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Open-Label, Multicenter Study of Combined Intrathecal Morphine and Ziconotide: Addition of Morphine in Patients Receiving Ziconotide for Severe Chronic Pain

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ABSTRACT

Objective. To assess the safety and efficacy of adding intrathecal morphine to intrathecal ziconotide in patients treated with stable ziconotide doses.

Design. Multicenter, open-label study with a 4-week morphine titration phase during which ziconotide was held constant and an extension phase during which dosing of either drug could vary.

Setting. Outpatient clinics.

Patients. Patients with suboptimal pain relief receiving stable ziconotide doses (≥4.8 μg/day) in one of two ongoing ziconotide trials.

Interventions. Ziconotide dosing remained constant during the titration phase; intrathecal morphine titration was based on each patient's daily systemic opioid dose at the study's start. During the extension phase, intrathecal ziconotide and morphine dosing were adjusted per investigator discretion.

Outcome Measures. Safety was assessed primarily via adverse events. Efficacy was analyzed via percentage change on the visual analog scale of pain intensity and in weekly systemic opioid consumption.

Results. Twenty-five patients enrolled. The most common (≥10% of patients in either study phase) study drug-related (i.e., ziconotide/morphine combination [or ziconotide monotherapy in the extension phase only]) treatment-emergent adverse events included dizziness, peripheral edema, pruritus, and nausea. From the initial visit to week 4, visual analog scale of pain intensity scores improved by a mean of 26.3% (95% confidence interval: 15.6%–37.1%) but varied during the extension phase (mean percentage change from the initial visit ranged from –0.4% at week 16 to –35.0% at week 72). Mean percentage decrease in systemic opioid consumption from the initial visit was 49.1% at week 4 and 51.2% at week 56 of the extension phase.

Conclusions. Intrathecal morphine, combined with stable intrathecal ziconotide doses, reduced pain in patients with previously suboptimal pain relief on ziconotide monotherapy.

Key Words. Ziconotide; Morphine; Intrathecal; Combination Therapy

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Introduction

Ziconotide is the first nonopioid intrathecal (IT) analgesic approved by the US Food and Drug Administration for the treatment of severe chronic pain in patients for whom IT therapy is warranted and who are intolerant of or refractory to other treatment, such as systemic analgesics, adjunctive therapies, or IT morphine. It is the synthetic equivalent of a 25–amino-acid peptide found in the venom of *Conus magus*, a marine snail. Ziconotide exerts its antinociceptive effects by binding to and directly blocking neuronal N-type, voltage-sensitive calcium channels, thereby inhibiting calcium influx and reducing the release of neurotransmitters [1–4]. Clinical trials have demonstrated the safety and efficacy of IT ziconotide monotherapy in treating severe chronic pain [5–7].

Currently, morphine and hydromorphone are considered first-line IT therapy for severe chronic pain [8]. In patients who do not respond to IT monotherapy, combinations of drugs are often employed. Theoretically, combining two mechanistically distinct drugs for IT therapy could result in additive effects. Morphine produces analgesia via presynaptic inhibition of neurotransmitter release from primary afferent terminals, which is mediated by decreased inward conductance of calcium ions, and via postsynaptic inhibition of secondary cells in the dorsal horn, which occurs by activation of postsynaptic potassium channels [9]. Results from animal studies have suggested that the combination of an N-type calcium channel blocker (such as ziconotide) and morphine may result in additive or synergistic analgesia [3,9,10]. The present study was conducted to evaluate the safety and efficacy of the combination of IT morphine and ziconotide in patients with severe chronic pain.

Methods

Objectives

This open-label, multicenter study was designed to assess the safety of adding progressively increasing amounts of IT morphine to IT ziconotide in patients being treated with a stable ziconotide dose. Other study objectives were to determine whether adding IT morphine to ziconotide provided additional pain relief compared with ziconotide alone, and to determine whether the addition of IT morphine allowed for a reduction in systemic opioid consumption.

Study Subjects

Patients were eligible for inclusion in the study if they had an implanted programmable SynchroMed® Infusion System (Medtronic, Inc., Minneapolis, MN) in place for the treatment of chronic pain and were receiving a stable IT ziconotide dose of at least 4.8 μg/day as monotherapy in one of two ongoing long-term clinical trials of ziconotide. Patients were also required to have suboptimal pain relief (i.e., visual analog scale of pain intensity [VASPI] score of ≥40 mm or residual pain not relieved by ziconotide and of a different nature than pain relieved by ziconotide) and to have no ongoing serious drug-related adverse events at the time of study entry. Signing an informed consent form before study participation and the use of adequate contraceptive methods by females of childbearing potential were also required for study participation. Study exclusion criteria included pregnancy or lactation, use of an investigational drug or device other than ziconotide within 30 days before initiation of the study drug, a known history of intolerance or hypersensitivity to IT morphine, and a condition contraindicating the use of IT analgesia.

Study Design

The study began with an initial visit, which was the termination visit from the ongoing ziconotide monotherapy trial. At the initial visit, patients underwent a complete physical examination, and a complete medical history was obtained. The initial visit was followed by a 4-week titration phase with weekly clinic visits, during which the patient's ziconotide dose remained unchanged from the previous study and the IT morphine dose was increased. At the end of the titration phase, patients could continue on combination therapy or ziconotide monotherapy in the extension phase or terminate from the study. During the extension phase, clinic visits were scheduled at a minimum of every 60 days, and unscheduled visits could occur for pump refill, dosage change, adverse-event assessment, or post-termination follow-up.

Study Drug

The dose of ziconotide remained constant during the titration phase. The starting dose and titration of IT morphine were based on the average daily dose of systemic opioids (converted to oral morphine equivalents) each patient was taking at the start of the study (Table 1). Upward titration of IT morphine was allowed only at scheduled weekly visits. Scheduled dose escalation of IT morphine

Table 1 Dose escalation schedule for intrathecal morphine (titration phase)

Average Daily Dose of Systemic Opioids at Start of Study as Oral Morphine Equivalents (mg/day)	Dose for Week 1 (mg/day)	Dose for Week 2 (mg/day)	Dose for Week 3 (mg/day)	Dose for Week 4 (mg/day)
<100	0.25	0.5	1.0	2.0
100–300	0.5	1.0	2.0	3.0
>300	1.0	2.0	3.0	4.0

was stopped if the patient experienced intolerable adverse events or significantly improved analgesia. During the extension phase, the dosing of ziconotide and IT morphine could be adjusted at study visits at the discretion of the investigator.

Safety Measurements

Adverse events were monitored at each visit throughout the study and assessed by the investigator as serious or nonserious; mild, moderate, or severe; and related or not related to the study drug (i.e., the combination of IT morphine and ziconotide [or ziconotide alone in the extension phase only]). Adverse events that were new in onset or aggravated in severity or frequency after initiation of the study drug were designated as treatment-emergent adverse events (TEAEs). Clinical laboratory evaluations, including blood chemistry and hematology tests, were performed at the initial visit, the week 4/early termination visit, every 60 days (±7 days) during the extension phase, and at the extension phase termination visit. Vital signs, including systolic and diastolic blood pressure, pulse rate, respiratory rate, and body temperature, were measured at each scheduled visit. A 12-lead electrocardiogram (ECG) was performed at the initial visit, the week 4/early termination visit, and the extension phase termination visit. The Mini Mental Status Examination (MMSE) assessed patients' level of cognition on a 0–30 scale, with 30 being the best possible score, and also assessed the patient's level of consciousness as alert, drowsy, stupor, or coma. The MMSE was administered at the initial visit, the week 4/early termination visit, and the extension phase termination visit. Concomitant medication use was assessed at all study visits.

Efficacy Measurements

The primary efficacy measure was the VASPI score, measured at all study visits during the titration phase and the extension phase. The VASPI is a 100-mm scale, with 0 mm representing no pain and 100 mm representing the worst pain imaginable. The Categorical Pain Relief Scale (CPRS) was also used to assess efficacy at the week 4/early termination visit and at the extension phase termination visit. Pain relief was rated on a 1–6 scale, with 1 being worse pain and 6 being complete pain relief. Additionally, the Clinical Global Impression (CGI) scale was used to assess efficacy at the week 4/early termination visit and the extension phase termination visit. On the CGI scale, satisfaction with therapy was rated from 0 (not at all) to 4 (completely). Overall pain control was rated from 0 (poor) to 4 (excellent). Patients were also asked to rate whether the combination of IT morphine and ziconotide provided additional pain relief compared with ziconotide alone. Additionally, at each study visit, patients were asked to provide an estimate of their weekly consumption of systemic opioids (which were then converted to oral morphine equivalents).

Statistical Analysis

Safety and efficacy analyses were performed using the all patients population (which included all patients who signed an informed consent form and received any study medication) for the titration phase analyses. The extension phase population (which included all patients who entered the extension phase) was used for the extension phase analyses.

Adverse events were coded into body systems and preferred terms using a sponsor-defined modified Coding Symbols for a Thesaurus of Adverse Reaction Terms, Fifth Edition, dictionary. The frequency and percentage of patients who reported TEAEs were summarized for both the titration and extension phases; TEAEs were also summarized by seriousness, severity, relationship to study drug, and time of first occurrence. Laboratory values and changes were summarized descriptively for the initial visit, the week 4/early termination visit, each scheduled extension phase visit (i.e., at 60-day intervals), and the extension phase termination visit.

Vital signs were summarized descriptively for each scheduled study visit, and the frequency and percentage of patients with abnormal vital sign

values were tabulated. ECG readings were summarized descriptively at the initial visit, the week 4/early termination visit, and the extension phase termination visit. Changes from the initial visit to the week 4/early termination visit and the extension phase termination visit were summarized descriptively. The MMSE total score was summarized descriptively for the initial, week 4/early termination, and extension phase termination visits. Change in total score from the initial visit at the week 4/early termination and the extension phase termination visits was summarized descriptively and with two-sided 95% confidence intervals (CIs) for the mean change. The frequency and percentage of patients experiencing all magnitudes of change in consciousness from the initial visit to the week 4/early termination and extension phase termination visits were summarized.

The efficacy analyses used observed data (i.e., missing data were not imputed unless otherwise specified). The primary efficacy variable was the percentage change in VASPI score from the initial visit to week 4. The primary efficacy analysis included descriptive statistics and two-sided 95% CIs for both the mean change and mean percentage change in VASPI score from the initial visit to week 4. Several secondary efficacy analyses were also performed. Change and percentage change in VASPI score from the initial visit to the week 4/early termination visit, using the last observation carried forward (LOCF) imputation method, as well as the change and percentage change in VASPI score from the initial visit to weeks 1, 2, and 3, and to each scheduled study visit during the extension phase, were analyzed via descriptive statistics and two-sided 95% CIs for the mean changes and mean percentage changes. The mean values of weekly systemic opioid consumption (converted to oral morphine equivalents) at the initial visit and the end of weeks 1, 2, 3, and 4 were summarized via descriptive statistics. The change and percentage change in weekly systemic opioid consumption for weeks 1, 2, 3, and 4, and for each scheduled study visit during the extension phase, compared with the initial visit, were summarized via descriptive statistics and two-sided 95% CIs for the mean changes and mean percentage changes. The correlation between the percentage changes from the initial visit to week 4 in weekly systemic opioid consumption and in VASPI score was calculated using the Pearson product–moment correlation and the Spearman rank correlation. Additionally, the frequency and percentage distributions of CPRS scores and CGI scores were calculated for the week 4/early termination visit and the extension phase termination visit.

Results

Patient Disposition, Baseline Characteristics, and Demographics

Twenty-five patients were screened, enrolled, and treated, and 23 patients completed the titration phase. Two patients (8.0%) prematurely discontinued the titration phase because of adverse events. A total of 24 patients entered the extension phase, including one patient who discontinued from the study during the titration phase but was allowed to re-enter the study on ziconotide monotherapy during the extension phase. Reasons for treatment termination during the extension phase included end of study (17 patients, 70.8%), adverse event (two patients, 8.3%), death (two patients, 8.3%), patient request/withdrawal of consent (one patient, 4.2%), and other reasons (two patients, 8.3%). Treatment duration totaled 2.1 patient-years in the titration phase and 23.9 patient-years in the extension phase, for a total of 26.0 patient-years for the entire study.

Patient baseline characteristics and demographics are shown in Table 2. The etiology of pain was nonmalignant for all 25 patients. Pain was due to failed back surgery syndrome for 10 patients (40.0% titration phase, 41.7% extension phase). Pain classifications (classifications not mutually exclusive) included neuropathic (88.0% titration phase, 91.7% extension phase), nociceptive (40.0% titration phase, 37.5% extension phase), and visceral (4.0% titration phase, 4.2% extension phase). The mean duration of pain was 15.0 years for patients in the titration phase and 15.4 years for patients in the extension phase. All 25 patients who entered the study had pain that was considered by investigators to be refractory to treatment.

Safety

For most patients, the ziconotide dose was stable during the titration phase; however, because two patients discontinued the study during the titration phase and four patients had changes in their ziconotide dose (two increased, two decreased) during the titration phase (protocol deviations), the median ziconotide dose varied. Median ziconotide doses were 8.12, 8.12, 6.48, 6.48, and 4.85 μg/day at baseline and weeks 1, 2, 3, and 4, respectively. The ziconotide dose was also relatively stable during the extension phase through

Table 2 Baseline characteristics and demographics

Characteristic	All Patients Population (N = 25)	Extension Phase Population (N = 24)
Age, mean (SD), years	57.4 (14.64)	56.4 (13.93)
Sex, N (%)		
Male	10 (40.0)	10 (41.7)
Female	15 (60.0)	14 (58.3)
Race, N (%)		
Caucasian	25 (100.0)	24 (100.0)
VASPI score, mean (SD), mm	70.3 (18.86)	71.3 (18.56)
Previous IT opioid therapy, N (%)		
Yes	18 (72.0)	17 (70.8)
No	7 (28.0)*	7 (29.2)*
MMSE total score, mean (SD)	28.3 (3.60)	28.9 (1.72)
Oral morphine equivalents at initial visit, median, mg/week	840.0	735.0
Initial visit IT ziconotide dose, median, mcg/day	8.12	6.75
Initial visit IT morphine dose, median, mg/day	0.25	0.25
Initial† IT morphine titration dose, N (%)		
0.07 mg/day	0	1 (4.2)
0.25 mg/day	12 (48.0)	12 (50.0)
0.252 mg/day	0	1 (4.2)
0.333 mg/day	0	1 (4.2)
0.5 mg/day	10 (40.0)	8 (33.3)
1 mg/day	3 (12.0)	1 (4.2)

* Two of these patients had never received previous IT morphine; however, information regarding other IT opioids in these patients was not available.
† Intended initial IT morphine titration dose is listed for the titration phase.
SD = standard deviation; VASPI = visual analog scale of pain intensity; IT = intrathecal; MMSE = Mini Mental Status Examination.

week 48 (median: 5.15 μg/day) but increased at week 56 (median: 24.20 μg/day); however, the dose at week 56 reflects the 13 patients who continued in the extension phase for 56 weeks before discontinuing treatment or the end of the study. Five patients converted to ziconotide monotherapy, and 19 patients continued with IT ziconotide/morphine combination treatment during the extension phase.

The median IT morphine dose was 0.25 mg/day at the initial visit and progressively increased during the titration phase, with median values of 0.25, 0.50, 1.00, and 1.25 mg/day at weeks 1, 2, 3, and 4, respectively. During the extension phase, the median IT morphine dose was 1.50 mg/day at week 8 and fluctuated from a high of 2.1 mg/day at week 56 to a low of 0 mg/day for each of the two patients who completed a week 72 visit.

At the time of study enrollment (i.e., before combination therapy), 44.0% of patients reported ongoing adverse events (i.e., ongoing from the patient's study of origin). Twenty-three patients (92.0%) reported at least one TEAE during the titration phase, and 24 patients (100.0%) reported at least one TEAE during the extension phase. The maximum severity of any TEAE was mild or moderate for 52.0% of patients in the titration phase and 45.8% of patients in the extension phase. The most commonly (≥5% of patients in either study phase) reported TEAEs that were considered related to the study drug are shown in Table 3. Most patients (22/25, 88.0%) first experienced a TEAE within 2 weeks of study entry.

During the titration phase, two patients (8.0%) reported six serious TEAEs, including accidental injury, ataxia, confusion, dehydration, subdural hematoma, and urinary tract infection, none of which were considered related to the study drug.

Table 3 Most commonly reported TEAEs (≥5% of patients in either study phase) considered related to study drug*

Adverse Event	Number (%) of Patients: Titration Phase (N = 25)	Number (%) of Patients: Extension Phase (N = 24)
Body as a whole		
Asthenia	1 (4.0)	2 (8.3)
Headache	2 (8.0)	1 (4.2)
Digestive system		
Nausea	4 (16.0)	1 (4.2)
Vomiting	2 (8.0)	0
Metabolic and nutritional system		
Edema	2 (8.0)	1 (4.2)
Peripheral edema	3 (12.0)	3 (12.5)
Nervous system		
Confusion	2 (8.0)	2 (8.3)
Dizziness	7 (28.0)	1 (4.2)
Somnolence	2 (8.0)	0
Skin and appendages		
Pruritus	6 (24.0)	0
Urogenital system		
Urinary retention	2 (8.0)	0

* Study drug refers to the combination of ziconotide and IT morphine or ziconotide alone (extension phase only).
TEAE = treatment-emergent adverse event.

During the extension phase, eight patients (33.3%) reported 16 serious TEAEs. One patient experienced three events of vasculitis; two patients experienced chest pain. Abnormal thinking, acute kidney failure, anemia, back pain, catheter site inflammation, cellulitis, congestive heart failure, constipation, hypoxia, pulmonary hypertension, and stupor were reported in one patient each. None of these serious TEAEs were considered related to the study drug.

Among the patients with serious TEAEs that were related to the central nervous system, one patient reported ataxia and confusion. Both of these events were considered possibly related to the patient's other conditions, including subdural hematoma, urinary tract infection, and dehydration, as well as concomitant medications (not specified). A serious TEAE of abnormal thinking was considered related to an intercurrent illness in another patient who also experienced an exacerbation of Behcet disease. A TEAE of stupor was considered related to an intercurrent illness in a patient who experienced congestive heart failure on the same day. This patient died the following day from severe cardiorespiratory failure secondary to congestive heart failure. The death was considered unrelated to the study drug. One other patient died during the study from neurovasculitis. This death was considered unrelated to the study drug.

Changes in laboratory values were generally unremarkable during the titration phase. Alkaline phosphatase levels rose by a mean of 9.1 U/L from the initial visit to the week 4/early termination visit. By the extension phase termination visit, mean change in alkaline phosphatase levels from the initial visit was down to 5.4 U/L. During the extension phase, some alterations in creatine kinase (CK) levels were noted. For the 22 patients with CK values available at both the initial visit and the week 4/early termination visit of the titration phase, increases in mean and median CK levels were not noted. For the 16 patients with CK values reported at both the initial visit and the extension phase termination visit, mean and median CK level increases were 90.1 and 9.5 U/L, respectively. High CK levels were noted in five of 22 patients (22.7%) at the initial visit and five of 18 patients (27.8%) at the extension phase termination visit. In all, 12 patients had elevated CK levels at least once during the study, four of whom had CK levels more than three times the upper limit of normal. In general, patients with elevated CK levels did not experience adverse events thought to be associated with CK elevation, with the possible exceptions of stomach cramps, fatigue, and chills in one patient and anemia and acute renal failure in another patient. All of these adverse events were considered by the investigator to be unrelated to ziconotide. The adverse event of anemia was considered related to another concomitant medication (not specified), and the renal failure was considered related to a pre-existing condition.

Some alterations in platelet counts were also noted during the extension phase. For the 14 patients with platelet counts reported at both the initial visit and the extension phase termination visit, the mean and median changes in platelet counts were 8.1×10^3/mcL and -12.5×10^3/mcL, respectively. Abnormally high platelet counts were seen in two of 23 patients (8.7%) at the initial visit and one of 15 patients (6.7%) at the extension phase termination visit.

Vital signs and ECG parameters were relatively stable during the study. The mean total MMSE score was relatively stable: 28.3 (range: 13–30) at the initial visit, 28.8 (range: 20–30) at the week 4/early termination visit, and 29.0 (range: 21–30) at the extension phase termination visit. The mean change in total MMSE score from the initial visit was 0.6 (95% CI: –0.2 to 1.4) at the week 4/early termination visit and 0.0 (95% CI: –0.4 to 0.5) for the extension phase termination visit. The level of consciousness subscale showed that most patients (24/25, 96.0%) were alert at the initial visit. One patient had an increase in consciousness level from the initial visit (drowsy) to the week 4/early termination visit (alert) and the extension phase termination visit (alert).

Efficacy

The primary efficacy analysis showed that VASPI scores improved by a mean of 26.3% (95% CI: 15.6%–37.1%) from the initial visit to week 4 (observed data), indicating a clinically significant reduction in pain intensity. For patients with VASPI scores available at both time points (N = 23), mean VASPI score was 70.6 mm (range: 42–100 mm) at the initial visit and 51.5 mm (range: 18–100 mm) at week 4 (observed data). Using the LOCF analysis, mean change in VASPI score from the initial visit to week 4/early termination (20.9 mm; 95% CI: 11.7–30.1 mm) and the corresponding mean percentage change (28.3%; 95% CI: 17.2%–39.3%) also showed clinically significant reductions in pain intensity. Mean changes in VASPI score from the initial visit to weeks 1, 2,

Table 4 VASPI score results (titration and extension phases)

Week	N	% Change in VASPI Score from Initial Visit, Mean (SD)	95% CI
Titration phase			
1	24	11.3 (31.67)	(–2.1, 24.6)
2	24	16.7 (34.36)	(2.2, 31.3)
3	23	17.3 (18.52)	(9.3, 25.3)
4	23	26.3 (24.93)	(15.6, 37.1)
Extension phase*			
8	24	9.7 (34.75)	(–5.0, 24.4)
16	24	–0.4 (37.86)	(–16.4, 15.5)
24	23	4.2 (39.22)	(–12.8, 21.2)
32	21	6.2 (34.87)	(–9.7, 22.1)
40	20	7.4 (51.58)	(–16.7, 31.5)
48	19	4.2 (40.75)	(–15.4, 23.9)
56	12	6.0 (32.60)	(–14.7, 26.7)
64	9	3.9 (27.89)	(–17.6, 25.3)
72	1	35.0 (NA)	NA

* Weeks 8 through 72 of the extension phase represent weeks 12 through 76 of total treatment with study drug, including the titration phase.
Note: increases (positive changes) indicate a reduction in pain intensity.
VASPI = Visual Analog Scale of Pain Intensity; SD = standard deviation; CI = confidence interval; NA = not applicable.

and 3 were 9.3, 14.7, and 12.9 mm, respectively; percentage changes in VASPI score during the titration and extension phases are shown in Table 4. Wide variations are evidenced by the standard deviations in percent change in VASPI score during the extension phase (Table 4).

Median systemic opioid consumption was 840.0 mg/week at the initial visit and decreased by a mean of 35.1%, 39.0%, 44.3%, and 49.1% at weeks 1, 2, 3, and 4, respectively. The Pearson product–moment correlation ($r = 0.2724$, $P = 0.2085$) and the Spearman rank correlation ($r = 0.3299$, $P = 0.1242$) indicated no statistically significant relationship between the decrease in systemic opioid consumption and improvement in VASPI score at week 4. Weekly systemic opioid consumption generally decreased during the extension phase; the mean percentage decrease from the initial visit was 37.9% at week 8; 24.5% at week 16; 0.2% at week 24; 11.5% at week 32; 42.1% at week 40; 49.2% at week 48; 51.2% at week 56; 49.7% at week 64; and 61.1% at week 72.

On the CPRS at week 4/early termination, no patients had complete pain relief, 17 patients (68.0%) had "moderate" or "a lot" of improvement in their pain, and eight patients (32.0%) had slight improvement or no change in their pain. At the extension phase termination visit, among the 18 patients with available data, 14 patients (77.8%) had "moderate" or "a lot" of improvement in their pain, while four patients (22.2%) had slight improvement or no change in their pain. Results for the CGI scale generally indicated good or better overall pain control and additional pain relief with combination therapy (compared with ziconotide monotherapy) (Table 5).

Discussion

The rationale for IT combination therapy is to combine drugs with different mechanisms of action so that afferent pain signals are interrupted at several different sites, thus producing additive or synergistic pain control. This combined effect may also allow for dose reduction of each individual drug, which may reduce drug intolerance.

Currently, there is a paucity of data regarding the safety of IT ziconotide/morphine combination therapy at various concentrations. Research in rats

Table 5 CGI results (titration and extension phases)

CGI Questions/Responses	Week 4/Early Termination Visit (N = 25), Number (%) of Patients	Extension Phase Termination Visit (N = 24)*, Number (%) of Patients
Satisfied with combination therapy		
Not at all	2 (8.0)	0
A little bit	1 (4.0)	1 (5.3)
Somewhat	10 (40.0)	5 (26.3)
A lot	8 (32.0)	11 (57.9)
Completely	4 (16.0)	2 (10.5)
Overall pain control		
Poor	2 (8.0)	1 (5.3)
Fair	6 (24.0)	4 (21.1)
Good	9 (36.0)	7 (36.8)
Very good	6 (24.0)	6 (31.6)
Excellent	2 (8.0)	1 (5.3)
Additional pain relief with combination therapy		
Yes	23 (92.0)	15 (88.2)
No	2 (8.0)	2 (11.8)

* Data were missing for five patients on both the "satisfied with combination therapy" and "overall pain control" measures and for seven patients on the "additional pain relief with combination therapy" measure. Percentages are based only on patients with nonmissing data.
CGI = Clinical Global Impression.

that were administered IT ziconotide and morphine in combination suggests that IT ziconotide may enhance the hypotensive effects of morphine [11]. Other animal model studies have included assessments of gastrointestinal motility and respiration in rats and mice receiving IT ziconotide combined with subcutaneous morphine [12]. The results of these studies suggest that ziconotide appears to potentiate the inhibition of gastrointestinal motility by morphine [12]. However, ziconotide in combination with subcutaneous morphine does not appear to induce respiratory depression or to increase the susceptibility of morphine-tolerant animals to respiratory depressant effects of morphine [12].

In the present study, adverse events reported during the titration phase were consistent with the safety profiles of IT morphine and ziconotide, which have considerable overlap. Combination treatment with IT ziconotide and IT morphine revealed no new or unexpected adverse events. The rate of discontinuation due to adverse events during the titration phase was low (8.0%), and only one patient chose not to continue into the extension phase of the study. TEAEs reported during the extension phase were generally similar to those reported in the titration phase.

Twenty-four patients were enrolled in the extension phase of the study. With the exception of five patients who converted back to ziconotide monotherapy, all patients continued with IT morphine/ziconotide combination treatment throughout the extension phase.

Elevated CK levels were noted in some patients during the study; however, such elevations were generally not associated with adverse events. Although the investigators did not consider CK elevations to be drug-related, it should be noted that elevated CK levels have been seen in 40% of patients in clinical studies of ziconotide, and the product labeling recommends that physicians periodically monitor serum CK levels in patients treated with ziconotide [13].

In the present study, combination treatment with ziconotide and IT morphine provided a significant reduction in pain intensity during the titration phase. Analysis of the primary efficacy variable showed a mean 26.3% reduction in VASPI score from the initial visit to week 4, and a supportive efficacy analysis using LOCF corroborated these findings. Reductions in pain intensity were seen as early as week 1 and progressively increased at weeks 2 and 3 as upward titration of IT morphine continued. As the majority of the patients in the study had previously received IT opioid therapy, it is unlikely that IT morphine was solely responsible for the VASPI score reductions noted during the study; VASPI score reductions were more likely attributable to IT ziconotide/morphine combination therapy.

Systemic opioid use decreased at each week during the titration phase, with an overall mean decrease of 49.1% from the initial visit to week 4, indicating that the improvement in VASPI scores was not caused by increased systemic opioid consumption. The reduction in systemic opioid use seen in this study is an important finding. Such a reduction may help reduce overall patient exposure to opioids, thereby reducing undesirable effects, including but not limited to tolerance, constipation, endocrine suppression, and opioid sleep-disordered breathing. Overall, mean percentage changes in VASPI scores showed widely variable pain relief with continued combination therapy during the extension phase. However, other secondary efficacy variables, including the CPRS and CGI scores, suggested meaningful improvement in pain relief during the extension phase. These results are particularly notable when considering that the patients in this study had a mean duration of pain of 15.0 years at study entry and that all patients were considered by the investigators to have pain that was refractory to treatment. However, it is also important to note that five patients converted back to ziconotide monotherapy during the extension phase of the study. Therefore, the improvements in VASPI, CGI, and CPRS scores during the extension phase reflect results from a mixed group of patients: those receiving combination therapy and those receiving ziconotide monotherapy.

Limitations of this study include its open-label design and small size. In order to confirm and further explore the findings of the current study, larger, more rigorous studies should be undertaken.

Although morphine is the "gold standard" IT opioid, this study cannot suggest that other opioids in combination with ziconotide would provide similar safety and efficacy results. Further studies are needed to determine the long-term safety and efficacy of all IT medications used in combination with ziconotide.

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