

Key Words: mood disorder, treatment efficacy, mood stabilizer, adjunctive treatment, Bipolar Disorder

Zonisamide for Bipolar Depression: A Randomized, Double Blind, Placebo-Controlled, Adjunctive Trial

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ABSTRACT ~ Objective: This is the first multicenter, double blind, randomized, placebo-controlled trial to evaluate the safety and efficacy of adjunctive zonisamide for the treatment of bipolar depression. **Experimental design:** One hundred two patients with bipolar disorder, type I or II in the depressed phase of illness were randomized to either adjunctive zonisamide or placebo. The study consisted of three phases, a 7 to 30 day screening and stabilization phase, 6 weeks of blinded treatment and a 1 to 3 week discontinuation phase. MADRS score was the primary outcome variable. Secondary outcome measures included the YMRS, CGI-S, CGI-I, Quality of Life Enjoyment and Satisfaction Questionnaire (Q-LES-Q), and an a priori analysis of response and remission. Metabolic parameters including weight, waist-hip ratio, body mass index, fasting glucose, cholesterol and triglyceride levels were also evaluated. Side effects were measured using the SAFTEE. **Principal observations:** There were no statistically significant differences in response between subjects treated with adjunctive zonisamide vs. placebo controls for the primary or secondary outcome measures. There were also no differences between the groups with regard to response rate or remission rate. **Conclusions:** In contrast to preliminary open label studies that suggested a role for zonisamide in bipolar depression, we could not confirm these results in a large double blind controlled study. *Psychopharmacology Bulletin. 2011;44(2):73-84.*

INTRODUCTION

Bipolar disorder is a common condition for which effective medical treatment is often lacking. Recent estimates of prevalence suggest that the various forms of bipolar disorder may affect more than 4% of the population.¹ The depressive phase of bipolar disorder is a significant source of morbidity for patients with this illness² and there is a lack of robust controlled data to guide treatment choices.

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Residual symptoms of depression or mania despite treatment with available medications are common and correlated with relapse.³⁻⁵ Additional medications, such as antidepressants are often added to the patient's regimen in response to continued symptoms. A recent study from the Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD) reported adjunctive administration of antidepressant drugs did not appear to convey significant clinical benefit.⁶

Zonisamide is broad-spectrum anticonvulsant, discovered in 1972 that became available for commercial use in Japan in 1989 and in the United States in 2000, as an adjunctive treatment for epilepsy. Several mechanisms have been proposed for zonisamide's anticonvulsant effects including dose related blockade of sodium channels, blockade of T-type calcium channels,⁷ low dose facilitation of serotonergic and dopaminergic transmission, dopaminergic inhibition at higher doses and carbonic anhydrase inhibition.⁸

Open-label and retrospective studies of adjunctive zonisamide have been conducted in bipolar disorder, which provided preliminary evidence for efficacy in both the manic⁹⁻¹¹ and the depressed,^{9,10,12-14} phases of the illness. Furthermore, weight gain and obesity are common side effects in the treatment of bipolar disorder. Mood stabilizers that may prevent weight gain or promote weight loss are highly desirable for the treatment of this disorder.¹⁵ In addition to the putative mood stabilizing effects of zonisamide, beneficial effects on weight and metabolic parameters have also been reported.¹⁵⁻¹⁸

Zonisamide appears to be generally well tolerated with a favorable side effect profile; sedation and dizziness are reported as common side effects with rare reports of more serious adverse events.⁸ One advantage of zonisamide over several currently available mood stabilizers is that it has fewer significant drug interactions. Zonisamide is inactivated by CYP3A4 dependent reduction and its clearance is increased by co-administration of carbamazepine, phenytoin and phenobarbital; a higher dose of zonisamide may be required in patients taking these medications.¹⁹

In light of the attractive preliminary data suggesting efficacy of zonisamide in mood disorders and its positive side effect profile, we conducted a multi-site, controlled trial of zonisamide augmentation in bipolar depression.

MATERIALS AND METHODS

Subjects

One hundred two subjects with bipolar disorder, type I or II, in the depressed phase of illness, meeting all inclusion and exclusion criteria,

were randomized to either adjunctive zonisamide or placebo at a 1:1 ratio. The ten participating sites recruited subjects from June 2, 2008 through November 10, 2008. All study sites were private outpatient research centers within the United States. Capital Clinical Research Associates (CCRA) was both a study site and the coordinating site for the study. All subjects were volunteers, age 18 to 65, who signed written informed consent. Diagnosis was made using DSM-IV criteria²⁰ as determined by the Mini International Neuropsychiatric Interview.²¹

At screening, subjects were required to have a score of 20 or greater on a structured interview version of the Montgomery Asberg Depression Rating Scale (MADRS)^{22,23} with duration of the current depressive episode for at least 4 weeks prior to study entry. Subjects were required to take a stable regimen of psychiatric medications for two weeks prior to the baseline visit, including mood stabilizers, antidepressants, antipsychotics or anticonvulsants. Subjects who were not taking psychiatric medications at screening could be treated by the research psychiatrist during the stabilization phase of the trial and were subsequently enrolled provided they continued to meet all inclusion and exclusion criteria. All subjects taking lithium or valproic acid were required to have minimum blood levels of 0.4 mEq/L and 50 mEq/L respectively.

Subjects with a score of >10 on the Young Mania Rating Scale (YMRS),²⁴ or those who experienced a decrease in MADRS score of 25% or more between screening and baseline visits, were excluded from the study. Other exclusion criteria included: a rating of >4 on the MADRS suicidal thoughts item, another Axis I disorder as a principal diagnosis in the 6 months prior to screening, significant medical problems, significantly abnormal screening laboratory values, a history of allergy to sulfonamides or related drugs, history of recurrent nephrolithiasis, pregnancy or lactation, a positive urine screen for illicit drugs, a history of substance abuse or dependency requiring specialized treatment in the 6 months prior to screening, participation in another research study within 2 weeks of screening, and a history of prior treatment with zonisamide. Subjects were also excluded if they had initiated a course of Cognitive Behavioral Therapy within one month of screening.

Study Design and Procedures

The study consisted of a screening and stabilization phase of up to 30 days, a treatment phase of six weeks, and a discontinuation phase of one to three weeks. All medications taken within 30 days of baseline were recorded and all medications for the current episode of depression were recorded and required to be at a stable dose for at least two weeks prior to baseline. Medications were to remain at stable, baseline dose,

for the duration of the study. During the study, patients were permitted adjunctive use of benzodiazepines (up to 2 mg of lorazepam or equivalents per day), zolpidem (up to 10 mg per day), zaleplon (up to 10 mg per day), eszopiclone (up to 3 mg per day), or ramelteon (8 mg per day) for insomnia. If benzodiazepines were being used for anxiety, they could be taken at higher doses as long as the dose was constant for two weeks prior to enrollment and throughout the study. Stimulant medications such as amphetamine, methylphenidate and modafinil were not allowed. No new therapies, pharmacological or non-pharmacological, such as light therapy or cognitive behavioral therapy, were permitted during the study. Patients were seen at Weeks 1, 2, 4 and 6 during the treatment phase. Telephone visits were scheduled at Weeks 3 and 5. During the discontinuation phase of the study, a telephone visit was scheduled at Week 7 (and Week 8 if needed) with a final study visit at Week 9. Table 1 presents a summary of study procedures at each visit.

At baseline, subjects were randomly assigned to either zonisamide or placebo in a 1:1 ratio. Study medication was begun at 100 mg a day and increased after one week to 100 mg twice a day (V3, week 1) and then to 100 mg each morning and 200 mg each evening after another week (V4, week 2). The dose of study medication was maintained at 300 mg a day for the remainder of the 6-week study. Patients unable to tolerate more than 100 mg per day were allowed to remain at that dosage. Likewise, patients who could not tolerate more than 200 mg per day were able to stay at that dosage. Patients whose dosage had been raised, but were unable to tolerate the higher dosage, had their daily dose lowered by 100 mg a day. At the end of the treatment phase the dose of study medication was tapered by 100 mg every seven days.

Generic zonisamide manufactured by Apotex was the active study drug and Avicel PH 105, a microcrystalline cellulose manufactured by CMF BioPolymer, was used for the placebo through out the study. A central pharmacy prepared the study drug. The randomization sequence was managed by a centralized IVRS facility. All study subjects, staff, raters and clinicians remained blind to study condition. The central pharmacy was the only party not blinded during the study. Information to break the blind was sent directly to the statistician by the central pharmacy at the end of the study.

Outcome Measures

Efficacy was assessed using a mixed model repeated measure analysis of variance (ANOVA) for the primary outcome variables, MADRS, and YMRS as well as the Clinical Global Impression-Severity (CGI-S) and Clinical Global Impression-Improvement (CGI-I).²⁵ A categorical

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TABLE 1

SUMMARY OF STUDY PROCEDURES AT EACH VISIT ZONISAMIDE AUGMENTATION FOR BIPOLAR DEPRESSION

WEEK	0	DAY 1	1	2	3	4	5	6	7(+8)	7-9
Visit	1	2	3	4	TC	5	TC	6	TC	7 (follow up)
Informed Consent	X									
MINI	X									
DSM-IV Criteria	X									
Labs ^{1,2}	X							X		
Physical exam	X							X		
ECG	X									
YMRS	X	X	X	X		X		X		X
MADRS	X	X	X	X		X		X		X
CGI-S	X	X	X	X		X		X		X
CGI-I			X	X		X		X		X
QIDS	X	X	X	X		X		X		X
Q-LES-Q	X	X	X	X		X		X		X
SAFTEE										
(SYMPTOM CHECKLIST)		X	X	X		X		X		X
Vital Signs	X	X	X	X		X		X		X
Weight/Height	X							X		
Waist-hip ratio	X							X		
Adverse events	X	X	X	X	X	X	X	X	X	X
Concomitant Medications	X	X	X	X	X	X	X	X	X	X
Dispense IP		X	X	X		X		X		
Collect IP			X	X		X		X		X

¹Screening and endpoint labs: serum chemistry, hematology, urinalysis, free T4, TSH, Lithium and Valproic acid levels for subjects taking these meds, serum pregnancy test for women of childbearing potential, urine drug test at screening only.

²Serum metabolic measures: fasting glucose, total cholesterol, HDL, VLDL, LDL and triglycerides.

analysis of treatment response and remission was also performed. Responders were defined as those patients with >50% reduction in their MADRS score between the Baseline and Discontinuation visits. Remission was defined as a MADRS score of <10 at endpoint.

Secondary outcome measures included: CGI-S, CGI-I and the Quality of Life Enjoyment and Satisfaction Questionnaire (Q-LES-Q).²⁶ Metabolic outcome measurements included weight, waist-hip ratio, body-mass index,^{27,28} and levels of plasma lipids, glucose and triglycerides. Safety was assessed using a standardized adverse event scale, the Systematic Assessment for Treatment Emergent Effects (SAFTEE).²⁹ The emergence of mania or hypomania was assessed using the YMRS. Basic descriptive statistics including the mean, standard deviation, variance and range were performed for all variables.

Paired T-tests were run comparing differences between groups for vital signs and metabolic measures.

Study population size was estimated from previous studies; 34 subjects in each of the two groups, zonisamide versus placebo, were needed for 80% statistical power to detect an effect size of 0.7 at a statistical significance level of 0.05. We planned to screen up to 200 subjects in order to enroll 100 and arrive at the total of 68, assuming a 68% completion rate.

RESULTS

One hundred and eighty-three subjects were screened and 102 were randomized to treatment; 79 subjects had a diagnosis of bipolar disorder, type I and 23 subjects with bipolar disorder, type II. Table 2 displays the characteristics of the two treatment groups. There were no statistical differences between groups at baseline for demographic variables, vital signs, metabolic measures, or the primary and secondary outcome variables. Of the 102 subjects enrolled, 52 were allocated to treatment with zonisamide and 50 to placebo. The mean dose of zonisamide was 277.6 mg/day, S.D. 51.1 mg. Two subjects in the zonisamide group were excluded from analysis for clinical reasons and one subject in the zonisamide group withdrew consent after baseline and did not start the study drug. Diagram 1 shows subject disposition through the trial.^{30,31} Ninety-two subjects completed the trial, 48 subjects from zonisamide group and 44 from placebo group.

There was no statistically significant difference between the zonisamide and the placebo-treated groups for change from baseline to endpoint on the MADRS scale; graph 1 shows MADRS vs. time for both groups. The mixed model repeated measures ANOVA showed no group-by-time interaction at any time point for the MADRS or for any of the secondary outcome measurements. Table 3 lists the results for MADRS, YMRS, CGI-S and CGI-I.

With regard to treatment response, 41.7% of patients treated with zonisamide experienced a 50% reduction in MADRS score, compared to 43.2% of placebo-treated patients ($p = 0.88$). The remission rates were 27.7% for zonisamide-treated and 25% for placebo-treated patients ($p = 0.77$). The mean dose of zonisamide for treatment responders was 275 mg/d and 279.5 mg/d for the non responders.

There were also no statistically significant differences between groups for the Q-LES-Q, systolic blood pressure, diastolic blood pressure, weight, waist hip ratio, fasting blood glucose, HDL cholesterol, LDL cholesterol, VLDL cholesterol, and triglycerides at study endpoint.

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TABLE 2

BASELINE CHARACTERISTIC TABLE: DEMOGRAPHICS ZONISAMIDE AUGMENTATION FOR BIPOLAR DEPRESSION

	ZONISAMIDE (N = 50) N = 41 BIPOLAR I N = 9 BIPOLAR II	PLACEBO (N = 50) N = 37 BIPOLAR I N = 13 BIPOLAR II	CHI SQUARE; DEGREES OF FREEDOM; PROBABILITY
Age (s.d.) ^a	43.1 (11.0)	41.4 (11.2)	-0.75; 98; 0.46 ^b
Gender	29 female 21 male	32 female 18 male	0.38; 1; 0.54
Race	23 Black 1 Hispanic 0 Other 26 White	21 Black 4 Hispanic 1 Other 24 white	2.97; 3; 0.40
Employment	3 full time 10 part time 1 retired 36 unemployed	5 full time 8 part time 0 retired 35 unemployed	1.70; 3; 0.64
Education (highest grade or degree)	1 grade 8 or less 9 some high school 19 high school 14 some college 6 college 0 post grad 0 other	3 grade 8 or less 13 some high school 10 high school 18 some college 4 college 1 post grad 1 other	7.41; 6; 0.28

^aTwo sample t-test for age analysis, Chi square test for all other demographics.

^bT-value; degrees of freedom; probability.

Employment data missing for 2 subjects in placebo group.

Education level data missing for 1 subject in zonisamide group.

Baseline characteristics were analyzed for all except 2 subjects in the zonisamide group: 1 subject excluded due to medication noncompliance and 1 was not on stable dose of meds for 2 weeks prior to baseline (protocol violation).

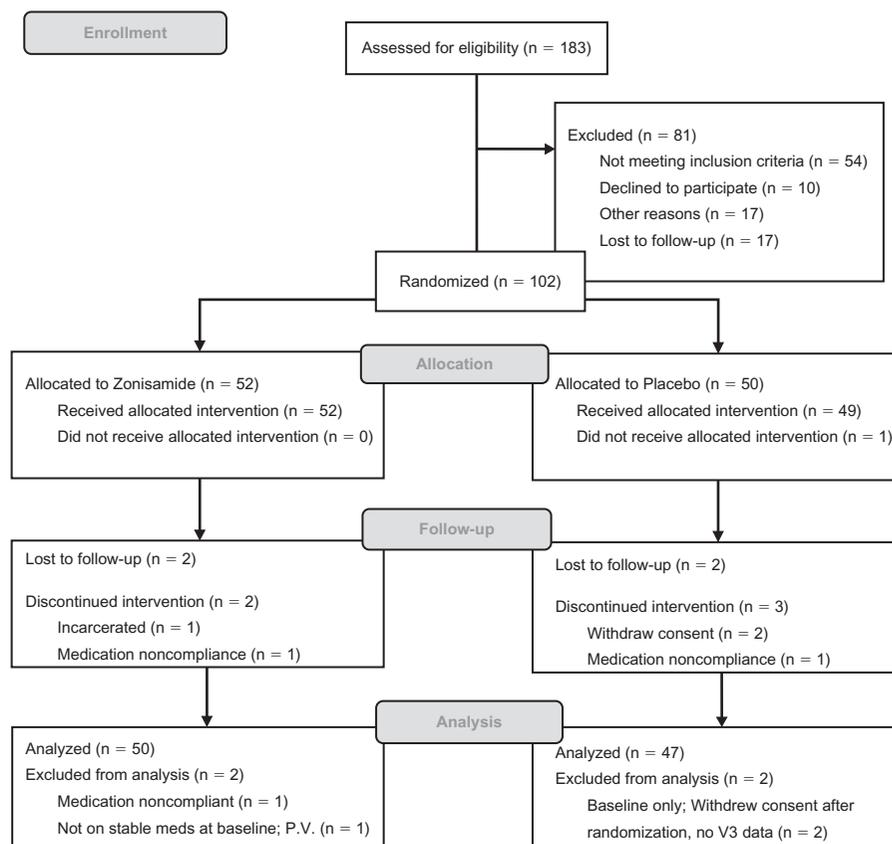
There was a modest, but significant, reduction in total cholesterol between baseline and endpoint for both treatment groups, but no statistical difference between the treatment groups.

Adverse events were uncommon in this study. Headache was the most common adverse event reported, which occurred in 16% of patients taking zonisamide and in 4% of patients taking placebo. Other side effects that were notably more common in the zonisamide group than in the placebo group were constipation (14% vs. 0%), and nausea (12% vs. 6%). Two serious adverse events were reported. One subject randomized to zonisamide was hospitalized voluntarily because of increased isolation, hallucinations, and aggressive behavior. Another subject from the placebo group was admitted because of passive suicidal ideations.

DIAGRAM 1

SUBJECT FLOW DIAGRAM
ZONISAMIDE AUGMENTATION FOR BIPOLAR DEPRESSION

PREPARED USING CONSORT FORMAT^{30,31}



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DISCUSSION AND CONCLUSION

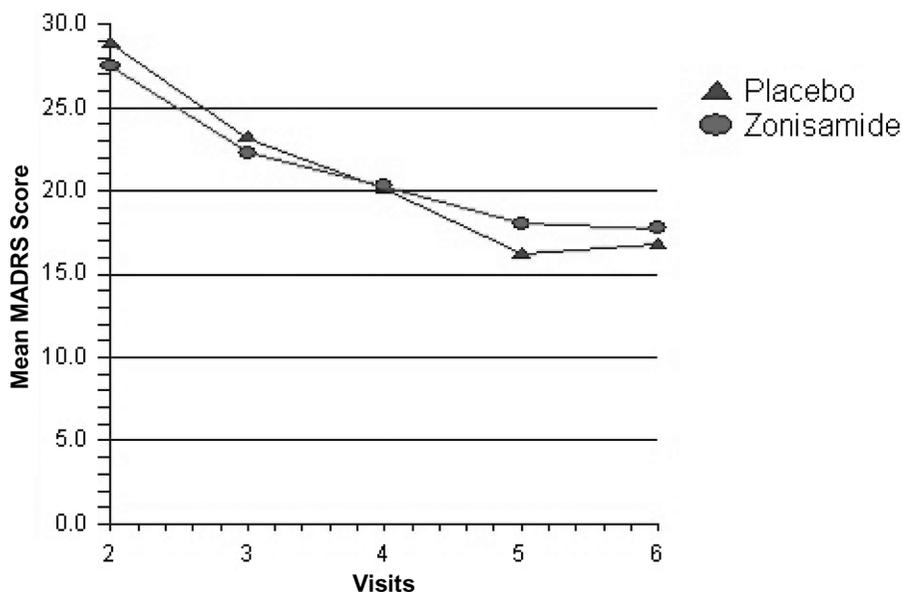
In contrast to earlier open label and retrospective trials,⁹⁻¹⁴ this multicenter, placebo-controlled study did not demonstrate zonisamide augmentation to be superior to placebo in patients with bipolar depression. McElroy et al.⁹ conducted the largest previous open label study of zonisamide augmentation in patients with bipolar disorder. Twenty-two patients with bipolar depression were enrolled in the 8-week acute treatment phase of the study; improvement was demonstrated on the CGI Scale modified for bipolar illness (CGI-BP-Depression-Severity) and on the Inventory for Depressive Symptomatology Scale (IDS) at a mean dose of 247 mg per day. In a retrospective chart review of 12 patients with bipolar depression treated for 6 weeks at a mean dose of 236 mg per day, Baldassano et al.¹⁴ reported that patients experi-

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GRAPH 1

MEANS OF MADRS GRAPH
ZONISAMIDE AUGMENTATION FOR BIPOLAR DEPRESSION

MEAN MADRS SCORES VS. TIME



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TABLE 3

OUTCOME MEASURES
ZONISAMIDE AUGMENTATION FOR BIPOLAR DEPRESSION
TABLE OF STUDY OUTCOME MEASURES AT BASELINE AND END POINT

RATING SCALE SCORES AT BASELINE AND END POINT: MEAN (S.D.)

	ZONISAMIDE	PLACEBO	F-VALUE: d.f.; PROBABILITY
MADRS Baseline	27.5 (4.7)	28.9 (5.3)	F(4,360) = 1.34, $p < 0.25$
MADRS V6	17.7 (10.7)	16.7 (9.6)	
YMRS Baseline	5.7 (2.3)	5.6 (2.7)	F(4,359) = 1.92, $p < 0.11$
YMRS V6	4.4 (3.5)	5.6 (4.2)	
CGI-Severity Baseline	4.4 (0.5)	4.5 (0.6)	F(6,534) = 0.72, $p < 0.64$
CGI-Severity V6	3.2 (1.3)	3.4 (1.4)	
CGI-Improvement (week 1/V3)	3.3 (0.7)	3.4 (0.8)	F(4,338) = 0.66, $p < 0.62$
CGI-Improvement V6	2.8 (1.2)	2.9 (1.4)	

enced a significant improvement on the Global Assessment of Functioning (GAF) scale, and that 50% of patients were considered to be treatment responders, although improvement in mean CGI-S scores was not statistically significant in this group. Anand et al.¹³ administered adjunctive zonisamide (up to 300 mg/day) to 10 patients with

treatment resistant bipolar depression in an open label 8-week trial. This study reported significant improvements on the Hamilton Rating Scale for Depression (HAM-D) and the CGI-I. Ghaemi et al.¹² found that open label zonisamide (mean dose = 222.5 mg) given for 8 weeks to 20 patients with bipolar depression was associated with significant improvement in MADRS scores, although 10 patients terminated from the study due to side effects.

The current study is the largest clinical trial of zonisamide given adjunctively for bipolar depression and is the only double blind, placebo-controlled study to be reported. Our study seems to conclusively demonstrate a lack of beneficial effect of zonisamide in bipolar depression. The dose of zonisamide administered in this study was not much different (mean dose 277.6 mg/d) from that in previously reported studies. However, there are several possible factors that may have produced a false-negative result, which must be considered carefully when interpreting these data. It is also possible that doses of zonisamide greater than 300 mg per day could be effective in bipolar depression. This hypothesis may be supported by studies that have shown improvement in manic symptoms and other disorders such as obesity and alcohol dependence with doses of zonisamide up to 600 mg per day.^{11,32-36}

Three of the four studies of augmentive zonisamide for bipolar depression referenced above administered zonisamide for longer than 6 weeks. While it is possible that we failed to detect a beneficial effect of zonisamide because of a relatively short study period of 6 weeks, the robust lack of effect seen here makes this interpretation unlikely. Only one of the above studies used the MADRS as the main outcome measurement.¹² While it is possible that differences between the MADRS and the scales used in the previous studies could have contributed to the lack of benefit seen in this study, we feel this interpretation is also unlikely since we also used a number of clinician-administered and self-report secondary outcome measures.

Finally, our study is consistent with many other recent studies of patients with affective disorders in that the placebo response was very high (43.2%). Possible reasons for the high placebo response rates seen in contemporary studies and methods for overcoming this problem with new trial designs have been reviewed recently by Fava et al.³⁷ ♣

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