

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
21-060

MEDICAL REVIEW



FDA CENTER FOR DRUG EVALUATION AND RESEARCH

DIVISION OF ANESTHETIC, CRITICAL CARE, AND ADDICTION DRUG PRODUCTS
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DIVISION DIRECTOR SUMMARY REVIEW AND RECOMMENDATION FOR APPROVAL

DATE: December 23, 2004

DRUG: Prialt (ziconotide, solution for intrathecal administration, 25 µg/mL and 100 µg/mL)

NDA: 21-060

NDA Code: Type 1P NDA

SPONSOR: Elan Pharmaceuticals

INDICATION: For the management of severe, chronic pain in patients in patients for whom intrathecal therapy is warranted

Prialt (ziconotide, solution for intrathecal administration, 25 µg/mL and 100 µg/mL) is the first product in the class of drugs known as conotoxins to be submitted for FDA evaluation for marketing. Conotoxins are naturally occurring peptides found in the venom of piscivorous marine snails such as the *Conus magnus*. Prialt is a synthetic version of one of those peptides and is thought to act by binding to N-type calcium channels on the primary nociceptive afferent nerves in the dorsal horn of the spinal cord, blocking excitatory neurotransmitter release in the primary afferent nerve terminals. Early clinical studies of ziconotide delivered intravenously were discontinued because healthy volunteers developed profound hypotension upon administration.

Elan Pharmaceuticals submitted the original application for NDA 21-060 in support of marketing approval for Prialt on December 28, 1999. An approvable letter was issued on June 27, 2000 citing deficiencies related to chemistry, manufacturing and controls (CMC), and the adequacy of the clinical trials to establish a safe and effective dosing regimen. The sponsor submitted a complete response to the approvable letter on January

26, 2001. This submission included reanalyses of the original clinical data, rather than a new clinical trial as requested in the first approvable letter. A second approvable letter, issued on July 25, 2001, cited persistent deficiencies in CMC, preclinical concerns related to possible embryofetal toxicity, and the inadequacy of the reanalyses of the clinical data to establish a safe dosing regimen. A complete response to the second approvable letter was submitted on June 25, 2004.

Review of the CMC portion of this submission was completed by Michael Theodorakis, Ph.D. Review of the pharmacology and toxicology data presented in this submission was completed by Suzanne R. Thornton-Jones, Ph.D. The sponsor has submitted a single additional study in support of the safety and efficacy of their product. A statistical review and evaluation was completed by Joan Buenconsejo, Ph.D. A detailed review of this study and of the safety of the product was performed by Lex Schultheis, M.D, Ph.D. Rigoberto Roca, M.D. contributed a secondary review for the clinical team. Additional consultation on this submission was obtained from The Center for Devices and Radiological Health (CDRH), the Microbiology Staff, the Division of Drug Marketing, Advertising and Communication (DDMAC), and the Office of Drug Safety (ODS).

Clinical Efficacy and Safety:

The original application and the reanalyses submitted as a response to the first approvable letter based the sponsor's findings of efficacy and safety on two clinical trials designed to evaluate Prialt in patients with severe, chronic pain due to AIDS or malignancy (Study 95-001 [001]) or due to a heterogeneous collection of non-malignant medical conditions (Study 96-002 [002]). The clinical review team found the data to be inadequate to support the safe and effective use of Prialt for the following reasons:

- In Study 001, inspection of one of the study sites by the Division of Scientific Investigation revealed that the patients at that site were unblinded to treatment due to study misconduct. This called into question the integrity of data monitoring at all study sites.
- The review team found that the dosing regimen had been changed while the studies were ongoing in order to improve tolerability to Prialt. As a consequence, too few subjects were treated with the dosing regimen proposed in the draft labeling to allow adequate assessment of efficacy and safety. While the Division's *post hoc* exploratory analysis of the subset of subjects treated with the proposed dosing regimen suggested that Prialt may be effective, too few patients were evaluable for the analysis to be conclusive.
- There was a high incidence of neuropsychiatric adverse events, many of which were serious and some of which appeared to be causally related to deaths during the clinical trials. These events were thought to be related to the rapid titration scheme initially used in the clinical trials, and to the high final doses employed in those trials.

The original application also included data from three open-label safety studies and four Phase 2 studies. Data from two, new open-label extension studies have been included in this submission.

Study 301 is a new study submitted by the sponsor to confirm the efficacy results observed in the short-term (5 to 6 days) trials, 001 and 002, and to establish that the slower titration schedule and relatively lower final doses used in this trial would confer a more acceptable safety profile.

Patients with chronic pain that had not been adequately controlled with a variety of intrathecally delivered analgesics, or who were intolerant to these drugs and to systemically administered opiates, were enrolled in Study 301 if their Visual Analogue Score Pain Index (VASPI) was greater than or equal to 50 mm on a scale of 100 mm. Subjects were weaned from their intrathecal medications and stabilized on oral opiates prior to randomization. They were then randomized to Prialt 0.10 µg/hr or placebo, delivered via an implanted SyncroMed Infusion System already in place. Subjects were titrated over a period of 21 days, to a dose that resulted in adequate analgesia or to a maximum dose of 0.9 µg/hr. Blinded treatment continued for three weeks.

The Intent-to-Treat population, consisting of all subjects who received at least one dose of study medication and who had at least one efficacy evaluation, was analyzed after three weeks of treatment. A last-observation-carried-forward methodology was employed for imputing missing data. The sponsor's analysis of the primary efficacy endpoint, change in VASPI score from baseline to study termination, revealed a statistically significant treatment effect for the Prialt subjects. Further analyses performed by the sponsor and the Division, using alternative methodologies for imputation of missing data, confirmed the finding of the original analysis.

The results of the Dr. Buenconsejo's analysis using a baseline-observation-carried-forward strategy for imputation of missing data are summarized in Dr. Roca's table (page 6 of his review), reproduced below:

VASPI Score (mm) at Week 3	Ziconotide N = 112	Placebo N = 108	p-value
Mean (SD)	69.8 (21.5)	75.8 (20.1)	
Percent change from baseline	12.2 (25.3)	5.4 (22.8)	0.0376

The review team also performed a responder analysis, defining a responder as a subject with at least a 30% improvement in VASPI score at Week 3 compared to baseline. In this analysis, all subjects with missing data were classified as non-responders. The results of this analysis are summarized in Dr. Roca's table (page 6 of his review), reproduced below:

	Ziconotide N = 112	Placebo N = 108	p-value	95% CI
Responder	18 (16.1 %)	13 (12.0%)	0.390	

95 % CI for responder	(8.8, 23.3)	(5.4, 18.6)	
Treatment difference in % of responders	4%		(-6.0, 14.1)

Secondary efficacy endpoints included:

- *Responder Analysis*
- *Other Analysis using VASPI Score:*
 - The percent change in VASPI score at the final visit at the end of treatment week 3 compared to baseline visit using observed data only (no LOCF).
 - The VASPI score (mm) change from baseline to termination visit (using LOCF).
 - The percent change in weekly VASPI scores reported at scheduled weekly treatment visits at the end of week 1 and week 2 and the final visit using observed data only (no LOCF).
 - Percent change in weekly VASPI scores reported at scheduled weekly treatment visits at the end of week 1 and week 2, with LOCF for early terminations.
 - Percent change in weekly VASPI scores at weekly treatment visits at the end of treatment week 1, week 2 and final visit, observed data only, without LOCF.
- *Weekly Opiate Consumption*
- *Clinical Global Impression (CGI):*
 - Clinical Global Impression Satisfaction with Therapy
 - Clinical Global Impression Overall Pain Control
- *Change in Global McGill Pain Questionnaire Scores:*
 - Change in Global McGill Total Score
 - Change in Global McGill Pain Intensity Scores
- *Change in Brief Pain Inventory (BPI)*
- *Sleep Pattern and Quality of Sleep*
- *Categorical Pain Relief Scale(CPRS)*
- *Change in Treatment Outcome Pain Survey Dimension Score (TOPS)*

The results of the analyses of these endpoints were generally supportive of the primary efficacy endpoint analyses.

The most significant concern that resulted from review of the original safety database was a high incidence of neuropsychiatric adverse events, many of which were serious, and some of which appeared to be causally related to fatalities in the clinical trials. Dr. Sharon Hertz, the primary medical reviewer for the initial application, defined this adverse event profile as a "ziconotide-induced syndrome of encephalopathy." Signs and symptoms of this "encephalopathy" included, but were not limited to: depression, suicidal ideation and completed suicide, ataxia, cognitive impairment, confusion and stupor, hallucinations, bizarre behavior, somnolence, dementia, amnesia, and aphasia. The sponsor convened a panel of specialists to evaluate these findings. That panel chose nine representative adverse event terms for their analysis. These terms were not inclusive of all of the events of concern noted in Dr. Hertz's review. The panel suggested the use of the term "neurocognitive impairment" rather than "encephalopathy" based upon their evaluation. However, the Division's review of the panel's analysis determined that it was incomplete and that their conclusions were not compelling. Therefore, additional safety data was requested in the second approvable letter.

Based upon his review of the data from the new study, Dr. Schultheis has determined that "...similar dysfunction of the central nervous system was present in Study 301 as in earlier high-dose rapid-titration trials." (page 13, Clinical Review) However, he found that, in general, patients appeared to tolerate these events, and that 90 of the 112 Prialt-treated subjects consented to continuing treatment in the open-label extension study. There were no deaths in Study 301. There were three deaths reported from one of the ongoing extension studies; but Dr. Schultheis determined that these three deaths were unlikely to have been related to treatment with Prialt. While 12% of Prialt-treated subjects experienced serious adverse events compared to 9% of placebo-treated subjects, the incidence of discontinuations due adverse events was 5% in both treatment groups. However, of these subjects who discontinued, 4 of the 6 in the Prialt arm had an event referable to the nervous system while only 1 of the 5 in the placebo arm had a CNS-referable event, opiate withdrawal. While the number of common adverse events related to the nervous system was high in both treatment groups, it was approximately 2.5 times higher in the Prialt group compared to the placebo group (485 vs. 195, respectively).

One other safety concern arose during review of the overall safety database for Prialt. This was elevation of creatine kinase (CK). In the initial safety database a high percentage of Prialt-treated subjects had elevated CK levels, many greater than 3 times the upper limit of normal. However, only a handful of those subjects had elevations that did not resolve, and only one subject had serious clinical consequences. For that subject, it appears that the etiology of his rhabdomyolysis was not related to Prialt exposure. In Study 301, five Prialt-treated subjects experienced CK levels that were three times the upper limit of normal. However, these elevations were not accompanied by clinical signs of renal failure, myocardial damage, myopathy or rhabdomyolysis, and they resolved upon discontinuation of treatment with study drug.

Nonclinical Safety:

Dr. Thornton-Jones has determined that there are no outstanding toxicological concerns at this time. She notes that ziconotide did not block hERG channels at concentrations up to 15 ng/mL. Also, all impurities have been adequately qualified.

Follow-up studies of the embryotoxicity confirmed that the apparent malformations seen in the earlier study were due to incomplete ossification and not to a teratogenic effect. However, embryolethality was noted in the new studies with a NOAEL of 0.5 mg/kg/day. This is 400 times the recommended dose for clinical use.

Chemistry, Manufacturing and Controls:

Dr. Theodorakis has determined that all of the outstanding concerns listed in the second approvable letter have been adequately addressed in this submission. At this time there are, however, some site inspections still pending. This issue will be addressed by Robert Meyer, M.D., Director, Office of Drug Evaluation II and signatory for this application, prior to any action being taken.

Nomenclature:

The sponsor's proposed Tradename, Prialt, was found to be acceptable by both the ODS and DDMAC review teams.

Discussion:

While the data submitted to this application do appear to have established the efficacy of Prialt, the treatment effect was at best meager, and was limited to a small subset of the subjects. To a large degree this is due to the profound toxicity that is often associated with exposure to this drug, and to the inability of most patients to tolerate that toxicity. These neuropsychiatric adverse events associated with Prialt would be completely unacceptable for most drug products. However, a number of factors may allow a determination that a reasonable risk to benefit balance exists for this product. With the slower titration and lower final doses administered in Study 301, the patients appeared to be better able to tolerate the neuropsychiatric adverse events, many subjects actually choosing to continue into the open-label extension study. The events appeared to be reversible with discontinuation of the drug; and there were no deaths in this study that were clearly attributable to these events. The most compelling argument, however, is that, for a few patients who had failed all other accepted therapies and who continued to experience excruciating, chronic pain, Prialt relieved their pain to a degree that allowed them to return to a more acceptable quality of life.

Significant elevations of CK were also noted across all studies. Fortunately, it was only in the earlier studies, those that employed a faster titration rate and a higher final dose, that these elevations were associated with clinical effects that might result in significant

morbidity or mortality. Additionally, in the most recent, slow-titration, lower-dose study, these elevations were reversible upon discontinuation of Prialt administration. Nevertheless, some form of monitoring for elevations in CK and the clinical signs and symptoms associated with myopathy, rhabdomyolysis and/or renal failure is necessary for patients being treated with Prialt.

There are also a number of potential pitfalls associated with the delivery of Prialt via an intrathecal infusion pump, including inadequate sterile technique, inadequate attention to the dosing instructions during initial use and when the dose is increased, and inadequate patient monitoring during chronic use. However, the administration of intrathecal drugs via implanted pumps is limited, by its very nature, to those physicians with expertise in this treatment technique and knowledge of the associated risks. It would essentially be negligence for an untrained, inexperienced practitioner to institute treatment with Prialt. In light of the harsh reality that there are always outliers who may not let the best interests of their patients provide their motivation and guide their treatment decisions, however, the most prudent path forward would appear to be limitation of the use of Prialt to those patients who had failed all other generally accepted treatments for their chronic, severe pain. Indeed, this is the patient population evaluated in Study 301.

Therefore, in consideration of the small but important patient population that is living with severe, chronic pain that is unresponsive to available, accepted treatments, I am reasonably confident that the risks associated with Prialt treatment are outweighed by its potential benefit. In order to assure the safe use of the product, however, the product labeling must clearly state the risk of severe neuropsychiatric adverse events and the potential for elevations of CK and associated serious, clinical consequences; and it must provide well-defined criteria for choosing appropriate patients for treatment, clear and cogent warnings regarding the proper administration of the product, appropriate instructions for monitoring of patients under treatment, and recommendations for when to discontinue treatment.

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Action recommended by the Division:

Approval, pending resolution of incomplete manufacturing site inspections

Bob A. Rappaport, M.D.
Director
Division of Anesthetic, Critical Care and Addiction Drug Products
Office of Drug Evaluation II, CDER, FDA

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/s/

Bob Rappaport
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MEDICAL OFFICER



FDA Center for drug evaluation and research
Division of Anesthetic, Critical Care, and Addiction Drug Products
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Medical Officer Team Leader Memorandum

Date: December 6, 2004
To: File, NDA 21-060
From: Rigoberto Roca, M.D.
Deputy Director
Division of Anesthetic, Critical Care and Addiction Drug Products
Re: NDA 21-060, Ziconotide
Response to Approvable Letter

Background

Ziconotide is a 25-amino acid peptide that is the synthetic equivalent of the a naturally occurring peptide found in the venom of the piscivorous marine snail *Conus magnus*. It is formulated as a sterile, preservative-free isotonic solution with a pH of 4.0-5.0, and is intended for intrathecal administration.

The applicant's proposed indication is the management of severe chronic pain in patients in whom intrathecal therapy is warranted. Ziconotide's mechanism of action is unknown, although animal studies suggest that it binds to N-type calcium channels on the primary nociceptive afferent nerves in the dorsal horn of the spinal cord, blocking excitatory neurotransmitter release in the primary afferent nerve terminals. It does not appear to have opioid features, and does not appear to block or potentiate opioid effects. In animal models of acute persistent and neuropathic pain, ziconotide appears to be an effective analgesic when administered by the intrathecal, epidural, intracerebroventricular or intravenous route. However, early clinical trials of systemically administered ziconotide were discontinued because of profound systemic hypotension.

Regulatory History

The original IND for ziconotide (IND 45,718) was filed in June 1994, and the NDA submitted on December 28, 1999. That application received an Approvable letter on July 25, 2001, based in part on insufficient data to demonstrate the safety and efficacy of ziconotide in the intended patient population. There were also deficiencies identified in the Pharmacology/Toxicology and Chemistry, Manufacturing, and Controls (CMC)

sections of the application. Complete details of the deficiencies identified can be found in the reviews of Drs. Sharon Hertz, Bob Rappaport and Cynthia McCormick, members of the clinical review team during the original review cycle.

The clinical deficiencies identified during the first review cycle included:

- There were insufficient data to assess the efficacy of the dosing regimen being recommended by the applicant, secondary to multiple dosing regimen modifications during the course of the clinical trials. These modifications had become necessary because of significant toxicity observed with the original regimens.
- Field investigation identified irregularities at one clinical site were suggestive of data unblinding, raising concerns about the integrity of the data. Exclusion of this study site in the reanalysis of the primary endpoint resulted in a treatment effect that was no longer significant in one of the pivotal trials.
- Significant protocol violations were identified which limited the ability to assess secondary outcome measures, as well as responsiveness to study drug.
- A dose effect for toxicity was identified in the clinical trials, however, the assessment of the safety profile was compromised by the inadequately defined dosing regimens used in the clinical trials.

The applicant submitted a complete response to the approvable action letter on June 25, 2004. As part of their response, the applicant has submitted the results from Study ELN92045-301, entitled "A Randomized, Double-Blind, Placebo-Controlled Study of Intrathecal Ziconotide in Adults with Severe Chronic Pain," which shall be referred to as Study 301 in this memorandum. The patient population studied was patients with severe pain despite multiple medications, including intrathecally administered opiates. Neuropathic pain was the predominant type of pain reported, with failed back surgery being the most common etiology.

The purpose of Study 301 was to confirm the efficacy results observed in the short-term (5-6 days) pivotal trials previously submitted (Studies 96-002 and Study 95-001) using a slower dose titration schedule over a three-week treatment period. This hypothesis was supported by the observation in an open-label long-term study (Study 98-022) that patients who were titrated over a longer period of time seemed to tolerate ziconotide better. The primary efficacy endpoint was stipulated to be the percent change in the visual analog score pain index (VASPI) score at the termination visit (at the end of Week 3) compared to the baseline visit. The visual analog scale was delimited by "0" representing "no pain experienced" and "100" representing worst pain imaginable.

Secondary objectives of Study 301 included a characterization of opiate withdrawal effects as patients were converted from intrathecal opiates to systemic opiates and quantification of the amount of opiates used during the trial.

The applicant also submitted data to address the pharmaco/toxicology and CMC deficiencies identified in the approvable letter.

Efficacy

The applicant submitted the data and the study reports from their previously submitted placebo-controlled trials, as well data from Study 352, an open-label extension trial available to patients who completed Study 301 who wished to continue on ziconotide. Therefore, Study 301 is the only new trial submitted by the applicant to support the efficacy of ziconotide.

Study Design

In order to be enrolled in Study 301, patients had to meet the following inclusion criteria:

1. male or female ≥ 18 years of age;
2. visual analog score pain index (VASPI) ≥ 50 mm;
3. chronic pain not adequately controlled and/or intolerant to systemic opioids and for whom intrathecal therapy was warranted;
4. have an implanted programmable SynchroMed Infusion System in place for the treatment of chronic pain;
5. willing to use appropriate contraceptive methods if they were of child-bearing potential.

The following conditions would make a patient ineligible for the study:

1. pregnancy or lactation;
2. use of an investigational drug other than ziconotide within 30 days prior to initiation of the study drug;
3. known hypersensitivity to ziconotide or any of its components;
4. a condition that would contraindicate the use of intrathecal analgesia (e.g., infection at the microinfusion injection site, uncontrolled bleeding diathesis, or spinal canal obstruction that impairs cerebrospinal fluid circulation).

The design of Study 301 stipulated that patients were to be weaned from their intrathecal medication and stabilized on oral opioids prior to randomization. Patients were then randomized to one of the following two arms:

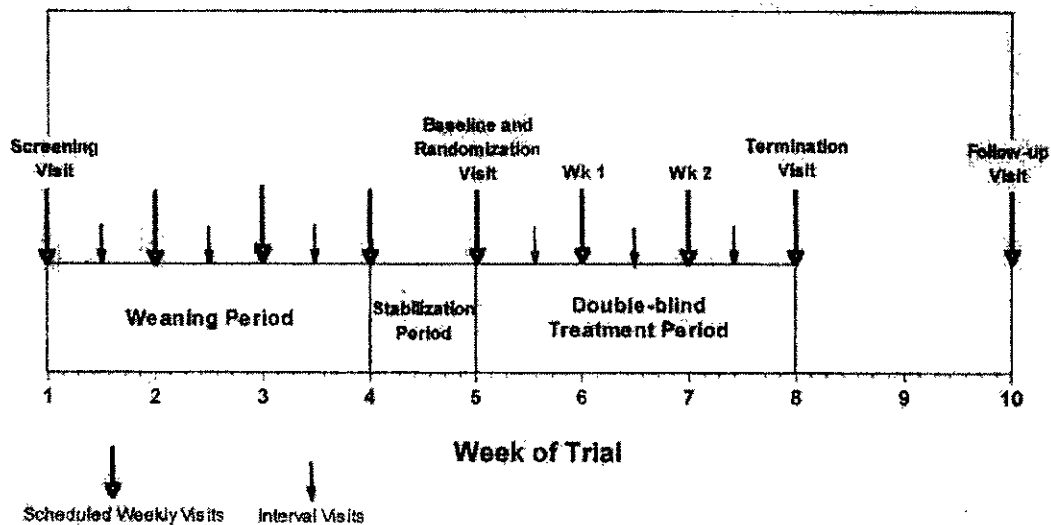
- Ziconotide 0.10 μ /hr (2.4 μ /day), or
- Placebo (the vehicle for ziconotide, including excipients)

Of note are the secondary inclusion criteria stipulating that in order to be randomized, a patient needed to still have a VASPI ≥ 50 mm, and to have been weaned off all intrathecal medications and stabilized on systemic analgesics for at least one week.

Patients were to be titrated over a period of 21 days, to a level that would achieve analgesia or to a maximum of 0.9 μ /hr. This differed from the previous studies (Study 96-002 and Study 95-001) where patients had been titrated to tolerability or a maximum dose of 2.4 μ /hr (per the final dosing regimen) over a period of 5 – 6 days.

The following schematic, reproduced from the applicant's submission illustrates the trial design.

Figure 1: Study 301 Schematic

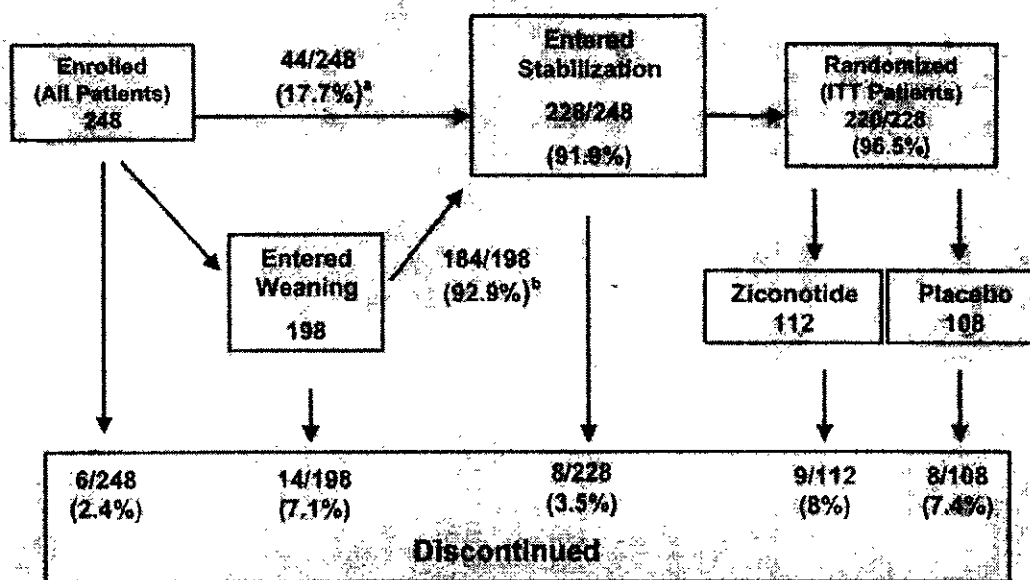


From I.8 V.005 P.143 Sponsor's NDA Submission 03, Vol 3.030 of 3.103, Section 17.1.1 Study Protocol N92045-301, Page 959

Study Results

Two hundred forty-eight patients were enrolled, 44 patients of which were able to enter the stabilization period directly because they were not on any intrathecal medications. Of the 204 patients that entered the weaning period, 20 did not make it to the stabilization period for a variety of reasons, most commonly an inability to wean from the intrathecal medication or patient request. Therefore, 228 patients entered the stabilization period. An additional 8 patients were discontinued during the stabilization period, leaving 220 patients eligible for randomization to either ziconotide or placebo. The diagram that follows is a representation of the patient disposition.

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The table below provides a summary of the patient disposition, starting from the point of randomization.

Summary of Patient Disposition and Study Termination - All Randomized Patients

	Ziconotide N = 112 n (%)	Placebo N = 108 n (%)	Total N = 220 n (%)
Patients treated with study drug	112	108	220
Completed study	112	108	220
Early discontinuation during treatment period	103 (92)	100 (93)	203 (92)
<i>Reason for discontinuation during treatment period</i>			
Lack of efficacy	2 (1.8)	2 (1.9)	4 (1.8)
Adverse event	6 (5.4)	5 (4.6)	11 (5.0)
Death	0	1 (0.9)	1 (0.5)
Subject request; voluntary withdrawal of consent	1 (0.9)	0	1 (0.5)
<i>Planned to participate in Open-label extension</i>			
Yes	90 (87.4)	95 (95)	185 (91.1)
No	13 (12.6)	5 (5.0)	18 (8.9)

Primary Efficacy Endpoint

The patient population utilized to assess for the primary efficacy endpoint was the intent-to-treat (ITT) population, which was defined as all patients who were randomized to one of the treatment groups. Utilizing a last-observation-carried-forward (LOCF) imputation method for missing data as was specified in the study protocol, the applicant was able to demonstrate a statistically significant reduction in the mean VASPI score measured after three weeks of treatment, 14.7% vs. 7.2% in the ziconotide and placebo treatment groups, respectively (p value = 0.04).

The applicant also used other imputation methods in an effort to assess the impact of missing data, including:

- Use of only observed data: only patients with Week 3 VASPI data were included.
- Imputing the median percent change from baseline to Week 3 obtained from all subjects as the outcome variable for patients missing VASPI data for Week 3
- Substituting the smallest percent improvement from baseline to Week 3 obtained from all subjects in the same treatment group for any missing VASPI data in Week 3

All of these alternative techniques yielded comparable results.

The techniques utilized by the applicant were intended to address the concern that the LOCF imputation technique may bias the magnitude of the treatment effect and inflate the Type I error when the drop-out is treatment related. However, the review team utilized other techniques to address this concern, including a baseline-observation-carried-forward (BOCF) imputation method to account for missing data and responder analyses.

The table below summarizes the results obtained when BOCF was utilized to evaluate the primary efficacy variable on the ITT population. The results were comparable results to what had been observed with the other methods.

VASPI Score (mm) at Week 3	Ziconotide N = 112	Placebo N = 108	p-value
Mean (SD)	69.8 (21.5)	75.8 (20.1)	
Percent change from baseline	12.2 (25.3)	5.4 (22.8)	0.0376

Additional analyses

A responder analyses, which defined a responder as someone who had at least 30% improvement in VASPI score at Week 3, compare to baseline, was performed by the review team. A mean pain reduction of at least 30% has been previously used in other clinical trials as representing a reduction that is clinically meaningful. In the analysis, all other patients are classified as non-responders, including those with missing data.

The results of this analysis on the ITT population are summarized in the table below.

	Ziconotide N = 112	Placebo N = 108	p-value	95% CI
Responder	18 (16.1 %)	13 (12.0%)	0.390	
95 % CI for responder	(8.8, 23.3)	(5.4, 18.6)		
Treatment difference in % of responders	4%			(-6.0, 14.1)

A weekly responder analysis based on percent decrease in mean score from baseline was also performed, using 10-percent increments, resulting in cumulative distributive functions of pain reduction by treatment group. In these analyses, patients who withdrew

from the study before the end of the week were classified as non-responders, regardless of the reason for the withdrawal, for that particular week and the succeeding weeks.

The following table summarizes the results of that analysis for the ITT population for Week 3 (with BOCF imputation technique). Focusing on the patients who reported at least a 30% decrease at Week 3, there were 18 in the ziconotide group, and 13 in the placebo.

	Ziconotide N = 112		Placebo N = 108	
	<i>n</i>	%	<i>n</i>	%
Any increase	22	20	31	29
None	28	25	27	25
> 0% decrease	62	55	50	46
≥10 % decrease	47	42	34	31
≥20 % decrease	31	28	22	20
≥30 % decrease	18	16	13	12
≥40 % decrease	12	11	9	8
≥50 % decrease	9	8	2	2
≥60 % decrease	5	4	2	2
≥70 % decrease	5	4	2	2
≥80 % decrease	4	4	2	2
≥90 % decrease	3	3	1	1
100 % decrease	2	2	1	1

The review team performed a similar response profile analysis for Week 1, also utilizing BOCF imputation techniques for missing data. The data suggest that patients on the ziconotide treatment group appeared to have an advantage in responding at Week 1 compared to placebo, but this advantage appeared to diminish over time. An analysis of when patients responded seemed to suggest that response to ziconotide may be seen relatively early, or not at all.

It must be emphasized that these secondary analyses were performed to try to discern additional information about the performance of ziconotide, but must be viewed with caution since they were not pre-specified analyses, and they have a substantial amount of statistical uncertainty.

Secondary Efficacy Endpoints

The applicant had several secondary endpoints of interest, including clinical global impression satisfaction with therapy, clinical global impression overall pain control, McGill pain questionnaire (overall and in pain intensity scores), brief pain inventory, sleep pattern and quality of sleep, categorical pain relief scores, and change in treatment outcome pain survey dimension score.

The results were scattered, with several of the analyses showing trends in favor of the ziconotide treatment groups, but not all achieving statistical significance. For additional details, please refer to Dr. Schultheis' review.

Opioid consumption

There was no significant difference in opioid consumption between the two treatment groups.

Safety

The safety data from the previously submitted studies have already been reviewed by the previous clinical review team. One of the concerns from Studies 95-001 and 96-002 was the incidence of neurological adverse events that was observed in those studies, potentially because of the rapid titration rate. One of the goals of Study 301 was to assess whether decreasing the titration rate and the maximum allowable dose would impact the safety profile. Dr. Schultheis reviewed the safety data from Study 301 and from the extension study (Study 352).

Deaths

There were no deaths reported for Study 301; three deaths were reported from Study 352 in the 120-Day Safety update. Dr. Schultheis's assessment was that it was unlikely that the deaths were related to ziconotide. In two cases, the rapidly evolving symptoms developed after a lengthy exposure to ziconotide and the patients had other potentially predisposing comorbid conditions. The third case occurred many days after a relatively limited amount of exposure to ziconotide.

Serious adverse events

More patients the ziconotide treatment group experienced serious adverse events (SAEs) than in the placebo group (12 % vs. 9%, respectively). The most common body system affected was nervous system, followed by body as a whole, then digestive and cardiovascular.

Discontinuation due to Adverse Events

The number of patients that discontinued due to adverse events were comparable between ziconotide and placebo, 6 (5.3%) and 5 (4.6%), respectively. However, 4 of the 6 patients on the ziconotide arm who discontinued had an event referable to the nervous system (agitation, dizziness, and tremors). Only 1 of the 5 patients on the ziconotide arm who discontinued had a nervous system adverse event, opiate withdrawal.

Common Adverse Events

In Study 301, of the 112 patients in the ziconotide treatment group, 108 reported experiencing an adverse event, compared to 99 of the 108 patients in the placebo treatment group. The body systems most affected is summarized in the table below.

<i>Body system</i>	Number of Adverse Events		Number of Patients Reporting Adverse Event	
	<i>Ziconotide</i>	<i>Placebo</i>	<i>Ziconotide</i> <i>N = 112</i> <i>n (%)</i>	<i>Placebo</i> <i>N = 108</i> <i>n (%)</i>
Nervous	485	195	98 (88)	76 (70)
Digestive	215	154	83 (74)	68 (63)
Whole body	192	143	76 (68)	60 (56)
Metabolic and nutritional	67	37	41 (37)	22 (20)
Skin and appendages	52	56	37 (33)	34 (31)
Urogenital	35	23	28 (25)	19 (18)
Respiratory	37	28	26 (23)	21 (19)
Special senses	33	30	26 (23)	18 (17)
Cardiovascular	32	26	25 (22)	20 (19)
Musculoskeletal	27	22	19 (17)	16 (15)
Hemic and lymphatic	7	3	4 (4)	3 (3)
Total	1182	717		

With respect to the adverse events that affected the nervous system, the type that were more frequently associated with ziconotide compared to placebo were dizziness, somnolence and confusion. The table below summarizes the types of nervous system adverse events that were reported.

<i>Type of Adverse Event</i>	Number of Adverse Events		Number of Patients Reporting Adverse Event	
	<i>Ziconotide</i>	<i>Placebo</i>	<i>Ziconotide</i> <i>N = 112</i> <i>n (%)</i>	<i>Placebo</i> <i>N = 108</i> <i>n (%)</i>
Dizziness	93	16	56 (50)	15 (14)
Somnolence	37	28	30 (27)	23 (21)
Confusion	30	7	22 (20)	6 (6)
Ataxia	20	2	19 (17)	2 (2)
Abnormal gait	25	2	18 (16)	2 (2)
Hypertonia	25	13	18 (16)	10 (9)
Memory impairment	16	2	14 (13)	2 (2)
Withdrawal symptoms	20	16	15 (13)	15 (14)
Dysesthesia	11	2	10 (9)	2 (2)
Tremor	10	3	9 (8)	3 (3)
Difficulty concentrating	6	1	5 (4)	1 (1)
Mental slowing	5	1	3 (3)	1 (1)
Total	298	93		

The more common adverse events affecting the digestive system were nausea, vomiting and anorexia. The body as a whole category is wide-ranging, with asthenia, pain, and chills being the most commonly reported adverse events associated with ziconotide.

Other abnormal findings

Six patients in the ziconotide treatment group experienced elevated uric acid levels; all were asymptomatic. Five patients in the ziconotide treatment group were noted to have elevations in creatinine kinase that were three times the upper limit of normal. These were not accompanied by clinical signs of renal failure, myocardial damage, or rhabdomyolysis.

Additional considerations

Throughout the entire drug development program for ziconotide, the Division has expressed to the applicant concern about the apparent safety profile of ziconotide. Study 301 was intended to help assess whether a slower titration rate and a lower maximum dose resulted in an adverse event profile that would allow more patients to tolerate the product.

The applicant has demonstrated that ziconotide is effective, as per the pre-specified primary efficacy endpoint of a significant reduction in the mean VASPI scored measured after three weeks of treatment. It also appears that the slower titration scheme seems to be better tolerated than the other regimens. However, the adverse event profile observed is still of significant concern, particularly the adverse events referable to the nervous system.

It is acknowledged that there is a patient population that could potentially benefit from ziconotide therapy; specifically, patients experiencing chronic, intractable pain who are candidates for intrathecal therapy. However, until additional experience is gained in how best to manage patients with ziconotide, perhaps the intended patient population should be limited to patients who are in chronic, intractable pain and who not only need intrathecal therapy, but who have also failed intrathecal morphine sulfate.

By virtue of ziconotide's formulation, and the recommended method of administration which requires an implanted programmable infusion system, it is extremely unlikely that ziconotide would be prescribed and/or used by general practitioners. However, language should be incorporated in the package insert to specifically note that practitioners using ziconotide should be well-acquainted with chronic pain management strategies and the use of intrathecally administered therapies.

If approved, the post-marketing experience will be very valuable in determining whether any changes, including additional restrictions, are warranted.

Recommendations

The applicant has demonstrated, using the pre-specified primary efficacy variable, that ziconotide is effective, and has a manageable safety profile. Ziconotide can be approved provided that appropriate language can be incorporated in the package insert that would identify the most appropriate patient population, as well as information regarding the appropriate safeguards that should be instituted when using ziconotide.

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Clinical Review

Application Type NDA
Submission Number 21,060
Submission Code AZ

Letter Date June 25, 2004
Stamp Date June 28, 2004
PDUFA Goal Date December 28, 2004

Reviewer Name Lex Schultheis, M.D., Ph.D.
Review Completion Date December 3, 2004

Established Name Ziconotide
(Proposed) Trade Name Prialt
Therapeutic Class Analgesic
Applicant Elan Pharmaceuticals

Priority Designation P

Formulation: sterile, preservative free, isotonic solution for intrathecal administration using an appropriate microinfusion device

Dosing Regimen: Prialt is to be initiated at 2.4 mcg/day (0.1 mcg/hr) and titrated to patient response. Doses may be increased by 2.4 mcg/day (0.1 mcg/hr) or less at intervals of 2 to 3 times per week, up to a recommended maximum of 19.2 mcg/day by Day 21.

Indication: Severe chronic pain requiring intrathecal therapy

Intended Population: Patients at least 18 years of age with severe chronic pain not adequately controlled and/or intolerant to systemic opioids and for whom IT therapy is warranted.

Table of Contents

1 EXECUTIVE SUMMARY.....	5
1.1 RECOMMENDATION ON REGULATORY ACTION	5
1.2 RECOMMENDATION ON POSTMARKETING ACTIONS.....	6
1.2.1 Risk Management Activity.....	6
1.2.2 Required Phase 4 Commitments.....	7
1.2.3 Other Phase 4 Requests	7
1.3 SUMMARY OF CLINICAL FINDINGS.....	7
1.3.1 Brief Overview of Clinical Program.....	7
1.3.2 Efficacy.....	9
1.3.3 Safety.....	10
1.3.4 Dosing Regimen and Administration.....	12
1.3.5 Drug-Drug Interactions.....	12
1.3.6 Special Populations.....	12
2 INTRODUCTION AND BACKGROUND.....	13
2.1 PRODUCT INFORMATION	13
2.2 CURRENTLY AVAILABLE TREATMENT FOR INDICATIONS	13
2.3 AVAILABILITY OF PROPOSED ACTIVE INGREDIENT IN THE UNITED STATES	13
2.4 IMPORTANT ISSUES WITH PHARMACOLOGICALLY RELATED PRODUCTS	14
2.5 PRESUBMISSION REGULATORY ACTIVITY	14
2.6 OTHER RELEVANT BACKGROUND INFORMATION.....	19
3 SIGNIFICANT FINDINGS FROM OTHER REVIEW DISCIPLINES.....	20
3.1 CMC (AND PRODUCT MICROBIOLOGY).....	20
3.2 ANIMAL PHARMACOLOGY/TOXICOLOGY	21
4 DATA SOURCES, REVIEW STRATEGY, AND DATA INTEGRITY.....	22
4.1 SOURCES OF CLINICAL DATA	22
4.2 TABLES OF CLINICAL STUDIES	22
4.3 REVIEW STRATEGY	23
4.4 DATA QUALITY AND INTEGRITY.....	23
4.5 COMPLIANCE WITH GOOD CLINICAL PRACTICES	24
4.6 FINANCIAL DISCLOSURES.....	24
5 CLINICAL PHARMACOLOGY.....	25
5.1 PHARMACOKINETICS.....	25
5.2 PHARMACODYNAMICS	26
5.3 EXPOSURE-RESPONSE RELATIONSHIPS.....	27
6 INTEGRATED REVIEW OF EFFICACY.....	28
6.1 INDICATION	28
6.1.1 Methods.....	28
6.1.2 General Discussion of Endpoints.....	28
6.1.3 Study Design.....	29
6.1.4 Efficacy Findings.....	33
6.1.5 Clinical Microbiology.....	40
6.1.6 Efficacy Conclusions.....	40
7 INTEGRATED REVIEW OF SAFETY.....	41
7.1 METHODS AND FINDINGS.....	41
7.1.1 Deaths.....	41

Clinical Review
Lex Schultheis, M.D., Ph.D.
NDA 21,060
Prialt (Ziconotide)

7.1.2 Other Serious Adverse Events	43
7.1.3 Dropouts and Other Significant Adverse Events	43
7.1.4 Other Search Strategies	45
7.1.5 Common Adverse Events	47
7.1.6 Less Common Adverse Events	55
7.1.7 Laboratory Findings	56
7.1.8 Vital Signs	58
7.1.9 Electrocardiograms (ECGs)	61
7.1.10 Immunogenicity	66
7.1.11 Human Carcinogenicity	66
7.1.12 Special Safety Studies	66
7.1.13 Withdrawal Phenomena and/or Abuse Potential	69
7.1.14 Human Reproduction and Pregnancy Data	70
7.1.15 Assessment of Effect on Growth	70
7.1.16 Overdose Experience	70
7.1.17 Postmarketing Experience	70
7.2 ADEQUACY OF PATIENT EXPOSURE AND SAFETY ASSESSMENTS	70
7.2.1 Description of Primary Clinical Data Sources (Populations Exposed and Extent of Exposure) Used to Evaluate Safety	71
7.2.2 Description of Secondary Clinical Data Sources Used to Evaluate Safety	72
7.2.3 Adequacy of Overall Clinical Experience	72
7.2.4 Adequacy of Special Animal and/or <i>In Vitro</i> Testing	72
7.2.5 Adequacy of Routine Clinical Testing	72
7.2.6 Adequacy of Metabolic, Clearance, and Interaction Workup	73
7.2.7 Adequacy of Evaluation for Potential Adverse Events for Any New Drug and Particularly for Drugs in the Class Represented by the New Drug; Recommendations for Further Study	73
7.2.8 Assessment of Quality and Completeness of Data	73
7.2.9 Additional Submissions, Including Safety Update	73
SUMMARY OF SELECTED DRUG-RELATED ADVERSE EVENTS, IMPORTANT LIMITATIONS OF DATA, AND CONCLUSIONS	74
7.4 GENERAL METHODOLOGY	76
7.4.1 Pooling Data Across Studies to Estimate and Compare Incidence	76
7.4.2 Explorations for Predictive Factors	76
7.4.3 Causality Determination	80
8 ADDITIONAL CLINICAL ISSUES	81
8.1 DOSING REGIMEN AND ADMINISTRATION	81
8.2 DRUG-DRUG INTERACTIONS	83
8.3 SPECIAL POPULATIONS	85
8.4 PEDIATRICS	85
8.5 ADVISORY COMMITTEE MEETING	85
8.6 LITERATURE REVIEW	85
8.7 POSTMARKETING RISK MANAGEMENT PLAN	86
8.8 OTHER RELEVANT MATERIALS	86
9 OVERALL ASSESSMENT	87
9.1 CONCLUSIONS	87
9.2 RECOMMENDATION ON REGULATORY ACTION	87
9.3 RECOMMENDATION ON POSTMARKETING ACTIONS	88
9.3.1 Risk Management Activity	88
9.3.2 Required Phase 4 Commitments	88
9.3.3 Other Phase 4 Requests	88
9.4 LABELING REVIEW	89
10 APPENDICES	91

Clinical Review
Lex Schultheis, M.D., Ph.D.
NDA 21,060
Prialt (Ziconotide)

10.1 REVIEW OF INDIVIDUAL STUDY REPORTS	91
10.1.1 Protocol ELN92045-301 "A Randomized Double-Blind, Placebo-Controlled Study of Intrathecal Ziconotide in Adults with Severe Chronic Pain" March 27, 2002.....	91
10.1.2 STUDY 95-01 Protocol Synopsis "A Multicenter, Phase II/III, Placebo Controlled Study Of SNX-111 (ziconotide) Administered Intrathecally To Patients With Chronic Malignant Pain."	109
10.1.3 STUDY 96-002 Protocol Synopsis "A Multicenter, Phase II/III, Placebo Controlled Study of SNX-111 (SNX) Administered Intrathecally To Patients With Chronic Non-Malignant Pain."	119
10.2 CONCLUSIONS FROM PREVIOUS NDA REVIEW OF STUDIES 95-001 AND STUDY 96-002	130
10.3 SUMMARY OF STUDIES IN THE SPONSOR'S INTEGRATED SUMMARY OF SAFETY	133
10.4 TIMING OF ONSET ADVERSE EVENTS	147
11 SPONSOR'S PROPOSED ANNOTATED PACKAGE INSERT.....	150
12 REFERENCES.....	177

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1 EXECUTIVE SUMMARY

1.1 Recommendation on Regulatory Action

In an adequate and well-controlled clinical trial (Study 301), ziconotide was used safely and was effective in patients with indwelling intrathecal infusion pumps who continued to have chronic severe pain despite other pharmacological regimens, including intrathecal opiates.

The evidence of effectiveness in Study 301 rests primarily upon:

- A demonstration of a statistically significant difference in the primary endpoint, a reduction in the Visual Analog Pain Score Index (VASPI) after three weeks of treatment with study drug compared to a baseline measurement following a period of weaning from other intrathecal medication and stabilization on oral opiates. The mean VASPI baseline was 80 in both the ziconotide and placebo parallel treatment groups where a score of 100 indicated the worst pain imaginable and 0 indicated no pain. The mean reduction in VASPI among patients treated with ziconotide was 14 compared with a reduction in VASPI score of 7 in the placebo-treated population. Fifty-four percent of patients in the ziconotide group compared to 46% of the placebo-treated patients had a reduction in pain by this assessment.
- A trend among the secondary efficacy endpoint variables that also supported efficacy of ziconotide. These variables included patients with a post-treatment reduction in VASPI of 30% (responders), categorical assessments of pain, and questionnaire measurements of effect of pain on quality of life, functionality and sleep. The findings from clinical trials (95-001 and 96-002) presented with the previous NDA submission and reviewed by Dr. Sharon Hertz generally supported efficacy of ziconotide in the treatment of chronic severe pain, but were not definitive because of flaws in protocol design and study conduct.

The evidence of safety profile of ziconotide is based upon:

- An absence of mortality among patients treated with ziconotide during Study 301.
- A similar incidence of serious adverse events between patients treated with ziconotide (13/112, 12%) and placebo (10/108, 9%). None of the serious adverse events among the patients treated with ziconotide in Study 301 required discontinuation of the drug.
- Reversibility of serious adverse events following discontinuation of ziconotide. All serious adverse events among ziconotide treated patients in Study 301 resolved except for a case of Hepatitis B that appeared to be unrelated to treatment.

The incidence of all adverse events was higher in patients treated with ziconotide (104/112, 93%) than placebo (89/108, 82%). The most common adverse events in the ziconotide treatment group were in the nervous system, body as a whole and metabolic and nutritional system. In particular, adverse events identified as more common among patients treated with

Clinical Review
Lex Schultheis, M.D., Ph.D.
NDA 21,060
Prialt (Ziconotide)

ziconotide included confusion, memory impairment, dizziness, ataxia and gait disturbance, urinary retention, hallucinations, vertigo, aphasia, tremor, elevated creatine kinase and hyperuricemia. The incidence of severe adverse events was higher with ziconotide (47/112, 42%) than with placebo (29/108, 27%), but the rate of discontinuation because of an adverse event was similar between ziconotide (6/112, 5%) and placebo treatment groups (5/108, 5%).

The qualitative aspects of the adverse event profile reported for Study 301 was generally similar to findings from previously submitted phase 3 trials reviewed by Dr. Sharon Hertz. A primary difference in treatment regimen between Study 301 and Studies 95-001 and 96-002 is that Study 301 stipulated a slower titration schedule because of preliminary evidence suggesting that this would reduce adverse events. Differences included 6 reports of asymptomatic hyperuricemia in the ziconotide group versus no reports in the placebo group and 2 cases of lower leg weakness unique to the ziconotide group. One of the patients described new onset lower leg weakness in the setting of preexisting Parkinson's disease and upper extremity weakness. The other patient with leg weakness was noted to have leg weakness on the screening neurological examination. Compared to Studies 95-001 and 96-002, Study 301 did exhibit a lower proportion of serious adverse events and dropouts. In contrast to the previous trials, no evidence of QT prolongation appeared among ziconotide treated patients in Study 301 compared with the placebo, although a thorough QT study was not performed.

In the greater population of patients with severe chronic pain, a small percentage of patients are expected to have a clinically significant benefit from treatment with ziconotide because the drug was associated with a high incidence of adverse events that limited tolerability, even among patients in whom efficacy was most clearly demonstrated. The use of ziconotide should be restricted to physicians who are skilled in the care of medically complex patients with chronic pain and to patients who have exhausted approved pharmacologic therapeutic options. Labeling guidance that will enable ziconotide treatment to be interrupted or discontinued early in the setting of a drug-related adverse event is expected to facilitate the safe use of ziconotide and enable treatment of patients who can benefit from this drug.

1.2 Recommendation on Postmarketing Actions

1.2.1 Risk Management Activity

Consideration should be given to constructing a safety registry including duration of treatment for patients treated with ziconotide. The interim report from the long-term open-label extension studies 352 suggests that few patients continue to use ziconotide for more than several months. Long-term administration safety data will be useful in predicting an expected duration of treatment with ziconotide, information that may be eventually incorporated into the product label.

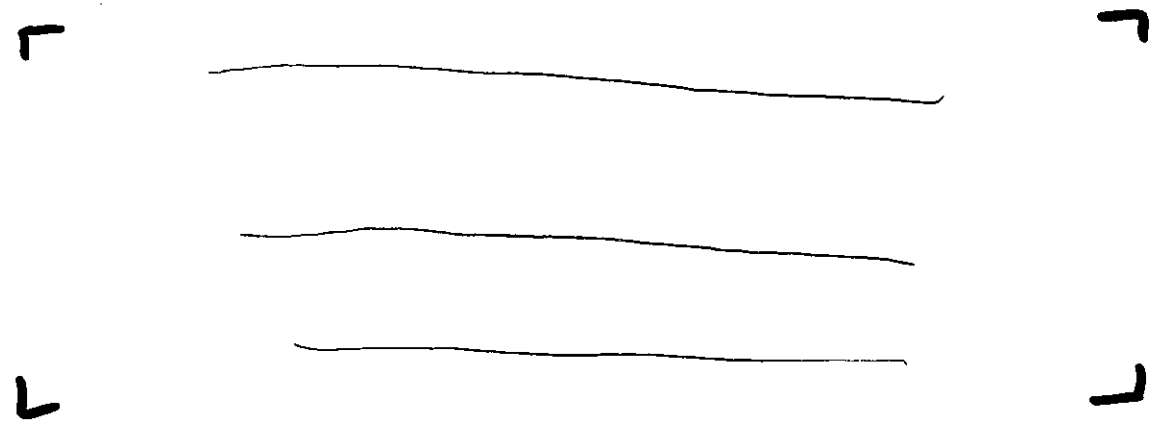
Consideration should also be given to restricted distribution of the drug to physicians or practice centers with recognized expertise in chronic administration of intrathecal pain medication.

1.2.2 Required Phase 4 Commitments

Study of ziconotide in pediatric patients should be deferred for five years while post-marketing safety data is accumulated.

The safety database should be extended among patients over 65 years of age. Study 301 only included 20 patients in this age group. Data from earlier studies suggest that the elderly may have an increased incidence of confusion, but there may be differential dosing requirements for efficacy also.

1.2.3 Other Phase 4 Requests



1.3 Summary of Clinical Findings

1.3.1 Brief Overview of Clinical Program

The sponsor submitted a one new randomized double-blinded placebo-controlled clinical trial with this resubmission of the NDA. This trial entitled "A randomized, double blind, placebo-controlled study of intrathecal ziconotide in adults with severe chronic pain" (ELN92045-301, Study 301) consisted of 112 patients exposed to ziconotide and 108 patients treated with placebo in the ITT population. The entry criteria required the patients to have severe chronic pain that was inadequately controlled pharmacologically, despite an indwelling mechanical pump that delivered intrathecal opiates. Following a period of weaning from existing intrathecal medication and stabilization on oral opiates, patients were started on either 0.05 mcg/hr or 0.1 mcg/hr of intrathecal ziconotide or intrathecal placebo (the vehicle for ziconotide with excipients). The new study stipulated a slower titration schedule over 21 days and a lower maximum dose of 0.9 µg/hr compared to the previous two studies (95-001, 96-002) with forced titration schedules in which ziconotide doses were increased until tolerability was exceeded or a maximum dose of 2.4 mcg/hr (per the final dosing regimen) over 5 to 6 days. The mean dose of ziconotide was 0.5 mcg/hr in study 95-001 and 0.83 mcg/hr in study 96-002 at the end of the titration phase. In study 301, ziconotide was titrated gradually over a three-week treatment period. In addition, ziconotide was titrated to early onset of analgesia rather than to assess the higher dose range of safety and efficacy as already observed in Studies 95-001 and 96-

Clinical Review
Lex Schultheis, M.D., Ph.D.
NDA 21,060
Prialt (Ziconotide)

002, and potentially to minimize serious adverse events (SAEs), withdrawals, and adverse events (AEs).

Efficacy was determined primarily by assessment of a statistically significant change in Visual Analog Pain Score Index (VASPI) compared with the "baseline" measurement at the end of the stabilization period. Secondary endpoints consisted of global assessments of pain, patient satisfaction, quality of life, functionality and sleep. Assessment of safety was based upon reported adverse events, changes in vital signs, laboratory testing, including measurements of creatine kinase and serial electrocardiograms with measurement of QT intervals.

A new open label trial (Study 352) included with this NDA submission was conducted consisting of 85 patients who participated in trial 301 who wished to be treated with ziconotide after Study 301 had concluded. The interim study report (240 days) was composed of 37 patients who had been treated with ziconotide in Study 301 and 48 patients who had been treated with placebo. Adverse event data and dosing information was evaluated to assess safety of long-term exposure and tolerance to ziconotide.

The sponsor provided the data and study reports from their previously submitted and reviewed placebo-controlled clinical trials designed to evaluate the safety and effectiveness of ziconotide by intrathecal administration to patients with chronic severe pain secondary to AIDS or malignancy (Study 95-001) or nonmalignant pain (Study 96-002). Unblinded treatment of patients by one investigator was revealed on an Agency visit to a trial site of Study 95-001, necessitating exclusion of data from that site and calling into question the data monitoring of the entire work. Review of the reported data further revealed that the dosing regimen was changed while the studies were ongoing to improve tolerability of ziconotide. This suggested that dose-ranging information and delineation of the temporal pharmacodynamic profile of ziconotide was still evolving as the phase three trials were begun. As a consequence, too few patients were treated with the dosing regimen that was proposed in the draft labeling to warrant a finding of efficacy or safety. Agency *post hoc* exploratory analysis of the subset of patients treated with the proposed draft labeling suggested that ziconotide may have been effective, but too few patients were evaluable for the analysis to be conclusive.

Five open-label studies were presented. Study 94-004 (n=9) was the sponsor's first intrathecal rising-dose feasibility study in patients with terminal cancer, AIDS or intractable neuropathic pain and was presented with the previous NDA submission. Study 95-002 (n=155) was an extension for patients who participated in the pivotal trials (95-001 and 96-002) included with the earlier NDA submission. An internal pump was not required in patients with pain from malignancy. Study 98-022 was a large (n=644) multicenter safety study in patients with chronic malignant or nonmalignant pain. Study 351 is a new extension study (n=78) in progress with patients from Study 95-002 and Study 98-022. Study 352 was a 14 month extension study (n=85) for patients from the pivotal study (301) for the current NDA submission.

Earlier explorations include 3 phase-two studies (96-003, 96-010 and 97-013) and a titration to response study (97-015) that were previously submitted and reviewed as part of the sponsor's earlier NDA submission.

1.3.2 Efficacy

This study was a randomized, double-blind, multicenter, placebo-controlled study to confirm the analgesic efficacy of ziconotide, intended to characterize opioid use before and during the double-blind treatment period. Clinical evaluation was performed at screening visit, during a weaning period of up to three weeks, a one week stabilization period, a baseline visit, a three-week double-blind treatment period, a termination visit, and a follow-up visit. The epoch of patient evaluation was up to 9 weeks including follow-up of two weeks or longer in the setting of adverse events.

On the screening visit, patients provided informed consent and were evaluated for study eligibility, including a VASPI score of ≤ 50 out of a maximum possible of 100 mm. Patients receiving intrathecal (IT) medications at screening were weaned and evaluated on scheduled weekly visits or other 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 proceeded directly to the stabilization protocol. Patients were stabilized on a systemic analgesic regimen consisting primarily of oral opiates over one week to allow for adequate assessment of baseline VASPI and opiate consumption. Next, the inclusion/exclusion criteria were reapplied on visit to establish a baseline assessment and perform randomization for treatment. Patients who met entry criteria were randomized in a 1:1 ratio and received either IT ziconotide or placebo (vehicle for ziconotide including excipients) 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 mcg/hr (2.4 mcg/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 mcg/hr.

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' indicated no pain and '100' indicated worst possible pain). The baseline VASPI score was the VASPI score taken immediately prior to infusion of the study drug. For patient dropouts, the sponsor used the last observation carried forward (LOCF) to impute missing value. The sponsor also presented a sensitivity analysis using several statistical alternatives to LOCF to replace missing data. The Agency Biometrics review team performed an analysis using baseline values for replacement of missing data (BOCF) and grouped patients who dropped-out before completion of the study with patients who did not improve VASPI scores over 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

Clinical Review
Lex Schultheis, M.D., Ph.D.
NDA 21,060
Prialt (Ziconotide)

different from that of the placebo group. A secondary analysis of patients who improved VASPI scores by 30% or more over baseline measurements (responder analysis)

A variety of other pain and quality of life assessments were used to characterize other aspects of the patient's pain and to validate the clinical relevance the VASPI measurement of pain intensity in the study sample such as concomitant opiate administration, the patient's responses to the Clinical Global Impression questionnaire (CGI), Brief Pain Inventory questionnaire, Global McGill Pain Questionnaire, Categorical Pain Relief Scale (CPRS), Sleep Questionnaire and Treatment Outcome Pain Survey (TOPS).

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 percent change instead of using LOCF. A statistically significant improvement in VASPI among patients treated with ziconotide compared with placebo was also observed in the Agency Biometrics review by Joan Buenconsejo, Ph.D. that utilized BOCF and scored VASPI in patient dropouts as baseline.

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'.

1.3.3 Safety

The extent of exposure for ziconotide has increased from 976 patients in the earlier submission of the NDA to 1254 listed in the ISS and the 120 Day Safety Update in the current submission. The safety analysis focused on the findings of Study 301 because of uncertainty in the dosing schedule in prior studies. A failure to account for loss of ziconotide due to adsorption to the pump surface or dead space in a ziconotide naïve pump in dosing further confounded interpretation of safety data from earlier studies. Adverse events reporting from previously submitted studies also suffered from a convoluted reporting path. Adverse events coded as related to the infusion device were not reported with the ISS of the previous NDA submission.

Clinical Review
Lex Schultheis, M.D., Ph.D.
NDA 21,060
Prialt (Ziconotide)

The sponsor counted patients enrolled in more than one study only once for AE summaries. Patients who received both ziconotide and placebo were also included in both respective groups for when reporting adverse events. These irregularities confounded analysis of pooled data except in gross qualitative terms.

The adverse event profile of ziconotide in this study appears grossly similar to the observations from previous studies. The principal safety concerns raised by Sharon Hertz, M.D. in her review of the sponsor's previous NDA submission were related to signs and symptoms of what she termed encephalopathy. A panel of specialists chosen by the sponsor suggested the term "neurocognitive impairment" based upon 9 symptoms representative of ziconotide-induced neurocognitive dysfunction. Terms chosen by the sponsor are: amnesia, aphasia, confusion, speech disorder and thinking abnormal. The panel selected the terms: amnesia, aphasia, confusion, delirium, encephalopathy, hallucinations, speech disorder, stupor and thinking abnormal. Adverse events included in Dr. Hertz's description of encephalopathy also included somnolence, dementia, and CNS depression. Other verbatim terms such as bizarre behavior and organic brain dysfunction were not included in lists produced by the sponsor or their expert panel.

Review of the verbatim descriptions of adverse events suggested that similar dysfunction of the central nervous system was present in Study 301 as in earlier high-dose rapid-titration trials. Fewer serious adverse events and discontinuations resulted from adverse events were apparent than in the earlier trials. Patients appeared to tolerate these symptoms and 90 of the 112 patients treated with ziconotide consented to continue the drug in the open label extension despite a high incidence of adverse events reported as severe or serious.

There appeared to be no differential pattern of presentation for adverse events among men and women. The study sample was mostly composed of Caucasians so that stratification of treatment effect by race was not possible. Certain neurological adverse events, such as confusion appeared more frequently among patients older patients ≥ 65 , while other adverse events such as elevation of creatine kinase (skeletal muscle fraction) appeared only among younger patients.

Testing at baseline and after three weeks of treatment did not reveal worsening depression among patients treated with ziconotide compared with placebo.

The principal laboratory abnormality associated with ziconotide use is an elevation of creatine kinase. This elevation was not related to electrocardiographic evidence or symptoms of myocardial ischemia or infarction. Nor was there lateralizing evidence of cerebrovascular accident among patients with CK elevation. The source tissue of increased creatine kinase is believed to be skeletal muscle, but the mechanism of enzyme release has not been established.

The safety profile of ziconotide indicates that it should be used in patients that will be monitored for signs of neurological adverse events that may include psychiatric abnormalities. Patients will require screening and monitoring for abnormalities on blood chemistry especially creatine kinase, therefore the drug may be associated with increased risk for some patients with preexisting renal insufficiency.

1.3.4 Dosing Regimen and Administration

There was no apparent relationship between dose and relative efficacy in Study 301. Neither was there a clear association between dose and the incidence of serious or severe adverse events in Study 301. A comparison between the incidence of adverse events reported in the rapid titration high initial dose trials (Study 95-001 and 96-002) revealed that 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. The mean infusion rate of Study 301 was about 0.26 mcg/hour, considerably lower than the proposed upper limit of 0.9 mcg/hour allowed in the protocol. The open label extension study 352 for patients who completed Study 301 exhibited gradual incremental increase in dose over 14 months.

1.3.5 Drug-Drug Interactions

No studies of drug-drug interaction were performed by the sponsor. A study of concomitant opiate administration during treatment with study drug during Study 301 indicated that efficacy findings associated with ziconotide could not be explained by increased opiate dosing. A reviewer's analysis of concomitant administration of antidepressant or anxiolytic medication with study drug did not reveal trends in the incidence adverse events.

1.3.6 Special Populations

The numbers of elderly patients studied in the pivotal trial (Study 301) was small so that definitive conclusions regarding relative risk with age are difficult. The incidence of neurocognitive disturbance (encephalopathy) associated with ziconotide was higher in patients at least 65 years old than among younger patients. No pediatric studies were conducted.

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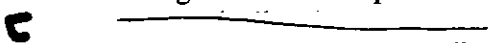
2 INTRODUCTION AND BACKGROUND

2.1 Product Information

- Description of the product:

Ziconotide is a water soluble synthetic equivalent of a naturally occurring peptide found in the venom of the piscivorous marine snail, *Conus magus*. This 25 amino acid peptide is formulated as a sterile, preservative free, isotonic solution with a pH of 4.0-5.0. The product's analgesic action is by specific blockade of calcium channels (N-type VSCC) necessary for depolarization induced neurotransmitter release, found in highest density within the substantia gelatinosa of the spinal cord. Specific binding of ziconotide has been found in the superficial laminae of the dorsal horn of the rat spinal cord, the site of primary nociceptive afferent synapses. Ziconotide had no opioid features and does not block or potentiate opioid effects. This mechanism for analgesia contrasts that of opioid induced analgesia which is attributed to the suppression of signal conduction by slow hyperpolarization of projection neurons.

Systemically administered ziconotide also has a profound sympatholytic effect which is felt to be due to its blockade of the N-type VSCC which prevents norepinephrine release from the presynaptic nerve terminal and results in a profound hypotension.

The early development plan for ziconotide included intrathecal administration for the management of chronic pain, epidural administration for management of acute pain and intravenous administration for neuroprotection. 



2.2 Currently Available Treatment for Indications

The proposed indication for ziconotide is management of severe chronic pain in patients in whom intrathecal therapy is warranted. The affected population is distinguished by symptoms of intractable severe pain that has not been controlled by more conservative therapy. The pathological etiology of the pain is known and observable, but is not amenable to surgical intervention. These patients are also free from drug habituation, psychiatric and other medical conditions that would render an implanted mechanical pump unsuitable.

The only Agency approved drug for treatment of pain by chronic intrathecal administration is morphine. Other medications administered intrathecally under IND or prescribed off-label for chronic pain include ketamine, midazolam, local anesthetics, and clonidine.

2.3 Availability of Proposed Active Ingredient in the United States

Ziconotide is currently unavailable for use in the United States.

2.4 Important Issues With Pharmacologically Related Products

Ziconotide is new molecular entity and there are no related products that are currently marketed. Efficacy of intrathecal ziconotide could not be established because one (95-001, Chronic Malignant Pain) of the two pivotal clinical trials was discovered by an FDA site inspection team to have been unblinded during execution. Clinical trials of intrathecal ziconotide performed under IND and previous NDA submission were notable for adverse events of the nervous system including a peculiar hallucination of oral "strings" that lead patients to cut themselves in an effort to remove the imagined oral appendages. Other cognitive disturbances were reported such as confusion, memory loss, speech impairment, nystagmus and disturbance of balance. There was inadequate data characterizing the neurological adverse events and documenting their reversibility. Hypotension, nausea and asthenia were also reported adverse events associated with ziconotide. Review of ECG data from clinical Study 98-022 submitted as part of an NDA 12/28/99 suggested that Qt prolongation may occur with ziconotide treatment, but baseline data was not available. Dose-finding of earlier work was inadequate because of adsorption of ziconotide to the lining of the indwelling pump, questions about the differential stability of the drug and the adsorbed product, and inability to assess the actual dosing in patients. These uncertainties lead to inappropriately high dosing at the beginning of the trials with subsequent reduction in dose. An evaluation of the safety of concomitant administration of opiate with ziconotide was lacking.

Other classes of conotoxin are undergoing preclinical investigations. Alpha-conotoxins may be more potent than α -conotoxin MVIIA used as a model for ziconotide.

2.5 Presubmission Regulatory Activity

The original IND for ziconotide, 45,718, was filed 6/30/94 by Neurex Corporation, for intrathecal administration in the management of severe, chronic pain in patients for whom intraspinal analgesic therapy is clinically indicated. Neurex was acquired by Elan Corporation in August of 1998.

In that same month, another IND amendment (serial no. 172) changed the diluent from a custom product to commercially available normal saline.

A briefing of the product development plan was presented to the Anesthetic And Life Support Drugs Advisory Committee in morning session on March 24, 1997.

The NDA submitted on 12/28/99 included two adequate and well-controlled clinical trials (95-001, chronic malignant pain and 96-002, chronic non malignant pain) and one supportive study (996-003). This application was not approved. Although these trials appeared to document effectiveness of ziconotide in two different patient populations, an FDA site visit discovered procedural irregularities in Study 95-001 that suggested that the data had become unblinded during conduct of the trial. When a reanalysis of the primary outcome measure for the study was performed, the treatment effect of ziconotide did not reach statistical significance. analysis of secondary efficacy endpoints was limited by a high number of protocol violations.

The apparent safety profile of ziconotide may not have been accurate because of inadequately defined dosing regimens in the pivotal trials, however a high incidence of reported serious adverse events would have diminished the usefulness of ziconotide had efficacy been adequately established. A dose-effect was related to toxicity. The incidence of death among

Clinical Review
Lex Schultheis, M.D., Ph.D.
NDA 21,060
Prialt (Ziconotide)

patients treated with ziconotide was twice as high as among placebo-treated patients. Certain neurological adverse events, described collectively as "encephalopathy" in earlier reviews had a delayed presentation associated with cumulative exposure. The incidence of serious adverse events was three times higher with ziconotide and patients were twice as likely to discontinue compared with patients treated with placebo. Other adverse events with increased frequency in ziconotide treatment arms, including nausea and vomiting, hypotension, urinary retention and elevations in CPK and creatinine were inadequately explored.

The sponsor submitted a response 1/26/01 to the Division action letter 6/27/00 with amendments 7/11/01 and 7/17/01. Following review of the amended application, the Division determined that the application was approvable provided that remaining deficiencies were satisfactorily addressed.

The deficiencies listed in the Agency 7/25/01 approvable letter are:

1. The data submitted do not adequately establish the effectiveness of this product for the proposed indication. The two pivotal trials, Studies 95-001 and 96-002, were not adequately designed to assess the effectiveness of ziconotide when used according to the titration regimen in the dosage and administration section of the proposed label. The specific reasons for the determination that these studies were inadequate were detailed in our letter dated June 27, 2000. The additional analyses requested for the pivotal trials were intended to complement a new, adequate and well controlled trial, not to replace such a trial.
2. The data submitted do not adequately establish the safety of this product for chronic administration. A risk-benefit analysis to establish the viability of ziconotide in the treatment of chronic malignant and non-malignant pain cannot be accomplished until the safety profile of the product has been adequately characterized. Specifically, deficiencies remain in the analysis and risk assessment as identified in the following items:
 - a. The analysis of adverse events reported fails to adequately address the problem of inconsistent mapping of similar events to different COSTART terms. This is particularly true regarding adverse events related to central nervous system toxicity.
 - b. The extent and reversibility of central nervous system toxicity has not been adequately addressed.
 - c. The data submitted have not adequately characterized the interaction between ziconotide and opiates, in particular the effects of coadministered opioids on safety and efficacy.
 - d. The extent to which the loss of drug substance associated with the lowest ziconotide concentration utilized during the trials with a ziconotide-naïve intrathecal pump impacts the safety and efficacy data obtained during the pivotal trials has not been adequately addressed.
 - e. A detailed analysis of treatment-emergent ECG findings, specifically QT

Clinical Review
Lex Schultheis, M.D., Ph.D.
NDA 21,060
Prialt (Ziconotide)

prolongation, has not been carried out.

3. The methodology used in the rat embryo-fetal study that demonstrated the absence of ischial and pubic bones in the highest dose group was not capable of distinguishing between absent bones and unossified cartilage. The possible contribution of maternal toxicity to these findings has not been fully explored.
4. Regarding the aseptic media fill process, the specifications set for sterility upon fill are not sufficiently rigorous to ensure sterility of this product for human intrathecal use.
5. The compatibility of the ziconotide solution with the Medtronic micro-infusion pump has not been adequately characterized and the controls ensuring the compatibility have not been adequately described.
6. The test method provided for the 2D-NMR test for the drug substance is inadequate, the drug substance specification does not include this test, and the analytical testing site performing this test has not been inspected due to missing information.
7. The acceptance criteria for impurities in the drug product is incomplete, lacking specifications for total impurities.

The Agency suggested that the sponsor complete the following to correct the outstanding deficiencies:

A. Submit the results of a new randomized, double-blind, placebo-controlled study of the safety and effectiveness of ziconotide conducted in the target population and at the dosing regimen (i.e., initial dose, dose titration schedule, and titration interval) proposed for marketing. The design of this study has been discussed in reference to IND submissions N200 dated February 27, 2001, and N206 dated April 22, 2001.

B. Submit a detailed and complete reanalysis of the safety data from Study 95-001 and Study 96-002 that adequately addresses the deficiencies noted in #1 (a), (b), (c), (d), and (e).

C. The results from the previous studies and the new placebo-controlled trial should be incorporated into the ISS segment in your future resubmission.

D. Perform a focused embryo-fetal development study in rats which will be capable of demonstrating whether the previous finding of absence of pubic and ischial bones was due to delayed bone maturation (ossification) or due to absence of bone and cartilage. The rat embryo-fetal development study should:

- i. Utilize the same experimental design as in the previously conducted rat embryofetal development study, including using the same supplier, strain, age, and weight of rat;
- ii. Include the following two treatment groups: vehicle and 15 mg/kg/day ziconotide;

Clinical Review
Lex Schultheis, M.D., Ph.D.
NDA 21,060
Prialt (Ziconotide)

L. Provide the address and CFN number of the _____ facility. Also provide the name of a contact person and a telephone number for that facility.

M. Provide updated stability data and statistical analysis of the data for the drug product.

N. Include an acceptance criterion for total impurities in the regulatory specifications for the drug product.

O. Include acceptance criteria for each individual impurity in the regulatory specification for the drug product. In addition, provide a general specification for unspecified impurities, e.g., "any unspecified impurity: less than 0.1%." In your response, provide data supporting the proposed impurity specifications.

1. Describe in detail any significant changes or findings in the safety profile.

2. When assembling the sections describing discontinuations due to adverse events, serious adverse events, and common adverse events, incorporate new safety data as follows:

- Present new safety data from the studies for the proposed indication using the same format as the original NDA submission.
- Present tabulations of the new safety data combined with the original NDA data.
- Include tables that compare frequencies of adverse events in the original NDA with the retabulated frequencies described in the bullet above.
- For indications other than the proposed indication, provide separate tables for the frequencies of adverse events occurring in clinical trials.

3. Present a retabulation of the reasons for premature study discontinuation by incorporating the drop-outs from the newly completed studies. Describe any new trends or patterns identified.

4. Provide case report forms and narrative summaries for each patient who died during a clinical study or who did not complete a study because of an adverse event. In addition, provide narrative summaries for serious adverse events.

5. Describe any information that suggests a substantial change in the incidence of common, but less serious, adverse events between the new data and the original NDA data.

6. Provide a summary of worldwide experience on the safety of this drug. Include an updated estimate of use for drug marketed in other countries.

7. Provide English translations of current approved foreign labeling not previously submitted.

Clinical Review
Lex Schultheis, M.D., Ph.D.
NDA 21,060
Prialt (Ziconotide)

2.6 Other Relevant Background Information

The IND under which ziconotide was studied for the management of pain, by intrathecal route under IND 45,718 _____ are active.

IND No.	Initial IND Submission	IND Holder	Status	Route	Indication
45,718	6/30/94	Elan Pharmaceuticals	Active	Intrathecal	Pain

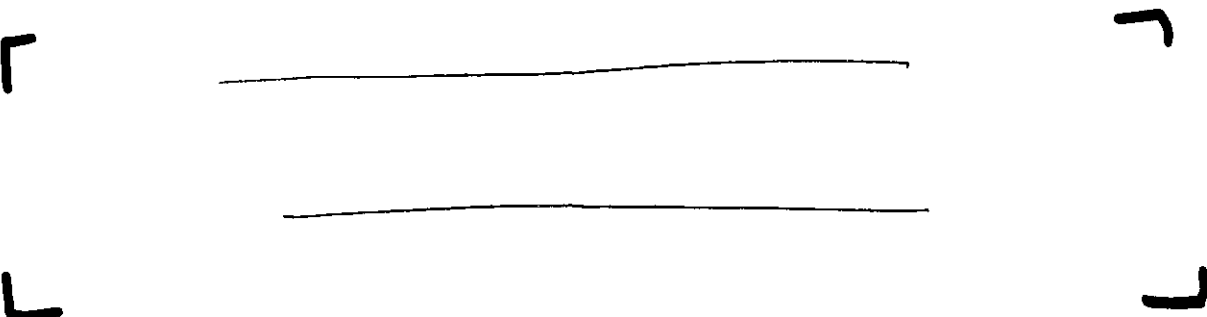
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3 SIGNIFICANT FINDINGS FROM OTHER REVIEW DISCIPLINES

3.1 CMC (and Product Microbiology)

A final CMC review is pending, however Dr. Michael Theodorakis has identified the principal chemistry issues. These include adequate characterization of impurities in the drug product for pharmacological/toxicological evaluation. by the sponsor and reviewed by CDRH. The preparation procedure of a ziconotide naïve pump to minimize drug adsorption during treatment was established. Drug stability data and manufacturing facilities were evaluated. A consult request submitted for microbiology review for the new 25 µg/mL formulation is pending.

The regulatory specifications for acceptance of the drug product were revised to include total impurities and individual limits for the impurities being monitored. All specified impurities that appear in the drug product during storage and in the pump have been qualified.



The first time that the infusion pump is filled with ziconotide, adsorption of drug to the interior surface of the pump can alter the concentration of drug in the reservoir. The process to prepare the pump for first time use was considered adequate to minimize unexpected changes to delivered dose resulting from adsorption. Subsequent refill of the pump with ziconotide was not expected to result in clinically significant dose changes resulting from drug adsorption.

Five manufacturing and quality control facilities for this NDA were acceptable to Compliance. Reports of the evaluation of three facilities are pending.

The stability data (12 lots) support the Applicant's request for an initial month expiration dating period for the 1 mL, 2 mL and 5 mL presentations of the 100 µg/mL strength injection when stored at 2°-8°C. For the 25 µg/mL (20 mL) strength injection stored at 2°-8°C, the Applicant provided month stability data (3 lots) and requested a 24 month expiration dating period. Based on the statistical analysis of the month data, the sponsor concluded that the 25 µg/mL was stable for at least months. Dr. Theodorakis recommended that this request be granted.

During the previous review cycle, Dr. Paul Stinavage recommended non-approval because of lack of evidence that the non-preserved injection solution in the pump will remain sterile of microbial growth when used in patients for 30 days.

3.2 Animal Pharmacology/Toxicology

A final review is pending. Dr. Suzanne Thornton's preliminary findings were related to three primary areas of clinical interest: the effect of ziconotide on cardiac repolarization, the potential for the ziconotide drug product impurities to cause neurotoxicity and the potential for ziconotide to cause fetal toxicity.

Ziconotide up to a concentration of 15 ng/mL did not block hERG [rapidly repolarizing potassium current (I_{KR}), slowly repolarizing cardiac potassium current (I_{KS}), and transient outward potassium current (I_{TO})] channels. These findings suggest that ziconotide will not cause QT prolongation.

No new toxicities were associated with administration of impurities when compared to a high dose of ziconotide (3 μ g/hr) when given as a continuous i.t. infusion in Beagle dogs. Toxicities which associated with both ziconotide and impurity administration included an increase in creatinine, a decrease in triglycerides, decrease in pituitary and ovary weights, increases in liver, thyroid and spleen weights. The common neurological signs observed with ziconotide were not observed with the impurities. These results suggest that impurities in the ziconotide drug product are unlikely to cause observed clinical neurological abnormalities or other toxicity in the drug doses used clinically.

Three embryo-fetal development studies were conducted where pregnant rats were administered ziconotide as continuous i.v. infusion. Embryoletality and fetal lethality were observed, however, at doses that were not necessarily dose-related. Common findings included clinical signs (ptosis, stained and thin fur around mouth and eyes and/or labored breathing, dehydration, tremors, hypersensitivity to touch or with handling, convulsions), decreases in body weights, body weight gains, and food consumption, decreases in gravid uterine weight, no/few evaluable fetuses or pups due to no live fetuses or pups due to complete resorptions of the litters in a narrow range of doses (1.5, 4.5, 15 mg/kg/day), increase in plasma concentrations with increase in dose. Only one study revealed fetal variations, apparently incompletely ossified pubic bones, at a dose of 15 mg/kg/day, which was transitory as there were no affects in offspring during the lactation period. The other studies failed to reveal any fetal or pup malformations or variations, even at doses greater than 15 mg/kg/day. A NOAEL of 0.5 mg/kg/day was established. These preclinical findings suggest that ziconotide has the potential for a high level of fetal toxicity, however at much higher doses than would be used clinically.

4 DATA SOURCES, REVIEW STRATEGY, AND DATA INTEGRITY

4.1 Sources of Clinical Data

NDA application submitted June 25, 2004.

Review of NDA submitted 6/2/2001 by Sharon Hertz, M.D.

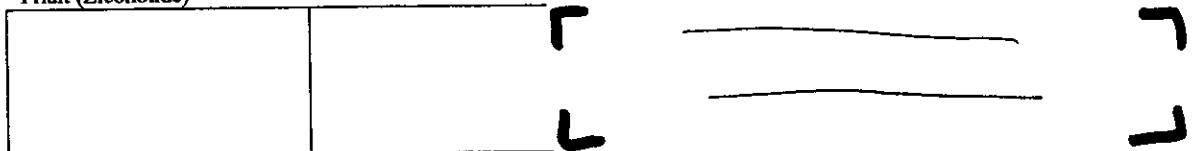
Team leader review (6/3/2000) of NDA submitted 2001 by Bob Rappaport, M.D.

Division Director's reviews (6/12/2000, 7/18/2001) of NDA by Cynthia McCormick, M.D.

Agency action Letter (7/25/01) by John Jenkins on NDA submission 02.

4.2 Tables of Clinical Studies

Study Number/Year Completed	Patients enrolled/No. Exposures to Ziconotide/No. in ITT Population	Study Design	Title
ELN2045-301/2003	248/112/220	Phase 3, pivotal trial Randomized Double-Blind, Placebo-Controlled in Patients with Chronic Back Pain	A Randomized Double-Blind, Placebo-Controlled Study of Intrathecal Ziconotide in Adults with Severe Chronic Pain
ELN 92045-351/ongoing	78/78/0	Open Label Extension from 95-002 and 98-022	An Open-Label, Long-Term, Multicenter Study of Ziconotide Administered Intrathecally
ELN92045-352/ongoing	85/85/0	Open Label Extension from Study 301	An Open-Label, Long-Term, Multicenter Study of Ziconotide Administered Intrathecally
98-022/2002	668/644/0	Open Label Safety study in patients with chronic malignant or nonmalignant pain	An Open-Label, Long-Term, Multicenter Study of Ziconotide Administered Intrathecally to Patients with Chronic Severe Pain



4.3 Review Strategy

A primary review of efficacy was conducted of the only new clinical trial submitted: study ELN2045-301 "A Randomized Double-Blind, Placebo-Controlled Study of Intrathecal Ziconotide in Adults with Severe Chronic Pain". The primary review of Sharon Hertz and secondary reviews by Bob Rappaport and Cynthia McCormick of the remaining clinical trials were consulted for evaluation of the sponsor's previously submitted trial reports. Consideration was given to potential support offered by data included in the previously submitted NDA December 28, 1999 (02), exclusive of patients treated by _____ because of concerns about trial integrity as described by Dr. Hertz in her review.

An evaluation of safety was primarily based upon data submitted with the current NDA, because the rate of upward dose titration is substantially below that used in earlier trials. An estimate of the relative safety between the dosing regimen used earlier and with the ELN2045-301 was performed.

For certain serious adverse events that were qualitatively similar in the earlier NDA submission and the current submission, the sponsor pooled safety data. My review of safety was based upon the findings from the new trial (ELN2045-301) because outstanding questions concerning the delivered dose of ziconotide because of adsorption to the lining of the indwelling pump confounded interpretation of the data collected earlier. Furthermore, agency review of earlier studies precipitated the current study of slow titration because risk associated with more rapid titration employed in the earlier studies was unacceptable.

A risk-benefit analysis was performed to evaluate the efficacy of ziconotide in clinical trial ELN2045-301 compared to the likely risks associated with its use and the potential to minimize serious risks.

4.4 Data Quality and Integrity

In general, the primary data source table in electronic format was legible, navigable and consistent when data was shared between tables. The sponsor's summary findings in the paper copy of the NDA submission were confirmed by review of the source data in most cases.

An inspection was conducted of three trial sites used for study 301 lead by principal investigators: Peter S. Kosek, Lynn R. Webster, and Michael Minehart. These sites were selected because of higher than average enrollment. A full report is pending, however no abnormalities in study conduct have been noted at the time of this review.

One inconsistency noted was in Table 33 located in I.8 V.002 on P.195-196 reporting the incidence of neurological adverse events stratified by type of adverse event, dose and duration of study drug. My review of the source data from the electronic data tables, which was confirmed

Clinical Review
Lex Schultheis, M.D., Ph.D.
NDA 21,060
Prialt (Ziconotide)

by Dr. Joan Buenconsejo of the Agency Biometric review team, yielded higher incidences than the sponsor's report.

Another difference was with Agency interpretation of dropouts. The sponsor included two patients who discontinued the study on the final day of the study in the subset of patients they classified as having demonstrated efficacy of ziconotide. In my analysis and in the review of Dr. Joan Buenconsejo these patients were not considered as having demonstrated efficacy. It is interesting to note that two additional patients classified as responders (> 30% improvement in the primary efficacy variable) elected not to continue treatment with ziconotide following conclusion of the pivotal trial (ELN92045-301) and were reported to having had adverse events in their CRF. These adverse events were not reported in the sponsor's electronic source table of Adverse Events because the date of report coincided with the termination of the placebo controlled trial. In my analysis, these patients were not considered to have withdrawn because of an adverse event in keeping with strict interpretation of the protocol, however they are mentioned here as a point of reference for later examination of the risk-benefit profile of ziconotide.

4.5 Compliance with Good Clinical Practices

The Sponsor has asserted that the clinical studies of ziconotide conducted by or sponsored by Élan Pharmaceuticals were conducted in compliance with the regulations for Institutional Review Boards (21 CFR 56) and Informed Consent (21 CFR 50), as well as state and local requirements for the conduct of clinical trials.

The sponsor indicated that the studies were reviewed by the applicable IRBs in accordance with the FDA's IND regulations and consent was obtained from participating subjects, and were completed in accordance with FDA regulations for Good Clinical Practice and the Helsinki Agreement for Ethical Principles for Medical Research Involving Human Subjects.

4.6 Financial Disclosures

To comply with 21CFR §54.4, Certification and Disclosure Requirements, the Sponsor submitted disclosure/certification information by Clinical Investigators for those investigators participating in Elan Study ELN92045-301, "A Randomized Double-Blind, Placebo-Controlled Study of Intrathecal Ziconotide in Adults with Severe Chronic Pain" A listing of those investigators who have self certified or been certified through site audits was included. In an effort to determine if participating investigators would be subject to disclosure, audits of all financial records were performed by the sponsor to determine if investigators participating in the above mentioned study met the disclosure requirements outlined in 21 CFR §54.4 (a)(3)(ii) and defined by §54.2 (f). The results of the audit revealed that no investigator received payments meeting the reporting requirements.

5 CLINICAL PHARMACOLOGY

5.1 Pharmacokinetics

No new pharmacokinetic trial reports were submitted with the current application. The sponsor's earlier submission included fourteen clinical trials which provided PK data. All 14 provided data on plasma levels, 3 attempted to quantify drug in the CSF and one in urine. These are summarized in Table 5.1-1.

Table 5.1-1 Matrices Sampled and Data Available in Ziconotide Human PK Studies

Study No.	Route	CSF PK	CSF Conc.	Plasma PK	Plasma Conc.	Urine Conc.
97-013	IT	yes			Yes	
94-004	IT				Yes	
95-001	IT				Yes	
96-002	IT				Yes	
96-003	IT				Yes	
95-002	IT				Yes	
93-001	IV			Yes		
93-002	IV			Yes		
93-003	IV			Yes		
94-001	IV		Yes	Yes		
95-002	IV			Yes		Yes
94-004	IV			Yes		
98-021	Epidural	Yes		Yes		
96-012	Epidural				Yes	

A blank cell indicates data not available. (From Sponsor's Prior submission Table 3.6-1, Vol. 2.2, P. 172)

CSF PK

CSF was sampled during three different studies, following the administration of ziconotide by IT, ED and IV routes. Study 97-013 was the primary PK study for the IT route and the only study to characterize the PK of ziconotide in the CSF following IT administration. This was an open label, pilot study of the PK, safety and analgesic profiles following a single one hour IT infusion in 23 patients (including one patient enrolled twice). The doses were 1, 5, 7.5 and 10 mcg. CSF samples were collected for 48 hours. Although the sponsor indicated AUC and Cmax were dose proportional, this was not supported by the results. AUC and Cmax actually decreased from the 7.5 to 10 mcg doses. Clearance and the volume of distribution also peaked with the 7.5 mcg dose. Half-life was the most stable measurement ranging from 5.3 h for the 1 mcg dose to 4.2 h for the 10 mcg dose.

Study 94-001 was a multicenter placebo controlled, phase II safety and feasibility study. Patients were dosed IV for 72 hours with one of 3 dose regimens; a constant 70 mg/d infusion or escalating infusions with maximum doses of 0.25 mg/kg/d or 1 mg/kg/d. Fifty two of 66 CSF

Clinical Review
Lex Schultheis, M.D., Ph.D.
NDA 21,060
Prialit (Ziconotide)

samples were drawn from 4-75 hours after the start of the infusion. The results demonstrated very large variability, C_{max} ranged from _____ AUC from 6 to 480 ng*h/mL, possibly explained by contamination with blood.

Study 98-021 was an open label, pilot study following a single 1 hour epidural infusion in 42 patients. Doses were 1, 2, 56, 10 and 20 mcg. Only 14 of 39 patients with CSF samples had quantifiable CSF ziconotide levels. The CSF-PK results were reported to be dose dependent by the sponsor, but the results from the 5 and 10 mcg doses were comparable for many parameters. A saturable transport mechanism across the meninges was postulated.

Overall, there was little consistency within the information obtained from attempting to quantify ziconotide in the CSF. No reliable PK parameters could be calculated from these results.

Plasma PK

Plasma PK was sampled during the 2 pivotal intrathecal studies, 95-001 and 96-002. Only 44% (22/50) of the patients in 95-001 and 30% (30/102) of patients in 96-002 had quantifiable plasma levels of ziconotide. The values were widely variable, as were dose rates, with only gross correlations between infusion rate and plasma level. During study 95-002, the open label extension from the pivotal trials, doses were maintained for the first 30 days. Plasma samples were drawn 48 hours after the first maintenance period was initiated. Only 13% of the plasma levels were above the quantitation limit. There was no correlation between the average hourly infusion rate and the presence of a quantifiable concentration. There were only 7 samples (5%) from intrathecal study 97-013 with quantifiable ziconotide plasma levels. Similar, highly variable findings were obtained from IT studies 94-004 and 96-003.

The plasma PK values from epidural studies 98-021 and 96-012 were more dose proportional than the CSF results according to the sponsor, but were only quantifiable in up to 75% of samples from any given dose.

Following IV administration, the PK results were less variable than by other routes of administration. The mean half life was 1.3 h from study 93-001 with doses from 0.3 to 10 mcg/kg/24h and 2.4 h from 93-002 with doses from 10 to 1000 mcg/kg/24 hr, demonstrating some dose dependence. The mean steady state volume of distribution was 30 liters from study 93-001 and 48 liters from 93-002. Clearance averaged 17 liters/h from study 93-001 and 14 liters/h from 93-002.

Urine concentration following IV infusion in study 94-002 was not sufficiently recoverable for comment.

5.2 Pharmacodynamics

A relationship between blood and/or CSF concentration and clinical effect was not clearly established. Intrathecal dosing, as empirically derived during clinical trials, was only loosely based upon measured concentrations in CSF or blood.

Clinical Review
Lex Schultheis, M.D., Ph.D.
NDA 21,060
Prialt (Ziconotide)

5.3 Exposure-Response Relationships

Clinical studies of measured drug exposure were of limited application in predicting clinical response. The dose, dose increment and titration interval were refined during phase 3 trials presented with the sponsor's previously submitted NDA. Previous Agency reviews of earlier Clinical Studies 95-001 and 96-002 identified frequent dose reductions, interruptions and discontinuations that were required because of adverse events. A previously unexpected potential relationship between ziconotide administration and QT prolongation was detected. The lack of a clear relationship between ziconotide concentration in body fluids and drug response during pharmacological testing necessitated that dose-effect be established an additional titration trial (Study 310). *Post-hoc* analysis of variations in the dosing regimen used in a subset of patients from Clinical Studies 95-001 and 96-002 were used by the sponsor to develop the titration schedule of Study 301 which forms the basis for the current review.

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6 INTEGRATED REVIEW OF EFFICACY

6.1 Indication

Ziconotide is indicated for management of severe chronic pain in patients in whom intrathecal therapy is warranted.

6.1.1 Methods

The primary source of data for the review of efficacy is sponsor's report of results from Study ELN92045-301, submitted for the first time with this NDA application. This study entitled "A Randomized, double-Blind, Placebo-Controlled Study of Intrathecal Ziconotide in Adults with Severe Chronic Pain" was conducted in patients who exhibited severe pain despite multiple medications including administration of intrathecal opiates by an indwelling pump. The most common pain mechanism in this study was neuropathic pain accounting for 76% of the patients in the ziconotide arm and 71% of the patients in the placebo arm. Failed back surgery was the most common etiology in the study and was reported for 61% for the patients in the ziconotide arm and 56% of the patients treated with placebo. The results were presented after analysis and summary by the sponsor in the paper archive of the application. The source data were also supplied in electronic tables for independent analysis by the Agency. The clinical review by the agency used analysis of the source data to confirm the sponsor's findings and identify inconsistencies when present.

As part of the Agency review, missing data from the source electronic tables was analyzed using baseline data for replacement rather than use of the last observation carried forward technique used by the sponsor as stipulated in the protocol. The best practice for statistical management of missing data in clinical trials to evaluate treatment of chronic pain has been evolving since the protocol was designed and the technique chosen for Agency review of ziconotide reflects the current consensus of opinion among Agency Biometrics experts.

Additional materials used for reference include the reviews of Drs. Sharon Hertz, Bob Rappaport and Cynthia McCormick who comprised the medical review team for the earlier NDA submission of ziconotide.

6.1.2 General Discussion of Endpoints

The primary efficacy endpoint for Study ELN92045-301 was the change in visual analog score pain index (VASPI) in measurements taken at baseline and at the end of three weeks of constant administration of either intrathecal saline (placebo) or ziconotide. Visual analog scales have been validated as a clinical tool to quantitatively assay pain as a continuous variable delimited by "no pain experienced = 0" and "worst pain imaginable = 100" as extrema. In both treatment groups the mean baseline VASPI score was 81.

A limitation of VAS scores is that statistically significant differences between central measures of treatment arms may be quantitatively small and be uninterpretable in terms of

Clinical Review
Lex Schultheis, M.D., Ph.D.
NDA 21,060
Prialt (Ziconotide)

clinical relevance. For this reason, the fraction of patients in each treatment arm who achieved a threshold in reduction of VAS scores that was postulated to be clinically relevant were to be analyzed as a secondary endpoint. The patients who achieved a 30 % reduction in VAS score were termed "responders" in Study 301. The magnitude of the threshold reduction in VAS and analysis of responders was based upon recommendations from Agency before the trial was conducted.

Other secondary endpoints were chosen to establish whether or not a reduction in VAS score associated with treatment was also manifested as global improvements in pain and in the patient's subjective assessment of their quality of life. Central measures of scores on questionnaires and an assessment of changes in pain using a categorical scale were analyzed as secondary efficacy variables to provide evidence to determine whether or not a reported reduction in VAS score was associated with a clinically meaningful improvement to patients in the treatment group. The assessment tools used were: CGI Satisfaction Score, CGI pain Score, Global McGill Pain Total Score, Global McGill Pain intensity Score, BPI Enjoyment of Life, Sleep Duration and Quality Score, Concomitant Opiate Administration Weekly Mean and total Cumulative dose. All have been commonly utilized as measurements of pain, quality of life and sleep respectively.

6.1.3 Study Design

Study 301 fulfills the regulatory criteria (21 CFR 314.126) for an adequate and well-controlled clinical trial based upon a randomized, double-blinded, parallel-group, placebo-controlled multicenter design.

Bias was minimized by randomizing 248 patients to one of two treatment arms after stabilization of pain management off intrathecal therapy, blinding 39 participating investigators and their patients to the treatment, prospective identification of efficacy endpoints and an adequate statistical analysis plan.

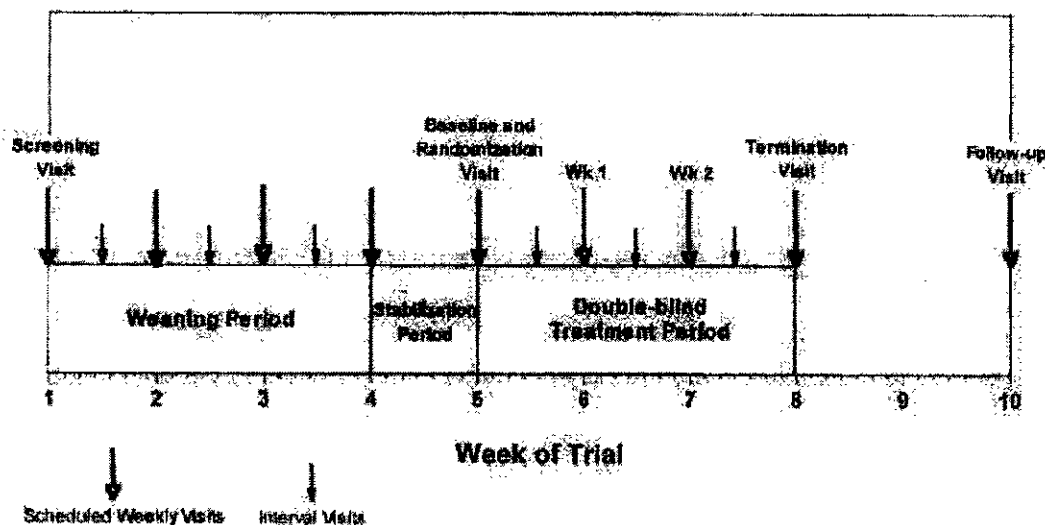
The control group consisted of patients randomized to treatment with intrathecal administration of the ziconotide vehicle including excipients (preservative free L-methionine and sodium chloride at pH 4.3 ± 0.2). The treatment groups were well matched with respect to baseline and screening pain characteristics, duration of pain, patient age and etiology of pain.

The duration of the treatment phase of Study 301 (three weeks) is evaluated for adequacy of exposure needed to establish an effective dose, for detection of tolerance and the spectrum of adverse events in patients likely to receive ziconotide for treatment of chronic pain over and extended period. Analysis of efficacy and safety within the dosing range of Study 301 did not suggest dose-related effects with a slow titration regimen. Expression of the range, severity and reversibility of likely adverse events associated with ziconotide was established by review of findings during Study 301, the 120 day safety update and subsequent open-label Study 352 composed of volunteers from Study 301. Tolerance to ziconotide could not be established, however incremental dosing adjustments persisted among patients who continued treatment with ziconotide in Study 352 following Study 301.

Entry criteria for Study 301 were sufficient to warrant a generalization of the findings among adult patients having chronic severe pain that has been intractable to alternative medical treatment including intrathecal morphine. At baseline, 96% of patients in the ziconotide group and 97% of patients in the placebo group were considered to have intractable pain refractory to available pharmacological treatment. The mean patient age was 53 years and the mean duration of pain was 14 years. The etiology of pain was failed back surgery in 61 % of the patients treated with ziconotide and 56% of the patients treated with placebo with 76% and 71% of the patients in the ziconotide and placebo groups, respectively, carrying a diagnosis of neuropathic pain.

Adequacy of dose finding was evaluated based upon ziconotide treated patients in Study 301 and ziconotide treated patients from Study 301 who continued in Study 352. A general comparison was made to the findings presented with Studies 95-001 and 96-002. Among ziconotide treated patients treated in Study 301, there was no clear dose effect related to efficacy or incidence of adverse events. A higher-dose fast-titration regimen used in Studies 96-001 and 96-002 appeared to be associated with increased efficacy and an increased frequency of adverse events, however dosing was not definitively established in these earlier studies because of uncertainty regarding the amount of drug adsorption in the indwelling pump. Patients who continued ziconotide treatment in Study 352 required an increasing dose over 14 months of administration.

Figure 6.1.3-1 Study 301 Schematic



From I.8 V.005 P.143 Sponsor's NDA Submission 03, Vol 3.030 of 3.103, Section 17.1.1 Study Protocol N92045-301, Page 959

Clinical Review
 Lex Schultheis, M.D., Ph.D.
 NDA 21,060
 Prialt (Ziconotide)
 Figure 6.1.3-2 Study 301 Assessments

Schedule of Events

Procedure	Screening Visit	Visit 1	Visit 2	Stabilization Visit	Baseline Visit (Randomization)	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7	Visit 8	Visit 9	Visit 10
Informed Consent	X												
Inclusion/Exclusion Criteria	X												
Medical/Personal History	X												
Physical Exam	X												
Neurological Assessment	X												
Vital Signs	X				X								
Lab Evaluations ^a	X				X								
Pregnancy Test ^b	X				X								
12-Lead ECG	X				X								
VASPR (Visual Analog Scale of Pain Intensity)	X	X		X	X	X							
Brief Pain Inventory (BPI)	X				X								
Mini-Mental State Examination (MMSE)	X				X								
Neurocognitive Assessment	X				X								
Concomitant Medication Review	X				X								
Randomization	X				X								
Baseline Assessment	X				X								
Baseline Physical Exam	X				X								
Baseline Neurological Examination	X				X								
Baseline Concomitant Medication	X				X								
Dropout/Withdrawal/Pump Interference				X	X	X	X	X	X	X	X	X	X
Patient Daily Diary (to be filled in)	X	X	X	X	X	X	X	X	X	X	X	X	X
Adverse Events		X	X	X	X	X	X	X	X	X	X	X	X
Concomitant Medication	X	X	X	X	X	X	X	X	X	X	X	X	X

From I.8 V.005 P.145 Sponsor's NDA Submission 03, Vol 3.030 of 3.103, Section 17.1.1 Study Protocol N92045-301, Page 961

- a Patients already weaned off IT opiates may proceed to stabilization after screening visit.
- b Scheduled weekly weaning visits; internal visits as needed. Pump is to be refilled on Study Day 14.
- c Stable dosing for at least one week on systemic opiates; IT opiates = 0 prior to Stabilization Visit.

Clinical Review
Lex Schultheis, M.D., Ph.D.
NDA 21,060
Prialt (Ziconotide)

- d Interval visits at least once and not more than twice each week. Visits must be at least 24 hours apart.
- e Blood chemistry and hematology at Screening, Baseline and Termination Visits. For all male patients, testosterone levels were to be obtained at Baseline.

For females of childbearing potential only:

- g VASPI at scheduled weekly visits during weaning and treatment periods.
- h Scheduled termination or early termination. If the patient does not wish to enroll in the open-label ziconotide study then survival is to be confirmed 30 days after last dose.
- i Pump is to be rinsed three times with fresh 5 mL preservative-free 0.9% Sodium Chloride Injection, UPS using new syringe for each rinse at the subject's last weaning visit.
- j Pump is to be rinsed three times with 2 mL of diluted Study Drug at the Randomization Visit.
- k Pump is to be refilled on Treatment Day 14. After pump refill the patient is to be contacted approximately 48hrs after refill for the assessment of adverse events.
- l The final VASPI score is to be obtained after a minimum of 48 hours of stable dosing.
- m If the patient wishes to enroll in the open-label ziconotide study, the Termination Visit assessments need to be immediately completed and completion confirmed by the CRO prior to unblinding. The site will be Instructed to call the IVRS to obtain the patient's assignment. Site is to contact the patient to schedule an office visit for enrollment in the open-label study.
- n Patients experiencing ongoing study-drug related adverse events at the time of ziconotide termination require follow-up visits at 2-week intervals until resolution of the adverse event. This follow-up visit can be an office visit or the investigator can contact the patient by phone.

**Appears This Way
On Original**

6.1.4 Efficacy Findings

Primary Efficacy Endpoint:

The sponsor reported a statistically significant ($p=0.04$) reduction in the mean Visual Analog Scale Pain Index (VASPI) measured after 3 weeks of treatment following stabilization in the Ziconotide group (14.7%) compared with the placebo group (7.2%). Missing data was imputed using last observation carried forward (LOCF) for the sponsor's analysis as stipulated by the protocol. Further sensitivity analysis of the primary efficacy endpoint was conducted by the sponsor using alternative methods to LOCF for management of missing data. Alternative methods to impute missing data for the analysis VASPI of Week 3 was performed by the sponsor. These included:

- a. Use of observed data only. Only subjects with Week 3 VASPI data were included.
- b. Imputing the median percent change from baseline to week 3 obtained from all subjects in the same treatment group as the outcome variable for subjects without Week 3 VASPI.
- c. The smallest percent improvement from baseline to Week 3 obtained from all subjects in the same treatment group was substituted for missing VASPI data in Week 3.

Analysis of changes in VASPI using these alternative techniques all yielded similar results.

During Agency biometrics review, an analysis of the primary efficacy endpoint using baseline carried forward replacement of missing data (BCFR) was conducted by Dr. Joan Buenconsejo. In this analysis, the baseline VASPI was substituted for missing data so that no improvement in VASPI was recorded for the patients affected. Her analysis, summarized in Table 6.1.4-4 supported the sponsor's finding of a statistically significant reduction in VASPI in the ziconotide-treated, but not the placebo-treated arm after three weeks.

Secondary Endpoints:

Responder Analysis:

Responders were defined by the protocol as patients having at least a 30% reduction in VASPI from baseline to week 3. The sponsor reported no statistically significant difference between ziconotide and placebo treatment arms using LOCF imputation of missing data, as stipulated by the protocol.

There was no clear difference in the incidence of responders treated with ziconotide compared to all patients who were responders when analyzed by gender or age. The number of patients who described their race as other than Caucasian was too small for analysis.

An analysis by Dr. Joan Buenconsejo of the Agency Biometrics review team using baseline observation determined that there was no significant difference in responders between ziconotide and placebo treatment groups using a BCFR technique to impute missing data. Her analysis of various percentages of reduction in VASPI revealed that there was no trend or

Clinical Review
Lex Schultheis, M.D., Ph.D.
NDA 21,060
Prialat (Ziconotide)

threshold reduction in VASPI that differentiated treatment arms. For example, the proportion of ziconotide patients with a 50% reduction in VASPI was larger by a statistically significant margin than the number of patients in the placebo arm, but not for patients with a 40% or 60% reduction in VASPI.

Further analysis by Dr. Buenconsejo revealed that different patients would have been defined as responders in week 1 or week 2 compared to week 3. This indicates that the VASPI score fluctuated over the course of the clinical trial among individual patients and that a persistent reduction of VASPI was not maintained among patients who exhibited early signs of improvement.

Other Analysis using VASPI Score:

The sponsor conducted several other analyses of the VASPI as stipulated by the protocol. These included:

- The percent change in VASPI score at the final visit at the end of treatment week 3 compared to baseline visit using observed data only (no LOCF).
- The VASPI score (mm) change from baseline to termination visit (using LOCF).
- The percent change in weekly VASPI scores reported at scheduled weekly treatment visits at the end of week 1 and week 2 and the final visit using observed data only (no LOCF).
- Percent change in weekly VASPI scores reported at scheduled weekly treatment visits at the end of week 1 and week 2, with LOCF for early terminations.
- Percent change in weekly VASPI scores at weekly treatment visits at the end of treatment week 1, week 2 and final visit, observed data only, without LOCF.

The findings were generally supportive of efficacy as determined by analysis of the primary efficacy endpoint. A more detailed analysis of the time-dependent variability of the VASPI is presented below in Tables 6.1.4-5 and 6.1.4-5 with a discussion in the associated **Summary of Primary and Secondary Efficacy Findings and Clinical Reviewer's Interpretation.**

Weekly Opiate Consumption:

The sponsor identifies a 26.8% median decrease in weekly opiate use from the pretreatment stabilization period to mean opiate consumption at week 3 for the ziconotide group compared to a 25% decrease in the placebo group as evidence that an improvement in VASPI score was not a result of increased opiate use.

The sponsor further describes a consistent weekly decline in mean opiate consumption in contrast to the absence of a similar trend in the placebo group. This difference in consistency of the trend toward reduced weekly opiate consumption between the ziconotide and placebo is not seen when reviewing median rather than mean data.

Table 6.1.4-1 Median Weekly Opiate Consumption Declined In Both Ziconotide and Placebo Treatment Groups

Clinical Review
 Lex Schultheis, M.D., Ph.D.
 NDA 21,060
 Prialt (Ziconotide)

	Ziconotide N =112	Placebo N=108
Pretreatment	1367 (0-14880)	1202 (0-11613) mg/day
Week 1	1354 (0-15584)	1116 (0-11067)
Week 2	1380 (0-14798)	1191 (0-9726)
Week 3	1000 (0-9560)	900 (0-9181)

Opiate consumption for each treatment group is presented as the **median (range) in mg oral opiate equivalents of morphine for each time period**. Data was abstracted from Study Report ELN92045-301, Sponsor's Tables 15.2.21-22 in I.8 V.003 P.102-104.

Clinical Global Impression (CGI):

Clinical Global Impression Satisfaction with Therapy:

Patients selected a representation of their overall satisfaction with study therapy at termination from a 5 point scale: 0 = not at all, 1 = a little bit, 2 = somewhat, 3 = a whole lot, 4 = completely.

The sponsor reported that 31/109 (28%) of the patients in the ziconotide group and 13/107 (12%) patients in the placebo group had either "a whole lot" or "complete satisfaction" with therapy at termination. The sponsor's analysis indicated a statistically significant difference between the treatment arms using the Mantel-Haenszel chi-square test (p=0.003).

Clinical Global Impression Overall Pain Control:

The CGI pain control scale also had five choices to indicate the patient's overall evaluation of pain control: 0= poor, 1 =fair, 2 =good, 3 = very good and 4 = completely.

Of the 109 patients in the ziconotide treatment group, 13 patients experienced "very good" or "excellent" overall pain control compared with 1 of the 107 placebo patients. The sponsor's analysis reported this difference as statistically significant (p=0.0004) using the Mantel-Haenszel chi-square test.

Change in Global McGill Pain Questionnaire Scores:

Change in Global McGill Total Score:

At baseline and termination, the patient was asked to quantify each of the 15 individual Global McGill pain descriptors as none (0), mild (1), moderate (2) or severe (3). The Global McGill Total Score is the sum of the scores from the 15 individual descriptors of pain. The mean change from baseline to termination was 3.2 in the ziconotide group and 0.6 in the placebo group. The sponsor reported a statistically significant improvement in the ziconotide group compared with the placebo group (p =0.03).

Change in Global McGill Pain Intensity Scores:

The patient was asked to assign their present pain intensity to one of the following categories: no pain (0), mild (1), discomforting (2), distressing (3) horrible (4) or excruciating

Clinical Review
 Lex Schultheis, M.D., Ph.D.
 NDA 21,060
 Prialt (Ziconotide)

(5). In the ziconotide group, 45/107 (42%) patients experienced improved pain by at least one unit from baseline to termination compared to 38 /106 (38%) of patients in the placebo group. The sponsor indicated that they were unable to demonstrate a statistically significant difference between treatment arms (p=0.051).

Change in Brief Pain Inventory (BPI):

This questionnaire was used to measure the interference of pain on mood, relations with other people, walking ability, sleep, normal work and enjoyment of life. The patient scored each item as: not at all (0), a little bit (1), moderately (2), quite a bit (3) or extremely (4) for the previous week. In the ziconotide group 46/109 patients (42%) experienced an improvement of at least one unit in the score for “enjoyment of life” from baseline to termination compared with 29/106 patients (27%) in the placebo group. This change was reported by the sponsor as statistically significant (P=0.02). All subset scores were associated with relative improvement among the ziconotide group compared to the placebo group, but the sponsor reported that the differences were not statistically significant.

Sleep Pattern and Quality of Sleep:

The current sleep pattern was ranked using a questionnaire to investigate the effect of pain on the pattern and quality of sleep and to determine if pain relief also resulted in improved sleep quality.

Table 6.1.4-2 Patients Receiving Ziconotide Exhibited Improvement in Pattern and Quality of Sleep

Parameter	Ziconotide (N = 112)	Placebo (N = 108)	p-value ^a
Current Sleep Pattern (uninterrupted) at			0.0067
<2 hours	20(18.5%)	29(27.1%)	
2 to 4 hours	45(41.7%)	55(51.4%)	
4 to 6 hours	33(30.6%)	18(16.8%)	
Over 6 hours	10(9.3%)	5(4.7%)	
Missing	4	1	
Pain Makes it Hard to Fall Asleep			0.6394
Yes	69(63.3%)	71(66.4%)	
No	40(36.7%)	36(33.6%)	
Missing	3	1	
Pain Wakes Me Up During the Night			0.0715
Yes	82(75.2%)	91(85.0%)	
No	27(24.8%)	16(15.0%)	
Missing	3	1	

Clinical Review
 Lex Schultheis, M.D., Ph.D.
 NDA 21,060
 Prialt (Ziconotide)

Overall Quality of Sleep			0.0059
Poor	45(41.7%)	61(57.0%)	
Fair	43(39.8%)	38(35.5%)	
Good	20(18.5%)	8(7.5%)	
Missing	~ 4	1	

^a Mantel-Haenszel chi-square test with 1 degree of freedom. Data Source: Section 15.2, Table 15.2.35

At baseline, the pattern and quality of sleep for the ziconotide and placebo groups were similar, but the sponsor reported statistically significant improvements in the number of hours of uninterrupted sleep ($p=0.0070$ and overall sleep quality ($p=0.006$) and evidence of fewer awakenings due to pain in the ziconotide group ($p=0.07$).

Categorical Pain Relief Scale(CPRS):

Table 6.1.4-3 Patients Receiving Ziconotide Exhibited Improvement in Categorical Pain Score

Parameter	Ziconotide (N = 112)	Placebo (N = 108)	p-value
CPRS at Termination			0.0596 ^a
Worse	35(32.1%)	27(25.2%)	
No Change	23(21.1%)	46(43.0%)	
Slight Improvement	22(20.2%)	19(17.8%)	
Moderate Improvement	12(11.0%)	11 (10.3%)	
A Lot of Improvement	15(13.8%)	3(2.8%)	
Complete Relief	2(1.8%)	1 (0.9%)	
Missing	3	1	

Note: CPRS scores are ranked as follows: 0 = worse, 1 = no change, 2 = a slight improvement, 3 = moderate improvement, 4 = a lot of improvement, and 5 = complete relief.

^a Mantel-Haenszel chi-square test with 1 degree of freedom for comparing ziconotide versus placebo at termination.

Data Source: Section 15.2, Table 15.2.31

Change in Treatment Outcome Pain Survey Dimension Score (TOPS):

The TOPS score had a range from 0 to 100 based upon a survey consisted of questions that examined the patient's perspective of pain, its impact on the patient's life and performance of usual activities. The Total Pain Experience was based upon five dimensions: pain symptoms, perceived family/social disability, lower body functional limitations, and objective work disability. The ziconotide arm exhibited a mean decrease (improvement) in TOPS score of 3.9 compared with a decrease of 1.8 in the placebo group. The trend suggesting improvement in the ziconotide group was not statistically significant.

Summary of Primary and Secondary Efficacy Findings and Clinical Reviewer's Interpretation:

The sponsor's data, as analyzed by the sponsor and by the Agency is consistent, demonstrating a statistically significant reduction in VASPI score among patients treated with ziconotide compared to placebo after three weeks of therapy. The mean difference in VASPI score between ziconotide and placebo treatment groups was small (7, using LOCF) and may not, by itself, reflect a meaningful improvement in pain. All secondary efficacy endpoints, designed to indicate the impact of therapy on global quality of life, sleep or functionality exhibited a trend toward improvement in the mean score of patients treated with ziconotide compared with placebo. The differences in the mean score of secondary efficacy variables or subsets of questions associated with secondary efficacy variables were often small so that the importance of improvement in an individual secondary efficacy endpoint was difficult to interpret.

A combined analysis of the primary and secondary efficacy results was performed by this reviewer to further estimate clinically meaningful impact of treatment with ziconotide by stratifying patients into subgroups based upon the degree of improvement in the primary and secondary efficacy endpoints. This analysis is intended to describe the distribution of outcome according to the magnitude of clinical benefit as an extension of responder analysis, but making use of the BCFR methods preferred by the Agency biometrics team reviewing this product.

Patients identified as having a reduction on VASPI < 30 % of baseline for the purpose of this analysis are termed as minimum responders. Patients with a reduction in VASPI of >= 30 % of baseline are identified as responders. The subgroup of responders who, in addition had an improvement of at least 2 categorical steps in McGill Pain Intensity Score, Sleep Scale, Categorical Pain Scale, Brief Pain Inventory and Clinical Global Impression of Pain Control are identified as patients with a large quantitative improvement in the primary efficacy variable supported by large improvement at least one secondary endpoint. This subgroup of patients is expected by this reviewer to have the most clinically relevant improvement during study drug treatment.

Table 6.1.4-4 Efficacy of Ziconotide on Primary Efficacy Endpoint (VASPI) Using Baseline Carried Forward Replacement of Missing Data

Efficacy of Ziconotide in Reducing VASPI

	Placebo (N=108)	Ziconotide (N=112)
Nonresponders*	58 (54%)	52 (46%)
All Responders*	50 (46%)	60 (54%)
Minimum Responders	37 (34%)	43 (38%)
Responders	13 (12%)	17 (15%)
Responders with marked improvement in at least one secondary efficacy endpoint	4 (4%)	12 (11%)

Nonresponders are defined as patients having no change or an increment in VASPI when comparing Baseline and Mean VASPI after the 3rd week of treatment. Imputation of missing VASPI data using BCFR was performed by Biometrics reviewer, Joan Buenconsejo, Ph.D.. Minimal responders are defined as having less than 30 % decrement

Clinical Review
 Lex Schultheis, M.D., Ph.D.
 NDA 21,060
 Prialt (Ziconotide)

in VASPI. Responders are defined as having at least a 30 % decrement in VASPI. Responders with marked improvement in at least one secondary efficacy endpoint have at least a 30% decrement in VASPI and an improvement of at least 2 categorical steps in McGill Pain Intensity Score, Sleep Scale, Categorical Pain Scale, Brief Pain Inventory and Clinical Global Impression of Pain Control. Imputation of missing data for the secondary efficacy endpoints was performed by the sponsor using last observation carried forward methodology. The data in each cell is displayed as number of patients (% of patients in treatment group). Statistically significant differences between Placebo and Ziconotide treatment ($P < 0.05$) are indicated by “*”.

Secondary endpoints:

1. CGI - Overall Pain Control Rating at Termination: Poor (0) Fair/Good (1-2) Very Good (≥ 3)
2. Change in McGill Pain Intensity at Termination from baseline: Worsen (< 0), No change ($=0$), Improve by 1 ($=1$), Improved by at least 2 (≥ 2)
3. Change in BPI at Termination from baseline: Worsen (< 0), No change ($=0$), Improve by no more than 4 (<5), Improved by at least 5 (≥ 5)
4. Change in Quality of Sleep at Termination from baseline: Worsen (< 0), No change ($=0$), Improve (>0)
5. Change in CPRS at Termination from baseline: Worsen (< 0), No change ($=0$), Improve (>0)
6. Change in TOPS at Termination from baseline: Worsen (< 0), No change ($=0$), Improve by no more than 9 (<10), Improved by at least 10 (≥ 10)
 - Improved in at least one secondary outcome ("second") is defined as: If one of the variables above is coded as "poor or worsening" OR if all variables are coded as "no change" then second=0 (no change/worsen) Else second=1 (improved in at least one secondary outcome).

Table 6.1.4-4 shows that treatment with ziconotide compared with placebo increased the incidence of patients who described substantial pain relief (3% difference in responders) and concomitant improvement in scores used to indicate improvement in quality of life (8% difference in responders with improvement in secondary endpoints). This increased incidence of a substantial clinical improvement following treatment with ziconotide compared with placebo represented a small percentage of the patients treated, so that among the patients who did improve, the improvement was modest. It also suggests treatment with ziconotide may result in a small percentage of patients that have substantial improvement in their pain and associated quality of life.

An additional analysis was performed during review (in collaboration with Dr. Joan Buenconsejo, Biometrics) to examine the pain reduction by ziconotide compared with placebo over the entire 3 week blinded treatment period of Study 301. Although the primary efficacy endpoint was related to pain reduction in the third week of treatment, some patients exhibited pain reduction in the first week. Table 6.1.4-5 illustrates the distribution of patients by their degree of pain control over the entire blinded treatment period. Ziconotide was associated with more frequent reduction in pain over three weeks than placebo.

Table 6.1.4-5 Time Course of Pain Reduction over 3 Weeks

	Ziconotide	Placebo
Responders in at Least One Out of Three Weeks	39 Pts (35%)	28 Pts (26%)
Mild Responders in Least One Out of Three Weeks	56 Pts (50%)	50 Pts (46%)
Non Responders in All Weeks	17 Pts (15%)	30 Pts (28%)

Data was abstracted from sponsor's electronic data tables.

Durability of pain reduction was also examined during review in collaboration with Dr. Joan Buenconsejo, Biometrics. In this analysis, patients who consistently improved from the first week, as shown by a reduction in VASPI over the following two weeks were defined as "Persistent". Patients who had a reduction of VASPI in the first week and failed to improve VASPI score over the following two weeks, but continued to show improvement over baseline were defined as "Moderately Persistent". Those patients who exhibited a reduction in VASPI in at least one of the first two weeks, but were no better than baseline in the third week were defined as "Worsening". Table 6.1.4-6 illustrates that the frequency with which an initial improvement in pain (first week) continued (through 3 weeks) was only slightly better with ziconotide than placebo. The incidence of worsening pain over three weeks, despite an initial improvement (first week) was also slightly higher with ziconotide than placebo. The difference in durability of pain reduction as an effect of treatment was only marginally different than placebo. This suggests that ziconotide could effect a predictable level of pain control in only a very limited number of patients during the 3 week trial treatment period.

Table 6.1.4-6 Durability of Improvement as Measured by Reduction in VASPI over Three Weeks of Blinded Treatment

	Ziconotide (N=112)	Placebo (N=108)
Persistent	13 (12%)	11 (10%)
Moderately Persistent	16 (14%)	11 (10%)
Worsening	10 (9%)	6 (6%)

Data was abstracted from sponsor's electronic data tables.

6.1.5 Clinical Microbiology

Consultative review is pending.

6.1.6 Efficacy Conclusions

Ziconotide is more effective than placebo in reducing chronic pain measured by VASPI after three weeks of treatment. Improvement in pain indicated by a reduction in VASPI was supported by secondary endpoints that reflected a global assessment of satisfaction, quality of life and sleep. The degree of pain reduction reported by patients who responded to ziconotide varied from week to week in the three week trial so that some patients who were responders in the first week did not respond in the second or third weeks and some patients who did not respond early, responded later. Slightly more than half of the patients treated with ziconotide compared to slightly less than half the patients treated with placebo had improvement in pain. This difference was statistically significant, but the average improvement was small and had little impact on their quality of life. A slightly higher percentage of patients treated with ziconotide than placebo exhibited a marked reduction in pain (responders) and also had improvement in global secondary efficacy variables. Among patients who improved the most, the trend suggested that incidence was higher with ziconotide than with placebo, but statistical significance was not established.

7 INTEGRATED REVIEW OF SAFETY

7.1 Methods and Findings

Safety data for Studies 95-001 and 96-002 were reviewed by Drs. Sharon Hertz, Bob Rappaport and Cynthia McCormick who comprised the clinical team for the earlier NDA submission of ziconotide. Clinical safety of ziconotide protocols under IND 45,718 have been reviewed by Dr. Elizabeth McNeil. The principal safety findings from these earlier studies are summarized briefly below, but the data from Study 301 is evaluated separately in detail. The rationale for presentation of findings and analysis of Study 301 separately is based upon the differences in dosing regimen between studies. The protocol stipulating slow titration and a low dose in Study 301 compared with earlier studies was in response to the high incidence of neurological adverse events observed previously, the high dropout rate with these studies and inadequate documentation of safety data which prevented determination of causality. An unfavorable/indeterminate risk profile was a principal reason that the ziconotide NDA was not approved at the last action. A review of findings reported from the open-label Study 352 which enrolled volunteers who elected to be treated with ziconotide after the conclusion of Study 301 is also presented in summary form.

7.1.1 Deaths

There were no deaths among patients treated with ziconotide during the conduct of ELN92045-301. There were three deaths reported in the 120 day safety update among patients in Study 352, the open-label extension trial following Study 301. The cause of death in cases 4-4 or 33-5 were unlikely to be related to ziconotide because rapidly evolving symptoms developed after a lengthy exposure to the drug and other medical conditions predisposed the patient to the mortal event. Patient 27-1 died after relatively limited exposure to ziconotide occurring many days after the last dose of ziconotide, so ziconotide is believed to be an unlikely cause of this patient's death.

Table 7.1.1-1 Patients Who Died While Treated With Ziconotide During Study 352

Study/ Patient Number	Age/ Gender	Days After Last Dose Until Death	Cumulative Dose of Ziconotide (mcg)	Cause of Death
4-4	70/F	1	852.58	Intoxication by the combined effects of Methadone, Alprazolam, and Paroxetine
27-1	53/M	20	11.54	Respiratory arrest

Clinical Review
 Lex Schultheis, M.D., Ph.D.
 NDA 21,060
 Prialt (Ziconotide)

33-5	571M	3	2503.07	Multiple System Organ Failure, Shock

Data was abstracted from the Sponsor's 120 Day Safety Update Report, Table 8.4.9-3
 Of all the patients exposed to ziconotide, 6% died during treatment at a rate of 12% per patient-year of treatment.

Table 7.1.1-2 Incidence of Death Among All Patients Treated with Ziconotide

	ISS	Safety Update
	Ever Received Ziconotide (N = 1202)	Ever Received Ziconotide (N = 1254)
Patient-Years of Exposure	571.28	661.90
Deaths	75(6.2%)	79(6.3%)
Death Rate by Patient-Years of Exposure	0.1313	0.1194

Data was abstracted from the Sponsor's 120 Day Safety Update Report, Table 8.4.9-3

Most patients who died during treatment with ziconotide received a rapid-titration regimen in studies reviewed by Dr. Hertz in the sponsor's earlier submission. Many of the treated patients were suffering from malignancy or AIDS.

Table 7.1.1-3 Patient Deaths by Study

Study	ISS	Safety Update
	Ever Received Ziconotide	Ever Received Ziconotide
94-004	6	6
94-004 Long-Term Extension	7	7
95-001	13	13
95-002	27	27
96-002	0	0
96-003	0	0
96-010	0	0
97-013	0	0
97-015	0	0
98-022	18	18
301	0	0
351	3	5
352	1	3
Total ¹	75/1202 (6.2%)	79/1254 (6.3%)

Clinical Review
 Lex Schultheis, M.D., Ph.D.
 NDA 21,060
 Prilact (Ziconotide)

^a Patients who participated in more than one study. Data was abstracted from the Sponsor's 120 Day Safety Update Report, Table 8.4.63.

7.1.2 Other Serious Adverse Events

Thirteen (12%) out of the total 112 patients treated with ziconotide in ELN92045-301 experienced 29 serious adverse events in contrast to 10 (9%) patients in the placebo group who experienced a total of 23 serious adverse events.

Table 7.1.2-1 Serious Adverse Events Among Patients Treated with Ziconotide or Placebo

Body System	Ziconotide Treated Patients N= 112			Placebo Treated Patients N=108		
	Serious AEs	Number of Patients (n)	Incidence n/112	Serious AEs	Number of Patients (n)	Incidence n/108
Urogenital	0	0	0%	3	3	3%
Skin & Appendages	0	0	0%	3	3	3%
Respiratory	2	2	2%	2	2	2%
Nervous system	11	9	8%	4	3	3%
Musculoskeletal	2	2	2%	0	0	0%
Metabolic and Nutrition	1	1	1%	3	2	2%
Digestive	3	3	3%	5	4	4%
Cardiovascular	3	3	3%	5	3	3%
Body as a Whole	7	6	5%	3	3	3%
Total	29			28		

Data was abstracted from sponsor's electronic adverse event tables.

7.1.3 Dropouts and Other Significant Adverse Events

Six patients treated with ziconotide in Study 301 discontinued treatment because of an adverse event and one additional patient treated with ziconotide withdrew consent. Five placebo patients discontinued because of an adverse event.

Table 7.1.3-1 Patients in Study 301 Treated with Ziconotide Who Were Discontinued Because of an Adverse Event.

Ziconotide Treated Group (N= 112)			
CASE_ID	Verbatim Description of Adverse Event	Body System	Phase of Study

Clinical Review
 Lex Schultheis, M.D., Ph.D.
 NDA 21,060
 Prialt (Ziconotide)

301000020000008	Agitation	Nervous System	Treatment
301000023000002	Severe Tremors Of Entire Body	Nervous System	Treatment
301000032000009	Dizziness	Nervous System	Treatment
301000035000003	Dizziness	Nervous System	Treatment
301000050000001	Hot Flashes	Cardiovascular System	Weaning
301000054000006	Nausea	Digestive System	Treatment

Data was abstracted from the sponsor's electronic data tables.

Table 7.1.3-2 Patients in Study 301 Treated with Placebo Who Were Discontinued Because of an Adverse Event.

Placebo Treated Group (N= 108)			
CASE_ID	Verbatim Description of Adverse Event	Body System	Phase of Study
301000003000002	Nausea	Digestive System	Treatment
301000020000005	Pruritus	Skin & Appendages	Treatment
301000022000001	Headache	Body As A Whole	Treatment
301000055000006	Nausea	Digestive System	Treatment
301000055000011	Opiate Withdrawal	Nervous System	Treatment

Data was abstracted from the sponsor's electronic data tables.

Most dropouts because of adverse events among patients during treatment with ziconotide in Study 301 were associated to symptoms related to the nervous system. Patients treated with placebo did not exhibit the same trend suggesting that the nervous system adverse events were actually caused by ziconotide rather than patient disease.

7.1.3.1 Overall profile of dropouts

Nearly equal numbers of patients in the ziconotide and placebo treatment groups withdrew from Study 301 before completion because of an adverse event, however 4 out of 6 patients in the ziconotide group discontinued because of symptoms related to the central nervous system not found in the patients in the placebo group who discontinued. Patients who prematurely discontinued study from the ziconotide group because of an adverse event related to the central nervous system constituted 4% (4/112) of eligible patients.

7.1.3.2 Adverse events associated with dropouts

The adverse events related to the nervous system most commonly associated with patients who discontinued Study 301 in the ziconotide treatment group included agitation, severe tremors of the whole body and dizziness. These adverse events resolved about two weeks after discontinuing study drug. Hot flashes during weaning of intrathecal opiates and nausea with vomiting during treatment with ziconotide also each resulted in one patient discontinuing Study 301. Nausea was also reported in the placebo treatment arm, as were symptoms of opiate withdrawal as reasons for discontinuing participation in Study 301.

7.1.3.3 Other significant adverse events

Six patients in the ziconotide group were reported to have elevated uric acid levels. All patients were asymptomatic and the clinical significance of this finding is unclear.

Five patients were reported to have elevations of creatine kinase exceeding three times the normal limit, but without clinical signs of stroke or myocardial damage. There were no associated signs of rhabdomyolysis or renal insufficiency.

Two patients treated with ziconotide developed new onset lower extremity weakness. One of the patients (site 8 pt 8) described new onset lower leg weakness in the setting of preexisting Parkinson's disease and upper extremity weakness. Symptoms had not completely resolved by the termination visit. The other patient (site 55 pt 5) had a preexisting history of failed back syndrome and was reported to have had leg weakness on the earlier screening neurological examination. The symptoms in this patient were transitory.

7.1.4 Other Search Strategies

Although the primary search strategy for adverse events focused on Study 301, the entire population of patients exposed to ziconotide was evaluated to assess the rate at which patients were discontinued from treatment. Even though these data were collected from patients with different underlying disease with wide ranging severity and prognosis they were related by the common symptom of intractable pain. Among all patients with various dosing regimens, 42% patients with intractable pain discontinued taking ziconotide because of a serious adverse event. This high rate of discontinuation is evidence of a high-level of risk among a broad spectrum of patients treated with the full range of dosing regimens tested.

Table 7.1.4-1 Serious Adverse Event Incidence and Event Rate Among all Patients Treated with Ziconotide.

	ISS	Safety Update
	Ever Received Ziconotide (N = 1202)	Ever Received Ziconotide (N = 1254)
	While Receiving Ziconotide (N ^b = 1202)	While Receiving Ziconotide (N ^b = 1254)
Patient Years of Exposure ^a	571.28	661.90
Patients with Serious Adverse	429(35.7%)	458(36.5%)

Clinical Review
 Lex Schultheis, M.D., Ph.D.
 NDA 21,060
 Prialt (Ziconotide)

Serious Adverse Event Rate by Patient Years of Exposure	0.7509	0.6919
Patients with Adverse Events Leading to Study Discontinuation	482(40.1%)	528(42.1%)
Rate of Adverse Events Leading To Discontinuation by Patient Years of Exposure	0.8437	0.7977

Data was abstracted from the Sponsor's 120 Day Safety Update Report, Table 8.4.62.

Another search strategy used in this review was an examination of the patients treated with ziconotide who had treatment interrupted because of symptoms of the nervous system.

Table 7.1.4-2 Ziconotide Treated Patients Among All Studies Who Had A Treatment Interruption Because of a Nervous System Adverse Event

Body System/ COSTART Term	ISS	Safety Update
	While Receiving Ziconotide ^a (N = 1202)	While Receiving Ziconotide (N = 1254)
Number of Patients with Any Event	591(49.2%)	642(51.2%)
Nervous System	423(35.2%)	462(36.8%)
Abnormal Gait	40(3.3%)	43(3.4%)
Agitation	13 (1.1%)	14(1.1%)
Anxiety	20(1.7%)	21(1.7%)
Aphasia	26(2.2%)	32(2.6%)
Ataxia	22(1.8%)	25(2.0%)
Cerebrospinal Fluid Abnormal	23(1.9%)	23(1.8%)
Confusion	138(11.5%)	149(11.9%)
Depression	20(1.7%)	22(1.8%)
Dizziness	79(6.6%)	87(6.9%)
Dysesthesia	18(1.5%)	19(1.5%)
Hallucinations	35(2.9%)	41(3.3%)
Memory Impairment	43(3.6%)	50(4.0%)
Meningitis	17(1.4%)	17(1.4%)
Nervousness	14(1.2%)	15(1.2%)
Nystagmus	32(2.7%)	33 (2.6%)
Paresthesia	21(1.7%)	23 (1.8%)

Somnolence	34(2.8%)	35(2.8%)
Speech Disorder	21(1.7%)	24(1.9%)
Stupor	13(1.1%)	13(1.0%)
Thinking Abnormal	27(2.2%)	29(2.3%)
Tremor	16(1.3%)	19(1.5%)
Vertigo	12(1.0%)	12(1.0%)
Special Senses	48(4.0%)	54(4.3%)
Abnormal Vision	23(1.9%)	26(2.1%)
Urogenital System	42(3.5%)	47(3.7%)
Urinary Retention	13(1.1%)	17(1.4%)

Data was abstracted from the Sponsor's 120 Day Safety Update Report, Table 8.4.62.

These data and the data in Table 7.1.4-2 indicate that the frequency of interruption in ziconotide treatment (51%) for an adverse event was higher than for serious adverse events (36%) and for permanent discontinuation of ziconotide (42%). This means that about 9% patients were able to return to ziconotide treatment despite an adverse event and that 15% of the patients interrupted treatment because of an adverse event that was determined to be less than serious. Adverse events related to the nervous system accounted for 37% of treatment interruptions. The most frequent cause of treatment interruption resulted from symptoms of mental confusion (12%).

7.1.5 Common Adverse Events

Of the 112 patients treated with ziconotide in Study 301, 108 were reported to have experienced an adverse event. Adverse events were reported in 99 patients among the Study 301 placebo population consisting of 108 patients.

7.1.5.1 Eliciting adverse events data in the development program

Checklists and verbatim assessments were used to characterize adverse events in the previously presented phase studies (95-001, 96-002), the new pivotal trial (301) and their extensions.

Differences in study design contributed to differences in frequency of assessment. For example, Studies 95-001 and 96-002 utilized a rapid titration regimen over a period of 5 to 6 days while Study 301 extended the period of titration to 3 weeks so investigator-patient contact was less frequent with Study 301 than in the earlier trials. The entire period of blinded treatment was of longer duration in Study 301. Both earlier and later studies allowed for an open-label extension period after the blinded study was terminated to collect safety information.

The characterization of neurological adverse events in Studies 95-001 and 96-002 was questioned in the review by Dr. Sharon Hertz because verbatim descriptions of very similar adverse events were sometimes grouped according to different COSTART preferred terms. This potential ambiguity when grouping similar events confounded interpretation of adverse event

Clinical Review
 Lex Schultheis, M.D., Ph.D.
 NDA 21,060
 Prialt (Ziconotide)

rates associated with study drug treatment. The sponsor subsequently utilized several different groupings of neurological adverse events in their analysis of safety data from Study 301 based upon Agency recommendations, a sponsor selected "panel of experts" and the sponsor's internally derived definitions. Differences in data organization between studies challenge a direct, simple comparison of certain adverse event rates between the previously submitted phase 3 trials and the current submitted clinical study.

7.1.5.2 Appropriateness of adverse event categorization and preferred terms

An issue of concern in the previous review by Dr. Hertz was the disparate categorization of nervous system adverse events that she felt may be combined to describe encephalopathy related to ziconotide. The sponsor subsequently convened its own panel of experts who concluded that a smaller set of preferred terms should be used describe symptoms of the nervous system caused by ziconotide. The incidence of neurological event is higher using the categorization previously used by Dr. Hertz than by the sponsor or their selected expert panel. Using any categorization scheme, the incidence of neurological adverse events is very high indicating that at least half the patients treated and perhaps as high as 71% experienced neurological adverse events with cognitive impairment among all patients tested with all dose-titration regimens.

Table 7.1.5-1 Comparison of the Incidence of Neurological Adverse Events among All Patients Treated with Ziconotide Using Categorization Defined by Prior FDA Review, Sponsor's Panel of Experts and Sponsor.

	ISS	Safety Update
	While Receiving Ziconotide . n = 1202	While Receiving Ziconotide . n = 1254
Non-specific Encephalopathy (FDA) (34 criteria)		
Any one event	820(68.2%)	884(70.5%)
Any two events	588(48.9%)	638(50.9%)
Any three events	391(32.5%)	430(34.3%)
Neurocognitive Dysfunction (Panel) (13 criteria)		
Any one event	645(53.7%)	703(56.1%)
Any two events	390(32.4%)	423(33.7%)
Any three events	181(15.1%)	204(16.3%)
Cognitive Impairment (Sponsor) (9 criteria)		
Any one event	625(52.0%)	681 (54.3%)
Any two events	334(27.8%)	362(28.9%)
Any three events	120(10.0%)	145(11.6%)

Data was abstracted from the Sponsor's 120 Day Safety Update Report, Table 8.4.59.

It was clear that however the neurological adverse events were grouped, the overall incidence of neurological adverse events among all trials with all dosing regimens was very high. It is against this background that the incidence of neurological adverse events that the incidence of neurological adverse events in Study 301 was compared.

Incidence of common adverse events

Table 7.1.5-1 Common Adverse Events

	Number of AEs		Number of Patients Having AEs		Incidence	
	Ziconotide	Placebo	Ziconotide	Placebo	Ziconotide	Placebo
Urogenital	35	23	28	19	25%	18%
Special Senses	33	30	26	18	23%	17%
Skin & Appendages	52	56	37	34	33%	31%
Respiratory	37	28	26	21	23%	19%
Nervous	485	195	98	76	88%	70%
Musculoskeletal	27	22	19	16	17%	15%
Metabolic & Nutritional	67	37	41	22	37%	20%
Hemic & Lymphatic	7	3	4	3	4%	3%
Digestive	215	154	83	68	74%	63%
Cardiovascular	32	26	25	20	22%	19%
Whole Body	192	143	76	60	68%	56%
Total	1182	717				

Data (includes reports from Weaning, Stabilization and Treatment phases) was abstracted by this reviewer from the sponsor's electronic table of adverse events.

These findings indicate that the most frequent adverse events were reported associated with the body systems described as the Nervous System, the Digestive system, the Body as a Whole and Metabolic and Nutritional systems. Among the most frequently reported adverse events, the incidence of adverse events involving the nervous system in the ziconotide treatment group was more than twice the incidence in the placebo group. There was a slightly higher incidence of adverse events among ziconotide treated patients compared with placebo treated patients in every body system except for Skin and Appendages.

7.1.5.4 Common adverse event tables

The reader is referred to Table 7.1.5-1 Common Adverse Events above.

7.1.5.5 Identifying common and drug-related adverse events

The sponsor's adverse event tables (I.8 V.002 P.171-173) were inspected by the reviewer for grossly identifiable findings of increased frequency of adverse events associated with ziconotide compared with patient treated with placebo. Patients exposed to ziconotide had a higher frequency of asthenia, abnormal gait, aphasia ataxia, confusion, dizziness, hallucinations, memory impairment, nystagmus, vertigo, hyperuricemia and urinary retention among adverse event reported by at least 2% of the patients in either treatment group. These adverse events were reported as having a statistically significant ($P < 0.05$, Fisher's Exact Test) increase in frequency among ziconotide patients compared with placebo patients. Statistical comparisons were not performed for every adverse event described when a small number of events were reported.

Additional analyses and explorations

The sponsor's analysis suggested that adverse events that might be related to ziconotide were concentrated in body systems classified as Nervous System, Digestive System, Body as a Whole and Metabolic and Nutritional system. This reviewer conducted an additional descriptive analysis on these body systems to more fully characterize possible related adverse effects of ziconotide that might not have been connected because of their infrequency the sponsor's segregation of adverse events into weaning/stabilization and treatment phases of the study. In the following analysis all data was abstracted from the sponsor's electronic adverse event tables and no distinction was made between phases of the study. The incidence of adverse events depicted below may differ slightly from the sponsor in cases (e.g. nausea) because some patients exhibited symptoms in more than one phase and were counted twice by the sponsor. Some adverse events that were not identified as occurring with a statistically significant difference in frequency between ziconotide and placebo treatment groups may appear more prominent in my description because adverse events having the same preferred name occurring in different phases were summed together.

Adverse events related to the nervous system that was more common with ziconotide included: abnormal gait, ataxia, confusion, difficulty concentrating, dizziness, dysesthesia, hypertonia, memory impairment, mental slowing, somnolence, tremor and withdrawal syndrome.

Table 7.1.5-2 Adverse Events of the Nervous System that Were More Common with Ziconotide than Placebo

	Number of AEs		Number of Patients Having AEs		Incidence	
	Ziconotide	Placebo	Ziconotide	Placebo	Ziconotide	Placebo
Abnormal Gait	25	2	18	2	16%	2%
Ataxia	20	2	19	2	17%	2%
Confusion	30	7	22	6	20%	6%
Difficulty Concentrating	6	1	5	1	4%	1%
Dizziness	93	16	56	15	50%	14%

Clinical Review
 Lex Schultheis, M.D., Ph.D.
 NDA 21,060
 Prialt (Ziconotide)

Dysesthesia	11	2	10	2	9%	2%
Hypertonia	25	13	18	10	16%	9%
Memory Impairment	16	2	14	2	13%	2%
Mental Slowing	5	1	3	1	3%	1%
Somnolence	37	28	30	23	27%	21%
Tremor	10	3	9	3	8%	3%
Withdrawal Syndrome	20	16	15	15	13%	14%
Total	298	93				

Data (includes reports from Weaning, Stabilization and Treatment phases) was abstracted by this reviewer from the sponsor's electronic table of adverse events.

Nausea and anorexia, and to a lesser extent vomiting, were also more common among patients treated with ziconotide than placebo.

Table 7.1.5-3 Adverse Events of the Digestive System Were More Common With Ziconotide than Placebo

	Number of AEs		Number of Patients Having AEs		Incidence Among All Patients	
	Ziconotide	Placebo	Ziconotide	Placebo	Ziconotide	Placebo
Nausea	93	56	63	45	56%	42%
Vomiting	32	24	26	21	23%	19%
Anorexia	18	10	16	8	14%	7%
Total	143	90				

Data (includes reports from Weaning, Stabilization and Treatment phases) was abstracted by this reviewer from the sponsor's electronic table of adverse events.

Table 7.1.5-4 Adverse Events of the Body as a Whole

	Number of AEs		Number of Patients Having AEs		Incidence Among All Patients	
	Ziconotide	Placebo	Ziconotide	Placebo	Ziconotide	Placebo
Accidental Injury	6	2	5	2	4%	2%
Asthenia	33	19	26	17	23%	16%
Chest Pain	13	3	9	3	8%	3%
Chills	17	14	15	10	13%	9%
Fever	10	7	9	5	8%	5%
Flu syndrome	6	1	5	1	4%	1%
Hormone Level Altered	4	1	4	1	4%	1%
Malaise	3	2	3	2	3%	2%
Pain	27	14	23	12	21%	11%

Data (includes reports from Weaning, Stabilization and Treatment phases) was abstracted by this reviewer from the sponsor's electronic table of adverse events.

Case report narratives of reported chest pain were reviewed and determined to be either musculoskeletal in origin or preceded actual administration of ziconotide.

Table 7.1.5-5 Adverse Events of the Metabolic and Nutritional System

	Number of AEs		Number of Patients Having AEs		Incidence Among All Patients	
	Ziconotide	Placebo	Ziconotide	Placebo	Ziconotide	Placebo
Creatine Kinase Increased	16	4	13	4	12%	4%
Creatinine Increased	2	1	2	1	2%	1%
Dehydration	5	3	5	3	4%	3%
Hyperlipidemia	6	5	6	5	5%	5%
Hyperuricemia	6	0	6	0	5%	0%

Data (includes reports from Weaning, Stabilization and Treatment phases) was abstracted by this reviewer from the sponsor's electronic table of adverse events.

- There were 10 reports of urine retention associated with ziconotide comprising an incidence of 8.9% compared to an incidence of 0% in the placebo treatment group.

Risk-Benefit Assessment Comparing Incidence of Adverse Events among Patients Stratified by Therapeutic Benefit.

As part of an overall strategy to assess risk associated with beneficial reduction of pain, the incidence of adverse events in the ITT population in ELN92045-301 was evaluated. While this analysis is performed on a subset of the entire safety population, Study 301 utilizes a dosing regimen that was demonstrated to be effective at reduced risk compared to rapid titration studies previously reviewed. Furthermore, the ITT population is considered because it represents a controlled subset of patients for whom an efficacy analysis can also be performed.

The incidence of serious adverse events is broken down by the degree of efficacy using the terminology introduced earlier according patients who were nonresponders, minimal responders and responders.

Table 7.1.5-6 Incidence of Serious Adverse Events Among the ITT Population

	Placebo (N=108)	Ziconotide (N=112)
Nonresponders	8/58 (14%)	6/52 (12%)
Minimum Responders	4/37 (11%)	3/43 (7%)
Responders	0/13 (0%)	4/17 (24%)

Data was abstracted by this reviewer from the electronic adverse event tables of the sponsor and a comprehensive table of ITT patients sorted by VASPI using BOCF provided by Dr. Buenconsejo of the Biometric team.

These findings suggest an increasing trend in the incidence of serious adverse events with increasing therapeutic effect of ziconotide. The incidence of serious adverse events decreased among patients with a similar reduction in VASPI while taking placebo.

Clinical Review
 Lex Schultheis, M.D., Ph.D.
 NDA 21,060
 Prialt (Ziconotide)

This review also examined the relationship of improvement in VASPI (Table 6.1.4-4, 6.1.4-6) to treatment in comparison to the concomitant opiate dose because opiates also have the potential to decrease VASPI and at the same time, increase adverse events with increasing effect as observed in Table 7.1.5-6. Although both the weekly dose and the cumulative opiate dose were higher for patients treated with ziconotide than for patients treated with placebo; the trend among ziconotide treated patients was toward a reduction in opiate administration, while a similar trend was observed among patients treated with placebo (Table 6.1.4-1) was less apparent. This suggests that the increase in serious adverse events observed with increasing treatment effect of ziconotide may not be simply attributed to an associated increase in concomitant opiate administration.

A similar analysis of the severe adverse events among the ITT population of Study 301 was performed.

Table 7.1.5-7 Incidence of Severe Adverse Events Among the ITT Population

	Placebo (N=108)	Ziconotide (N=112)
Nonresponders	18/58 (31%)	21/52 (40%)
Minimum Responders	9/37 (24%)	20/43 (47%)
Responders	2/13 (15%)	6/17 (35%)

Data was abstracted by this reviewer from the electronic adverse event tables of the sponsor and a comprehensive table of ITT patients sorted by VASPI using BOCF provided by Dr. Buenconsejo of the Biometric team.

The incidence of severe adverse events did not appear to increase with increasing therapeutic effect of ziconotide. In the placebo treatment group, the incidence of severe adverse events declined with VASPI scores, perhaps indicating a relationship between patient disease and the severity of reported adverse events. As the pain experienced by placebo-treated patients improved, other symptoms became less troublesome. The ziconotide treatment group did not clearly exhibit a similar trend.

Table 7.1.5-8 Duration and Dose at Onset of Selected Adverse Events

		Median Day	Median Duration	Median Dose at Onset	Cumulative
Adverse Event of	Incidence	at Onset	at Offset	(mcg/hr)	Dose at Onset
Particular Interest	n (%)	(range)	(range)	(range) ^a	(mcg) (range) ^b
Abnormal Gait (including Ataxia)					
Ziconotide (N=112)	35 (31.2%)	4.5 (0-24)	5 (1-43)	0.20 (0.1-0.4)	12.0 (0-186)
Placebo (N=108)	4 (3.7%)	8.5 (1-13)	5.5 (5-6)	0.15 (0.1-0.3)	26.4 (2-48)

Clinical Review
 Lex Schultheis, M.D., Ph.D.
 NDA 21,060
 Prialt (Ziconotide)

Abnormal Vision (Including Amblyopia)					
Ziconotide (N=112)	13 (11.6%)	8.0 (0-30)	5.5 (1-60)	0.20 (0.1-0.6)	19.2 (0-206)
Placebo (N=1 08)	4 (3.7%)	15.0 (6-38)	6 (2-15)	0.33 (0.2-0.6)	54.0 (18-383)
Aphasia or Speech Disorder					
Ziconotide (N=112)	19 (17.9%)	16.0 (4-24)	13 (3-43)	0.30 (0.1-0.6)	81.6 (12-151)
Placebo (N=1 08)	3 (2.8%)	7.0 (2-26)	1.5 (1-2)	0.15 (0.2-0.3)	22.8 (5-109)
Asthenia (including Myasthenia)					
Ziconotide (N=112)	29 (25.9%)	3.0 (0-30)	4 (1-35)	0.15 (0.1-0.6)	9.6 (0-178)
Placebo (N=1 08)	18 (16.6%)	5.5 (0-32)	7 (4-37)	0.15 (0.1-0.6)	16.3 (0-304)
Confusion					
Ziconotide (N=112)	22 (19.6%)	9.5 (0-24)	6 (1-24)	0.28 (0.1-0.6)	40.8 (0-206)
Placebo (N=1 08)	5 (5.5%)	13.0 (4-32)	2.5 (1-6)	0.28 (0.1-0.6)	64.8 (10-304)
Dizziness					
Ziconotide (N=112)	56 (50%)	3.0 (0-24)	6 (1-33)	0.15 (0.1-0.6)	7.2 (0-151)
Placebo (N=1 08)	15 (13.9%)	4.0 (0-26)	1 (1-9)	0.14 (0.1-0.6)	9.9 (0-154)
Hypotension (including Postural Hypotension)					
Ziconotide (N=112)	5 (4.5%)	2.5 (0-16)	10 (1-36)	0.15 (0.1-0.5)	6.0 (0-84)
Placebo (N=1 08)	1 (0.9%)	5.0 (5-5)	4	0.10 (0.1-0.1)	7.2 (7-7)
Memory Impairment or Amnesia					
Ziconotide (N=112)	17 (15.2%)	7.5 (2-29)	6 (2-60)	0.16 (0.1-0.6)	23.6 (0-268)
Placebo (N=108)	2 (1.8%)	22.0 (22-22)	Unknown	0.56 (0.6-0.6)	174.8 (175-175)
Nausea (including Vomiting and Nausea and Vomiting)					
Ziconotide (N=112)	66 (58.9%)	6.0 (1-342)	5 (1-74)	0.13 (0.1-0.4)	9.6 (0-227)
Placebo (N=1 08)	49 (45.4%)	4 1-30)	4 (1-55)	0.15 (0.1-0.6)	16.8 (0-214)
Nystagmus					
Ziconotide (N=112)	9 (8.0%)	8.0 (4-16)	10.5 (3-43)	0.16 (0.1-0.7)	19.2 (5-14)
Placebo (N=1 08)	0 (0.0%)	0 (0.0)	0	0 (0.0)	0 (0.0)
Somnolence					
Ziconotide (N=112)	30 (26.8%)	4.0 (0-24)	6 (1-37)	0.11 (0.1-0.5)	9.6(0-132)
Placebo (N=1 08)	23 (21.3%)	6.0 (0-32)	5 (2-42)	0.20 (0.1-0.6)	21.0 (0-304)

Clinical Review
 Lex Schultheis, M.D., Ph.D.
 NDA 21,060
 Prialt (Ziconotide)

Thinking Abnormal (Including Difficulty Concentrating and Mental Slowing)					
Ziconotide (N=112)	10 (8.9 %)	4.0 (0-18)	6 (3-23)	0.12 (0.1-0.5)	9.6 (0-122)
Placebo (N=1 08)	3 (2.7%)	10.0 (10-10)	3.5 (1-6)	0.30 (0.3-0.3)	45.6 (46-46)
Urinary Retention					
Ziconotide (N=112)	10 (8.9%)	7.5 (1-24)	10 (1-27)	0.15 (0.0-0.6)	16.8 (0-202)
Placebo (N=1 08)	0 (0.0%)	0 (0.0)	0	0 (0.0)	0 (0.0)

Data was abstracted from sponsor's electronic tables for Adverse Events with corrections of sponsor's Table 33 from I.8 V.002 P.195-196. Calculations were confirmed by Dr. Buenconsejo, Biometrics Reviewer.

7.1.6 Less Common Adverse Events

Less common adverse events that were not represented in the placebo treatment group included symptoms related to the nervous system (number of reported AEs in parenthesis): Abnormal oral sensations(1), akathisia(1), amnesia(5), convulsion(1), dysarthria(2), hallucinations(9), hyperesthesia(3), nystagmus(11), paralysis(2), paranoid reaction(1), peripheral neuritis(2), sleep disorder other than somnolence(1), twitching(5), and vertigo(9). These adverse events constituted 11% of all adverse events reported with ziconotide and were observed in 34 patients, 30% of population treated with ziconotide in Study 301.

Less common adverse events related to the digestive system that occurred with ziconotide, but not with placebo included (number of reported AEs in parenthesis): colitis (1), esophagitis (2), fecal incontinence (1), glossitis (2), hepatitis (1), intestinal obstruction (1) and abnormal liver function tests (1) observed in 9 patients, 8% of the ziconotide treatment group in Study 301.

Under the system classification Body as a Whole, adverse events that were reported in association with ziconotide, but not with placebo included: catheter site pain(1), cellulitis(1), face edema(1), neck pain(4), overdose(2), pump site pain(2), and suicide attempt(1).

Within the category termed Metabolic and Nutritional System, adverse events associated with ziconotide, but not placebo included: Bun increased(1), Healing abnormal(1), Hyperuricemia(6), Liver fatty deposit(1), SGOT increased(1), and weight gain (1).

Urinary retention (10) was reported exclusively with ziconotide in Study 301.

7.1.7 Laboratory Findings

7.1.7.1 Overview of laboratory testing in the development program

Preclinical studies did not reveal significant laboratory abnormalities with central neuraxial administration of ziconotide.

Earlier clinical studies revealed few abnormalities in laboratory testing. The previously submitted phase 3 trial reports noted elevations in creatine kinase in a small number of patients.

Study 301 and the earlier submitted study reports from Study 95-001 and 96-002 documented laboratory findings in blood chemistry and hematology measured at screening, baseline and termination visits.

7.1.7.2 Selection of studies and analyses for drug-control comparisons of laboratory values

The laboratory data from Study 301 was used for the focus of this review because the back-pain patients in this study may have fewer metabolic abnormalities than cancer or AIDS patients that were previously studied. The duration of blinded treatment was also longer in Study 301 than in earlier work, thereby affording a better opportunity to observe abnormalities caused by the study drug. Earlier review by the agency also documents the findings from Studies 95-001 and Study 96-002.

7.1.7.3 Standard analyses and explorations of laboratory data

7.1.7.3.1 Analyses focused on measures of central tendency

The sponsor conducted an analysis of differences between ziconotide and placebo treated patients based upon mean and median values measured in standard hematological and chemistry blood tests (including LFTs and creatinine). No clinically significant differences were noted.

7.1.7.3.2 Analyses focused on outliers or shifts from normal to abnormal

A histogram constructed from all measured values is used in this review to illustrate the overall distribution of the data. The laboratory value is found along the abscissa and matched with the number of times the value was reported along the ordinate. This display is used to visually identify skewness of data sample and illustrate outlier values as points displaced from the main body of data along the abscissa.

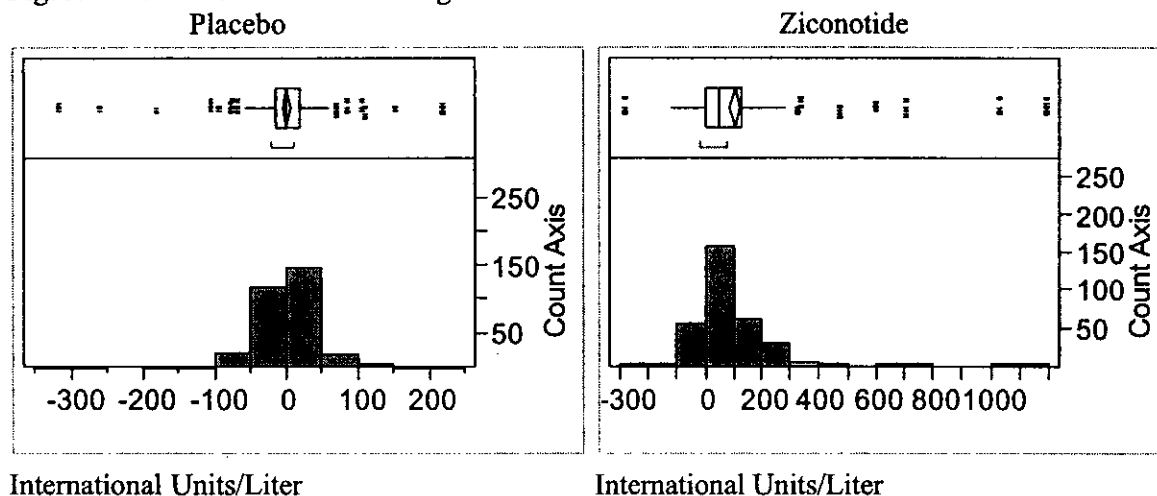
Measures of central tendency and variation are displayed for comparison by the schematic just above the distribution histogram. The ends of the box depict the limits of the 25th and 75th quartiles containing 50% of the data. The line across the middle of the box identifies the median and the center of the diamond identifies the mean. The horizontal points of the diamond indicate the 95% confidence interval of the mean. The lines extending horizontally from the ends of the box identify the data values from the upper and lower quartile plus 1.5 times

Clinical Review
 Lex Schultheis, M.D., Ph.D.
 NDA 21,060
 Prialt (Ziconotide)

the interquartile range. The bracket along the edge of the box identifies the densest 50% of the observations.

A small number of patients treated with ziconotide, but not placebo, exhibited clinically significant changes in measured serum creatine kinase.

Figure 7.1.7-1 Distribution of Change in Creatine Kinase



7.1.7.3.3 Marked outliers and dropouts for laboratory abnormalities

Among the outlier patients with marked elevations in creatine kinase, EKG abnormalities were investigated for signs of cardiac ischemic disease. In particular the presence of Q-waves, T-wave inversion, axis shift, bundle branch block or interventricular conduction delay was considered to be a potential sign of cardiac ischemic disease. Table 7.1.7-2 illustrates that no patient developed Q-waves and other signs of coronary disease were inconsistently noted. With the magnitude of release of creatine kinase (CK) seen in patient number 301000007000007, significant signs of congestive failed might be expected if the source of creatine kinase was the heart. Similarly, the affected patients did not have cerebral infarction that could account for the observed CK elevation. The source of CK elevation is likely to be skeletal muscle even though new onset severe muscle weakness was not highlighted symptom in the study report. Many of the patients reported muscle pain, however the pain often resolved without normalization of the creatine kinase level.

Creatine kinase from earlier studies was fractionated in cases of elevation and found to be in the skeletal muscle fraction.

Table 7.1.7-2 Patients with Large Changes in Creatine Kinase Associated With Ziconotide

Case_ID	Baseline CK	Treatment CK	EKG Q/T/A/B/D	Age	Gender
301000007000007	621	1815	N/N/N/N/N	47	Male
301000016000002	443	661	N/N/Y/N/N	45	Male
301000035000006	635	1672	N/N/Y/Y/Y	44	Male

Clinical Review
Lex Schultheis, M.D., Ph.D.
NDA 21,060
Prialt (Ziconotide)

301000041000009	106	817	N/Y/Y/N/Y	40	Male
301000041000010	98	707	N/N/Y/Y/Y	46	Male

Data was abstracted by this reviewer from sponsor's electronic tables for laboratory values and ECG.

EKG Q/T/A/B/D Y refers to the presence and N the absence of : Q waves (Q), T-wave inversion (T), Axis Shift(A), Bundle branch block or interventricular conduction delay (B), and Dysrhythmias (D)

7.1.7.4 Additional analyses and explorations

Minor changes in platelet concentration and uric acid level were also noted in some patients, however they are believed to be of no clinical consequence.

7.1.8 Vital Signs

7.1.8.1 Overview of vital signs testing in the development program

Preclinical and early clinical testing was notable for hypotension resulting from intravenous administration of ziconotide.

In previously submitted study reports of phase 3 trials 95-001 and 96-002, hemodynamic orthostasis was noted, especially with rapid titration and high doses of ziconotide. This effect appeared to be less frequent and severe in a small number of patients who were treated with more gradual titration and lower maximum dosing.

Vital sign testing was performed in Study 301 at Screening, Baseline, at least weekly during the treatment phase and at Termination. Special attention was given to assessment for signs of orthostasis because it had been associated with rapid titration to high doses in earlier studies.

7.1.8.2 Selection of studies and analyses for overall drug-control comparisons

Study 301 was the primary focus of this review because the slow-titration schedule was expected to reduce risks of earlier regimens. The blinded treatment interval was also extended compared to earlier trials so that the effect of a longer cumulative exposure on vital signs could be evaluated.

7.1.8.3 Standard analyses and explorations of vital signs data

7.1.8.3.1 Analyses focused on measures of central tendencies

The sponsor presented changes in mean and median heart rate, body temperature, and blood pressure associated with ziconotide and placebo. There were no clinically meaningful differences.

7.1.8.3.2 Analyses focused on outliers or shifts from normal to abnormal

As part of this review, a histogram constructed from all measured values was used to illustrate the overall distribution of the data. The laboratory value is found along the abscissa and matched with the number of times the value was reported along the ordinate. This display is used to visually identify skewness of data sample and illustrate outlier values as points displaced from the main body of data along the abscissa.

Measures of central tendency and variation are displayed for comparison by the schematic just above the distribution histogram. The ends of the box depict the limits of the 25th and 75th quartiles. The line across the middle of the box identifies the median and the center of the diamond identifies the mean. The horizontal points of the diamond indicate the 95% confidence interval of the mean. The lines extending horizontally from the ends of the box identify the data values from the upper and lower quartile plus 1.5 times the interquartile range. The bracket along the edge of the box identifies the densest 50% of the observations.

There were no clinically meaningful differences between ziconotide and placebo-treated patients.

7.1.8-1 Figure Distribution of Changes in Heart Rate

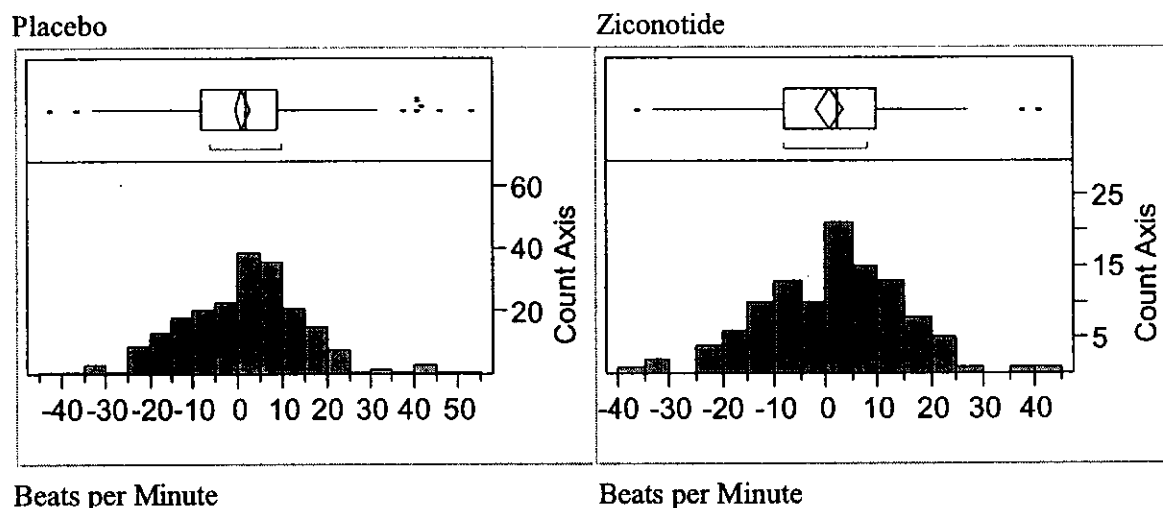


Figure 7.1.8-2 Distribution of Changes in Systolic Blood Pressure

Placebo

Ziconotide

Clinical Review
 Lex Schultheis, M.D., Ph.D.
 NDA 21,060
 Prialt (Ziconotide)

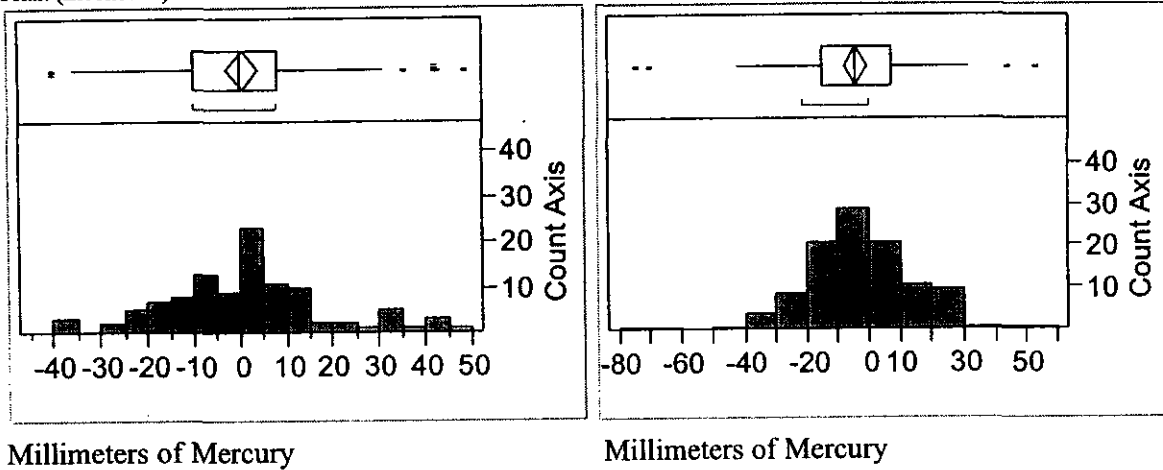


Figure 7.1.8-3 Distribution of Changes in Diastolic Blood Pressure

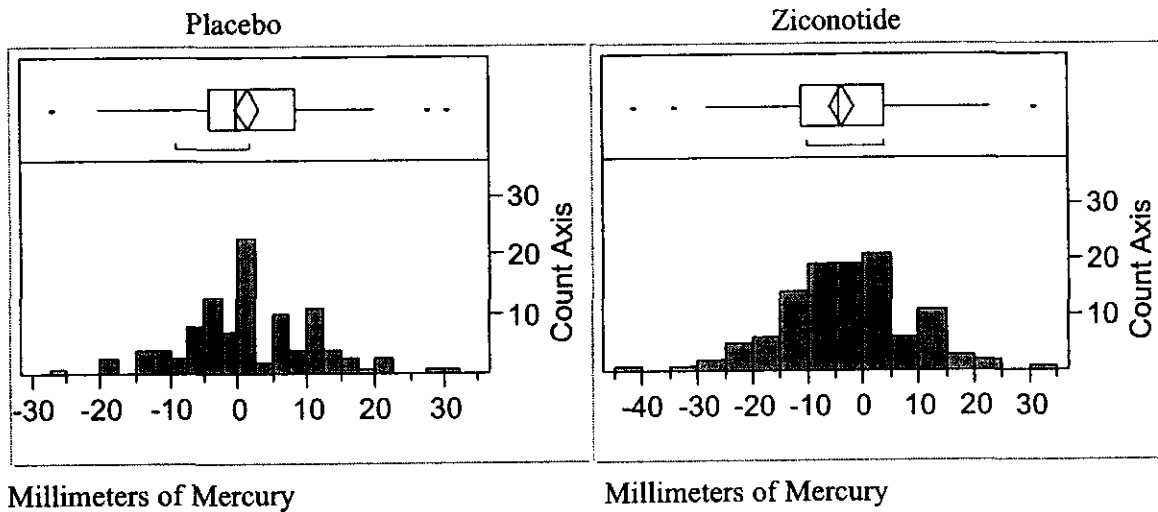
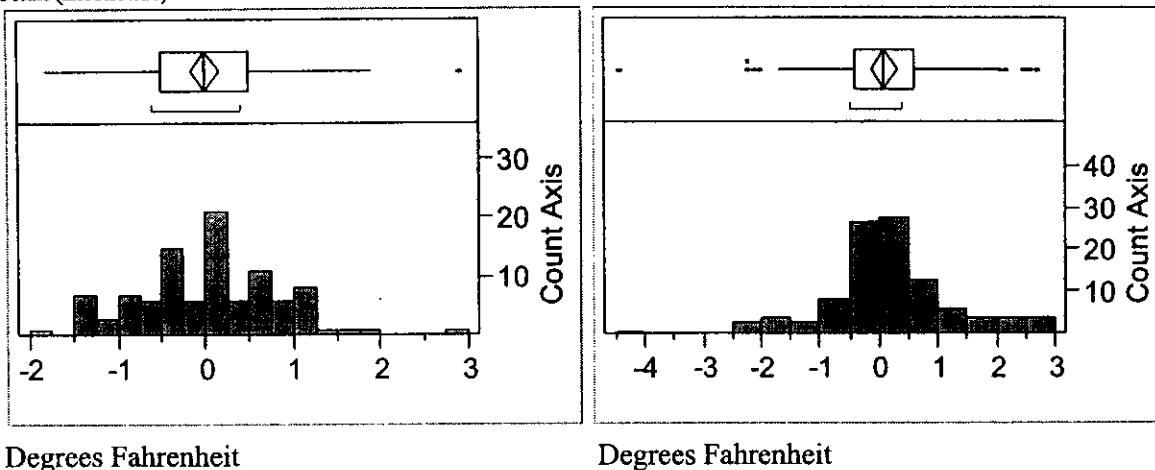


Figure 7.1.8-4 Distribution of Changes in Body Temperature

Placebo

Ziconotide



7.1.8.3.3 Marked outliers and dropouts for vital sign abnormalities

For heart rate, diastolic blood pressure, systolic blood pressure and body temperature the data distribution showed little skewness (mean approximately equal to median). There were also no evident patient outliers, individuals with values much higher or lower than expected when compared to the distribution of data seen in the patients treated with placebo.

7.1.8.4 Additional analyses and explorations

The lack of skewness and outliers in measured changes in blood pressure and heart rate suggest that changes were not clinically noteworthy in Study 301. Vitals signs were only assessed during the relatively infrequent visits to the investigator and not with postural changes so it was not possible to capture signs of orthostasis when it is most exaggerated, such as upon arising from supine to standing upon awakening.

7.1.9 Electrocardiograms (ECGs)

7.1.9.1 Overview of ECG testing in the development program, including brief review of preclinical results

Preclinical studies of ziconotide up to a concentration of 15 ng/mL did not block hERG [rapidly repolarizing potassium current (I_{KR}), slowly repolarizing cardiac potassium current (I_{KS}), and transient outward potassium current (I_{TO})] channels.

Examination of line listings of ECG data for Study 98-022 by Dr. Sharon Hertz in an earlier review cycle revealed descriptors of QT/QTc prolongation for 58 subjects.

An ECG analysis was performed for Study 301 including baseline and treatment measurements using 12 leads. This protocol was not a thorough QT study, incorporating sequential measurements following dose adjustment and sophisticated methods of QT correction

Clinical Review
Lex Schultheis, M.D., Ph.D.
NDA 21,060
Prialt (Ziconotide)

for heart rate. It appears from the reviewer's back calculation of QTc assessments recorded in the CRFs that method of correction for heart rate was not standardized.

7.1.9.2 Selection of studies and analyses for overall drug-control comparisons

Study 301 was used for determination of QT changes associated with ziconotide because of better control over dosing and more systematic collection of ECG in every patient studied than in earlier studies.

7.1.9.3 Standard analyses and explorations of ECG data

7.1.9.3.1 Analyses focused on measures of central tendency

The sponsor presented mean and median QT and QTc intervals with heart rate, PR and QRS waveform ECG intervals collected during assessment at screening, baseline and termination visits. The reported changes in QT and QTc were similar for patients treated with ziconotide and for patients treated with placebo.

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Table 7.1.9-1 Measures of Central Tendency of QT in Patients treated with Ziconotide vs. Placebo

Parameter	Ziconotide			Placebo		
	Screening (N=107)	Baseline (N=107)	Study Termination ^b (N=107)	Screening Baseline ^a (N=106) (N=106)	Study Termination (N=106)	
QT Interval (milliseconds)						
N	105	105	105	106	106	106
Mean (SD)	395.8 (30.91)	395.0 (36.75)	389.4 (30.28)	393.6 (36.18)	384.0 (39.10)	384.1
Median (Range)	400.0 (320-480)	400.0 (300-500)	400.0 (320-480)	400.0 (300-480)	380.0 (320-480)	400.0 (320 - 480)
Change from Baseline						
N			105		106	
Mean (SD)			-5.7 (32.83)		0.1 (31.79)	
Median (Range)			0.0 (-140-80)		0.0 (-80-80)	

Note: Statistics and abnormalities were calculated only for patients who had measures at screening, baseline, and study termination. ^a Baseline was the last non-missing measure before the first dose in Study 301.

^b Termination was the last non-missing measure taken in Study 301.

Data were abstracted from sponsor's Study Report I.8 V.54 P. 120.

Clinical Review
 Lex Schultheis, M.D., Ph.D.
 NDA 21,060
 Prialt (Ziconotide)

Table 7.1.9-2 Measures of Central Tendency of QTc in Patients treated with Ziconotide vs. Placebo

Parameter	Ziconotide			Placebo		
	Screening (N=107)	Baseline ^a (N=107)	Study Termination (N=107)	Screening (N=106)	Baseline ^a (N=106)	Study Termination (N=106)
QTc Interval (milliseconds)						
N	105	105	105	106	106	106
Mean (SD)	423.6 (30.43)	428.1 (30.89)	428.4 (28.44)	420.0 (30.95)	426.4 (27.00)	422.9 (27.77)
Median (Range)	425.0 (351 -514)	425.0 (363-511)	426.0 (360 - 500)	416.0 (332 - 500)	426.0 (360-518)	425.0 (358-503)
Change from Baseline						
N			105			106
Mean (SD)			0.3 (28.92)			-3.5 (29.12)
Median (Range)			3.0 (-90 - 77)			-2.5 (-86 - 74)

Note: Statistics and abnormalities were calculated only for patients who had measures at screening, baseline, and study termination. Baseline was the last non-missing measure before the first dose in Study 301.

^bTermination was the last non-missing measure taken in Study 301.

Data were abstracted from sponsor's Study Report I.8 V.54 P. 121.

Analyses focused on outliers or shifts from normal to abnormal

A histogram constructed from all measured values was used to illustrate the overall distribution of the data. The laboratory value is found along the abscissa and matched with the number of times the value was reported along the ordinate. This display is used to visually identify skewness of data sample and illustrate outlier values as points displaced from the main body of data along the abscissa.

Measures of central tendency and variation are displayed for comparison by the schematic just above the distribution histogram. The ends of the box depict the limits of the 25th and 75th quartiles. The line across the middle of the box identifies the median and the center of the diamond identifies the mean. The horizontal points of the diamond indicate the 95% confidence interval of the mean. The lines extending horizontally from the ends of the box identify the data values from the upper and lower quartile plus 1.5 times the interquartile range. The bracket along the edge of the box identifies the densest 50% of the observations.

Figure 7.1.9-1 Distribution of Absolute QT Changes from Baseline

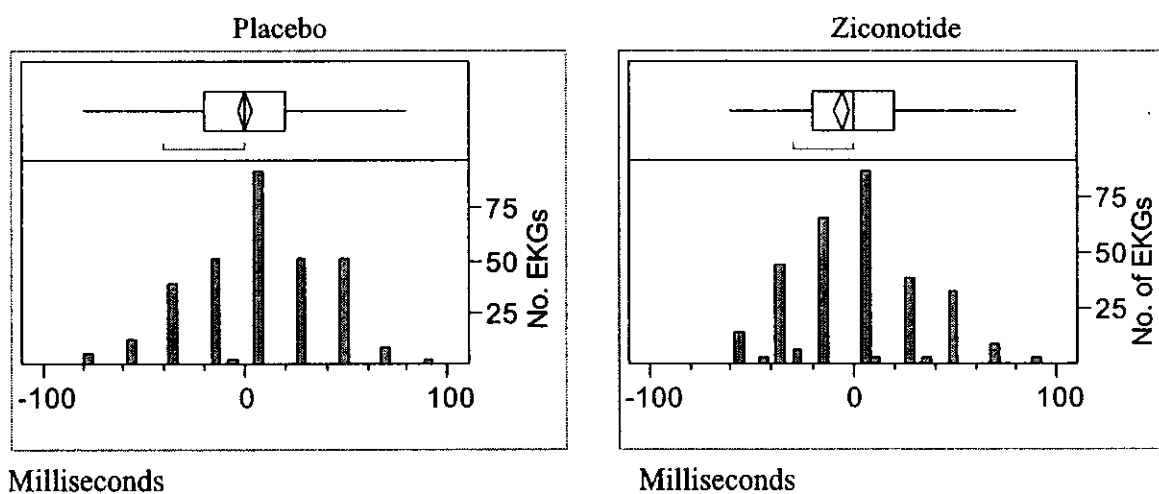
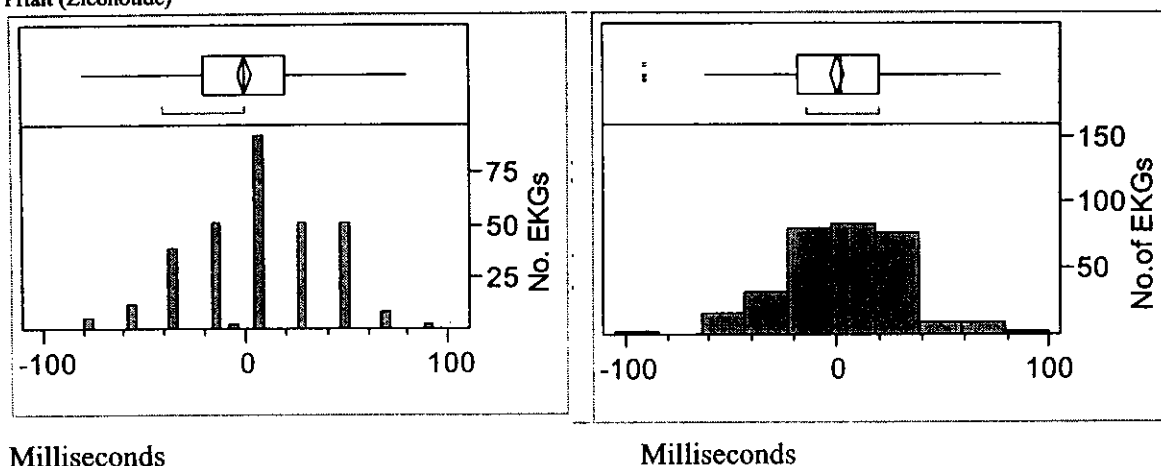


Figure 7.1.9-2 Distribution of QTc Changes from Baseline

Placebo

Ziconotide



There was no obvious outlier group among ziconotide-treated patients with prolonged QT or QTc as measured. Chronic administration of ziconotide did not appear to prolong QTc in this population.

As part of the review, the QT correction was checked on CRFs were sparsely selected from the electronic data set from patients with serious adverse events. The reported data suggested that correction technique used was variable. Some QT intervals appeared to have been corrected by Bazett's methods, others by Fredericia's method and others by unidentifiable techniques. There was no positive control for QT prolongation. Despite this limitation, both mean uncorrected QT measurements and "corrected" QT intervals did not appear to be prolonged, nor was there a suggestion of prolongation among the outlier data.

7.1.9.3.3 Marked outliers and dropouts for ECG abnormalities

No patients were discontinued from Study 301 for EKG abnormalities.

7.1.9.4 Additional analyses and explorations of ECG data

No additional studies were performed.

7.1.10 Immunogenicity

No studies were performed.

7.1.11 Human Carcinogenicity

No studies were performed.

7.1.12 Special Safety Studies

Evaluation of Cognition Using the Mini Mental Examination

Clinical Review
 Lex Schultheis, M.D., Ph.D.
 NDA 21,060
 Prialt (Ziconotide)

A mini mental examination was performed at baseline and termination to assess the impact of ziconotide therapy on cognition. At baseline, the mean and median total scores were comparable between treatment groups. Mental function as measured by the MMSE was normal for the great majority of patients, although there were a number of patients with abnormally low scores at baseline.

At termination, the median values of the total score were again comparable between the treatment groups, and the mean change from baseline was -0.4 for ziconotide and -0.1 for placebo. There was no statistically significant difference between the treatment groups in the change from baseline to termination.

Table 7.1.12-1 Mini Mental Status Evaluation at Baseline and Termination Safety Population

	Ziconotide (N = 112)	Placebo (N = 108)
Total Score at Baseline ^a		
N	112	108
Mean (SO)	29.0 (1.65)	29.2 (1.43)
Median (Range)	30.0 (21 - 30)	30.0 (24 - 30)
Total Score at Termination ^a		
N	107	107
Mean (SO)	28.6 (2.75)	29.1 (1.80)
Median (Range)	30.0 (7 - 30)	30.0 (16 - 30)
Change in Total Score from Baseline at Termination ^{a,b}		
N	107	107
Mean (SO)	-0.4 (2.54)	-0.1 (1.44)
Median (Range)	0.0 (-21 - 4)	0.0 (-8 - 3)
Level of Consciousness Along a Continuum at Baseline ^c		
N	110	108
Mean (SO)	1.1 (0.28)	1.0 (0.19)
Median (Range)	1.0 (1 - 3)	1.0 (1 - 2)
Level of Consciousness Along a Continuum at Termination ^c		
N	107	107
Mean (SO)	1.1 (0.41)	1.0(0.21)
Median (Range)	1.0(1-3)	1.0 (1 - 2)
Change in level of Consciousness Along a Continuum from Baseline at Termination ^{b,c}		
N	105	107
Mean (SO)	0.1 (0.37)	0.0 (0.22)
Median (Range)	0.0(-1-1)	0.0(-1-1)

Data Source is sponsor's Study Report ELN92045-301 I. 8 V. 002 P. 247

The maximum possible total score was 32. A "Total Score" (32 maximum) is sum of scores from these individual items: orientation on date (max. score of 5), orientation on place (max. score of 5), registration (max. score of 3), attention and calculation (max. score of 5), recall (max. score of 5), and language (max. score of 9). b Change = (Baseline score - score at current visit).Improvement was indicated by an increase from baseline to termination.

c Level of consciousness along a continuum is scored as follows: 1 = alert, 2 = drowsy,

Clinical Review
Lex Schultheis, M.D., Ph.D.
NDA 21,060
Prialt (Ziconotide)

3 = stupor, 4 = coma. The level of consciousness score is not included in the total MMSE score.

There were several patients with substantial decrements in both treatment groups, as indicated by the ranges. A total of six patients had decrements in MMSE total score from baseline to termination of greater than 3 points. Four of these patients received ziconotide and two received placebo.

One patient (site 20, patient ID 12) in the ziconotide group had a decrement of -21. This patient had a screening MMSE total score of 26, a baseline total score of 28, and a termination total score of 7. At the termination MMSE evaluation, the patient had ongoing AEs of confusion, abnormal gait, aphasia, and asthenia.

Two patients in the ziconotide group had a decrease in MMSE of 6 points. Ongoing adverse events for one patient (site 5, patient ID 1) at the study termination MMSE included anxiety, anorexia, depression, mental slowing, nausea, speech disorder, and memory impairment.

The other patient (site 40, patient ID 3) in the ziconotide group had adverse events that included nausea, confusion, ataxia, accidental injury, incoordination, and aphasia.

Patient 40/6 in the ziconotide group had a decrease of 4 points. There were no ongoing adverse events ongoing at the time of final MMSE evaluation.

In the placebo group, one patient (site 32, patient ID 10) had a decrease of 6 points but no there were no ongoing adverse events. The other patient (site 41, patient ID 13) in the placebo group had a decrease of 8 points with adverse events that included abdominal pain, constipation, and insomnia.

Evaluation of Depression Using the Hamilton Depression Scale

The HAM-D is a questionnaire used to assess the patient's feelings with regard to the following items: depressed mood, feelings of guilt, suicide, insomnia, work and activities, retardation, agitation, anxiety, somatic symptoms, genital symptoms, hypochondriasis, loss of weight, and insight. The score ranges from 0 (least depressed) to 52 (most depressed). Scores of 10-13 are associated with mild depression, scores of 14-17 are mild to moderate, and scores >17 are indicative of severe depression.

At baseline, the median scores for the ziconotide and placebo groups were 13.0 and 11.0 respectively. The wide range of baseline values with maximum values of 32 and 30 indicates that some patients in both treatment groups were severely depressed and that, on average, the patient population was mildly depressed.

At termination, there was a slight improvement in the ziconotide group and a slight worsening in the placebo group, but this difference was not statistically significant ($p=0.3$, two-sample t-test). Again, the range of scores was wide.

The HAM-D results are consistent with other assessments of depression during the study. In the 46-Symptom Checklist at screening, 68% of patients in the safety population reported depression during the few months prior to study entry. In the screening medical history, 68% of patients gave a history of depression. A total of 62% of patients were taking antidepressants during the pretreatment period. However, depression was reported as an adverse event for only 3% (5/177) of patients during the weaning period, and for 3% (3/112) of ziconotide patients and 5% (5/108) of placebo patients during the treatment period.

Therefore, the Study 301 patient population had a high prevalence of depression by a variety of measures, and ziconotide did not appear to worsen depression over the three-week study period.

Table 7.1.12-2. Hamilton Rating Scale - "Total Score" and "Depressed Mood" At Baseline and Termination - Safety Population

	Ziconotide (N=112)	Placebo (N = 108)
Total Score at Baseline a		
N	112	108
Mean (SO)	13.3 (6.74)	11.5 (6.20)
Median (Range)	13.0 (0 - 32)	11.0 (0 - 30)
Total Score at Termination a		
N	106	106
Mean (SO)	12.8 (7.26)	12.0(6.13)
Median (Range)	13.0 (0 - 31)	11.0 (2 - 27)
Change in Total Score from Baseline at Termination b		
N	106	106
Mean (SO)	-0.3 (5.42)	0.4 (4.24)
Median (Range)	0.0 (-14 -14)	1.0(-10-11)
95% CI of Mean	-1.4 - 0.7	-0.4 - 1.2
Depressed Mood at Baseline		
Absent	35 (31.3%)	39(36.1%)
Indicated only on questioning	42 (37.5%)	41 (38.0%)
Spontaneously reported verbally	18(16.1%)	17 (15.7%)
Communicates non-verbally	15 (13.4%)	11 (10.2%)
Reports Virtually only	2 (1.8%)	0

Data Source is sponsor's Study Report ELN92045-301 I. 8 V. 002 P. 249

a "Total Score" is sum of scores from seventeen individual items: depressive mood (0-4), feelings of guilt (0-4), suicide (0-4), insomnia early (0-2), insomnia middle (0-2), insomnia late (0-2), work and activities (0-4), retardation (0-4), agitation (0-2), anxiety-psychic (0-4), anxiety-somatic (0-4), somatic symptom (GI) (0-2), somatic symptoms (general) (0-2), genital symptoms (0-2), hypochondriasis (0-4), loss of weight (0-2), and insight (0-4).

b Change = (Baseline score - score at current visit). Therefore, a positive change from baseline to termination indicated improvement.

7.1.13 Withdrawal Phenomena and/or Abuse Potential

There is no abuse potential for ziconotide because it is administered intrathecally by an indwelling pump programmed by a physician to deliver the prescribed dose.

Withdrawal phenomena were not reported following discontinuation of ziconotide.

7.1.14 Human Reproduction and Pregnancy Data

No data were developed to assess the impact on human reproduction in patients treated with ziconotide. Pregnancy was an exclusion criterion for clinical trials.

7.1.15 Assessment of Effect on Growth

Preclinical studies indicated that ziconotide is toxic to the fetus, but at doses several orders of magnitude above doses used in clinical practice. Ossification of the pelvis was delayed in rats, but was eventually completed resulting in normal bone.

No data was developed to assess the effect of ziconotide on human growth and development because clinical trials were restricted to mature adults.

7.1.16 Overdose Experience

In Study 301, the maximum allowed dose was not received by any patient. Nor was the allowed rate of titration exceeded. In the strict sense, no overdoses occurred during Study 301.

While no true overdoses occurred during this trial, titration of the infusion downward did occur during the treatment phase numerous times. Titration of the infusion downward may be a subtle indicator that the risk exceeded the benefit to an individual patient because the maximum intended effect of the drug was complete relief of pain. A likely rationale for a prescribed reduction in rate of study drug administration in an individual patient is that the degree of pain relief was not of as much individual clinical value as amelioration of undesired effects potentially related to the drug. Other explanations of individualized downward dose titration are also possible and precluded analysis of downward dose titration because documentation of the investigators rationale behind individual dose adjustments was not presented.

7.1.17 Postmarketing Experience

Ziconotide has not been marketed.

7.2 Adequacy of Patient Exposure and Safety Assessments

A principal concern with the previous NDA submission was that rapid dose titration was unsafe and that there were too few patients studied at slower titration rates to make an assessment of efficacy when slow titration was used. The ITT population of 112 patients exposed to slow titration of ziconotide in Study 301 was sufficient to evaluate the safety and efficacy of this dosing regimen in chronic pain patients. The exposed patient population in Study 301 is expected to be representative of adult patients with severe chronic pain based upon their entry requirements for high VASPI score at baseline and duration and mechanism of chronic pain. The duration of exposure of patients treated with ziconotide in Study 301 was extended to 14 months in the open label Study 352 thereby enabling an assessment of the risks and benefits of long-term ziconotide after slow titration.

Study 301 is supported by over 1200 patients that have been exposed to ziconotide with various dosing regimens. This database was sufficient to characterize the type of adverse events

Clinical Review
Lex Schultheis, M.D., Ph.D.
NDA 21,060
Prialt (Ziconotide)

expected in the general population. Efficacy findings in earlier studies may be evaluated for general supportive evidence of pain relief with ziconotide.

7.2.1 Description of Primary Clinical Data Sources (Populations Exposed and Extent of Exposure) Used to Evaluate Safety

7.2.1.1 Study type and design/patient enumeration

The primary source of clinical data is an adequate and well-controlled clinical trial (ELN92045-301) conducted with a double-blinded, randomized parallel group design in 112 patients treated with ziconotide and 108 patients treated placebo.

7.2.1.2 Demographics

The fraction of men and women was also similar in both treatment arms of Study 301. There were 53 men (47%) and 59 women (53%) in the group treated with ziconotide. The placebo arm consisted of 55 men (51%) and 53 women (49%). Study 301 has a sufficient number of men and women to determine whether there are gender differences to ziconotide treatment.

Racial diversity of patients in Study 301 patients was very limited. Of 220 evaluable patients, 107 (96%) in the ziconotide group and 99 patients (92%) in the placebo group identified themselves as Caucasian. This study is insufficiently diverse to identify racial differences associated with ziconotide treatment, however there are no data to support that are expected racial differences in symptoms or response to treatment.

The mean age in the ziconotide treatment arm was 53 years and the mean duration of pain was 14 years. In the placebo group the mean age was 55 years and mean duration of pain was 15 years. Twenty patients (18%) in the ziconotide group and 22 patients (20%) in the placebo group were 65 years or older. The diversity of age groups studies is sufficient to determine the effect of ziconotide in adults. The number of elderly patients is only sufficient to make preliminary assessments of safety in the elderly population.

7.2.1.3 Extent of exposure (dose/duration)

The treatment phase of Study 301 lasted, 3-weeks when patients who had been stabilized off intrathecal medication received an intrathecal ziconotide or placebo infusion beginning at 0.1 mcg/hr with upward dose titration in increments from 0.05 mcg to 0.1 mcg/hr at intervals not less than 24 hours to treat chronic pain. The maximum dose was to have been no more than 0.9 mcg/hour. During conduct of the study the mean ziconotide dose at the end of three weeks was 0.26 mcg/hour so the upper boundary of dosing was not achieved. The extent of exposure is sufficient to make assessments of safety and efficacy of ziconotide dosing for treatment of chronic pain. Data available from earlier studies and extended treatment of patients completing Study 301 who participated in open-label study 352 provides sufficient supportive information to assess the consequences of long-term administration of ziconotide.

7.2.2 Description of Secondary Clinical Data Sources Used to Evaluate Safety

7.2.2.1 Other studies

The results of Study 352, an open-label extension for patients completing Study 301 were examined to identify consequences of long-term exposure to Ziconotide. The sponsor's Integrated Summary of Safety Tables amended to include the 120 Day Safety Update was reviewed to identify the timing of onset and resolution of adverse events with long-term use of ziconotide. These table include data from trials that were submitted with previously reviewed NDA for ziconotide.

7.2.2.2 Postmarketing experience

Ziconotide has not been marketed.

7.2.2.3 Literature

The published report in the Journal of the American Medical Association (1/7/2004) based upon clinical Study 95-001 of patients with intractable pain from cancer or AIDS was reviewed. (Intrathecal ziconotide in the treatment of Refractory Pain in Patients with Cancer or AIDS: Randomized Controlled Trial., P. Staats et al. JAMA vol 291 # 1 pp 63-70) This publication did not comment on or remove subjects from a study site (Principal Investigator: Yearwood , second author) determined to have become unblinded during the conduct of the study.

7.2.3 Adequacy of Overall Clinical Experience

Over 1200 patients exposed to ziconotide have been studied in clinical trails. A table of all studies in the ISS containing the number of patient by study, study design and dosing regimen by study is included in the Appendix (10.3). The ISS was further extended by a 120-day Safety Update that extended the information available regarding long-term exposure. The database is sufficient to make an assessment of safety.

7.2.4 Adequacy of Special Animal and/or *In Vitro* Testing

The review by Dr. Suzzane Thornton indicates that while there is a significant body of evidence to indicate that a generalized delay in ossification of the pubic area bones is a result of A repeated analysis indicated that the bones were unossified so that their apparent absence was an artifact of the initial staining procedure.

7.2.5 Adequacy of Routine Clinical Testing

Routine testing of vital signs, laboratory measurements, emotional and cognitive assessment and physical examination was broad enough and sufficiently sophisticated to capture adverse events based upon prior preclinical and accumulating clinical experience with

ziconotide. The study drug was administered chronically for three weeks during the treatment phase of Study 301. The assessments for emotional/cognitive parameters and ECG bracketed the treatment phase of Study 301. More frequent assessments may have been desirable because of the fluctuating course of symptoms (Table 6.1.4-5) and the likelihood of dose titration, however no striking abnormalities were discovered in the data collected, so the clinical testing was most likely adequate.

7.2.6 Adequacy of Metabolic, Clearance, and Interaction Workup

No new study of ziconotide metabolism, clearance and interaction was presented with this submission. Earlier studies of metabolism, clearance and interaction were complicated because ziconotide is administered in low doses directly into the intrathecal compartment and is virtually undetectable in plasma or urine. Being a small peptide, ziconotide is believed to be rapidly metabolized locally. More thorough evaluation of drug disposition and interaction appears to be impractical and unnecessary.

7.2.7 Adequacy of Evaluation for Potential Adverse Events for Any New Drug and Particularly for Drugs in the Class Represented by the New Drug; Recommendations for Further Study

The types of adverse events reported with the current submission are similar to the adverse events previously reported with the prior review cycle. It is not expected that additional testing will reveal new adverse events unlike those that have been reported because the doses, duration of treatment and underlying pathology in the anticipated population to be treated has been characterized. While the pathophysiological mechanisms of adverse symptoms associated with ziconotide, especially neurocognitive (or encephalopathic) disorders and elevation of serum creatine kinase (skeletal muscle) are not established, methods to identify and treat these abnormalities are sufficiently well characterized.

7.2.8 Assessment of Quality and Completeness of Data

The sponsor's data was of sufficient quality and completeness to be reviewed. Site visit of three trial sites from Study 301 did not reveal procedural abnormalities. Minor discrepancies occurred during review with the sponsor's calculation of the incidence of adverse events in Table 33 located in I.8 V.002 P. 195-196. (Results of this review concurred by Dr. Joan Buenconsejo, Agency Biometrics team). Several patients treated with ziconotide who completed Study 301 as responders did not proceed directly into Study 352. Initial inspection of their electronic data files suggested that adverse events prevented their further participation, however treatment with ziconotide appears to have been temporarily interrupted at the end of Study 301. Differences in analysis and interpretation encountered during the review and inspection of the sponsor's study report were not of sufficient magnitude to change the meaning of the results.

7.2.9 Additional Submissions, Including Safety Update

Results abstracted from the sponsor's 120 day Safety Update report are identified throughout this review and compared with safety findings from Study 301.

Summary of Selected Drug-Related Adverse Events, Important Limitations of Data, and Conclusions

The following table, derived from Study 301, illustrates selected symptoms most likely related to ziconotide administration. The primary limitation of these data is that the duration of exposure was limited to that of the controlled study. Some ziconotide related symptoms may worsen or abate with extended exposure, however it is not possible to clear determine the evolution of symptoms without a control group in a longer-term study. Despite the clinical significance of the symptoms most likely related to ziconotide and the potential for creatine kinase elevations (skeletal) to occur, adverse events could be diagnosed and treated. Ziconotide may be administered safely in carefully selected patients by practitioners who are skilled in pain management using indwelling intrathecal administration.

Table 7.3-1 Duration and Dose at Onset of Selected Adverse Events

		<i>Median Day</i>	<i>Median Duration</i>	<i>Median Dose at Onset</i>	<i>Cumulative</i>
<i>Adverse Event of</i>	<i>Incidence</i>	<i>at Onset</i>	<i>at Offset</i>	<i>(mcg/hr)</i>	<i>Dose at Onset</i>
<i>Particular Interest</i>	<i>n (%)</i>	<i>(range)</i>	<i>(range)</i>	<i>(range) *</i>	<i>(mcg) (range) *</i>
Abnormal Gait (including Ataxia)					
Ziconotide (N=112)	35 (31.2%)	4.5 (0-24)	5 (1-43)	0.20 (0.1-0.4)	12.0 (0-186)
Placebo (N=1 08)	4 (3.7%)	8.5 (1-13)	5.5 (5-6)	0.15 (0.1-0.3)	26.4 (2-48)
Abnormal Vision (including Amblyopia)					
Ziconotide (N=112)	13 (11.6%)	8.0 (0-30)	5.5 (1-60)	0.20 (0.1-0.6)	19.2 (0-206)
Placebo (N=1 08)	4 (3.7%)	15.0 (6-38)	6 (2-15)	0.33 (0.2-0.6)	54.0 (18-383)
Aphasia or Speech Disorder					
Ziconotide (N=112)	19 (17.9%)	16.0 (4-24)	13 (3-43)	0.30 (0.1-0.6)	81.6 (12-151)
Placebo (N=1 08)	3 (2.8%)	7.0 (2-26)	1.5 (1-2)	0.15 (0.2-0.3)	22.8 (5-109)
Asthenia (including Myasthenia)					
Ziconotide (N=112)	29 (25.9%)	3.0 (0-30)	4 (1-35)	0.15 (0.1-0.6)	9.6 (0-178)
Placebo (N=1 08)	18 (16.6%)	5.5 (0-32)	7 (4-37)	0.15 (0.1-0.6)	16.3 (0-304)
Confusion					
Ziconotide (N=112)	22 (19.6%)	9.5 (0-24)	6 (1-24)	0.28 (0.1-0.6)	40.8 (0-206)
Placebo (N=1 08)	5 (5.5%)	13.0 (4-32)	2.5 (1-6)	0.28 (0.1-0.6)	64.8 (10-304)
Dizziness					
Ziconotide (N=112)	56 (50%)	3.0 (0-24)	6 (1-33)	0.15 (0.1-0.6)	7.2 (0-151)

Clinical Review
 Lex Schultheis, M.D., Ph.D.
 NDA 21,060
 Prialt (Ziconotide)

		Median Day	Median Duration	Median Dose at Onset	Cumulative
Adverse Event of	Incidence	at Onset	at Offset	(mcg/hr)	Dose at Onset
Particular Interest	n (%)	(range)	(range)	(range) ^a	(range) ^b
Placebo (N=1 08)	15 (13.9%)	4.0 (0-26)	1 (1-9)	0.14 (0.1-0.6)	9.9 (0-154)
Hypotension (Including Postural Hypotension)					
Ziconotide (N=112)	5 (4.5%)	2.5 (0-16)	10 (1-36)	0.15 (0.1-0.5)	6.0 (0-84)
Placebo (N=1 08)	1 (0.9%)	5.0 (5-5)	4	0.10 (0.1-0.1)	7.2 (7-7)
Memory Impairment or Amnesia					
Ziconotide (N=112)	17 (15.2%)	7.5 (2-29)	6 (2-60)	0.16 (0.1-0.6)	23.6 (0-268)
Placebo (N=108)	2 (1.8%)	22.0 (22-22)	Unknown	0.56 (0.6-0.6)	174.8 (175-175)
Nausea (including Vomiting and Nausea and Vomiting)					
Ziconotide (N=112)	66 (58.9%)	6.0 (1-342)	5 (1-74)	0.13 (0.1-0.4)	9.6 (0-227)
Placebo (N=1 08)	49 (45.4%)	4 1-30)	4 (1-55)	0.15 (0.1-0.6)	16.8 (0-214)
Nystagmus					
Ziconotide (N=112)	9 (8.0%)	8.0 (4-16)	10.5 (3-43)	0.16 (0.1-0.7)	19.2 (5-14)
Placebo (N=1 08)	0 (0.0%)	0 (0.0)	0	0 (0.0)	0 (0.0)
Somnolence					
Ziconotide (N=112)	30 (26.8%)	4.0 (0-24)	6 (1-37)	0.11 (0.1-0.5)	9.6(0-132)
Placebo (N=1 08)	23 (21.3%)	6.0 (0-32)	5 (2-42)	0.20 (0.1-0.6)	21.0 (0-304)
Thinking Abnormal (Including Difficulty Concentrating and Mental Slowing)					
Ziconotide (N=112)	10 (8.9 %)	4.0 (0-18)	6 (3-23)	0.12 (0.1-0.5)	9.6 (0-122)
Placebo (N=1 08)	3 (2.7%)	10.0 (10-10)	3.5 (1-6)	0.30 (0.3-0.3)	45.6 (46-46)
Urinary Retention					
Ziconotide (N=112)	10 (8.9%)	7.5 (1-24)	10 (1-27)	0.15 (0.0-0.6)	16.8 (0-202)
Placebo (N=1 08)	0 (0.0%)	0 (0.0)	0	0 (0.0)	0 (0.0)

Data was abstracted from sponsor's electronic tables for Adverse Events with corrections of sponsor's Table 33 from I.8 V.002 P.195-196. Calculations were confirmed by Dr. Buenconsejo, Biometrics Reviewer.

7.4 General Methodology

7.4.1 Pooling Data Across Studies to Estimate and Compare Incidence

Pooled safety data from all studies of intrathecal ziconotide was examined in tabular format provided with the sponsor's 120 day Safety Update Report as an amended ISS. These data were an extension of the ISS.

7.4.1.1 Pooled data vs. individual study data

Significant differences in the dosing regimen between Study 301 and earlier clinical trials of ziconotide made it difficult to precisely compare the incidence of adverse events, timing of adverse event onset and resolution between studies. Moreover, Study 301 included a longer titration-treatment phase than earlier phase 3 studies. Review of the ISS in comparison with the adverse event electronic event table available with Study 301 indicates that the type of adverse events seen in Study 301 were representative of the adverse events seen in the entire ISS.

7.4.1.2 Combining data

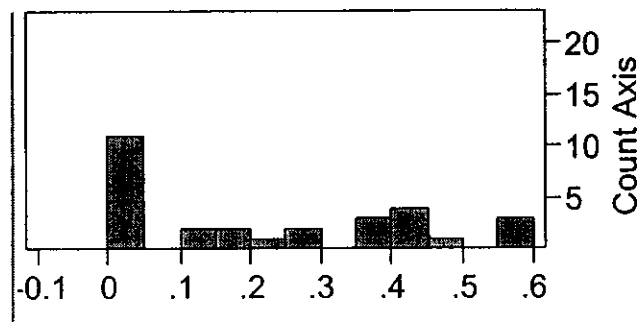
No new types of adverse events were presented in the pooled data compared with safety database of Study 301. Analysis of the pooled data revealed that while most adverse events presented themselves for the first time within the first few weeks of treatment, some patients experienced their first symptoms after months.

7.4.2 Explorations for Predictive Factors

7.4.2.1 Explorations for dose-dependency for adverse findings

The number of serious adverse events was not related to the hourly infusion rate of ziconotide.

Table 7.4.2-1 Rate of Serious Adverse Events Associated with Hourly Rate of Ziconotide Infusion

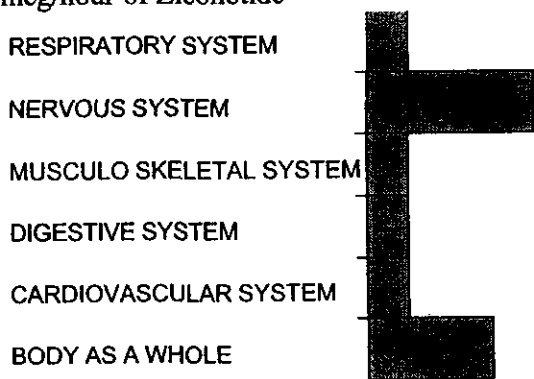


Clinical Review
Lex Schultheis, M.D., Ph.D.
NDA 21,060
Prialt (Ziconotide)
Dose of Ziconotide in mcg/hour at Onset of Adverse Event

“Count Axis” refers to the number of serious adverse events reported at each dosing level
Data was abstracted from the sponsor’s electronic data tables of adverse events and dosage for Study 301.

The type of serious adverse event was also analyzed as part of this review according to body system. Figure 7.4.2-1 depicts the distribution of adverse events by body system at the lowest dose range (0.05 mcg/hour). Serious adverse events in the Nervous System and in Body as a Whole tended to predominate at each dosing level.

Figure 7.4.2-1 Distribution of Serious Adverse Events by Body System Occurring at Dose 0.5 mcg/hour of Ziconotide



Data was abstracted from the sponsor’s electronic data tables.

Just as for serious adverse events, the incidence of severe adverse events did not appear to increase with the hourly dose of ziconotide. The median dose of ziconotide at onset of all adverse events ranged from 0.11 mcg/hr to 0.3 mcg/hr and was lowest for somnolence. The median cumulative dose at onset was lowest for hypotension (6 mcg) and dizziness (7.2 mcg). As seen in earlier trials, the median dose of initial onset of adverse events was low when compared to the entire range of dosing used.

Explorations for time dependency for adverse findings

In Study 301 the median time of onset of adverse events was within the first week of treatment. Adverse events of cognition including memory, confusion, speech difficulty tended to occur later than dizziness or nausea. Dr. Robert Meyer inquired about the possibility that adverse events such as mental slowing, confusion or memory impairment may have confounded the ability to describe pain for efficacy analysis (12/1/04). A detailed description of the timing of adverse events in relation to efficacy parameters was compiled by Dr. Joan Buenconsejo (Biometrics team) and is presented in the Appendix.

Among all ziconotide treated patients in the 120 day safety update report, cognitive disturbances occurred for the first time to patients over the entire range of treatment.

Clinical Review
 Lex Schultheis, M.D., Ph.D.
 NDA 21,060
 Prialat (Ziconotide)

Table 7.4.2-2 First Occurrence of Adverse Events in Patients who Received Ziconotide for >90 days with Adverse Events Reported for >60 (5%) Total Patients Who Ever Received Ziconotide. Data is Taken from All Intrathecal Clinical Studies 120 Day Safety Update (N = 445)

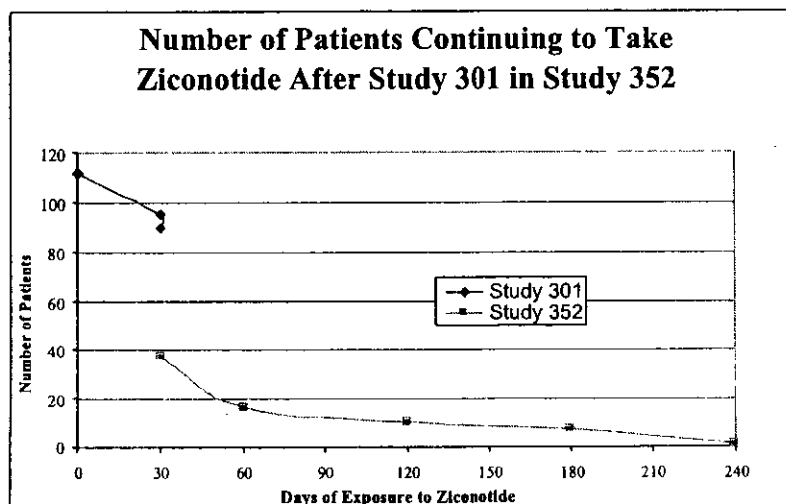
Body System/ COSTART Term	Time of First Occurrence of Adverse Event ^a				
	0 to <30 days	30 to <90 days	90 to <180 days	180 to <365 days	>_365 days
Nervous System (cont'd)	361	39	13	3	4
Cerebrospinal Fluid Abnormal	25	2	1	0	0
Hallucinations	20	44	22	7	9
Thinking Abnormal	10	17	9	10	6
Tremor	28	13	10	5	6
Vertigo	17	2	2	10	6

Data was abstracted from the sponsor's 120 day Safety Update Report.

The median duration of most adverse events following cessation of ziconotide among patients in Study 301 who did not continue treatment on open-label Study 352 was one or two weeks although there were cases of nausea, memory impairment and abnormal vision that lasted at least 45 days.

This review also examined the dropout rate of patients who received ziconotide in Study 301 and decided to continue ziconotide during the subsequent open label trial, Study 352. It is recognized that some patients may have delayed entry into Study 352 and were not captured in the interim study report and that all discontinuations resulted from intolerance to the drug. Despite the limitations of the data, it is striking that of the 90 patients who were treated with ziconotide in Study 301 and consented to continue into Study 352, only 37 continued with ziconotide immediately. Furthermore, a persistent decline in the fraction of patients who continued treatment over following months was also apparent. These trends have many possible explanations, however they suggest that the real benefit was to a small fraction of patients who were able to tolerate the drug for an extended period.

Figure 7.4.2-1 Discontinuation Rate of Ziconotide Therapy over 240 Days of Exposure



Data was abstracted from the sponsor's electronic data tables from Study 301 and from I. 8 V.015 P.069 (report of Study ELN92045-352).

7.4.2.3 Explorations for drug-demographic interactions

The composition of each treatment group in Study 301 was overwhelmingly Caucasian, so no exploration of drug vs. race was undertaken.

The adverse event rate was 94 % from male and 92 % for female patients taking ziconotide. The only notable difference by body system in adverse events was related to the digestive system with 64% of female and 55% of male patients reporting an adverse event.

The overall incidence of adverse events was similar for patients < 65 years of age (92%) as for older patients (95%). Certain adverse events occurred more frequently among patients at least 65 years old compared to younger patients.

Table 7.4.2-3 Adverse Events At Least 10 % More Frequently Among Patients At Least 65 Years Old.

Adverse Event	Incidence among Patients ≥ 65 Years Old	Incidence among Patients < 65 Years Old
Abnormal Gait	35%	11%
Dizziness	60%	45%
Diplopia	15%	1%
Abdominal Pain	15%	3%
Peripheral Edema	15%	3%
Insomnia	15%	4%
Paralysis	10%	0%

Data was Abstracted from Sponsor's Study Report ELN92045-301 I.8 V. 002 P.186

Some Adverse events were reported more frequently among younger patients.

Table 7.4.2.-4 Adverse Events At Least 10 % More Frequently Among Patients Younger Than 65 Years Old.

Adverse Event	Incidence among Patients ≥ 65 Years Old	Incidence among Patients < 65 Years Old
Creatine Kinase	0%	13%
Hypertonia	0%	12%
Chills	0%	11%

Data was Abstracted from Sponsor's Study Report ELN92045-301 I.8 V. 002 P.186

7.4.2.4 Explorations for drug-disease interactions

No studies of drug-disease interaction were performed, because the placebo and ziconotide treatment groups were well-matched in terms of underlying disease.

7.4.2.5 Explorations for drug-drug interactions

No studies of drug-drug interactions were performed by the sponsor. An analysis of drug-drug interaction between ziconotide and the two most commonly prescribed concomitant drug classes: anxiolytics and antidepressants were performed as part of this review of adverse events.

In Study 301, the most commonly reported concomitant non-opiate medications were antidepressants (70%) and anxiolytics (46%). These were reported for 57% and 34 % of patients, respectively in the placebo group. Opiate use was 98% of patients in the ziconotide groups and 97% of the placebo group. The most common opiates were oxycodone and morphine, reported as used by 33% and 31% of patients in the ziconotide group. Oxycodone and morphine were reported used by patients in the placebo group as 24% and 37 %, respectively.

7.4.3 Causality Determination

Adverse events of the nervous system that indicated impaired cognition and consciousness only presented with ziconotide. These adverse events have been variously described as encephalopathy by the Agency or neurocognitive impairment by the sponsor. Their association with ziconotide and complete lack of association with placebo despite similar demographics, disease and type of concomitant medication in both treatment arms indicates that ziconotide is the cause of this effect. Furthermore, the symptoms resolve after ziconotide is discontinued.

Elevations of creatine kinase of noncardiac or cerebral origin are also associated with ziconotide, but not placebo treatment. The mechanism behind this elevation is unknown, but it appears to be caused by ziconotide in a minority of patients.

Clinically significant urinary retention is more commonly associated with ziconotide than placebo. Although concomitant opiates may cause urinary retention and opiates were given in higher doses in the ziconotide group, the difference in opiate dose may not account for the increased incidence in urinary retention among ziconotide treated patients.

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8 ADDITIONAL CLINICAL ISSUES

8.1 Dosing Regimen and Administration

The dosing regimen used in Study 301 was a low starting dose and slow-titration regimen following weaning from other intrathecal medication. The 20 mL reservoir pump was to have been filled with 0.25 mcg/mL ziconotide and refilled on study day 14. The starting dose was stipulated to be 0.10 mcg/hr with upward titration no more frequently than every 24 hours. The maximum upward titration dose increment was 0.1 mcg/hr, with a minimum of 0.05 mcg/hr. The dosing goal was to have been within the range of 0.35 mcg/hr to 0.90 mcg/hr by the end of 3 weeks. The median maximum dose at the end of three weeks was lower than the protocol target.

Table 8.1-1 cross-references the measured level of efficacy and the frequency of serious or severe adverse events to the maximum and cumulative dose of ziconotide. This comparison indicates that only a very small fraction of patients responded with a marked reduction in their pain and improvement in quality of life without a severe adverse event. Among the patients with the most benefit, the maximum dose at three weeks and cumulative dose received were unrelated to the clinical measures of efficacy or safety in this study. In addition, among patients with a minimum quantifiable improvement in efficacy, the maximum dose at three weeks and the cumulative dose were not substantially different than patient without clinical benefit. In summary, there was no trend or pattern with the dosing regimen used in Study 301 that related dose of ziconotide to improved efficacy or incidence of major adverse events. This absence of dose-effect suggests that patients who respond to ziconotide will require little titration and that there is no safety advantage to lower dosing within the dose range used over the duration of this study.

Table 8.1-1 Dosing Regimen and Administration

Efficacy			Safety		Dosing	
Patients With a Reduction in VASPI (Incidence)			Patients with Serious AEs (Incidence)	Patients with Severe AEs (Incidence)	Maximum Dose in Third Week Median (Range)	Cumulative Dose Median (Range)
	Placebo (N=108)	Ziconotide (N=112)	Ziconotide (N=112)		Ziconotide (N=112)	Ziconotide (N=112)
Nonresponders	58/108 (54%)	52/112 (46%)	6/52 (12%)	21/52 (40%)	0.26 (0.05-0.7)	131 (7-529)
Minimum Responders	37/108 (34%)	43/112 (38%)	3/43 (7%)	20/43 (47%)	0.25 (0.05-0.8)	151 (31-370)
Responders	13/108 (12%)	17/112 (15%)	4/17 (24%)	6/17 (35%)	0.17 (0.05-0.6)	106 (41-397)
Responders who improved two steps in at least one secondary efficacy	3/108 (3%)	14/112 (13%)	4/12 (29%)	5/14 (36%)	0.21 (0.05-0.5)	108 (57-397)

Clinical Review
 Lex Schultheis, M.D., Ph.D.
 NDA 21,060
 Prialat (Ziconotide)

Efficacy			Safety		Dosing	
Patients With a Reduction in VASPI (Incidence)			Patients with Serious AEs (Incidence)	Patients with Severe AEs (Incidence)	Maximum Dose in Third Week Median (Range)	Cumulative Dose Median (Range)
	Placebo (N=108)	Ziconotide (N=112)	Ziconotide (N=112)		Ziconotide (N=112)	Ziconotide (N=112)
endpoint						

Data was abstracted from sponsor's electronic data tables.

The secondary endpoints:

1. CGI - Overall Pain Control Rating at Termination: Poor (0) Fair/Good (1-2) Very Good (≥ 3)
2. Change in McGill Pain Intensity at Termination from baseline: Worsen (< 0), No change ($=0$), Improve by 1 ($=1$), Improved by at least 2 (≥ 2)
3. Change in BPI at Termination from baseline: Worsen (< 0), No change ($=0$), Improve by no more than 4 (<5), Improved by at least 5 (≥ 5)
4. Change in Quality of Sleep at Termination from baseline: Worsen (< 0), No change ($=0$), Improve (>0)
5. Change in CPRS at Termination from baseline: Worsen (< 0), No change ($=0$), Improve (>0)
6. Change in TOPS at Termination from baseline: Worsen (< 0), No change ($=0$), Improve by no more than 9 (<10), Improved by at least 10 (≥ 10)

Improved in at least one secondary outcome ("second") is defined as:

If one of the variables above is coded as "poor or worsening" OR if all variables are coded as "no change" then second=0 (no change/worsen)

Else second=1 (improved in at least one secondary outcome).

Data was abstracted from sponsor's electronic data tables for Study 301.

The entire ziconotide treatment population from all completed studies was also evaluated for evidence of a dose-relationship to specific adverse events. The median dose at the onset of an adverse event ranged from 0.2 to 0.3mcg/hr and occurred after less than 30 days of treatment so the cumulative dose was low.

Table 8.1-2 Time and Dose Relationship to Onset of Selected Adverse Events

Adverse Event	While Receiving Ziconotide (N = 1254)			
	Number of Patients	Median No. Days to Onset	Median Dose at Onset (mcg/hr)	Median Cumulative Dose at Onset (mcg)
Abnormal Gait (Including Ataxia)	377	5	0.20	28.36

Clinical Review
 Lex Schultheis, M.D., Ph.D.
 NDA 21,060
 Prialt (Ziconotide)

Amblyopia (including Abnormal)	254	8	0.20	35.76
Aphasia or Speech Disorder	285	25	0.30	153.93
Asthenia (Including Myasthenia)	373	14	0.20	59.57
Confusion	415	22	0.26	127.93
Dizziness	651	4	0.20	15.69
Hypotension (Including Postural)	179	5	0.30	44.61
Memory Impairment or	288	29	0.22	153.64
Nausea (Including Vomiting or Nausea and Vomiting)	692	4	0.20	13.96
Nystagmus	339	5	0.25	29.21
Somnolence	349	10	0.20	48.43
Thinking Abnormal (including Difficulty Concentrating and Mental)	187	25	0.21	147.27
Urinary Retention	174	6	0.20	33.19

Data was abstracted from sponsor's Table 8.4.8-15 of the 120 Day Safety Update report.

8.2 Drug-Drug Interactions

No drug-drug interaction studies were conducted by the sponsor except for an analysis of concomitant opiate administration as a secondary endpoint in Study 301. Three patients in Study 301 were also treated with intranasal ketamine as an analgesic, however there was insufficient data to make a determination about potential synergistic effect.

The most commonly administered concomitant medications were antidepressants and anxiolytics. In this review, the incidence of adverse events and serious adverse events was compared among patients taking these concomitants because they were the most commonly administered and because these agents cross the blood-brain barrier and may interact with ziconotide in the central nervous system.

Table 8.2-1 illustrates the relationship of adverse events to patient groups with and without concomitant treatment with antidepressants. An increase in serious and nonserious adverse events is present when antidepressants are taken with either ziconotide or placebo.

Table 8.2-1 Incidence of Adverse Events Among Patients Taking Antidepressants

Patents with Adverse Events	Patients with Serious Adverse Events

Clinical Review
 Lex Schultheis, M.D., Ph.D.
 NDA 21,060
 Prialt (Ziconotide)

Ziconotide + Antidepressant 79 pts (71%) [out of 112 pts]	73 pts (92%) [out of 79 pts]	10 pts (13%) [out of 79 pts]
Ziconotide No Antidepressant 33 pts (30%) [out of 112 pts]	31 pts (90%) [out of 33 pts]	3 pts (9%) [out of 33 pts]
Placebo + Antidepressant 62 pts (57%) [out of 108 pts]	51 pts (82%) [out of 62 pts]	5 pts (8%) [out of 62 pts]
Placebo No Antidepressant 46 pts (43%) [out of 108 pts]	38 pts (76%) [out of 46 pts]	5 pts (11%) [out of 46 pts]

Analysis was performed on the ITT sample during the treatment phase of Study 301, 112 ziconotide treated patients and 108 placebo treated patients. Percentages reflect the fraction of patients in each subset. Data was abstracted from sponsor's electronic data tables.

Table 8.2-2 illustrates the relationship of adverse events to patient groups with and without concomitant treatment with anxiolytics. An increase in serious but not all adverse events is present when anxiolytics are taken with either ziconotide or placebo.

Table 8.2-2 Incidence of Adverse Events Among Patients Taking Anxiolytics

	Patients with Adverse Events	Patients with Serious Adverse Events
Ziconotide + Anxiolytic 55 pts (49%) [out of 112 pts]	50 pts (91%) [out of 55 pts]	9 (16%) [out of 55 pts]
Ziconotide No Anxiolytic 57 pts (51%) [out of 112 pts]	54 pts (95%) [out of 57 pts]	4 (7%) [out of 57 pts]
Placebo + Anxiolytic 37 pts (34%) [out of 108 pts]	31 pts (84%) [out of 37 pts]	5 (14%) [out of 37 pts]
Placebo No Anxiolytic 71 pts (66%) [out of 108 pts]	58 pts (82%) [out of 71 pts]	5 (7%) [out of 71 pts]

Analysis was performed on the ITT sample during the treatment phase of Study 301, 112 ziconotide treated patients and 108 placebo treated patients. Percentages reflect the fraction of patients in each subset. Data was abstracted from sponsor's electronic data tables.

Clinical Review
Lex Schultheis, M.D., Ph.D.
NDA 21,060
Prialt (Ziconotide)

Administration of any concomitant medication is expected to increase adverse events. If there is no interaction between medications then the incidence of adverse events would be expected to be the sum of adverse event rate for each medication when given separately. Potentiation of risk by a medication when coadministered with another medication is expected to result in an adverse event rate that is more than the sum of the rates of the individual medications when administered alone. In the case of ziconotide and coadministered anxiolytics the serious adverse event rate was similar to the rate when anxiolytics were given with placebo. Antidepressants coadministered with ziconotide resulted in a serious adverse event rate that was higher than the rate when placebo and antidepressants were given. This difference is probably not clinically significant because it is similar in magnitude to the difference between the serious adverse event rates for placebo groups treated with and without anxiolytics.

8.3 Special Populations

The number of elderly patients was too limited to perform a specific dose analysis.

8.4 Pediatrics

No studies were conducted in the pediatric population.

8.5 Advisory Committee Meeting

A presentation of information about ziconotide was made by the Agency to closed session of the Scientific Advisory Committee meeting on March 24, 1997. This presentation was to inform the committee rather than to solicit committee advice.

8.6 Literature Review

A publication in the Journal of the American Medical Association presented findings of clinical Study 95-001 of patients with intractable pain from cancer or AIDS on 1/7/2004. (Intrathecal ziconotide in the treatment of Refractory Pain in Patients with Cancer or AIDS: Randomized Controlled Trial., P. Staats et al. JAMA vol 291 # 1 pp 63-70). The authors included the principal investigator who was discovered by the Agency to have permitted unblinded treatment of patients at his clinical site. The publication did not mention the part of the study was unblinded.

The authors reported that of the evaluable population, 67 (98.5%) of 68 patients receiving ziconotide and 38 (95%) of 40 patients receiving placebo were taking opiates at baseline (median morphine equivalent dosage of 300 mg/day for the ziconotide group and 600 mg/day for the placebo group; $p=0.63$ based upon mean values), and 36 had used intrathecal morphine. Mean (SD) VASPI scores were 73.6 (1.8) mm in the ziconotide group and 77.9 (2.3) mm in the placebo group ($P=0.18$). Mean VASPI scores improved 53.1% (95% confidence interval[CI], 44.0%-62.2%) in the ziconotide group and 18.1% (95% CI, 4.8%-31.4%) in the placebo group ($p<0.001$), with no loss of efficacy of ziconotide in the maintenance phase. Pain relief was moderate to complete in 52.9% of patients in the ziconotide group compared with 17.5% in the placebo group ($p<0.001$). Five patients receiving ziconotide achieved complete pain relief, and 50% of patients receiving ziconotide responded to therapy compared with 17.5% of those

Clinical Review
Lex Schultheis, M.D., Ph.D.
NDA 21,060
Prialt (Ziconotide)

receiving placebo ($p=0.001$). The authors concluded from the results that ziconotide provided statistically and clinically significant analgesia in patients with pain from cancer or AIDS.

During the titration phase, 4 (10%) of the 40 patients receiving placebo reported a total of 4 serious adverse events, and 22 (30.6%) of the 72 receiving ziconotide in the safety group reported a total of 31 serious adverse events. The most common serious adverse events among patients who received ziconotide during titration were confusion, somnolence and urinary retention. Starting at lower dosages, using smaller dose increments and increasing the interval between dose titrations tended to reduce the frequency of most adverse events. The frequency of occurrence of confusion was not directly related to dose. Death rates were similar between ziconotide and placebo treatment groups.

Confusion occurred more frequently among patients who were 60 years old or older than among younger patients.

There was no clear difference between ziconotide or placebo treatment groups in terms of gender or race at baseline, efficacy or adverse events.

8.7 Postmarketing Risk Management Plan

This product is expected to be used by a limited number of practitioners who regularly treat patients with intrathecal medication for chronic pain. Post marketing data could be collected to improve the estimated

8.8 Other Relevant Materials

No other materials were consulted.

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9 OVERALL ASSESSMENT

9.1 Conclusions

Ziconotide is more effective than placebo in reducing chronic pain measured by VASPI after three weeks of treatment. Improvement in pain indicated by a reduction in VASPI was supported by secondary endpoints that reflected a global assessment of satisfaction, quality of life and sleep. The degree of pain reduction reported by patients who responded to ziconotide varied from week to week in the three week trial so that some patients who were responders in the first week did not respond in the second or third weeks and some patients who did not respond early, responded later. The incidence of serious or severe adverse events is highest among patients with most pain reduction. A comparison of safety and efficacy findings among patients stratified by the degree of efficacy suggests that a small percentage of patients treated with ziconotide who exhibited a high level of pain control will also have improvement in their quality of life despite a high incidence of serious or severe adverse events. Slightly more than half of the patients treated with ziconotide compared to slightly less than half the patients treated with placebo had improvement in pain, but the average improvement was small and had little impact on their quality of life. There is no clear relationship between maximum dose or cumulative dose of ziconotide and efficacy or safety when using the slow titration regimen of Study 301 so that titration of ziconotide beyond the range studied in trial 301 may not be necessary nor desirable.

In comparing the safety of the titration schedules used for Study 301 and the earlier Studies 95-001, 96-002, a sentinel finding is the relative rate of withdrawal because of an intolerable adverse event. When the slow titration regimen of Study 301 was used, 5.4% of the patients treated with ziconotide and 4.6 % of the placebo-treated patients were discontinued because of an intolerable adverse event. In contrast, the fast-titration method used in earlier studies resulted in 13.5% of the ziconotide and 3.7% of the placebo-treated patients discontinuing participation because of an adverse event. While it is recognized that there are clinical differences between the patient populations in rapid-titration and slow-titration studies, and significant flaws in data collection and analysis complicate interpretation of fast-titration studies, it is concluded that rapid-titration should be reserved for situations where compassionate care is more important than patient safety.

9.2 Recommendation on Regulatory Action

Ziconotide is approvable for patients with chronic severe pain who have indwelling pumps for intrathecal administration and who have exhausted alternatives for medical treatment. The label should specify dosing guidelines for slow titration and provide guidance for careful and frequent patient monitoring.

9.3 Recommendation on Postmarketing Actions

Consideration should be given to constructing a safety registry including duration of treatment for patients treated with ziconotide. The interim report from the long-term open-label extension studies 352 suggests that few patients continue to use ziconotide for more than several months. Long-term administration safety data will be useful in predicting an expected duration of treatment with ziconotide, information that may be eventually incorporated into the product label.

Consideration should also be given to restricted distribution of the drug to physicians or practice centers with recognized expertise in chronic administration of intrathecal pain medication.

9.3.1 Risk Management Activity

[Redacted]

9.3.2 Required Phase 4 Commitments

Study of ziconotide in pediatric patients should be deferred while post-marketing safety data is accumulated.

The safety database should be extended among patients over 65 years of age. Study 301 only included 20 patients in this age group. Data from earlier studies suggest that the elderly may have an increased incidence of confusion, but there may be differential dosing requirements for efficacy also..

9.3.3 Other Phase 4 Requests

[Redacted]

Clinical Review
Lex Schultheis, M.D., Ph.D.
NDA 21,060
Prialt (Ziconotide)

9.4 Labeling Review

- The Clinical Trials section should have all quantitative efficacy, safety and dosing information from rapid-titration Studies 95-001 and 96-002 deleted because the findings from these trials were inadequate to stand alone. A statement in the section on Study 301 should describe that pain reduction was variable during the course of treatment with ziconotide.
- The Indication and Usage section should reflect that ziconotide is to be used in patients who cannot tolerate approved intrathecal alternative pain medication or who have pain that is refractory to intrathecal alternative medication. There is considerable clinical experience with intrathecal morphine in pain management, however safety data is still emerging, especially at higher doses. There is reason to suspect that intrathecal ziconotide may have increased risk than morphine so the indication should reflect the concept that ziconotide should be considered after alternative drugs. The findings of Study 301 support this premise because most patients that were studied had failed treatment with intrathecal opiates.
- The Contraindications section should include a statement that ziconotide is not to be coadministered with other intrathecal medication.
- The Warnings section should indicate that severe cognitive or emotional changes may result from ziconotide administration. A statement should be included advising interruption or discontinuation of ziconotide treatment if these reactions occur. The potential for serious adverse reactions with ziconotide treatment may justify a boxed warning. In the previously submitted phase 3 trials, ziconotide was associated with a higher death rate than placebo. In Study 301 patients treated with ziconotide described cognitive disorders that may have the potential to result in serious injury.
- The Precautions section will require editorial changes.
- The Pediatric and Geriatric use sections will require editorial changes to comply with standards in the CFR.
- The Adverse Reactions section should have the side by side comparison of adverse events in fast titration and slow titration studies removed. This comparison promotes the concept that the fast titration schedule may be used safely.
- The Dosage and Administration section should have references to the fast titration schedule deleted. A statement should be included that controlled studies of pain relief have not been conducted for more than three weeks duration. The dosing range should reflect the doses tested (rather than planned) during the slow titration trial.

Comments to Applicant

Advice to the sponsor is under internal discussion at the date of this review.

Clinical Review
Lex Schultheis, M.D., Ph.D.
NDA 21,060
Prialt (Ziconotide)

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10 APPENDICES

10.1 Review of Individual Study Reports

10.1.1 Protocol ELN92045-301 "A Randomized Double-Blind, Placebo-Controlled Study of Intrathecal Ziconotide in Adults with Severe Chronic Pain" March 27, 2002

10.1.1.1 Study Plan Synopsis

10.1.1.1.1 Rationale:

In protocols 96-002 and 95-001 ziconotide was titrated to an effective dose over 5-6 days. In the open-label trial (98-022 An Open-Label, Long-Term Safety and Tolerability Study of Ziconotide Administered Intrathecally to Patients With Chronic, Severe Pain) in which over 650 patients were studied, ziconotide was titrated over a period of four weeks. This study demonstrated that ziconotide appeared to be better tolerated by patients when titrated over a longer period of time. Therefore, in the current study, ziconotide was to have been titrated more slowly than in the pivotal trials (96-002 and 95-001) and more rapidly than in the long-term safety trial(98-022) to confirm the efficacy and safety profile of ziconotide using a slower titration schedule.

10.1.1.1.2 Objectives:

Primary: To confirm the positive efficacy results observed in the short term (5-6 days) pivotal trials (96-002 and 95-001) using an alternative slower dose titration schedule over a three week treatment period.

Secondary: To characterize opiate withdrawal effects during conversion from Intrathecal (IT) to systemic opiate therapy and to quantify the amount of concomitant opiate usage during the trial.

10.1.1.1.3 Population:

The number of patients to be randomized was stipulated to be 220.

Inclusion Criteria

Primary Inclusion (Screening Visit)

Patients were to be able to read, understand, and voluntarily sign the Institutional Review Board (IRB) approved, written informed consent document prior to the performance of any study-specific procedures;

Patients were to be male or female at least 18 years of age;

VASPI score greater than or equal to 50 mm;

Patients were to have severe chronic pain not adequately controlled and/or intolerant to systemic opioids and for whom intrathecal therapy is warranted;

Patients were to be willing and able to comply with the protocol, and able to maintain the Patient Daily Diary for Opioid Consumption;

Patients were to have an implanted programmable SynchroMed Infusion System in place for the treatment of chronic pain;

Female patients of childbearing age were to agree to use adequate, appropriate contraceptive methods.

Secondary Inclusion (Baseline and Randomization Visit)

Patients were to have a VASPI score greater than or equal to 50 mm;

At randomization, patient was to be weaned off all ITT medications and stabilized on systemic analgesics for at least one week.

Exclusion Criteria

Patient was pregnant or lactating;

Patient was on an investigational drug other than ziconotide or device within 30 days prior to the initiation of study drug;

Patients with a known hypersensitivity to ziconotide or any of its components;

Patients with a condition that would contraindicate the use of IT analgesia, including the presence of infection at the microinfusion injection site, uncontrolled bleeding diathesis and spinal canal obstruction that impairs circulation of CSF.

Design:

Screening: Eligibility and baseline measurements, begin Patient Daily diary for Opiate Consumption (PDD)

Weaning: (only for eligible patients on other intrathecal medications) weaning off IT medications and converting IT opiates to a combination of one long-acting opiate for stable dosing and fast-acting opiate as rescue analgesic

Stabilization Period: 1-week pre treatment stabilization of baseline VASPI and opioid consumption. The SynchroMed pump was to have been rinsed with preservative-free 0.9% Normal Saline, USP to remove residual drug

Baseline Visit: Secondary screening, baseline measurements and randomization of patients. Initiation of study drug infusion was to have begun after the infusion pump was been rinsed three times with 2 mL randomized study medication.

Double-blind Treatment Period: Scheduled weekly treatment visit for evaluation and titration of study drug and at least one and no more than two interval visits per week to allow for adequate dose titration. A one day visit window was to have been allowed. The starting dose was stipulated to be 0.10 mcg/hr. The titration time interval for upward titration was not to be more frequent than every 24 hours. The maximum upward titration dose increment is 0.1 mcg/hr, with a minimum of 0.05 mcg/hr. The dose was to be increased for insufficient analgesia in the absence of clinically concerning AEs. There was to have been no restriction on downward titration in dose or interval to manage unacceptable AEs. The dosing goal was to have been within the range of 0.35 mcg/hr to 0.90 mcg/hr by the end of 3 weeks. The pump was to have been refilled on study day 14 with a subsequent assessment of adverse events 48 hours later. A minimum 48 hour period of stable dosing was to precede the final VASPI assessment on the termination visit.

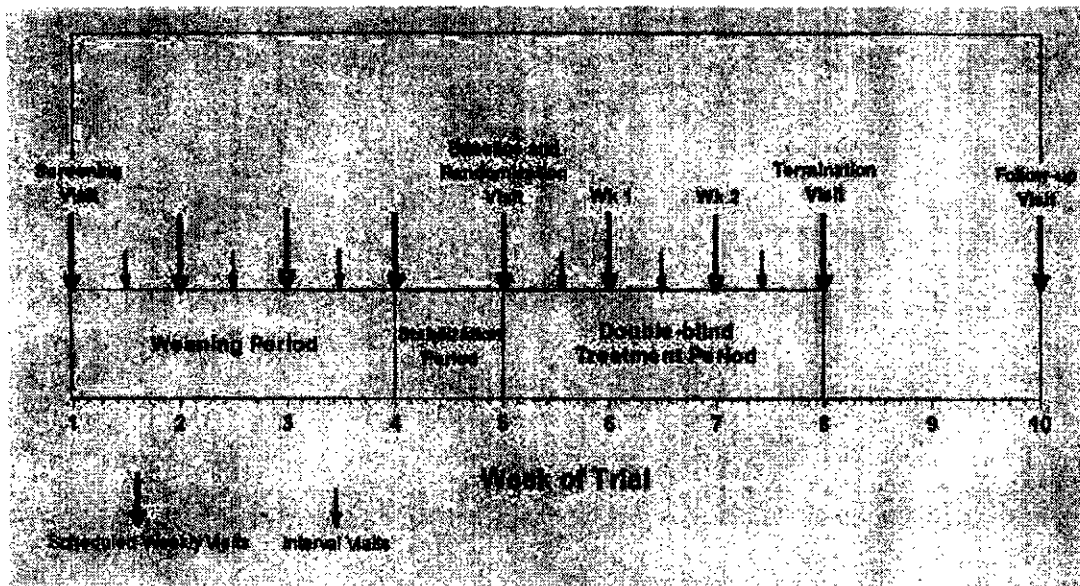
Termination Visit: An assessment of all safety and efficacy parameters was to have been performed.

Follow-up Visit: An evaluation of ongoing treatment emergent AEs or abnormal laboratory values was to be continued until time of resolution. Follow-up visits for treatment emergent AEs were to occur at 2 week intervals.

Trial Exit Options: All patients were to have the option of receiving intrathecal ziconotide without blinding at the conclusion of this trial. The blind was to have been removed after all termination visit safety and efficacy parameters were documented, the CRF was assessed by the CRO for completeness and the patient scheduled for an office visit for enrollment in the open-label trial.

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Figure 10.1.1.1.4-1 Schematic of Trial Design



From I.8 V.005 P.143 Sponsor's NDA Submission 03, Vol 3.030 of 3.103, Section 17.1.1 Study Protocol N92045-301, Page 959

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 NDA 21,060
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10.1.1.1.4 Assessments
 Table 10.1.1.1.5-1 Schedule of Assessments

Procedure	Schedule of Events						
	Screening Visit*	Baseline Visits	Randomization Visit	Baseline Visit (randomization)	Scheduled Weekly Visits	Weekly Visits	Follow-up Visit (2 weeks post-termination of study drug)
Informed Consent	X						
Inclusion/Exclusion Criteria	X			X			
Medical/Pain History	X						
Physical Exam	X						
Neurological Assessment	X			X			
Vital Signs	X			X			
Lab Evaluations*	X			X			
Pregnancy Test	X			X			
12-Lead ECG	X		X	X			
VASPP/Visual Analog Scale of Pain Intensity				X			
Brief Pain Inventory (BPI)				X			
Milv Mental Status Evaluation (MMSE)				X			
Hamilton Depression Rating Scale (HamD)				X			
Categorical Pain Relief Scale (CPRS)				X			
Global Medical Pain Score	X			X			
Treatment Outcome Pain Survey (TOPS)				X			
Global Global Impression				X			
Sleep Characteristics				X			
Dose Adjustment/Pump refill/Refill				X		X	
Patient diary/diary (pains use)	X			X		X	
Adverse Events		X		X		X	
Concomitant Medication		X		X		X	

10.1.1.1.6 Analysis Plan

10.1.1.1.6.1 Primary Efficacy Endpoint

The primary endpoint was stipulated to be the percent change in the VASPI score from the baseline visit to the termination visit (at the end of week 3) compared to the baseline visit.

10.1.1.1.6.2 Secondary Efficacy Endpoints

Using the VASPI Score

- Patients who complete the 3 week-treatment period with a 30% improvement from baseline are successes, all others are treatment failures.
- The percent change in VASPI score at the final visit at the end of treatment week 3 compared to baseline visit using observed data only (no LOCF).
- The VASPI score (mm) change from baseline to termination visit (using LOCF).
- The percent change in weekly VASPI scores reported at scheduled weekly treatment visits at the end of week 1 and week 2 and the final visit using observed data only (no LOCF).
- Percent change in weekly VASPI scores reported at scheduled weekly treatment visits at the end of week 1 and week 2, with LOCF for early terminations.
- Percent change in weekly VASPI scores at weekly treatment visits at the end of treatment week 1, week 2 and final visit, observed data only, without LOCF.

Using Opiate Consumption Rate

- Weekly absolute opiate consumption converted to oral morphine equivalents.
- Percent change in weekly opiate consumption from the PDD (with reconciliation) at weekly treatment visits at the end of the treatment week 1, treatment week 2, and final visit compared to pretreatment stabilization week.

Using Functional or Global Measures

- Percent change in brief Pain inventory (BPI) and categorical pain relief scores at the final visit compared to baseline and to screening.
- Global satisfaction score for efficacy and tolerability of study drug by patient at final visit.
- Global McGill Pain Questionnaire Score (Short Form) and Clinical Global Impression at final visit.
- TOPS at screening, baseline, and termination visit and sleep questionnaire at baseline and termination visits.

10.1.1.1.6.3 Statistical Analysis

The null hypothesis was to have been fulfilled if the difference in mean percent change in VASPI from baseline to the final visit at the end of week 3 with LOCF is not statistically

significant. The alternative hypothesis is that the mean percent change in VASPI is different for the ziconotide group compare with the placebo group.

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

Primary Efficacy Analysis:

The primary efficacy variable: $(\text{VASPI Baseline value} - \text{VASPI Value at week 3}) / \text{VASPI Baseline value} \times 100$ with LOCF

The baseline VASPI was to have been taken immediately prior to the infusion of the study drug.

The difference in treatment between groups was to have been compared using a two sided, two sample t-test at the 5% level of significance. Consistency across centers was to have been investigated by examining the treatment differences and corresponding 95% confidence intervals in individual centers.

Secondary Efficacy Analyses:

Percent Change in weekly VASPI at the end of Week 1 and Week 2 with LOCF for early terminations.

Percent change in weekly VASPI at the end of Week 1 and Week 2 and final visit, observed data only without LOCF.

Percent change in weekly opiate consumption (short acting as rescue medications and all opiates used) compared to baseline.

Percent change in Brief Pain Inventory (BPI) Score at the Final Visit compared to Baseline and Screening.

All continuous secondary efficacy variables will be analyzed using two-sample t tests; discrete variables were to have been analyzing using the two-sample binomial test or Pearson's chi-square test.

10.1.1.2 Protocol Amendments

Amendment 1: July 25, 2002

Male patients and their partner(s) of childbearing age are stipulated to use adequate, appropriate contraceptive methods. ((Sponsor's Summary of Patient Eligibility Criteria, (I.8 V.005 P.1023)).

The pump is stipulated to be rinsed three times with fresh 5 mL preservative-free 0.9% Sodium Chloride Injection, UPS using new syringe for each rinse at the subject's last weaning visit (I.8 V.005 P.1030, 1036) and Sponsor's Section 6.5.2).

For subject's receiving high concentrations of opiate solutions

- At the end of the weaning period, when the opiate-containing solution is exchanged for the saline. Active drug was to be infused until the dead volume was replaced with saline.
For a typical dead volume [the dead space is defined as the distance from the pump to the IT space and the volume is calculated at the time of the pump/catheter implant] of 0.4 mL, and a flow rate of 96 microliters/day, it could take as long as 7 days for opiate infusion to end and the saline to reach the catheter tip. This problem would have been compounded in the case of high concentration opiate solution opiate solutions where significant amounts of opiate could have been delivered from the dead volume.

The investigator was to dilute the opiate solution midway through the weaning period to avoid high opiate concentrations at the end of weaning.

The investigator was to exchange the opiate solutions for saline a few days before the end of the weaning period, so that the last of the active drug was infused before the start of the stabilization period. In this way the patient will undergo a one-week stabilization period with only saline infusion.

Patients who decided not to receive intrathecal ziconotide upon completion of ELN92045-301 were to have the contents of their pump removed at the Termination visit. Prior to a patient entering into the open-label trial, the treating physician was to have been unblinded. At the Initial Visit for the open-label trial, patients randomized to ziconotide were to have the contents of their pump reservoir replaced with study drug for the open-label extension (ELN92045-352).

- At the beginning of the Double-blind treatment period, when saline is exchanged for test drug solution, saline was to have been infused until the test drug solution replaced the dead volume. To avoid confounding titration of the test drug and resultant high initial dose of the test drug, the dead volume of the catheter and the pump was to have been calculated exactly and a Priming or Purge Bolus performed to expel the saline from the dead space in the infusion system.

A sleep questionnaire was added. (I.8 V.005 P.1051)

A 12 Lead EKG was included in the Baseline/Randomization Visit. (I.8 V.005 P.1053)

In addition, administrative changes were made to the protocol.

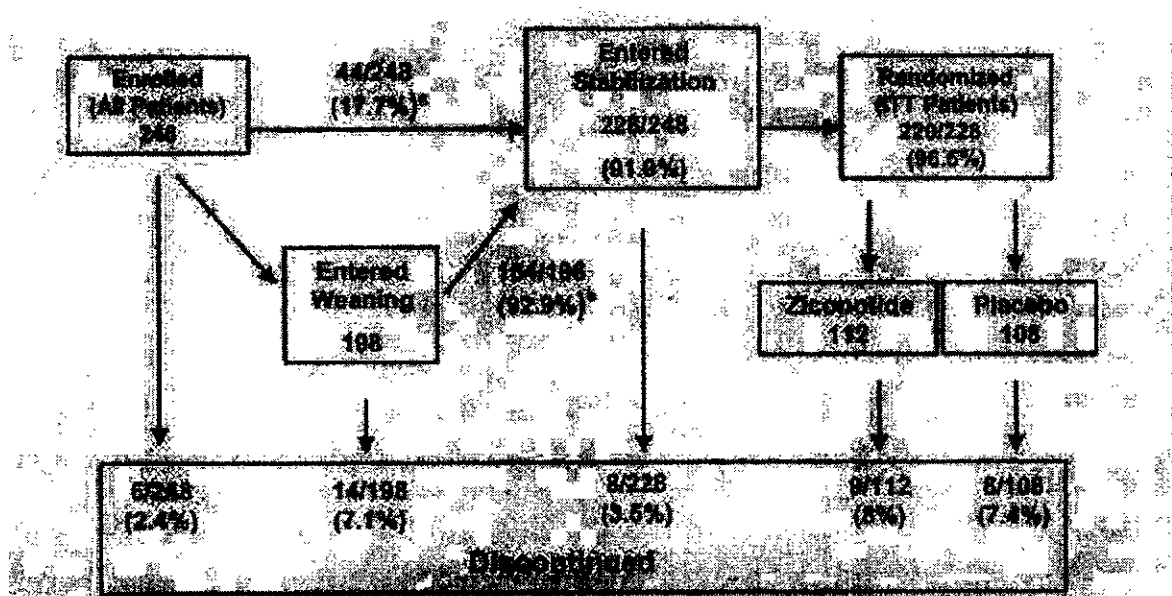
Amendment 2: October 02, 2003

Administrative changes were made to the protocol.

10.1.1.3 Conduct of Study

10.1.1.3.1 Patient Disposition

Figure 10.1.1.3.1-1 Disposition Schematic



^a There were 44 patients who did not need to be weaned from IT medications and directly entered the stabilization period.

^b There were 184 patients who completed the weaning period and then entered the stabilization period. Of these, 177 patients completed the stabilization period and were randomized to treatment.

From Sponsor's Report ELN92045-301 I. V. 002 P. 005, 006, 007, 008

Protocol Violations

Table 10.1.1.3-1 Summary of Patient Disposition and Study Termination - All Enrolled Patients

	Ziconotide	Placebo	Total
Enrolled ^a	NA	NA	248 (100.0%)

Clinical Review
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NDA 21,060
{Prialt (Ziconotide)}

	Ziconotide	Placebo	Total
Did not Meet Screening Inclusion/Exclusion Criteria ^b	NA	NA	8(3.2%)
Dropped out Before Weaning ^o	NA	NA	6(2.4%)
Entered the Weaning Period ^d	NA	NA	198 (100.0%)
Completed Weaning Period	NA	NA	184(92.9%)
Discontinued During Weaning Period	NA	NA	14(7.1%)
Reason for Discontinuation During Weaning Period ^o			
Unable to Wean from IT Analgesics	NA	NA	4(2.0%)
No Longer Meets Inclusion/Exclusion Criteria	NA	NA	1 (0.5%)
Non-Compliant	NA	NA	2 (1.0%)
Adverse Event	NA	NA	2(1.0%)
Subject Request; Voluntary Withdrawal of Consent	NA	NA	5(2.5%)
Other	NA	NA	2(1.0%)
Entered the Stabilization Period	NA	NA	228 (100.0%)
Completed Stabilization Period	NA	NA	220 (96.5%)
Discontinued During Stabilization Period	NA	NA	8(3.5%)
Reason for Discontinuation During Stabilization Period			
No Longer Meets Inclusion/Exclusion Criteria	NA	NA	1 (0.4%)
Adverse Event	NA	NA	1 (0.4%)
Other	NA	NA	6(2.6%)
Met Baseline Criteria	NA	NA	220(100.%)
Randomized	112 (100.0%)	108 (100.0%)	220 (100.0%)
Patients Treated with Study Drug	112 (100.0%)	108 (100.0%)	220 (100.0%)
Completed Study	103(92.0%)	100(92.6%)	203(92.3%)
Early Discontinuation During Treatment Period	9(8.0%)	8(7.4%)	17(7.7%)
Reason for Early Discontinuation During Treatment Period			
Lack of Efficacy	2(1.8%)	2(1.9%)	4(1.8%)
Adverse Event	6(5.4%)	5(4.6%)	11 (5.0%)
Death	0	1 (0.9%)	1 (0.5%)
Subject Request; Voluntary Withdrawal of Consent	1 (0.9%)	0	1 (0.5%)
Planned to Participate in Open-label Extension			

Clinical Review
 Lex Schultheis, M.D., Ph.D.
 NDA 21,060
 {Prialt (Ziconotide)}

	Ziconotide	Placebo	Total
Yes	<u>90(87.4%)</u>	<u>95(95.0%)</u>	185 (91.1%)
No	<u>13(12.6%)</u>	<u>5(5.0%)</u>	<u>18(8.9%)</u>

Note: NA = all patients who entered the screening, weaning, and stabilization periods, but were not yet randomized.

^a All patients who signed the consent form.

^b Four patients (58/1, 58/2, 25/5, 33/2) not meeting screening inclusion/exclusion criteria were randomized into the study; these patients are included in Section 10.2.

Reasons include no longer meets inclusion/exclusion criteria (3 patients), and subject request/voluntary withdrawal of consent, noncompliant, and other (1 patient each) (Sponsor's Study report Appendix 17.2.1, Listing 17.2.1.1).

^d Forty-four patients who were not receiving any IT medications did not enter the weaning phase but entered the stabilization phase directly from screening (IT pump contained no active medication - saline only).

^e Patients with multiple reasons for discontinuation are counted in more than one subcategory.

^f Patient 21/3122.

^g Includes only randomized patients who completed study.

10.1.1.3.2 Demographics/Group Comparability

The study population had a mean age of 54 years, ranging from 27-86 with a similar distribution in age in both treatment groups. The study population was nearly evenly divided between males and female in both treatment groups. The population was almost exclusively Caucasian.

Reference Sponsor's study report ELN92045-301 I.8 V.002 P.113, 114

Dosing Information

The median ziconotide dose at week 3 was 0.25 mcg/hr (range 0-0.8 mcg/hr).

Reference Sponsor's Study report ELN92045-301 I.8 V.002 P.158

Concomitant Medications

Only one patient was not taking opiates at the outset of therapy. In the ziconotide group the most frequently referenced non-opiate medications were antidepressants 70% and anxiolytics 46%. In the placebo group use of these drugs were reported for 57% and 34% of the patients respectively.

Reference Sponsor's Study report ELN92045-301 I.8 V.002 P.161

10.1.1.3.5 Unplanned Analysis

No interim analysis was conducted.

10.1.1.3.6 Sponsor's Efficacy Results

10.1.1.3.6.1 Primary Efficacy Results

The sponsor reported a statistically significant percent reduction in the mean VASPI among patients treated with Ziconotide compared to patients treated with placebo during the third week as compared to the Baseline measurement. There was no significant difference between the Baseline measurements of VASPI between the Ziconotide and the Placebo treatment groups.

Table 10.1.1.3.6.1-1 Percent Change in VASPI Score From Baseline at Week 3 (LOCF) - ITT Population

Parameter	Ziconotide	Placebo	p-value
VASPI Score at Baseline (mm)			
N	112	108	
Mean (SD)	80.7 (14.98)	80.7 (14.91)	
Median (range)	85.0 (50 - 100)	81.5 (51 - 100)	
VASPI Score at Week 3 (mm)			
N	112	108	
Mean (SD)	67.9 (22.89)	74.1 (21.28)	
Median (range)	70.0 (0 - 100)	75.5 (0 - 100)	
Change in VASPI Score from Baseline at Week 3 ^a			0.0360 ^b
N	112	108	
Mean (SD)	14.7 (27.71)	7.2 (24.98)	
Median (range)	9.2 (-45 - 100)	2.3 (-51 - 100)	

^a Percent change = $100 \times (\text{VASPI score at baseline} - \text{VASPI score at Week 3}) / (\text{VASPI score at baseline})$. Positive values represent improvement in pain.

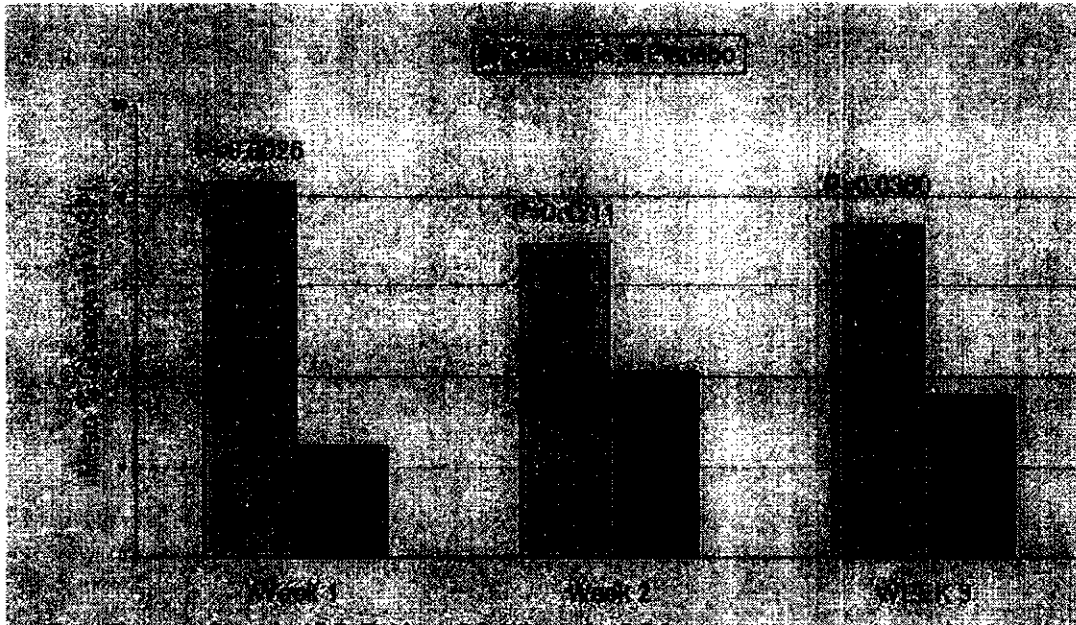
^b Treatment difference was tested using the two-sample t-test.

From Sponsor's Study Report ELN92045-301, I. 8 V. 002 P. 128

10.1.1.3.6.2 Secondary Efficacy Results

Week by Week Change in VASPI

Figure 10.1.1.3.6.2-1 Mean Change in VASPI by Week



From Sponsor's Study Report 301 Section 15.2, Tables 15.2.1-3

Responder Analysis

Table 10.1.1.3.6.2-1 : Treatment Responders at Week 3 - ITT Population

	Ziconotide (N = 112)	Placebo (N = 108)	p-value
Responder ^a to Ziconotide	18(16.1%)	13(12.0%)	0.390 ^d
Nonresponder to Ziconotide	94(83.9%)	95(88.0%)	
95% CI for % of Responders ^b	(8.8%,23.3%)	(5.4%, 18.6%)	
Treatment Difference in % of Responders	4.0%		
95% CI for Treatment Difference in % of Responders ^b	(-6.0%,14.1%).		

^a Responders were defined as those patients who had at least 30% improvement in VASPI score from baseline at Week 3 and all other patients including those with missing VASPI data at Week 3 were classified as non-responders.

^b 95% binomial confidence interval with continuity correction.

Treatment difference is for ziconotide minus placebo.

^d Two sample binomial test.

Data Source: Sponsor's Study Report 301 Section 15.2, Table 15.2.18

Sponsor's Sensitivity Analysis of Primary Efficacy Variable

Table 10.1.1.3.6.2-2 :P-values of the Results of Primary and Other Efficacy Analyses of Percent Change and Change in VASPI at Weeks 1, 2 and 3

	Week 1	Week 2	Week 3
Change VASPI (LOCF)	0.0026	0.1211	0.0360
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

* Primary Efficacy Outcome

Note: All p-values represent comparisons between treatment groups.

Data Source: Sponsor's Study Report Section 15.2, Tables 15.2.1 through 15.2.9

Opiate Consumption

Table 10.1.1.3.6.2-3 Mean Value and Percent Change in Weekly Opiate Consumption From Pretreatment Stabilization at Week 3 (Treatment Period) - ITT Population

Parameter	Ziconotide	Placebo	p-value
Weekly Opiate Consumption (mg) During Pretreatment Stabilization Period ^a			
N	112	108	
Mean (SD)	2101.1 (2353.11)	1876.1 (2145.54)	
Median (range)	1366.8 (0 - 14880)	1202.1 (0 - 11613)	
Weekly Opiate Consumption (mg) During Week 3 (Treatment Period) ^a			0.7475
N	107	101	
Mean (SD)	1524.3 (1626.75)	1452.6 (1578.86)	
Median (range)	1000.0 (0 - 9560)	900.0 (0 - 9181)	
Change from Pretreatment Stabilization at Week 3 (Treatment Period) ^b			0.4371
N	107	101	
Mean (SD)	-23.7 (56.16)	-17.3 (61.14)	
Median (range)	-28.6 (-100 - 400)	-25.0 (-100 - 406)	

Parameter	Ziconotide	Placebo	p-value
Spearman's Rank Correlation Coefficient between % Change in Opiate Consumption at Week 3 and Percent Change in Observed VASPI at Week 3			
N	95	91	
Correlation Coefficient	-0.1076	-0.2738	
p-value ^d	0.2993	0.0086	

^a Weekly absolute opiate consumption was converted to oral morphine equivalent.

^b Percent change = (weekly opiate consumption at current visit - pretreatment stabilization weekly opiate consumption)/(pretreatment stabilization weekly opiate consumption) x 100.

Treatment difference was tested using the two-sample t-test.

^d The p-value is reported for testing the null hypothesis that there is no association between percentage change in weekly opiate consumption from pretreatment stabilization at Week 3 and percentage change in observed VASPI at Week 3 (a two-tailed test). Decrease in pain and increase in opiate use were both calculated as positive changes.

Data Source: Sponsor's Study Report Section 15.2

McGill Pain Score

Table 10.1.1.3.6.2-4 :Change in the Global McGill Pain Total Score and Present Pain Intensity Score From Baseline at Termination - ITT Population

Parameter	Ziconotide (N = 112)	Placebo (N = 108)	p-value
Change in Global McGill Pain Total Score ^a			
N	108	107	0.0259 ^b
Mean (SD)	3.2 (8.71)	0.6 (8.24)	
Median (range)	2.0 (-16 - 35)	0.0 (-22 - 25)	
95% CI of Mean	1.6-4.9	-0.9-2.2	
Change in Global McGill Present Pain Intensity ^a			0.0508
Worsen by >_2 units	1 (0.9%)	6(5.7%)	
Worsen by 1 unit	14(13.1%)	15(14.2%)	
Unchanged	47(43.9%)	47(44.3%)	
Improved by 1 unit	29(27.1%)	30(28.3%)	
Improved by >>-2 units	16(15.0%)	8(7.5%)	
Missing	5 ^c	2	

Note: Total score is sum of scores from fifteen individual descriptors of pain (Throbbing, Shooting, Sharp, Cramping, Gnawing, Hot-burning, Aching, Heavy, Tender, Splitting, Tiring exhausting, Sickening, Fearful, and Punishing-cruel). Each descriptor of pain is

scored as 0 = none, 1 = mild, 2 = moderate, and 3 = severe. Global McGill Present Pain Intensity was scored as follows: 0 = no pain, 1 = mild, 2 = discomforting, 3 = distressing, 4 = horrible, and 5 = excruciating.

^a Change = (Baseline score - score at termination).

^b Treatment difference was tested using the Two-sample t-test. Mantel-Haenszel chi-square test with 1 degree of freedom.

Data Source: Sponsor's Study Report Section 15.2

McGill Global Score

Table 10.1.1.3.6.2-5 : Clinical Global Impression at Termination - ITT Population

Parameter	Ziconotide (N = 112)	Placebo (N = 108)	p-value ^a
Satisfaction with Therapy ^b at Termination n (%)			
Satisfaction ^b			0.0027
Not at all	37(33.9%)	55(51.4%)	
A little bit	17(15.6%)	16(15.0%)	
Somewhat	24(22.0%)	23(21.5%)	
A lot	23(21.1%)	8(7.5%)	
Completely	8(7.3%)	5(4.7%)	
Missing	3	1	
Overall Pain Control Rating ^c at Termination n (%)			0.0004
Poor	46(42.2%)	60(56.1%)	
Fair	19(17.4%)	28(26.2%)	
Good	31(28.4%)	18(16.8%)	
Very Good	9(8.3%)	0	
Excellent	4(3.7%)	1 (0.9%)	
Missing	3	1	

^a Mantel-Haenszel chi-square test with 1 degree of freedom.

^b Clinical Global Impression of Satisfaction Rating: 0 = not at all, 1 = a little bit, 2 = somewhat, 3 = a lot, and 4 = completely.

Clinical Global Impression of Overall Pain Control Rating: 0 = poor, 1 = fair, 2 = good, 3 = very good, and 4 = excellent.

Data Source: Sponsor's Study Report Section 15.2

Categorical Pain Score

Table 10.1.1.3.6.2-6 : Categorical Pain Relief Scale at Termination - ITT Population

Parameter	Ziconotide (N = 112)	Placebo (N = 108)	p-value
CPRS at Termination			0.0596 ^a
Worse	35(32.1%)	27(25.2%)	
No Change	23(21.1%)	46(43.0%)	
Slight Improvement	22(20.2%)	19(17.8%)	
Moderate Improvement	12(11.0%)	11 (10.3%)	
A Lot of Improvement	15(13.8%)	3(2.8%)	
Complete Relief	2(1.8%)	1 (0.9%)	
Missing	3	1	

Note: CPRS scores are ranked as follows: 0 = worse, 1 = no change, 2 = a slight improvement, 3 = moderate improvement, 4 = a lot of improvement, and 5 = complete relief.

^a Mantel-Haenszel chi-square test with 1 degree of freedom for comparing ziconotide versus placebo at termination.

Data Source: Sponsor's Study Report Section 15.2

Sleep Score

Table 10.1.1.3.6.2-6 : Sleep Pattern and Quality of Sleep at Termination - ITT Population

Parameter	Ziconotide (N = 112)	Placebo (N = 108)	p-value ^a
Current Sleep Pattern (uninterrupted) at Termination			0.0067
<2 hours	20(18.5%)	29(27.1%)	
2 to 4 hours	45(41.7%)	55(51.4%)	
4 to 6 hours	33(30.6%)	18(16.8%)	
Over 6 hours	10(9.3%)	5(4.7%)	
Missing	4	1	
Pain Makes it Hard to Fall Asleep			0.6394
Yes	69(63.3%)	71(66.4%)	
No	40(36.7%)	36(33.6%)	
Missing	3	1	
Pain Wakes Me Up During the Night			0.0715
Yes	82(75.2%)	91(85.0%)	
No	27(24.8%)	16(15.0%)	
Missing	3	1	
Overall Quality of Sleep			0.0059
Poor	45(41.7%)	61(57.0%)	

Clinical Review
Lex Schultheis, M.D., Ph.D.
NDA 21,060
{Prialt (Ziconotide)}

Fair	43(39.8%)	38(35.5%)	
Good	20(18.5%)	8(7.5%)	
Missing ~	.	1	

^a Mantel-Haenszel chi-square test with 1 degree of freedom.
Data Source: Sponsor's Study Report Section 15.2

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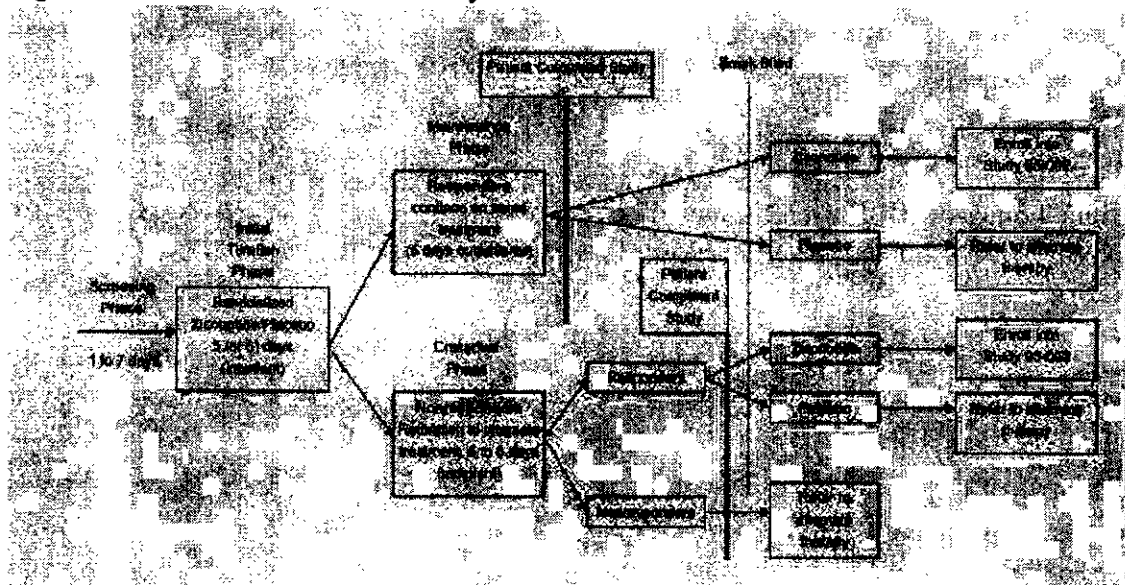
10.1.2 STUDY 95-01 Protocol Synopsis "A Multicenter, Phase II/III, Placebo Controlled Study Of SNX-111 (ziconotide) Administered Intrathecally To Patients With Chronic Malignant Pain."

10.1.2.1 Synopsis

10.1.2.1.2 Objective: To compare the effect of increasing doses of IT SNX to placebo in chronic malignant pain and assess the safety of increasing doses of IT SNX.

10.1.2.1.3 Study Design: The study was to be a multicenter, multi-national, randomized, double blind, parallel, placebo controlled trial. The primary efficacy endpoint was to be obtained at the end of the initial titration period. The second phase of the study was to include a crossover period for a subset of patients from which several secondary endpoints were to be obtained.

Figure 10.1.2.1.3-1 Schematic of Study



From Sponsor's Study Report

Inclusion Criteria:

1. Patients with chronic intractable pain from malignancy or AIDS
2. Patients who have an intrathecal catheter and/or Medtronic SynchroMed infusion System in place, or whose next line of therapy would require placement of such a device
3. The patient has been slowly tapered and discontinued from intrathecal medications, stabilized on oral or systemic analgesics for at least 3 d prior to enrollment in the study.
4. Life expectancy of at least 1 month. If implantation of a SynchroMed pump is considered, life expectancy should be greater than 3 months.

5. Average Visual Analog Scale Pain Intensity (VASPI) over past 3 days on oral or systemic opioids of at least 50.
6. 18 yo or older, limited enrollment of patients at least 10 y of age at some centers
7. Women must not be pregnant or breastfeeding. Women must be postmenopausal or if of child bearing potential, using an acceptable method of contraception.

Exclusion Criteria:

1. Sepsis
2. CHF, sinus bradycardia with greater than 1st degree block, asthma, syncope
3. Mini-mental status exam of <24 or diagnosis of dementia/delirium
4. Investigational drug study within 30 d
5. Prior SNX study
6. Physical or psychological problem precluding pump implantation or use of external pump
7. Intrathecal catheters above T1
8. Implanted infusion pumps or catheters other than SynchroMed system

Enrollment of 120 patients was planned.

During the screening period, patients were to be stabilized on a systemic analgesic regimen for at least 3 days prior to study enrollment. Patients receiving intrathecal therapy were to be tapered off all intrathecal medication for a minimum of 3 days prior to beginning study medication.

During the pre-infusion period, patients would then be randomized to SNX or placebo and begin a blinded 5 day initial titration as inpatients. Patients tolerating the study drug after 48 h were to be permitted discharge to home for the remainder of the initial titration phase. The primary efficacy endpoint was to be measured at the end of this titration period.

Randomization was to be 2:1 SNX to placebo, and stratified by etiology of chronic pain (AIDS vs. cancer), and history of intrathecal opioid use. Randomization was also to be stratified by center, with a block size of three within a center

The following definitions were provided by the sponsor to determine treatment assignments at the conclusion of the initial titration period and to assist with decisions concerning dosage adjustment.

1. Responders - patients experiencing a $\geq 30\%$ drop in VASPI (an average of the last 2 measurements taken within a 2 h period or 3 if the first 2 measurements differ by greater than 15 mm) compared with baseline in the setting of stable or decreasing regimen of concurrent opioid analgesics and no change in the type of concurrent opioid analgesics.
2. Non-responders - patients experiencing $< 30\%$ drop in VASPI or a 30% drop in the setting of increased opioid analgesics including a change in type of opioid analgesic
3. Early responders - patients who demonstrate a response prior to 144 h of study medication infusion, on initial or crossover arms
4. Onset of analgesia - a minimum of 20% improvement from baseline VASPI with confirmation by categorical pain relief scale, without an increase in opioids

At the conclusion of the 5 day initial titration period:

1. Responders were to continue on the same treatment for a 5 day maintenance period as out-patients. At the end of the 5 day maintenance period the treatment assignments were to be unblinded:
 - 1a. Responders to SNX were to be enrolled in a long term study
 - 1b. Responders to placebo were to be discontinued from the study.
2. Non-responders were to be crossed over to the alternate treatment still blinded and titrated for up to 5 d. At the end of the 5 day crossover period, the treatment assignments were to be unblinded:
 - 2a. Non-responders to SNX were to be discontinued from the study.
 - 2b. Non-responders to placebo were to be discontinued from the study.
 - 2c. Placebo responders were to be discontinued from the study.
 - 2d. SNX responders from this period were to be offered enrollment in a long term study.

Study Medication

The study drug was to be SNX-111 acetate in vehicle with L-methionine and NaCl, pH 4.3 +/- 0.2. The placebo and diluent were the same as vehicle.

The dosing regimen was changed three times during the study. The initial dose of drug for any given patient was to be based on weight in the original protocol, starting with 0.005 mcg/kg/h up to a maximum dose of 0.3 mcg/kg/h, titrated upward every 12 h.

Time (hours)	Original, 1/23/96 (mcg/kg/h)	Revision 1 6/11/96 (mcg/h)
0 - 12	0.005	0.4
12 - 24	0.008	0.6
24 - 36	0.013	0.9
36 - 48	0.021	1.5
48 - 60	0.034	2.4
60 - 72	0.055	3.9
72 - 84	0.089	6.2
84 - 96	0.144	10.1
96 - 108	0.233	16.3
108 - 120	0.300	21.0

Time (hours)	Revision2, 10/25/96 (mcg/h)	Revision 3, 2/21/97 (mcg/h)
0 - 24	0.4	0.1
24 - 48	0.6	0.2
48 - 72	0.9	0.3
72 - 96	1.5	0.6
96 - 120	2.4	1.2
120 - 144 prn	3.9	2.4

Subjects were to be titrated to toxicity according to the original protocol. Beginning with Revision 2, the dose titration interval was changed from 12 hours to 24 hours. Beginning with

revision 3, patients were to be titrated to efficacy. Also once the onset of analgesia was reached, the dose was to be held an additional 24 h to permit the full analgesic effect to occur. Any dose could be held an additional 24 h before further increase, at the investigator's discretion. A dose was to be maintained or reduced as needed based on the appearance of lateral gaze nystagmus, a change in baseline confusion, or the appearance of other adverse events (AE's) thought to be related to study drug.

Concomitant Medication:

No intrathecal medications were to be allowed.

Pain and Functionality Assessment Scales:

Visual Analog Scale Pain Intensity (VASPI) - a standard 100 mm visual analog scale

Visual Analog Scale Pain Relief (VASPR) - from the Memorial Pain Assessment Card ranging from "No relief of pain" to "Complete relief of pain"

Mood Score - from the Memorial Pain Assessment Card: visual analog scale for mood ranging from "Worst mood" to "Best mood".

Tursky Description - from the Memorial Pain Assessment Card: 4 category scale: No Pain; Just Noticeable, Mild Or Weak; Moderate Or Strong; Severe Or Excruciating

Category Pain Relief Scale (CPRS) a 6 point categorical scale from 0 - "My pain is now WORSE compared to before the infusion started." to 5 - "I have COMPLETE RELIEF of my pain compared to before the infusion started"

Wisconsin Brief Pain Inventory Scale (WBPI) - a series of 6 descriptions of function: mood, relationships with other people, walking ability, sleep, normal work and enjoyment of life, scored on a 0 (not at all) to 4 (extremely) categorical scale.

Karnofsky Performance Status Scale Score

10.1.2.1.4 Efficacy Analysis

Primary Efficacy Analysis:

The primary efficacy endpoint was to be the percent change of VASPI from baseline to the end of the initial titration phase = $[(\text{baseline VASPI} - \text{final VASPI})/\text{baseline VASPI}] \times 100$.

The primary efficacy endpoint was to be analyzed using a 2-way ANOVA model with treatment, intrathecal opioid use history and treatment-by- intrathecal opioid use history. The evaluable population was to be used for this analysis.

10.1.2.2 Conduct of the Study

10.1.2.2.1 Disposition

Of the 112 patients enrolled and treated, 108 met evaluability criteria. Sixty eight of these initially received ziconotide, 40 placebo. However, the ITT population included 71 patients who received ziconotide.

Ninety eight of 112 patients enrolled in the study carried the diagnosis of cancer. These patients were evenly distributed in the two treatment groups, 86.8% in the ziconotide group and 90% in the placebo group. The remainder of patients enrolled in the study had AIDS.

Initial titration phase: Of the 72 patients receiving ziconotide, 11 withdrew during titration phase. Of the 40 patients initially receiving placebo, 3 discontinued during the initial titration. One additional patient in each initial titration group completed titration but did not enter a second phase.

Maintenance phase: Forty eight patients initially treated with ziconotide who completed initial titration entered maintenance. Of these, 9 discontinued the study during maintenance. There were no early discontinuations among the 11 patients initially treated with placebo that entered the maintenance phase.

Crossover phase: Three of the 12 patients crossed over from ziconotide to placebo and 8 of the 25 patients crossed over from placebo to ziconotide discontinued the study early.

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Table 10.1.2.2.1-1 Patient Disposition

	Initial Treatment Assignment	
	Ziconotide	Placebo
Number of Patients Randomized	71	40
All Treated Patients ^a	72 (100.0%)	40 (100.0%)
Safety Population	72 (100.0%)	40 (100.0%)
ITT Population	71 (98.6%)	40 (100.0%)
Evaluable Population	68 (94.4%)	40 (100.0%)
Reasons for Being Non-evaluable		
Not Randomized	1 (1.4%)	
Insufficient VASPI data	3 (4.2%)	
Number of Patients Who Completed the Study	47 (65.3%)	29 (72.5%)
Initial Titration Phase		
Completed Phase and Entered Second Phase	60 (83.3%)	36 (90.0%)
Completed Phase and Did Not Enter 2nd Phase	1 (1.4%)	1 (2.5%)
Primary Reason for Early Termination:		
Intolerable Adverse Event ^b	5 (6.9%)	2 (5.0%)
Withdrawal Requested by Patient	2 (2.8%)	0 (0.0%)
Unrelated Medical Condition	2 (2.8%)	0 (0.0%)
Infection ^c	0	1 (2.5%)
System Related (Pump/Catheter)	1 (1.4%)	0
Ineffective Drug Therapy / Loss of Effect	1 (1.4%)	0
Other	0	0
Maintenance Phase ^d		
Entered Phase	48 (66.7%)	11 (27.5%)
Completed Phase	39 (54.2%)	11 (27.5%)
Primary Reason for Early Termination		
Intolerable Adverse Event ^e	4 (5.6%)	0
Withdrawal Requested by Patient	1 (1.4%)	0
Death on Study ^f	2 (2.8%)	0
Ineffective Drug Therapy/Loss of Effect	1 (1.4%)	0
Other ^g	1 (1.4%)	0
Crossover Phase ^h		
Entered Phase	12 (16.7%)	26 (65.0%)
Completed Phase	7 (9.7%)	18 (45.0%)
Primary Reason for Early Termination		
Intolerable Adverse Event ⁱ	3 (4.2%)	8 (20.0%)
Withdrawal Requested by Patient	1 (1.4%)	0
Other ^j	1 (1.4%)	0

a Patient 5047-74 was not randomized but received open-label ziconotide on compassionate basis.

b One placebo patient (Patient 5047-49) discontinued due to an adverse event associated with the device.

c One placebo patient (Patient 5006-75) discontinued due to an infection associated with the device.

d Patients who completed the initial titration phase and underwent the maintenance phase continued to receive their initial treatment.

e Three ziconotide patients (Patients 501-87, 5025-74, and 5097-50) discontinued due to adverse events associated with the device

- f Patient 5009-74 died of ovarian carcinoma, unrelated to drug. Patient 5025-49 died after a suicide attempt, possibly related to drug.
 g Other included Patient 5006-73 (Patient went home on Day 6 with complete relief of pain).
 h Patients who were nonresponders, during the initial titration phase were crossed over to receive the opposite treatment during the crossover phase. Includes Patient 5014-49 who crossed over to ziconotide after maintenance on placebo.
 i Two placebo patients receiving ziconotide during the crossover phase (Patients 5002-25 and 5025-73) discontinued due to adverse events associated with the device.
 j No reason was specified.
 Data Source: review Sharon Hertz, M.D. 6/2/00

10.1.2.2.2 Sponsor's Efficacy Analysis

Primary Efficacy Analysis

The primary efficacy measure was the percent change in VASPI score from baseline to end of initial titration. For the evaluable group, the VASPI decreased by 53% for patients initially treated with ziconotide and by 18% for patients initially treated with placebo, a statistically significant difference. These results are presented in Table 10.1.2.2.2-1. This difference remained statistically significant when the baseline VASPI was taken into account and when the concurrent use of opioids was taken into account.

Table 10.1.2.2.2-1 Percent Change in VASPI Score from Baseline to the End of Initial Titration Phase - Evaluable Population (From sponsor's Table 9.1 Vol. 2.096, P. 135)

Parameter	Initial Treatment Assignment		p-value ^a
	Ziconotide (N= 68)	Placebo (N=40)	
VASPI Score at Baseline (mm)			0.183 (0.921)
Mean (SE)	73.6 (1.83)	77.9 (2.31)	
Median (range)	75.0 (27 - 100)	79.5 (45 - 99)	
VASPI Score at End of Initial Titration (mm)			
Mean (SE)	34.2 (3.48)	61.0 (4.89)	
Median (range)	27.0 (0-99)	70.3 (4 - 100)	
% change VASPI score at End of Initial Titration ^b			0.0002 (0.337)
Mean (SE)	53.1 (4.63)	18.1 (6.77)	
Median (range)	62.3 (-26 -100)	7.8 (-62 - 96)	
95% CI for Mean ^c	(44.0, 62.2)	(4.8, 31.4)	
95% CI for Mean Difference ^c	(18.9, 51.1)		

a Treatment difference was tested using the 2-way ANOVA model with treatment, intrathecal opioid use history, and treatment by intrathecal opioid use history interaction as factors. The p-value for treatment-by-intrathecal opioid use history interaction is given in parentheses (see Appendix 13).

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

c Data were pooled across strata when calculating the 2-sided 95% confidence intervals for individual treatment mean and for treatment difference (ziconotide-placebo) in mean percent change in VASPI score at the end of the initial titration phase.

Data Source: Review by Sharon Hertz

Therapeutic dose level

The dosages at the time of onset of analgesia was evaluated by initial dose for patients who received ziconotide during the initial titration period and these are summarized in Table 10.1.2.2.2-2. Patients receiving an initial dose of ≤ 0.1 mc g/h reached the onset of analgesia at a mean dose of 0.48 mc g/h. Patients receiving an initial dose of >0.1 mc g/h reached the onset of analgesia at a mean dose of 3.12 mc g/h. The original and first 2 amended dosing regimens started dosing at higher doses, with only 12 hours between titration steps, and incorporated a forced titration to toxicity. By waiting only 12 hours between titration steps it is possible that many patients were titrated to the next dose level before experiencing the full effect of the lower dose. As a result, the onset of analgesia would be attributed to a higher dose in these patients. Instructions to end the forced titration and lower the starting dose to 0.1 mc g/h were part of revision 3, dated 2/21/97.

Patients beginning titration with an initial dose >0.1 mc /h. The dosing instructions to titrate to toxicity with titration at 12 hour intervals likely also impacted the final dose as well.

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Table 10.1.2.2.2-2 Ziconotide Dosing Information during Initial Titration Phase (From sponsor's Table 9.5 Vol. 2.096, P. 148)

Parameter	Initial Dose		Total
	<0.1 mcg/h	> 0.1 mcg/h	
Dose at End of Initial Titration (mcg/h) ^a			
n	39	29	68
Mean (SE)	0.52(0.09)	1.34(0.33)	0.87(0.16)
Median	0.3	0.8	0.6
Range	0.074 - 2.400	0.200 - 9.360	0.074 - 9.360
Cumulative Dose During Initial Titration (mcg) ^b			
n	39	29	68
Mean (SE)	36.90 (4.25)	167.83 (34.25)	92.74 (16.66)
Median	26.63	95.79	56.53
Range	6.80 - 116.80	36.15 - 880.55	6.80 - 880.55
Dose at Onset of Analgesia (mcg/h) ^c			
n	39	29	68
Mean (SE)	0.48(0.09)	3.12(0.95)	1.60(0.43)
Median	0.2	1.5	0.6
Range	0.10-2.40	0.20-20.58	0.10-20-58

a The last non-zero dose level administered during the initial titration phase was reported.

b The cumulative dose mcg/h at the end of the initial titration phase with K distinct doses was estimated as: [dose level 1 (mcg/hr) x duration of dose level 1 (hours) and dose level 2 mcg x duration of dose level 2 (hours) +...+ dose level K (mcg/hr) x duration of dose level K (hours)].

c Onset of analgesia was defined as when the percent change in VASPI was >20% and the CPRS score was 2:2 (i.e., at least a slight improvement). For patients who did not have onset of analgesia, the maximum dose level during the initial titration phase was used.

Data Source. Review by Sharon Hertz

Period of treatment

The assignment into either the maintenance phase or crossover for the alternate therapy during the second period of the study was based on the investigator's assessment of whether a patient was a responder or nonresponder. This assessment was performed incorrectly for 21 patients. Of the 49 patients initially treated with ziconotide and placed in maintenance, 15 were incorrectly assigned. Of the 11 placebo treated patients placed in maintenance, 2 were incorrectly assigned. As a result of these errors, the data from the maintenance group was not assessed further.

Patients determined to be nonresponders at the end of the initial titration period were to be crossed over to the alternate treatment. Of the 7 ziconotide treated patients crossed over to placebo, one was incorrectly assigned. Of the 26 placebo treated patients crossed over to ziconotide, 3 were incorrectly assigned. The mean percent change in VASPI score during the initial titration period was negligible for these nonresponders regardless of treatment group. Placebo nonresponders crossed over to ziconotide for the second treatment period responded with a mean percent change in VASPI score of 44.9%. This is comparable to the 53% reduction in mean VASPI score at the end of the initial titration for patients initially treated with ziconotide.

Responder Rate

As noted in the protocol, the definition of a responder was established at the beginning of the trial and served as a means of determining the nature of the second phase of treatment. There were many errors by the investigators in determining which patients met these criteria. The sponsor reviewed the CRF's and determined which patients truly met the responder criteria (derived data). The difference in proportion of responders between treatment groups is statistically significantly greater for the ziconotide treated group.

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10.1.3 STUDY 96-002 Protocol Synopsis "A Multicenter, Phase II/III, Placebo Controlled Study of SNX-111 (SNX) Administered Intrathecally To Patients With Chronic Non-Malignant Pain."

10.1.3.1. Synopsis

10.1.3.1.1 Objective: To assess the safety and efficacy of increasing doses of IT SNX in chronic non-malignant pain compared to placebo

10.1.3.1.2 Study Design:

Figure 10.1.3.1.2-1 Schematic of Study

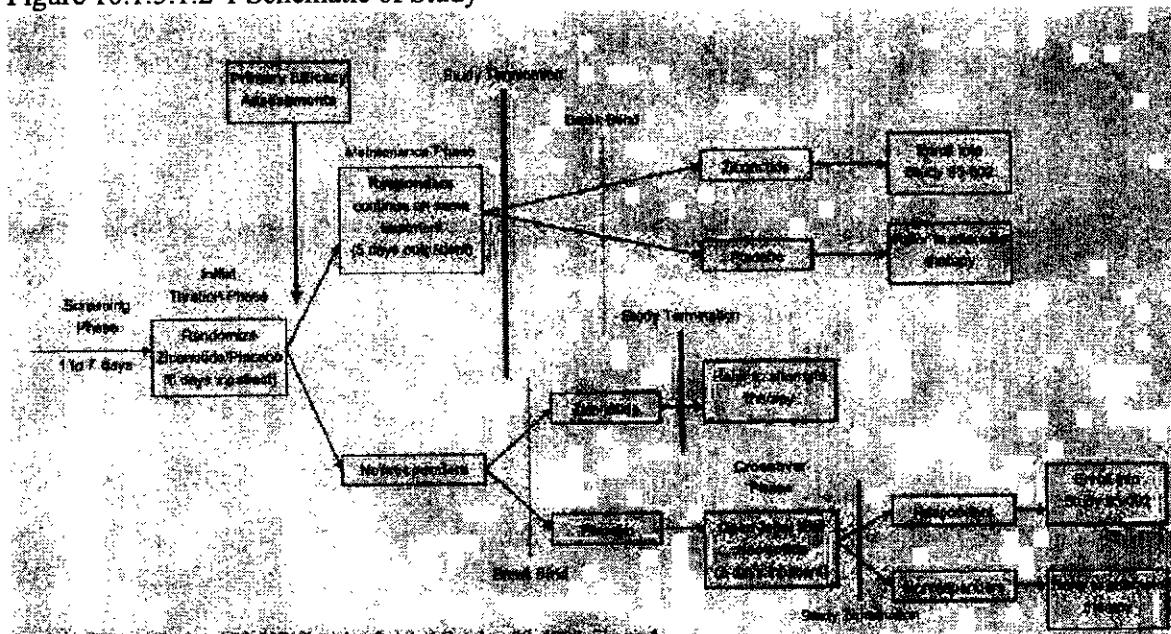


Figure is from sponsor's study report

Inclusion Criteria:

1. Patients with chronic non-malignant pain who have intrathecal catheters and/or Medtronic SynchroMed infusion System in place, or whose next line of therapy would require placement of such devices.
2. The patient has been slowly tapered and discontinued from intrathecal medications, stabilized on oral or systemic analgesics for at least 3 d prior to enrollment in study.
3. Medically capable of having a pump and /or temporary catheter implanted.
4. Average VASPI over past 3 days on oral or systemic opioids of at least 50
5. At least 18 years of age.
6. Women must not be pregnant or breastfeeding. Women must be postmenopausal or if of child bearing potential, using an acceptable method of contraception.

7. History of unsatisfactory response to systemic opioids and has tried at least 2 of the following: NSAIDs, antidepressants, anticonvulsants or topical agents.
8. History of a failed a course of physical therapy where appropriate.

Exclusion Criteria:

1. Sepsis
2. CHF, sinus bradycardia with greater than 1st degree block, asthma, syncope
3. Diagnosis of dementia/delirium, somatization d/o, hypochondriasis, Munchausen's syndrome, inadequately treated affective d/o. If these are possible, patient must be evaluated and cleared by a psychiatrist.
4. Investigational drug study within 30 d
5. Physical or psychological problem precluding pump implantation or use of external pump
6. Intrathecal catheters above T1
7. Implanted infusion pumps or catheters other than SynchroMed system

Enrollment of 170 patients was planned.

During the screening period, patients were to be stabilized on a systemic analgesic regimen for at least 3 d prior to study enrollment. Patients receiving intrathecal therapy were to be tapered off all intrathecal medication for a minimum of 3 days prior to beginning study medication.

During the pre-infusion period, patients would then be randomized to SNX or placebo and begin a blinded 6 day initial titration as inpatients. The primary efficacy endpoint was to be measured at the end of this titration period.

Randomization was to be 2:1 SNX to placebo, and stratified by central vs. peripheral pain syndrome. Randomization was also to be stratified by center, with a block size of three within a center.

The following definitions were provided by the sponsor to determine treatment assignments at the conclusion of the initial titration period and to assist with decisions concerning dosage adjustment.

1. Responders - patients experiencing a $\geq 30\%$ drop in VASPI (an average of the last 2 measurements taken within a 2 h period or 3 if the first 2 measurements differ by greater than 15 mm) compared with baseline in the setting of stable or decreasing regimen of concurrent opioid analgesics and no change in the type of concurrent opioid analgesics.
2. Non-responders - patients experiencing $< 30\%$ drop in VASPI or a 30% drop in the setting of increased opioid analgesics including a change in type of opioid analgesic
3. Early responders - patients who demonstrate a response prior to 144 h of study medication infusion, on initial or crossover arms
4. Onset of analgesia - a minimum of 20% improvement from baseline VASPI with confirmation by categorical pain relief scale, without an increase in opioids

At the conclusion of the 6 day initial titration period:

3. Responders were to continue on the same treatment for a 5 day maintenance period as out-patients. At the end of the 5 day maintenance period the treatment assignments were to be unblinded:
 - 1a. Responders to SNX were to be enrolled in a long term study
 - 1b. Responders to placebo were to be discontinued from the study.
4. Non-responders were to have the medication assignment unblinded:
 - 2a. Non-responders to SNX were discontinued from the study.
 - 2b. Non-responders to placebo were to be crossed over, open-label, to SNX and titrated as in-patients for 5 days.
 - 2b(i). SNX responders from this period were to be offered enrollment in a long term study.
 - 2b(ii). SNX non-responders were to be discontinued from the study.

Study Medication:

The study drug was to be SNX-111 acetate in vehicle with L-methionine and NaCl, pH 4.3 +/-0.2. The placebo and diluent were the same as vehicle.

The dosing regimen was changed twice during the study, the details are described below in the protocol amendments. The 3 dosing regimens used are presented below.

Table 10.1.3.1.2-1 Changes to Dosing Regimen

Time (Hours)	Original (mcg/h)	Revision 1, 10/21/96 (mcg/h)	Revision 2, 2/21/97 (mcg/h)
0-24h	0.4	0.4	0.1
24-48	0.9	0.6	0.2
48-72	1.8	0.9	0.3
72-96	3.4	1.5	0.6
96-120	5.3	2.4	1.2
120-144	7.0	3.9	2.4

Table from Review by Dr. Sharon Hertz

Subjects were to be titrated to efficacy at titration intervals of 24 h. As of revision 1, once the onset of analgesia began, the dose was to be held an additional 24 h to permit the full analgesic effect to occur. Also as of revision 1, any dose could have been held an additional 24 h before further increase, at the investigator's discretion. A dose was to be maintained or reduced as needed based on the appearance of lateral gaze nystagmus, a change in baseline confusion, or the appearance of other adverse events (AE's) thought to be related to study drug.

Concomitant Medication:

No intrathecal medications were to be allowed.

Pain and Functionality Assessment Scales:

Visual Analog Scale Pain Intensity (VASPI) - a standard 100 mm visual analog scale

Category Pain Relief Scale (CPRS) a 6 point categorical scale from 0 - "My pain is now WORSE compared to before the infusion started." to 5 - "I have COMPLETE RELIEF of my pain compared to before the infusion started"

Wisconsin Brief Pain Inventory Scale (WBPI) - a series of 6 descriptions of function: mood, relationships with other people, walking ability, sleep, normal work and enjoyment of life, scored on a 0 (not at all) to 4 (extremely) categorical scale.

McGill-Melzack Pain Questionnaire (Vol. 2.107, P. 069) -a tool consisting of 3 major classes of word descriptors--sensory, affective and evaluative--that are used by patients to specify subjective pain experience, along with an intensity scale and other items to determine the properties of pain experience. The 3 major measures are: (1) the pain rating index, based on two types of numerical values that can be assigned to each word descriptor, (2) the number of words chosen; and (3) the present pain intensity based on a 1-5 intensity scale

Short Form Sickness Impact Profile (Vol. 2.107, P. 072)- a list of 20 statements, patients check off those that describe them on the day they are responding to the evaluation. Includes statements such as: "I am going out less to visit people", "I often moan and groan in pain or discomfort", "I walk more slowly".

Primary Efficacy Analysis:

The primary efficacy endpoint was to be the percent change of VASPI from baseline to the end of the initial titration phase = $[(\text{baseline VASPI} - \text{final VASPI})/\text{baseline VASPI}] \times 100$.

The primary efficacy endpoint was to be analyzed using a 2-way ANOVA model with treatment, center and treatment-by-center as interactions. Student's t-test was to be used to test significance of the mean percent change in VASPI from baseline to the end of the initial titration phase for each treatment group. This primary efficacy analysis was to be performed on the evaluable population.

10.1.3.2 Conduct of Study

Patient enrollment took place from 8/19/96 through 2/10/98. A total of 43 investigators at 43 centers enrolled patients. Nine investigators were responsible for enrolling 10 or more patients each. The remaining 33 centers enrolled less than 10 patients per center.

The planned interim analysis by an independent party was performed on 12/15/97. Over 200 patients had already been enrolled at that time, but the interim database consisted of 104 patients. The estimate of the standard deviation was revised and it was determined that to have 90% power for detecting the originally specified treatment difference of 30% with a 2:1 ration of ziconotide treated patients to placebo, a total of 80 patients would be required. The sample size already exceeded this 200 patients.

10.1.3.2.1 Disposition

Seven of the 264 patients randomized to study drug were not treated. Seventy three patients discontinued the study early. Eight patients in each group were considered unevaluable by the sponsor. Forty of the remaining 170 patients randomized to ziconotide discontinued during the initial titration period; 8 during the maintenance period. Seven of the remaining 87 patients randomized to placebo discontinued the study during the initial titration period and 18 after crossing over to ziconotide. One patient initially randomized to ziconotide whose treatment was interrupted by a dislodged catheter was randomized a second time, receiving placebo under a new patient number. Of note there is one patient excluded from the ITT population, included in the safety population that cannot be accounted for. Based on the definitions of the populations, the assumption is that this patient was felt to have insufficient VASPI to be included in the ITT.

The most common reason for early study discontinuation was intolerable adverse events. This accounted for 15.9% of the early discontinuations from the ziconotide group and 1% of the early discontinuations from the placebo group during initial titration. During the maintenance period, 19.5% of ziconotide treated patients discontinued the study due to adverse events. During the crossover period (from placebo to ziconotide) 19.5% of patients discontinued the study due to adverse events.

10.1.3.2.2 Sponsor's Efficacy Results

Primary Efficacy Analysis:

The primary efficacy parameter was the mean percent change in VASPI from baseline to the end of the initial titration phase and this information is summarized in Table 7.28. The mean percent change in VASPI for the ziconotide group was 30.7% reported by sponsor (31.7% by this reviewer's calculation). This was significantly different from zero and from the mean percent change of 6.2% by sponsor (6.8% this reviewer's calculation) in the placebo group.

Table 10.1.3.2.2 Percent Change in VASPI Score From Baseline to the End of Initial Titration Phase - Evaluable Population (From sponsor's Table 9.1 Vol. 2.107, P. 126)

Parameter	Ziconotide	Placebo	p-value
VASPI Score at Baseline (mm)			0.018 (0.178). ^a
n	159	79	
Mean (SE)	80.2 (1.09)	76.8 (1.54)	
Median (range)	82.0 (33 - 100)	76.0 (50 - 100)	
VASPI Score at End of Initial Titration (mm)			
n	159	79	
Mean (SE)	54.8 (2.65)	71.6 (2.60)	
Median (range)	62.0 (0 - 100)	77.0 (17 - 100)	
% Change in VASPI Score at End of Initial Titration ^b			0.0002 (0.324). ^a
n	159	79	
Mean (SE)	30.7 (3.47)	6.2 (3.24)	
Median (range)	23.8 (-113 - 100)	1.1 (-62 - 80)	
95% CI for Mean ^c	(23.9, 37.5)	(-0.1, 12.6)	

Parameter	Ziconotide	Placebo	p-value
95% CI for Mean Difference ^c	(15.2, 33.8)		

a. Treatment difference was tested using the 2-way ANOVA model with treatment, center, and treatment-by-center interaction as factors. The p-value for treatment-by-center interaction is given in parentheses (see Appendix 13).

b. Percent change = $100 \times (\text{VASPI score at baseline} - \text{VASPI score at end of initial titration}) / (\text{VASPI score at baseline})$. Positive values represent improvement in pain.

c. Data were pooled across centers when calculating the 2-sided 95% confidence intervals for individual treatment mean and for treatment difference (ziconotide - placebo) in mean percent change in VASPI score at the end of the titration phase.

Note: Only patients having non-missing data at both baseline and the end of the initial titration phase were included in the analysis.

Note: Evaluable Patients 6057-101, 6063-102, and 6081-101 in the ziconotide group were excluded from the analysis as these patients did not have VASPI scores at both baseline and at the end of initial titration.

Data Source: Review Sharon Hertz

Dose Range

An analysis of the percent change in VASPI from baseline to the end of the initial titration period by the dose range at the time of VASPI measurement was performed. This was not a planned analysis. The numbers in these subgroups were too small for statistical comparisons. There was difference in the mean percent change in VASPI for the $> 0.2, \leq 0.3$ mcg/h range between treatment groups which may be a function of only 3 placebo treated patients in the comparator group. There was also no difference in the mean percent change in VASPI between treatment groups for the >2.0 mcg/hr dose range. This may reflect either a ceiling effect for the ziconotide or may indicate that patients not responding at lower doses were too refractory to respond even at this higher dose range.

Drug-Disease Interaction

The mean percent change in VASPI was analyzed for effects by either pain syndrome or pain classification. Pain syndrome refers to whether the pain was due to a central or peripheral lesion. Pain classification refers to whether the pain was neuropathic or nonneuropathic in etiology. There was no effect of pain syndrome; patients with either central or peripheral pain syndromes who received ziconotide had a significant greater decrease in pain than patient who received placebo as indicated by a greater change in mean percent change VASPI.

Patients with neuropathic pain who received ziconotide had a greater percent change in VASPI than patients who received placebo. However, while there was a trend to greater change in the ziconotide treated group, there was no statistically significant difference between treatment groups for patients with non-neuropathic pain. The sponsor indicates that there were far fewer patients in the non-neuropathic pain group, 28, than the neuropathic pain group, 185, and that may be why a statistically significant difference was not seen.

Therapeutic Dose Level:

The sponsor performed an evaluation to determine the dose of ziconotide which produced the therapeutic effect. This would be the dose level at the end of the initial titration and was an unplanned analysis. The analysis was stratified by initial dose. Patients starting with an initial dose of >0.1 mc g/h reached a considerably higher final dose than those started on ≤ 0.1 mc g/h. The earlier dosing regimens began with higher doses than later revised dosing regimens. The

sponsor proposes that there may have been an overshooting of the time of onset of analgesia during the earlier dose titration schedules as adequate time for the full effect of the dose to become apparent was not allotted between dose changes. The sponsor used median rather than mean values for this table due to the large ranges of the dose values.

Table 10.1.3.2.2 Ziconotide Dosing Information During Initial Titration Phase (From Table 9.4 Vol. 2.107, P. 137)

Parameter	≤ 0.1 mcg/hr	>0.1 mcg/hr	Total
n	122	40	162
Dose Level at End of Initial Titration (mcg/hr) ^a			
Median	0.400	0.920	0.469
Range	0.019 - 2.400	0.200 - 9.600	0.019 - 9.600
Cumulative Dose Received During Initial Titration (mcg) ^b			
Median	45.68	99.6	51.44
Range	4.31-122.51	8.93 - 453.55	4.31 - 453.55
Dose Level at Onset of Analgesia (mcg/hr) ^c			
Median	0.30	0.80	0.45
Range	0.00 - 2.40	0.00 - 9.60	0.00 - 9.60

a The last non-zero dose level administered during the initial titration phase was reported.

b The cumulative dose (mcg) at end of initial titration phase with K distinct doses was estimated as: [dose level 1 (mcg/h) x duration of dose level 1 (hours) + dose level 2 (mcg/h) x duration of dose level 2 (hours) +...+ dose level K (mcg/h) x duration of dose level K (hours)].

c Onset of analgesia was defined as when the percentage change in VASPI was >20% and the CPRS score was >-2 (i.e., at least a slight improvement). For patients who did not have onset of analgesia, the maximum dose level received during the initial titration phase was used.

Data Source: NDA Review by Dr. Sharon Hertz

Efficacy Summary:

This study is submitted as one of two pivotal efficacy trials in the previous NDA. Subjects were randomized to ziconotide or placebo for the initial titration. Following this phase there was a regimen to crossover nonresponders to placebo but the assessments of response to ziconotide and placebo included many errors by the individual investigators. The primary efficacy variable was measured at the end of the initial titration phase and was not affected by this problem.

The ziconotide treated group was found to have a slightly but significantly higher baseline pain intensity score and was receiving a greater amount of opioids at baseline. Even with these factors taken into account, the ziconotide treated group had a greater reduction in mean percent change in VASPI than the placebo group and this reached statistical significance. Concurrent opioid use, when factored in, had no effect on this result.

There was a steady trend of increasing mean percent change in VASPI over the six day titration period for the ziconotide treated patients, but only a small and fluctuating change with

the placebo treated patients. When stratified by initial dose, the patients who began ziconotide on ≤ 0.1 mcg/h had a statistically significant greater change in mean percent change VASPI, but not those with an initial titration dose of > 0.1 ug/h. There was a comparable size change in mean percent change of VASPI compared to the placebo treated patients for this group as for the lower initial dose group, but this difference did not reach significance. Analyses stratified by the final dose range resulted in varying results that may have been affected by several small group sizes. Patients receiving > 2 mcg/h ranges did not demonstrate a greater mean percent change in VASPI placebo treated patients. This may be due to a ceiling effect of the ziconotide or a reflection of patients who have intractable pain that did not respond to the ziconotide.

There was no effect of prior intrathecal morphine use, central vs. peripheral pain syndromes. Patients with nonneuropathic pain type did not have a significant treatment effect, but patients treated with ziconotide with neuropathic pain did demonstrate a greater mean percent change in VASPI than placebo treated patients.

Overall, the use of intrathecal ziconotide in chronic, nonmalignant pain appears to be effective, but may depend on the underlying type of pain.

Studies 95-001 and 96-002, were very similar in design. Study 96-002 began enrollment 5 months after 95-001 and they ran concurrently for 18 months until 96-002 ended enrollment 5 months prior to 95-001. The patient populations differed, chronic malignant pain due to cancer or AIDS in study 95-001 compared to chronic non-malignant pain in 96-002, but both populations included patients with neuropathic and non-neuropathic pain. Both studies incorporated several protocol changes reflecting lower initial doses, slower titration of dose and lower maximum dose and the final dosing schedule was the same for both studies.

In light of the similarities between the two studies, a side by side comparison of the results was performed by Dr Hertz.

The populations used for the final efficacy analyses in both studies were modified from the total patient populations to reflect only patients from the final dosing protocol and exclude the patients from sites 501 and 6090 due to a breach in blinding at those sites. Reanalyses were performed for the percent change in VASPI, absolute change in VASPI, categorical pain relief scale and responder rate, but not the WBPI scales. The disposition and demographics were not recalculated to reflect these changes. The population used for the results will be indicated for each area to minimize confusion.

Primary Efficacy Evaluation (Reanalysis Population)

With respect to pain relief in response to ziconotide, there were a number of differences between the 2 pivotal studies and these are summarized in Table 10.1.3.1.2-2. These results represent the patients treated with the final dose schedule and exclude patients from study sites 501 and 6090.

Table 10.1.3.1.2-2 Comparison of Studies 95-001 and Study 96-002

	95-001		96-002	
	Ziconotide	Placebo	Ziconotide	Placebo

Percent Change In VASPI At The End Of The Initial Titration Phase					
Evaluable	% change in VASPI				
	N	32	17	117	61
	Mean (SE)	42.4 (7.32)	18.9 (9.0)	29.4 (3.74)	6.4 (3.75)
	Median (range)	47.6 (-26-95)	3.1 (-24-96)	19.9 (-54-100)	1.1 (-62-79)
	p-value	0.058		0.004	
ITT	% change in VASPI				
	N	34	17	119	64
	Mean (SE)	39.5 (7.17)	18.9 (9.0)	29.6 (3.69)	6.0 (3.59)
	Median (range)	43.0 (-26-95)	3.1 (-24-96)	20.2 (-54-100)	1.1 (-62-79)
	p-value	0.08		<0.001	
Treatment Responders ^b					
Evaluable	N	32	17	102	53
	Responder	15 (46.9%)	3 (17.6%)	32 (31.4%)	8 (15.1%)
	Nonresponder	17 (53.1%)	14 (82.4%)	70 (68.6%)	45 (84.9%)
	p-value	0.023		0.131	

a. categories are worse, on change, slight improvement, moderate improvement, a lot of improvement or complete relief.

b. Treatment responder defined as

1. $\geq 30\%$ decrease in VASPI from baseline
2. No increase in dose of concomitant opioids
3. No change in the type of concomitant opioid (even if equivalent dose)

For the evaluable population, the difference in the mean % change in VASPI in study 95-001 between ziconotide and placebo treated patients was 23.5%, this did not reach statistical significance. The difference in study 96-002 was 23.0% and this did reach statistical significance.

Dr. Sharon Hertz examined the listings of adverse events and reassigned the COSTART terms of clinically and physiologically related signs and symptoms. This resulted in the adverse events mapped by the sponsor to the terms confusion, thinking abnormal, delirium, amnesia being mapped by Dr. Hertz to encephalopathy. Similarly, the adverse events mapped by the sponsor to nausea, nausea and vomiting, and vomiting were mapped by this reviewer to the term nausea and/or vomiting. The adverse events mapped by the sponsor to gait abnormality, incoordination, cerebellar syndrome, ataxia were mapped by this reviewer to ataxia. The adverse events of motor weakness and limb weakness mapped to by the sponsor to myasthenia were remapped to weakness. Lastly, suicidal ideation and suicidal gestures mapped to by the sponsor to depression were remapped as suicidal ideation/gesture. The result of this re-mapping is displayed in Table 10.1.3.1.2-3. The most striking difference from this re-mapping is the considerably larger proportion of patients (5.7%) exhibiting Encephalopathy as a serious adverse event.

Table 10.1.3.1.2-3 Serious Adverse Events For Selected Remapped COSTART Terms, All Intrathecal Studies

New Term	While Receiving Ziconotide (N=704)		While Receiving Placebo (N=151)	
Ataxia	6	0.9%	1	0.7%

Clinical Review
 Lex Schultheis, M.D., Ph.D.
 NDA 21,060
 (Prialt (Ziconotide))

Encephalopathy	40	5.7%	1	0.7%
Nausea and/or vomiting	13	1.8%	0	0.0%
Suicidal ideation/gesture	6	0.9%	1	0.7%
Weakness	3	0.4%	2	1.6%

The most common serious adverse events occurring during the double blinded, placebo controlled period of the two pivotal studies are summarized in Table 8.6. The patients were divided by initial dose group, to better approximate the final dosing regimen. This is useful because the final dosing protocol prescribed significantly lower doses than the original protocols. As a result and demonstrated in Table 8.6, the frequencies of adverse events was influenced by the initial dose/ different dosing protocols, with the patients who received lower initial doses exhibiting fewer adverse events. The SAE's that occurred most frequently overall involved the nervous and digestive systems, particularly confusion, dizziness and nausea.

The adverse events leading to study discontinuation are summarized by event in Table 10.1.3.1.2-4. This table represents this reviewer's determination of the primary adverse event resulting in study discontinuation when this could be discerned from the narratives. From this table it can be seen that encephalopathy consisting of the individual complaints or findings of confusion, memory impairment, thinking abnormal and delirium, was the most common AE leading to study discontinuation with 76 patients (26.4%). Additionally, hallucinations, depression/ suicidal ideation, anxiety, psychosis/bizarre behavior and hostility constitute an additional 22 patients (7.5%) and are arguably extensions of encephalopathy. This results in 100 patients (33.8%) of early discontinuations due to encephalopathy, or 11.3% of the entire intrathecal ziconotide treated population discontinuing their respective studies early due to an encephalopathy related adverse event. These figures do not take into account the number of patients within the "Multiple AEs" group which, as explained above, includes a variety of encephalopathy related adverse events. This was the next most common adverse event leading to early study discontinuation. When taken together, dizziness, ataxia, vertigo and vestibular toxicity accounted for 29 discontinuations (9.8%).

Table 10.1.3.1.2-4 Adverse Event Resulting in Study Termination

	All IT Studies, Ziconotide		Pivotal trials (while receiving)	
			Ziconotide	Placebo
Number Of Patients Terminating Study Early Due To Adverse Event.	295	100%	67	7
Adverse Event				
Encephalopathy includes confusion, thinking abnormal, disorientation, somnolence, stupor	76	26.4%	12	1
Multiple AEs identified as contributing (includes vestibular symptoms, nausea, confusion, headache)	36	12.0%	0	
Nausea and/or Vomiting	16	5.4%	7	
Paresthesias/Dysesthesias	14	4.7%	4	
Dizziness	13	4.4%	9	
Indeterminate from narrative	13	4.4%	0	
Meningitis	12	4.1%	4	

Clinical Review
 Lex Schultheis, M.D., Ph.D.
 NDA 21,060
 (Prialt (Ziconotide))

Ataxia	10	3.4%	4	
Other Infection	7	2.4%	3	2
Device Problem (includes leaking catheters)	7	2.4%	2	
Increased Pain	7	2.4%	1	1
Anxiety (includes panic attacks)	6	2.0%	0	
Auditory/Sensory Hallucinations	6	2.0%	0	
Depression/Suicidal ideation/Suicide	5	1.7%	1	
Headache	5	1.7%	2	1
Nystagmus alone	5	1.7%	1	
Psychosis/Bizarre Behavior	5	1.7%	0	
Vertigo	4	1.4%	3	
Vision blurred, Diplopia (2 each)	4	1.4%	2	
CK increased	3	1.0%	0	
Orthostatic Hypotension/Hypotension (2 each)	3	1.0%	0	
Progression of Cancer	3	1.0%	0	
Urinary Retention/ Urinary Incontinence (1/2)	3	1.0%	1	
Weakness	3	1.0%	1	1
Other - two each: <u>Involuntary Movements</u> , Laboratory Value Abnormal, <u>Peripheral Edema</u> , <u>Vestibular Toxicity</u>	9	3.1%	2	
Other - one each: Allergic rash, Abnormal Ejaculation, <u>Aphasia</u> , <u>Atrial Fibrillation</u> , Cardiac, Chest wall rigidity, <u>Convulsion</u> , Death from Unknown Cause, Dry Mouth, <u>Dysarthria</u> , <u>Dyspnea</u> , <u>Fever</u> , Gastroenteritis, Hostility, Insomnia, <u>Leg Cramp</u> , <u>Malaise</u> , Malignant Hyperthermia, Overdose (methadone), Oral thrush, Pulmonary Embolus, Stomatitis, Syncope, Taste Perversion	22	7.5%	8	1 (fever)

Sponsor Table 9.2.8.9 (vol. 5.002, P. 307) provides individual information on the 200 patients who discontinued due to an adverse event including infection from all 9 of the intrathecal studies and has been included in the safety review appendix.

In addition to patients discontinuing from studies due to adverse events, there were 373 of 887 patients (42.1%) for whom study drug was temporarily or permanently stopped due to an adverse event. (See IT Table 9.2.8.10, Vol. 5.002 P. 310). Again, it can be seen that the adverse events related to encephalopathy such as confusion and amnesia, vestibular toxicity such as dizziness, abnormal gait and nystagmus and nausea are the most common reasons for study drug to be temporarily or permanently stopped.

In particular, nausea and/or vomiting, abnormal gait, dizziness, confusion, nystagmus, somnolence and urinary retention were more frequent in the ziconotide group.

As demonstrated in Table 10.1.3.1.2-4, there was a mild trend for increasing adverse event frequency overall with increasing dose. Nystagmus, Abnormal Vision, Ataxia, Pain, Abnormal Gait and Confusion, urinary retention were the individual AE's that trended to an increased incidence with increasing cumulative dose. Several important adverse events did not seem to increase with increasing dose including: postural hypotension, nausea, vomiting, constipation.

Adverse Events By Initial Dose

Patients beginning the study on a larger initial dose, were generally on higher hourly rates and received a greater cumulative dose. Patients starting on >1.0 mcg/h of ziconotide were more likely than patients beginning on a lower dose to have fever, postural hypotension, confusion, and urinary retention. This differs from the profile of adverse events most frequent by cumulative dose and suggests that the dose rate rather than the cumulative dose or initial rate may be the more important dosing factor related to the appearance of adverse events.

Of these 679 patients, 676 experienced the first occurrence of AE's within the first 3 months of drug exposure and the majority of these were within the first month. The only AE which was not represented most often within the first 30 d was hallucinations, which occurred for the first time most commonly from 30-90 days.

When the patients who were treated for greater than 3 months were separated from the overall group, the majority of patients, 157 out of 159, still experienced the first occurrence of an adverse event within the first 30 d of treatment. However, there were several AE's with a higher incidence after one month of treatment. These included asthenia, confusion, depression, hallucinations, thinking abnormal and taste perversion.

Adverse Events first occurring for the first time after 3 months of treatment were very infrequent. These included increased salivation, stomatitis, tooth disorder and tongue disorder, delirium, hostility, manic reaction, neurosis and personality disorder.

10.2 Conclusions from Previous NDA Review of Studies 95-001 and Study 96-002

The following findings are from the review of Dr. Sharon Hertz following her analysis of Studies 95-001 and 96-002:

The results of studies 95-001 and 96-002 had to be reanalyzed excluding patients from earlier dosing regimens that differed from the final dosing regimen and did not reflect the manner in which ziconotide would be utilized in clinical practice. These two studies shared the same design for the initial titration period lasting 5-6 days. Additional patients had to be excluded from a site that was found on inspection to be unblinded. As a result of this reanalysis, for study 95-001, the primary efficacy variable, mean percent change in VASPI, failed to show a statistically significant difference between the ziconotide treated patients and the placebo treated patients, for either the ITT or evaluable populations. There were limited secondary endpoints provided with this reanalysis. The only secondary endpoint that reached statistical significance was the number of patients who met the sponsor's definition of a responder which was greater for the ziconotide treated patients. It is important to note that the number of patients available for comparison in the reanalysis representing patients treated in the planned manner of ziconotide use was only 34.

The results from the reanalysis for study 96-002 were less affected by the reanalysis. The mean percent change in VASPI at the end of the initial titration phase for evaluable and ITT populations and the category pain relief scale demonstrated a statistically significant improvement in favor of the ziconotide treated patients compared to placebo. However, the number of responders did not differ significantly between treatment groups.

Based on these results, there is only one pivotal trial that demonstrates efficacy, study 96-002. As the size of the treatment effect in study 95-001 was comparable to study 96-002, it appears that 95-001 was inadequate to demonstrate efficacy, possibly due to the small number of patients. Alternatively, ziconotide does not produce an adequate analgesic effect and the statistically significant results from study 96-002 are not reproducible or clinically meaningful.

There were other differences between the outcomes of these two studies based on the original analyses submitted with the NDA. Eighty three percent of patients completed the initial titration phase of 95-001 while only 48.2% completed the initial titration phase in 96-002. Older patients (≥ 60 years) treated with ziconotide in study 95-001 demonstrated a greater difference in mean percent change in VASPI from placebo, while younger patients (< 60 years) in 96-002 demonstrated a greater effect. Women demonstrated a greater placebo effect in 95-001, men in 96-002. Patients with a history of prior intrathecal morphine use treated with ziconotide differed less from placebo than IT morphine naïve patients in 95-001, but more in 96-002. In 96-002, patients with neuropathic pain treated with ziconotide had a statistically significantly greater mean percent change in VASPI compared to placebo treated patients, but for patients with non-neuropathic pain, the difference did not reach significance. In 95-001, the AIDS patients with primarily neuropathic pain did not have a statistically significant treatment effect, while the cancer patients with mixed etiologies of pain did demonstrate a statistically significant treatment effect.

The populations in the two studies were different. Patients in 95-001 were enrolled with chronic malignant pain due to cancer or AIDS, in 96-002 with chronic nonmalignant pain. However, the differences in the outcomes of these two studies underscores the lack of a clear picture of the efficacy profile of ziconotide. The presence of effects of age, gender, or etiology of pain on the efficacy of ziconotide are unclear.

These uncertain efficacy results must be evaluated in the setting of the safety profile of ziconotide. Twice as many deaths occurred in patients who had been exposed to ziconotide than those only exposed to placebo. Three times as many patient experienced serious adverse events while receiving ziconotide than placebo. Serious adverse events involved the nervous system more than 3 times as often while receiving ziconotide than while receiving placebo and included dizziness, nystagmus, confusion and somnolence. Encephalopathy including confusion, abnormal thinking, amnesia, and somnolence, as a serious adverse event was 8 times more common while receiving ziconotide than placebo. The encephalopathy was not explored with respect to duration or reversibility. Nausea and/or vomiting, dyspnea, hypotension and postural hypotension, and urinary retention as serious adverse events occurred only in ziconotide treated patients.

Patients receiving ziconotide were twice as likely to discontinue or terminate early from a study as patients receiving placebo. Of the 32% of ziconotide treated patients discontinuing early, 63.6% of patients did so due to adverse events. Of these ziconotide treated patients discontinuing early, 33.8% did so due to encephalopathy related adverse events or put another way, 11.3% of patients treated with ziconotide discontinued early from their respective studies due to an encephalopathy related adverse event. This included anything from somnolence to confusion, stupor, and auditory or sensory hallucinations.

As for adverse events in general, nausea and/or vomiting, encephalopathy, ataxia, somnolence, motor weakness, anxiety, muscle cramps, depression, agitation, hypotension, postural hypotension were all much more frequent in patients while receiving ziconotide. Fever, postural hypotension, nausea, vomiting, abnormal gait, confusion, dizziness, nystagmus, somnolence, urinary retention were all statistically more frequent in patients while receiving ziconotide than while receiving placebo.

Patients receiving ziconotide had more frequent elevations in CPK than patients receiving placebo, reaching 4.2% at study termination, and 11% when CPK at any visit was evaluated. Patients receiving ziconotide were more likely to have a rise in creatinine above 1.2 and greater than 0.3 mg/dl than placebo. The clinical and physiological significance of these changes is unclear.

There is insufficient evidence to confirm efficacy of ziconotide when used in the dosing range planned, while there is evidence of a considerable potential for toxicity.

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Clinical Review
 Lex Schultheis, M.D., Ph.D.
 NDA 21,060
 Prialt (Ziconotide)

10.3 Summary of Studies in the Sponsor's Integrated Summary of Safety

Table 10.3 Table of All Intrathecal Clinical Studies - ISS

Protocol Number Principal Investigator(s) Country(ies) Study Start/Stop Dates	Objective /Stud Design	Diagnosis or Other Criteria for Inclusion	Total n Race (%C/%Afr/%O)	Gender Males/Females n/n (%/%)	Mean Age (Years) Age Range (Min - Max)	Treated N Per R.,Group	Drug Regimen	Duration of Treatment	Summary of Safety Results	Location of Report, Listings,& CRF(Vol/P)
Double-Blind, Placebo-Controlled Clinical Studies										
95-001 32 Investigators; see Appendix 10 of individual study report for complete list. Australia Netherlands USA March 1996/July 1998	Efficacy and safety of ziconotide dose titration Phase II/III, randomized, double-blind, placebo- controlled, "fast titration" for 5 to 6 days	Patients with chronic, malignant pain (AIDS or cancer patients)	112 ziconotide: 72 placebo: 40 ITT Population: 111 (87%/8%/5%) ziconotide: 71 (83%/11%/6%) placebo: 40 (95%/3%/3%) Final Dosing Regimen population: 59 patients	ITT Population a: 56/55 (50%/50%) ziconotide: 36/35 (51%/49%) placebo: 20/20 (50%/50%)	ITT Population: 55.5 (24-85) ziconotide: 54.8 (24-81) placebo: 56.6 (33-85)	Ziconotide: 72 Placebo: 40 Final Dosing Regimen population: Ziconotide: 40 Placebo: 19	Intrathecal ziconotide (0.1 mcg/hr to a max of 2.4 mcg/hr) ^b placebo	120 or 144 hr, nonrespon- ders (based on protocol definition) may be crossed over to the opposite treatment; responders continue initial treatment for 5-day, blinded maintenance phase; ziconotide responders may enter 95-002	% of Patients while receiving ziconotide: AEs: Initial Titration: 97.2% Maintenance: 66.7% Crossover: 84.6% SAEs: 41.8% DC/AEs: 12.2% Total # of Deaths (either treatment): 15 patients (10 ziconotide, 5 placebo)	Original NDA Report: V006, p. 011 Listings: V008, p.002 CRF: V014, p.199

Note: C = Caucasian / Afr = African / O = Other

^a Demographic data available for ITT population only; one additional patient was included in the safety population.

^o See ISS Section and 8.4.3.2.1.1 and 8.4.3.2.1.2 for complete dosing information for Studies 95-001 and 96-002, respectively. ^{*} Includes all data in the database as of 30 May 2003.

^o Twenty-two patients initially enrolled; however, two patients who initially received 5 mcg also participated in the 7.5 mcg dose group. Therefore, a total of 24 cases were evaluated.

Clinical Review
 Lex Schultheis, M.D., Ph.D.
 NDA 21,060
 {Prialt (Ziconotide)}

Table 10.3 Table of All Intrathecal Clinical Studies - ISS (cont'd)

Protocol Number Principal Investigator(s) Country(ies) Study Start/Stop Dates	Objective /Study Design	Diagnosis or Other Criteria for Inclusion	Total n Race (%C/%Afr/%O)	Gender Males/Females n/n (%/%)	Mean Age (Years) Age Range (Min - Max)	Treated N Per R _n Group	Drug Regimen	Duration of Treatment	Summary of Safety Results	Location of Report, Listings, & CRF(Vol/P)
Double-Blind, Placebo-Controlled Clinical Studies (Continued)										
96-002 43 Investigators; see Appendix 10 of individual study report for complete list. Australia Austria Belgium Switzerland USA January 1995/ February 1998	Efficacy and safety of ziconotide dose titration Phase II/III, randomized, double-blind, placebo-controlled, titration to response	Chronic, non-malignant pain	All Treated: 256 ziconotide: 170 Placebo: 86 ITT Population: 255 (95%/2%/3%) ziconotide: 169 (96%/2%/2%) placebo: 86 (94%/1%/5%) Final Dosing Regimen population: 198	ITT Population: 143/112 (56%/44%) ziconotide: 94/75 (56%/44%) placebo: 49/37 (57%/43%)	ITT Population: 52.0 (22-82) ziconotide: 51.6 (22-82) placebo: 52.8 (25-79)	Ziconotide: 170 Placebo: 86 Final Dosing Regimen population: Ziconotide: 130 Placebo: 68	IT ziconotide (0.1 to a maximum of 2.4 mcg/h) ^b placebo Intrathecal ziconotide (0.1 to 2.4 mcg/h) ^b placebo	144 hr, nonresponders to placebo may cross over to active treatment; responders continue initial treatment in a 5-day, blinded maintenance phase; ziconotide responders may enter 95-002	% of Patients while receiving ziconotide: AEs: Initial Titration: 94.7% Maintenance: 59.8% Crossover: 94.0% SAEs: 16.5% DC/AEs: 14.1% Total # of Deaths (either treatment): None	Original NDA Report: V017, p. 012 Listings: V018, p. 034 CRF: V027, p.208

Note: C = Caucasian / Afr = African / O = Other

^a Demographic data available for ITT population only; one additional patient was included in the safety population.

^b See ISS Section and 8.4.3.2.1.1 and 8.4.3.2.1.2 for complete dosing information for Studies 95-001 and 96-002, respectively. ^{*} Includes all data in the database as of 30 May 2003. Twenty-two patients initially enrolled; however, two patients who initially received 5 mcg also participated in the 7.5 mcg dose group. Therefore, a total of 24 cases were evaluated.

Clinical Review
 Lex Schultheis, M.D., Ph.D.
 NDA 21,060
 {Prialt (Ziconotide)}

Table 10.3 Table of All Intrathecal Clinical Studies - ISS (cont'd)

Protocol Number Principal Investigator(s) Country(ies) Study Start/Stop Dates	Diagnosis or Other Criteria for Inclusion			Total n Race (%C/%Afr/%O)	Gender Males/Females n/n (%/%)	Mean Age (Years) Age Range (Min - Max)	Treated N Per R., Group	Drug Regimen	Duration of Treatment	Summary of Safety Results
Placebo-Controlled Clinical Studies (Continued)										
Double-Blind, 301 39 investigators; see Appendix 17.1.4 of individual study report for complete list. August 2002/ November 2003	Confirmation of positive efficacy results observed in Studies 95-001 and 96-002 Phase III, randomized, double-blind, placebo- controlled "slow titration" to response	Severe chronic pain, unresponsive to current therapy	220 ziconotide: 112 placebo: 108 ziconotide: (96%/1%/ 4%) placebo: (92%/ 3%/ 6%) ITT	Total: 108/112 (49%/51%) ziconotide: 53/59 (47%/53%) placebo: 55/53 (51%/49%)	Total: 53.7 (27-86) ziconotide: 52.5 (30-84) placebo: 54.8 (27-86)	112 108 ITT	IT ziconotide (0.1 to 0.9 mcg/hr) placebo	Up to nine % of Patients weeks, while receiving consisting of a ziconotide three-week AEs: 92.9% weaning phase, a SAEs: 11.6% one-week stabilization DC/AEs: 4.5% phase, a three-week Total # of treatment Deaths phase, and (either two-week treatment): follow-up 1 patient phase (placebo)	NDA Report: V 007, p.002 Listings: See Item 11 CRF: V 006, p.002	

Note: C = Caucasian / Afr = African / O = Other

* Demographic data available for ITT population only; one additional patient was included in the safety population.

See ISS Section and 8.4.3.2.1 and 8.4.3.2.1.2 for complete dosing information for Studies 95-001 and 96-002, respectively. Includes all data in the database as of 30 May 2003. Twenty-two patients initially enrolled; however, two patients who initially received 5 mcg also participated in the 7.5 mcg dose group. Therefore, a total of 24 cases were evaluated.

Clinical Review
 Lex Schultheis, M.D., Ph.D.
 NDA 21,060
 (Prialt (Ziconotide))

Table 10.3 Table of All Intrathecal Clinical Studies - ISS (cont'd)

Protocol Number Investigator(s) Country(ies) Study Start/Stop Dates	Objective /Study Design	Diagnosis or Other Criteria for Inclusion	Total n Race (%C/%Afr/%O)	Gender Males/Females n/n (%/%)	Mean Age (Years) Age Range (Min - Max)	Treated n Per R., Group	Drug Regimen	Duration of Treatment	Summary of Safety Results	Location of Report, Listing & CRF (Vol/Pg)
Long-Term, Open-Label Clinical Studies (Continued)										
95-002	Long-term safety,	Chronic, intractable pain	155 (95%/3%/1%)	74/71 (51%/49%)	55.0 (24-85)	155	ITT ziconotide	Open;	AEs: 98.7%	NDA
42	Investigations; tolerability, and efficacy	(malignant and non-malignant)	Study of origin: 95-001: 44 (91%/7%/2%)	Study of origin: 95-001: 19/25 (43%/57%)	Study of origin: 95-001: 56.7 (24-85)		individual dose based on experience in previous study	termination based on clinical judgment and/or patient request	SAES: 51.6% DC/AEs: 39.4%	Report: V 029, p.274 Listings: See Item 11
	Phase III, open-label, entry limited to responders		96-002: 101 (97%/2%/1%)	96-002: 55/46 (55%/45%)	96-002: 54.3 (24-80)				Deaths: 27 patients	
Australia										
Austria										CRF:
Belgium										V 029,
Switzerland										p.130
USA										
June 1996/June 2002										

Note: C = Caucasian / Afr = African / O = Other

a Demographic data available for ITT population only; one additional patient was included in the safety population.

See ISS Section and 8.4.3.2.1.1 and 8.4.3.2.1.2 for complete dosing information for Studies 95-001 and 96-002, respectively. ° Includes all data in the database as of 30 May 2003. Twenty-two patients initially enrolled; however, two patients who initially received 5 mcg also participated in the 7.5 mcg dose group. Therefore, a total of 24 cases were evaluated.

Clinical Review
 Lex Schultheis, M.D., Ph.D.
 NDA 21,060
 {Prialt (Ziconotide)}

Table 10.3 Table of All Intrathecal Clinical Studies - ISS (cont'd)

Protocol											
Number											
Principal Investigator(s)											Location of
Country(ies)		Diagnosis or Other	Total n	Gender	Mean Age (Years)	Treated n					Reporting
Study Start/Stop Dates	Objective / Study Design	Criteria for Inclusion	Race (%C/%Afr/%O)	Males/Females n/n (%/%)	Age Range (Min - Max)	Per R. Group	Drug Regimen	Duration of Treatment	Summary of Safety Results		& C (Vol/I
Long-Term, Open-Label Clinical Studies (Continued)											
98-022	Assess long term safety and tolerability	Chronic, severe, nonmalignant or malignant pain	644 (94%/2%/5%)	315/329 (49%/51%)	52.1 (16-88)	644	IT ziconotide starting dose of 0.1 mcg/hr, titrated to response at a rate less than or equal to 10.1 mcg/hr per 24 hrs	Open; termination based on clinical judgment and/or patient request	AEs: 99.7% SAES: 36.2% DC/AEs: 61.0%		SNIR Repe V 0 p. 0 i Listin See Item 11 CRF: V 049, p.305
68 investigative sites; see Appendix 16.1.4 of individual study report for complete list.											
USA											
October 1998/ August 2002											

Note: C = Caucasian / Afr = African / O = Other

* Demographic data available for ITT population only; one additional patient was included in the safety population.

^b See ISS Section and 8.4.3.2.1.1 and 8.4.3.2.1.2 for complete dosing information for Studies 95-001 and 96-002, respectively. Includes all data in the database as of 30 May 2003.

^d Twenty-two patients initially enrolled; however, two patients who initially received 5 mcg also participated in the 7.5 mcg dose group. Therefore, a total of 24 cases were evaluated.

Clinical Review
 Lex Schultheis, M.D., Ph.D.
 NDA 21,060
 (Prialt (Ziconotide))

Table 10.3 Table of All Intrathecal Clinical Studies - ISS (cont'd)

Protocol Number Principal Investigator(s) (ies) Study Start/Stop Dates	Objective / Study Design	Diagnosis or Other Criteria for Inclusion	Total n Race (%C/%Afr/%O)
Long-Term, Open-Label Clinical Studies (Continued)			
351 ^a	Provide access to ziconotide to those patients completing long-term ziconotide therapy in ongoing trials	Ziconotide -treated patients receiving therapy in ongoing trials	78 (99%/0%/1%)
19	Investigators; see Appendix 17.1.4 of individual study report for complete list.	those patients receiving therapy in ongoing trials	
USA	95-002 and 98-022		
April 2002 / Ongoing	Phase III, open-label, long term, study		

Note: C = Caucasian / Afr = African / O = Other

^a Demographic data available for ITT population only; one additional patient was included in the safety population.

^b See ISS Section and 8.4.3.2.1.1 and 8.4.3.2.1.2 for complete dosing information for Studies 95-001 and 96-002, respectively. Includes all data in the database as of 30 May 2003.

Clinical Review
 Lex Schultheis, M.D., Ph.D.
 NDA 21,060
 (Prialt (Ziconotide))

Twenty-two patients initially enrolled; however, two patients who initially received 5 mcg also participated in the 7.5 mcg dose group. Therefore, a total of 24 cases were evaluated.

Table 10.3 Table of All Intrathecal Clinical Studies - ISS (cont'd)

Protocol					
Number					
Principal Investigator(s)					
Country(ies)		Diagnosis	Total n		Mean Age Treated
Study		or Other		Gender	(Years) n
Start/Stop	Objective /	Criteria for	Race	Males/Females	Age Range Per R,
Notes	Study Design	Inclusion	(%C/%Afr/%O)	n/n (%/%)	(Min - Max) Group Drug Regimen
Long-Term, Open-Label Clinical Studies (Continued)					
1 ^a	Assess long	Severe,	85	47/38	52.5
	term safety	chronic	(97%/1%/2%)	(55%/45%)	(31 -84)
	and	pain			
Investigators:	tolerability				
Appendix					
1.4 of	Phase III,				
Individual study	open-label,				
Port for	long term,				
Complete list.	study for				
A	patients from				
	Study 301				
August 2002 /					
going					

Note: C = Caucasian / Afr = African / O = Other

^a Demographic data available for ITT population only; one additional patient was included in the safety population.

^b Includes all data in the database as of 30 May 2003.

Twenty-two patients initially enrolled; however, two patients who initially received 5 mcg also participated in the 7.5 mcg dose group. Therefore, a total of 24 cases were evaluated.

Clinical Review
 Lex Schultheis, M.D., Ph.D.
 NDA 21,060
 {Prialt (Ziconotide)}

Table 10.3 Table of All Intrathecal Clinical Studies - ISS (cont'd)

Protocol										
Number										
Principal Investigator(s)			Total n							Location of Report, Listings & CRF (Vol/Pg)
Country(ies)		Diagnosis or Other Criteria for Inclusion	Race (%C/%Afr/%O)	Gender Males/Females n/n (	Mean Age Treated (Years) n	Age Range Per R. (Min - Max) Group	Drug Regimen	Duration of Treatment	Summary of Safety Results	
Study Start/Stop Dates	Objective / Study Design									
Other Studies										
96-003	Pilot evaluation of safety and efficacy for acute post-operative pain	Acute post-operative pain	30 (83%/13%/3%)	j 13/17 (43%/x/57%)	63 (39-84)	30	IT	Up to 72 hr	Percent of patients while receiving ziconotide	Original NDA Report: V067, p. 004
4 investigative sites; see Appendix 16.1.4 of individual study report for complete list. USA	Phase II, randomized, double-blind, placebo-controlled		ziconotide 0.7 mcg/h: 12 (75%/17%/8%)	ziconotide: 0.7 mcg/h: 5/7 (42%/58%)	ziconotide: 0.7 mcg/h: 63.5 (48-81)	12	7.0 mcg/h (high dose) placebo		SAEs: None DC/AEs: 20.8%	Listings: V068, p. 002 CRF: V069, p. 119
			ziconotide 7.0 mcg/h: 6 (100%/0%/0%)	ziconotide 7.0 mcg/h: 3/3 (50%/50%)	ziconotide 7.0 mcg/h: 57.5 (39-67)	6			Deaths: None	
October 1996/November 1997			placebo: 12 (83%/17%/0%)	placebo: 5/7 (42%/58%)	placebo: 64.8 (45-84)	12				

Note: C = Caucasian / Afr = African / O = Other

* Demographic data available for ITT population only; one additional patient was included in the safety population.

b* Includes all data in the database as of 30 May 2003.

Clinical Review
 Lex Schultheis, M.D., Ph.D.
 NDA 21,060
 (Prialt (Ziconotide))

*Twenty-two patients initially enrolled; however, two patients who initially received 5 mcg also participated in the 7.5 mcg dose group. Therefore, a total of 24 cases were evaluated.

Table 10.3 Table of All Intrathecal Clinical Studies - ISS (cont'd)

Protocol					
Number					
Principal Investigator(s)			Total n		
Country(ies)		Diagnosis I		Mean Age	Treated
Study		or Other	Gender	(Years)	n
Start/Stop	Objective /	Criteria for Race	Males/Females	Age Range	Per R _x
Dates	Study Design	Inclusion (%C/%Afr/%O)	n/n (%%)	(Min - Max)	Group Drug Regimen
Other Studies (Continued)					
96-010	Evaluation of	Chronic,	1	1/0 44	IT ziconotide
	safety and	intract-	(100%/0%/0%)	(100%/0%)	0.2-3.4
One	efficacy of	able, non-			mcg/hr
investigator	increasing	malignant			
	doses of	pain			
	ziconotide				
USA					
	Phase II,				
December	open-label,				
1996/	titration to				
February 1997	response				

Note: C = Caucasian / Afr = African / O = Other

*Demographic data available for ITT population only; one additional patient was included in the safety population.

Clinical Review
 Lex Schultheis, M.D., Ph.D.
 NDA 21,060
 {Prialt (Ziconotide)}

^b. Includes all data in the database as of 30 May 2003. Twenty-two patients initially enrolled; however, two patients who initially received 5 mcg also participated in the 7.5 mcg dose group. Therefore, a total of 24 cases were evaluated.

Table 10.3 Table of All Intrathecal Clinical Studies - ISS (cont'd)

Protocol Number Investigator(s) Country(ies) Study Start/Stop Dates	Objective / Study Design	Diagnosis or Other Criteria for Inclusion	Total n Race (%C/%Afr/ %O)	Gender Males/ Females n/n (%/%)	Mean Age (Years) Age Range (Min - Max)	Treated n Per R., Group	Drug Regimen	Duration of Treatment	Summary of Safety Results
Other Studies (Continued)									
97-013	PK profile, safety, and efficacy of a range of bolus doses	Chronic non- malignant or malignant pain	24 ^d (92%/8%/0%)	12/12 (50%/50%)	1 mcg : 47.6 (40-61)	5	Intrathecal infusion ziconotide (i.e., bolus dose); completers final dosing cohort and/or 5 mcg open-label titration	1-hr AEs: 87.5% SAEs: 12.5% DC/AEs: None Deaths: None	Original NDA Report: V061, p.002 Listings: V062, p.430 CRF: V062, p.142
USA			1 mcg: 5 (100%/0%/0%)	1 mcg: 3/2 (60%/40%)			1 mcg may enter		
March 1998/August 1999	Phase II, open-label, pilot study		5 mcg: 8 (100%/0%/0%)	5 mcg: 4/4 (50%/50%)	5 mcg: 50.8 (31 -65)	8	7.5 mcg (83%/17%/0%)		
			7.5 mcg: 6 (83%/17%/0%)	7.5 mcg: 3/3 (50%/50%)	7.5 mcg: 43.0 (31 -54)	6	7.5 mcg		
			10 mcg: 5 (80%/20%/0%)	10 mcg: 2/3 (40%/60%)	10 mcg:	5	10 mcg		

Note: C = Caucasian / Afr = African / O = Other

Clinical Review
 Lex Schultheis, M.D., Ph.D.
 NDA 21,060
 {Prialt (Ziconotide)}

^a Demographic data available for ITT population only; one additional patient was included in the safety population.

^b Includes all data in the database as of 30 May 2003.

^d Twenty-two patients initially enrolled; however, two patients who initially received 5 mcg also participated in the 7.5 mcg dose group. Therefore, a total of 24 cases were evaluated.

Table 10.3 Table of All Intrathecal Clinical Studies - ISS (cont'd)

Protocol Number (Country)	Principal Investigator(s) Study Start/Stop Dates	Objective / Study Design				Diagnosis or Other Criteria for Inclusion	Total n Race (%C% Afr/% O)	Gender (Males/ Female n/n (%/%)	Mean Age (Years) Range (Min - Max)	Treatment Drug Regimen	Duration of Treatment	Summary of Safety Results	Location of Report, Listings, & CRF (Vol/Pg)
Other Studies (Continued)													
97-013		PK profile,	Chronic	24 °	12/12				Intrathecal	1-hr infusion	AEs: 87.5%	Original	
		safety, and	non-						ziconotide	(i.e., bolus		NDA	

Clinical Review
 Lex Schultheis, M.D., Ph.D.
 NDA 21,060
 (Prialt (Ziconotide))

	efficacy of a	malignant	(92% /8%/0 %)	(50%/50 %)			bolus:	dose);	SAEs: 12.5%	
	range of	or						completers		Report:
USA	bolus doses	malignant	1 mcg: 5	1 mcg: 3/2	1 mcg: 47.6	5	1 mcg	may enter	DC/AEs: None	V061,
		pain	(100 %/0 %/0 %)	(60%/40 %)	(40- 61)			final dosing		p.002
March 1998/August	Phase II, open-label,		5 mcg: 8	5 mcg: 4/4	5 mcg: 50.8	8	5 mcg	cohort and/or open-label	Deaths: None	Listings:
1999	pilot study		(100 %/0 %/0 %)	(50%/50 %)	(31 - 65)			titration		V062, p.430
			7.5 mcg: 6	7.5 mcg: 3/3	7.5 mcg: 43.0	6	7.5 mcg			CRF:
			(83% /17%/ 0%)	(50%/50 %)	(31 - 62)					V062, p.142
			10	10 mcg:	10 mcg: 49.2	5	10 mcg			
			(80% /20%/ 0%)	(40%/60 %)	(31 - 62)					

Note: C = Caucasian / Afr = African / O = Other

Demographic data available for ITT population only; one additional patient was included in the safety population.

. Includes all data in the database as of 30 May 2003.

Twenty-two patients initially enrolled; however, two patients who initially received 5 mcg also participated in the 7.5 mcg dose group. Therefore, a total of 24 cases were evaluated.

Clinical Review
 Lex Schultheis, M.D., Ph.D.
 NDA 21,060
 {Prialt (Ziconotide)}

Table 10.3 Table of All Intrathecal Clinical Studies - ISS (cont'd)

Protocol Number	Investigator(s)	Country(ies)	Study	Start/Stop Dates	Objective 1	Criteria for Inclusion	Race (%C/%Afr/%O)	Gender Males/Females n/n (%/%)	Mean Age Treated (Years) n	Age Range Per R. (Min - Max) Group	Drug Regimen
97-015	Two Investigators:	USA	Phase III, open-label, titration to response	June 1997/ September 1997	Establish safety and efficacy or increasing doses of ziconotide	Chronic, nonmalignant pain (100%/0%/0%)	1 (100%/0%/0%)	1/0 (100%/0%)	66	1	Intrathecal ziconotide 0.04-0.3 mcg/hr

Note: C = Caucasian / Afr = African / O = Other

* Demographic data available for ITT population only; one additional patient was included in the safety population.

See ISS Section and 8.4.3.2.1.1 and 8.4.3.2.1.2 for complete dosing information for Studies 95-001 and 96-002, respectively. ^a Includes all data in the database as of 30 May 2003. Twenty-two patients initially enrolled; however, two patients who initially received 5 mcg also participated in the 7.5 mcg dose group. Therefore, a total of 24 cases were evaluated.

10.4 Timing of Onset Adverse Events

Table 10.4-1 Timing of Onset of Adverse Events in Study 301

	Placebo					
	<= 7 days		8 - 14 days		> 14 days	
	Responder	Non-responder	Responder	Non-responder	Responder	Non-responder
Total	13	95	17	91	13	95
Body as a Whole	3 (23%)	19 (20%)	3 (18%)	9 (10%)	3 (23%)	8 (8%)
Abdominal Pain	0	1 (1%)	0	1 (1%)	1 (8%)	0
Asthenia	0	6 (6%)	0	2 (2%)	1 (8%)	4 (4%)
Back Pain	0	2 (2%)	0	2 (2%)	0	3 (3%)
Chest Pain	0	0	0	2 (2%)	0	0
Chills	1 (8%)	3 (3%)	0	1 (1%)	0	0
Fever	0	3 (2%)	1 (6%)	0	0	0
Headache	0	8 (8%)	0	3 (3%)	1 (8%)	1 (1%)
Pain	1 (8%)	3 (3%)	0	2 (2%)	1 (8%)	1 (1%)

	Ziconotide					
	<= 7 days		8 - 14 days		> 14 days	
	Responder	Non-responder	Responder	Non-responder	Responder	Non-responder
Total	24	88	22	90	17	95
Body as a Whole	9 (38%)	25 (28%)	2 (9%)	14 (16%)	1 (6%)	13 (14%)
Abdominal Pain	0	0	0	6 (7%)	0	0
Asthenia	3 (13%)	12 (14%)	0	3 (3%)	1 (6%)	6 (6%)
Back Pain	0	2 (2%)	0	2 (2%)	0	0
Chest Pain	0	3 (3%)	1 (5%)	2 (2%)	0	2 (2%)
Chills	2 (8%)	5 (6%)	0	1 (1%)	1 (6%)	1 (1%)
Fever	2 (8%)	2 (2%)	1 (5%)	0	1 (6%)	2 (2%)
Headache	3 (17%)	9 (10%)	0	2 (2%)	0	2 (2%)
Pain	1 (4%)	7 (8%)	1 (5%)	3 (3%)	0	0

Clinical Review
 Lex Schultheis, M.D., Ph.D.
 NDA 21,060
 {Prialt (Ziconotide)}

	Placebo					
	<= 7 days		8 - 14 days		> 14 days	
	Responder	Non-responder	Responder	Non-responder	Responder	Non-responder
Total	13	95	17	91	13	95
Nervous System	5 (38%)	31 (33%)	4 (24%)	9 (10%)	0	6 (6%)
abnormal gait	1 (8%)	1 (1%)	0	0	0	0
agitation	0	2 (2%)	0	0	0	1 (1%)
anxiety	0	3 (3%)	0	2 (2%)	0	0
aphasia	0	0	0	1 (1%)	0	0
ataxia	0	0	0	2 (2%)	0	0
confusion	0	1 (1%)	1 (6%)	1 (1%)	0	2 (2%)
depression	0	4 (4%)	0	1 (1%)	0	0
difficulty concentrating	0	0	0	1 (1%)	0	0
dizziness	1 (8%)	9 (9%)	0	0	0	4 (4%)
dry mouth	0	2 (2%)	0	0	0	0
dysthesia	1 (8%)	1 (1%)	0	0	0	0
hallucinations	0	0	0	0	0	0
hypertonia	1 (8%)	2 (2%)	0	0	2 (15%)	0
insomnia	2 (15%)	7 (7%)	2 (12%)	2 (2%)	0	0
memory impairment	0	0	0	0	0	1 (1%)
nervousness	0	4 (4%)	0	0	0	0
nystagmus	0	0	0	0	0	0
paresthesia	0	2 (2%)	0	1 (1%)	0	0
somnolence	0	8 (8%)	1 (6%)	5 (5%)	1 (8%)	1 (1%)
speech disorder	1 (8%)	0	0	0	0	1 (1%)
tremor	0	2 (2%)	0	0	0	0
vertigo	0	0	0	0	0	0
withdrawal syndrome	1 (8%)	2 (2%)	0	3 (3%)	1 (8%)	0
	Ziconotide					
	<= 7 days		8 - 14 days		> 14 days	
	Responder	Non-responder	Responder	Non-responder	Responder	Non-responder
Total	24	88	22	90	17	95
Nervous System	16 (67%)	35 (40%)	4 (18%)	16 (18%)	2 (12%)	18 (19%)
abnormal gait	3 (13%)	7 (8%)	0	3 (3%)	0	4 (4%)
agitation	1 (4%)	2 (2%)	0	1 (1%)	0	1 (1%)
anxiety	2 (8%)	3 (3%)	1 (5%)	0	2 (12%)	2 (2%)

Clinical Review
 Lex Schultheis, M.D., Ph.D.
 NDA 21,060
 {Prial (Ziconotide)}

aphasia	0	2 (2%)	0	1 (1%)	0	6 (6%)
ataxia	1 (4%)	10 (11%)	1 (5%)	5 (6%)	0	1 (1%)
confusion	3 (13%)	5 (6%)	0	3 (3%)	0	9 (9%)
depression	0	0	0	3 (3%)	0	0
difficulty concentrating	0	4 (5%)	0	0	0	1 (1%)
dizziness	10 (42%)	29 (33%)	0	10 (11%)	0	4 (4%)
dry mouth	1 (4%)	1 (1%)	1 (5%)	1 (1%)	0	1 (1%)
dyssthesia	3 (13%)	2 (2%)	0	1 (1%)	1 (6%)	1 (1%)
hallucinations	0	3 (3%)	0	2 (2%)	0	3 (3%)
hypertonia	0	6 (7%)	1 (5%)	2 (2%)	0	2 (2%)
insomnia	0	3 (3%)	0	2 (2%)	0	2 (2%)
memory impairment	3 (13%)	3 (3%)	2 (9%)	0	1 (6%)	4 (4%)
nervousness	1 (4%)	3 (3%)	0	1 (1%)	0	3 (3%)
nystagmus	1 (4%)	3 (3%)	0	4 (4%)	0	1 (1%)
paresthesia	1 (4%)	4 (5%)	1 (5%)	0	0	2 (2%)
somnolence	5 (21%)	10 (11%)	2 (9%)	2 (2%)	1 (6%)	5 (5%)
speech disorder	0	0	0	3 (3%)	1 (6%)	6 (6%)
tremor	0	3 (3%)	0	2 (2%)	1 (6%)	1 (1%)
vertigo	3 (13%)	4 (5%)	0	1 (1%)	0	0 (0%)
withdrawal syndrome	1 (4%)	2 (2%)	1 (5%)	0	0	0 (0%)

Data was compiled from sponsor's electronic data tables by Dr. Joan Buenconsejo.

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_____ § 552(b)(4) Trade Secret / Confidential

_____ § 552(b)(5) Deliberative Process

_____ § 552(b)(5) Draft Labeling

Clinical Review
Lex Schultheis, M.D., Ph.D.
NDA 21,060
Prialt (Ziconotide)

12 REFERENCES:

Intrathecal ziconotide in the treatment of Refractory Pain in Patients with Cancer or AIDS:
Randomized Controlled Trial., P. Staats et al. JAMA vol 291 # 1 pp 63-70

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/s/

Lester Schultheis
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Rigoberto Roca
12/23/04 04:28:39 PM
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FDA CENTER FOR DRUG EVALUATION AND RESEARCH
DIVISION OF ANESTHETIC, CRITICAL CARE, AND ADDICTION DRUG PRODUCTS
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DIVISION DIRECTOR'S REVIEW AND RECOMMENDATION FOR ACTION

DATE: July 18, 2001
NDA: 21-060
DRUG PRODUCT: PRIALT (ziconotide) 100 mcg/mL, 1,2,5,10 mL vials
SPONSOR: Élan Pharmaceuticals
SUBMISSION: Complete Response to Approvable Letter (of June 26, 2000)
DATE RECEIVED: January 26, 2001

Background

This submission is a complete response to an approvable letter (6/27/00) issued for NDA 20-060 for ziconotide for intrathecal administration for the treatment of pain. The previous review identified significant deficiencies. There remain many of the same problems, which this submission did not adequately address. They will be summarized below.

Chemistry Manufacturing and Controls

One significant problem identified during the first review cycle was stability throughout the dosing regimen. A thorough analysis of mechanisms leading to a decrease in ziconotide concentration in the Synchronmed micro-infusion pump was submitted. These provided an understanding of the quantity and mechanisms of drug loss in the pump reservoir. The mechanisms included adsorption, dilution (equilibration with system dead volumes) and chemical degradation. Efforts to eliminate adsorption have been investigated. [

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The sponsor has developed two sets of dosing instructions to allow for these very different settings. Nevertheless the compatibility of the ziconotide solution with the Medtronic micro-infusion pump has not been fully characterized even with this submission and the controls ensuring the compatibility have not been adequately described. Further information will be requested.

Appropriate analytical methods for assuring the activity of the drug substance on lot-to-lot release have been submitted at this cycle. They include the 2 dimensional NMR and a binding assay. The test method provided for the 2D-NMR test for the drug substance, however, is inadequate, the drug substance specification is incomplete for this test and the analytical testing site performing this test has not been inspected due to missing information.

Finally, the only remaining deficiency is that the acceptance criteria for impurities in the drug product lack individual specifications and specifications for total impurities. These will be requested for the in-pump specifications as well.

The division has received confirmation (6/27/01) from CDRH that the infusion pump through which this product will be administered is an approved device.

Microbiology

In the previous cycle there had been inadequate evaluation of the potential for Ziconotide to support microbial growth if contamination were to occur in the pump. This was critical to resolve because of the pump's placement in the intrathecal space the need for reentry on a regular basis to refill the pump with drug, and the risk of infection of the meninges. Microbiology studies were indeed performed and provided a profile that should assure the safe delivery of the product if the pump is refilled under strict aseptic technique. A filter is present in the system, although, if inoculation were to occur, this will likely provide only temporary protection against colonization. The need for strict aseptic technique should be included in the package insert.

The manufacturing method in the new facility has been determined to be acceptable, however the specifications for sterility are not sufficiently tight to provide assurance that the drug will not contain microbes. Therefore the sponsor will be required to provide new specifications ensuring that the vials on media fill using modern aseptic fill technique are sterile, that is, limits of <0.1% contamination.

Nonclinical Safety

During the first review cycle concerns arose as to whether the findings in the rat reproductive toxicology study, namely absent pubic and ischial bone, and absence of certain vertebral bodies (caudal region), represented teratogenicity. This remains unresolved. The possible contribution of maternal toxicity has not been fully addressed even with the literature articles submitted during this review cycle. In addition the proper staining techniques were not used to distinguish between delayed ossification and actual absence of bone. Therefore it is prudent, in the interest of understanding the nature of these findings and for proper labeling of this product, to require that a focused rat embryo-fetal study capable of demonstrating whether the previous finding of absence of

pubic and ischial bones and absence of certain vertebral bodies was due to delayed bony maturation (ossification) or due to absence of bone and cartilage. The study requested will require definitive staining techniques of cartilage and bone. Insofar as there was not adequate toxicokinetics (TK) in the NDA study, the study was a non-GLP study, it would be essential to obtain TK in the new study. Correlation of these findings with maternal toxicity will be critical.

Clinical Efficacy and Safety

The principle clinical deficiencies found in the original submission can be summarized as inadequate evidence for clinical effectiveness of intrathecal ziconotide for the treatment of pain in the target population and incomplete assessment of safety at the proposed dosing regimen.

The results of inadequate dose finding leading to changes in regimen throughout the trials, the adsorption of drug to the lining of the pump reservoir resulting in inability to assess actual dosing, and other significant problems with the studies in the original NDA are well described in Dr. Hertz's current and previous reviews. The remedy that was required in the original approvable letter was the conduct of a new adequate and well-controlled trial demonstrating effectiveness at the dosing regimen proposed for marketing. It was cautioned that this study should be initiated only after the concerns raised by the differential stability of the drug product and the adsorption of the drug substance have been satisfactorily addressed. These have been nearly all addressed as of this response. However, the sponsor did not conduct a new clinical trial, but rather requested the trial as phase 4 commitment. This was not accepted since the trial would be a necessary component for the determination of efficacy.

It was thought that a detailed and complete reanalysis of the safety and efficacy of ziconotide could be performed in the subset of patients in Studies 001 and 002 who were treated with the final revision of the dosing regimen. It was thought that this would provide supporting evidence of efficacy and safety. Élan, instead, submitted only reanalyses of the two previously submitted trials including one in which a *post hoc* subgroup analysis was performed and which was not previously found acceptable as the basis for the finding of effectiveness. No new analyses were performed that had not been previously reviewed. The request to view the new dosing regimen as a surrogate endpoint was not accepted, since the dosing regimen provides the input against which pain control is compared. There is no surrogate endpoint within this resubmission.

The sponsor will again be directed to perform a randomized double blind placebo-controlled clinical trial of the effectiveness and safety of ziconotide using a dosing regimen that can be tolerated. The study should also evaluate the impact on effectiveness of the coadministration of opiate analgesics.

The failure to study the safety of concomitant opiate administration with ziconotide, failure to do an adequate characterization of the CNS side effects and determination of reversibility, failure to adequately define a safe and effective dosing regimen, and the inadequate reporting of essential clinical data in the CRFs all remain as deficiencies.

Upon review of the new safety update Dr. Hertz identified an additional safety finding of QT prolongation that was not previously analyzed and will need further analysis and potentially further study. Identification of the actual dose delivered to individual patients will be an important component to the reanalysis of the safety database.

In summary the data submitted still do not adequately establish the safety of this product for chronic administration. The adverse events have not been appropriately evaluated to link them with the dosing regimen recommended in the labeling, and to characterize their true incidence and establish causality in the studied patient population.

In summary, many of the same critical deficiencies are present in this application. The sponsor will again be notified of the deficiencies and steps required to remedy them.

Division's Recommendation for Action: Approvable

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/s/

Cynthia McCormick
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MEDICAL OFFICER



FDA CENTER FOR DRUG EVALUATION AND RESEARCH

DIVISION OF ANESTHETIC, CRITICAL CARE, AND ADDICTION DRUG PRODUCTS
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Medical Officer Review Response to Approvable Letter

NDA:	21-060
Serial No.:	N00BZ
Drug Name:	Ziconotide
Sponsor:	Elan Pharmaceuticals
Review Date:	6/15/01
Date of Submission:	1/26/01
Date of Receipt:	1/29/01
Reviewer:	Sharon Hertz, M.D.
Project Manager:	Laura Governale, Pharm.D.

SUMMARY:

This submission represents the sponsor's complete response to the June 27, 2000 Approvable Letter issued following the review of the December 28, 1999 original NDA submission. The sponsor has failed to provide an adequate response to key clinical deficiencies identified in the Approvable Letter including failure to adequately replicate the finding of efficacy, failure to provide a thorough analysis of safety findings, and failure to clarify uncertain drug exposure due to drug/pump interactions.

To confirm the finding of efficacy in the intended patient population, a new clinical trial was deemed necessary. The pivotal trials submitted in support of efficacy failed to provide substantial evidence of efficacy in large part due to design flaws, particularly, inadequate Phase 2 dose finding resulting in multiple protocol modifications during the Phase 3 trials. The sponsor has requested that they be allowed to perform this additional study post-marketing and has submitted a reanalysis of prior efficacy data. The review of this reanalysis failed to provide additional evidence of efficacy. In addition to providing information on efficacy, the new trial is needed prior to marketing to define a safe approach to drug titration that can be incorporated into the product label.

Problems identified in the analysis of safety data included an inadequate evaluation of CNS-related adverse events. A proposed method for reanalysis suggested by the Agency, utilizing groupings of related adverse event terms, was rejected by the sponsor and the issue remains outstanding. Additional documentation of details surrounding the cause of death of patients who died during the clinical trials was attempted by the sponsor, but no significant additional information was provided.

Ziconotide, a peptide, adsorbs to the surface of the implantable SynchroMed pump, resulting in a reduction in available active drug in the reservoir of ziconotide-naïve pumps. Additional drug is lost in ziconotide-naïve pumps due to the filling of a fixed dead space. For pumps initially filled with a 10 ug/ml concentration of ziconotide solution during the pivotal trials, these sources of drug loss went unrecognized and patients were exposed to less drug than expected. The actual amount of drug exposure for these patients depends on many factors including the rate of titration and time to first pump refill. The period of uncertain drug exposure coincides with the study period used for efficacy measurements and for the initial safety assessments. The sponsor was requested to quantitate the actual drug exposure for these patients and assess the impact on relevant safety and efficacy assessments. This reanalysis was not performed. The sponsor did provide a more detailed analysis of safety and efficacy based on the patient population exposed to the final dosing regimen, but failed to incorporate the impact of reduced drug exposure as outlined above.

An analysis of the effects of coadministered opioids on safety and efficacy was lacking in detail and failed to provide meaningful conclusions. A review of overdoses of ziconotide demonstrated no serious or irreversible adverse events resulting from the limited number of events identified. An evaluation of potential withdrawal symptoms from discontinuation of ziconotide did not identify any evidence of a withdrawal syndrome.

An update of safety data was provided. No differences in the overall incidences of adverse events were identified in a review of this updated Integrated Summary of Safety.

Further attempts to collect and confirm financial disclosure resulted in an adequate reporting that did not reveal any financial interactions resulting in a potential for conflict of interest or bias from study investigators.

This application remains approvable, pending adequate and complete responses to the clinical deficiencies identified in the original NDA review.

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BACKGROUND:

The current submission represents a complete response to the June 27, 2000 Approvable Letter. The original NDA submission dated December 28, 1999, was found to have clinical and chemistry deficiencies. The clinical deficiencies included failure of one of the pivotal efficacy trials to demonstrate efficacy by the primary efficacy outcome measure, inadequate documentation of safety data, and uncertain drug exposure. The chemistry issues contributing to the approvable decision included questions of drug adsorption to the pump, differential stability of the drug product at different concentrations, a question of the drug product's ability to sustain microbial growth, and selection of an appropriate analytical method to assess drug substance activity.

The sponsor reports that "the issues and concerns listed in the Approvable Letter including supportive data and reports (NDA Resubmission)" are present in this submission. The sponsor has submitted a reanalysis of the efficacy data without data from a new trial. The safety data has been reanalyzed and updated to address the clinical issues enumerated in the Approvable Letter. In addition, the sponsor has put forth a proposal for Accelerated Approval of ziconotide and a request for Orphan Drug Designation has been filed.

DEFICIENCIES AND RESPONSE

This review will be organized according to the deficiencies identified and the corrective actions outlined by the Agency.

Deficiency:

1. The data submitted in the NDA are inadequate to support a definitive conclusion that ziconotide will be safe and effective in the target patient population using the dosing regimen recommended in the proposed draft labeling. While the two Phase 3 placebo-controlled studies (Study 95-001 and Study 96-002) were on their face adequately designed to evaluate the safety and effectiveness of ziconotide by intrathecal administration, insufficient attention was given to dose-ranging for safety and effectiveness and to delineation of the temporal pharmacodynamic profile of the drug prior to initiation of these studies. These failures resulted in the use of an initial dosing regimen (i.e., initial dose, dose titration schedule, and titration interval) in both studies that was associated with an unacceptably high rate of serious adverse events and patient withdrawals. The dosing regimen was significantly modified (e.g., changes in initial dose and dose escalation schedule, changes in dosing interval, change from dose escalation to toxicity to dose escalation to analgesia, etc.) on several occasions while these two studies were ongoing in an attempt to find a more tolerable dosing strategy. As a result, only a relatively small number of patients were treated with the final dosing regimen, which most closely approximates the dosing regimen proposed in the draft labeling.

Analysis of the subset of patients enrolled in Study 95-001 and Study 96-002 who were treated with the final dosing strategy (after exclusion of patients enrolled at the clinical sites where unblinding may have occurred) suggested that ziconotide may be effective for management of severe chronic pain (i.e., the primary endpoint of percent change in visual analog scale of pain intensity (VASPI) for ziconotide-treated patients was statistically significantly different from

placebo in Study 96-002 and there was a trend favoring ziconotide versus placebo in Study 95-001).

Interpretation of the data from this subset of patients, however, is limited due to the following factors:

- (a) This analysis represents a post-hoc subset of patients that was not pre-specified in the protocol and, as such, this analysis is best considered exploratory and not confirmatory of effectiveness of the final dosing regimen.*
- (b) The small number of patients who were treated with the final dosing regimen in these two studies limits the conclusions that can be reached regarding the safety and tolerability of the final dosing regimen.*

Corrective Action: A. (1) Submit the results of a new randomized, double-blind, placebo-controlled study of the safety and effectiveness of ziconotide at the dosing regimen (i.e., initial dose, dose titration schedule, and titration interval) proposed for marketing conducted in the target population proposed for labeling. This study should be initiated only after the concerns raised by the differential stability of the drug product and the adsorption of the drug substance to the pump reservoir have been satisfactorily addressed (see Item D., below). The dosing regimen used in this study should take into account the actual drug delivered during the previous two placebo-controlled studies so as to provide corroborating evidence of effectiveness for the previously studied regimen. You are strongly encouraged to consult the Division of Anesthetic, Critical Care, and Addiction Drug Products regarding the design of the new clinical trial prior to initiation of the trial.

Response:

The sponsor has submitted the following response to this deficiency:

1. An argument that the original data from studies 96-002 and 95-001 is sufficient to support efficacy because data from a site found to have questions concerning data integrity due to unblinding should not be excluded as those results do not differ from the remainder of the results.
2. A request for Accelerated Approval based on the argument that data from subjects studied under different, earlier dosing protocols should be considered a surrogate endpoint for the analgesic effect of ziconotide administered according to later protocols.
3. An argument that a new study to confirm efficacy should be performed following approval, as a post-marketing commitment.

Comments:

The argument for including data from a study site with questionable data integrity had been addressed in the original NDA review by Dr. Stella Grosser of the Division of Biometrics. In short, data from the site in question was found to be of uncertain quality due to unblinding during an investigation by the Division of Scientific Investigation. As a result, the Agency has excluded this data from the efficacy analysis. As discussed by Dr. Grosser, the efficacy results

from this site are similar to the results of the remainder of the efficacy population does not lessen the concerns about the integrity of the data.

The argument for Accelerated Approval based on Subpart H was been rejected by the Agency and communicated to the sponsor in a teleconference on February 6, 2001. The use of a post hoc argument about surrogate endpoints for the purpose of salvaging a pivotal trial that failed to adequately demonstrate efficacy, followed by a post-marketing study, fails to address the basic clinical deficiencies of the original NDA submission outlined in the Approvable letter. Data obtained from early titration protocols found to be too aggressive, which resulted in a high rate of adverse events, does not represent a surrogate endpoint. Use of a surrogate endpoint is not indicated when an appropriate, direct primary endpoint can be evaluated. The pivotal trials completed were flawed due to inadequate dose-finding prior to commencing these studies. Furthermore, it appears that the final dosing regimen from these pivotal trials is still too aggressive. According to the sponsor, during a face-to-face meeting between the Agency and the sponsor on August 17, 2000, greater patient tolerance was observed using a slower titration during the open-label trial, 98-022. The sponsor expressed reluctance to utilize the final titration schedule from the pivotal trials in a new study, now that a safer approach to titration has been demonstrated. This underscores the point that we do not yet have adequate information to direct physicians in the proper use of this product.

The proposed protocol in the current submission, EP111-325, reflects the dosing regimen utilized during the final protocol amendments for the two original pivotal trials. A protocol synopsis submitted 2/23/01, Serial No. 200, describes a less aggressive dose titration and supercedes the prior draft protocol. This latter synopsis describes a starting dose of 0.1 ug/h with increments of from 0.05ug/hr to 0.1 ug/hr, at intervals no more frequent than 48 hours, and a maximum dosage of 0.9 ug/h. This may represent a better titration. An agreement was reached between the sponsor and the Agency during the February 6, 2001 teleconference that if the latter study protocol yielded evidence of efficacy, the dosing regimen from this trial would be used for labeling purposes.

In order to provide adequate and appropriate information for the purpose of confirming that ziconotide is safe and effective in the planned manner of use, in the intended patient population, it is necessary for the sponsor to conduct a clinical trial prior to approval.

Deficiency:

1 (c) Analysis of the subset of patients who received the final dosing regimen has not been extended to include the secondary endpoints that were specified in the protocol nor to include standard analyses of safety and effectiveness generally reported in a complete clinical trial report (e.g., patient demographics, duration of exposure, adverse events, etc.).

Corrective Action: A.(2) Submit a detailed and complete reanalysis of the subset of patients in Study 95-001 and Study 96-002 who were treated with the final revision of the dosing regimen that adequately address the deficiencies noted in item #1 (c), (d), (e), and (f) above or a subset that reasonably conforms to the proposed labeling, after the issues of actual drug delivery to patients have been addressed. You are

strongly encouraged to consult the Division of Anesthetic, Critical Care, and Addiction Drug Products regarding the reanalyses of Study 95-001 and Study 96-002 prior to conducting the requested reanalyses.

Response:

I) EFFICACY:

The sponsor has submitted a reanalysis of efficacy data for the subset of patients treated under the final dosing regimen in the pivotal trials, Study 95-001 and Study 96-002, and a pooled analysis to evaluate patient subsets. The request for a reanalysis of the subset of patients who received the dosing under the final regimen was intended to complement the analysis of results from a new clinical trial. This approach is inadequate in lieu of a new clinical trial. The data reanalyses and analysis of pooled data have been reviewed by Dr. Stella Grosser from the Division of Biometrics. The results do not differ from the results submitted in the original NDA review.

II) SAFETY:

a. Extent of Exposure:

The population for the ISS has increased to 976 patients treated with ziconotide in the current submission from 704 at the time of the NDA 120-day safety update due to ongoing enrollment in open-label studies. The placebo exposure is unchanged. Of the 368 patients enrolled in the double-blind, placebo-controlled studies, 257 were treated under the final dosing schedule, 170 received ziconotide, 87 received placebo. It is unclear if the patients considered low-dose in this group were those beginning with a dose of ≤ 0.1 ug/hr, or if they were actually treated under the final dosing schedules. Regardless, no accounting for the loss of ziconotide due to adsorption of drug onto the pump surface or loss due to the dead space for patients receiving their initial drug exposure with the 10 ug/ml concentration was performed; nor was there an identification of those patients who might be affected by this. Updates on dosing information, patient disposition, demographics, and baseline characteristics were provided

b. Adverse Events

The sponsor has submitted an amended ISS updating the prior ISS with information from studies ongoing at the time of NDA submission, and has also addressed some of the issues raised in the Approvable Letter. The cutoff dates for this ISS Amendment were August 8, 2000 for Study 95-002 and July 31, 2000 for Study 98-022. Adverse events occurring subsequent to the cutoff dates for the ISS Amendment through December 15, 2000 were submitted in appendices to this Amendment.

The methodology of reporting adverse events for this ISS Amendment was the same as applied to the original NDA submission and 120-day Safety Update with a few exceptions. Summaries of adverse events were provided for the entire population, the initial, placebo-controlled, double-blind titration period in the pivotal studies, and the open-label studies; but in this amendment, a summary for the low-dose population from the placebo-controlled, double-blind period of the pivotal trials was also provided. This review will focus on differences in the results for the entire population compared with the original review, and the results for the low-dose population.

The sponsor coded adverse event terms to preferred terms using the COSTART thesaurus, 5th edition, 1995. For terms that did not match the thesaurus exactly the sponsor's medical monitor determined the best match possible. The sponsor counted patients enrolled in more than one study only once for all AE summaries and patients who received both ziconotide and placebo in both respective groups for AE summaries. For studies 95-001, 96-002, 95-002 and 97-013 the investigator categorized AE's and SAE's according to relationship to study drug or device. As a result, adverse events ascribed to the device were submitted to the Medtronic PMA SynchroMed infusion system supplement, and not this ISS Amendment or the original NDA. However, in response to Agency comments, cases of meningitis during these studies, originally reported only in the Medtronic PMA supplement, have been included in the current submission. (Note: The reviewer's original NDA evaluation did include the reports of meningitis in the PMA supplement as well as those in the NDA.).

Adverse events from the entire intrathecal population were evaluated based on whether they occurred while patients were receiving ziconotide or while they were receiving placebo. The sponsor has presented these adverse events in IT Table 8.8.2.7-1 (Vol. 10.7, P. 163). Adverse events that occurred more than once were only counted the first time for this table. This table also presents the number of adverse events by body system. For patients with more than one adverse event in a given body system, only the first was counted for this table.

Many of the patients in the double-blind studies were crossed over from ziconotide or placebo to the alternate treatment. Adverse events for these subjects were reported separately based on the treatment the patient received while the event occurred. As a result, the adverse events are reported for the "while receiving ziconotide" group or for the "while receiving placebo" group. Adverse events were extremely common occurring in nearly all of the patients in the "while receiving ziconotide" group, (96.8%), and in 76.2% of patients in the "while receiving placebo" group, as demonstrated in Table 1. This is not significantly changed from the original NDA. Also, as presented in the original NDA, patients experienced more adverse events per patient while receiving ziconotide than while receiving placebo. This has been demonstrated in two ways. The total number of adverse events in Table 8.8.2.7-1 for the 976 patients while receiving ziconotide was 9751, an average of 10 adverse events per patient. The total number of adverse events for the 151 patients in the "while receiving placebo" group was 385, an average of 2.5 adverse events per patient. Similarly, for the 976 patients in the "while receiving ziconotide" group, there were 4494 adverse events by body system, so that on the average each patient had adverse events involving 4.6 body systems. For the 151 patients in the "while receiving placebo" group, there were 282 adverse events by body system, an average of 1.9 per patient. The patients in the "while receiving ziconotide" group were under treatment for a longer period of time than those receiving placebo which would account for some of this greater frequency of adverse events.

Table 1

COSTART Term	While Receiving Ziconotide (N = 976)	While Receiving Placebo (N = 151)
Number Of Patients With Any Event	945 (96.8%)	115 (76.2%)
Adverse Event by Body System	4494 (4.6/patient)	282 (1.9/patient)
Individual Adverse	9751 (10 AE/patient)	385 (2.5 AE/patient)

The most common AE's involved the Nervous System (88.5% ziconotide group, 41.1% placebo group), Body As A Whole (73.8% and 39.1%, respectively) And Digestive System (70.8% and 35.1%, respectively). The most common individual AE's in the "while receiving ziconotide" group were dizziness (51.6%), nausea (48.7%), headache (33.2%), confusion (31.7%), nystagmus (29.8%), somnolence (25.1%), pain (24.3%) and abnormal gait (21.6%). The only AE's reported for more than 20% of patients in the "while receiving placebo" group were nausea (20.5%), still less than half as frequent, and headache (20.5%) which was similar to the ziconotide group.

A criticism of the original NDA ISS by the Agency was that the sponsor mapped adverse event verbatim terms of similar symptoms to different COSTART terms. This effectively dilutes the appearance of adverse events. In particular, this was true for adverse events related to encephalopathy and this is discussed in greater detail below.

The sponsor has listed other clearly related adverse events as separate entries in the Adverse Event tables. For example, Table 8.8.2.7-1 (Vol. 10.7, p. 163) lists both "Lab test abnormal" and "Laboratory test abnormal", "Vasodilatation" and "Vasodilation", "Mucous membrane disorder" and "Mucus membrane disorder", "Injection site pain", "Injection site inflammation", "Injection site reaction", and "Injection site hypersensitivity", "Cardiovascular disorder" and "Coronary artery disorder", "Gastritis" and "Gastroenteritis", all as separate entries in this table.

Table 8.8.2.7-1 (Vol. 10.7, p. 163), Adverse Events, was reviewed. There were no clinically relevant changes in the incidences of individual adverse events compared to the original NDA review.

Table 2 lists those adverse events that were found to be statistically significantly different between treatment groups during the initial titration period of the two pivotal studies, 95-001 and 96-002. Information from the double-blind population from the original NDA review, and now additionally from the low-dose population, has been included. When these analyses were extended to the low-dose population, most of the comparisons remained statistically significantly different with a higher frequency of adverse events occurring in the ziconotide-treated patients. The smaller number of subjects would be one factor for the changes in p-values. The adverse events nausea and/or vomiting, abnormal gait, dizziness, confusion, nystagmus, somnolence and urinary retention were particularly more frequent in the ziconotide group.

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Table 2 Comparisons of Adverse Events in Ziconotide-treated Patients and Placebo Patients - Double-Blind, Placebo-Controlled Clinical Studies - Initial Titration Phase

COSTART Term	All Patients			Low-Dose Group		
	Ziconotide N = 242	Placebo N = 126	p-value	Ziconotide (N = 170)	Placebo (N = 87)	p-value
Number of Patients with Any Adverse Event	231 95.5%	91 72.2%	<0.0001 ^a	160 94.1%	63 72.4%	0.0001 ^a
Body as a Whole	118 48.8%	44 34.9%	0.0117 ^b	78 45.9%	28 32.2%	0.0341 ^b
Fever	32 13.2%	5 4.0%	0.0055 ^a	16 9.4%	4 4.6%	not done
Cardiovascular System	69 28.6%	17 13.5%	0.0011 ^a	44 25.9%	12 13.8%	0.0264 ^a
Postural Hypotension	37 15.3%	7 5.6%	0.0063 ^a	23 13.5%	6 6.9%	0.1449
Digestive System	156 64.5%	44 34.9%	<0.0001 ^b	106 62.4%	28 32.2%	0.0001
Nausea	104 43.0%	24 19.0%	<0.0001 ^b	72 42.4%	15 17.2%	0.0001 ^a
Vomiting	37 15.3%	7 5.6%	0.0063 ^a	23 13.5%	3 3.4%	0.0146 ^a
Nervous System	204 84.3%	49 38.9%	<0.0001 ^b	141 82.9%	39 44.8%	0.0001 ^b
Abnormal Gait	56 23.1%	3 2.4%	<0.0001 ^a	38 22.4%	3 3.4%	0.0001 ^a
Confusion	35 14.5%	7 5.6%	0.0097 ^a	20 11.8%	4 4.6%	0.0714 ^a
Dizziness	127 52.5%	17 13.5%	<0.0001 ^a	86 50.6%	15 17.2%	0.0001 ^a
Nystagmus	101 41.7%	15 11.9%	<0.0001 ^a	70 41.2%	12 13.8%	0.0001 ^a
Somnolence	38 15.7%	7 5.6%	0.0042 ^a	22 12.9%	5 5.7%	0.0873 ^a
Special Senses	57 23.6%	6 4.8%	<0.0001 ^a	43 25.3%	6 6.9%	0.0003 ^a
Amblyopia	22 9.1%	2 1.6%	not done	18 10.6%	2 2.3%	0.0244 ^a
Urogenital System	66 27.3%	8 6.3%	<0.0001 ^a	142 24.7%	6 6.9%	0.0003 ^a
Urinary Retention	40 16.5%	2 1.6%	<0.0001 ^a	24 14.1%	2 2.3%	0.0019 ^a

a Treatment difference is tested using Fishers Exact Test.

b Treatment difference is tested using the CMH general association test controlling for study.

Studies include: 95-001 and 96-002.

Source: Sponsor's Table 8.8.2.7.9, Vol. 2.93, 249. Table 8.8.2.7-9, Vol. 10.7, P. 231

i) Adverse Events by Subgroup

Effects Of Age

Among the total population, patients < 60 years of age and patients ≥ 60 years of age reported similar AE's, and this was true for both treatment groups. Patients ≥ 60 reported more confusion (43.9%) compared with patients <60 (26.3%). (Table 8.8.2.7-5 vol. 10.7, P. 211). This was unchanged from the original NDA submission.

Among the low-dose population, the differences between age groups was less notable, presumably at least in part due to the smaller group sizes. (Table 8.8.2.7-15, Vol. 10.7, p. 262.) In the listing of adverse events by age groups of <65 years, 65-74 years and ≥75 years (Table 7.5b, Appendix 2, Vol. 10.10, P. 49), among ziconotide-treated patients, there were only 28 and 17 patients in the two older age groups, respectively, compared with 125 patients in the lower age group. The uneven group sizes preclude detailed analysis. However, 29.4% of patients >75 years experienced confusion compared with 10.4% and 7.1% for the two younger age groups.

Effects of Gender

Among the entire population, the adverse event profiles for women and men were similar (Table 8.8.2.7-6, vol. 10.7, P. 217). The AE's at least 5% more common in women receiving

ziconotide were nausea, 54.4% in women compared with 43.2% in men, vomiting (20.0% vs. 14.2%), peripheral edema (14.7% vs., 8.8%), and dizziness (55.3% vs. 48.2). There were no significant differences in these findings among the low-dose population (Table 8.8.2.7-15, Vol. 10.7, p. 282).

Effects of Race

There were few non-Caucasian patients (68) compared with Caucasian (908) among those receiving ziconotide. There was a greater frequency of fever (32.4%) in non-Caucasian patients compared with Caucasian (17.4%). This was the only difference greater than 10%. The large imbalance in enrollment of non-Caucasian patients precludes meaningful comparisons. This imbalance was even greater in the low-dose population, with 161 Caucasian patients and 9 non-Caucasian patients.

ii) Time To First Occurrence Of AE

Of the 945 patients who received ziconotide, 936 experienced the first occurrence of any AE within 1 month of treatment. The handling of this adverse event data suffered the same shortcomings as the general adverse event data, with no attempt by the sponsor to reconcile similar adverse events mapped to different COSTART terms.

While most of the adverse events occurred for the first time within 30 days of starting treatment with ziconotide, there were many adverse events which continued to appear after longer periods of exposure. Of particular relevance to this drug product, was the first occurrences of confusion with 58 first occurrences between 30 and 90 days, compared to 226 in the first 30 days. For depression, there were 21 first occurrences between 30 and 90 days compared with 62 occurrences in the first 30 days and for hallucinations there were 28 first occurrences between 30 and 90 days and 49 during the first 30 days. There were also first occurrences of emotional liability (8) and paranoid reaction (10) between 30 and 90 days, compared with 24 and 13 occurrences in the first 30 days, respectively (Vol. 10.7, p. 181).

Among patients on therapy for more than three months, most adverse events were apparent within the first three months of treatment. However, accidental injury, amnesia, confusion, depression, hallucinations, and CK increased were several adverse events that continued to occur for the first time as far out as 180 days.

Table 3 Time of First Occurrence of AE

COSTART Term	0 to < 30 days	30 to < 90 days	90 to < 180 days	180 days
Accidental Injury	22	8	6	11
Amnesia	76	11	12	7
Confusion	85	25	15	7
Depression	38	11	10	8
Hallucinations	33	15	10	3
Creatine Kinase Increased	19	2	4	2

Source: Table 8.8.2.7-3, Vol. 10.7, P. 187

iii) Adverse Events By Cumulative Dose

As discussed in the original NDA review, several adverse events occurred more frequently with greater cumulative doses or higher doses at onset of therapy. These included nystagmus,

abnormal vision, ataxia, abnormal gait, urinary retention, and confusion. An analysis of the low-dose population mirrored this finding (Table 8.8.2.7-13, 8.8.2.7-14 Vol. 10.7, P. 255, 258).

iv) Sponsor's Review of Adverse Events of Particular Interest

The sponsor identified 10 adverse events as being of particular clinical interest during the blinded reviews of safety data during the pivotal trials. These are: abnormal gait (including ataxia), amblyopia (including abnormal vision), asthenia (including myasthenia), confusion, dizziness, hypotension (including postural hypotension), nausea (including vomiting or nausea and vomiting), nystagmus, somnolence and urinary retention. These adverse events were all more common in patients receiving ziconotide. Among the low-dose patients, the following adverse events were more common among the ziconotide-treated patients than placebo-treated patients: dizziness (50.6% vs., 17.2%), nausea, including vomiting or nausea and vomiting, (52.4% vs. 20.7%), nystagmus (41.2% vs. 13.8%), and abnormal gait, including ataxia, (29.4% vs. 4.6%). The sponsor provided tables with median days to adverse event onset, median dose at onset and median cumulative dose at onset. Table 4 provides information representing the entire ziconotide-treated population followed by Table 5 with the information for the low-dose population. The median number of days to the onset of all adverse events were greater for the full population compared to the low-dose group, but the low-dose group would only have information collected for the first five to six day treatment period. The median doses at onset for all these adverse events were smaller for the full population. The median cumulative doses at onset were similar for all of these adverse events except confusion and somnolence, which were higher for the low-dose group.

Table 4 Time and Dose Relationship of Events of Particular Clinical Interest to Ziconotide Treatment-All IT Clinical Studies (N=945)

AE (n)	While Receiving Ziconotide		
	Median No. Days to Onset ^a	Median Dose at Onset ^a (ug/hr)	Median Cumulative Dose at Onset ^b (ug)
Abnormal gait (including ataxia) (285)	6.00	0.20	20.04
Amblyopia (including abnormal vision) (191)	6.00	0.20	21.17
Asthenia (including myasthenia) (256)	9.00	0.15	17.44
Confusion (309)	15.00	0.20	5.91
Dizziness (504)	4.00	0.20	12.00
Hypotension (incl. postural hypotension) (144)	4.00	0.30	16.99
Nausea (incl. vomiting, nausea and vomiting) (535)	3.00	0.15	9.36
Nystagmus (291)	6.00	0.25	21.04
Somnolence (245)	6.50	0.20	16.59
Urinary retention (138)	5.00	0.20	20.14

a For patients who experienced more than one occurrence of the event, the day/dose level associated with the first occurrence of the event was used.

b The cumulative dose (ug) at onset of the first reported event with K distinct doses was estimated as: [dose level 1 (ug/hour) x duration of dose level 1 (hours) + dose level 2 (ug/hour) x duration of dose level 2 (hours) + dose level K (ug/hour) x duration of dose level K (hours)].

Studies include: 94-004, 95-001, 95-002, 96-002, 96-003, 96-010, 97-013, 97-015, and 98-022.

Source: Table 8.8.2.7-8, Vol. 10.7, P. 227

Table 5 Time and Dose Relationship of Events of Particular Clinical Interest to Ziconotide Treatment- Low-Dose Patient Population (N=170)

AE (n)	While Receiving Ziconotide		
	Median No. Days to Onset ^a	Median Dose at Onset ^{a,b} (ug/hr)	Median Cumulative Dose at Onset ^c (ug)
Abnormal gait (including ataxia) (50)	4.00	0.45	22.87
Amblyopia (including abnormal vision) (26)	4.00	0.30	18.31
Asthenia (including myasthenia) (16)	4.00	0.25	17.31
Confusion (20)	4.00	0.30	15.80
Dizziness (86)	3.00	0.30	11.83
Hypotension (including postural hypotension) (33)	3.00	0.30	12.65
Nausea (incl. vomiting, nausea and vomiting) (89)	2.00	0.20	6.90
Nystagmus (70)	4.00	0.30	15.34
Somnolence (22)	3.00	0.30	10.03
Urinary retention (24)	3.50	0.30	20.01

a For patients who experienced more than one occurrence of the event, the day/dose level associated with the first occurrence of the event was used.

b Patients who had the occurrence of the event after the last infusion are not included in the calculation.

c The cumulative dose (ug) at onset of the first reported event with K distinct doses was estimated as: [dose level 1 (ug/hour) x duration of dose level 1 (hours) + dose level 2 (ug/hour) x duration of dose level 2 (hours) + dose level K (ug/hour) X duration of dose level K (hours)].

Studies include: 96-002 and 95-001.

Source: Table 8.8.2.7-21, Vol. 10.7, P. 278

One problem with the analysis of adverse events by dose and time to onset is that the ziconotide population consists of subjects who were titrated onto study drug according to several different titration protocols. Early subjects in the pivotal trials were titrated more aggressively than the low-dose group. Subjects first receiving ziconotide in study 98-022 may have been titrated similarly to the low-dose group or even more slowly. These differences preclude meaningful interpretation of these results.

v) Focused Adverse Event Reviews

Encephalopathy

As noted above, a criticism of the original NDA ISS by the Agency was that the sponsor mapped adverse event verbatim terms of similar symptoms to different COSTART terms. In particular, this was true for adverse events related to encephalopathy. Although the Agency provided the sponsor with a list of 30 encephalopathy related adverse events, the sponsor has redefined related adverse events, listing just 5 AEs they designate as the cardinal features of cognitive dysfunction. A panel of ziconotide investigators and neurologists was convened by the sponsor to establish a consensus that there was no specific "ziconotide CNS syndrome." The term "neurocognitive impairment" was suggested as a term preferable to encephalopathy. This panel chose a list of 9 symptoms representative of ziconotide-induced neurocognitive dysfunction. Terms chosen by the sponsor are: amnesia, aphasia, confusion, speech disorder, and thinking abnormal. Terms chosen by the panel are: amnesia, aphasia, confusion, delirium, encephalopathy, hallucinations, speech disorder, stupor and thinking abnormal. Terms chosen by this reviewer not included by the sponsor or panel were: somnolence, dementia, and CNS depression. Bizarre behavior, a verbatim term, was excluded by the sponsor and panel. Terms related to both psychiatric conditions, as well as organic brain dysfunction, were also excluded from the sponsor's and panel's symptom lists.

The sponsor additionally generated a table looking at “specificity ratios” for different definitions of this syndrome (Table 8.8.2.7-31, Vol. 10.7, P. 326). In actuality, the sponsor generated incidence ratios for ziconotide vs. placebo-treated patients. Based on this reviewer’s original analysis for the NDA review, 65% of ziconotide-treated patients experienced any one of the adverse events associated with encephalopathy compared with 22.5% of placebo-treated patients. When analyzed according to those adverse event terms associated with “neurocognitive impairment” by the panel of investigators and experts convened by the sponsor, 51.4% of ziconotide-treated patients and 10.6% of placebo-treated patients exhibited any one of the 9 listed events. For the sponsor generated group, 49.6% of ziconotide-treated patients and 9.3% of placebo-treated patients experienced any one of the 5 listed adverse events.

The symptoms of cognitive dysfunction described by any of the three different lists of adverse events are not specific for a “syndrome.” These symptoms are simply evidence of central nervous system effects of ziconotide that affect the processes involved in clarity of thought, memory, level of consciousness, mood and behavior. The patient populations studied, patients with chronic pain due to malignant and non-malignant etiologies of pain, are often treated with several CNS active medications that could result in adverse events reflective of encephalopathy. As a result, both placebo and ziconotide treated patients would be expected to exhibit these symptoms. For the current application, it is important to recognize the markedly greater frequency of these adverse events in patients receiving ziconotide compared to placebo. By using different COSTART terms for similar adverse events which reflect similar underlying processes, the sponsor has diluted the appearance of the encephalopathy. By remapping these terms, this reviewer found that approximately two thirds of patients treated with ziconotide experienced at least one of these symptoms. When this reviewer analyzed the causes of study discontinuation in the original NDA, it was found that the most common reasons for a patient to prematurely discontinue study participation were: confusion, memory impairment, delirium, hallucinations, depression/ suicidal ideation, anxiety, psychosis/bizarre behavior, and hostility.

These findings indicate that treatment with ziconotide results in a clinically significant number of adverse events affecting clarity of thought, memory, level of consciousness, mood and behavior. This can be called encephalopathy or neurocognitive dysfunction. Regardless of the title, patients and prescribers will need to be adequately informed of the high rate of these adverse events so that adequate precautions can be taken to ensure patient safety.

Neuropsychiatric Adverse Events

The sponsor prepared tables mapping adverse events related to neuropsychiatric symptoms to a sponsor-defined dictionary prepared for another drug development program. Table 6 combines the sponsor’s tables for the entire population and the low-dose population. As can be seen, there were many more occurrences among the ziconotide-treated patients, particularly when patients treated with the more aggressive early dosing paradigms are included. Review of the low-dose patients compared to concurrently enrolled placebo patients reveals that all of the adverse events identified below were more common in the ziconotide-treated patients than placebo-treated patients with the exception of anxiety, difficulties in word expression, and tiredness. While the sponsor has made a distinction between adverse events related to

neurocognitive impairment and neuropsychiatric impairment, this is an artificial construct. The adverse events listed below are common to organic conditions, including drug-induced encephalopathy, that impair the neurocognitive function of the brain.

Table 6 Neuropsychiatric Adverse Events.

	All Patients				Low-Dose Patients, Controlled Trials			
	Ziconotide N=976		Placebo N=151		Ziconotide N= 170		Placebo N= 87	
Neuropsychiatric And Cognitive Dysfunction	650	66.60%	37	24.50%	65	38.20%	23	26.40%
Agitation/Irritability	65	6.7	1	0.7	3	1.8	1	1.1
Anger/Aggression	19	1.9	0	0	1	0.6	0	0
Anxiety	118	12.1	8	5.3	7	4.1	7	8
Apathy	6	0.6	0	0	0	0	0	0
Confusion	309	31.7	10	6.6	20	11.8	4	4.6
Depression	105	10.8	1	0.7	4	2.4	1	1.1
Difficulties In Verbal Expression	166	17	3	2	5	2.9	3	3.4
Difficulty Concentrating	124	12.7	1	0.7	4	2.4	0	0
Euphoria	2	0.2	0	0	1	0.6	0	0
Insomnia	114	11.7	3	2	10	5.9	1	1.1
Nervousness	87	8.9	5	3.3	9	5.3	3	3.4
Paranoid Behavior	30	3.1	0	0	1	0.6	0	0
Psychosis	6	0.6	0	0	0	0	0	0
Somnolence	245	25.1	10	6.6	22	12.9	5	5.7
Tiredness	153	15.7	5	3.3	6	3.5	4	4.6

Source: Appendix 2, Table 25.1 and 25.3, Vol. 10.11, P. 239

Reversibility of Confusion

At the request of the Agency, the sponsor evaluated the reversibility of the CNS adverse reactions to ziconotide. However, the sponsor chose to limit the analysis to the term confusion, omitting any of the other terms contributing to the "neurocognitive dysfunction" syndrome discussed above, and this resulted in an analysis of limited usefulness. The sponsor conducted the analysis with data from trial 98-022. The adverse event data was searched for instances of confusion for which the drug was discontinued. This information is presented in Listing 13, found in Vol. 10.51, P. 81. Within this limited analysis, the sponsor identified 65 patients with 78 events. There is no discussion or information on the dose of ziconotide associated with the ongoing confusion or if there was an association with a change in dosing. The sponsor's comments state that one patient had no resolution, but the information in Listing 13 indicates that 13 patients had ongoing symptoms. One patient's symptom was attributed to "Ritalin, Alzheimer's/ Parkinsons." Listing 13 does not provide information on etiology for the other unresolved patients. For the 64 events with "consistent dates of resolution of confusion and dates of drug discontinuation", the sponsor calculated a mean time to resolution of 10 days with a range of 0 to 38 days.

Cognitive Assessments

During Studies 95-001 and 96-002, patients underwent cognitive assessments including Trail Making, Parts A and B, and Digit Symbols tests. These tests were administered at baseline and

following the end of the initial titration phase. No clinically meaningful changes were noted by the sponsor. However, patients with CNS-related adverse events such as confusion and somnolence were unable to complete the testing at the end of the titration phase. As a result, the patients who experienced the greatest disturbance of cognitive function were excluded from this analysis and only those without cognitive adverse events, or with only mild cognitive impairment were included. The resulting analysis does not provide a meaningful assessment of cognitive disturbances due to ziconotide-induced adverse events and is not considered further.

Meningitis

The sponsor provided a listing of 40 patients with meningitis in the ISS Amendment and one additional case following the cutoff date for the amendment. The listing was compared to the patients with meningitis identified in the original review. Eight new cases were identified subsequent to the 120-day safety update. All seven patients listed in the ISS Amendment had external pumps. Patients 12-1561 and 12-1563 had multiple CSF leaks from their systems placing them at high risk for infection. Patient 12-1559 had the external catheter in place for 35 days and patient 12-1488 for 17 days. The external catheter systems have an increasing risk for infection when in place for longer than 14 days. There were neither narratives nor CRFs provided for patients 63-1485 and 123-1555. Patient 5007-049 was identified as a SAE of meningitis in the post ISS Amendment cutoff date information in Appendix 7. No further information was provided.

Table Additional Cases of Meningitis

Patient Number	Underlying Diagnosis	Treatment at Onset	Pump Type	Organism Identified	Reviewer's Comments
12-1488	Post laminectomy pain syndrome	Ziconotide	External	Gram negative organisms	Meningitis day 17
12-1559	Chest wall trauma, thoracostomy	Ziconotide	External	No organism identified	Leak day 3 Meningitis day 35
12-1561	Post lumbar laminectomy pain syndrome	Ziconotide	External	Gram negative rods	Leaks days 2, 12. Meningitis day 22
12-1563	Post cervical laminectomy pain syndrome	Ziconotide	External	Gram negative rods	Leaks days 3, 7, 9 Meningitis day 13
12-1571	Headache-r/o meningitis	Ziconotide	External	Negative culture	Meningitis day 3, no CSF information provided
63-1485	Severe post herpetic syndrome	Ziconotide	External	Staphylococcus epidermidis	No narrative or CRF
123-1555	Cancer, left chest epithelioid hemangioendothelioma	Ziconotide	External	Streptococcus viridans	No narrative or CRF
5007-049	NA			NA	NA

Source: Sponsor's Table 8.8.2.7-32, Vol. 10.7, P. 329

It appears to be unlikely that ziconotide contributed to the occurrence of meningitis in patients 12-1561 and 12-1563. However, the possibility that the ability of ziconotide to sustain microbial growth contributed to the remaining cases of meningitis cannot be confirmed or excluded based on available information.

The sponsor provided a table of the incidence of meningitis by pump type and study (Table 8.8.2.7-33, Vol. 10.7, p. 332). There were 11 cases of meningitis during the double-blind

studies in total. All occurred in patients with external pump systems, none in patients with internal pumps. Seven of the cases occurred in ziconotide-treated patients with external pumps (N=138) and four cases were in placebo-treated patients with external pumps (N=70). The remaining 29 cases occurred in open-label, uncontrolled studies: 27 in patients with external pumps and 2 in patients with internal pumps. This information suggests that the occurrence of meningitis is related to the risk of meningitis associated with external pumps, rather than a ziconotide related risk. Were ziconotide-mediated microbial growth the primary factor resulting in meningitis, with or without contaminated or colonized internal pumps, then it would be expected that cases of meningitis would be occurring after weeks or months in the internal pump population as well as the external pump population.

Hypersensitivity

The sponsor was asked by the Agency to address the issue of potential hypersensitivity to ziconotide. The results of early guinea pig systemic and passive cutaneous anaphylaxis studies suggested that hypersensitivity may be a clinical problem. The intrathecal doses of ziconotide are very small, reaching approximately 30 ug/day at the maximum suggested infusion rate of 2.4 ug/hr. As a result of these small CNS doses, the systemic exposure to IT ziconotide is extremely low. Citing re-exposure as the most likely situation for the development of a hypersensitivity reaction the sponsor has performed a focused review of adverse events occurring for the first time in patients who have been exposed to ziconotide a second time following an interval off drug. The design of Study 98-022 permits a "drug holiday" for up to 30 days. One hundred and eighty patients enrolled in this study had an interruption in ziconotide therapy.

The sponsor reports there have been no occurrences of anaphylaxis and this term is not found in the adverse event database. In a compilation of first occurrences of adverse events following re-exposure to ziconotide (Appendix 2, Table 26, Vol. 10.11, P. 242), the following adverse events which may be related to a hypersensitivity reaction were noted:

Allergic reaction	1 (0.6%)
Generalized edema	1 (0.6%)
Vasodilation	4 (2.2%)
Tongue edema	1 (0.6%)
Edema	7 (3.9%)
Asthma	2 (1.1%)
Pruritus	11 (6.1%)
Rash	19 (10.6%)

In the narratives (Appendix 4, Vol. 10.52, p. 27) and Table 8.8.2.8-14, there is a report of Patient 082-1439 discontinuing study participation due to a hypersensitivity reaction. The details of this reaction were not provided. Patient 164-1458 discontinued study participation due to a rash.

vi) Drug-Drug Interactions

The sponsor chose the following drug classes for subgroup analysis: antidepressants, antiepileptics, anxiolytics, diuretics, neuroleptics and sedatives. The sponsor did not perform a subgroup analysis of opioids as almost all patients took opioids during the trials.

The sponsor found that adverse events that were also indications for the medication class were more frequent in patients taking medications for that indication, i.e. depression in patients taking antidepressants. There were no clusters of adverse events with an increased frequency for any class of medications evaluated.

c) Deaths

The sponsor has provided information on deaths from all studies and from the ongoing studies up to the cutoff dates of August 8, 2000 for Study 95-002 and July 31, 2000 for Study 98-022. Additional information for the 2 ongoing studies through December 15, 2000 was summarized separately and submitted as Appendix 7.

There were 64 deaths in total reported in the original NDA review including the 8 patients reported in the 120-day Safety Update and the 120-day Safety Update Appendix 6. Two of these patients had never received ziconotide. In the current ISS Amendment including Appendix 7, there were 4 additional deaths reported among patients receiving ziconotide. This results in a total of 68 deaths, including the 2 patients who received only placebo.

The cause of death for the four additional deaths are described in the following summarized narratives.

Patient 63-1485 was an 81 year old man with a history "severe post herpetic syndrome" and a history of coronary artery disease. Seventy days after beginning ziconotide, the patient was diagnosed with meningitis and hospitalized. During the hospitalization, the patient underwent a cardiac work-up and while off cardiac medications, experienced a myocardial infarction, dying 6 days later due to complications. From the available information, this death does not appear related to exposure to ziconotide.

Patient 78-1246 was a 48 year old man with chronic pain due to a spinal cord injury, who committed suicide by an overdose of oral Dilaudid. The patient had chronic pain due to a thoracic spinal cord injury. According to the narrative, the patient had tried suicide by overdose once in his past. The patient began study drug 7/13/99, underwent L4-5 discectomy on 2/16/00 even though some degree of relief from study medication was noted. The surgery failed to improve the patients symptoms. The patient died on . . . due to the overdose. There is insufficient data available to determine if ziconotide could have contributed to the patient's state of mind leading to the suicide.

Patient 172-1427 was a 64 year old man with chronic pain due to failed lower back syndrome, and with a history of COPD, Barrett's esophagus and depression. The patient was found dead at home. An autopsy revealed coronary artery disease as an immediate cause of death. From the available information, this death does not appear related to exposure to ziconotide.

Patient 122-1615 was a 73 year old woman with metastatic breast cancer who died following the . — cutoff date. The cause of death was listed as progression of cancer, dehydration. There is insufficient data available to determine if ziconotide could have contributed to the patient's cause of death.

At the time of the NDA review, there was insufficient information on 20 of the patient deaths to establish if ziconotide contributed to the cause of death. At the request of the Agency, the sponsor attempted to gather all available hospital records concerning deaths. For those patients without hospital records, the principal investigators were requested to provide additional records. Information for 35 patients has been obtained. Some of the entries provide some additional information, but for many, the cause of death is still simply attributed to progression of disease. This may reflect all that is available in the investigators' records for these cancer patients.

d) Serious Adverse Events

Serious Adverse Events for the entire group of patients exposed to intrathecal ziconotide are reported in Table 8.8.2.8-6 (Vol. 10.8, P. 026). Each patient with more than one SAE/body system is reported only once so the incidences represent conservative values. Furthermore, and more importantly, this table fails to capture all of the SAE's, only those identified by the CRFs as SAE's.

Serious Adverse Events occurred in 340 of 976 patients (34.8%) while receiving ziconotide. this value is unchanged from the original NDA review. According to the sponsor, the most common SAE's while receiving ziconotide were confusion (4.1%), meningitis (2.4%), pneumonia (2.0%), fever (1.7%) and pain (1.7%). Dizziness and urinary retention were reported in $\geq 1.5\%$ of patients in the original NDA, (2.0% and 1.6%, respectively), but dropped to 1.3% and 1.4%, respectively, in the current submission. Meningitis was not reported by the sponsor as a frequent SAE in the original NDA, possibly because the occurrences were reported to the PMA initially. The frequency of the remainder of serious adverse events remained unchanged from the original NDA. The reporting of adverse events remains limited as the sponsor failed to combine like adverse events such as confusion and thinking abnormal into meaningful categories, thereby underestimating the frequency of what are likely the same or related clinical events.

The incidence of serious adverse events during the double-blind studies, when compared between patients titrated on the final, slower titration schedule and the entire group of patients in the double-blind initial titration phase, generally demonstrate a lower occurrence in the former patients. However, similar adverse events were again represented in many different terms so the overall rates are diluted.

Table 8 SAEs in Double-Blind, Placebo-Controlled Clinical Studies - Initial Titration Phase

COSTART Term	Ziconotide				Placebo	
	Low-dose Group N=170		Total N = 242		Total N = 126	
Number of Patients with Any Event	27	15.91%	49	20.2%	6	4.8%
Body as a Whole	2	1.2%	5	2.1%	2	1.6%
Cardiovascular System	3	1.8%	6	2.5%	0	0.0%
Digestive system	3	1.8%	5	2.1%	0	0.0%
Nervous System	15	8.8%	26	10.7%	3	2.4%
Respiratory System	3	1.8%	5	2.1%	1	0.8%
Special Senses	4	2.4%	8	3.3%	0	0.0%
Urogenital System	4	2.4%	6	2.5%	0	0.0%

Studies include: 95-001 and 96-002.

Data Source: Sponsor's Table 8.8.2.8-7, Vol. 10.8, p. 035.

e) Adverse Events Leading To Discontinuation

In this ISS Amendment, the sponsor provided two discussions of adverse events leading to study discontinuation, 1) AEs including infection leading to study discontinuation, and 2) AEs for which study drug was temporarily or permanently stopped. The former represents patients for whom "Intolerable AE" or "Infection" were checked as the primary reason for discontinuation on the study termination page of the CRF. For the extension portion of study 94-004, this information was on another CRF page and was included in the data for AE leading to D/C where the sponsor deemed it appropriate. The latter represents all AEs for which the action taken listed on the CRF AE page was "Stopped."

A total of 368 of 976 patients (37.7%) discontinued or terminated early from a study while receiving ziconotide due to adverse events. This includes 227 of the 567 patients (40.0%) enrolled in study 98-022. These percentages do not differ significantly from the review of the NDA including the 120-day Safety Update.

During the review of the original NDA, an extensive evaluation of 298 narratives for the patients who discontinued study participation due to adverse events was performed. A subset of narratives were found to have misclassified reasons for study discontinuation. These misclassifications were not corrected by the sponsor for the current submission.

Within the current submission, 101 of the patients in Sponsor's Table 8.8.2.8-13 (Vol. 10.8, p. 73, Patients who Discontinued from the Study due to AEs - All intrathecal Clinical Studies) had no narratives provided. In addition, there were narratives for four patients in Appendix 4 who were not listed in Table 8.8.2.8-13.

The sponsor has failed to adequately address the issue of discontinuations due to adverse events in the current submission. There are numerous missing narratives and an inadequate analysis of the actual reasons for study discontinuation.

The sponsor's table 8.8.2.8-14 lists the reasons for temporary or permanent stopping of study drug. The most common reasons (>3.0%) were: confusion (11.7%), dizziness (7.4%), nausea (5.3%), abnormal gait (4.0%), speech disorder (3.6%), headache (3.4%), and amnesia (3.3%).

Overall, based on the sponsor's comments, ziconotide was temporarily or permanently stopped due to adverse events in 467 of 976 patients (47.8%).

f) Clinical Labs, Vital Signs, ECG

Clinical Laboratory Evaluations

The results for the analysis of serum chemistry tests were presented in Table 8.8.2.9-2 (Vol. 10.8, P. 144). This table is comparable to Table 9.2.9.2 (Item 9, Electronic volume 5, p. 335), submitted in the NDA 120-day Safety Update. In comparing these two tables, two inconsistencies were noted. First, the number of subjects in the column "Ever Received Ziconotide" decreased from the 120-day safety update to the current submission. For example, there was an "n" of 596 for ALT in Table 9.2.9.2, but only 569 in Table 8.8.2.9-2. Given the ongoing enrollment in Study 98-022, the number of patients ever exposed to ziconotide should have increased. If the newer patients did not have laboratory values to evaluate, at the very least, the number of patients in the table should have remained the same, not decreased. Second, in many instances, the number of abnormal results decreased from the 120-day safety update to the current submission. The number of ALT values that changed from normal to abnormally high was 42 in Table 9.2.9.2, and 35 in Table 8.8.2.9-2.

These problems were also present in the hematology data presented in Table 8.8.2.9-3 (Vol. 10.8, P. 150).

The sponsor's threshold analysis evaluating lab values outside predetermined numerical ranges, and in the case of liver enzymes and CK greater than three times the upper limit of normal, was reviewed for chemistry values (Table 8.8.2.9-7, Vol. 10.8, p. 159) and hematology values (Table 8.8.2.9-8, Vol. 10.8, p. 160). These values did not change appreciably from the 120-day safety update.

Vital signs

The data on vital signs did not change appreciably from the original NDA review.

Electrocardiogram evaluations

No EKG changes to abnormal and clinically significant were reported. On review of Appendix 3, Listing 8.0, it was noted that the ECG abnormalities from study 98-022 were not assessed for clinical relevance as were the ECG abnormalities from the other studies. Fifty eight patients were found with QTC prolongation subsequent to beginning treatment with study medication. Values for these abnormalities were not provided and have been requested from the sponsor. The sponsor indicated that EKG abnormalities detected by a central reader and not by individual investigators were not counted as adverse events.

Deficiency:

1 (d) The analyses submitted for the entire patient population studied and for the subset of patients who received the final dosing regimen have not adequately addressed the contribution of coadministered opiate analgesics to the safety and effectiveness of ziconotide. The analyses have also not adequately addressed the

potential for opiate overdose and/or withdrawal during initiation and maintenance of treatment with ziconotide.

Response:

Effects of Coadministered Opioids on Safety-Adverse Events by Opioid Use

The sponsor has prepared an analysis of adverse events by opioid use at the end of the initial titration phase for all of the patients treated during the double-blind, placebo-controlled trials and for the low-dose population. The patients were dichotomized into two groups, those above and those below the median opioid usage and the frequency of adverse events were compared. There was no information provided on what was found to be the actual median opioid usage, on the amount of ziconotide usage of the two groups, or if there were any trends within subgroups such as those receiving high doses of both ziconotide and opioids or relatively high doses of one or the other. The analysis provided is not meaningful in the current form.

Effects of Coadministered Opioids on Efficacy

The sponsor performed the efficacy reanalyses on data pooled from the two studies and it will not be considered further at this time.

Overdose

The sponsor has identified 11 patients who experienced unintentional overdoses of IT ziconotide, one more case than in the NDA and 120-day safety update. There were no deaths or permanent injury resulting from any of these overdoses. The adverse events resulting from the overdoses are presented in Table 9.

Table 9 Patients With an Intrathecal Ziconotide Overdose -120-Day Safety Update (From Sponsor's Table 8.8.2.14-1, Vol. 10.8, P. 208)

Study #	Patient Number	Dosing Error	Symptoms
94-004	500-501	0.7 ug/h (titrated q4h, not q24h)	Generalized myoclonic contractions, nystagmus, tremor
95-001	5007-049	31.25 ug/hr, pump error	Sedation
95-001	5025-074	1.1 ug/h not 0.1 ug/h on day 3	Nausea and vomiting
95-002	6071-104	0.417 ug/h (incomplete dosing prior 4-8 w due to catheter dislodgment)	Gait disturbances, photosensitivity and dizziness
95-002	6077-101	1.46 ug/h from 1 ug/h, titrated	Hypotension and neurological symptoms
96-002	6067-104	2.4ug/h from 0.6 u g/h, pump error	Confusion, nystagmus, garbled speech, found slumped over a bedside table
96-002	6069-105	stable on 1.3 ug/h, found with multiple pill sin mouth.	Confusion
98-022	119-1070	0.6ug/h from 0.3 ug/h, concentration of drug increased, pump rate not adjusted	Gait unsteadiness, word-finding difficulties, dizziness
98-022	147-1289	5.0 ug/h instead of 0.1 ug/h, pump error	Light headedness and gait unsteadiness
98-022	161-1343	4.8 ug bolus, pump error	General weakness light headedness, nausea, diaphoresis
98-022	123-1269	bolus error	No symptoms were provided in the narrative

Withdrawal Effects

The sponsor evaluated the adverse events with onset on the day of or after discontinuation of ziconotide. No pattern of adverse events could be detected as a result of ziconotide discontinuation. A review of adverse events associated with opioid withdrawal including chills, diarrhea, tremor, and sweating, found fewer of these after stopping ziconotide as compared to the entire ziconotide population. Of the entire population, there were 26 adverse event reports of withdrawal syndrome, 2 of which occurred in patients receiving placebo. The sponsor reports most of these were associated with a reduction in opioid dose.

Deficiency:

1 (e) The data submitted and the analyses performed do not readily allow a determination of the dose and concentration over time administered to individual patients nor of the protocol amendment under which they were treated. The data submitted and the analyses performed also do not allow identification of the actual dose of ziconotide delivered to individual patients. This issue arises from the variable in vitro stability of the drug product depending on the concentration of drug product and the type of infusion pump studied, the variable in vitro stability data depending on the diluent used, and the dosing instructions provided to investigators that allowed for use of a single fill of the pump reservoir for up to 30 days, which are at odds with the refill instructions proposed in the draft labeling and the stability data. This uncertainty regarding the dose of ziconotide that was actually delivered to patients during the clinical trials makes it impossible to write a dosing and administration section of the labeling that will assure the safe and effective use of the product under the conditions of use (e.g., initial fill time, refill timing, use of saline diluent, etc.) proposed in the draft labeling.

Response:

The sponsor submitted Item 8.8, Appendix 1, Vol. 005, p233, which consists of two tables: Table 1: Study 95-001 Low-Dose Patient Population and Table 2: Study 96-002 Low-Dose Patient Population. The columns of these tables are: Investigator/(Site #), Patient Number, First Dose Date, and Dose (ug/hr). While these tables do identify which patients began titration with 0.1 ug/h, they do not identify under which dosing regimen titration occurred, as some patients beginning at this dose were titrated more aggressively than the final dosing regimen dictated. The investigators were permitted to increase or decrease the rate of ziconotide infusion as needed. There is no means for correlating the drug dosage and efficacy scores.

The issue of the impact of adsorption on the actual amount of drug delivered has not been adequately addressed. In response to this issue, the sponsor cites the proposed Labeling-FPP, Item 4, CMS in the current submission, Vol. 001, p. 001, and Item 8.8 Appendix 1, Vol. 005, p. 233. The sponsor also refers to the responses to Items C and D.

In the labeling, there is reference to 180 subjects in the chronic nonmalignant pain study and 49 patients in the chronic malignant pain study who were started on 0.1 ug/h. The original, complex refill instructions have been replaced by a table indicating proper refill intervals. The

label states that the initial refill of a ziconotide naïve pump should take place after no more than 14 days, with subsequent refills permitted at a maximum interval of 60 days. There is no explanation for the 14 day maximum refill interval for ziconotide naïve pumps. The solution is only available as a 100 ug/ml concentration, to be diluted as needed with preservative free normal saline.

In Item 4, CMC, the sponsor reports that their investigation into the causes of the apparent adsorption of the drug substance. [REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED] Because the most dramatic effect occurs with the 10 ug/ml concentration, the sponsor has eliminated the 10 ug/ml concentration from the product line. The initial dosing instructions in the label direct the physician to dilute the 100ug/ml solution to 25 ug/ml. The conclusion by the sponsor is that no alteration of the drug product or pump reservoir is necessary.

What is missing from the sponsor's response is the following analysis. Given that many patients began treatment with the 10 ug/ml concentration solution, at a rate of 0.1 ug/h, what dose of medication did the patients actually receive taking into account the [REDACTED]

[REDACTED] This would also depend on how rapidly the patients were titrated to higher dosing rates and on how soon the pumps were refilled at the same or higher concentrations. Based on the information provided in Item 4, patients may have been dosed with [REDACTED] less than believed, or in cases of refills beyond 14 days, even less. This would create a bias in the safety data as patients would be experiencing adverse events attributed to a higher dose than they were actually receiving. Patients receiving doses comparable to those reported, but using the 100 ug/ml dose could be expected to demonstrate a higher rate of adverse events than patients in the two completed pivotal trials. It is also possible that the dose associated with efficacy for patients responding at lower doses [REDACTED]

Deficiency:

1 (f) Numerous instances of inadequate documentation of important clinical information on the case report forms for patients enrolled in the two Phase 3 studies makes it difficult, and sometimes impossible, to adequately evaluate the specific details of adverse events and to make a reasonable assessment of causality.

Response:

The sponsor indicates that all available hospital records for patients who died in IT ziconotide trials have been obtained and are presented in Item 8.8, Appendix 8, Vol. 49, p. 240. Complete narratives are in Item 8.8, Appendix 4, Vol. 49, p. 001 for the period between the IT 120-day

Safety update and the ISS Amendment. Item 8.8, Appendix 7, Vol. 0.49, p. 231 contains narratives for the events between the ISS Amendment and December 15, 2000.

All of the submitted information was reviewed. Item 8.8, Appendix 4 is composed of the narratives for the period between the 120-day ISS update and the ISS Amendment. Several of these narratives are missing important information. Patient 0121559 developed meningitis, but no CSF culture results are reported. Patients 0121488, 0121561, 0121563 also developed meningitis, and while the CSF results report Gram negative rods, no final identification of the bacteria is provided. This information is extremely important given the concerns that ziconotide might support bacterial growth. Patient 0121571 was "ruled out" for meningitis, but no CSF results were provided, except that the culture was negative for growth. The patient was treated with antibiotics and the timing of the antibiotics and the CSF sampling are unclear. Given the information available, it cannot be concluded that the patient did not have meningitis. Patient 0351309 is reported to have received ziconotide at an initial infusion of 0.01 ug/hr, later increased to 0.02 ug/h. No protocol has specified such a low dosage rate, suggesting an error in the reporting of this narrative.

Item 8.8 Appendix 7 is composed of a listing of the deaths and SAEs reported between the data cutoff dates for the ISS and December 15, 2000. Only two narratives were provided, including one patient (1521557) with an agitated depression requiring neuromuscular blockade, intubation and ultimately electroconvulsive therapy.

Item 8.8, Appendix 8 is composed of a listing of patient deaths and hospital records for these patients. There are still narratives with too little information to determine whether a relationship existed between study drug and the cause of death. Several representative examples of these narratives are Patients 501-76, 501-77, 501-79, and 501-87, who were receiving study drug and died. The cause of death was noted as progression of metastatic disease with no detail concerning the proximate events surrounding the patients' deaths. The reason for study drug discontinuation for patient 501-84 was not provided and the patient subsequently died 6 days later, with the cause listed as progression of malignant disease. It is unclear from this index which, if any, of these narratives actually have any additional information from the narratives submitted with the original NDA submission.

Deficiency

2: Appropriate documentation has not been provided for financial disclosure as required under 21 CFR 54.4 and 314.50(k) for Studies 95-001 and 96-002.

Corrective Action B: Provide the appropriate documentation for financial disclosure required for Studies 95-001 and 96-002 under 21 CFR 54.4.

Response

In the current submission, I. 19, Vol. 01, p. 273, the sponsors has supplied updated financial disclosure information by clinical investigators. In the table provided, for studies 95-002, 98-022, 98-023, and 98-029, it can be seen that all of the Principle Investigators have supplied the self-certification forms to Elan. Most of the Secondary Investigators have also returned the self-certification forms for most sites. **C**

In a submission dated _____ the sponsor provided financial disclosure information for studies 95-001 and 96-002 updated following the submission of the original NDA. In a submission dated _____ the sponsor submitted the Financial Disclosure information for studies 95-002, 98-021, 98-022, 98-023, and 98-029. In addition, a "Master Payees List" was provided, for the years 1997-1999. Form 3454 was provided for the studies, certifying that Elan had not entered into any financial arrangement with the investigators, whereby the value of compensation to the investigator could be affected by the outcome of the study. To supplement the self-certification process, as only 63% of the investigator sites had responded, the Finance departments for all business units of Elan Pharmaceuticals, Ltd., have conducted an audit of all financial records and payments regarding investigators participating in these studies. The audit revealed that two investigators, _____ have received payments cumulatively exceeding \$25,000. These payments were study-related investigator payments and/or study expense reimbursements. No other payments or practices were found that would trigger disclosure as defined by 21 CFR 54.2 (a), (b), or (c).

The sponsor has attempted with due diligence to collect the pertinent and necessary financial disclosure information. None of the information presented raises any cause for concern with respect to financial arrangements made during these studies.

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Sharon Hertz
7/12/01 02:55:14 PM
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Bob Rappaport
7/17/01 05:42:51 PM
MEDICAL OFFICER

I agree with Dr. Hertz's conclusions and recommendations that this response does not adequately address all of the deficiencies and that the application remains approvable



FDA CENTER FOR DRUG EVALUATION AND RESEARCH

DIVISION OF ANESTHETIC, CRITICAL CARE, AND ADDICTION DRUG PRODUCTS
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Tel:(301)443-3741

Medical Officer Review

IND: 45,718

Serial No.: 200

Protocol: Synopsis

Review Date:

Drug Name: Ziconotide

Sponsor: Elan Pharmaceutical

Type of Submission: Protocol Synopsis

Date of Submission: 2/23/01

Date of Receipt: 2/26/01

Reviewer: Sharon Hertz, M.D.

Project Manager: Laura Governale, Pharm.D.

Background: The Division of Anesthetics, Critical Care and Addiction Drug Products reviewed NDA 21-060, submitted December 28, 1999, and found that the application was approvable. In addition to numerous chemistry issues, the Division found that efficacy had only been demonstrated in one of two clinical efficacy trials. The sponsor was informed that a new adequate and well controlled trial demonstrating efficacy would be needed for approval of the application. In a meeting to discuss the results of this review with the sponsor on August 17, 2000, the sponsor indicated that there could be difficulty repeating the study design previously used, even with the final established dosing regimen. While this regimen was an improvement over the original dosing regimen in 95-001 and 96-002, the pivotal clinical trials, according to the clinical consultants present representing the sponsor, it may still be too aggressive resulting in adverse events and less tolerance of ziconotide, than the slower titration utilized in the open-label 98-022. As a result of these comments, and in the interest of pursuing the most efficient study capable of demonstrating efficacy and providing information needed for adequate instruction on how to use ziconotide, the Division suggested a study using the most ideal dosing titration. One study using the dosing regimen the sponsor believed would be the safest and best tolerated, which demonstrated efficacy, would be accepted as a second adequate and well controlled trial to complement Study 96-002.

Title: A Randomized, Double-blind, Placebo-controlled 3 Week Study of Intrathecal Ziconotide in Adults with Severe, Chronic, Intractable Pain

Indication: Severe, chronic, intractable pain

Objective:

Primary: Confirm the efficacy of ziconotide using an alternative, slower titration schedule

Secondary: More closely characterize opiate withdrawal effects during conversion from intrathecal to systemic opiate therapy

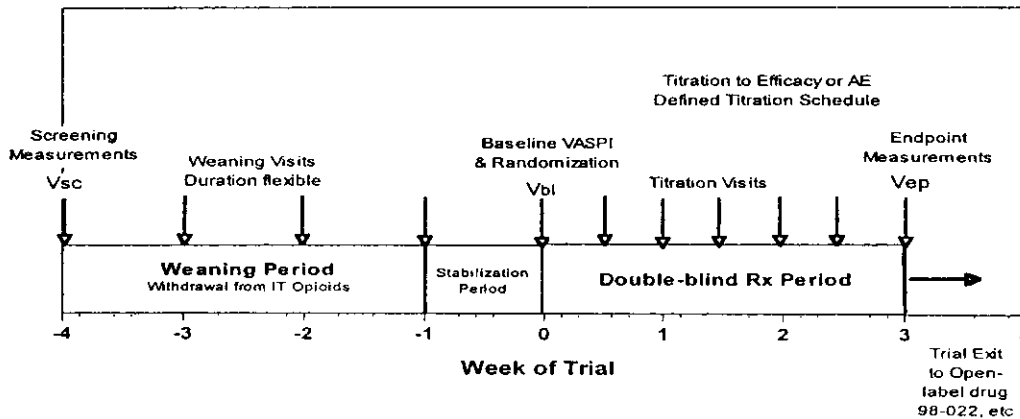
Accurately quantitate the amount of concomitant opiate usage during treatment

Study Design: randomized, double-blind, placebo-controlled

Study Duration: 7 weeks

Study Schematic:

Overview of Confirmatory Trial Design



Population: N=220

Inclusion Criteria:

1. Male, female, ≥ 18 years of age
2. Severe, chronic, intractable pain not adequately controlled by and/or intolerant to systemic opioids and intrathecal (IT) therapy is warranted
3. VASPI ≥ 50 mm at screening and baseline
4. Implanted SynchroMed infusion system with catheter tip at appropriate location

Exclusion Criteria:

1. Pregnancy or Lactation
2. Inadequately controlled psychiatric conditions

Conduct of Study:

- Pre-treatment weaning off all IT medications - up to 3 weeks
- Pre-treatment stabilization on systemic opioids - 1 week
- Scheduled Titration - 3 weeks
 - Starting dose: 0.1 ug/h, maximum increase: 0.1 ug/hr, minimum increase: 0.05ug/hr to a maximum of 0.9 ug/h
 - Decreases prn AEs
 - Upward titration at biweekly schedule visits or more frequently prn. No more frequent than q 48 hours
 - Ziconotide 100 ug/ml in 5 ml vials, diluted to 25 ug/ml for rate of ≥ 0.1 ug/h, to 10 ug/ml for rate of <0.1 ug/hr

Outcome Measures:

Efficacy:

- Pain intensity - VAS (VASPI)
- Weekly opiate use by daily patient diary
- Hours of sleep
- QOL and/or functional scale at Screening, Baseline and Last Visit
- Global measure such as Clinical Global Impression (CGI) by patient at last visit

Safety:

- AE's, Vital signs
- MMSE
- Labs at Screening, Baseline and Final Visits
- PE and EKG at Screening and Final Visits.

Statistical Analysis:

Primary efficacy endpoint: % change in VASPI at Final Visit compared to Baseline with LOCF

Secondary efficacy endpoints:

- AUC for all repeated VASPI's zicon vs. placebo for completed patients
- Change in VASPI at Final Visit from Baseline
- % Change in weekly opiate consumption compared to Pretreatment Stabilization Week
- % Change QOL/functional scale at Final Visit from Baseline
- % Change CGI at Final Visit from Baseline
- % Responders ($\geq 30\%$ reduction in VASPI) at Final Visit from Baseline or at least 30% reduction in average daily VASPI at the end of Week 3 from Baseline

Sample size is based on 80% power, $p < 0.05$, to detect at least a 15% difference in % change in VASPI, 2-sample t-test with SD of 39.5% for both treatment groups.

The primary analysis will be on the ITT population, with a 2-way ANOVA. Early terminations will be handled as LOCF.

Comments: The overall design described in this protocol synopsis appears appropriate to meet the stated objectives. Adequate safety monitoring appears planned.

There should be a period of stabilization of at least 48 hours prior to the final assessment at the end of the three week titration period. According to the statistical reviewer, the sponsor should consider methods for the handling of missing data other than LOCF that can avoid the bias in favor of the study drug that occurs with this method.

The full protocol will need to be reviewed prior to a final opinion.

Medical Officer

Date

CC: Original IND
HFD-170 Division File, B. Rappaport, L. Governale, S. Hertz

NDA: 21-060

Drug Name: Ziconotide

Trade Name: N/A

Formulation: Solution For Intrathecal Infusion

Sponsor: Elan Pharmaceuticals

Type of Submission: New Drug Application

Date of Submission: 12/28/99

Date of Receipt: 12/28/99

Date of Addendum: 6/14/00

Reviewer: Sharon Hertz, M.D.

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SECTION 12.0 ADDENDUM.....3
SECTION 12.1 PEDIATRIC STUDIES.....3
SECTION 12.2 FINANCIAL DISCLOSURE.....3
SECTION 12.3 DEVICE RELATED ADVERSE EVENTS.....4
SECTION 12.4 ADDITIONAL CASE REPORT - ADVERSE EVENT.....10
SECTION 12.5 MISCELLANEOUS.....11
SECTION 13.0 CONCLUSION.....11

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SECTION 12.0 ADDENDUM

SECTION 12.1 PEDIATRIC STUDIES

The sponsor has submitted a request for a full waiver of all requirements for pediatric assessment for ziconotide. The sponsor indicates that an attempt was made to enroll pediatric patients over 10 years of age, by contacting over 45 investigative sites. Only one patient less than 18 years of age was enrolled. It is important to note that the protocol amendment to permit enrollment of children 10 years of age and older was dated 10/30/97 and study enrollment was closed on 3/9/98.

As the safety and efficacy of ziconotide in an adult chronic pain population is not yet fully defined and the utility of this drug in that population is also unclear, it is recommended that the evaluation of ziconotide in pediatric chronic pain patients be deferred this time. Should a clear pattern of benefit and use in adults become apparent, it can then be determined if there is a potential role for the use of ziconotide in the pediatric chronic pain population and the practicality of study in the pediatric population can then be determined.

SECTION 12.2 FINANCIAL DISCLOSURE

The sponsor submitted only financial disclosure information for clinical studies ongoing or that started after _____. This was a result of a miscommunication by the Agency. A request for full financial disclosure for all studies was requested by teleconference on _____ a response from Sheldon Mullins of Elan Pharmaceuticals reported that the forms would take time to send out and complete and might be available for review by mid June.

Financial disclosure information at the time of this review was submitted for studies _____

According to the sponsor, financial disclosure/certification forms were sent to all investigators listed on Form 1572, who had not previously submitted financial disclosure information. Not all investigators have responded. The sponsor sent duplicate financial disclosure/certification forms to all investigators that had not responded, by FedEx and with prepaid addressed return envelopes and a tracking record. The sponsor is attempting to contact nonresponders and those who are no longer participating in the clinical trials.

In addition, the sponsor has performed internal audits by the Finance departments from each business unit of Elan Pharmaceuticals, Ltd. This audit included all financial records and payments regarding investigators participating in the studies noted above. The audit also included all payments made to investigators, sub-investigators and other external study-related personnel, for all studies conducted by Elan pharmaceuticals, _____ Elan Diagnostics, _____ Elan Pharmaceutical Research Corporation and Elan-UK.

As of the NDA submission dated _____ the sponsor had identified through internal audits two investigators who received substantial payments (cumulatively over \$25,000) since _____. These were _____ both of whom participated in clinical study _____. These were study related payments or expense reimbursements and the sponsor provided an accounting of these payments.

The sponsor has submitted a form FDA 3454 for each of the studies noted above. A form 3455 has been submitted for a _____ clinical study _____, had indicated that he received "unrestricted educational grants to support laboratory research unrelated to ziconotide". Study _____ contributed _____ patients for the database of _____ patients (this includes _____ patients participating in _____ studies). There are 14 of 76 sites for which all certification was through Elan audits indicating no self certification by the investigators. The Investigators providing the largest number of subjects to this study, _____ have submitted financial disclosure forms for themselves and all sub-investigators from their sites.

Study _____ contributed _____ patients to the safety database. There were no self certifications for any of the investigators from 7 of the 56 sites. There was no one investigator that provided a substantial proportion of patients to this study. The Investigators providing the largest number of subjects to this study, _____ have submitted financial disclosure forms for themselves and all sub-investigators from their sites. _____ had submitted a financial disclosure form for himself, but there was one self-certification form missing for _____ subinvestigators at this site.

SECTION 12.3 DEVICE RELATED ADVERSE EVENTS

The devices in the PMA supplement used in the clinical studies were the following:
SynchroMed pump models _____

Catheter models: _____
These devices are commercially available.

The external pump used was the CADD Micro® _____ Infusion System, _____ and is commercially available.

Table 1 demonstrates the distribution of patients among the studies along with the number of patients with internal and external pumps.

Table 1 Summary table of Elan Pharmaceuticals /Medtronic sponsored clinical studies.

Protocol Number	Study Title	Number of Study Centers	Number Patients Enrolled	Patients with SynchroMed Infusion System	Patients With An External Infusion System	Age Range in Years	Mean (Median) Age In Years	Sex (M/F)	Study Treatment Days Range (Median)
95-001	A Multicenter, Phase II/III, Placebo Controlled Study Of Ziconotide Administered Intrathecally To Patients With Chronic Malignant Pain	32	112	27	85	24-85	55.5 (57.0)	M = 56 F = 55	0 - 11 Days Completed
95-002	An Open-Label, Long-Term Safety and Efficacy Study of Ziconotide Administered Intrathecally to Patients Suffering From Chronic Pain Using the SynchroMed Infusion System or The Sims Deltec CADD-Micro Pump	40	155 ²	154	4 ¹	24-85	55(56)	M = 77 F = 78	3,- 1283 Days (81) Ongoing
96-002	A Multicenter, Phase II/III Placebo Controlled Study Of Ziconotide Administered IT To Patients With Chronic Nonmalignant Pain	43	257	129	128	22-82	52(51)	M = 143 F = 112	0 - 11 Days Completed
96-010	A Phase II Study of Ziconotide Administered Intrathecally to Patients with Nonmalignant Pain	1	1	1	NA ³	NA ³	44	M = 1	25 Days Completed
97-013	A Phase II, Single Center, Open-Label Pilot Study Of Ziconotide Administered IT By Bolus Injection (1-Hour Infusion) To Patients Suffering From Chronic Pain	1	Part A 22 Part B 11 ⁴	17 6	5 5	31-65	48.7(48.5) 52 (54)	11/11 4/7	1 -Hour Infusion 1-6 Days Completed
97-015	An Open-Label, Dose Escalation Study of Ziconotide Administered Intrathecally to Patients with Nonmalignant Pain.		1	1	NA ³	NA ³	66	M = 1	21 Days Completed
98-022	A Multicenter, Phase II/III, Open-Label, Long-Term Safety and Tolerability Study of Ziconotide Administered IT To Patients with Chronic, Severe Pain	69	483	372 ⁵		16-84	51.6 (50)	M = 246 F = 237	0.28-389 Days (51.8) Ongoing

- 1 Three of the four patients were later implanted with the SynchroMed Infusion System
 2 These patients were previously enrolled in protocols 95-001 or 96-002
 3 NA = Not Applicable
 4 These patients were a subset of the 22 patients in Part A.
 5 2 patients with a SynchroMed infusion system experienced an AE but the data for the device had not been entered into the data base prior to the lock.
 Source: (From Sponsor's Table 2, P. 6, 120-day safety Update)

The device related adverse events were defined as "procedure related" if occurring within 60 days of implantation or were directly attributable to the surgical, refill or programming procedure. "System related" events were defined as occurring 60 days or more after implant or directly attributable to the device performance. End of battery life was reported in the CRF's but not in the adverse events as this was an expected event.

The adverse events attributed to the infusion system were reported to the PMA Supplement _____ amendment for the SynchroMed infusion system for studies co-sponsored by Elan Pharmaceuticals and Medtronic. A total of 244 SynchroMed infusion pumps and 238 Medtronic catheters were used in Elan/Medtronic co-sponsored studies, 95-001, 95-002, 96-002, 97-013, 96-010, 97-015. The adverse events from study 94-004 were all reported in the NDA submission.

The adverse events from the one study sponsored by Elan Pharmaceuticals alone were reported to Medtronic by Elan. A total of 380 SynchroMed pumps and 381 Medtronic catheters were used in the Elan sponsored study, 98-022.

External Device Safety Summary Studies 95-001, 96-002 and 95-002

The external device related adverse events were reviewed from the original PMA/S submission. The adverse events associated with the use of external devices were only provided for studies 95-001, 96-002 and 95-002. There were 213 patients who used the CADD Micro pump with external catheter during these studies. Of these 213 patients, there were 119 (55.9%) with a total of 209 external device related adverse events. The most common adverse events were spinal headache/ headache (23.0%), CSF leak (16.4%), catheter dislodgment/migration (8.9), disconnected from pump (6.1%), and meningitis (5.2%). The reports of meningitis were discussed in full detail in SECTION 8 of the body of the medical officer's review.

A breakdown of the adverse events associated with the external device are provided in Table 2.

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Table 2. Device Related Adverse Events, Studies 95-001, 96-002 and 95-002, External Pump

Adverse Event	Number of Adverse Events (% of AE's)	Number Patients with Device Related Event ¹ (% of All Patients)
System ²		
Pump (No infusion, pump alarm)	2 (1.0%)	2 (0.9%)
Battery failure	1 (0.5%)	1(0.5%)
Procedural ³		
Pump (Under infusion, no infusion, High pressure alarm)	5 (2.4%)	5 (2.3%)
Catheter (Kink, disconnected from pump, puncture/cut, fracture/break, dislodgment/migration, leak at catheter juncture occlusion, segments disconnected)	61 (29.2%)	55 (25.6%)
Spinal Site/Tract (CSF leak, spinal headache/headache, back pain, paresthesia, left foot drop, lumbar drainage, spinal subdural hematoma, catheter placement failure, leg pain, leakage at catheter site, catheter site redness and leakage)	112 (53.6%)	107 (50.2%)
Programming/Refill (error, no infusion)	6 (2.9%)	6 (2.8)
Infection/ Infection Related (catheter infection, catheter site infection, lumbar site infection, meningitis, encephalopathy, cellulitis, fever)	19 (9.1%)	19 (8.9%)
Other (drug leak at filter, skin irritation, emesis)	3 (1.4%)	3 (1.4%)
Grand total external device adverse events	209	

¹ Percent of the 213 patients with an external system who experienced each adverse event at least once

² System Related: the adverse event occurred 60 days or more post implant and/or was directly attributable to the device performance

³ Procedure Related: the adverse event occurred within the first 60 days after implant and/or was directly attributable to the surgical, refill or programming procedure

Internal Device Related Adverse Events

The internal device related adverse events for study 97-013 were reviewed from the original PMA/S submission. The internal device related adverse events from studies 95-001, 96-002, 95-002 and 98-022 were reviewed from the 120-day safety update.

Studies 95-001, 96-002 and 95-002

There were a total of 230 unique patients implanted with SynchroMed pumps in Studies 95-001, 96-002 and 95-002. Within this group, there was a total of 62 adverse events in 41 of the 230 patients (17.8%). There were 154 patients with an implanted Medtronic system in study 95-002, and 32 of these patients (20.8%) with device related adverse events. These adverse events are reported in Table 3. For study 95-002 which was ongoing at the time of the 120-day safety update, there were 3 additional adverse events between the PMA/S submission cutoff date of 11/2/99 and the 120-day safety cutoff date of 2/21/00. These consisted of one programming error, and 2 increased pump pressure readings during 2 refill procedures on one pump. Further monitoring of this pump has revealed no further incidents. Studies 95-001 and 96-002 were completed as of the

11/2/99 cutoff date. The line listings for the individual adverse events from 95-002 were available and were reviewed.

Table 3 Device Related Adverse Events in Studies 95-001, 96-002, 95-002, Internal Pump

Adverse Event	Number Device Related Adverse Events (% of AE's)		Number Patients With Device Related AEs (% of All Patients)	
	95-002 N=47	95-001, 96-002, 95-002 N=62	95-002 N=154	95-001, 96-002, 95-002 N=230
Procedural				
Pump pocket (includes pocket seroma, erosion, erythema, pump shifted, inverted, tilted, refill port inaccessible, ecchymosis, pain, incisional pain)	17 (36%)	17 (27.4%)	17 (11.0%)	17 (7.3%)
Catheter (kink, disconnect)	2 (4.2%)	2 (3.2%)	2 (1.2%)	2 (1.0%)
Spinal site/Tract (spinal headache, back wound drainage, paresthesia, radicular pain)	7 (14.8%)	9 (14.5%)	7 (4.4%)	9 (3.9%)
Programming/Refill (programming error, tubing disconnected from needle, increased pump pressure)	12 (25.5%)	16 (25.8%)	9 (5.7%)	13 (7.0%)
System				
Programmer (printer malfunction)	1 (2.0%)	1 (1.6%)	1 (0.6%)	1 (0.4%)
Catheter (dislodgment/ migration, disconnected)	3 (6.4%)	7 (11.3%)	3 (1.9%)	7 (3.0%)
Spinal Site/Tract (Catheter tract pain)	1 (2.1%)	1 (1.6%)	1 (0.6%)	1 (0.4%)

According to the line listings (listing 1, p. 16, 120-day safety update), 12 of the 47 adverse events were serious, 6 resulted in initial or prolonged hospitalization, 3 surgery, 1 pump replacement and 2 intervention to prevent impairment damage. All of the adverse events resolved except for one patient with unchanged painful pump position, one patient with an unchanged tilted pump and one patient with the sequelae of pump requiring explantation and replacement. There was tremendous overlap and inconsistency in this line listing. According to an accounting by this reviewer, there were 14 serious adverse events, listed in Table 4.

Table 4 Serious Device Related Adverse Events, Studies 95-001, 96-002 and 95-002

Adverse Event	Number Of Patients
Pump explanted and replaced	5
Pump explanted	2
Surgical exploration/ repair or replacement of catheter	3
Systemic antibiotics	3
Hospitalization for pain medication	1

Study 98-022

There were 372 patients with internal pump systems in study 98-022. Sixty nine patients (18.5%) had a total of 107 device related adverse events. These were reported with different terminology than the Elan/Medtronic co-sponsored studies and are reported below in Table 5. The line listings of the individual adverse events were reviewed.

Table 5 Device Related Adverse Events, Study 98-022, Internal Pump

	Number Device Related Adverse Events (% of AE's)	Number Patients With Device Related AEs (% of All Patients)
Adverse Event	98-022 N=107	98-022 N=372
Procedural		
Pump pocket (includes pocket seroma, pump inverted, tingling & burning, bruising incision site, open wound, pain, erythema, r/o infection)	32 (29.9%)	32 (8.6%)
Catheter (dislodgment/migration, fracture, poor pump/catheter connection)	3 (2.8%)	3 (0.1%)
Spinal site/Tract (spinal headache, lumbar seroma, CSF leak, open wound, pain, swelling, tenderness at catheter insertion site)	38 (35.5%)	35 (10.2%)
Programming/Refill (programming error)	3 (2.8%)	3 (0.1%)
Infection/infection related (pocket infection, lumbar infection, cellulitis, surgical wound infection, meningitis, abdominal incision site infection)	10 (9.3%)	10 (2.7%)
Other (post anesthetic effect)	1 (0.9%)	1 (0.3%)
System		
Pump Pocket (pain, incisional pain, pocket seroma, erythema, skin sensitivity, swelling, tingling & burning, unconfirmed fluid around pump)	12 (11.2%)	12 (3.2%)
Catheter (dislodgment/ migration, fracture/break)	5 (4.7%)	5 (1.3%)
Spinal Site/Tract (CSF leak, pain at catheter insertion site)	2 (1.9%)	2 (0.5%)
Infection/Infection related (pocket infection)	1 (0.9%)	1 (0.3%)

Fourteen of the 107 device related adverse events from 98-022 were reported as serious. There were 9 patients with hospitalization required/prolonged for pump or catheter explant/revision. Additionally, there were 2 patients requiring treatment for spinal headache or CSF leaks, one patient requiring pain management and two patients requiring pocket fluid aspiration/repair.

Study 97-013

There were 22 patients enrolled in study 97-013. Two of these patients enrolled in a second dose cohort as well. Seventeen of these patients used external pumps, 7 (41.1%) of whom experienced 14 device related adverse events. Of the 11 patients in the second part of the protocol, 6 used external pumps, 2 (33.3%) of whom had a total of 3 device related adverse events. All of these adverse events were considered procedural. Combining both parts of the study, 6 were catheter related, 6 spinal site/tract, 3 infection related, and 2 were filter problems. Five of these adverse events were considered serious, requiring prolonged hospitalization for treatment of aseptic meningitis (1), fever (1) and elevated CSF white cell count (1) occurring in the same patients, CSF leak (1) and spinal headache (1) occurring in the same patient.

There were 7 patients who used a combination of an internal SynchroMed system and an external CADD-Micro pump. One of these patients had a device related adverse event, a dislodged needle.

There were no device related adverse events in studies 96-010 and 97-015.

Reviewer's Summary

With external pumps, the most common adverse events were related to the spinal site and tract, occurring in 50.2% of patients. An additional 25.6% of patients had adverse events related to problems with the catheter. The sponsor reports an incidence of 8.9% for infection related adverse events in this group. Meningitis was included in the reporting of device related adverse events, but has been discussed in detail in the main body of the safety review of the NDA.

For the internal pumps, adverse events occurring in the greatest proportion of patients were those related to pump pocket problems in 7.3% of patients in studies 95-001, 96-002 and 95-002 and 8.6% of patients in study 98-022. Spinal site and tract related problems occurred in 3.9% of patients in studies 95-001, 96-002 and 95-002 and 10.2% of patients in study 98-022. When serious, the adverse events required prolonged hospitalization for systemic antibiotics, pain management or surgical intervention to repair or replace pumps or catheters.

SECTION 12.4 ADDITIONAL CASE REPORT - ADVERSE EVENT

The sponsor has submitted a safety report, dated _____ of a 47 year old woman with a history of chronic pain due to "peripheral neuritis" who developed shortness of breath, muscle spasms, muscle pain and weakness. The patient had been receiving intrathecal ziconotide for 6 months. The dose at the time of adverse event was 0.475 ug/h. The patient was hospitalized on _____. The EKG on _____ revealed a prolonged QT interval of 376/504 msec. The serum CPK was 1516 IU/L on _____ 2101 IU/L on _____, and peaked at 2298 IU/L (date unspecified). The potassium was 3.2 mmol/L on _____. The peak ESR was 25 mm/h (date unspecified). A chest x-ray and pulmonary function tests were normal. A needle EMG were "weakly suggestive of a generalized,

non-inflammatory myopathy". The patient's symptoms worsened following hospitalization. The patient was treated with Ultram, Baclofen, Celebrex, OxyContin, aspirin, Prevacid, Percocet, Toradol and Albuterol. Study drug was decreased to 0.35 ug/hr on _____ and discontinued on _____. The symptoms were resolved by _____.

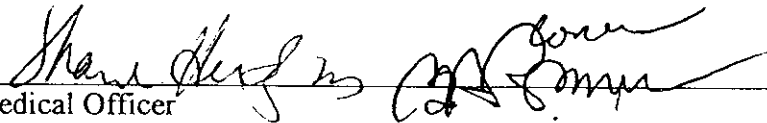
Comments: This adverse event of muscle pain and weakness is consistent with a drug induced myopathy due to ziconotide.

SECTION 12.5 MISCELLANEOUS

The safety update review is incorporated into the primary medical review

SECTION 13.0 CONCLUSION

The device related adverse events were notable for the high frequency of occurrence of spinal site and tract, and catheter related events for the external pump and the pump pocket and spinal site and tract related events for the internal pump. However, these events were not of a sufficient severity and not of an unexpected nature to result in a change to the overall conclusions delineated in the medical officer's review dated 6/2/00.


Medical Officer _____ Date 6/14/00

- CC: Original NDA
HFD-170 Division File
HFD-170
B. Rappaport
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MEMORANDUM

DATE: June 12, 2000

FROM: Cynthia G. McCormick, MD, Director *Cynthia McCormick MD*
Division of Anesthetic, Critical Care and Addiction Drug Products
Office of Drug Evaluation II, CDER, FDA

TO: John K. Jenkins, M.D., Director
Office of Drug Evaluation II, CDER, FDA

File, NDA # 21-060 Ziconotide Injectable

RE: Recommended Nonapproval Action

This memorandum conveys my endorsement of the review team's recommendation that Elan Pharmaceutical's NDA # 21-060 ziconotide injectable should not be approved. I agree that the NDA fails to provide sufficient evidence to support the conclusion that ziconotide will be safe and effective for use under the conditions recommended in its proposed labeling.

Background

NDA 21-060 is a marketing application submitted by Elan Pharmaceuticals on December 28, 1999 for ziconotide injectable, a new drug product for intrathecal administration by implanted, programmable pump for the treatment of severe, chronic pain.

Ziconotide (SNX-111) is a synthetic peptide, which has been demonstrated to be an antagonist at the presynaptic N-type (neuron-specific) voltage-sensitive calcium channels in the central nervous system and spinal cord, predominantly distributed to superficial laminae of the dorsal horns, where virtually all nociceptive afferents terminate. Its specific activity in the processing of nociceptive information, interpreted as pain at the cortical level, is not well worked out, but it is thought that ziconotide blocks neurotransmitter release at the spinal cord level thus preventing

propagation of pain signals to the cortex. As such, it might be expected to have a "nonspecific" effect on pain of peripheral origin. The drug was found to have antinociceptive activity in animal spinal injury models of peripheral neuropathy. Based on the adverse event profile of this drug in both preclinical and clinical studies, it is likely that ziconotide has activity at cortical sites as well.

This drug was developed for intrathecal administration because of poor blood-brain barrier (BBB) permeability and significant hypotension when delivered intravenously. Due to these constraints limiting its delivery to the intrathecal (and potentially the epidural) route via an implantable pump, the focus of development has narrowed to include only advanced pain therapy. Thus, the size of the NDA with its relatively small safety data base for a new molecular entity reflect potentially very limited use in painful conditions (malignant and nonmalignant) for which intraspinal therapy is reserved.

Ziconotide's development was discussed at a closed meeting of the Anesthetics and Life Support Advisory Committee (ALSAC) on March 24, 1997 in an effort by Neurex Corporation, the IND¹ holder at that time, to brief the committee and to solicit advice about the future direction of the clinical development plan. The committee's discussions about evaluation of ziconotide in acute pain, evaluation of the metabolic profile and evaluation of the PK/PD relationship were not followed, since these suggestions do not appear to have been feasible or practicable. Discussions surrounding the preservative-free status of ziconotide and the need to evaluate the potential for microbial contamination and growth, is not fully reflected in this NDA nor is the Committee's suggestion to study drug-drug interactions with chemotherapeutic agents, likely to be co-administered with this drug in patients with chronic malignant pain.

Subsequent to the advisory committee meeting there were routine meetings and teleconferences with the Division of Anesthetics, Critical Care and Addicition Drug Products in advance of the NDA submission in which agreement was reached on what would be an acceptable size for the NDA safety database and the priority review status of the NDA. These discussions and agreements are reflected in the meeting minutes supporting this action package.

Chemistry Manufacturing and Controls²

Drug Substance. There have been adequate data pertaining to the method of preparation, isolation, and purification of the drug substance and these have been found acceptable. The identity and purity and assay of the biological activity (calcium channel efflux bioassay) of the primary reference standard have been satisfactorily supported with data. Regarding the analysis

¹ IND # 45,718, Ziconotide for intrathecal administration

² The 1994 Guidance for Industry for the Submission of Chemistry, Manufacturing and Controls Information for Synthetic Peptide substances was available for this application.

of the drug substance, regulatory specifications and testing procedures for lot-to-lot release of the drug substance have not been resolved. The sponsor was given a choice among four test methods: [REDACTED]

[REDACTED] These have all been demonstrated to be reasonable surrogates for biological activity of the peptide. At this time the sponsor has not identified which of these methods will be used for lot-to-lot analysis, although any of these methods would be acceptable.

Drug Product. [REDACTED]

In determining the shelf life of ziconotide, there had to be adequate assurance that sustained biological activity correlated with the chemical stability of the product as assessed by the standard quantitative assays performed. [REDACTED]

[REDACTED] The shelf life of 24 months at 2-8° C was adequately supported by the data provided.

The stability of the drug product was evaluated *in vitro* within the device for a 30-day period at 37° C. In addition accelerated stability was obtained for [REDACTED]. There was adequate evaluation of the product's stability in the pump under conditions simulating the clinical setting, however, biological activity was not evaluated in this protocol as noted above. Thus one is only indirectly able to make a reliable assessment of the efficacy of the drug product for human intrathecal use.

The review team has delineated additional parameters that affected the product's stability, namely concentration and previous fill. Concentrations below 25 µg/ml are not stable for the full 30-day reservoir capacity. This was true for ziconotide-naïve pumps as well as previously filled pumps, however the stability of the drug product was slightly greater in previously ziconotide-filled pumps. The package insert has included a table that outlines the life of the drug product at various concentrations and the frequency required to refill the pump given a specific concentration.

These stability issues coupled with the need to titrate drug slowly to limit adverse events (described in the clinical reviews) have resulted in a complex paradigm for filling and programming the device, which could predictably lead to medication errors. In addition, the need for more frequent filling increases the risk of microbial contamination in the pump and therefore the intrathecal space.

The — impurities, which have been identified with degradation of this drug product, are below the thresholds that would require qualification (according to the ICH3B Guidance) for a new molecular entity. The thresholds for requiring qualification of impurities in peptide products have not been established. The impurities measured for this product are sufficiently low, assuming a maximum _____ as to not require qualification. (See CMC memorandum of 6/12/00).

The assay for extractables from the catheter has been the source of contradiction within the application. The sponsor stated that there were no substances extracted from the catheter, however, the HPLC chromatograms submitted included peaks labeled as extractables. In addition the AAI report stated clearly that an extraneous peak was present and that it appeared only in samples pumped through the catheter. The sponsor will be required to resolve this apparent contradiction and provide identification of this substance apparently extracted from the catheter.

Compatibility testing. Tests for compatibility with pump components and nine other likely co-administered intrathecal medications were performed. These included liroresal, bupivacaine, morphine, fentanyl, hydromorphone, clonidine, and sufentanil. No incompatibilities were identified.

Sterility/Microbiological Issues. Sterility of the drug product is attained by aseptic fill, because the peptide is heat sensitive. Media fill testing revealed numbers of contaminated vials in excess of that expected to assure adequate sterility of the drug product by aseptic fill. The company will be required to adjust its specifications to meet Agency standards for a parenteral agent to assure adequate sterility on filling.

Endotoxin levels estimated at the highest infusion rate are within the Agency's accepted limits (0.2 EU/kg/hr maximum) for an intrathecal formulation.

³ As Dr. Theodorakis notes in his review the stability was assessed by quantitative measurement of the drug substance, and did not include measurement of impurities or assay of biological activity.

All spinal anesthetics are currently preservative-free due to neurotoxicity associated with many preservatives. Therefore, this product, a peptide in aqueous solution, also without preservative, may have the potential to support bacterial growth. This is of particular concern since this product is administered via pump and refilled every 30 days, providing the opportunity to introduce microbial contamination with each refill. The testing of a spectrum of microbials injected into reconstituted ziconotide produced results that called into question the testing procedures, since all agents tested showed abrupt death of microbials after three days. Because these tests could not be considered definitive, the question of the drug product's potential to sustain microbial growth on contamination has not been satisfactorily answered. The one contaminant that demonstrated considerable growth was _____

Since the data from these tests were considered by the microbiology reviewer to be unreliable it is not possible at this time to conclude that this product will be safe for human intrathecal use.

The clinical safety database was not sufficiently large to provide assurance of the safety of this product relative to its sterility, nor is examination of the clinical safety database for evidence of meningitis/sepsis the most sensitive measure of the potential for this drug product to support microbial growth. Furthermore the clinical trial environment, characterized by limited administration and carefully monitored procedures, may not be fully reflective of the ultimate clinical environments in which this drug may be administered.

Until adequate assurance that the intrathecally administered drug product has sustained sterility, either by the addition of a non-toxic preservative, or by some other means, it should not be approved. The sponsor of this product did not explore during development the possibility that some preservative exists that is not toxic to the spinal cord as suggested at the ALSAC meeting in 1997. The remedy for this problem may entail reformulation of the drug product as well as potentially nonclinical safety testing (bridging studies) and additional clinical safety and efficacy testing.

Inspections: The inspections have all been successful except for one. The site that performed the _____ testing for bulk drug substance was not prepared for inspection, causing the inspection to be cancelled. The drug cannot be approved without a satisfactory inspection of this site.

The Devices: The reliability of the devices to accurately deliver drug for the duration of use was evaluated. The maximum duration of testing was 30 days. The devices, which have been approved and marketed for 10 years, continue to meet the approved specifications with Ziconotide.

Biopharmaceutics

The pharmacokinetics of intrathecal (IT) Ziconotide have been evaluated in six clinical trials, and combined with studies of epidural and intravenous administration, some with quantification, have helped to characterize the profile of this drug, but only in a very limited way. Ziconotide is 100% bioavailable to the CNS when administered intrathecally. It is recovered in plasma after IT administration, but plasma levels are extremely low. It was hoped that the plasma PK profile could be examined both to better understand any systemic toxicity that might occur, and also to provide a mechanism to correlate with CSF levels and potentially pharmacodynamic effects following intrathecal administration. The latter correlation was not achieved, however. The time course of the pharmacodynamic effect was also not effectively correlated with CSF levels.

Based on Study 97-013, the CSF PK of ziconotide is linear following a 1-hour infusion and mean terminal elimination half-life was 4.5 hours.

Metabolism: Metabolites of ziconotide have not been identified. It was not found to be technically feasible to label and track the breakdown products of this peptide from metabolism by proteases, as only one of the resultant by-products would potentially retain the label.

Effect on CSF PK. Drug interaction studies were conducted with drugs known to affect CNS production, drugs likely to be co-administered, and with other Ca^{++} channel antagonists. No evidence of drug-drug interactions with these agents was found.

Efficacy

The evidence for efficacy was provided by two double-blind, placebo-controlled, effectively parallel, short-term trials comparing ziconotide with placebo, Studies 95-001 (chronic malignant pain) and 96-002 (chronic nonmalignant pain). The sponsor asserts that these studies both provide evidence for efficacy of ziconotide administered intrathecally. These are fully and carefully discussed in the Clinical and Statistical Reviews and Supervisory Memo by Dr. Rappaport. The details will not be repeated in this memo, therefore. I will focus mainly on Study 95-001 since that is the study, which is under question by the review team as potentially a failed trial.

Both studies were characterized by a randomization to a placebo or ziconotide IT titration phase lasting approximately 5 days, after which the primary assessment of efficacy was made. Patients were allowed to continue to receive any opiate or non-opiate analgesics, except for intrathecal medication. The titration period was followed by a more complicated follow-on period with

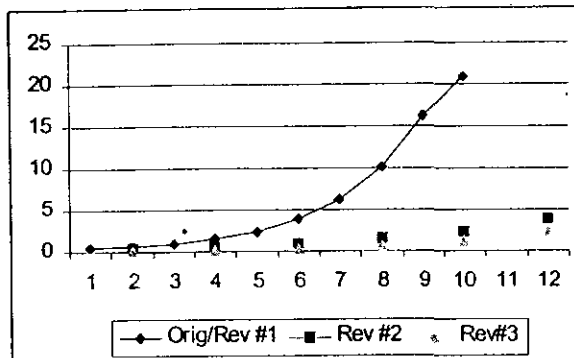
potential to crossover to a second randomized comparison, however the primary analysis of efficacy was determined by the first period, and the review team has concentrated its focus on this period. The primary efficacy variable was response defined percent improvement from baseline in the VASPI (visual analog scale of pain intensity), a 100-point scale. Secondary variables included other measures of pain relief, as well as a measure of percent change in opiate from baseline to the end of the Initial Titration Phase. It could be argued that a 5-day study in chronic pain is inappropriately brief. However, given the technical problems associated with delivery of placebo through a device for a prolonged period of time, and thus difficulty recruiting from a small population, longer trials are not as readily performed. Nevertheless, the fact remains that these are adjunctive trials and patients do not go without medication. Efficacy demonstrated as early as 5 days should be a reasonable surrogate, although tolerance cannot be ruled out in a trial of this short duration.

The problem of inadequate dose finding during development resulted in problems with the design and the conduct of both pivotal trials. The inappropriately high dosing at the beginning of the trials and stepwise reduction in dose to the last cohorts of the trials is well described in the primary medical review by Dr. Hertz and by Dr. Rappaport in his secondary review. The decision of the review team to accept as the primary cohort for efficacy analysis the cohort who received medication delivered according to the final protocol amendment (the low dose group), slow titration from a lower dose and to a lower maximum, is reasonable. For inclusion of all groups (high and low dose) in the final efficacy analysis may have led to an erroneous conclusion if the "high dose responders" carried the effect. It is important to know whether the low dose is an effective dose, since the sponsor proposes to label the drug for the lower more readily tolerated dose (infusion rate).

The figure below is a graphic representation of the table in Dr.Hertz's primary medical review (p.24/136) delineating the potential dosing of patients during Study 95- 001 with the original protocol and the subsequent three revisions. The potential dosing and upward titration described in the original protocol (calculated by body weight) would be almost identical to that in protocol revision #1 if one were to assume a 70-kg patient. The potential dosing for revisions 2 and 3 are also very similar as shown in the graph on the following page, except for a slightly lower starting dose, and the paradigm shift to dose to efficacy in revision 3 as opposed to dosing to toxicity in the previous iterations of the protocol.

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Figure 1. Potential dosing under each of the Protocol Revisions of Study 95-001



y-axis 0-26 µg/hr ziconotide IT infusion

x-axis 1-12 corresponds to each titration step, where each integer represents 12 hr

The sponsor has not made it clear whether any patients actually achieved maximum dosing in any of the dosing paradigms described. If the average dose achieved by patients was close to or within the range of the final dosing regimen, it might be argued that these patients should have been included in the analysis of efficacy. The table on the following page summarizes the patient enrollment under each revision.

Protocol	Total N (ITT)	Ziconotide	Placebo
Original	111	71	40
Revision 1	Unk	Unk	Unk
Revision 2	Unk	Unk	Unk
Revision 3	59	40	19
Revision 3- ~~site~~	51	34	17

The review team did not have access to the data regarding the actual doses received under each of these revisions, however, and it could not be teased out of the available tables or data sets provided by the sponsor. The sponsor had some difficulty in readily providing the breakdown of patients who were treated under revision 3, the dosing paradigm described in the label. In order to make an assessment of their similarity, this information should have been provided. The review team is of the mind that the patient tolerance and therefore the actual dosing under revisions 2 and three were sufficiently dissimilar to have led to the final protocol change. Therefore, I concur with the team's decision to treat this group as the primary focus for analysis of efficacy.

The effect of the rate of titration appears to have played an important role in the ultimate doses associated with analgesia in patients receiving ziconotide. Dr Hertz makes the case that patients beginning with low-dose infusion (slower titration) achieved analgesia with lower doses of ziconotide administered than patients in the earlier parts of both studies who underwent q12 hour (more rapid) titration.

The sponsor did not adequately and effectively evaluate the potential beneficial effects of the drug since it did not make appropriate observations in pilot studies to identify a tolerable dose escalation scheme and also to learn that the onset of effect may be slower than anticipated, i.e., 24 hours rather than 12 hours. The effect of this latter oversight was that in both efficacy trials a portion of the patients were titrated to potentially higher doses than needed by failing to allow the effect to occur before increasing the dose. If steps had not been taken to eliminate those patients in the earlier protocols, where forced titration on a q12 hour schedule limited only by adverse events was the rule, the outcome might have been linked to higher doses than needed. This is an important point in view of the adverse safety profile associated with this drug.

The problem of the site where unblinding was a likely (although not fully proven) occurrence makes little difference in the final outcome, however the data do not appear to be vastly different in the _____ site. The review team proposes to reject these possibly unreliable data in the formulation of a regulatory decision where the risk benefit margin is so low. Not only is their recommendation a prudent one but also examining the results without these data point out how marginal the effect really is, as the statistical significance of the study is lost without them. I can find no compelling reason to include these data in the analysis.

The results of Study 95-001 were not unequivocal, and the study's power is lost when the analysis of the final cohort, with the questionable data from the _____ site removed. Thus, there is no confirmatory evidence of the drug's clinical effect. The numerical difference in % change in VASPI is noted, however, the difference has lost its statistical significance. This is shown in the table on the following page, which was extracted from Dr. Rappaport's supervisory memo dated June 3, 2000 (after amendment 4/22/00, Table 1, volume 2.097, table 9.1 p.69 , 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)	42.4 (7.32)	18.9 (9.0)	53.1 (4.63)	18.1 (6.77)
	Median (range)	56.1 (-26-95)	3.1 (-24-96)	62.3 (-26-100)	7.8 (-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 (range)	43.0 (-26-95)	3.1 (-24-96)	62.0 (-26-100)	7.8 (-62-96)
		p-value for treatment difference	0.080		<.001

In both studies the effect of concomitant opiates was evaluated as a secondary measure. At the meeting of the ALSAC on 3/24/97, there was considerable speculation as to whether ziconotide

has the effect of blunting the analgesic effect of opiates or has a morphine (or opiate-) sparing effect, thus opiate dose can be reduced following treatment. One of the principal investigators suggested that there was a potentiating effect of ziconotide on the opiates, and that there was a need to balance titration of ziconotide with morphine (or other opiates)—because ziconotide appeared to have the effect of reducing requirements for MS. He also described a withdrawal effect as requirements for opiates decreased, often treated with more opiates, resulting in more adverse events. This effect on opiates is an important consideration and depending on whether the use of opiates increases or decreases in the trial, the efficacy results could potentially be affected. The baseline comparability of ziconotide and placebo groups with regard to opiates at baseline was made for both studies. The analysis was not, however, performed on the primary analysis group, that is the low dose, slow titration groups (last protocol revision). It appeared that on initial randomization for both studies, there was a slight preponderance of higher dose opiates in the ziconotide patients. This was not a statistically significant difference. The mean percent change in opiate use at the end of titration phase was -9.9 morphine equivalents for the ziconotide group and 5.1 morphine equivalents for the placebo group, indicating a decline in opiate use in the ziconotide treated patients. No statistical analysis was done on these results.

Safety—Nonclinical

The sponsor requested waiver of carcinogenicity studies on the grounds that (1) ziconotide is an endogenous peptide and (2) the study of intrathecal carcinogenicity is not technically feasible. The division argued that the peptide is not endogenous to humans and therefore could potentially be a human carcinogen, but concurred that the studies would likely not be feasible. The problem was brought before the Pharmacology Toxicology Coordinating Committee (PTCC) on May 20, 1999, which proposed an alternative stepwise evaluation, beginning with genotoxicity testing, and the in vitro Syrian Hamster Embryo (SHE) Cell transformation test and if positive, the TG.AC test. The genotoxicity panel and SHE cell testing were negative. While these studies provide some assurance, they do not eliminate the potential of carcinogenicity with prolonged use.

Antigenicity was evaluated in appropriate animal models (guinea pigs) of anaphylaxis and was weakly demonstrated. It was used to inform the clinical safety evaluation.

Reproductive toxicity studies were performed, using IV administration to maximize blood levels and assess the worst case, knowing that human plasma levels following IT administration are negligible. Segment II studies revealed the potential for teratogenicity in a dose-related fashion. The anomalies were largely developmental anomalies related to the skeletal system, but major anomalies of brain and heart were also described. These findings will ultimately need to be reflected in labeling if and when as this product gains approval in the future.

Safety—Clinical

The safety data base for this product as described by Dr. Hertz, might have been adequate in terms of total exposures (slightly over 1000 by all routes, including intravenous) providing information about the systemic and central toxicity of this product. The bulk of exposure (887) was by the intrathecal route. The specific dose-by-duration tables are provided by Dr. Hertz's review. The chronic exposure fell short of what was agreed upon and what might be expected for an NDA for a drug used chronically. The six-month exposure included 140 patients and the one-year exposure was only 37 patients. These small numbers make it difficult to assess the long-range toxicity of this product. It was recognized from the onset that the likelihood of being able to obtain the numbers recommended by the ICH E1A guidance is small, since the population under study is largely terminal patients. But as Dr. Hertz has described in her review, this is not exclusively the population under study.

Deaths Dropouts Serious Adverse Events. The deaths reported in this NDA (60 total) were mostly in the ziconotide group and in most cases attributable to underlying disease. However, in many cases insufficient information was provided to assess the cause of death. The sponsor should review source documents and provide to the NDA a more complete assessment of these deaths.

The adverse event profile of this drug includes a plethora of CNS findings, including encephalopathy and cerebellar outflow tract signs, possible effects on muscle with unexplained CPK elevations in the absence of specific myopathic symptoms, urinary retention, autonomic symptoms, and other symptoms which may need to be further evaluated as possible drug interactions, such as withdrawal syndrome. The effect of dose on these events has not been adequately worked up by the sponsor, and may be significantly different at the high dose rapid infusion rates compared to the low as suggested by the attrition rates due to adverse events as a function of dose and infusion noted during the clinical trials.

CNS toxicity. A nonspecific encephalopathy was recorded among patients receiving ziconotide. Findings included cognitive as well as psychiatric symptoms. They ranged from mild to so severe as to limit participation in studies (over one quarter of ziconotide patients). Specific dose-relatedness was not well worked out, and these patients were not followed to resolution, so that reversibility could not be assessed. Dr. Hertz made an effort to readjudicate the safety data as it related to CNS side effects, and made every effort to avoid repetition of reports. It would appear, based on her analysis, that this is a significant effect which increases in patients who initiated treatment on a higher dose. The actual dose (or infusion rate) at which these symptoms emerged could not be ascertained. The contribution of concomitant medications, such as opiates, to these CNS symptoms, was also not evaluated. The sponsor needs to carefully tease out the effects of dose, infusion rate, and concomitant medication on the severity of this encephalopathy. In addition, reversibility should be evaluated.

Drug-Drug Interactions.

Opiates. Since ziconotide was administered against a background of opiates, and there were reports of an opiate interaction both in the NDA and by the sponsor at the advisory committee meeting, this should have been carefully worked out. There was an apparent effect on opiates when ziconotide was begun, such that some patients went into withdrawal due to rapid tapering of opiates or possibly withdrawal may have been precipitated by the drug itself. This is an important finding which was not evaluated by the sponsor, and which should have been thoroughly investigated so that the appropriate directions could be conveyed in the package insert to avoid serious complications of treatment that might be predicted and avoided.

Chemotherapeutic agents. Interactions with chemotherapeutic agents as had been requested by the ALSAC were not specifically analyzed by the sponsor. This should be examined in the existing safety database and specifically examined prospectively in future trials.

Potential for Contamination and microbial growth. Intrathecal products in which preservatives have been used have historically had difficulty with adverse events such as severe back pain limiting their use. The possibility that ziconotide may support bacterial growth was not fully examined and because there is the chance of introducing microbials with each refill of the pump, this is a critical deficiency. While currently approved intrathecal drugs do not contain preservative, the possibility that one exists that is not neurotoxic has not been explored.

Meningitis was reported in the IT ziconotide studies mainly in patients who had external pumps. The actual number of patients who were treated with implanted pumps was fairly high, but may not be sufficient to provide assurance that meningitis is an uncommon event. Iatrogenic/nosocomial meningitis should be assessed in future studies.

Possible Hypersensitivity. Since ziconotide is a peptide and therefore potentially antigenic, it was tested and found to be positive in two animal models of anaphylaxis. There were no clinical reports of anaphylaxis in the NDA, however the safety database for ziconotide was rather small, fewer than 1000 patents, and therefore incapable of detecting an incidence any less than 0.1%. Surveillance to detect ziconotide-specific IgG or IgE antibodies was not specifically reported in the NDA, even though the sponsor indicated at the 1997 ALSAC meeting that this would be done.

Abuse Liability. The abuse potential of this compound has been evaluated fully and it has been found to have no abuse liability. No scheduling action is required in this area.

The reliability of safety data and documentation of serious adverse events and deaths in this NDA was questioned by Dr. Hertz, the medical officer who reviewed this NDA, who notes by way of example that many, but not all, cases of meningitis failed to be reported as serious adverse events, since they were considered by the sponsor to be complications of the device. In other ways the safety data suffered from lack of specific use of terminology to describe CNS adverse events.

Data Integrity/Financial Disclosure

The problem of the unblinded site is a significant one. The DSI investigator asserts that at least one site in the _____ center the study coordinator mixed drug, was therefore unblinded, and then had unlimited contact with patients and the principal investigator. This site contributed considerable data to the two pivotal studies. There was sufficient opportunity for the study coordinator to have introduced bias into the study either by contributing to the unblinding of patients and investigator, or so as to have unintentionally biased the primary outcome measures of the study by talking with patients. There were some uncorroborated reports that the study coordinator assisted in obtaining measurements. Since the endpoints were not objective or measured endpoints, bias is a real threat to the integrity of a trial such as this. To avoid drawing conclusions based on potentially unreliable data, the review team reasonably and cautiously eliminated these data from the primary efficacy analyses. This affected not only the outcome of the efficacy trials but also potentially the safety data as well. One additional site (_____) was found to have been unreliable due to absence of primary source documents a significant shortcoming. The sponsor had already eliminated this site upon making this discovery on its own. The DSI team considered, but was unable to provide evidence, that there was a systemic problem with the conduct of the studies, that is, inadequate monitoring of policies and standard procedures, in this NDA.

The reliability of safety data and documentation of serious adverse events and deaths in this NDA was questioned by Dr. Hertz, the medical officer who reviewed this NDA, who notes by way of example that many, but not all, cases of meningitis failed to be reported as serious adverse events, since they were considered by the sponsor to be complications of the device. The extent of problems such as this could not be easily estimated.

The required financial disclosure for the two pivotal studies was not provided by the sponsor, despite diligent attempts to obtain that information. This is a critical deficiency in view of the data integrity problems encountered in these studies.

Regulatory

This sponsor was notified that the division would be reviewing this NDA under a priority status at a teleconference held on February 16, 1999 in advance of the pre NDA Meeting. While the reasons for the division granting a priority review for this application are not well described in the minutes of that meeting, it was based on the fact that the _____ for which intraspinal therapy was required due to its advanced nature, and which was determined to be a severe, debilitating condition associated with irreversible morbidity. Closer examination of the entry criteria of the pivotal studies does clearly not support this conclusion, nor do the objectives of the trial and

outcome measures demonstrate an effect on morbidity. Nevertheless, the NDA was reviewed with priority status, as originally agreed.

This application was filed as a new NDA under 505 (b)(1), while some of the data were generated by _____ some by Neurex Corporation, and the NDA filed by Elan, a right of reference was provided for the data not generated by Elan.

A consultation was requested of FDA's General Counsel regarding the acceptability of proposed labeling which included the trademark or brand names of the pumps that were used in the clinical studies. Appropriate footnoting was recommended to eliminate confusion as to whether the manufacturer of the drug and the pumps were the same, since they were not. Further, the division was advised that the labeling of the pumps should be consistent with the ultimate labeling of the device. There were no other specific conditions attached to using the name of the pumps in the product labeling.

Nomenclature

Approval of the proposed tradename _____ was not recommended by the consulting team from OPDRA because of the similarity to Zofran in written orders, as well as the potentially similar context in which these drugs will be used. If Ziconotide were accidentally administered intravenously, significant hypotension and death could result, based on the early clinical studies of intravenous administration. If Zofran were inadvertently administered intrathecally, the effect on the meninges and spinal cord, and ultimately brain, could not be predicted, since it has not been evaluated.

Summary and Recommended Action

The recommendation to "not approve" ziconotide turns on the failure of the firm to provide reliable and affirmative evidence that it is safe and effective, to provide accurate estimates of the incidence of serious risks in the proposed dosing range, to provide evidence that the intrathecal product will not support the growth of microorganisms, and that reasonable and clear directions for use can be written based on clinical trial data establishing efficacy at a safe and tolerated dosing regimen. One must acknowledge that there is an important distinction between lack of evidence to demonstrate safety and efficacy and affirmative evidence to demonstrate that the drug is either unsafe or ineffective. It is expected that the case for the drug's safety and efficacy as delivered by the implanted intrathecal device can eventually be made.

I concur with the review team that approval should not be granted for this product.

E.C.NDA #21-060 (000) Ziconotide Injectable



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DIVISION OF ANESTHETIC, CRITICAL CARE, AND ADDICTION DRUG PRODUCTS
HFD-170, Room 9B-45, 5600 Fishers Lane, Rockville MD 20857 Tel:(301)443-3741

MEMORANDUM

DATE: June 3, 2000

TO: File, NDA 21-060

FROM: Bob A. Rappaport, M.D.
 Deputy Director, DACCADP
 Team Leader, Anesthetic Drug Group

RE: Supervisory Review of NDA 21-060, Ziconotide

BACKGROUND:

NDA 21-060, ziconotide injectable, was submitted by Elan Pharmaceuticals on December 28, 1999. Ziconotide is a synthetic equivalent of a naturally occurring peptide found in the venom of the marine snail, *Conus magus*. This 25 amino acid peptide is freely soluble in water and the drug product is formulated as a sterile, preservative free, isotonic solution with a pH of 4.0-5.0. Ziconotide is a neuron specific calcium channel blocker that selectively blocks the N-type, voltage-sensitive calcium channels which are involved in the mediation of pain. It is indicated for intrathecal use via an implantable pump for the treatment of severe, chronic pain, of malignant or nonmalignant origin.

5

→ The IND for intrathecal administration (45,718) was submitted to this

Division on June 30, 1994. **C**

C An Anesthetics and Life Support Advisory Committee meeting was held in 1997 during which ziconotide (then known as SNX-111) was discussed during the morning session. This was essentially a briefing for the committee on the development plan for this novel analgesic product.

The clinical studies of the effectiveness and safety of this new formulation have been reviewed [submitted June 2, 2000] by Sharon Hertz, M.D. The application has also been reviewed by Stella Grosser, Ph.D. and Thomas Permutt, Ph.D. (biostatistics), Shinja Kim, Ph.D. (clinical pharmacology and biopharmaceutics), David A. Brase, Ph.D. (pharmacology/toxicology), Michael Theodorakis, Ph.D. (chemistry), Chien-Hua Niu, Ph.D. (protein chemistry), Paul Stinavage, Ph.D. (microbiology), Hung Trinh, MD (CDRH) and Michael Klein, Ph.D. (abuse liability). In this memo, I will briefly review the effectiveness and safety data summarized in the primary clinical review and make appropriate recommendations for action on the NDA.

EFFECTIVENESS:

Evidence of efficacy has been submitted in two adequate and well-controlled clinical studies 95-001 and 96-002, and one supportive study 96-003.

Study 95-001 [001]:

This was a randomized, double-blind, placebo-controlled, parallel-group study conducted at 32 centers in the U.S. (30 sites), Australia (1 site), and the Netherlands (1 site). One hundred eleven patients with chronic pain due to malignancies or AIDS were randomized to receive treatment with either ziconotide or placebo in a ratio of 2:1. Randomization was stratified within each of the centers by etiology of the pain (cancer or AIDS) and by history of intrathecal opioid use.

During the Screening Phase, patients were stabilized on an analgesic regimen for at least three days prior to enrollment in the double-blind phase. Intrathecal medications were discontinued for at least three days prior to beginning study medication. The initial portion of the study consisted of a blinded five day titration with study medication or placebo. The dosing regimens used for this titration are discussed below. Patients who tolerated treatment for 48 hours were allowed to continue in the trial as outpatients. The primary efficacy evaluation and some of the secondary efficacy evaluations were performed at the end of this titration phase. Responders were defined as having a greater than or equal to 30% decrease from their baseline pain measurement with no increase in concurrent opioid use and no change in opioid type. Non-responders were crossed over to receive the other treatment while responders were maintained on their original drug; and the blind was not broken. Pain assessments were repeated after 5 more days.

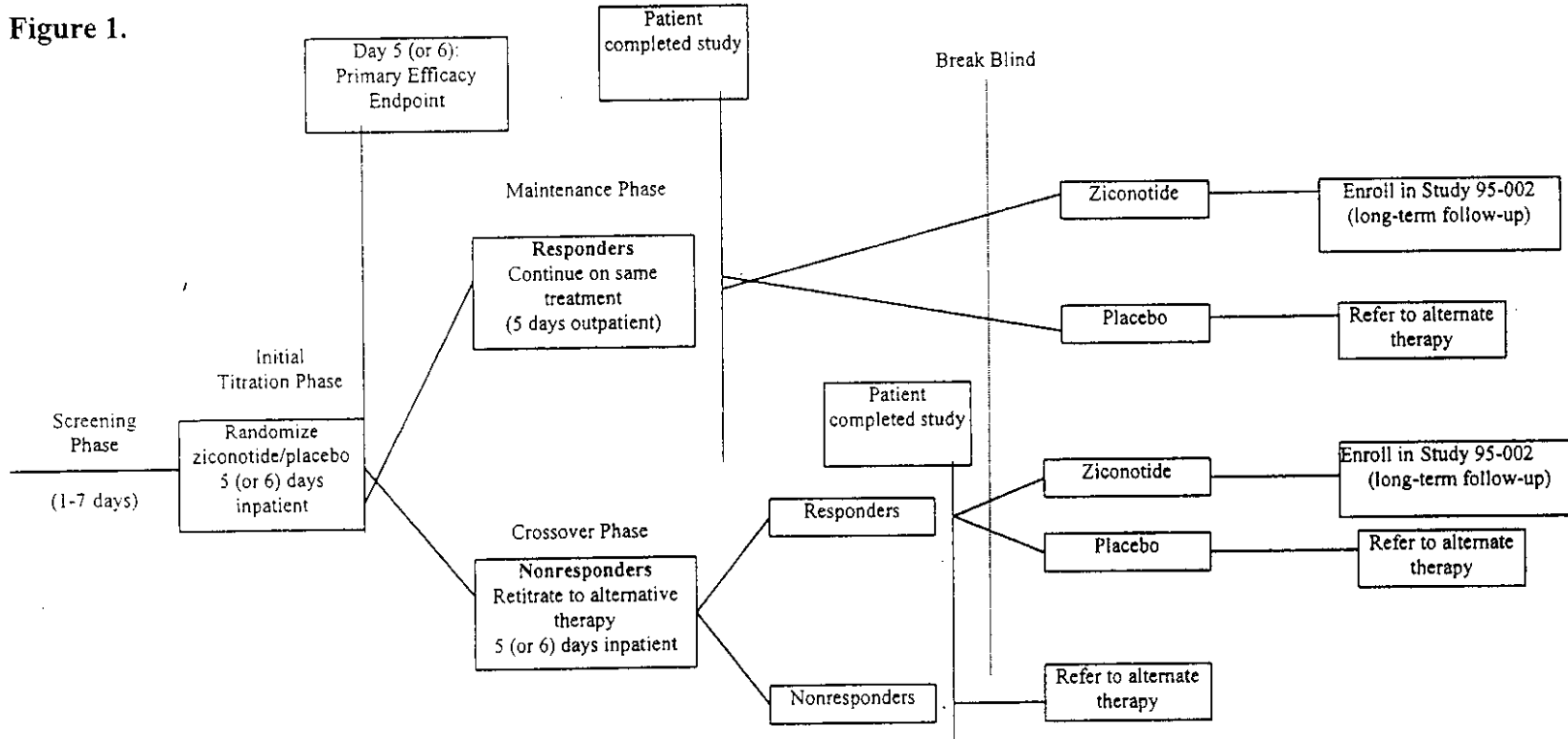
The flow chart copied and modified from the sponsor's ISE, Volume 002, page 053 has been reproduced below:

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Study 001 Design

Figure 1.



The dosing regimen changed three times during the study, each time due to an excessive number of intolerable adverse events. The original protocol (January 23, 1996) called for a regimen which started with 0.005 $\mu\text{g}/\text{kg}/\text{h}$ titrated upward every 12 hours in a forced titration to intolerable adverse events. This dose escalation schedule, based on the Fibonacci series, is summarized in the sponsor's dosing table from the original protocol, Vol. 2.104, page 121 of the NDA, and reproduced in a modified version below:

**Table 1. Dose Escalation
Schedule Original Protocol**

Time (hours)	Dose ($\mu\text{g}/\text{kg}/\text{h}$)
0-12	0.005
12-24	0.008
24-36	0.013
36-48	0.021
48-60	0.034
60-72	0.055
72-84	0.089
84-96	0.144
96-108	0.233
108-120	0.300

Revision 1 (June 11, 1996) removed the weight basis for dose determination, thereby changing the dosing range to 0.4 $\mu\text{g}/\text{h}$ to 21.0 $\mu\text{g}/\text{h}$. *Revision 2* (October 25, 1996) lowered the maximum dose in the initial titration regimen to 2.4 $\mu\text{g}/\text{h}$ and included an additional optional escalation to 3.9 $\mu\text{g}/\text{h}$. This revision also changed the timing of dosage adjustments from no more frequently than every 12 hours to no more frequently than every 24 hours. *Revision 3* (February 21, 1997) lowered the initial dose to 0.1 $\mu\text{g}/\text{h}$, with optional escalation to 2.4 $\mu\text{g}/\text{h}$. Also, subjects were now titrated to efficacy and at the onset of analgesia the dose was held for an additional 24 hours to permit the full analgesic effect to occur. Any dose could be held for an additional 24 hours at the investigator's discretion. The dose was reduced if lateral gaze nystagmus, a change in mental status, or other adverse events thought to be related to study drug were noted. The actual dosing schedules based on the three revisions are summarized below:

Table 2. Dose Escalation Schedules after Revisions 1, 2 and 3

Study Hour	Revision 1 (ug/h)	Revision 2 (ug/h)	Revision 3 (ug/h)
0-12	0.4	0.4	0.1
12-24	0.6		
24-36	0.9	0.6	0.2
36-48	1.5		
48-60	2.4	0.9	0.3
60-72	3.9		
72-84	6.2	1.5	0.6
84-96	10.1		
96-108	16.3	2.4	1.2
108-120	21.0		
120-144		3.9	2.4

The protocol specified primary measure of efficacy was the percent change in Visual Analogue Scale Pain Intensity [VASPI]¹ from baseline to the end of the Initial Titration Phase, analyzed using a 2-way ANOVA model with treatment, history of intrathecal opioid use, and treatment-by-history of intrathecal opioid use as variables. The sponsor based this analysis on the Evaluable population. The sponsor also planned a number of supportive statistical analyses of the primary measure of efficacy which are summarized on page 27 of Dr. Hertz's review.

Although an interim analysis to confirm the planned sample size was intended based on the protocol, it was not performed as the results from an interim analysis in Study 002 were applied to this study as well. The sample size was revised downward from 165 to 105 evaluable patients on the assumption that the lower variability than expected that was seen in Study 002 would also be seen in this study.

The protocol specified secondary efficacy parameters included:

- Change in VASPI score from baseline to the end of the Initial Titration Phase
- Change in Karnofsky Performance Score² from baseline to the end of the Initial Titration Phase.
- Category Pain Relief Scale [CPRS]³ at the end of the Initial Titration Phase

¹ VASPI was reported by patients marking their pain intensity on a 100 mm horizontal line where 100 mm equaled the worst possible pain and 0 mm equaled the least possible pain intensity.

² Karnofsky Performance Status Scale:

100	Normal; no complaints, no evidence of disease
90	Able to carry on normal activity; minor signs or symptoms of disease
80	Normal activity with effort; some signs or symptoms of disease
70	Cares for self, but unable to carry on normal activity or to do active work
60	Requires occasional assistance, but is able to care for most of personal needs
50	Requires considerable assistance and frequent medical care
40	Disable; requires special care and assistance
30	Severely disabled, hospitalization is indicated although death is not imminent
20	Very ill, hospitalization and active supportive care necessary
10	Moribund
0	Dead

Best Possible Copy

- Change in Wisconsin Brief Pain Inventory Scale [WBPIIS]⁴ subsets from baseline to the end of the Initial Titration Phase
- Change in Visual Analog Scale of Pain Relief [VASPAR]⁵ from preinfusion to the end of the Initial Titration Phase and at study termination
- Change in Mood Score⁶ from preinfusion to the end of the Initial Titration Phase and at study termination
- Change in Tursky Description⁷ from preinfusion to the end of the Initial Titration Phase and at study termination
- Proportion of patients responding to treatment at the end of the Initial Titration Phase
- Proportion of patients responding to ziconotide at the end of the Crossover Phase
- Change in tactile allodynia parameters from baseline to the end of the Initial Titration Phase
- Mean percentage change in VASPI and Karnofsky Score from baseline to end of Maintenance Phase
- Percent change in opioid use from baseline to the end of the Initial Titration Phase.

Results:

A total of 111 patients were randomized. One further patient was not randomized, but did receive ziconotide on a compassionate basis and has been included in the Safety database. Three patients were not included in the Evaluable data set due to insufficient VASPI data; although all 3 completed the Initial Titration Phase of the study. The following table summarizes the patient disposition during the titration phase:

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³ CPRS is a 6 point categorical scale from 0 = "My pain is now WORSE compared to before the infusion started." to 5 = "I have COMPLETE RELIEF of my pain compared to before the infusion started."

⁴ WBPIIS is a series of 6 description of function: mood, relationships with other people, walking ability, sleep, normal work, and enjoyment of life, scored on a 0 (not at all) to 4 (extremely) categorical scale.

⁵ VASPAR ranges from "No relief of pain" to "Complete relief of pain." (from "Memorial Pain Assessment Card" from Clinical Practice Guidelines for Management of Cancer Pain published by AHCP, March 1994)

⁶ Mood Score is visual analog score ranging from "worst mood" to "best mood." (from "Memorial Pain Assessment Card")

⁷ Tursky Description is 4 category scale: no pain; just noticeable, mild or weak; moderate or strong; severe or excruciating. (from "Memorial Pain Assessment Card")

Table 3.

	Ziconotide	Placebo
Patients Randomized	71	40
All Treated Patients	72	40
Safety Population	72	40
Intent-to-Treat [ITT] Population	71	40
Evaluable Population	68	40
Reasons for Being Non-evaluable:		
Not Randomized	1	
Insufficient VASPI data ⁸	3	

[based on Table 7.4, page 32 of Dr. Hertz's review]

Of the 72 patients who received ziconotide, 11 withdrew during the Initial Titration Phase. Of the 40 patients who initially received placebo, 3 withdrew during the Initial Titration Phase. The reasons for withdrawal are summarized below:

Table 4.

Primary Reason for Early Termination:	ziconotide	Placebo
Intolerable Adverse Event ^a	5 (6.9%)	2 (5.0%)
Withdrawal Requested by Patient	2 (2.8%)	0 (0.0%)
Unrelated Medical Condition	2 (2.8%)	0 (0.0%)
Infection ^b	0	1 (2.5%)
System Related (Pump/Catheter)	1 (1.4%)	0
Ineffective Drug Therapy / Loss of Effect	1 (1.4%)	0

a One placebo patient (Patient 5047-49) discontinued due to an adverse event associated with the device.

b One placebo patient (Patient 5006-75) discontinued due to an infection associated with the device.

[based on Table 7.4, page 30 of Dr. Hertz's review]

The baseline demographics of the two study groups were, in general, similar. While the mean baseline opioid analgesic consumption (in morphine equivalents) was greater in the ziconotide group, this difference did not reach statistical significance.

⁸ Three possible criteria for defining adequacy: 1) one or more scores after receiving at least 96 hours treatment in Initial Titration Phase; 2) have remained at their final dose prior to termination of Initial Titration Phase for at least 12 hours and have one or more scores at the end of those 12 hours; 3) or, have terminated from study due to adverse event and have one or more score on the last dose or the penultimate dose prior to termination of the Initial Titration Phase

Primary Efficacy Analyses:

Two concerns arose during the review period which required reassessment of the sponsor's analyses, and ultimately, reanalysis of the efficacy data. The first concern was based on the revisions which occurred in the dosing regimen during the course of the study. The sponsor's proposed labeling recommends a paradigm for titration of dose, rather than a fixed dosing regimen, based on the regimen used in the study only after implementation of Revision 3. Subjects in this study who were treated under the earlier dosing regimens may have received much higher doses than are recommended in the proposed labeling. Indeed, the revisions were undertaken, and these higher doses not recommended, due to an excessive number of intolerable adverse events. While efficacy may have been established at those higher doses, the risk to benefit relationship was clearly unacceptable. Therefore, Drs. Hertz, Grosser and Permutt chose to request reanalysis of the efficacy data using only the subjects treated under Revision 3.

The second concern was based on the field inspection report of a center _____ that participated in both Study _____. That report documented irregularities which may have compromised the integrity of the data. Specifically, the investigator for _____ had contracted with a CRO. The primary study coordinator for that CRO was directly involved in the preparation and administration of study drug and titration of study drug dosage, and assisted in the assessment of efficacy outcome measures. Thus, the Division of Scientific Investigations [DSI] considered this site to be unblinded, and based on their finding, this data was excluded from the final analyses.

The table located on page 7 of Dr. Permutt's review summarizes and compares the results of the primary efficacy analysis performed on the entire study population and on the subjects treated under Revision 3, excluding those at the _____ site. That table has been modified and reproduced below:

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Table 5.

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 (range)	56.1 (-26-95)	3.1 (-24-96)	62.3 (-26-100)	7.8 (-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 (range)	43.0 (-26-95)	3.1 (-24-96)	62.0 (-26-100)	7.8 (-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.)

While there was only a modest change in the observed difference between the groups from the analysis of the entire study population to the analysis of the more limited population, the difference was no longer supported by statistical significance. Of note, when the Evaluable patient population is used for the analysis, the p-value is borderline. However, when the ITT is analyzed, the p-value clearly indicates lack of statistical significance. The difference between these two populations consists of just two subjects. Patient 5015-51 was excluded from the evaluable population due to insufficient VASPI data. The patient had leakage from the catheter and study drug was discontinued between 24 and 48 hours after the infusion was started. No VASPI was performed after study drug was discontinued. Patient 5047-74 was not randomized and received study drug on an open-label basis.

The following *supportive analyses* performed by the sponsor on the primary outcome measure were based on the data set from the full group of subjects randomized. No reanalyses were performed with the pre-Revision 3 or ~~_____~~ site subjects excluded.

- The sponsor analyzed the percent change in VASPI by initial dose. The percent change in VASPI was statistically significantly greater for the ziconotide group compared to the placebo group for both the subjects started at less than or equal to 0.1 $\mu\text{g/h}$ and the subjects started at more than 0.1 $\mu\text{g/h}$ ($p = 0.042$ and 0.001 , respectively).
- The sponsor also found that the mean percent change in VASPI score from baseline to the end of titration was greater for the ziconotide group compared to the placebo group at all dose ranges. Dose range was defined as the rate of administration at the time when the final efficacy assessment was performed for the Initial Titration Phase

of the study. However, the numbers in the individual dose range groups were too small for statistical comparison.

- The sponsor found a statistically significant difference between the treatment groups ($p = 0.01$) in the mean percent change in VASPI score from baseline to the score taken on each subsequent treatment day. The scores in the ziconotide group increased progressively from 17.5% to 55.1%. The scores in the placebo group showed no consistent trend.
- No interactions were noted with prior intrathecal opioid use or based on a diagnosis of cancer vs. AIDS. The findings related to demographic subgroup analyses will be discussed in comparison to the results from Study 002 later in this review.

Secondary Efficacy Analyses:

Following completion of the Initial Titration Phase of the study, Responders from either arm of that phase were entered into a Maintenance Phase and continued on their same treatment for 5 days. Nonresponders were entered into a Crossover Phase and changed to the alternate therapy for 5 to 6 days. The blind was not broken until the end of these phases and the data was to be used for supportive and secondary efficacy analyses. Sixty ziconotide treated and 36 placebo subjects entered these second phases of the study. Forty-six of the ziconotide treated and 29 of the placebo subjects completed those phases. The following table summarizes the disposition of those patients:

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Table 6.

Maintenance Phase		
Entered Phase	48 (66.7%)	11 (27.5%)
Completed Phase	39 (54.2%)	11 (27.5%)
Primary Reason for Early Termination		
Intolerable Adverse Event ^a	4 (5.6%)	0
Withdrawal Requested by Patient	1 (1.4%)	0
Death on Study ^b	2 (2.8%)	0
Ineffective Drug Therapy/Loss of Effect	1 (1.4%)	0
Other ^c	1 (1.4%)	0
Crossover Phase		
Entered Phase	12 (16.7%)	26 (65.0%)
Completed Phase	7 (9.7%)	18 (45.0%)
Primary Reason for Early Termination		
Intolerable Adverse Event ^d	3 (4.2%)	8 (20.0%)
Withdrawal Requested by Patient	1 (1.4%)	0
Other ^e	1 (1.4%)	0

a Three ziconotide patients (Patients 501-87, 5025-74, and 5097-50) discontinued due to adverse events associated with the device

b Patient 5009-74 died of ovarian carcinoma, unrelated to drug. Patient 5025-49 died after a suicide attempt, possibly related to drug.

c Other included Patient 5006-73 (Patient went home on Day 6 with complete relief of pain).

d Two placebo patients receiving ziconotide during the crossover phase (Patients 5002-25 and 5025-73) discontinued due to adverse events associated with the device.

e No reason was specified.

Data Source: Appendix 2, Table 1.2

[based on Table 7.4, page 32 of Dr. Hertz's review]

In addition, there were 21 protocol violations characterized by incorrect assignment into the secondary phases of the study. The most common reason for the erroneous assignments was, according to the sponsor, incorrect assessment of responder status by the investigators. Of the 49 patients in the ziconotide treatment group placed in the Maintenance Phase, 15 were incorrectly assigned. Of the 11 patients in the placebo group placed in the Maintenance Phase, 2 were incorrectly assigned. Of the 7 patients in the ziconotide group placed in the placebo group in the Crossover Phase, 1 was incorrectly assigned. Of the 26 patients in the placebo group placed in the ziconotide group in the Crossover Phase, 3 were incorrectly assigned.

Due to the small numbers of patients in the secondary phases of the study, and due to the large number of significant protocol violations, this reviewer considers this data suspect for use in the assessment of effectiveness.

- Ziconotide dosing requirements:

Dr. Hertz's Table 7.12, page 41 of her review, summarizes three of the secondary outcome measures initially defined as "subgroup analyses of the primary outcome variable" in the protocol. It has been modified and reproduced below:

Table 7.

Parameter	Initial Dose		Total
	≤0.1 ug/h	> 0.1 ug/h	
Dose at End of Initial Titration (ug/h) ^a			
N	39	29	68
Mean (SE)	0.52(0.09)	1.34(0.33)	0.87(0.16)
Median	0.3	0.8	0.6
Range	0.074 - 2.400	0.200 - 9.360	0.074 - 9.360
Cumulative Dose During Initial Titration (ug) ^b			
N	39	29	68
Mean (SE)	36.90 (4.25)	167.83 (34.25)	92.74 (16.66)
Median	26.63	95.79	56.53
Range	6.80 - 116.80	36.15 - 880.55	6.80 - 880.55
Dose at Onset of Analgesia (ug/h) ^c			
N	39	29	68
Mean (SE)	0.48(0.09)	3.12(0.95)	1.60(0.43)
Median	0.2	1.5	0.6
Range	0.10-2.40	0.20-20.58	0.10-20-58

a The last non-zero dose level administered during the Initial Titration Phase was reported.

b The cumulative dose ug/h at the end of the Initial Titration Phase with K distinct doses was estimated as: {dose level 1 (ug/hr) x duration of dose level 1 (hours) and dose level 2 ug x duration of dose level 2 (hours) + ... + dose level K (ug/hr) x duration of dose level K (hours)}.

c Onset of analgesia was defined as when the percent change in VASPI was >20% and the CPRS score was 2:2 (i.e., at least a slight improvement). For patients who did not have onset of analgesia, the maximum dose level during the Initial Titration Phase was used.

Data Source. Appendix 2, Table 8.1

The data in this table indicate that the patients treated under the earlier, more aggressive dosing regimens required more drug before achieving analgesia. This is not unexpected in light of the fact that for two out of the three earlier dosing regimens starting at greater than 0.1 µg/h, the patients were initially treated at 12-hour intervals and the full analgesic effect of any single dose may not have been achieved before the dose was increased to the next level, resulting in the administration of higher dosages and greater cumulative quantities of study drug.

- Change in VASPI score from baseline to the end of the Initial Titration Phase:

The table located on page 8 of Dr. Permutt's review summarizes and compares the results of this secondary efficacy analysis on the Initial Titration Phase performed on the entire study population and on the subjects treated under Revision 3, excluding those at the _____ site. That table has been modified and reproduced below:

Table 8.

Population	Parameter	Rev3 without		Entire study	
		Ziconotide	Placebo	Ziconotide	Placebo
Evaluable	N	32	17	68	40
	Mean (SE)	32.4 (5.68)	15.6 (7.63)	39.4 (3.61)	16.9 (5.61)
	Median (range)	37.3 (-14-87)	2.5 (-16-91)	45.0 (-17-99)	7.5 (-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 (range)	28.3 (-14-87)	2.5 (-16-93)	44.5 (-17-99)	7.5 (-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.)

- Change in Karnofsky Performance Score from baseline to the end of the Initial Titration Phase:

There were no differences between treatment groups in the Karnofsky Performance Score at the end of the Initial Titration Phase (or at the end of the secondary phases). Dr. Hertz's Table 7.16, page 44 of her review, summarizes the results.

- CPRS at the end of the Initial Titration Phase:

The following table summarizes the results from the CPRS:

Table 9.

Parameter	Ziconotide	Placebo	p-value
	N=54	N=31	
Category Pain Relief Scale			<0.001
Worse	4 (5.9%)	7 (17.5%)	
No Change	9 (13.2%)	8 (20.0%)	
Slight Improvement	5 (7.4%)	9 (22.5%)	
Moderate Improvement	7 (10.3%)	1 (2.5%)	
A Lot of Improvement	24 (35.3%)	6 (15.0%)	
Complete Relief	5 (7.4%)	0 (0.0%)	
Missing	14 (20.6%)	9 (22.5%)	

Data Source: Appendix 2, Table 9.1

[based on Table 7.14, page 40 of Dr. Hertz's review]

When reanalyzed using only the Revision 3 subjects and excluding the subjects, the differences are no longer statistically significant.

- WBPIS subsets from baseline to the end of the Initial Titration Phase:

There were no differences between the treatment groups with respect to any of the subsets. Dr. Hertz's Table 7.15, page 43 of her review, summarizes the results.

- VASPAR, Change in Mood Score, and Tursky Description from preinfusion to the end of the Initial Titration Phase and at study termination:

The VASPAR, Change in Mood Score, and Tursky Description all demonstrated improvement in pain relief, mood and pain description for both treatment groups. Although the changes were larger for the ziconotide group, the sponsor did not perform inferential statistics on the data.

- Proportion of patients responding to ziconotide at the end of the Initial Titration Phase and at the end of the Crossover Phase:

The sponsor readjudicated the patients assessed as responders by the investigators based on review of the CRF's. The difference in the proportion of responders between the treatment groups was statistically significantly greater for the ziconotide treated subjects. Dr. Hertz's Table 7.18, page 45 of her review, summarizes those results and has been modified and reproduced below:

Table 10.

Parameter	Initial Treatment Assignment	
	Ziconotide (N=68)	Placebo (N=40)
Number of Responders (%)	34 (50.0%)	7 (17.5%)
Number of Nonresponder (%)	34 (50.0%)	33 (82.5%)
95% CI for Percent Responders	(37.6%, 62.4%)	(7.3%, 32.8%)
Treatment Difference in Percent Responder	32.5%	
95% CI for Treatment Difference in % Responder	(15.8%, 49.2%)	
p-value	0.001	

Data Source: Appendix 2, Tables 11.11

Eight of 26 patients crossed over from placebo to ziconotide met the criteria for responders. None of the nonresponders crossed over to placebo responded. The difference in the proportion of responders between ziconotide and placebo during the Crossover Phase was comparable to that found in the Initial Titration Phase.

- Change in tactile allodynia parameters from baseline to the end of the Initial Titration Phase:

The numbers studied for this endpoint were far too small for an accurate analysis.

- Mean percentage change in VASPI and Karnofsky Score from baseline to end of maintenance phase:

The mean percentage changes in the Karnofsky Score were minimally different for the two treatment groups. The mean percent change in VASPI at the end of the Maintenance Phase was 69.4 for the ziconotide group and 57.5 for the placebo group. No statistical analysis was performed on this data.

- Percent change in opioid use from baseline to the end of the Initial Titration Phase:

The mean percent change in opioid use at the end of the Initial Titration Phase was -9.9 morphine equivalents for the ziconotide group and +5.1 morphine equivalents for the placebo patients. No statistical analysis was performed by the sponsor.

Study 96-002 [002]:

This was a randomized, double-blind, placebo-controlled, parallel-group study conducted at 43 centers. Thirty-six of those sites were in the U.S. The other 7 centers were located in Austria (1 site), Australia (1 site), Belgium (4 sites), and Switzerland (1 site). Two hundred sixty-four patients with chronic non-malignant pain were randomized to receive treatment with either ziconotide or placebo in a ratio of 2:1. Randomization was stratified by central vs. peripheral pain syndrome.

During the Screening Phase, patients were stabilized on an analgesic regimen for at least three days prior to enrollment in the double-blind Phase. Intrathecal medications were discontinued for at least three days prior to beginning study medication. The initial portion of the study consisted of a blinded six day titration with study medication or placebo. The dosing paradigms used for this titration are discussed below. The primary efficacy evaluation and some of the secondary efficacy evaluations were performed at the end of this Initial Titration Phase. Responders were defined as having a greater than or equal to 30% decrease from their baseline pain measurement with no increase in concurrent opioid use and no change in opioid type.

Responders remained blinded for an additional 5 days of treatment on the same treatment. The blind was then broken and Responders to placebo were discontinued from the study, while responders to ziconotide were enrolled in a long-term study. Non-responders from the Initial Titration Phase were unblinded and those in the ziconotide group were discontinued from the study, while those in the placebo group were crossed over to treatment with ziconotide on an open-label basis for 5 days. After the 5 days, non-

responders were discontinued and responders were offered enrollment in a long-term study.

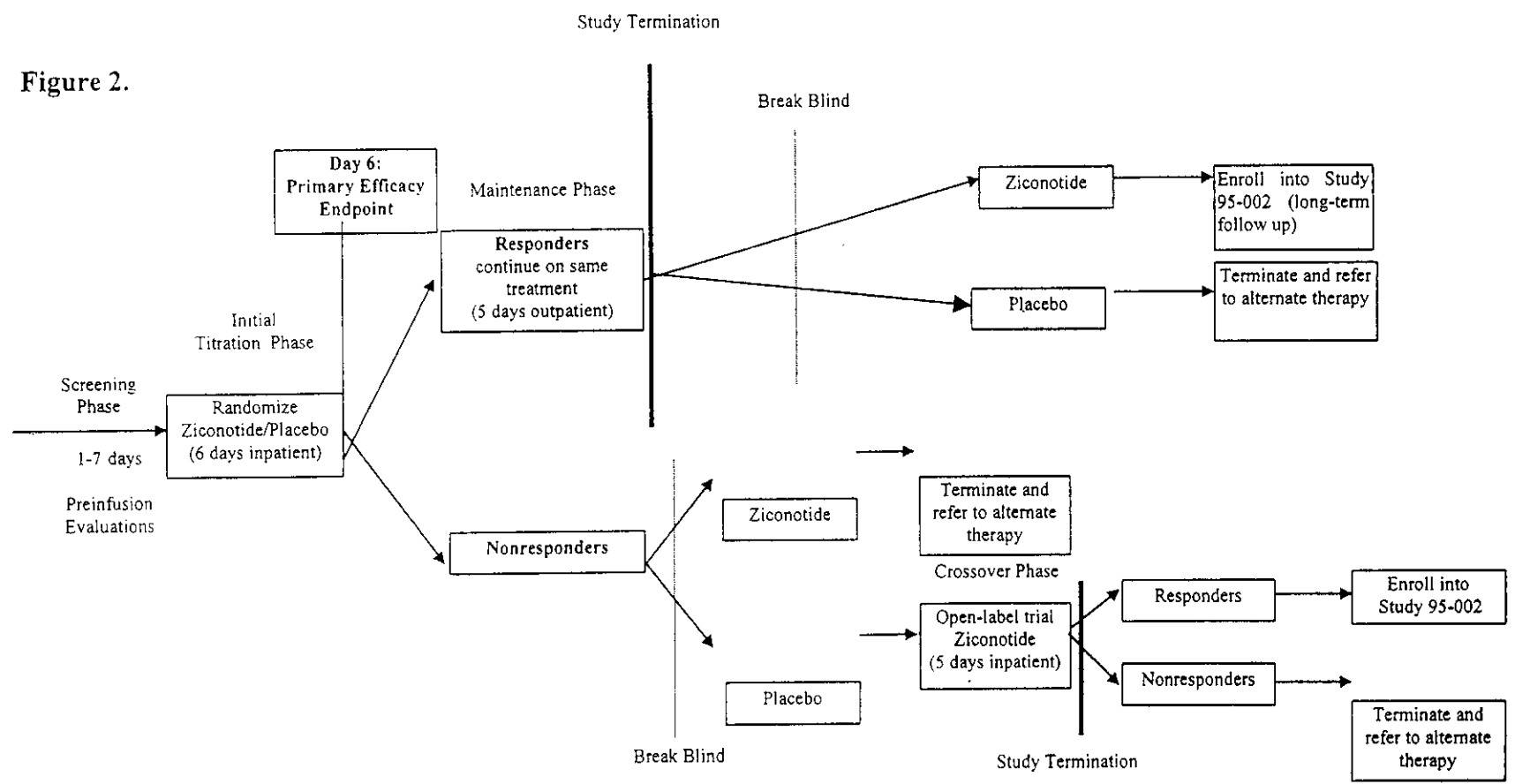
The flow chart copied and modified from the sponsor's ISE, Volume 002, page 057 has been modified and reproduced below

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Study 002 Design

Figure 2.



The dosing regimen changed twice during the study, both times due to an excessive number of intolerable adverse events. The original protocol (May 17, 1996) called for a regimen which started with 0.4 µg/h titrated upward every 24 hours to efficacy, to a maximum dose of 7.0 µg/h. *Revision 1* (October 28, 1996) changed the maximum dose at 144 hours from 7.0 µg/h to 3.9 µg/h. This revision also stipulated that, at the onset of analgesia, the dose was to be held an additional 24 hours to permit the full analgesic effect to occur. Also, any dose could be held for an additional 24 hours at the investigator's discretion. The dose was reduced if lateral gaze nystagmus, a change in mental status, or other adverse events thought to be related to study drug were noted. *Revision 2* (February 21, 1997) reduced the dose titration range from 0.4 – 3.9 µg/h to 0.1 – 2.4 µg/h. The actual dosing schedules based on the two revisions are summarized below:

Table 11. Dose Escalation Schedules: Original and Revisions 1 and 2

Study Hour	Original (ug/h)	Revision 1 (ug/h)	Revision 2 (ug/h)
0-24	0.4	0.4	0.1
24-48	0.9	0.6	0.2
48-72	1.8	0.9	0.3
72-96	3.4	1.5	0.6
96-120	5.3	2.4	1.2
120-144	7.0	3.9	2.4

The protocol specified primary measure of efficacy was the percent change in VASPI from baseline to the end of the Initial Titration Phase, analyzed using a 2-way ANOVA model with treatment, center, and treatment-by-center as variables. The sponsor based this analysis on the Evaluable population. The sponsor also planned a number of supportive statistical analyses of the primary measure of efficacy which are summarized on pages 51-52 of Dr. Hertz's review.

An independent interim analysis to confirm the planned sample size, based on the protocol, was performed and indicated that the variability was lower than had been predicted. The sample size was then fixed at the pre-specified, pre-interim analysis number.

The protocol specified secondary efficacy parameters included:

- Change in VASPI score from baseline to the end of the Initial Titration Phase
- Percent change in McGill Pain⁹ Score from baseline to the end of the Initial Titration Phase.

⁹ The McGill-Melzick Pain Questionnaire is a tool consisting of three major classes of word descriptors (sensory, affective, and evaluative) that are used to specify subjective pain experience; it also includes an intensity scale and other items to determine the properties of pain experience. The three major measures are: 1) the pain rating index, based on two types of numerical values that can be assigned to each word descriptor; 2) the number of words chosen; and 3) the present pain intensity on a 1-5 scale.

- CPRS at the end of the Initial Titration Phase
- WBPIS subsets from baseline to the end of the Initial Titration Phase
- Proportion of patients responding to treatment at the end of the Initial Titration Phase
- Proportion of patients responding to ziconotide at the end of the Crossover Phase
- Change in tactile allodynia parameters from baseline to the end of the Initial Titration Phase
- For patients in Maintenance Phase: Percent change in VASPI and percent change in McGill Pain Score from baseline to study termination
- For patients in Crossover Phase: Percent change in VASPI from baseline to study termination
- Percent change in opioid use from baseline to the end of the Initial Titration Phase.

Results:

A total of 264 patients were randomized. The following table summarizes the patient disposition during the titration phase:

Table 12.

	Ziconotide	Placebo
Patients Randomized	175	89
All Treated Patients	170	87
Safety Population ^a	170	86
Intent-to-Treat [ITT] Population ^b	169	86
Evaluable Population	162	79
Reasons for Being Non-evaluable:		
Lack of Source Documentation	7	5
Investigation Drug Within 30 Days of Study	0	1
IT Medication Within 3 Days of Enrollment	2	2
Insufficient VASPI Data	1	1

^a The safety population included patients who had received any amount of study medication at any time during the study except for Patient6087-106 who had been, at first, randomized to ziconotide and then randomized to placebo.

^b While this group decreased by one patient who probably had insufficient VASPI data, the documentation required to make that assessment is still pending from the sponsor as of 6/1/00

[based on Tables 7.23 and 7.24, pages 55-57 of Dr. Hertz's review]

Of the 170 patients who received ziconotide, 40 withdrew during the Initial Titration Phase. Of the 87 patients who initially received placebo, 7 withdrew during the Initial Titration Phase. The reasons for withdrawal are summarized below:

Table 13.

Primary Reason for Early Termination:	Ziconotide	Placebo
Noncompliance by Patient	0	1
Intolerable Adverse Event ^a	27	1
Withdrawal Requested by Patient	0	1
Unrelated Medical Condition	0	1
Administrative or Investigator Decision	1	1
Infection ^b	1	1
System Related (Pump/Catheter)	4	1
Ineffective Drug Therapy / Loss of Effect	5	0
Other ^c	2	0

a Three ziconotide patients (6058-101, 6059-111, and 6067-101) and one placebo patient (6079-106) discontinued due to adverse events associated with the device.

b Device adverse events.

c Other includes: Patient 6066-102 - non-responder to active drug, 6087-105 no intrathecal catheter CSF flow
Data Source: Appendix 2, Table 1.1

[based on Table 7.24, pages 56-57 of Dr. Hertz's review]

The baseline demographics of the two study groups were, in general, similar. While the mean baseline opioid analgesic consumption (in morphine equivalents) was greater in the ziconotide group, this difference did not reach statistical significance. In addition, The baseline VASPI score and the WBPIS Mood score were statistically significantly higher in the ziconotide group. The following table summarizes those results:

Table 14.

Pain Assessments	Ziconotide (N = 162)	Placebo (N=79)	p-value
VASPI Score (mm)			0.022
Mean (SE)	80.2 (1.09)	76.8 (1.54)	
Median (range)	82.0 (33.0-100-0)	76.0 (50.0-100-0)	
WBPIS - Mood			0.012
n	160	79	
Mean (SE)	2.9(0.08)	2.5(0.12)	
Median (range)	3.0 (0.0-4.0)	3.0 (0.0-4.0)	

[based on Table 7.27, page 60 of Dr. Hertz's review]

Primary Efficacy Analyses:

Based on the same two concerns discussed in this review on page 9 in relation to Study 001, the patient population deemed most appropriate for analysis of efficacy by Drs. Hertz, Grosser and Permutt consisted of a considerably smaller subset of the original Evaluable (or ITT) population described by the sponsor.

The table located on page 6 of Dr. Permutt's review summarizes and compares the results of the primary efficacy analysis performed on the entire study population and on the subjects treated under Revision 2, excluding those at the _____ site. That table has been modified and reproduced below:

Table 15.

Population	Parameter	Rev2 without _____		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 (range)	19.9 (-54-100)	1.1 (-62-79)	23.8 (-113-100)	1.1 (-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 (range)	20.2 (-54-100)	1.1 (-62-79)	25.6 (-113-100)	1.1 (-62-80)
		p-value treatment difference	<0.001		<.001

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

Each of the analyses showed a statistically significant difference in favor of the ziconotide treated patients. An ANCOVA was performed to adjust for the higher mean baseline VASPI score in the ziconotide group. The mean percent change in VASPI score remained statistically significantly greater for the ziconotide group compared to the placebo group for both the Evaluable and ITT populations ($p < 0.001$ for both comparisons).

The following *supportive analyses* performed by the sponsor on the primary outcome measure were based on the data set from the full group of subjects randomized. No reanalyses were performed with the pre-Revision 2 or _____ site subjects excluded.

- The sponsor analyzed the percent change in VASPI by initial dose. The percent change in VASPI was statistically significantly greater for the ziconotide group compared to the placebo group for the subjects started at less than or equal to 0.1 $\mu\text{g/h}$ ($p = 0.002$). While the percent change in VASPI was larger for the ziconotide group compared to the placebo group for the subjects started at greater than 0.1 $\mu\text{g/h}$, the difference did not reach statistical significance.
- The sponsor found that the mean percent change in VASPI score from baseline to the end of titration was greater for the ziconotide group compared the placebo group at only four out of the six dose ranges. Dose range was defined as the rate of

administration at the time when the final efficacy assessment was performed for the Initial Titration Phase of the study. However, the numbers in the individual dose range groups were too small for statistical comparison.

- The sponsor found a statistically significant difference between the treatment groups in the mean percent change in VASPI score from baseline to the score taken on each subsequent treatment day. The scores in the ziconotide group increased progressively from 6.9% to 29.9%. The scores in the placebo group showed no consistent trend. The treatment difference was significant by ANOVA with a p-value of 0.009.
- No interactions were noted with prior intrathecal morphine use or concurrent opioid use. The findings related to demographic subgroup analyses will be discussed in comparison to the results from Study 001 later in this review.

Secondary Efficacy Analyses:

Following completion of the Initial Titration Phase of the study, Responders from either arm of that phase were entered into a Maintenance Phase and continued on their same treatment for 5 days. The blind was not broken until the end of this phase and the data was to be used for supportive and secondary efficacy analyses. Nonresponders were unblinded, entered into a Crossover Phase and changed to the alternate therapy for 5 to 6 days. Eighty-two ziconotide treated and 12 placebo subjects entered the blinded Maintenance Phase of the study. Seventy-four of the ziconotide treated and all 12 of the placebo subjects completed the Maintenance Phase. The following table summarizes the disposition of those patients:

Table 16.

Maintenance Phase		
Entered Phase	82	12
Completed Phase	74	12
Primary Reason for Early Termination		
Intolerable Adverse Event ^a	4	0
Infection	1	0
System Related (Pump/Catheter)	2	0
Ineffective Drug Therapy/Loss of Effect	1	0

Data Source: Appendix 2, Table 1.1

[based on Table 7.24, page 57 of Dr. Hertz's review]

In addition, there were 20 protocol violations characterized by incorrect assignment into the second phases of the study. All 20 consisted of ziconotide non-responders who were entered into the Maintenance Phase.

- Ziconotide dosing requirements:

Dr. Hertz's Table 7.37, page 69 of her review, summarizes three of the secondary outcome measures initially defined as "subgroup analyses of the primary outcome variable" in the protocol. It has been modified and reproduced below:

Table 17.

Parameter	≤ 0.1 ug/hr	>0.1 ug/hr	Total
N	122	40	162
Dose Level at End of Initial Titration (ug/hr) ^a			
Median	0.400	0.920	0.469
Range	0.019 - 2.400	0.200 - 9.600	0.019 - 9.600
Cumulative Dose Received During Initial Titration (ug) ^b			
Median	45.68	99.6	51.44
Range	4.31-122.51	8.93 - 453.55	4.31 - 453.55
Dose Level at Onset of Analgesia (ug/hr) ^c			
Median	0.30	0.80	0.45
Range	0.00 - 2.40	0.00 - 9.60	0.00 - 9.60

a The last non-zero dose level administered during the initial titration phase was reported.

b The cumulative dose (ug) at end of initial titration phase with K distinct doses was estimated as: [dose level 1 (ug/h) x duration of dose level 1 (hours) + dose level 2 (ug/h) x duration of dose level 2 (hours) + ... + dose level K (ug/h) x duration of dose level K (hours)].

c Onset of analgesia was defined as when the percentage change in VASPI was >20% and the CPRS score was >-2 (i.e., at least a slight improvement). For patients who did not have onset of analgesia, the maximum dose level received during the initial titration phase was used.

Data Source: Appendix 2, Table 8. 1

The data in this table indicate that the patients treated under the earlier, more aggressive dosing regimens required more drug before achieving analgesia. This is not unexpected in light of the fact that for two out of the three earlier dosing regimens starting at greater than 0.1 µg/h and the full analgesic effect of any single dose may not have been achieved before the dose was increased to the next level, resulting in the administration of higher dosages and greater cumulative quantities of study drug.

- Change in VASPI score from baseline to the end of the Initial Titration Phase:

The table located on page 6 of Dr. Permutt's review summarizes and compares the results of this secondary efficacy analysis on the Initial Titration Phase performed on the entire study population and on the subjects treated under Revision 2, excluding those at the site. That table has been modified and reproduced below:

Table 18.

Population	Parameter	Rev2 without		Entire study	
		Ziconotide	Placebo	Ziconotide	Placebo
Evaluable	N	117	61	159	79
	Mean (SE)	23.8 (2.97)	5.1 (2.61)	25.4 (2.65)	5.2 (2.36)
	Median (range)	16.5 (-35-96)	1.0 (-36-61)	19.0 (-52-98)	1.0 (-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 (range)	17.5 (-35-96)	1.0 (-36-61)	19.5 (-52-98)	1.0 (-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)

- Percent change in McGill Pain Score from baseline to the end of the Initial Titration Phase:

The mean percent change in the McGill Pain Score was greater for the ziconotide treated patients (23.6) compared to the placebo treated patients (9.0). This difference was statistically significant with a p-value of 0.01.

- CPRS at the end of the Initial Titration Phase:

The following table summarizes the results from the CPRS:

Table 19.

Parameter	Ziconotide	Placebo	p-value
	N=162	N=79	
Category Pain Relief Scale			0.001
Worse	14 (8.6%)	10 (12.7%)	
No Change	55 (34.0%)	48 (60.8%)	
Slight Improvement	23 (14.2%)	7 (8.9%)	
Moderate Improvement	21 (10.3%)	1 (2.5%)	
A Lot of Improvement	34 (21.0%)	10 (12.7%)	
Complete Relief	5 (7.4%)	4 (5.1%)	

Data Source: Appendix 2, Tables 9.1, 10.1

[based on Table 7.34, page 66 of Dr. Hertz's review]

The differences remain statistically significant when the analysis is performed on the data set excluding the patients from the earlier dosing regimens and those treated at the site.

- WPBIS subsets from baseline to the end of the Initial Titration Phase:

Table 20.

Parameter	Ziconotide (N=162)	Placebo (N=79)	p-value
Change In WPBIS – Mood			0.003
Worsen By $\geq$ 2 Units	3 (1.9%)	5 (6.3%)	
Worsen By 1 Unit	13 (8.0%)	8 (10.1%)	
Unchanged	38 (23.5%)	32 (40.5%)	
Improved By 1 Unit	43 (26.5%)	18 (22.8%)	
Improved By $\geq$ 2 Units	47 (29.0%)	14 (17.7%)	
Missing	18 (11.1%)	2 (2.5%)	
Change In WPBIS – Walking Ability			0.044
Worsen By $\geq$ 2 Units	14 (8.6%)	2 (2.5%)	
Worsen By 1 Unit	20 (12.3%)	5 (6.3%)	
Unchanged	48 (29.6%)	27 (34.2%)	
Improved By 1 Unit	21 (13.0%)	22 (27.8%)	
Improved By $\geq$ 2 Units	34 (21.0%)	18 (22.8%)	
Missing	25 (15.4%)	5 (6.3%)	
Change In WPBIS – Sleep			0.001
Worsen By $>$ 2 Units	5 (3.1%)	2 (2.5%)	
Worsen By 1 Unit	18 (11.1%)	12 (15.2%)	
Unchanged	31 (19.1%)	40 (50.6%)	
Improved By 1 Unit	41 (25.3%)	15 (19.0%)	
Improved By $\geq$ 2 Units	50 (30.9%)	8 (10.1%)	
Missing	17 (10.5%)	2 (2.5%)	
Change In WPBIS – Enjoyment Of Life			0.010
Worsen By $\geq$ 2 Units	2 (1.2%)	2 (2.5%)	
Worsen By 1 Unit	14 (8.6%)	12 (15.2%)	
Unchanged	48 (29.6%)	30 (38.0%)	
Improved By 1 Unit	31 (19.1%)	18 (22.8%)	
Improved By $\geq$ 2 Units	47 (29.0%)	12 (15.2%)	
Missing	20 (12.3%)	5 (6.3%)	

Treatment difference was tested using the CMH row mean scores test controlling for center. The category 'missing' was excluded when calculating the p-value. Appendix 2, Table 10.1

[modified and reproduced from Table 7.27, page 60 of Dr. Hertz's review]

- Proportion of patients responding to ziconotide at the end of the Initial Titration Phase and at the end of the Crossover Phase:

The sponsor readjudicated the patients assessed as responders by the investigators based on review of the CRF's. The difference in the proportion of responders between the treatment groups was statistically significantly greater for the ziconotide treated subjects. Dr. Hertz's Table 7.36, page 68 of her review, summarizes those results and has been modified and reproduced below:

Table 21.

Parameter	Initial Treatment Assignment	
	Ziconotide (N=162)	Placebo (N=79)
Number of Responders (%)	54 (33.3%)	11 (13.9%)
Number of Nonresponder (%)	108 (66.7%)	68 (86.1%)
95% CI for Percent Responders	(26.1%, 40.6%)	(6.3%, 21.6%)
Treatment Difference in Percent Responder	19.4%	
95% CI for Treatment Difference in % Responder	(8.9%, 29.9%)	
p-value	0.002	

Data Source: Appendix 2, Tables 11.1 and s11.1

Sixteen of 61 patients crossed over from placebo to ziconotide met the criteria for responders. The responder rate during the Crossover Phase was comparable to that found in the Initial Titration Phase.

- Change in tactile allodynia parameters from baseline to the end of the Initial Titration Phase:

For the 33 evaluable patients in this analysis, 23 were in the ziconotide group and 10 were in the placebo group during the Initial Titration Phase. There was little overall change and no statistically significant difference between the groups ($p = 0.53$).

- For patients in Maintenance Phase: Percent change in VASPI and percent change in McGill Pain Score from baseline to study termination:

The percent change in VASPI at study termination was 61.8 for the ziconotide group and 37.9 for the placebo group. No data regarding the McGill Pain Score at study termination was provided by the sponsor.

- For patients in Crossover Phase: Percent change in VASPI from baseline to study termination:

This was an unblinded phase of the study. No inferential or descriptive statistics were discussed in the application.

- Percent change in opioid use from baseline to the end of the Initial Titration Phase:

While a few outlier values complicated the interpretation of this data (see Dr. Hertz's discussion on pages 68-69 of her review), regardless of the conditions of analysis, the ziconotide treated patients did not have a larger percent increase in opioid use than the placebo treated patients. With the outliers excluded, the ziconotide group demonstrated a small decrease in opioid use.

- Pain Classification and Syndrome:

Dr. Hertz's Table 7.32, page 65 of her review, summarizes this data and has been modified and reproduced below:

Table 22.

Parameter	Ziconotide		Placebo		p-value
	n	Mean (SE)	n	Mean (SE)	
Pain Syndrome					<0.001 (0.693) ^a
Central	64	28.2 (4.75)	32	7.3 (4.95)	
Peripheral	90	31.2 (4.97)	45	6.0 (4.48)	
Pain Classification					0.054 (0.353) ^a
Neuropathic	124	31.6 (3.70)	61	8.1 (3.76)	
Non-neuropathic	17	6.6 (14.23)	11	-1.7 (7.92)	

a Treatment difference was tested using the 2-way ANOVA with treatment, pain syndrome (pain classification) and treatment by pain syndrome (pain classification) interaction as factors. The p-value for treatment by pain syndrome (pain classification) interaction is presented in the parenthesis.

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

Note: Percent change = $100 \times (\text{VASPI at baseline} - \text{VASPI at end of initial titration}) / (\text{VASPI at baseline})$.

Positive values represent improvement in pain.

Data Source: Appendix 2, Tables 9.8 and 9.9

While there was not a statistically significant interaction for pain classification and treatment, the apparent treatment effect was larger for the neuropathic compared to the nonneuropathic pain patients. There was a statistically significant interaction for pain syndrome and treatment with peripheral pain apparently being more responsive to ziconotide than central pain.

Studies Supportive of Efficacy:

Only **Study 96-003** was appropriately designed to provide supportive data for the IT route of administration of ziconotide for the treatment of pain. In this pilot study, 30 patients undergoing elective orthopedic or pelvic surgery were enrolled and randomized, 12 to receive ziconotide 0.7 µg/h, 6 to receive ziconotide 7.0 µg/h, and 12 to receive placebo. Treatments were administered either by intrathecal catheter with an external pump for a period of up to 72 hours.

The primary efficacy outcome measures were the daily dose of PCA morphine equivalents and the average hourly use of PCA morphine equivalents. Secondary outcome variables were the VASPI and the CPRS. Intrathecal ziconotide appeared to be more effective than placebo with significantly less PCA morphine equivalents use from 24 to 48 hours after the start of the infusion. The high and low dose ziconotide groups approached a significant difference. The mean daily VASPI scores were lower or equal for the ziconotide treated patients throughout the infusion period.

Subgroup Analyses of Efficacy:

The two tables which follow were copied from the sponsor's electronic version of the study reports by Dr. Permutt and can be found in his review on pages 9 and 10:

Table 23.

[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

Table 24.

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

As can be seen from these tables, in Study 002, there is a marked difference between the less than 60 year old and greater than or equal to 60 year old patients, with the later being apparently less responsive to ziconotide. In Study 001, the results for the age-by-treatment effects are again large, but in the opposite direction. Women appeared to be more responsive to ziconotide than men in both studies. In addition, the small non-white population in each study appeared to be more responsive to placebo than ziconotide. These findings are difficult to interpret in light of the uncertainty of the overall efficacy results for the two studies, the contradictory findings in the age analyses, and the small populations available for analysis.

SAFETY:

The sponsor has submitted 20 clinical studies in support of safety: 9 IT, 7 intravenous and 4 epidural. Four of those studies (IT Studies 95-002 and 98-022; epidural studies 98-023 and 98-029) were ongoing at the time of the submission and data from them has been included in the 120-Day Safety Update. Dr. Hertz's Table 8.1, page 80 of her review, briefly summarizes the IT studies, three of which (95-001, 96-002 and 96-003) I have described above. The other six IT studies were uncontrolled, open-label safety and pharmacokinetic evaluations.

A total of 887 patients have been treated with ziconotide via the IT route of administration. Dr. Hertz's Table 9.1, page 129 of her review, summarizes the duration of treatment and cumulative dose exposure for the IT patients. It has been modified and reproduced below:

Table 25.

Duration of Treatment (Days) ^a	Number of Patients (N = 887)	Cumulative Dose of Ziconotide (ug)		
		Mean (SD)	Median	Range
0 to <30	445 (50.2%)	113.7 (279.9)	52.5	0.1-4625.0
30 to <90	203 (22.9%)	646.3 (2230.4)	302.1	64.8 - 30742.7
90 to <180	140 (15.8%)	1168.9 (1424.7)	729.0	122.0 - 8312.4
180 to <360	62 (7.0%)	2362.6 (3278.3)	1476.1	289.8 - 23749.7
≥360	37 (4.2%)	9731.6 (17282.6)	3889.5	918.9 - 80559.7

^a Each group is mutually exclusive.

Note: Includes all data in the database as of 21 February 2000 for Study 95-002 and 23 February 2000 for Study 98-022.

Studies include: 94-004, 95-001, 95-002, 96-002, 96-003, 96-010, 97-013, 97-015, and 98-022.

Data Source: Appendix 1, IT Table 1.7.

Dr. Hertz's Table 9.2, page 130 of her review, summarizes the mean duration of treatment, initial and final doses, and cumulative dose for the entire population of patients exposed to ziconotide to date. It has been modified and reproduced in part, below:

Table 26.

	Ever Received Ziconotide (N = 887)
Number of Days of Treatment^a	
Mean (PE)	91.49 (5.24)
Median (Range)	34.83 (0.06 - 1288.17)
Initial Dose Level Received (ug/hr)	
Mean (SE)	0.33(0.04)
Median (Range)	0.106 (0.004 - 10.000)
Last Dose Level Received (ug/hr)	
Mean (SE)	0.89(0.08)
Median (Range)	0.290 (0.001 - 38.100)
Cumulative Dose (ug)^b	
Mean (SE)	960.51 (142.88)
Median (Range)	196.67 (0.10 - 80559.65)

a Number of days while patients were receiving study drug.

b The cumulative ziconotide/placebo dose level was estimated by (dose level 1 x duration of dose level 1) +(dose level 2 x duration of dose level 2) + ... + (dose level K x duration of dose level K), if K distinct ziconotide infusions were received.

Note: Includes all data in the database as of 21 February 2000 for Study 95-002 and 23 February 2000 for Study 98-022

Studies include: 94-004, 95-001, 95-002, 96-002, 96-003, 96-010, 97-013, 97-015, and 98-022.

Data Source: Appendix 1, IT Table 3.1.

The average hourly dosing for all patients treated with IT ziconotide, excluding the new data from the 120-Day Safety Update, is summarized in Dr. Hertz's Table 5.6, page 14 of her review and has been modified and reproduced below. Dr. Hertz notes that, "There was no significant change in the average hourly dosing from the IT ISS and the 120 day safety update."

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Table 27.

		Ziconotide	
		Initial Dose ≤ 0.1 ug/h	Initial Dose > 0.1 ug/h
All patients	N	548	156
	Mean (SE)	0.42 ug/h (0.038)	1.78 ug/h (0.191)
	Median (Range)	0.24 ug/h (0.01 - 16.62)	0.74 ug/h (0.12 - 10.00)
Week 1	N	548	156
	Mean (SE)	0.27 ug/h (0.014)	1.82 ug/h (0.191)
	Median (Range)	0.17 ug/h (0.01 - 3.91)	0.76 ug/h (0.12 - 10.00)
Week 2	N	407	74
	Mean (SE)	0.33 ug/h (0.030)	0.84 ug/h (0.170)
	Median (Range)	0.20 ug/h (0.01 - 8.36)	0.46 ug/h (0.03 - 12.20)
Weeks 3 & 4	N	346	62
	Mean (SE)	0.43 ug/h (0.063)	0.57 ug/h (0.064)
	Median (Range)	0.24 ug/h (0.01 - 19.03)	0.38 ug/h (0.01 - 2.33)
Month 2	N	272	51
	Mean (SE)	0.45 ug/h (0.076)	0.63 ug/h (0.110)
	Median (Range)	0.24 ug/h (0.02 - 19.02)	0.36 ug/h (0.10 - 4.52)
Month 4	N	138	22
	Mean (SE)	0.49 ug/h (0.064)	0.66 ug/h (0.166)
	Median (Range)	0.23 ug/h (0.05 - 10.00)	0.29 ug/h (0.13 - 2.54)
Month 6	N	72	12
	Mean (SE)	0.42 ug/h (0.063)	0.90 ug/h (0.276)
	Median (Range)	0.25 ug/h (0.01 - 3.60)	0.39 ug/h (0.12 - 2.82)
Month 12	N	28	8
	Mean (SE)	0.33 ug/h (0.059)	1.23 ug/h (0.426)
	Median (Range)	0.23 ug/h (0.08 - 1.42)	0.77 ug/h (0.12 - 3.14)
Month 18	N	10	6
	Mean (SE)	0.32 ug/h (0.068)	1.28 ug/h (0.576)
	Median (Range)	0.27 ug/h (0.08 - 0.74)	0.64 ug/h (0.12 - 3.29)
Month 24	N	3	3
	Mean (SE)	0.30 ug/h (0.005)	2.32 ug/h (0.743)
	Median (Range)	0.30 ug/h (0.29 - 0.31)	2.80 ug/h (0.86 - 3.29)

Deaths:*Intrathecal Studies:*

Fifty-eight of the deaths reported in the ISS occurred in patients "ever" exposed to ziconotide. An additional 2 deaths in ziconotide exposed patients were reported in Appendix 6¹⁰ to the NDA. These 58 deaths represent an incidence of 8.2%. Thirty-five of the patients who died did so either while ziconotide was being infused or on the same day that the infusion was discontinued. Only 2 deaths occurred in patients who never

¹⁰ Appendix 6 included data from the period when the database was locked through submission of the NDA

received ziconotide, for an incidence of 4.5%. Of the 58 deaths in ziconotide treated patients reported in the body of the ISS, 51 (87.9%) occurred in patients with chronic malignant pain and 7 (12.1%) occurred in patients with chronic non-malignant pain.

Dr. Hertz reviewed the CRF's and narratives for the patients who died to determine if exposure to ziconotide might have been a direct or indirect cause of any of those deaths. For 20 of those patients, there was insufficient information make that assessment. Those 20 patients were all being treated for chronic malignant pain and their CRF's listed "progression of underlying cancer" as the cause of death.

Dr. Hertz found that for 33 of the patients who died, and for whom the narratives and CRF's suggested that ziconotide was non-contributory in those deaths, she was unable to definitively exclude ziconotide as having directly or indirectly contributed to the deaths. Her Table 8.2 (page 82 of her review) clusters those patients by the most proximate or serious adverse event described as occurring prior to the patient's death. Encephalopathy and respiratory failure are the most common of these adverse events, occurring in 8 and 6 out of 26 malignant pain patients and 0 and 0 out of 7 non-malignant pain patients, respectively.

In regard to the patients with *malignant pain*, the three examples [Patients: 100-101, 123-1181, and 5009-53] summarized by Dr. Hertz on pages 82 and 83 of her review are suggestive of deaths likely to be attributable to progression of underlying disease. However, Dr. Hertz was able to determine that 4 of the patients with malignant pain [Patients: 100-103, 200-202, 100-102, and 5007-79] were likely to have died due to causes other than exposure to study drug; and 2 other patients [Patients: 501-73 and 5032-74] might well have died, at least indirectly, due to exposure to ziconotide. Thus, it appears that 7 of the 33 indeterminate deaths were unlikely to be related to study drug, 2 may well have been related to exposure to study drug, and the remaining 17 remain obscure.

On reviewing Dr. Hertz's summary narratives (pages 83 and 84 of her review) on the 7 *non-malignant pain* patients who died, it appears as if 3 of those subjects [Patients 6055-104, 6066-103, and 6068-101] were likely to have died due to progression of underlying disease or toxicity due to medications given concomitantly with ziconotide. For the other 4 patients, the cause of death is less clearcut. Patients 91-1009, 122-1112 and 0661081 were all possible suicides. Patient 035-1276 was found dead and had no obvious cause of death.

Six more non-malignant pain patients died after the primary database was locked and were reported in the 120-Safety Update. Based on Dr. Hertz's summary narratives (page 131-132 of her review) on these 6 patients, it appears as if 3 of them [Patients: 6055-102, 157-1399 and 63-1485] were likely to have died of causes unrelated to ziconotide exposure. One patient [6093-105] died of cardiac arrest of unclear etiology. The other two patients [066-1441 and 172-1427] were found dead without a clearcut cause.

Epidural Studies:

Only 1 patient has died thus far during the Epidural Studies. That patient's death was believed to be due to peritonitis which developed after pelvic surgery for metastatic ovarian cancer.

Intravenous Studies:

Fifty-four out of 175 (31%) patients exposed to ziconotide compared to 21 out 125 (17%) patients exposed to placebo died in the IV studies. In the Traumatic Brain Injury studies, the majority of the patients died as a result of their head trauma as would be expected. Although not listed as the actual cause of death, except for 2 of the placebo patients and 1 ziconotide treated patient, hypotension (i.e. shock) was documented as an adverse event for 10 of these patients who had been treated with ziconotide and 1 of the placebo patients. Thus, 18% of the ziconotide treated patients who died had hypotension as an adverse event compared to 5% of the placebo treated patients.

Discontinuations:*Intrathecal:*

When the population of all patients studied in the IT trials is considered (inclusive of the new data from the 120-Day Safety Update), approximately 33% of the ziconotide treated patients compared to 6% of placebo patients were discontinued due to intolerable adverse events. Dr. Hertz reviewed narratives for these patients. Based on that review she determined that many of the adverse events leading to discontinuation had been misclassified or misattributed. Thus, she readjudicated the submitted information and found that the most frequent (> 5%) adverse events resulting in discontinuation from the study were (see Dr. Hertz's Table 8.13, page 94 of her review):

Encephalopathy*	26.4%
Multiple Adverse Events	12.0%
Nausea and/or Vomiting	5.4%

*including confusion , thinking abnormal, disorientation, somnolence, stupor

In the controlled clinical trials, 28% ziconotide treated patients and 16% placebo patients were discontinued due to adverse events. Dr. Hertz's Table 8.13, page 94 of her review, summarizes those events. The most frequent of the events occurring with significantly greater frequency in the ziconotide compared to the placebo treated patients were: encephalopathy (5% vs. 3%), dizziness (4% vs. 0), and nausea and/or vomiting (3% vs. 0).

Epidural:

Nine patients have discontinued the epidural studies due to adverse events. One of those patients had been treated with placebo. Of the ziconotide treated patients, one discontinued due to headache, paresthesias and leg pain, and was also listed as a serious adverse event. The other patients discontinued due to: hypotension (2), intractable pain (1), confusion (1), nausea (1), "nausea, vomiting and injection site pain" (1), and "somnolence, confusion, anxiety and nausea" (1).

Intravenous:

In the CABG studies, 88.5% of those receiving ziconotide completed the study. Only 1 patient discontinued early due to an adverse event, namely hypotension. Amongst the TBI patients, 50.9% of those receiving ziconotide completed the study. The incidence of death was high in both the ziconotide and placebo patients (29.7% and 14.4%, respectively). Four percent of the ziconotide treated patients discontinued due to intolerable adverse events, while 3.2% of the placebo patients discontinued for this reason.

The incidence of orthostatic hypotension appeared to be higher in the ziconotide treated patients; and clinically significant supine hypotension was seen in the study drug treated patients. This development program was discontinued due to the frequent occurrence of intolerable adverse events.

Serious Adverse Events:*Intrathecal:*

Serious adverse events occurred in 34% of all ziconotide treated patients and 12% of the placebo patients. The most common serious adverse events in the ziconotide treated patients were: confusion (4%), dizziness (2%), pneumonia (2%), and urinary retention (2%). The most common serious adverse events in the placebo patients were: myasthenia and ileus (1% each).

Dr. Hertz reviewed the listing of serious adverse events and found that similar adverse events were mapped to different COSTART terms; especially those attributable to the central nervous system. She chose to adjudicate the assignments, resulting in the sponsor's terms 'confusion', 'thinking abnormal', 'delirium', and 'amnesia', all being included under the umbrella term, 'encephalopathy.' Similarly, Dr. Hertz remapped the sponsor's terms 'nausea', 'vomiting', and 'nausea and vomiting' to the term 'nausea and/or vomiting.' The sponsor's 'gait abnormality', 'incoordination', cerebellar syndrome', and 'ataxia', were included under the term 'ataxia.' 'Motor weakness' and 'limb weakness' were remapped from 'myasthenia' to 'weakness.' Finally, 'suicidal

ideation' and 'suicidal gestures' were remapped from 'depression' to 'suicidal ideation/gesture.'

Based on her readjudication of the serious adverse events, Dr. Hertz found that 'encephalopathy' occurred with a greater frequency (6% vs. 1%) in the ziconotide treatment group. 'Nausea and/or vomiting' also occurred more often (2% vs. 0) in the ziconotide group.

Serious adverse events occurring in greater than or equal to 1% of patients separated by initial dosing regimen in the double-blind, placebo-controlled, pivotal trials are summarized in Dr. Hertz's Table 8.6, page 87-88 of her review, which has been modified and reproduced below:

Table 28.

COSTART Term	Ziconotide						Placebo	
	≤ 0.1 ug/h N= 166		> 0.1 ug/h N = 76		Total N = 242		Total N = 126	
Number of Patients with Any Event	25	15.1%	24	31.6%	49	20.2%	6	4.8%
Body as a Whole	2	1.2%	3	3.9%	5	2.1%	2	1.6%
Carcinoma of Lung	0	0.0%	2	2.6%	2	0.8%	0	0.0%
Cardiovascular System	3	1.8%	3	3.9%	6	2.5%	0	0.0%
Hypotension	1	0.6%	1	1.3%	2	0.8%	0	0.0%
Postural Hypotension	0	0.0%	2	2.6%	2	0.8%	0	0.0%
Digestive system	3	1.8%	2	2.6%	5	2.1%	0	0.0%
Nausea	0	0.0%	2	2.6%	2	0.8%	0	0.0%
Nervous System	14	8.4%	12	15.8%	26	10.7%	3	2.4%
Abnormal Gait	1	0.6%	1	1.3%	2	0.8%	0	0.0%
Confusion	2	1.2%	5	6.6%	7	2.9%	0	0.0%
Convulsion	3	1.8%	0	0.0%	3	1.2%	0	0.0%
Dizziness	5	3.0%	2	2.6%	7	2.9%	0	0.0%
Nystagmus	0	0.0%	2	2.6%	2	0.8%	0	0.0%
Somnolence	1	0.6%	2	2.6%	3	1.2%	0	0.0%
Respiratory System	3	1.8%	2	2.6%	5	2.1%	1	0.8%
Carcinoma of Lung	0	0.0%	2	2.6%	2	0.8%	0	0.0%
Dyspnea	2	1.2%	1	1.3%	3	1.2%	0	0.0%
Special Senses	4	2.4%	4	6.3%	8	3.3%	0	0.0%
Amblyopia	1	0.6%	2	2.6%	3	1.2%	0	0.0%
Urogenital System	3	1.8%	3	3.9%	6	2.5%	0	0.0%
Urinary Retention	3	1.8%	3	3.9%	6	2.5%	0	0.0%

Dr. Hertz readjudicated the serious adverse events for the controlled clinical trials as she had for the overall clinical population, as described above. Based on this remapping, she

found that 'encephalopathy' (4.5% vs. 0) and 'nausea and/or vomiting' (4.5% vs. 0) occurred with greater frequency in the ziconotide treated patients.

Epidural:

Thirteen out of the total number of 223 subjects (5.8%) experienced serious adverse events. Dr. Hertz's Table 8.26, page 121 of her review, summarizes those events. Only hypotension and GI hemorrhage have occurred more than once; and the blind remains intact for those patients.

Intravenous:

Supine and orthostatic hypotension during intravenous administration of ziconotide appeared to be dose related. There were 5 (19%) ziconotide treated patients and 1 (20%) placebo treated patient in the CABG studies who experienced serious adverse events. The most common of those was hypotension, occurring in 3 of the ziconotide treated patients.

The incidence of serious adverse events in the Phase 2 TBI studies was 41% for the ziconotide group and 28% for the placebo group. The TBI trials were discontinued due to the finding of an increased mortality rate in the ziconotide treated patients. Dr. Hertz's Table 8.30, page 125 of her review, summarizes the serious adverse events in those studies. The most frequent of those events occurring with significantly greater frequency in the ziconotide vs. the placebo treated patients were: hypotension (8% vs 2%), intracranial hypertension (6% vs. 2%), heart arrest (5% vs. 2%), and brain edema (3% vs. 0).

Other Adverse Events:

The most common adverse events for the "while receiving ziconotide" population were: dizziness (50.6%), nausea (44.9%), headache (29.7%), confusion (28.4%), and somnolence (22.3%). The only adverse events occurring in more than 20% of patients while being treated with placebo were nausea (20.5%) and headache (20.5%).

Dr. Hertz readjudicated the assignments of adverse event COSTART terms in some cases. Based on that remapping, she has summarized her findings in Table 8.15 on page 96 of her review. That table has been modified and reproduced below:

Table 29.

New Term	While Receiving Ziconotide (N=704)		While receiving Placebo (N=151)	
Agitation	36	(5.1%)	0	(0.0%)
Anxiety	69	(9.8%)	5	(3.3%)
Ataxia	220	(31.2%)	4	(2.6%)
Muscle Cramps	53	(7.5%)	3	(2.0%)
Depression	51	(7.2%)	1	(0.7%)
Dizziness	352	(50.0%)	14	(9.3%)
Encephalopathy	276	(39.2%)	10	(6.6%)
Nausea and/or Vomiting	357	(50.7%)	35	(23.2%)
Somnolence	157	(22.3%)	9	(6.0%)
Motor Weakness	81	(11.5%)	3	(2.0%)

Dr. Hertz's Table 8.16, pages 97-98 of her review, summarizes the common adverse events which occurred with the greatest frequency in the ziconotide patients. It has been modified and reproduced below:

Table 30.

COSTART Term	Ziconotide N = 242		Placebo N = 126		p-value
Number of Patients with Any Adverse Event	231	95.5%	91	72.2%	<0.0001 ^a
Body as a Whole	118	48.8%	44	34.9%	0.0117^b
Accidental Injury	6	2.5%	3	2.4%	
Asthenia	13	5.4%	4	3.2%	
Chest Pain	8	3.3%	3	2.4%	
Fever	32	13.2%	5	4.0%	0.0055 ^a
Headache	39	16.1%	26	20.6%	0.2737 ^b
Malaise	5	2.1%	0	0.0%	
Pain	23	9.5%	4	3.2%	
Cardiovascular System	69	28.6%	17	13.5%	0.0011^a
Hypertension	6	2.5%	2	1.6%	
Hypotension	17	7.0%	4	3.2%	
Postural Hypotension	37	15.3%	7	5.6%	0.0063 ^a
Tachycardia	5	2.1%	1	0.8%	
Digestive System	156	64.5%	44	34.9%	<0.0001^b
Anorexia	10	4.1%	1	0.8%	
Constipation	40	16.5%	16	12.7%	0.3361 ^b
Diarrhea	15	6.2%	6	4.8%	
Nausea	104	43.0%	24	19.0%	<0.0001 ^b
Nausea and Vomiting	19	7.9%	3	2.4%	
Vomiting	37	15.3%	7	5.6%	0.0063 ^a
Metabolic and Nutritional System	13	5.4%	3	2.4%	
Musculoskeletal System	24	9.9%	2	1.6%	
Myasthenia	20	8.3%	2	1.6%	

Table 30. (continued)

COSTART Term	Ziconotide N = 242		Placebo N = 126		p-value
Nervous System	204	84.3%	49	38.9%	<0.0001^b
Abnormal Gait	56	23.1%	3	2.4%	<0.0001 ^a
Agitation	5	2.1%	1	0.8%	
Amnesia	7	2.9%	0	0.0%	
Ataxia	19	7.9%	2	1.6%	
Confusion	35	14.5%	7	5.6%	0.0097 ^a
Dizziness	127	52.5%	17	13.5%	<0.0001 ^a
Hypertonia	12	5.0%	2	1.6%	
Incoordination	10	4.1%	0	0.0%	
Insomnia	15	6.2%	2	1.6%	
Nervousness	15	6.2%	3	2.4%	
Nystagmus	101	41.7%	15	11.9%	<0.0001 ^a
Paresthesia	12	5.0%	4	3.2%	
Reflexes Decreased	5	2.1%	1	0.8%	
Somnolence	38	15.7%	7	5.6%	0.0042 ^a
Speech Disorder	10	4.1%	3	2.4%	
Thinking Abnormal	9	3.7%	0	0.0%	
Twitching	5	2.1%	1	0.8%	
Withdrawal Syndrome	5	2.1%	2	1.6%	
Vertigo	12	5.0%	0	0.0%	
Respiratory System	29	12.0%	12	9.5%	0.4407^b
Dyspnea	10	4.1%	4	3.2%	
Lung Disorder	5	2.1%	0	0.0%	
Rhinitis	5	2.1%	0	0.0%	
Skin and Appendages	31	12.8%	13	10.3%	0.6118^a
Sweating	10	4.1%	4	3.2%	
Special Senses	57	23.6%	6	4.8%	<0.0001^a
Abnormal Vision	14	5.8%	0	0.0%	
Amblyopia	22	9.1%	2	1.6%	
Diplopia	12	5.0%	0	0.0%	
Photophobia	5	2.1%	0	0.0%	
Taste Perversion	5	2.1%	0	0.0%	
Urogenital System	66	27.3%	8	6.3%	<0.0001^a
Urinary Incontinence	6	2.5%	1	0.8%	
Urinary Retention	40	16.5%	2	1.6%	<0.0001 ^a
Urinary Tract Infection	10	4.1%	0	0.0%	
Urination Impaired	13	5.4%	3	2.4%	

a Treatment difference is tested using Fishers Exact Test.

b Treatment difference is tested using the CMH general association test controlling for study.

Studies include: 95-001 and 96-002.

Data Source: Appendix I, IT Table 4.2.

Of note are the numerous adverse events occurring with an increased clinical and/or statistical frequency in the ziconotide treated patients, many of which are effects on the central, and possibly autonomic, nervous system. Dr. Hertz readjudicated the

assignments of adverse event COSTART terms in some cases. Based on that remapping, she has summarized her findings in Table 8.17 on page 98 of her review. That table has been modified and reproduced below:

Table 31.

New Term	While Receiving Ziconotide (N=242)	While receiving Placebo (N=126)
Ataxia	84 (34.7%)	5 (4.0%)
Muscle Cramps	13 (5.4%)	2 (1.6%)
Encephalopathy	49 (20.2%)	9 (7.1%)
Nausea and/or Vomiting	127 (52.5%)	29 (23.0%)

In her Table 8.18, pages 99 of her review, Dr. Hertz has summarized the data on the incidence of the more common adverse events (occurring in at least five ziconotide treated patients) at various cumulative ziconotide doses. That table has been modified and reproduced below:

Table 32.

Cumulative Dose	Ziconotide									
	≤ 4 ug		> 4 and ≤ 9.72 ug		> 9.72 and ≤ 20.49 ug		>20.49 and ≤ 44.55 ug		> 44.55 ug	
	N = 242		N = 241		N = 234		N = 211		N = 138	
COSTART Term	N	%	N	%	N	%	N	%	N	%
Patients with Any Event	112	46.3%	123	51.0%	134	57.3%	120	56.9%	89	64%
Digestive System	48	19.8%	49	20.3%	33	14.1%	48	22.7%	31	22%
Vomiting	7	2.9%	5	2.1%	10	4.3%	5	2.4%	11	8%
Nervous System	51	21.1%	80	33.2%	86	36.8%	74	35.1%	67	49%
Abnormal Gait	2	0.8%	9	3.7%	12	5.1%	21	10.0%	15	11%
Ataxia	1	0.4%	3	1.2%	2	0.9%	4	1.9%	9	7%
Confusion	5	2.1%	5	2.1%	5	2.1%	8	3.8%	13	9%
Nystagmus	13	5.4%	16	6.6%	27	11.5%	24	11.4%	27	20%
Special Senses	12	5.0%	16	6.6%	10	4.3%	13	6.2%	12	9%
Abnormal Vision	1	0.4%	2	0.8%	2	0.9%	3	1.4%	6	4%
Amblyopia	4	1.7%	2	0.8%	7	3.0%	5	2.4%	4	3%
Urogenital System	7	2.9%	12	5.0%	17	7.3%	21	10.0%	15	11%
Urinary Retention	5	2.1%	6	2.5%	11	4.7%	14	6.6%	5	4%

In her Table 8.19, page 100 of her review, Dr. Hertz summarizes the most frequent adverse events (occurring in at least 5% of the patients receiving ziconotide) by starting dose subgroups and less than or equal to 0.1 µg/h and greater than 0.1 µg/h. That table has been modified and reproduced below:

Table 33.

COSTART Term	≤0.1 ug/h (N = 166) ^a		> 0.1 ug/h (N = 76) ^a	
Number of Patients with Any Event	157	94.6%	74	97.4%
Body as a Whole	73	44.0%	45	69.2%
Asthenia	6	3.6%	7	9.2%
Fever	16	9.6%	16	21.1%
Cardiovascular System	42	25.3%	27	35.5%
Postural Hypotension	20	12.0%	17	22.4%
Musculoskeletal System	12	7.2%	12	15.8%
Nervous System	140	84.3%	64	84.2%
Confusion	18	10.8%	17	22.4%
Hypertonia	11	6.6%	1	1.3%
Vertigo	11	6.6%	1	1.3%
Respiratory System	16	9.6%	13	17.1%
Lung Disorder	0	0.0%	5	6.6%
Urogenital System	40	24.1%	26	34.2%
Urinary Retention	22	13.3%	18	23.7%
Urinary Tract Infection	4	2.4%	6	7.9%
Urination Impaired	13	7.8%	0	0.0%

^a Represents the number of patients who had study drug initiated at that dose level.

Note: Body system totals include all patients with adverse events of the specified body systems, as listed in Appendix 1, IT Table 6.3, not solely those presented in this table.

Studies include: 95-001 and 96-002. Data Source: Appendix 1, IT Table 6.3.

Of further interest, while most adverse events occurred within the first 30 days of treatment, hallucinations occurred more frequently at 30 to 90 days. For patients treated for greater than 3 months, again the majority of the adverse events occurred within the first 30 days. However, asthenia, confusion, depression, hallucinations, abnormal thinking and taste perversion occurred more frequently after one month of treatment. Increased salivation, stomatitis, tooth disorders, tongue disorders, delirium, hostility, manic reaction, neurosis and personality disorder all occurred, at least one time for the first time, after 3 months of treatment.

Ten cases of overdose of intrathecal ziconotide resulted in predominantly CNS symptoms as is documented in Dr. Hertz's Table 8.21, page 95 of her review. While meningitis did occur frequently in the ziconotide treated patients (~30/887 = 3%), most of the patients who contracted CSF infections had external pumps.

During her review of the laboratory data, Dr. Hertz noted a possibly excessively high incidence of elevated CPK serum levels (see further discussion under Laboratory Values,

below). Based on this finding, she undertook an analysis looking for evidence of a drug related myopathic process. However, the limited number of patients with CPK elevations for whom narratives were available, limited the value of this analysis.

Dr. Hertz also became concerned about the frequent occurrence of an apparent encephalopathic process in the ziconotide treated patients. She found that 100 out of the 887 (11%) patients ever exposed to ziconotide discontinued from a study early due to an adverse event of Encephalopathy. Twenty-two patients discontinued due to hallucinations, depression/suicidal ideation, anxiety, psychosis/bizarre behavior, or hostility. Review of Dr. Hertz's brief narrative summaries for 18 patients with this encephalopathic syndrome (pages 113 through 115 of her review) certainly support her hypothesis that it is a drug related toxicity, with the majority of the events resolving with discontinuation of study drug.

Laboratory Values:

While she was unable to document evidence of a drug associated myopathy, Dr. Hertz did carefully review the CPK data and has summarized that data in Table 8.23, page 116, of her review. That table has been modified and reproduced below:

Table 34.

	While on Ziconotide N=1046	While on Placebo N=151
Normal at onset, increased during infusion	212 (20.2%)	18 (11.9%)
Increased to >189 IU/L, <600 IU/L	169 (16.2%)	12 (7.9%)
Increased to >600 IU/L	43 (4.1%)	5 (3.3%)
Elevated at onset (>189 IU/L), increased during infusion	52 (5.0%)	1 (0.01%)
Increased to <600 IU/L	27 (2.6%)	1 (0.7%)
Increased to >600 IU/L	25 (2.4%)	0
Elevated at onset (>189 IU/L), decreased during study	34 (3.3%)	10 (6.6%)

Source: Appendix 2, IT listing 7.2.11 (Vol. 5.36)

The consistently higher incidence of elevations in the ziconotide treated patients raises the possibility of an undefined toxicity manifesting as a myopathic process.

When Dr. Hertz looked at change in creatinine, she found that 3.7% of the ziconotide treated patients and 1.3% of placebo treated patients experienced an increase in serum creatinine of at least 0.3 (and above 1.2 mg/dl), supporting the need for possible further evaluation and routine monitoring of renal function.

No other laboratory abnormalities were found to be more common or excessively abnormal in the ziconotide treated patients.

Vital Signs:

Dr. Hertz's review of the vital sign and EKG data in the application documented that no abnormalities were found to be more common or of particular clinical concern in the ziconotide compared to the placebo treated patients.

COMMENTS:

The sponsor has submitted two placebo-controlled trials as evidence of effectiveness of ziconotide in the treatment of chronic, malignant and non-malignant pain. These two trials, performed in two different patient populations, initially appeared to document effectiveness of the product when administered as a regimen involving titration to tolerability or effect. However, the high incidence of serious adverse events suggestive of CNS toxicity would have diminished the value of ziconotide even in the setting of exquisite effectiveness. As the dosing regimens were changed in the course of the trials in response to toxicity, it became apparent during the Division's review that the data from the earlier dosing regimens could not be used to support an analysis of effectiveness. Not only were these earlier regimens discontinued due to the intolerable adverse events associated with administration of the drug at those levels, but the sponsor had included dosing recommendations in the package insert which were based only on the final, lower and slower dosing regimens.

Additional data in these studies were found to be unacceptable when a field investigation of one study site, used in both studies, documented irregularities strongly suggestive of unblinding which may have compromised the integrity of the data. When a reanalysis of the primary outcome measure was performed on the two pivotal efficacy trials, the findings of a statistically significant treatment effect for ziconotide persisted in the non-malignant pain study (96-002); but the treatment effect in the malignant pain study (95-001) no longer reached statistical significance. While a borderline p-value of 0.058 resulted for the analysis of Study 95-001 when it was performed using the data from the Evaluable population, the p-value resulting from the same analysis on the ITT population was clearly unacceptable ($p = 0.080$).

Data acceptable for evaluation of efficacy from the secondary outcome measures was limited by a high incidence of significant protocol violations, and the fact that the limited study population described above was not used in a reanalysis of most of these endpoints. The protocol violations in question were of notable concern, both in relation to the safety and effectiveness of ziconotide: i.e., for both studies, the investigators had difficulty in assessing responsiveness to study drug.

Analyses of subgroup data only added to the apparent inadequacy of the sponsor's development plan for ziconotide. Variation in effect was seen by age, race and sex. While the numbers were small and the statistical reliability unclear, an interaction cannot be ruled out. While some indication of an increased effect for peripheral, neuropathic pain was found in Study 96-002, the neuropathic pain patients in Study 95-001 did not have a statistically significant treatment effect.

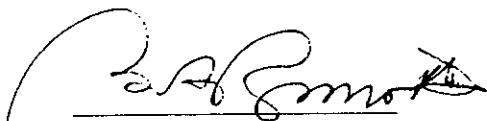
The apparent safety profile of ziconotide may be somewhat inaccurate due to the sponsor's use of inadequately defined dosing regimens in their large clinical trials. Certainly, a dose effect for toxicity has been documented. The most common (5 - 40%), and potentially concerning toxicity seen in the intrathecal studies, encephalopathy, appears to be a delayed effect and may be associated with cumulative exposure. The incidence of death during the intrathecal clinical development program was twice as high for the ziconotide treated patients compared to the placebo treated patients. The incidence of serious adverse events appears to be at least three times as high in the ziconotide treated patients; and patients receiving ziconotide were twice as likely to have discontinued from the intrathecal studies. Increased frequencies of nausea and vomiting, multiple CNS toxicities, hypotension, urinary retention, CPK elevations, and elevations in serum creatinine, have not been adequately explored or addressed.

The sponsor has recommended a dosing regimen not supported by data documenting that it is safe and effective. This application offers some suggestion that ziconotide provides analgesia for chronic, malignant and non-malignant pain. However, how to achieve an adequate level of analgesia, in a variety of populations, while avoiding significant toxicity, has not been adequately characterized. The data that have been included in this application have been collected, analyzed and presented in a rather careless and casual manner; and much of the data that would have been necessary in order to clearly and accurately define the safety and effectiveness profiles of the product have not even been carefully delineated.

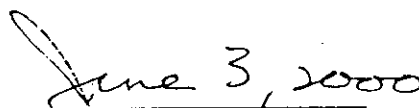
The fact that the sponsor was unable to replicate effectiveness may have been due to loss of power to detect an effect, an inappropriate patient population, or a general lack of care in the performance of the studies. However, one cannot rule out the possibility that ziconotide is simply not effective in the setting of malignant pain. While the sponsor will no doubt argue that effectiveness was established in the patients treated under the earlier dosing regimens in that study, that efficacy was achieved at the cost of intolerable toxicity. Without an adequate characterization of the dose/effect and dose/toxicity responses, this product cannot safely be used to treat even the most stable patient. While this Division is well aware of the need for novel, potent analgesic products to treat the large group of patients with intractable chronic pain and/or intolerable side effects from their opioid analgesics, that, in and of itself, is not a sufficient excuse for approving a potentially dangerous product which has been inadequately evaluated. The risk of a patient with an implanted intrathecal pump being sent home and developing serious CNS toxicity clearly outweighs the questionable effectiveness which has been demonstrated for this product.

RECOMMENDATIONS:

I concur with Dr. Hertz that this application should not be approved.



Bob A. Rappaport, M.D.



June 3, 2000
June 3, 2000

Cc: Original NDA 21-060
HFD-170: Division File
HFD-170:
McCormick
Rappaport
Hertz
Permutt
Grosser
Kim
Brase
Theodorakis
Governale

Ziconotide
NDA 21-060

NDA: 21-060

Drug Name: Ziconotide

Trade Name: N/A

Formulation: Solution For Intrathecal Infusion

Sponsor: Elan Pharmaceuticals

Type of Submission: New Drug Application

Date of Submission: 12/28/99

Date of Receipt: 12/28/99

Date Review Completed: 6/2/00

Reviewer: Sharon Hertz, M.D.

**Appears This Way
On Original**

TABLE OF CONTENTS

SECTION 1.0 MATERIALS UTILIZED IN REVIEW	5
SECTION 1.1 MATERIALS FROM NDA/IND.....	5
SECTION 1.2 RELATED REVIEWS AND CONSULTS	5
SECTION 1.3 OTHER RESOURCES.....	6
SECTION 2.0 BACKGROUND.....	6
SECTION 2.1 INDICATION	6
SECTION 2.2 RELATED INDS.....	7
SECTION 2.3 REGULATORY HISTORY.....	7
SECTION 3.0 CMC.....	8
SECTION 4.0 PRECLINICAL TOXICOLOGY AND PHARMACOLOGY	9
SECTION 5.0 CLINICAL DATA SOURCES	10
SECTION 5.1 INTRATHECAL CLINICAL INVESTIGATIONS	11
SECTION 5.1.1 DESCRIPTION OF CLINICAL STUDIES - IT.....	11
SECTION 5.1.2 DEMOGRAPHICS - IT.....	11
SECTION 5.1.3 EXTENT OF EXPOSURE -IT.....	12
SECTION 5.2 OTHER SOURCES.....	15
SECTION 5.2.1 EPIDURAL CLINICAL INVESTIGATIONS	15
SECTION 5.2.1.1 Description Of Studies - ED	15
SECTION 5.2.1.2 Demographics - ED.....	16
SECTION 5.2.1.3 Extent Of Exposure -ED.....	17
SECTION 5.2.2 INTRAVENOUS CLINICAL INVESTIGATIONS	17
SECTION 5.2.2.1 DESCRIPTION OF STUDIES - IV.....	18
SECTION 5.2.2.2 Demographics and Baseline Characteristics - IV.....	19
SECTION 5.2.2.3 Extent of exposure - IV.....	19
SECTION 6.0 HUMAN PHARMACOKINETICS AND PHARMACODYNAMICS.....	20
SECTION 7.1 OVERVIEW OF CLINICAL STUDIES.....	22
SECTION 7.2 SUMMARY OF STUDIES PERTINENT TO EFFICACY.....	22
SECTION 7.2.1 STUDY 95-001.....	22
SECTION 7.2.1.1 Protocol Synopsis.....	22
SECTION 7.2.1.2 Statistical Analysis:.....	26
7.2.1.2.1 Patient Populations:.....	26
7.2.1.2.2 Planned Analyses:.....	27
SECTION 7.2.1.3 Protocol Amendments:.....	28
SECTION 7.2.1.4 Results.....	29
7.2.1.4.1 Conduct of study:.....	29
7.2.1.4.2 Disposition:.....	31
7.2.1.4.3 Unplanned Analyses Include.....	33
7.2.1.4.4 Baseline Characteristics.....	33
7.2.1.4.5 Sponsor's Efficacy Results.....	37
7.2.1.4.6 Reviewer's Efficacy Summary:.....	46
SECTION 7.2.2 STUDY 96-002.....	47
SECTION 7.2.2.1 Protocol Synopsis.....	47
SECTION 7.2.2.2 Statistical Analysis:.....	50
7.2.2.2.1 Patient Populations:.....	50
7.2.2.2.2 Planned Analyses:.....	51
SECTION 7.2.2.3 Protocol Amendments:.....	52

SECTION 7.2.2.4	Results	53
7.2.2.4.1	Conduct of study	53
7.2.2.4.2	Disposition	55
7.2.2.4.3	Unplanned Analyses	57
7.2.2.4.4	Demographic and Baseline Characteristics	57
7.2.2.4.5	Sponsor's Efficacy Results	61
7.2.2.4.6	Reviewer's Efficacy Summary	70
SECTION 7.2.3	STUDY 96-003	70
SECTION 7.2.3.1	Protocol Synopsis	70
SECTION 7.3	ADDENDUM	71
SECTION 7.4	COMPARISON OF STUDIES 95-001 AND 96-002	74
SECTION 8.0	SAFETY FINDINGS	79
SECTION 8.1	METHODS:	79
SECTION 8.2	INTRATHECAL CLINICAL INVESTIGATIONS	79
SECTION 8.2.1	DEATHS - IT	81
SECTION 8.2.2	SERIOUS ADVERSE EVENTS - IT	85
SECTION 8.2.3	DISPOSITION - IT	88
SECTION 8.2.3.1	Adverse Events Leading To Discontinuation - IT	92
SECTION 8.2.4	ADVERSE EVENTS - IT	95
SECTION 8.2.4.1	Overall Adverse Events	95
SECTION 8.2.4.2	Adverse Events By Cumulative Dose	98
SECTION 8.2.4.3	Adverse Events By Initial Dose	99
SECTION 8.2.4.4	Time To First Occurrence Of AE	100
SECTION 8.2.4.5	Adverse Events by Subgroup	101
SECTION 8.2.4.6	Overdoses	102
SECTION 8.2.5	ADVERSE EVENTS OF SPECIAL INTEREST -IT	103
SECTION 8.2.6	CLINICAL LABORATORY EVALUATIONS - IT	115
SECTION 8.3	EPIDURAL ISS	119
SECTION 8.3.1	DEATHS -ED	120
SECTION 8.3.2	SERIOUS ADVERSE EVENTS - ED	120
SECTION 8.3.3	DISPOSITION - ED	121
SECTION 8.3.3.1	Adverse Events leading to study discontinuation - ED	121
SECTION 8.3.3.2	Other dropouts - ED	121
SECTION 8.3.4	ADVERSE EVENTS - ED	122
SECTION 8.3.5	CLINICAL LABORATORY EVALUATIONS - ED	122
SECTION 8.4	INTRAVENOUS ISS	123
SECTION 8.4.1	DEATHS - IV	123
SECTION 8.4.2	SERIOUS ADVERSE EVENTS - IV	124
SECTION 8.4.3	PATIENT DISPOSITION - IV	126
SECTION 8.4.3.1	Adverse Events Leading To Study Discontinuation - IV	127
SECTION 9.0	120-DAY SAFETY UPDATE	129
SECTION 9.1	INTRATHECAL STUDIES	129
SECTION 9.1.1	DEMOGRAPHICS - IT	129
SECTION 9.1.2	PATIENT EXPOSURE - IT	129
SECTION 9.1.3	DEATHS	130
SECTION 9.1.3.1	Suicide	132
SECTION 9.1.4	PATIENT DISPOSITION	132
SECTION 9.1.5	SERIOUS ADVERSE EVENTS	133
SECTION 9.1.6	ADVERSE EVENTS	133
SECTION 9.2	EPIDURAL STUDIES	134

SECTION 9.3 INTRAVENOUS STUDIES 134
SECTION 10.0 CONCLUSIONS 134
SECTION 11.0 RECOMMENDATIONS AND REVIEWER SIGNATURE 136

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On Original**

SECTION 1.0 MATERIALS UTILIZED IN REVIEW

1. NDA 21-060 submission 12/28/99
2. IND 45,718 submitted by Neurex Corporation, assumed by Elan Pharmaceutical Corporation
3. ~~_____~~
4. Transcript of the Anesthetic And Life Support Drugs Advisory Committee- March 24, 1997
5. Case report forms from all studies submitted to the NDA.
6. The following responses to requests for information:

Date of submission	Date received	Description
2/18/00	2/22/00	Response to request for additional information in paper and electronic format.
3/22/00	3/23/00	Response to information requested during teleconference on 3/10/00.
3/31/00	4/3/00	Missing case report tabulations in print and in electronic format for Study C96-003; 10 volumes
4/6/00	4/7/00	Response to clinical questions faxed to sponsor on 4/4/00
4/17/00	4/18/00	Response to request for reanalysis of primary and secondary efficacy variables for patients treated under final protocol revision for 95001 and 96002
4/20/00	4/24/00	Response to information on QA monitoring, overall conduct of studies
4/20/00	4/21/00	Submission of SAS transport data from prior request for data reanalysis, 89 volumes
4/24/00	4/25/00	Submission of the 120-day safety update in paper and electronic format, data and Case Report Forms; Medtronic 120-day safety Update
5/10/00	5/10/00	Response to request for clarification of discrepancy in number of meningitis cases reported

SECTION 1.1 MATERIALS FROM NDA/IND

The NDA submission consists of 775 volumes containing the preclinical and clinical data. Included as part of the clinical materials are summaries and data listings for 20 clinical studies; 9 intrathecal, 7 intravenous and 4 epidural.

Clinical trial reports from the individual trials were submitted as MS Word files. Case report forms for the subjects experiencing serious adverse events, deaths and adverse events leading to study discontinuation and case report form tabulations were submitted in print and as SAS transport files.

SECTION 1.2 RELATED REVIEWS AND CONSULTS

A microbiology consult was obtained. Please refer to the chemistry review for details.

SECTION 1.3 OTHER RESOURCES

SECTION 2.0 BACKGROUND

Ziconotide is a synthetic equivalent of a naturally occurring peptide found in the venom of the piscivorous marine snail, *Conus magus*. It is hydrophilic and freely soluble in water and is formulated as a sterile, preservative free, isotonic solution, with a pH of 4.0-5.0.

Ziconotide represents a novel approach to analgesia. Ziconotide is a neuron specific calcium channel blocker (N-type VSCC) that crosses the blood brain barrier. The mechanism of analgesic action of ziconotide is the selective blockade of N-type VSCCs which are found in highest density within the substantia gelatinosa of the spinal cord. It is believed that they control calcium fluxes necessary for depolarization induced neurotransmitter release. Specific binding sites for ziconotide have been found in the superficial laminae of the dorsal horn of the rat spinal cord, the site of primary nociceptive afferent synapses. Ziconotide had no opioid features and does not block or potentiate opioid effects. This mechanism for analgesia contrasts that of opioid induced analgesia which is attributed to the suppression of signal conduction by slow hyperpolarization of projection neurons.

The ability of ziconotide to cross the BBB and inhibit the cycle of calcium influx, neurotransmitter release and calcium accumulation that leads to cell death. However, ziconotide also has a profound sympatholytic effect which is felt to be due to its blockade of the N-type VSCC which prevents norepinephrine release from the presynaptic nerve terminal. This sympatholytic effect results in a profound hypotension has limited the usefulness of systemically administered ziconotide and resulted in a termination of the clinical trials of ziconotide to investigate its neuroprotective effects in _____

The early development plan for ziconotide included intrathecal administration for the management of chronic pain, epidural administration for short term acute pain and intravenous administration for neuroprotection. Cerebral ischemia during coronary artery bypass graft surgery and severe traumatic brain injury were the clinical models used to evaluate the neuroprotective effects.

SECTION 2.1 INDICATION

The sponsor proposes ziconotide by the intrathecal route for, "the management of severe, chronic pain in patients for whom intraspinal therapy is warranted." (Vol. 2.1, P. 077)

SECTION 2.2

RELATED INDS

The IND under which ziconotide was studied for the management of pain, by intrathecal route under IND 45,718

IND No.	Initial IND Submission	IND Holder	Status	Route	Indication
45,718	6/30/94	Elan Pharmaceuticals	Active	Intrathecal	Pain

SECTION 2.3

REGULATORY HISTORY

The original IND for ziconotide, 45,718, was filed 6/30/94 by Neurex Corporation, for use in the management of severe, chronic pain in patients

Neurex was acquired by Elan Corporation in August of 1998. The production of the drug product was changed to with an IND amendment (serial no. 168) in August of 1999. In that same month, another IND amendment (serial no. 172) changed the diluent from a custom product to commercially available normal saline.

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SECTION 3.0 CMC

Ziconotide is the synthetic equivalent of a 25 amino acid, polybasic peptide found in the venom of the piscivorous marine snail *Conus magus*. It has been developed as a new chemical entity by Elan Pharmaceuticals. The chemical name is ω -conotoxin MVIIA.

Ziconotide is a white powder that is soluble in water. _____

The drug product, Ziconotide Solution, Preservative Free, contains 0.1 mg/ml of ziconotide in an isotonic saline solution containing L-methionine as an antioxidant. The drug product is supplied in single dose, 2, 5, _____ ml _____ vials. There are both 1 and 2 ml volumes available. _____ Sodium _____ are used to adjust the pH.

The sponsor proposes that ziconotide is compatible with approved, commercially available, implantable infusion pumps and extracorporeal pumps. In particular, ziconotide stability and recovery from pumps as a function of time at room temperature or _____ as appropriate, using drug product held for _____ months at recommended storage conditions. Ziconotide diluted with sodium chloride remains stable within _____ of the initial concentration 0, _____ days in ziconotide naïve pumps and _____ days in previously ziconotide exposed pumps when starting with the _____ concentration. The 25 ug concentration remains within specifications for 14 days in ziconotide naïve pumps and >30 days in ziconotide exposed pumps.

Based on preliminary findings of the chemistry review for this NDA, there are several outstanding issues. It is not clear that the shelf lives proposed for the different volume vials are fully supported by data available at this time. The stability data did not include results of the binding assay for the peptide as well as total impurities. The microbiology consultation suggested nonapproval for this product. Reference to the full Chemistry review is suggested for further detail.

SECTION 4.0 PRECLINICAL TOXICOLOGY AND PHARMACOLOGY

There were numerous preclinical studies of ziconotide. The preclinical pharmacology explored the effects of ziconotide by intracerebroventricular (ICV), intravenous (IV), intrathecal (IT), subcutaneous (SQ) and intraperitoneal (IP) routes. Dose dependent tremors were exhibited in rodents and dogs of central origin that was reversible following cessation of treatment and abated at times with continued treatment. In rats, IV administration was able to produce a dose dependent hypotension due at least in part to sympatholysis and not found with IT or oral administration. Intraperitoneal and subcutaneous administration produced less hypotension than IV. The hypotension following IV infusion responded to pressors. Dogs appeared less susceptible to the hypotension. There was inhibition of GI motility in the rat by IV route.

There was dose dependent analgesia following IT, ICV and IV administration in most rat pain models but with variable effect in mechanical allodynia models. There was also a reduction of joint inflammation and paw inflammation following intra-articular, IV and SQ administration. A neuroprotective effect was demonstrated following IV and ICV administration in several rodent models. No cross tolerance with morphine was found in rat models.

Second degree AV block was noted in two dog studies (6 of 16 in study CTBR 54156, 1 out of 10 in study CTBR 55068).

Ziconotide was variably antigenic in systemic anaphylaxis assays in guinea pigs.

Reproductive toxicology studies in rats revealed a NOAEL for reproductive performance at 0.125 mg/kg/h, but higher doses did result in retarded ossification of the pelvic girdle. There was no teratogenicity in rabbits. Maternal toxicity was demonstrated at 0.19 mg/kg/h and higher.

Genotoxicity studies with the Ames assay, mouse lymphoma assay, mouse micronucleus assay and SHE cell assay were negative.

In summary, ziconotide produced analgesia in a wide variety of animal pain models by multiple routes of administration. Ziconotide reduced inflammatory edema by systemic and local routes, but not by the IT route. Ziconotide demonstrated a neuroprotective effect by IT, ICV and IV routes in central and peripheral nerve injury models. Other than a characteristic shaking behavior felt to be centrally mediated, the only other major organ system effect demonstrated was systemic hypotension. Abuse liability and physical dependence in *in vitro* and *in vivo* models predict ziconotide is not likely to have abuse or physical dependence potential.

SECTION 5.0 CLINICAL DATA SOURCES

The sponsor has submitted 20 clinical studies; 9 intrathecal, 7 intravenous and 4 epidural. Sixteen studies were completed as of the ISS cut off date. Data from 2 ongoing intrathecal studies were submitted, for study 95-002 through 4/30/99 and for study 98-022 through 9/9/99. For ongoing epidural studies, 98-023 and 98-029, data through 9/9/99 was included. Deaths and serious adverse events (SAE's) reported after the cutoff dates through 12/1/99 were submitted in Appendix 6.

As of the cutoff dates, 1341 unique patients were administered ziconotide and/or placebo. Of these, 704 patients were exposed to intrathecal ziconotide. Ninety one were still blinded at the time of preparation of this ISS. The disposition of these patients is summarized in Table 5.1.

Table 5.1 Distribution of Studies in the Ziconotide Clinical Program
From Sponsor's Table 8.8.1.1 (Vol. 2.93, P. 089)

Study Category	Study Numbers	Number of Patients/Volunteers			
		No. of Studies	Ziconotide	Placebo	Total ^a
Intrathecal					
Double - Blind, Placebo Controlled					
Chronic Pain	95-001, 96-002	2	335	32 ^a	367 ^a
Acute Post-op Pain	96-003	1	18	12	30
Open-Label					
Chronic Pain	94-004, 95-002, 96-010, 97-013, 97-015, 98-022	6	351 ^b	0	351 ^b
Subtotal		9	704	44	748
Intravenous					
Double - Blind, Controlled					
Volunteers	93-001, 93-002, 93-003	3	79	25	104
CABG	94-002, 95-004	2	26	5	31
Traumatic Brain Injury	94-001, 1009-002/1009-003	2	175	125	300
Subtotal		7	280	155	435
Epidural					
Double - Blind, Placebo Controlled					
Acute Post-op Pain	96-012, 98-023	2	17	8	116 ^c
Open-Label					
Chronic Pain	98-021 ^d , 98-029	2	37	0	37
Volunteers	98-021 ^d	1	7	0	7
Subtotal		4	61	8	160
Total		20	1043^c	207	1341^c

a. One patient enrolled in a second study (98-022) and received ziconotide; therefore, only 44 patients never received ziconotide in the Intrathecal Clinical Studies.

b. All patents enrolled in Study 95-002 were previously enrolled in Study 95-001 or 96-002; therefore, the 155 patients enrolled in Study 95-002 are not included in this total. Three patients enrolled in Study 98022 had received ziconotide in a previous study and therefore these patients are not counted in this total

c. Study 98-023 is an ongoing blinded study and the treatment assignment of the 91 patients is unknown; d. therefore, the 91 patients are only counted in the total column of this table. Study 98-021 enrolled volunteers as well as patients with chronic pain.

e. Two patients received ziconotide in both an intrathecal and an epidural study and are therefore only counted once in the ziconotide total and the overall total.

Data Source: Individual Clinical Trial Reports.

SECTION 5.1 INTRATHECAL CLINICAL INVESTIGATIONS

SECTION 5.1.1 DESCRIPTION OF CLINICAL STUDIES - IT

The intrathecal studies submitted for this section are presented in Table 5.2. Study 98-022 and study 95-002, an open label extension of studies 95-001 and 96-002, were ongoing at the time of NDA submission.

Table 5.2 Intrathecal Ziconotide Studies - All Patients (From sponsor's Table 8.2.1, Vol. 2.091, P. 155)

Study Number	Study Designs	Protocol-Specified Dose	Patient/Subject	No. of Subjects ^a
Controlled Intrathecal Studies-Chronic Pain				
95-001	Phase II/III Placebo-controlled, safety and efficacy	0.1-2.4 ug/h ^b	Chronic malignant pain	112
96-002	Phase II/III Placebo-controlled, safety and efficacy	0.1-2.4 ug/h ^b	Chronic nonmalignant pain	257
Controlled Intrathecal Studies-Acute Pain				
C96-003	Phase II-Pilot, Placebo-controlled	0.7, 7.0 ug/h	Acute post-op pain	30
Uncontrolled Intrathecal Studies				
94-004	Phase I/II-Pilot, open-label	0.3-300 ng/kg/h	Chronic pain	31
95-002	Phase III-Long-term, open-label, safety	0.1-2.4 ug/h	Chronic pain	155 ^c
C96-010	Phase II, Open-label, safety and efficacy	0.2-3.4 ug/h	Chronic, nonmalignant pain	1
C97-013	Phase II-PK	1, 5, 7.5, 10 ug	Chronic pain	22
C97-015	Phase II, Open-label, safety and efficacy	0.04-0.1 ug/h	Chronic, nonmalignant pain	1
C98-022	Phase II-Open-label, long-term Safety	0.1 ug/h, titration to response	Chronic severe pain	500 ^d

a Indicates subjects enrolled or treated in the studies.

b Final protocol amendment, higher dosing in earlier protocol amendments

c These patients previously participated in Study No. 95-001 or 96-002.

d Planned enrollment for ongoing studies.

SECTION 5.1.2 DEMOGRAPHICS - IT

The crossover design of some of the studies resulted in many patients being exposed to both ziconotide and placebo. The sponsor has presented the demographics for patients categorized in the following 3 groups: 1. ever exposed to ziconotide, 2. patients ever exposed to placebo and 3. patients only exposed to placebo (never exposed to ziconotide). This is summarized in Table 5.3. Overall, the groups were very similar, with the "never received ziconotide" group slightly older and the "ever received ziconotide" group a little heavier.

Table 5.3 Demographics and Baseline Characteristics by Study Drug Exposure, All Patients
(From Sponsor's Tables 8.8.2.6.1, 8.8.2.6.2, and 8.8.2.6.3, Vol. 2.93 P. 183, 187)

Parameter	All IT Studies			Initial Controlled Titration, Pivotal Trials		
	Ever Received Ziconotide (N = 704)	Ever Received Placebo (N = 151)	Never Received Ziconotide (N = 44)	Ziconotide (N = 242)	Placebo (N = 126)	Total (N = 368)
Age (year)						
n	704	151	44	242	126	368
Mean (SE)	52.5 (0.52)	55.1 (1.09)	56.8 (1.96)	52.7 (0.91)	54.0 (1.13)	53.1 (0.72)
Median (Range)	51.0 (16.0-85.0)	53.0 (25.0-85.0)	54.0 (34.0-84.0)	51.5 (22.0-82.0)	52.0 (25.0-85.0)	52.0 (22.0-85.0)
<60 years	488 (69.3%)	94 (62.3%)	24 (54.5%)	163 (67.4%)	84 (66.7%)	247 (67.1%)
>60 years	216 (30.7%)	57 (37.7%)	20 (45.5%)	79 (32.6%)	42 (33.3%)	121 (32.9%)
Gender						
Male	364 (51.7%)	84 (55.6%)	25 (56.8%)	132 (54.5%)	69 (54.8%)	201 (54.6%)
Female	340 (48.3%)	67 (44.4%)	19 (43.2%)	110 (45.5%)	57 (45.2%)	167 (45.4%)
Race						
Caucasian	654 (92.9%)	142 (94.0%)	38 (86.4%)	223 (92.1%)	119 (94.4%)	342 (92.9%)
Black	23 (3.3%)	4 (2.6%)	3 (6.8%)	12 (5.0%)	2 (1.6%)	14 (3.8%)
Hispanic	12 (1.7%)	4 (2.6%)	3 (6.8%)	6 (2.5%)	4 (3.2%)	10 (2.7%)
Asian	10 (1.4%)	1 (0.7%)	0 (0.0%)	1 (0.4%)	1 (0.8%)	2 (0.5%)
Other	4 (0.6%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Missing	1 (0.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Weight (kg)						
n	631	134	43	236	121	357
Mean (SE)	79.9 (0.8)	76.4 (1.6)	75.3 (2.98)	77.3 (1.20)	77.1 (1.68)	77.2 (0.98)
Median (Range)	78.5 (40 - 174.8)	75.5 (43 -127.3)	75.0 (43 -115.9)	76.9 (41-127.5)	76.4 (43- 127.3)	76.8 (41 -127.5)
Height (cm)						
n	640	137	43	236	120	356
Mean (SE)	170.6 (0.44)	170.6 (1.06)	169.8 (1.94)	171.4 (0.71)	169.7 (1.15)	170.8 (0.61)
Median (Range)	170.2 (110.0-203.2)	170.2 (124.5-203.2)	170.2 (142.2-193.0)	171.8 (144.8-200.9)	170.2 (124.5-203.2)	170.2 (124.5 -203.2)

a. Treatment difference was tested using the 2-way ANOVA model with treatment, study, and treatment-by-study interaction as factors. The p-value for the treatment-by-study interaction is given in parentheses.

b Treatment difference was tested using the CMH general association test controlling for study.

c For Caucasian versus Other (Black, Hispanic, and Asian combined). Studies include: 95-001 and 96-002.

Data Source: Appendix 1, IT Table 2.3.

Overall, the patient populations of those who “ever received ziconotide”, “ever received placebo” and “never received ziconotide” were well balanced for baseline and demographic characteristics including age, gender, race, height and weight.

SECTION 5.1.3 EXTENT OF EXPOSURE -IT

Study drug exposure is summarized in Tables 5.4 and 5.5. Overall exposure was 136.4 person years for ziconotide. As of the cutoff dates, 46.9% of the patients had been exposed for 30 days

or more. The median duration of treatment was 28.0 days, the mean 78.9 days. The mean cumulative dose of ziconotide was 909.4 ug. The maximum cumulative dose was 73,484 ug.

Table 5.4 Duration Of Treatment With Intrathecal Ziconotide, All Patients (From sponsor's Table 8.8.2.4.5, Vol. 2.093, P. 154)

Duration of Treatment (Days)	Number of Patients (N = 704)	Cumulative Dose of Ziconotide (ug)		
		Mean (SD)	Median	Range
0 to <30	381 (54.1%)	119.7 (292.3)	58.4	0.1 - 4625.0
30 to <90	163 (23.2%)	758.3 (2494.1)	317.8	19.7- 30742.7
90 to <180	103 (14.6%)	1347.5 (1719.3)	718.6	163.6 - 10161.9
180 to <360	23 (3.3%)	1999.5 (1324.9)	1658.9	624.3 - 6062.9
>360	34 (4.8%)	8419.4 (15464.9)	3301.2	918.9 - 73,484.2

Note: Includes all data for all patient visits through 30 April 1999 for Study 95-002 and all data in the database as of 9 September 1999 for Study 98-022.

Studies include: 94-004, 95-001, 95-002, 96-002, 96-003, 96-010, 97-013, 97-015, and 98-022.

Data Source: Appendix 1, IT Table 1.7.

Table 5.5 Dosing Information, All Patients Who Ever Received Intrathecal Ziconotide. (From Sponsor's Table 3.1, Vol. 2.215, P. 032)

	Ever on Ziconotide (N=704)	
	Mean (SE)	Median (Range)
Number of Days on Study Drug	78.87 (5.27)	27.98 (0.06 - 1041.17)
Initial Dose Level Received (ug/h)	0.39 (0.05)	0.100 (0.004 - 10.000)
Last Dose Level Received (ug/h)	1.04 (0.09)	0.300 (0.001 - 38.100)
Cumulative Dose (ug) ^a	909.44 (152.29)	169.98 (0.10 - 73484.16)

a. The cumulative Ziconotide /Placebo dose level was estimated by (dose level 1 x duration of dose Level 1) + (dose Level 2 x duration of dose Level 2) + (dose level K x duration of dose level K), if K distinct infusions were received.

The extent of dosing by the average hourly dose is presented in Table 5.6. Patients were segregated by starting dose. Those patients starting on doses of >0.1 ug/h, were generally maintained on a higher dose. This may reflect the constraints of different dosing schedules within and between protocols during titration. The hourly dosing decreased over time for this group, particularly after the first week, remaining higher than the dosing of those starting on ≤ 0.1 ug/h. What is also demonstrated by Table 5.6, is that a fairly wide range of hourly doses persisted even among those patients remaining on ziconotide for greater than 12 months.

Table 5.6 Average hourly dosing - All intrathecal studies (From Sponsor's Table 3.5, Vol. 2.215, P. 036)

		Ziconotide	
		Initial Dose $\leq$ 0.1 ug/h	Initial Dose $>$ 0.1 ug/h
All patients	N	548	156
	Mean (SE)	0.42 ug/h (0.038)	1.78 ug/h (0.191)
	Median (Range)	0.24 ug/h (0.01 - 16.62)	0.74 ug/h (0.12 - 10.00)
Week 1	N	548	156
	Mean (SE)	0.27 ug/h (0.014)	1.82 ug/h (0.191)
	Median (Range)	0.17 ug/h (0.01 - 3.91)	0.76 ug/h (0.12 - 10.00)
Week 2	N	407	74
	Mean (SE)	0.33 ug/h (0.030)	0.84 ug/h (0.170)
	Median (Range)	0.20 ug/h (0.01 - 8.36)	0.46 ug/h (0.03 - 12.20)
Weeks 3 & 4	N	346	62
	Mean (SE)	0.43 ug/h (0.063)	0.57 ug/h (0.064)
	Median (Range)	0.24 ug/h (0.01 - 19.03)	0.38 ug/h (0.01 - 2.33)
Month 2	N	272	51
	Mean (SE)	0.45 ug/h (0.076)	0.63 ug/h (0.110)
	Median (Range)	0.24 ug/h (0.02 - 19.02)	0.36 ug/h (0.10 - 4.52)
Month 4	N	138	22
	Mean (SE)	0.49 ug/h (0.064)	0.66 ug/h (0.166)
	Median (Range)	0.23 ug/h (0.05 - 10.00)	0.29 ug/h (0.13 - 2.54)
Month 6	N	72	12
	Mean (SE)	0.42 ug/h (0.063)	0.90 ug/h (0.276)
	Median (Range)	0.25 ug/h (0.01 - 3.60)	0.39 ug/h (0.12 - 2.82)
Month 12	N	28	8
	Mean (SE)	0.33 ug/h (0.059)	1.23 ug/h (0.426)
	Median (Range)	0.23 ug/h (0.08 - 1.42)	0.77 ug/h (0.12 - 3.14)
Month 18	N	10	6
	Mean (SE)	0.32 ug/h (0.068)	1.28 ug/h (0.576)
	Median (Range)	0.27 ug/h (0.08 - 0.74)	0.64 ug/h (0.12 - 3.29)
Month 24	N	3	3
	Mean (SE)	0.30 ug/h (0.005)	2.32 ug/h (0.743)
	Median (Range)	0.30 ug/h (0.29 - 0.31)	2.80 ug/h (0.86 - 3.29)

Exposure during the double blind, initial titration period of studies 95-001 and 96-002 represent placebo controlled data. This is summarized in Table 5.7 and is again segregated by initial dose. Again, it can be seen that patients starting on higher doses ended on higher doses, with greater overall cumulative doses.

Table 5.7 Ziconotide exposure by Initial Dose Group, Patients during the initial, double blind, placebo controlled period of the controlled trials. (From Sponsor's Table 8.8.2.4.8, Vol. 2.093, P. 161)

Parameter	Ziconotide (N = 242)		
	≤ 0.1 ug/h (n = 166)	>0.1 ug/h (n = 76)	Total (n = 242)
Number of Days			
Mean (SE)	5.63 (0.08)	5.63 (0.28)	5.63 (0.10)
Median (Range)	5.95 (0.77 - 9.05)	5.74 (0.96 - 22.50 ^c)	5.93 (0.77 - 22.50)
Initial Dose Level (ug/hr)			
Mean (SE)	0.10 (0.00)	0.36 (0.01)	0.18 (0.01)
Median (Range)	0.10 (0.010 - 0.100)	0.40 (0.102 - 0.480)	0.0 (0.010 - 0.480)
Dose Level at End (ug/hr) ^a			
Mean (SE)	0.72 (0.06)	1.57 (0.22)	0.99 (0.08)
Median (Range)	0.30 (0.019 - 2.400)	0.90 (0.10 - 9.60)	0.519 (0.019 - 9.60)
Cumulative Dose ^b (ug)			
Mean (SE)	49.81 (2.55)	144.54 (16.43)	79.56 (6.12)
Median (Range)	40.48 (1.85-122.51)	100.20 (8.93 - 880.55)	52.76 (1.85 - 880.55)

a. The last non-zero dose level administered during the initial titration phase was reported.

b. The cumulative dose (ug) at the end of initial titration phase, with K distinct doses was estimated as: [dose level 1 (ug/hr) x duration of dose level 1 (hours) + dose level 2 (ug/hr) x duration of dose level 2 (hours) + ... + dose level K (ug/hr) x duration of dose level K (hours)].

c. The one outlying value of 22.5 d represents one patient (501-49) who left the study due to meningitis and reentered following treatment, receiving study drug a total of 10 d.

Studies include: 95-001 and 96-002.

Data Source: Appendix 1, Table 3.2.

SECTION 5.2 OTHER SOURCES

SECTION 5.2.1 EPIDURAL CLINICAL INVESTIGATIONS

The section on the investigation of ziconotide by epidural route was reviewed from the 120-day safety review.

SECTION 5.2.1.1 Description Of Studies - ED

A total of 4 clinical trials were conducted to study epidural administration of ziconotide as summarized in Table 5.8. 96-012 was a pilot study in acute postoperative pain, 98-021 was a pharmacokinetic study with both chronic pain patients and healthy volunteers. Study 98-023 was a dose-response study in patients with acute postoperative pain and 98-029 was a long term study in patients with chronic pain.

Table 5.8 Epidural studies (From sponsor's Table 8.2.1, Vol. 2.091, P. 155)

Study Number	Study Designs	Protocol-Specified Dose	Patient/Subject	No. of Subjects ^a
96-012	Phase II Placebo controlled, pilot	0.7 or 7 ug/h	Acute post-op pain	25
98-021	Phase II PK	2,5,10,20 ug single 60 min infusion	Chronic severe pain	42 ^b
98-023	Phase II/III Placebo controlled, dose response	2, 7, and 20 ug/h	Surgical pain	240 ^b
98-029	Open label safety	0.2 ug/h titration to patient response	Chronic severe pain	200

a Indicates subjects enrolled or treated in the studies.

b These patients previously participated in Study No. 95-001 or 96-002.

Study 96-012

This was to be a phase II, double blind, placebo controlled pilot study in patients undergoing elective total hip or knee replacement, elective retropubic radical prostatectomy or elective abnormal hysterectomy. The patients were to have an epidural catheter for surgical anesthesia. A morphine IV PCA was to be available for rescue. Patients were to be randomly assigned to either 0.7ug/h or 7ug/h of ziconotide by continuous epidural infusion for 48 h.

Study 98-012 was to be a phase I/II open label PK study. Five fixed doses, 1, 2, 5, 10, and 20 ug, were to be administered by short epidural infusion to healthy volunteers and chronic pain patients. The primary objectives were to characterize the 24 h CSF and plasma PK profiles. The secondary objectives were to evaluate safety and efficacy in chronic pain due to cancer or AIDS. The dose was to be infused over 60 minutes (1ml/h) followed by a 30 minute saline flush.

Study 98-023 was to be a phase II/III randomized, double blind, placebo controlled, parallel group study of safety and efficacy of 3 different doses in acute pain due to elective total knee or total hip replacement. A morphine PCA was to be available for rescue. Ziconotide was to be administered at 0.2ml/h at concentrations of 2, 7, or 20 ug/h or placebo for 48 h.

Study 98-029 was to be a phase II open label study to evaluate the long term safety of epidural ziconotide in patients with chronic malignant or nonmalignant pain in outpatients. Patients were to receive a continuous epidural infusion of ziconotide starting at a rate of 0.2 ug/h, titrated to efficacy no more frequently than q 24hour, by increments of ≤ 0.2 ug/h.

SECTION 5.2.1.2 Demographics - ED

The demographics for the epidural studies are summarized in Table 5.9. As can be seen there were fewer men than women in the two smaller studies, but overall there was a preponderance of Caucasian subjects.

Table 5.9 Demographics, All Epidural Studies

Study	96-012	98-012	98-023	98-029
n	25	46	150	2
Mean Age (years)	60 (range 23-87)	43-51 across 5 groups (range 20-67)	65 (range 20-91)	
Sex	9 male (36%)	20 male (43%)	74 male (49%)	NA
Race	22 Caucasian	33 Caucasian 5 African American 1 Hispanic 3 other.	128 Caucasian 17 African American 4 Hispanic 1 Asian	NA

SECTION 5.2.1.3 Extent Of Exposure -ED

A total of 219 subjects have participated in an epidural study. Given that study 98-023 is still blinded, the estimated number of unique subjects exposed to ziconotide is 173.

Table 5.10 Epidural Extent of Exposure -Epidural 120-Day Safety Update patient disposition overview ED, 120 day safety update (From Sponsor's Tables 9.3.4.1 and Vol. 5.2, P. 387)

Study (n= Subjects)	Treatment Arms	Patients/Group ^a	Mean Duration (h)	Mean Cumulative Ziconotide Dose (ug)
96-012 (25)	Placebo	8	41.8	0
	0.7 ug/hr	9	42.0	29.4
	7.0 ug/hr	8	41.7	291.7
98-021 ^a (42)	1 ug	6	1	1.00
	2 ug	9	1	1.98
	5 ug	10	1	4.68
	10 ug	11	1	10.06
	20 ug	10	1	20.70
98-023 (150)	A	36	45.9	Not Available (Study Blinded)
	B	41	46.3	
	C	38 ^d	44.4	
	D	35	46.4	
98-029 ^c	0.2 - 2 ug/h	2	12 - 94 d	182.9 - 2771.0
Subjects = 219		Cases = 223		

a Four patients with chronic pain participated in the study twice. Thus, the 10 ug group includes one case who previously participated in the 2 ug group and one who previously participated in the 5-ug group, and the 20 ug group includes two cases who previously participated in the 2-ug group.

b Estimated duration of exposure.

c Patient 012-1503 previously participated in IT Study 98-022.

d For one patient, the study drug infusion start time was missing. This patient was not included in the mean duration calculation.

Data Source: Study reports for Studies 96-012 and 98-021; Appendix 2, Epidural Patient Data Listing 2.1 for Study 98-023; Appendix 2, Epidural Patient Data Listing 1 for Study 98-029.

SECTION 5.2.2 INTRAVENOUS CLINICAL INVESTIGATIONS

This section was reviewed from the IV ISS in the original NDA submission. No new data was presented in the 120-day safety review.

SECTION 5.2.2.1 DESCRIPTION OF STUDIES - IV

A total of 7 intravenous studies were conducted under 8 protocols. The subjects included normal volunteers, patients undergoing coronary artery bypass graft (CABG) surgery and patients with severe traumatic brain injury (TBI). An 8th study in stroke patients was terminated prior to patient enrollment. Three of the studies were phase I in normal volunteers, 2 were phase II in CABG patients and 2 were phase II in TBI patients.

The dose levels ranged from 0.0003 to 1.29 mg/kg/24hr (~ 0.875 to 3, 000 ug/hr) for up to 72 h compared with 0.02 to 21 ug/h for the intrathecal route. Details of the seven intravenous studies used to supply safety information are presented in Table 5.11.

Table 5.11 Intravenous studies from sponsor's (From Sponsor's Table 8.2.1 Vol. 2.091, P. 155)

Study Number	Study Designs/ Protocol-Specified Dose
93-001 Phase I - Randomized, Double Blind, Placebo Controlled, Dose Escalation Study Of Ziconotide Administered Intravenously To Healthy Male Volunteers	N= 40 (30 drug, 10 placebo) Low dose, safety 0.3, 1, 3.3, 10 ug/kg/24 h, x 24h
93-002 Phase I - Randomized, Double Blind, Placebo Controlled, Dose Escalation Study Of Ziconotide Administered Intravenously To Healthy Male Volunteers	N=56 High dose, safety 10, 30, 60, 125, 250, 500, 1000 ug/kg/24 h
93-003 Phase I - One Label, Placebo Controlled, Pilot Hemodynamic And PK Study Of ziconotide Administered Intravenously To Healthy Male Volunteers	N=8 6 dose levels 1, 3.3, 10 ug/kg/24h x 6h; 1-10 ug/kg/24hr ramped over 6h
94-001 Phase II - Multicenter, Randomized, Double Blind, Placebo Controlled, Dose Tolerance Trial Of Ziconotide Administered Intravenously To Patients With Moderate To Severe Head Injuries	N=68, 3/dose group; 1/placebo group 62.5/125/250 or 250/500/1000 ug/kg/24h, each dose for 24h, blinded or open label 70 mg/d x 72h
94-002 Phase II - Randomized, Double Blind, Placebo Controlled, Dose Escalation Study Of Ziconotide Administered Intravenously To Patients Undergoing Elective CABG Surgery With Cardiopulmonary Bypass	N=16, 3/dose group; 1/placebo group Safety Load/Main. 62.5/15, 125/30, 250/60, 500/0 ug/kg/24h, initially over < 11h, changed to <5 h to decrease risk of hypotension
95-004 Phase II - Randomized, Double Blind, Dose Escalation Study Of Ziconotide Administered Intravenously To Patients Undergoing Elective CABG Surgery With Cardiopulmonary Bypass	N=15 Safety Load/Main. 15/5, 30/10, 45/15 ug/kg/h
1009-002 (North American arm) 1009-003 (European arm) Phase II/III Multicenter, Randomized, Double Blind, Placebo Controlled Trial Of Ziconotide Administered Intravenously To Patients With Moderate To Severe Head Injury	N=232 Safety and efficacy 60 mg/24h Enrollment paused May, 1998 when a difference in the 14 day mortality between groups appeared, p< 0.04, and terminated November, 1998, due to a lack of a positive effect on the primary efficacy variable.

a Indicates subjects enrolled or treated in the studies.

SECTION 5.2.2.2 Demographics and Baseline Characteristics - IV

The baseline characteristics between ziconotide treated and placebo treated patients in the normal volunteer, phase I studies were similar between groups without notable difference (Table 8.8.3.6.1, Vol. 2.94, P. 054).

The baseline characteristics between ziconotide treated and placebo treated patients in the phase II, CABG studies were similar between groups except the placebo patients began with a slightly higher blood pressure (136.8/67.6 vs. 122.6/62.2 ziconotide group) and lower respiratory rate (7.8 vs. 13.5/min ziconotide group) (Table 8.8.3.6.2, Vol. 2.94, P. 057).

The baseline characteristics between ziconotide treated and placebo treated patients in the phase II, TBI studies were similar between groups without notable difference (Table 8.8.3.6.3, Vol. 2.94, P. 060).

SECTION 5.2.2.3 Extent of exposure - IV

Table 5.12 demonstrates the intravenous ziconotide exposure for volunteers, CABG and TBI patients.

Table 5.12 Cumulative Dose and Duration of Dosing for Subjects in All Intravenous Studies (From Sponsor's Tables 8.8.3.4.2, 8.8.3.4.4, 8.8.3.4.6 Vol. 2.94, P. 043)

Patient Population	Total No. of Patients Exposed to Ziconotide	Intravenous Patients		
		Dose Rate ^a (ug/h) Mean (SD) Median (Min-Max)	Cumulative Dose (ug) Mean (SD) Median (Min-Max)	Duration of Dosing (hr) Mean (SD) Median (Min-Max)
Clinical Pharmacology Healthy Volunteers	79	498(968)	11,788 (23,292)	20.5(7.16)
		36	835	24
CABG Surgery Patients	26	1013(854)	3426(2800)	4.2(2.5)
		710	2216	3.8
Traumatic Brain Injury Patients	175	2458(739)	150,578 (61,116)	62(20)
		2532	179,380	70

^a Some or all patients in Studies 93-002, 93-003, 94-002, 95-004, 94-001 and 1009-002 /1009-003 had more than one infusion rate (e.g., Study 93-002 ramping scheme with up to 7 infusion rates). For these patients, their dose rate was calculated based on total cumulative dose and total infusion duration and the mean, median, min and max value presented are based on these patient averages.

Studies include: 93-001, 93-002, 93-003, 94-002, 95-004, 94-001 and 1009-002/1009-003

Data Source: Item 6; Individual Pharmacokinetic Reports 94-002 and 95-004 and Appendix 4, Attachment A.

SECTION 6.0 HUMAN PHARMACOKINETICS AND PHARMACODYNAMICS

Fourteen clinical trials provided PK data. All 14 provided data on plasma levels, 3 attempted to quantify drug in the CSF and one in urine. These are summarized in Table 6.1.

Table 6.1 Matrices Sampled and Data Available in Ziconotide Human PK Studies (From Sponsor's Table 3.6-1, Vol. 2.2, P. 172)

Study No.	Route	CSF PK	CSF Conc.	Plasma PK	Plasma Conc.	Urine Conc.
97-013	IT	yes			Yes	
94-004	IT				Yes	
95-001	IT				Yes	
96-002	IT				Yes	
96-003	IT				Yes	
95-002	IT				Yes	
93-001	IV			Yes		
93-002	IV			Yes		
93-003	IV			Yes		
94-001	IV		Yes	Yes		
95-002	IV			Yes		Yes
94-004	IV			Yes		
98-021	Epidural	Yes		Yes		
96-012	Epidural				Yes	

A blank cell indicates data not available.

CSF PK

CSF was sampled during three different studies, following the administration of ziconotide by IT, ED and IV routes. Study 97-013 was the primary PK study for the IT route and the only study to characterize the PK of ziconotide in the CSF following IT administration. This was an open label, pilot study of the PK, safety and analgesic profiles following a single one hour IT infusion in 23 patients (including one patient enrolled twice). The doses were 1, 5, 7.5 and 10 ug. CSF samples were collected for 48 hours. Although the sponsor indicated AUC and Cmax were dose proportional, this was not supported by the results. AUC and Cmax actually decreased from the 7.5 to 10 ug doses. Clearance and the volume of distribution also peaked with the 7.5 ug dose. Half life was the most stable ranging from 5.3 h for the 1 ug dose to 4.2 h for the 10 ug dose.

Study 94-001 was a multicenter placebo controlled, phase II safety and feasibility study in patients with TBI. Patients were dosed IV for 72 hours with one of 3 dose regimens; a constant 70 mg/d infusion or escalating infusions with maximum doses of 0.25 mg/kg/d or 1 mg/kg/d. Fifty two of 66 CSF samples were drawn from 4-75 hours after the start of the infusion. The results demonstrated very large variability, Cmax ranged from _____, AUC from 6 to 480 ng*h/ml, possibly explained by contamination with blood.

Study 98-021 was an open label, pilot study following a single 1 hour epidural infusion in 42 patients. Doses were 1, 2, 5, 10 and 20 ug. Only 14 of 39 patients with CSF samples had quantifiable CSF ziconotide levels. The CSF PK results were reported to be dose dependent by

the sponsor, but the results from the 5 and 10 ug doses were comparable for many parameters. A saturable transport mechanism across the meninges was postulated.

Overall, there was little consistency within the information obtained from attempting to quantify ziconotide in the CSF. No reliable PK parameters could be calculated from these results.

Plasma PK

Plasma PK was sampled during the 2 pivotal intrathecal studies, 95-001 and 96-002. Only 44% (22/50) of the patients in 95-001 and 30% (30/102) of patients in 96-002 had quantifiable plasma levels of ziconotide. The values were widely variable, as were dose rates, with only gross correlation's between infusion rate and plasma level. During study 95-002, the open label extension from the pivotal trials, doses were maintained for the first 30 days. Plasma samples were drawn 48 hours after the first maintenance period was initiated. Only 13% of the plasma levels were above the quantitation limit. There was no correlation between the average hourly infusion rate and the presence of a quantifiable concentration. There were only 7 samples (5%) from intrathecal study 97-013 with quantifiable ziconotide plasma levels. Similar, highly variable findings were obtained from IT studies 94-004 and 96-003.

The plasma PK values from epidural studies 98-021 and 96-012 were more dose proportional than the CSF results according to the sponsor, but were only quantifiable in up to 75% of samples from any given dose.

Following IV administration, the PK results were less variable than by other routes of administration. The mean half life was 1.3 h from study 93-001 with doses from 0.3 to 10 ug/kg/24h and 2.4 h from 93-002 with doses from 10 to 1000 ug/kg/24 hr, demonstrating some dose dependence. The mean steady state volume of distribution was 30 liters from study 93-001 and 48 liters from 93-002. Clearance averaged 17 liters/h from study 93-001 and 14 liters/h from 93-002.

Urine concentration following IV infusion in study 94-002 was not sufficiently recoverable for comment.

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SECTION 7.0 EFFICACY FINDINGS

SECTION 7.1 OVERVIEW OF CLINICAL STUDIES

The sponsor has submitted two studies to the NDA in support of the claim of efficacy in the management of pain, studies 95-001 and 96-002. Both were multicenter, randomized, double blind, placebo controlled studies. Protocol 95-001 evaluated the efficacy of ziconotide in patients with pain due to malignancy and AIDS. Protocol 96-002 evaluated the efficacy of ziconotide in patients with chronic non-malignant pain. In both protocols, patients were either about to begin intrathecal analgesics or who were already receiving intrathecal analgesics. Those patients already receiving intrathecal analgesics were stabilized on systemic opioids. Patients were randomized to ziconotide or placebo for a 5 to 6 day titration at which point the primary efficacy endpoint was measured, percent change in Visual Analog Scale Pain Intensity (VASPI) score. Secondary efficacy endpoints were produced during this initial titration phase and later maintenance or crossover phases.

Five additional studies were submitted as support for the efficacy claim. Study C96-003 was a small study of intrathecal ziconotide in acute postoperative pain and a brief review follows the review of 96-002. Studies 94-004, C97-013 and 95-002 were open label studies and C96-012 was a single dose study of epidural ziconotide. The results of these trials are not considered for the efficacy review but will be incorporated into the safety review.

SECTION 7.2 SUMMARY OF STUDIES PERTINENT TO EFFICACY

SECTION 7.2.1 STUDY 95-001

SECTION 7.2.1.1 Protocol Synopsis

Title: A Multicenter, Phase II/III, Placebo Controlled Study Of SNX-111 Administered Intrathecally To Patients With Chronic Malignant Pain.

Objective: to compare the effect of increasing doses of IT SNX to placebo in chronic malignant pain and assess the safety of increasing doses of IT SNX.

Study Design: The study was to be a multicenter, multi-national, randomized, double blind, parallel, placebo controlled trial. The primary efficacy endpoint was to be obtained at the end of the initial titration period. The second phase of the study was to include a crossover period for a subset of patients from which several secondary endpoints were to be obtained.

Inclusion Criteria:

1. Patients with chronic intractable pain from malignancy or AIDS
2. Patients who have an intrathecal catheter and/or Medtronic SynchroMed infusion System in place, or whose next line of therapy would require placement of such a device
3. The patient has been slowly tapered and discontinued from intrathecal medications, stabilized on oral or systemic analgesics for at least 3 d prior to enrollment in the study.
4. Life expectancy of at least 1 month. If implantation of a SynchroMed pump is considered, life expectancy should be greater than 3 months.

5. Average Visual Analog Scale Pain Intensity (VASPI) over past 3 days on oral or systemic opioids of at least 50.
6. 18 yo or older, limited enrollment of patients at least 10 y of age at some centers
7. Women must not be pregnant or breastfeeding. Women must be postmenopausal or if of child bearing potential, using an acceptable method of contraception.

Exclusion Criteria:

1. Sepsis
2. CHF, sinus bradycardia with greater than 1st degree block, asthma, syncope
3. Mini-mental status exam of <24 or diagnosis of dementia/delirium
4. Investigational drug study within 30 d
5. Prior SNX study
6. Physical or psychological problem precluding pump implantation or use of external pump
7. Intrathecal catheters above T1
8. Implanted infusion pumps or catheters other than SynchroMed system

Enrollment of 120 patients was planned.

During the screening period, patients were to be stabilized on a systemic analgesic regimen for at least 3 d prior to study enrollment. Patients receiving intrathecal therapy were to be tapered off all intrathecal medication for a minimum of 3 days prior to beginning study medication.

During the pre-infusion period, patients would then be randomized to SNX or placebo and begin a blinded 5 day initial titration as inpatients. Patients tolerating the study drug after 48 h were to be permitted discharge to home for the remainder of the initial titration phase. The primary efficacy endpoint was to be measured at the end of this titration period.

Randomization was to be 2:1 SNX to placebo, and stratified by etiology of chronic pain (AIDS vs. cancer), and history of intrathecal opioid use. Randomization was also to be stratified by center, with a block size of three within a center

The following definitions were provided by the sponsor to determine treatment assignments at the conclusion of the initial titration period and to assist with decisions concerning dosage adjustment.

1. Responders - patients experiencing a $\geq 30\%$ drop in VASPI (an average of the last 2 measurements taken within a 2 h period or 3 if the first 2 measurements differ by greater than 15 mm) compared with baseline in the setting of stable or decreasing regimen of concurrent opioid analgesics and no change in the type of concurrent opioid analgesics.
2. Non-responders - patients experiencing < 30% drop in VASPI or a 30% drop in the setting of increased opioid analgesics including a change in type of opioid analgesic
3. Early responders - patients who demonstrate a response prior to 144 h of study medication infusion, on initial or crossover arms
4. Onset of analgesia - a minimum of 20% improvement from baseline VASPI with confirmation by categorical pain relief scale, without an increase in opioids

At the conclusion of the 5 day initial titration period:

1. Responders were to continue on the same treatment for a 5 day maintenance period as out-patients. At the end of the 5 day maintenance period the treatment assignments were to be unblinded:
 - 1a. Responders to SNX were to be enrolled in a long term study
 - 1b. Responders to placebo were to be discontinued from the study.
2. Non-responders were to be crossed over to the alternate treatment still blinded and titrated for up to 5 d. At the end of the 5 day crossover period, the treatment assignments were to be unblinded:
 - 2a. Non-responders to SNX were to be discontinued from the study.
 - 2b. Non-responders to placebo were to be discontinued from the study.
 - 2c. Placebo responders were to be discontinued from the study.
 - 2d. SNX responders from this period were to be offered enrollment in a long term study.

Study Medication:

The study drug was to be SNX-111 acetate in vehicle with L-methionine and NaCl, pH 4.3 +/- 0.2. The placebo and diluent were the same as vehicle.

The dosing regimen was changed three times during the study. The initial dose of drug for any given patient was to be based on weight in the original protocol, starting with 0.005 ug/kg/h up to a maximum dose of 0.3 ug/kg/h, titrated upward every 12 h.

Time (hours)	Original, 1/23/96 (ug/kg/h)	Revision 1 6/11/96 (ug/h)
0 - 12	0.005	0.4
12 - 24	0.008	0.6
24 - 36	0.013	0.9
36 - 48	0.021	1.5
48 - 60	0.034	2.4
60 - 72	0.055	3.9
72 - 84	0.089	6.2
84 - 96	0.144	10.1
96 - 108	0.233	16.3
108 - 120	0.300	21.0

Time (hours)	Revision 2, 10/25/96 (ug/h)	Revision 3, 2/21/97 (ug/h)
0 - 24	0.4	0.1
24 - 48	0.6	0.2
48 - 72	0.9	0.3
72 - 96	1.5	0.6
96 - 120	2.4	1.2
120 - 144 pm	3.9	2.4

Subjects were to be titrated to toxicity according to the original protocol. Beginning with Revision 2, the dose titration interval was changed from 12 hours to 24 hours. Beginning with revision 3, patients were to be titrated to efficacy. Also once the onset of analgesia was reached, the dose was to be held an additional 24 h to permit the full analgesic effect to occur. Any dose

could be held an additional 24 h before further increase, at the investigator's discretion. A dose was to be maintained or reduced as needed based on the appearance of lateral gaze nystagmus, a change in baseline confusion, or the appearance of other adverse events (AE's) thought to be related to study drug.

Concomitant Medication:

No intrathecal medications were to be allowed. Rescue medication was to be systemic opioids and adjuvant analgesics/sedatives as needed. Physical therapy and acupuncture were to be permitted. Any change in concomitant or rescue analgesic type was to be considered an increase in medication even if the total dose remained the same.

Study Schematic:

Table 7. 1 (From Sponsor's Table 7.1, Vol. 5.096, P. 61)

Procedure	Screening Phase	Infusion	Both Initial Titration and Crossover Phase, If Applicable		Maintenance - Responders to Initial Therapy	Study Termination	2 Week Post Study F/U Visit ^a
			Inpatient Treatment	120 H Post Infusion	5 Day Outpatient Treatment		
Written Informed Consent	X						
Medical History	X						
D/C Intrathecal Medication	X						
Concomitant Medication	X	X	X	X	X	X	
Mini Mental Status Exam	X						
Complete PE, neuro exam	X	X		X		X	
Vital Signs Measurements	X ^b	X	q 8h	X		X	
3-day VASPI (average)	X						
Digit Symbol and Trail Making, Parts A and B		X		X		X	
Laboratory Evaluations	X					X	X ^c
Electrocardiogram	X						
Pregnancy Test	X						
Plasma for Ziconotide Levels	X			X		X	
Administration of Study Drug			X				
Pain Assessments	X	X	X ^d	X		X	
WBPI ^e	X	X		X		X	
CPRS ^f			q 24h ^g	X			
VASPR ^h , Mood score, Tursky description of Memorial Pain Card	X	X	X			X	
Karnofsky Performance Scale		X		X		X	
Adverse Events			X	X	X	X	X ^f
Break Blind						X	
Evaluate for Long-Term Study						X	

- a. For patients not enrolling in the long-term extension study.
- b. Including orthostatic vital signs measurements
- c. If unresolved, clinically significant, lab abnormalities or AE's present at discharge
- d. Q 24 h, VASPI, Memorial Pain Card, tactile allodynia if applicable
- e. Wisconsin Brief Pain Inventory Scale
- f. Category Pain Relief Scale
- g. And at onset of analgesia
- h. Visual Analog Scale Pain Relief

Pain and Functionality Assessment Scales:

Visual Analog Scale Pain Intensity (VASPI) - a standard 100 mm visual analog scale

Visual Analog Scale Pain Relief (VASPR) - from the Memorial Pain Assessment Card ranging from "No relief of pain" to "Complete relief of pain"

Mood Score - from the Memorial Pain Assessment Card: visual analog scale for mood ranging from "Worst mood" to "Best mood".

Tursky Description - from the Memorial Pain Assessment Card: 4 category scale: No Pain; Just Noticeable, Mild Or Weak; Moderate Or Strong; Severe Or Excruciating

Category Pain Relief Scale (CPRS) a 6 point categorical scale from 0 - "My pain is now WORSE compared to before the infusion started." to 5 - "I have COMPLETE RELIEF of my pain compared to before the infusion started"

Wisconsin Brief Pain Inventory Scale (WBPI) - a series of 6 descriptions of function: mood, relationships with other people, walking ability, sleep, normal work and enjoyment of life, scored on a 0 (not at all) to 4 (extremely) categorical scale.

Karnofsky Performance Status Scale Score:

- 100 Normal, no complaints; no evidence of disease
- 90 Able to carry on normal activity; minor signs or symptoms of disease
- 80 Normal activity with effort, some signs or symptoms of disease
- 70 Cares for self but unable to carry on normal activity or to do active work
- 60 Requires occasional assistance but is able to care for most of personal needs
- 50 Requires considerable assistance and frequent medical care
- 40 Disabled; requires special care and assistance
- 30 Severely disabled; hospitalization is indicated although death not imminent
- 20 Very ill; hospitalization and active supportive care necessary
- 10 Moribund
- 0 Dead

SECTION 7.2.1.2 Statistical Analysis:

7.2.1.2.1 Patient Populations:

The sponsor has provided the following definitions of the evaluable, intent-to-treat and safety populations. The sponsor has planned to use the evaluable population for the efficacy analysis.

- The evaluable population was to be those patients having met all inclusion criteria and none of the exclusion criteria, no more than minor protocol violations, and at least one of the following: 1. at least one VASPI score after at least 4 full days of treatment, 2. have reached final dose prior to termination of the initial titration phase for at least 12 h, and had at least one VASPI at the end of the 12 h, 3. if terminated due to intolerable AE's, had at

least one VASPI score on the last dose or dose prior to termination of the initial titration phase

- The intent-to-treat population consists of patients who received any amount of study medication, and had a baseline and at least one follow-up VASPI score during the initial titration phase.
- The safety population includes all patients having received any study medication

All statistical tests were to be 2 sided and considered significant with a p-value of ≤ 0.05 .

7.2.1.2.2 Planned Analyses:

Baseline and demographic characteristics: The baseline characteristics compared between groups were to be: demographics, medical diagnosis (cancer vs. AIDS) and disease characteristics; preinfusion pain assessments, analgesic equivalents of opioids at baseline and preinfusion Karnofsky Performance Status Scale score.

- Cochran Mantel Haenszel (CMH) tests controlled for intrathecal opioid use history for categorical data
- Two-way ANOVA models with treatment, intrathecal opioid use history and treatment-by-intrathecal opioid use history interaction for continuous data

Primary Efficacy Analysis:

The primary efficacy endpoint was to be the percent change of VASPI from baseline to the end of the initial titration phase = $[(\text{baseline VASPI} - \text{final VASPI})/\text{baseline VASPI}] \times 100$.

The primary efficacy endpoint was to be analyzed using a 2-way ANOVA model with treatment, intrathecal opioid use history and treatment-by-intrathecal opioid use history. The evaluable population was to be used for this analysis.

Supportive Analyses of the Primary Efficacy Variable:

The supportive analyses on the primary efficacy variable were to include:

1. The Student's Matched Pair t-test was to be used to test significance of the mean percent change in VASPI from baseline to the end of the initial titration phase for each treatment group.
2. A 2-sided asymptotic 95% confidence interval for the overall treatment difference in the means of the primary efficacy variable calculated for the evaluable population with data pooled across all strata.
3. Analysis of the primary efficacy variable for three additional patient populations:
 - a. The ITT population
 - b. evaluable and ITT populations with an initial dose ≤ 0.1 ug/h
 - c. evaluable ITT patients with an initial dose >0.1 ug/h
4. Treatment difference in the primary efficacy variable for evaluable patients using 2-way ANOVA model including treatment, dose level at final assessment, interaction of treatment by dose level.
5. Subgroup analyses of the primary efficacy variable with descriptive summaries for: diagnosis, gender, age, race.

Secondary Efficacy Variables:

The secondary efficacy variables are summarized in Table 7.2.

Table 7.2 Secondary Efficacy Variables (From Sponsor's Table 7.3, Vol. 2.096, P. 095)

Variable(s)	Statistical Model
Change in VASPI score at the end of the initial titration phase Change in Karnofsky Performance Score from baseline to the end of the initial titration phase	2-way ANOVA with treatment, intrathecal opioid use history and treatment by intrathecal opioid use history interaction
Other assessments including VASPR, Mood score and Tursky description at preinfusion, at the end of the initial titration phase and at study termination	Descriptive statistics
Proportion of treatment responders at the end of the initial titration phase	CMH test (general association) stratified by intrathecal opioid use history and 95% symmetrical CI using binomial distribution (pooled across strata) for the treatment difference in the proportion of responders
Proportion of patients responding to ziconotide at the end of the crossover phase among patients under going the crossover phase	Conditional probability estimated as: (ziconotide responders in the crossover phase/ number of patents in the crossover phase); 95% symmetrical CI using binomial distribution (pooled across strata)
Change in tactile allodynia parameters from baseline to the end of initial titration phase	Descriptive statistics
Among patients in maintenance: mean % change in VASPI and change in Karnofsky Score from baseline of initial titration phase to end of maintenance	Descriptive statistics
Among those patients who did crossover: mean % change in VASPI and change in Karnofsky score from baseline of initial titration phase to end of crossover	Descriptive statistics
Percent change in opioid use at the end of the initial titration phase	Descriptive statistics; plot in % change in opioid use vs. primary efficacy variable; linear correlation with % change in VASPI

Interim Analysis:

An interim analysis was to be performed on the first 100 patients who complete the blinded phase by an independent third party to confirm planned sample sizes. Based on results, more but not fewer were to be enrolled. No p-value penalty was planned because conduct and design was not to be changed nor the study stopped and significance claimed.

SECTION 7.2.1.3 Protocol Amendments:

Original protocol - 1/23/96

- initial dosing - 0.005 ug/kg/h titrated to max of 0.3 ug/kg/h titrated q 12h.

Administrative change 1 - 2/15/96

- change references from day 5 to day 6, from day 10 to day 11
- change reference to single panel label to double panel label
- CRO information provided

- Revision 1 - 6/11/96
- remove dosing by weight, initial dose 0.4 ug/h to maximum of 21 ug/h
 - add Category Pain Relief Score to pain assessments

Administrative change 2 - 7/16/96

- clarify procedure for breaking blind in an emergency
- clarify that study drug is mixed in the syringes provided for administration through the external pump
- eliminate q 12 h WPIS as inpatient
- clarify reporting of SAE's

- Revision 2 - 10/25/96
- dosing change, to initial dose of 0.4 mg titrated to 2.4 mg/h at 120 h, maximum of 3.9 ug/h
 - change timing of the pain assessments from q 12 to q 24 h
 - change the inpatient period from a minimum of 5 d to minimum of 2 d

- Revision 3 - 2/21/97
- expanded inclusion criteria to allow non-terminal cancer/AIDS patients
 - dose decreased to 0.1 to 1.2 ug/h at 120 h, maximum of 2.4 ug/h
 - dose could be maintained for 24h or reduced as indicated

- Revision 4 - 10/30/97
- add patients as young as 10 years old to inclusion criteria
 - clarify error in description of randomization
 - clarify typing errors
 - changes to contact pages

- Revision 5 - 2/19/98
- revise statistical considerations, decrease N from 200 to 120
 - clarify timing of study termination visit
 - add intersecting hexagon figure to appendix D (MMSE)
 - Section 3.0: definition of responder changed from a "30% drop" to "≥ 30% drop"

SECTION 7.2.1.4 Results

7.2.1.4.1 Conduct of study:

The first patient was enrolled on 3/12/96 and the last patient completed the study on 7/22/98. Enrollment was closed on 3/9/98. A total of 32 investigators at 32 centers participated.

Protocol Violations:

There were twenty three patients with protocol violations which could potentially impact the primary efficacy variable. Four of these patients had 2 protocol violations each. These are summarized in Table 7.3.

Table 7.3 Protocol violations.

Violation	Total	Ziconotide	Placebo
Inclusion/exclusion criteria violations:			
Co-existing heart disease/asthma	6	2	4
Pre-existing dementia	2	2	
Illiterate	2	2	
Catheter tip above T10	2	1	1
Non-patent spinal canal	1		1
Other investigational drug within 30d	2		2
Had not failed systemic opioids	1	1	
Lack of source documentation - no answer recorded re: withdrawn from all intrathecal meds	2		2
Lack of VASPI data			
Preinfusion score under anesthesia	1	1	
No VASPI from study termination	1	1	
Titration begun before score completed	1	1	
Not randomized, open label	1	1	
Unblinded at incorrect point in study	1		
Incorrectly crossed over to ziconotide after placebo maintenance		1	

*Some patients had more than one violation

On review of the CRF's, it was determined by this reviewer that the only protocol violation that actually would impact the primary efficacy outcome variable was the one patient not randomized and given study drug in an open label manner. The sponsor has already excluded that patient from the evaluable population and from the ITT population.

Of the remaining patients with protocol violations:

- Two patients with preexisting dementia one (5005-73) actually scored a 25 on the MMSE (above the exclusion criterion of 24) and the other patient (5024-73) scored 17 but was also illiterate limiting the reading and writing elements of the exam.
- Two patients with exposure to other investigational drugs (5029-49, 5508-50) had actually been granted exemptions for radiation therapy, not investigational drugs.
- Two patients with missing documentation, (5007-51, 5007-75), no answer to the criterion of withdrawal from intrathecal medication, had not received prior intrathecal medication.
- Two patients with catheter tips above T10, (5005-50, 5029-49), were granted exemptions for their preexisting intrathecal catheters and pumps.
- Three patients were lacking VASPI data. One patient (501-82) had a preinfusion (baseline) score taken with the patient still under anesthesia and one patient (5009-52) started drug infusion before the preinfusion VASPI score was completed. For these two patients, the screening VASPI scores were used as baseline scores. One patient (5003-49) had no study termination VASPI score as he was obtunded at the time of termination. The last available VASPI was used in place of the termination score.

- One patient (5006-49) was a nonresponder and was unblinded after the initial titration period.
- One patient (5014-49) received placebo during the initial titration and maintenance phases, but then was crossed over to receive ziconotide during the crossover phase. The results from this patient were interpreted for study 95-001 as a placebo responder and used for safety. The patient was then enrolled into 95-002.

There were an additional 21 protocol violations characterized by incorrect assignment into the second period of the study. Following the initial titration period, nonresponders were to be crossed over for titration with the alternate therapy and responders were to be entered into a maintenance period. These assignments and the results of pain assessments during this second phase of the study were to provide information for supportive and secondary efficacy analyses. The most common reason for the incorrect assignment was incorrect assessment of responder status by the investigator. These protocol violations did not impact the primary efficacy variable.

7.2.1.4.2 Disposition:

Of the 112 patients enrolled and treated, 108 met evaluability criteria. Sixty eight of these initially received ziconotide, 40 placebo. However, the ITT population included 71 patients who received ziconotide. The disposition of the patients enrolled is detailed in Table 7.4.

Initial titration phase: Of the 72 patients receiving ziconotide, 11 withdrew during titration phase. Of the 40 patients initially receiving placebo, 3 discontinued during the initial titration. One additional patient in each initial titration group completed titration but did not enter a second phase.

Maintenance phase: Forty eight patients initially treated with ziconotide who completed initial titration entered maintenance. Of these, 9 discontinued the study during maintenance. There were no early discontinuations among the 11 patients initially treated with placebo that entered the maintenance phase.

Crossover phase: Three of the 12 patients crossed over from ziconotide to placebo and 8 of the 25 patients crossed over from placebo to ziconotide discontinued the study early.

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Table 7.4 Patient Disposition (From sponsor's Tables 8.1 and 8.3, Vol. 2.096, P. 112, 117)

	Initial Treatment Assignment	
	Ziconotide	Placebo
Number of Patients Randomized	71	40
All Treated Patients ^a	72 (100.0%)	40 (100.0%)
Safety Population	72 (100.0%)	40 (100.0%)
ITT Population	71 (98.6%)	40 (100.0%)
Evaluable Population	68 (94.4%)	40 (100.0%)
Reasons for Being Non-evaluable		
Not Randomized	1 (1.4%)	
Insufficient VASPI data	3 (4.2%)	
Number of Patients Who Completed the Study	47 (65.3%)	29 (72.5%)
Initial Titration Phase		
Completed Phase and Entered Second Phase	60 (83.3%)	36 (90.0%)
Completed Phase and Did Not Enter 2nd Phase	1 (1.4%)	1 (2.5%)
Primary Reason for Early Termination:		
Intolerable Adverse Event ^b	5 (6.9%)	2 (5.0%)
Withdrawal Requested by Patient	2 (2.8%)	0 (0.0%)
Unrelated Medical Condition	2 (2.8%)	0 (0.0%)
Infection ^c	0	1 (2.5%)
System Related (Pump/Catheter)	1 (1.4%)	0
Ineffective Drug Therapy / Loss of Effect	1 (1.4%)	0
Other	0	0
Maintenance Phase ^d		
Entered Phase	48 (66.7%)	11 (27.5%)
Completed Phase	39 (54.2%)	11 (27.5%)
Primary Reason for Early Termination		
Intolerable Adverse Event ^e	4 (5.6%)	0
Withdrawal Requested by Patient	1 (1.4%)	0
Death on Study ^f	2 (2.8%)	0
Ineffective Drug Therapy/Loss of Effect	1 (1.4%)	0
Other ^g	1 (1.4%)	0
Crossover Phase ^h		
Entered Phase	12 (16.7%)	26 (65.0%)
Completed Phase	7 (9.7%)	18 (45.0%)
Primary Reason for Early Termination		
Intolerable Adverse Event ⁱ	3 (4.2%)	8 (20.0%)
Withdrawal Requested by Patient	1 (1.4%)	0
Other ^j	1 (1.4%)	0

a Patient 5047-74 was not randomized but received open-label ziconotide on compassionate basis.

b One placebo patient (Patient 5047-49) discontinued due to an adverse event associated with the device.

c One placebo patient (Patient 5006-75) discontinued due to an infection associated with the device.

d Patients who completed the initial titration phase and underwent the maintenance phase continued to receive their initial treatment.

e Three ziconotide patients (Patients 501-87, 5025-74, and 5097-50) discontinued due to adverse events associated with the device

f Patient 5009-74 died of ovarian carcinoma, unrelated to drug. Patient 5025-49 died after a suicide attempt, possibly related to drug.

g Other included Patient 5006-73 (Patient went home on Day 6 with complete relief of pain).

h Patients who were nonresponders, during the initial titration phase were crossed over to receive the opposite treatment during the crossover phase. Includes Patient 5014-49 who crossed over to ziconotide after maintenance on placebo.

i Two placebo patients receiving ziconotide during the crossover phase (Patients 5002-25 and 5025-73) discontinued due to adverse events associated with the device.

j No reason was specified.

Data Source: Appendix 2. Table 1.2

7.2.1.4.3 Unplanned Analyses Include

1. Diagnosis and disease status variables data were sparse for treatment by intrathecal opioid use history. The CMH was not controlled for this, instead a CMH general association test was used.
2. Only treatment emergent AE's were summarized by study phase. A data listing of non-treatment emergent events was added. This change was made after unblinding the study.
3. Within group changes and between group differences in lab data were to be inferentially analyzed but were not, since not collected at crossover so parallel analysis between ziconotide vs. placebo was not possible. changes from screening to study termination were summarized descriptively.
4. ANCOVA was also to be performed for mean percent change in VASPI score from baseline to the end of the initial titration phase, with treatment, intrathecal opioid use history and treatment-by-intrathecal opioid use history interaction, baseline VASPI score and percent change in opioid use at the end of initial titration.
5. Treatment difference in daily percent change of VASPI score from baseline for the evaluable patients using a repeated measures ANOVA model including treatment, intrathecal opioid use history and interaction of treatment by intrathecal opioid use history.
6. CPRS at the end of the initial titration phase by CMH test (row mean score statistics) stratified by center.
7. Change in WPIS Subsets from baseline to the end of the initial titration phase by CMH test (row mean score statistics) stratified by center.

The planned interim analysis was not performed. The interim analysis of study 96-002 revealed a sufficiently robust response to study drug that the interim analysis for study 95-001 was deemed unnecessary and the number of patients enrolled in study 95-001 was terminated at 120 rather than the planned 200.

7.2.1.4.4 Baseline Characteristics

Diagnoses:

Ninety eight of 112 patients enrolled in the study carried the diagnosis of cancer. These patients were evenly distributed in the two treatment groups, 86.8% in the ziconotide group and 90% in the placebo group. The remainder of patients enrolled in the study had AIDS.

Demographics

The two treatment groups were similar with respect to the basic demographic characteristics of age, gender, Karnofsky score, and absence of nystagmus. Forty two percent of patients were 60 years of age or older, further age breakdown was not provided. These results are summarized in Table 7.5.

Table 7.5 Demographic and Baseline Characteristics (From sponsor's Table 8.5 -Evaluable Population)

Parameters	Initial Treatment Assignment		p-Value
	Ziconotide (N = 68)	Placebo (N = 40)	
Age (years) Mean (SE) Median (range)	55.3 (1.72) 57.5 (24.0-81.0)	56.6 (2.07) 56.0 (33.0-85.0)	0.777 (0.667) ^a
Gender Male Female	34 (50.0%) 34 (50.0%)	20 (50.0%) 20 (50.0%)	0.974 ^b
Race Caucasian Black Hispanic Asian	57 (83.8%) 8 (11.8%) 3 (4.4%) 0	38 (95.0%) 1 (2.5%) 0 1 (2.5%)	0.086 ^{b,c}
Diagnosis Cancer AIDS	59 (86.8%) 9 (13.2%)	36 (90.0%) 4 (10.0%)	0.619
Nystagmus Absent Present Missing	28 (41.2%) 5 (7.4%) 35 (51.5%)	14 (35.0%) 0 26 (65.0%)	0.107 ^b
Smoke Cigarettes Yes No Missing	6 (8.8%) 26 (38.2%) 36 (52.9%)	6 (15.0%) 9 (22.5%) 25 (62.5%)	0.123
Karnofsky Performance Score n Mean (SE) Median (range)	62 64.4 (1.92) 70.0 (30.0-90.0)	38 60.5 (2.41) 60.0 (30.0-90.0)	0.334 (0.711) ^a

Prior analgesic use

The mean baseline amount of opioid analgesics in morphine equivalents was greater in the ziconotide group, 6.2 g/d than the placebo group, 4.2 g/d, but this difference did not reach statistical significance. See Table 7.6.

Prior Intrathecal Morphine

Prior use of intrathecal morphine was identified pre hoc a potential source of bias. There were anticipated differences between patients who were naïve to intrathecal morphine compared with those having prior exposure to intrathecal morphine. The IT morphine naïve group would require implantation of external IT infusion systems, IT morphine experienced patients might already have implanted pumps. The IT morphine experienced patients would have to be withdrawn from the IT morphine prior to the study and stabilized on an oral or other systemic opioid regimen. To avoid this potential source of bias, randomization at the time of patient enrollment was stratified by prior treatment with intrathecal morphine. As a result, there was

comparable representation of IT morphine experienced and naïve in the two treatment groups, amounting to approximately one third of each treatment group.

This information is summarized in Table 7.6.

Table 7.6 Baseline analgesic status. (From sponsor's Table 8.6 1. 8, V. 096, P. 121)

Pain Characteristic	Initial Treatment Assignment		p-value (by CMH general association test)
	Ziconotide (N=68)	Placebo (N=40)	
Oral Morphine Equivalent (g/day)			0.634 (0.893)
Mean (SE)	6.2 (3.31)	4.2 (1.20)	
Median (range)	0.3 (0.0-201.8)	0.6 (0.0-30.0)	
Currently Receiving Systemic Analgesics			0.847
Yes	64 (94.1%)	38 (95.0%)	
No	4 (5.9%)	2 (5.0%)	
Currently Have SynchroMed Pump in Place			0.903
Yes	16 (23.5%)	9 (22.5%)	
No	52 (76.5%)	31(77.5%)	
Ever Been on Intrathecal Morphine			0.779
Yes	22 (32.4%)	14 (35.0%)	
No	46 (67.6%)	26 (65.0%)	
Pain Responsive to Intrathecal Morphine			0.909
Yes	9/22 (40.9%)	6/14 (42.9%)	
No	13/22 (59.1%)	8/14 (57.1%)	

Data Source: Appendix 2, Table 4.1

Baseline Pain Scores

The preinfusion pain assessment scores were similar between groups as demonstrated in Table 7.7.

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Table 7.7 Preinfusion Pain Assessments by Intrathecal Opioid Use History - Evaluable Population (From sponsor's Table 8.7, Vol. 2.096)

Pain Assessments	Initial Treatment Assignment		p-value
	ziconotide (N=68)	Placebo (N=40)	
VASPI Score (mm)			0.183 (0.921) ^a
n	68	40	
Mean (SE)	73.6(1.83)	77.9(2.31)	
Median (range)	75.0 (27.0-100.0)	79.5 (45.0-99.0)	
WPIS - Mood ^b			0.400
n	63	37	
Mean (SE)	2.4(0.15)	2.6(0.17)	
Median (range)	3.0 (0.0-4.0)	3.0 (1.0-4.0)	
WPIS - Relationship with Other People			0.479
n	63	37	
Mean (SE)	2.2 (0.14)	2.4 (0.16)	
Median (range)	2.0 (0.0-4.0)	2.0 (1.0-4.0)	
WPIS - Walking Ability			0.734
n	62	37	
Mean (SE)	2.9 (0.14)	2.8 (0.21)	
Median (range)	3.0 (0.0-4.0)	3.0 (0.0-4.0)	
WPIS - Sleep			0.238
n	63	37	
Mean (SE)	2.7 (0.15)	3.0 (0.17)	
Median (range)	3.0 (0.0-4.0)	3.0 (0.0-4.0)	
WPIS - Normal Work			0.472
n	61	35	
Mean (SE)	3.3 (0.13)	3.5 (0.14)	
Median (range)	4.0 (0.0-4.0)	4.0 (1.0-4.0)	
WPIS - Enjoyment of Life			0.37
n	63	37	
Mean (SE)	3.1(0.13)	3.3 (0.13)	
Median (range)	3.0 (0.0-4.0)	4.0 (1.0-4.0)	

a Treatment difference was tested using the 2-way ANOVA model with treatment, intrathecal opioid use history, and treatment by intrathecal opioid use history interaction as factors. The p-value for the treatment by intrathecal opioid use history interaction is given in parentheses.

b By CMH row mean scores test controlling for IT opioid use history)

Data Source: Appendix 2, Table 5.1

Concomitant Medications

The most frequent concomitant medications during the preinfusion and initial titration periods were opioids, laxatives antidepressants, anxiolytics, peptic ulcer drugs, antiepileptics, antipsychotics, antibacterials, antipruritics, propulsives, other analgesics and antipyretics, stomatological preparations, hypnotics and sedatives. The ziconotide group used more systemic antihistamines, primarily meclizine for dizziness and antipsychotics for nausea and more acetaminophen as fever was present more often in this group.

An excess in systemic antibiotics in the ziconotide group could not be explained by the sponsor.

7.2.1.4.5 Sponsor's Efficacy Results

Primary Efficacy Analysis

The primary efficacy measure was the percent change in VASPI score from baseline to end of initial titration. For the evaluable group, the VASPI decreased by 53% for patients initially treated with ziconotide and by 18% for patients initially treated with placebo, a statistically significant difference. These results are presented in Table 7.8. This difference remained statistically significant when the baseline VASPI was taken into account and when the concurrent use of opioids was taken into account.

Table 7.8 Percent Change in VASPI Score from Baseline to the End of Initial Titration Phase - Evaluable Population (From sponsor's Table 9.1 Vol. 2.096, P. 135)

Parameter	Initial Treatment Assignment		p-value ^a
	Ziconotide (N= 68)	Placebo (N=40)	
VASPI Score at Baseline (mm)			0.183 (0.921)
Mean (SE)	73.6 (1.83)	77.9 (2.31)	
Median (range)	75.0 (27 - 100)	79.5 (45 - 99)	
VASPI Score at End of Initial Titration (mm)			
Mean (SE)	34.2 (3.48)	61.0 (4.89)	
Median (range)	27.0 (0-99)	70.3 (4 - 100)	
% change VASPI score at End of Initial Titration ^b			0.0002 (0.337)
Mean (SE)	53.1 (4.63)	18.1 (6.77)	
Median (range)	62.3 (-26 -100)	7.8 (-62 - 96)	
95% CI for Mean ^c	(44.0, 62.2)	(4.8, 31.4)	
95% CI for Mean Difference ^c	(18.9, 51.1)		

a Treatment difference was tested using the 2-way ANOVA model with treatment, intrathecal opioid use history, and treatment by intrathecal opioid use history interaction as factors. The p-value for treatment-by-intrathecal opioid use history interaction is given in parentheses (see Appendix 13).

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

c Data were pooled across strata when calculating the 2-sided 95% confidence intervals for individual treatment mean and for treatment difference (ziconotide -placebo) in mean percent change in VASPI score at the end of the initial titration phase.

Data Source: Appendix 2, Table 9. 1, and Appendix 13

Subgroup Analyses Supportive of the Primary Efficacy Analysis

ITT population

The mean percent change in VASPI score from baseline to the end of the initial titration period for the ITT population was 51% for the ziconotide group and 18% for the placebo group; this was statistically significant. This statistically significant difference remained when the baseline VASPI score differences were taken into account.

Initial Dose

The mean percent change in VASPI score from baseline to the end of the initial titration period was analyzed by initial dose. The percent change in VASPI score was significantly greater for

the ziconotide group than placebo at both ≤ 0.1 ug/h and >0.1 ug/h initial doses. These results are presented in Table 7.9.

Table 7.9 Mean Percent Change in VASPI Score at End of Initial Titration Phase by Initial Dose and by Dose Range - Evaluable Population (From sponsor's Tables 9.3 and 9.4, Vol. 2.096, P. 145)

Initial Dose Group	Ziconotide		Placebo (N = 40)		p-value
	N	Mean (SE)	N	Mean (SE)	
≤ 0.1 ug/h	38	44.9(6.21)	21	21.1 (8.93)	0.042 (0.455) ^b
>0.1 ug/h	29	64.1(6.52)	19	14.8 (10.50)	0.001 (0.490) ^b
Dose Range at VASPI^a					
< 0.2 ug/hr	21	51.2(7.28)	2	38.6 (49.70)	
$> 0.2, \leq 0.3$ ug/h	7	58.9 (12.51)	4	47.3 (27.75)	
$> 0.3, \leq 0.6$ ug/h	16	56.2(7.97)	7	29.9 (17.37)	
$> 0.6, \leq 1.0$ ug/h	8	83.0(9.22)	0	--	
> 1.0 ug/h, ≤ 2.0 ug/h	9	41.7 (16.15)	11	11.3 (11.64)	
> 2.0 ug/h	7	26.6 (19.83)	16	7.7(9.65)	
All Dose Ranges	68	53.1(4.63)	40	18.1 (6.77)	0.016 (0.569) ^c

a. The dose range refers to the administration rate when the final efficacy assessment in the initial titration phase was made.

b. Treatment difference for initial dose group was tested using the 2-way ANOVA model with treatment, intrathecal opioid use history, and treatment by intrathecal opioid use history interaction as factors.

c. Treatment difference for dose range was tested using the 2-way ANOVA with treatment, dose range, and interaction of treatment by dose range as factors. The p-value for the interaction is presented in parentheses. Dose range >0.6 and < 1.0 was combined with dose range >1.0 and <2.0 for analysis due to the missing cell.

Data Source: Appendix 2, Tables 9.3, 9.4, Table 9.7

The patients in the initial dose group of ≤ 0.1 ug/h had a mean percent change in VASPI of 44.9 compared with 64.1 for the patients in the initial dose group of >0.1 ug/h. In addition, the difference in the mean percent change in VASPI between treatment groups was 23.8 for the initial dose group of ≤ 0.1 ug/h compared with 49.3 for the initial dose group of >0.1 ug/h suggesting greater efficacy with the higher dose regimen represented by the higher initial dose.

Dose Range

The mean percent change in VASPI score from baseline to end of initial titration period by dose range at the time of VASPI measurement at the end of titration was analyzed. These results are present in Table 7.9. There was a greater change in VASPI for the ziconotide group than for the placebo group at all dose ranges but the number of patients in each group at each dose was too small to permit individual statistical comparisons.

Treatment Day

For the ziconotide group, the mean percent change in VASPI from the score at baseline to the score taken on each treatment day, 1 through 5 or 6, increased progressively from 17.5% to 55.1%. For the placebo group, there was no consistent trend as the mean percent change in VASPI score varied between 17.9% and 26.1%. The difference between treatment groups was statistically significant ($p=0.010$).

Demographic subgroups

Age

There was no effect of age on the mean percent change in VASPI scores for patients initially treated with ziconotide, but among patients in the placebo treated group, there was a greater change for patients <60 years old as demonstrated in Table 7.10. The significance of this is unclear.

Table 7.10 Mean Percent Change in VASPI Score at End of Initial Titration Phase by Demographic Subgroups - Evaluable Population (From Sponsor's Table 9.6 Vol. 2.96, P. 150)

Demographic Subgroup	Initial Treatment Assignment			
	n	Ziconotide Mean (SE)	n	Placebo 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

Gender

There was a greater mean percent change in VASPI for the female patients in both the ziconotide and the placebo treated groups, so that the between treatment group differences for male and female patients was not significantly different.

Race

There was an effect of race on the primary outcome measure. While overall, the ziconotide treated patients scored greater changes in the mean percent change in VASPI score than the placebo treated patients, the "other than Caucasian" patients treated with placebo had a greater mean percent change in VASPI than the corresponding ziconotide treated patients. There were however, only 2 patients in this placebo subgroup.

Prior intrathecal Morphine Use:

There was no effect of prior intrathecal opioid use on the response to ziconotide. (See Table 9.7, Vol. 2.096, P. 151.)

Drug-Disease Interactions

There was a significant change in mean percent change in VASPI score for both cancer and AIDS patients treated with ziconotide compared with placebo treated patients. This change was slightly greater for the cancer patients than the AIDS patients.

There were no drug-center interactions.

Secondary Efficacy Parameters:

Percent Change In Opioid Use

The percent change in daily opioid use at the end of the initial titration phase represented a very large range, due to several outlying values, from -100 to 6645.7% in the ziconotide group and -100 to 1680.8% in the placebo group. As shown in Table 7.11, there was a slight decrease in opioid use in the ziconotide treated group and a small increase in the placebo treated group. No statistical comparison was performed by the sponsor. The sponsor also performed supplemental analyses, one excluding outliers with more than a 100% change and one excluding outliers with more than a 1000% change. These supplemental analyses again demonstrated a slight decrease in the amount of opioid use in the ziconotide group and a slight increase in the placebo group. (See Tables S12.1.1 and S2.1.2, Appendix 2 v2.097, P. 101)

Table 7.11 Percent Change in Daily Opioid Use at the End of the Initial Titration Phase - Evaluable Population (From Sponsor's Table 9.17 Vol. 2.096, P. 170)

Parameter	Ziconotide	Placebo
Mean Percent Change in Opioid Use at End of Initial Titration		
n	68	40
Mean (SE)	-9.9 (6.9)	5.1 (10.1)
Median (range)	-10.1 (-100.0-100)	0.0(-100.0-100)

Data Source: Appendix 2, Table S12. 1.1

Therapeutic dose level

The dosages at the time of onset of analgesia was evaluated by initial dose for patients who received ziconotide during the initial titration period and these are summarized in Table 7.12. Patients receiving an initial dose of ≤ 0.1 ug/h reached the onset of analgesia at a mean dose of 0.48 ug/h. Patients receiving an initial dose of >0.1 ug/h reached the onset of analgesia at a mean dose of 3.12 ug/h. The original and first 2 amended dosing regimens started dosing at higher doses, with only 12 hours between titration steps, and incorporated a forced titration to toxicity. By waiting only 12 hours between titration steps it is possible that many patients were titrated to the next dose level before experiencing the full effect of the lower dose. As a result, the onset of analgesia would be attributed to a higher dose in these patients. Instructions to end the forced titration and lower the starting dose to 0.1 ug/h were part of revision 3, dated 2/21/97.

Patients beginning titration with an initial dose >0.1 ug/h also ended titration at a higher dose than patients starting with an initial dose of ≤ 0.1 ug/h. The dosing instructions to titrate to toxicity with titration at 12 hour intervals likely also impacted the final dose as well.

Table 7.12 Ziconotide Dosing Information during Initial Titration Phase (From sponsor's Table 9.5 Vol. 2.096, P. 148)

Parameter	Initial Dose		Total
	≤0.1 ug/h	> 0.1 ug/h	
Dose at End of Initial Titration (ug/h) ^a			
n	39	29	68
Mean (SE)	0.52(0.09)	1.34(0.33)	0.87(0.16)
Median	0.3	0.8	0.6
Range	0.074 - 2.400	0.200 - 9.360	0.074 - 9.360
Cumulative Dose During Initial Titration (ug) ^b			
n	39	29	68
Mean (SE)	36.90 (4.25)	167.83 (34.25)	92.74 (16.66)
Median	26.63	95.79	56.53
Range	6.80 - 116.80	36.15 - 880.55	6.80 - 880.55
Dose at Onset of Analgesia (ug/h) ^c			
n	39	29	68
Mean (SE)	0.48(0.09)	3.12(0.95)	1.60(0.43)
Median	0.2	1.5	0.6
Range	0.10-2.40	0.20-20.58	0.10-20-58

a The last non-zero dose level administered during the initial titration phase was reported.

b The cumulative dose ug/h at the end of the initial titration phase with K distinct doses was estimated as: [dose level 1 (ug/hr) x duration of dose level 1 (hours) and dose level 2 ug x duration of dose level 2 (hours) +...+ dose level K (ug/hr) x duration of dose level K (hours)].

c Onset of analgesia was defined as when the percent change in VASPI was >20% and the CPRS score was 2:2 (i.e., at least a slight improvement). For patients who did not have onset of analgesia, the maximum dose level during the initial titration phase was used.

Data Source. Appendix 2, Table 8.1

Period of treatment

The assignment into either the maintenance phase or crossover for the alternate therapy during the second period of the study was based on the investigator's assessment of whether a patient was a responder or nonresponder. This assessment was performed incorrectly for 21 patients. Of the 49 patients initially treated with ziconotide and placed in maintenance, 15 were incorrectly assigned. Of the 11 placebo treated patients placed in maintenance, 2 were incorrectly assigned. As a result of these errors, the data from the maintenance group will not be assessed further.

Patients determined to be nonresponders at the end of the initial titration period were to be crossed over to the alternate treatment. Of the 7 ziconotide treated patients crossed over to placebo, one was incorrectly assigned. Of the 26 placebo treated patients crossed over to ziconotide, 3 were incorrectly assigned. The mean percent change in VASPI score during the initial titration period was negligible for these nonresponders regardless of treatment group. Placebo nonresponders crossed over to ziconotide for the second treatment period responded with a mean percent change in VASPI score of 44.9%. This is comparable to the 53% reduction in mean VASPI score at the end of the initial titration for patients initially treated with ziconotide. These results are presented in Table 7.13.

Table 7.13, Evaluable Patients Who Underwent The Crossover Phase (From Sponsor's Table 9.10, Vol. 2.096, P. 156.)

Parameter	Initial Treatment Assignment	
	Ziconotide (N=12)	Placebo (N=26)
Mean % Change In VASPI From Baseline To The End Of Initial Titration (SE)	0.2 (5.26)	-3.1 (5.67)
Mean % Change In VASPI From Baseline To Study Termination (SE) (After crossover period)	4.2 (6.75)	44.9 (8.65)

Change in VASPI score and CPRS

The results of the mean absolute change in VASPI score and mean change in CPRS, from baseline to the end of the initial titration, are presented in Table 7.14. These analyses were performed on the evaluable population. Only 54 of 68 evaluable patients in the ziconotide group and only 31 of 40 in the placebo group had complete CPRS data. There were statistically significant changes in favor of greater pain relief for the ziconotide treated group by both scales.

Table 7.14 Absolute change in VASPI and CPRS - Evaluable Population (from Sponsor's Tables 9.11, 9.13 Vol. 2.096, P. 158, 160)

Parameter	Initial Treatment Assignment		p-value
	Ziconotide N = 68	Placebo N = 40	
Change in VASPI Score (mm)			0.002 (0.453) ^a
Mean (SE)	39.4(3.61)	16.9 (5.61)	
Median (range)	45.0 (-17 - 99)	7.5 (-34 - 93)	
	N=54	N=31	
Category Pain Relief Scale			<0.001
Worse	4 (5.9%)	7 (17.5%)	
No Change	9 (13.2%)	8 (20.0%)	
Slight Improvement	5 (7.4%)	9 (22.5%)	
Moderate Improvement	7 (10.3%)	1 (2.5%)	
A Lot of Improvement	24 (35.3%)	6 (15.0%)	
Complete Relief	5 (7.4%)	0 (0.0%)	
Missing	14 (20.6%)	9 (22.5%)	

^a Treatment difference was tested using the 2-way ANOVA model with treatment, intrathecal opioid use history, and treatment by intrathecal opioid use history interaction as factors. The p-value for treatment-by-intrathecal opioid use history interaction is given in parentheses.

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

Data Source: Appendix 2, Table 9.1

There was no effect of prior intrathecal opioid use for the results of the absolute change in VASPI score for the ziconotide treated group. There was however, an effect of prior intrathecal opioid use on the results of the absolute change in VASPI score for the placebo group with patients having a history of IT morphine use demonstrating a greater change in the VASPI score than the IT morphine naive group.

WBPIS

There were no differences between the ziconotide and placebo treated groups with respect to any of the WBPIS subsets: Mood, Relationship with Other People, Walking Ability, Sleep, Normal

Work, or Enjoyment of Life (p-values ranged from 0.39 to 0.98). The sponsor explains this lack of difference as a possible artifact, that the WPBIS correlates better with worst pain rather than with the repeated pain measures.

Table 7.15 Change In the Wisconsin Brief Pain Inventory Subsets (WPBIS) at the End of the Initial Titration Phase -Evaluable Population (From Sponsor's Table 9.14 Vol. 2.096, P. 163)

Parameter	Initial Treatment Assignment				p-value
	Ziconotide N=68		Placebo N = 40		
Change in WPBIS - Mood					0.984 ^a
Worsened by ≥ 2 units	7	10.3%	6	15.0%	
Worsened by 1 unit	12	17.6%	6	15.0%	
Unchanged	22	32.4%	12	30.0%	
Improved by 1 unit	6	8.8%	3	7.5%	
Improved by ≥ 2 units	4	5.9%	4	10.0%	
Missing	17	25.0%	9	22.5%	
Change in WPBIS - Relationship with Other People					0.596
Worsened by ≥ 2 units	12	17.6%	5	12.5%	
Worsened by 1 unit	8	11.8%	7	17.5%	
Unchanged	22	32.4%	12	30.0%	
Improved by 1 unit	4	5.9%	3	7.5%	
Improved by ≥ 2 units	4	5.9%	3	7.5%	
Missing	18	26.5%	10	25.0%	
Change in WPBIS - Walking Ability					0.444
Worsened by ≥ 2 units	7	10.3%	4	10.0%	
Worsened by 1 unit	11	16.2%	3	7.5%	
Unchanged	24	35.3%	16	40.0%	
Improved by 1 unit	5	7.4%	4	10.0%	
Improved by ≥ 2 units	4	5.9%	3	7.5%	
Missing	17	25.0%	10	25.0%	
Change in WPBIS - Sleep					0.480 ^a
Worsened by ≥ 2 units	15	22.1%	7	17.5%	
Worsened by 1 unit	10	14.7%	6	15.0%	
Unchanged	20	29.4%	13	32.5%	
Improved by 1 unit	4	5.9%	2	5.0%	
Improved by ≥ 2 units	3	4.4%	3	7.5%	
Missing	16	23.5%	9	22.5%	
Change in WPBIS - Normal Work					0.390 ^a
Worsened by ≥ 2 units	7	10.3%	2	5.0%	
Worsened by 1 unit	4	5.9%	4	10.0%	
Unchanged	18	26.5%	13	32.5%	
Improved by 1 unit	4	5.9%	2	5.0%	
Improved by ≥ 2 units	0	0.0%	1	2.5%	
Missing	35	51.5%	18	45.0%	
Change in WPBIS - Enjoyment of Life					0.889 ^a
Worsened by ≥ 2 units	9	13.2%	7	17.5%	
Worsened by 1 unit	11	16.2%	4	10.0%	
Unchanged	23	33.8%	14	35.0%	
Improved by 1 unit	5	7.4%	5	12.5%	
Improved by ≥ 2 units	2	2.9%	0	0.0%	
Missing	18	26.5%	10	25.0%	

a. Treatment difference was tested using the CMH row mean scores test stratified by intrathecal opioid

use history. The category "missing" was excluded when calculating the P-value.
 Data Source: Appendix 2, Table 10. 1

Karnofsky Performance Status Score

There were no differences between treatment groups in the Karnofsky Performance Status Score at the end of the initial titration phase (p=0.93) (or at the end of maintenance and crossover phases) compared to baseline for the evaluable population.

Table 7.16 Change in Karnofsky Performance Status Score at the End of the Initial Titration, and Maintenance Phases - Evaluable Population (From Sponsor's Table 9.15, Vol. 2.096, P. 166)

Parameter	Initial Treatment Assignment		p-value
	Ziconotide	Placebo	
Karnofsky Performance Status Scale Score at Baseline ^a			
n	46	25	
Mean (SE)	65.7(2.28)	58.0(2.89)	
Median (range)	70.0 (30 - 90)	60.0 (30 - 80)	
Change in Karnofsky Performance Status Scale Score from Baseline to End of Initial Titration Phase			0.935 (0.935) ^b
n	46	25	
Mean (SE)	0.2(1.44)	0.4(1.22)	
Median (range)	0.0 (40 - 20)	0.0 (-10 - 20)	
Change in Karnofsky Performance Status Scale Score from Baseline to End of Maintenance Phase			
n	38	10	
Mean (SE)	3.4(1.52)	5.0(4.01)	
Median (range)	0.0 (-30 - 20)	0.0 (-20 - 20)	

a. Baseline is presented for patients with end of initial titration reading.

b. Treatment difference was tested using the 2-way ANOVA model with treatment, intrathecal opioid use history, and treatment by intrathecal opioid use history interaction as factors. The p-value for treatment by intrathecal opioid use history interaction is given in parentheses.

Note: Scale 0 (dead) - 100 (normal).

Data Source: Appendix 2, Tables 10.3 and 10.4

VASPR and Memorial Pain Assessment Card

The VASPR and the Tursky description and Mood Score of the Memorial Pain Assessment Card all demonstrated improvement in pain relief, mood and pain description for both treatment groups. The changes were larger for the ziconotide group but the sponsor did not perform inferential statistics.

Table 7.17 VASPR, Mood Score, and Tursky Description at End of Initial Titration Phase - Evaluable Patients (From Sponsor's Table 9.16 Vol. 2.096, P. 168)

Parameter	Initial Treatment Assignment			
	Ziconotide		Placebo	
	Preinfusion	End of Initial Titration	Preinfusion	Titration End of Initial
VASPR^a				
n	62	68	37	39
Mean (SE)	30.0 (2.8)	63.6 (3.8)	20.5 (2.9)	42.2 (5.3)
Median (range)	24.0 (0 - 100)	73.0 (0 - 100)	14.0 (0 - 63)	28.0 (1 - 99)
Mood Score				
n	63	68	38	39
Mean (SE)	49.6 (3.1)	60.7 (3.2)	33.2(3.7)	52.3(4.9)
Median (range)	54.0 (5 -100)	64.0 (1 -100)	31.0 (1 - 94)	58.0 (1 - 100)
Tursky Description				
No pain	1 (1.5%)	7 (10.3%)	0 (0.0%)	1 (2.5%)
Just Noticeable, Mild or Weak	2 (2.9%)	27 (39.7%)	1 (2.5%)	8 (20.0%)
Moderate or Strong	40 (58.8%)	26 (38.2%)	20 (50.0%)	9 (47.5%)
Severe or Excruciating	21 (30.9%)	8 (11.8%)	17 (42.5%)	10 (25.0%)
Missing	4 (5.9%)	0 (0.0%)	2 (5.0%)	2 (5.0%)

a. Scale for VASPR: 0 (no relief of pain) to 100 (complete relief of pain),

Mood: 0 (worst mood) to 100 (best mood).

Data Source: Appendix 2, Table 10.5

Responder Rate

As noted in the protocol, the definition of a responder was established at the beginning of the trial and served as a means of determining the nature of the second phase of treatment. There were many errors by the investigators in determining which patients met these criteria. The sponsor reviewed the CRF's and determined which patients truly met the responder criteria (derived data). These results are presented in Table 7.18. The difference in proportion of responders between treatment groups is statistically significantly greater for the ziconotide treated group.

Table 7.18 Number (%) of Patients Who Responded to Treatment at the End of the Initial Titration Phase - Evaluable Population (From Sponsor's Table 9.18 Vol. 2.096, P. 172)

Parameter	Initial Treatment Assignment	
	Ziconotide (N=68)	Placebo (N=40)
Number of Responders (%)	34 (50.0%)	7 (17.5%)
Number of Nonresponder (%)	34 (50.0%)	33 (82.5%)
95% CI for Percent Responders	(37.6%, 62.4%)	(7.3%, 32.8%)
Treatment Difference (Ziconotide-Placebo) in Percent Responders ^a	32.5%	
95% CI for Treatment Difference in % Responder ^a	(15.8%, 49.2%)	
p-value ^b	0.001	

^a Treatment difference was tested using the CMH general association test controlling for intrathecal opioid use history.

b Symmetric confidence intervals are calculated using the binomial distribution.
 Data Source: Appendix 2, Tables 11.11

During the second period of treatment following crossover of placebo nonresponders to ziconotide, 8 of 26 (30.8%) patients met the criteria for responders. None of the 12 ziconotide nonresponders crossed over to placebo were responders. The difference in the proportion of responders between the ziconotide and placebo groups during the crossover period is comparable to the initial titration period.

There was a larger proportion of ziconotide treated patients with a history of IT morphine exposure who met the criteria for responder than those who were IT morphine naïve. These results are presented in Table 7.19. Among patients treated with ziconotide, both IT morphine experienced and naïve groups still demonstrated a greater proportion of patients meeting the criteria for responder than the respective placebo treated patients.

Table 7.19 Patients Who Responded to Treatment at the End of the Initial Titration Phase by Intrathecal Opioid Use History- Evaluable Population (From sponsor's Table 9.21 Vol. 2.096, P. 175.)

Parameter	Initial Treatment Assignment			
	Ziconotide		Placebo	
	IT Morphine Experienced (N = 22)	IT Morphine Naive (N = 46)	IT Morphine Experienced (N = 14)	IT Morphine naïve (N = 26)
Initial Titration Phase				
Responder	13 (59.1%)	21 (45.7%)	4 (28.6%)	3 (11.5%)
Nonresponder	9 (40.9%)	25 (54.3%)	10 (71.4%)	23 (88.5%)
95% CI for % Responder ^a	(36.4%, 79.3%)	(30.9%, 61.0%)	(8.4%, 58.1%)	(2.4%, 30.2%)

a Symmetric confidence intervals are calculated using the binomial distribution

7.2.1.4.6 Reviewer's Efficacy Summary:

This study is presented by the sponsor as one of two pivotal efficacy trials. There was a problem with the study design in that the individual investigators had difficulty determining the correct treatment assignment for the second treatment period. This problem had no effect on the primary efficacy variable, mean percent change in VASPI score, measured at the end of the initial treatment period, nor on secondary efficacy variables that were also measured at the end of the initial titration period.

This study demonstrated that treatment with intrathecal ziconotide was superior to treatment with placebo for the relief of chronic pain due to malignancy and AIDS. This treatment effect was independent of supplemental opioid use, baseline demographic factors and baseline pain scores. There was concordance between the primary efficacy variable of mean percent change in VASPI, as well as by the secondary measures CPRS and absolute change in VASPI score. The reduction in VASPI increased over the 5 day titration period for the ziconotide treated group. There was no improvement in functionality as demonstrated by the lack of difference in the WBPIS scores between the treatment groups. There was a dose related effect evidenced by a

greater change in the mean percent change in VASPI for patients beginning titration with >0.1 ug/h compared with patients beginning with an initial dose of ≤0.1 ug/h.

Based on this study, intrathecal ziconotide in doses from 0.1 to 2 ug/h appears to be effective in providing relief from chronic pain due to malignancy and AIDS.

SECTION 7.2.2 STUDY 96-002

SECTION 7.2.2.1 Protocol Synopsis

Title: A Multicenter, Phase II/III, Placebo Controlled Study Of SNX-111 (SNX) Administered Intrathecally To Patients With Chronic Non-Malignant Pain.

Objective: To assess the safety and efficacy of increasing doses of IT SNX in chronic non-malignant pain compared to placebo

Inclusion Criteria:

1. Patients with chronic non-malignant pain who have intrathecal catheters and/or Medtronic SynchroMed infusion System in place, or whose next line of therapy would require placement of such devices.
2. The patient has been slowly tapered and discontinued from intrathecal medications, stabilized on oral or systemic analgesics for at least 3 d prior to enrollment in study.
3. Medically capable of having a pump and /or temporary catheter implanted.
4. Average VASPI over past 3 days on oral or systemic opioids of at least 50
5. At least 18 years of age.
6. Women must not be pregnant or breastfeeding. Women must be postmenopausal or if of child bearing potential, using an acceptable method of contraception.
7. History of unsatisfactory response to systemic opioids and has tried at least 2 of the following: NSAIDs, antidepressants, anticonvulsants or topical agents.
8. History of a failed a course of physical therapy where appropriate.

Exclusion Criteria:

1. Sepsis
2. CHF, sinus bradycardia with greater than 1st degree block, asthma, syncope
3. Diagnosis of dementia/delirium, somatization d/o, hypochondriasis, Munchausen's syndrome, inadequately treated affective d/o. If these are possible, patient must be evaluated and cleared by a psychiatrist.
4. Investigational drug study within 30 d
5. Physical or psychological problem precluding pump implantation or use of external pump
6. Intrathecal catheters above T1
7. Implanted infusion pumps or catheters other than SynchroMed system

Enrollment of 170 patients was planned.

During the screening period, patients were to be stabilized on a systemic analgesic regimen for at least 3 d prior to study enrollment. Patients receiving intrathecal therapy were to be tapered off all intrathecal medication for a minimum of 3 days prior to beginning study medication.

During the pre-infusion period, patients would then be randomized to SNX or placebo and begin a blinded 6 day initial titration as inpatients. The primary efficacy endpoint was to be measured at the end of this titration period.

Randomization was to be 2:1 SNX to placebo, and stratified by central vs. peripheral pain syndrome. Randomization was also to be stratified by center, with a block size of three within a center.

The following definitions were provided by the sponsor to determine treatment assignments at the conclusion of the initial titration period and to assist with decisions concerning dosage adjustment.

1. Responders - patients experiencing a $\geq 30\%$ drop in VASPI (an average of the last 2 measurements taken within a 2 h period or 3 if the first 2 measurements differ by greater than 15 mm) compared with baseline in the setting of stable or decreasing regimen of concurrent opioid analgesics and no change in the type of concurrent opioid analgesics.
2. Non-responders - patients experiencing $< 30\%$ drop in VASPI or a 30% drop in the setting of increased opioid analgesics including a change in type of opioid analgesic
3. Early responders - patients who demonstrate a response prior to 144 h of study medication infusion, on initial or crossover arms
4. Onset of analgesia - a minimum of 20% improvement from baseline VASPI with confirmation by categorical pain relief scale, without an increase in opioids

At the conclusion of the 6 day initial titration period:

3. Responders were to continue on the same treatment for a 5 day maintenance period as out-patients. At the end of the 5 day maintenance period the treatment assignments were to be unblinded:
 - 1a. Responders to SNX were to be enrolled in a long term study
 - 1b. Responders to placebo were to be discontinued from the study.
4. Non-responders were to have the medication assignment unblinded:
 - 2a. Non-responders to SNX were discontinued from the study.
 - 2b. Non-responders to placebo were to be crossed over, open-label, to SNX and titrated as in-patients for 5 days.
 - 2b(i). SNX responders from this period were to be offered enrollment in a long term study.
 - 2b(ii). SNX non-responders were to be discontinued from the study.

Study Medication:

The study drug was to be SNX-111 acetate in vehicle with L-methionine and NaCl, pH 4.3 +/- 0.2. The placebo and diluent were the same as vehicle.

The dosing regimen was changed twice during the study, the details are described below in the protocol amendments. The 3 dosing regimens used are presented below.

Time (Hours)	Original (ug/h)	Revision 1, 10/21/96 (ug/h)	Revision 2, 2/21/97 (ug/h)
0-24h	0.4	0.4	0.1
24-48	0.9	0.6	0.2
48-72	1.8	0.9	0.3
72-96	3.4	1.5	0.6
96-120	5.3	2.4	1.2
120-144	7.0	3.9	2.4

Subjects were to be titrated to efficacy at titration intervals of 24 h. As of revision 1, once the onset of analgesia began, the dose was to be held an additional 24 h to permit the full analgesic effect to occur. Also as of revision 1, any dose could have been held an additional 24 h before further increase, at the investigator's discretion. A dose was to be maintained or reduced as needed based on the appearance of lateral gaze nystagmus, a change in baseline confusion, or the appearance of other adverse events (AE's) thought to be related to study drug.

Concomitant Medication:

No intrathecal medications were to be allowed. Rescue medication was to be systemic opioids and adjuvant analgesics/sedatives as needed. Physical therapy and acupuncture were to be permitted. Any change in concomitant or rescue analgesic type was to be considered an increase in medication even if the total dose remained the same.

Table 7.20 Schedule of Events (From sponsor's Table 7.1, Vol. 2.096)

Procedure			Initial Titration and Crossover Phase		Maintenance		
	Screening phase	Pre-infusion	Inpatient Treatment	144 Hours Post-infusion	Outpatient Treatment 5 Days	Study Termination	2 Week Post-study F/U Visit
Written Informed Consent	X						
Medical History	X						
D/C Intrathecal Medication	X						
Concomitant Medication	X	X	X	X	X	X	
Complete PE, neuro exam	X	brief				X	
Vital Signs (incl. orthostatics)	X	X	q 8h	X		X	
12-Lead Electrocardiogram	X					X	
3-day VASPI (average)	X						
Exam for nystagmus	X		X				
Trails A and B, Digit Symbol Test		X		X		X	
Laboratory Evaluations	X					X	pm
Pregnancy Test	X						
Plasma Ziconotide Levels	X			X		X	
Study Drug Administration			X				
VASPI		X	q 24h	X ^b		X	
CPRS ^c		X	q24h			X	
WBPI ^d		X				X	
McGill Pain Questionnaire		X				X	
Allodynia assessment	X					X	
QOL Assessments ^a	X	X					
Adverse Events			X	X	X	X	pm
Break Blind				non-responders		for pts on maintenance	
Eval. for Long-Term Study						X	

- a. Quality of Life (QOL) assessments: Sickness Impact Profile Short form and the Pain Disability Index.
- b. VASPI scores at termination are performed twice within 2h, if the difference is greater than 15, a 3rd score will be taken. All 3 scores must be measured within 4 h.
- c. Category Pain Relief Scale
- d. Wisconsin Brief Pain Inventory Scale

Pain and Functionality Assessment Scales:

Visual Analog Scale Pain Intensity (VASPI) - a standard 100 mm visual analog scale

Category Pain Relief Scale (CPRS) a 6 point categorical scale from 0 - "My pain is now WORSE compared to before the infusion started." to 5 - "I have COMPLETE RELIEF of my pain compared to before the infusion started"

Wisconsin Brief Pain Inventory Scale (WBPI) - a series of 6 descriptions of function: mood, relationships with other people, walking ability, sleep, normal work and enjoyment of life, scored on a 0 (not at all) to 4 (extremely) categorical scale.

McGill-Melzack Pain Questionnaire (Vol. 2.107, P. 069) -a tool consisting of 3 major classes of word descriptors--sensory, affective and evaluative--that are used by patients to specify subjective pain experience, along with an intensity scale and other items to determine the properties of pain experience. The 3 major measures are: (1) the pain rating index, based on two types of numerical values that can be assigned to each word descriptor, (2) the number of words chosen; and (3) the present pain intensity based on a 1-5 intensity scale

Short Form Sickness Impact Profile (Vol. 2.107, P. 072)- a list of 20 statements, patients check off those that describe them on the day they are responding to the evaluation. Includes statements such as: "I am going out less to visit people", "I often moan and groan in pain or discomfort", "I walk more slowly".

SECTION 7.2.2.2 Statistical Analysis:

7.2.2.2.1 Patient Populations:

The sponsor has provided the following definitions of the evaluable, intent-to-treat and safety populations. The sponsor has planned to use the evaluable population for the efficacy analysis.

- The evaluable population was to be those patients having met all inclusion criteria and none of the exclusion criteria, no more than minor protocol violations, and at least one of the following: 1. at least one VASPI score after at least 4 full days of treatment, 2. have reached final dose prior to termination of the initial titration phase for at least 12 h, and had at least one VASPI at the end of the 12 h, 3. if terminated due to intolerable AE's, had at least one VASPI score on the last dose or dose prior to termination of the initial titration phase
- The intent-to-treat population consists of patients who received any amount of study medication, and had a baseline and at least one follow-up VASPI score during the initial titration phase.

- The safety population includes all patients having received any study medication with the exception of patient 6087-106 who represents the second randomized patient number for one patient.

All statistical tests were to be 2 sided and considered significant with a p-value of ≤ 0.05 .

Stratification:

Statistical analyses will be stratified by history of intrathecal opioid use.

For analyses including center as a stratification or adjustment factor, sites enrolling fewer than 9 subjects were to be pooled.

7.2.2.2.2 Planned Analyses:

Baseline and demographic characteristics: The baseline characteristics compared between groups were to be: demographics, characteristics of pain at screening, preinfusion pain assessments, analgesic equivalents of opioids at baseline.

- Cochran Mantel Haenszel (CMH) tests controlled by center for categorical data.
- Two-way ANOVA models with treatment, center and treatment-by-center interaction for continuous data..

Primary Efficacy Analysis:

The primary efficacy endpoint was to be the percent change of VASPI from baseline to the end of the initial titration phase = $[(\text{baseline VASPI} - \text{final VASPI})/\text{baseline VASPI}] \times 100$.

The primary efficacy endpoint was to be analyzed using a 2-way ANOVA model with treatment, center and treatment-by-center as interactions. Student's t-test was to be used to test significance of the mean percent change in VASPI from baseline to the end of the initial titration phase for each treatment group. This primary efficacy analysis was to be performed on the evaluable population.

Supportive Analyses of the Primary Efficacy Variable:

The supportive analyses on the primary efficacy variable were to include:

6. A 2-sided asymptotic 95% confidence interval for the overall treatment difference in the means of the primary efficacy variable calculated for the evaluable population with data pooled across all centers
7. Analysis of the primary efficacy variable for three additional patient populations:
 - d. The ITT population
 - e. evaluable patients with an initial dose ≤ 0.1 ug/h
 - f. ITT patients with an initial dose ≤ 0.1 ug/h
8. Treatment difference in the primary efficacy variable for evaluable patients using 2-way ANOVA models: including treatment, dose level at final assessment, interaction of treatment by dose level; treatment, pain syndrome and interaction of treatment by pain syndrome; and treatment, pain class, and interaction of treatment by pain class.
9. Treatment difference in daily percent change of VASPI score from baseline for the evaluable patients using a repeated measures ANOVA model including treatment, center and interaction of treatment by center.

10. Subgroup analyses of the primary efficacy variable: Descriptive summaries for gender, age, race and prior intrathecal morphine use.

Secondary Efficacy Analyses:

The planned secondary efficacy analyses are presented in Table 7.21.

Table 7.21 Secondary Efficacy Variables (From Sponsor's Table 7.3, Vol. 2.107 P. 091)

Variable(s)	Statistical Model
Change in VASPI score at the end of the initial titration phase	2-way ANOVA with treatment and center as factors and treatment-by-center interaction
% change from baseline in McGill Pain Score to the end of the initial titration phase	2-way ANOVA with treatment and center as factors and treatment-by-center interaction
Category Pain Relief Scale (CPRS) at the end of the initial titration phase	CMH test (row mean score statistics) stratified by center
Change in Wisconsin Brief Pain Inventory Subset (WBPIIS) from baseline to the end of the initial titration phase	CMH test (row mean score statistics) stratified by center
Proportion of treatment responders at the end of the initial titration phase	CMH test (general association) stratified by center and 95% CI (pooled across centers) for the treatment difference in the proportion of responders
Proportion of patients responding to ziconotide at the end of the crossover phase among patients under going the crossover phase	Conditional probability estimated as: (ziconotide responders in the crossover phase - number of patents undergoing the crossover phase); conditional 95% CI (pooled across centers)
Change in tactile allodynia parameters from baseline to the end of initial titration phase	Descriptive statistics; 2-way ANOVA with treatment, center factors and the treatment-by-center interaction for treatment difference in area
Among patients in maintenance: % change in VASPI and % change in McGill Pain Score from baseline of initial titration phase to study termination	Descriptive statistics
Among those patients who did crossover: % change in VASPI from baseline of initial titration phase to study termination	Descriptive statistics
Percent change in opioid use at the end of the initial titration phase	Descriptive statistics; plot in % change in opioid use vs. primary efficacy variable; linear correlation with % change in VASPI

Interim Analysis:

A sponsor blinded, third party interim analysis was to be performed on the first 50-100 patients in the evaluable population to confirm assumptions underlying the planned sample sizes. There was no plan to stop the study early or to change study conduct or design so no p-value penalty was planned.

SECTION 7.2.2.3 Protocol Amendments:

Original protocol date: 5/17/96

Administrative change 1: 8/16/96

- add EKG at day 6 for SNX nonresponders, day 11 for all SNX patients
- add Categorical Pain Relief Scale, McGill Pain Questionnaire and Wisconsin Brief Pain Inventory
- correction to short form sickness impact profile
- change VASPI to be consistent with other SNX studies

Administrative change 2: 8/30/96

- change approximate number of study sites and add Belgium sites
- replace section in which the SynchroMed referred only to applications in the US
- remove inclusion that patients speak English
- Add Biopharm contact
- Add that Belgium regulations will be followed

Amendment 1 10/28/96

- modify dose escalation
- add Pain Disability Index
- Add Quality of life analysis
- change routine pain assessment to q 24 h

Amendment 2 2/21/97

- changes in the minimum and maximum dose and dosing regimen based on additional information that analgesic effect and AE's have occurred at lower doses than in earlier studies.
- sections have been edited for clarity
- patients without implanted pump were added as eligible for long term extension
- decision trees were added

Administrative Change 3 11/14/97

- clarification of the randomization procedure
- revision of the statistical section to reflect changes in patient enrollment and add secondary analyses based on 2/21/97 revision
- clarification of concomitant opioid use analysis
- add information of the stability for SNX in the external pump
- For the definition of onset of analgesia, a $\geq 20\%$ drop from baseline in VASPI and CPRS ≥ 2 was to be used, without taking concomitant opioids into account as this was not calculated daily.

SECTION 7.2.2.4 Results

7.2.2.4.1 Conduct of study

Patient enrollment took place from 8/19/96 through 2/10/98. A total of 43 investigators at 43 centers enrolled patients. Nine investigators were responsible for enrolling 10 or more patients each. The remaining 33 centers enrolled less than 10 patients per center.

The planned interim analysis by an independent party was performed on 12/15/97. Over 200 patients had already been enrolled at that time, but the interim database consisted of 104 patients. The estimate of the standard deviation was revised and it was determined that to have 90% power for detecting the originally specified treatment difference of 30% with a 2:1 ration of ziconotide treated patients to placebo, a total of 80 patients would be required. The sample size already exceeded this 200 patients.

Protocol Deviations:

There were 20 patients with protocol deviations and these are summarized in Table 7.22.

Table 7.22 Summary of Protocol Deviations

Protocol Deviation	Number of Patients
Protocol deviations at study entry or during the initial titration period:	
Re-randomized to placebo from ziconotide	1
Inclusion/exclusion criteria violations:	18
Not withdrawn from intrathecal medication by 3d prior to enrollment ^a	5
Patient has congestive heart failure, sinus bradycardia, etc. ^b	8
VAS not >50 ^b	3
Patient has a previously implanted programmable medical device other than a SynchroMed pump ^c	2
Other ^c	4
Re-randomized to placebo from ziconotide	1

a. Listing 3.1, Appendix 3, Vol. 2.108

b. Listing 1.2, Appendix 3, Vol. 2.108

There were 18 patients with violations of inclusion and exclusion criteria.

- Five patients were not withdrawn from intrathecal medication at least 3 days prior to the start of study medication. One patient, 6054-101, was started on study medication on the third day following withdrawal of prior intrathecal medication and was included in the evaluable population by the sponsor. Patient 6054-102 and the remaining 3 patients who were from site 6076, were not included in the evaluable population.
- Three patients did not have documented VASPI scores >50 at screening. Two of these patients, 6062-102 and 6093-105, did not have VASPI scores documented at screening at all. These patients did have VASPI scores > 50 at preinfusion (baseline). The third patient, 6071-103, had a VASPI of 39 at screening, but this was felt to be uncharacteristically low. An exception was granted and the preinfusion VASPI score was >50. All 3 patients were included in the evaluable population.
- Four patients failed to meet a total of 5 of the inclusion/exclusion criteria: one patient had a missing response to the exclusion of pregnancy/lactating, one had participated in another investigational drug study within 30 days and this same patient also had an implanted infusion pump/catheter other than SynchroMed, one did not sign the consent form prior to study, and one could not read, understand and sign consent form. These patients were included in the evaluable population.
- Eight patients violated the exclusion criterion of prior history of congestive heart failure, sinus bradycardia, etc. These patients were included in the evaluable population.

One patient, 6087-105, who was initially randomized to ziconotide discontinued the trial due to a problem with the indwelling catheter dislodging. The patient was re-enrolled in the study with a second randomized number, 6087-106 with which the patient received placebo. This second enrollment is excluded from the evaluable population.

There were 16 patients considered non-evaluable by the sponsor. The reasons patients were excluded from the evaluable population are summarized in Table 7.23. There was a lack of source documentation available for all 12 of the patients enrolled at study site 6076. Seven of these patients were randomized to ziconotide and 5 to placebo. The sponsor has excluded all 12 of these patients from the evaluable population.

Table 7.23 Patients Excluded From the Evaluable Population (From Sponsor's Table 8.3, Vol. 2.096)

	Initial Treatment Assignment			
	Ziconotide		Placebo	
Non-evaluable Patients	8	(4.7%)	8	(9.2%)
Reasons Patients Were Not Eligible for the Evaluable Population ^a				
Lack of Source Documentation	7	(4.1%)	5	(5.7%)
Started Investigational Drug Within 30 Days of Study	0	(0.0%)	1	(1.1%)
IT Medication Used Within 3 Days Prior to Enrollment	2	(1.2%)	2	(2.3%)
Insufficient VASPI Data ^b	1	(0.6%)	1	(1.1%)

a. A patient may be reported in more than one category.

b. The three criteria were: have one or more VASPI scores after receiving at least 4 full days (96 hours) of treatment during the initial titration phase; have remained at their final dose prior to termination of the initial titration phase for at least 12 hours and have one or more VASPI scores at the end of the 12-hour period; or have terminated from the study due to intolerable adverse events and have one or more VASPI scores on the last dose or, the penultimate dose prior to termination of the initial titration phase.

Data Source: Appendix 2, Table 1.2

Following the initial titration period, patients were determined to be responders or nonresponders to the initial treatment. Assignment to maintenance or crossover during the second treatment period was based on this responder determination. There were many incorrect determinations of responder status resulting in incorrect assignment to treatment during the second treatment period. As the primary efficacy variable was assessed at the end of the initial titration period and the blind was broken at the end of the initial titration, these errors did not impact the primary efficacy variable. A total of 27 patients were assigned to the incorrect treatment during the second treatment period.

7.2.2.4.2 Disposition

Seven of the 264 patients randomized to study drug were not treated. Seventy three patients discontinued the study early. Eight patients in each group were considered unevaluable by the sponsor, the reasons are noted in Table 7.19. Forty of the remaining 170 patients randomized to ziconotide discontinued during the initial titration period; 8 during the maintenance period. Seven of the remaining 87 patients randomized to placebo discontinued the study during the

initial titration period and 18 after crossing over to ziconotide. One patient initially randomized to ziconotide whose treatment was interrupted by a dislodged catheter was randomized a second time, receiving placebo under a new patient number. This information is summarized in Table 7.24.

Of note there is one patient excluded from the ITT population, included in the safety population that cannot be accounted for by this reviewer. Based on the definitions of the populations, the assumption is that this patient was felt to have insufficient VASPI to be included in the ITT, but this cannot be confirmed by this reviewer. A late inquiry was made to the sponsor to resolve this unknown, but was too late for this review. The information will be provided in an addendum.

The most common reason for early study discontinuation was intolerable adverse events. This accounted for 15.9% of the early discontinuations from the ziconotide group and 1% of the early discontinuations from the placebo group during initial titration. During the maintenance period, 19.5% of ziconotide treated patients discontinued the study due to adverse events. During the crossover period (from placebo to ziconotide) 19.5% of patients discontinued the study due to adverse events.

Table 7.24 Summary of Patient Disposition by Treatment Randomization (From sponsor Table 8.1 and 8.3, Vol. 2.107, P. 105, 112)

Population	Initial Treatment Assignment	
	Ziconotide	Placebo
Number of Patients Randomized	175	89
Number of Patents Randomized but not Treated ^a	5	2
Number of Patients Randomized and Treated	170 (100.0%)	87 (100.0%)
Safety Population ^b	170 (100.0%)	86 (98.9%)
ITT Populations ^c	169 (99.4%)	86 (98.9%)
Evaluable Population ^d	162 (95.3%)	79 (90.8%)
Non-evaluable Patients	8 (4.7%)	8 (9.2%)
Number of Patients Completed Study	122 (71.8%)	62 (71.3%)
Initial Titration Phase		
Completed Phase and Entered Second Phase	82 (48.2%)	79 (90.8%)
Completed Phase and Did Not Enter 2nd Phase	48 (28.2%)	1 ^e (1.1 %)
Primary Reason for Early Termination		
Noncompliance by Patient	0	1 (1.1 %)
Intolerable Adverse Event ^f	27 (15.9%)	1 (1.1 %)
W/D Requested by Patient or Legal Rep.	0	1 (1.1 %)
Unrelated Medical Condition	0	1 (1.1 %)
Administrative or Investigator Decision	1 (0.6%)	1 (1.1 %)
Infection ^g	1 (0.6%)	1 (1.1 %)
System-Related (Pump / Catheter)	4 (2.4%)	1 (1.1%)
Ineffective Drug Therapy / Loss of Effect	5 (2.9%)	0 (0.0%)
Other ^h	2 (1.2%)	0 (0.0%)

Table continues:

Table 7.24 Continued

Population	Initial Treatment Assignment	
	Ziconotide	Placebo
Maintenance Phase ¹		
Entered Phase	82 (48.2%)	12 (13.8%)
Completed Phase	74 (43.5%)	12 (13.8%)
Primary Reason for Early Termination		
Intolerable Adverse Event	4 (2.4%)	0 (0.0%)
Infection ^g	1 (0.6%)	0 (0.0%)
System-Related (Pump / Catheter)	2 (1.2%)	0 (0.0%)
Ineffective Drug Therapy / Loss of E	1 (0.6%)	0 (0.0%)

- a. Patients 6076-102, 6076-105, 6083-103, 6083-106, and 6074-106 were randomized to the ziconotide group but were not treated and Patients 6081-103 and 6054-104 were randomized to the placebo group and not treated.
- b. The safety population included patients who had received any amount of study medication at any time during the study except for Patient 6087-106 who had been randomized first to ziconotide as patient 6087-105 and then re-randomized to placebo as patient to ziconotide as patient 6087-106.
- c. The ITT population included patients who had received any amount of study medication with at least a baseline VASPI and one f/u VASPI during the initial titration phase.
- d. The evaluable population included patients who met the inclusion and exclusion criteria of the study, did not substantially violate the protocol and had sufficient VASPI data.
- e. Patient 6059-110, a placebo nonresponder, did not enter the crossover phase but was terminated inadvertently from the study at the end of the initial titration phase. The case report form for this patient was incorrectly marked as "study completed."
- f. Three ziconotide patients (6058-101, 6059-111, and 6067-101) and one placebo patient (6079-106) discontinued due to adverse events associated with the device.
- g. Device adverse events.
- h. Other includes: Patient 6066-102 - non-responder to active drug, 6087-105 no intrathecal catheter CSF flow
- i. Those patients who completed the initial titration phase and underwent the maintenance phase continued on their initial treatment.

NA = not applicable

Data Source: Appendix 2, Table 1.1

7.2.2.4.3 Unplanned Analyses

Additions and changes to the planned analyses:

- The percent change in VASPI from baseline on each day was analyzed by repeated measures analyses rather than separately for the initial titration phase.
- Lab data was analyzed with descriptive statistics.
- Calculating oral morphine equivalents and the change in opioid type were added
- for the calculation of the percent change in McGill-Melzack Global scores only questions with non-missing scores were included.
- Only treatment emergent AE's were summarized.
- Inferential statistics on the primary efficacy variable, evaluable and ITT patients were added.
- Rather than 20%, all AE's reported by 10% or more were analyzed inferentially

7.2.2.4.4 Demographic and Baseline Characteristics

The demographic characteristics of the two treatment groups were comparable for age, race, gender and presence of nystagmus and are summarized in Table 7.25.

Table 7.25 Demographic and Baseline Characteristics -Evaluable Population (From sponsor's Table 8.4, Vol. 2.107, P. 114)

Parameters	Ziconotide (N = 162)	Placebo (N=79)	p-Value
Age (years)			0.741 (0.575) ^a
Mean (SE)	51.7 (1.11)	52.9 (1.41)	
Median (range)	50.0 (22.0 - 82.0)	51.0 (25.0 - 79.0)	
Gender			0.612 ^b
Male	89(54.9%)	47(59.5%)	
Female	73(45.1%)	32(40.5%)	
Race			0.483 ^{b, c}
Caucasian	155 (95.7%)	74 (93.7%)	
Black	4 (2.5%)	1 (1.3%)	
Hispanic	2 (1.2%)	4 (5.1%)	
Asian	1 (0.6%)	0 (0.0%)	
Nystagmus ^d			0.581 ^b
Absent	85 (52.5%)	42 (53.2%)	
Present	6 (3.7%)	4 (5.1%)	
Missing	71 (43.8%)	33(41.8%)	

a. Treatment difference was tested using the 2-way ANOVA model with treatment, center, and treatment-by-center interaction as factors. The p-value for treatment-by-center interaction is given in parentheses.

b. Treatment difference was tested using the CMH general association test controlling for center.

c. For Caucasian versus Other (Black, Hispanic, and Asian combined).

d. Nystagmus information was not collected prior to June 1997.

Data Source: Appendix 2, Table 3.1

Baseline Pain Characteristics:

The two treatment groups were similar with respect to the characteristics of pain at screening as demonstrated in Table 7.26. This includes the type of pain syndrome, pain classification, prior treatment within intrathecal morphine, and duration of pain. The ziconotide group had a higher mean daily amount of oral morphine equivalents, but the standard error was large and the difference did not reach statistical significance.

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Table 7.26 Summary of Characteristics of Pain at Screening - Evaluable Population (From sponsor's Table 8.5 Vol. 2.107, P. 115)

Pain Characteristic	Ziconotide (N =162)	Placebo (N = 79)	p-value
Pain Syndrome			0.902 ^a
Central	65(40.1%)	32 (40.5%)	
Peripheral	92(56.8%)	45 (57.0%)	
Unknown	5 (3.1%)	2 (2.5%)	
Pain Classification			0.6558 ^a
Neuropathic	126(77.8%)	61 (77.2%)	
Non-neuropathic ^b	17(10.5%)	11 (13.9%)	
Missing	19(11.7%)	7 (8.9%)	
Ever Been on Intrathecal Morphine			0.2620 ^a
Yes	91 (56.2%)	49 (62.0%)	
No	71 (43.8%)	29 (36.7%)	
Missing	0 (0.0%)	1 (1.3%)	
Pain Responsive to Intrathecal Morphine ^c			0.3048 ^a
Yes	47(51.6%)	29 (59.2%)	
No	44(48.4%)	20 (40.8%)	
Duration of Pain			0.122 ^d
< 6 months	1 (0.6%)	0 (0.0%)	
6 months to 1 year	4 (2.5%)	0 (0.0%)	
> 1 year	157(96.9%)	79(100%)	
Oral Morphine Equivalents (mg/day)			0.705 (0.759) ^a
Mean (SE)	405.1 (60.64)	330.5 (48.81)	
Median (range)	165.0 (0 - 5758.8)	180.0 (0 - 2160.0)	

a Treatment difference was tested using the CMH general association test controlling for center.

b Non-neuropathic includes visceral, somatic mixed, and other pain classifications.

c The percent was calculated using the number of patients who had ever been on intrathecal morphine as the denominator.

d Treatment difference was tested using the CMH row mean scores test controlling for center.

Data Source: Appendix 2, Table 4.1

Baseline Pain Scores:

Among the baseline pain assessments, there were statistically significant differences noted between treatment groups as demonstrated in Table 7.27. The baseline VASPI score and the WBPIS Mood score were significantly higher for the ziconotide treated group than for the placebo.

Table 7.27 Summary of Preinfusion Pain Assessments -Evaluable Population (From sponsor's Table 8.6 Vol. 2.107, P. 117)

Pain Assessments	Ziconotide (N = 162)	Placebo (N=79)	p-value
VASPI Score (mm) ^a			0.022(0.319)
Mean (SE)	80.2 (1.09)	76.8 (1.54)	
Median (range)	82.0 (33.0-100-0)	76.0 (50.0-100-0)	
WPIS - Mood ^c			0.012 ^d
n	160	79	
Mean (SE)	2.9(0.08)	2.5(0.12)	
Median (range)	3.0 (0.0-4.0)	3.0 (0.0-4.0)	
WPIS - Relationship With Other People'			0.928 ^d
n	159	79	
Mean (SE)	2.3(0.10)	2.3(0.13)	
Median (range)	2.0 (0.0-4.0)	3.0 (0-0-4-0)	
WPIS - Walking Ability			0.388 ^d
n	150	77	
Mean (SE)	3.0(0.09)	3.1(0.12)	
Median (range)	3.0 (0.0-4-0)	3.0 (0-0-4-0)	
WPIS - Sleep ^c			0.196 ^d
n	160	79	
Mean (SE)	2.9(0.08)	2.7(0.12)	
Median (range)	3.0 (0-0-4-0)	3.0 (0.0-4-0)	
WPIS - Normal Work ^c			0.653 ^d
n	145	75	
Mean (SE)	3.3(0.08)	3.3(0.12)	
Median (range)	4.0 (0.0-4.0)	4.0 (0.0-4.0)	
WPIS - Enjoyment of Life			0.256 ^d
n	159	78	
Mean (SE)	3.2(0.07)	3.1(0.12)	
Median (range)	3.0 (0-0-4-0)	3.0 (0.0-4-0)	
Global McGill Pain Score			0.370 (0.854) ^b
n	135	71	
Mean (SE)	37.8(1.05)	37.3(1.52)	
Median (range)	38.0 (13.0-65-0)	36.0 (6.0-64.0)	

a VASPI scale: 0 mm (least possible pain) to 100 mm (worst possible pain).

b Treatment difference was tested using the 2-way ANOVA model with treatment, center, and treatment-by-center interaction as factors. The p-value, for the treatment-by-center interaction is given in parentheses.

c A 5-point scale: 0 = not at all; 1 = a little bit; 2 = moderately; 3 = quite a bit; 4 = extremely.

d Treatment difference was tested using the CMH row mean scores test controlling for center.

e For the McGill Pain Score questionnaire and scales see Appendix D of the study protocol in Appendix 6 of this report. Data Source: Appendix 2, Table 5.1

Concomitant medications

During the preinfusion and initial titration periods, the most commonly reported medications were opioids, antidepressants, antiepileptics, other analgesics and antipyretics, anxiolytics, laxatives, hypnotics and sedatives, muscle relaxants (centrally acting) and drugs for the treatment of peptic ulcer. These were generally similar between the two treatment groups. See Table 8.7 (Vol. 2.107, P. 121) and Table 8.8 (Vol. 2.107, P. 123).

7.2.2.4.5 Sponsor's Efficacy Results

Primary Efficacy Analysis:

The primary efficacy parameter was the mean percent change in VASPI from baseline to the end of the initial titration phase and this information is summarized in Table 7.28. The mean percent change in VASPI for the ziconotide group was 30.7% reported by sponsor (31.7% by this reviewer's calculation). This was significantly different from zero and from the mean percent change of 6.2% by sponsor (6.8% this reviewer's calculation) in the placebo group.

Table 7.28 Percent Change in VASPI Score From Baseline to the End of Initial Titration Phase - Evaluable Population (From sponsor's Table 9.1 Vol. 2.107, P. 126)

Parameter	Ziconotide	Placebo	p-value
VASPI Score at Baseline (mm)			0.018 (0.178) ^a
n	159	79	
Mean (SE)	80.2 (1.09)	76.8 (1.54)	
Median (range)	82.0 (33 - 100)	76.0 (50 - 100)	
VASPI Score at End of Initial Titration (mm)			
n	159	79	
Mean (SE)	54.8 (2.65)	71.6 (2.60)	
Median (range)	62.0 (0 - 100)	77.0 (17 - 100)	
% Change in VASPI Score at End of Initial Titration ^b			0.0002 (0.324) ^a
n	159	79	
Mean (SE)	30.7 (3.47)	6.2 (3.24)	
Median (range)	23.8 (-113 - 100)	1.1 (-62 - 80)	
95% CI for Mean ^c	(23.9, 37.5)	(-0.1, 12.6)	
95% CI for Mean Difference ^c	(15.2, 33.8)		

a. Treatment difference was tested using the 2-way ANOVA model with treatment, center, and treatment-by-center interaction as factors. The p-value for treatment-by-center interaction is given in parentheses (see Appendix 13).

b. Percent change = $100 \times (\text{VASPI score at baseline} - \text{VASPI score at end of initial titration}) / (\text{VASPI score at baseline})$. Positive values represent improvement in pain.

c. Data were pooled across centers when calculating the 2-sided 95% confidence intervals for individual treatment mean and for treatment difference (ziconotide - placebo) in mean percent change in VASPI score at the end of the titration phase.

Note: Only patients having non-missing data at both baseline and the end of the initial titration phase were included in the analysis.

Note: Evaluable Patients 6057-101, 6063-102, and 6081-101 in the ziconotide group were excluded from the analysis as these patients did not have VASPI scores at both baseline and at the end of initial titration.

Data Source: Appendix 2, Table 9.1 and Appendix 13

Subgroup Analyses Supportive of the Primary Efficacy Analysis

ITT population

The mean percent change in VASPI score from baseline to the end of the initial titration period for the ITT population was 31.2% for the ziconotide group and 6.0% for the placebo group; this was statistically significant.

When an ANCOVA was performed to adjust for a higher mean baseline VASPI score for the ziconotide group, the mean percent change in VASPI score was again significantly greater for

the ziconotide group than the placebo group with evaluable and ITT populations ($p < 0.001$ for both comparisons). This information is summarized in Table 7.29.

Table 7.29 (From Appendix 2, Table s9.2, ITT population, Vol. 2.108, P. 027)

Parameter	Ziconotide	Placebo	p-value
VASPI Score at Baseline (mm)			0.021 (0.286) ^a
n	164	86	
Mean (SE)	80.2 (1.06)	76.9 (1.47)	
Median (range)	81.0 (33 - 100)	76.0 (50 - 100)	
VASPI Score at End of Initial Titration (mm)			
n	164	86	
Mean (SE)	54.4 (2.60)	71.9 (2.47)	
Median (range)	61.8 (0 - 100)	76.5 (17 - 100)	
% Change in VASPI Score at End of Initial Titration ^b			<0.001 (0.273) ^d
n	164	86	
Mean (SE)	31.2 (3.41)	6.0 (3.05)	
Median (range)	25.6 (-113 - 100)	1.1 (-62 - 80)	
95% CHI for Mean ^c	(24.6, 37.9)	(-0.1, 11.9)	
95% CI for Mean Difference ^c	(16.3, 34.2)		

a. Treatment difference was tested using the 2-way ANOVA model with treatment, center, and treatment-by-center interaction as factors. The p-value for treatment-by-center interaction is given in parentheses.

b. Percent change = $100 \times (\text{VASPI score at baseline} - \text{VASPI score at end of initial titration}) / (\text{VASPI score at baseline})$. Positive values represent improvement in pain.

c. Data is pooled across centers when calculating the 2-sided 95% confidence intervals for individual treatment mean and for treatment difference (ziconotide - placebo) in mean percent change in VASPI score at the end of the titration phase.

d. Treatment difference is tested using the 2-way ANCOVA model with baseline VASPI, treatment, center and treatment-by-center interaction as factors. The p-value for treatment-by-center is given in the parentheses.

Initial Dose

The mean percent change in VASPI from baseline to the end of the initial titration period was also analyzed by initial dose. This analysis differs from that planned; mean percent change in VASPI from baseline to the end of the initial titration period for initial dose of < 0.1 ug/hr for the evaluable and ITT populations. The ziconotide group demonstrated a significantly larger percent change in VASPI compared to placebo for the lower initial dose group. Although the difference in mean percent change in VASPI between ziconotide and placebo treated patients was comparable between the dosing groups, 25.2 for the ≤ 0.1 ug/h group and 23.1 for the 0.1 ug/h group, this difference between treatment groups for the higher initial dose group did not reach statistical significance. The number of patients in the higher dose group was much smaller than the lower initial dose group. These results are presented in Table 7.30.

Table 7.30 Mean Percent Change in VASPI Score at the End of the Initial Titration Phase by Initial Dose and Dose at Measurement - Evaluable Population (From sponsor's Tables 9.2 and 9.3, Vol. 2.107, P. 134, 135)

Initial Dose	Ziconotide		Placebo		p-value ^a
	n	Mean (SE)	n	Mean (SE)	
<0.1 ug/hr	120	31.8 (3.79)	66	6.6 (3.47)	0.002 (0.753)
>0.1 ug/hr	39	27.4 (8.09)	13	4.3 (9.06)	0.161 (0.152)
Dose range at evaluation ^b					
≤ 0.2 ug/h	39	41.5 (6.54)	11	0.3 (9.08)	
> 0.2, ≤ 0.3 ug/h	31	36.8 (9.08)	3	40.7 (5.86)	
> 0.3, ≤ 0.6 ug/h	28	38.0 (8.04)	8	26.0 (14.35)	
> 0.6, ≤ 1.0 ug/h	9	29.7 (12.52)	4	-14.0 (19.06)	
> 1.0, ≤ 2.0 ug/h	23	32.9 (8.28)	11	3.6 (6.74)	
>2.0 ug/hr	29	1.2 (6.64)	42	4.2 (3.84)	
All Dose Ranges	159	30.7 (3.47)	79	6.2 (3.24)	0.004 (0.51)

a Treatment difference was tested using the 2-way ANOVA model with treatment, center, and treatment-by-center interaction as factors. The p-value for treatment-by-center interaction is given in parentheses.

b The dose range refers to the administration rate when the final efficacy assessment in the initial titration phase was made.

Note: Only patients having non-missing data at both baseline and at end of initial titration were included in the analyses. Positive values represent improvement in pain.

Appendix 2. Tables 9.3, 9.4, 9.7

Dose Range

An analysis of the percent change in VASPI from baseline to the end of the initial titration period by the dose range at the time of VASPI measurement was performed. This was not a planned analysis. These results are presented in Table 7.27. The numbers in these subgroups were too small for statistical comparisons. There was difference in the mean percent change in VASPI for the > 0.2, ≤ 0.3 ug/h range between treatment groups which may be a function of only 3 placebo treated patients in the comparator group. There was also no difference in the mean percent change in VASPI between treatment groups for the >2.0 ug/hr dose range. This may reflect either a ceiling effect for the ziconotide or may indicate that patients not responding at lower doses were too refractory to respond even at this higher dose range.

Treatment Day

The percent change in VASPI score from baseline to the end of the initial titration, by treatment day increased steadily from days 1 through 6, from 6.9 to 29.9 for the ziconotide group. For the placebo group, there was no overall trend with values ranging between 3.9 and 7.5. The treatment difference was significant by ANOVA at p=0.009.

Demographic Subgroup

Review of the mean percent change in VASPI score at the end of the initial titration by demographic subgroup revealed differences within the placebo group, but not within the ziconotide treated group as demonstrated in Table 7.31.

Table 7.31 Mean Percent Change in VASPI Score at the End of the Initial Titration Phase by Demographic Subgroup -Evaluable Population (From Sponsor's Table 9.5 Vol. 2.107, P. 138)

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 = $100 \times (\text{VASPI score at baseline} - \text{VASPI score at end of initial titration}) / (\text{VASPI score at baseline})$. Positive values represent improvement in pain.

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

Age

There was a greater placebo effect within the ≥60 years of age group (16.3%) than <60 years of age (2.1%). The mean percent change in VASPI for the different age groups within the ziconotide treated group only differed by 2.5%. The difference between treatment groups therefore, was greater for the < 60 years of age group (29.3%) compared with ≥60 years (12.6%). The significance of this is unclear.

Gender

There was a modest difference between the genders. There was a greater response to placebo in the male group by 8.7% and to ziconotide by 2.5%, but the overall between treatment group differences were not significantly different for the 2 genders.

Prior IT Morphine Use

There was not effect of prior IT morphine use on the mean percent change in VASPI score for either treatment group. (Table 9.6, Vol. 2.107, P. 139).

Concurrent Opioid Use

The effect of concurrent use of opioids on the treatment effect was analyzed by an ANCOVA including baseline VASPI score, percent change in opioid use at the end of the initial titration phase, treatment, center and interaction of treat-by-center as factors. The treatment effect remained significant at a p-value of 0.001. There was no relationship between the mean percent change in VASPI and the percent change in opioid use.

Drug-Disease Interaction

The mean percent change in VASPI was analyzed for effects by either pain syndrome or pain classification. Pain syndrome refers to whether the pain was due to a central or peripheral lesion. Pain classification refers to whether the pain was neuropathic or nonneuropathic in etiology. There was no effect of pain syndrome; patients with either central or peripheral pain syndromes

who received ziconotide had a significant greater decrease in pain than patient who received placebo as indicated by a greater change in mean percent change VASPI.

Patients with neuropathic pain who received ziconotide had a greater percent change in VASPI than patients who received placebo. However, while there was a trend to greater change in the ziconotide treated group, there was no statistically significant difference between treatment groups for patients with non-neuropathic pain. The sponsor indicates that there were far fewer patients in the non-neuropathic pain group, 28, than the neuropathic pain group, 185, and that may be why a statistically significant difference was not seen. These results are summarized in Table 7.32.

The difference in mean percent change in VASPI for patients treated ziconotide compared to patients treated with placebo was comparable for patients with central and peripheral pain syndromes as summarized in Table 7.32.

Table 7.32 Mean Percent Change in VASPI Score at the End of the Initial Titration Phase by Pain Characteristics - Evaluable Population (From Sponsor's Table 9.7, Vol. 2.107, P. 141)

Parameter	Ziconotide		Placebo		p-value
	n	Mean (SE)	n	Mean (SE)	
Pain Syndrome					<0.001 (0.693) ^a
Central	64	28.2 (4.75)	32	7.3 (4.95)	
Peripheral	90	31.2 (4.97)	45	6.0 (4.48)	
Pain Classification					0.054 (0.353) ^a
Neuropathic	124	31.6 (3.70)	61	8.1 (3.76)	
Non-neuropathic	17	6.6 (14.23)	11	-1.7 (7.92)	

a Treatment difference was tested using the 2-way ANOVA with treatment, pain syndrome (pain classification) and treatment by pain syndrome (pain classification) interaction as factors. The p-value for treatment by pain syndrome (pain classification) interaction is presented in the parenthesis.

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

Note: Percent change = $100 \times (\text{VASPI at baseline} - \text{VASPI at end of initial titration}) / (\text{VASPI at baseline})$. Positive values represent improvement in pain.

Data Source: Appendix 2, Tables 9.8 and 9.9

There were no drug-center interactions.

Secondary Efficacy Parameters:

Maintenance Phase

As noted previously, there were 20 patients considered by the sponsor to be ziconotide nonresponders mistakenly entered into maintenance. The results from these patients were included in the analysis of the maintenance phase by the sponsor limiting the utility of these results. The ziconotide treated patients maintained the greater mean percent change in VASPI than the placebo treated patients at the study termination present at the end of the initial titration phase as demonstrated in Table 7.33.

Table 7.33 Percent Change in VASPI Score at the End of the Maintenance Phase - Evaluable Population (From Sponsor's Table 9.8, Vol. 107, P. 143)

Parameter	Initial Treatment Assignment	
	Ziconotide	Placebo
No. of Evaluable Patients Who Underwent the Maintenance Phase	77	12
Percent Change in VASPI Score from Baseline to End of Initial Titration		
n	76	12
Mean (SE)	62.1(3.53)	55.2(4.89)
Median (range)	65.2 (-21.5 - 100.0)	55.3 (31.8 - 80)
Percent Change in VASPI Score from Baseline of Initial Titration Phase to Study Termination		
n	74	12
Mean (SE)	61.8(4.08)	37.9 (9.66)
Median (range)	70.6 (-44.3 - 100.0)	40.2 (-9.8 - 89.8)

Note: Only patients having non-missing data at both baseline and end of maintenance phase were in this analysis.
 Note: Ziconotide pts 6054-101, 6060-113, and 6088-105 had no VASPI score at the end of the maintenance phase.
 Data Source: Appendix 2, Table 10.2 and Appendix 13

Change in VASPI, CPRS, McGill Pain Questionnaire

The results of treatment group comparisons for the mean absolute change in VASPI score, the change in CPRS, and the Global McGill Pain scores are presented in Table 7.34. These analyses were performed on the evaluable population. All 3 analyses demonstrated greater improvements in pain relief/greater reductions in pain intensity for the ziconotide treated group compared to the placebo group and these were statistically significant.

Table 7.34 Secondary Pain Analyses - VASPI, CPRS, McGill Pain Questionnaire (From Sponsor's Tables 9.10, 9.11, 9.12, Vol. 2.107, P.145-7)

Parameter	Ziconotide (N = 162)	Placebo (N = 79)	p-value
Change in VASPI Score ^a			<0.001
n	159	79	(0.212) ^b
Mean (SE)	25.4 (2.65)	5.2 (2.36)	
Median (range)	19.0 (-52 - 98)	1.0 (-36 - 80)	
CPRS categories n (%)			0.001 ^c
Worse	14 (8.6%)	10 (12.7%)	
No Change	55 (34.0%)	48 (60.8%)	
Slight Improvement	23 (14.2%)	7 (8.9%)	
Moderate Improvement	21 (13.0%)	10 (12.7%)	
A Lot of improvement	34 (21.0%)	4 (5.1%)	
Complete Relief	15 (9.3%)	0	
% Change in Global McGill Pain Score			0.014
n	135	71	(0.692) ^b
Mean (SE)	23.6 (3.89)	9.0 (3.51)	
Median (range)	17.9 (-150.0-100.0)	8.5 (-100.0-81.8)	

- a. Patients 6057-101, 6063-102, and 6081-101 had no VASPI score at the end of the initial titration phase and were not included in the analysis.
- b. Treatment difference was tested using the 2-way ANOVA model with treatment, center, and treatment-by-center interaction as factors. The p-value for treatment-by-center interaction is given in parentheses.
- c. Treatment difference was tested using the CMH row mean scores test controlling for center.
- Data Source: Appendix 2. Tables 9.1, 10.1

WBPIS

The categories of the WBPIS are: Mood, Walking Ability, Sleep, and Enjoyment of Life. The 5 rating choices are Worsen By ≥ 2 Units, Worsen By 1 Unit, Unchanged, Improved By 1 Unit, and Improved By ≥ 2 Units. A missing category is also present. The ziconotide group demonstrated a significantly greater percentage of scores in the Improved By ≥ 2 Units choice for all categories except for the Walking subset. The WBPIS results are presented in Table 7.35.

Table 7.35 Change in the Wisconsin Brief Pain Inventory Subsets (WBPI) at the End of the Initial Titration Phase Evaluable Population (From sponsor's Table 9.13 Vol. 2.107, P. 148)

Parameter	Ziconotide (N=162)	Placebo (N=79)	p-value a
Change In WBPI - Mood			0.003
Worsen By ≥ 2 Units	3 (1.9%)	5 (6.3%)	
Worsen By 1 Unit	13 (8.0%)	8 (10.1%)	
Unchanged	38 (23.5%)	32 (40.5%)	
Improved By 1 Unit	43 (26.5%)	18 (22.8%)	
Improved By ≥ 2 Units	47 (29.0%)	14 (17.7%)	
Missing	18 (11.1%)	2 (2.5%)	
Change In WBPI - Walking Ability			0.044
Worsen By ≥ 2 Units	14 (8.6%)	2 (2.5%)	
Worsen By 1 Unit	20 (12.3%)	5 (6.3%)	
Unchanged	48 (29.6%)	27 (34.2%)	
Improved By 1 Unit	21 (13.0%)	22 (27.8%)	
Improved By ≥ 2 Units	34 (21.0%)	18 (22.8%)	
Missing	25 (15.4%)	5 (6.3%)	
Change In WBPI - Sleep			0.001
Worsen By > 2 Units	5 (3.1%)	2 (2.5%)	
Worsen By 1 Unit	18 (11.1%)	12 (15.2%)	
Unchanged	31 (19.1%)	40 (50.6%)	
Improved By 1 Unit	41 (25.3%)	15 (19.0%)	
Improved By ≥ 2 Units	50 (30.9%)	8 (10.1%)	
Missing	17 (10.5%)	2 (2.5%)	
Change In WBPI - Enjoyment Of Life			0.010
Worsen By ≥ 2 Units	2 (1.2%)	2 (2.5%)	
Worsen By 1 Unit	14 (8.6%)	12 (15.2%)	
Unchanged	48 (29.6%)	30 (38.0%)	
Improved By 1 Unit	31 (19.1%)	18 (22.8%)	
Improved By ≥ 2 Units	47 (29.0%)	12 (15.2%)	
Missing	20 (12.3%)	5 (6.3%)	

a Treatment difference was tested using the CMH row mean scores test controlling for center. The category 'missing' was excluded when calculating the p-value. Appendix 2, Table 10.1

Responder Rate:

The definition of Responder was established in the study protocol as those patients who 1) experienced a $\geq 30\%$ drop in VASPI score compared to baseline; 2) had stable or decreased concomitant opioid analgesics; and 3) had opiate type unchanged from preinfusion if receiving opiates. There were many patients who were incorrectly classified by the investigators as responders. The sponsor reviewed the CRF's and reassessed the responder status of the patients. Based on the determination by the sponsor, 33% of the 162 patients initially titrated to ziconotide were responders, and 14% of the patients in the placebo group were responders, and this difference reached statistical significance. This information is summarized in Table 7.36.

Table 7.36 Number (%) of Patients Who Responded to Treatment During the Initial Titration Phase - Evaluable Population (From sponsor's Table 9.15 Vol. 2.107, P. 153)

Parameter	Derived Response	
	Ziconotide (N = 162)	Placebo (N = 79)
Responder a n (%)	54 (33.3%)	11(13.9%)
Nonresponder	108 (66.7%)	68 (86.1%)
95% CI for % Responders ^a	(26.1, 40.6%)	(6.3, 21.6%)
Treatment Difference and 95% CI in % Responders ^a	19.4% (8.9%, 29.9%)	
p-value ^b	0.002	

a. Data were pooled across centers when calculating the 2-sided 95% CI. Treatment difference is for ziconotide-placebo.

b. Treatment difference was tested using the CMH general association test controlling for center. Appendix 2, Tables 11.1 and s11.1

The placebo nonresponders from the initial titration period were to be crossed over to ziconotide in an unblinded manner. Of the 68 placebo nonresponders, 61 entered the crossover phase to ziconotide. Sixteen of these 61 patients met the criteria as responders to ziconotide, for a responder rate of 26%. This is close to the 33% responder rate from the group initially titrated on ziconotide in a blinded manner.

Tactile Allodynia:

A total of 44 patients had measurements made to detect tactile allodynia (Appendix 3, Listing 3.5). Of these 44 patients, 4 had pain ratings of 0, no pain; and 6 had only one measurement. One patient had contradictory information consisting of an initial patient pain rating of 0 but a measured area of allodynia followed by a second patient rating of 4 with a smaller area of allodynia. Of the remaining 33 patients considered evaluable, 23 received ziconotide and 10 received placebo during the initial titration phase. There was little change overall, and no significant difference between treatment groups ($p=0.53$). (Table 9.17, Vol. 2.107, P. 155)

Percent Change In Opioid Use:

There were a few large outlying values in the percent change in opioid use; the range was -100.0% to 2246.2%. The sponsor compared the mean percent change for all patients and found a mean percent increase in daily opioid use of 25.7% for the ziconotide group compared to 24.3% for the placebo group. A second analysis excluded patients with a percent change greater than 1000%. This resulted in the exclusion of 3 patients from the ziconotide group and none from the placebo group. The mean percent change in daily opioid use was -5.3% for the ziconotide group compared to the 24.3% for the placebo group. A third analysis set the percent

change for patients with no opioid use at baseline, but opioid use at the end of the initial titration at 100% and any >100% change at 100. This affected 8 patients in the ziconotide group and 10 in the placebo group. This resulted in a mean percent change in daily opioid use of -9.3% for the ziconotide group and 6.8% for the placebo group.

Overall, regardless of the conditions of the analysis, the ziconotide group did not have a larger percent increase in opioid use than the placebo group and without the outliers, demonstrated a small decrease in opioid use.

Therapeutic Dose Level:

The sponsor performed an evaluation to determine the dose of ziconotide which produced the therapeutic effect. This would be the dose level at the end of the initial titration and was an unplanned analysis. The analysis was stratified by initial dose. As seen in Table 7.37, patients starting with an initial dose of >0.1 ug/h reached a considerably higher final dose than those started on ≤ 0.1ug/h. The earlier dosing regimens began with higher doses than later revised dosing regimens. The sponsor proposes that there may have been an overshooting of the time of onset of analgesia during the earlier dose titration schedules as adequate time for the full effect of the dose to become apparent was not allotted between dose changes. The sponsor used median rather than mean values for this table due to the large ranges of the dose values.

Table 7.37 Ziconotide Dosing Information During Initial Titration Phase (From Table 9.4 Vol. 2.107, P. 137)

Parameter	≤ 0.1 ug/hr	>0.1 ug/hr	Total
n	122	40	162
Dose Level at End of Initial Titration (ug/hr) ^a			
Median	0.400	0.920	0.469
Range	0.019 - 2.400	0.200 - 9.600	0.019 - 9.600
Cumulative Dose Received During Initial Titration (ug) ^b			
Median	45.68	99.6	51.44
Range	4.31-122.51	8.93 - 453.55	4.31 - 453.55
Dose Level at Onset of Analgesia (ug/hr) ^c			
Median	0.30	0.80	0.45
Range	0.00 - 2.40	0.00 - 9.60	0.00 - 9.60

a The last non-zero dose level administered during the initial titration phase was reported.

b The cumulative dose (ug) at end of initial titration phase with K distinct doses was estimated as: [dose level 1 (ug/h) x duration of dose level 1 (hours) + dose level 2 (ug/h) x duration of dose level 2 (hours) + ... + dose level K (ug/h) x duration of dose level K (hours)].

c Onset of analgesia was defined as when the percentage change in VASPI was >20% and the CPRS score was >-2 (i.e., at least a slight improvement). For patients who did not have onset of analgesia, the maximum dose level received during the initial titration phase was used.

Data Source: Appendix 2, Table 8. 1

7.2.2.4.6 Reviewer's Efficacy Summary:

This study is submitted as one of two pivotal efficacy trials. Subjects were randomized to ziconotide or placebo for the initial titration. Following this phase there was a regimen to crossover nonresponders to placebo but the assessments of response to ziconotide and placebo included many errors by the individual investigators. The primary efficacy variable was measured at the end of the initial titration phase and was not affected by this problem.

The ziconotide treated group was found to have a slightly but significantly higher baseline pain intensity score and was receiving a greater amount of opioids at baseline. Even with these factors taken into account, the ziconotide treated group had a greater reduction in mean percent change in VASPI than the placebo group and this reached statistical significance. Concurrent opioid use, when factored in, had no effect on this result.

There was a steady trend of increasing mean percent change in VASPI over the six day titration period for the ziconotide treated patients, but only a small and fluctuating change with the placebo treated patients. When stratified by initial dose, the patients who began ziconotide on ≤ 0.1 ug/h had a statistically significant greater change in mean percent change VASPI, but not those with an initial titration dose of >0.1 ug/h. There was a comparable size change in mean percent change of VASPI compared to the placebo treated patients for this group as for the lower initial dose group, but this difference did not reach significance. Analyses stratified by the final dose range resulted in varying results that may have been affected by several small group sizes. Patients receiving > 2 ug/h ranges did not demonstrate a greater mean percent change in VASPI placebo treated patients. This may be due to a ceiling effect of the ziconotide or a reflection of patients who have intractable pain that did not respond to the ziconotide.

There was no effect of prior intrathecal morphine use, central vs. peripheral pain syndromes. Patients with nonneuropathic pain type did not have a significant treatment effect, but patients treated with ziconotide with neuropathic pain did demonstrate a greater mean percent change in VASPI than placebo treated patients.

Overall, the use of intrathecal ziconotide in chronic, nonmalignant pain appears to be effective, but may depend on the underlying type of pain.

SECTION 7.2.3 STUDY 96-003

SECTION 7.2.3.1 Protocol Synopsis

Study 96-003 was a small pilot study in patients with acute postoperative pain. The study design was randomized, double blinded and placebo controlled. Thirty patients were enrolled, 12 received ziconotide, 0.7 ug/h, 6 received ziconotide 7.0 ug/h and 12 patients received placebo via intrathecal catheter and external pump. Duration of treatment was up to 72 hours. Patients included those undergoing elective total hip replacement, elective retropubic radical prostatectomy or elective abdominal hysterectomy. The primary efficacy variables were daily dose of PCA morphine equivalents each 24 h post op and average hourly use of PCA morphine equivalents. VASPI was a secondary efficacy variable along with CPRS.

The results showed that the intrathecal ziconotide was more effective than placebo, as demonstrated by significantly less PCA morphine equivalents during from 24 to 48 hours after the start of infusion. Pairwise comparisons demonstrated a significant difference between the high dose ziconotide and placebo. The high and low dose ziconotide groups approached a significant difference ($p=0.81$). Mean daily VASPI scores were lower or equal for the ziconotide treated patients compared with the scores of the placebo treated patients throughout the infusion period.

SECTION 7.3

ADDENDUM

As noted, there were several protocol changes for studies 95-001 and 96-002 resulting in changes to the dosing regimen. For study 95-001, the original protocol called for study drug to be initiated at 0.0005ug/kg/h, titrating to a maximum of 0.3 ug/kg/hr with dose changes every 12 hours. Six months into the study, the first revision changed the dose schedule to 0.4 ug/h, titrated up to 21 ug/h. The titration continued until toxicity appeared. The third protocol revision changed the initial dose to 0.1 ug/h with a maximum of 2.4 ug/h and titration occurring no sooner than every 24h. Furthermore, patients were titrated to efficacy not toxicity. For study 96-002, the dosing was initiated with 0.4 ug/h and titrated to effect up to 7.0 ug/h. This was reduced to 0.1 ug/h, titrated to a maximum of 2.4 ug/h in the second revision. The marked differences in these dosing schedules within each study effectively translated into patients being exposed to very different treatment conditions, particularly early in study 95-001. To evaluate the efficacy of ziconotide under the anticipated conditions of use if approved, a separate analysis was requested including only those patients dosed under the final dosing revision. The sponsor had performed analyses based on the initial dose, but this did not exactly match the specified population. The final study population treated under the final protocol revisions consisted of 38 patient initially titrated with ziconotide and 19 patients with placebo for study 95-001 and for study 96-002, 124 patients initially titrated with ziconotide and 65 patients with placebo.

The result of this reanalysis is summarized in Tables 7.38 and 7.39. The size of the treatment effect for the primary efficacy variable, mean percent change in VASPI, remained statistically significantly better for the ziconotide treated patients in the Evaluable population ($p=0.05$ from 0.042). For the ITT population, the alpha power of the treatment effect changed from $p=0.59$ to 0.068. The change in CPRS and number of responders both remained statistically significant. For study 96-002, the mean percent change in VASPI and the change in CPRS remained greater remained for the ziconotide treated group at statistically significant levels, although the number of responders lost statistical significance ($p=0.91$).

Table 7.38 - 95-001 Efficacy Endpoints by Report Analysis and Protocol Revision 3 with and without Site 501 Data

		Report Analysis Initial Dose <0.1 ug/hr		Patient Treated Under Protocol Revision 3		Revision 3 Without Site 501	
Population	Parameter	Ziconotide	Placbo	Ziconotide	Placbo	Ziconotide	Placebo
Percent Change^b in VASPI at End of Initial Titration Phase							
Evaluable	n	39	21	38	19	32	17
	Mean (SE)	44.9 (6.21)	21.1 (8.93)	44.5 (6.36)	20.1 (9.46)	42.4 (7.32)	18.9 (9.0)
	Median (range)	57.2 (-26 - 95)	3.1 (-35 -96)	56.1 (-26 - 95)	3.1 (-35 -96)	47.6 (-26 - 95)	3.1 (-24 - 96)
	p-value	0.042 (0.455) ^a		0.050 (0.602) ^a		0.058 (0.604) ^a	
Intent-to-Treat	n	41	21	40	19	34	17
	Mean (SE)	42.4 (6.16)	21.1 (8.93)	41.9 (6.30)	20.1 (9.46)	39.5 (7.17)	18.9 (9.0)
	Median (range)	55.1 (-26-95)	3.1 (-35 - 96)	53.3 (-26 -95)	3.1 (-35 -96)	43.0 (-26 - 95)	3.1 (-24 - 96)
	p-value	0.059 (0.550) ^a		0.068 (0.703) ^a		0.080 (0.716) ^a	
Category Pain Relief Scale							
Evaluable	n	68	40	38	19	32	17
	Worse	4 (5.9%)	7 (17.5%)	3 (7.9%)	5 (26.3%)	3 (9.4%)	5 (29.4%)
	No Change	9 (13.2%)	8 (20.0%)	7 (18.4%)	4 (21.1%)	7 (21.9%)	3 (17.6%)
	Slight Improvement	5 (7.4%)	9 (22.2%)	5 (13.2%)	4 (21.1%)	4 (12.5%)	4 (23.5%)
	Moderate Improvement	7 (10.3%)	1 (2.5%)	5 (13.2%)	1 (5.3%)	4 (12.5%)	1 (5.9%)
	A Lot of Improvement	24 (35.3%)	6 (15%)	17 (44.7%)	5 (26.3%)	13 (40.6%)	4 (23.5%)
	Complete Relief	5 (7.4%)	0 (0%)	1 (2.6%)	0 (0%)	1 (3.1%)	0 (0%)
	Missing	14 (20.6)	9 (22.5%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
	p-value	<0.0010 ^c		0.033 ^c		0.056 ^c	
Treatment Responders							
Evaluable	n	68	40	38	19	32	17
	Responder	34 (50%)	7 (17.5%)	18 (47.4%)	4 (21.1%)	15 (46.9%)	3 (17.6%)
	Non-responder	34 (50%)	33 (82.5%)	20 (52.6%)	15 (78.9%)	17 (53.1%)	14 (82.4%)
	p-value	0.001 ^d		0.034 ^d		0.023 ^d	

a 2-way ANOVA model with treatment, intrathecal opioid use history, and treatment by intrathecal opioid use history interaction as factors. The p-value for treatment by intrathecal opioid use history interaction is given in parentheses.

b % change = (VASPI at baseline - VASPI at end of initial titration) / (VASPI at baseline) × 100. Positive numbers indicate an improvement in pain scores.

c CMH row mean scores test stratified by intrathecal opioid use history. The category "missing" was excluded when calculating the p-value.

d CMH general association test stratified by intrathecal opioid use history.

Data Source: Appendix A: Attachment A, Items 3 (Table 9.3) and 4 (Table 9.5); Appendix D: 95-001 Clinical Trial Report, Appendix 2, Tables 9.3, 9.5 10. 1, and 11. 1.

Table 7.39 - 96-002 Efficacy Endpoints by Report Analysis and Protocol Revision 2 with and without Site 6090 Data

		Report Analysis Initial Dose ≤0.1 ug/hr		Patient Treated Under Protocol Revision 2		Revision 2 Without Site 6090	
Population	Parameter	Ziconotide	Placebo	Ziconotide	Placebo	Ziconotide	Placebo
Percent Change^b in VASPI at End of Initial Titration Phase							
Evaluable	n	120	66	124	65	117	61
	Mean (SE)	31.8 (3.79)	6.6 (3.47)	30.7 (3.64)	6.0 (3.56)	29.4 (3.74)	6.4 (3.75)
	Median (range)	20.4 (-54 -100)	1.7 (-62 -79)	22.2 (-54 -100)	1.1 (-62 -79)	19.9 (-54 -100)	1.1 (-62 -79)
	p-value	0.002 (0.753) ^a		0.001 (0.816) ^a		0.004 (0.872) ^a	
Intent-to-Treat	n	122	69	126	68	119	64
	Mean (SE)	31.9 (3.73)	6.3 (3.34)	30.9 (3.59)	5.7 (3.42)	29.6 (3.69)	6.0 (3.59)
	Median (range)	23.9 (-54 -100)	1.4 (-62 -79)	24.6 (-54 -100)	1.1 (-62 -79)	20.2 (-54 -100)	1.1 (-62 -79)
	p-value	0.001 (0.787) ^a		<0.001 (0.843) ^a		<0.001 (0.891) ^a	
Category Pain Relief Scale							
Evaluable	n	162	79	109	57	102	53
	Worse	14 (8.6%)	10 (12.7%)	10 (9.2%)	6 (10.5%)	10 (9.8%)	5 (9.4%)
	No Change	55 (34.0%)	48 (60.8%)	35 (32.1%)	35 (61.4%)	34 (33.3%)	33 (62.3%)
	Slight Improvement	23 (14.2%)	7 (8.9%)	17 (15.6%)	5 (8.8%)	17 (16.7%)	5 (9.4%)
	Moderate Improvement	21 (13.0%)	10 (12.7%)	13 (11.9%)	9 (15.8%)	12 (11.8%)	8 (1.1%)
	Lot of Improvement	34 (21.0%)	4 (5.1%)	25 (22.9%)	2 (3.5%)	20 (19.6%)	2 (3.8%)
	Complete Relief	15 (9.3%)	0 (0%)	9 (8.3%)	0 (0%)	9 (8.8%)	0 (0%)
	p-value	0.001 ^c		0.003 ^c		0.017 ^c	
Treatment Responders							
Evaluable	n	162	79	109	57	102	53
	Responder	54 (33.3%)	11 (13.9%)	36 (33.0%)	8 (14.0%)	32 (31.4%)	8 (15.1%)
	Non-responder	108 (66.7%)	68 (86.1%)	73 (67.0%)	49 (86.0%)	70 (68.6%)	45 (84.%)
	p-value	0.002 ^d		0.091 ^d		0.131 ^d	

a Treatment difference is tested using 2-way ANOVA model with treatment, center and treatment-by-center interaction as factors. The p-value for treatment-by-center interaction is given in parentheses

b.% change = (VASPI at baseline - VASPI at end of initial titration) / (VASPI at baseline) x 100. Positive numbers indicate an improvement in pain scores.

c CMH row mean scores test controlling for center.

d CMH general association test controlling for center.

Data Source: Appendix A: Attachment A, Items 3 (Table 9.3) and 4 (Table 9.5); Appendix E: 96-002 Clinical Trial Report, Appendix 2, Tables 9.3, 9.5 10. 1, and 11. 1.

However, the result of routine inspections of study sites revealed a problem at site 501 from study 95-001. The investigator for site 501 was the same as for 6090 from study 96-002. The primary investigator had contracted with a CRO, and the primary study coordinator from this CRO, a pharmacist, was directly involved in the preparation and administration of study drug, titration of study drug dose and assisted in the assessment of outcome measures. This resulted in her being unblinded and for this reason, the patient data from this site has been excluded from the efficacy analysis for studies 95-001 and 96-002. The data was not removed from the safety database. This resulted in 12 ziconotide and 5 placebo treated patients removed from the patient population of 95-001 and 11 ziconotide and 4 placebo treated patients removed from the population of study 96-002. Because the first reanalysis of patients limited to the final dosing protocol already excluded some of the patients from this site, only an additional 6 ziconotide treated patients and 2 placebo treated patients were removed from the efficacy population of study 95-001 and 7 ziconotide treated and 4 placebo treated patients from the efficacy population of study 96-002.

For study 95-001, as a result of this reanalysis, the alpha level for the mean percent change in VASPI comparing ziconotide and placebo treated patients was 0.058 for the evaluable population and 0.080 for the ITT population. The difference between the evaluable and ITT populations was the exclusion of 2 patients: patient 5015-51 was excluded from the evaluable population due to insufficient VASPI data. The patient had leakage from the catheter and study drug was discontinued between 24 and 48 hours after the infusion was started. No VASPI was performed when study drug was discontinued. Patient 5047-74 was not randomized and received study drug open label.

The difference in the change in CPRS loses its statistical significance although the difference in the number of treatment responders remains statistically significantly different.

For study 96-002, the differences in mean percent change in VASPI and CPRS remain statistically significant, and the difference in number of responders remains without statistical significance.

SECTION 7.4 COMPARISON OF STUDIES 95-001 AND 96-002

The two pivotal studies, 95-001 and 96-002, were very similar in design. Study 96-002 began enrollment 5 months after 95-001 and they ran concurrently for 18 months until 96-002 ended enrollment 5 months prior to 95-001. The patient populations differed, chronic malignant pain due to cancer or AIDS in study 95-001 compared to chronic non-malignant pain in 96-002, but both populations included patients with neuropathic and non-neuropathic pain. Both studies incorporated several protocol changes reflecting lower initial doses, slower titration of dose and lower maximum dose and the final dosing schedule was the same for both studies.

In light of the similarities between the two studies, a side by side comparison of the results was performed by this reviewer.

The populations used for the final efficacy analyses in both studies were modified from the total patient populations to reflect only patients from the final dosing protocol and exclude the patients from sites 501 and 6090 due to a breach in blinding at those sites. Reanalyses were performed for the percent change in VASPI, absolute change in VASPI, categorical pain relief scale and responder rate, but not the WBPI scales. The disposition and demographics were not recalculated to reflect these changes. The population used for the results will be indicated for each area to minimize confusion.

Disposition (Entire Population)

Only 48.2% of the patients in 96-002 completed the initial titration phase and entered the second phase, compared to 83.3% of the patients in study 95-001. The most common reason for early termination was intolerable adverse events in both studies.

Demographic And Baseline Characteristics (Entire Population)

The demographic and baseline characteristics were similar with respect to age and gender. There was a slightly greater proportion of African American patients in 95-001, 7.6%, compared with 2.1% in study 96-001. Overall, both study populations were primarily Caucasian. Neither study had any statistically significant differences in demographic and baseline characteristics between their ziconotide and placebo treated groups.

Baseline Medication

Oral Opioid Equivalents (Entire Population)

The patients with chronic malignant pain in study 95-001 were on a considerably higher mean baseline oral morphine equivalent, 6.2 g/d for the ziconotide treated group and 4.2g/d for the placebo group, than the patients with chronic non-malignant pain in study 96-002 with 0.4 g/d for the ziconotide treated patients and 0.33 g/d for the placebo treated group.

Intrathecal Morphine Experience (Entire Population)

As an inclusion criterion for both studies, patients must have been at the point in their pain management where they were already receiving intrathecal opioids or the use of intrathecal opioids was to be the next step. In study 95-001, 33.3% of the patients had been on intrathecal morphine (36/108), proportionately distributed between ziconotide and placebo treatment groups. In study 96-002, 58.1% of patients had ever been on intrathecal morphine (140/241), 56% of the ziconotide treated group and 62% of the placebo group. This difference between treatment groups in 96-002 did not reach statistical significance. Of those who had ever been on intrathecal morphine, 41.2% of the patients in 95-001 had pain responsive to the intrathecal morphine, compared with 54.3% of the patients in 96-002. Twenty three percent of the patients in study 95-001 had a SynchroMed pump in place at the time of the study. This information is not available for study 96-002.

Concomitant Medication At Preinfusion (Entire Population)

Opioids were the most common concomitant medication at preinfusion for both studies, but were more common for patients in 95-002 (91.7%) than 96-002 (75.4%). Patients in 96-002 were more frequently on antidepressants (60.8%) than patients in 95-001 (50%).

Baseline Assessments (Entire Population)

The WPBIS represents a 5 point scale assessing the degree to which a patient's pain interfered with various activities including Mood, Walking Ability, Normal Work, Enjoyment of life, and sleep. The scoring ranges from 0 (not at all) to 4 (extremely). As demonstrated in Table 7.40, these scores were similar between the studies but overall, were slightly greater in study 96-002. The mood score for the ziconotide treated patients was higher than the placebo treated patients and this did reach statistical significance.

Table 7.40

WPBIS Assessment	95-001		96-002	
	Ziconotide	Placebo	Ziconotide	Placebo
	Mean (SE)	Mean (SE)	Mean (SE)	Mean (SE)
Mood	2.4 (0.15)	2.6 (0.170)	2.9 (0.08)	2.5 (0.12)
Walking Ability	2.9 (0.14)	2.8 (0.21)	3.0 (0.09)	3.1 (0.12)
Normal Work	3.3 (0.13)	3.5 (0.14)	3.3 (0.08)	3.3 (0.12)

Baseline Pain Scores (Reanalysis Population)

The mean preinfusion VASPI for ziconotide treated patients in 95-001 was 73.4 and for placebo treated patients 78.6. This did not differ statistically. In study 96-002, the ziconotide treated patients mean preinfusion VASPI was 80.6 compared to 74.8 for the placebo group and this difference did reach statistical significance.

Primary Efficacy Evaluation (Reanalysis Population)

With respect to pain relief in response to ziconotide, there were a number of differences between the 2 pivotal studies and these are summarized in Table 7.41. These results represent the patients treated with the final dose schedule and exclude patients from study sites 501 and 6090.

Table 7.41

		95-001		96-002	
		Ziconotide	Placebo	Ziconotide	Placebo
Percent Change In VASPI At The End Of The Initial Titration Phase					
Evaluable	% change in VASPI				
	N	32	17	117	61
	Mean (SE)	42.4 (7.32)	18.9 (9.0)	29.4 (3.74)	6.4 (3.75)
	Median (range)	47.6 (-26-95)	3.1 (-24-96)	19.9 (-54-100)	1.1 (-62-79)
	p-value	0.058		0.004	
ITT	% change in VASPI				
	N	34	17	119	64
	Mean (SE)	39.5 (7.17)	18.9 (9.0)	29.6 (3.69)	6.0 (3.59)
	Median (range)	43.0 (-26-95)	3.1 (-24-96)	20.2 (-54-100)	1.1 (-62-79)
	p-value	0.08		<0.001	
Treatment Responders^b					
Evaluable	N	32	17	102	53
	Responder	15 (46.9%)	3 (17.6%)	32 (31.4%)	8 (15.1%)
	Nonresponder	17 (53.1%)	14 (82.4%)	70 (68.6%)	45 (84.9%)
	p-value	0.023		0.131	

a. categories are worse, on change, slight improvement, moderate improvement, a lot of improvement or complete relief.

b. Treatment responder defined as

1. $\geq 30\%$ decrease in VASPI from baseline
2. No increase in dose of concomitant opioids
3. No change in the type of concomitant opioid (even if equivalent dose)

For the evaluable population, the difference in the mean % change in VASPI in study 95-001 between ziconotide and placebo treated patients was 23.5%, this did not reach statistical significance. The difference in study 96-002 was 23.0% and this did reach statistical significance.

Secondary Efficacy Evaluation - Responder Rate (Reanalysis Population)

In contrast to the primary efficacy variable, the number of patients meeting the criteria as responders was significantly greater for the ziconotide treated patients in study 95-001 compared to placebo, but no in study 96-002. The results are comparable for the ITT population

Secondary Efficacy Evaluation - Initial Dose (Entire Population)

When the original study population was evaluated for the mean percent change in VASPI at the end of the initial titration period, the ziconotide treated patient in study 95-001 had a 53.1% change compared with the placebo group's 18.1% change for a difference of 33%. The ziconotide treated patients in 96-002 had a mean percent change in VASPI at the end of the initial titration of 30.7% compared to 6.2% for the placebo treated patients, a difference of 24.5%. In comparing patients who began titration with an initial dose >0.1 ug/h to those with an initial dose ≤ 0.1 ug/h, an interesting difference between the 2 studies can be seen. Patients beginning with a higher initial dose in study 95-001 had a greater difference in percent change in VASPI compared to placebo than patients starting in the lower dose group. However, in study 96-002, patients with the higher initial dose and those with the lower initial dose both had comparable differences in percent change in VASPI. This difference was statistically significant for the lower initial dose group, but not for the higher dose group.

Table 7.42 Mean Percent Change In VASPI Score At The End Of The Initial Titration Phase By Initial Dose- Evaluable Population

Initial dose group	95-001		96-002	
	Ziconotide	Placebo	Ziconotide	Placebo
<0.1 ug/h				
N ^a	39	21	120	66
Mean (SE)	44.9 (6.21)	21.1 (8.93)	31.8 (3.79)	6.6 (3.47)
p-value	0.042		0.002	
>0.1 ug/h				
N ^a	29	19	39	13
Mean (SE)	64.1 (6.52)	14.8 (10.5)	27.4 (8.09)	4.3 (9.06)
p-value	0.001		0.161	

a Only patients with non-missing data at baseline and the end of titration were included.

From Table 9.3, Vol. 2.96, P. 145, Table 9.2, Vol. 107, P. 134

Secondary Efficacy Evaluation - Demographics (Entire Population)

The percent change in VASPI by demographic group also showed differences between the 2 studies. In particular, the difference between ziconotide and placebo treated patients was larger for the ≥ 60 year old patients in 95-001 and greater for the <60 year old patients in study 96-002. These differences appear to arise from differences in the placebo groups with younger patients in

95-001 and older patients in 96-002 having greater placebo effects. For gender, there was a greater placebo effect in women in study 95-001, and in men in 96-002, but the differences between treatment groups were similar.

Table 7.43 Mean Percent Change In VASPI Score At The End Of The Initial Titration Phase By Demographic group - Evaluable Population

Initial dose group	95-001		96-002	
	Ziconotide	Placebo	Ziconotide	Placebo
Age <60 years				
N	39	23	114	56
Mean (SE)	51.6 (6.19)	24.2 (9.10)	31.4 (3.82)	2.1 (3.53)
Age ≥ 60 years				
N	29	17	45	23
Mean (SE)	55.2 (7.08)	9.6 (10.06)	28.9 (7.62)	16.3 (6.71)
Gender - Male				
N	34	20	88	47
Mean (SE)	44.1 (6.90)	12.3 (8.07)	32.6 (4.23)	9.8 (4.84)
Gender - Female				
N	34	20	71	32
Mean (SE)	62.1 (5.88)	23.9 (10.94)	28.3 (5.77)	1.1 (3.54)

Source: Table 9.6, Vol. 2.96, P. 150; Table 9.5, Vol. 107, P. 138

Prior IT Morphine (Reanalysis Population)

There was an effect of prior intrathecal morphine use on the revised study population in study 95-001 but not in 96-002. In study 95-001, patients who were IT morphine experienced and treated with ziconotide had a mean percent change in VASPI that was greater than placebo by 17.7, while IT morphine-naïve ziconotide treated patients had a difference from placebo of 30.7. For study 96-002, the difference in mean percent change in VASPI for ziconotide treated patients who were IT morphine experienced compared to placebo treated patients was 25.6 and for IT morphine naïve ziconotide treated patients compared with placebo treated patients the difference was 22.

Drug-Disease Interaction (Entire Population)

The ziconotide treated cancer patients in study 95-001 had a larger difference in mean percent change VASPI compared to placebo treated patients than the AIDS patients, the difference between treatment groups was 36.8 for the cancer patients and 22.4 for the AIDS patients. The cancer patients had many etiologies responsible for their pain, the AIDS patients primarily neuropathic pain.

In study 96-002, the ziconotide treated patients with neuropathic pain had a significant difference in mean percent change in VASPI from placebo treated patients. There was no significant difference for the patients with non-neuropathic pain.

SECTION 8.0 SAFETY FINDINGS

SECTION 8.1 METHODS:

The sponsor has submitted 20 clinical studies in support of safety; 9 intrathecal, 7 intravenous and 4 epidural. Sixteen studies were completed as of the ISS cut off date. Data from 2 ongoing intrathecal studies were submitted, for study 95-002 through 4/30/99 and for study 98-022 through 9/9/99. For ongoing epidural studies, 98-023 and 98-029, data through 9/9/99 was included. Deaths and serious adverse events (SAE's) reported after the cutoff dates through 12/1/99 were submitted in Appendix 6.

The safety data has been provided in sections based on route of delivery as agreed upon by the Agency and the sponsor.

For the epidural studies, the sponsor summarized the objectives, methods, and safety results for each of the four studies separately due to differences in study populations, doses administered, fixed vs. titrated dosing and study design.

This review of the safety of ziconotide in the exposed population is based on the information provided by the sponsor in the ISS and the study summaries for the individual trials. Narrative summaries of deaths, serious adverse events (SAE's) and discontinuations were reviewed. Original tabular summaries were examined.

The sponsor coded adverse event terms to preferred terms using the COSTART thesaurus, 5th edition, 1995. Terms that did not match the thesaurus exactly were matched by the sponsor's medical monitor to generate a modified COSTART dictionary. The sponsor counted patients who were enrolled in more than one study only once for all AE summaries and patients who received both ziconotide and placebo in each group for AE summaries. For studies 95-001, 96-002, 95-002 and 97-013 the investigator categorized AE's and SAE's according to relationship to study drug or device. The sponsor has not included AE's ascribed to the device in this ISS. The device information was submitted to the Medtronic PMA supplement of the SynchroMed infusion system. There was no distinction between device and drug AE's for the other IT studies.

SECTION 8.2 INTRATHECAL CLINICAL INVESTIGATIONS

The intrathecal studies submitted for this section are presented in Table 8.1. Study 98-022 and study 95-002, an open label extension of studies 95-001 and 96-002, were ongoing at the time the ISS was submitted.

Table 8.1 Intrathecal Ziconotide Studies - All Patients (From sponsor's Table 8.2.1, Vol. 2.091, P. 155)

Study Number	Study Designs	Protocol-Specified Dose	Patient/Subject	No. of Subjects ^a
Controlled Intrathecal Studies-Chronic Pain				
95-001	Phase II/III Placebo-controlled, safety and efficacy	0.1-2.4 ug/h	Chronic malignant pain	112
96-002	Phase II/III Placebo-controlled, safety and efficacy	0.1-2.4 ug/h	Chronic nonmalignant pain	257
Controlled Intrathecal Studies-Acute Pain				
C96-003	Phase II-Pilot, Placebo-controlled	0.7, 7.0 ug/h	Acute post-op pain	30
Uncontrolled Intrathecal Studies				
94-004	Phase I/II-Pilot, open-label	0.3-300 ng/kg/h	Chronic pain	31
95-002	Phase III-Long-term, open-label, safety	0.1-2.4 ug/h	Chronic pain	155 ^b
C96-010	Phase II, Open-label, safety and efficacy	0.2-3.4 ug/h	Chronic, nonmalignant pain	1
C97-013	Phase II-PK	1, 5, 7.5, 10 ug	Chronic pain	22
C97-015	Phase II, Open-label, safety and efficacy	0.04-0.1 ug/h	Chronic, nonmalignant pain	1
C98-022	Phase II-Open-label, long-term Safety	0.1 ug/h, titration to response	Chronic severe pain	500 ^c

^a Indicates subjects enrolled or treated in the studies.

^b These patients previously participated in Study No. 95-001 or 96-002.

^c Planned enrollment for ongoing studies

Study 95-002 An Open Label, Long Term Safety And Efficacy Study Of Ziconotide Administered Intrathecally To Patients Suffering From Chronic Pain Using The SynchroMed Infusion System Of The Sims Deltec CADD Micro Pump

This study was to be an open label extension for patients who demonstrated a response to ziconotide in one of the controlled pivotal trials, 95-001 or 96-002. Patients receiving ziconotide via an external pump were eligible to be implanted with a SynchroMed Infusion System as part of this study. Patients were to be managed on their fixed optimal therapeutic dose, the last dose received during the trial of origin, provided there was adequate pain control, no increase in concurrent analgesic medication and no unacceptable AE's. After the initial 30 day period, dose increases were to be permitted, up to a 2 fold increase every 12 hours.

Study 98-022 An Open Label, Long Term Safety And Tolerability Study Of Ziconotide Administered Intrathecally To Patents With Chronic, Severe Pain

Patients with chronic severe nociceptive and/or neuropathic pain of central or peripheral origin were to be eligible. Treatment was started at 0.1 ug/h titrated by no more than 0.1 ug/h every 24 hours to efficacy. No maximum dosage was specified by the protocol. A single voluntary interruption of ziconotide infusion was to be permitted for up to 30 days. This was because in prior ziconotide trials, patients who terminated study participation would request reentry after several weeks off after realizing that the drug had provided pain relief.

Study 94-004 A Phase I/II, Open Label, Rising Dose, Safety And Feasibility Study Of SNX-111 Administered Intrathecally To Patients With Chronic Intractable Pain

This was to be dose ranging study starting with 0.3ng/kg/hr, and a maximum dose of 300 ng/kg/hr. Titration was to be based on pain relief and the presence of intolerable adverse events. The initial titration period lasting 7 days was to be as an inpatient with an option for a long term extension for patients with at least 24 hours of satisfactory pain relief.

Study 97-013 A Phase II, Pilot Study Of Ziconotide Administered By Bolus Injection To Patients With Chronic Pain

This was a single center, open label pilot study. Part A assess PK, safety and analgesic profiles of ziconotide over 48 following a 1 hour intrathecal infusion. Patients were eligible with chronic malignant pain. The doses were to be 1, 5, 25, 50 and 100 ug, but the study was amended and the doses were 1, 5, 7.5 and 10 ug as 10 ug was the maximally tolerated dose.

Only one patient was enrolled in each of the 2 following studies:

Study 96-010 A Phase II Study Of Ziconotide Administered Intrathecally To Patients With Chronic Nonmalignant Pain

Study 97-015 An Open Label, Dose Escalation Study Of Ziconotide Administered By Intrathecally To Patients With Chronic Nonmalignant Pain

SECTION 8.2.1 DEATHS - IT

The sponsor has provided information on deaths from all studies and from the ongoing studies up to the cutoff dates: for 95-002, 4/30/99, and 98-022, 9/9/99. Additional information for the 2 ongoing studies through 12/1/99 was summarized separately and submitted as Appendix 6

There were 58 deaths reported in the body of the submission and 2 in Appendix 6 for a total of 60 deaths. (Appendix 6 represents data submitted to the NDA between the 9/9/99 cutoff date and 12/1/99.) Fifty eight of the deaths occurred in the group of 704 patients who had "ever received ziconotide". This represents an incidence of 8.2%. Thirty five of the patients died either while ziconotide was still being infused or on the same day that the ziconotide infusion was discontinued.

Two deaths occurred in the group of 44 patients who "never received ziconotide" for an incidence of 4.5%. One of these patients, 5029-49, died due to progression of adenocarcinoma of unknown origin 13 days after the last dose of study medication. The other patient, 5009-75, had a diagnosis of metastatic breast carcinoma and died 40 days after completing the study. The death was not noted as a serious AE and details of the death are not available for review.

Of the 58 deaths occurring in patients who were ever on ziconotide, 51 (87.9%) occurred in patients with chronic pain of malignant origin and the remaining 7 (12.1%) occurred in patients with chronic pain of non-malignant origin. The narratives, selected CRF's and lab results for these patients were reviewed and an attempt was made to determine if ziconotide could have contributed to the cause of death.

Of the 58 deaths in patients ever on ziconotide there were 20 patients for whom the patient narratives and CRF's provided too little information to assess any possible association between the cause of death and ziconotide. These 20 patients all enrolled with chronic malignant pain and the cause of death provided in the patient narrative and CRF simply stated progression of underlying cancer with no further comment.

There were 33 patients for whom the patient narratives and CRF's suggest that there was no contribution of ziconotide to the cause of death. However, there was not enough detailed information for this reviewer to definitively exclude a direct or indirect effect of the ziconotide contributing to the cause of death. Twenty six of these patients had metastatic cancer, 7 had pain of non-malignant origin. The cause of death for the 26 cancer patients was attributed to disease progression and complications from advanced metastatic cancer by the investigators and sponsor. The most proximate or serious adverse events described in the patient narratives and on the CRF's prior to death in these patients and the patients with non-malignant pain are presented in Table 8.2. As can be seen, encephalopathy and respiratory failure were the overwhelmingly most common AE's preceding death in these patients, but these are also common antecedents to death in terminal cancer patients.

Table 8.2 Adverse Events Prior to Death

Adverse event	Chronic malignant pain	Chronic non-malignant pain
Encephalopathy including delirium, confusion and mental status change	8	0
Respiratory failure including effusions and pulmonary edema/volume overload	6	0
Pneumonia including aspiration	2	1
Liver failure including metastatic invasion	2	0
Multisystem failure	1	0
Acute renal failure	0	1
SVT/Possible arrhythmia/Syncope	3	0
Sepsis	1	0
Meningitis	1	0
Suicide	1	2
Overdose	0	1
Coronary artery thrombosis/cardiac arrest	0	1
Found dead, no autopsy	0	1

Three examples of the patients with malignant disease classified in this group (death unlikely related to ziconotide) are detailed below for illustration.

- Patient 100-101 was a 57 year old man who enrolled in study 94-004 with a history of metastatic chondrosarcoma. The patient had numerous skeletal lytic lesions associated with fractures involving the pelvis, femoral neck, humerus and lumbar vertebral bodies; invasion of the vertebral metastases into the thecal sac, bilateral lower extremity edema, and adrenal metastases. The patient completed the initial phase of the study during which ziconotide was titrated from 1 ng/kg/h to 300 ng/kg/h, resulting in a final dose of 38.1 ug/h in this 127 kg man. Four days later the patient died due to respiratory arrest, attributed to aspiration pneumonia resulting from increased opiate consumption. The patient had been receiving

intravenous morphine sulfate at 0.5 mg/h with intermittent 2 mg boluses prn. Disorientation that began while on ziconotide persisted beyond study completion. It can not be determined if a ziconotide related encephalopathy contributed to the patient's death but this seems unlikely given the 4 days separating drug discontinuation and death and the patient was also receiving parenteral morphine.

- Patient 123-1181 was a 53 year old man who enrolled in study 98-022 with a history of metastatic renal cell carcinoma. The patient developed paranoia, disorientation and increased cancer pain 19 days after starting ziconotide. The drug was stopped 10 days later due to persisting confusion. The adverse events were ongoing and the patient died 18 days after cessation of ziconotide. Death was attributed to cardiopulmonary collapse due to the cancer. The patient was also taking oxycodone IR, oxycodone SR, methadone and celecoxib at the time of death. The dosages are not available from the CRF. While it is possible that the confusion persisting after discontinuation of study drug was due to a ziconotide related encephalopathy, the 18 days between drug discontinuation and death make this seem unlikely.
- Patient 5009-53 was a 57 year old man who enrolled in study 95-002 following 95-001 with a history of metastatic lung cancer. The patient had progressive paresis due to spinal cord compression at T1. While on Day 37 of ziconotide, the patient developed dyspnea, progressing to respiratory insufficiency and death attributed to spinal cord compression from tumor advancement. The patient was receiving ziconotide at a rate of 6.67 ug/h at the time of death along with morphine sulfate 1260 mg/day by intravenous route. While it is possible that the ziconotide contributed to the dyspnea, the patient's dose was relatively stable over time fluctuating between 6.25 and 7.92 ug/h in the weeks prior to the patients death and there were other factors, particularly the very large morphine dose and the spinal cord compression that are more likely contributing causes.

The 7 deaths in patients with chronic pain of non-malignant origin can be considered less expected than the patients with malignant pain. Based on the available information summarized below there is no evidence of any clear contribution by ziconotide to the cause of death for any of these patients. However, as can be seen, information is limited so the possibility of a contribution by ziconotide can not be definitively excluded.

- Patient 6055-104, a 65 year old woman, entered the study with chronic back pain. This patient had a history of hypertension, diabetes, peripheral neuropathy, COPD, gastritis and bowel obstruction. On _____, 3 days prior to start of study drug, the patient's BUN and creatinine were 36 and 3.0. On _____ 12 days after initiating therapy with ziconotide, the BUN and creatinine were 35 and 2.9. The patient developed acute renal failure on _____ while still receiving ziconotide and died in hospice care 8 days later after refusing dialysis. There is no information on the renal function between _____. The patient had been on numerous medications including OxyContin, Percocet, oxybutinin, amitriptyline, Premarin, and Glucotrol.
- Patient 6066-103, a 61 year old woman, had pain due to "end stage multiple sclerosis" (App 3, Vol. 2.275, P. 306). This patient died due to pneumonia, and had a history of several episodes of pneumonia prior to study drug infusion, including just one month prior to the start of the study.
- Patient 6068-101, a 69 year old man, entered the study with failed back syndrome and died after a cardiac arrest. An autopsy was performed and found the cause of death to be

“coronary atherosclerosis with acute thrombosis and contributing hypertension.” (Appendix 3, Vol. 2.275, P. 337)

- Patient 91-1009, a 37 year old man, enrolled with a history of atypical facial pain. The patient withdrew from the study on _____ 11 days after initiating therapy with ziconotide due to lack of pain relief. The patient committed suicide on _____ by unspecified means.
- Patient 122-1112, a 46 year old woman, enrolled with a history of “neck and bilateral upper extremity pain, s/p cervical anterior fusion, Low back pain and bilateral lower extrem. pain s/p lumbar laminectomy w/ the formation of adhesive arachnoiditis” (CRF, page 5). The patient had a history of chronic opioid use. Ten days after starting ziconotide, the patient was found dead from a methadone overdose, with an empty bottle of methadone by her side. This patient is counted by the sponsor as a suicide.
- Patient 035-1276, a 72 year old woman, enrolled with a history of failed back syndrome. The patient also had a history of labile blood pressure. The patient was found dead in her bed on Day 24 of treatment. No autopsy was performed and the cause of death is unknown.
- Patient 0661081, a 61 year old man, enrolled with a history of ilioinguinal neuralgia and depression. Six months after initiating treatment, the patient attempted suicide by gun shot to the head and died the following day.

There were 4 patient narratives which documented sufficient information to attribute death to a cause other than study drug. The causes of death for these patients were massive hemoptysis (100-103), sepsis (200-202), hemorrhagic brain metastases (100-102), brain metastases (5007-79).

There were 2 patients for whom the information in the patient narratives and the investigator’s assessment are suggestive of a possible contribution between the ziconotide and the cause of death. Both of these patients had an encephalopathy at the time of death:

- Patient 501-73 enrolled with metastatic cervical cancer. The patient developed psychosis 17 days after beginning ziconotide which was ongoing until death 47 days after beginning ziconotide. It is unclear if either ziconotide or brain metastases contributed to the patient’s psychosis and death.
- Patient 5032-74 enrolled with invasive squamous cell cancer of the head and neck. The patient developed delirium with multifocal myoclonus 5 days after starting ziconotide and the ziconotide was discontinued that same day. The patient was also on escalating doses of morphine sulfate at the time. The patient died due to aspiration pneumonia 5 days later and it was suggested by the investigator that either the morphine or the ziconotide contributed to the mental status change placing the patient at risk for the aspiration.

Suicides/suicide attempts

There were 5 suicide attempts, 3 completed suicides and 2 patients with suicidal ideation during the intrathecal clinical trials. Nine of these 10 patients were among the 704 who had ever received ziconotide (1.3%) and the remaining 1 patient was from the group of 151 patients who had received placebo (0.7%). Within the controlled trials, one patient on placebo had suicidal ideation, 1 patient on ziconotide had suicidal ideation and one patient on ziconotide had a completed suicide. Two of these patients had histories of suicidal ideation prior to the study and two patients had prior histories of depression. Table 8.3 provides further information on these patients.

Table 8.3 Summary of Suicidal Events (Modified From Sponsor's Table 8.8.2.8.4 Vol. 2.93, P. 324)

Investigator-Patient #	Etiology Of Pain	Suicidal Event	Comments
5013-49	Prostate Cancer, Metastatic	Suicidal ideation	Day 4 on placebo. History of suicidal ideation 6 months prior to study
5025-49	Squamous Cell Cancer, Metastatic	Completed suicide, Gunshot	Day 8 on ziconotide, met criteria for responder
5007-49	Neuro-Fibrosarcoma	Suicide attempt, Drug overdose	Day 1012 on ziconotide. Complained of work related stress
6605-101	Post Traumatic Calcaneal Osteomyelitis	Suicidal tendency	Day 5 ziconotide. suicidal ideation began. Placed on a rapid opioid taper as study was started
91-1009	Atypical Facial Pain	Completed suicide, Unknown means	25 days following discontinuation, 11 days on ziconotide
122-1112	Failed Back Syndrome	Completed Suicide, Methadone overdose	No further information available, 10 days on ziconotide
94-1125	Failed Back Syndrome	Suicide attempt, Drug overdose	No further information available, 22 days on ziconotide
135-1163	Refractory Occipital Neuralgia	Suicide gesture, Unknown means	H/o depression, details of gesture NA, 57 days on ziconotide
118-1078	Spinal Cord Injury With Partial Paraplegia	Suicide attempt, Xanax overdose	H/o depression and occasional suicidal ideation, 61 days on ziconotide
123-1181	Renal Cell Carcinoma, Metastatic	Suicide attempt, Dextroamphetamine overdose	No further information available, 18 days on ziconotide

Data Source Appendix 2, IT Patient Data Listings 1.1, 2.2.4.1, and 4.4.

SECTION 8.2.2 SERIOUS ADVERSE EVENTS - IT

Serious Adverse Events for the entire group of patients exposed to intrathecal ziconotide are reported in Table 8.8.2.8.5 (Vol. 2.227, P. 328). Each patient with more than one SAE/body system is reported only once so the incidences represent conservative values. Furthermore, and more importantly, this table fails to capture all of the SAE's, only those identified by the CRF's as SAE's. For example, under the COSTART term death, only 3 patients are reported as SAE's, however, there were 35 deaths while receiving ziconotide according to Table 8.8.2.8.3 Patient Deaths (Vol. 2.93, P. 319) (out of 58 deaths in patients who "ever received ziconotide").

Serious Adverse Events occurred in 240/704 patients (34.1%) while receiving ziconotide compared to 18/151 (11.8%) of patients while receiving placebo. According to the sponsor, the most common SAE's while receiving ziconotide were confusion (4.1%), dizziness (2.0%), pneumonia (2.0%) and urinary retention (1.6%). While receiving placebo, the most common SAE were myasthenia and ileus, 1.3% each, and no other SAE occurred in more than one patient while receiving placebo. Serious Adverse events occurring in 1% or greater of the patients are presented in Table 8.4.

**Table 8.4 Serious Adverse Events in $\geq 1\%$ of Patients - All Intrathecal Clinical Studies
(Modified From sponsor's Table 8.8.2.8.5, Vol. 2.93 P. 328)**

COSTART Term	Ziconotide N = 704		Placebo N = 151	
	Number of Patients	Percentage	Number of Patients	Percentage
Number of Patients with Any Event	240	34.10%	18	11.90%
Body as a Whole	79	11.20%	4	2.60%
Fever	9	1.30%	0	
Headache	8	1.10%	1	0.70%
Digestive System	33	4.70%	2	11.30%
Nausea	7	1.0%	0	0.00%
Cardiovascular System	22	3.10%	0	0.00%
Metabolic and Nutritional Disorder	9	1.30%	1	0.70%
Musculoskeletal System	12	1.70%	3	2.00%
Nervous System	107	15.20%	6	4.00%
Confusion	29	4.10%	0	0.00%
Dizziness	14	2.00%	0	0.00%
Meningitis	10	1.40%	1	0.70%
Somnolence	9	1.30%	0	0.00%
Thinking Abnormal	8	1.10%	0	0.00%
Respiratory System	37	5.30%	4	2.60%
Dyspnea	9	1.30%	0	0.00%
Pneumonia	14	2.00%	1	0.70%
Skin and Appendages	10	1.40%	0	0.00%
Special Senses	12	1.70%	0	0.00%
Urogenital System	30	4.30%	1	0.70%
Urinary Retention	11	1.60%	0	0.00%

Note: A patient may be included in both the 'While Receiving Ziconotide*' and the 'While Receiving Placebo' columns, but are only counted once per column total.

Studies include: 94-004, 95-001, 95-002, 96-002, 96-003, 96-010, 97-013, 97-015, and 98-022.

Data Source: Appendix 1. IT Table 10.1.

After review of the IT Listing 4.4 Serious Adverse Events (Drug Only) and IT Listing 4.5 Adverse Event Verbatim Mappings (Appendix 2, Vol. 2.227) this reviewer found that similar adverse events were mapped to different COSTART terms. This was particularly true of the adverse events involving the central nervous system. For example, patients who demonstrated manifestations of an encephalopathy including confusion, not making sense while speaking, memory problems or delirium were mapped to a variety of COSTART terms including confusion, thinking abnormal, amnesia. This results in many terms with small incidences representing an adverse event with a larger incidence.

This reviewer examined the listings of adverse events and reassigned the COSTART terms of clinically and physiologically related signs and symptoms. This resulted in the adverse events mapped by the sponsor to the terms confusion, thinking abnormal, delirium, amnesia being mapped by this reviewer to encephalopathy. Similarly, the adverse events mapped by the sponsor to nausea, nausea and vomiting, and vomiting were mapped by this reviewer to the term nausea and/or vomiting. The adverse events mapped by the sponsor to gait abnormality, incoordination, cerebellar syndrome, ataxia were mapped by this reviewer to ataxia. The adverse

events of motor weakness and limb weakness mapped to by the sponsor to myasthenia were remapped to weakness. Lastly, suicidal ideation and suicidal gestures mapped to by the sponsor to depression were remapped as suicidal ideation/gesture. The result of this re-mapping is displayed in Table 8.5. The most striking difference from this re-mapping is the considerably larger proportion of patients (5.7%) exhibiting Encephalopathy as a serious adverse event.

Table 8.5 Serious Adverse Events For Selected Remapped COSTART Terms, All Intrathecal Studies

New Term	While Receiving Ziconotide (N=704)		While Receiving Placebo (N=151)	
Ataxia	6	0.9%	1	0.7%
Encephalopathy	40	5.7%	1	0.7%
Nausea and/or vomiting	13	1.8%	0	0.0%
Suicidal ideation/gesture	6	0.9%	1	0.7%
Weakness	3	0.4%	2	1.6%

The most common serious adverse events occurring during the double blinded, placebo controlled period of the two pivotal studies are summarized in Table 8.6. The patients were divided by initial dose group, to better approximate the final dosing regimen. This is useful because the final dosing protocol prescribed significantly lower doses than the original protocols. As a result and demonstrated in Table 8.6, the frequencies of adverse events was influenced by the initial dose/ different dosing protocols, with the patients who received lower initial doses exhibiting fewer adverse events. The SAE's that occurred most frequently overall involved the nervous and digestive systems, particularly confusion, dizziness and nausea.

Table 8.6 Serious Adverse Events in $\geq 1\%$ of Patients by Initial Dose Group -Double-Blind, Placebo-Controlled Clinical Studies - Initial Titration Phase (Modified from Sponsor's Table 8.8.2.8.6, Vol. 2.93)

COSTART Term	Ziconotide						Placebo	
	≤ 0.1 ug/h N= 166		> 0.1 ug/h N = 76		Total N = 242		Total N = 126	
Number of Patients with Any Event	25	15.1%	24	31.6%	49	20.2%	6	4.8%
Body as a Whole	2	1.2%	3	3.9%	5	2.1%	2	1.6%
Carcinoma of Lung	0	0.0%	2	2.6%	2	0.8%	0	0.0%
Cardiovascular System	3	1.8%	3	3.9%	6	2.5%	0	0.0%
Hypotension	1	0.6%	1	1.3%	2	0.8%	0	0.0%
Postural Hypotension	0	0.0%	2	2.6%	2	0.8%	0	0.0%
Digestive system	3	1.8%	2	2.6%	5	2.1%	0	0.0%
Nausea	0	0.0%	2	2.6%	2	0.8%	0	0.0%
Nervous System	14	8.4%	12	15.8%	26	10.7%	3	2.4%
Abnormal Gait	1	0.6%	1	1.3%	2	0.8%	0	0.0%
Confusion	2	1.2%	5	6.6%	7	2.9%	0	0.0%
Convulsion	3	1.8%	0	0.0%	3	1.2%	0	0.0%
Dizziness	5	3.0%	2	2.6%	7	2.9%	0	0.0%
Nystagmus	0	0.0%	2	2.6%	2	0.8%	0	0.0%
Somnolence	1	0.6%	2	2.6%	3	1.2%	0	0.0%

Table continues

Table 8.6 continued

COSTART Term	≤ 0.1 ug/h N= 166		> 0.1 ug/h N = 76		Total N = 242		Total N = 126	
Respiratory System	3	1.8%	2	2.6%	5	2.1%	1	0.8%
Carcinoma of Lung	0	0.0%	2	2.6%	2	0.8%	0	0.0%
Dyspnea	2	1.2%	1	1.3%	3	1.2%	0	0.0%
Special Senses	4	2.4%	4	6.3%	8	3.3%	0	0.0%
Amblyopia	1	0.6%	2	2.6%	3	1.2%	0	0.0%
Urogenital System	3	1.8%	3	3.9%	6	2.5%	0	0.0%
Urinary Retention	3	1.8%	3	3.9%	6	2.5%	0	0.0%

Note: One additional patient (Patient 6076-108) experienced a serious adverse event of abdominal pain which was noted after database closure and is not included in any of the summary tables or IT Patient Data Listings in Appendices 1 and 2. This patient is presented in IT Table 8.8.2.8.7 in the text of the IT ISS and has been noted in the text preceding IT Table 8.8.2.8.6.

Studies include: 95-001 and 96-002.

Data Source: Appendix 1, IT Table 10.2.

The same process of reassigning the COSTART terms of clinically and physiologically related signs and symptoms was performed on the serious adverse events from the initial titration period of the controlled trials. This primarily affected the categories of Ataxia, Encephalopathy and Nausea and/or Vomiting and the results for the entire group of patients are presented in table 8.7. The most striking difference from this re-mapping is the considerably larger proportion of patients (4.5%) exhibiting Encephalopathy as a serious adverse event.

Table 8.7 Remapped Serious Adverse Events, Controlled Trials, Initial Titration Period

New Term	While Receiving Ziconotide (N=242)		While Receiving Placebo (N=126)	
Ataxia	3	1.2%	1	0.8%
Encephalopathy	11	4.5%	0	0.0%
Nausea and/or vomiting	4	1.7%	0	0.0%

SECTION 8.2.3 DISPOSITION - IT

Of the 748 patients participating in intrathecal ziconotide trials, there were 704 unique patients who ever received ziconotide and 44 patients who "never received ziconotide". This includes 610 patients who were initially assigned to ziconotide during the first study, 93 patients who were crossed over from placebo to ziconotide during their first study and one patient who received placebo during the first study participation (patient 5519-25 in study 95-001) and ziconotide during the second study participation (study 98-022).

Of the 168 patients who entered a second study, 158 patients received ziconotide during participation in both studies. This consists of all 155 patients in study 95-002, (48 from study 95-001 and 107 from study 96-002) and 3 patients from 98-022 (2 originally from study 96-002 and one from 97-013). There was one patient who received ziconotide in study 98-022 that had previously received placebo in study 95-001. The sponsor has also included 9 patients from the extension portion of 94-004 as participating in a second study.

There were 862 cases of ziconotide exposure. This is a result of participation in more than one study, and includes the 704 patients who received ziconotide during their original study participation, plus the 158 patients who received ziconotide for the second time during participation in a second study.

The disposition of patients from all of the intrathecal studies is summarized in Table 8.8. The sponsor made the determination of study completion from the CRF study termination page. Different terms were used for the reason for study termination across studies so the termination choices used for this ISS represent an aggregate across studies. As explained below, there are differences in the categorization of cause of study termination between the sponsor and this reviewer. The re-categorization by this reviewer is presented in italics in Table 8.8.

The protocol for study 98-022 presents a problem for interpretation of disposition and safety data. Within the study protocol, a voluntary interruption of ziconotide infusion for up to 30 days is permitted. The sponsor has determined that any patients in the 30 day interruption at the time of data cutoff would be considered ongoing for the purposes of safety. This can potentially inflate the duration and exposure data, and since there are no AE's for this period, bias the incidence of AE's in favor of the study drug (Vol. 2.93, P 168).

As can be seen, there were many more patients in the "ever received ziconotide" group discontinuing study participation due to intolerable adverse events than patients who "never received ziconotide".

Table 8.8 Disposition of patients from All IT Studies (From Sponsor's tables 8.8.2.5.2 and 8.8.2.5.1, Vol. 2.93 P. 174)

Reason	Study of Origin		Second Study
	Ever Received Ziconotide	Never Received Ziconotide	Ever Received Ziconotide
All Treated Patients	703 (100.0%) ^a	45 (100.0%)	168 (100.0%) ^b
Study Completed ^c	277 (39.4%) 278 (39.5%)	33 (73.3%)	
Ongoing	200 (28.4%) ^d	0	24 (14.3%)
Terminated or Discontinued	226 (32.1%) 225 (32.0%)	12 (26.7%)	135 (80.4%)
Primary Reason for Early Termination or Discontinuation			
Non-compliance by Patient	1 (0.1%)	1 (2.2%)	
Intolerable Adverse Event	141 (20.1%) 143 (20.3%)	4 (8.9%)	59 (35.1%)
Withdrawal Requested by Patient or Legal Representative	11 (1.6%) 12 (1.7%)	1 (2.2%)	24 (14.3%)
Unrelated Medical Condition	2 (0.3%)	1 (2.2%)	2 (1.2%)
Administrative or Investigator Decision	1 (0.1%)	1 (2.2%)	2 (1.2%)
Death on Study	3 (0.4%)	0	23 (13.7%)
Infection	2 (0.3%) 3 (0.4%)	1 (2.2%)	
System Related (Pump/Catheter)	8 (1.1%) 13 (1.8%)	1 (2.2%) 2 (4.4%)	
Ineffective Drug Therapy/Loss of Effect	37 (5.3%) 38 (5.4%)	0	24 (14.3%)
Other ^e	20 (2.8%) 10 (1.4%)	2 (4.4%) 0	1 (0.6%)

Note: Figures in italics represent the reviewer's assessments.

- a. In this summarisation, Patient 5519-25, who received placebo in the study of origin (95-001) and then ziconotide in a second study (98-022), is counted in the 'never received ziconotide' column
 - b. Includes 9 patients in the long-term extension portion of Study 94-004, for whom disposition data was collected not on the Study Termination Page of the CRF, but on other CRF pages. Data for these 9 patients are not included in this table.
 - c. Not applicable for patients participating in the ongoing Long-Term, Open-Label Clinical Studies.
 - d. Patient 10-715 in Study 98-022 was still considered to be ongoing as of the data cut-off. However, because the patient discontinued in the study of origin this patient is counted as discontinued in IT Table 8.8.2.5.1 and as ongoing in IT Table 8.8.2.5.2,
 - e. Reasons (e.g., intrathecal catheter no CSF flow, catheter fell out prior to end of study, etc.) are listed in App 2, IT Patient Data Listing 2.1.
- Data Source: Appendix 1, IT Table 1.2 and 1.2.1.

The Patient Data Listing 2.1 (Appendix 2, Vol. 2.218, P. 188), the Patient Narratives (Appendix 3, Vol 2.274, 2.275 and 2.276) and the CRF's were reviewed to determine the causes behind the early termination of the 23 patients categorized in Table 7 in the "Other" group. These results are summarized in Table 8.9. There is no information as to the cause of study termination for 8 of these patients and an un-interpretable phrase in Listing 2.1 for 3 of the patients. Six of the patients had catheter problems and one had the battery of his/her external pump removed. Six of the patients had reasons for study termination that could be grouped in one of the categories under Primary Reasons for Study Termination, including two patients with intolerable adverse events, one with meningitis, one who withdrew consent, one with lack of pain relief and one who according to the patient narrative, completed the study

Table 8.9 Explanation Of "Other" Reason For Study Termination

	Study of Origin		Second Study
	Ever Received Ziconotide	Never Received Ziconotide	Ever Received Ziconotide
No Explanation, Narrative Or CRF Provided	8		
Catheter Out or Occluded, Pump Problem	5	2	
Reason For Study Termination Not "Other"	6		
Includes:			
Meningitis Due To Infected Catheter	1		
Completed Study	1		
Intolerable Adverse Event	2		
Withdrew consent	1		
Lack of pain relief	1		
Uncertain ^a	2		1

- a. Explanation of "other" in Listing 2.1 consists of incomplete phrases:
 Patient 203-999 - "medication initiated after surgical incision, syringe disco"
 Patient 6066-102 - "pt receiving active drug 2nd was a non-responder, term"
 Patient 6066-119 - "saline was placed in SynchroMed pump on 2/5 intole"

The sponsor pointed out that the patient population consisted of sick cancer patients many of whom were considered terminal at study entry along with the chronic non-malignant pain patients. The disposition for patients in the two controlled trials during the randomized, double blinded initial titration phase is summarized in Table 8.10. This data controls for the severity of illness within the study population when evaluating the disposition of the patients. During this initial titration period, the randomization prevents bias by patient characteristic this is supported by the demographic information in the efficacy review. The ziconotide treated patients

demonstrated a greater frequency of early study termination, and the predominant reason for this early termination was intolerable adverse events.

Table 8.10 Disposition of Patients from the Double-Blind, Placebo-Controlled Clinical Studies - Initial Titration Phase (From Sponsor's Table 8.8.2.5.4, Vol. 2.93 P. 177)

Reason	Ziconotide	Placebo
All Treated Patients ^a	242 (100.0%)	126 (100.0%)
Initial Titration Phase Completed	191 (78.9%)	117 (92.9%)
Early Termination or Discontinued from Initial Titration Phase	51 (21.1%)	9 (7.1%)
Primary Reason for Early Termination from Initial Titration Phase		
Non-compliance by Patient	0	1 (0.8%)
Intolerable Adverse Event ^b	32 (13.2%)	3 (2.4%)
Withdrawal Requested by Patient or Legal Representative	2 (0.8%)	1 (0.8%)
Unrelated Medical Condition	2 (0.8%)	1 (0.8%)
Administrative or Investigator Decision	1 (0.4%)	1 (0.8%)
Infection ^c	1 (0.4%)	1 (0.8%)
System Related (Pump/Catheter)	5 (2.1%)	1 (0.8%)
Ineffective Drug Therapy/Loss of Effect	6 (2.5%)	0
Other ^d	2 (0.8%)	0

a. Includes Patient No. 5047-74 in Study 95-001, who was not randomized but received open-label ziconotide.

b. Three ziconotide patents (6058-101, 609-111, and 6067-101) and two placebo patents (5047-49 and 6079-106) discontinued due to adverse events associated with the device.

c. Device adverse events.

d. Other includes: Patient was a nonresponder to active drug (6066-102) and intrathecal catheter no CSF flow (6087-105).

Studies include: 95-001 and 96-002.

Data Source: Appendix 1, IT Table 1.3; Appendix 2, IT Patient Data Listing 2.1.

As can be seen in Table 8.11, although there was a larger proportion of patients terminating or discontinuing early from the group consisting of all of the intrathecal studies than from the initial controlled titration period of the 2 pivotal studies, the breakdown of the reasons for early termination are very similar. The primary difference appears to be a greater proportion of patients in the total group, who terminated early due to ineffective drug therapy/loss of effect. The primary reason for early study termination for both treatment groups was intolerable adverse events. Furthermore, the "ever received ziconotide" group and the "ziconotide" group from the pivotal trials both had a larger number of early withdrawals than the respective placebo comparator groups.

Table 8.11 Early Termination of Discontinuation, All IT Studies

Reason	Study of Origin, All IT Studies		Second Study	Initial Controlled Titration, Pivotal Trials	
	Ever Received Ziconotide	Never Received Ziconotide	Ever Received Ziconotide	Ziconotide	Placebo
All treated patients (100%)	703	45	168	242	126
Early termination or discontinuation	225 (32.0%)	12 (26.7%)	135 (80.4%)	51 (21.1%)	9 (7.1%)
Primary Reason for Early Termination or Discontinuation (% of Early termination group)					
Non-compliance by Patient	1 (0.4 %)	1 (8.3%)	0	0	1 (11.1%)
Intolerable Adverse Event	143 (63.6%)	4 (33.3%)	59 (43.7%)	32 (62.7%)	3 (33.3%)
Withdrawal Requested by Patient /Legal Representative	12 (5.3%)	1 (8.3%)	24 (17.8%)	2 (3.9%)	1 (11.1%)
Unrelated Medical Condition	2 (0.9%)	1 (8.3%)	2 (1.5%)	2 (3.9%)	1 (11.1%)
Administrative or Investigator Decision	1 (0.4 %)	1 (8.3%)	2 (1.5%)	1 (2.0%)	1 (11.1%)
Death on Study	3 (1.3%)	0	23 (17.0%)	0	
Infection	3 (1.3%)	1 (8.3%)	0	1 (2.0%)	1 (11.1%)
System Related-Pump/ Catheter	13 (6.0 %)	2 (16.7%)	0	5 (9.8%)	1 (11.1%)
Ineffective Drug Therapy/ Loss of Effect	38 (16.8%)	0	24 (17.7%)	6 (2.5%)	0
Other ^c	10 (4.4%)	0	1 (2.7%)	2 (3.9%)	0

SECTION 8.2.3.1 Adverse Events Leading To Discontinuation - IT

This section of the safety review was created based on the total information available in the 120 day safety update

Patients who ended study participation due to Adverse Events were captured by the sponsor as patients for whom “Intolerable AE” or “Infection” were checked as the primary reason for discontinuation on the study termination page of the CRF. For the extension portion of study 94-004, this information was on another CRF pages and was included in the data for AE leading to D/C where the sponsor deemed it appropriate.

A total of 295 (33.3%) out of the 887 patients who ever received ziconotide discontinued or terminated early from a study while receiving ziconotide due to adverse events. Six of these patients discontinued from both 95-001 or 96-002 and again from 95-002. These patients were counted only once in the 295 patients. The sponsor points out that they captured 4 additional patients included in the 295, who discontinued for an adverse event but this was not recorded as such on the CRF’s. Nine patients of the 151(6.0%) who “ever received placebo”, discontinued while receiving placebo.

Table 8.12 Number of Patients who Discontinued from a Study Due to Adverse Events (including Infection) by Study - All Intrathecal Clinical Studies (Modified from sponsor’s IT Table 9.2.8.8, Vol. 5.002, P. 232)

Study	While Receiving Ziconotide			While Receiving Placebo
	IT ISS (N=704)	IT 120 Day Safety Update (N=887)	New Patients not in IT ISS (N=183)	
94-004	10	10		
94-004 Long-Term Extension	3 ^a	3 ^a		-
95-001	17	17		6
95-002	58 ^b	59 ^b		-
96-002	50	50		2
96-003	5 ^c	5 ^c		1
96-010	1	1		-
97-013	0	0		-
97-015	1	1		-
98-022	61 ^d	155	28	-
Total	200/704 (28.4%)	295/887 (33.3%)	28/183 (15.3%)	9/151 (6.0%)

a. Includes Patients 100-107, 300-301, and 400-405. Disposition data for the long-term extension portion of Study 94-004 were not recorded on the Study Termination Page of the CRF but were recorded on other pages of the CRF and are presented in the 94-004 Final Clinical Study Report.

b. Includes six patients (5019-73, 5025-74, 5029-74, 6052-102, 6060-113, 6080-107) who discontinued while receiving ziconotide in the study of origin.

c. Includes 2 patients (204-69 and 204-71) who were noted to have an adverse event at the time of discontinuation, although the reason for discontinuation was not recorded as adverse event or infection on the Study Termination Page of the CRF.

d. Includes one patient (91-1009) who was noted to have an adverse event at the time of discontinuation and one patient (91-1019) who died, although the reason for discontinuation was not recorded as adverse event or infection on the Study Termination Page of the CRF.

Studies include: 94-004, 95-001, 96-002, 96-002, 96-003, 96-010, 97-013, 97-015, and 98-022

Data Source: Appendix 2, IT Patient Data Listing 2.1 and the 94-004 Final Clinical Study Report

The narratives for the 200 patients from the IT ISS who discontinued study participation due to adverse events were reviewed. Ninety eight of the narratives from the safety update including amended narratives from the 200 patients and patients not previously included in the IT ISS were reviewed. Four narratives were not provided. Seventeen (17.3%) of the 98 narratives described reasons for study discontinuation which were misclassified. Most commonly, all or some of the adverse events attributed as the cause for study discontinuation were described as having resolved completely from weeks to months before study drug discontinuation or predated the onset of study drug administration. Many of the narratives identified multiple AEs as contributing to study discontinuation and the narratives do not provide sufficient information to establish if any one AE was more contributory than the others. Within this category, the adverse events most often included were nausea, vomiting, dizziness, paresthesias, confusion, headache and blurred vision.

The adverse events leading to study discontinuation are summarized by event in Table 8.13. This table represents this reviewer's determination of the primary adverse event resulting in study discontinuation when this could be discerned from the narratives. From this table it can be seen that encephalopathy consisting of the individual complaints or findings of confusion, memory impairment, thinking abnormal and delirium, was the most common AE leading to study discontinuation with 76 patients (26.4%). Additionally, hallucinations, depression/

suicidal ideation, anxiety, psychosis/bizarre behavior and hostility constitute an additional 22 patients (7.5%) and are arguably extensions of encephalopathy. This results in 100 patients (33.8%) of early discontinuations due to encephalopathy, or 11.3% of the entire intrathecal ziconotide treated population discontinuing their respective studies early due to an encephalopathy related adverse event. These figures do not take into account the number of patients within the "Multiple AEs" group which, as explained above, includes a variety of encephalopathy related adverse events. This was the next most common adverse event leading to early study discontinuation. When taken together, dizziness, ataxia, vertigo and vestibular toxicity accounted for 29 discontinuations (9.8%)

Table 8.13 Adverse Event Resulting in Study Termination

	All IT Studies Ziconotide		Pivotal trials (while receiving)	
			Ziconotide	Placebo
Number Of Patients Terminating Study Early Due To Adverse Event.	295	100%	67	7
Adverse Event				
Encephalopathy includes confusion, thinking abnormal, disorientation, somnolence, stupor	76	26.4%	12	1
Multiple AEs identified as contributing (includes vestibular symptoms, nausea, confusion, headache)	36	12.0%	0	
Nausea and/or Vomiting	16	5.4%	7	
Paresthesias/Dyesthesias	14	4.7%	4	
Dizziness	13	4.4%	9	
Indeterminate from narrative	13	4.4%	0	
Meningitis	12	4.1%	4	
Ataxia	10	3.4%	4	
Other Infection	7	2.4%	3	2
Device Problem (includes leaking catheters)	7	2.4%	2	
Increased Pain	7	2.4%	1	1
Anxiety (includes panic attacks)	6	2.0%	0	
Auditory/Sensory Hallucinations	6	2.0%	0	
Depression/Suicidal ideation/Suicide	5	1.7%	1	
Headache	5	1.7%	2	1
Nystagmus alone	5	1.7%	1	
Psychosis/Bizarre Behavior	5	1.7%	0	
Vertigo	4	1.4%	3	
Vision blurred, Diplopia (2 each)	4	1.4%	2	
CK increased	3	1.0%	0	
Orthostatic Hypotension/Hypotension (2 each)	3	1.0%	0	
Progression of Cancer	3	1.0%	0	
Urinary Retention/ Urinary Incontinence (1/2)	3	1.0%	1	
Weakness	3	1.0%	1	1
Other - two each: <u>Involuntary Movements</u> , <u>Laboratory Value Abnormal</u> , <u>Peripheral Edema</u> , <u>Vestibular Toxicity</u>	9	3.1%	2	
Other - one each: <u>Allergic rash</u> , <u>Abnormal Ejaculation</u> , <u>Aphasia</u> , <u>Atrial Fibrillation</u> , <u>Cardiac</u> , <u>Chest wall rigidity</u> , <u>Convulsion</u> , <u>Death from Unknown Cause</u> , <u>Dry Mouth</u> , <u>Dysarthria</u> , <u>Dyspnea</u> , <u>Fever</u> , <u>Gastroenteritis</u> , <u>Hostility</u> , <u>Insomnia</u> , <u>Leg Cramp</u> , <u>Malaise</u> , <u>Malignant Hyperthermia</u> , <u>Overdose (methadone)</u> , <u>Oral thrush</u> , <u>Pulmonary Embolus</u> , <u>Stomatitis</u> , <u>Syncope</u> , <u>Taste Perversion</u>	22	7.5%	8	1 (fever)

Sponsor Table 9.2.8.9 (vol. 5.002, P. 307) provides individual information on the 200 patients who discontinued due to an adverse event including infection from all 9 of the intrathecal studies.

In addition to patients discontinuing from studies due to adverse events, there were 373 of 887 patients (42.1%) for whom study drug was temporarily or permanently stopped due to an adverse event. (See IT Table 9.2.8.10, Vol. 5.002 P. 310). Again, it can be seen that the adverse events related to encephalopathy such as confusion and amnesia, vestibular toxicity such as dizziness, abnormal gait and nystagmus and nausea are the most common reasons for study drug to be temporarily or permanently stopped.

SECTION 8.2.4 ADVERSE EVENTS - IT

SECTION 8.2.4.1 Overall Adverse Events

The information on the incidence of adverse events is presented for the entire intrathecal population and separately for patients in the pivotal studies, during the initial, placebo controlled, double blinded titration period. The sponsor analyzed a third group, patients in the long term open label studies, but this group was not be included in the body of the safety review by this reviewer as it offers no additional information beyond that gained from the entire group of patients.

Adverse events from the entire intrathecal population were evaluated based on if they occurred while patients were receiving ziconotide or while they were receiving placebo. The sponsor has presented these adverse events in IT Table 8.8.2.7.1 (Vol. 2.93 P. 196). Adverse events that occurred more than once were only counted the first time for this table. This table also presents the number of adverse events by body system. For patients with more than one adverse event in a given body system, only the first was counted for this table.

Adverse events were extremely common while on ziconotide, occurring in nearly all of the patients (96.4%), and in 76.2% of patients while on placebo, Table 8.14. However, patients experienced more adverse events per patient while receiving ziconotide than while receiving placebo. This is demonstrated two ways. The total number of adverse events in Table 8.8.2.7.1 for the 704 patients while receiving ziconotide was 6008, an average of 8.5 adverse events per patient. The total number of adverse events for the 151 patients while receiving placebo was 385, an average of 2.5 adverse events per patient. Similarly, for the 704 patients while receiving ziconotide, there were 2865 adverse events by body system, so that on the average of each patient had adverse events involving 4.1 body systems. For the 151 patients while receiving placebo, there were 282 adverse events by body system, an average of 1.9 per patient.

Table 8.14

COSTART Term	While Receiving Ziconotide (N = 704)	While Receiving Placebo (N = 151)
Number Of Patients With Any Event	679 (96.4%)	115 (76.2%)
Adverse Event by Body System	2865 (4.1/patient)	282 (1.9/patient)
Individual Adverse	6008 (8.5 AE/patient)	385 (2.5 AE/patient)

The most common AE's involved the Nervous System, Body As A Whole And Digestive System. The most common individual AE's in the while receiving ziconotide group were dizziness (50.6%), nausea (44.9%), headache (29.7%), confusion (28.4%), somnolence (22.3%). The only AE's reported for more than 20% of patients while receiving placebo were nausea (20.5%), still less than half as frequent than while receiving ziconotide and headache (20.5%) which was similar to the ziconotide group.

After review of Table 8.8.2.7.1 and the COSTART mapping terms, this reviewer determined that similar adverse events were mapped to different COSTART terms diluting the appearance of some of these AE's. Nausea, vomiting and nausea and vomiting were mapped to nausea and/or Vomiting. Confusion, thinking abnormal, delirium, amnesia were mapped to encephalopathy. Gait Abnormality, incoordination, cerebellar syndrome, and ataxia were mapped to ataxia. Limb weakness mapped to myasthenia was remapped to weakness. The term hypertonia included a variety of adverse events from stiffness to muscle spasms. Muscle spasms were remapped to muscle cramps as noted below in Table 8.15.

Table 8.15 Remapped AE's, all IT patients

New Term	While Receiving Ziconotide (N=704)		While receiving Placebo (N=151)	
Agitation	36	(5.1%)	0	(0.0%)
Anxiety	69	(9.8%)	5	(3.3%)
Ataxia	220	(31.2%)	4	(2.6%)
Muscle Cramps	53	(7.5%)	3	(2.0%)
Depression	51	(7.2%)	1	(0.7%)
Dizziness	352	(50.0%)	14	(9.3%)
Encephalopathy	276	(39.2%)	10	(6.6%)
Nausea and/or Vomiting	357	(50.7%)	35	(23.2%)
Somnolence	157	(22.3%)	9	(6.0%)
Motor Weakness	81	(11.5%)	3	(2.0%)

There were 32 reports of CSF abnormality for the while receiving ziconotide group which included 11 cases of leaking catheters.

Table 8.16 presents the adverse events information from the placebo controlled, double blinded initial titration period of the two pivotal studies, 95-001 and 96-002. The blinded nature of this study period and the proportionately larger placebo control group provides a better comparator for these adverse events than available for the entire population. The sponsor has performed tests for statistical significance for some of the adverse events with larger between group differences.

Based on the statistical comparisons, there were statistically significant differences with a greater incidence of many adverse events in the ziconotide group. In particular, nausea and/or vomiting, abnormal gait, dizziness, confusion, nystagmus, somnolence and urinary retention were more frequent in the ziconotide group.

Table 8.16. Adverse Events in $\geq 2\%$ of Ziconotide Treated Patients and Greater than in Placebo Patients - Double-Blind, Placebo-Controlled Clinical Studies - Initial Titration Phase (From Sponsor's Table 8.8.2.7.9, Vol. 2.93, 249)

COSTART Term	Ziconotide N = 242		Placebo N = 126		p-value
	Number	Percentage	Number	Percentage	
Number of Patients with Any Adverse Event	231	95.5%	91	72.2%	<0.0001 ^a
Body as a Whole	118	48.8%	44	34.9%	0.0117^b
Accidental Injury	6	2.5%	3	2.4%	
Asthenia	13	5.4%	4	3.2%	
Chest Pain	8	3.3%	3	2.4%	
Fever	32	13.2%	5	4.0%	0.0055 ^a
Headache	39	16.1%	26	20.6%	0.2737 ^b
Malaise	5	2.1%	0	0.0%	
Pain	23	9.5%	4	3.2%	
Cardiovascular System	69	28.6%	17	13.5%	0.0011^a
Hypertension	6	2.5%	2	1.6%	
Hypotension	17	7.0%	4	3.2%	
Postural Hypotension	37	15.3%	7	5.6%	0.0063 ^a
Tachycardia	5	2.1%	1	0.8%	
Digestive System	156	64.5%	44	34.9%	<0.0001^b
Anorexia	10	4.1%	1	0.8%	
Constipation	40	16.5%	16	12.7%	0.3361 ^b
Diarrhea	15	6.2%	6	4.8%	
Nausea	104	43.0%	24	19.0%	<0.0001 ^b
Nausea and Vomiting	19	7.9%	3	2.4%	
Vomiting	37	15.3%	7	5.6%	0.0063 ^a
Metabolic and Nutritional System	13	5.4%	3	2.4%	
Musculoskeletal System	24	9.9%	2	1.6%	
Myasthenia	20	8.3%	2	1.6%	
Nervous System	204	84.3%	49	38.9%	<0.0001^b
Abnormal Gait	56	23.1%	3	2.4%	<0.0001 ^a
Agitation	5	2.1%	1	0.8%	
Amnesia	7	2.9%	0	0.0%	
Ataxia	19	7.9%	2	1.6%	
Confusion	35	14.5%	7	5.6%	0.0097 ^a
Dizziness	127	52.5%	17	13.5%	<0.0001 ^a
Hypertonia	12	5.0%	2	1.6%	
Incoordination	10	4.1%	0	0.0%	
Insomnia	15	6.2%	2	1.6%	
Nervousness	15	6.2%	3	2.4%	
Nystagmus	101	41.7%	15	11.9%	<0.0001 ^a
Paresthesia	12	5.0%	4	3.2%	
Reflexes Decreased	5	2.1%	1	0.8%	
Somnolence	38	15.7%	7	5.6%	0.0042 ^a
Speech Disorder	10	4.1%	3	2.4%	
Thinking Abnormal	9	3.7%	0	0.0%	
Twitching	5	2.1%	1	0.8%	
Withdrawal Syndrome	5	2.1%	2	1.6%	

Table 8.16 continued

COSTART Term	Ziconotide N = 242		Placebo N = 126		p-value
Vertigo	12	5.0%	0	0.0%	
Respiratory System	29	12.0%	12	9.5%	0.4407^b
Dyspnea	10	4.1%	4	3.2%	
Lung Disorder	5	2.1%	0	0.0%	
Rhinitis	5	2.1%	0	0.0%	
Skin and Appendages	31	12.8%	13	10.3%	0.6118^a
Sweating	10	4.1%	4	3.2%	
Special Senses	57	23.6%	6	4.8%	<0.0001^a
Abnormal Vision	14	5.8%	0	0.0%	
Amblyopia	22	9.1%	2	1.6%	
Diplopia	12	5.0%	0	0.0%	
Photophobia	5	2.1%	0	0.0%	
Taste Perversion	5	2.1%	0	0.0%	
Urogenital System	66	27.3%	8	6.3%	<0.0001^a
Urinary Incontinence	6	2.5%	1	0.8%	
Urinary Retention	40	16.5%	2	1.6%	<0.0001 ^a
Urinary Tract Infection	10	4.1%	0	0.0%	
Urination Impaired	13	5.4%	3	2.4%	

a Treatment difference is tested using Fishers Exact Test.

b Treatment difference is tested using the CMH general association test controlling for study.

Studies include: 95-001 and 96-002.

Data Source: Appendix 1, IT Table 4.2

Upon re-mapping clinically and physiologically related adverse events to the same heading, the differences between the ziconotide and placebo treated groups is even greater for some adverse events as noted in Table 8.17. As above, abnormal gait, ataxia, incoordination, cerebellar syndrome were grouped under Ataxia. Muscle spasms and cramps were removed from Hypertonia and grouped under muscle cramps. Confusion, thinking abnormal, encephalopathy, delirium, amnesia were grouped under encephalopathy.

Table 8.17 Adverse Events remapped to related Terms, Initial Titration Period, Pivotal Trials

New Term	While Receiving Ziconotide (N=242)	While receiving Placebo (N=126)
Ataxia	84 (34.7%)	5 (4.0%)
Muscle Cramps	13 (5.4%)	2 (1.6%)
Encephalopathy	49 (20.2%)	9 (7.1%)
Nausea and/or Vomiting	127 (52.5%)	29 (23.0%)

SECTION 8.2.4.2 Adverse Events By Cumulative Dose

As demonstrated in table 8.18, there was a mild trend for increasing adverse event frequency overall with increasing dose. Nystagmus, Abnormal Vision, Ataxia, Pain, Abnormal Gait and Confusion, urinary retention were the individual AE's that trended to an increased incidence with increasing cumulative dose. Several important adverse events did not seem to increase with increasing dose including: postural hypotension, nausea, vomiting, constipation.

Table 8.18 Number of Patients With Adverse Events by Cumulative Dose (ug) at Onset of Event -Adverse Events Reported by ≥ 5 Ziconotide-Treated Patients at Any Cumulative Dose Range Double-Blind, Placebo-Controlled Clinical Studies -Initial Titration Phase (From Sponsor's Table 8.8.2.7.11, Vol. 2.93, P. 263)

Cumulative Dose	Ziconotide									
	≤ 4 ug		> 4 and ≤ 9.72 ug		> 9.72 and ≤ 20.49 ug		> 20.49 and ≤ 44.55 ug		> 44.55 ug	
	N = 242		N = 241		N = 234		N = 211		N = 138	
COSTART Term	N	%	N	%	N	%	N	%	N	%
Patients with Any Event	112	46.3%	123	51.0%	134	57.3%	120	56.9%	89	64%
Digestive System	48	19.8%	49	20.3%	33	14.1%	48	22.7%	31	22%
Vomiting	7	2.9%	5	2.1%	10	4.3%	5	2.4%	11	8%
Nervous System	51	21.1%	80	33.2%	86	36.8%	74	35.1%	67	49%
Abnormal Gait	2	0.8%	9	3.7%	12	5.1%	21	10.0%	15	11%
Ataxia	1	0.4%	3	1.2%	2	0.9%	4	1.9%	9	7%
Confusion	5	2.1%	5	2.1%	5	2.1%	8	3.8%	13	9%
Nystagmus	13	5.4%	16	6.6%	27	11.5%	24	11.4%	27	20%
Special Senses	12	5.0%	16	6.6%	10	4.3%	13	6.2%	12	9%
Abnormal Vision	1	0.4%	2	0.8%	2	0.9%	3	1.4%	6	4%
Amblyopia	4	1.7%	2	0.8%	7	3.0%	5	2.4%	4	3%
Urogenital System	7	2.9%	12	5.0%	17	7.3%	21	10.0%	15	11%
Urinary Retention	5	2.1%	6	2.5%	11	4.7%	14	6.6%	5	4%

SECTION 8.2.4.3 Adverse Events By Initial Dose

As noted above, patients beginning the study on a larger initial dose, were generally on higher hourly rates and received a greater cumulative dose. With that in mind, Table 819 demonstrates that patients starting on >1.0 ug/h of ziconotide were more likely than patients beginning on a lower dose to have fever, postural hypotension, confusion, and urinary retention. This differs from the profile of adverse events most frequent by cumulative dose and suggests that the dose rate rather than the cumulative dose or initial rate may be the more important dosing factor related to the appearance of adverse events.

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Table 8.19 Adverse Events Reported by Initial Dose Group -Reported by at Least 5% of Patients Receiving Ziconotide in Either Dose Group - Double-Blind, Placebo-Controlled Clinical Studies - Initial Titration Phase (From Sponsor's Table 8.8.2.7.12, Vol. P. 265)

COSTART Term	Ziconotide			
	≤0.1 ug/h (N = 166) ^a		> 0.1 ug/h (N = 76) ^a	
Number of Patients with Any Event	157	94.6%	74	97.4%
Body as a Whole	73	44.0%	45	69.2%
Asthenia	6	3.6%	7	9.2%
Fever	16	9.6%	16	21.1%
Cardiovascular System	42	25.3%	27	35.5%
Postural Hypotension	20	12.0%	17	22.4%
Musculoskeletal System	12	7.2%	12	15.8%
Nervous System	140	84.3%	64	84.2%
Confusion	18	10.8%	17	22.4%
Hypertonia	11	6.6%	1	1.3%
Vertigo	11	6.6%	1	1.3%
Respiratory System	16	9.6%	13	17.1%
Lung Disorder	0	0.0%	5	6.6%
Urogenital System	40	24.1%	26	34.2%
Urinary Retention	22	13.3%	18	23.7%
Urinary Tract Infection	4	2.4%	6	7.9%
Urination Impaired	13	7.8%	0	0.0%

a Represents the number of patients who had study drug initiated at that dose level.

Note: Body system totals include all patients with adverse events of the specified body systems, as listed in Appendix 1, IT Table 6.3, not solely those presented in this table.

Studies include: 95-001 and 96-002. Data Source: Appendix 1, IT Table 6.3

SECTION 8.2.4.4 Time To First Occurrence Of AE

Of the 704 patients participating in intrathecal studies, there were 679 with adverse events. Of these 679 patients, 676 experienced the first occurrence of AE's within the first 3 months of drug exposure and the majority of these were within the first month. The only AE which was not represented most often within the first 30 d was hallucinations, which occurred for the first time most commonly from 30-90 days. Vol. 2.93 P. 209 IT Table 8.8.2.7.2

When the patients who were treated for greater than 3 months were separated from the overall group, the majority of patients, 157 out of 159, still experienced the first occurrence of an adverse event within the first 30 d of treatment. However, there were several AE's with a higher incidence after one month of treatment. These included asthenia, confusion, depression, hallucinations, thinking abnormal and taste perversion. Vol. 2.93 P. 213 IT Table 8.8.2.7.3

Adverse Events first occurring for the first time after 3 months of treatment were very infrequent. These included increased salivation, stomatitis, tooth disorder and tongue disorder, delirium, hostility, manic reaction, neurosis and personality disorder.

SECTION 8.2.4.5 Adverse Events by Subgroup

Effects Of Age

Overall, patients < 60 years of age and patients $\geq$ 60 years of age reported similar AE's and this was true for both treatment groups. Patients less than 60 reported more headache and more musculoskeletal system adverse events. Patients $\geq$ 60 reported, more cardiovascular system and respiratory system adverse events but confusion and urinary tract infection were the only individual AE more frequent in patients greater than 60 years. (Table 8.8.2.7.5 vol. 2.93, P. 213).

The adverse events by age in the group of patients during the initial titration of the two pivotal trials look very similar to the total group. Minor differences include a greater proportion of the following adverse events in the $\geq$ 60 y group nausea and vomiting, vomiting, confusion, dizziness, nystagmus, and in the Respiratory system overall.

Effects of Gender

Overall the adverse event profile for women and men was very similar (IT Table 8.8.2.7.6, vol. 2.93, P. 236). The AE's at least 5% more common in women receiving ziconotide were nausea, peripheral edema, dizziness and somnolence. In the while receiving placebo group, women also had greater frequencies of nausea, dizziness and somnolence but not peripheral edema.

The gender differences for the population during the controlled and blinded initial titration period of the pivotal trials were similar to the total population (see Vol. 2.93 P. 272 IT Table 8.8.2.7.14).

Effects of Race

Overall, there were considerably fewer non-Caucasian patients enrolled in the studies as demonstrated in Table 8.20. There were only 9 non-Caucasian patients in the placebo group, too few for meaningful comparisons. The adverse event profile was similar between Caucasian and non-Caucasian patients, although the later had an overall greater incidence of AE's. The Caucasian group had more frequent Cardiovascular system adverse events but no particular adverse event explained this difference. The Other race group demonstrated more frequent fever, digestive system overall, constipation, nausea, vomiting, anemia, amnesia, depression, emotional lability and urinary retention than the control group.

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Table 8.20 Patients with Adverse Events by Race Reported by at Least 5% of Patients While Receiving Ziconotide And With At Least A 5% Difference Between Race Groups- All Intrathecal Studies (From Sponsor's Table 8.8.2.7.7 Vol. 2.93, P. 241)

COSTART Term	While Receiving Ziconotide				While Receiving Placebo			
	Caucasian N = 654		Other ^a N = 50		Caucasian N = 142		Other ^a N = 9	
Number of Patients with Any Event	630	96.3%	49	98.0%	106	74.6%	9	100.0%
Body as a Whole	49	68.7%	38	76.0%	52	36.6%	7	77.8%
Fever	118	18.0%	15	30.0%	6	4.2%	3	33.3%
Cardiovascular System	182	27.8%	9	18.0%	26	18.3%	1	11.1%
Digestive System	436	66.7%	38	76.0%	49	34.5%	4	44.4%
Constipation	95	14.5%	11	22.0%	15	10.6%	1	11.1%
Nausea	287	43.9%	29	58.0%	27	19.0%	4	44.4%
Vomiting	86	13.1%	13	26.0%	11	7.7%	0	0.0%
Hemic and Lymphatic System	32	4.9%	5	10.0%	8	5.6%	0	0.0%
Anemia	17	2.6%	5	10.0%	6	4.2%	0	0.0%
Nervous System	554	84.7%	43	86.0%	59	41.5%	3	33.3%
Amnesia	85	13.0%	9	18.0%	0	0.0%	0	0.0%
Anxiety	69	10.6%	2	4.0%	8	5.6%	0	0.0%
Aphasia	30	4.6%	5	10.0%	0	0.0%	0	0.0%
Depression	42	6.4%	6	12.0%	1	0.7%	0	0.0%
Emotional Lability	15	2.3%	5	10.0%	0	0.0%	0	0.0%
Urogenital System	213	32.6%	20	40.0%	9	6.3%	2	22.2%
Urinary Retention	89	13.6%	10	20.0%	1	0.7%	1	11.1%

^a Other includes missing race classification

Note: Body system totals include all patients with adverse events of the specified body system, as listed in Appendix 1, IT Table 9. 1, not solely those presented in this table

Note: A patient may be included in both the 'While Receiving Ziconotide' and the 'While Receiving Placebo' columns, but is only counted once per column total.

Studies include: 94-004, 95-001, 95-002, 96-002, 96-003, 96-010, 97-013, 97-015, and 98-022.

Data Source: Appendix 1, IT Table 9. 1.

There were too few non-Caucasian patients in the controlled trials for a meaningful comparisons of adverse events by race. In the ziconotide group there were 223 Caucasian patients and 10 non-Caucasian patients. In the placebo group, 119 Caucasian patients and 7 non-Caucasian patients. (IT Table 8.8.2.7.15 Vol. 2.93 P. 274)

SECTION 8.2.4.6 Overdoses

There were 10 overdoses of intrathecal ziconotide, primarily due to programming errors of the pump. There were no deaths or permanent injury resulting from any of these overdoses. The adverse events resulting from the overdoses are presented in Table 8.21.

Table 8.21 Patients With an Intrathecal Ziconotide Overdose -120-Day Safety Update (From Sponsor's Table 9.2.12.1, Vol. 5.2, P. 369)

Study #	Patient Number	Dosing Error	Symptoms
94-004	500-501	0.7 ug/h (titrated q4h, not q24h)	Generalized myoclonic contractions, nystagmus, tremor
95-001	5007-049	31.25 ug/hr, pump error	Sedation
95-001	5025-074	1.1 ug/h not 0.1 ug/h on day 3	Nausea and vomiting
95-002	6071-104	0.417 ug/h (incomplete dosing prior 4-8 w due to catheter dislodgment)	Gait disturbances, photosensitivity and dizziness
95-002	6077-101	1.46 ug/h from 1 ug/h, titrated	Hypotension and neurological symptoms
96-002	6067-104	2.4ug/h from 0.6 u g/h, pump error	Confusion, nystagmus, garbled speech, found slumped over a bedside table
96-002	6069-105	stable on 1.3 ug/h, found with multiple pill sin mouth.	Confusion
98-022	119-1070	0.6ug/h from 0.3 ug/h, concentration of drug increased, pump rate not adjusted	Gait unsteadiness, word-finding difficulties, dizziness
98-022	147-1289	5.0 ug/h instead of 0.1 ug/h, pump error	Light headedness and gait unsteadiness
98-022	161-1343	4.8 ug bolus, pump error	General weakness light headedness, nausea, diaphoresis

SECTION 8.2.5 ADVERSE EVENTS OF SPECIAL INTEREST -IT

There were several adverse events that prompted a more focused review. Meningitis is a concern with chronic intrathecal drug administration, particularly because the drug products do not contain any preservatives or antibacterial agents. The large number of patients with encephalopathy along with reports of bizarre behavior and hallucinations resulted in closer examination of the reports of psychosis, and hallucinations. Direct CNS dosing of the ziconotide prompted review of the reports of convulsions.

Meningitis

There were a total of 16 out of 887 patients with meningitis reported as SAEs in the 120 d safety update. Ten cases out of 704 patients had been reported in the original ISS report and 2 cases in the sponsor's Appendix 6 of the 120 day safety update. After review of the patient narratives for the intrathecal studies from the IT ISS, the IT 120 day safety update and the list of additional SAEs in Appendix 6 of the 120 day safety update, this reviewer identified 31 patients with meningitis. There were no narratives provided for the 2 patients identified in Appendix 6 of the 120 day safety update.

An inquiry was made to the sponsor concerning the discrepancies noted. The response from the sponsor, dated 5/10/00, indicated that the discrepancy "stems from the way adverse events were collected and analyzed in the pivotal trials... Many of the cases of meningitis in those trials were clearly related to external intrathecal catheters and were reported as device complications." The

sponsor provided Table 8.22 which was to be inclusive of all cases of meningitis. The last column of the table was added by and contains this reviewer's comments. It is important to note that many of the patients with external pumps were on prophylactic antibiotics, a possible contributing factor for some or all of the aseptic CSF cultures. The sponsor's table documents 32 patients identified with meningitis. Two of these patients, were not considered to have meningitis by this reviewer. Patient 400-406 had fever and negative cultures without a documented CSF pleocytosis and described as a presumed meningitis by the sponsor in the narrative, while patient 135-1209 had a parameningeal infection. Two patients were counted by this reviewer as having meningitis but were not included in the sponsor's response. Patients 063-1485 and 123-1555 were listed in Table 6.1, the Appendix 6 of the 120-day safety update (Vol 5 52, P349), as having meningitis. No narratives for these 2 patients were provided.

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Table 8.22 (From Sponsor's Update of IT Table 9.2.7.15 Listing of Meningitis Cases, Response to Reviewer's Inquiry Dated 5/10/00)

Study Number	Patient Number	Underlying Diagnosis	Treatment	Pump Type	Breach ^a	Organism identified	Data Source/ Preferred Term	When Meningitis Diagnosed/ Comments
94-004	102	Colon Cancer with brain metastasis	Ziconotide	External		Staphylococcus epidermidis	IT Listing 4.4 (SAE) /Meningitis	Day 20
94-004	107	Brachial avulsion and plexopathy	Ziconotide	External	Yes	Gram positive cocci	IT Listing 4.4 (SAE) /Fever	Day 2
94-004	403	Colon carcinoma with fistula and brain metastasis	Ziconotide	External	Yes	E. coli	IT Listing 4.4 (SAE) / CSF Abnormal	Day 4/ No breach according to narrative
94-004	405	AIDS neuropathy	Ziconotide	External		Staphylococcus epidermidis and S. warneri	IT Listing 4.4 (SAE) /Meningitis	Month 3
94-004	406	Peripheral neuropathy	Ziconotide	External		Negative cultures	IT Listing 4.4 (SAE) / Fever	Not considered meningitis by this reviewer
95-001	501-49	Breast Cancer	Ziconotide	External		Streptococcus mitis	Medtronic PMA/Meningitis	Day 3
95-001	5002-25	AIDS	Ziconotide	External		Enterobacter cloacae	Medtronic PMA/Meningitis	Day 7
95-001	5006-75	AIDS	Placebo	External	Yes	Staphylococcus and Corynebacterium	Medtronic PMA/Meningitis	Day 7 study, day 2 ziconotide
95-001	5012-73	Lung Cancer	None ^b	External		Enterococcus vancomycin resistant	Medtronic PMA/Meningitis	10 days after catheter explanted
95-001	5025-73	Breast Cancer	Ziconotide	External		Staphylococcus aureus	Medtronic PMA/Meningitis	Day 7 study, day 1 ziconotide
95-001	5029-27	AIDS	Placebo	External		Aseptic meningitis	IT Listing 4.4 (SAE)	Day 6 study, day 1 ziconotide/catheter tip grew Staph. Epidermidis
95-001	5097-50	Breast Cancer	Ziconotide	External	Yes	Klebsiella oxytoca, Enterobacter, Strep. mitis	Medtronic PMA/Meningitis	Day 8
96-002	6058-101	Failed back syndrome	Ziconotide	External	Yes	Acinetobacter baumannii	Medtronic PMA/Meningitis	2 days after ziconotide discontinued
96-002	6059-108	Failed back syndrome	None ^b	External	Yes	Negative cultures	Medtronic PMA/Meningitis	7 days after study discontinued, had been on antibiotics
96-002	6060-113	Low back pain	Ziconotide	External	Yes	Staphylococcus epidermidis	Medtronic PMA/Meningitis	Day 10
96-002	6090-105	Failed back syndrome	None ^b	External	Yes	Streptococcal meningitis	Medtronic PMA/Meningitis	One day after catheter removed

Table continues.

Table 8.22 continued

95-002	501-75	Hodgkin's lymphoma	Ziconotide	Internal		Bacterial meningitis	IT Listing 4.4 (SAE)/Meningitis	Month 3
95-002	6086-103	Multiple Sclerosis	Baclofen	External	Yes	Staphylococcus aureus	Medtronic PMA/ Meningitis	3 days after ziconotide discontinued
97-013	713	Low Back Pain	Ziconotide	External	Yes	Aseptic meningitis	IT Listing 4.4 (SAE)/ Meningitis	Day 1/ Treated with antibiotics for 8h prior to CSF examination
98-022	12-1189	Laminectomy pain syndrome	None ^b	External	Yes	Gram negative bacteria	IT Listing 4.4 (SAE)/ Meningitis	6 days after explantation of catheter
98-022	12-1190	Skin cancer and post-laminectomy syndrome	Ziconotide	Internal		Negative cultures, seroma fluid - Staph. epidermidis	IT Listing 4.4 (SAE)/ Meningitis	2 months after internal pump implanted
98-022	12-1378	Chronic back and leg pain	Ziconotide	External		Negative cultures	IT Listing 4.4 (SAE)/ Meningitis	day 5
98-022	91-1032	Lymphoma and post-herpetic neuralgia	Ziconotide	External		Enterococcus sp.	IT Listing 4.4 (SAE)/ Meningitis	Day 14
98-022	101-1088	Lumbar radiculopathy	Ziconotide	External	Yes	Not stated	IT Listing 4.4 (SAE)/ Meningitis	Day 8
98-022	134-1253	Failed back syndrome	None ^b	External	Yes	Negative cultures	IT Listing 4.4 (SAE)/ Meningitis	3 days after study completed
98-022	135-1087	Chronic pancreatitis	Ziconotide	External	Yes	Not stated	IT Listing 4.4 (SAE)/ Meningitis	Day 9
98-022	135-1100	Failed back syndrome	Ziconotide	External	Yes	Staphylococcus sp. methicillin resistant	IT Listing 4.4 (SAE)/ Meningitis	day 13
98-022	135-1127	Lumbosacral radiculopathy, Hep. C	Ziconotide	External	Yes	Staphylococcus aureus	IT Listing 4.4 (SAE)/ Meningitis	day 4
98-022	135-1192	Failed back syndrome	Ziconotide	External	Yes	Aseptic meningitis (Acinetobacter contaminant)	IT Listing 4.4 (SAE)/ Meningitis	day 12
98-022	135-1209	Failed back syndrome	Ziconotide	External	Yes	Parameningeal infection	IT Listing 4.1 (AE)/ Meningitis	Not considered meningitis by this reviewer
98-022	138-1350	Post-traumatic injury	Ziconotide	External	Yes	Negative cultures	IT Listing 4.4 (SAE)/ Meningitis	day 5
98-022	148-1430	Failed Back Syndrome	Ziconotide	External	Yes	Bacterial Meningitis. (gram positive cocci, bacillus)	IT Listing 4.4 (SAE)/ Meningitis	Narrative not found by reviewer

a Documented breach of administration system prior to diagnosis of meningitis

b Occurred 48 hours or more after study drug stopped.

Data Source: Medtronic Premarket Approval (P860004/SO44) and Appendix 2 IT Patient Data Listings 4.1, 4.4 and 4.7.

The following are summaries of the available narratives and information for patients diagnosed with meningitis:

1. Patient 100-102, a 72 year old woman with metastatic colon cancer, was diagnosed with meningitis on day 20, 2 days after being diagnosed with hemorrhagic brain metastases. The CSF culture grew *S. epidermidis*. The patient improved with antibiotics but died 3 weeks later, attributed to the brain metastases.
2. Patient 100-107, a 43 year old Hispanic man, was enrolled for intractable pain due to phantom pain, with allodynia, hyperesthesia and hyperalgesia of his residual left upper limb. The patient had a history of HTN, cardiomyopathy, congestive heart failure, coronary angioplasty, chronic A-fib, TIA, and frequent episodes of diaphoresis. The patient had an intrathecal catheter at _____ placed for the study, the date is unclear and began the study on _____. The patient developed neck pain on day 2 and fever on day 9. A diagnosis of meningitis "secondary to catheter disconnection" was made. CSF examination revealed 1880 WBC, "93% gran", "heavy polys, rare gm + cocci in pairs". The patient was started on IV antibiotics and the meningitis was resolved by day 34.
3. Patient 400-403, a 47 year old Caucasian woman, had intractable pain due to metastatic carcinoma of the colon, including brain mets. The patient had inflamed skin due to fecal leakage from colovaginal fistulas. Ziconotide was started _____ via an _____ intrathecal catheter and on day 4, she complained of back pain, headache, neck pain and stiffness. The catheter was removed, and CSF culture grew *E. coli*. The meningitis responded to treatment with Vancomycin and claforan.
4. Patient 400-405, 54 year old Caucasian man, had intractable pain due to HIV related neuropathy, and a history of hemophilia, hepatitis B and C and bilateral knee replacements. The patient began ziconotide on 11/10/95. On _____ the patient developed nausea and vomiting and was diagnosed with bacterial meningitis. CSF cultures grew *S. epidermidis* and *S. warneri*. The meningitis resolved by _____ after treatment with antibiotics.
5. Patient 501-49, a 62 year old Caucasian woman, had metastatic breast cancer. The patient developed fever on day 3 of treatment with ziconotide. The CSF culture grew *S. viridans*, *S. pneumoniae* and *S. mitis*. The patient was treated with antibiotics and the meningitis resolved. Study drug was continued except for two brief periods when it was held due to confusion and dizziness.
6. Patient 501-75, a 24 year old woman with end stage Hodgkin's lymphoma began treatment with ziconotide _____. She was diagnosed with bacterial meningitis _____ after being found unresponsive at home. The patient had been in a terminal care program and died on _____.
7. Patient 5002-25, a 38 year old Caucasian man with AIDS, initially received placebo and then crossed over to ziconotide on day 5. On day 7, the patient complained of a moderate spinal headache and was diagnosed with meningitis. The catheter and medication were discontinued. CSF examination revealed a glucose of 5, a protein of 474, and no organisms.

on gram stain. No CSF cell count or culture results were provided. The patient recovered with treatment.

8. Patient 5006-75, a 51 year old Caucasian woman with metastatic breast cancer, was noted to have a CSF leak on day 1. On day 5 the study ended and the patient was diagnosed with meningitis. The CSF was reported to be cloudy, and the meningitis resolved with antibiotics. No further details about the infection were provided.
9. Patient 5012-73, 67 year old Caucasian woman with lung cancer, was diagnosed with meningitis 10 days after study conclusion and explantation of the catheter. The CSF examination revealed 2000 WBCs and the cultures were negative for growth. No further details about the infection were provided. The meningitis resolved with antibiotics.
10. Patient 5025-73, a 51 year old Caucasian woman with metastatic breast cancer, started on ziconotide day 7 following treatment with placebo. Later that day, the patient developed fever, confusion and back pain. Antibiotics were started, and the intrathecal catheter removed. The CSF culture was reported as growing "Staphylococcus organisms". No further information was provided.
11. Patient 5029-27, a 37 year old Caucasian man with AIDS, developed fever and headache one day after crossing over from ziconotide to placebo. Meningitis was diagnosed, cultures were reported to be negative but the catheter tip grew out *S. epidermidis*. The patient was discharged with antibiotics.
12. Patient 5097-50, a 51 year old Caucasian woman with metastatic breast cancer, noted leakage from the intrathecal catheter on day 6. After missing an appointment on day 7, the patient was found on day 8 with fever and altered mental status. CSF gram stain revealed gram negative rods, and gram stain from the catheter revealed gram negative and positive rods. The patient improved with antibiotics.
13. Patient 6058-101, a 50 year old Caucasian woman with failed back syndrome, developed sudden onset of headache and confusion on day 9 of ziconotide treatment. The CSF culture grew *Acinetobacter baumannii*. The patient was treated with antibiotics and improved.
14. Patient 6059-108, a 50 year old Caucasian man with Marfan's syndrome and back pain, was noted to have CSF leak one day after starting placebo. The leak was managed with the application of collodion to the site. The catheter became disconnected day 4 after repositioning to alleviate leg paresthesia. Treatment was crossed over to ziconotide on day 6 and the study was completed on day 12. The patient had been treated with prophylactic cefazolin during study drug infusion. Seven days after ziconotide was discontinued, the patient developed meningitis. CSF examination revealed a glucose of 34, protein of 112 and many polymorphonuclear cells on gram stain. The CSF cultures were negative. The patient was treated with antibiotics and the meningitis resolved.
15. Patient 6060-113, a 54 year old Caucasian woman with intractable low back pain, was on maintenance with ziconotide at home. The catheter disconnected day 8 and was reconnected

by the patient. The pump battery failed and patient was off drug for approximately 8 h. On day 10, the patient was diagnosed with meningitis. CSF examination revealed a glucose of 34, protein of 82 and WBC of 1340. The CSF cultures grew *S epidermidis*. The meningitis resolved with antibiotics.

16. Patient 6086-103, a 59 year old woman with multiple sclerosis, was admitted for pump implantation 27 days after starting study 96-002. Study drug was discontinued permanently 1 week later and meningitis was diagnosed 3 days following study drug discontinuation. CSF examination revealed gram positive cocci. The meningitis resolved with antibiotics.
17. Patient 6090-105, a 51 year old Caucasian woman with intractable low back pain and failed back surgery, completed the study with catheter removal on day 11. At home a CSF leak developed with headache and nausea. The patient received an epidural blood patch and IV ceftriaxone. The following day, she developed fever, became unresponsive, and was diagnosed with streptococcal meningitis that resolved with antibiotics.
18. Patient 10-713, a 42 year old man with chronic low back pain, developed fever the day of ziconotide infusion. Antibiotics were started and a CSF sample was drawn 6.5 hours later. The CSF revealed 775 WBC with protein of 77 mg/dl and glucose of 74 mg/dl. Cultures were negative. The patient recovered with antibiotic treatment.
19. Patient 012-1189, a 71 year old woman, was noted to have a CSF leak 5 days after study drug was started. Ziconotide was stopped 10 days later, and the patient was diagnosed with meningitis 6 days after explantation of what was noted to be a fractured catheter. CSF examination revealed a protein of 12.31 mg/100 ml, WBC of 13.92 K/ccm and gram negative bacteria. The meningitis resolved with treatment.
20. Patient 012-1190, a 59 year old woman with post laminectomy syndrome began ziconotide on _____ had an internal pump implanted on _____ was diagnosed with meningitis. CSF cultures were negative, but CSF WBC was elevated. Seroma aspirate grew *S epidermidis*. The intrathecal catheter and pump were removed and the meningitis resolved with treatment.
21. Patient 012-1378, a 72 year old man with history of chronic back and left leg pain, HTN, and status post CABG, was diagnosed with meningitis on day 5 of ziconotide administration. CSF examination revealed "75% polymorphonuclear leukocytes" "CSF cultures revealed no specific organism". The patient responded to antibiotic treatment.
22. Patient 091-1032, a 65 year old man with post-herpetic neuralgia, developed fever, catheter site redness and meningitis 14 days after starting study drug. CSF examination revealed 858 WBC, a protein of 75 and a glucose 59. The CSF culture was positive for gram positive cocci in pairs and *Enterococcus* species, also present on the catheter tip culture. The meningitis resolved with treatment.

23. Patient 101-1088, a 40 year old man with failed back syndrome, developed meningitis one day after reconnecting his catheter on study day 7. The infection resolved with treatment. No further details were provided.
24. Patient 134-1253, a 79 year old man with history of failed back syndrome developed a CSF leak on day 4 of treatment and "taped it up" on his own. On day 6, ziconotide was discontinued due to a CSF leak from a partially dislodged catheter. Three days later, the patient was diagnosed with meningitis with CSF examination revealing 376 WBC, 69% polymorphonuclear cells, a glucose of 45 and a protein of 115. No organisms were seen on gram stain. The patient had been on prophylactic antibiotics. The meningitis resolved with antibiotics.
25. Patient 135-1087, a 60 year old man, was diagnosed with meningitis 9 days after starting study drug. The meningitis was "ongoing" at the time of the report, (6 months later) and no further details were provided.
26. Patient 135-1100, a 44 year old woman, developed meningitis 13 days after starting study drug. The patient had CSF leakage from an unspecified site on day 2. CSF culture grew methicillin resistant Staphylococcus. The meningitis resolved with treatment.
27. Patient 135-1127, a 44 year old man with lumbosacral radiculopathy and history of Hepatitis C, was diagnosed with meningitis on day 4 of treatment with ziconotide, after his catheter had disconnected. CSF examination was reported to be cloudy and culture was positive for S. aureus. The meningitis resolved with treatment.
28. Patient 135-1192, a 43 year old woman, was noted to have a CSF leak 9 days after starting treatment, and was treated with a blood patch. Three days later, the patient developed a "chemical meningitis" with incoherence, obtundation and fever. CSF grew possible contaminant, no information was provided on CSF cell count or chemistry. An epidural abscess was diagnosed 2 days later and debrided. It was determined to be "atypical adipose tissue". The patient was discharged with IV antibiotics and all ultimately resolved.
29. Patient 138-1350, a 44 year old man with history of seizure disorder, DVT and scoliosis due to trauma, developed meningitis on day 5 of treatment, 3 days after an accidental catheter disconnection. CSF examination revealed cloudy fluid, glucose of 48, protein of 238, 3520 WBC of which 92% were neutrophils and 80 RBC. CSF cultures and gram stain were negative for bacteria or yeast. The meningitis responded to antibiotic treatment.
30. Patient 063-1485, an 81 year old man, began ziconotide on — and was noted as having meningitis in Table 6.1 of the safety update, Vol. 5, P. 350 but no narrative was provided. The patient was hospitalized on —. No details of the meningitis were provided. The patient died during the hospitalization from a myocardial infarction.
31. Patient 123-1555 was noted as having meningitis in Table 6.1 of the safety update, Vol. 5, P. 350 but no narrative was provided.

32. Patient 148-1430 was noted in the 5/10/00 correspondence as a patient with failed back syndrome, diagnosed with bacterial meningitis characterized by gram positive cocci, bacillus. No narrative was provided.

In summary, of the 887 patients ever exposed to ziconotide, 32 patients (3.6%) were diagnosed with meningitis. Two of these patients were clearly documented to have internal pumps at the time of diagnosis, 28 had external pumps and the type of pump is unknown for 2 patients. Of the 28 patients with external pumps, 19 patients had some type of breach of the intrathecal catheter system, typically a brief disconnection of the catheter or tubing that could increase the risk for bacterial contamination. All of the patients had received ziconotide by the time meningitis was diagnosed including 3 patients who were diagnosed on day 1 of ziconotide exposure (2 of these 3 had received placebo prior to ziconotide).

CPK

To further evaluate the clinical significance of the CPK elevations, the available patient narratives for patients with serious adverse events, adverse events leading to study discontinuation and deaths were explored for reports of CPK elevation, weakness or muscle pain. Ten such narratives were found among the IT ISS, IT 120-day safety update and Appendix 6 of the 120-day safety update. The first two narrative summaries describe CPK elevations with reasons other than ziconotide. Narratives 3 through 7 are patients with elevated CPK's and no other identifiable reason for the elevation. The remaining 3 narratives describe patients with symptoms of weakness or pain but no CPK elevations

1. Patient 134-1131, a 36 year old woman with history of hip fracture, severe malnutrition, unexplained CPK elevations and chronic pain syndrome began study drug on _____. The patient was found unresponsive in a closet, _____ "where she appeared to have been for several hours". The patient had a CPK of >16,000 IU/L and was treated for rhabdomyolysis and acute tubular necrosis that were ongoing at the time of reporting. _____
2. Patient 879-1136, a 65 year old woman with cervicogenic headache, intractable neck and upper extremity pain, had a CPK of 194 IU/L at screening. Drug was started by internal pump 6 weeks later. After 3 weeks of treatment, the CPK was 197 IU/L. That day the patient presented with fever of 106, decreased level of consciousness, trembling, tachycardia, and a blood pressure of 159/122. Cultures of blood, urine and CSF were negative. Urine drug screen was positive for methadone and phenothiazine metabolites. CSF glucose was 80 mg/100 ml, protein 30 mg/100 ml and gram stain was negative. The patient was diagnosed with neuroleptic malignant syndrome and improved with treatment of fluids, Dantrolene, versed, Narcan and Tylenol. Her CPK was 924 IU/L 3 days later.
3. Patient 6073-104, a 66 year old Caucasian woman with peripheral neuropathy pain, was noted to have an elevated CPK of 653 IU/L on day 11, and 918 IU/L on day 20, along with confusion and lower extremity ataxia. The symptoms resolved after discontinuation of ziconotide, the CPK normalized 42 days after ziconotide was discontinued.
4. Patient 6601-101, a 40 year old woman with failed back syndrome, developed upper and lower extremity muscle pain during her 10th month of treatment. The patient's CPK was 209

U/L. The pain improved and the CPK normalized to 129 U/L after study drug was discontinued. The CPK levels reported in Appendix 2, IT Listing 7.2.10 were also elevated to a maximum of 520 IU/L earlier in treatment, 28 days after beginning the study.

5. Patient 157-1424, a 60 year old woman with history of cervical stenosis, coronary artery disease, vitamin B6 deficiency s/p partial gastrectomy and depression developed an elevated CPK 2 months after beginning ziconotide. MM and MB fractions were elevated and resolved after drug was discontinued. The CPK levels reported in Appendix 2, IT Listing 7.2.10 demonstrate an elevated value of 437 IU/L on day 42 of the study, and a normal value of 45 on day 53.
6. Patient 157-1451, a 41 year old man with history of hypertension, migraine, anxiety and depression developed an elevation of CPK during the fourth week of ziconotide treatment. Study drug was discontinued the same day. The CPK levels reported in Appendix 2, IT Listing 7.2.10 demonstrate an elevated value of 1008 IU/L on day 24 of the study, returning to normal on day 63.
7. Patient 066-1349, a 47 year old woman, initiated intrathecal ziconotide treatment. On the patient presented to a local ER with shortness of breath and muscle spasms. She was diagnosed with polymyalgia rheumatica and hypokalemia (3.2 mmol/L). Her EKG revealed a prolonged QT interval of 376/504 msec. Her ESR was 25 mm/h. The patient's CPK was 1516 IU/L on , and 2101 IU/L on . EMG revealed a non-inflammatory myopathy. Ziconotide was discontinued and "the events resolved". The CPK levels reported in Appendix 2, IT Listing 7.2.10 were all normal for this patient up to but the elevated CPK occurred later than the cutoff date for this listing and was reported in Appendix 6.
8. Patient 6091-101, a 39 year old Caucasian woman with Arnold Chiari syndrome, had neurogenic pain involving the entire right side of the body. After crossing over to ziconotide from placebo, the patient developed blurred vision, urinary retention, dizziness, inability to ambulate, and inability to raise her arms above her head due to weakness. Drug was discontinued but the patient later enrolled in study 95-002. The CPK levels reported in Appendix 2, IT Listing 7.2.10 were all normal for this patient.
9. Patient 123-1303, a 50 year old man with history of multiple sclerosis, left lower extremity weakness and neurogenic bladder, developed increased muscle weakness in his legs on day one. The drug was discontinued 13 days later and the weakness continued at the time of reporting. The CPK levels reported in Appendix 2, IT Listing 7.2.10 were all normal for this patient.
10. Patient 139-1324, an 80 year old woman with history of post laminectomy pain, developed leg weakness and aching legs 14 days after beginning ziconotide. The patient also developed nystagmus and ataxia. Leg weakness and aching legs continued at the time of reporting. The CPK levels reported in Appendix 2, IT Listing 7.2.10 were all normal for this patient.

Convulsions

Unprovoked seizures would be an extremely important adverse event to warn prescribers and patients about. There were a total of 7 patients with reported convulsions in the adverse events data from the IT 120-day safety update, 3 of which were considered serious adverse events in the 120-day safety update. The following two narratives were found and summarized

1. Patient 5015-51, a 30 year old Hispanic woman with metastatic cervical carcinoma was noted to have a CSF leak on day 1. The catheter was explanted the next day, antibiotics were begun, but the patient became febrile with cellulitis at the catheter site the next day. Ofloxacin replaced the cephalexin and the infection resolved. Two days later, the patient had two brief convulsive seizures. No further information is available.
2. Patient 5029-74 50 year old Caucasian woman with metastatic colon cancer. The patient had a convulsion on day 3, with an unremarkable work-up including CT and CSF exam and culture. The patient was concurrently on morphine by IV PCA in daily dose of 4000-6000 mg.
3. Patient 094-1020 was noted as having generalized seizures in Table 6.1 of the safety update, Vol. 552, P. 350 but no narrative was provided.

Encephalopathy with Psychiatric Manifestations

Encephalopathy in its many manifestations from confusion and memory loss to hallucinations and bizarre behavior represents an important component of the adverse event profile for intrathecal ziconotide by virtue of the frequency in which it occurred. In the original IT ISS, of the 704 patients who ever received ziconotide, 5.7% of patients experienced Encephalopathy as a serious adverse event. Of the 295 patients in the 120 day safety update database of 887 patients who ever received ziconotide, 100 (33.8%) discontinued from a study early due to an adverse event of Encephalopathy. This constitutes 11.3% of the entire intrathecal ziconotide treated population discontinuing their respective studies early due to an Encephalopathy related adverse event. Some of these adverse events were more serious than others. There were 22 patients who discontinued early due to adverse events of hallucinations, depression/ suicidal ideation, anxiety, psychosis/bizarre behavior or hostility.

Below are brief summaries of 17 narratives available for these patients and for the last patient identified, comments from Table 6.1 of the 120-day safety update

1. Patient 6063-102, a 36 year old woman with chronic pain due to gunshot wound to the spinal cord, developed lethargy, garbled speech, excessive sleepiness, impaired coordination and hallucinations on day 5. Symptoms resolved within 24 hours of study drug discontinuation.
2. Patient 149-1313, a 38 year old woman with history of failed back syndrome and sleep disorder, developed feelings of paranoia 3 weeks after starting ziconotide along with garbled speech, both of which resolved after 1 week off treatment.
3. Patient 118-1049, a 49 year old man with history of intractable lumbar radiculopathy, developed sensory hallucinations described as strings and tags hanging from his gums on

_____ after beginning ziconotide _____ The patient had previously developed confusion, memory loss and irritability. Symptoms resolved 5 days after ziconotide was discontinued.

4. Patient 118-1178, a 32 year old woman with history of reflex sympathetic dystrophy, MVP, tachycardia, chronic UTI, elevated liver function tests, developed psychotic symptoms including hallucinations, thought disorganization and paranoid delusions on _____ after starting ziconotide on _____. Study drug was discontinued _____ and symptoms resolved _____ after treatment with Risperdal was started _____.
5. Patient 123-1116, a 38 year old woman, developed auditory hallucinations, date unspecified, while receiving ziconotide which resolved after the drug was stopped
6. Patient 135-1197, a 35 year old man with history of back pain, developed auditory hallucinations after 5 months on ziconotide which resolved following study drug discontinuation.
7. Patient 5009-78, a 62 year old man with metastatic prostate cancer, developed increasing somnolence, pulmonary embolus and left frontal stroke on day 30 of treatment. On day 35 of treatment, the patient developed increased anxiety, confusion, slurred speech and dysphasia, later visual and auditory hallucinations. The stroke and PE were diagnosed after hospitalization on day 38 and drug was discontinued
8. Patient 5011-50, a 61 year old woman with metastatic breast cancer developed psychosis 1 day after ziconotide was discontinued for acute gastroenteritis
9. Patient 501-73, a 38 year old woman with metastatic cervical cancer, developed psychosis on day 17. No further details were provided.
10. Patient 5020-49, a 45 year old man with bladder cancer, enrolled with burning pain in both legs. The patient developed auditory and visual hallucinations on day 1 following titration of the ziconotide dose. The symptoms resolved with a decrease in dose.
11. Patient 6062-101, a 656 year old man with intractable peripheral non-neuropathic pain developed auditory hallucinations, music and then voices on day 71 of ziconotide treatment. The hallucinations persisted through treatment with "tiotixene", but did resolve after discontinuation of study drug
12. Patient 6063-101, a 39 year old man with peripheral neuropathy, developed hallucinations on day 4 of ziconotide treatment which resolved one day after drug discontinuation.
13. Patient 6063-102, a 36 year old woman with chronic pain due to gunshot wound, to the spinal cord, developed lethargy, garbled speech, excessive sleepiness, impaired coordination and hallucinations on day 5. She later became unable to respond verbally, described in the narrative as a "catatonic-like state". Symptoms resolved within 24 hours of study drug discontinuation.

14. Patient 6076-106, a 70 year old woman with failed back syndrome, developed “psychotic behavior” characterized by disorientation to time and place, abnormal behavior (picking at clothes). The date of onset was not specified. The patient required hospitalization for this behavior. The patient remained on study drug for an addition 2 months, and the psychosis resolved after ziconotide and morphine were discontinued.
15. Patient 6076-112, a 39 year old man with central neuropathic pain developed “bizarre behavior”. No further detail is provided.
16. Patient 6090-109, a 77 year old man with failed back syndrome, developed agitation, combativeness and paranoia, on day 77. The symptoms resolved with treatment using haloperidol and lorazepam and discontinuation of the ziconotide.
17. Patient 93-1098, a 65 year old man with history of neuropathic pain, and failed back syndrome, developed intermittent dizziness, confusion and hallucinations during titration to restart ziconotide, after a 1 month pause in treatment. The drug had been held due to EKG changes that resolved during this time period.
18. Patient 1124-1461 was noted as having auditory hallucinations and a suicide attempt in Table 6.1 of the 120-day safety update, Vol. 5, 52, P. 350 but no narrative was provided.

SECTION 8.2.6 CLINICAL LABORATORY EVALUATIONS - IT

This section reports on data that includes in the initial IT ISS and the 120-day safety update

CPK

Based on the sponsor’s review of the data, (see Table 9.2.9.5, Vol. 5.2, p. 344), in patients who ever received ziconotide (N=903), there were 9 patients (1%) with CPK > 3X ULN at screening, and 27 (4.2%) at study termination. There were 4 patients (0.6%) with CPK > 594 IU/L at study termination, none at screening. Among the “never received ziconotide” group (N=44), the only CPK abnormality at screening or termination was 1 patient (2.3%) with a CPK >3X ULN at screening. The sponsor also found among the patients who ever received ziconotide, 91 patients (11%) with CPK >3X ULN at any visit, 5 (0.6%) with CPK > 594 IU/L. There was only one each for the “never received ziconotide” group (Table 9.2.9.7, Vol. 5.2, p. 347)

This reviewer examined IT Listing 7.2.11 and found that among the 1046 cases of ziconotide exposure (887 unique patients, 159 participating in 2 studies), there were 68 patients (6.2%) with a CPK greater than 600 IU/L at any visit after screening, while receiving ziconotide. The CPK information is summarized in Table 8.23. Forty three of these patients (4.1%) began the study with a normal CPK, 25 (2.4%) with an elevated CPK that rose further during the study. Of the 151 patients in the while receiving placebo group, there were 5 (3.3.0%) with a CPK >600 IU/L at any visit, all of whom began the study with a normal CPK. As can be seen in Table 8.22, there were additional patients in both groups with CPK elevations that were <600 IU/L.

For patients with an increase in CPK > 600 IU/L, there were 13 CRF’s available for review, these were patients in the while receiving ziconotide group. Eight of these patients had no

identifiable explanation for the elevated CPK. One of these 8 had an adverse event of muscle pain noted in the CRF (135-1101). Five of these patients had trauma/surgery/acute renal failure to explain the elevated CPK. Three CRF's with CPK elevations <600 IU/L and chosen for sustained elevations in CPK over several measurements were available for review. Of these patients, 2 had adverse events of lower extremity weakness noted (6090-103, 6090-107) and one had muscle pain noted (6601-101). Only one of the CRF's for the while on placebo patients with CPK > 600 IU/L were found to review. This patient (6087-101) was noted to have violent body movements without loss of consciousness on the day of the elevated CPK.

Table 8.23 Abnormal CPK Laboratory Values

	While on Ziconotide N=1046	While on Placebo N=151
Normal at onset, increased during infusion	212 (20.2%)	18 (11.9%)
Increased to >189 IU/L, <600 IU/L	169 (16.2%)	12 (7.9%)
Increased to >600 IU/L	43 (4.1%)	5 (3.3%)
Elevated at onset (>189 IU/L), increased during infusion	52 (5.0%)	1 (0.01%)
Increased to <600 IU/L	27 (2.6%)	1 (0.7%)
Increased to >600 IU/L	25 (2.4%)	0
Elevated at onset (>189 IU/L), decreased during study	34 (3.3%)	10 (6.6%)

Source: Appendix 2, IT listing 7.2.11 (Vol. 5.36)

In Table 9.2.9.2 (Vol. 5.2) the sponsor reported 87 patients in the ever received ziconotide group and 4 in the "never received ziconotide" group that had CPK values which changed from normal at screening to high at termination. This reviewer counted patients with CPK values that changed from normal at screening to abnormal at some point while receiving study drug and found 212 patients (20.2%) with CPK values that changed from normal to high while receiving ziconotide and 18 patients (11.9%) while receiving placebo.

Serum Creatinine

The sponsor has chosen greater than 2 mg/dl as the threshold for an abnormal creatinine level and has provided this information for the patients at screening and termination in table 9.2.9.5 and at any visit, Table 9.2.9.7. At study screening, there were 12 patients ever exposed to ziconotide out of 907, with a creatinine > 2.0 mg/dl and 13 at study termination. There were no patients with creatinine >2 from the never exposed to ziconotide group at screening or termination. At any visit, there were 19 patients ever exposed to ziconotide with creatinine >2.0 and still none from the never exposed to ziconotide group.

This reviewer examined IT Listing 7.2.12, (Vol. 5.37) and found that while on ziconotide, there were 7 patients (0.7%) with creatinine >2 at screening, and 1 patient (0.7%) while on placebo. The denominators used were 1046 cases of ziconotide exposure (887 unique patients and 159 enrolled in a second study), and 151 patients while receiving placebo. As not all of these patients necessarily had full data, the percentages are conservative and may be artificially low. There were 9 patients from the while receiving ziconotide group (0.9%), with a creatinine >2 mg/dl from any time after screening during the study and one patient (0.7%) while on placebo.

In IT Table 9.2.9.2 (vol. 5.2, P. 337) the sponsor indicates that there were 17 patients in the while receiving ziconotide group who went from normal to abnormally high creatinine, none in the “never received ziconotide” group.

A creatinine of 2, while definitely abnormal is not as sensitive an indicator of renal damage as a change in creatinine. This reviewer examined IT Listing 7.2.12, (Vol. 5.37) and counted the number of patients with a change in creatinine that went above 1.2 mg/dl, and represented a difference of at least 0.3. There were 33 patients (3.7%) in the while receiving ziconotide group who met these criteria, and 2 (1.3%) in the while receiving placebo group.

AST

In Table 9.2.9.7, the sponsor reports 1 patient with AST >108 IU/L, 27 >3X ULN of the “ever received ziconotide” group and none for the “never received ziconotide” group. This reviewer examined IT Listing 7.2.3 (Vol. 5.32) and found 17 patients (1.6%) (assuming the 1046 denominator) in the “ever received ziconotide” group with a serum AST >108 IU/L after screening, 13 of whom were normal at screening, 3 elevated, but for whom the increase was more than 50%. Patients with significantly elevated AST on screening without significant change during the study were excluded. There were 2 patients (1.3%) in the “ever received placebo” group with AST >108 IU/L while receiving placebo.

There were 120 patients in the “ever received ziconotide” group (11.5%) with a normal AST at screening and an abnormal AST at some time during the study and 10 (6.6%) in the while receiving placebo group.

In Table 9.2.9.2 (Vol. 5.2), the sponsor reports 56 patients whose AST changed from normal at screening to abnormally high at study termination and none in the placebo group.

WBC

In Table 9.2.9.8 (Vol. 5.2), the sponsor reports 11 (1.3%) patients who “ever received ziconotide” with a WBC of <2.5 K/cmm at any time, 3 (6.8%) from the “never received ziconotide” group. This reviewer counted 12 patients (1.1%) who “ever received ziconotide” in IT listing 7.2.31 (vol. 5.46) with WBC <2.5 K/cmm at any time, and one patient (0.7%) who “ever received placebo”. There were an additional 4 patients in the “ever received ziconotide” group who began the study with a WBC <2.5 K/cmm.

Vital signs

This section reports on data that includes in the initial IT ISS and the 120-day safety update. The sponsor used the following threshold values, summarized in Table 8.24, to define clinically significant change in vital signs.

Table 8.24 Clinically Significant Vital Sign Abnormalities- Threshold Values -IT 120-Day Safety Update (Table 9.2.10.1, Vol. 5.2, P. 351)

Vital Sign Parameter	Threshold Value
Systolic blood pressure	absolute value <100 mmHg >30 mmHg decrease from Baseline
Diastolic blood pressure	absolute value <60 mmHg >20 mmHg decrease from Baseline
Orthostatic systolic blood pressure	>30 mmHg decrease from supine SBP as compared to the standing SBP
Orthostatic diastolic blood pressure	>20 mmHg decrease from supine DBP as compared to the standing DBP
Heart rate	absolute value <50 bpm absolute value > 120 bpm

Based on these threshold criteria, the sponsor reported a total of 20.5% of the 887 unique patients who “ever received ziconotide” had a decrease of systolic BP of > 30 mmHg from baseline at any visit, and 23.7 % of these patients had a > 20 mmHg decline in diastolic BP. Among the 44 patients who “never received ziconotide” 15.9% of the 44 patients had the same magnitude of change in systolic BP and diastolic BP (Table 9.2.10.3, Vol. 5.2, P. 355).

Electrocardiogram evaluations

This section reports on data that includes in the initial IT ISS and the 120-day safety update.

EKGs were performed for all studies except 94-004. Patients were counted more than once if they participated in more than one study. The sponsor describes that the number of possible cases for patients who received ziconotide is 1015. 856 unique patients and 159 patients participating in a second study. However, in Table 9.2.11.1 (Vol. 5.2, P. 33), N is 560. There is no explanation for the missing 456 cases.

The clinical investigators evaluated the EKGs and determined if they were normal, abnormal and not clinically significant or abnormal and clinically significant for all studies except 98-022 for which a central, independent cardiologist read and recorded all of the studies.

As presented in table 9.2.11.1, of the 560 cases, there were 311 normal baseline records, 244 abnormal but not clinically significant and 5 abnormal and clinically significant. At study termination, there were 299 normal EKGs, 258 abnormal but not clinically significant and 3 abnormal and clinically significant. Only one record is reported as changing to abnormal and clinically significant. There were only 21 EKGs for the nerve received ziconotide group and none changed to abnormal and clinically significant.

In reviewing the patient narratives, there were only two patients this reviewer could identify with an EKG report considered to be either a serious adverse event or an adverse event leading to early study termination.

1. Patient 93-1098, a 65 year old man with history of neuropathic pain, and failed back syndrome, had a baseline EKG with LBBB, left atrial enlargement with long QT interval of 473 msec. One month after beginning the study, the EKG revealed PVCs, right axis deviation, diffuse T wave abnormalities and anterior infarct and after an additional 5 days,

left anterior fascicular block, QT interval "long for rate", nonspecific inferior T wave abnormalities and anterior infarct. Ziconotide was discontinued and the Q-wave abnormalities were resolved on an EKG from 6 weeks after beginning the study. Study drug was restarted 8 weeks after starting the study. Although symptomatic with intermittent dizziness, confusion and hallucinations during titration, no EKG was performed. Five months after the patient started the study, the EKG was reported as normal sinus rhythm, left atrial enlargement and anterior infarct.

- 2 Patient 118-1364, a 39 year old woman with history of fibromyalgia, hypertension, asthma, and multiple other symptoms, entered the study on _____. A screening EKG revealed anteroseptal ST segment depression and T wave inversion that was unchanged on _____. On _____, the EKG revealed T wave inversion with ST segment depression in V1-V3. A myocardial infarction was ruled out and exercise Thallium stress test was negative. Ziconotide was discontinued on _____. A cardiac catheterization on _____ revealed "normal coronary anatomy", normal left ventricular systolic function and elevated right sided pressures felt to be consistent with possible cardiomyopathy.

SECTION 8.3 EPIDURAL ISS

This section was reviewed from the 120-day safety update. The four epidural ziconotide studies are summarized below.

Study 96-012

This was to be a phase II, double blind, placebo controlled pilot study in patients undergoing elective total hip or knee replacement, elective retropubic radical prostatectomy or elective abnormal hysterectomy. The patients were to have an epidural catheter for surgical anesthesia. A morphine IV PCA was to be available for rescue. Patients were to be randomly assigned to either 0.7ug/h or 7ug/h of ziconotide by continuous epidural infusion for 48 h. As positive efficacy results were found after the first portion of the study, the planned second, higher dose portion was not performed.

Study 98-012 was to be a phase I/II open label PK study. Five fixed doses, 1, 2, 5, 10, and 20 ug, were to be administered by short epidural infusion to healthy volunteers and chronic pain patients. The primary objectives were to characterize the 24 h CSF and plasma PK profiles. The secondary objectives were to evaluate safety and efficacy in chronic pain due to cancer or AIDS. The dose was to be infused over 60 minutes (1ml/h) followed by a 30 minute saline flush.

Study 98-023 was to be a phase II/III randomized, double blind, placebo controlled, parallel group study of safety and efficacy of 3 different doses in acute pain due to elective total knee or total hip replacement. A morphine PCA was to be available for rescue. Ziconotide was to be administered at 0.2ml/h at concentrations of 2, 7, or 20 ug/h or placebo for 48 h.

Study 98-023 The study is ongoing and is still blinded. One hundred and fifty patients have been enrolled so far. The mean age is 65 (range 20-91), 74 are male, 128 are white, 17 black, 4 Hispanic and 1 Asian. For the purpose of data handling, patients were categorized into the 4 treatment groups, 36 were enrolled in group A, 41 in group B, 38 in group C and 35 in group D.

This was performed by a statistician at _____ all _____ personnel and Elan personnel remain blinded to the treatment group assignments.

Study 98-023

At the time of data cutoff, 150 patients had been enrolled, randomized and exposed to study drug. Seven patients were granted protocol exceptions for inclusion or exclusion criteria by the medical monitor, and one patient was noted to be a protocol violation for violation of the ASA score exclusion criterion. A total of 133 patients (89%) completed the 48 h drug infusion period, although 4 disposition forms were not available by the cut off. The primary reason for early termination for 7 patients was adverse event, for the remaining 6, other. The designation of other represented inadequate pain control under the study conditions for 5 of the 6 patients, and for one patient it was requested to remove catheter

SECTION 8.3.1 DEATHS -ED

There was one death during the 4 epidural studies. Patient 13064, randomized to ziconotide 0.7 ug/h in study 96-012, underwent a hysterectomy and bilateral salpingo-oophorectomy for ovarian cancer. The patient developed peritonitis which was fatal

SECTION 8.3.2 SERIOUS ADVERSE EVENTS - ED

There was a total of 13 patients out of the total number of 223 cases (5.8%) who experienced 26 serious adverse events. These 13 patients are detailed in Table 8.25. Most of the serious adverse events occurred in patients participating in studies that are ongoing and still blinded.

Table 8.25 Serious Adverse Events, Epidural Studies

Study/Patient ID	SAE
During Ziconotide Infusion	
98-021 1542684	Leg Pain
98-029 0911501	Uncontrolled Nausea And Vomiting (Patient Also On Chemotherapy)
During Blinded Study Drug Infusion	
98-023 1152654	Hypotension, Pulmonary Edema
1092802	Hypotension, Respiratory Depression, Unresponsiveness
1152643	Hypotension
1102608	Abdominal Distension And Ileus
Following Completion Of Ziconotide Infusion	
96-012 13064	Peritonitis Resulting In Death
20018	Atrial Fibrillation
Following Completion Of Blinded Study Drug Infusion	
98-023 1022849	Pulmonary Embolism
104857	Colonic Polyps, Colonic Ulcers, Diverticula, GI Bleeding, Internal Hemorrhoids
1082642	DVT, Hip Dislocation
1152654	Acute Renal Failure, Right Sided Heart Failure, Thrombocytopenia
1152655	Increased Depression, Upper GI Bleed
Placebo	
96-012 10061	Pulmonary Edema

Source: Table 9.3.8.1, Vol. 5.2, P. 410

Table 8.26 provides a summary of the serious adverse events in the epidural studies by event and treatment group. Hypotension, GI hemorrhage and pulmonary edema were the most common adverse events.

Table 8.26 Serious Adverse Events - Epidural Studies

Adverse Event	Patients Received Ziconotide	Patient Received Placebo	Study Drug Blinded
Abdominal Distention			1
Acute Renal Failure			1
Atrial Fibrillation	1		
Colonic Polyps			1
Colonic Ulcers			1
Deep Vein Thrombophlebitis			1
Depression			1
GI Diverticula			1
GI Hemorrhage			2
Hip Dislocation			1
Hypotension			3
Hypoventilation			1
Ileus			1
Leg Pain	1		
Peritonitis	1		
Pulmonary Edema		1	1
Pulmonary Embolus			1
Rectal Disorder- Internal Hemorrhoids			1
Right Sided Heart Failure			1
Stupor (Unresponsiveness)			1
Thrombocytopenia			1
Uncontrolled Nausea And Vomiting			1

SECTION 8.3.3 DISPOSITION - ED

SECTION 8.3.3.1 Adverse Events leading to study discontinuation - ED

Nine patients have terminated epidural studies due to adverse events. One patient had received placebo and terminated due to fever, pulmonary edema and dyspnea. One patient who had received ziconotide, 1542684, terminated due to headache, paresthesias, and leg pain, listed under SAE's. The remaining 7 patients were in the blinded study. Two of these patients terminated due to hypotension, one each intractable pain, confusion and nausea. The last 2 patients had multiple AE's, 1 patient with nausea, vomiting and injection site pain, and 1 with somnolence, confusion, anxiety and nausea.

SECTION 8.3.3.2 Other dropouts - ED

The two patients enrolled in study 98-029 as of the 120-day safety update have both discontinued study participation. Patient 0121503 received epidural ziconotide for 93.9 days and then withdrew consent and discontinued from the study. This patient had previously participated in

IT study 98-022 as patient 012-1015. Patient 0911501 received epidural ziconotide for 12.2 days and then required catheter removal for safety concerns.

SECTION 8.3.4 ADVERSE EVENTS - ED

AE information was available for 220 of the 223 cases exposed to study drug. A total of 749 adverse events were reported, the most common were nausea, fever and anemia (ED Table 9.3.7.2, Vol. 5.2, P. 395). Adverse events affecting the nervous system reached 65% of ziconotide treated patients in 96-012, compared to 25% of placebo treated patients in that study. For adverse events affecting the digestive system up to 53% of the ziconotide treated patients in study 96-012 compared to 25% of placebo treated patients

SECTION 8.3.5 CLINICAL LABORATORY EVALUATIONS - ED

There were no additions to this section in the 120-day safety update.

Study 96-012 provides placebo controlled, double blinded information. Review of the laboratory results revealed 2 patients in the ziconotide 0.7 ug/h group with a normal to high change in ALT, none in placebo, 6 patients with normal to high changes in AST, 1 placebo, 3 in the 0.7 ug/h and 2 in the 7.0 ug/h ziconotide groups. There were normal to high LDH elevations in 3 patients in the 7.0 ug/h ziconotide group. There were across group elevations in CK, lowering of hemoglobin and hematocrit and an across decrease in albumin. There were no changes in creatinine.

In the results from study 98-021, there were only sporadic changes to the lab values except for an across the board increase in CK.

In the laboratory results from study 98-023, there were across group decreases in albumin, protein, hematocrit and hemoglobin and calcium, and increase in CK.

These changes are all consistent with those seen in patients undergoing surgery.

SECTION 8.3.6 VITAL SIGNS

From study 96-012, both of the ziconotide treated groups demonstrated declines in systolic and diastolic blood pressures 1, 2 and 3 hours after infusion of study drug was started, greater in the 7.0 ug/h group. There placebo was a decrease in systolic and diastolic blood pressure for the placebo treated group as well for the first 2 hours after drug infusion, comparable to the 0.7 ug/h ziconotide group.

The blood pressure results from Study 98-012 are less consistent with post infusion declines in systolic blood pressure for the 1, 2, and 10 ug infusions there were greater than for the 20 ug infusion. There was little change in systolic blood pressure in the 5 ug infusion group. Changes in diastolic blood pressure were similar.

The blood pressure results for study 98-023 revealed declines during the 48 hour infusion for groups A and C that was gone by 72 hours.

SECTION 8.4 INTRAVENOUS ISS

This section was reviewed from the IV ISS of the original NDA submission. No new information was provided in the 120 day safety update

During the TBI studies, in a protocol revision to study 94-001 dated 6/5/95 and in a change to the Investigator Brochure dated 3/20/95, the sponsor changed the reporting of hypotension from an adverse event to not an adverse event "provided therapeutic countermeasures (adequate intravenous fluid administration and proactive use of vasopressors) for hemodynamic management proved effective" (Vol. 2.94, P. 032). This revision would have impacted studies 95-004 and 1009/002 and 1009./003 which were started subsequent to the revision. Studies 93-00, 93-002 and 93-003 were completed prior to this revision. The sponsor did not indicate whether 94-002 was impacted by this revision.

SECTION 8.4.1 DEATHS - IV

There were no deaths from the phase I, normal volunteer studies.

There was only one death in the phase II CABG studies, a patient who died in cardiac arrest from arrhythmias. 14 hours after initiating treatment with placebo.

There were 75 patients who died during the Phase II TBI studies. Fifty four of these patients received ziconotide. The causes of death were summarized in Table 8.27.

Table 8.27 Cause of Death, IV TBI Studies (Based on Table 8.8.3.8.2, Vol. 2.94, P. 123)

Cause Of Death	Ziconotide (N=175)	Placebo (N=125)
Result of head trauma	41	7
Complications Of TBI	25	2
Increased Intracranial Pressure	9	5
Herniation	7	3
Cardiopulmonary Arrest	3	3
Multiorgan Failure/Trauma	3	1
ARDS	2	1
Sepsis	1	2
Shock	1	2
Other: ruptured aorta, acute renal failure, support withdrawn	1	2
Unknown	2	0
Total Number Of Deaths	54 (30.9%)	21 (16.8%)

Based on the causes of death from Table 8.8.3.8.2 (Vol. 2.94, P. 123), it appears that a total of 3 patients, only one on ziconotide died from hypotension. However, 10 of these patients experienced systolic hypotension according to the patient narratives and this can contribute to a drop in cerebral perfusion pressure and increased cerebral ischemia, edema and intracranial pressure. Systolic hypotension was noted in the narrative of one of the placebo patients.

According to an analysis by the sponsor, mean arterial pressure was lower in the ziconotide treated group than the placebo group and it was these patients who demonstrated a higher mortality rate.

SECTION 8.4.2 SERIOUS ADVERSE EVENTS - IV

Table 8.28 presents a summary of the Deaths, SAE's and AE's leading to early study discontinuation.

Table 8.28 Deaths, Serious Adverse Events And Adverse Events Leading To Early Discontinuation, All IV Studies (From Sponsor's Table 8.8.3.8.1, Vol 2 94, P. 119)

	Phase I Safety Studies		Phase II CABG Studies		Phase II TBI Studies	
	Ziconotide (N=79)	Placebo (N=25)	Ziconotide (N=26)	Placebo (N=5)	Ziconotide (N=175)	Placebo (N=125)
Deaths	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%) ^a	52 (29.7%) ^b	18 (14.4%)
Serious Adverse Events	1 (1.3%)	0 (0.0%)	5 (19.2%)	1 (20.0%)	71 (40.6%)	35 (28.0%)
Adverse Events Leading to Study Discontinuation	9 (11.4%)	0 (0.0%)	1 (3.8%)	0 (0.0%)	7 (4.0%)	4 (3.2%)

a No ziconotide treated or placebo treated patients were noted on the study termination page of the CRF to have discontinued from the CABG studies due to death; one placebo patient (patient No. 1/3 in Study 94-002) had an adverse event resulting in death that occurred after study completion (See Table 8.8.3.8.3)

b 52 ziconotide treated patients and 18 placebo treated patients were noted on the study termination page of the CRF to have discontinued from the TBI studies due to death; overall, 54 ziconotide treated patients and 21 placebo treated patients had adverse events resulting in death (See Table 8.8.3.8.2)

Data Source Appendix I, IV Tables 1, 7, 17, 24, 34, and 41.

The occurrence of supine and orthostatic hypotension during studies of intravenous ziconotide was significant and dose related. An interim analysis of adverse events and outcome during the TBI trials resulted in the determination that the patients treated with ziconotide had a greater mortality than those treated with placebo and lead to discontinuation of these trials.

There was only one patient from the phase I, safety studies with a serious AE. This subject experienced hypotension, with supine and standing BP dropping from 133/78 and 144/88 to 107/61 and 51/29, occurring 2.5 hours after initiation of ziconotide infusion.

There were 5 ziconotide treated (19.2%) patients with SAE's and one placebo treated patient (20.0%) with an SAE in the CABG phase II studies. The SAE's are detailed in Table 8.29. All of these events occurred after the completion of study drug infusion.

Table 8.29 Serious Adverse Events - CABG studies

Adverse Event	Ziconotide	Placebo
Hypotension	3	
atelectasis	1	
pleural effusion	1	
cerebrovascular accident	1	
Post-operative mediastinal bleeding	1	
Death		1

There were many more serious adverse events in the phase II TBI studies among the ziconotide treated patients 40.6% (71/175) compared with the placebo treated patients 28.0% (35/125). There were more SAE's involving the cardiovascular system and nervous system in the ziconotide treated group as noted in Table 8.30. In particular, there was more heart arrest (4.6% ziconotide vs. 1.6% placebo), hypotension (8.0% ziconotide vs. 1.6% placebo), and intracranial hypertension (6.3% ziconotide vs. 1.6% placebo).

Table 8.30 Serious Adverse Events in at least 1% of ziconotide treated patients - TBI Studies (From Sponsor's Table 8.8.3.8.4, Vol. 2.94, P. 130)

COSTART Term	Ziconotide N = 175		Placebo N = 125	
	Number	Percentage	Number	Percentage
Number of Patients With Any Event	71	40.6%	35	28.0%
Body As A Whole	18	10.3%	8	6.4%
Aggravation Reaction	2	1.1%	1	0.8%
Fever	2	1.1%	0	0.0%
Hydrocephalus	3	1.7%	0	0.0%
Sepsis	6	3.4%	3	2.4%
Cardiovascular System	26	14.9%	10	8.0%
Heart Arrest	8	4.6%	2	1.6%
Hypotension	14	8.0%	2	1.6%
Endocrine System	3	1.7%	0	0.0%
SIADH	2	1.1%	0	0.0%
Metabolic and Nutritional Disorder	4	2.3%	3	2.4%
Musculoskeletal System	3	1.7%	1	0.8%
Nervous System	31	17.7%	12	9.6%
Brain Edema	6	3.4%	0	0.0%
Cerebral Infarct	5	2.9%	3	2.4%
CNS Depression	3	1.7%	1	0.8%
Intracranial Hypertension	11	6.3%	2	1.6%
Ischemia Cerebellar	2	1.1%		0.0%
Meningitis	2	1.1%	1	0.8%
Subarachnoid Hemorrhage	2	1.1%	0	0.0%
Subdural Hematoma	2	1.1%	1	0.8%
Respiratory System	18	10.3%	16	8.0%
Aspiration Pneumonia	3	1.7%	1	0.8%
Pneumonia	8	4.6%	5	4.0%
Respiratory Distress Syndrome	3	1.7%	2	1.6%
Special Senses	3	1.7%	3	2.4%
Mydriasis	2	1.1%	1	0.8%
Urogenital System	2	1.1%	2	1.6%

Studies include: 94-001 and 1009-002/1009-003.

Data Source: Appendix I, IV Table 41.

SECTION 8.4.3 PATIENT DISPOSITION - IV

Study subject disposition is summarized in Table 8.310. There were considerably more patients discontinuing the study due to adverse events in the ziconotide treated compared to placebo treated subjects in the normal volunteer group and the TBI patients. There was no difference between treatment groups in the CABG patients

Table 8.31 Summary of Disposition of Subjects - All Intravenous Studies (From Sponsor's Table 8.8.3.5.1, 8.8.3.5.2, 8.8.3.5.3 Vol. 2.94 P. 048)

	Normal Volunteers		CABG		TBI	
	Ziconotide n (%)	Placebo n (%)	Ziconotide n (%)	Placebo n (%)	Ziconotide n (%)	Placebo n (%)
All Subjects Enrolled	79	25	26	5	175	125
Subjects Enrolled, but Not Treated	0	0	0	0	0	0
Study Completed	69 (87.3%)	23 (92.0%)	23 (88.5%)	4 (80.0%)	89 (50.9%)	77 (61.6%)
Early Termination or Discontinued	10 (12.7%)	2 (8.0%)	3 (11.5%)	1 (20.0%)	86 (49.1%)	48 (38.4%)
Primary Reason for Early Termination or Discontinuation ^a						
Intolerable Adverse Event	9 (11.4%)	0 (0.0%)	1 (3.8%)	0 (0.0%)	7 (4.0%)	4 (3.2%)
Withdrawal Requested by Subject	1 (1.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Death on Study	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	52 (29.7%) 54 (30.9%) ^c	18 (14.4%) 21 (16.8%) ^c
Other ^b	0 (0.0%)	2 (8.0%)	2 (7.7%)	1 (20.0%)	27 (15.4%)	26 (20.8%)

a Early termination from Studies 93-001 and 93-002 was defined as withdrawal prior to the completion of the 4-day study. Early termination from 93-003 was defined as withdrawal prior to the completion of the 2-day study. Early termination from Studies 94-002 and 95-004 was defined as withdrawal prior to 48 hours post infusion. Early termination from Study 94-001 was defined as withdrawal prior to the completion of the 28-day study. Early termination from Study 1009-002/1009-003 was defined as withdrawal prior to six months after the end of infusion

b Two placebo patients in Study 93-001 discontinued for reason specified as "Study was stopped" per Appendix 2 IV Patient Data Listing 2. Per Appendix 2, IV Patient Data Listing 17, all 3 patients from Study 94-002 who withdrew for "other" reasons, terminated the study early due to a "protocol change". Reasons for early termination for patients terminating the studies early due to "Other" included lost to follow-up, study stopped, patient not available for follow-up, patient refused visit, patient relocated, and other miscellaneous reasons as specified in Appendix 2, IV

c In section 8.8.3.8.2.3, the sponsor provides actual figures on the number of deaths, not just those reported on the study termination page of the CRF's

Patient Data Listing 32

Studies include 93-001, 93-002, 93-003, 94-002 and 95-004, 94-001 and 1009-002/1009-003

Data Source: Appendix 1, IV Table 1, 17, 34

A total of 87.3% of the normal volunteers participating in the phase I studies completed the studies. In the phase I trials, intolerable adverse events were the most common cause for early termination, responsible for 9 of the 10 early terminations. One patient, not included in the safety database was discontinued early due to A-fib occurring during placement of a Swan-Ganz catheter prior to administration of study drug.

Among patients in the CABG studies, 88.5% of those receiving ziconotide completed the study. Of the 3 early discontinuations, 1 was due to intolerable adverse event, hypotension. The other two patients discontinued due to reasons categorized as "other" and are attributed to a "protocol Change" Vol. 2.94, P. 049).

Among the TBI patients, 50.9% completed the studies, and 61.6% of the placebo patients completed. The main reason for early study termination for patients receiving ziconotide was death, occurring in 52 patients (29.7%) compared with 18 placebo patients (14.4%). Fifteen percent of ziconotide patients terminated study participation early due to "other" reasons compared with 20.8% of placebo patients. Seven (4.0%) of the ziconotide treated patients discontinued due to intolerable adverse events compared with 4 (3.2%) of the placebo treated patients. (Note: there are 11 patients listed as discontinuations due to adverse events from study 94-001, and 12 from study 1009-003, Vol. 2.274, P. 260, P. 135).

SECTION 8.4.3.1 Adverse Events Leading To Study Discontinuation - IV

Among normal volunteers receiving ziconotide, 7 subjects in study 93-001 and one subject in 93-003 discontinued dosing due to "significant" orthostatic hypotension without a reflex increase in heart rate, and symptoms associated with hypotension including syncope with asystole. One subject discontinued early in study 93-002 due to hypotension while recumbent. The one remaining early termination from the ziconotide group was by patient request. One patient, not included in the safety database was discontinued early due to A-fib occurring during placement of a Swan-Ganz catheter prior to administration of study drug.

There was one ziconotide treated patient in the phase II CABG studies who discontinued due to hypotension.

Among the TBI patients, seven (4.0%) of the ziconotide treated patients discontinued due to intolerable adverse events compared with 4 (3.2%) of the placebo treated patients as summarized in Table 8.32. (Note: In the patient narratives, there are 11 patients listed as discontinuations due to adverse events from study 94-001, and 12 from study 1009-003, Vol. 2.274, P. 260, P. 135).

Of the 23 patients identified in the narratives who discontinued due to adverse events, 2 were placebo patients who discontinued due to hypokalemia and abnormal LFT's. Of the remaining 21 patients, 12 terminated the study early for hypotension, one to avoid the risk of hypotension, one of ran ischemic leg, one of hypoxia, and 2 due to adverse events attributed to the pressors needed to counteract ziconotide induced hypotension.

Table 8.32 Adverse Events Leading To Early Study Discontinuation

	Ziconotide treated	Placebo treated
Total	21	2
Hypotension	12	
Pressor Related AE	2	
Pump Error/Ziconotide OD/Hypotension	1	
Tachycardia	1	
Hypoxia	1	
Ischemic Leg	1	
Risk Of Hypotension	1	
Drug Stopped For Brain Death Evaluation	1	
Abnormal LFT's		1
Hypokalemia		1
Uncertain From Narrative	1	

**Appears This Way
On Original**

SECTION 9.0 120-DAY SAFETY UPDATE

SECTION 9.1 INTRATHECAL STUDIES

The cutoff dates for the 120-day IT safety update are as follows:

Study 95-002 - 2/21/00

Study 98-022 - 2/23/00

SECTION 9.1.1 DEMOGRAPHICS - IT

There were no significant changes in the demographic and baseline characteristics between the IT ISS and the 120-day safety update. This includes age, gender, race, weight and height.

SECTION 9.1.2 PATIENT EXPOSURE - IT

A total of 931 unique patients were enrolled in intrathecal studies as of the cut off date. A total of 887 patients had received ziconotide, 151 received placebo. Forty four of the placebo patients never received ziconotide. Of the 887 patients, 704 were reported in the original IT ISS, and 183 represent new patients enrolled in Study 98-022 subsequent to the cut off date for the IT ISS. There were no new patients enrolled and treated with placebo subsequent to the IT ISS. The placebo values are therefore unchanged and will not be repeated.

As summarized in Table 9.1, approximately half of the patients (50.2%) were exposed to ziconotide for a period of 1-29 days compared with 54% from the IT ISS and 26.9% had received ziconotide for ≥ 90 days compared to 22.7% from the IT ISS.

Table 9.1 Number of Patients Receiving IT Ziconotide by Maximum Duration of Treatment - All Intrathecal Clinical Studies -IT 120-Day Safety Update (From Sponsor's Table 9.2.4.6, Vol. 5.2, P. 110)

Duration of Treatment (Days) ^a	Number of Patients (N = 887)	Cumulative Dose of Ziconotide (ug)		
		Mean (SD)	Median	Range
0 to <30	445 (50.2%)	113.7 (279.9)	52.5	0.1-4625.0
30 to <90	203 (22.9%)	646.3 (2230.4)	302.1	64.8 - 30742.7
90 to <180	140 (15.8%)	1168.9 (1424.7)	729.0	122.1 - 8312.4
180 to <360	62 (7.0%)	2362.6 (3278.3)	1476.1	289.8 - 23749.7
≥ 360	37 (4.2%)	9731.6 (17282.6)	3889.5	918.9 - 80559.7

a Each group is mutually exclusive

Note: Includes all data in the database as of 21 February 2000 for Study 95-002 and 23 February 2000 for Study 98-022.

Studies include: 94-004, 95-001, 95-002, 96-002, 96-003, 96-010, 97-013, 97-015, and 98-022.

Data Source: Appendix 1, IT Table 1.7.

The duration of treatment ranges from 0.6 to 1288.2 days, with a mean of 91.5 days as demonstrated in Table 9.2. This compares with a mean of 79 days and upper limit of the range of 1042 days from the IT ISS. The range of final dose rates ranges from 0.001ug/h to 38.0 ug/h reflecting various protocol initial and final dose levels and this is unchanged from the IT ISS. The mean last dose level received was 0.89 ug/h, lower than the 1.04 ug/h from the ISS and the

median was 0.29 ug/h which is unchanged from the IT ISS. The mean cumulative dose was 960.5 ug compared with 909 ug from the IT ISS.

Table 9.2 Dosing Information -All Intrathecal Clinical Studies -IT 120-Day Safety Update (From Sponsor's Table 9.2.4.7 Vol. 5.2, P. 112)

	Ever Received Ziconotide (N = 887)	Never Received Ziconotide ^a (N=44)
Number of Days of Treatment ^b		
Mean (PE)	91.49 (5.24)	6.59(0.65)
Median (Range)	34.83 (0.06 - 1288.17)	6.10 (0.26 - 13.53)
Initial Dose Level Received (ug/hr)		
Mean (SE)	0.33(0.04)	0.12(0.02)
Median (Range)	0.106 (0.004 - 10.000)	0.100 (0.000 - 0.400)
Last Dose Level Received (ug/hr)		
Mean (SE)	0.89(0.08)	1.88(0.68)
Median (Range)	0.290 (0.001 - 38.100)	0.357 (0.000 - 21.000)
Cumulative Dose (ug) ^c		
Mean (SE)	960.51 (142.88)	263.69 (101.80)
Median (Range)	196.67 (0.10 - 80559.65)	63.32 (0.00 - 3261.35)

a Placebo in dose equivalents

b Number of days while patients were receiving study drug.

c The cumulative ziconotide/placebo dose level was estimated by (dose level 1 x duration of dose level 1) + (dose level 2 x duration of dose level 2) + ... + (dose level K x duration of dose level K), if K distinct ziconotide infusions were received

Note: Includes all data in the database as of 21 February 2000 for Study 95-002 and 23 February 2000 for Study 98-022

Studies include: 94-004, 95-001, 95-002, 96-002, 96-003, 96-010, 97-013, 97-015, and 98-022

Data Source: Appendix 1, IT Table 3.1.

The average hourly dosing for the first 4 weeks demonstrates that patients beginning their initial titration with doses >0.1 ug/h rapidly titrated down while those beginning titration with doses ≤0.1 ug/h slowly titrated up. The doses were similar between the two groups by week 12 according to the sponsor. There was no significant change in the average hourly dosing from the IT ISS and the 120 day safety update.

SECTION 9.1.3 DEATHS

Fifty eight deaths were reported among the 704 patients who ever received ziconotide in the original IT ISS. There were 6 additional deaths reported in the 120-day safety update. Four of these were never previously reported, 2 of these were previously reported in Appendix 6 of the IT ISS. There were an additional 2 deaths in reported Appendix 6 of the 120 day safety update, see Table 9.3. This results in a total of 64 deaths (7.2%) among the 887 patients exposed to ziconotide.

Table 9.3 Deaths among patients who ever received ziconotide

Source of Data	Number Of Deaths Of Patients Who Ever Received Ziconotide
NDA - IT SS, cutoff 9/9/99	56
NDA - IT SS Appendix 6, 9/9/99 through 12/1/99	2
120-day IT safety update, cutoff Study 95-002 - 2/21/00 Study 98-022 - 2/23/00	4
120-day IT safety update Appendix 6, through 4/21/00	2
Total	64

The 6 additional deaths were patients who received ziconotide and enrolled with chronic, nonmalignant pain. One patient died from a myocardial infarction occurring during hospitalization for meningitis. One patient died of cardiogenic shock from an acute myocardial infarction. One patient died of a ruptured thoracic dissecting aortic aneurysm. Of the 3 remaining patients, 1 died from a cardiac arrest and two were found dead at home, but details concerning these patients deaths were not provided. Brief narratives of the deaths of these 6 patients with non-malignant pain are provided below.

1. Patient 6055-102, a 72 year old man, had a history of chronic low back pain, peripheral vascular disease, hypertension, CAD and repair of abdominal aortic aneurysm. He enrolled in 96-002 on _____ and 95-002 on _____. On _____, the patient died from a ruptured dissecting thoracic aorta.
2. Patient 6093-105, a 50 year old man with reflex sympathetic dystrophy enrolled in 96-002 on _____ and 95-002 on _____. On _____, the patient died from a cardiac arrest. No autopsy information was provided.
3. Patient 066-1441 was a 61 year old man with history of hiatal hernia, aspiration pneumonia, "bilateral foot neuropathy", depression, started ziconotide _____. The patient was found dead in his bed on _____, one day after diagnosis of possible stool impaction. No further information was provided.
4. Patient 63-1485 was an 81 year old man with history of coronary artery disease. the patient began ziconotide on _____. Meningitis was diagnosed on _____ and study drug was discontinued. on _____ "the patient underwent 'cardiac challenge' testing. The patient's cardiac medications were discontinued at that time." On _____ the patient experienced a myocardial infarction with pulmonary edema. He required ventilatory support for one day. A cardiac catheterization on _____ revealed 40% ostial left main artery stenosis with distal filling defect, complex 90% mid right coronary artery stenosis, 75-90% left anterior descending artery stenosis. The patient became unresponsive following respiratory difficulty, was placed on comfort measures and died on _____.
5. Patient 157-1399 was a 66 year old man with a history of cervical and lumbar radiculopathy, type II diabetes mellitus, hypertension, cerebrovascular accident and hyperlipidemia. Ziconotide was initiated on _____ and was discontinued on _____ when the patient was hospitalized for dehydration. Six days later, the patient was readmitted with an acute myocardial infarction. The patient Had an pulmonary edema and required ventilatory support. The patient was on pressors for cardiogenic shock and died on _____.
6. Patient 172-1427, was a 64 year old man with a history of COPD, GERD with Barrett's esophagus and depression. The patient started receiving ziconotide on _____. The patient

was found dead at home on . — An autopsy was scheduled, but no report was available at the time of this report.

SECTION 9.1.3.1 Suicide

There were 3 additional suicide related adverse events, 2 in the 120 update and 1 in Appendix 6 of the 120 day update. One patient with a history of pudendal neuralgia and prostate cancer had suicidal thoughts and one with ilioinguinal neuralgia and depression completed suicide by gunshot wound to head. This results in a total of 5 suicide attempts, 4 completed suicides and 2 patients with suicidal ideation among the 887 patient exposed to intrathecal ziconotide. There was one patient reported in the original IT ISS with suicidal ideation who had been treated with placebo.

SECTION 9.1.4 PATIENT DISPOSITION

Forty four percent of the patients terminated or discontinued the study early, compared with 32% from the IT ISS. The most common reason for early study discontinuation was intolerable adverse event, responsible for 236 terminations (26.6% of the total population or 60.3% of the early discontinuations). This compares with 20.3% of the total IT ISS population discontinuing early due to intolerable adverse events. Ineffective drug therapy was the next most common accounting for 11.1% compared with 5.3% from the IT ISS. This information is summarized in Table 9.4.

Table 9.4 Summary of Disposition of Patients Based on Study of Origin - All Intrathecal Clinical Studies -IT 120-Day Safety Update (From Sponsor's Table 9.2.5.1 Vol. 5.2, P. 126)

Reason	Ever Received Ziconotide		Never Received Ziconotide	
	Count	Percentage	Count	Percentage
All Treated Patients ^a	886	100.0%	45	100.0%
Study Completed ^b	278	31.4%	33	73.3%
Ongoing	217	24.5%	0	0.0%
Early Termination or Discontinued	391	44.1%	12	26.7%
Primary Reason for Early Termination or Discontinuation				
Non-compliance by Patient	2	0.2%	1	2.2%
Intolerable Adverse Event	236	26.6%	4	8.9%
Withdrawal Requested by Patient or Legal Representative	11	1.2%	1	2.2%
Unrelated Medical Condition	2	0.2%	1	2.2%
Administrative or Investigator Decision	1	0.1%	1	2.2%
Death on Study ^c	3	0.3%	0	0.0%
Infection	2	0.2%	1	2.2%
System Related (Pump/Catheter)	12	1.4%	1	2.2%
Ineffective Drug Therapy / Loss of Effect	98	11.1%	0	0.0%
Other ^d	24	2.7%	2	4.4%

a In this summarization, Patient 5519-25, who received placebo in the study of origin (95-001) and then ziconotide in a second study (98-022), is counted in the "never received ziconotide" column.

b Not applicable for patients participating in the ongoing Long-Term, Open-Label Clinical Studies.

c For Study 98-022, deaths were captured on the Adverse Event CRF page but not the Study

Termination CRF page. There were nine patient deaths in Study 98-022 which can be found in IT Patient Data Listing 2.2.

d Reasons (e.g., intrathecal catheter no CSF flow, catheter fell out prior to end of study, etc.) are listed in Appendix 2, IT Patient Data Listing 2.1.

Note: For all 155 patients in Study 95-002 and 5 patients in Study 98-022 who participated in more than one intrathecal study, this table only includes disposition data for the first study.

Note: Includes all data as of the cutoff date of 21 February 2000 for Study 95-002 and 23 February 2000 for Study 98-022.

Studies include: 94-004, 95-001, 96-002, 96-003, 96-010, 97-013, 97-015, and 98-022.

Data Source: Appendix 1, IT Table 1.2.

Among the 169 patents who entered a second study, 82.8% were discontinued at the time of the 120 day safety update. Thirty six percent of these patients discontinued due to adverse events.

Adverse events leading to study discontinuation from the IT ISS are discussed in SECTION 8.2.3.1.

SECTION 9.1.5 SERIOUS ADVERSE EVENTS

Serious adverse events were reported for 282 of the 887 patients (31.8%) who were exposed to ziconotide and included in the 120 day safety update. This includes the 240 of the 704 patients from the initial IT ISS and 28 of the 183 patients not previously included in the IT ISS.

Additionally, 41 patients with serious adverse events were reported in Appendix 6 of the 120 Safety update. This results in 323 of the 887 patients (36.4%) who ever received intrathecal ziconotide as having at least one serious adverse event

Table 9.2.8.5 (Vol. 5.002, p. 260) of the 120 day safety update lists the number and percent of patients with serious adverse events for the 704 patients from the IT ISS, the 887 patients from the IT 120 day safety update and 183 patients not including in the IT ISS. This table was reviewed. The frequencies of the individual adverse events and adverse events by body system in the IT 120 day safety update population are similar without any notable deviations to the IT ISS.

The constellation of terms used for encephalopathy still constitute the largest number of SAE's confusion 4 (0.5%), amnesia 1 (0.1%), confusion 31 (3.5%), delirium 2 (0.2%), encephalopathy 2 (0.4%). The terms used for the more severe forms of mental status changes, psychosis 6 (0.7%), hallucinations 2 (0.2%), paranoid reaction 1 (0.2%), manic reaction 2 (0.2%) also remain notable but without significant change from the IT ISS. Nausea 4 (0.5%), nausea and vomiting 5 (0.6%) and vomiting 4 (0.5%) are also when taken together, still important and again, unchanged from the IT ISS. The terms used to refer to ataxia including abnormal gait 4 (0.5%), ataxia 1 (0.1%), are unchanged, but incoordination was changed to 0 and cerebellar syndrome was changed to ischemia cerebellar

SECTION 9.1.6 ADVERSE EVENTS

There were 824 out of 887 patients with adverse events, 92.9% comparable to the 96.4% from the IT ISS. The frequency of the individual adverse events did not change appreciably from the IT ISS.

The effects of age group and gender remain clinically insignificant and unchanged from the IT ISS.

SECTION 9.2 EPIDURAL STUDIES

The information presented in SECTIONS 5 and 8 for the epidural studies was obtained from the 20-day safety update. The epidural studies were ongoing with little information available in the original NDA submission for this route of administration.

SECTION 9.3 INTRAVENOUS STUDIES

No new information from intravenous studies was submitted in the 120-day safety update.

SECTION 10.0 CONCLUSIONS

As discussed in Section 7.3, the results of studies 95-001 and 96-002 had to be reanalyzed excluding patients from earlier dosing regimens that differed from the final dosing regimen and did not reflect the manner in which ziconotide would be utilized in clinical practice. These two studies shared the same design for the initial titration period lasting 5-6 days. Additional patients had to be excluded from a site that was found on inspection to be unblinded. As a result of this reanalysis, for study 95-001, the primary efficacy variable, mean percent change in VASPI, failed to show a statistically significant difference between the ziconotide treated patients and the placebo treated patients, for either the ITT or evaluable populations. There were limited secondary endpoints provided with this reanalysis. The only secondary endpoint that reached statistical significance was the number of patients who met the sponsor's definition of a responder which was greater for the ziconotide treated patients. It is important to note that the number of patients available for comparison in the reanalysis representing patients treated in the planned manner of ziconotide use was only 34.

The results from the reanalysis for study 96-002 were less affected by the reanalysis. The mean percent change in VASPI at the end of the initial titration phase for evaluable and ITT populations and the category pain relief scale demonstrated a statistically significant improvement in favor of the ziconotide treated patients compared to placebo. However, the number of responders did not differ significantly between treatment groups.

Based on these results, there is only one pivotal trial that demonstrates efficacy, study 96-002. As the size of the treatment effect in study 95-001 was comparable to study 96-002, it appears that 95-001 was inadequate to demonstrate efficacy, possibly due to the small number of patients. Alternatively, ziconotide does not produce an adequate analgesic effect and the statistically significant results from study 96-002 are not reproducible or clinically meaningful.

There were other differences between the outcomes of these two studies based on the original analyses submitted with the NDA. Eighty three percent of patients completed the initial titration phase of 95-001 while only 48.2% completed the initial titration phase in 96-002. Older patients

(≥60 years) treated with ziconotide in study 95-001 demonstrated a greater difference in mean percent change in VASPI from placebo, while younger patients (<60 years) in 96-002 demonstrated a greater effect. Women demonstrated a greater placebo effect in 95-001, men in 96-002. Patients with a history of prior intrathecal morphine use treated with ziconotide differed less from placebo than IT morphine naive patients in 95-001, but more in 96-002. In 96-002, patients with neuropathic pain treated with ziconotide had a statistically significantly greater mean percent change in VASPI compared to placebo treated patients, but for patients with non-neuropathic pain, the difference did not reach significance. In 95-001, the AIDS patients with primarily neuropathic pain did not have a statistically significant treatment effect, while the cancer patients with mixed etiologies of pain did demonstrate a statistically significant treatment effect.

The populations in the two studies were different. Patients in 95-001 were enrolled with chronic malignant pain due to cancer or AIDS, in 96-002 with chronic nonmalignant pain. However, the differences in the outcomes of these two studies underscores the lack of a clear picture of the efficacy profile of ziconotide. The presence of effects of age, gender, or etiology of pain on the efficacy of ziconotide are unclear.

These uncertain efficacy results must be evaluated in the setting of the safety profile of ziconotide. Twice as many deaths occurred in patients who had been exposed to ziconotide than those only exposed to placebo. Three times as many patients experienced serious adverse events while receiving ziconotide than placebo. Serious adverse events involved the nervous system more than 3 times as often while receiving ziconotide than while receiving placebo and included dizziness, nystagmus, confusion and somnolence. Encephalopathy including confusion, abnormal thinking, amnesia, and somnolence as a serious adverse event was 8 times more common while receiving ziconotide than placebo. The encephalopathy was not explored with respect to duration or reversibility. Nausea and/or vomiting, dyspnea, hypotension and postural hypotension, and urinary retention as serious adverse events occurred only in ziconotide treated patients.

Patients receiving ziconotide were twice as likely to discontinue or terminate early from a study as patients receiving placebo. Of the 32% of ziconotide treated patients discontinuing early, 63.6% of patients did so due to adverse events. Of these ziconotide treated patients discontinuing early, 33.8% did so due to encephalopathy related adverse events or put another way, 11.3% of patients treated with ziconotide discontinued early from their respective studies due to an encephalopathy related adverse event. This included anything from somnolence to confusion, stupor, and auditory or sensory hallucinations.

As for adverse events in general, nausea and/or vomiting, encephalopathy, ataxia, somnolence, motor weakness, anxiety, muscle cramps, depression, agitation, hypotension, postural hypotension were all much more frequent in patients while receiving ziconotide. Fever, postural hypotension, nausea, vomiting, abnormal gait, confusion, dizziness, nystagmus, somnolence, urinary retention were all statistically more frequent in patients while receiving ziconotide than while receiving placebo.

Patients receiving ziconotide had more frequent elevations in CPK than patients receiving placebo, reaching 4.2% at study termination, and 11% when CPK at any visit was evaluated. Patients receiving ziconotide were more likely to have a rise in creatinine above 1.2 and greater than 0.3 mg/dl than placebo. The clinical and physiological significance of these changes is unclear.

In conclusion, there is insufficient evidence to confirm efficacy of ziconotide when used in the dosing range planned, while there is evidence of a considerable potential for toxicity.

SECTION 11.0 RECOMMENDATIONS AND REVIEWER SIGNATURE

NDA 21-060, ziconotide by intrathecal administration for the management of severe, chronic pain in patients for whom intraspinal therapy is warranted, should not be approved.

Sharon H. Hertz, M.D.