Clinical Trial Results of the Prometra System

Study Objectives

The purpose of this clinical investigation was to demonstrate the accuracy, safety and effectiveness of the Prometra® pump system for the intrathecal infusion of preservative-free morphine sulfate (Infumorph) in the treatment of chronic intractable pain.

Study Overview

The Prometra's Utilization in Mitigating Pain (PUMP) study was conducted under a US FDA IDE (G060192). The PUMP study was a non-randomized, open-label, multi-center study. Enrollment for the study included patients suffering from cancer pain or chronic, non-malignant pain with a pain score of 4/10 or greater, or patients who needed a pump replaced and had a documented history of pain relief with intrathecal morphine sulfate infusion.

The PUMP study began on March 10, 2007 when the first patient was enrolled. The study enrolled a total of 110 patients at seven clinical sites. Sites included:

- Pain Institute of Tampa (Tampa, Florida), John Barsa, MD
- Center for Pain Relief (Charleston, West Virginia), Timothy Deer, MD
- Pain Control Network (Louisville, KY), Elmer Dunbar, MD
- Lowell General Hospital (Lowell, Massachusetts), Gopala Dwarakanath, MD
- Center for Interventional Pain Management (St. Louis, Missouri), Gurpreet Padda, MD
- Center for Clinical Research (Winston-Salem, North Carolina), Richard Rauck, MD
- Fox Chase Pain Management Associates (Jenkintown, Pennsylvania), Steven Rosen, MD

Methodology

All subjects were implanted with the Prometra pump system and all subjects received treatment with intrathecal morphine. Subjects were evaluated on a monthly basis for the first six months (Acute Phase). After completion of the Month 6 visit, subjects entered the Long-Term Phase of the study and continued to attend follow-up visits on a quarterly basis until the study device was explanted, became commercially available, or the patient expired.

Acute Phase

- First 6 months
- Monthly Evaluation

Long-Term Phase

- After 6 months until explanted or the device is commercially available
- Quarterly evaluation

Demographics

The demographics for the patient population are similar to what has been reported in other studies involving intrathecal drug delivery systems. Table 1 summarizes the demographic information for the PUMP study.

Table 1: Patient Demographics

Demographic	Population (N=110)
Gender	**N (%)**
Male	59 (54%)
Female	51 (46%)
Age (years)	
N	110
Mean	55.6
SD	13.3
Median	54.6
Range	28-84
Race	**N (%)**
White	104 (95%)
Black or African American	5 (5%)
Hispanic	1 (1%)

Pain History

A slight majority of patients enrolled had neuropathic pain only. The most common causes of pain in the study were post-lumbar spine surgery with pain and intractable back pain. The proportion of patients whose pain was nonmalignant vs. cancer pain is consistent with other studies involving IDDs.

Table 2: Patient Pain History

Variable	(N=110)
Duration of Pain (N ± SD)	**12.4 ± 10.0 years**
Pain Category	**N (%)**
Neuropathic	64 (58)
Nociceptive	12 (11)
Both	34 (31)
Causes of Pain[1]	**N (%)**
Chronic Regional Pain Syndrome	24 (22)
Vertebral Body Compression Fractures	6 (6)
Post Lumbar Spine Surgery with Pain	60 (55)
Post Cervical Spine Surgery with Pain	14 (13)
Post Thoracotomy Pain Syndrome	3 (3)
Arachnoiditis	26 (24)
Intractable Back Pain	57 (52)
Cancer Pain	3 (3)
Other	70 (64)

[1] Percentages may add up to greater than 100% because patients may be counted in more than one category.

Evaluations of Objectives

There were three objectives of the study. The study was designed to evaluate the accuracy, safety and efficacy of the Prometra pump system.

1. To demonstrate that the Prometra pump system accurately delivers medication in the intrathecal space as programmed, accuracy was evaluated using the following key measurements:
   a. **Reservoir Volume (expected volume):** volume of medication calculated to remain in the pump according to the volume that was previously programmed for delivery
   b. **Returned Volume (actual delivered volume):** volume of medication physically removed from the pump
   c. **DP Ratio:** The ratio of delivered drug to programmed drug or (actual to expected volume) summed cumulatively for all fill/refills, including any unscheduled visits per patient
   d. **Refill Volume:** volume of medication injected into the pump
   e. Accuracy was considered met if the 90% confidence limits on the DP ratio were within the 85% to 115% range
2. To demonstrate the safety of the Prometra pump system, safety was evaluated using the following data:
   a. The device-related serious adverse events (SAE) post implant.
   b. The tabulation of the incidence of device complications.

Study Results

Accuracy

The Delivered to Programmed (DP) ratio was calculated as the ratio of the actual delivered drug to the programmed delivered drug. The DP ratio was calculated per patient and averaged together to get the monthly DP ratios.

The table below displays the results of the analysis of the DP ratio. These results summarize 1,730 refills as of December 21, 2009.

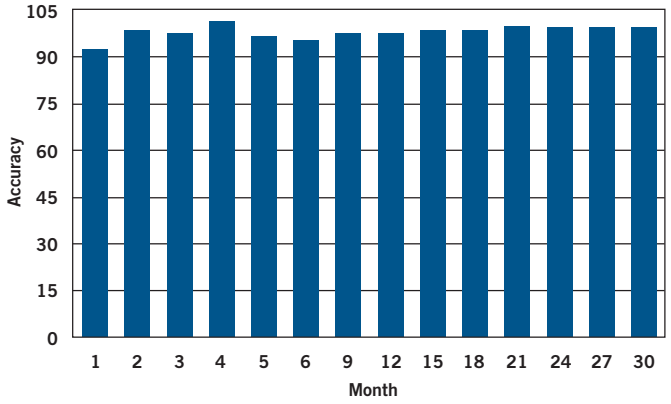
Table 3: Analysis of Delivered-Programmed (DP) Drug Volume Ratios

Per Patient DP Ratio	(N=110)
N	107*
Mean	96.8
Standard Deviation	5.5
Median	97
90% confidence interval of mean	95.9 – 97.7

*Three patients had their pump explanted prior to having a refill.

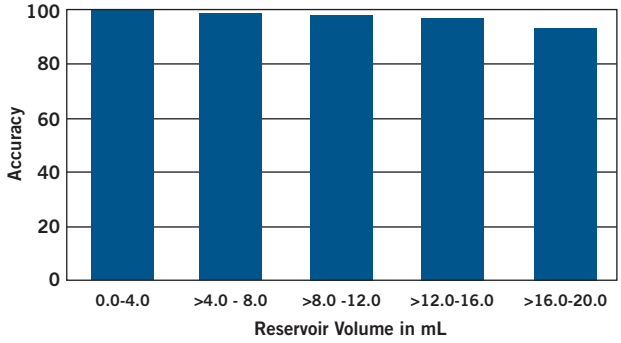
Prometra's accuracy remained well within the 85 – 115% range for each month over the course of treatment as demonstrated by Figure 1 below and table 3 above. Accuracy was reported to be greater than 95% at all months, with the exception of Month 1, which was over 92%. At 2.5 years post implant (30 months) Prometra's accuracy not only remained above industry standards, but accuracy also improved over time, which can be seen in figure 1.

Figure 1: Accuracy by Month



Reservoir volume did not have an effect on Prometra's accuracy. The graph below illustrates the pump's accuracy over several different reservoir volume categories. The accuracy remained over 90% despite a high or low reservoir return volume. Prometra's drug delivery is unaltered by both an increase in reservoir pressure when the pump is full and a decrease in reservoir pressure when the pump is empty, creating accurate drug flow throughout the dosing-cycle from refill to refill.

Figure 2: Accuracy by Reservoir Volume



Safety

Adverse events were collected in both the acute phase and long-term follow up phase. The adverse events collected during each phase are illustrated below.

Acute Phase

- All adverse events were collected, including those listed in the Long-Term Phase

Long-Term Phase

- Device Related Adverse Events (DRAE)
- Serious Adverse Events (SAE)
- Unanticipated Adverse Device Events (UADE)

Definitions

1. **Device Related Adverse Events (DRAE)** – an adverse event that is reported to be possibly, probably or definitely related to the device or study procedure.
2. **Serious Adverse Events (SAE)** – an adverse event that is deemed to be serious. It is considered serious if there are any untoward medical occurrences that require overnight hospitalization, require prolongation of existing hospitalization, result in persistent or significant disability or incapacity, are life-threatening, or result in death.
3. **Unanticipated Adverse Device Events (UADE)** – an adverse event that was not expected based upon studies of other commercially available replacement product.

Serious adverse events were tracked in order to determine the pump's safety. Although 274 patients experienced an SAE, the large majority were not Device Related. Many of the SAEs were related to procedural pain or health conditions that the patient had prior to the Prometra pump system implant.

During the study only three patients were reported to have a Device-Related Serious Adverse Event. One patient experienced implant site cellulitis and the second experienced an extradural abscess. Third patient had hip fracture from fall. Although the adverse events were suspected to be related to the device, such adverse events are not unusual in patients receiving this therapy.

No unanticipated adverse events were observed during the trial. In addition, no pump failures occurred and no granulomas were observed during the study.

Conclusions

The purpose of this clinical study was to demonstrate the accuracy, safety and efficacy of the Prometra pump system for the chronic intrathecal infusion Infumorph solution in the treatment of chronic intractable pain. One hundred ten patients were successfully implanted with the Prometra pump at seven clinical sites.

Every endpoint was achieved. Specifically, the Prometra pump system accurately delivers the volume of medication that is programmed for delivery, as exemplified by a delivered-programmed (DP) ratio of 95.9 – 97.7%, which is well within the endpoint limits of 85% - 115%.

The Prometra pump system was also shown to provide safe therapy to this patient population. No unanticipated adverse device effects or deaths attributed to the Prometra pump system have occurred. Adverse events and device complications reported in this study are consistent with what has been documented in other studies involving implantable drug delivery systems. No pump failures occurred and no granulomas were observed during the study.

*Individual results may vary. Not every individual will experience the same benefits. See Indications, safety, and warnings for associated with intrathecal drug delivery.

INDICATIONS: The Prometra Programmable Infusion System is indicated for intrathecal infusion of Infumorph® (preservative-free morphine sulfate sterile solution) or preservative-free sterile 0.9% saline solution (Sodium Chloride Injection, USP). **DRUG INFORMATION:** Refer to the Infumorph labeling for a complete list of indications, contraindications, warnings, precautions, dosage administration information and screening procedures. **CONTRAINDICATIONS:** Implantation of this device is contraindicated when: The presence of infection is known or suspected; contraindications relating to Infumorph must be observed and followed per the approved drug labeling. **WARNINGS:** (1) Use of unapproved drugs (e.g., drug cocktails, pharmacy compounded drugs, morphine with preservatives, etc.) with the Prometra pump could result in pump failure and/or serious adverse events including death. (2) Patients should not undergo MRI or other magnetic or other magnetic therapies. Failure to empty the pump prior to exposure to MRI environment could result in drug overdose that could lead to serious patient injury or death. **PRECAUTIONS:** Safety and effectiveness for use in pediatric patients under 22 years old has not been investigated or established. Caution: Federal Law (USA) restricts this device to sale by or on the order of a physician. **Complete Prometra Instructions for Use and Infumorph drug labeling must be reviewed prior to use.**

Rx Federal Law (USA) restricts this device to sale by or on the order of a physician.

Flowonix™

Implanting Confidence®

Flowonix Medical Inc.
500 International Drive, Suite 200
Mount Olive, New Jersey 07828
973.426.9229 · 973.426.0035 (fax)
www.flowonix.com

PL-15018