

# Dose Ratio Optimization with Zonisamide SR and Bupropion SR for Weight Loss

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## ABSTRACT

**Background:** Zonisamide with bupropion has been shown to cause weight loss but the optimal dose ratio is unknown. A novel sustained-release (SR) zonisamide was tested in combination with bupropion SR in six different dose ratios vs. placebo.

**Methods:** A double-blind, placebo-controlled trial randomized 623 healthy obese subjects equally to one of the seven treatment groups: Z120mg/B280mg, Z120/B360, Z240/B280, Z240/B360, Z360/B280, Z360/B360, or placebo. A minimalist ancillary therapy comprised of diet instruction as well as advice on behavior modification and exercise was included. Dosage titration occurred during Weeks 1 through 8, and maintenance dosage was administered from Weeks 9 through 24. Data collected during this 24-week period were included in the primary analysis. An additional 24 weeks of open label treatment continued per protocol.

**Results:** The results of the primary analysis on the percent change from baseline total body weight at the Week 24 visit are summarized in Figure 1. All active treatment groups showed statistically significant weight loss in comparison with placebo (P <0.001), while percentage weight loss at the two highest dosages (Z360/B280 and Z360/B360) were statistically significantly superior to that observed with the Z120/B280, the lowest active dosage tested.

**Conclusions:** The extent of weight loss with the combination treatment increased with higher ZB dosage. Five of the six active ZB groups (including the highest Z360/B360) exhibited a rate of discontinuation rate due to an adverse event comparable to that seen with placebo.

## INTRODUCTION

Empatic™ is a combination of zonisamide SR (Z) with bupropion SR (B) in Phase II development for weight loss. This combination approach is designed to promote hypothalamic proopiomelanocortin (POMC) activity (appetite reduction and stimulation of energy expenditure) while blocking a parallel compensatory pathway (Agouti-related Peptide or AgRP).

## OBJECTIVES

**Primary:** To compare the mean percentage and absolute change from baseline to Week 24 in total body weight of multiple regimens of the ZB combination in the treatment of uncomplicated obesity.

**Secondary:** (1) To evaluate numbers and proportions of subjects losing at least 5% of baseline body weight at 24 weeks; (2) To evaluate mean changes in obesity-associated cardiovascular risk factors at 24 weeks and; (3) To assess the safety and tolerability of combination therapy compared with placebo and identify an optimal regimen(s) to use in Phase III trials.

## METHODS

A double-blind, placebo-controlled multi-center trial randomized 623 healthy, non-diabetic, obese subjects to either: Z120/B280, Z120/B360, Z240/B280, Z240/B360, Z360/B280, Z360/B360, or placebo. At baseline, 12 and 24 weeks, subjects were provided an exercise prescription and a hypocaloric diet representing a deficit of 500 kcal/day. Four hundred eighty subjects completed 24 weeks of treatment.

## STATISTICAL METHODS

The primary efficacy endpoint of percentage weight loss was analyzed using the adjusted least squares from an ANCOVA model that included the percentage weight loss from baseline to Week 24 as the dependent variable, treatment group as a fixed effect and the baseline body weight as a covariate. The secondary endpoint of proportion of responders was analyzed using a logistic regression model with proportion of subjects as the dependent variable, treatment as a fixed effect and baseline body weight as a covariate. Dunnett's adjustment was used for ZB treatment comparisons with placebo and a Tukey's adjustment was used for each pairwise ZB treatment comparisons. Adverse events (AEs) were summarized using descriptive statistics and differences in discontinuation rates due to AEs were analyzed using a Chi-square test.

Missing data for efficacy endpoints was imputed using the last observation carried forward (LOCF) method.

## RESULTS

Statistically significant greater weight loss was observed across each of the six ZB arms compared with placebo on

the primary outcome measure of percent change in body weight between baseline and Week 24 for the Full Analysis Set (also called intent-to-treat). There is linear trend across the six combination dosage groups for a greater mean percent weight loss between baseline and Week 24 as doses were increased.

The incidence of treatment-emergent AEs leading to discontinuation across five of the six dosage groups (including the highest Z360/B360) was not statistically significantly different from that seen with placebo. However, the rates of discontinuation attributed to an AE were somewhat more common in the higher dose pairings. Among the most frequent adverse events were: headache, nausea, insomnia, and dry mouth. Of note, the incidence of AEs leading to early discontinuation with the zonisamide SR formulation was much lower than those seen in study OT-102, conducted with immediate release zonisamide (14.0% pooled rate with 16.9% at the highest dose versus 37% seen in the previous study).<sup>1</sup> The overall all-cause discontinuation rate was 22.3%. No serious adverse event (SAE) was attributed by the investigators to any of the six investigational treatments.

Figure 1: Empatic™ Efficacy at Week 24

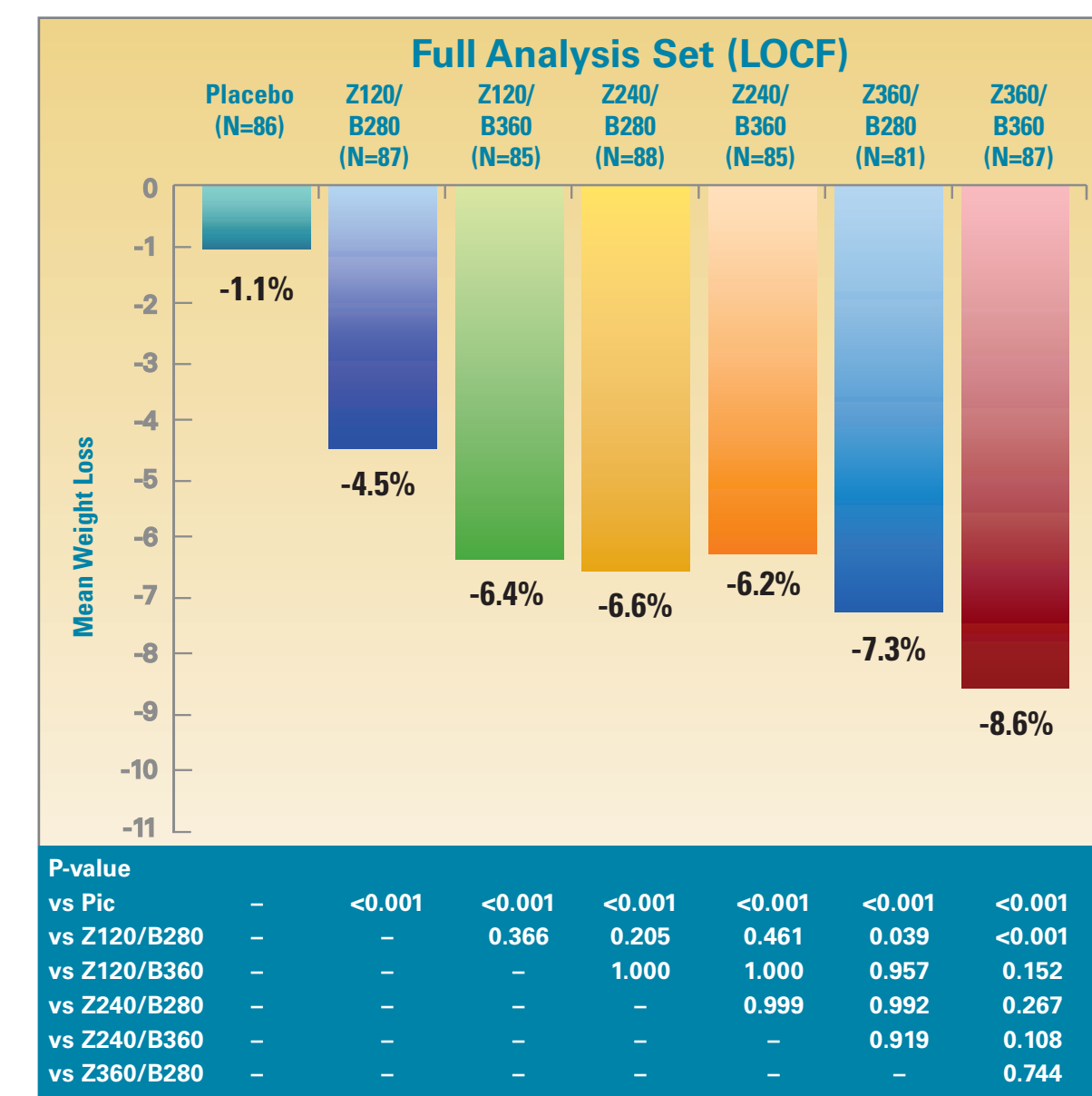


Figure 2: Empatic™ 5% Responder Analysis Full Analysis Set

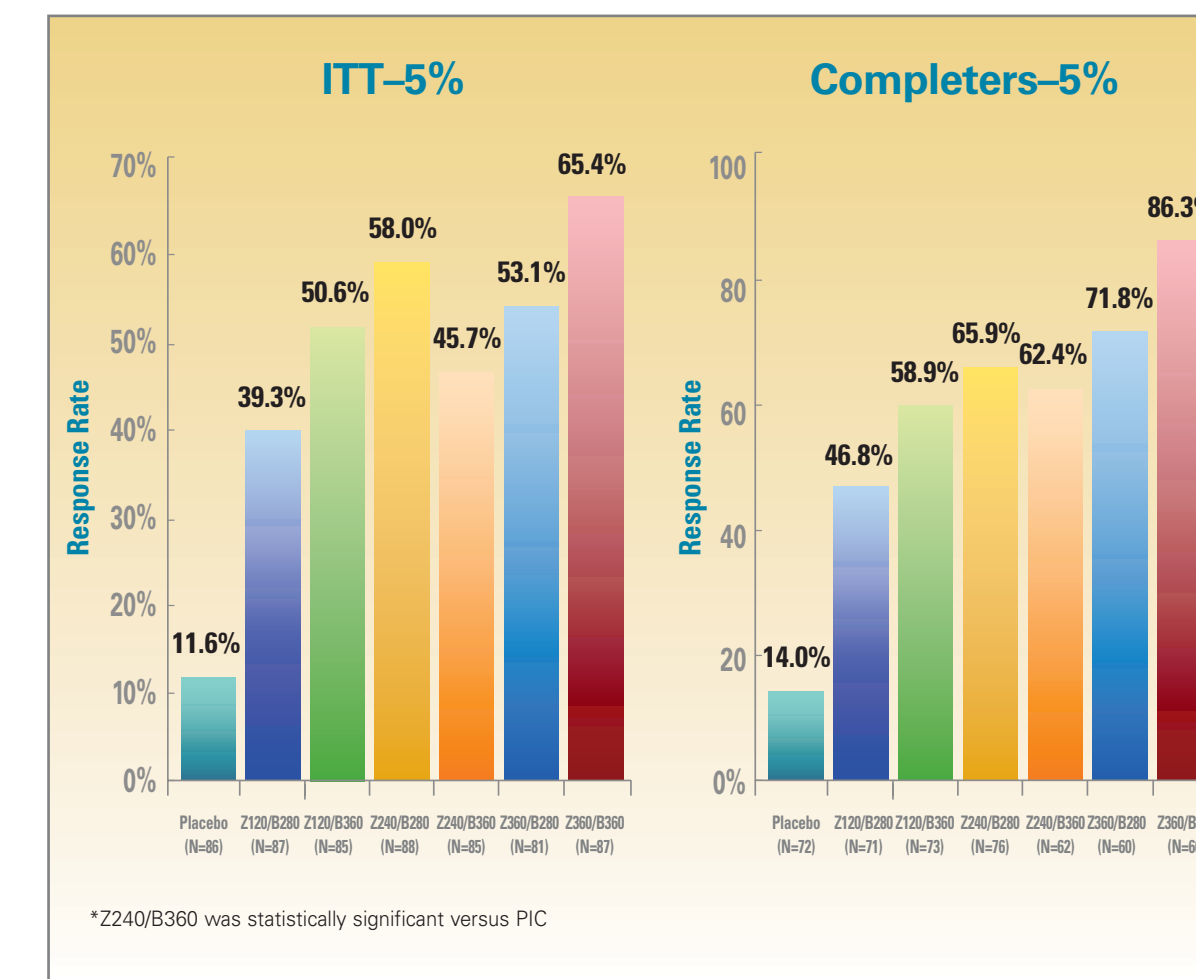


Figure 3: Empatic™ Mean Weight Loss over 24 Weeks (Observed Cases)

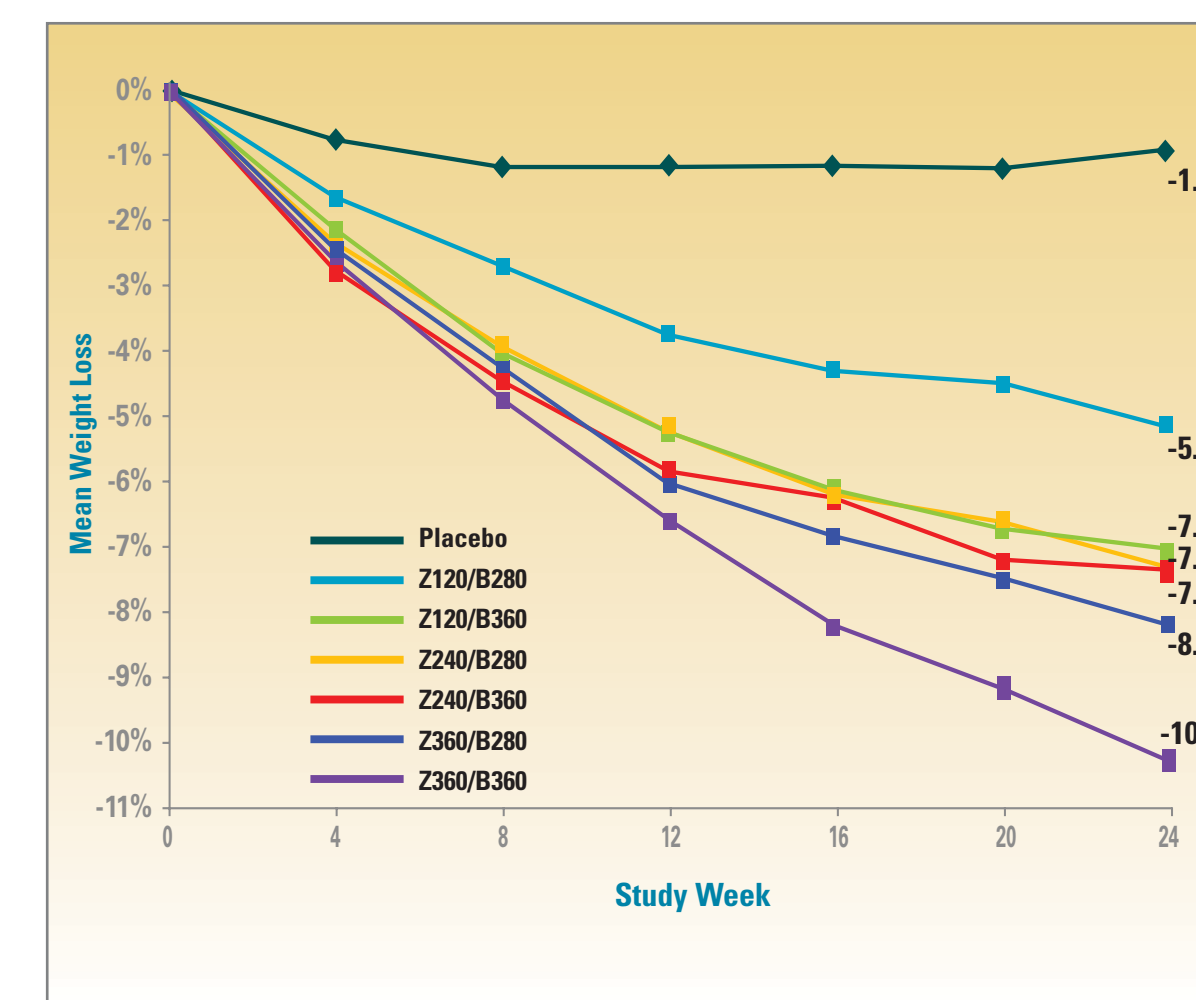


Table 1: Empatic™ Discontinuation Due to AE

	Treatment Group						
	Plc	Z120/B280	Z120/B360	Z240/B280	Z240/B360	Z360/B280	Z360/B360
Number Of Subjects	88	87	87	90	87	83	89
Discontinuation due to AE	9.1%	10.3%	9.2%	10.0%	20.7%	16.9%	16.9%
Anxiety	1.1%	0%	1.1%	1.1%	2.3%	0%	3.4%
Dizziness	1.1%	0%	0%	0%	2.3%	2.4%	0%
Headache	0%	2.3%	0%	1.1%	4.6%	1.2%	2.2%
Insomnia	0%	1.1%	1.1%	1.1%	2.3%	2.4%	3.4%
Irritability	0%	0%	0%	0%	3.4%	1.2%	0%
Nausea	2.3%	3.4%	1.1%	0%	3.4%	2.4%	4.5%

## SUMMARY and CONCLUSIONS

All six combinations of zonisamide SR and bupropion SR were more effective than placebo across all treatment arms for the primary outcome measure of percentage change between baseline and Week 24, as well as, for secondary categorical weight loss response (≥5%, ≥10%). Weight loss associated with the two highest dose combinations Z360/B280 and Z360/B360 was particularly robust and statistically superior to that of the lowest dose combination (Z120/B280). Consistent with the proposed mechanism of action of the ZB combination, all six dosage groups showed evidence of continuing downward weight loss trajectories at Week 24. Dry mouth, insomnia, headache, and nausea were the most commonly seen AEs. Five of the six active ZB groups (including the highest Z360/B360) exhibited a discontinuation rate due to an AE comparable to that seen with placebo. One or more ZB dose ratios will be compared to the individual monotherapies and placebo in an upcoming weight loss trial.

## REFERENCES

<sup>1</sup>Greenway F, Anderson J, Atkinson R, Fujioka K, Gadde KM, Gupta A, O'Neil PM, Schumacher D, Smith D, Whitehouse MJ, Cruickshank S, Guttadauria M. Bupropion and Zonisamide for the treatment of obesity. Obesity 14(suppl.):A17, 2006.