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STATISTICAL REVIEW(S)

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STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA/Serial Number: 21060/N_000
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Applicant: Elan Pharmaceuticals, Inc.
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1. EXECUTIVE SUMMARY

The applicant, Elan Pharmaceuticals Inc., has proposed the use of PRIALT (ziconotide) for the management of severe chronic pain. The overall study objective of this new amendment is to confirm the efficacy results observed in the short-term (5 to 6 days) controlled trials (95-001 and 96-002) using an alternative slower dose titration schedule over a three-week treatment period. The secondary objectives of this study were to characterize opiate withdrawal effects during conversion from IT to systemic opiate therapy, and to quantify the amount of concomitant opiate usage during the trial. The evidence taken collectively from Study 301 and 96-002 reviewed indicated statistical support favoring ziconotide treatment over placebo in the management of pain (Table 1). Furthermore, the significant difference in the primary efficacy variable in Study 301 did not appear to be confounded by the use of concomitant opioids, as the use of opioid decreased in both treatment groups from baseline to termination, with a larger decrease observed in the ziconotide group than in the placebo group.

Based on my review, no statistical issue appeared to be of concern except for the choice of imputation method in the primary efficacy analysis. However, because the applicant provided several alternatives and presented sensitivity analyses that showed the results were consistent (except when WOCF was used), this lessened my concern. Nevertheless, as an added check, I performed two additional analyses that are regarded as fairly conservative. One was imputing subject who dropped out using baseline observation carried forward approach, and the other was assuming those who dropped out as nonresponders in the responder analysis.

In study 301, analysis using BOCF showed that there was a statistically significant difference in mean percent change from baseline of VASPI score between ziconotide-treated patients and placebo-treated patients at Week 3 (termination), favoring the ziconotide-treated group. In order for subjects in the two old studies (95-001 and 96-002) to be comparable to the new study, the applicant included all randomized low-dose patients in Studies 95-001 and 96-002, excluding patients from _____ site. The reason for exclusion of _____ site is due to the irregularities found related to blinding that could compromise the integrity of the data. Similar to the conclusion presented by the applicant in the previous submissions, there was a statistically significant difference in mean percent change from baseline of VASPI score between ziconotide-treated patients and placebo-treated patients at termination, favoring the ziconotide-treated group in Study 96-002. However, the treatment difference remains questionable in Study 95-001.

Although both the fast titration and slow titration regimens demonstrated a greater improvement in the proportion of responders (at least 30 percent change in pain reduction) with ziconotide treatment over placebo that was consistent with the difference in mean percent change in VASPI scores, it appeared that the treatment difference was more prominent in the fast titration studies. This could mean that ziconotide is more effective on individuals when titration is fast. However, this regimen could potentially be more toxic compared to a slow titration regimen. This is further examined by Dr. Schultheis.

Another conclusion may be drawn from Study 301: patients responded well at Week 1 when the slow titration regimen was employed. Quantitatively, subjects in the ziconotide group responded well at Week 1 (Ziconotide 24 [21%], Placebo 13[12%]), but only a few continued to respond (Ziconotide 7, Placebo 3) up to Week 3 (Figure 4). On the other hand, it appears that there is no difference in the number of new responders at Week 2 (Ziconotide 10, Placebo 10) or Week 3 (Ziconotide 5, Placebo 5) between the ziconotide-treated group and the placebo group.

Table 1: Collective Evidence - Mean Percent Change in VASPI Score (SE) and Proportion of Responders (>=30% pain reduction), by Study

	Mean (SD)		% Change		p-value
	Placebo	Active	Placebo	Active	
Study 301 at Week 1					
N	108	112	108	112	
Baseline VASPI score	80.7 (14.9)	80.7 (15.0)			
Observed	75.1 (20.6)	65.9 (26.6)	5.4 (26.8)	17.5 (31.0)	0.0033*
BOCF	75.6 (20.1)	67.0 (26.4)	5.0 (25.7)	16.6 (30.4)	0.0026*
Responders			13 (12%)	24 (21%)	
Study 301 at Week 2					
N	108	112	108	112	
Baseline VASPI score	80.7 (14.9)	80.7 (15.0)			
Observed	72.5 (21.0)	68.9 (23.9)	8.4 (25.0)	13.6 (28.5)	0.1667*
BOCF	73.9 (20.8)	69.6 (23.6)	7.5 (23.8)	12.9 (27.9)	0.1269*
Responders			17 (16%)	22 (20%)	
Study 301 at Week 3					
N	108	112	108	112	
Baseline VASPI score	80.7 (14.9)	80.7 (15.0)			
Observed	74.2 (20.7)	67.8 (21.8)	6.4 (24.7)	14.4 (26.9)	0.0369*
BOCF	75.8 (20.1)	69.8 (21.5)	5.4 (22.8)	12.2 (25.3)	0.0376*
Responders			13 (12%)	18 (16%)	
Study 95-001					
N	17	33	17	33	
Baseline VASPI score	78.6 (14.1)	73.7 (14.8)			
Observed	63.0 (30.8)	42.3 (30.8)	18.9 (37.1)	41.1 (41.4)	0.0695†
BOCF	63.0 (30.8)	42.3 (30.8)	18.9 (37.1)	41.1 (41.4)	0.0459†
Responders			5 (29%)	19 (58%)	
Study 96-002					
N	64	119	64	119	
Baseline VASPI score	75.0 (13.0)	80.7 (12.9)			
Observed	70.2 (22.6)	56.7 (32.6)	6.0 (28.8)	29.6 (40.2)	<0.0001‡
BOCF	70.2 (22.6)	56.7 (32.6)	6.0 (28.8)	29.6 (40.2)	0.0001‡
Responders			12(19%)	51 (41%)	
Pooled					
N	81	152	81	152	
Baseline VASPI score	75.8 (13.3)	79.2 (13.6)			
Observed	68.7 (24.5)	53.6 (32.6)	8.7 (30.9)	32.1 (40.6)	<0.0001‡
BOCF	68.7 (24.5)	53.6 (32.6)	8.7 (30.9)	32.1 (40.6)	<0.0001‡
Responders			17 (21%)	70 (45%)	

*p-values with no adjustments

†p-values adjusted for baseline VASPI scores

‡p-values adjusted for study and baseline VASPI score

1.1 Conclusions and Recommendations

In view of the statistical findings generated from the analyses conducted by the applicant and by me, I conclude that ziconotide is efficacious for the management of severe chronic pain under a slower dose titration schedule over a three-week period. However, as indicated in my review, the safety of the study drug must also be established. Ultimately, the benefit must outweigh the risk this study drug may have to potential patients.

1.2 Brief Overview of Clinical Studies

Ziconotide is a calcium channel blocker proposed for the management of severe, chronic, opioid-refractive pain. It is a synthetic version of a naturally-occurring peptide found in the venom of the marine snail, *Conus magus*; this venom alters neuromuscular function in prey.

More than twenty clinical studies, varying in their design, route of administration, and indication, were carried out in the development of this drug. Review of these studies for the NDA resulted in an approvable letter, dated 27 June 2000. An amendment was submitted in response in January 2001 and the information presented in this submission did not provide sufficient evidence to conclude that ziconotide is efficacious under labeled conditions. A new amendment was submitted in 28 June 2004 in response to the July 2001 letter, and is the subject of this review of evidence concerning efficacy of ziconotide in treating chronic pain.

According to the reviews of Drs. Grosser and Permutt on the original NDA submission and the resubmission, the original NDA submission contained two studies relevant to efficacy, 95-001 and 96-002. Study 95-001 was a multicenter, phase II/III, placebo-controlled study of SNX-111 administered intrathecally to patients with chronic malignant pain. Study 96-002 was a multicenter, phase II/III, placebo controlled study of SNX-111 administered intrathecally to patients with chronic non-malignant pain. Both were short-term trials, lasting 5 or 6 days. The primary efficacy outcome was percent change in VASPI (visual analog scale pain index). In the course of review, two problems were discovered. Mid-study protocol changes led to differing titration paradigms within trials. Moreover, field investigation of a center that participated in both studies 96-002 and 95-001 revealed irregularities that could compromise the integrity of the data, especially issues related to blinding. Thus only data from patients treated under the final version of the protocol were considered for the efficacy analysis, and data from compromised site were excluded. Under these conditions, one study, 96-002, successfully showed ziconotide to be effective while study 95-001 did not. The June 2000 approvable letter requested the submission of "results of a new randomized, double-blind, placebo-controlled study of the safety and effectiveness of ziconotide at the dosing regimen ... proposed for marketing conducted in the target population proposed for labeling." In addition, the letter pointed out that a detailed and complete reanalysis, including secondary endpoints, of the subset of patients included in the final efficacy analysis of Studies 95-001 and 96-002 needed to be done. The applicant, in response to the request, provided the reanalysis of the data gathered in Studies 95-001 and 96-002, including results of pooling data from the two studies. They offered an argument for the adequacy of these original data in proving efficacy. As a result, the amendment did not provide any new data. While there were analyses that were not in the original submission, Dr. Grosser and Dr. Permutt had carried out those analyses in the review of the original submission. Therefore, under the January 2001 amendment, there was still insufficient evidence to conclude that ziconotide is efficacious under the labeled conditions.

In this new amendment dated 28 June 2004, the applicant submitted study ELN92045-301 (hereafter referred to as "Study 301") to confirm the efficacy of ziconotide seen in the two Phase II/III double-blind placebo-controlled trials (Studies 95-001 and 96-002) and to evaluate the safety profile using a slower

titration regimen and a lower maximum dose. This submission is in response to the July 2001 letter by the agency. The new study used a slower titration schedule over 21 days and a lower maximum dose of 0.9 µg/hr compared to the previous two studies with forced titration schedules in which ziconotide doses were increased to tolerability or a maximum dose of 2.4 µg/hr (per the final dosing regimen) over 5 to 6 days. The mean dose of ziconotide was 0.5 µg/hr in study 95-001 and 0.83 µg/hr in study 96-002 at the end of the titration phase. Therefore, in study 301, ziconotide was titrated more slowly than in studies 95-001 and 96-002. A three-week treatment period was chosen to allow for more gradual titration of ziconotide. In addition, ziconotide was titrated to early onset of analgesia rather than assess the higher dose range of safety and efficacy as already observed in Studies 95-001 and 96-002, and potentially to minimize SAEs, withdrawals, and adverse events (AEs).

The applicant's overall study objective of this new amendment is to confirm the efficacy results observed in the short-term (5 to 6 days) controlled trials (95-001 and 96-002) using an alternative slower dose titration schedule over a three-week treatment period. The secondary objectives of this study were to characterize opiate withdrawal effects during conversion from IT to systemic opiate therapy, and to quantify the amount of concomitant opiate usage during the trial.

1.3 Statistical Issues and Findings

I conclude that treatment with ziconotide produces lower mean pain score at endpoint, as well as Week 1 compared to placebo. A brief summary of the findings is displayed in Table 1.

My conclusions were formulated after an in-depth analyses of treatment responders. These analyses were post-hoc; the purpose was to validate conclusions and to understand the treatment effects over time and using different definitions of responders.

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2. INTRODUCTION

2.1 Overview

This is a review of the clinical data in patients with chronic pain as submitted in NDA 21-060, serial number 000, for Prialt (ziconotide).

Ziconotide is a calcium channel blocker proposed for the management of severe, chronic, opioid-refractive pain. It is a synthetic version of a naturally-occurring peptide found in the venom of the marine snail, *Conus magus*; this venom alters neuromuscular function in prey.

More than twenty clinical studies, varying in their design, route of administration, and indication, were carried out in the development of this drug. Review of these studies for the NDA resulted in an approvable letter, dated 27 June 2000. An amendment was submitted in response in January 2001 and the information presented in this submission did not provide sufficient evidence to conclude that ziconotide is efficacious under labeled conditions. A new amendment was submitted 28 June 2004 in response to the July 2001 letter, and is the subject of this review of evidence concerning efficacy of ziconotide in treating chronic pain.

Currently the applicant, Elan Pharmaceuticals, is seeking approval to market Prialt (ziconotide) for the treatment of severe chronic pain. The overall study objective of this new amendment is to confirm the positive efficacy results observed in the short-term (5 to 6 days) controlled trials (95-001 and 96-002) using an alternative slower dose titration schedule over a three-week treatment period. The secondary objectives of this study were to characterize opiate withdrawal effects during conversion from IT to systemic opiate therapy, and to quantify the amount of concomitant opiate usage during the trial.

The focus of this statistical review is on the new clinical study (ELN92045-301) conducted in patients with severe chronic pain. Results from the two clinical studies (95-001 and 96-002) will also be discussed.

2.2 Data Sources

This statistical review is based on data submitted in study ELN92045-301, and from the integrated summary of efficacy for three studies (ELN92045-301, 95-001 and 96-002).

The electronic part of the submission of this NDA can be found on the internal network drive of \\Cdsub1\n21060\N_000\2004-06-25A\

Hardcopy is provided for the clinical study report (Studies ELN92045-301, 95-001 and 96-002)

The electronic datasets for all the studies are under \\Cdsub1\n21060\N_000\2004-06-25A\crt\datasets

3. STATISTICAL EVALUATION

3.1 Evaluation of Efficacy (ELN92045-301)

Study Design

This study was a randomized, double-blind, multicenter, placebo-controlled study to confirm the analgesic efficacy of ziconotide, to characterize opioid use before and during the double-blind treatment period, and to evaluate the safety of the specified titration schedule in adult patients. The study duration was up to 9 weeks (including a two-week or longer follow-up period to assess ongoing drug-related AEs) per patient. The study consisted of a screening visit, a weaning period, a stabilization period, a baseline visit, a double-blind treatment period, a termination visit, and a follow-up visit.

During the screening visit, patients provided informed consent and were screened for study eligibility (including a VASPI score of ≤ 50 mm). Patients receiving intrathecal (IT) analgesics and/or other IT medications at screening were weaned from such medications during the weaning period, which continued for up to three weeks and included scheduled weekly visits and interval visits as needed.

During the weaning period, IT opiates were converted to systemic opiates. Patients who were not receiving any other IT medications at screening could proceed straight to the stabilization period without any weaning visits. Patients were stabilized on a systemic analgesic regimen during the one-week stabilization period in order to allow for adequate assessment of baseline VASPI and opiate consumption. During the baseline/randomization visit, the inclusion/exclusion criteria were reviewed. Patients who met study entry criteria were randomized in a 1:1 ratio and received either IT ziconotide or placebo for the three-week double-blind treatment period. Scheduled weekly treatment visits and interval visits were performed to evaluate patients during dose titration. The starting dose was 0.10 $\mu\text{g/hr}$ (2.4 $\mu\text{g/day}$) and the dose was gradually increased. By the end of the three-week double-blind treatment period, the final dose did not exceed 0.9 $\mu\text{g/hr}$.

Study Objective

The primary objective of this study was to confirm the efficacy results observed in the short-term (5 to 6 days) controlled trials (95-001 and 96-002) using an alternative slower dose titration schedule over a three-week treatment period. The secondary objectives of this study were to characterize opiate withdrawal effects during conversion from IT to systemic opiate therapy, and to quantify the amount of concomitant opiate usage during the trial.

Efficacy Parameters:

The primary efficacy variable for this study was the percent change in Visual Analog Scale Pain Intensity (VASPI) score at Week 3 from baseline. The VASPI was used to quantify the patient's pain intensity on a continuous scale using a 100-mm horizontal line ('0' indicates no pain and '100' indicates worst possible pain). The baseline VASPI score was the VASPI score taken immediately prior to infusion of the study drug. If a patient withdrew early from the study, the applicant used the last observation carried forward (LOCF) to impute missing value.

The percentage change from baseline to Week 3 was computed as:

$$\left[\frac{(\text{Baseline} - \text{Week 3})}{\text{Baseline}} \right] \times 100$$

A positive value represents an improvement from baseline.

The primary efficacy analysis includes ITT patients who were randomized into one of the two study treatment groups. The two treatment groups were compared using a two-sided, two sample t-test at the

5% level of significance. The primary null hypothesis tested was that the mean percent change in VASPI score from baseline to Week 3 of the ziconotide group was not different from that of the placebo group. The corresponding alternative hypothesis was that the mean percent change in VASPI score from baseline to Week 3 of the ziconotide group was different from that of the placebo group.

A variety of other pain and quality of life assessments were used to characterize other aspects of the patient's pain and to support the measurement of pain intensity as the primary efficacy assessment such as the patient's responses to the Clinical Global Impression questionnaire (CGI), Brief Pain Inventory questionnaire, Global McGill Pain Questionnaire, Categorical Pain Relief Scale (CPRS), and Treatment Outcome Pain Survey (TOPS).

Applicant's Summary of Results

For the primary efficacy variable, the mean percent change in VASPI score from baseline to Week 3 (LOCF) of 14.7% in the ziconotide group was significant improvement over the mean percent change of 7.2% for the placebo group ($p=0.0360$; two sample t-test). Onset of efficacy was demonstrated as early as Week 1 (LOCF), with a mean percent change in VASPI score of 16.6% in the ziconotide group compared with 5.0% for the placebo group ($p=0.0026$). The percent change at Week 2 favored ziconotide but was not statistically significant. The primary efficacy outcome measure results were confirmed based on the sensitivity analyses for the observed Week 3 VASPI values, imputing the median change, and imputing the smallest ("worst") percent change instead of using LOCF.

The significant difference in the primary efficacy variable did not appear to be confounded by the use of concomitant opioids, as the use of opioids decreased in both treatment groups from baseline to termination, with a larger decrease observed in the ziconotide group than in the placebo. The clinical significance of the positive results from the primary efficacy variable favoring ziconotide over placebo was supported by analyses of multiple secondary efficacy outcome measures, including the CGI satisfaction rating, the CGI Pain control rating, the Global McGill Pain Total Score, the Global McGill Pain Intensity Score, and the CPRS. The clinical significance of the efficacy of ziconotide in the treatment of severe chronic pain was further supported by the statistically significant changes noted in sleep duration, sleep quality, and BPI 'enjoyment of life'.

Detailed Review of Study 301

Study 301 was a randomized, double-blind, multicenter, placebo-controlled study to confirm the analgesic efficacy of ziconotide, to characterize opioid use before and during the double-blind treatment period, and to evaluate the safety of the specified titration schedule in adult patients. The study duration was up to 9 weeks (including a two-week or longer follow-up period to assess ongoing drug-related AEs) per patient.

For the ITT efficacy analysis of the percent change in VASPI, 110 patients randomized into each of the two treatment groups (a total of 220 randomized patients) will provide 80% power, at the two-sided 5% significance level, to detect a treatment difference of at least 15 percentage points in the percent change of the VASPI between treatment and placebo groups at the last visit from baseline. The sample sizes were estimated based on the use of a two-sample t-test with a standard deviation of 39.5% for both treatment groups (estimated from the two previous efficacy studies: 95-001 and 96-002).

A total of 248 patients signed the informed consent form and were enrolled in the study. Forty-four patients (18% of 248 enrolled) entered the stabilization period directly because they did not need to be weaned from IT medications, while 198 (80%) patients entered the weaning period prior to stabilization, of which 184 (93%) completed the weaning period. Two hundred twenty patients completed the

stabilization period and were randomized; 112 were randomized to ziconotide and 108 were randomized to placebo. The study was conducted at 39 sites, all sites having less than 18 patients. Protocol deviation information was provided but was not clear.

Dosing with ziconotide was started at 2.4 µg/day (0.1 µg/hr) and the dose could be increased by 2.4 µg/day (0.1 µg/hr) two to three times/week (minimum titration interval 24 hours) to a maximum allowable dose of 21.6 µg/day (0.9 µg/hr). The mean final dose at the end of the trial at 21 days was 6.9 µg/day (0.29 µg/hr).

Table 2: Summary of Patient Disposition and Study Termination - All Enrolled Patients

	Ziconotide	Placebo	Total
Enrolled			248 (100%)
Did not meet screening inclusion/exclusion criteria			8 (3%)
Dropped out before weaning			6 (2%)
Entered Weaning Period			198 (100%)
Completed Weaning			184 (93%)
Entered Stabilization Period ¹			228 (100%)
Completed Stabilization Period			220 (97%)
Met Baseline criteria			220 (100%)
Randomized	112	108	220
Patients treated with study drug	112 (100%)	108 (100%)	220 (100%)
Early Discontinuation	9 (8%)	8 (7%)	17 (8%)
Lack of efficacy	2 (2%)	2 (2%)	4 (2%)
Adverse Event	6 (5%)	5 (5%)	11 (5%)
Death	0	1 (0.9%)	1 (0.5%)
Subject Request: Voluntary Withdrawal of consent	1 (0.9%)	0	1 (0.5%)
Completed Study	103 (92%)	100 (93%)	203 (92%)
Planned to participate in open-label extension	90 (87%)	95 (95%)	185 (91%)

¹ Includes 184 patients who completed weaning and 44 patients who were not receiving any IT medications and who did not enter weaning phase
* Source: Volume 002 Section 10.1 Table 6

Demographic and baseline characteristics of age, sex, race, weight, and height were comparable between the two treatment groups. In the ziconotide group, the mean age was 52 years (range: 30 to 84 years) with the majority of patients (82%) under 65 years of age. The group was comprised of 47% males and 53% females. Most patients (96%) were Caucasian. The mean oral morphine equivalent¹ during the pretreatment stabilization period was 300.2 mg/d and the median was 195.3 mg/d (range: 0 to 2126 mg/d). In the placebo group, the mean age was 55 years (range: 27 to 86 years) with the majority of

¹ Oral Morphine Equivalent – the individual doses of opiates were converted to oral morphine equivalents using conversion factors published in review articles, textbooks, and drug package inserts. I.8.V.009 p.340

patients (80%) under 65 years of age. The group was comprised of 51% males and 49% females. The majority of patients (92%) were Caucasian. The mean oral morphine equivalent during the pretreatment stabilization period was 268.0 mg/d and the median was 171.7 mg/d (range: 0 to 1659 mg/d). Both groups were comparable with respect to mean vital sign measurements (systolic and diastolic blood pressure, pulse, and body temperature). Most importantly, using a 100 mm Visual Analog Scale of Pain Intensity (VASPI) where 100 mm = worst possible pain, mean baseline pain scores were 80.7 in both the ziconotide and placebo groups (Table 4).

The applicant provided a summary table for pain characteristics at screening for the ITT population. The treatment groups were generally comparable with respect to etiology and duration of pain, pain classification, mean duration of pain, pain refractory to treatment, and pain due to failed back surgery syndrome. The majority of patients (97%) entered the study with pain that was considered refractory to treatment by the Investigator. The pain was described as neuropathic (76% ziconotide, 71% placebo), nociceptive (36% PRIALT, 32% placebo), mixed pain (33% ziconotide, 40% placebo) and degenerative (28% ziconotide, 31% placebo). Patients may have had more than one pain etiology. The most common pain etiology (58%) was failed back surgery syndrome (FBSS). The mean duration of pain was 13.9 years for the ziconotide group vs. 15.0 years for the placebo group (range 1.6 to 63 years for all patients).

The applicant also provided summary tables on the mean VASPI scores and percent change in VASPI scores at Week 1, at Week 2, and at Week 3 using LOCF, as well as summary results from sensitivity analyses using several other imputation methods (observed cases only, WOCF, and median change). As outlined in Table 3, there was significant improvement in mean percent change in VASPI score from baseline to Week 3 (LOCF) in the ziconotide group compared to the placebo group ($p=0.0360$). This result was confirmed based on the sensitivity analyses for the observed Week 3 VASPI values, imputing median change, and using change in VASPI score (LOCF). There is also some agreement between LOCF and when smallest ("worst") percent change is used at Week 3.

Table 3: P-values¹ of the results of primary and other efficacy analyses of percent change and change in VASPI at Weeks 1, 2, and 3

Parameter	Week 1	Week 2	Week 3
% Change VASPI (LOCF)	0.0026	0.1211	0.0360 ²
% Change VASPI (Observed)	0.0033	0.1667	0.0369
% Change VASPI (Imputing median)	0.0021	0.1194	0.0156
% Change VASPI (Imputing smallest/worst)	0.0005	0.0399	0.0642
Change VASPI (LOCF)	0.0042	0.1256	0.0320

¹ All p-values represent comparisons between treatment groups

² Primary efficacy outcome

* Source: Volume 002 Section 10.1 Table 24

Although the mean percent change in VASPI score from baseline to Week 3 in the ziconotide group was a significant improvement over the mean percent change in VASPI score in the placebo group using these imputation techniques in handling the missing data, methods like LOCF may bias magnitude of treatment effects, the associated standard errors, and may inflate Type 1 error when drop-out is treatment-related. Therefore, additional analyses were conducted and presented in Tables 4 and 5 and Figures 1 to 3.

The first analysis used baseline observation carried forward (BOCF) to impute missing data. The advantage of this approach is that it assumes that those who drop out will get no change in their VASPI scores from baseline. The analysis of weekly mean percent change in VASPI score showed a statistically

significant difference between the ziconotide treated-group and the placebo at Week 1 and Week 3 (Table 4). Quantitatively, the ziconotide-treated group showed a favorable pain reduction score compared to the Placebo group at all weeks.

Table 4: Mean and Percent Change in VASPI Score at Weeks 1, 2, and 3 (BOCF) - ITT Population

Parameter	Ziconotide	Placebo	p-value
VASPI Score at Baseline (mm)			
N	112	108	
Mean (SD)	80.7 (15.0)	80.7 (14.9)	
Median (range)	85.0 (50 – 100)	81.5 (51 – 100)	
VASPI Score at Week 1 (mm)			
N	112	108	
Mean (SD)	67.0 (26.4)	75.6 (20.1)	
Percent change from baseline	16.6 (30.4)	5.0 (25.7)	0.0026
VASPI Score at Week 2 (mm)			
N	112	108	
Mean (SD)	69.6 (23.6)	73.9 (20.8)	
Percent change from baseline	12.9 (27.9)	7.5 (23.8)	0.1269
VASPI Score at Week 3 (mm)			
N	112	108	
Mean (SD)	69.8 (21.5)	75.8 (20.1)	
Percent change from baseline	12.2 (25.3)	5.4 (22.8)	0.0376

I also carried out additional analyses including weekly responder analyses based on percent decrease in mean pain score from baseline. The percent decrease was classified in 10-percent increments (e.g. =10%, =20%,..., =100% pain reduction) that will give you cumulative distribution functions of pain reduction by treatment groups. In these analyses, patients who withdrew from the study before the end of a week regardless of the reason for withdrawal were classified as non-responders at that particular week and the succeeding weeks.

Figures 1 to 3 present the proportion of responders at weekly time points for all the various definitions of responder considered. Inspection of these graphs suggests that there are apparent differences in the proportion of responders between the two treatment groups in most of the definitions of responder considered. This difference is most evident at Week 1 and Week 3. This implies that higher proportions of subjects in the ziconotide-treated groups were treatment responders compared to the placebo-treated group when different definitions of responder (based on different percent pain reduction) were used.

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Table 5: Percentage Change in Week 3 Mean VASPI Score (BOCF) - ITT Population

	PLACEBO		ZICONOTIDE	
	Total	%	Total	%
Any increase	31	29%	22	20%
None	27	25%	28	25%
> 0 % decrease	50	46%	62	55%
= 10%	34	31%	47	42%
= 20%	22	20%	31	28%
= 30%	13	12%	18	16%
= 40%	9	8%	12	11%
= 50%	2	2%	9	8%
= 60%	2	2%	5	4%
= 70%	2	2%	5	4%
= 80%	2	2%	4	4%
= 90%	1	1%	3	3%
=100%	1	1%	2	2%

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Figure 1: Response Profile at Week 1 (BOCF) - ITT Population

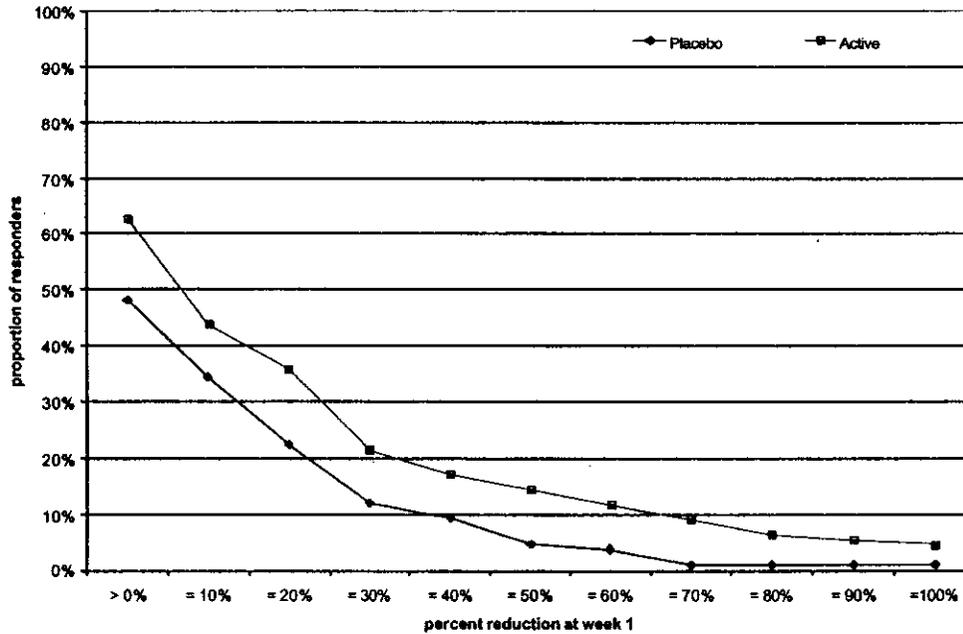


Figure 2: Response Profile at Week 2 (BOCF) - ITT Population

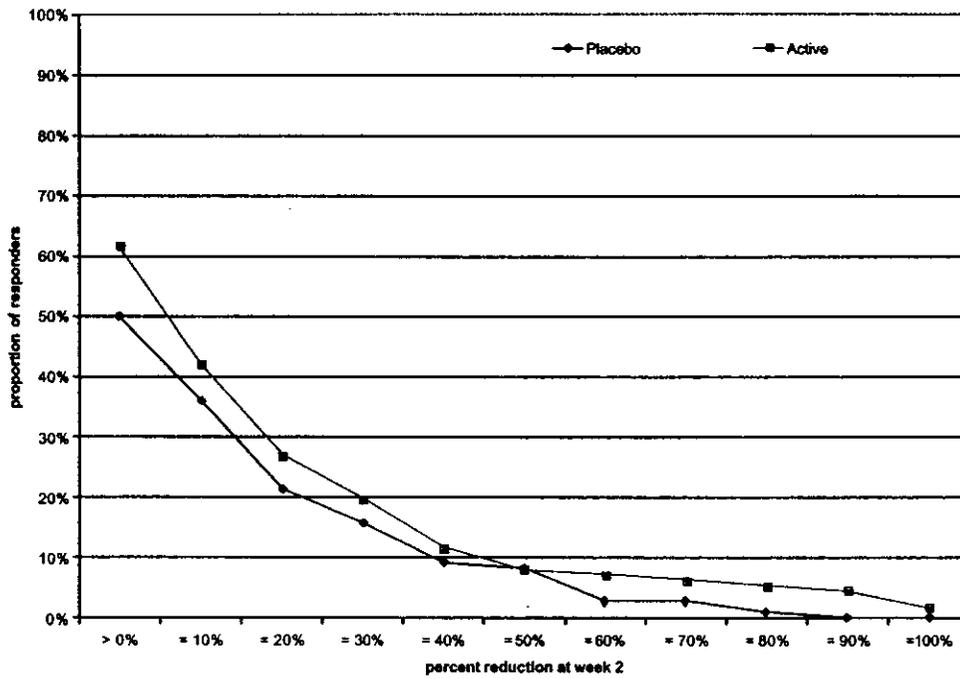
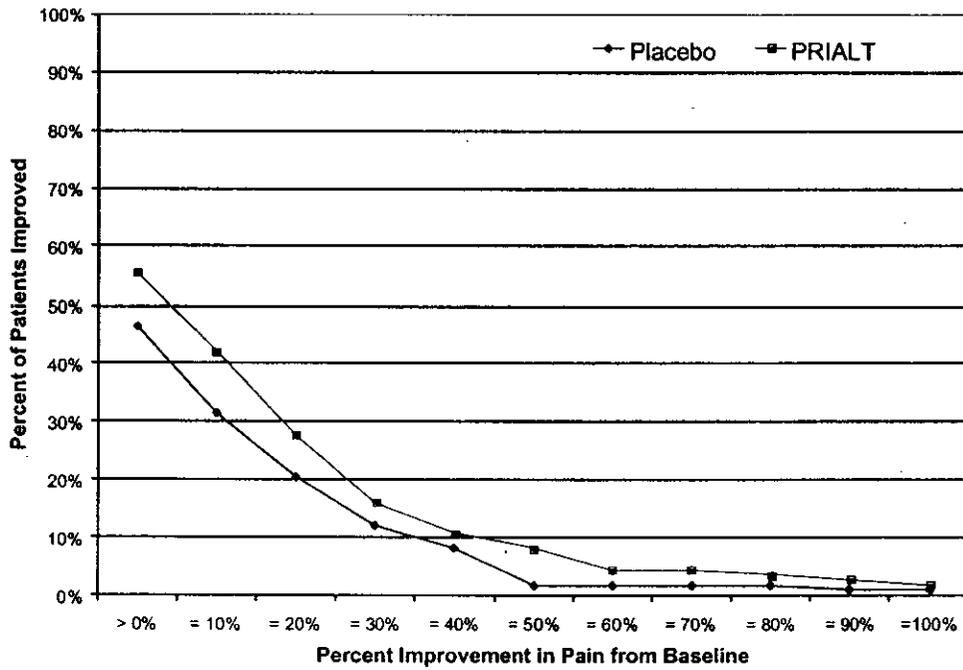


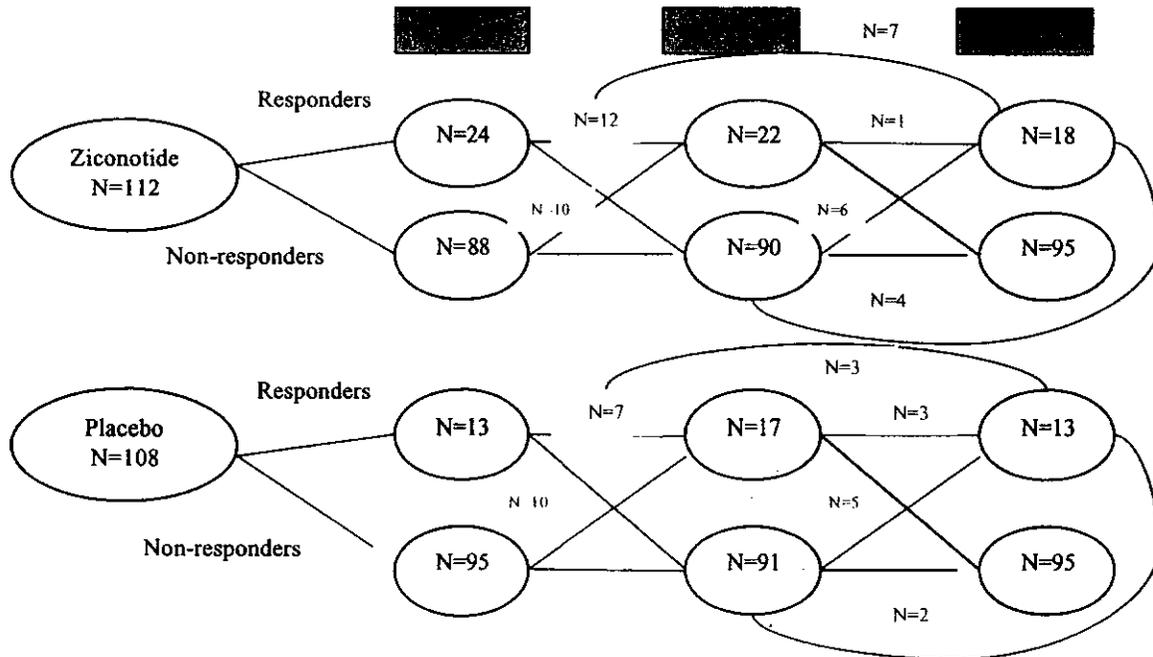
Figure 3: Response Profile at Week 3 (BOCF) - ITT Population



There were a total of 31 subjects (18 ziconotide, 13 placebo) who had at least 30% mean pain reduction at the end of the study. Figure 4 presents the distribution of these patients from the beginning of the study (week 1) to the end of the study (week 3). The obvious difference between treatment groups is the number of responders at Week 1 and how much these responders continued to respond at Week 2 and Week 3 (in red). Seven out of 18 subjects (41%) responded from the beginning to end in the ziconotide group, and only 3 out of 13 subjects (23%) in the placebo group. Otherwise, there is no difference in the proportion of responders between the treatment groups among subjects who did not respond at Week 1 and eventually responded at Week 2 or Week 3.

Therefore, from this descriptive summary, subjects in the ziconotide group had an advantage in responding at Week 1 over the placebo. The advantage diminishes as time goes by. However, there are still chances of patients responding in either treatment groups at Week 2, but this chance does not carry over to the end of the Week 3. As an illustration (in green), among those in ziconotide who did not respond at Week 1, 10 responded at Week 2, but only one (6%) carried over to respond at Week 3. Similarly, those in placebo, 10 responded at Week 2, but only three (23%) carried over to respond at Week 3. Furthermore, one can also look at the number of new responders at each week: at Week 1, 24 (21%) responded in ziconotide versus only 13 (12%) from placebo group; However, at Week 2 and Week 3, the percent new responders among the ziconotide group are not different among the placebo group (Week 2: 10 ziconotide, 10 placebo; Week 3: 6 ziconotide, 5 placebo). These numbers must be interpreted with caution as they are subject to substantial statistical uncertainty, but they suggest that responses to ziconotide may be seen relatively early or not at all.

Figure 4: Diagram of Responders at Weeks 1, 2 and 3



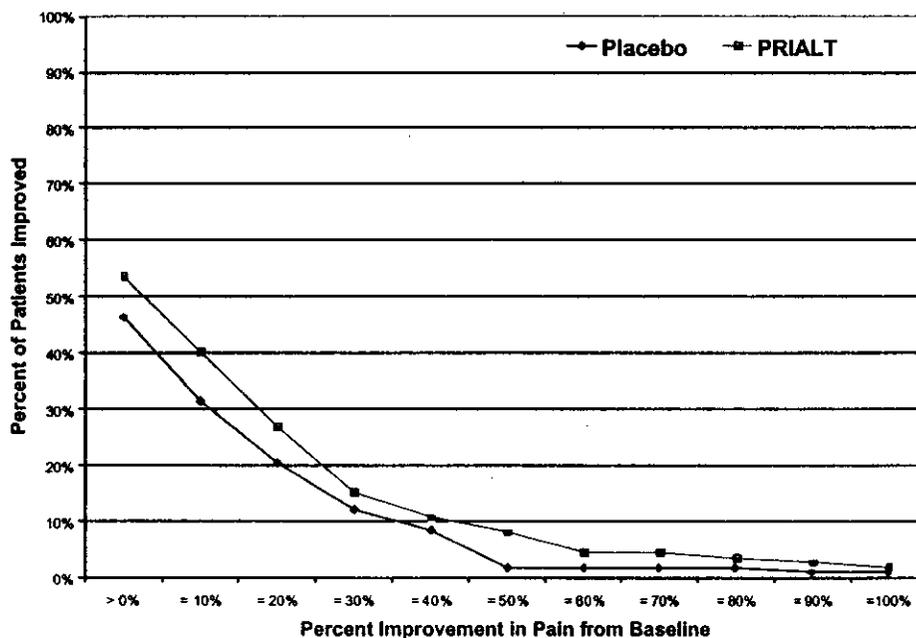
For a more stringent definition of responders at the end of the study, subjects who dropped out in the study, regardless of the time of drop-out, are considered failures. This implies that those who dropped out after Week 3 are considered non-responders at Week 3. Of the 31 subjects who had at least 30% mean pain reduction at the end of the study, one subject dropped out after Week 3 due to adverse event. Using this new definition, there is still a small difference in the proportion of responders between the placebo and ziconotide group (Table 6 and Figure 5). Additional results from the responder analysis are presented in the Appendix when subjects who did not continue to join in the open-label study (Study 352) are also considered non-responders.

Table 6: Revised Percentage Change in Week 3 Mean VASPI Score (BOCF) - ITT Population

	PLACEBO		ZICONOTIDE	
	Total	%	Total	%
Any increase	31	29%	22	20%
None	27	25%	30	27%
> 0 % decrease	50	46%	60	54%
= 10%	34	31%	45	40%
= 20%	22	20%	30	27%
= 30%	13	12%	17	15%
= 40%	9	8%	12	11%
= 50%	2	2%	9	8%
= 60%	2	2%	5	4%
= 70%	2	2%	5	4%
= 80%	2	2%	4	4%
= 90%	1	1%	3	3%
=100%	1	1%	2	2%

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Figure 5: Revised Response Profile at Week 3 (BOCF) - ITT Population



Descriptive statistics on the secondary variables are summarized and presented in Table 7. A higher percentage of subjects in the ziconotide group did improve in at least one secondary outcome variables without any worsening conditions compared to subjects in the placebo group (Ziconotide 33%, Placebo 19%, $p=0.0142$). A larger proportion of subjects in the ziconotide group had at least a fair/good CGI overall pain control score at termination compared to the placebo group. Furthermore, improvement in McGill Pain Intensity score from baseline, in BPI score from baseline, in pain relief score from CPRS, and pain outcome survey score from TOPS also favored the ziconotide-treated group compared to the placebo group. Lastly, a higher percentage of subjects taking ziconotide had improvement in sleep quality compared to subjects in the placebo group. Inspection of the mean CGI overall pain control score at termination, as well as mean changes from baseline across different secondary outcomes also showed treatment difference favoring ziconotide-treated subjects (i.e. higher mean score) (Figures 6–8).

Table 7: Descriptive Statistics on the Secondary Variables (BOCF) - ITT Population

	Placebo	Ziconotide
Total	108	112
CGI ¹ Overall Pain Control at Termination (%)		
Poor	60 (56%)	46 (42%)
Fair/Good	46 (43%)	50 (46%)
Very Good	1 (1%)	13 (12%)
Change in McGill Pain Intensity (%)		
Worsen	21 (20%)	15 (14%)
No Change	47 (44%)	47 (44%)
Improved by 1	30 (28%)	29 (27%)
Improved by = 2	8 (8%)	16 (15%)
Change in BPI ² (%)		
Worsen	45 (42%)	38 (35%)
No Change	15 (14%)	8 (7%)
Improved by < 5	35 (33%)	37 (34%)
Improved by = 5	11 (10%)	26 (24%)
Change in Quality of Sleep (%)		
Worsen	16 (15%)	12 (11%)
No Change	79 (74%)	61 (57%)
Improved	12 (11%)	35 (32%)
Change in CPRS ³ (%)		
Worsen	23 (22%)	14 (13%)
No Change	43 (40%)	37 (34%)
Improved	41 (38%)	57 (53%)
Change in TOPS ⁴ (%)		
Worsen	45 (42%)	34 (31%)
No Change	1 (1%)	1 (1%)
Improved by < 10	41 (38%)	46 (42%)
Improved by = 10	20 (19%)	28 (26%)
Outcome (%) ⁵		
Worsen/no change	88 (81%)	75 (67%)
Improved	20 (19%)	37 (33%)

¹ Clinical Global Impression Score

² Brief Pain Inventory

³ Categorical Pain Relief Scale

⁴ Treatment Outcome Pain Survey

⁵ Improved outcome is defined as subjects who had at least one successful secondary outcome with NO worsening condition.

Figure 6: Mean CGI Score at Termination

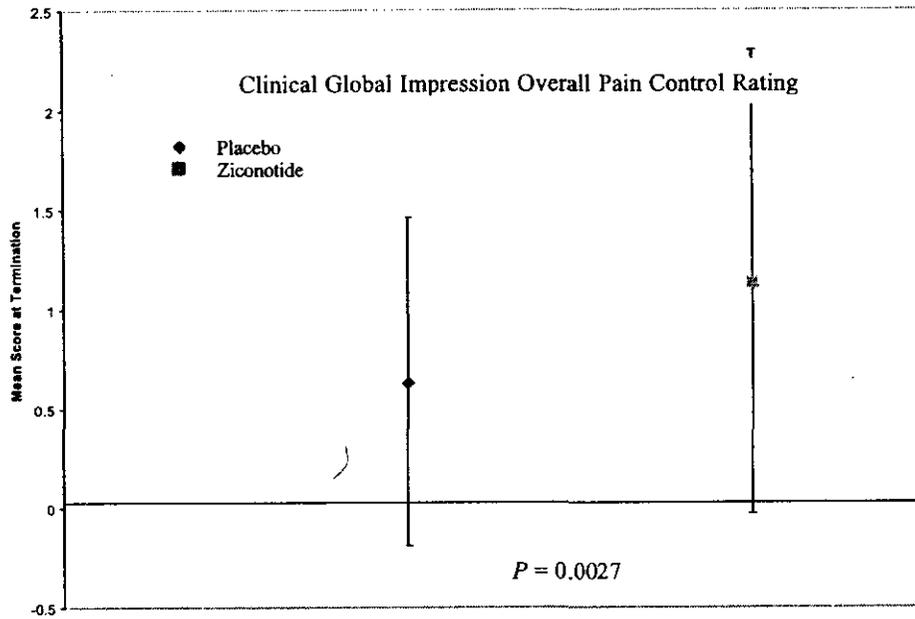


Figure 7: Mean Change in McGill Pain Intensity, BPI, and Quality of Sleep Score (SD) from Baseline

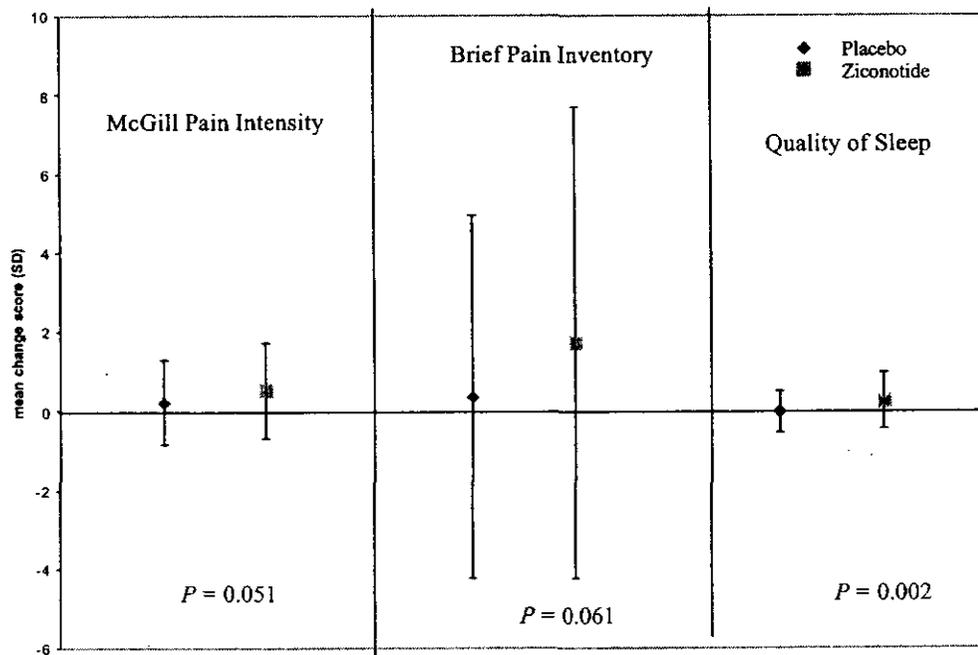
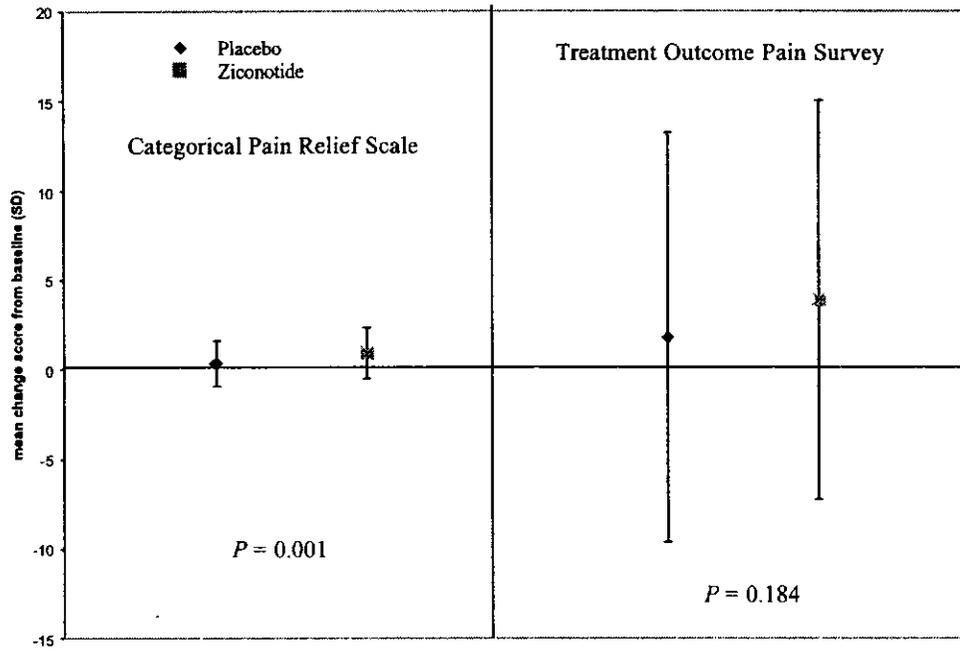


Figure 8: Mean Change in CPRS and TOPS Score (SD) from Baseline



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In summary, more than 90% of randomized patients successfully completed the study. The overall mean percent change in VASPI score at Week 3 using baseline observation carried forward (BOCF) was 12.2 in the ziconotide group and 5.4 in the placebo group ($p = 0.038$). Although the mean change in VASPI score was significantly different between the ziconotide and the placebo group, the proportion of responders (with at least 30% pain reduction) between the two treatment groups were not much different (Ziconotide 16% Placebo 12%). The difference in the proportion of responders was a little less when a stringent definition of responder was used (Ziconotide 15% Placebo 13%). When at least one successful secondary outcome with no worsening conditions was considered among the responders, the difference more clearly favored the ziconotide-treated subjects. Thus, subjects responding to ziconotide were more likely also to have an improvement in at least one quality of life outcome than subjects responding to placebo (Ziconotide 13% Placebo 3%). I conclude, therefore, that ziconotide was effective in reducing pain as well as improving quality of life in at least a small subgroup of the population in the study. Characteristics of these patients will be explored further.

Table 8: Summary of Results from Study 301

	Ziconotide	Placebo	Total
Enrolled			248 (100%)
Randomized	112	108	220
Completed Study	103 (92%)	100 (93%)	203 (92%)
Early Discontinuation	9 (8%)	8 (7%)	17 (8%)
Lack of efficacy	2 (2%)	2 (2%)	4 (2%)
Adverse Event	6 (5%)	5 (5%)	11 (5%)
Death	0	1 (0.9%)	1 (0.5%)
Subject Request: Voluntary Withdrawal of consent	1 (0.9%)	0	1 (0.5%)
Mean Percent Change in VASPI Score at Week 3 (SD)	12.2 (25.3)	5.4 (22.8)	
Responder (%) ¹ at Week 3	18 (16%)	13 (12%)	31 (14%)
Plus at least one successful secondary outcomes ²	15 (13%)	3 (3%)	18 (8%)
New Responder (%) ³ at Week 3	17 (15%)	13 (12%)	27 (12%)
Plus at least one successful secondary outcomes	14 (13%)	3 (3%)	17 (8%)

¹ Responders are defined as subjects with at least 30% pain reduction at Week 3 using the ITT population

² Subjects who are identified as responders and who have at least one successful secondary outcome with NO worsening condition in others

³ Responders are defined as subjects with at least 30% pain reduction at Week 3 and who did not dropped out of the study

The following table summarizes the demographic and baseline characteristics of subjects who responded to treatment (i.e. at least 30% pain reduction). The characteristics of the responders are not extremely different from the characteristics of the non-responders (e.g. sex, height and weight). Since most randomized subjects were Caucasians and under 65 years of age, the small difference found between responders and non-responders in these characteristics may not be meaningful.

The mean opiate consumption at Week 3 and the mean change of opiate consumption from pretreatment stabilization were substantially lower among the responders compared to non-responders. However, only a small difference can be seen in the change in opiate consumption between the ziconotide-treated group and the placebo group, slightly favoring the ziconotide group. This indicates that concomitant opioid use did not account for the differences in proportion of responders between the ziconotide-treated and placebo-treated groups.

Table 9: Demographic and Baseline Characteristics of Responders (BOCF) - ITT Population

	Total		Ziconotide		Placebo	
	Responder	Non-Responders	Responder	Non-Responders	Responder	Non-Responders
N (%)	31	189	18	94	13	95
Female (%)	17 (55%)	95 (50%)	9 (50%)	50 (53%)	8 (62%)	45 (47%)
Caucasian (%)	26 (84%)	180 (95%)	16 (89%)	91 (97%)	10 (77%)	89 (94%)
Age < 65	23 (74%)	155 (82%)	13 (72%)	79 (84%)	10 (77%)	76 (80%)
Weight (kg)	89.0 (27.6)	87.2 (21.0)	96.0 (29.1)	86.4 (21.5)	78.5 (22.2)	88.1 (20.5)
Height (cm)	168.1 (14.1)	171.6 (10.7)	168.7 (15.3)	171.8 (9.9)	167.1 (12.7)	171.3 (11.5)
Mean Opiate Consumption (mg)						
Pretreatment						
Stabilization	2234	1951	2629	2000	1689	1902
Week 1	1913	1922	2247	2016	1450	1828
Week 2	1738	1953	1915	2002	1493	1904
Week 3	1361	1512	1555	1518	1092	1506
Mean % Change from Pretreatment						
Stab to Week 3 (SD)	38.4 (37.0)	17.5 (61.1)	39.7 (39.6)	20.4 (58.6)	36.5(34.6)	14.5 (63.8)

Review and Comparison to Studies 95-001 and 96-002

The design of the two pivotal studies (95-001 and 96-002) were very similar; they were conducted simultaneously and with some of the same investigators. Study 95-001 was a multicenter, phase II/III, placebo-controlled study of SNX-111 administered intrathecally to patients with chronic malignant pain. Study 96-002 was a multicenter, phase II/III, placebo controlled study of SNX-111 administered intrathecally to patients with chronic non-malignant pain. Both were short-term trials, lasting 5 or 6 days. The primary efficacy outcome was percent change in VASPI (visual analog scale pain index) between the baseline and end of initial titration phase VASPI scores. The baseline VASPI score for a patient was the score taken immediately prior to initiation of infusion of the study drug. The final VASPI score at the end of the blinded, initial titration phase was the average of the last two VASPI scores (or the last three VASPI scores, if the third confirmatory measurement was done) obtained at the end of the initial titration phase (typically 120 hours for study 95-001 and 144 hours for Study 96-002). The percentage change from the baseline value was computed as:

$$\left[\frac{(\text{Baseline} - \text{End of Initial Titration Phase})}{\text{Baseline}} \right] \times 100$$

A positive value represents an improvement from baseline.

For the purpose of the integrated summary of efficacy, the applicant defined Week 3 to be the end of the initial titration phase in Study 301. In the analyses, the applicant included all the randomized patients (ITT population in Study 301 and all randomized low-dose patients in Studies 95-001 and 96-002, excluding patients from _____ site. The reason for exclusion of _____ site is due to the irregularities found related to blinding that could compromise the integrity of the data.

Table 10 presents the results from the primary efficacy analysis using baseline observation carried forward (BOCF) on these three studies. Both the fast titration and slow titration regimens demonstrated a statistically significantly greater improvement in mean percent change in VASPI score with ziconotide treatment over placebo that corresponds to the applicant's claim. As was the case in the applicant's review, the treatment effect was most pronounced in the fast titration studies, where an aggressive dose titration over 5 to 6 days occurred in hospitalized patients with a mean dose of 0.794 µg/hr at the endpoint and a maximum dose up to 2.40 µg/hr. While statistically significant, the treatment difference in the slow titration study was less than with the fast titration, most likely resulting from the lower mean dose of 0.287 µg/hr at the endpoint and maximum dose of 0.9 µg/hr with dose titration occurring over a three-week period in outpatients until early onset of analgesia.

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Table 10: Results of Primary and Other Efficacy Analyses of Percent Change in VASPI for Low Dose Fast Titration (Studies 95-001 and 96-002 combined) and Slow Titration (Study 301) Studies

	Mean (SD)		% Change		p-value
	Placebo	Active	Placebo	Active	
Study 301					
N	108	112			
Baseline VASPI score	80.7 (14.9)	80.7 (15.0)			
Observed	74.2 (20.7)	67.8 (21.8)	6.4 (24.7)	14.4 (26.9)	0.0369*
BOCF	75.8 (20.1)	69.8 (21.5)	5.4 (22.8)	12.2 (25.3)	0.0376*
Study 95-001					
N	17	33			
Baseline VASPI score	78.6 (14.1)	73.7 (14.8)			
Observed	63.0 (30.8)	42.3 (30.8)	18.9 (37.1)	41.1 (41.4)	0.0695†
BOCF	63.0 (30.8)	42.3 (30.8)	18.9 (37.1)	41.1 (41.4)	0.0459†
Study 96-002					
N	64	119			
Baseline VASPI score	75.0 (13.0)	80.7 (12.9)			
Observed	70.2 (22.6)	56.7 (32.6)	6.0 (28.8)	29.6 (40.2)	<0.0001‡
BOCF	70.2 (22.6)	56.7 (32.6)	6.0 (28.8)	29.6 (40.2)	0.0001‡
Pooled					
N	81	152			
Baseline VASPI score	75.8 (13.3)	79.2 (13.6)			
Observed	68.7 (24.5)	53.6 (32.6)	8.7 (30.9)	32.1 (40.6)	<0.0001‡
BOCF	68.7 (24.5)	53.6 (32.6)	8.7 (30.9)	32.1 (40.6)	<0.0001‡

*p-values with no adjustments

†p-values adjusted for baseline VASPI scores

‡p-values adjusted for study and baseline VASPI score

As shown in the detailed review section of Study 301, the onset of efficacy was at Week 1 even at a lower dose of ziconotide in the slow titration study. The clinical significance of the improvement in VASPI score was confirmed by the improvements in multiple protocol-specified secondary efficacy variables.

In terms of proportion of responders, visual inspection of the graphs on each fast titration studies (Study 95-001 and 96-002), as well as the pooled study, suggest that the cumulative distributions between ziconotide-treated group and the placebo are different (Figures 9 to 11; Tables 11 to 13). This implies that higher proportions of subjects in the ziconotide-treated groups were treatment responders compared to the placebo-treated group when different definitions of responder (based on different percent pain reduction) were used.

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Figure 9: Response Profile at the End of the Initial Titration Phase, Study 95-001

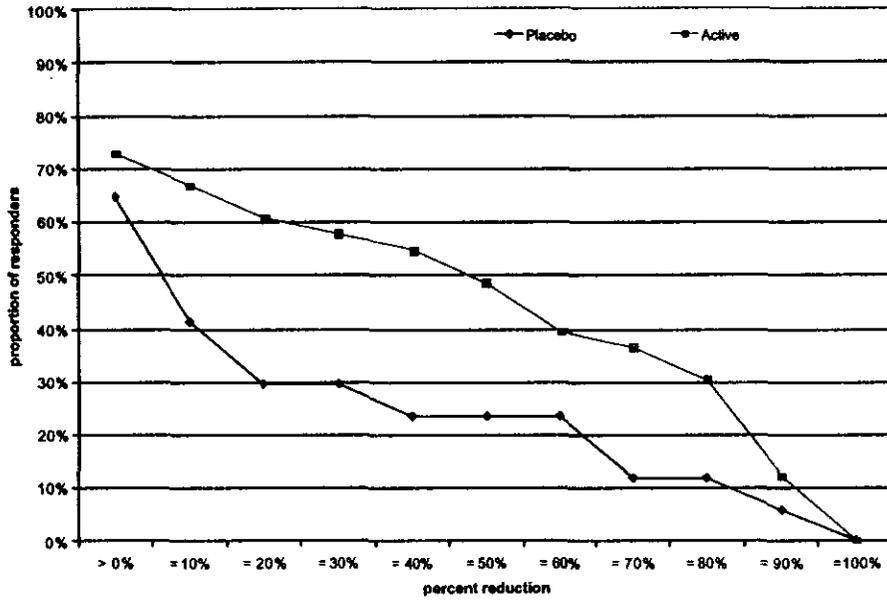


Figure 10: Response Profile at the End of the Initial Titration Phase, Study 96-002

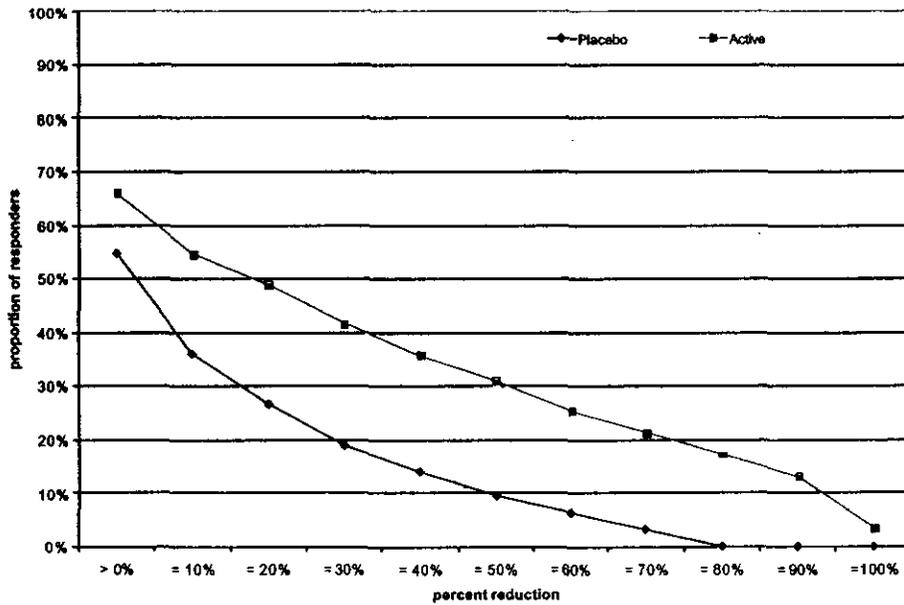


Table 11: Percentage Change in Mean VASPI Score Using BOCF - ITT population (Study 95-001)

	PLACEBO		ZICONOTIDE	
	Total	%	Total	%
Any increase	5	29%	8	24%
None	1	6%	1	3%
> 0 % decrease	11	65%	24	73%
= 10%	7	41%	22	67%
= 20%	5	29%	20	61%
= 30%	5	29%	19	58%
= 40%	4	24%	18	55%
= 50%	4	24%	16	48%
= 60%	4	24%	13	39%
= 70%	2	12%	12	36%
= 80%	2	12%	10	30%
= 90%	1	6%	4	12%
=100%	0	0%	0	0%

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Table 12: Percentage Change in Mean VASPI Score using BOCF - ITT Population (Study 96-002)

	PLACEBO		ZICONOTIDE	
	Total	%	Total	%
Any increase	27	42%	39	32%
None	2	3%	3	2%
> 0 % decrease	35	55%	81	66%
= 10%	23	36%	67	54%
= 20%	17	27%	60	49%
= 30%	12	19%	51	41%
= 40%	9	14%	44	36%
= 50%	6	9%	38	31%
= 60%	4	6%	31	25%
= 70%	2	3%	26	21%
= 80%	0	0%	21	17%
= 90%	0	0%	16	13%
=100%	0	0%	4	3%

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Figure 11: Response Profile at the End of the Initial Titration Phase, Pooled Studies (95-001 and 96-002)

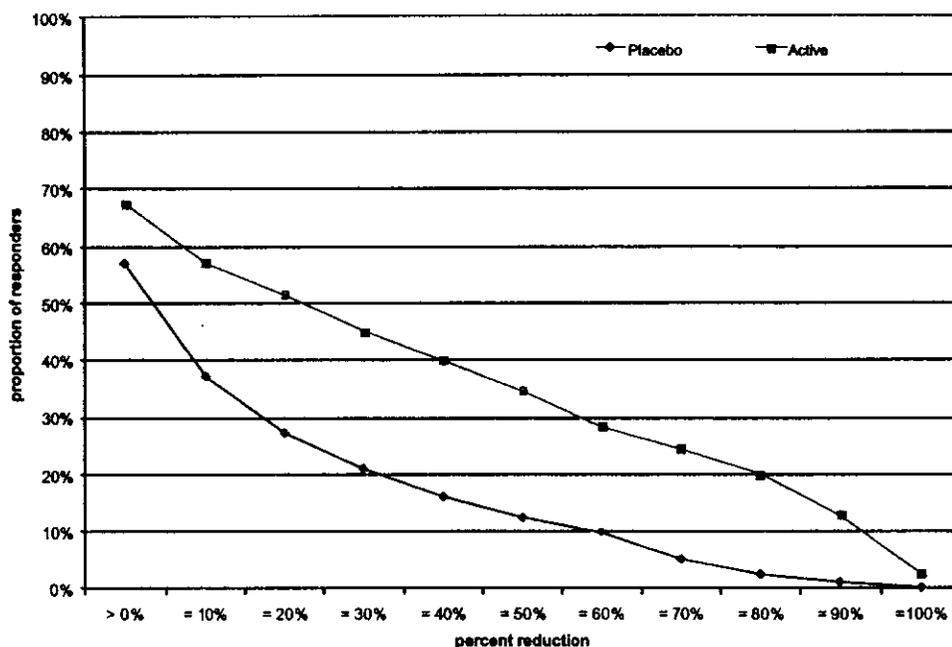


Table 13: Percentage Change in Mean VASPI Score using BOCF (Pooled Studies) - ITT Population

	PLACEBO		ZICONOTIDE	
	Total	%	Total	%
Any increase	32	40%	47	30%
None	3	4%	4	3%
> 0 % decrease	46	57%	105	67%
= 10%	30	37%	89	57%
= 20%	22	27%	80	51%
= 30%	17	21%	70	45%
= 40%	13	16%	62	40%
= 50%	10	12%	54	35%
= 60%	8	10%	44	28%
= 70%	4	5%	38	24%
= 80%	2	2%	31	20%
= 90%	1	1%	20	13%
= 100%	0	0%	4	3%

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Results and Conclusions

Although both the fast titration and slow titration regimens demonstrated a greater improvement in proportion of responders (at least 30 percent change in pain reduction) with ziconotide treatment over placebo that was consistent with the difference in mean percent change in VASPI scores, it appeared that the difference between treatment groups, as well as the proportions of responders, were most pronounced in the fast titration studies.

Table 14: Proportion of Responders, by Study

	TOTAL		PLACEBO		ZICONOTIDE	
	Total	%	Total	%	Total	%
Study 301	31	14%	13	12%	18	16%
Study 95-001	24	48%	5	29%	19	58%
Study 96-002	63	34%	12	19%	51	41%
Pooled (Study 95-001 and 96-002)	87	37%	17	21%	70	45%

The applicant in their report identified several differences between ziconotide-treated patients in the slow titration (Study 301) and fast titration studies 95-001 and 96-002 that may affect the difference in treatment response. Here are some of the differences identified by the applicant:

1. The design of Study 301 required up to a 7-week period with IT therapy for approximately 50% of patients. This may have increased the likelihood of selecting a more refractory to treat, more severely ill pain population willing to be treated with no IT drugs or placebo for such long duration
2. A greater proportion of patients in Study 301 had non-neuropathic pain than in Studies 95-001 or 96-002.
3. It appears that patients Study 301 had a longer duration of pain before receiving ziconotide.

In summary, ziconotide is effective in treating severe chronic pain. Although it appears that it is effective via fast titration regimen, it is important to note that only one fast titration study (96-002) successfully showed effectiveness based on the original efficacy review, as well as in Table 8. Pooling the two fast-titration studies may have demonstrated efficacy, but the safety of these two studies remains problematic.

The applicant, in response to the approvable letter, provided an amendment that included a new study that addressed concerns posed by the Agency. The new study used a slower titration schedule over 21 days and a lower maximum dose of 0.9 µg/hr compared to the previous two studies with forced titration schedules in which ziconotide doses were increased to tolerability or a maximum dose of 2.4 µg/hr (per the final dosing regimen) over 5 to 6 days. The mean dose of ziconotide was 0.5 µg/hr in study 95-001, and 0.83 µg/hr in study 96-002 at the end of the titration phase. Therefore, in study 301, ziconotide was titrated more slowly than in studies 95-001 and 96-002. A three-week treatment period was chosen to allow for more of analgesia rather than assess the higher dose range of safety and efficacy as already observed in Studies 95-001 and 96-002, and potentially to minimize SAEs, withdrawals, and adverse events (AEs).

Based on the review of efficacy in this new study, it appears that ziconotide is effective in treating severe chronic pain. The clinical significance of the improvement in VASPI score was also confirmed by the improvements in multiple protocol-specified secondary efficacy variables. In terms of the opiate consumption, the significant difference in the primary efficacy variable did not appear to be confounded by the use of concomitant opioids, as the use of opioids decreased in both treatment groups from pretreatment

stabilization to termination, with a larger decrease observed in the ziconotide group than in the placebo group.

Although the study drug was shown to be effective, the safety of the study drug must also be established. Dr. Lester Schultheis will provide a detailed review of the safety of ziconotide resulting from Study 301 and he will present its significance compared to the previous two studies.

3.2 Evaluation of Safety

Applicant's Summary of Results

The adverse event profile of ziconotide in this study is consistent with the results observed in the previous studies. However, the lower dose and slow titration regimen resulted in fewer SAEs and discontinuations due to AEs. Many of the anticipated AEs in ziconotide-treated patients were mild to moderate and well tolerated in this severely ill, chronic pain population. In most cases, AEs resulted in no changes in study drug dose. In spite of this AE profile, there was a clear benefit for this severely ill patient population. Of patients who received ziconotide, 87.4% expressed a desire to continue to receive the medication in an open-label follow-up study (Study 352).

A detailed review of the safety profile of ziconotide can be found in Dr. Lester Schultheis' review.

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4. FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

Separate analyses by age, race, and sex were carried out in Study 301, as well as those two previous studies (Studies 95-001 and 96-002). Baseline observation carried forward was used to impute missing data. The results based on the subgroup population across different studies are so variable that interactions are difficult to interpret. For instance, in study 301, the difference between ziconotide and placebo in patients over 65 years was more than (at least 6 percentage points) in patients under 65. Similarly when studies 95-001 and 96-002 are pooled together, the age-by-treatment interaction was also large, but this time in the opposite direction. Opposite treatment difference were shown in male and female groups between Study 301 (slow titration) and Pooled Study (Fast Titration). Because there are substantial statistical uncertainties due to lack of power and small sample size in each subgroup, these make the interaction difficult to interpret. Therefore it is difficult to be confident whether there is real demographic variation in the effect or there is not.

Table 15: Mean Percent Change in VASPI Score at the End of the Initial Titration Phase by Age (BOCF) - Low Dose Fast Titration (Studies 95-001 and 96-002) and Slow Titration (Study 301) Studies

	Ziconotide		Placebo	
	n	Mean (SE)	n	Mean (SE)
Study 301				
Age < 65	92	10.1 (25.0)	86	4.4 (21.5)
Age = 65	20	21.6 (25.0)	22	9.3 (27.5)
Study 95-001				
Age < 65	22	39.9 (41.3)	10	32.6 (42.7)
Age = 65	11	43.5 (43.5)	7	-0.6 (13.6)
Study 96-002				
Age < 65	92	29.6 (39.2)	50	2.6 (27.0)
Age = 65	27	29.7 (44.3)	14	18.2 (32.3)
Pooled (95-001 and 96-002)				
Age < 65	114	31.6 (39.6)	60	7.6 (31.8)
Age = 65	38	33.7 (44.0)	21	11.9 (28.6)

Table 16: Mean Percent Change in VASPI Score at the End of the Initial Titration Phase by Sex (BOCF) - Low Dose Fast Titration (Studies 95-001 and 96-002) and Slow Titration (Study 301) Studies

	Ziconotide		Placebo	
	n	Mean (SE)	n	Mean (SE)
Study 301				
Male	53	13.2 (26.1)	55	2.7 (19.7)
Female	59	11.3 (24.8)	53	8.1 (25.5)
Study 95-001				
Male	18	34.0 (40.6)	12	21.4 (34.0)
Female	15	49.5 (42.2)	5	12.8 (47.6)
Study 96-002				
Male	70	31.3 (38.4)	37	9.9 (32.9)
Female	49	27.3 (43.0)	27	0.6 (21.3)
Pooled (95-001 and 96-002)				
Male	88	31.8 (38.6)	49	12.7 (33.2)
Female	64	32.5 (43.5)	32	2.5 (26.3)

Table 17: Mean Percent Change in VASPI Score at the End of the Initial Titration Phase by Race (BOCF) - Low Dose Fast Titration (Studies 95-001 and 96-002) and Slow Titration (Study 301) Studies

	Ziconotide		Placebo	
	n	Mean (SE)	N	Mean (SE)
Study 301				
Caucasian	107	12.0 (25.4)	99	4.5 (22.5)
Others	5	15.3 (26.2)	9	15.4 (25.1)
Study 95-001				
Caucasian	30	39.4 (41.1)	16	14.1 (32.4)
Others	3	57.9 (50.1)	1	95.8
Study 96-002				
Caucasian	114	29.8 (40.8)	60	3.2 (26.6)
Others	5	24.5 (25.2)	4	47.6 (31.4)
Pooled (95-001 and 96-002)				
Caucasian	148	31.8 (40.9)	76	5.5 (28.0)
Others	8	37.0 (37.1)	5	57.2 (34.7)

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5. SUMMARY AND CONCLUSIONS

5.1 Statistical Issues and Collective Evidence

Based on my review, no statistical issue appeared to be of concern except for the choice of imputation method in the primary efficacy analysis. However, because the applicant provided several alternatives and presented sensitivity analyses that showed the results were highly robust (except when WOCF was used), this lessened my concern. Nevertheless, as an added check, I performed two additional analyses that are regarded as fairly conservative. One was imputing subject who dropped out using baseline observation carried forward approach, and the other was assuming those who dropped-out as non-responders in the responder analysis. Summary of the results is presented in Table 18 (similar to Table 1).

In study 301, analysis using BOCF showed that there is statistically significant difference in mean percent change of VASPI score from baseline between ziconotide-treated patients and placebo-treated patients at Week 3 (termination), favoring the ziconotide-treated group. In order for subjects in the two old studies (95-001 and 96-002) to be comparable to the new study, the applicant included all randomized low-dose patients in Studies 95-001 and 96-002, excluding patients from [REDACTED] site. Similar to the conclusion presented by the applicant in the previous submissions, there is a statistically significant difference in mean percent change of VASPI score from baseline between ziconotide-treated patients and placebo-treated patients at termination, favoring the ziconotide-treated group in Study 96-002. Meanwhile, treatment difference remained to be questionable in Study 95-001.

Although both the fast titration and slow titration regimens demonstrated a greater improvement in proportion of responders (at least 30 percent change in pain reduction) with ziconotide treatment over placebo that was consistent with the difference in mean percent change in VASPI scores, it appeared that the treatment difference was more prominent in the fast titration studies. This could mean that ziconotide is more effective on individuals when titration is fast. However, this regimen could potentially be more toxic compared to a slow titration regimen.

Another conclusion may be drawn from Study 301: patients responded well at Week 1 when the slow titration regimen was employed. Quantitatively, subjects in the ziconotide group responded well at Week 1 (Ziconotide 24 [21%], Placebo 13[12%]), but only a few continued to respond (Ziconotide 7, Placebo 3) up to Week 3 (Figure 4). On the other hand, it appears that there is no difference in the number of new responders at Week 2 (Ziconotide 10, Placebo 10) or Week 3 (Ziconotide 5, Placebo 5) between the ziconotide-treated group and the placebo group. In terms of the opiate consumption in Study 301, the significant difference in the primary efficacy variable did not appear to be confounded by the use of concomitant opioids, as the use of opioids decreased in both treatment groups from pretreatment stabilization to termination, with a larger decrease observed in the ziconotide group than in the placebo group.

5.2 Conclusions and Recommendations

In view of the statistical findings generated from the analyses conducted by the applicant and by me, I conclude that ziconotide is efficacious for the management of severe chronic pain. However, as indicated in my review, the safety of the study drug must also be established.

Table 18: Collective Evidence - Mean Percent Change in VASPI Score (SE) and Proportion of Responders (>= 30% pain reduction), by Study

	Mean (SD)		% Change		p-value
	Placebo	Active	Placebo	Active	
Study 301 at Week 1					
N	108	112	108	112	
Baseline VASPI score	80.7 (14.9)	80.7 (15.0)			
Observed	75.1 (20.6)	65.9 (26.6)	5.4 (26.8)	17.5 (31.0)	0.0033*
BOCF	75.6 (20.1)	67.0 (26.4)	5.0 (25.7)	16.6 (30.4)	0.0026*
Responders			13 (12%)	24 (21%)	
Study 301 at Week 2					
N	108	112	108	112	
Baseline VASPI score	80.7 (14.9)	80.7 (15.0)			
Observed	72.5 (21.0)	68.9 (23.9)	8.4 (25.0)	13.6 (28.5)	0.1667*
BOCF	73.9 (20.8)	69.6 (23.6)	7.5 (23.8)	12.9 (27.9)	0.1269*
Responders			17 (16%)	22 (20%)	
Study 301 at Week 3					
N	108	112	108	112	
Baseline VASPI score	80.7 (14.9)	80.7 (15.0)			
Observed	74.2 (20.7)	67.8 (21.8)	6.4 (24.7)	14.4 (26.9)	0.0369*
BOCF	75.8 (20.1)	69.8 (21.5)	5.4 (22.8)	12.2 (25.3)	0.0376*
Responders			13 (12%)	18 (16%)	
Study 95-001					
N	17	33	17	33	
Baseline VASPI score	78.6 (14.1)	73.7 (14.8)			
Observed	63.0 (30.8)	42.3 (30.8)	18.9 (37.1)	41.1 (41.4)	0.0695†
BOCF	63.0 (30.8)	42.3 (30.8)	18.9 (37.1)	41.1 (41.4)	0.0459†
Responders			5 (29%)	19 (58%)	
Study 96-002					
N	64	119	64	119	
Baseline VASPI score	75.0 (13.0)	80.7 (12.9)			
Observed	70.2 (22.6)	56.7 (32.6)	6.0 (28.8)	29.6 (40.2)	<0.0001‡
BOCF	70.2 (22.6)	56.7 (32.6)	6.0 (28.8)	29.6 (40.2)	0.0001‡
Responders			12(19%)	51 (41%)	
Pooled					
N	81	152	81	152	
Baseline VASPI score	75.8 (13.3)	79.2 (13.6)			
Observed	68.7 (24.5)	53.6 (32.6)	8.7 (30.9)	32.1 (40.6)	<0.0001‡
BOCF	68.7 (24.5)	53.6 (32.6)	8.7 (30.9)	32.1 (40.6)	<0.0001‡
Responders			17 (21%)	70 (45%)	

*p-values with no adjustments

†p-values adjusted for baseline VASPI scores

‡p-values adjusted for study and baseline VASPI score

Appendix

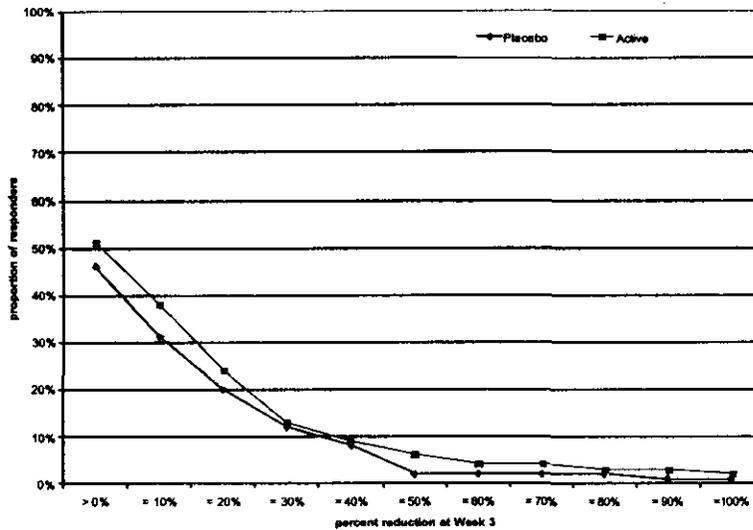
For the most stringent definition of responders at the end of the study, subjects who dropped out in the study, regardless of the time of drop-out, were considered failures. Furthermore, subjects who were identified as responders previously but did not join the open-label study were also considered failures. Of the 31 patients in Table 5 who were classified as responders with 30% pain reduction at Week 3, only 27 remained as responders based on this new definition of responder (Placebo 13, Ziconotide 14). Using this new definition, there is clearly only a small difference in the proportion of responders between the placebo and ziconotide group (Table A and Figure A).

Table A: Revised Percentage Change in Week 3 Mean VASPI Score (BOCF) - ITT Population

	PLACEBO		ZICONOTIDE	
	Total	%	Total	%
Any increase	31	29%	22	20%
None	27	25%	33	29%
> 0 % decrease	50	46%	57	51%
= 10%	34	31%	42	38%
= 20%	22	20%	27	24%
= 30%	13	12%	14	13%
= 40%	9	8%	10	9%
= 50%	2	2%	7	6%
= 60%	2	2%	4	4%
= 70%	2	2%	4	4%
= 80%	2	2%	3	3%
= 90%	1	1%	3	3%
=100%	1	1%	2	2%

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Figure A: Revised Response Profile at Week 3 (BOCF) - ITT Population



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S. Edward Nevius
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Statistical Review and Evaluation

NDA 21-060

Name of drug: ziconotide (SNX-111)

Applicant: Elan

Indication: intrathecal administration for pain

Documents reviewed: N00BZ volumes 001-004

Project manager: Laura Governale

Medical officer: Sharon Hertz, M.D.

Classification: amendment

Dates: received 29 January 2001; user-fee goal (6 months) 31 July 2001

Reviewer: Stella Grosser

Introduction

Ziconotide is a calcium channel blocker proposed for the management of severe, chronic, opioid-refractive pain. It is the synthetic equivalent of a naturally occurring peptide found in the venom of a marine snail, *Conus magus*; this venom alters neuromuscular function in prey.

Twenty clinical studies, varying in their design, route of administration, and indication, were carried out in the development of this drug. Review of these studies for the NDA resulted in an approvable letter, dated 27 June 2000. An amendment was submitted in response in January 2001. This amendment is the subject of this review of evidence concerning efficacy of ziconotide in treating chronic pain.

Original submission

The original NDA contained two studies relevant to efficacy, 95-001 and 96-002. Study 95-001 was a multicenter, phase II/III, placebo controlled study of SNX-111 administered intrathecally to patients with chronic malignant pain. Study 96-002 was a multicenter, phase II/III, placebo controlled study of SNX-111 administered intrathecally to patients with chronic non-malignant pain. Both were short-term trials, lasting 5 or 6 days. The primary efficacy outcome was percent change in VASPI (visual analog scale pain index). In the course of review, two problems were discovered. Mid-study protocol changes led to differing titration paradigms within trials. Moreover, field investigation of a center that participated in both studies 96-002 and 95-001 revealed irregularities that could compromise the integrity of the data, especially issues related to blinding.

Thus, only data from patients treated under the final version of the protocol were considered for the efficacy analysis, and data from the compromised site were excluded. Under these conditions, one study, 96-002, successfully showed ziconotide to be effective while study 95-001 did not. For more details on the design and analysis of these studies,

see the original efficacy review.

This amendment

The June 2000 approvable letter requested the submission of "results of a new randomized, double blind, placebo-controlled study of the safety and effectiveness of ziconotide at the dosing regimen ... proposed for marketing conducted in the target population proposed for labeling." In addition, the letter pointed out that a detailed and complete reanalysis, including secondary endpoints, of the subset of patients included in the final efficacy analysis of Studies 95-001 and 96-002 needed to be done.

In reply, in this amendment, the sponsor provides the reanalysis of the data gathered in Studies 95-001 and 96-002, including results of pooling data from the two studies. They offer an argument for the adequacy of these original data in proving efficacy. This argument is discussed below.

There are no data from new clinical studies in this submission.

Sponsor suggests that site was not unblinded and its data should be included in efficacy analysis

The sponsor compares patients treated under the final protocol dosing revision with and without Investigator [REDACTED] patients (the suspect site) (Section 8.7.4.3.2.2). They point out that

[t]he exclusion of patients from [REDACTED] site made little difference in the overall pattern of treatment response for both studies ... [F]indings indicate that the loss of statistical significance when Investigator [REDACTED] patients are removed is due to a decrease in patient numbers and not to bias from results at this site. Overall, these analyses indicate that data from the [REDACTED] site did not bias the efficacy results and support [REDACTED] statement that he had remained blinded during the initial titration period [the relevant part of the study].

Note that in the original statistical review of efficacy, Dr. Permutt and I also remark that the data from [REDACTED] do not appear to be much different in terms of apparent treatment effect size from those at other centers. However, effect size at a particular site relative to data from the rest of the study patients implies nothing about the quality of the data from that the site. Here data quality was determined by considerations external to the data, namely the findings of the Division of Scientific Investigations. Including data of uncertain quality from the [REDACTED] site does not lessen the uncertainty about the effect size in the study as a whole and the increase in statistical significance is spurious. I also note that secondary efficacy outcomes, such as absolute change in VASPI, CPRS and percent responders, show the same patterns in size, direction and certainty as the percent change in VASPI (positive effect of ziconotide, clinically relevant magnitude, statistically significant in 96-002 but not in 95-001 without the inclusion of the [REDACTED] site).

Sponsor suggests that efficacy based on a surrogate endpoint was shown

In response to FDA criticism of the mid-study changes in dosing, the sponsor argues that

the analgesic effect across several dosing regimens can be viewed as a surrogate endpoint for the analgesic effect of ziconotide administered at the more precise dosing regimen ... [Z]iconotide has an effect on a clinical endpoint that is different from but highly predictive of the endpoint that would support traditional approval.

The effect across several dosing regimens, in my view, is not a surrogate endpoint. Variable dosing regimens are surrogate input, not outcome. The distinction is between surrogate measures of the effect of a given regimen (where the most meaningful outcome is too hard to observe) and reasonable, direct, measures of the effect of something other than what the sponsor is proposing to give. While there is a fair amount of literature, guidance, and regulation pertaining to the former situation, the situation here falls into the latter category. The endpoints measured, change and percent change in VASPI at 5 or 6 days, remain the same throughout as per protocol and in themselves would be acceptable to support approval. There appears to be at most a narrow therapeutic window for ziconotide, where the benefits of pain relief outweigh safety concerns. The sponsor has not fully established where this window is for the population and how to find it for the individual.

Conclusions

There are no new data presented in this amendment. While there are analyses that were not in the original submission, they are similar to analyses either that the sponsor submitted in response to questions or that Dr. Permutt and I carried out in the course of the original review. This information was thus considered in drawing our earlier conclusion as well as reconsidered in reviewing this amendment. There is still insufficient evidence to conclude that ziconotide is efficacious under the labeled conditions.

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Statistical Review and Evaluation

NDA 21-060

Name of drug: ziconotide (SNX-111)

JUN 6 2000

Applicant: Elan

Indication: intrathecal administration for pain

Documents reviewed: volumes 2.091-2.214

amendment 4/22/00

electronic data and programs

Project manager: Laura Governale

Medical officer: Sharon Hertz, M.D.

Classification: 1P

Dates: received 28 December 1999; user-fee goal (6 months) 28 June 2000

Reviewers: Stella Grosser, Thomas Permutt

INTRODUCTION

Ziconotide (SNX-111) is a calcium channel blocker proposed for the management of severe, chronic, opioid-refractory pain. It is the synthetic equivalent of a naturally occurring peptide found in the venom of a marine snail, *Conus magus*; this venom alters neuromuscular function in prey.

Twenty clinical studies, varying in their design, route of administration, and indication, were carried out in the development of this drug. Routes of administration were intrathecal, epidural or intravenous; the primary use proposed is intrathecal administration with an implanted pump device. Designs included double-blind, placebo-controlled; long-term, open-label; and a variety of phase II supportive studies. The bulk of the subjects in these studies suffered from chronic pain; the study populations also included patients with acute post-operative pain, coronary artery bypass graft patients, traumatic brain injury patients and normal volunteers.

This review addresses evidence concerning efficacy of ziconotide in treating chronic pain. There are two relevant studies, 95-001 and 96-002. Study 95-001 was a multicenter, phase II/III, placebo-controlled study of SNX-111 administered intrathecally to patients with chronic malignant pain. Study 96-002 was a multicenter, phase II/III, placebo-controlled study of SNX-111 administered intrathecally to patients with chronic non-malignant pain. Both were short-term trials. Administered dose level varied within trials; this aspect of the protocols is described in more detail below.

DESIGN OF PIVOTAL EFFICACY STUDIES

The designs of the two pivotal efficacy studies were very similar; they were conducted simultaneously and with some of the same investigators. Study 95-001 was a multicenter, phase II/III, placebo controlled study of SNX-111 administered intrathecally to patients with chronic malignant pain, either cancer or AIDS-related. One hundred eleven patients were randomized to receive initial treatment with either ziconotide or placebo in a ratio of 2:1 ziconotide:placebo, resulting in 71 ziconotide and 40 placebo patients. The evaluable population of 108 included 95 (88%) cancer patients. The sponsor stated that an additional patient who received open label ziconotide was included in the safety population for this study. This patient apparently was included in the intent-to-treat analysis of efficacy as well. Randomization was stratified within each of 32 centers by etiology of the pain and by history (yes or no) of intrathecal opioid use. Study duration was approximately 32 days and consisted of a screening phase (1 to 7 days), a double-blind initial titration phase (5 or 6 days), a double-blind maintenance or a double-blind crossover phase (5 days), and follow-up assessment (14 days).

The initial titration phase consisted of five days with an option to continue to a sixth day for those patients who were tolerating the medication but had not achieved adequate analgesia. Data for primary efficacy evaluation, as well as some secondary efficacy measures, were collected at the end of this phase. Notwithstanding the maintenance or crossover phase, therefore, the study had a simple, parallel-group design as concerns the primary efficacy analysis.

At the end of the titration phase, patients were crossed over to the other treatment unless they had responded well to the treatment they had been on, as defined by at least a 30% decrease from the baseline pain measurement with no increase in concurrent opioid usage and no change in opioid type. Patients and staff remained blind as to the initial treatment assignment. Pain assessments were repeated after 5 days of this maintenance phase, but this later phase played no part in the primary analysis of efficacy.

Study 96-002 was a multicenter, phase II/III, placebo controlled study of SNX-111 administered intrathecally to patients with chronic non-malignant pain. Two hundred sixty-four patients across 42 centers were randomized to receive initial treatment with either ziconotide or placebo in a ratio of 2:1 ziconotide:placebo. Seven patients received no treatment, leaving 170 treated with ziconotide group and 87 with placebo. Study duration was approximately 32 days and consisted of a screening phase (1 to 7 days), a double-blind initial titration phase (6 days), a double blind maintenance or a double-blind crossover phase (5 days), and follow-up assessment (14 days).

As in study 95-001, data for primary efficacy evaluation, as well as some secondary efficacy measures, were collected at the end of the initial titration phase, so that the study was a simple, parallel-group study as far as the primary analysis of efficacy is concerned.

As in study 95-001, responders at this point in the trial were defined by the sponsor as those patients with at least a 30% decrease from the baseline pain measurement with no increase in concurrent opioid usage and no change in opioid type. Unlike study 95-001, the blind was broken for non-responders after the initial titration phase and only placebo non-responders were crossed over during the maintenance phase to receive ziconotide. (Patients who had received ziconotide were terminated from the study.)

Efficacy (evaluable) population: The evaluable population consisted of patients who met the inclusion and exclusion criteria of the study, did not substantially violate the protocol, and met at least one of the following three criteria:

1. had at least one visual analog scale pain intensity (VASPI) score after receiving at least 4 full days (96 hours) of study drug during the initial titration phase;
2. had reached their final dose prior to termination of the initial titration phase for at least 12 hours and had at least one VASPI score at the end of the 12-hour period; or
3. had terminated from the study due to an intolerable adverse event and had at least one VASPI score on the last or the second-last dose prior to termination of the initial titration phase.

Intent-to-Treat population: The intent-to-treat population included patients who had received any amount of study medication (either ziconotide or placebo) and had a baseline VASPI score and at least one follow-up VASPI score during the initial titration phase. There was also one patient in 95-001 who received a full course of study medication during the initial titration phase but was unblinded the entire period.

Due to protocol changes and inspection issues, the sizes of what we consider to be the most appropriate populations for evaluation of efficacy were substantially reduced. These changes are described below and led to final sample sizes for evaluating efficacy as follows:

	95-001		96-002	
	ITT	eval.	ITT	eval
Ziconotide	34	32	119	117
Placebo	17	17	64	61
Total	51	49	183	181

Interim sample size change in 95-001: An interim analysis of study 96-002 was conducted for the purpose of increasing the sample size if necessary. Instead, it indicated that variability was lower than predicted (the expectation was that it might be higher than what was found in the earlier pilot studies). Accordingly, the sample size for 96-002 was then fixed at the pre-specified, pre-interim analysis number, but the sample size for 95-001 was revised downward from 165 to 105 evaluable patients on the assumption that this lower variability also would be found in this patient population.

PROTOCOL CHANGES AND INSPECTION ISSUES

For two reasons, we think the most relevant populations for analysis are a subset of all patients treated. Field investigation of a center ██████ that participated in both studies 96-002 and 95-001 revealed irregularities that could compromise the integrity of the data, especially issues related to blinding. After consultation with the Division of Scientific Investigations, we consider it most appropriate to exclude data from ██████ in the analysis of both studies. While this was one of the largest sites, it still represents a fairly small proportion of all patients. Furthermore, the data from ██████ do not appear to be much different in terms of apparent treatment effect from those at other centers. Thus, analysis with or without ██████ leads to essentially similar conclusions.

A more substantial problem concerns revisions to the protocol, especially as regards the dosing paradigm. As noted above, the initial treatment period, on which efficacy was evaluated, involved titration of the dose. Accordingly, the proposed labeling recommends not a fixed dose but a paradigm for titration. Unfortunately, at different points in each study, radically different titration paradigms were used. In particular, patients treated under early versions of each protocol may have received much higher doses than recommended in the proposed label, and these doses are not proposed to be recommended because of adverse experiences in the early part of each trial. The experience at these higher doses, therefore, is not very relevant to determination of efficacy under the proposed paradigm.

In *study 95-001*, there were three revisions to the protocol affecting the dosing titration regimen:

- Under the original protocol (23 January 1996), infusion of ziconotide or placebo was initiated at a dose of 0.005 µg/kg/h (5 ng/kg/h) and was titrated up to a maximum dose of 0.3 µg/kg/h (300 ng/kg/h). Dose increases were made at 12-hour intervals, using an escalation schedule based on the Fibonacci series (1, 1, 2, 3, 5, 8, ...). The titration was to be continued upward until the appearance of intolerable adverse events that might be related to study drug.
- *Revision No. 1* (11 June 1996) removed the weight basis for dose determination, therefore changing the dose range to 0.4 µg/h to 21.0 µg/h.

- *Revision No. 2* (25 October 1996) lowered the maximum dose in the initial titration regimen to 2.4 µg/h, with an additional optional escalation to 3.9 µg/h.
- *Revision No. 3* lowered the initial dose to 0.1 µg/h and the maximum initial titration from 2.4 to 1.2 µg/h, with optional escalation to 2.4 rather than 3.9 µg/h. Also, the interval for dose adjustments was changed from 12 hours to 24 hours.

In addition, patients treated before Revision 3 of the protocol underwent forced titration, in which study drug was titrated to toxicity, whereas under the final version escalation was to be stopped if acceptable relief was obtained.

In *study 96-002*, there were 2 revisions to the protocol, again affecting the dosing regimen:

- Under the original protocol (17 May 1996), infusion of ziconotide or placebo was initiated at a dose of 0.4 µg/h and was titrated to effect up to a maximum dose of 7.0 µg/h.
- *Revision No. 1* (28 October 1996) modified the maximum dose at 144 hours from 7.0 µg/h to 3.9 µg/h based on a blinded review of adverse event data which indicated that the most frequently reported events were occurring at lower doses than in previous studies.
- *Revision No. 2* (21 February 1997) was generated because the onset of analgesic effect appeared to be occurring at lower doses than predicted in previous studies. The onset of nystagmus, dizziness, and confusion were also observed to be occurring at lower doses than in previous studies. Therefore, the dose titration range was lowered from 0.4 µg/h-3.9 µg/h to 0.1 µg/h-2.4 µg/h.

Most of the patients in *study 96-002* were treated under the final revision, but only about half the patients in *study 95-001* were treated under the final version of the protocol. The draft labeling proposes to recommend a titration scheme that corresponds to the final version for both studies.

PRIMARY EFFICACY ANALYSIS

The primary measure of efficacy was the percent change in visual analog scale pain intensity (VASPI) from baseline to the end of the initial titration phase. VASPI was reported by patients, who marked their pain on a 100 mm horizontal line where 100 mm = worst possible pain and 0 mm = least possible pain. The baseline score was a single measurement, whereas the final score was the mean of two measurements no more than two hours apart (or three measurements, if the two differed by more than 15 mm and there was a third measurement). Because of some questions about interpretability of the percent change, we also report summary statistics for the numerical change from baseline (not as percent); but the results are

essentially similar. The protocol amendments did not address statistical analysis. Presumably it was intended to lump patients from all versions of the protocol together in analysis, and this was in fact the analysis reported in the submission.

In study 95-001, the primary test of treatment difference was a 2-way ANOVA with treatment, opioid use history (yes or no), and treatment-by-opioid interaction as factors. In study 96-002, treatment difference was tested using a 2-way ANOVA with treatment, center, and treatment-by-center interaction as factors. The smallest centers were pooled into three pseudo-centers for the purpose of this analysis, with the choice of pseudo-center for each center depending on the type of pain treated at the center (one pseudo-center for central pain, another for peripheral pain, and a third for both). The reasons for the differences in covariates are not clear, but each protocol unambiguously specified an acceptable analysis for the study concerned.

STUDY 96-002

The VASPI results for study 96-002 are shown in the two tables below. We report both the protocol-specified primary measure, percent change, and the absolute change from baseline. We also show both what we think is the most relevant population (final version of the protocol, without the ~~site~~) and the whole population.

Population	Parameter	Rev2 without site		Entire study	
		Ziconotide	Placebo	Ziconotide	Placebo
Evaluable	% reduction in VASPI				
	N	117	61	159	79
	Mean (SE)	29.4 (3.74)	6.4 (3.75)	30.7 (3.47)	6.2 (3.24)
	Median	19.9	1.1	23.8	1.1
	(range)	(-54-100)	(-62-79)	(-113-100)	(-62-80)
	p-value for treatment difference	0.004		<0.001	
Intent-to-treat	N	119	64	164	86
	Mean (SE)	29.6 (3.69)	6.0 (3.59)	31.2 (3.41)	6.0 (3.05)
	Median	20.2	1.1	25.6	1.1
	(range)	(-54-100)	(-62-79)	(-113-100)	(-62-80)
		p-value treatment difference	<0.001		<0.001

(From amendment 4/22/00, Table 2 and volume 2.107, Table 9.1, p. 292 and Table 9.3 p. 293.)

Population	Parameter	Rev2 without █████		Entire study	
		Ziconotide	Placebo	Ziconotide	Placebo
Evaluable	Reduction in VASPI				
	N	117	61	159	79
	Mean (SE)	23.8 (2.97)	5.1 (2.61)	25.4 (2.65)	5.2 (2.36)
	Median	16.5	1.0	19.0	1.0
	(range)	(-35-96)	(-36-61)	(-52-98)	(-36-80)
	p-value for treatment difference	0.001		<0.001	
Intent-to-treat	N	119	64	164	86
	Mean (SE)	24.0 (2.92)	4.8 (2.50)	25.7 (2.59)	5.0 (2.22)
	Median	17.5	1.0	19.5	1.0
	(range)	(-35-96)	(-36-61)	(-52-98)	(-36-80)
		p-value for treatment difference	<0.001		<0.001

(From amendment 4/22/00 Appendix C, Table 9.3 and Table 9.5.)

The range of experiences in both treatment groups was very wide. In the ziconotide group the median change from baseline was between 15 and 20 mm on the 100-mm scale, depending on the definition of the population, whereas the median change in the placebo group was near zero. The difference between treatments was statistically significant for either the raw or percent change, for either the evaluable or intent-to-treat populations, and whether █████ patients and those treated before the final protocol revision were included or excluded.

STUDY 95-001

The next two tables show the results for reduction in VASPI from study 95-001. Here again, we report the patients treated under the final version of the protocol excluding the █████ site as well as the whole population. The percent reduction was primary according to the protocol, but we also show the absolute change from baseline.

Population	Parameter	Rev3, without 		Entire study	
		Ziconotide	Placebo	Ziconotide	Placebo
Evaluable	% reduction in VASPI				
	N	32	17	68	40
	Mean (SE)	42.4 (7.32)	18.9 (9.0)	53.1 (4.63)	18.1 (6.77)
	Median	56.1	3.1	62.3	7.8
	(range)	(-26-95)	(-24-96)	(-26-100)	(-62-96)
	p-value for treatment difference	0.058		<0.001	
Intent-to-treat	N	34	17	71	40
	Mean (SE)	39.5 (7.17)	18.9 (9.0)	51.4 (4.59)	18.1 (6.77)
	Median	43.0	3.1	62.0	7.8
	(range)	(-26-95)	(-24-96)	(-26-100)	(-62-96)
		p-value for treatment difference	0.080		<.001

(From amendment 4/22/00, Table 1 and volume 2.097, table 9.1, p. 69 and table 9.2 p. 71.)

Population	Parameter	Rev3 without 		Entire study	
		Ziconotide	Placebo	Ziconotide	Placebo
Evaluable	Reduction in VASPI				
	N	32	17	68	40
	Mean (SE)	32.4 (5.68)	15.6 (7.63)	39.4 (3.61)	16.9 (5.61)
	Median	37.3	2.5	45.0	7.5
	(range)	(-14-87)	(-16-91)	(-17-99)	(-34-93)
	p-value for treatment difference	0.083		0.002	
Intent-to-treat	N	34	17	71	40
	Mean (SE)	30.2 (5.56)	15.6 (7.63)	38.4 (3.57)	16.9 (5.61)
	Median	28.3	2.5	44.5	7.5
	(range)	(-14-87)	(-16-93)	(-17-99)	(-34-93)
		p-value for treatment difference	0.110		0.003

(From amendment 4/22/00, Appendix B, Table 9.3 p. 2, Table 9.5 p. 2.)

Here the numerical differences between treatment groups were somewhat larger than in study 96-002, but they were not so clearly statistically significant because the numbers of patients were smaller. From the standpoint of hypothesis testing, patients randomized to ziconotide or placebo, regardless of the dosing paradigm, give some information about the effectiveness of ziconotide. Thus, the hypothesis that ziconotide has no effect at any dose can be confidently rejected. It remains theoretically possible that it is effective only when used according to early versions of the protocol, where it was found also to be too toxic for further study. There is nothing to suggest such a threshold effect, however. The observed difference between ziconotide and placebo under the final protocol was only modestly less than for all patients combined, even though it was not statistically significant.

On the other hand, this study provides very limited information about the effectiveness of ziconotide when used according to the proposed directions. When analysis is confined to patients treated in this manner, the results do not reach the usual standard of statistical significance. There is thus less than the usually required amount of information on benefits to be weighed against the risks of the drug.

DEMOGRAPHICS

Separate analyses by age, race and sex were carried out in both of the principal efficacy studies. The two tables below are copied from the electronic version of the study reports. Some differences were numerically impressive. In study 96-002 the difference between ziconotide and placebo in patients over 60 was less than half that in patients under 60. In study 95-001 this age-by-treatment interaction was almost as large but in the opposite direction. In both studies the difference between treatments was more for women than for men. Also, the small nonwhite population in each study did better on placebo than on ziconotide.

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**[96-002] Mean Percent Change in VASPI Score at the End of
the Initial Titration Phase by Demographic Subgroup -
Evaluable Population**

Demographic Subgroup	Ziconotide		Placebo	
	n	Mean (SE)	n	Mean (SE)
Age				
< 60 Years of age	114	31.4 (3.82)	56	2.1 (3.53)
≥ 60 Years of age	45	28.9 (7.62)	23	16.3 (6.71)
Gender				
Male	88	32.6 (4.23)	47	9.8 (4.84)
Female	71	28.3 (5.77)	32	1.1 (3.54)
Race				
Caucasian	152	30.8 (3.60)	74	4.4 (3.15)
Other	7	29.3 (11.27)	5	33.6 (18.53)

Note: Patients 6057-101, 6063-102, and 6081-101 had no VASPI score at the end of the initial titration phase and were not included.

Note: Percent change = 100 x (VASPI score at baseline - VASPI score at end of initial titration) / (VASPI score at baseline). Positive values represent improvement in pain.

Data Source: Appendix 2, Tables 9.10, 9.11, and 9.12

**[95-001] Mean Percent Change in VASPI Score at End of Initial
Titration Phase by Demographic Subgroups - Evaluable
Population**

Demographic Subgroup	Ziconotide		Placebo	
	n	Mean (SE)	n	Mean (SE)
Age				
< 60 Years	39	51.6 (6.19)	23	24.4 (9.10)
≥ 60 Years	29	55.2 (7.08)	17	9.6 (10.06)
Gender				
Male	34	44.1 (6.90)	20	12.3 (8.07)
Female	34	62.1 (5.88)	20	23.9 (10.94)
Race				
Caucasian	57	48.9 (5.23)	38	14.2 (6.53)
Other	11	75.1 (6.11)	2	92.3 (3.51)

Note: Percent change = (VASPI score at baseline - VASPI score at end of initial titration) / (VASPI score at baseline) x 100.

Data Source: Appendix 2, Tables 9.9, 9.10, and 9.11

These interactions are difficult to interpret. They are, of course, subject to substantial statistical uncertainty. The trials were designed statistically only to show a positive effect of ziconotide on average across all groups, and one of them arguably failed even in this. So, as

usual, it is impossible to be confident either that there is real demographic variation in the effect or that there is not. The observed variation, however, serves to underscore the fact that there is minimal quantitative information about the effectiveness of ziconotide. There are no trials at fixed doses, only titration studies; and there were six different titration schemes used at various times in the two studies. At best, there may be barely enough information to establish dosing recommendations for the "average" patient, and dosing recommendations for important subgroups would be speculative.

We note in this context that even the opposite directions in the two studies of the age-by-treatment interaction, which might otherwise suggest that they were due to random variation, are not very reassuring in view of the differences between the protocols and between versions of the same protocol. It is not inconceivable that, on average, elderly patients received relatively more effective doses in study 95-001 and less effective doses in study 96-002. Again, we do not suggest that there is persuasive evidence that this is the case. Rather, there is a general paucity of evidence about precisely what the effects of ziconotide are, at what doses, and in what populations.

CONCLUSIONS AND RECOMMENDATIONS

The application reports two studies of efficacy of intrathecal ziconotide (SNX-111). Study 96-002 showed an effect that was clearly statistically significant. Study 95-001 appeared to show an effect as well. However, when analysis was restricted to the population treated under conditions proposed to be recommended in the label, the results of study 95-001 were not statistically significant. Taken together, the two studies clearly show that ziconotide is an active agent at least at some doses. Nevertheless, they do not meet the usual standard of replication of significant results under the labeled conditions. The benefits under these conditions of use are poorly quantified and must be weighed against substantial risks, which are discussed in the medical officer's review.

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Numerically impressive variation in effect was seen by age, race and sex. The numbers of patients were too small for these apparent interactions to be statistically reliable, but neither can the possibility of strong interactions be excluded with any confidence.

Description of the clinical trials in labeling should reflect the subpopulation that was treated according to the dosing paradigm that is to be recommended.

for *Thomas Permutt 6/5/00*
Stella Grosser, Ph.D.
Mathematical Statistician

Thomas Permutt 6/5/00
Thomas Permutt, Ph.D.
Mathematical Statistician (Team Leader)

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HFD-170/Governale, Hertz, Rappaport, McCormick, Grosser, Permutt

HFD-170/division file