ± 15.4	
Week 12 absolute change	−1.4 ± 1.7	−6.3 ± 1.7		−6.3 ± 2.1		−13.6 ± 2.6	
LS mean (95% CI) difference		−4.6 (−9.6, 0.3)	0.064	−4.8 (−10.1, 0.5)	0.077	−11.4 (−17.7, −5.2)	<0.001
Diastolic blood pressure*, mmHg							
Baseline	70.8 ± 8.4	71.4 ± 6.4		73.1 ± 6.5		70.4 ± 8.6	
Week 12 absolute change	−1.3 ± 1.0	−1.8 ± 0.9		−2.0 ± 1.2		−4.1 ± 1.6	
LS mean (95% CI) difference		−0.5 (−3.2, 2.2)	0.706	−0.9 (−3.9, 2.0)	0.525	−2.3 (−5.7, 1.1)	0.179
Pulse rate*, bpm							
Baseline	74.8 ± 8.6	77.5 ± 9.6		75.0 ± 8.2		77.2 ± 3.7	
Week 12 absolute change	0.3 ± 1.3	−1.8 ± 1.1		1.0 ± 1.2		0.3 ± 1.1	
LS mean (95% CI) difference		−2.2 (−5.2, 0.8)	0.150	0.6 (−2.7, 3.9)	0.725	−0.3 (−4.1, 3.4)	0.853
Leptin, µg/l							
Baseline	54.9 ± 27.9	53.9 ± 27.4		52.9 ± 28.4		51.5 ± 21.9	
Week 12 absolute change	6.9 ± 4.1	−21.2 ± 2.5		−25.2 ± 3.2		−26.6 ± 4.1	
LS mean (95% CI) difference		−28.0 (−35.9, −20.0)	<0.001	−32.1 (−40.2, −24.0)	<0.001	−35.4 (−45.6, −25.2)	<0.001
Adiponectin, mg/l							
Baseline	4.0 ± 2.4	4.6 ± 2.6		4.0 ± 2.2		3.7 ± 1.7	
Week 12 absolute change	0.1 ± 0.3	2.2 ± 0.4		2.7 ± 0.3		3.2 ± 0.5	
LS mean (95% CI) difference		1.9 (1.0, 2.8)	<0.001	2.6 (1.7, 3.5)	<0.001	3.2 (2.1, 4.3)	<0.001

Baseline (day 1) data are mean ± standard deviation. Week 12 data are mean ± standard error for change from baseline (day 1) to week 12 for the per protocol population. Treatment effect and p values represent analysis of covariance for LS mean change from baseline for beloranib versus placebo. SI conversion factors: cholesterol, 0.0259; triglycerides, 0.0113. hsCRP, high-sensitivity C-reactive protein; LS, least squares.

*Body fat mass (bioimpedance), waist, hip, and ambulatory blood pressure monitoring (ABPM) measurements were obtained at screening (baseline) and week 12. ABPM per protocol population: 0.6 mg beloranib n = 15; 1.2 mg beloranib n = 11; 2.4 mg beloranib n = 7; placebo n = 14.

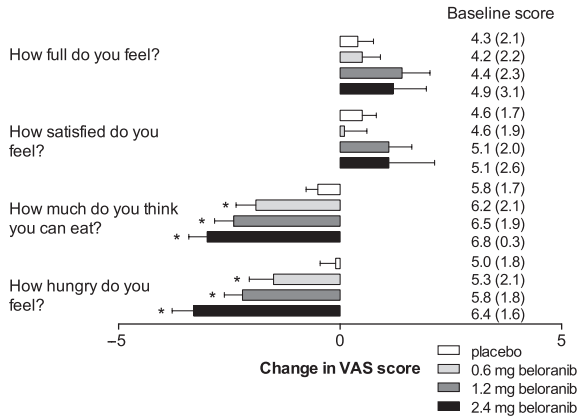

Figure 2. Change from baseline in appetite and eating behaviour according to eight-question visual analogue scale (VAS) scores. Absolute change in appetite and eating behaviour according to eight-question VAS scores. Data are mean (standard error of the mean) for the change in score from baseline (day 1) to week 12 for the per protocol population. Baseline score numbers are mean (standard deviation). *$p < 0.05$ for change from baseline for beloranib versus placebo at week 12, assessed by analysis of covariance.

There were no deaths or serious adverse events considered by the investigators to be related to the study drug. There were no clinically significant changes in laboratory findings, ECG measurements or vital signs. Semen analysis and sex hormones (follicle-stimulating hormone, luteinizing hormone, testosterone, sex hormone-binding globulin and inhibin B) were assessed in male participants during the study and at 3 months after the study, and no differences were observed in patients who received beloranib treatment.

A total of 24 (16%) participants withdrew early from the study because of adverse events. The rate of study withdrawal because of adverse events was highest in the 2.4 mg beloranib group (17/35 participants). There were nine sleep-related adverse events (mostly insomnia) that led to withdrawal from the study. These were associated with higher doses of beloranib: 1.2 mg beloranib (1/37 participants) and 2.4 mg beloranib (8/35 participants).

A similar number of participants reported adverse events across treatment groups (Table 3). Injection site-related adverse events were mostly mild and occurred at a similar incidence rate among all the beloranib and placebo groups. Sleep-related and gastrointestinal adverse events were more frequent with the 2.4 mg dose of beloranib than placebo. Adverse events were generally mild to moderate in severity and transient in nature.

An increase in PSQI total scores occurred early in the study in all beloranib treatment groups and was most prominent in the 2.4 mg beloranib group. There was an incremental increase in PSQI total scores with the highest doses of beloranib that peaked at week 3 [mean (s.d.) score change from baseline: 0.6 mg beloranib, 0.7 (2.8); 1.2 mg beloranib, 2.8 (3.8); 2.4 mg beloranib, 4.5 (4.6); and placebo −0.6 (2.2)]. Mean PSQI scores returned to baseline by weeks 8–13. The mean (range) week 12 scores were generally similar for 0.6 mg beloranib [−0.1 (−6 to 6)], 1.2 mg beloranib [0.4 (−3 to 3)] and placebo [−0.3 (−8 to 7)], with a small increase in the 2.4 mg beloranib group [1.6 (−3 to 6)]. A similar trend occurred in the PSQI category indicating increased sleep latency. There was no change in PSQI scores with placebo.

Table 3. Number of participants reporting adverse events with incidence ≥10% with any beloranib group versus placebo.

	Placebo	Beloranib		
		0.6 mg	1.2 mg	2.4 mg
	n = 38	n = 37	n = 37	n = 35
Gastrointestinal disorders				
Diarrhoea	6 (15.8)	5 (13.5)	5 (13.5)	11 (31.4)
Dry mouth	0	2 (5.4)	1 (2.7)	4 (11.4)
Nausea	10 (26.3)	8 (21.6)	11 (29.7)	16 (45.7)
Vomiting	4 (10.5)	3 (8.1)	1 (2.7)	8 (22.9)
General disorders and administrative site conditions				
Injection site pruritus	1 (2.6)	4 (10.8)	3 (8.1)	5 (14.3)
Injection site reaction	3 (7.9)	1 (2.7)	3 (8.1)	7 (20.0)
Nervous system disorders				
Dizziness	2 (5.3)	2 (5.4)	2 (5.4)	9 (25.7)
Headache	15 (39.5)	18 (48.6)	12 (32.4)	10 (28.6)
Psychiatric disorders				
Abnormal dreams	3 (7.9)	10 (27.0)	6 (16.2)	6 (17.1)
Depression	0	2 (5.4)	4 (10.8)	0
Insomnia	8 (21.1)	8 (21.6)	11 (29.7)	17 (48.6)
Sleep disorder (other)	6 (15.8)	2 (5.4)	7 (18.9)	10 (28.6)
Other				
Cough	0	1 (2.7)	2 (5.4)	4 (11.4)
Decreased appetite	7 (18.4)	11 (29.7)	12 (32.4)	9 (25.7)
Hot flush	0	4 (10.8)	2 (5.4)	8 (22.9)
Pruritis	1 (2.6)	4 (10.8)	0	0

Data are n (%) for the safety population (participants who received at least one dose of study drug). Adverse events are listed using the Medical Dictionary for Regulatory Activities (or MedDRA) preferred terms and grouped by System Organ Class.

There were no treatment differences in heart rate as measured by 24-h Holter monitoring scores or ABPM (Table 2, Figure S2). There was a decrease in mean systolic blood pressure in all beloranib groups as measured by ABPM, and the reduction was statistically significant in the group that received the highest dose of beloranib (2.4 mg; $p = 0.0006$).

Discussion

In the present phase II study of beloranib, we observed a dose-dependent weight loss that continued for the duration of the 12-week study. The reduction in body weight was rapid and progressed through to week 12, suggesting that further weight reduction may occur with continued treatment. Weight loss with beloranib was associated with dose-dependent reductions in body mass as well as a reduction in waist and hip circumference. Consistent with weight loss, beloranib was also associated with clinically and statistically significant improvements in many cardiometabolic risk factors, including LDL and HDL cholesterol, triglyceride and hsCRP levels, and systolic blood pressure. Notably, there were no deleterious effects on any measured cardiovascular risk factors.

The 0.6 and 1.2 mg doses of beloranib were generally well tolerated and adverse events were mostly mild and transient; however, the highest 2.4 mg dose resulted in more sleep-related

early study withdrawals and adverse events that were primarily attributable to increased sleep latency. Consistent with previous experience [10], the most common adverse events with beloranib were sleep-related or gastrointestinal in nature and were dose-dependent. The discontinuation rate was greater in the group of participants who received the highest dose of beloranib (2.4 mg), the primary reason for which was sleep disturbance; however, for the participants in this treatment group who remained in the study, the incidence of sleep disturbance (measured by adverse event reporting and the PSQI) decreased to baseline incidence by weeks 8–12.

Weight loss with beloranib is attributed to altered lipid biosynthesis and utilization and decreased caloric intake. MetAP2 inhibition is hypothesized to reduce lipid and cholesterol biosynthesis and increase fatty acid mobilization and lipid utilization [14,15]. This is consistent with the observed increase in adiponectin (a catabolic hormone) and β-hydroxybutyrate (a product of free fatty acid metabolism) in beloranib-treated participants compared with placebo [16]. Reduced caloric intake also probably contributed to weight loss, as the beloranib-treated participants reported a marked reduction in hunger and prospective food intake and were more likely to report adverse events of decreased appetite. The mechanism of sleep disturbances with beloranib is unknown but may suggest a state of transient hyperarousal [17] or may be caused by acute and significant weight loss.

The rapid reduction in body weight observed with beloranib is consistent with previous observations [10]. Although weight loss of ~1 kg/week occurred with the highest dose of 2.4 mg, clinically meaningful weight loss of 5.5 and 6.9 kg (5.3 and 6.7%) occurred at week 12 with the lower doses of 0.6 and 1.2 mg, which were better tolerated. For all doses, body weight continued to decrease throughout the 12-week study, suggesting that further weight loss may be possible with continued administration.

Historically, most obesity medications produce mean weight loss of ≤5%, although a few cause greater weight loss [6,18]. The combination therapy, phentermine/topiramate, produces the greatest mean weight loss of medications currently approved by the US Food and Drug Administration for long-term weight management [19,20]. Similarly to beloranib, weight loss with phentermine/topiramate is dose-dependent, although the highest dose of phentermin/topiramate produces mean weight loss of <8% at 12 weeks of treatment [19].

The only other treatment that produces greater and more rapid mean weight loss than obesity medications is bariatric surgery (which requires patients to adhere to a very low-calorie liquid diet for 2–4 weeks after surgery) [21]. Bariatric surgery, which includes gastric bypass, sleeve gastrectomy and adjustable gastric banding, is the only obesity treatment that causes at least 15% weight loss over >1 year of follow-up [22–24]. Bariatric surgery also improves blood glucose, lipids and blood pressure, and helps prevent, improve or resolve obesity-related conditions and diseases including type 2 diabetes, cardiovascular disease and some cancers, and reduces mortality [22–27]. Although the safety of bariatric surgery continues to improve as laparoscopic procedures become more common, bariatric surgery is still associated with significant complications and a peri-operative mortality rate of ~0.1–0.3% [22,28,29].

In the present study, weight loss and improvements in obesity-related cardiometabolic risk factors were observed after 12 weeks of beloranib treatment and in the absence of any diet, exercise or behavioural counselling. In addition, beloranib was associated with a dose-dependent reduction in sense of hunger and prospective food intake. Although this study was not powered to allow for statistical comparisons between doses, these preliminary results indicate that beloranib produces clinically significant weight loss in the absence of any dietary intervention and without the risk of surgery. Whether weight loss with beloranib is similar to currently approved obesity treatments such as bariatric surgery remains to be determined.

The present 12-week study was designed to provide preliminary data to inform the design of future studies and included a relatively small number of participants consisting primarily of white women without type 2 diabetes. Additional longer studies are necessary to confirm the efficacy and safety of beloranib for weight loss and change in cardiometabolic risk factors in a larger and more diverse patient population, as well as in patients with obesity-related diseases such as type 2 diabetes. Additionally, although the 2.4 mg beloranib appeared to be safe, it was not well tolerated in some participants. It remains to be seen whether dose-titration during the first few weeks of administration will improve the tolerability of this higher dose of beloranib.

In this phase II study, beloranib produced statistically significant and clinically meaningful weight loss in obese participants for up to 12 weeks in the absence of any dietary or exercise intervention. Weight loss was associated with a corresponding reduction in body fat mass, and statistically significant improvements in cardiometabolic risk factors, including waist circumference, lipids and blood pressure, were observed compared with placebo. Beloranib appeared safe and generally well tolerated at doses <2.4 mg, with sleep disturbance and gastrointestinal adverse events occurring more frequently with the highest dose of beloranib compared with placebo. Overall, adverse events were generally mild to moderate and resolved over the course of the study. These results support further investigation of twice weekly subcutaneous injection with beloranib for weight loss as a potential alternative to bariatric interventions.

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Conflict of Interest

J. K., S. L., F. d. L., J. M., J. P., S. S., and B. S. have no conflict of interest. D. K. and J. V. are employees of Zafgen, Inc. T. H. is an employee of, holds stock in, and is a director at Zafgen, Inc.

D. K., J. K., S. L., F. d. L., J. M., F. P., S. S. and B. S. either participated in study conception and design and/or data collection. D. K., J. K., B. S., J. P., S. L. and T. H. participated in data analysis. D. K., J. K., S. L., F. d. L., J. M., F. P., S. S., B. S., T. H., and J. V.

contributed to drafting of the manuscript or critical revision for important intellectual content. All authors approved the final version to be published. D. K. and T. H. had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

Supporting Information

Additional Supporting Information may be found in the online version of this article:

Figure S1. Patient enrolment and outcomes.

Figure S2. Mean blood pressure at week 12.

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