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Zonisamide for Weight Reduction in Obese Adults A 1-Year Randomized Controlled Trial

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SUMMARY

Background—Obese individuals who have failed to achieve adequate weight loss with lifestyle changes have limited non-surgical therapeutic options. We evaluated the efficacy and tolerability of zonisamide, an antiepileptic drug, for enhancing weight loss in obese patients receiving diet and lifestyle guidance.

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Conflict of Interest Disclosures: All authors have completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. DrGadde reported receiving grants from Bristol Myers Squibb, Forest Laboratories, National Institute of Diabetes and Digestive and Kidney Diseases, Pfizer and Vivus in the past 36 months. He has been awarded several patents in the name of his institution for use of zonisamide as monotherapy and in combination with other drugs for treatment of obesity as well as weight gain associated with psychotropic drugs; these patents have been licensed to Orexigen Therapeutics by his institution. Consequent to the licensing agreement, Dr Gadde owns equity in Orexigen, which is developing zonisamide and bupropion combination therapy for obesity, based on his patents. However, to the best of DrGadde's knowledge, no commercial entity has announced plans to develop zonisamide monotherapy for obesity or other applications claimed in his patents. Dr Allison has had financial interests with Arena Pharmaceuticals, EnteroMedics, Frontiers Foundation, Federal Trade Commission, Jason Pharmaceuticals, Kraft Foods, Mead Johnson Nutrition, Mead Johnson & Company, Medifast, Orexigen Therapeutics, Sage Publications, University of Arizona, University of Wisconsin, Vivus, Wolters Kluwer Pharma Solutions, and Paul, Pfizer, Weiss, Wharton and Garrison LLP. Dr Bray reported that he has been a consultant to Abbott Laboratories and Takeda Global Research Institute; is an advisor to Medifast, Herbalife, and Global Direction in Medicine; and has received royalties for the *Handbook of Obesity*. No other authors provided any financial disclosures.

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Methods—This was a 1-year randomized, double-blind, placebo-controlled trial conducted between January 2006 and September 2011 at Duke University Medical Center. Patients were 225 obese (mean [SD] body mass index 37.6 [4.9]) women (134 [59.6%]) and men (91 [40.4%]) without diabetes. Interventions were daily dosing with placebo (n=74), zonisamide 200 mg (n=76), orzonisamide 400 mg (n=75), in addition to diet and lifestyle counseling by a dietitian for 1 year. Primary outcome was change in body weight at 1-year.

Results—Of the 225 randomized patients, 218 (97%) provided 1-year follow-up assessments. Change(least-squares mean) in body weight was -4.0 kg (−3.7%; 95% CI, −5.8 kg to −2.3 kg) for placebo, −4.4 kg (−3.9%; −6.1 to −2.6, *P*=.79 *vs* placebo) for zonisamide 200 mg, and −7.3 kg (−6.8%; −9.0 to −5.6, *P*=.009 *vs* placebo) for zonisamide 400 mg. In the categorical analysis,23 (31%) on placebo, 26 (34%; *P*=.71) on zonisamide 200 mg, and 41 (55%; *P*=.007) onzonisamide 400 mg achieved ≥5% weight loss; for ≥10% weight loss, the corresponding numbers were 6 (8%), 17 (22%; *P*=.022), and 24 (32%; *P*=.001). Gastrointestinal, nervous system and psychiatric adverse events occurred at a higher incidence with zonisamide than with placebo.

Conclusion—Zonisamide 400 mg/d moderately enhanced weight loss achieved with diet and lifestyle counseling, but had a high incidence of adverse events.

Keywords

randomized controlled trial; obesity; weight loss; antiobesity drugs; weight loss drugs; zonisamide; antiepileptic drugs

INTRODUCTION

Diet and exercise are often recommended as first-line treatment for obese patients, but long-term results are not impressive.[1,2] Although intensive lifestyle interventions of the type tested in the Diabetes Prevention Program[3] and Look AHEAD[4] trials have demonstrated approximately 6–8% weight loss over a year, these are difficult to implement in primary care settings and third-party payers rarely reimburse.[5] Orlistat and lorcaserin, the only monotherapy drugs currently approved for long-term management of obesity achieve about 3 kg weight loss relative to placebo after 1 year.[6,7] Thus, for obese patients who fail to achieve adequate benefit from lifestyle therapies, there is a dire need for additional non-surgical therapeutic options. Zonisamide is an antiepileptic drug that demonstrated weight loss efficacy in obese adults(−5.9 kg vs −0.9 kg) in a 16-week trial with further weight loss in the additional 16-week extension phase.[8] In that trial, zonisamide dose was titrated to 400 mg/d for all patients by week 7, and to 600 mg/d for patients not losing at least 5% weight. A subsequent review of the data showed that patients with inadequate weight loss at 400 mg had no appreciable additional weight loss at 600 mg. However, since the dose was raised to 400 mg regardless of the degree of weight loss, it was not known whether a lower dose would have been just as effective over longer duration. Furthermore, placebo treatment led to weight loss of only 0.9 kg suggesting that the lifestyle intervention in that trial was not very effective. This trial was designed to answer two questions: 1) Does addition of zonisamide400 mg/d augment weight loss achievable with a fair quality lifestyle intervention that could be administered in a primary care setting? 2) Is a zonisamide lower dose (200 mg/d) also efficacious?

This report describes a long-term randomized controlled trial testing the efficacy and tolerability of two zonisamide doses (200 mg and 400 mg) in obese adults, also receiving diet and lifestyle counseling.

METHODS

Study Design and Randomization

This was a randomized, double-blind, parallel-group, three-arm trial, conducted between January 2006 and September 2011 at Duke University Medical Center, Durham, North Carolina. Eligible patients were randomly assigned in a 1:1:1 ratio to receive once-daily treatment with placebo, zonisamide 200 mg, or zonisamide 400 mg for 1-year. Additionally, all patients received diet and lifestyle counseling.

Randomization, facilitated by a pseudo-number generator, with a permuted block size of nine and stratification for gender, was implemented by the medical center's Investigational Drug Service (IDS). Study drugs were dispensed by IDS as identically appearing capsules, and investigators and patients remained masked to treatment assignment until all patient visits and data entry were completed.

Patients

All patients gave written informed consent. Duke University's institutional review board approved the protocol.

Eligible patients were 18 to 65 years old with body-mass index (BMI) ranging from 30 to 50 kg/m^2. Key exclusion criteria were diabetes mellitus, serious or unstable medical illness; renal calculi history; diabetes mellitus; current major depression, alcohol or drug abuse; score ≥11 on depression subscale of the Hospital Anxiety and Depression Scale (HADS);[9] psychosis or bipolar disorder or severe personality disorders; suicidality; antipsychotics or mood stabilizers; other psychotropic medications if taken for less than 3 months; and taking zonisamide or other antiepileptic drugs (see eMethods for details). Patients were recruited via local area advertisements, hospital website listings, and physician referrals. Patients were given a small stipend for travel expenses (maximum $180 for one year).

Study Drugs

Zonisamide 100 mg and placebo capsules were prepared in accordance with Good Manufacturing Practice (GMP) guidelines in Duke Compounding Facility with active pharmaceutical ingredient (Sochinaz SA, Switzerland, distributed by Bachem Americas, King of Prussia, Pennsylvania) plusdextrose as an inactive ingredient. Identical-looking placebo capsules contained dextrose.

Each capsule contained zonisamide 100 mg or placebo, with patients and study staff blinded to contents. Dose was gradually titrated upward as follows: 1 capsule for 15 days, 2 during days 16–30, 3 capsules during days 31–45, and 4 from day 46 onward. The entire dose was taken at night. Blinded dose reduction was allowed and dose increase could be withheld. Patients had the option to discontinue the drug and remain in the study receiving only diet and lifestyle counseling. Compliance was assessed by comparing the number of capsules dispensed and returned.

Diet and Lifestyle Intervention

The study aimed to achieve at least 3% weight loss for all participants. Hence, all patients received diet and lifestyle counseling to promote weight loss. This included an individualized diet plan to reduce daily energy intake by 500 kcal from the energy requirements calculated using Mifflin-St Jeorresting metabolic rate equation.[10] Diet compositions were consistent with U.S. Department of Agriculture Guidelines, and patients were advised to consume 50% of their calories from carbohydrates, 20% from protein, and 30% from fat. Complex carbohydrates, whole grains, dietary fiber, and lean proteins were

emphasized and subjects were also taught to minimize consumption of saturated and trans fats. Patients were asked to record and monitor their daily caloric intake with a food diary, and at monthly study visits, they met with a registered dietitian for 30 minutes to discuss their progress, any perceived challenges, and receive individualized counseling and educational materials. Topics discussed included goal setting, planning healthy meals, understanding food labels, supermarket shopping, snacking and dining out, and basic guidance to increase aerobic exercise and strength training. All patients in the study were encouraged to exercise and while a specific exercise program was not prescribed, the dietitian discussed strategies for increasing physical activity such as walking at lunch breaks, wearing a pedometer to track steps and setting weekly physical activity goals. Other areas covered were decision-making, managing social situations, barriers to healthy eating, coping strategies, and relapse prevention.

Visits and assessments

Following randomization and drug dispensing, visits occurred twice in the first month, and at monthly intervals thereafter. Assessments included body weight, BP, heart rate, waist circumference, clinical and laboratory evaluations, concomitant medications, treatment compliance, adverse events (AEs), HADS depression subscale, and a suicidal ideation question.

Primary and Secondary Outcomes

The primary outcome, pre-specified in the protocol, was absolute change in body weight in kilograms. Secondary outcomes included proportions of patients achieving 5% and 10% weight loss, and changes in waist circumference, blood pressure, lipids, and other relevant blood tests. Safety outcomes included frequency of adverse events and HADS depression score change.

Statistical analysis

Power analysis, based on the assumption that relative to placebo, zonisamide 400 mg and 200 mg groups would lose 3% and 1.5%, respectively, indicated that 75 patients per treatment group, with primary endpoint data available for 65 patients at one year, would provide over 92% power to detect differences *vs* placebo at a 0·05 significance level (2-tailed).

Primary analysis was conducted on the intention-to-treat (ITT) sample of all randomized patients. The primary endpoint was weight loss at 1-year, Month-12 weight minus baseline weight, in kilograms. Using ANCOVA, the resulting difference score was regressed on a three-level proxy variable (1 = placebo; 2 = 200 mg; 3 = 400 mg) denoting randomization status; to control for differences in initial body weight. Baseline weight and gender were included as a covariates. Efficacy, testing the overall difference between groups, was evaluated using a 2-degree-of-freedom test. Based on a significant omnibus test, pair-wise contrasts between treatments were subsequently tested using closed (step-down) testing with P values of 0.05 or less indicating significance.

Missing data are a potential source of bias.[11] Many past imputation strategies, including last observation carried forward (LOCF) and completer analysis, often provide biased results[12] and are no longer favored relative to full likelihood-based and multiple imputation procedures, both of which are less subject to bias and inconsistencies under satisfying assumptions.[13] For this study, missing data for the primary analysis were augmented using multiple imputations in a two-step process. Based on available weight data from all randomized subjects, an initial imputation based on a Markov Chain Monte Carlo algorithm was used to establish a monotone missing data pattern. Missing values in the monotone

dataset were subsequently multiply imputed (m = 5 imputations) in a second step using regression procedures as described by Rubin and Schenker.[14] The primary Month-12 outcome measure was calculated using the imputed datasets and analyzed using ANCOVA regressions as described above; data from the five analyses were subsequently combined into single estimates and tested as described by Schafer.[15] Two secondary sensitivity analyses were used: An imputation using traditional LOCF procedures to replace the missing Month-12 data point, and a completers-based approach restricted to full-dose compliant (80%) patients (FDC) with Month-12 data (n=139). The latter two analyses facilitate comparisons with earlier published studies.

For responder analyses, two dichotomous outcome measures were calculated identifying patients with ≥5% and ≥10% weight loss. The latter measures were modeled with logistic regressions that included the three-level group proxy (described above) and a baseline weight covariate, with omnibus testing preceding pairwise tests as before.

Analyses of secondary outcomes were based on intent-to-treat ANCOVAs. Difference scores from baseline to endpoint (Month-12) for each measure were regressed on the three-level proxy denoting group while controlling for the baseline value of the same measure. Contrasts were subsequently estimated in models, which had a significant overall treatment effect.

Results

Patients

Two-hundred sixty patients signed consent forms and 225 patients were randomly assigned to 3 treatment groups – 74 to placebo, 76 to 200 mg, and 75 to 400 mg. Reasons for not randomizing 35 screed patients, and subsequent flow are depicted in Figure 1. Twenty patients discontinued placebo, 25 discontinued 200 mg, and 13 discontinued 400 mg. However, some patients who discontinued the drug remained in the study and completed all visits, and 41 patients that discontinued the drug returned for their 1-year visit to complete final assessments. Thus, primary endpoint assessment was available for 71 assigned to placebo, 73 assigned to 200 mg, and 74 assigned to 400 mg, leaving only 7 of 225 lost to follow-up.

Patient characteristics at baseline, shown in Table 1, were similar among the 3 groups. We enrolled 40% men and 37% ethnic minorities. Mean age and BMI were43 years, and 37.6 kg/m^2, respectively. Approximately 21% had depression history and 9% were on antidepressants.

Weight loss

Patients assigned to zonisamide 400 mg lost more weight than those assigned to placebo whereas 200 mg dose was not superior to placebo. In the primary MI analysis, weight changes (least-squares [LS] mean) were −4.0 kg (95% CI −5·8% to −2.3)for placebo, −4.4 kg (−6.1 to −2.6, P=.79) for 200 mg, and −7.3 kg (−9.0 to −5.6, P=.009) for 400 mg; corresponding %weight changes were −3.7%, −3.9%, and −6.8%, respectively. LOCF analysis showed similar weight change (Table 2), and full-dose compliant (FDC) patients showed greater weight loss with similar between-group differences.

In the categorical MI analyses, 23 (31.1%) patients assigned to placebo achieved ≥5% weight loss compared with 26 (34.2%, P=.72 *vs* placebo)and 41 (54.7%, P=.007 *vs* placebo) assigned to 200 mg and 400 mg, respectively; for ≥10% weight loss, the corresponding figures were 6 (8.1%), 17 (22.4% [P=.023]), and 24 (32.0% [P<.001]), respectively.

Weight Changes for Patients Who Dropped Out and Returned

Table 4 shows weight changes for the 41 patients (placebo = 15, 200 mg = 15, 400 mg = 11) who dropped out, but returned at 1-year. Weight gain was observed in all treatment groups, most notably for the 400 mg group. Mean (SD) weight changes were 1.4% (3.1) for placebo patients, 0.7% (3.5) for 200 mg (P *vs* placebo = 0.35), and 4.9% (3.4) for 400 mg (P *vs* placebo = 0.008).

Secondary Outcomes

Waist circumference decreased in all treatment groups; there was a greater decrease with 400 mg than with placebo. Changes in blood pressure, heart rate, fasting glucose, and lipids were favorable with all treatments without significant between-group differences. Although 400 mg led to a statistically significant (P=.007) greater reduction in glycated hemoglobin, the change was not clinically significant. There were no significant changes in hepatic enzymes and serum bicarbonate.

Adverse Events

This trial was not powered to detect differences in adverse events. Given the relatively small sample, we combined adverse events of similar nature into broader categories (e.g., terms such as sadness, crying, depression, depressed mood were combined as ‘depression-related’). As shown in Table 3, altered taste, constipation, diarrhea, dry mouth, headache, fatigue, nausea/vomiting, somnolence, fatigue, headache, language/speech problems, impaired attention/concentration, memory problems, and anxiety-related and depression-related adverse events were more frequent with one or both of the zonisamide doses. HADS depression scores were <3 (within normal) at all time points in all treatment groups. No patients developed major depressive disorder and none had suicidal ideation or panic attacks. Most neuropsychiatric adverse events were mild in severity and all events resolved quickly upon dose reduction or drug discontinuation.

A total of 14 patients discontinued study drug due to adverse events – 4 on placebo (1 patient each for mental slowing, memory impairment, tactile hallucinations, and stomach ache), 6 on 200 mg (2 headache, 1 memory impairment, 1 muscle weakness, 1 irritability, 1 depressed mood), and 4 on 400 mg (1 headache, 1 somnolence, 1 memory impairment, 1 depressed mood). Drug (400 mg) was stopped for one patient who became pregnant; she delivered a normal healthy baby at full-term. A total of 12 patients completed the study on reduced dose (1 on placebo, 2 on 200 mg, and 9 on 400 mg).

Discussion

To our knowledge, this is the first RCT examining the long-term efficacy of zonisamide for weight reduction. Zonisamide 400 mg/d led to 3.3 kg greater weight loss than diet and lifestyle intervention alone. Zonisamide 200 mg/d was not efficacious.

A unique feature of this trial is the high retention. Of 48 patients who dropped out, 41 returned at 1-year time-point, leaving only 7 of 225 randomized patients lost to follow-up. Not surprisingly, MI and LOCF imputation procedures showed almost identical results as few data were missing. Historically, dropout rates have generally been in the range of 30–50% in pharmaceutical weight loss trials, including recent long-term trials.[16–19] Interestingly, in the COR-BD trial that tested the addition of naltrexone + bupropion or placebo to intensive behavior modification, 42% withdrew early in the behavior modification (plus placebo) group and 12% cited an adverse event for discontinuation,[20] Simons-Morton et al[21] criticized obesity trials with the argument that high attrition introduces a bias, and randomization does not serve its purpose when data from patients who

have not adhered to treatment are not analyzed. A counter argument is that physicians are interested in treatment effects among patients that adhere to it and not the effect of being assigned to a treatment.

Various statistical models are employed in obesity RCTs to make up missing data, the most common being LOCF. Food and Drug Administration (FDA), in its guidance to industry,[22] recommends LOCF, which implicitly assumes that patients who withdraw early in a trial would have maintained the same weight at study exit as at the time of withdrawal. Other statistical imputation procedures make less restrictive assumptions for the individual patient or the assigned group based on patterns of weight change prior to dropout. Although some imputation procedures are superior to others, it is important to recognize that all imputation approaches make assumptions, some of which are inherently untestable (e.g., that data are missing at random).[15]

Observations of weight change among the 41 patients in this trial, who dropped out early, but returned for final assessment at 1-year, demonstrate that most obese patients gain weight or regain their lost weight after they drop out from a clinical trial, calling into question the results from trials with high dropout rates and the validity of commonly used imputation procedures in obesity RCTs. As seen in Table 4, many patients who lost substantial weight prior to drop out regained considerable weight by 1-year visit. The 11 dropouts in the 400 mg group gained almost 5% weight on the average when they returned at 1-year.

There were no extraordinary efforts in this trial that could explain the high retention. There were no extended screening visits to ensure patients were serious about participation. Patients were educated about time and commitment required for participation, and that they needed to make changes to their diet and lifestyle without which drug therapy would not help. They were counseled to have realistic expectations about what could be achieved over a year. Very few patients were excluded during screening. They were told that if they withdrew early, they would be requested to return for 1-year visit to complete final assessments, which would be valuable for the study's success. There was no coercion and the stipend offered was minimal.

Historically, most obesity RCTs enrolled primarily white women. This trial enrolled a fair number of men (40%) and ethnic minorities (37%).

A notable limitation of this trial is that most patients did not have significant weight-related comorbidities. At baseline, patients had normal blood pressure, lipids, and glycemic measures. Reduction in risks associated with obesity is most demonstrable when patients with risk factors are enrolled. This is a consideration for future investigation.

In a preliminary trial by Gadde et al.,[8] zonisamide achieved 5 kg greater weight loss than placebo (5.9 kg *vs* 0.9 kg) over 16 weeks. The current RCT examined whether zonisamide, could enhance long-term weight loss achievable with a good quality diet and lifestyle intervention that is implementable in a primary care clinical setting. In contrast to the previous trial, placebo group in the current RCT achieved an impressive 4 kg weight loss. Our lifestyle intervention was not as intensive as the ones administered in DPP,[3] Look AHEAD,[4] and COR-BMOD[20] trials, and could be easily incorporated into primary care practices.

Although, zonisamide 400 mg/d demonstrated moderate efficacy of a magnitude similar to orlistat[6] and lorcaserin,[7] neuropsychiatric adverse events (mood changes and memory problems) occurred at a higher frequency relative to placebo. Hence, for treatment of obesity, the drug's benefit-to-risk ratio needs thoughtful and cautious assessment. The

results of our trial must be considered in the context of our follow-up procedures, which were markedly different from those of typical weight loss trials.

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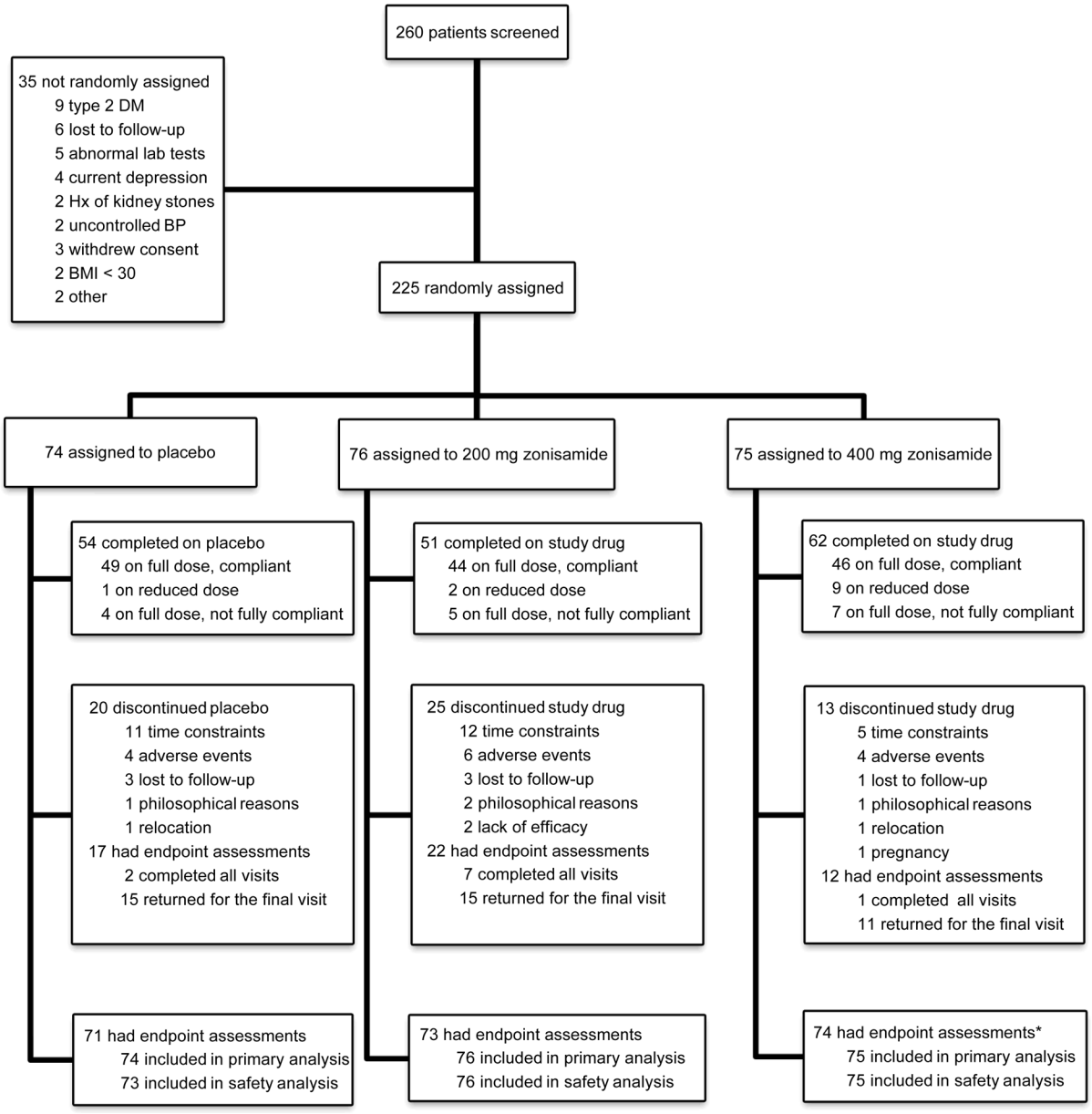

Figure 1. Flow of Patient Screening, Randomization, and Disposition

*One patient became pregnant and had drug discontinued at Month 5. She was followed to the end of the study, but actual data for months 6 through 12were replaced by imputed values.

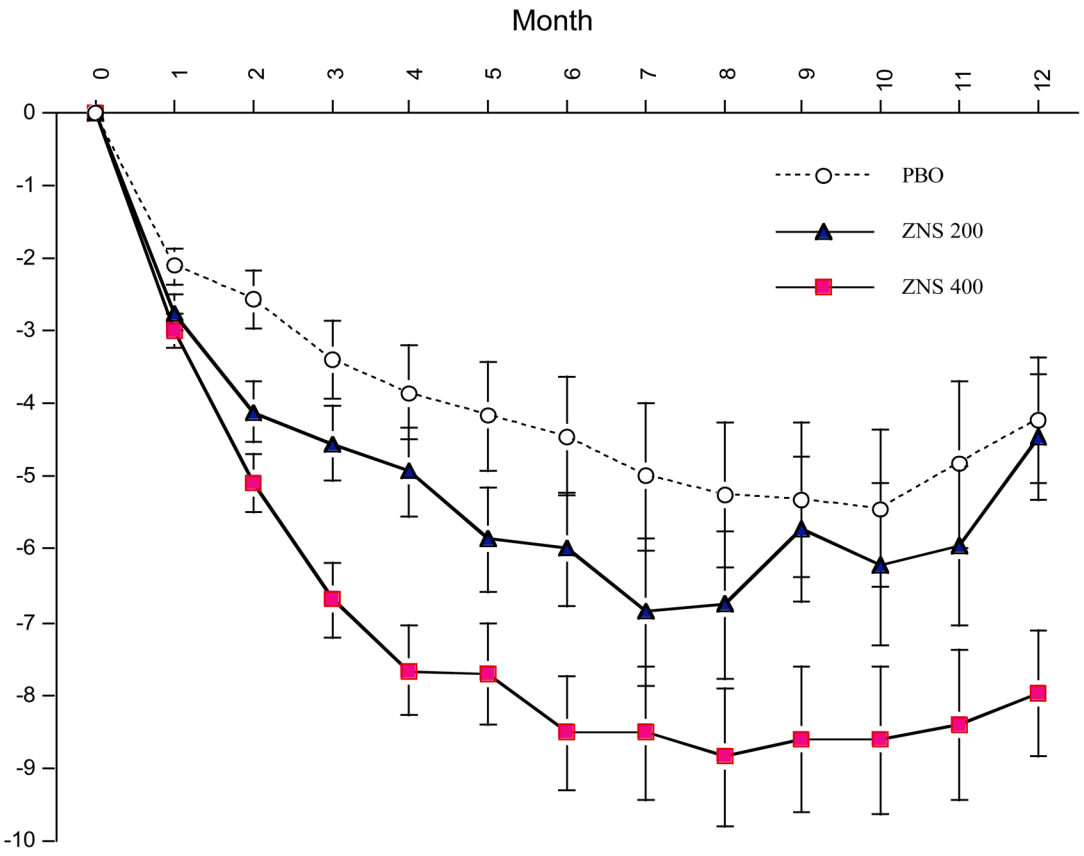

Figure 2.
Abbreviations: ZNS, zonisamide. Depicted as least-square means (SE). For one patient who was found to be pregnant at Month 5, data collected between Month 6 and Month 12 are not included.

Table 1

Patient Characteristics by Treatment Group

	Placebo (n = 74)	ZNS 200 mg (n = 76)	ZNS 400 mg (n = 75)
Age, y	43.5 (10.3)	44.2 (10·1)	42.3 (10·0)
Women, No. (%)	44 (59.5%)	45 (59.2%)	45 (60.0%)
Race, No. (%)			
White	49 (66.2%)	48 (63.2%)	45 (60.0%)
Black	23 (31.1%)	27 (35.5%)	27 (36.0%)
Other	2 (2.7%)	1 (1·3%)	3 (4.0%)
Married, No. (%)	47 (63.5%)	48 (63.2%)	44 (58.7%)
Obese for >10 years, No. (%)	45 (60.8%)	50 (65.8)	47 (62.7)
Family history of obesity, No. (%)	55 (74.3%)	49 (64.4)	41 (54.7)
Psychiatric history, No. (%)	18 (24.3%)	17 (22.4%)	23 (30.7%)
Taking antidepressant, No. (%)	6 (8.1%)	5 (6.6)	9 (12%)
Weight, kg	110.7 (18·8)	111.4 (21.0)	109.0 (14.9)
Body mass index, kg/m^2	37.8 (5.2)	37.5 (5.1)	37.7 (4·4)
Waist circumference, cm	113·1 (13.3)	114.3 (15.7)	112.8 (11.7)
Blood pressure, mm Hg			
Systolic	120.6 (13·7)	124·2 (14.0)	119·9 (12.1)
Diastolic	78.8 (9·7)	81.2 (9.1)	80·4 (9·3)
Heart rate, bpm	73.0 (10.4)	75.4 (11·1)	72·4 (10·2)
Total cholesterol, mg/dL	197.1 (32.8)	189.4 (31.9)	189.4 (28.1)
LDL cholesterol, mg/dL	122.4 (31.8)	116.0 (30.1)	116.9 (29.6)
HDL cholesterol, mg/dL	51.0 (12.4)	50.0 (13.4)	48.4 (11.9)
Triglycerides, mg/dL	125.8 (66.1)	124.7 (81.5)	117.7 (58.6)
Fasting glucose, mg/dL	93.9 (14.4)	95.0 (10.8)	93.6 (11.0)
Glycatedhemoglobin, %	5.6 (0.4)	5·6 (0·5)	5·6 (0·5)

Unless otherwise stated, values as mean (SD). Abbreviations: HDL, high-density lipoprotein; LDL, low-density lipoprotein; ZNS, zonisamide.

Table 2

Changes in Weight and Secondary Parameters

Outcome Variable	Placebo (n = 74)	ZNS 200 mg (n = 76)	p value *vs* placebo	ZNS 400 mg (n = 75)	p value *vs* placebo
Weight, kg					
MI analysis (n = 74, 76, 75)	−4.0 (−5.9, −2.7)	−4.4 (−6.1, −2.6)	.79	−7.3 (−9.0, −5.6)	.009
LOCF analysis (n = 74, 76, 75)	−4.0 (−5.7, −2.2)	−4.3 (−6.0, −2.6)	.78	−7.4 (−9.1, −5.7)	.006
FDC analysis (n= 49, 44, 46)	−5.1 (−7.4, −2.8)	−6.0 (−8.4, −3.5)	.62	−9.1 (−11.5, −6.7)	.019
Weight, %					
MI analysis	−3.7 (−5.3, −2.1)	−3.9 (−5.4, −2.3)	.88	−6.8 (−8.4, −5.3)	.006
LOCF analysis	−3.7 (−5.2, −2.1)	−3.8 (−5.3, −2.2)	.87	−6.9 (−8.5, −5.4)	.004
FDC analysis	−4.7 (−6.8, −2.6)	−5.4 (−7.6, −3.2)	.66	−8.7 (−10.8, −6.5)	.009
Patients with >5% weight loss, No. (%)					
MI analysis	23 (31.1)	26 (34.2)	.72	41 (54.7)	.007
LOCF analysis	22 (29.7)	25 (32.9)	.66	41(54.7)	.003
FDC analysis	21 (42.9)	17 (38.6)	.76	30 (65.2)	.030
Patients with >10% weight loss, No. (%)					
MI analysis	6 (8.1)	17 (22.4)	.023	24 (32.0)	<.001
LOCF analysis	5 (6.8)	17 (22.4)	.010	25 (33.3)	<.001
FDC analysis	5 (10.2)	13 (29.5)	.020	18 (39.1)	.002
Waist circumference, cm	−4.8 (−6.6, −3.1)	−6.1 (−7.8, −4.3)	.33	−8.5 (−10.2, −6.8)	.003
Systolic BP, mm Hg	−0.6 (−2.9, −1.7)	−4.4 (−6.7, −2·1)	.025	−1.9 (−4·1, 0·4)	.46
Diastolic BP, mm Hg	−1.5 (−3.2, 0.1)	−3.6 (−5.3, −2.0)	.08	−3.9 (−5.5, −2.3)	.048
Heart rate, bpm	−2.7 (−4.6, −0.9)	−2.0 (−3.9, −0.1)	.58	−2.4 (−4.2, −0.5)	.76
Total cholesterol, mg/dL	−1.9 (−7.2, 3.4)	4.1 (−1.0, 9.2)	.11	−0.1 (−5.0, 4.9)	.62
LDL cholesterol, mg/dL	−2.0 (−6.7, 2.7)	1.7 (−2.8, 6.3)	.26	−0.3 (−4.7, 4.1)	.60
HDL cholesterol, mg/dL	2.5 (0.7, 4.3)	1.5 (−0.3, 3.2)	.44	3.4 (1.7, 5.1)	.49
Triglycerides, mg/dL	−11.3 (−22.6, 0.0)	0.7 (−10.1, 11.5)	.13	−11.7 (−22.2, −1.1)	.96
Fasting glucose, mg/dL	−2.6 (−5.1, 0.0)	−1.4 (−3.9, 1.2)	.51	−3.5 (−5.9, −1.0)	.63
Glycatedhaemoglobin, %	−0.01 (−0.07, 0.05)	−0.05 (−0.12, 0.01)	.38	−0.13 (−0.19, −0.07)	.007
ALT, mg/dL	−0.8 (−3.5, 2.0)	−0.3 (−3.0, 2.4)	.79	−1.3 (−3.9, 1.4)	.81
Creatinine, mg/dL	−0.03 (−0.06, −0.01)	0.01 (−0.01, 0.03)	.016	0.02 (−0.00, 0.04)	.003

Unless otherwise stated, analyses are for 218 patients who had 1-year endpoint assessments. Abbreviations: ALT, alanine amino transferase; BP, blood pressure; HDL, high-density lipoprotein; FDC, full-dose compliant; LDL, low-density lipoprotein; LOCF, last observation carried forward; MI, multiple imputation; ZNS, zonisamide.

Table 3

Adverse events

Event Number of patients (%)	Placebo (n = 74)	ZNS 200 mg (n = 76)	ZNS 400 mg (n = 75)
Altered taste	0 (0)	4 (5.3)	4 (5.3)
Dry mouth	3 (4.1)	5 (6.6)	1 (1.3)
Nausea/vomiting	4 (5.3)	4 (5.3)	10 (13.3)
Constipation	2 (2.7)	2 (2.6)	5 (6.7)
Diarrhea	1 (1.4)	2 (2.6)	4 (5.3)
Anxiety-related	2 (2.7)	5 (6.6)	7 (9.3)
Depression-related	3 (4.1)	3 (3.9)	5 (6.7)
Impaired attention/concentration	1 (1.4)	1 (1.3)	4 (5.3)
Impaired memory	1 (1.4)	5 (6.6)	8 (10.7)
Language/speech problems	1 (1.4)	3 (3.9)	6 (8.0)
Headache	5 (6.8)	8 (10.5)	14 (18.7)
Fatigue	2 (2.7)	4 (5.3)	7 (9.3)
Somnolence	3 (4.1)	9 (11.8)	6 (8.0)
Insomnia	1 (1.4)	4 (5.3)	1 (1.3)
Infections	10 (13.5)	8 (10.5)	15 (20.0)
Musculoskeletal problems	9 (12.2)	11 (14.5)	8 (10.7)

Adverse events reported by at least 5% patients in any of the treatment groups are shown.

Table 4

Weight Change of Patients Who Withdrew Early and Returned for 1-Year Visit

	Treatment	Dropout month	Weight change at dropout, kg (%)	Weight change from dropout time to return at 1-year, kg (%)
1	Placebo	8	−8.8 (−7.6)	3.4 (3.2)
2	Placebo	4	−0.5 (−0.3)	−9.2 (−6.0)
3	Placebo	9	−5.7 (−5.5)	2.9 (3.0)
4	Placebo	8	2.8 (3.1)	4.9 (5.2)
5	Placebo	4	0.2 (0.1)	−0.5 (−0.3)
6	Placebo	1	0.8 (0.6)	−4.6 (−3.2)
7	Placebo	7	−8.4 (−5.8)	5.4 (4.0)
8	Placebo	8	−4.1 (−3.2)	4.4 (3.6)
9	Placebo	4	−1.0 (0.7)	2.6 (1.9)
10	Placebo	4	−2.8 (−2.5)	5.3 (4.8)
11	Placebo	8	−9.2 (−6.8)	2.4 (1.9)
12	Placebo	6	−9.0 (−7.5)	3.4 (3.1)
13	Placebo	6	0.3 (0.2)	0.2 (0.1)
14	Placebo	2	−1.2 (−1.2)	0.3 (0.3)
15	Placebo	1	−4.1 (−3.3)	−0.5 (−0.4)
16	200 mg	5	0.7 (0.6)	−4.8 (−4.6)
17	200 mg	9	6.4 (5.0)	−4.3 (−3.2)
18	200 mg	7	−2.6 (−2.6)	−0.4 (−0.4)
19	200 mg	6	3.0 (2.7)	5.0 (4.4)
20	200 mg	8	−7.3 (−7.0)	−4.1 (−4.2)
21	200 mg	4	3.3 (2.8)	4.5 (3.8)
22	200 mg	9	−2.6 (−2.3)	−2.1 (−1.9)
23	200 mg	9	−6.2 (−6.7)	−0.8 (−0.9)
24	200 mg	9	−4.4 (−4.4)	5.6 (5.8)
25	200 mg	7	−0.7 (−0.8)	2.3 (2.8)
26	200 mg	6	−1.0 (−1.1)	2.1 (2.4)
27	200 mg	3	−0.5 (−0.4)	8.0 (6.3)
28	200 mg	4	1.5 (1.4)	−1.5 (−1.4)
29	200 mg	6	3.3 (2.2)	0.2 (0.1)
30	200 mg	6	−5.2 (−3.1)	1.3 (0.8)
31	400 mg	6	−14.1 (−11.7)	7.3 (6.9)
32	400 mg	5	−2.1 (−1.8)	1.9 (1.7)
33	400 mg	7	−12.5 (−12.2)	10.2 (11.3)
34	400 mg	7	−3.5 (−3.9)	3.8 (4.5)
35	400 mg	2	−2.1 (−1.9)	2.3 (2.1)
36	400 mg	9	3.8 (3.6)	−0.2 (−0.2)

	Treatment	Dropout month	Weight change at dropout, kg (%)	Weight change from dropout time to return at 1-year, kg (%)
37	400 mg	2	−1.8 (−1.5)	2.0 (1.7)
38	400 mg	4	−28.4 (−21.9)	6.4 (6.3)
39	400 mg	9	−15.1 (−13.7)	4.4 (4.6)
40	400 mg	9	−28.5 (−24.4)	7.5 (8.5)
41	400 mg	5	−11.5 (−10.6)	5.8 (6.0)

200 mg and 400 mg refer to zonisamide doses.