CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-060

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

NDA 21-060
Ziconotide

July 17, 2001

Biopharm Review:

No review required this cycle (2nd cycle).

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

Date: June 1, 2000

To: Dr. Cynthia G. McCormick
Director, Division of Anesthetic, Critical Care
and Addiction Drug Products (HFD-170)

From: Michael Klein, Ph.D. Michael Klein 6/1/00
Office of the Center Director
Controlled Substance Staff (HFD-009)

Through: Dr. Deborah B. Lederman 6/5/00
Director, Controlled Substance Staff (HFD-009)

Subject: NDA # 21-060. Ziconotide: Abuse Liability Review
Sponsor: Elan Pharmaceuticals

This memorandum is in response to the request of the Division of Anesthetic, Critical Care, and Addiction Drug Products, to review the abuse liability sections of NDA # 21-060.

SUMMARY

The abuse liability assessment volumes of NDA # 21-060 (ziconotide) were submitted to HFD-170 for review. The proposed indication for ziconotide is for the management of severe, chronic pain in patients for whom intraspinal therapy is warranted.

Pharmacodynamic interactions of ziconotide with morphine were evaluated. Unlike other calcium channel antagonists, in drug interaction studies with morphine, ziconotide did not shift the dose-response curve or exacerbate respiratory depression in preclinical studies. Ziconotide also had no effect on development of tolerance to the antinociceptive properties of chronically administered morphine.

The sponsor reported that respiratory depression was not observed in clinical trials with ziconotide, as is associated with μ-opioids. Nor was there an indication of tolerance development, signs and symptoms of withdrawal or craving upon discontinuation of ziconotide following short term or long term use in these trials.

The sponsor submitted the drug to the College on Problems of Drug Dependence (CPDD) for evaluation in a standard battery of abuse liability testing and found no abuse potential.

Tests that were conducted are described in the APPENDIX. The animal study results showed that ziconotide does not have a μ-opioid profile. Ziconotide did not substitute completely for morphine. There was no demonstration of dependence.

[redacted]

CONCLUSION:

1. The chemical formulation and its limited restricted availability in the clinical setting limits the likelihood for diversion or an illicit market that could be the source of the drug to be abused.
2. Ziconotide does not have the properties or characteristics of a μ-opioid.
3. Most study results are based upon animal abuse liability studies and published literature.
4. [redacted]

cc: Original NDA file 21-060
HFD-009/LeidermanD
HFD-009/MoodyC
HFD-009/KleinM
HFD-170/McCormickC
HFD-170/RappoportB
HFD-170/GovernaleL/SchumakerC

APPENDIX

CPDD Test Results:

1. Ziconotide (at concentrations of 1 nM to 30 μM) decreased twitch magnitude in the electrically-stimulated mouse *vas deferens* preparation. The concentration-effect curve for this response was not shifted by the μ-opioid antagonist, naltrexone (100 nmol). Thus, ziconotide is a potent, highly efficacious agonist in the mouse *vas deferens* preparation. These results suggest that ziconotide is not a μ-opioid, since naltrexone had no effect.
2. *In vitro* evaluation: In the binding affinity study using monkey brain cortex membranes, ziconotide failed to produce significant displacement of tritiated μ-, δ-, or κ-opioid receptor ligands. These findings were obtained in displacing the specific equilibrium binding of (a) 1.0 nM [^{3}H]DAGO (μ selective), 1.0 nM [^{3}H]pCl-DPDPE (δ-selective), and 1.5 nM [^{3}H]U69,593 (κ-selective) in membranes from monkey brain cortex suspended in 50 mM Tris.HCl buffer (pH 7.4) containing 150 mM NaCl. Weak binding (Ki 1190 nmol) to the δ-opioid receptor was observed. For the μ-receptor there was 1.5% inhibition at 6μM and for the δ- receptor there was 0.3% inhibition at 6μM. Ziconotide failed to produce significant displacement of any tritiated ligand.
3. Single dose suppression test determines the ability of a drug to suppress signs of withdrawal in rhesus monkeys which have been made dependent by chronic administration of morphine. Ziconotide (0, 0.25, and 1.0 mg/kg IV) in this test, produced a partial, dose-dependent reduction of the abstinence syndrome. A dose of 2.0 mg/kg was no more effective than the 1.0 mg/kg dose in attenuating withdrawal signs. Therefore, it appears that ziconotide cannot substitute completely for morphine. The lack of a clear dose-response relationship in this assay typically is not seen with opioids and suggests that the partial suppression of morphine withdrawal by ziconotide is nonspecific.
4. Drug Discrimination Test: Monkeys that are physically dependent on morphine were trained to discriminate between saline and naltrexone. Ziconotide was evaluated for its ability to block morphine withdrawal (i.e., substitute for morphine). After substitution of ziconotide for a daily morphine injection, selection of the naltrexone-appropriate lever is intended to indicate discrimination by morphine withdrawal differences, and selection of the saline-appropriate lever should indicate that the test drug has μ-opioid receptor agonist properties and can attenuate morphine withdrawal. Ziconotide did not attenuate the discrimination of morphine withdrawal at doses (up to 0.032 mg/kg IV).
5. Self-Administration: Ziconotide self-administration was evaluated in rhesus monkeys experienced in self-administration of alfentanil (N=3). Doses ranging from 1 ng/kg to 0.01 mg/kg IV were tested. There was no indication that ziconotide had any effects different from those produced by saline. Higher doses were not tested because of concerns about the drug's hypotensive effects.

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_____ § 552(b)(5) Draft Labeling

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW

NDA 21-060 **Submission Date:** 12/28/99 and 4/28/2000
Drug and Formulation: Ziconotide Preservative Free Injection for Intrathecal use, 100 µg/ml in 1, 2, 5 [redacted] ml fill vials.
Sponsor: Elan Pharmaceuticals, South San Francisco, CA 94080
Type of Submission: Original NDA, 1P **Reviewer:** Shinja R. Kim, Ph.D.

SYNOPSIS:

Ziconotide is the synthetic equivalent of a 25 amino acid polybasic peptide (ω-conopeptide MVIIA) found in the venom of the *piscivorous* marine snail, Conus magus; with a molecular weight of 2639 daltons. Ziconotide is the first of a new class of calcium channel blockers that selectively block neuronal N-type, voltage-sensitive calcium channels (VSCCs), which are involved in the mediation of pain. It is indicated for intrathecal (IT) use for the management of severe, chronic, nociceptive, and/or neuropathic pain of central (spinal or thalamic) and/or peripheral origin.

This NDA contains fourteen clinical trials (6, 6 and 2 studies for IT, IV and epidural routes, respectively) that provide PK information: three studies quantified drug in cerebrospinal fluid (CSF), fourteen studies measured plasma ziconotide, and one measured drug in the urine. Substantial effort has been made to characterize the concentration-time profile of ziconotide within the CSF, as it is the most accessible fluid in close proximity to ziconotide's putative site of action, *i.e.*, the dorsal horn of the spinal cord.

Ziconotide PK in CSF following IT infusion are of primary importance (for efficacy) (Study 97-013), whereas plasma exposure after IT dosing is considered to be secondary for efficacy, although important for systemic safety (Study Nos. 95-001, 96-002, 94-004, 95-002). The characterization of plasma PK following IV route of administration is necessary since ziconotide, which is injected intrathecally, is expected to be eventually recovered in plasma and eliminated further. Similarly, CSF and plasma PK of ziconotide after epidural dosing are of some value, only for characterization of drug disposition in a situation where drug intended for the IT space is inadvertently administered epidurally. Urinary excretion data after IV infusion is of minor significance since plasma concentrations are very low after IT infusion. Plasma and CSF samples from these studies were assayed using an RIA procedure with a quantification limit of [redacted] in plasma and CSF.

The summary review of this NDA from the Clinical Pharmacology and Biopharmaceutics perspective is shown below, with questions that are generally sought pertinent to section 6:

What was the logic behind the route of administration chosen [IT] for ziconotide?

The sponsor pointed out that this decision was made based on two reasons. (a) Significant hypotension accompanied IV dosing. (b) The site of action for analgesia was on the central side of the blood-brain barrier (dorsal horn of the spinal cord) and this peptide was expected to demonstrate poor CNS penetrability. Therefore, administration by IT route may be necessary for efficacy.

What are the current recommended management methods for chronic pain?

A brief outline of the World Health Organization (WHO) analgesic ladder is presented below as a stepwise treatment program.

Step 1: Nonopioid analgesics (e.g., nonsteroidal anti-inflammatory drugs) ± adjuvants.

Step 2: Weak opioids for mild to moderate pain (e.g., codeine and hydrocodone) ± nonopioids/adjuvants.
Step 3: Strong opioids for moderate to severe pain (e.g., morphine and hydromorphone) ± nonopioids/adjuvants.
Step 4: Neurostimulation and/or intraspinal therapy.
Step 5: Neuroablative procedures for pain unresponsive to the above.

Advanced pain therapy involves more invasive therapies (i.e., steps 4 and 5) for patients with pain that is not satisfactorily managed by systemic analgesics. However, treatment of chronic pain by systemic analgesics may be limited by side effects and/or by the development of tolerance (e.g., opioids). Therefore, ziconotide is likely to be used at step 4.

What is the proposed dose and how was this determined?

"Dosing should be initiated at no more than 0.1 μg/hr and titrated to patient response. The dose should not be increased more often than once in a 24 hour period and by not more than 0.1 μg/hr per increment. Dose increases in increments of less than 0.1 μg/hr are acceptable. Few patients respond to ziconotide doses above 2.4 μg/hr."(Draft labeling)

Study 97-013 was the pivotal study and the only study to characterize PK of ziconotide in CSF after an IT dose. The results of study 97-013 appear to support the efficacy of the product and the selected dosing regimen; however, the dose recommendation should be based on the established safety and efficacy of its use in humans, and the medical officer will review these issues based on all pivotal safety and efficacy studies.

Is the clinical trial(s) formulation the same as the to-be marketed?

All clinical trials conducted for this NDA used the to-be marketed formulation except studies with intravenous (IV) route of administration (there were 6 studies). Therefore only two studies with IV dosing, which are relevant to characterize PK of ziconotide in plasma, are reviewed.

Were the pharmacokinetics of the drug characterized adequately?

Ziconotide has been delivered via three routes of administration (IT, epidural and IV) and ziconotide concentrations have been quantified in three body fluids (CSF, plasma, and urine). The summary of the integrated pharmacokinetics (PK) from the three routes of administration are presented below;

1. ***Intrathecal Dose***

Cerebrospinal fluid (CSF): based on study 97-013.

- Following a 1-hr IT infusion of 1-10μg dose, CSF concentrations increased with dose but was not dose proportional.
- The CSF PK of ziconotide was variable.
- The clearance (CL) of ziconotide from CSF following IT administration (median 0.26, mean 0.38, range: 0.08-2.93 mL/min), was found to be equivalent to bulk rostral flow of CSF (0.35-0.37 mL/min). Ziconotide was distributed into an apparent CSF volume (median 99 mL) that was intermediate between spinal cord CSF volume (75 mL) and total CSF volume (140 mL). The median terminal elimination half-life in CSF was 4.5 hours (range: 2.9-6.5 hours).

Plasma:

- Plasma ziconotide concentrations following IT infusion (0.1-7.0 μg/hr doses, infused up to six days) were quantifiable in [redacted] of cases and exhibited mean concentrations of < 0.2 ng/mL.

- The mean and median plasma bioavailability following a one-hour IT infusion were < 10%.

2. Intravenous Dose

CSF: No information available.

Plasma:
- Ziconotide has been administered as an IV infusion to healthy men at rates up to 1000-fold greater than IT infusion rates (not all reviewed). Based on study 93-001, the average (range) CL, V_{ss}, and $t_{1/2}$ were 17 L/hr (12-26 L/hr), 30 L (18-40 L) and 1.3 hr (0.7-1.9 hr), respectively. Additionally, PK of ziconotide was linear and dose-proportional.

3. Epidural Dose

CSF:
- Following a one-hour epidural infusion of 1-20 μg of ziconotide, CSF PK appears to be nonlinear. The median CSF bioavailability of the epidural dose was generally < 1%, which was consistent with the existence of a capacity-limited transport system for ziconotide through meninges (which has been characterized in *in vitro* studies using primate meninges).

Plasma:
- Measurable plasma levels of ziconotide following chronic epidural infusion were quantifiable in about [redacted] of cases and were generally [redacted] (study 96-012).
- The $\%F_{plasma}$ following a one-hour epidural infusion ranged from [redacted], with a median value of 0.0% and mean of 26%, based on all samples, below and above quantifiable concentrations (study 98-021).

4. Disposition

- Preliminary analyses, based on selected subjects from the ziconotide data base, have suggested that renal or hepatic dysfunction had no effect on ziconotide disposition. However, the number of subjects was too small to make any definitive conclusion.
- Less than 1% of ziconotide is recovered intact in human urine following IV infusion.
- Primary degradation route for ziconotide is through ubiquitous peptidases that are present in most organs (*in vivo* rat study, 98-5037). On the other hand, *in vitro* incubation studies, 764-02654 and 93-5027 (these studies are for validation of RIA methods) suggest that no appreciable metabolism of ziconotide occurs within CSF or plasma. Therefore, it appears that degradation of ziconotide mainly occurs in tissues/organs.
- Ziconotide was 53% bound, nonspecifically, in human plasma over the concentration range of 1-10,000 ng/mL (RR764-03035).

Is PK-PD of ziconotide characterized and does this support the proposed dose?

- Traditional PK-PD modeling (e.g., CSF or plasma concentrations with PD) was not performed due to insufficient data, instead correlative analyses (Spearman Rank correlation) were conducted (e.g., relationship of PK parameters with efficacy variables, VASPI).
- Following IT infusion to chronic pain patients, CSF exposure (AUC and C_{max}) correlated with efficacy (Study 97-013).

- Ziconotide in plasma following IT infusions was not correlated with efficacy endpoints. Similarly, very little efficacy was observed following a one-hour epidural ziconotide infusion (Study 98-021).
- The dose recommendation should be based on the established safety and efficacy of its use in humans. Based on PK-PD (efficacy) results (i.e., 97-013), the sponsor's proposed dosing regimen seems to be appropriate. However, the safety/efficacy issues with ziconotide have not been evaluated by this reviewer (review by a medical officer).

What are the factors that are likely to affect the pharmacokinetics of ziconotide?

The sponsor did not prospectively study the effect of demographics, renal or hepatic dysfunction or interaction with other drugs on the pharmacokinetics of ziconotide, but performed statistical analysis (nonparametric) of the PK data based on selected patients from the clinical PK studies. The results are summarized as follows.

Demographics: Demographic factors (sex, race, age, height and weight) which may contribute to inter-patient differences in the PK of ziconotide are summarized below, however note that no definitive conclusions can be made because findings were based on a small number of patients.

Effect on CSF PK

- The CL of ziconotide following IT or epidural dosing was unaffected by race, height, weight, sex, and age based on limited number of patients.
- The literature describes increased CSF volume in adult males with increasing age, apparently due to cortical atrophy. Consistent with this physiologic change, the CSF distribution volume of ziconotide was significantly larger in males than in females following IT dosing of 1-10 μg.

Effect on plasma PK after IT or Epidural infusions

- Sex, age, race, height, and weight had no influence on plasma PK of ziconotide following IT or epidural dosing.
- Similarly, the plasma CL and $\%F_{plasma}$ of ziconotide following IT and epidural infusions were apparently unaffected by these demographic variables.

Effect on plasma PK after IV infusions

- Following high IV doses producing plasma ziconotide concentrations several orders of magnitude greater than those experienced after IT or epidural dosing, the CL of ziconotide from plasma was shown to decrease with increased age over the range of 19-49 years. Similarly, the terminal $t_{1/2}$ in plasma decreased with age (available data limited to males).
- No changes in plasma CL were apparent with race, height, or weight.
- Conclusions regarding sex differences in plasma PK at high exposures remain undefined.

Renal Dysfunction:

Renal dysfunction was defined, per the sponsor, by the occurrence of creatinine >2.0 mg/dL and/or BUN (blood urea nitrogen) >40 mg/dL at any time during participation in a ziconotide study. Seven individuals with renal dysfunction were identified (under these criteria) from studies 98-022, 95-001 and 96-002 (among investigated database, study Nos. 94-004, 95-001, 96-002, 95-002 and 98-002). However, plasma ziconotide concentration data was available only for 2 of the 7 patients, and neither of these patients had quantifiable plasma ziconotide. The sponsor stated that this analysis suggested that the impairment of function of this end-organ was unlikely to significantly impact the blood levels of ziconotide after IT dosing. However, this conclusion is premature since the number of patients

with renal dysfunction was too small. Note: Subjects with renal or hepatic dysfunction were excluded from studies 97-013, 98-021 or the IV PK studies.

Hepatic Dysfunction:

The criteria for hepatic dysfunction are defined, per the sponsor as meeting one or more of the following;

- ALT (SGPT) three-fold in excess of upper limit of normal
- AST (SGOT) three-fold in excess of upper limit of normal
- Total bilirubin >3.0 mg/dL

Fourteen individuals with the signs of hepatic dysfunction were identified from the ziconotide database (94-004, 95-001, 96-002, 95-002 and 98-002), but plasma sample concentration data was available only for 5 of the 14 patients. Among these 5 patients, ziconotide plasma concentrations were below limit of quantitation in 3 patients. In other 2 patients, ziconotide plasma concentrations were [redacted] and were within the same range as those of the other patients, with normal organ function. The sponsor stated that this result was expected for ziconotide since proteases and peptidases are broadly distributed throughout the body.

Overall, however, definitive conclusions regarding the impact of renal or hepatic impairment on ziconotide PK can not be made since the number of patients with hepatic or renal dysfunction was too small (even though, plasma ziconotide concentrations following IT infusion were low). In addition, differences in PK in patients with normal organ function *vs.* organ dysfunction based on one concentration (although steady state concentration) is inadequate.

Drug Interaction:

Patients were selected from participating clinical pharmacology studies who were concomitantly taking other drugs, which may exhibit potential influence on the PK of ziconotide. Then, plasma ziconotide concentrations from these patients were compared with those of patients who were receiving only ziconotide. Drugs that were considered for evaluation of potential influence on PK of ziconotide are listed below:

1. Drugs which reduce CSF formation – e.g., furosemide (3 patients), bumetanide (2 patients) and omeprazole (3 patients). The results show that furosemide use could possibly elevate CSF exposure of ziconotide and reduce CSF CL values (qualitatively).

2. Protease inhibitors including ACE inhibitors - e.g., HIV protease inhibitor (12 patients), lisinopril, benazepril and moexipril (1 patient each). The results show that plasma concentrations of ziconotide in these patients were similar to those who were taking none of these drugs.

3. Other Calcium channel antagonists – e.g., verapamil (6 patients), nifedipine (2 patients) and amlodipine (2 patients). The results were the same as #2.

Based on these data analyses, it can be concluded that there was no evidence of drug interaction with these drugs, except furosemide. However, overall, larger trials are required to confirm these observations.

Has the sponsor adequately validated the bioanalytical methodology used in the clinical trials of ziconotide?

The sponsor developed and validated RIA methods for the quantification of plasma and CSF ziconotide concentrations, but not for the human urine; ziconotide concentrations in the urine were measured by using the same (validated) RIA method for plasma. The limit of quantification was [redacted] in plasma or CSF, with linear range of [redacted] Specificity studies with ziconotide have not been performed with (validated) RIA method (due to no known cross-reactants available per sponsor). Precision and accuracy were within the agency's generally accepted criteria.

Is the NDA acceptable from a pharmacokinetic perspective?

CSF pharmacokinetics of ziconotide following single 1-hour IT and Epidural routes of administration using the to-be marketed formulation are characterized. However, the following items are considered as deficiencies from OCPB point of view:

- The assay method used has not been shown to be specific. Therefore, the assay method is not considered optimal.
- Steady state CSF PK of ziconotide is not characterized following IT or epidural (and IV) route of administration.
- Mass balance in humans is missing. Urine data to provide excretion information has been submitted. However, this data is considered not adequate, because (1) urine collection time (study design) was not sufficient. (2) analytical method used to quantify ziconotide concentration in urine was not validated.
- PK profiles for 'special populations' are not sufficiently evaluated.

However, overall, these deficiencies should be evaluated and some requirements waived taking into consideration the nature/chemistry of ziconotide as well as the indication and route of administration of this drug. It is difficult to radio-label this compound appropriately to evaluate mass balance. This further complicates the measurement of metabolites.

COMMENT TO THE SPONSOR:

A more specific assay method for ziconotide needs to be developed and used for future studies.

RECOMMENDATION:

The NDA 21-060 is acceptable from the Clinical Pharmacology and Biopharmaceutics perspective. Please forward the above comment to the sponsor.

Shinja R. Kim, Ph.D.
Division of Pharmaceutical Evaluation II

RD Signed by Ramana Uppoor, Ph.D.
FT [signature] for Ramana Uppoor 6/2/00
Ramana Uppoor, Ph.D.

cc: NDA (21,060), HFD-170 (Divisional File; Governale, Hertz), HFD-850 (Lesko), HFD-870 (Kim, Uppoor, HuangS), CDR (Barbara Murphy)

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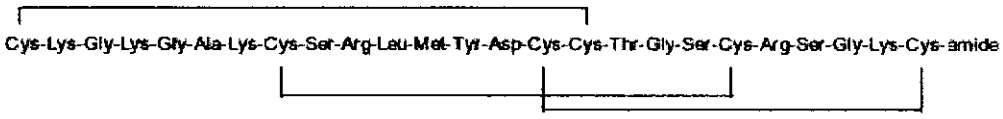
BACKGROUND

Ziconotide is a 25 amino acid, polybasic peptide containing three disulfide bridges with a molecular weight of 2639 daltons and a molecular formula of $C_{102}H_{172}N_{36}O_{32}S_7$. The amino acid sequence and disulfide bridging pattern are given below:



Ziconotide blocks the N-type calcium channel, which is one of at least 5 known subtypes of voltage-sensitive calcium channels (VSCCs), (L, N, O/P/Q, R, and T) that are expressed in neurons and other cells. Three pharmacologic effects of the N-type VSCC blocking action of ziconotide include the following:

- Blocks neurotransmitter release from primary afferent neurons in the superficial laminae (Rexed laminae I and II) of the dorsal horn, the site at which axons of first-order peripheral nociceptive afferents synapse with second-order afferent neurons.
- Modulates neuronal excitability by blocking N-type calcium channels on cell bodies and on dendritic shafts and spines, which may have an effect on persistent pain states associated with CNS hyper-excitability.
- Blocks neurotransmitter release from peripheral sympathetic efferents and directly reduces sympathetic tone (blood pressure).

Therefore, the primary route of ziconotide administration mode is IT in order to maximize analgesic effect and minimize systemic drug concentrations, which will curtail the potential for peripherally mediated adverse events primarily hypotension. The product is formulated as a sterile, preservative-free, isotonic solution for intrathecal (IT) administration via an appropriate, programmable microinfusion device after dilution to the appropriate concentration with 0.9% sodium chloride injection, USP.

Bioavailability (CSF): Injection into both the IT and epidural spaces is extravascular. Hence, drug may leave those spaces, migrate through blood vessel walls, and enter blood. Drug, which is injected into the epidural space, may also enter CSF after crossing the dura and arachnoid. Lastly, intravenously injected drug may cross the blood-brain barrier and enter CSF. Due to the existence of the blood-brain barrier, ziconotide (a relatively large, charged, hydrophilic molecule) must be injected directly into the CSF (IT) or adjacent to it (epidural), since it will only slowly and incompletely be transported there following intravenous injection. Unfortunately, CSF PK following IV infusion was not computed due to contamination of CSF samples with blood, per the sponsor (Study 94-001). In a PK study in dogs it was reported that CSF bioavailability was 0.01% following an IV bolus dose of 100 μg/kg ziconotide compared to IT dose, indicative of limited penetration of ziconotide into CSF (Study TY-96-019).

OVERVIEW OF HUMAN DOSING STUDIES

FORMULATION

Each mL of Trade Name contains 1 mg of ziconotide base with excipients. The excipients are listed along with their function in Table 1:

Table 1: Excipients

Component	Formulation	Function
Sodium Chloride, USP		
L Methionine, USP		
HCl, NF		
NaOH, NF		
Water for Injection, USP		

INTRATHECAL ADMINISTRATION

Six IT studies (97-013, 94-004, 95-001, 96-002, 96-003 and 95-002) involved the collection of ziconotide clinical pharmacology data. Study 97-013 characterized the CSF PK of ziconotide (single dose), whereas all of the studies (including 3 patients from study 97-013) evaluated ziconotide levels in plasma. All of these studies were performed in pain patients and five of the six studies (i.e., except 96-003) enrolled chronic pain patients.

97-013: The Part A was an open-label, pilot study that assessed the PK, safety, and analgesic profiles of ziconotide administered as a single one-hour IT infusion. Twenty-two patients were enrolled in the study and assigned to 1 μg, 5 μg, 7.5 μg, or 10 μg dose groups. CSF and plasma concentrations were collected for 48 hours following a one-hour infusion. Patients began at 0.1 μg/hr and could titrate up to 2.4 μg/hr. The open-label extension study, Part B, involved the administration of ziconotide by IT infusion for six days, and the primary objective was to explore whether efficacy or safety measures following a one-hour infusion (Part A) could predict outcomes following a continuous infusion (Part B).

Ziconotide PK in CSF: The results indicated that both $AUC_{\infty, CSF}$ and $C_{max, CSF}$ increased with increasing dose (however, 'PK linearity' could not be confirmed). The median CL was 0.26 mL/min, with a % CV of 150%, equivalent to the rate of CSF bulk flow in the adult humans (0.35 mL/min). The median V_d of 99 mL (170% CV) is intermediate between total CSF volume (140 mL) and spinal cord volume (75 mL). The mean half-life was 4.6 hr (20% CV). The CSF PK parameters derived from this Part A study are displayed in Table 2.

Ziconotide concentrations in Plasma: Only three patients (out of 23 patients) had plasma samples above the ziconotide assay limit of . The sponsor stated that three patients had $\%F_{plasma}$ (plasma bioavailability) values of (referenced plasma AUC_{∞} from Study 93-001), while that in others was 0.0% (no detectable concentration). Therefore, the median $\%F_{plasma}$ was 0.0%, with a mean ± SD of 8.4 ± 24.5%, and a range of following IT doses of 1 to 10 μg.

PK-PD: Effect-site PK-PD modeling was not performed (due to insufficient data), instead, Spearman-rank correlation coefficient test was carried out as a measurement of association of PK-PD relationship ($\alpha = 0.05$). The results are summarized as follows: (1) The CSF AUC_{∞} was well correlated with VASPID, SPID, and the TOTPAR scores. (2) Exhibited a trend in dose-related analgesic effect. (3) The CSF C_{max} results were similar to those of CSF AUC_{∞}, but the correlations

were not as robust. (4) Analgesic response occurred in 1/5 (20%), 2/8 (25%), 3/6 (50%), and 2/5 (40%) responders in the 1, 5, 7.5 and 10 μg dose groups, respectively. (5) Overall, a strong positive correlation was observed for the CSF exposure parameters, while dose (infusion rate) exhibited very little relationship to analgesic response.

Table 2: CSF PK following a single 1-hour IT dose (Study 97-013)

Dose (μg)	N		AUC_∞ (ng hr/mL)	CL (mL/min)	$t_{1/2}$ (hr)	Vd (mL)	Cmax (ng/mL)
1	5	Mean	83.6 ± 27.6	0.22 ± 0.06	5.3 ± 0.8	99.1 ± 36.5	16.4 ± 6.4
		Median	75.2	0.22	5.3	79.8	16.1
		Range		[redacted]			
5	8	Mean	318 ± 74.7	0.27 ± 0.06	4.5 ± 0.8	106 ± 29.5	68.2 ± 20.3
		Median	310	0.27	4.4	99.1	68.2
		Range		[redacted]			
7.5	6	Mean	608 ± 520	0.68 ± 1.11	4.4 ± 1.0	290 ± 520	132 ± 92.1
		Median	515	0.25	4.7	97.1	105
		Range		[redacted]			
10	4[a]	Mean	539 ± 205	0.34 ± 0.12	4.2 ± 0.8	121 ± 38.3	122 ± 47.5
		Median	497	0.34	4.2	124	118
		Range		[redacted]			
Overall	23	Mean	NA	0.38 ± 0.56	4.6 ± 0.9	155 ± 263	NA
		Median		0.26	4.5	99.2	
		Range		[redacted]			

[a] One patient of the five treated did not provide evaluable PK data.
NA = Not applicable.

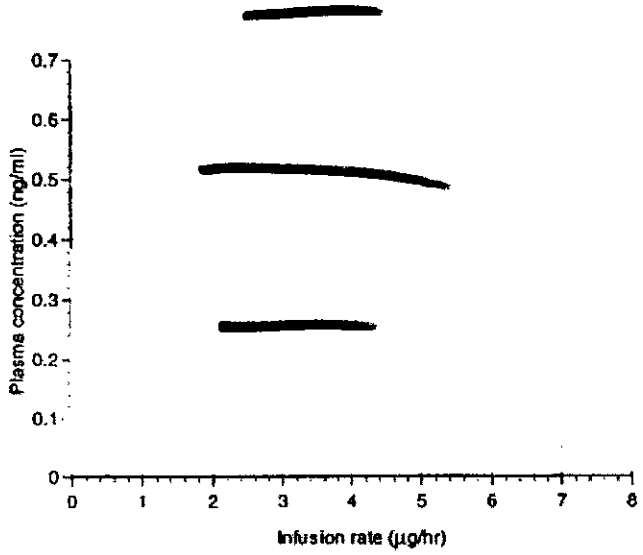
Part B: The predicted steady state C_{ss} in CSF averaged 43 ± 54 ng/ml (based on CSF CL rates of subjects, from Part A and their highest infusion rates). The results showed that this (predicted) C_{ss} was a poor indicator for PD (i.e., none of the efficacy variables with C_{ss} were statistically significant at $p = 0.05$).

95-001: This was one of the pivotal placebo controlled IT ziconotide Phase II/III efficacy and safety study in patients with chronic malignant pain. In the initial phase, patients received 5-6 days of IT infusion beginning at a dose of 0.1 μg/hr, and the infusion rate was periodically titrated upward to effect up to a maximum dose of 2.4 μg/hr. A plasma sample was obtained from patients on day 5 or 6 (one sample per patient). Fifty-six percent (28/50) of patients had plasma ziconotide levels below the limit of detection. The remaining 22 patients (44%) had concentrations ranging from [redacted] with average of 0.202 ± 0.497 ng/mL. The mean cumulative dose of ziconotide infused over 6 days was 42 ± 34 μg in the patients with levels below detection [redacted]
The corresponding values were 180 μg ± 210 μg (median: 96 μg, range: 31-880 μg) in patients with quantifiable ziconotide in plasma. On average, a higher cumulative ziconotide dose was observed in patients with measurable drug in plasma. Efficacy: The sponsor reported that the primary efficacy measure of % change in VASPI (Visual Analog Scale Pain Intensity) at the end of initial titration decreased by 53% from the baseline in patients treated with ziconotide, while that in patients treated with placebo the decrease was 18%. This difference was statistically significant.

96-002: This was one of the other pivotal IT ziconotide efficacy and safety study. The design was identical to Study 95-001, except that this study was carried out in patients with chronic non-

malignant pain. Ziconotide concentrations in plasma samples, which were obtained on Day 6, were below the limit of quantitation in 72/102 patients [redacted] and above the quantitation limit in [redacted] of patients. The average plasma concentration in these 30 individuals was 0.137 ± 0.138 ng/mL. Quantifiable values ranged from [redacted] and corresponding infusion rates ranged from 0.1 to 7.0 µg/hr. Both ziconotide infusion rate and cumulative ziconotide dose were statistically different between the two groups of patients with and without measurable drug in plasma ($p<0.0001$). Correlative analyses demonstrated that infusion rate and cumulative dose were equally good predictors of ziconotide exposure/concentration in blood ($p<0.0005$): Individuals with higher ziconotide infusion rates were more likely to exhibit quantifiable ziconotide in plasma, and the magnitude of the concentration was proportional to the infusion rate as shown in figure below.

Figure 1. Relationship between measurable Day 6 plasma concentration and infusion rate



Efficacy: The sponsor reported that the primary efficacy measure of % change in VASPI at the end of initial titration decreased by 30.7%from the base line in patients treated with ziconotide, while that in patients treated with placebo the decrease was 6.2%, which was a statistically significant difference.

95-002: This was an open-label study in which patients who had successfully participated in a previous ziconotide studies (95-001 and 96-002) were eligible. During the first 30 days, the patient was maintained on his/her fixed optimal therapeutic dose. Infusion rates ranged from 0.1 to 2.4 µg/hr. After the initial 30-day fixed dose period, dose increases were not to exceed a 2-fold increase every 12 hours. Blood samples for determination of ziconotide concentration were drawn 48 hours after the first maintenance period was initiated. The study is currently ongoing, so this analysis represents an interim look at the data. The mean ± SD day on which the plasma was taken was 45 ± 43 days (median of 29 days), with a range of 2 to 275 days. Patients had received an average of 565 µg of IT ziconotide, with a range of [redacted] at the time the plasma sample was taken. Eighteen samples (13%) were above the quantitation limit, and the quantifiable concentrations averaged 0.0932 ± 0.0476 ng/mL. The hourly infusion rate of the patients presenting with quantifiable ziconotide in plasma averaged 0.28 ± 0.15 µg/hr (ranged [redacted]), while that of

non-quantifiable plasma ziconotide averaged 0.45 ± 0.50 µg/hr (range of [redacted]). The range of hourly IT infusion rate of the patients presenting with and without quantifiable ziconotide in plasma were of opposite trend, suggesting that infusion rate was not a good predictor for exhibiting quantifiable plasma ziconotide (however, this is only interim data). Over all, the percentage of quantifiable concentrations, as well as the magnitude of the concentrations observed here were similar to those following IT infusion for 5 or 6 days (Study Nos. 95-001 and 96-002). This interim data suggests that plasma exposure is low following IT infusion.

94-004: This was an open-label, rising -dose study in patients with chronic intractable pain. Thirty-one patients were enrolled in this trial that continued up to 7 days. The starting dose was 0.3 ng/kg/hr and titration to maximum dose of 300 ng/kg/hr (21 µg/hr for a 70 kg person). Of the 23 patients for whom plasma samples were obtained during ziconotide infusion, 10 had concentrations ranging from [redacted] (43% of samples). The average infusion rate of the patients reporting quantifiable ziconotide in plasma was 130 ± 110 ng/kg/hr (9.1 ± 7.7 µg/hr for a 70 kg person).

96-003: This was a pilot, phase II, randomized, placebo-controlled study of IT administered ziconotide in post-operative analgesia. Patients received an infusion of placebo or ziconotide at a rate of 0.7 or 7.0 µg/hr for 3 days. In the low dose group, 20% of plasma samples contained ziconotide at the end of the infusion (mean of detectable levels = 0.065 ng/mL), whereas samples from the entire 7.0 µg/hr group had quantifiable drug (average = [redacted]). Therefore, it appeared that higher infusion rates were associated with a greater occurrence of quantifiable ziconotide in plasma.

EPIDURAL ADMINISTRATION

Two epidural ziconotide studies were performed. Study No. 98-021 characterized the CSF PK of ziconotide (single dose), whereas both studies, 98-021 and 96-012, characterized the plasma concentrations of ziconotide following epidural dosing.

98-021: This was an open-label, pilot study in 42 subjects to assess the PK, safety, and analgesic profiles of ziconotide administered as a single one-hour epidural infusion. The subjects were assigned to 1, 2, 5, 10 or 20 µg dose groups.

CSF PK: The CSF PK of ziconotide demonstrated nonlinearity and dose-dependence, purportedly due to saturation of the ziconotide transport system from the epidural space and across the meninges (i.e., capacity-limited carrier-mediated transport of ziconotide from the epidural space into CSF). The summarization of CSF PK is presented in Table 3.

Plasma PK: Plasma PK analyses were based on 16 subjects since the plasma ziconotide concentrations were below limit of quantitation at all times in 23 subjects (59% of subjects, total n=39). Ziconotide plasma PK was linear. The plasma CL/F was constant (median 398 mL), as was Vd/F (median 48 L). The median plasma $t_{1/2}$ was 1.7 hours and median T_{max} was 1.5 hours. The $\%F_{plasma}$ ranged from [redacted], with a median value of 0.0% and mean of 26% (based on all samples, below and above quantifiable concentrations). These results support the lack of a saturable transport system involved in the absorption of ziconotide into blood capillaries of the spine.

PK-PD: The results from the PK-PD analysis are summarized as follows: (1) Very little efficacy was observed in this trial, probably because little ziconotide was transported into CSF following the short one-hour epidural infusion. No dose-response relationship was observed with these efficacy endpoints. (2) Neither the CSF C_{max} nor AUC_{∞} were positively-correlated with any efficacy endpoints. (3) The overall efficacy PK-PD findings are considered to be of little value and are attributed to low and variable CSF exposure following the 1-hour epidural ziconotide infusion.

Table 3: CSF Ziconotide Pharmacokinetics Following Epidural Infusion (Study 98-021)

Parameter (units)	Dose Group					All doses (N=14)
	1 µg (N=1)	2 µg (N=1)	5 µg (N=2)	10 µg (N=5)	20 µg (N=5)	
AUC/D (ng•hr/mL/µg)						
mean ± SD	6.27	0.807	0.365 ± 0.410	0.384 ± 0.607	0.053 ± 0.052	0.714 ±1.65
range			(0.075-0.655)	(0.057-1.47)	(0.005-0.131)	0.0052 - 6.27
median (N)	6.27 (1)	0.807 (1)	0.365 (2)	0.148 (5)	0.041 (5)	0.106 (14)
C_{max}/D (ng/mL/µg)						
mean ± SD	1.63	0.226	0.137 ± 0.123	0.117 ± 0.206	0.0271 ± 0.0286	0.203 ± 0.432
range						
median (N)	1.63 (1)	0.226 (1)	0.137 (2)	0.026 (5)	0.0099 (5)	0.046 (14)
T_{max} (hr)						
mean ± SD	2.0	1.5	1.8 ± 0.4	2.3 ± 1.0	2.2 ± 1.0	2.1 ± 0.84
range						
median (N)	2.0(1)	1.5(1)	1.8 (2)	2.0 (5)	2.0 (5)	2.0 (14)
CL/F (mL/min)						
mean ± SD	2.66	20.7	124 ± 139	144 ± 108	1140 ± 1340	480 ± 908
range						
median (N)	2.66 (1)	20.7 (1)	124 (2)	112 (5)	406 (5)	165 (14)
$\%F_{csf}$ (%)						
mean ± SD	8.83	1.14	0.51 ± 0.58	0.54 ± 0.86	0.07 ± 0.07	1.00 ± 2.33
range						
median (N)	8.83 (1)	1.14 (1)	0.51 (2)	0.21 (5)	0.06 (5)	0.15 (14)
V_d/F (mL)						
mean ± SD	420	6050	3260	47,900 ± 46,100	34,100 ± 30,900	32,700 ± 38,100
range						
median (N)	420 (1)	6050 (1)	3260 (1)	25,100 (5)	22,700 (3)	23,800 (11)
$T_{1/2}$ (hr)						
mean ± SD	1.82	3.38	1.48	3.63 ± 1.77	1.53 ± 0.83	2.71 ± 1.57
range						
median (N)	1.82 (1)	3.38 (1)	1.48 (1)	2.85 (5)	1.97 (3)	2.44 (11)

N = number of patients with quantifiable ziconotide in CSF for whom this PK parameter could be calculated.

96-012: In this pilot study, patients were treated with placebo or ziconotide at doses of 0.7 µg/hr or 7.0 µg/hr by epidural infusion for 48 hours, at which point plasma was sampled. Quantifiable concentrations of ziconotide were present in 5 of the 9 low-dose (0.7 µg/hr) and in 6 of 8 high-dose (7 µg/hr) ziconotide patients. Plasma ziconotide concentrations ranged from [redacted] with average of [redacted] The data from this pilot study did not support the conclusion that higher infusion rates are associated with a greater incidence of quantifiable plasma ziconotide.

Summary of the CSF and plasma bioavailability of ziconotide results following IT and epidural dose is shown in the Table 4;

Table 4: CSF and plasma bioavailability of ziconotide after IT and epidural dose

Study No.	N	Route	Matrix	%F				PK
				Median	Mean	Min	Max	Linear
97-013	23	IT	plasma	0.0	8.4	[redacted]		yes
98-021	14	epidural	CSF	0.15	1.00			no
98-021	16	epidural	plasma	0.0	26.0			yes

*Exceeds 100% because calculated across studies.

INTRAVENOUS ADMINISTRATION

Six IV ziconotide studies were performed to characterize PK using an early formulation (i.e., not the same as the to-be marketed fromulation). Hence, only two studies, 93-001 and 94-002, are reviewed: $\%F_{plasma}$ was based on 93-001 and urine data was obtained from 94-002. Plasma samples were collected from all studies, and CSF samples were collected from the Study 94-001. However, CSF PK was not calculated from this study due to contamination with blood (per the sponsor), therefore this study was not reviewed.

93-001: This was the first ziconotide study in humans, and the objectives were to characterize the PK and safety of escalating IV infusions of ziconotide in healthy male adults. There were 4 dose groups (0.3, 1.0, 3.3 and 10 μg/kg/24 hr) with 6 subjects per group. Results based on all groups except the 0.3 μg/kg/24hr (plasma concentrations were not measurable in 5/6 volunteers) are summarized as follows: (1) Overall CL exhibited a mean value of 17 L/hr (range 12-26 L/hr). (2) The overall mean V_{ss} was 30 L (range 18-40 L). (3) Overall $t_{1/2}$ averaged 1.3 hr (range 0.7-1.9 hr). (4) PK of ziconotide was linear and dose-proportional. Note: The data from this study was used to calculate the fraction of IT or epidural dose which was recoverable in plasma ($\%F_{plasma}$).

94-002: Patients undergoing coronary artery bypass graft (CABG) were administered IV infusions of ziconotide in a placebo-controlled, double-blind, randomized, rising-dose tolerance study. Sixteen patients received a one-hour loading infusion (range 2.6 to 10.4 μg/kg/hr) followed by a maintenance infusion for up to 11 hours (range 0.62 to 2.5 μg/kg/hr). Average values for CL, $t_{1/2}$ and V_{ss} were 10.7 ± 1.7 L/hr, 1.3 ± 0.7 hour and 11.5 ± 3.3 L, respectively. CL and V_{ss} were significantly different than those of healthy volunteers (Study 93-001). The sponsor stated that these differences are probably associated with the abnormal physiologic condition of patients during CABG surgery (hemodilution, hypotension and hypothermia) as well as age effect (the CABG patients were substantially older than the healthy volunteers in 93-001).

Urine data: Of the 24 urine samples collected, 18 were analyzed. The concentration of drug in urine ranged from nondetectable to [redacted], with a mean concentration of 0.24 ng/mL. The corresponding plasma concentrations ranged from [redacted] The average percentage of ziconotide recovered in urine was [redacted] and the renal CL was < 0.1% of total CL following IV infusion. However in interpretation of the data one needs to be cautious due to study design and assay problems (See individual study 94-002 review).

Summary results of quantifiable plasma concentrations following IT and epidural ziconotide infusions are presented in Table 5.

Table 5: Plasma concentrations after IT and epidural infusions

Study No.	Infusion Rates µg/hr	Route	No. of PK Patients[a]	>QL %Samples	>QL %Patients	Mean	Median	Quantifiable Concentrations (ng/mL) Min	Max
95-001	0.1–14.1	IT	50			0.165	0.0681		
96-002	0.1–7.0	IT	102			0.137	0.0681		
94-004	0.7–7.0	IT	24			1.05	0.747		
95-002	0.04–2.7	IT	80			0.0932	0.073		
96-003	0.7–7.0	IT	16			0.174	0.111		
97-013	1.0–10.0[b]	IT	23			0.0745	0.061		
98-021	1.0–20.0[b]	Epidural	39			0.178	0.141		
96-012	0.7–7.0	Epidural	17			NA	NA	NA	

NA = Not available.

[a] Number of cases providing PK data may have differed from number of patients in the study.

[b] One-hour infusion implies that concentrations are not at steady-state; all other infusions were ≥48 hours.

IMPACT OF DEMOGRAPHIC FACTORS ON PK OF ZICONOTIDE

Demographics: Demographic factors (sex, race, age, height and weight) which may have impact on ziconotide exposure in CSF and plasma were examined in 7 studies (97-013, 95-001, 96-002, 94-004 by IT dose; 98-021 by epidural dose; 93-001 and 93-002 by IV dose). The results are summarized below:

GENDER

CSF PK: The results based on studies 97-013 and 98-021 are summarized as follows;

- Study 97-013 (IT) employed nearly equal number of males and females out of a total of 23 subjects. Sex was significantly related to CSF V_d ($p = 0.0373$). The median apparent CSF volume in males was 127 mL (range: 61-1350 mL) while that in females was 87 mL (range: 34-164 mL). The sponsor stated that this result could be due to two reasons (based on literature): (1) Males generally have larger bodies with larger brains so more fluid is needed to cover their brain matter. (2) Male brains atrophy at a faster rate than do female brains as aging proceeds, leaving more intracranial space to fill with fluid in order to maintain pressure.
- Sex was not associated with any difference in other ziconotide CSF PK parameters including CL. Therefore, gender difference in V_d seems to have minimal impact for IT dosing, because CSF CL determines the steady state CSF concentration following IT dosing.

Plasma PK: Comparison was made based on (IT dose) studies 95-001, 96-002 and 94-004 (detectable plasma concentration found in 37 males and 32 females). The data revealed no apparent differences between males and females. Sex was not associated with any difference in ziconotide plasma PK parameters.

AGE

CSF PK: Patients in the study 97-013 had an average age of 48 years (range: 31-65 years; n=1 with 65 years), and the data showed that none of the CSF PK parameters were significantly associated with age at the $p = 0.05$ level. The best correlation was between CSF volume and age ($p = 0.1277$). This relationship possibly indicates a trend toward increasing CSF volume with age.

Plasma PK:

- Based on 69 patients (n=16 with age ≥ 65 years) with mean age of 55 years (IT dose in study nos. 95-001, 96-002 and 95-004), there were no significant differences as a function of age.
- In Phase I study 93-001 (IV administration) in 40 healthy male volunteers, age ranged between 19 and 49 years. The correlations indicated that individuals with increased age had longer $t_{1/2}$ of ziconotide in plasma ($R = 0.63$, $p = 0.0073$). Changes in CL and V_d were not observed.
- In study 93-002 (IV administration), the age range studied was between 19 and 45 years (n = 56; healthy male volunteers). Correlative analyses suggested that the volunteers demonstrated reduced CL with increased age ($R = -0.33$, $p = 0.0325$). Related findings were a longer elimination $t_{1/2}$ of ziconotide in plasma ($R = 0.43$, $p = 0.0043$) and a higher dose-normalized C_{ss} ($R = 0.36$, $p = 0.0192$).

Overall, it appears that increase in age causes increase in $t_{1/2}$ of ziconotide in plasma. There were only 16 (detectable plasma levels; IT dose) geriatric (≥ 65 years old) patients in the ziconotide database and very few plasma samples were obtained. Therefore, definitive conclusion can not be made with respect to PK differences between geriatric and non-geriatric patients based on this data.

RACE

Effect of race on CSF and plasma PK: The number of subjects for the CSF PK evaluation were 31 Caucasians and 7 non Caucasians, and correspondingly for the plasma PK were 128 for Caucasians and 22 non Caucasians. The results showed that no significant differences were observed among different races (however this observation can not be applied for general population because this observation was based on small number of samples).

HEIGHT

CSF PK:

- In study 97-013, analyses of the effect of height on CSF PK were based on 23 patients whose height ranged from 59-74 inches. The correlations revealed no significant associations at the $p = 0.05$ level.

Plasma PK:

- Both, IT (95-001, 96-002 and 95-004) and epidural infusion (98-021) studies showed that height did not affect ziconotide concentrations in plasma.
- Following an IV study (93-001), height had significant relationship with Css/D ($R = -0.63$, $p = 0.0015$) and CL ($R = 0.52$, $p = 0.0330$). Height ranged from 148-184 cm in these subjects (healthy volunteers). These data suggest that taller individuals have increased plasma CL of ziconotide and reduced steady-state ziconotide concentrations after a 24-hour infusion of study drug. The sponsor stated that the reason for the significant correlations is the small sample size and nonrandom assignment to groups. Note: C_{ss} (not dose-normalized) failed to reveal a relationship with height ($p = 0.2955$).
- No statistically significant relationships were observed between height and plasma PK parameters in another IV study (93-002). The sponsor stated that the combined results lead to the expectation that ziconotide PK in CSF and plasma are likely to be unaffected by height.

WEIGHT

CSF PK:

- None of the correlation coefficients showed significant associations with weight in studies 97-013 (range: 110-266 pounds) or 98-021 (range: 123-258 Lbs.).

Plasma PK:

- No statistically significant correlations of plasma PK parameters and weight were revealed in studies 98-021, 95-001, 96-002, 95-004 or 93-001.
- In 93-001 (23 subjects), the correlations showed that CL_{ss} increased with increasing weight ($R = 0.59$, $p = 0.012$). The overall study mean CL_{ss} was 16.8 L/hr with a range of individual values of 12.0–22.6 L/hr. In study 93-002 (42 subjects), no statistically significant findings were revealed in the correlative analysis with CL_{ss} ($R = 0.14$, $p = 0.37$). The sponsor concluded that plasma CL following high IV dose showed no clinically significant changes with weight.

NONCLINICAL STUDIES: The following information is from the sponsor's report (not reviewed except plasma protein binding and red blood cell partitioning).

Plasma protein binding and red blood cell Partitioning: Ziconotide plasma protein binding and the blood partitioning were characterized in *in vitro* studies including human plasma (Study Nos. [redacted] 764-03035, [redacted] 43767 and [redacted] 48031). The results can be concluded as follows: (1) Nonspecific binding was negligible. (2) The mean % of ziconotide specifically bound to human plasma proteins was 53.3% (ranged 50-58%) over the range of 1.0-10,000 ng/mL (53.6% in rats and 62.1% in dogs). (3) About 40% of ziconotide in whole blood partitions into red blood cells in all species studied. All available data for red blood cell partitioning and plasma protein binding of ziconotide suggest that these phenomena are nonspecific and that displacement from any of these sites, if it occurs, is unlikely to significantly impact the PK of ziconotide since protein binding is low.

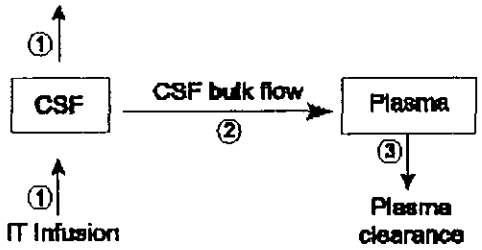
Distribution studies: Central nervous system tissue Flux: *In vitro* study, 98-5028, was performed to evaluate the binding of [^{125}I]-ziconotide to meningeal tissues and the permeability of [^{125}I]-ziconotide through the spinal meninges using monkeys. The results showed that (1) [^{125}I]-ziconotide bound with low affinity to sites determined to be specific to a ziconotide analogue in both pia-arachnoid and dura membrane homogenates. (2) Diffusion of [^{125}I]-ziconotide through intact meninges (dura-arachnoid-pia) was nonlinear and occurred in two phases, an early phase (0-2 hours) and a late phase (3-5 hours). The dura flux was linear with an IC_{50} of 0.7 μM (1820 ng/mL). The pia-arachnoid flux was nonlinear and the flux changed over time, exhibiting an average flux of 48 μM (125,000 ng/mL). Also in vivo microdialysis of ziconotide in the rat hippocampus was performed in order to determine the diffusion of the peptide in the extracellular space (Study No. 98-5037). For these studies [^{125}I]-ziconotide was perfused into the hippocampus for 2.5 hours at a concentration of 270 μM (700,000 ng/mL). Approximately 80% of infused radiolabeled ziconotide remained within 0.5 mm of the dialysis probe, and all of the detectable radioactivity was within 1 mm of the probe, indicating only limited diffusion of ziconotide within the brain's extracellular space when administered in this manner. Overall, these results suggested that ziconotide bound to, and was transported through, mammalian meninges by a capacity-limited transport system.

Animal metabolism studies: The expected consequence of the metabolism of ziconotide is degradation to individual amino acids. Numerous peptidases are likely to act on ziconotide (literature search). The metabolism of ziconotide was studied in brain and plasma after IV administration of [^{125}I]-ziconotide to rats (Study 98-5037). The time-course of intact [^{125}I]-ziconotide in plasma and brain after IV injection showed a rapid decrease after 20 minutes, to undetectable levels 2-24 hours

after injection. Significant amounts of [^{125}I]-ziconotide and free [^{125}I]-tyrosine, as well as smaller amounts of unlabeled material, were found in both plasma and brain. Stable, discrete proteolytic remnants were not observed in plasma or blood. These findings indicate that ziconotide is cleaved endogenously in the brain at multiple sites via multiple peptidases to yield its constituent amino acids. Also in that study, [^{125}I]-ziconotide was infused by a microdialysis probe to rat hippocampus for two hours to further characterize the metabolism of ziconotide in rat brain. The metabolism of ziconotide in the brain after dialysis was similar to that seen in brain after IV administration of the drug (multiple peptide fragments). The proportion of administered radioactivity recovered as intact drug increased with dose, suggesting that degradation of ziconotide in brain was rate-limiting at very high concentrations.

Expected modes of ziconotide degradation (study NC0201): According to the sponsor, protein drugs appear to be developed with little knowledge about the sites of metabolism (e.g., site of cleavage, the order of hydrolytic degradation sites or the nature of the peptidases involved), unlike small molecule drugs whose exact metabolic pathways are known, (i.e., cytochrome P450 3A). Thus, for protein molecules, it is generally accepted that after the first specific hydrolysis occurs, further degradation is likely to occur by relatively nonspecific events (i.e., proteolysis by endopeptidase and exopeptidase) proceeding through to complete digestion. The sponsor indicated that this kind of degradation is supported by studies, 98-5037, 764-02654, 93-5027, and concluded that ziconotide was cleaved endogenously, at multiple sites via multiple peptidases to amino acids, although exact degradation sites for ziconotide are not known. The sponsor also stated that the complete characterization of the proteolytic pathway has only been successfully accomplished for peptides containing 1-2 internal cleavage sites (Newcomb, *et al.*, 1991), and ziconotide can generate up to 45 linear fragments.

Renal Excretion: Proteins with size < 25,000 Da, are filtered through glomerular capillaries. The size, conformation, and charge of the protein are important contributors to the magnitude of renal elimination for that protein. After glomerular filtration, the protein is delivered to the proximal tubule. The protein is then rapidly endocytosed and hydrolyzed to constituent amino acids which are then transported to the interstitial compartment. The amino acids are then reabsorbed into the systemic circulation. For most peptides, and for ziconotide (Study No. 94-002), <1% escapes into urine. It is thought to be nearly impossible to saturate the renal elimination processes for small molecular weight proteins. In general, because of the efficient renal peptide recovery system, urinary excretion provides a significant underestimation of renal CL. Additionally, the very low $\%F_{plasma}$ following IT infusion, probably precludes a significant role for renal clearance. Fate of Ziconotide after IT infusion is shown in figure below: routes 1, 2 and 3 represent diffusion, CSF bulk flow (to blood) and systemic clearance, respectively.



ANALYTICAL METHODOLOGY

Radioimmunoassay (RIA) was developed to characterize ziconotide PK in the clinical pharmacology studies. The assay was validated for human plasma and CSF, but not for human urine. Table 6

summarizes information on the limit of quantitation, analytical range, and specificity of the RIA method.

Table 6: *In Vivo* Ziconotide analytical methods summary (PK studies)

Clinical Study No.	Submission Date	Body Fluid Matrix	Route	Method	Assay Sensitivity ng/mL	Assay Specificity
97-013	3/10/98	CSF	IT	RIA		
		plasma	IT	RIA		
94-004	6/30/94	plasma	IT	RIA		
95-001	2/15/96	plasma	IT	RIA		
95-002	2/15/96	plasma	IT	RIA		
96-002	7/23/96	plasma	IT	RIA		
96-003	7/10/96	plasma	IT	RIA		
98-021	8/28/98 10/2/98	CSF	epidural	RIA		
		plasma	epidural	RIA		
96-012	8/15/97	plasma	epidural	RIA		
93-001	3/11/93	plasma	IV	RIA		
93-002	10/13/93	plasma	IV	RIA		
93-003	2/8/94	plasma	IV	RIA		
94-001	6/8/94	plasma	IV	RIA		
		CSF	IV	RIA		
94-002	6/17/94	plasma	IV	RIA		
		urine	IV	RIA		
95-004	11/22/95	plasma	IV	RIA		

The RIA applied to these samples is based on the ability of unlabeled ziconotide to compete with ^{125}I-ziconotide for antibody binding sites.

Ziconotide incubated in rat brain has been shown to exhibit numerous degradation products, and not one "primary" metabolite (Study 98-5037). It is not known whether any particular ziconotide proteolytic cleavage product cross-reacts in this assay. The sponsor stated that "it is unlikely that the assay quantifies degradation products of ziconotide, since protease digestion (hydrolysis) commonly results in loss of tertiary (three-dimensional) structure, which would preclude antibody binding to ziconotide. Nevertheless, since specificity studies with ziconotide hydrolysis products have not been performed with this assay, the results presented here may represent combined parent molecule and partially digested degradation product. Thus, the RIA results should be interpreted to be ziconotide concentration equivalents." All of the data reported in the NDA represents total drug concentrations and unbound drug was not quantified in any study. Precision and accuracy are determined by replicate analyses of human plasma quality control pools prepared at three concentrations spanning the calibration range. Precision is measured as the % coefficient of variation (%CV) of the set of values determined for each pool. Accuracy is expressed as the % difference of the mean value for each pool from the theoretical concentration. The mean for each quality control pool was calculated from runs. The acceptance criteria were determined by taking ±10% of the mean or ±2 standard deviations, whichever was greater.

ANTI-ZICONOTIDE ANTIBODIES: Ziconotide is a peptide of a nonprimate species and therefore is capable of eliciting an antibody response in humans which would likely alter its PK in plasma. Serum IgG and IgE antibody levels were measured in samples from healthy volunteer subjects and patients. An RIA method was applied for the detection of anti-ziconotide IgE antibodies. An ELISA method was used for the detection of IgG antibodies. Table 7 summarizes information on the limit of quantitation, analytical range, and specificity of the RIA method and presents the human studies that provided samples to which the RIA or ELISA methods were applied. According to the sponsor, no elevations of ziconotide specific IgG or IgE antibodies were detected.

Table 7: Antibody detection analytical methods summary (PK studies)

Clinical Study No.	Submission Date	Method	Measures	Assay Sensitivity	Assay Specificity
97-013	3/10/98	RIA			
		ELISA			
95-002	2/15/96	RIA			
		ELISA			
93-001	3/11/93	RIA			
		ELISA			
93-002	10/3/93	RIA			
		ELISA			

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Note: Strikeouts and underlined text indicate this reviewer's suggested preliminary labeling comments (deletions and additions respectively).

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APPENDIX

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97-013: A Phase II, Single Center, Open-Label Pilot Study of Ziconotide (SNX-111) Administered Intrathecally by Bolus Injection (1-hour Infusion) to Patients with Chronic Pain (Part A), with an Optional Open-Label 6-Day Intrathecal Infusion (Part B)

Reference: Volume 58 – 63
Investigators:
Study Location:

Formulation: The lot number of ziconotide and diluent used in this study were IIIV14B and IIIV15B, respectively.

Objective: The main objective of this two part study was to assess the pharmacokinetics (PK), safety, and analgesic profiles of escalating single bolus doses of ziconotide administered intrathecally as a short (1-hour) infusion to patients. The objective of part B was to explore whether efficacy or safety measures following a 1-hour infusion (part A) could predict outcomes following a 144-hour IT infusion.

Study Design: This was a Phase II, single center, open-label, pilot study in subjects (age ≥ 18 years) with chronic pain of a neurological basis or chronic pain resulting from an underlying malignant condition (e.g., cancer or AIDS) and/or its treatment. Twenty-two patients were enrolled in study-part A and assigned to 1 μg, 5 μg, 7.5 μg, and 10 μg dose groups. Two patients who received the 5 μg dose were subsequently re-enrolled and received the 7.5 μg dose (total of 24). All patients within each cohort received the same dose as 1-hour, 1-ml infusion followed by a saline flush to ensure complete administration of the entire dose. Any patients who received ziconotide in one of the first four cohorts could elect to participate in the final dosing cohort after 1-week washout period. The ziconotide dose used in the final cohort was to be selected based on safety and efficacy responses to previous ziconotide doses. CSF samples were obtained through the intrathecal catheter placed for study drug administration (following a saline flush) or through the catheter access port. After completion of the 1-hour infusion, patients were evaluated with periodic pain assessments while awake for 48 hours. Except for the first 2 hours after ziconotide administration, patients continued to receive their current continuous regimen of systemic analgesics. Concomitant intrathecal or epidural medications were not permitted for the entire duration of the study. Rescue analgesics could include administration of systemic opioids or other analgesics, except ketorolac. The open-label extension study, Part B, enrolled eleven chronic pain patients who had recently completed the PK-pharmacodynamics study of IT ziconotide (Part A). This study involved the administration of ziconotide by IT infusion for 6 days. Patients began at 0.1 μg/hr and could titrate up to 2.4 μg/hr. However, neither CSF nor plasma samples were collected from Part B of this study.

Criteria for Evaluation:
Pharmacokinetics: Cerebrospinal fluid and plasma samples were obtained at 0 (pre-infusion), 1.5, 2, 4, 6, 8, 12 and 24 hours after study drug initiation for determination of ziconotide levels and to estimate PK parameters in the respective media. Estimated PK parameters include area under the CSF concentration-time curve to infinity [AUC_∞], maximum CSF concentration [C_{max}], time to maximum CSF concentration [t_{max}], CSF clearance [CL], CSF volume of distribution [V_d] and CSF terminal half-life [$t_{½}$].
Efficacy: Primary efficacy assessments were measured at pre-infusion, 0.5, 1, 1.5, 2, 3, 4, 5, 6, 7, 8, 12, 16, 20, 24, 32, 40, and 48 hours after the start of the study drug infusion. Primary efficacy parameters are Visual Analog Scale of Pain Intensity (VASPI; e.g., change from baseline in the VASPI at 2 hrs

following the start of the 1-hr infusion), Visual Analog Scale of Pain Intensity Difference (VASPID), maximum change from baseline VASPID during the first 4 hrs (MAXVASPID), summed VASPID (SPID), Category Pain Relief Scores (CPRS), MAXCPRS, summed CPRS (TOTPAR), duration, onset and response. The range of VASPI and CPRS were no pain (0 mm) to worst pain (100 mm) and worse than usual pain (0) to complete relief of pain (6), respectively. Secondary efficacy parameters are analgesia and overall analgesia, which were assessed through 48 hrs at various times.
Safety: Clinical laboratory tests, vital signs monitoring, physical/neurological examinations, electrocardiograms, and reports of adverse events.

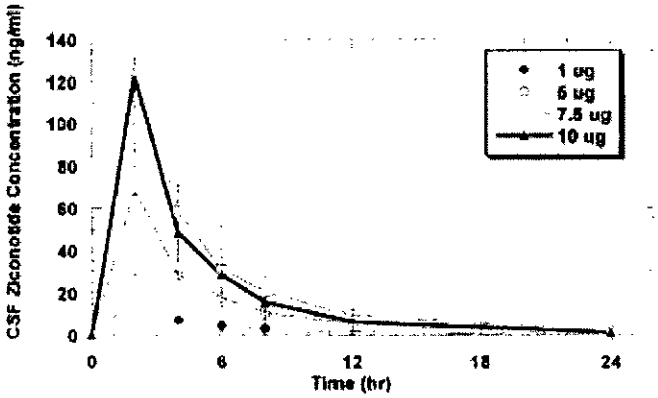
Analytical Methodology:
Assay Method: Radioimmunoassay (RIA)
Assay Sensitivity: The limit of quantitation (QL) was [redacted]
[redacted] CSF sample volume).
Assay Precision/Accuracy: The inter-day values %CV (& %RE) of ziconotide QC samples (CSF; plasma) for low [redacted]

Statistical methods: Part A: Descriptive PK parameters at different ziconotide dose levels. Statistical analysis was performed to assess linearity of CSF PK parameters by computation of the Spearman-rank correlation coefficient. Also, Spearman-rank correlation coefficient test was used as measure of association of PK-PD relationships. Part B: Correlative analyses of efficacy and safety parameters collected in Part B were compared to those of Part A.

Results and Discussion:

CSF Concentrations: The mean CSF concentration-time profile is shown in Figure 1 based on 23 subjects; in one subject (#17305), CSF concentrations increased after 6 hours (while plasma concentrations remained below the QL). The sponsor declared this data is aberrant, and thus omitted this data from the PK analyses. In addition, PK analysis was based on data without 1.5 hour samples (sponsor stated that because 1.5 hr-samples were not obtained from all patients, also stated that there was no difference in PK analysis with or without this 1.5 hr data). Figure 1 shows the mean ziconotide CSF concentration-time curves for 4 dose groups.

Figure 1. The Mean Ziconotide CSF Concentrations as a Function of Time



The overall CSF PK parameter values are listed in Table 1. Dose normalized AUC_∞ (i.e., AUC_∞/D) and C_{max} (C_{max}/D), CL and V_d are displayed in Figures 2-3.

Table 1. CSF pharmacokinetic parameters for ziconotide (n = 23)

Dose (μg)	N		AUC_∞ (ng hr/mL)	CL (mL/min)	$t_{1/2}$ (hr)	Vd (mL)	Cmax (ng/mL)
1	5	Mean	83.6 ± 27.6	0.22 ± 0.06	5.3 ± 0.8	99.1 ± 36.5	16.4 ± 6.4
		Median	75.2	0.22	5.3	79.8	16.1
		Range					
5	8	Mean	318 ± 74.7	0.27 ± 0.06	4.5 ± 0.8	106 ± 29.5	68.2 ± 20.3
		Median	310	0.27	4.4	99.1	68.2
		Range					
7.5	6	Mean	608 ± 520	0.68 ± 1.11	4.4 ± 1.0	290 ± 520	132 ± 92.1
		Median	515	0.25	4.7	97.1	105
		Range					
10	4[a]	Mean	539 ± 205	0.34 ± 0.12	4.2 ± 0.8	121 ± 38.3	122 ± 47.5
		Median	497	0.34	4.2	124	118
		Range					
Overall	23	Mean	NA	0.38 ± 0.56	4.6 ± 0.9	155 ± 263	NA
		Median		0.26	4.5	99.2	
		Range					

[a] One patient of the five treated did not provide evaluable PK data.
NA = Not applicable.

Figure 2. Dose normalized AUC_∞ (left) and C_{max} (right) in subjects.

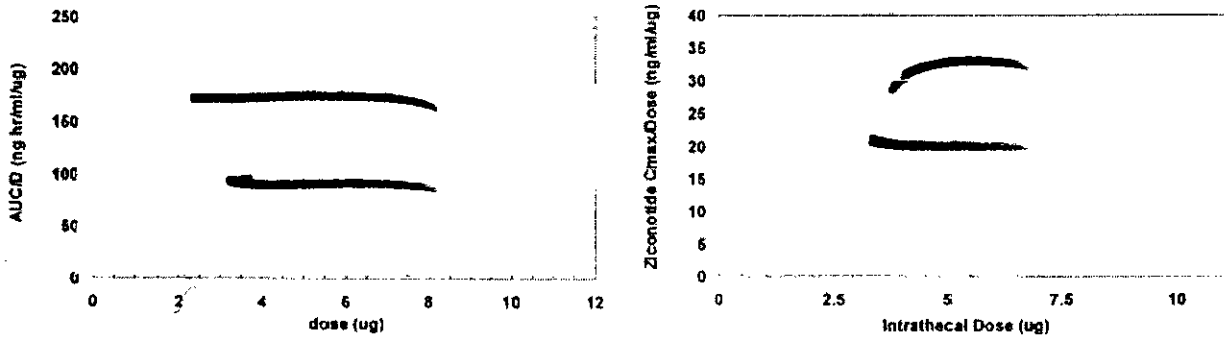


Figure 3. Clearance (left) and volume of distribution (right) in subjects.

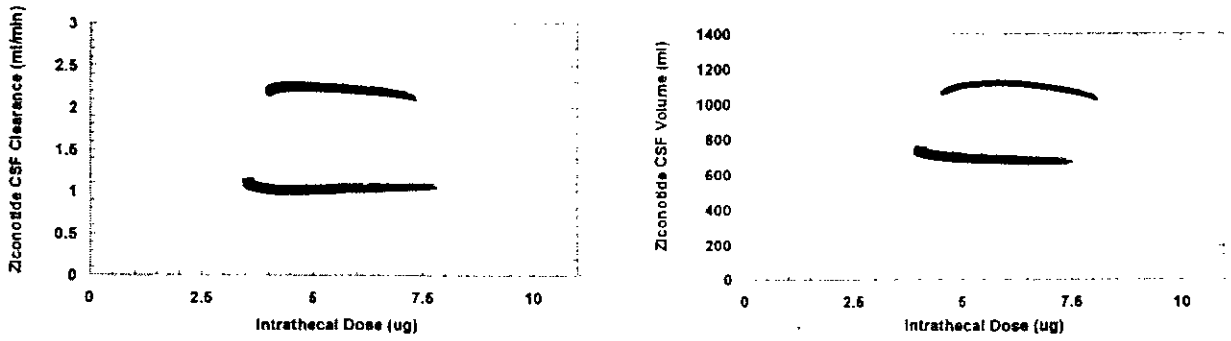


Table 2 lists the results of the linearity analysis using Spearman-rank correlation coefficient, at p-value >0.05, between dose and PK parameters.

Table 2. Dose proportionality of CSF PK parameters

Parameter	Units	Spearman R	p-value
AUC_∞/D	ng•hr/mL/μg	-0.32	0.1432
C_{max}/D	ng/mL/μg	[redacted]	0.5675
CL	mL/min	0.32	0.1373
Vd	mL	0.09	0.6767
$T_{1/2}$	hr	-0.35	0.1003

However, 'dose-proportionality' can not be confirmed, because this statistical analysis method is considered less than satisfactory when there is high variability in PK parameter values. Further, Figure 1 seems to show non-linearity.

Ziconotide Concentrations in Plasma: Only three patients had plasma samples above the ziconotide assay QL of [redacted] (Table 3). Except one case (#17295), quantifiable plasma concentrations of ziconotide occurred at later times suggesting that a lag time occurred between maximum lumbar CSF and maximum plasma ziconotide concentration. Since 20/23 patients exhibited below QL drug in plasma, their $\%F_{plasma}$ (plasma bioavailability) was 0.0%. The other three patients had $\%F_{plasma}$ values of [redacted]. The median $\%F_{plasma}$ was 0.0%, with a mean ± SD of 8.4 ± [redacted], following IT doses of 1 to 10 μg. The overall data demonstrates a dose-dependence, with the $\%F_{plasma}$ values > 0.0% coming from IT ziconotide doses ≥ 7.5 μg. The reference for plasma exposure was derived from the IV ziconotide infusion in study **93-001**.

Table 3. Plasma ziconotide concentrations in patients with conc. above the QL.

Patient ID	Dose (μg)	Sampling Time (hr)	Plasma Concentration (ng/mL)	CSF Concentration (ng/mL)	CSF/plasma Concentration Ratio
17205	7.5	4	[redacted]		
17115	7.5	4			
		6			
		8			
17295	10	1.5			
		2			
		4			

Efficacy (pain assessments):

Table 4 and 5 present mean and median VASPID and CPRS scores through 48 hours, respectively, along with MAXVASPID (maximal pain intensity difference) and MAXCPRS (maximal categorical pain relief) scores through 4 hours post-infusion.

Table 4. VASPI difference (VASPID) scores through 48 hrs post-infusion

Times	1 μg		5 μg		7.5 μg		10 μg	
	Mean±SD	Median	Mean±SD	Median	Mean±SD	Median	Mean±SD	Median
Max[1] 4 hrs	8.4±12	3	14±26	8.5	28.8±26	23	16.2±22	6
Sum[2] 2 hrs	1.0±11	0	1.9±29	0	20.4±20	17.5	11.1±25	1
Sum[2] 4 hrs	4.5±49	0	18.4±82	11.3	67.9±62	54	29.5±72	4.5
Sum[2] 8 hrs	15.9±84	6	69.8±19	23.8	183.4±166	141	58.2±160	6
Sum[2] 48 hrs	-366±544	-337	466±128	320.8	1145±1496	503	467±875	96
Effect[3] (hrs)	4.2±6.5	-	13.1±19	-	39.3±17	-	9.9±21.3	-

[1]Maximum through [2]Summed through [3]Duration of effect

Table 5. CPRS through 48 hrs post-infusion

Times	1 μg		5 μg		7.5 μg		10 μg	
	Mean±SD	Median	Mean±SD	Median	Mean±SD	Median	Mean±SD	Median
Max[1] 4 hrs	2.2±1.1	2	1.8±1.2	1.5	2.7±1.0	2	2.0±1.2	2
Sum[2] 2 hrs	1.8±0.5	2	2.3±1.1	2	2.8±0.9	2.5	2.5±1.1	2
Sum[2] 4 hrs	4.6±1.5	4	4.9±2.7	4.8	7.4±2.9	6	5.7±3.3	4
Sum[2] 8 hrs	7.8±1.5	8	11.1±6.7	9	13.4±3.8	12	11.1±5.9	8
Sum[2] 48 hrs	46.6±15	43	68.3±21	59.3	89.8±76	60.5	80.7±46	56

[1]Maximum through [2]Summed through

Ziconotide exhibited a dose-related analgesic effect, although the analgesic response was lower in the 10 μg dose group than 7.5 μg dose group as shown in Tables 4-5. Also, statistically significant correlation was observed between the CSF ziconotide AUC_∞ and several indices of efficacy (see Attachment 1, page 31). PK-PD correlation was positive and significant, suggesting that higher exposure was associated with increased efficacy.

Analgesic response occurred in 1/5 (20%), 2/8 (25%), 3/6 (50%), and 2/5 (40%) responders in the 1, 5, 7.5 and 10 μg dose groups, respectively. The analgesic responder(s) is defined as a patient showing at least a 30% improvement from baseline in his/her VASPI score during the first 4 hours after the start of study drug infusion, therefore, it appears that the responder rate is higher for the two highest dose groups compared with the two lowest dose groups. The onset of analgesia averaged 4.0 hours in this trial, with a median value of 1.5 hours and a range of 0.5 to 24 hours.

Part B: PK-PD analyses and the predicted C_{ss} were performed using the primary PK parameters (i.e., CL, V_d and $t_{1/2}$) derived in Part A. The efficacy endpoints were the same as for Part A. The time element associated with each parameter was not considered in these analyses. Instead, all Part A efficacy endpoints were correlated with all Part B efficacy endpoints, e.g., VASPID1 (A) with VASPID24 (B), VASPID48 (B), VASPID72 (B), VASPID96 (B), VASPID120 (B) and VASPID144 (B), etc.

$\underline{C_{ss}}$: The predicted maximum C_{ss} (calculated by, CSF C_{ss} = each subject's highest IT infusion rate /each subject's CSF CL which was obtained from Part A) averaged 43 ± 54 ng/ml with median of 19.4 ng/ml and ranged from 6 to 181 ng/ml. However, the results showed that this (predicted) C_{ss} was a poor indicator for the PD. The sponsor suggested that the rationale of the poor relationship between C_{ss} and PD was due to (1) restriction of 'dose-escalation' dosing regimen (i.e., dose was increased

only q24hrs), and (2) CSF PK variability was high, and additionally there may be a change in physiology in patients, since there was a time lapse of 6 months between Part A and B.

Efficacy: All parameters following acute administration failed to reveal statistically significant correlations with chronic infusion parameters (efficacy and safety endpoints), defined by $p < 0.05$ (e.g., The best correlation was achieved for time to MAXVASPID between Parts A and B with p value of 0.39).

Serum Antibody Assay Results: The sponsor reported that 13 serum antibody assessments (2 patients from part A and 11 patients from part B) for these patients uniformly demonstrated a lack of IgG and IgE antibody response to ziconotide up to six months post-exposure (Appendix A25 of NDA).

Summary of results:

- The overall median CSF AUC_∞/D for a 1-hour infusion was 63.8 ng•hr/ml/μg with range of 5.7-210 ng•hr/ml/μg.
- The highest CSF ziconotide concentration (C_{max}) seen in any patient was 367 ng/mL in the 7.5 μg dose group at 1.5 hours, and the overall median C_{max}/D for a 1-hour infusion was 13.4 ng/ml/μg (range . [redacted]).
- After a single 1-hour infusion of ziconotide both AUC_∞ and C_{max} of CSF increased with increasing dose, however, 'dose-proportionality' can not be confirmed (analysis method used considered not valid).
- The median CL was 0.26 mL/min (range 0.08-2.93 mL/min); median Vd was 99 mL (range 34-1350 mL) and the median half-life was 4.5 hr (range 2.9-6.5 hr).
- Quantifiable plasma concentrations occurred in only 3 patients, all of who received the two highest ziconotide doses (7.5 μg and 10 μg). These plasma concentrations occurred within 8 hours of intrathecal administration. The sponsor stated that $\%F_{plasma}$ of the IT doses ranged from [redacted] with a mean of 8.4%.
- After a single 1-hour infusion ziconotide generally exhibited a dose-related analgesic effect, although the analgesic response was lower in the 10 μg dose group than in the 7.5 μg dose group.
- Analgesic response (defined as at least a 30% improvement from baseline in the VASPI score by 4 hr) occurred in 1/5 (20%), 2/8 (25%), 3/6 (50%), and 2/5 (40%) of patients in the 1, 5, 7.5 and 10 μg dose groups, respectively.
- A significant correlation was observed between AUC_∞ of CSF and VASPID values at different time points during the study. A similar but weaker correlation pattern was observed with C_{max}.
- Short-term IT ziconotide infusions produced efficacy and safety profiles that were not predictive of continuous infusion outcomes.
- Predicted maximum steady state CSF ziconotide concentration (using subject's highest IT infusion rate and subject's CSF CL, that was obtained from Part A) ranged from 6 to 180 ng/mL with a median of 43 ng/mL. Pharmacodynamic (PD) parameters were not correlated well with this predicted C_{ss}.

Comments: (1) $\%F_{plasma}$ (calculated based on AUC_∞) of 24.7%, for the one of 3 subjects who showed plasma samples above BLQ, seems inadequate (or impossible) since this subject had only one data point. (2) Evaluation of dose proportionality for the PK of ziconotide by confidence intervals would be more meaningful rather than using p-value (0.05), especially when there was high inter-subject variability (%CV).

Attachment 1: PK-PD relationship – Efficacy Parameters

F PK parameter	Efficacy Variable	Spearman R	p-value
CL	VASPID 1.0	-0.48	0.0255
	TOTPAR 2.0	-0.45	0.0400
	ONSET	0.66	0.0204
Vd	VASPID 0.5	-0.43	0.0477
	TOTPAR 1.0	-0.46	0.0339
T1/2	none	--	--
AUC∞	VASPID 1.5	0.53	0.0108
	VASPID 2	0.43	0.0439
	VASPID 12	0.44	0.0408
	VASPID 16	0.46	0.0330
	VASPID 24	0.49	0.0217
	VASPID 32	0.61	0.0028
	VASPID 40	0.61	0.0025
	VASPID 48	0.72	0.0002
	SPID 1.0	0.43	0.0486
	SPID 1.5	0.48	0.0228
	SPID 2	0.52	0.0128
	SPID 16	0.43	0.0446
	SPID 20	0.47	0.0280
	SPID 24	0.47	0.0282
	SPID 32	0.49	0.0210
	SPID 40	0.53	0.0117
	SPID 48	0.56	0.0068
	TOTPAR 1.0	0.66	0.0011
	TOTPAR 1.5	0.64	0.0016
	TOTPAR 2.0	0.63	0.0024
	TOTPAR 3	0.46	0.0384
	TOTPAR 6	0.48	0.0262
	TOTPAR 7	0.46	0.0381
	TOTPAR 12	0.46	0.0344
	TOTPAR 16	0.49	0.0240
	TOTPAR 48	0.51	0.0184
C_{max}	VASPID 32	0.48	0.0245
	VASPID 40	0.48	0.0224
	VASPID 48	0.64	0.0014
	SPID 0.5	0.44	0.0384
	SPID 40	0.45	0.0351
	SPID 48	0.48	0.0229
	TOTPAR 1.0	0.59	0.0045
	TOTPAR 1.5	0.48	0.0270
	TOTPAR 2.0	0.54	0.0109
	TOTPAR 6	0.48	0.0294
	TOTPAR 7	0.51	0.0173
	TOTPAR 8	0.47	0.0323
	TOTPAR 12	0.5	0.0217
	TOTPAR 16	0.52	0.0149
	TOTPAR 20	0.45	0.0403
	TOTPAR 24	0.44	0.0484
	TOTPAR 48	0.5	0.0222

95-001: A Multicenter, Phase II/III, Placebo-Controlled Study of SNX-111 Administered Intrathecally to Patients with Chronic malignant Pain.

Reference: Volume 79
Investigators: Multicenter
Study Location: Multiple sites (clinical)

Objective:

To assess the efficacy and safety of increasing dose of ziconotide administered intrathecally by comparing it with placebo in patients with chronic malignant pain.

Test Product, Dose, and Batch Number:

Solution A - Ziconotide, 0.1 μg/hr to 2.4 μg/hr, NUT001, 111V14B
Solution B - Placebo and diluent, NUP001, NUP002, 111V15B

Study Design:

This trial was a randomized, double-blind, placebo-controlled, multicenter, multinational study with a partial open-label crossover phase. After completing a 1- to 7-day screening phase, patients were randomized in a 2-to-1 ziconotide-to-placebo ratio and received 5 (or 6) days of treatment in the initial titration phase. Infusion of ziconotide or placebo began at a dose of 0.1 μg/hr and was titrated up to 1.2 μg/hr at 120 hours, with an option to continue an additional day and titrate to a maximum dose of 2.4 μg/hr (or initiated at a dose of 0.4 μg/hr and titrated up to 21 μg/hr prior to 21 February 1997). At the conclusion of the initial titration phase, responders to therapy (patients who experienced a ≥30% decrease in Visual Analog Scale of Pain Intensity (VASPI) compared with baseline in the setting of either a stable or decreasing regimen of concurrent opioid analgesics) continued to receive blinded treatment during a 5-day maintenance phase, while nonresponders entered a 5- (or 6-) day crossover phase and were retitrated to the opposite blinded treatment. At the conclusion of the maintenance and crossover phases, the study was terminated and the blind was broken for responders. All responders to ziconotide were eligible to enroll in a long-term open-label extension study (Protocol No. 95-002).

Criteria for Evaluation:

Pharmacokinetics: Blood samples were obtained for ziconotide assay at the end of initial IT infusion (generally Day 5 or Day 6). In general, only one blood sample was collected from each patient.
Efficacy: Primary efficacy was measured by the percent change in VASPI score from baseline to the end of the initial titration phase. Secondary efficacy assessments included percent change in VASPI scores at the end of the maintenance and crossover phases, change in VASPI score, other pain scales, mean percent change in opioid use, and percent responders to treatment. Other pain scales included the following: Category Pain Relief Scale (CPRS), Wisconsin Brief Pain Inventory Subtest (WBPIS), Karnofsky Performance Status Scale, Visual Analog Scale of Pain Relief (VASPR), Mood Score, Tursky Description, and for affected patients, tactile allodynia evaluations.
Safety: Safety measurements included adverse events, serious adverse events, discontinuations due to adverse events, clinical laboratory evaluations, nystagmus assessments, vital sign measurements, and cognitive assessments (Digit Symbol and Trail Making, Parts A and B). **Note: Efficacy and Safety will be reviewed by the Medical officer since PK-PD was not evaluated in this study.

Analytical Methodology:
Assay Method: Radioimmunoassay (RIA)
Assay Sensitivity: The range of quantitation for a [redacted] undiluted sample is [redacted] with a lower limit of quantitation (LLQ) of [redacted]
Assay Precision/Accuracy: The inter-assay coefficients of variation of the QC samples (0.1, 2 and 6 ng/mL) for the analytical runs ranged from [redacted] with % differences from theoretical ranging from [redacted]

Statistical Methods:

Two-way ANOVA, ANCOVA, Cochran-Mantel-Haenszel test, and Fisher's Exact Test were used for efficacy and safety analyses.

Results and Discussion:

Plasma concentrations that were sampled at the end of initial IT infusion (generally Day 5 or Day 6) were available in 50 patients. Twenty-eight of the 50 patients (56%) had plasma ziconotide concentrations below quantitation limit of [redacted]. In the remaining 22 (44%) patients, the mean ± SD of plasma concentrations was 0.202 ± 0.496 ng/mL (range 0.0405-2.4 ng/mL). The mean ± SD, median and range of the cumulative dose of ziconotide during 6 days in these 22 patients were 179.73 ± 211.62 μg, 96.15 μg and 30.8-880.5 μg, respectively. Corresponding values in the patients with below quantification limit were 41.61 ± 34.17 μg, . [redacted] respectively. The mean ± SD concentration, median concentration and mean dose for the plasma ziconotide concentrations in female patients (n=18; age between 26-80 years) were 0.214 ± 0.551 ng/mL, 0.064 ng/mL and 2.227 μg/day, respectively. Corresponding values in male patients (n=12; age between 25-77 years) were 0.092 ± 0.052 ng/mL, 0.072 ng/mL and 1.869 μg, respectively. Similarly, corresponding values for patients age below 60 years (n=17) and ≥ 60 years (n=13) were 0.217 ± 0.564 ng/mL, 0.069 ng/mL, 1.663 μg and 0.096 ± 0.091 ng/mL, 0.059 ng/mL, 2.635 μg, respectively. The mean ± SD and median plasma ziconotide concentrations in 8 patients who had crossed over from initial placebo to ziconotide treatment were 0.0635 ± 0.0359 ng/mL and 0.0494 ng/mL, respectively. On average, a measurable drug in plasma was observed in patients who had higher cumulative ziconotide dose.

Efficacy: The sponsor reported that 53% of patients in the ziconotide group had moderate to complete pain relief as measured by VASPID compared to only 17.5% for the placebo group ($p < 0.001$).

Comment: It appears that there may be sex as well as age effect on PK of ziconotide.

96-002: A Multicenter, Phase II/III, Placebo-Controlled Study of SNX-111 Administered Intrathecally to Patients with Chronic Nonmalignant Pain

Reference: Volume 79
Investigators: Multicenter
Study Location: Multiple sites (clinical)

[redacted]

Objective:

To assess the efficacy, safety and tolerability of increasing dose of ziconotide administered intrathecally by comparing it with placebo in patients with chronic nonmalignant pain.

Test Product, Dose, and Batch Number:

Solution A - Ziconotide, 0.1 μg/hr to 2.4 μg/hr (0.4 to 7.0 μg/hr prior to 28 October 1996), NUT001, 111V14B
Solution B – Placebo and diluent, NUP001, NUP002, 111V15B

Study Design:

This trial was a randomized, double-blind, placebo-controlled, multicenter, multinational study with a partial open-label crossover phase. After completing a 3- to 7-day screening phase, patients were randomized in a 2-to-1 ziconotide-to-placebo ratio and received 6 days of treatment in the initial titration phase. Infusion of ziconotide or placebo began at a dose of 0.1 μg/hr and was titrated by specified increments no more often than every 24 hours up to 2.4 μg/hr at 144 hours (or initiated at a dose of 0.4 μg/hr and titrated up to 7.0 μg/hr at 144 hours prior to 21 February 1997). At the conclusion of the initial titration phase, responders to therapy (patients who experienced a ≥30% decrease in Visual Analog Scale of Pain Intensity (VASPI) compared with baseline in the setting of either a stable or decreasing regimen of concurrent opioid analgesics) continued to receive blinded therapy during a 5-day maintenance phase as outpatients, while nonresponders had their study medication blind broken. Nonresponders to ziconotide were terminated from the study. Nonresponders to placebo were crossed over to 5-day open-label ziconotide treatment as inpatients and the titration regimen was repeated. All responders to ziconotide were eligible to enroll into a long-term open-label extension trial (Protocol No. 95-002). Patients who were not eligible or did not choose to participate in the long-term extension protocol returned 2 weeks after completion of the study for reassessment of any adverse events or laboratory abnormalities that were clinically significant at discharge.

Criteria for Evaluation:

Pharmacokinetics: Blood samples were obtained for ziconotide assay on Day 6 and Day 11. In general, only one blood sample was collected from each patient.
Efficacy: Mean percent change of the final initial titration phase VASPI score from the baseline score for the ziconotide group compared to the placebo group using treatment and investigator as factors (primary endpoints). However, review of the Efficacy and Safety will be referred to the Medical officer since PK-PD was not evaluated in this study.

Analytical Methodology:

Assay Method: Radioimmunoassay (RIA)
Assay Sensitivity: The range of quantitation for a [redacted] undiluted sample is [redacted] with a lower limit of quantitation (LLQ) of [redacted]

Assay Precision/Accuracy: The inter-assay coefficients of variation of the QC samples (0.1, 2 and 6 ng/mL) for the analytical runs ranged from [redacted] with % differences from theoretical ranging from - [redacted]

Statistical Methods:

(Unweighted) linear regression analysis of plasma concentrations versus infusion rate or cumulative dose.

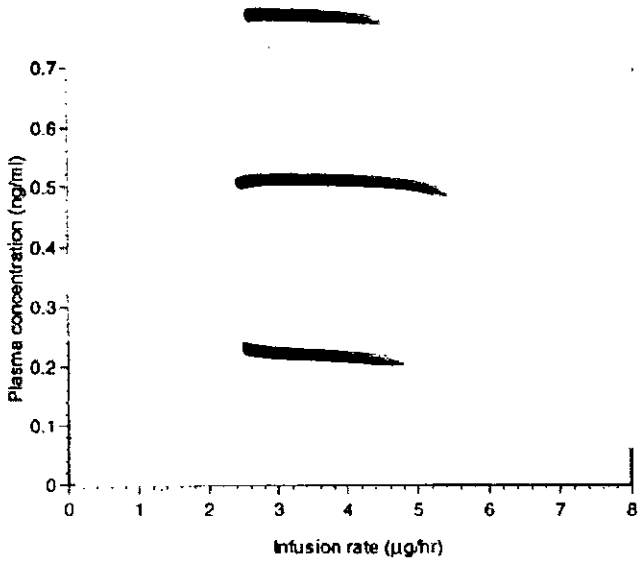
Results and discussion:

Plasma concentrations were sampled on Day 6 and Day 11 in this trial. However, the sponsor decided not to include Day 11 samples for PK analysis because only 12% of the total Day 11 samples were quantifiable (i.e., above LQ of [redacted]). Also plasma clearance of ziconotide was not calculated in this study since only one blood sample was obtained from each patient.

Patients on Day 6 (102 individuals) received continuous IT administration of ziconotide as an infusion rate of 0.1 to 0.7 μg/hr through Day 6 of the study. Among 102 individuals, 30 (29.4%) had levels above quantitation limit. The average plasma concentrations in these 30 individuals was 0.137 ± 0.138 ng/mL (range [redacted]) with a median of 0.0861 ng/mL.

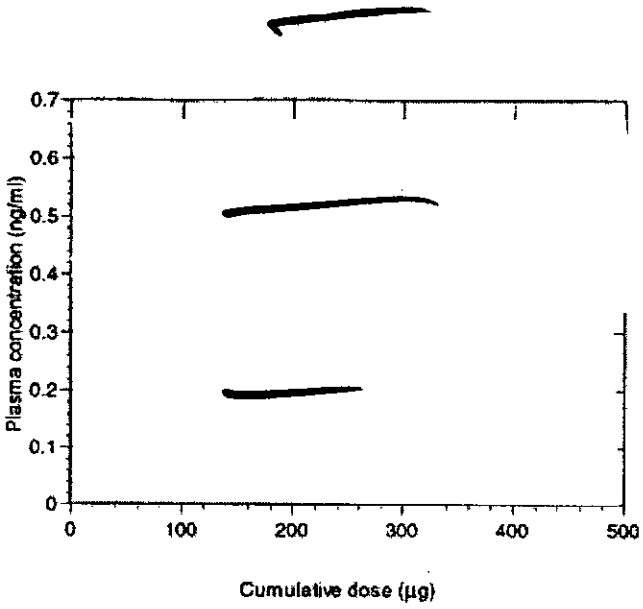
Relationship of infusion rate to plasma concentration: The average Day 6 infusion rate among the 102 patients in this analysis was 1.1 ± 1.1 μg/hr, with a median of 0.6 μg/hr (range of 0.1-7 μg/hr). In these 30 patients who had quantifiable plasma concentrations, mean infusion rate was 2.1 ± 1.4 μg/hr, with a median of 2.1 μg/hr and range of [redacted] The relationship between measurable Day 6 plasma concentration and infusion rate is plotted in Figure 1, and the results ($R^2 = 0.71$) support the observation that the administration of ziconotide IT at higher infusion rate is associated the attainment of greater plasma exposure.

Figure 1. Relationship between measurable Day 6 plasma concentration and infusion rate



Relationship of cumulative infusion dose to plasma concentration: The average cumulative ziconotide dose in the 102 patients was 76.6 ± 64.1 μg, with a median of 56.7 μg. In those 30 patients who had quantifiable plasma concentrations, cumulative doses, median and range values were 132 ± 84 μg, 114 μg and [redacted] respectively. The patients with undetectable plasma concentrations received cumulative doses of 53.5 ± 33.6 μg, median 41.7 μg and range [redacted] The relationship between Day 6 plasma concentration and cumulative dose is plotted in Figure 2, and the results ($R^2 = 0.77$) suggest that the administration of higher cumulative doses of ziconotide IT is associated with greater peripheral exposure.

Figure 2. Relationship between measurable Day 6 plasma concentration and cumulative dose



Summary of the results:

- Plasma ziconotide concentrations were below the limit of quantitation in about [redacted] of patients with an infusion rate of 0.1-7 μg/hr after six days of IT infusion of ziconotide.
- Patients with quantifiable ziconotide concentrations on Day 6 were receiving the drug at a mean infusion rate of 2.1 μg/hr and had received a mean total dose of 132 μg. The average plasma concentrations in these individuals was 0.137 ± 0.138 ng/mL (ranged [redacted]) with a median of 0.0861 ng/mL.
- Day 6 plasma concentrations were highly correlated with respect to infusion rate ($R^2 = 0.71$) or cumulative dose ($R^2 = 0.77$) within the studied IT doses.

Comment:

The sponsor should include Day 11 blood samples of patients with quantifiable ziconotide concentrations (i.e., addition of 14-15 patients) for PK analysis (compare this data with Day 6 or use all available data for PK analysis, even though it was not optimal condition).

95-002: An Open-Label, Long-Term Safety and Efficacy Study of SNX-111 Administered Intrathecally to Patients Suffering from Chronic Pain Using the SynchroMed® Infusion System or the Sims Deltec CADD-Micro Pump.

Reference: Volume 79
Investigators: Multicenter
Study Location: Multiple sites (clinical)

Objective:

To assess the long-term safety, efficacy, and tolerability of ziconotide administered intrathecally to patients who suffer from chronic, intractable pain and have participated in a previous Elan ziconotide study (either Study 95-001 or Study 96-002).

Test Product, Dose, and Batch Number:

Ziconotide, 0.1 μg/hr to 2.4 μg/hr, intrathecally, batch numbers NUT001, 111V14B, and 111V03C diluent, batch numbers NUP001, NUP002, and 111V15B.

Study Design:

This is an open-label, long-term, multicenter study conducted in 155 patients with malignant (cancer or AIDS) or nonmalignant (noncancer) chronic pain who had demonstrable analgesic response to ziconotide in previous controlled pivotal trials (95-001 or 96-002). Unless already implanted, patients are implanted with the Medtronic SynchroMed infusion system; however, patients with malignant disease are also permitted to receive study drug via an external pump. Patients receive study drug via one of these administration systems on a long-term basis. During the first 30 days of this long-term extension study, patients are maintained on their optimal therapeutic dose (based upon the previous study) (infusion rates ranged from 0.1 μg/hr to 2.4 μg/hr). After the initial 30-day fixed-dose period, dose increases are not to exceed a 2-fold increase per 12-hour period. Blood samples for determination of ziconotide concentration were drawn 48 hours after the first maintenance period was initiated.

Criteria for Evaluation:

Pharmacokinetics: Blood samples were obtained for ziconotide assay at the end of initial IT infusion (generally Day 5 or Day 6). In general, only one blood sample was collected from each patient.
Efficacy: The mean %change in the Visual Analog Scale Pain Intensity (VASPI), Karnofsky Scores, Quality of Life assessments, Pain Disability Index (PDI) and the Sickness Impact Profile scores (SIP-20).
Safety: Safety measurements included adverse event monitoring, clinical laboratory evaluations, vital signs measurements, changes in the electrocardiogram, changes in nystagmus, physical and other neurological examinations.

Analytical Methodology:

Assay Method: Radioimmunoassay (RIA)
Assay Sensitivity: The range of quantitation for a 0.1 mL undiluted sample is [redacted] with a lower limit of quantitation (LLQ) of [redacted]

Assay Precision/Accuracy: The inter-assay coefficients of variation of the QC samples (0.1, 2 and 6 ng/mL) for the analytical runs ranged from [redacted] with % differences from theoretical ranging from [redacted]

Statistical Methods:

Summary statistics were tabulated on all variables of interest. No inferential statistics were computed in this interim report.

Results and Discussion:

One blood sample was collected from the majority of patients, a few provided two samples (total 144 samples), and overall summary of data is shown in the table below.

	study day	Infusion rate µg/hr	cum. dose µg
mean	45	0.43	565
SD	43	0.47	1122
median	29	0.30	193
min		[redacted]	
max			

Eighteen samples (13%) from thirteen patients were above the quantitation limit and the remainder were below the assay limit of [redacted] The quantifiable concentrations averaged 0.0932 ± 0.0476 ng/ml (ranged [redacted]). The hourly infusion rate of the patients presenting with quantifiable ziconotide in plasma averaged 0.28 ± 0.15 µg /hr and ranged [redacted]. The hourly infusion rate of the patients presenting with unquantifiable plasma ziconotide averaged 0.45 ± 0.50 µg/hr, and exhibited a [redacted] range of infusion rate [redacted] Therefore, it appears that infusion rate was not a good predictor for exhibiting quantifiable plasma ziconotide since range of hourly infusion rates for quantifiable samples were within the range of hourly infusion rates for unquantifiable samples.

In terms of the magnitude of the concentrations or dose received in this trial, results were similar to those following IT infusion for a few days (studies 95-001 and 96-002). Hence, this interim data suggests that plasma exposure does not increase with duration of IT ziconotide infusion.

Comment: No steady state ziconotide concentrations in CSF were obtained.

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.

Reference: Volume 79
Investigators: Multicenter
Study Location: Multiple sites (clinical)

Formulation Lot Number: Ziconotide NUR001, NUT001, diluent NUP001

Objective: To assess the efficacy, safety and tolerability of increasing dose of ziconotide administered intrathecally to patients with chronic intractable pain and an unsatisfactory response to opioid therapy.

Study Design: This was an open-label, rising-dose study in 31 patients (16 women and 15 men) with mean (±SD) age of 56.6±14.4 years. Subjects were hospitalized for up to 7 days. The intrathecal dose of SNX-111 was titrated based on the patient's clinical response; the dose could be tripled at intervals of 24 to 48 hours, with a starting dose of 0.3 ng/kg/hr and maximum dose of 300 ng/kg/hr. Pain was assessed at 4-hour intervals throughout the in-hospital period.

Criteria for Evaluation:
Pharmacokinetics: Blood samples were obtained for ziconotide assay at the end of the in-hospital observation period. In general, only one blood sample was collected from each patient.
Efficacy/Safety: Visual Analog Scale of Pain Intensity (VASPI), Visual Analog Scale of Pain Relief (VASPR), maximal analgesic effect, the pattern of satisfaction or dissatisfaction reported by patients and adverse events as a safety endpoint. Note: the medical officer will review the Efficacy and Safety (no PK-PD assessment performed).

Analytical Methodology:
Assay Method: Radioimmunoassay (RIA)
Assay Sensitivity: The range of quantitation for a 0.1 mL undiluted sample is [redacted] with a lower limit of quantitation (LLQ) of [redacted]
Assay Precision/Accuracy: The assay for accuracy of the QC samples (1, 2 and 6 ng/mL) ranged from [redacted] (precision was not reported).

Statistical Methods: Descriptive statistics were computed for the efficacy and safety analyses.

Results: Twenty-three plasma samples were obtained after the initiation of ziconotide. Of the 23 samples, 10 samples (43%) had concentrations above detectable levels of ziconotide. These concentrations ranged from [redacted] The average infusion rate of the patients reporting detectable ziconotide in plasma was 130 ± 110 ng/kg/hr (9.1 ± 7.7 µg/hr for 70 kg person).

96-003: A Multicenter, Phase II, Placebo-controlled, Pilot Study of Ziconotide (SNX-111) Administered Intrathecally to Patients with Acute Postoperative Pain.

Reference: Volume 79
Investigators: Multicenter
Study Location: Multiple sites (clinical)

Objective:

The objective of this pilot study was to assess the safety and analgesic effectiveness of ziconotide administered intrathecally to patients with acute postoperative pain.

Test Product, Dose, and Batch Number:

Solution A - Ziconotide, NUT001
Solution B – Placebo and diluent, NUP001, NUP002

Study Design:

This trial was a Phase II, four-center, randomized, double-blind, placebo-controlled pilot study. The target population included patients undergoing elective total hip replacement surgery, elective retropubic radical prostatectomy, or elective abdominal hysterectomy. Patients in each of the operative populations were randomly assigned to receive placebo, 0.7 µg/hr ziconotide (low dose), or 7.0 µg/hr ziconotide (high dose) for 48 to 72 hours. All patients had intrathecal catheters in place for surgical anesthesia. Drug was delivered using an external pump. Infusion began intraoperatively, after the administration of intrathecal anesthesia and before surgical incision, and continued postoperatively. Rescue analgesia was limited to administration of IV morphine using a patient-controlled analgesia (PCA) pump.

Patient Disposition: A total of 34 patients were enrolled (12 in the placebo group; 13 in the 0.7 µg/hr ziconotide group; and 9 in the 7.0 µg/hr ziconotide group). Four patients were not treated, and a total of 30 patients were treated with test medication (12 with placebo, 12 with 0.7 µg/hr ziconotide, and 6 with 7.0 µg/hr ziconotide). A total of 19 patients completed treatment (9 on placebo, 8 on 0.7 µg/hr ziconotide, and 2 on 7.0 µg/hr ziconotide). Six patients discontinued treatment early with adverse events (1 on placebo, 1 on 0.7 µg/hr ziconotide, and 4 on 7.0 µg/hr ziconotide). Five patients discontinued early for reasons not associated with adverse events (2 on placebo and 3 on 7.0 µg/hr ziconotide).

Criteria for Evaluation:

Pharmacokinetics: Blood samples were obtained on Study Day 1 (preinfusion), on Study Day 3 (just before the end of infusion of study medication), and on Study Day 4 (at the time of discharge), or whenever the patient was discontinued from the study.

Efficacy: The primary efficacy variables were the daily dose of patient-controlled analgesia (PCA) morphine equivalents administered during each 24-hour postoperative period, the total PCA morphine equivalent use during the inpatient study period, and the average hourly use of PCA morphine equivalents. The secondary efficacy variables were the mean daily Visual Analog Scale of Pain Intensity (VASPI) and the mean daily Category Pain Relief Scale (CPRS) scores of each treatment group during the inpatient study period.

Analytical Methodology:
Assay Method: Radioimmunoassay (RIA)
Assay Sensitivity: The range of quantitation for a 0.1 mL undiluted sample is [redacted] with a lower limit of quantitation (LLQ) of [redacted]
Assay Precision/Accuracy: The inter-assay coefficients of variation of the QC samples (0.1, 2 and 6 ng/mL) for the analytical runs ranged from [redacted] with % differences from theoretical ranging from [redacted]

Statistical Methods:

No statistical analysis was performed with plasma concentrations.

Results and discussion:

None of the placebo samples nor any of the pre-infusion samples had detectable levels of ziconotide from total of 74 samples collected. In the 0.7 µg/hr group, 2/10 patients sampled had quantifiable ziconotide levels at the end of the infusion (mean of detectable ziconotide concentrations: 0.065 ng/mL). On the other hand, 6/6 patients in the 7.0 µg/hr group had quantifiable levels of ziconotide at the end of the infusion (mean concentration: 0.23 ng/mL). Only a single plasma sample (from a 7.0 µg/hr patient) taken at discharge contained quantifiable level of ziconotide.

98-021: A Phase I/II Pharmacokinetic Study of Ziconotide Administered by Short Epidural Infusion to Normal Subjects and Patients with Chronic Pain.

Reference: Volume 64 - 70
Investigators: Multicenter
Study Location: Multiple sites (clinical)

Objectives: The primary objective of the present study was to characterize the 24-hr CSF and plasma pharmacokinetic profiles following a short (1-hour) epidural infusion of ziconotide in up to five different treatment cohorts consisting of both normal volunteers and chronic pain patients. The secondary objectives were to evaluate the efficacy and safety of the tested doses, through pharmacokinetic-pharmacodynamic (PK-PD) analyses.

Formulation and method of drug delivery: The active drug and the diluent lot numbers were 111V03C and 111V15B, respectively. A temporary epidural catheter and an external, programmable infusion system that has been approved for use in epidural applications was used to deliver study drug. The epidural catheter was inserted up to 24 hours prior to initiation of study treatment. The external infusion pump was programmed to deliver study medication at a constant rate (1 mL/hr).

Study Design: This was a Phase I/II, multicenter, open-label study designed to assess the pharmacokinetics, safety and analgesic profiles of five different doses of ziconotide administered epidurally by short infusion. In this study, 42 subjects were enrolled (≥ 18 years of age) and assigned to 1 μg, 2 μg, 5 μg, 10 μg, and 20 μg dose groups. Of these, four patients were subsequently re-enrolled. Hence, there were a total of 46 cases of drug administration. Subjects had a temporary epidural catheter placed prior to administration of study drug. Each dose of ziconotide was administered as a single 1-hour epidural infusion, followed by a 30-minute saline flush to complete study drug administration (epidural catheter was removed after the saline flush). For all subjects, CSF samples were obtained through a temporary intrathecal catheter. Blood samples were also collected at the same time-points as the CSF samples. For 48 hours after completion of the 1-hour infusion, patients were evaluated with periodic pain assessments while awake. Except for the first 4 hours after ziconotide administration, patients continued to receive their current continuous regimen of systemic analgesics. Concomitant intrathecal or epidural medications were not permitted for the entire duration of the study. Rescue analgesics could include administration of systemic opioids or other analgesics, except ketorolac.

Criteria for Evaluation:
Pharmacokinetics: CSF and blood samples were obtained for ziconotide assay at 1, 1.5, 2, 4, 6, 8, 12 and 24 hr after initiation of study drug infusion. PK parameters to be estimated include area-under-the-concentration-time-curve (AUC_∞), peak concentration (C_{max}), time of peak concentrations (t_{max}), apparent clearance (CL/F), apparent volume of distribution (V_d/F), elimination half-life ($t_{½}$), and bioavailability (%F in CSF or in plasma).
PK-PD Efficacy (patients only): Efficacy variables included pain intensity differences (PID), measured using a visual analog scale of pain intensity (VASPI), and categorical pain relief scale (CPRS) at serial time points following treatment, summed pain intensity differences (SPID), summed pain relief scores (TOTPAR), Overall analgesia through 48 hours, Duration, Onset and Response. VASPI was assessed at preinfusion, and the VASPI and CPRS were also assessed at 0.5, 1, 1.5, 2, 3, 4, 5, 6, 7, 8, 12, 16, 20, 24, 32, 40, and 48 hrs after the start of the study drug infusion. The VASPI

scores were recorded on a visual analog scale of 0 mm (no pain) to 100 mm (worst pain imaginable). Other efficacy variables were assessed at various times.
Safety: Reported adverse events and serial measurements of vital signs, electrocardiograms, and routine laboratory tests. The relationship of CSF and plasma PK to adverse event incidence and changes in vital signs was characterized (review by medical officer).

Analytical Methodology:
Assay Method: Radioimmunoassay (RIA)
Assay Sensitivity: The range of quantitation for a 0.1 mL undiluted sample is [redacted] with [redacted] as the lower limit of quantitation (LLQ).
Assay Precision/Accuracy: The inter-day assay coefficients of variation of the QC samples (ranged 0.2-12.5 ng/mL) ranged from [redacted] with percent differences from theoretical ranging from [redacted]

Pharmacokinetic Data analyses: Epidurally-administered drug is absorbed into blood and transported through the dura and arachnoid into the cerebrospinal fluid. The plasma bioavailability of epidural ziconotide ($\%F_{plasma}$) was calculated by comparing the dose-normalized AUC_∞ (plasma) from the present study to that obtained in a study 93-001, which involved IV ziconotide infusion:

$$100 \times \left(AUC_{\infty epi}/D_{epi}/AUC_{\infty iv}/D_{iv}\right) = \%F_{plasma}$$

where the subscripts epi and iv denote the parameters associated with the epidural (C98-021) or the intravenous (93-001) studies, respectively. The pharmacokinetics of ziconotide were linear and dose-proportional in study 93-001, so the overall study plasma AUC_∞/D value of 0.0524 ng•hr/mL/μg was used in the calculations. A $\%F_{plasma}$ value was calculated for each case in the present study, even if the subject exhibited no quantifiable ziconotide in plasma following epidural ziconotide infusion ($\%F_{plasma} = 0.0\%$).

Likewise, the CSF bioavailability of epidural ziconotide ($\%F_{csf}$) was calculated by comparing the dose-normalized AUC_∞ (CSF) from the present study to that obtained in the IT ziconotide PK study (Study C97-013):

$$100 \times \left(AUC_{\infty epi}/D_{epi}/AUC_{\infty it}/D_{it}\right) = \%F_{csf}$$

Where the subscripts epi and it denote the parameter associated with the epidural (C98-021) or the intrathecal (C97-013) studies, respectively. The pharmacokinetics of ziconotide were linear and dose-proportional in study C97-013, so the overall study average CSF AUC_∞/D value of 71 ng•hr/mL/μg was used. An individual $\%F_{csf}$ value was calculated for each case, even if CSF concentrations were below the level of quantitation throughout the epidural study ($\%F_{csf} = 0.0\%$).

Statistical methods:

Results (descriptive PK parameter values) for this study were summarized by ziconotide dose level. PK-PD correlative analyses were performed using the Spearman Rank Correlation computation.

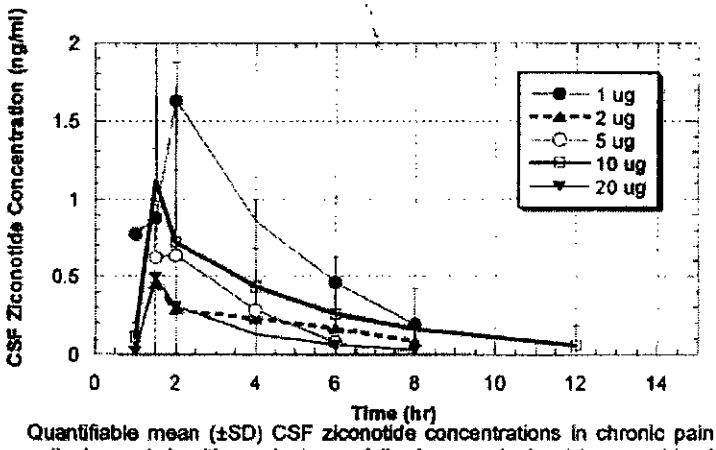
Results and Discussion:
Subjects: There were four early terminations. Thirty-one pain patients were included in the efficacy analysis and 39 subjects in the PK and PK-PD analyses. Seven healthy volunteers were enrolled in

this study and were distributed unevenly among dose groups. Two normal volunteers were in the 5 µg dose group (20% of participants), three were in the 10 µg dose group (27%), and one each in the 2 and 20 µg dose group (12.5% and 10%, respectively). The 1 µg dose group did not include any healthy volunteers.

CSF Pharmacokinetics

Cerebrospinal fluid concentrations were below the limit of quantification at all times for 25 of the 39 (64%) subjects whose PK concentration-time data sets were analyzed (therefore, CSF PK analyses were based on 14 subjects). The fraction of individuals displaying quantifiable ziconotide in CSF was related to dose, with 17%, 14%, 25%, 56%, and 56% of cases in the 1 µg, 2 µg, 5 µg, 10 µg, and 20 µg dose groups, respectively, exhibiting quantifiable drug. The majority of samples with quantifiable ziconotide were obtained between 1.5 and 6 hours after the epidural infusion. A plot of the mean ziconotide CSF concentration-time profiles, by dose group, is shown in Figure 1.

Figure 1. Mean ziconotide CSF concentration-time profiles per Dose



Quantifiable mean (±SD) CSF ziconotide concentrations in chronic pain patients and healthy volunteers following a single 1-hour epidural ziconotide infusion (N=14).

As shown in Figure 1, the 1 µg dose group exhibited the highest exposure, and the 20 µg group the lowest exposure (and exposure was quite variable), therefore, dose proportionality was not apparently demonstrated with mean exposure data. Table 1 summarizes the CSF PK of ziconotide for quantifiable subjects following a 1-hour EPI infusion.

Linearity of CSF Ziconotide PK: The results based on Spearman rank correlation coefficient (R), the CSF pharmacokinetics of ziconotide, except t_{max} and $t_{1/2}$, following a 1-hour EPI infusion were nonlinear and dose-dependent over the 20-fold dosage range studied here (Table 2).

Table 1: CSF Ziconotide Pharmacokinetics Following Epidural Infusion

Parameter (units)	Dose Group					All doses (N=14)
	1 µg (N=1)	2 µg (N=1)	5 µg (N=2)	10 µg (N=5)	20 µg (N=5)	
AUC/D (ng•hr/mL/µg)						
mean ± SD	6.27	0.807	0.365 ± 0.410	0.384 ± 0.607	0.053 ± 0.052	0.714 ±1.65
range			(0.075-0.655)	(0.057-1.47)	(0.005-0.131)	0.0052 - 6.27
median (N)	6.27 (1)	0.807 (1)	0.365 (2)	0.148 (5)	0.041 (5)	0.106 (14)
C_{max}/D (ng/mL/µg)						
mean ± SD	1.63	0.226	0.137 ± 0.123	0.117 ± 0.206	0.0271 ± 0.0286	0.203 ± 0.432
range						
median (N)	1.63 (1)	0.226 (1)	0.137 (2)	0.026 (5)	0.0099 (5)	0.046 (14)
T_{max} (hr)						
mean ± SD	2.0	1.5	1.8 ± 0.4	2.3 ± 1.0	2.2 ± 1.0	2.1 ± 0.84
range						
median (N)	2.0(1)	1.5(1)	1.8 (2)	2.0 (5)	2.0 (5)	2.0 (14)
CL/F (mL/min)						
mean ± SD	2.66	20.7	124 ± 139	144 ± 108	1140 ± 1340	480 ± 908
range						
median (N)	2.66 (1)	20.7 (1)	124 (2)	112 (5)	406 (5)	165 (14)
$\%F_{csf}$ (%)						
mean ± SD	8.83	1.14	0.51 ± 0.58	0.54 ± 0.86	0.07 ± 0.07	1.00 ± 2.33
range						
median (N)	8.83 (1)	1.14 (1)	0.51 (2)	0.21 (5)	0.06 (5)	0.15 (14)
V_d/F (mL)						
mean ± SD	420	6050	3260	47,900 ± 46,100	34,100 ± 30,900	32,700 ± 38,100
range						
median (N)	420 (1)	6050 (1)	3260 (1)	25,100 (5)	22,700 (3)	23,800 (11)
$T_{1/2}$ (hr)						
mean ± SD	1.82	3.38	1.48	3.63 ± 1.77	1.53 ± 0.83	2.71 ± 1.57
range						
median (N)	1.82 (1)	3.38 (1)	1.48 (1)	2.85 (5)	1.97 (3)	2.44 (11)

N = number of patients with quantifiable ziconotide in CSF for whom this PK parameter could be calculated.

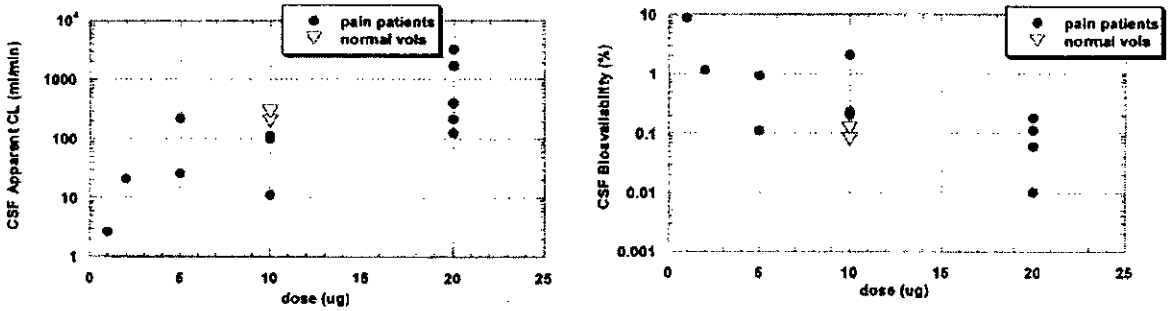
Table 2. Assessment of Dose-dependency of CSF PK

Parameter	Units	N	Spearman R	p-value
AUC∞/D	ng•hr/mL/µg	14	-0.70	**0.0051**
AUC	ng•hr/mL	14	-0.41	0.1503
C_{max}/D	ng/mL/µg	14	-0.64	**0.0145**
C_{max}	ng/mL	14	-0.37	0.1869
T_{max}	hr	14	0.12	0.6795
CL/F	mL/min	14	0.70	**0.0051**
%Fcsf	%	14	-0.72	**0.0034**
Vd/F	mL	11	0.59	0.0574
$T_{1/2}$	hr	11	-0.16	0.6305

Statistically significant findings are shaded and bolded
N = number of subjects for whom this PK parameter could be calculated

PK comparison between Healthy volunteers and Patients: Ziconotide CSF PK was compared in healthy normal volunteers and chronic pain patients, using CL/F (Figure 3, left) and $\%F_{csf}$ (Figure 3, right). These parameter values from normal volunteers fell among the values observed for pain patients. However, the small sample size inherent in this data set obviates statistical analyses and the power to make definitive conclusions.

Figure 3. Comparison of CSF CL/F (left) and %Fcsf (right) in Healthy volunteers and Pain patients.



Plasma Pharmacokinetics

Plasma PK analyses were done using 16 subjects since the plasma ziconotide concentrations were below assay limit of quantification at all times for 23 of the 39 (59% of subjects) subjects. The fraction of individuals displaying quantifiable ziconotide in plasma was apparently related to dose, with 0.0%, 0.0%, 50%, 67%, and 67% of cases in the 1 µg, 2 µg, 5 µg, 10 µg, and 20 µg dose groups, respectively, exhibiting quantifiable drug. Figure 4 shows the quantifiable mean plasma ziconotide concentrations in chronic pain patients and healthy volunteers following a single 1-hour epidural ziconotide infusion (n=16). Table 3 summarizes the mean plasma PK parameter values based on these data, and linearity analysis of plasma ziconotide PK parameters are summarized in Table 4.

Figure 4. Mean Ziconotide Plasma Concentration as a Function of Time and Dose

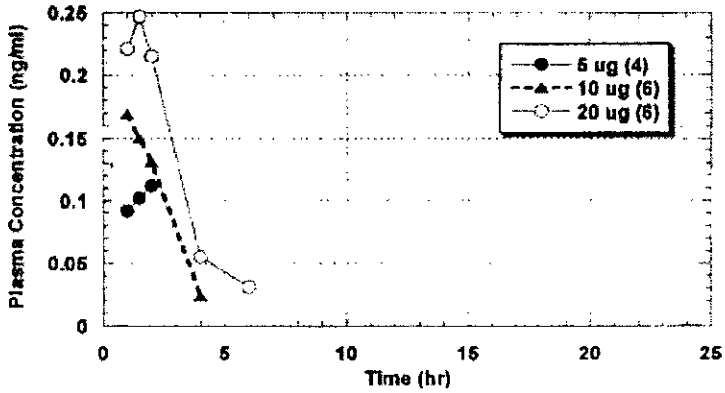


Table 3. Plasma Ziconotide Pharmacokinetics Following Epidural Infusion

parameter (units)	Dose Group					all doses (N=16)
	1 µg (N=0)	2 µg (N=0)	5 µg (N=4)	10 µg (N=6)	20 µg (N=6)	
AUC/D (nghr/ml/µg)						
mean ±SD	na	na	0.0398 ± 0.0101	0.0414 ± 0.0191	0.0365 ± 0.0242	0.0392 ± 0.0185
range			0.0306 - 0.0532	0.0134 - 0.0706	0.0080 - 0.0691	0.0080-0.0706
median (N)			0.0376 (4)	0.0434 (6)	0.0397 (6)	0.0421 (16)
C_{max}/D (ng/mL/µg)						
mean ± SD	na	na	0.0220±0.00249	0.0193±0.00597	0.0139±0.00691	0.0179±0.0064
range						
median (N)			0.0218 (4)	0.0203 (6)	0.0152 (6)	0.0191 (16)
T_{max} (hr)						
mean ± SD	na	na	1.9 ± 0.3	1.3 ± 0.4	1.3 ± 0.3	1.4 ± 0.4
range						
median (N)			2.0 (4)	1.0 (6)	1.5 (6)	1.5 (16)
CL/F (mL/min)						
mean ± SD	na	na	439 ± 104	527 ± 368	878 ± 829	637 ± 563
range						
median (N)			448 (4)	384 (6)	422 (6)	397 (16)
$\%F_{plasma}$ (%)						
mean ± SD	na	na	75.9 ± 19.4	79.2 ± 36.9	69.8 ± 46.2	74.9 ± 35.6
range						
median (N)			71.8 (4)	83.0 (6)	75.8 (6)	80.0 (16)
Vd/F (mL)						
mean ± SD	na	na	68,700	98,400± 114,000	127,000± 91,000	116,000± 98,600
range						
median (N)			68,700 (1)	49,000 (5)	113,000 (6)	69,400 (12)
$T_{1/2}$ (hr)						
mean ± SD	na	na	1.46	3.92 ± 5.90	2.08 ±1.12	2.88 ± 3.76
range						
median (N)			1.46 (1)	1.62 (5)	1.84 (6)	1.69 (12)

N indicates the number of subjects for whom this PK parameter could be derived with plasma conc. data.
na = not applicable (plasma ziconotide not quantifiable).

Table 4. Assessment of Dose-dependence of Plasma Pharmacokinetics

Parameter	Units	N	Spearman R	p-value
AUC∞/D	ng•hr/mL/µg	16		0.9816
AUC	ng hr/mL	16		**0.0405**
C_{max}/D	ng/mL/µg	16		**0.0239**
C_{max}	ng/mL	16		**0.0109**
T_{max}	hr	16		0.0908
CL/F	mL/min	16		0.9816
$\%F_{plasma}$	%	16		0.9816
Vd/F	mL	12		0.4807
$T_{1/2}$	hr	12		0.4351

Statistically significant findings are bolded and shaded.
N = number of subjects for whom this PK parameter could be calculated

Pharmacokinetic-Pharmacodynamic Analyses of Efficacy Data

The primary objectives of this study included the performance of PK-PD analyses of efficacy endpoints with both CSF and plasma pharmacokinetic data. Although it is generally believed that analgesic efficacy is derived from CSF ziconotide exposure, this analysis provides the opportunity to assess this hypothesis through correlation analyses with both CSF and plasma data. The correlation analyses (SAS version 6.12) were limited to subjects with quantifiable drug in CSF or plasma so that these results could be compared to those obtained following IT ziconotide infusion (Study C97-013, part A). Correlation coefficients and statistical significance were determined, with significance set at $p<0.05$.

Pain assessment: The mean MAXVASPID through 6 hours after initiation of study drug infusion was lowest for the 10 μg and 20 μg groups (10.5 and 17.0), and highest for the 1 μg, 2 μg and 5 μg dose groups (26.0, 19.5 and 28.5, respectively). Mean SPID, MAXCPRS and TOTPAR generally followed the same rank order as the MAXVASPID values. The 1 μg dose group had the highest proportion of responders at 48 hours (66.7%), and the 20 μg dose group had the smallest proportion of responders (0%). The combined results suggest that the greatest efficacy was observed in the 1 μg dose group.

CSF Pharmacokinetics and Analgesic Effect

Very little efficacy was observed in this trial, probably because little ziconotide was transported into CSF following the 1-hour EPI infusion. The CSF C_{max} and AUC exhibited some significant, negative, correlations with efficacy parameters, suggesting that lower CSF exposure was associated with increased efficacy, an unlikely event. The overall efficacy PK-PD findings are considered to be of little value and are attributed to low and variable CSF exposure following the 1-hour EPI ziconotide infusion.

Plasma Pharmacokinetics and Analgesic Effect

PK-PD correlations between plasma PK and efficacy revealed a few statistically significant correlations as listed below;

- TOTPAR through 20 hours with CL/F ($R = -0.55$, $p=0.0428$), AUC_∞ ($R = 0.54$, $p=0.0470$), $\%F_{plasma}$ ($R = 0.55$, $p=0.0428$). These results implied that individuals who cleared the drug more quickly from plasma or who absorbed less drug into blood tended to exhibit reduced efficacy at 20 hours. However, significant correlations were not apparent at other time-points, these findings (i.e., at the 20-hour) are considered spurious.
- TOTPAR through 0.5 hr with: V_d/F ($R=0.70$, $p=0.0247$), $t_{1/2}$ ($R=0.65$, $p=0.0434$). These results suggested that individuals who had a larger plasma distribution volume demonstrated greater efficacy at the earliest time-point. Clinically, ziconotide typically requires some time to act (95-001, 96-002), so it is unlikely that true analgesia existed 30 minutes after epidural administration.
- The classic exposure parameters (dose, AUC_∞, C_{max}) were not successfully correlated with any other of the VASPID, SPID, CPRS or TOTPAR scores following the 1-hour EPI infusion. Therefore, it may be concluded that plasma ziconotide exposure was not correlated in any significant manner with efficacy following a 1-hour EPI infusion to pain patients.

Concomitant medications: The results with concomitant medications that have the potential to affect either the pharmacokinetics or pharmacodynamics of ziconotide are as follows;

- Subject (#8792083) was prescribed furosemide for edema. This subject had the 2nd highest ziconotide CSF AUC_∞/D (1.47 ng•hr/ml/μg) and the 2nd highest C_{max}/D (0.485 ng/ml/μg)

following 10 μg dose. This suggested that there was a potential association with reduced ziconotide CSF clearance.

- Coadministration of ziconotide with angiotensin converting enzyme (ACE) inhibitors, such as benazepril, lisinopril and moexipril (1 patient each) did not suggest any relationship (i.e., interaction) with ziconotide.
- Coadministration of amlodipine (2 patients), nifedipine (2 patients) and verapamil (L-type calcium channel antagonists) (6 patients), also did not suggest any interaction with ziconotide.

Summary of results

CSF pharmacokinetics

- $AUC_{\infty, csf}$/dose, $C_{max, csf}$/dose and CL_{csf}/F demonstrated nonlinearity and dose-dependency following EPI administration. Nonlinearity of these parameters can be explained by capacity-limited transport of ziconotide from the epidural space into CSF. Consequently, $\%F_{csf}$, which relates with AUC /C_{max}, showed nonlinearity.
- The median and mean CSF ziconotide bioavailability following epidural infusion were 0.15% and 1.00% (range 0.01 to 8.83 %), respectively.
- The median CSF ziconotide clearance was 165 mL/min (range 2.66 to 3230 mL/min), which is much higher than the estimated human CSF bulk flow rate of 0.35 to 0.37 mL/min and greatly exceeds the estimated ziconotide human CSF median CL value of 0.26 mL/min based on IT administration (97-013). The median CSF distribution volume of ziconotide was 23,800 mL (range 420 to 118,339 mL), which was different than the predicted CSF volume in adult humans of 130 ± 30 mL, or the human CSF ziconotide volume of 99 mL. Therefore, the results appear to be due to very low CSF bioavailability (i.e., CL/F or V_d/F).
- The observation of nonlinearity of ziconotide pharmacokinetics in CSF following epidural administration can be explained simply by the dose-dependent CSF bioavailability of EPI ziconotide.

Plasma pharmacokinetics

- Ziconotide was quantifiable in plasma only within the three highest dosing cohorts (5, 10 and 20 μg). Overall, about 35% of patients had quantifiable drug in CSF and 41% had quantifiable drug in plasma.
- In contrast to CSF, plasma ziconotide pharmacokinetics were dose-proportional, except Cmax; Cmax was not well-characterized due to infrequent plasma sampling, so the nonlinearity documented for this parameter is questionable. This general linearity result supports the conclusion that ziconotide was absorbed from the EPI site into blood through a mechanism which does not involve a specific transporter. The path may be either directly through capillary endothelium, or via an indirect path utilizing the lymphatic system.
- The ziconotide $T_{max, plasma}$ was about 1.5 hours, slightly earlier than the 2.0 hour average for the CSF data.
- The plasma bioavailability of ziconotide ($\%F_{plasma}$) following a one-hour epidural infusion ranged from 0.0-136% with a mean value of 0.0% and mean of 26% (based on all samples, below and above limit of detection).
- The data demonstrated that angiotensin converting enzyme inhibitors did not affect plasma ziconotide clearance. The concomitant use of other calcium channel antagonists did not appear to affect the plasma pharmacokinetics of ziconotide.

- The characterization of ziconotide pharmacokinetics based on quantifiable concentrations results in an over-estimation of AUC and C_{max}, and therefore an under-estimation CL/F. The alternative (substitution of zero for BQL values) would produce under-estimated AUC and C_{max} values, resulting in over-estimated CL/F values.

Analgesia

- Niether CSF/plasma Cmax or CSF/plasma AUC_{∞} were positively correlated with any efficacy endpoints. Therefore, it appears that the PK-PD efficacy analyses support the general hypothesis that ziconotide must achieve quantifiable CSF concentrations for a significant period of time to elicit analgesic responses.

Conclusions:

- The CSF bioavailability of epidural ziconotide following a 1-hour infusion was very low and apparently saturable, resulting in nonlinear CSF pharmacokinetics. The combined results of this study support the observation that ziconotide is carried into CSF through a capacity-limited transport system. On the other hand, the plasma pharmacokinetics of ziconotide were dose-proportional, suggesting that ziconotide is absorbed from the epidural space into blood through a system that is not saturated.
- Epidural doses of 1-20 µg ziconotide resulted in very little CSF exposure, which was associated with weak efficacy and a lack of significant PK-PD relationships with CSF exposure.

96-012: A Multicenter, Phase II, Placebo-controlled Pilot Study of Ziconotide (SNX-111) Administered Epidurally to Patients with Acute Postoperative Pain.

Reference: Volume 80 (only for analytical report)
Investigators: Multicenter
Study Location: Multiple sites (clinical)

Test Product, Dose, Mode of Administration, and Lot Number: Ziconotide administered by continuous epidural infusion at either 0.7 µg/hr or 7.0 µg/hr. Lot Number NUT001.
Reference Therapy, Dose, Mode of Administration, and Lot Number: The placebo solution was identical to the active solution, except for the absence of the drug. Lot Number NUP002.

Objectives: To assess the safety and analgesic effectiveness of ziconotide administered by the epidural route in the management of postoperative pain.

Study Design: This phase II study was a randomized, double-blind, placebo-controlled, pilot study that was conducted at five sites, involving 25 patients (mean age of 60 years; range 23-87 years). Patients were treated with placebo or ziconotide at doses of 0.7 µg/hr or 7.0 µg/hr. Study drug was to be administered by epidural infusion for 48 hours. All patients had access to rescue analgesia as intravenous (IV) morphine by patient-controlled analgesia (PCA).

Criteria for Evaluation:
Pharmacokinetics: Ziconotide levels in plasma were obtained at baseline and just before the end of 48 hour-infusion. Optional samples for ziconotide in CSF were also collected just before the end of 48 hour-infusion.
Efficacy: The primary efficacy measure was the total amount of rescue analgesic medication used (measured as PCA IV morphine equivalents) during the first and second 24-hour periods following surgery and during the entire 48-hour study drug infusion period. Secondary efficacy measures included Visual Analog Scale of Pain Intensity (VASPI) and Categorical Pain Relief Scale (CPRS) scores.
Safety: Reported adverse events, laboratory assessments, vital signs measurements, and ECG results.

Analytical Methodology:
Assay Method: Radioimmunoassay (RIA)
Assay Sensitivity: The limit of quantitation (LLQ) was [redacted]
Assay Precision/Accuracy: The Replicate analysis of the QC ([redacted] had a between assay %RSD of [redacted] and a %RE of [redacted] Similarly, that of within assay %RSD was [redacted] and a %RE was [redacted]

Statistical methods: Statistical analysis was performed for efficacy but not for PK.

Results: Sixty-four samples from the 25 study patients were analyzed; none of the plasma samples from placebo-treated patients and none of the preinfusion (i.e., baseline) samples showed quantifiable concentrations of ziconotide (the lower limit of quantitation is [redacted]). Optional CSF samples, at the end of study drug infusion for analysis of ziconotide concentrations, were not collected (no explanation was presented). Quantifiable concentrations of ziconotide were present in 5 of the 9 low-dose (0.7 µg/hr) and in 6 of 8 the high-dose (7 µg/hr) ziconotide patients. Plasma ziconotide concentrations ranged from [redacted]

93-001: A randomized, double-blind, placebo-controlled, rising-dose safety and tolerability study of SNX-111 in healthy male volunteers.

Reference: Volume 71 – 73
Investigators: [redacted]
Study Location: [redacted]

Objective:

(1) To assess the safety and tolerability of single, escalating doses of SNX-111, in healthy, adult, male volunteers. (2) To obtain information on the pharmacokinetics of SNX-111 during and after continuous IV infusion in healthy subjects with no known hepatic or renal dysfunction.

Study Design:

This was a Phase I, first time in man, double-blind, randomized and placebo-controlled study in a total of 40 normal healthy male volunteers with a mean (range) age of 32.3 (20.1-48.6) years. The subjects were randomly divided into 5 groups: 10 μg/kg (Group 1 and Group 5), 0.3 μg/kg (Group 2), 1 μg/kg (Group 3), or 3.3 μg/kg (Group 4). The subjects (8 per dose group, 6 on SNX-111 and 2 on placebo) received continuous, constant rate, 24-h IV infusions (administered and monitored by an electronic infusion pump) via an indwelling IV catheter inserted in the lower part of the forearm at, or below, the antecubital area. A minimum interval of 1 week between dose groups was required to allow assessment of the safety and tolerability of the drug before proceeding to the next higher dose.

Drug supplies:

SNX-111 for Injection (Lot No. NUX002) was provided by Neurex as a sterile, [redacted] in vials containing 25 mg (peptide content) for reconstitution with 5 mL of Sterile Water for Injection (final concentration: 5 mg/mL). The reconstituted drug, then, was transferred into [redacted] containing 0.9% Sodium Chloride for Injection, [redacted] which were administered sequentially to achieve a 24-h continuous IV infusion. Subjects assigned to the placebo group received infusion of the vehicle only.

Criteria for Evaluation:

Pharmacokinetics: Blood samples were obtained at 0 (pre-infusion), and 15 min, 30 min, 1, 2, 4, 8, 12, 16 and 24 hrs after the start of the infusion, and 5 min, 15 min, 30 min, 1 h, 1.5 h, 2 h, 4 h, 6 h, 8 h, 10 h, 12 h, 16 h, and 24 h after the end of the infusion. Estimated PK parameters include Area under the plasma concentration-time curve to last detectable concentration [AUC_{0-t}] as well as to infinity [AUC_{∞}], steady state plasma concentration [CP_{ss}], Clearance [CL], Volume of distribution at steady state [V_{ss}], Area under the moment curve [AUMC], Mean residence time [MRT] and terminal half-life [$t_{½}$].

Safety: Blood pressure, ECG, EEG, Clinical laboratory tests, physical/neurological examinations, Affective/cognitive test, neurological examination, CNS functioning test and reports of adverse events.

Analytical Methodology:

Assay Method: Radioimmunoassay (RIA)

Assay Sensitivity: The limit of quantitation (LQ) was [redacted] for 0.1 ml sample volume).
Assay Precision/Accuracy: The precision of QC [redacted]), expressed as % relative standard deviation (%RSD), ranged from [redacted] and accuracy ranged from [redacted] on QC samples.

Statistical methods:

Descriptive statistics (mean, standard deviation, minimum, maximum, and change from baseline) were computed for each dose group. If statistical comparisons between active drug and placebo were appropriate, one-way analysis of variance or Fisher's exact test was used. In such cases, the 10 subjects receiving placebo were combined into a single treatment group and were compared with the 6 subjects receiving active treatment in each dose group.

Results:

Ziconotide plasma concentrations were not measurable (below LQ) in 5/6 subjects following the 0.3 μg/kg/24 hr dose, therefore, the sponsor did not include the data from group 2 for PK analysis. In addition 2 subjects did not complete the study due to adverse events, so only the data from 22 subjects are included for the PK analysis.

The 2-compartment PK open model with linear elimination best described Ziconotide plasma concentration-time data. However, noncompartmental model also provided similar PK parameter values. The results of the mean PK parameter values by these two models are listed in Table 1.

Table 1. Pharmacokinetic parameters for ziconotide (n = 22)

Parameter	Noncompartmental Model	2-Compartmental Model
AUC_∞ [a] (ng•h/mL)		
mean	5.1	5.36
range	[redacted]	
Cp_{ss} [b] (ng/mL)		
mean	0.20	0.20
range	[redacted]	
CL (L/hr)		
mean	16.9	16.2
range	[redacted]	
V_{ss} (L)		
mean	30.2	30.5
range	[redacted]	
V_d (L)		
mean	-	63.8
range	[redacted]	
$t_{1/2}$ (h)		
mean	1.26	1.22
range	[redacted]	
MRT (h)		
mean	1.82	1.92
range	[redacted]	

[a]Dose-normalized (i.e., AUC_∞/Dose; $AUMC_\infty$/Dose)
[b]Dose-normalized observed (i.e., Cp_{ss}/Dose)

Figure 1 shows individual observed plasma ziconotide concentration at steady state (Cp_{ss}) versus infusion rate (left panel), and individual estimates of AUC_∞ versus dose in subjects (right panel). Similarly, Figure 2 shows individual clearance estimates from 2-compartment model versus clearance estimates from D/AUC_∞ (left), and individual AUC_∞ estimates from 2-compartment model versus AUC_∞ estimates from noncompartmental modeling in subjects (right).

Figure 1. Individual Observed Cp_{ss} *vs.* Infusion Rate (left panel), and Individual estimates of AUC_∞ *vs.* Dose in healthy volunteers (right panel).

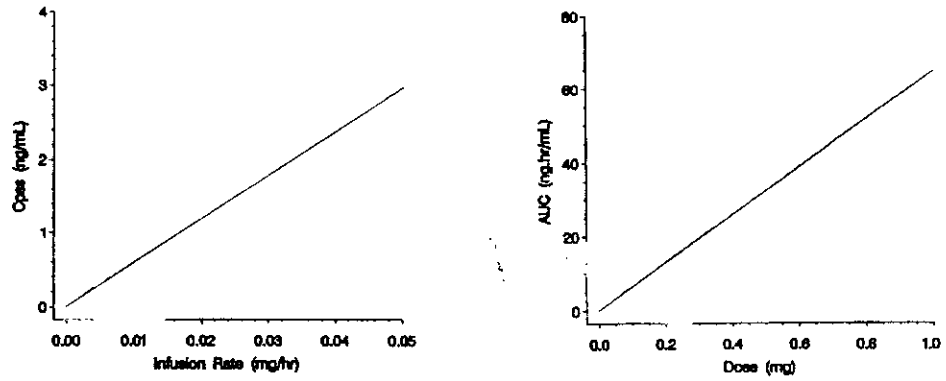
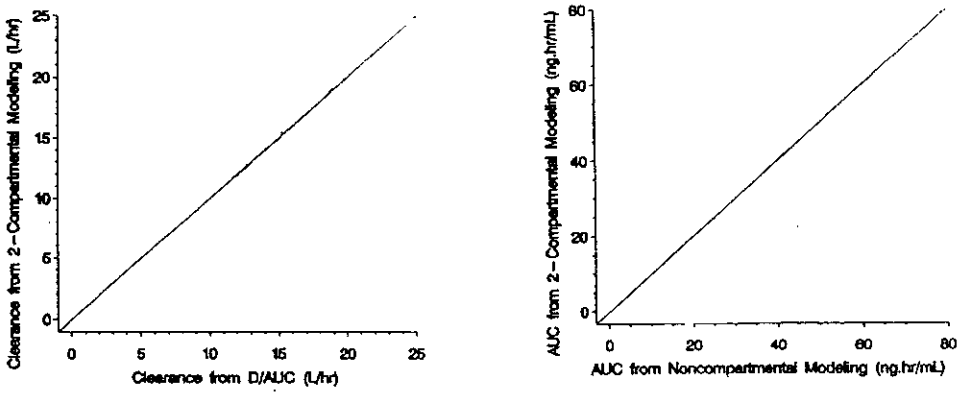


Figure 2. Individual Clearance estimates from 2-compartment model *vs.* Clearance estimates from D/AUC_∞ (left), and Individual AUC_∞ estimates from 2-compartment model *vs.* AUC_∞ estimates from Noncompartmental modeling in healthy volunteers (right).



The table below listed the primary PK parameter values per each group. Based on the results, it may be concluded that the plasma PK of ziconotide following IV infusion of between 1-10 μg/kg/24 hr to healthy male volunteers was linear and dose proportional.

Group	µg/kg/24 hr	CL (L/hr)	Vss (L)	$T_{1/2}$ (hr)
1 (N=6)	10	18.6 ± 2.2	30.0 ± 3.9	1.1 ± 0.1
2 (N=6)	0.3	--	--	--
3 (N=6)	1	17.1 ± 3.6	33.2 ± 4.7	1.3 ± 0.3
4 (N=5)	3	15.2 ± 0.1	32.3 ± 4.2	1.5 ± 0.2
5 (N=5)	10	16.6 ± 2.8	30.1 ± 5.2	1.3 ± 0.3

Summary of results:

- The dose normalized mean ± SD for Cp_{ss} was 0.2 ± 0.01 ng/mL.
- The dose normalized mean ± SD for AUC_∞ was 4.26±1.71 ng•h/mL by Noncompartmental model analysis.
- The mean (range) clearance was estimated to be 16.2 (11.7-21.8) L/hr.
- The mean (range) volume of distribution at steady state was 30.5 (18.6-47.0) liters.
- The overall mean (range) elimination half-life was 1.2 (0.75-1.6) hours.
- The mean (range) AUC_∞ was estimated to be 23.3 (4.6-66.7) ng•hr/mL.
- The mean (range) MRT was 1.9 (1.2-3.2) hours.
- It appears that plasma PK of ziconotide following IV infusion of between 1-10 µg/kg/24 hr to healthy male volunteers seems to be linear and dose proportional.
- Two-compartment model as well as Noncompartmental model produced similar PK parameter values for Ziconotide plasma concentrations.

Comments:

The drug formulation used in this study is not the same as the one to-be-marketed. Assessment of dose-proportionality of plasma ziconotide for PK parameters was done without any statistical analysis.

94-002: A Phase II, Placebo-Controlled, Double-Blind, Randomized, Rising Dose-Tolerance Study of SNX-111 Administered Intravenously to Patients Undergoing Elective Coronary Artery Bypass Graft Surgery With Cardiopulmonary Bypass.

Reference: Volume 81
Investigators:
Study Location: [redacted]

Formulation:

Ziconotide as a sterile, [redacted] Lot No. NUX002 (not the to-be marketed formulation), which was reconstituted in 0.9% Sodium Chloride Injection. Patients assigned to the control group received infusions of 0.9% Sodium Chloride only.

Objective:

To determine the maximum tolerated dose of ziconotide, administered by IV infusion, in patients undergoing elective coronary artery bypass graft (CABG) surgery with cardiopulmonary bypass (CPB), with specific emphasis on management of the known hemodynamic effect of systemic hypotension. Additionally, to evaluate PK characteristics of ziconotide.

Study Design:

This phase II study was a randomized (2:1 ratio of the ziconotide : placebo), double-blind, placebo-controlled, rising-dose study that was conducted at one site in 13 male and 3 female patients of age ≥ 75 years (mean of 60.4 years). Patients were treated at one of the following loading rate/maintenance rate: 0/0 (placebo), 62.5/15, 125/30, 250/60, 500/125, 1000/250, 2000/500 and 4000/1000 μg/kg/day, contingent upon acceptable hypotension management at the previous rate level. Loading dose infusion was administered 1 hour before CPB. Following the completion of the 1-hour loading dose and just before the beginning of CPB, a maintenance dose infusion was initiated and continued for 11 hours, for a total 12-hour study drug infusion period.

Criteria for Evaluation:

Pharmacokinetics: Blood samples were obtained before, during, and following the infusion. Estimated PK parameters include Clearance [CL], Volume of distribution at steady state [V_{ss}], Mean residence time [MRT] and terminal half-life [$t_{½}$].
Clinical: The primary endpoint for stopping dose escalation was hypotension that could not be managed with IV fluids or intermittent bolus administration of α-agonists, or the occurrence of serious or unexpected adverse events.

Analytical Methodology:

Assay Method: Radioimmunoassay (RIA)
Assay Sensitivity: The limit of quantitation was [redacted] ml sample size).
Assay Precision/Accuracy: The precision of QC, expressed as % relative standard deviation (%RSD), ranged from [redacted] and accuracy ranged from [redacted] in QC samples.

Pharmacokinetic Analysis:

PK parameters were estimated by noncompartmental methods (SAS), one or 2 compartment model (NONMEM). The results from this study were compared to those observed in healthy volunteers using Meta analysis: $Cp_{ss,\ observed}$ and $AUC_{0-\infty}$ were linearly regressed with infusion rate and dose, respectively to determine whether $Cp_{ss,\ observed}$ and $AUC_{0-\infty}$ were proportional to rate and dose, respectively.

Results and Discussion:

The following mean PK parameters values were observed:

Parameter	Method of Analysis	Mean	(%RSD)
* CL = D/AUC (L/hr)	Noncompartmental	10.7	15.6
CL = $R_0/Cp_{ss,observed}$ (L/hr)	Noncompartmental	10.8	20.6
CL (L/hr)	2-Compartmental	10.9	14.1
t½ using MRT (hr)	Noncompartmental	1.25	28.8
* t½ using MRT (hr)	2-Compartmental	1.69	32.6
Vd_{ss} (L)	Noncompartmental	11.5	29.0
* Vd_{ss} (L)	2-Compartmental	26.3	31.5

* Recommended method for parameter determinations (see text)

Results, by meta analysis, of comparison between patients (94-002) and healthy volunteers (study 93-001 and 93-002, reviewed first one only) are shown in the table below:

Subject Type	n	Clearance (L/hr)			Slope estimate		Mean age (yr)	Mean weight (kg)
		Mean	%RSD	Range	Cp_{ss}-Rate	AUC-Dose		
CABG patients	9	10.7	15.6	[redacted]	84.2	90.6	59.2	81.1
Healthy volunteers	60	15.3	17.9	[redacted]	55.3	60.2	29.1	79.9
Combined	69	14.7	20.7				33.0	80.0

Cp_{ss}-Rate = $Cp_{ss,\ observed}$ versus infusion rate AUC-Dose = AUC versus Dose

Clearance and Cp_{ss} from this study were significantly different than those from healthy volunteers ($p = 0.0001$). However, most of patients were older compared to the healthy volunteers, as shown in the table. Therefore, it appears that this difference is due to the effect of age.

Amendment to protocol:

The original protocol called for a 1 hour loading infusion followed by an 11 hour maintenance infusion at the following escalating dose levels: 125/30, 250/60, 500/125, 1000/250, 2000/500, and 4000/1000 µg/kg/24 hr. Four patients were treated under the original protocol; the highest dose administered before the protocol was amended was 250/60 µg/kg/24 hr.

The amended protocol reduced the duration of the maintenance infusion to 3-4 hours (administered until 1 hour after decannulation), and lowered the dose levels to the following escalating infusion rates: 62.5/15, 125/30, 250/60, 500/125, 1000/250, 2000/500, and 4000/1000 µg/kg/24 hr. Twelve subjects were treated under the amended protocol. The highest loading dose administered was 500 µg/kg/24 hr, with the maintenance infusion omitted for this dosing level. Dose

escalation was contingent upon acceptable safety and tolerability assessments at the previous dose level.

Pharmacokinetic Sampling and Data analysis Methods for urine data:

Under the original protocol, urine samples were collected for PK assays from 0-to-6-hour, 6-to-12-hour (i.e., from beginning to the end of infusion), and 12-to-18-hour interval (postinfusion). Under the amended protocol, urine samples were collected only until the end of the infusion. Urine samples were analyzed by the same method as plasma samples, and by the same laboratory.

Urinary ziconotide PK parameters, such as, total amount of ziconotide excreted in urine, percentage of ziconotide dose excreted, and renal clearance were to be calculated for each patient for each urine collection interval: The amount of ziconotide excreted in the urine was calculated as the urinary concentration of ziconotide multiplied by the urine volume. Ziconotide renal clearance for each urine collection interval was calculated as the amount of ziconotide excreted divided by the area under the plasma ziconotide concentration-time curve (AUC) for the same time period as the urine collection.

Analytical Methods:

A validated RIA for plasma ziconotide assay was used to determine urine ziconotide concentrations with the only modification to the procedure in which 0.1 mL of urine was used instead of plasma to prepare standard and unknowns.

Results and Discussion:

Of the 24 urine samples collected, 18 were analyzed. Renal clearance was estimable for 9 subjects (10 collection periods). The concentration of ziconotide RIA equivalents in urine ranged from nondetectable (i.e., < [redacted], with a mean concentration of 0.24 ng/mL (the corresponding plasma concentrations ranged from [redacted]). The percentage of the IV ziconotide dose that was excreted in urine ranged from [redacted], with a mean of 0.025%. The renal clearance for subject #004 was about 1% of total plasma clearance. In all other cases, calculable renal clearance values were < 0.1% of total clearance. Ziconotide was detected in the urine of 2 of 5 subjects in the placebo group, at concentrations of [redacted] respectively.

The urinary excretion of intact ziconotide in this trial appears to be low, however, this interpretation must be used cautiously for the following reasons: 1) analytical method used, was not validated for the analysis of the urinary ziconotide concentrations. 2) There was not a good correlation between the administered dose and the measured concentrations of ziconotide in the urine. 3) There are no data on the stability of ziconotide in urine. 4) The period of urine collection was not uniform in all patients, and especially in patients with amended protocol, did not encompass the entire period of drug elimination. 5) Measurable ziconotide levels in the urine samples from two placebo patients were detected (the sponsor suspects that this could be due to mislabeling or contamination of the sample at the hospital or in the laboratory).

The sponsor concluded that there is no evidence for any appreciable urinary excretion of intact ziconotide in this population of CABG patients treated with intravenous infusion of ziconotide.

Overall: (1) Plasma ziconotide concentration-time data were best represented by a 2-compartmental open PK model, however noncompartmental model also provided similar parameter values. (2) Clearance decreases with increasing age. (3) < 1% of the dose was excreted unchanged in the urine (using unvalidated assay). (4) The drug formulation used in this study is not the same as the to-be-marketed formulation.