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## **A Randomized, Double-blind, Placebo-controlled Study of Intrathecal Ziconotide in Adults With Severe Chronic Pain**

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**ABSTRACT**

Safety and efficacy data of slow intrathecal (IT) ziconotide titration for the management of severe chronic pain are presented. Patients randomized to ziconotide (n=112) or placebo (n=108) started IT infusion at 0.1 mcg/h (2.4 mcg/d), increasing gradually (0.05-0.1 mcg/h increments) over 3 weeks with ziconotide mean dose at termination of 0.29 mcg/h (6.96 mcg/d). Statistical significance was noted for VASPI mean percentage improvement, baseline to Week 3 [ziconotide (14.7%) versus placebo (7.2%; p=0.036)] and many of the secondary efficacy outcomes measures. Significant adverse events (AEs) reported in the ziconotide group were: dizziness, confusion, ataxia, abnormal gait, and memory impairment. Discontinuation rates for AEs and serious AEs were comparable for both groups. Slow titration of ziconotide, a non-opioid analgesic, to a low maximum dose resulted in significant improvement in pain and was better tolerated than in two previous controlled trials that used a faster titration to a higher mean dose.

**Key words:** intrathecal therapy, non-opioid, chronic pain, ziconotide

## INTRODUCTION

Many patients with severe chronic pain fail to receive satisfactory pain relief with systemic or intrathecal (IT) opioid therapy (1-4). There are various limitations to the effectiveness of opioids in this population, including the risk of addiction and abuse (5, 6), the potential for loss of efficacy due to the development of tolerance (1, 6), adverse events (AEs) (6, 7), and catheter tip granuloma (8). Furthermore, pain is often either refractory or minimally responsive to opioid treatment (1, 6).

The non-opioid analgesic ziconotide has been developed as a new treatment for patients with severe chronic pain who are intolerant of and/or refractory to other analgesic therapies. Ziconotide is the synthetic equivalent of a 25-amino-acid polybasic peptide found in the venom of the marine snail *Conus magus* (9). In rodents, ziconotide acts by binding to neuronal N-type voltage-sensitive calcium channels (10, 11), thereby blocking neurotransmission from primary nociceptive afferents. Ziconotide produces potent antinociceptive effects in animal models (12) and its efficacy has been demonstrated in human studies (13).

Two previous randomized, placebo-controlled trials using IT ziconotide enrolled over 350 patients with severe, chronic, treatment-refractory malignant (14) and nonmalignant pain (15, 16). The starting dose in these studies was 0.4 mcg/h (9.6 mcg/d), which was subsequently lowered to 0.1 mcg/h (2.4 mcg/d) due to unexpected intolerance. The dose was increased daily to a maximum dose of 2.4 mcg/h (57.6 mcg/d) in these hospitalized patients, according to a fixed defined titration schedule, over 5 to 6 days until analgesia was obtained or intolerance developed. The mean final ziconotide dose was 0.91 mcg/h (21.8 mcg/d) for the malignant pain trial and 1.02 mcg/h (24.5 mcg/d) for

the nonmalignant pain trial (16). In both studies, the ziconotide-treated patients experienced a statistically and clinically significant reduction in pain compared to placebo patients. However, pain relief was accompanied by a high incidence of serious adverse events (SAEs) and frequent discontinuations due to AEs.

The current randomized, controlled trial was designed to evaluate the safety and efficacy of ziconotide utilizing a slower titration schedule and lower maximum dose than was used in the two previous controlled trials. To allow a more gradual titration of ziconotide, the current double-blind study was conducted over a 3-week period, with a longer time interval between dose increases, smaller dose increments, and a lower maximum dose.

## **METHODS**

### ***Study Design***

This double-blind, placebo-controlled, 2-arm, randomized study consisted of an initial screening visit, a 3-week weaning period from all IT drugs, a 1-week stabilization period, and a 3-week double-blind treatment period. During the initial screening visit, patients provided written informed consent and were evaluated for study eligibility. Eligible patients receiving IT analgesics or other IT medications at screening were gradually weaned from all IT medications over a 3-week period. As IT opioids were withdrawn, they were replaced with systemic opiates for pain control before entering the stabilization period, during which only preservative-free saline was administered in the IT pump. Patients not taking any IT medications at screening proceeded directly to the stabilization period. All patients were stabilized on systemic analgesics and other non-IT medications for at least 1 week prior to administration of the study drug. At the end of the

stabilization period (baseline), patients were randomized in a 1:1 ratio to receive ziconotide or placebo. The 3-week, double-blind treatment period required weekly treatment visits, with interval visits (1 or 2 times per week) as necessary, to adjust dose based upon patient response and to evaluate safety during dose titration.

### ***Study Participants***

Patients were recruited from 39 centers in the US. Each investigator's Institutional Review Board approved the study protocol. To be eligible for screening, patients were required to have severe chronic pain that was inadequately controlled by systemic and/or IT analgesics with a Visual Analog Scale of Pain Intensity (VASPI) (17-19) score  $\geq 50$  mm and pain of any etiology that warranted the use of IT therapy. Patients were also required to have a programmable SynchroMed<sup>®</sup> infusion system implanted prior to study enrollment. Exclusion criteria included pregnancy or lactation, investigational drug or device use within 30 days prior to screening, known sensitivity to ziconotide, and contraindications to IT therapy. There were no exclusions for coexisting medical or psychiatric conditions and all systemic medications, including opioids and other analgesics, were allowed.

Patients were eligible for randomization if they met the following inclusion criteria at baseline (i.e., after the screening and stabilization period): a VASPI score  $\geq 50$  mm, successful discontinuation of all IT medications, and a stabilized regimen of systemic analgesics and other necessary medications.

### ***Drug Administration***

During the 3-week double-blind treatment period, patients received ziconotide at a starting dose of 0.1 mcg/h (2.4 mcg/d) or placebo at the equivalent infusion rate, which

was gradually titrated upward by 0.05 to 0.10 mcg/h (1.2 to 2.4 mcg/d) increments until patients attained analgesia or reported intolerance. At least 24 hours was required between each dose increase but downward titration was allowed at any time to improve tolerability. The maximum allowable dose was 0.9 mcg/h (21.6 mcg/d) by the end of the treatment period. Patients could receive other systemic medications, including opioids, as clinically indicated, but no IT medications other than the study drug were permitted.

### ***Efficacy and Safety Measures***

The primary efficacy outcome was the mean percentage changes in VASPI score from baseline to Week 3. The mean percentage changes in VASPI from baseline to Weeks 1 and 2 were secondary efficacy outcomes. Other secondary efficacy measurements included the Clinical Global Impression (CGI) of Patient Satisfaction and CGI Overall Pain Control (20), the Categorical Pain Relief Scale (CPRS) (21), and the percentage of treatment responders at termination. Treatment responders were defined as patients with a 30% or greater decrease in VASPI scores from baseline to end of Week 3. All other patients, including those with data missing at Week 3, were classified as nonresponders. Other secondary efficacy measures included changes from baseline to termination on the Global McGill Pain Relief Questionnaire and the scores from subscales of the Brief Pain Inventory (BPI). Quality of life assessments included a sponsor-defined sleep questionnaire and the Treatment Outcomes in Pain Survey (TOPS) (22).

To quantify concomitant opiate use, patients recorded opiate consumption in a daily diary that was converted to oral morphine equivalents using standard conversion

factors. Mean weekly opiate consumption during Weeks 1, 2, and 3 was compared with that during the pretreatment stabilization period.

A complete medical history and a physical and neurological examination were performed at the screening visit. The following safety measurements were performed at screening, baseline, and termination: laboratory evaluations (chemistry and hematology), vital signs, 12-lead electrocardiogram (ECG), Mini Mental State Examination (MMSE) (23) and the Hamilton Depression Scale (HAM-D) (24). For women of childbearing potential, pregnancy tests were done at screening and termination. At every clinic visit, patients were assessed for AEs and SAEs and changes in concomitant medication use. In addition, if patients were experiencing a study drug related AE at the end of the study, they required follow-up visits at 2-week intervals until the event resolved or to a new chronic baseline. Data collected at the end of the stabilization period (baseline) served as the pretreatment values for safety and efficacy measures.

### ***Statistical Analysis***

For the primary efficacy measure, the planned sample size of 110 randomized patients in each group provided 80% power to detect a between treatment group difference of at least 15 percentage points in the mean percentage change as measured on the VASPI from baseline to Week 3. The sample size was estimated based on the use of a two-sample *t*-test with a standard deviation (SD) of 39.5% for both treatment groups (estimated from the two previous efficacy controlled trials) at the 5% level of significance. Statistical analyses were performed using SAS version 8.2 (SAS Institute Inc, Cary, NC). The ITT population included all randomized patients (N=220) and was utilized for all safety analyses, the primary efficacy analysis, and the secondary efficacy

analyses of VASPI. Analyses for all remaining efficacy parameters utilized observed data only. Baseline and demographic characteristics were compared between the two treatment groups using two-sample *t*-tests for continuous variables, chi-square tests for categorical variables with all expected cell counts  $\geq 5$ , and Fisher's exact test for categorical variables with at least 1 expected cell count  $< 5$ .

The mean percentage change from baseline to each weekly visit on the VASPI was compared between treatment groups using the two-sample *t*-test, incorporating LOCF. A number of sensitivity analyses were also performed to investigate possible bias introduced by using the LOCF method, including observed case analysis (i.e., no imputation), imputing the median percentage change from all patients in the same treatment group at each weekly visit, and imputing the smallest (i.e., "worst") percentage change from all patients in the same treatment group at each weekly visit. The proportion of VASPI responders in the two treatment groups was compared using the two-sample binomial test.

The distribution of CGI responses in the two treatment groups was compared using the Mantel-Haenszel chi-square test (1 degree of freedom) assuming equally spaced scores for the CGI categories. Two-sample *t*-tests were used to compare the change from baseline in the Global McGill Pain Relief total score and the change from baseline in the TOPS total pain experience score at the termination visit between the two treatment groups. The Mantel-Haenszel chi-square test (1 degree of freedom) was used to compare the two treatment groups on the CPRS and sleep questionnaire responses at termination, and the change from baseline to termination on the BPI sub-scales. The percentage

change in weekly opiate consumption from the pretreatment stabilization period to Week 3 was compared between the two treatment groups using a two-sample *t*-test.

A modified COSTART (Coding Symbols for a Thesaurus of Adverse Reaction Terms) dictionary was used to code AEs into body systems and preferred terms; for AEs reported by 10% or more patients in either treatment group, the number of AEs reported were compared between treatment groups using Fisher's exact test. The total number of SAEs reported and the number of discontinuations due to AEs were compared between the treatment groups using the chi-square test. The two treatment groups were compared with respect to their mean change from baseline to termination in total MMSE and HAM-D scores using the two-sample *t*-test. Within each treatment group, McNemar's test was used to test laboratory changes from normal to abnormal (low or high) and vice-versa from baseline.

All statistical tests were two-sided, and results were considered statistically significant if  $p \leq 0.05$ .

## RESULTS

Figure 1 summarizes the disposition of patients in the study. Of the 248 patients enrolled at screening, 220 were randomized to study drug (112 ziconotide, 108 placebo). The majority of screened patients (79.8%;  $n=198$ ) were receiving IT morphine and/or other IT drugs and required weaning. The weaning process was successful in 92.9% of these patients and only 14 patients dropped out during weaning due to inability to tolerate withdrawal of IT drugs, AEs, non-compliance, or at the patient's request. There were 44 patients who enrolled with only saline in their pumps and they proceeded directly into the stabilization period. Stabilization on systemic analgesics and other non-IT medications

was successful for 96.5% of patients who entered this period. The dropout rate after randomization during the double-blind treatment period was essentially equal between the ziconotide (8.0%) and placebo (7.4%) groups; the reason for discontinuation was due primarily to AEs or lack of efficacy.

There were no significant differences between the two groups at randomization on demographic and pain history variables (Table 1). This patient population had severe chronic pain as evidenced by an extremely high mean VASPI score of 80.7 mm and a mean duration of pain of 14 to 15 years. The majority of the pain was classified as neuropathic, and failed back surgery syndrome (FBSS) was the single most common etiology of pain (58%).

The majority of patients (97%) were considered refractory to treatment by their physicians and 90% had already been treated with IT morphine. More than one IT drug had already been used by 58% of the patients prior to enrollment. Other prior therapies included oral opiates (99%), spinal cord stimulation (40%), spinal surgery (67%), neuroablation (10.5%), physical therapy (94%), and a wide variety of behavioral and psychological interventions. The median amount of systemic opiates taken during the stabilization period was 183 mg/d (range: 0-2126 mg/d) expressed as oral morphine equivalents.

With the exception of IT medications, all other medications were allowed during the treatment period. Patients took an average of 12 non-opioid medications during the treatment period. Opioids were the most commonly used medication during blinded treatment, used by 98% of patients. In descending order, the most commonly used opiates were: oxycodone +/- acetaminophen (41%), morphine (34%), hydrocodone +/-

acetaminophen (28%), methadone (24%), fentanyl (18%), and hydromorphone (13%).

Other adjuvant medications included antidepressants (64%), anticonvulsants (48%), muscle relaxants (42%), anxiolytics (40%), nonsteroidal anti-inflammatory drugs (34%), and sedative hypnotics (27%).

### *Efficacy*

The initial dose of blinded study drug was 0.1 mcg/h (2.4 mcg/d). At Week 3, the mean dose was 0.29 mcg/h (6.96 mcg/d) for the ziconotide group and 0.44 mcg/h (10.56 mcg/d) for the placebo group. The maximum dose used by any ziconotide-treated patient was 0.8 mcg/h (19.2 mcg/d) and the maximum dose used by any placebo patient was 0.9 mcg/h (21.6 mcg/d).

In the primary efficacy analysis, VASPI scores improved from baseline to Week 3 by a mean of 14.7% in the ziconotide-treated group and 7.2% in the placebo group ( $p=0.036$ ; Figure 2). The onset of efficacy was observed among ziconotide-treated patients at Week 1, with a mean percent improvement on the VASPI of 16.6%, compared to a mean percent improvement of 5.0% among the placebo patients ( $p=0.0026$ ). At Week 2, the mean percent improvement in VASPI scores for the ziconotide-treated group (13.8%) was greater than that for the placebo group (8.2%), but this difference was not statistically significant ( $p=0.12$ ). Results from the sensitivity analyses were not appreciably different from those results seen when the LOCF method was used. The proportion of treatment responders (i.e., those with at least 30% VASPI score improvement) did not differ significantly between groups (16.1% for ziconotide, 12.0% for placebo,  $p=0.39$ ) at Week 3.

At study termination, 28.4% of patients in the ziconotide group reported “a lot” or “complete” satisfaction with therapy on the CGI Satisfaction scale, compared with 12.1% of patients in the placebo group ( $p=0.0027$ ) (Figure 3a). On the CGI Overall Pain Control measure, 11.9% of ziconotide-treated patients reported “very good” or “excellent” pain control at study termination, compared with 0.9% of placebo-treated patients ( $p=0.0004$ ) (Figure 3b). Results of other secondary efficacy and quality of life parameters are presented in Table 2.

The change in the Global McGill Pain Relief total score was significantly reduced in the ziconotide group compared to the placebo group ( $p=0.026$ ). The CPRS showed a trend in favor of ziconotide but the difference did not reach significance ( $p=0.0596$ ). The impact of pain on quality of life, assessed using the TOPS questionnaire did not show a significant difference in mean change between the two treatment groups after only 3 weeks of treatment (ziconotide mean 3.9 (SD=11.13); placebo mean 1.8 (SD=11.44);  $p=0.1837$ ). The TOPS total pain experience score was 67.6 for ziconotide and 67.5 for placebo patients at study termination. The normative score for a healthy population was 14.2 and for a pain clinic population was 63.4 (22). Thus, the study population was severely impaired by pain and had a poor quality of life as measured by the TOPS. Finally, using a sponsor-defined sleep questionnaire, sleep pattern (uninterrupted hours of sleep and sleep quality) were both significantly improved by ziconotide treatment compared to placebo (Table 2). Most of the BPI sub-scales were not improved by treatment; specifically, no statistically significant difference between treatment groups was found for the following sub-scales: sleep, relations, work, mood, and walking. However, the enjoyment of life sub-scale of the BPI showed a statistically significant

improvement for ziconotide; 42.2% of ziconotide-treated patients improved by at least one unit from baseline to termination compared with 27.4% for placebo-treated patients ( $p=0.019$ ). (Table 3)

In the ziconotide group, there was a 23.7% mean decrease in weekly opiate use (in morphine equivalents) from pretreatment stabilization to Week 3, compared to a 17.3% decrease in the placebo group ( $p=0.44$ ). Mean weekly opiate consumption for the ziconotide group was 2101 mg (SD, 2353 mg) during pretreatment stabilization and 1524 mg (SD, 1627 mg) at Week 3. For the placebo group, mean weekly opiate consumption was 1876 mg (SD, 2146 mg) during pretreatment stabilization and 1453 mg (SD, 1579 mg) at Week 3. Since opiate consumption decreased in both treatment groups, the improvements in VASPI cannot be explained by increases in opiate use.

### ***Safety***

During the treatment period, 92.9% of patients in the ziconotide group and 82.4% of patients in the placebo group reported AEs ( $p=0.023$ ). The severity of AEs reported was primarily mild or moderate (ziconotide, 83.6%; placebo, 83.8%). The AEs most frequently occurring during the 3-week treatment period in either group are listed in Table 4. The AEs related to the central nervous system (CNS), such as dizziness, confusion, ataxia, abnormal gait, and memory impairment, were significantly reported more frequently in the ziconotide-treated patients than in placebo-treated patients (Table 4). The median time to onset for the most commonly reported ziconotide-related AEs (i.e., dizziness, nausea, confusion, ataxia, and asthenia) ranged from 3.0 to 9.5 days (Table 5). The median ziconotide dose at the time of AE onset ranged narrowly from 0.11 to 0.30 mcg/h (2.6 to 7.2 mcg/d) and thus AEs occurred at the therapeutic doses. For

patients reporting AEs at the end of the treatment period, the time to resolution for most of these AEs was within 1 to 2 weeks of drug discontinuation.

During the treatment period, 11.6% of ziconotide patients (13/112) reported a total of 19 SAEs and 9.3% of placebo patients (10/108) reported a total of 25 SAEs ( $p=0.57$ ). Serious AEs were considered study drug related by the investigator in 1.8% of ziconotide patients (2/112) and in 1.9% of placebo patients (2/108). Ziconotide-related SAEs included chest pain, hypertension, ataxia, dizziness, and neuralgia. No cases of anaphylaxis or hypersensitivity to ziconotide were reported.

The discontinuation rate due to AEs during the treatment period was comparable in the ziconotide ( $n=6$ , 5.4%) and placebo groups ( $n=5$ , 4.6%;  $p=0.80$ ). An additional three patients in each group discontinued treatment for other reasons: two ziconotide and two placebo patients due to lack of efficacy; one ziconotide patient voluntarily withdrew consent; and one placebo patient with a history of severe obstructive pulmonary disease and heart failure died from ventricular fibrillation.

At baseline, the mean MMSE total scores were similar between treatment groups (ziconotide, 29.0; placebo, 29.2). No significant difference between treatment groups was seen for the change in total MMSE score from baseline to termination (ziconotide, -0.4; placebo, -0.1;  $p=0.21$ ). Similar results were seen with the HAM-D total score. At baseline the mean total score was 13.3 for ziconotide and 11.5 for placebo. The mean change from baseline to termination was -0.3 for ziconotide and 0.4 for placebo ( $p=0.25$ ).

No clinically significant changes in vital signs or ECGs were noted in either treatment group from baseline to termination.

In ziconotide-treated patients, statistically significant shifts from normal at baseline, to above normal at termination were reported for uric acid, lactate dehydrogenase, and creatine kinase (CK). Two of the ziconotide-treated patients had CK levels greater than 3 times the upper limit of normal (ULN) at baseline (198 IU/L). These two patients plus an additional 3 patients had elevations in CK levels greater than 3 times the ULN at study endpoint. Of these 5 patients, only one experienced a SAE (hypokalemia), which the investigator reported as not related to ziconotide. Four of these patients did report muscular symptoms such as myalgia and muscle cramps during ziconotide treatment. No placebo patients had CK elevations greater than 3 times the ULN at baseline or termination. All other changes in blood chemistry values from baseline were relatively small in both groups and had no apparent trends.

## DISCUSSION

The management of patients with severe chronic pain poses a challenge to clinicians. The complexity of chronic pain having nociceptive, neuropathic, or mixed nosology can make diagnosis and long-term treatment difficult (25). These patients are often intolerant to and/or refractory to currently available treatments including IT opiates, thus demonstrating a need for new non-opioid analgesics.

This is the third double-blind, placebo-controlled study with ziconotide that formed the basis of the recent approval by the US Food and Drug Administration. Ziconotide appears to be the most studied IT analgesic with a total of 583 patients in randomized, double-blind, placebo-controlled clinical trials. In the current study, almost all of the 220 patients (96.8%) were determined by their physicians to be refractory to existing analgesic treatments. In three quarters of these patients, neuropathic pain was a significant component or the sole type of their pain. Even with the use of concomitant oral opiate medication in >98% of patients, ziconotide effectively reduced pain after 3 weeks of treatment with the onset of significant efficacy observed at Week 1 (Figure 2).

Although there was a statistically significant difference between the ziconotide and placebo groups in the primary efficacy analysis, mean percentage change in VASPI at Week 3 using LOCF, the magnitude of the improvement was small in both treatment groups. Nevertheless, this outcome was confirmed by the sensitivity analyses that did not use LOCF. Moreover, the clinical significance of this improvement in VASPI is supported by statistically significant differences between the two treatment groups in a number of secondary outcome measures such as CGI Satisfaction, CGI Overall Pain Control, and the Global McGill Pain Relief total score. The magnitude of the

improvement in VASPI score was also smaller in this study than in the two previous controlled trials. This difference is most likely due to the lower doses used in this study (mean dose 0.29 mcg/h, maximum dose 0.8 mcg/h) compared with those used in the two previous studies [mean doses of 0.91 and 1.02 mcg/h (range 21.8-24.5 mcg/d), maximum dose 2.4 mcg/h (57.6 mcg/d)]. It may also be the result of the greater number of refractory patients enrolled or the longer treatment duration of 3 weeks in an outpatient setting in this study compared to the 5 to 6 days in the hospital in the previous two studies.

In the current study, low dropout rates were observed, not only during the weaning (7.1%) and stabilization (3.5%) periods, but also during the 3-week placebo-controlled treatment phase (8.0% ziconotide, 7.4% placebo). This finding is in contrast to the two previous controlled, fast-titration trials, in which discontinuation rates of 32.4% and 28.4% were observed during the double-blind treatment phase. The improved retention rate in this study is likely a result of the low-dose, slow titration schedule, which allowed for individualization of dose by the physician for each patient. Moreover, the majority of patients receiving ziconotide in the current trial (87%) expressed a desire to continue receiving the medication in an open-label follow-up study.

Compared with the two previous controlled trials of ziconotide, not only was the discontinuation rate low, but the overall safety profile was improved. Although the overall frequency of AEs was similar, fewer SAEs and AEs leading to discontinuations were reported. In the two previous studies using a fixed, high-dose, fast titration schedule, many patients initiating treatment at >0.1 mcg/h (2.4 mcg/d) reported rapid onset of AEs, particularly nervous-system related SAEs. In the previous malignant pain

study, 22 ziconotide-treated patients (30.6%) reported 31 SAEs during the initial titration period, 14 (45.2%) of which involved the nervous system and were considered ziconotide-related by the investigator (5 moderate, 9 severe) (15). In the previous nonmalignant pain study, 28 ziconotide-treated patients (16.5%) reported 45 SAEs during the initial titration period, 20 (44.4%) of which involved the nervous system and were considered ziconotide-related by the investigator (2 mild, 7 moderate, 11 severe) (16). In the current trial, two (1.8%) patients reported SAEs that were considered ziconotide-related by the investigator (chest pain, hypertension, ataxia, dizziness and neuralgia); the majority of reported AEs were mild or moderate, and did not lead to discontinuation from the study. This finding suggests that increasing ziconotide doses slowly and in small increments on an individualized patient basis is the best way to achieve analgesia with an improved safety profile.

The US prescribing information for ziconotide contains a box warning for severe psychiatric symptoms and neurologic impairment (26). Compared with the two previous studies, the current study had a higher incidence of AEs related to higher cortical functions such as confusion and memory impairment. Such differences could be attributable to the longer duration of the current study and the higher cumulative dose over 3 weeks compared to only 5 to 6 days in the two previous controlled trials. However, results from the MMSE in the current study indicated no substantial changes in mental status and no significant differences between the ziconotide and placebo groups.

Elevations in CK levels greater than 3 times the ULN were noted in 5 ziconotide-treated patients at termination. Such CK elevations appear to be related to ziconotide, but their etiology remains unclear. For some patients, CK levels rose during the weaning and

stabilization periods, suggesting that CK level elevations were not attributable to ziconotide therapy alone. Although there did not appear to be any clinical sequelae of CK elevations in these patients, further investigation of the possible consequences of elevated CK levels in ziconotide-treated patients would be warranted.

The time course of ziconotide's observable pharmacologic action appears to develop more slowly than the kinetics of the distribution of ziconotide into the cerebrospinal fluid (CSF). The median time to onset of the most commonly reported AEs ranged from 3 to 9.5 days. In contrast, the half-life of ziconotide in human CSF is 4.6 hours (26), suggesting that an approximation to steady-state CSF concentration is achieved within 24 hours (approximately 5 half-lives). In the current study, dose changes could be made 2 to 3 times per week and no more frequently than every 24 hours. The relatively slow onset of AEs suggests that increments in the dosing of ziconotide be made no more frequently than weekly.

The apparent lag between CSF pharmacokinetics and the pharmacodynamics of ziconotide may reflect the drug's slow penetration into the CNS parenchyma. Consistent with ziconotide's molecular weight of approximately 2500 d and its polycationic nature, microdialysis studies in rat brain with radioiodinated ziconotide have shown that no detectable ziconotide diffused more than 1 mm from the dialysis probe in two hours of perfusion (27). The slow diffusion of ziconotide in neural tissue may also explain the slower-than-expected time course of resolution of AEs with discontinuation of ziconotide therapy. As stated above, based on the 4.6-hour CSF half-life of the drug, pharmacologically active concentrations of ziconotide would be expected to be cleared within 24 hours. However, for patients experiencing AEs at the end of their treatment

period, the time to resolution for most of these AEs was up to two weeks after ziconotide discontinuation. Other factors, such as a slow-off rate for ziconotide binding to its receptor (based upon animal studies), the N-type calcium channel, may also contribute to the slow reversal of AEs. The above result suggests that the full impact of reductions in ziconotide dosing may not be seen for several days. If an AE occurs, ziconotide can be immediately discontinued without the occurrence of withdrawal effects as seen (26).

Finally, the median ziconotide dose at the time of AE onset ranged narrowly from 0.11 to 0.30 mcg/h (2.6 to 7.2 mcg/d), consistent with the observation that time of onset for most AEs was within the first week of ziconotide therapy at the starting dose of 0.1 mcg/h (2.4 mcg/d). As mentioned above, efficacy was demonstrated in the first week of treatment. These results suggest that when titrating ziconotide, the starting dose should be no greater than 0.1 mcg/h (2.4 mcg/d). It should not be surprising that efficacy and AEs begin to manifest at similar doses. Because of the very high specificity of ziconotide for its target, efficacy and AEs are both likely due to inhibition of N-type calcium channels. Thus, as the results of the current study show, ziconotide has a narrow therapeutic index and must be administered carefully in order to provide maximum benefit for the patient.

## **Conclusion**

Ziconotide, a new non-opioid analgesic, reduced pain as measured by the VASPI in patients with severe chronic pain who were intolerant of and/or refractory to treatment with other analgesics including IT morphine. Using the slow dose titration regimen starting at 0.1 mcg/h (2.4 mcg/d) and titrating to a mean dose of 0.29 mcg/h (6.96 mcg/d) over 3 weeks, the degree of pain relief was less than that noted in the two previous controlled trials of ziconotide, but better patient retention and an improved safety profile

were observed (15, 16). Taken together, the 3 controlled trials demonstrate that, in order to achieve the best overall treatment outcome, slow titration of ziconotide at low doses is necessary to identify each patient's individualized therapeutic window. As the most comprehensively studied IT analgesic in controlled trials, ziconotide appears to have a place in the management of severe chronic pain.

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**Table 1. Patient Baseline and Demographic Characteristics**

	Ziconotide (N=112)	Placebo (N=108)	p-value*
Age, y			
Mean (SD)	52.5 (12.12)	54.8 (11.48)	0.15 ( <i>t</i> )
Sex, No. (%) of Patients			
Male	53 (47.3)	55 (50.9)	0.59 ( $\chi$ )
Female	59 (52.7)	53 (49.1)	
Race, No. (%) of Patients			
Caucasian	107 (95.5)	99 (91.7)	0.44 (E)
Black	1 (0.9)	3 (2.8)	
Hispanic	3 (2.7)	5 (4.6)	
Asian	1 (0.9)	0	
Other	0	1 (0.9)	
Pain classification, No. (%) of Patients <sup>†</sup>			
Neuropathic	85 (75.9)	77 (71.3)	0.44 (C)
Nociceptive	40 (35.7)	35 (32.4)	0.61 (C)
Mixed	37 (33.0)	43 (39.8)	0.30 (C)
Peripheral	17 (15.2)	10 (9.3)	0.18 (C)
Degenerative	31 (27.7)	33 (30.6)	0.64 (C)
Post-traumatic	16 (14.3)	21 (19.4)	0.31 (C)
Duration of pain, y			
Mean (SD)	13.87 (10.17)	14.95 (9.60)	0.42 ( <i>t</i> )
Refractory to treatment, No. (%) of Patients			
Yes	108 (96.4)	105 (97.2)	1.00 (E)
No	4 (3.6)	3 (2.8)	
Oral morphine equivalent use during pretreatment stabilization period, mg/d <sup>‡</sup>			
Mean (SD)	300.2 (336.16)	268.0 (306.51)	0.46 ( <i>t</i> )
Baseline VASPI score, mm			
Mean (SD)	80.7 (15.0)	80.7 (14.9)	0.98 ( <i>t</i> )

\*From two-sample *t*-tests (*t*) for continuous variables, chi-square tests (C) for categorical variables with all expected cell counts  $\geq 5$ , and Fisher's exact test (E) for categorical variables with at least 1 expected cell count  $< 5$ .

†A patient may have more than 1 pain classification.

\*Oral morphine equivalent (mg/d) was calculated using oral morphine equivalent during stabilization period divided by number of days.

**Table 2. Results of Various Secondary Efficacy Parameters**

Parameter	Ziconotide (N=112)	Placebo (N=108)	p-value
Global McGill Pain Relief Questionnaire Total Score			
N	108	107	
Mean (SD) change*	3.2 (8.71)	0.6 (8.24)	0.0259†
CPRS Rating at Termination, No. (%) of Patients			
Worse	35 (32.1)	27 (25.2)	0.0596‡
No change	23 (21.1)	46 (43.0)	
Slight improvement	22 (20.2)	19 (17.8)	
Moderate improvement	12 (11.0)	11 (10.3)	
A lot of improvement	15 (13.8)	3 (2.8)	
Complete relief	2 (1.8)	1 (0.9)	
Missing	3	1	
TOPS Total Pain Experience Score			
N	109	107	
Mean (SD) change*	3.9 (11.13)	1.8 (11.44)	0.1837†
Sleep Pattern (Uninterrupted) at Termination, No. (%) of Patients			
<2 hours	20 (18.5)	29 (27.1)	0.0067‡
2-4 hours	45 (41.7)	55 (51.4)	
4-6 hours	33 (30.6)	18 (16.8)	
>6 hours	10 (9.3)	5 (4.7)	
Missing	4	1	
Overall Quality of Sleep, No. (%) of Patients			
Poor	45 (41.7)	61 (57.0)	0.0059‡
Fair	43 (39.8)	38 (35.5)	
Good	20 (18.5)	8 (7.5)	
Missing	4	1	

Note: All p-values are based analyses using only non-missing data.

\*Baseline score minus score at termination

† Two-sample *t*-test

‡ Mantel-Haenszel chi-square test, df=1

**Table 3. Brief Pain Inventory (BPI) Subscales**

	Ziconotide (N=112)	Placebo (N=108)	p-value±
	n (%)	n (%)	
BPI Mood, Change from Baseline at Termination			0.5798
Worsened by ≥ 2 units	7 (6.4)	7 (6.6)	
Worsened by 1 unit	29 (26.6)	20 (18.9)	
Unchanged	31 (28.4)	48 (45.3)	
Improved by 1 unit	26 (23.9)	24 (22.6)	
Improved by ≥ 2 units	16 (14.7)	7 (6.6)	
Missing	3	2	
BPI Relations with Other People, Change from Baseline at Termination			0.158
Worsened by ≥ 2 units	10 (9.3)	10 (9.4)	
Worsened by 1 unit	17 (15.7)	21 (19.8)	
Unchanged	36 (33.3)	47 (44.3)	
Improved by 1 unit	29 (26.9)	15 (14.2)	
Improved by ≥ 2 units	16 (14.8)	13 (12.3)	
Missing	4	2	
BPI Walking Ability, Change from Baseline at Termination			0.9161
Worsened by ≥ 2 units	12 (11.3)	6 (5.9)	
Worsened by 1 unit	18 (17.0)	17 (16.7)	
Unchanged	33 (31.1)	45 (44.1)	
Improved by 1 unit	25 (23.6)	21 (20.6)	
Improved by ≥ 2 units	18 (17.0)	13 (12.7)	
Missing	6	6	
BPI Sleep, Change from Baseline to Termination			0.1412
Worsened by ≥ 2 units	12 (11.0)	4 (3.8)	
Worsened by 1 unit	15 (13.8)	24 (23.1)	
Unchanged	40 (36.7)	51 (49.0)	
Improved by 1 unit	20 (18.3)	16 (15.4)	
Improved by ≥ 2 units	22 (20.2)	9 (8.7)	
Missing	3	4	
BPI Normal Work, Change from Baseline at Termination			0.2646
Worsened by ≥ 2 units	11 (10.2)	7 (6.7)	
Worsened by 1 unit	14 (13.0)	16 (15.2)	
Unchanged	39 (36.1)	52 (49.5)	
Improved by 1 unit	28 (25.9)	24 (22.9)	
Improved by ≥ 2 units	16 (14.8)	6 (5.7)	
Missing	4	3	
BPI Enjoyment of Life, Change from Baseline at Termination			0.0188
Worsened by ≥ 2 units	10 (9.2)	9 (8.5)	
Worsened by 1 unit	13 (11.9)	20 (18.9)	
Unchanged	40 (36.7)	48 (45.3)	
Improved by 1 unit	24 (22.0)	19 (17.9)	
Improved by ≥ 2 units	22 (20.2)	10 (9.4)	
Missing	3	2	

± Mantel-Haenszel chi-square test (assuming equally spaced scores), df=1

**Table 4. AEs Most Frequently Reported During the Treatment Period (Incidence  $\geq$  10% in Either Treatment Group)**

Adverse Event	Patients, No. (%)	
	Ziconotide (N=112)	Placebo (N=108)
Any AE	104 (92.9)*	89 (82.4)
Dizziness	53 (47.3)*	14 (13.0)
Nausea	46 (41.1)	33 (30.6)
Asthenia	25 (22.3)	13 (12.0)
Somnolence	25 (22.3)	16 (14.8)
Diarrhea	21 (18.8)	18 (16.7)
Confusion	20 (17.9)*	5 (4.6)
Ataxia	18 (16.1)*	2 (1.9)
Headache	17 (15.2)	13 (12.0)
Vomiting	17 (15.2)	14 (13.0)
Abnormal gait	17 (15.2)*	2 (1.9)
Memory impairment	13 (11.6)*	1 (0.9)
Pain	12 (10.7)	8 (7.4)
CK increased	12 (10.7)	4 (3.7)
Pruritis	9 (8.0)	11 (10.2)
Insomnia	7 (6.3)	13 (12.0)

\*Occurred with significantly greater frequency with ziconotide versus placebo administration,  $p \leq 0.05$  (Fisher's exact test).

**Table 5: Time to Onset of AEs (Ziconotide-treated patients only)**

Adverse Events of Particular Interest	Incidence n (%)	Median Day at Onset (range)	Median Dose (mcg/h) at Onset (range)
Abnormal gait (including ataxia)	34 (30.4%)	4.5 (0-24)	0.20 (0.1-4.0)
Abnormal vision (including amblyopia)	11 (9.8%)	8.0 (0-30)	0.20 (0.1-0.6)
Aphasia or speech disorder	19 (17.0%)	16.0 (4-24)	0.30 (0.1-0.6)
Asthenia (including myasthenia)	27 (24.1%)	3.0 (0-30)	0.15 (0.1-0.6)
Confusion	20 (17.9%)	9.5 (0-24)	0.28 (0.1-0.6)
Dizziness	53 (47.3%)	3.0 (0-24)	0.15 (0.1-0.6)
Memory impairment or amnesia	16 (14.3%)	7.5 (2-29)	0.16 (0.1-0.6)
Nausea (including vomiting and/or nausea)	53 (47.3%)	4.0 (0-32)	0.13 (0.1-0.4)
Nystagmus	9 (8.0%)	8.0 (4-16)	0.16 (0.1-0.7)
Somnolence	25 (22.3%)	4.0 (0-24)	0.11 (0.1-0.5)
Thinking abnormal (including difficulty concentrating and memory slowing)	8 (7.1%)	4.0 (0-18)	0.12 (0.1-0.5)
Urinary retention	10 (8.9%)	7.5 (1-24)	0.15 (0.0-0.6)

## FIGURE LEGENDS

Figure 1. Patient disposition and termination by treatment group. \*44 patients did not require weaning of IT medications and entered the stabilization period directly.

†184 patients completed the weaning period and entered the stabilization period.

Figure 2. Mean percentage change in VASPI score from baseline to Weeks 1, 2, and 3 using the LOCF imputation method. The primary efficacy outcome was the mean percentage change in VASPI score from baseline to Week 3

Figure 3. CGI at termination. For Satisfaction With Therapy (a) and Overall Pain Control (b), the difference between the 2 treatment groups was statistically significant ( $p=0.0027$  and  $p=0.0004$ , respectively; Mantel-Haenszel chi-square test with one degree of freedom, assuming equally spaced scores).

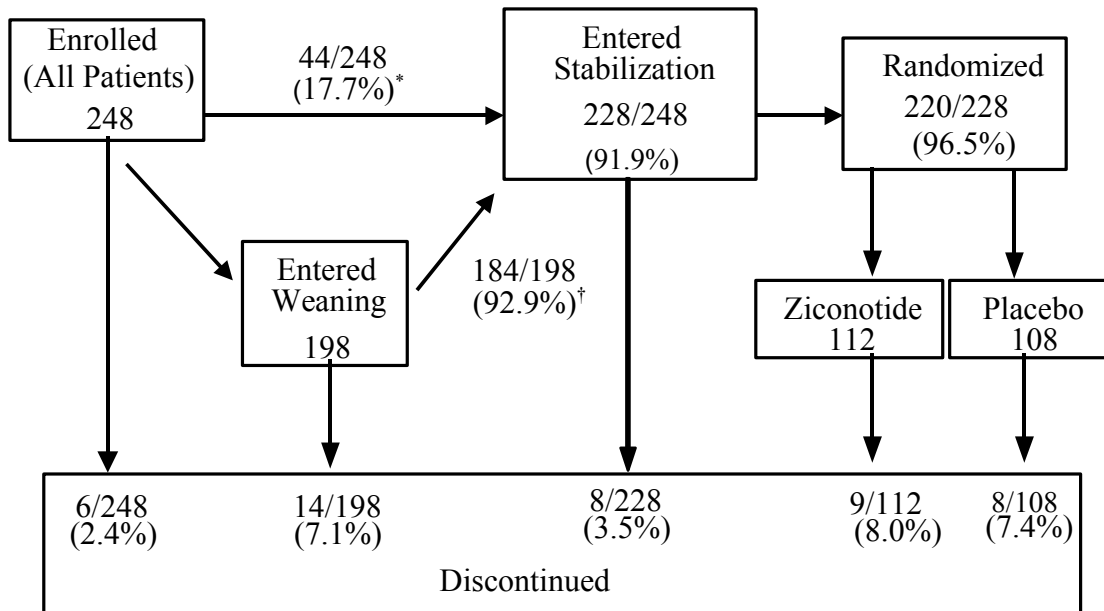


Figure 1

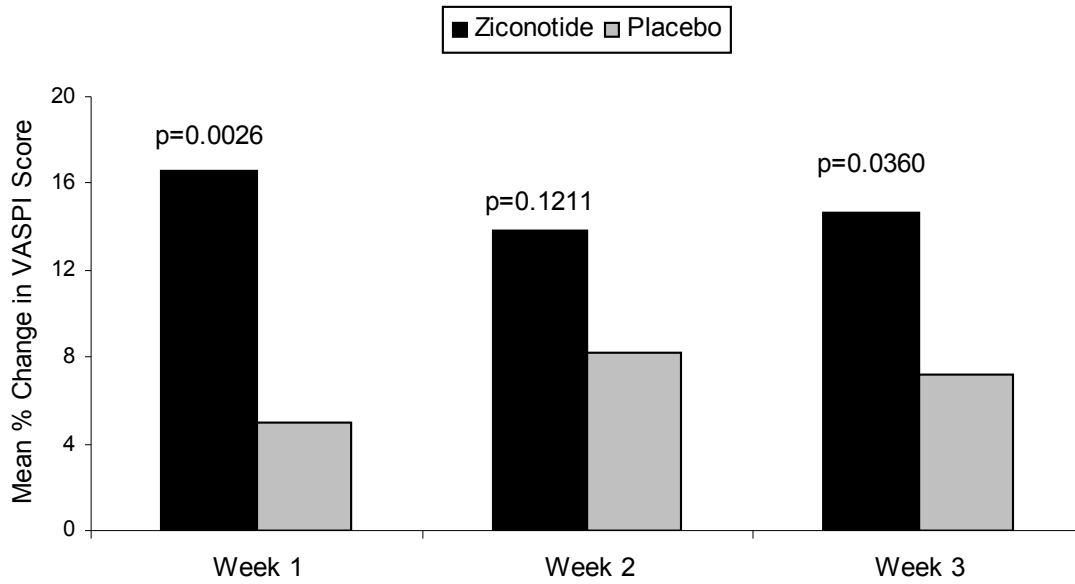
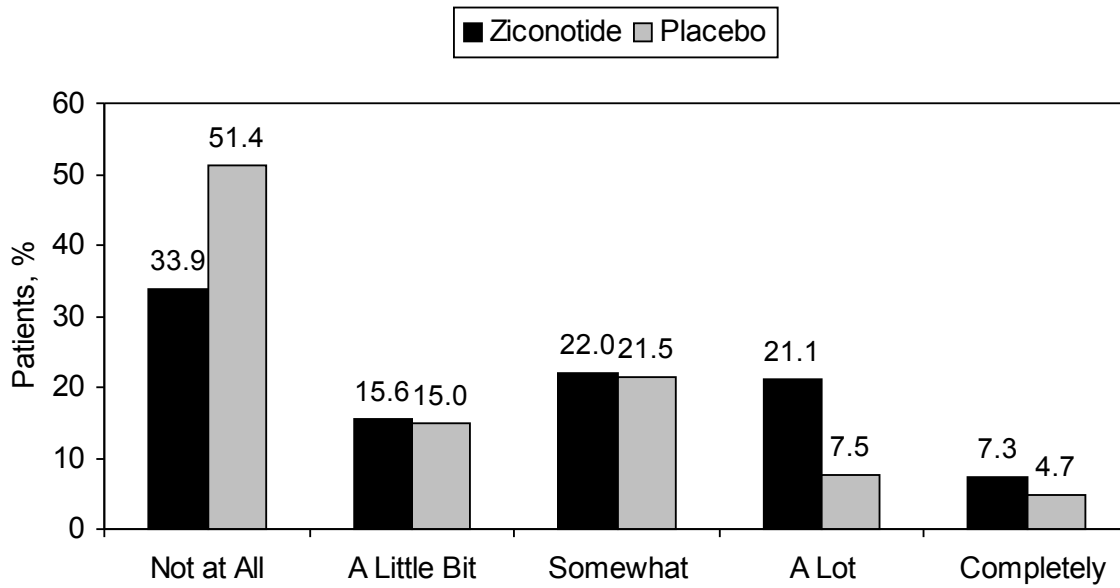
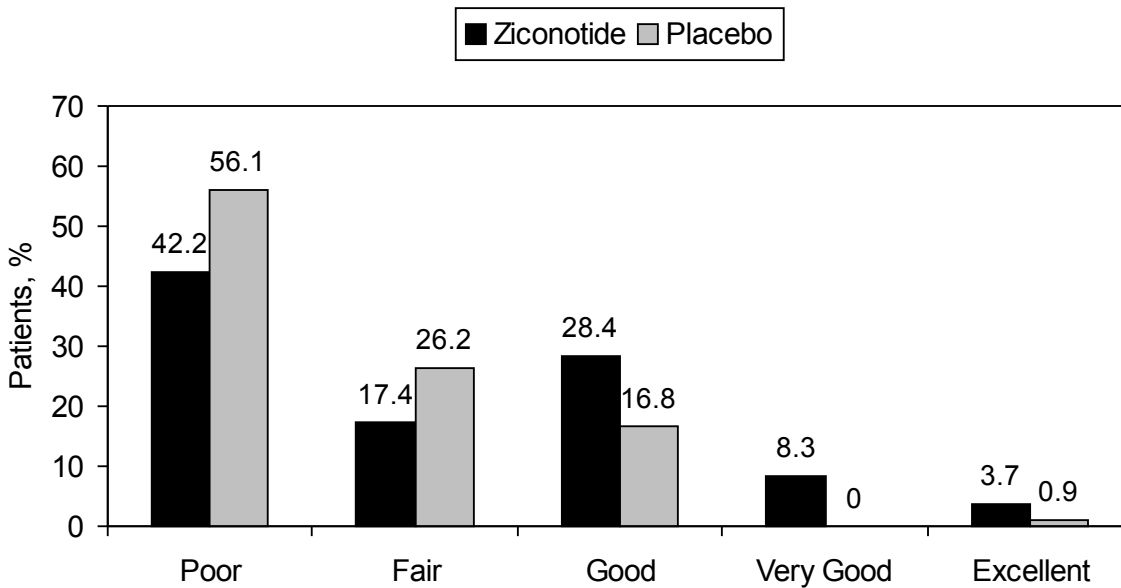


Figure 2



(a) CGI Satisfaction



(b) CGI Pain Control

Figure 3