MALLINCKRODT PHARMACEUTICALS, INC

INVESTIGATIONAL NEW DRUG PROTOCOL

INTRATHECAL HYDROMORPHONE HCL 10 MG/ML

PROTOCOL NUMBER CNS-HYD202US

VERSION 7.0 DATED 01 AUGUST 2016

AMENDMENT REVISING PRIOR VERSION 6.0 DATED 24 JUNE 2016

A Phase 3, Open-Label, Single-Arm Study To Assess The Safety Of Hydromorphone Hydrochloride Delivered By Intrathecal Administration

SPONSOR:

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CONFIDENTIAL

SUMMARY OF CHANGES FROM VERSION 6.0 TO VERSION 7.0

DATED 01 AUGUST 2016

This protocol amendment was required to allow dose adjustments immediately for subjects rolling over from the CNS-HYD201US study, to clarify that the study is open to all subjects in CNS-HYD201US who are randomized, or drop out prior to randomization, and the different procedures to be followed by subjects enrolling from CNS-HYD201US depending upon whether they were randomized subjects, or had dropped out prior to randomization. These and other changes are listed below:

1. Version is changed from v6.0 to v7.0 and protocol re-dated as appropriate. Title page, headers and footers are revised appropriately.

2. Protocol Synopsis, Study Design Section, last paragraph, was changed to allow dose adjustments from the beginning of enrollment, if clinically indicated.

3. Protocol Synopsis, Study Design Section, last paragraph, was changed to clarify that those subjects dropping out of CNS-HYD201US prior to randomization will need to do all assessments in the CNS-HYD202US trial. Their assessments for CNS201 will not carry over.

4. Section 1.4, Study Rationale, first paragraph, was revised to clarify that the CNS-HYD202US study is open to all subjects in CNS-HYD201US who are randomized, or drop out prior to randomization.

5. Section 3.1, Description of Trial Design, eleventh paragraph, was revised to allow dose adjustments from the beginning of enrollment, if clinically indicated.

6. Section 3.5.1.1, Titration to a Therapeutic Dose of Hydromorphone Hydrochloride was revised to allow dose adjustments from the beginning of enrollment, if clinically indicated.

7. Section 9.2, Baseline Evaluations, third paragraph, was revised to clarify the different procedures to be followed by subjects enrolling from CNS-HYD201US depending upon whether they were randomized subjects, or had dropped out prior to randomization.

8. Minor edits were made to correct grammar and spelling errors.

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LIST OF ABBREVIATIONS

ABBREVIATION	DEFINITION
AE	Adverse event
AUC	Area under the plasma concentration-time curve
$AUC_{0-\infty}$	Area under the plasma concentration curve-time from time 0 to infinity
AUC_{0-t}	Area under the plasma concentration-time curve from time 0 to the last quantifiable concentration
BPI	Brief Pain Inventory
CLcr	Creatinine Clearance
CFR	Code of Federal Regulations
cGMP	Current Good Manufacturing Practices
CMP	Complete Metabolic Panel
CNS	Central Nervous System
COWS	Clinical Opiate Withdrawal Scale
CRF	Case Report Form
CRU	Clinical Research Unit
CSF	Cerebrospinal Fluid
CT	Computed Tomography
%cv	Percent Coefficient of Variation
CTCAE	Common Terminology Criteria for Adverse Events (v. 4.03)
EC	Ethics Committee
FDA	Food and Drug Administration
g	Gram
GABA	Gamma-Aminobutyric Acid
GCP	Good Clinical Practice(s)
ICF	Informed Consent Form
ICH	International Conference on Harmonization

ABBREVIATION	DEFINITION
IRB	Institutional Review Board
IT	Intrathecal Injection
ITT	Intent-To-Treat
IP	Investigational Product
kg	Kilogram
L	Liter
MedDRA	Medical Dictionary for Regulatory Activities
mcg	Microgram
MFD	Maximum Feasible Dose
mg	Milligram
mL	Milliliter
MRI	Magnetic Resonance Imaging
NCI	National Cancer Institute
NDA	New Drug Application
PGIC	Patient's Global Impression of Change
PI	Principal Investigator
PTM	Personal Therapy Manager
SAE	Serious Adverse Event
U.S.	United States (of America)
USP	United States Pharmacopeia
VASPI	Visual Analog Scale of Pain Intensity
WHODD	World Health Organization Drug Dictionary

INVESTIGATOR STATEMENT

I have read and understand the protocol and agree to implement the study in accordance with the procedures set forth in the protocol and in accordance with the Sponsor's guidelines, all applicable government regulations, and the International Conference on Harmonization Good Clinical Practice Guidelines E6 (ICH-GCP).

I will maintain accurate source documents from which data are transcribed onto case report forms and accurate drug accountability records that show the receipt and disposition of all study drugs.

I will provide adequate protocol training to my associates, colleagues, and employees assisting in the conduct of the study.

I will obtain Institutional Review Board/Ethics Committee (IRB/EC) approval of the protocol and Informed Consent Form prior to enrollment of subjects in the study. I understand that any modifications to the protocol made during the course of the study must first be approved by the IRB/EC prior to implementation except when such modification is made to remove an immediate hazard to the subject.

I will ensure that a fully executed IRB-approved Informed Consent Form is obtained from each subject prior to initiation of any study procedures.

I will report (within 24 hours) any serious adverse event, regardless of relationship to study drug, or pregnancy that occurs during the course of the study, in accordance with the procedures described in Section 13.2 of the protocol. I will notify the Sponsor if I become aware that a partner of a study subject becomes pregnant while the subject was receiving this study drug.

I will submit all protocol inclusion/exclusion violations to the medical monitor for approval prior to enrollment of the subject in the study.

I will allow the Sponsor and its agents, as well as the United States (U.S.) Food and Drug Administration (FDA) and other regulatory agencies to inspect study facilities and pertinent records at reasonable times and in a reasonable manner, ensuring subject confidentiality. If I am notified that this study is to be inspected by a regulatory agency, I will notify the Sponsor as soon as possible thereafter (no later than 1 week).

This protocol contains information that is proprietary to the Sponsor. The information contained herein is provided for the purpose of conducting a clinical trial for the Sponsor.

The contents of this protocol may be disclosed to study personnel under your supervision and to your IRB/EC. The contents of this protocol may not be disclosed to any other parties (unless such disclosure is required by government regulations or laws) without the prior written approval of the Sponsor.

_____ _____

Investigator's Signature Date

<table>
<tr><th colspan="2">PROTOCOL SYNOPSIS</th></tr>
<tr><td>Study title</td><td>A Phase 3, Open-Label, Single-Arm Study to Assess the Safety of Hydromorphone Hydrochloride Delivered by Intrathecal Administration (CNS-HYD202US)</td></tr>
<tr><td>Sites</td><td>Up to 30</td></tr>
<tr><td>Study Drug</td><td>Hydromorphone hydrochloride 2 mg/mL and 10 mg/mL</td></tr>
<tr><td>Indication</td><td>Preservative free hydromorphone hydrochloride injection for intrathecal use is indicated for the management of pain not responsive to non-narcotic analgesics. Hydromorphone hydrochloride administered intrathecally, provides pain relief for extended periods without attendant loss of motor, sensory or sympathetic function.</td></tr>
<tr><td>Objectives</td><td><u>Primary objective</u>:
To evaluate the long-term (12-month) safety of a hydromorphone hydrochloride given by the intrathecal route of administration.</td></tr>
<tr><td>Study Design</td><td>This is an open-label, single-arm study to evaluate the safety of hydromorphone hydrochloride given by continuous intrathecal infusion using an implantable pump device. This clinical trial will be conducted at up to 30 clinical trial sites that are experienced with the use of intrathecal opioids. This study will enroll both subjects on a current opioid (eg, morphine or hydromorphone hydrochloride) intrathecal medication as well as naïve subjects not currently on intrathecal opioid medications. Dosing regimens allowed in this study will include simple continuous, complex continuous and Personal Therapy Manager (PTM) dosing.
For subjects entering the trial already on a therapeutic dose of hydromorphone hydrochloride, the hydromorphone hydrochloride will be replaced by the study drug (hydromorphone hydrochloride for intrathecal injection) on a 1:1 basis without dose adjustment or optional titration days. The subject is considered at a therapeutic dose and will start the study on Day 1.
Subjects converted from an intrathecal opioid therapy other than hydromorphone hydrochloride to the study drug will be dosed with the study drug according to the following conversion scheme:
<table>
<tr><th>Subject on Morphine or on another Opioid [3]</th><th>Conversion Ratio</th></tr>
<tr><td>Dose ≤ 30 mg IT morphine <u>and</u> tolerating therapy well</td><td>1 : 6 [1]</td></tr>
<tr><td>Dose > 30 mg IT morphine <u>or</u> subject has significant side effects on morphine</td><td>1 : 12 [2]</td></tr>
</table>
[1]Conversion is based on mg-morphine equivalence such that for each 6 mg morphine sulfate the dose is converted to 1 mg hydromorphone hydrochloride.
[2] Conversion is based on mg-morphine equivalence such that for each 12 mg morphine sulfate the dose is converted to 1 mg hydromorphone hydrochloride.
[3] Convert the opioid to mg-morphine equivalent dose first. Then convert to hydromorphone hydrochloride based on mg-morphine equivalent dose using the conversion scheme.

Subjects who are converted directly to the study drug based on the 1:6 morphine-equivalence ratio are, by definition, at a therapeutic dose and must start the study on Day 1 without titration. Dose adjustments may be performed at subsequent visits, based on the investigator discretion.
For subjects converted using 1:12 conversion ratio, due to safety considerations, the conversion will be followed by up to five (5) optional titration days (Titration Days A, B, C, D and E) to achieve a therapeutic dose before starting Day 1. These optional titration days may be three (3) to fourteen (14) days apart.
In subjects receiving an intrathecal opioid in combination with another drug(s) prior to the enrollment of the study, the intrathecal opioid will be converted directly to the study medication (see the conversion scheme above) while the dose of the other drug(s) used in the combination should be kept the same.</td></tr>
</table>

Study Design (Continued)

The conversion will take place by removing the current intrathecal opioid therapy in the pump and then replacing the contents with study hydromorphone hydrochloride for intrathecal injection. At the discretion of the investigator the pump reservoir may be rinsed with preservative free sterile saline or study medication (hydromorphone hydrochloride for intrathecal injection).

Dose adjustments may occur for any subject during the study, either on scheduled or unscheduled visit after study Day 1, as needed based on the following scheme:

Dose of Hydromorphone Hydrochloride IT	Maximum Dose Adjustment
0.1 to 0.5 mg/day	50 %
> 0.5 mg/day	25 %

As needed, additional intrathecal concomitant medications may be added to the therapy to optimize pain control (see Section 3.6.2).

Subjects who are naïve to intrathecal analgesics will have the pumps filled initially with a 2 mg/mL hydromorphone hydrochloride for intrathecal injection. Naïve subjects will be initiated on a dose between 0.1 mg/day and 0.5 mg/day, based on their current opioid dose and the discretion of the investigator. These subjects will be allowed up to five (5) optional titration days to achieve a therapeutic dose of hydromorphone prior to starting the long term safety period on Day 1 of this study. These optional titration days may be three (3) to fourteen (14) days apart. It is suggested that prior to a dose adjustment above 1 mg/day, the pump should be drained and refilled with 10 mg/mL hydromorphone hydrochloride and pump speed adjusted to achieve the target dose. Dose adjustments may continue as needed to optimize the therapy. After achieving a therapeutic dose of hydromorphone hydrochloride, additional intrathecal concomitant medications may be added to the therapy to optimize pain control for these subjects (see Section 3.6.2).

Subjects continuing on therapy from the CNS-HYD201US trial may remain at their current dose of hydromorphone hydrochloride or may have a dose adjustment if clinically indicated, beginning at Day 1 of this study. Subjects who were titrated off hydromorphone hydrochloride as part of the CNS-HYD201US control arm will be titrated back to a therapeutic dose using one or more optional titration days prior to Day 1 of this study.

A maximum dose 10 mg/day intrathecal hydromorphone hydrochloride is permitted at any time during this study. For subjects on PTM dosing regimens, the maximum daily dose will include the combined continuous dose and the allowed maximum PTM dose. All subjects should be contacted by telephone 24 hours after initiating study medication of hydromorphone hydrochloride.

Subjects may be given FDA approved oral supplemental opioid medication and other FDA approved non-opioid medications to help manage pain during the 12 month treatment.

Subjects will remain on therapy for a total of 12 months or until discontinuation from the study. During this continuous dosing period, dose adjustments (up or down) are permitted to manage pain or side effects provided the maximum 10 mg/day dose of hydromorphone hydrochloride is not exceeded. All medications administered must be recorded. At no time may a contraindicated treatment (see Section 3.6.3) be administered in combination with hydromorphone hydrochloride. Subjects will be assessed for pain intensity using a VASPI instrument at each study visit.

Subjects will be evaluated for side effects and clinical complications associated with the use of intrathecal hydromorphone hydrochloride. Signs and symptoms of a suspected granuloma will be monitored; examples of these include but are not limited to radicular pain and loss of drug efficacy.

If there are clinical signs or symptoms identified which may indicate an inflammatory mass formation, an MRI (with and without contrast) or CT myelogram should be performed (with consent of the subject) to evaluate the potential presence of a granuloma as opposed to other catheter related problems that may result in reduced delivery or clinical symptoms. Events will be classified by duration and concentration of intrathecal hydrophone hydrochloride. Events that may be related to a granuloma will be classified as confirmed granuloma or suspected granuloma.

Dosage and dose regimen	0.1 mg/day to 10 mg/day based on dose titration
Sample size	Approximately 350 subjects to be enrolled to complete at least 300 subjects with 6 months and 100 subjects with 12 months of study drug treatment.
Duration of subject participation	Approximately 12 months
Study population	Subjects requiring intrathecal opioid treatment to manage chronic moderate-to-severe intractable pain, 18 to 75 years of age.
Main Inclusion Criteria	Subjects must meet <u>all</u> of the following criteria to be included: 1. Subjects must be at least 18 years of age and no more than 75 years old. 2. Clinically diagnosed with moderate-to-severe intractable pain for at least a 6-month period. 3. Subject is reasonably expected to benefit from intrathecal pain medication and has a SynchroMed II programmable intrathecal pump. 4. Subject agrees to sign a Pain Treatment Agreement (Narcotic Contract) limiting narcotic prescriptions to the study medication prescribed by the investigator. 5. Subject must be cognitively intact and, in the opinion of the investigator, capable of participation in the trial. 6. Female subjects of child-bearing potential must agree to use a medically acceptable and effective double-barrier method of birth control. 7. Subjects who can receive an MRI (with and without contrast) or CT myelogram. 8. Provides written Ethics Committee approved informed consent. 9. Willing to comply with all study procedures and requirements.
Main Exclusion Criteria	Subjects meeting <u>any</u> of the following criteria will be excluded: 1. Women who are pregnant or breast-feeding 2. Subject has any known or suspected allergy to hydromorphone hydrochloride or to the materials of the infusion pump or intrathecal catheter. 3. Subject has a history of dependence and abuse of opioids, stimulants, alcohol, or benzodiazepines, as defined by DSM-IV criteria, within the past year (physical dependence on prescribed opioid analgesics is allowed but abuse of opioids according to DSM-IV is not permitted, ie, opioid addiction for recreational use). 4. Subjects who show signs of active systemic infection. 5. Subjects with a metastatic cancer to the spinal canal or a known central nervous system contraindication to intrathecal therapy. 6. Subjects have a condition requiring diathermy procedures. 7. Subject has a life expectancy of less than 12 months. 8. Subjects who are unable or unwilling to return to all of the required follow-up visits. 9. As a result of medical review and physical examination, the Investigator considers the subject unfit for the study.

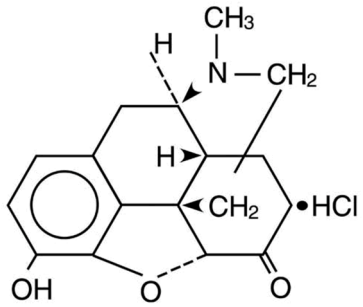
Study Visit Schedule (See Appendix A: Schedule of Study Procedures)	Subjects will be screened and evaluated for study participation prior to administration of any study medications. After signing an informed consent, and confirming eligibility and conformance with all entry criteria, the subject will be enrolled in the trial. For trial subjects participating in the CNS-HYD201US trial only baseline assessments that are not already conducted as part of the CNS-HYD201US trial Day 119 or Study Termination assessments will be performed. However, those subjects dropping out of CNS-HYD201US prior to randomization will need to do all assessments and meet all subject selection criteria in the CNS-HYD202US trial. Their assessments for CNSHYD201US will not carry over. Subjects entering the CNS-HYD202US study may either stay on their current hydromorphone hydrochloride therapy, be directly switched to hydromorphone hydrochloride from other opioid therapies, or will be titrated onto hydromorphone hydrochloride therapy as needed. Naïve subjects will need to be titrated to a therapeutic dose that is well tolerated prior to starting intrathecal combination therapy. All other subjects on combination therapies may maintain their combination therapy regimen upon conversion to study medication. Subjects will return to the clinic according to the schedule in Appendix A to have dose adjustments and study evaluations. For subjects converted to a hydromorphone hydrochloride equivalent dose based on a 1:12 ratio, who require titration prior to achieving a therapeutic dose of hydromorphone hydrochloride, up to five (5) optional titration days are allowed prior to starting Day 1 of the study. The subject may continue dose adjustments to optimize treatment during the 365 day continuous dosing period to evaluate long-term safety of intrathecal hydromorphone hydrochloride.
Study Duration	It is planned that each subject will participate in the study for approximately 12 months with expanded access after this period permitted at the discretion of the subject and attending physician and Mallinckrodt Pharmaceuticals. Overall duration of the study may be up to approximately 24 months not including the expanded access, depending on the rate of enrollment and number of subjects enrolled.
Safety Assessments	Subjects will be assessed throughout the study for adverse events and potential clinical signs and symptoms of a granuloma. Safety will be assessed through collection of AEs and SAEs during the conduct of the trial. At each visit, the subject will be queried for any AEs that differ from their baseline condition at the time of enrollment into the trial. The use of intrathecal morphine has been associated in rare cases with a granuloma at the catheter tip that can result in serious neurological impairment, including paralysis. In this study, the potential for a granuloma will be assessed at each visit to the investigator. If a granuloma is suspected based on clinical signs and symptoms, an MRI (with and without contrast) or CT myelogram should be obtained to evaluate if a granuloma is present. Clinical signs and symptoms that may indicate a granuloma include: • A sudden decrease in therapeutic response requiring increased daily doses that is not attributed to other assignable causes (eg, mechanical failures, catheter movement or catheter blockages). • Unexplained pain at the dermatomal level of the catheter tip. • Unexplained neurological deficit or dysfunction that could be due to compression of the spinal cord at the level of a catheter tip. For the purpose of this study, confirmed granuloma is an intramural extra-medullary mass at the catheter tip that is confirmed by an MRI (with and without contrast) or CT myelogram as read by central independent radiologist, or by surgery. If only clinical signs are detected, but the granuloma or mass cannot be verified by MRI (with and without contrast) or CT myelogram, and no other cause can be determined, the event will be classified as a suspected granuloma. During the trial, all SAEs reported to the investigator shall be reported to the Sponsor or their delegate within 24-hours of the event being reported to the investigator. The investigator will be asked to provide an assessment of severity of the event and an opinion as to the cause.

Primary Endpoint	Safety of intrathecal hydromorphone hydrochloride as assessed through collection of AEs and SAEs during the conduct of the trial. Particular attention will be paid to: • The rate of confirmed granulomas verified by MRI (with and without contrast), CT myelogram or by surgery. • The rate of suspected granulomas that cannot be verified by MRI (with and without contrast), CT myelogram or surgery.
Secondary Endpoints	The following Secondary Endpoints will be assessed. Each of these endpoints will be evaluated at each study visit. • Change in the Visual Analog Scale Pain Intensity (VASPI) overtime. • Change in the Brief Pain Inventory (BPI) (1, 2) overtime. • Change in the Patient Global Impression of Change (PGIC) (3) overtime.
Statistical Methodology	Categorical data will be summarized by number and percentage. Continuous data will be summarized by sample size, mean, median, standard deviation, minimum value, and maximum value. No formal statistical testing is planned for this open-label safety trial. All data will be presented by study drug concentration (2 mg/mL and 10 mg/mL) and all subjects combined. Subject disposition and demographics will be summarized. Safety will be evaluated based on incidence (number and percentage) of treatment-emergent AEs and SAEs summarized overall and by severity and by relationship to study treatment. Vital signs and vital sign changes will be analyzed as appropriate (with clinically meaningful vital sign abnormalities reported and analyzed as AEs). Incidence (number and percentage) and rate (including 95% confidence interval) of granuloma will be summarized for suspected and confirmed granulomas. Study objectives will be met when 300 subjects complete 6 months and 100 subjects complete 12 months of intrathecal hydromorphone therapy. For the purpose of the study report, the analyses may occur any time after the study submission objectives are met. At the time of submission, some subjects may still be receiving study treatment. Therefore, any subsequent safety data collected on those subjects will be submitted via a safety update, unless other format is requested by Regulatory Authorities.

1.0 INTRODUCTION

1.1 Background

Hydromorphone hydrochloride is potent mu-agonist opioid analgesic that was first marketed in the United States in the 1920s. It is primarily used to relieve moderate to severe pain and has been a primary treatment for this indication by both oral and injection routes of administration (4, 5). Dilaudid® was first marketed as an intravenous form of hydromorphone hydrochloride in January 1984 and is now widely generic, with more than 25 years of experience in the market in the United States. The oral Dilaudid® 8 mg formulation (NDA 19-892) was approved in 1992, followed by the 2 mg and 4 mg strengths in 2007. Other oral products, such as Palladone and Exalgo, have been approved by the Agency; however, intravenous use of hydromorphone hydrochloride is the most common and well-studied dosage form.



Hydromorphone Hydrochloride

While used off label for intractable pain by continuous intrathecal administration using implanted drug infusion pumps, this route of administration has never been approved by the United States Food and Drug Administration (FDA). There are also no well-controlled clinical trials that have demonstrated the safety and effectiveness of intrathecal hydromorphone hydrochloride in a manner that is compliant with FDA regulations and guidelines. The Sponsor is pursuing the formal development of a preservative free intrathecal hydromorphone hydrochloride formulation. This development program will provide evidence of safety and efficacy for approval by the FDA and will be manufactured under cGMP conditions with a formulation proven to be compatible with intrathecal pumps.

The only FDA approved opioid analgesic for continuous intrathecal use is Infumorph (morphine). The FDA has also approved one non-opioid analgesic for intrathecal use, Prialt® (ziconotide), which is not widely used given the significant side effects and high cost. As a result, off-label use of unapproved products is common for intrathecal administration. Some estimates are that hydromorphone hydrochloride is used by the intrathecal route of administration in up to 25,000 persons in the United States and is primarily obtained through poorly controlled pharmacy-based compounding, pharmacy compounding or by manipulation of Dilaudid-HP® (hydromorphone hydrochloride for injection, approved for IV infusion), which

adds significant risk to the treatment of subjects. Combinations with other unapproved drugs, such as clonidine, gabapentin, or bupivacaine, are also common.

The purpose of this protocol (CNS-HYD202-US) is to support the safety of intrathecal hydromorphone hydrochloride given by continuous intrathecal administration using an implantable programmable intrathecal infusion pump. The results of this protocol will be used to support submission and approval of intrathecal hydromorphone hydrochloride from the US FDA for use in subjects with chronic intractable pain.

1.2 Nonclinical Assessments

1.2.1 Pharmacology

Hydromorphone is a phenanthrene-derivative structural analog of morphine; it is essentially "dehydroxylated morphine." It may be produced in the body by N-demethylation of hydrocodone. The oral bioavailability is roughly 30%-40%. After intramuscular administration of hydromorphone, the analgesic onset is about 10-20 minutes, the time to peak analgesic effect is roughly 30-60 minutes, the analgesic duration is about 3-5 hours, and the elimination half-life is roughly 2-3 hours. Hydromorphone has a strong affinity for the mu opioid receptor and is as relatively hydrophilic as morphine sulfate. The oral-to-parental ratio is about 5:1 and when administered parenterally, roughly 1.5 mg of hydromorphone is equivalent to 10 mg of morphine. The major metabolic pathways of hydromorphone are similar to morphine and predominantly in the liver via glucuronidation (eg, hydromorphone -3-glucuronide (H3G], hydromorphone -6 glucuronides [H6G]). H3G is similar to M3G, being devoid of analgesic activity and potentially leading to a range of dose-dependent neuroexcitatory side effects (eg, allodynia, myoclonus, seizures) (5).

Analgesic effect and mechanism of action

Tejwani and Rattan determined that hydromorphone acts as an agonist at the mu-opioid receptor in a study comparing the efficacy of intrathecal hydromorphone and buprenorphine to suppress thermal nociception in male Sprague-Dawley rats. An additional objective was to understand whether hydromorphone binds and act as agonists to mu-, delta-, and kappa-spinal opioid receptors (6). Plummer et al demonstrated that the analgesic effect of intrathecal opioids, including hydromorphone, is linear based on a log(dose)-response in relationship to their clearance from the cerebrospinal fluid (7).

Allen et. al. measured the full analgesic dose and the maximum tolerated dose for a variety opioids in dogs with chronic intrathecal delivery. Drugs examined were morphine sulfate, hydromorphone, D/L-methadone, L-methadone, D-methadone, fentanyl, [d-Ala2,N-Me-Phe4,Gly5-ol]-enkephalin (DAMGO), naloxone, or saline. Six-hour intrathecal infusion of agonists resulted in a time-dependent increase in thermal escape latency. At higher concentrations, dose-limiting motor dysfunction and sedation occurred, and hypersensitivity occurred. (8).

Histamine release

Guedes et. al. found that intravenous hydromorphone hydrochloride induced minimal histamine release. They compared plasma histamine concentrations, behavioral and cardiovascular parameters following intravenous administration of hydromorphone hydrochloride and morphine in conscious dogs. Plasma histamine concentration, noninvasive oscillometric blood pressure, heart rate and rhythm were evaluated. Median plasma histamine increased significantly only after the higher dose of morphine. Maximum plasma histamine measured was 0.8 ng/mL after saline and, after the lower and higher doses, respectively, 10.2 and 9.7 ng/mL for hydromorphone hydrochloride, and 440 and 589 ng/mL for morphine. One dog became hypotensive immediately after receiving the highest dose of morphine. Occasional ventricular premature contractions occurred in one dog with both opioids and dosages. No dogs vomited or defecated, but all salivated profusely with both opioids. Neuroexcitation occurred in four dogs following each opioid (9).

In conclusion, the analgesic properties and mechanism of action of intrathecal hydromorphone hydrochloride as a potent agonist of the mu-opioid receptor is well understood and documented in the literature (4). The analgesic potency of hydromorphone hydrochloride via the intrathecal route versus systemic is believed to be approximately six to ten fold higher than morphine and this potency may be in part related to the clearance from the cerebrospinal fluid (10, 11). The ratio of analgesic dose to the maximum tolerated dose was studied in the dog and was found to be 1 to 3 for intrathecal hydromorphone, thus there is an adequate margin of safety by this route of administration (11). Hydromorphone was found to differ from morphine in being a negligible inducer of histamine release in the dog and may be associated with fewer side effects related to histamine release (12).

1.2.2 Toxicology

1.2.2.1 Mutagenic and Carcinogenic Toxicity

No carcinogenicity studies have been conducted in animals with hydromorphone according to the US product insert (physician labeling) for Dilaudid-HP®. Hydromorphone was not mutagenic in the in vitro Ames reverse mutation assay, or in the human lymphocytes chromosome aberration assay. Hydromorphone was not clastogenic in the in vivo mouse micronucleus assay.

1.2.2.2 Genetic and Teratogenicity Studies

No effects on fertility, reproductive performance, or reproductive organ morphology were observed in male or female rats given oral doses of hydromorphone by intravenous administration up to 7 mg/kg/day.

1.3 Clinical Experience

1.3.1 Overview of Clinical Pharmacology

Hydromorphone hydrochloride is a pure opioid agonist with the principal therapeutic activity of analgesia. A significant feature of the analgesia is that it can occur without loss of consciousness. Opioid analgesics also suppress the cough reflex and may cause respiratory depression, mood changes, mental clouding, euphoria, dysphoria, nausea, vomiting and electroencephalographic changes. Many of the effects described below are common to the class of mu-opioid analgesics, which includes morphine, oxycodone, hydrocodone, codeine, and fentanyl.

Opioids can interact with drugs that increase the effects of serotonin. These include antidepressants such as selective serotonin reuptake inhibitors (SSRIs), serotonin and norepinephrine reuptake inhibitors (SNRIs), tricyclic antidepressants (TCAs), triptans, 5-HT3 receptor antagonists, drugs that effect the serotonin neurotransmitter system (eg., mirtazapine, trazodone, tramadol), monoamine oxidase (MAO) inhibitors, (those intended to treat psychiatric disorders and also others, such as linezolid and intravenous methylene blue). The interaction could cause a rare but potentially life-threatening condition called serotonin syndrome. Subjects taking an opioid along with a serotonergic medicine should seek medical attention immediately if symptoms such as agitation; hallucinations; rapid heart rate; fever; excessive sweating; shivering or shaking; muscle twitching or stiffness; trouble with coordination; and/or nausea, vomiting, or diarrhea are experienced. The symptoms generally start within several hours to a few days of taking an opioid with another medication that increases the effects of serotonin in the brain, but symptoms may occur later, particularly after a dose increase[53].

Taking opioids may lead to a rare, but serious condition called adrenal insufficiency in which the adrenal glands do not produce adequate amounts of the steroid hormone, cortisol, particularly during stressful conditions. Subjects should seek medical attention if symptoms of adrenal insufficiency such as nausea, vomiting, loss of appetite, fatigue, weakness, dizziness, or low blood pressure are experienced.

Long-term use of opioids may be associated with decreased sex hormone levels. Subjects should inform the study doctor if they experience signs or symptoms of low libido, impotence, erectile dysfunction, lack of menstruation, or infertility.

Central Nervous System (CNS)

The precise mode of analgesic action of opioid analgesics is unknown. However, specific CNS opiate receptors have been identified, and opioids are believed to express their pharmacological effects by combining with these receptors. Hydromorphone depresses the cough reflex by direct effect on the cough center in the medulla. Hydromorphone produces respiratory depression by direct effect on brain stem respiratory centers. The mechanism of respiratory depression also involves a reduction in the responsiveness of the brain stem respiratory centers to increases in carbon dioxide tension. Hydromorphone causes miosis. Pinpoint pupils are a common sign of

opioid overdose, but are not pathognomonic (eg, pontine lesions of hemorrhagic or ischemic origin may produce similar findings). Marked mydriasis rather than miosis may be seen with hypoxia in the setting of Dilaudid® injection or Dilaudid-HP® overdose.

Gastrointestinal Tract and Other Smooth Muscle

Gastric, biliary, and pancreatic secretions are decreased by opioids such as hydromorphone. Hydromorphone causes a reduction in motility associated with an increase in tone in the gastric antrum and duodenum. Digestion of food in the small intestine is delayed and propulsive contractions are decreased. Propulsive peristaltic waves in the colon are decreased, and tone may be increased to the point of spasm. The end result is constipation. Hydromorphone can cause a marked increase in biliary tract pressure as a result of spasm of the sphincter of Oddi.

Cardiovascular System

Hydromorphone hydrochloride may produce hypotension as a result of either peripheral vasodilation, release of histamine, or both. Other manifestations of histamine release and/or peripheral vasodilation may include pruritus, flushing, and red eyes. Effects on the myocardium after intravenous administration of opioids are not significant in normal persons, vary with different opioid analgesic agents and vary with the hemodynamic state of the subject, state of hydration and sympathetic drive.

1.3.2 Overview of Clinical Pharmacology

Distribution

At therapeutic plasma levels, hydromorphone is approximately 8-19% bound to plasma proteins. After an intravenous bolus dose, the steady state of volume of distribution [mean (%cv)] is 302.9 (32%) liters.

Metabolism

Hydromorphone is extensively metabolized via glucuronidation in the liver, with greater than 95% of the dose metabolized to hydromorphone-3-glucuronide along with minor amounts of 6-hydroxy reduction metabolites.

Elimination

Only a small amount of the hydromorphone dose is excreted unchanged in the urine. Most of the dose is excreted as hydromorphone -3-glucuronide along with minor amounts of 6-hydroxy reduction metabolites. The systemic clearance is approximately 1.96 (20%) liters/minute. The terminal elimination half-life of hydromorphone after an intravenous dose is about 2.3 hours.

Hepatic Impairment

After oral administration of hydromorphone hydrochloride at a single 4 mg dose orally, the mean exposure to hydromorphone (C_{max} and $AUC_{0-\infty}$) is increased 4 fold in subjects with moderate (Child-Pugh Group B) hepatic impairment compared with subjects with normal hepatic function. Due to increased exposure of hydromorphone, subjects with moderate hepatic impairment should be started at a lower dose and closely monitored during dose titration. The pharmacokinetics of hydromorphone in subjects with severe hepatic impairment has not been studied. A further increase in C_{max} and AUC of hydromorphone in this group is expected. As such, the starting dose should be even more conservative and the dose titration should be more cautious than with persons with non-impaired liver function.

Renal Impairment

After oral administration of hydromorphone hydrochloride at a single 4 mg oral dose, mean exposure to hydromorphone (C_{max} and AUC_{0-48}) is increased in subjects with impaired renal function by 2-fold, in moderate (CLcr = 40 - 60 mL/min) renal impairment and 3-fold in severe (CLcr < 30 mL/min) renal impairment compared with normal subjects (CLcr > 80 mL/min). In addition, in subjects with severe renal impairment hydromorphone appeared to be more slowly eliminated with a longer terminal elimination half-life (40 hr) compared to subjects with normal renal function (15 hr). Subjects with moderate renal impairment should be started on a lower dose. Starting doses for subjects with severe renal impairment should be even lower. Subjects with renal impairment should be closely monitored during dose titration.

Pediatrics

Pharmacokinetics of hydromorphone hydrochloride has not been well evaluated in children.

Geriatric

The effect of age on the pharmacokinetics of hydromorphone hydrochloride has not been adequately evaluated.

Gender

Gender has little effect on the pharmacokinetics of hydromorphone hydrochloride. Females appear to have a higher C_{max} (25%) than males with comparable AUC_{0-24} values. The difference observed in C_{max} may not be clinically relevant.

Pregnancy and Nursing Mothers

Hydromorphone crosses the placenta. Hydromorphone is also found in low levels in breast milk, and may cause respiratory compromise in newborns when administered during labor or delivery.

1.3.3 Overview of Efficacy and Safety

Efficacy of Intrathecal Hydromorphone:

There is extensive literature on the use of intrathecal hydromorphone hydrochloride use in subjects with intractable pain. These reports have also led to the common use of hydromorphone hydrochloride in practice, with either compounded hydromorphone hydrochloride being used for intrathecal delivery or Dilaudid® for injection being filled into intrathecal pumps often with manipulation of the formulation. The off-label use of intrathecal hydromorphone hydrochloride is discussed in an article by Lee et. al. (13) that evaluated literature in support of hydromorphone hydrochloride, but concludes that the risk of unlicensed use of hydromorphone hydrochloride as an intrathecal product may pose more risks than the potential benefit.

Several review articles and management guidelines have also been published that compare the use of intrathecal morphine and hydromorphone hydrochloride, including the dose, efficacy, and safety. Guidelines for intrathecal drug delivery for the management of pain have been published by several major pain management organizations (13-16).

A review article entitled “Hydromorphone for Acute and Chronic Pain” (16) reports data from 48 studies (3510 participants). Of these studies 5 of the 48 studies were placebo-controlled, 43 of 48 studies compared hydromorphone hydrochloride use with other opioids, bupivacaine and with itself with different formulations and routes of administration including intrathecal. The author concludes that hydromorphone hydrochloride appears to be a more potent analgesic, but that there is little difference between morphine and hydromorphone hydrochloride in terms of efficacy, adverse effect profile and subject preference.

Other review articles also provide important data on the of intrathecal opioids, including hydromorphone hydrochloride (11, 12, 17-28). The use in children is also examined and provides some evidence of the effectiveness of intrathecal hydromorphone hydrochloride in the pediatric population (29). These articles also establish a conservatively safe starting dose for intrathecal hydromorphone hydrochloride is 0.5 mg/day with titration up to 10 mg/day. The rate of titration was also evaluated and even a rapid titration of 2 mg/day appeared to be safe and acceptable. These articles considered hydromorphone hydrochloride as a first line treatment by the intrathecal route of administration. The publication also suggests a maximum concentration for the formulation used in the intrathecal pump of 30 mg/mL to avoid increased risk of granulomas. These articles also look at retrospective evaluations of intrathecal hydromorphone hydrochloride use and the efficacy in severe pain populations. The general conclusions presented were that intrathecal hydromorphone hydrochloride is safe and at least as effective as morphine, with the potential for some benefits.

Although there are no randomized controlled studies of hydromorphone hydrochloride administered intrathecally, there are retrospective and prospective studies that have specifically examined the efficacy and safety of intrathecal hydromorphone hydrochloride alone or in combination (29-35).

Anderson et al (36) retrospectively reviewed 37 subjects with chronic nonmalignant pain managed with intrathecal hydromorphone hydrochloride after failure of intraspinal morphine. All subjects suffered from severe nonmalignant pain, most from failed lumbosacral spine operations (19/37; 51%). Morphine was replaced with hydromorphone hydrochloride because of pharmacological complications (21/37; 57%) or inadequate analgesic response (16/37; 43%) after an average of 11 months of intrathecal therapy. Adverse events, particularly nausea and vomiting, pruritus, and sedation were reduced by hydromorphone hydrochloride in most subjects. Peripheral edema was improved by hydromorphone hydrochloride but tended to recur with prolonged hydromorphone hydrochloride exposure. Analgesic response was improved by at least 25% in six of 16 subjects who were switched to hydromorphone hydrochloride because of poor pain relief. Du Pen et al (14) retrospectively reviewed 24 subjects with noncancer-related chronic pain receiving hydromorphone hydrochloride monotherapy. Average pain scores decreased significantly ($p = 0.03$).

Dominguez et al (37) found that half of 86 subjects in a retrospective review required either a switch to hydromorphone hydrochloride from morphine or adjuvants were added to morphine by 18 months after initiation of intrathecal morphine therapy. Ackerman et. al. (33) retrospectively examined intrathecal clonidine and combination opioid/clonidine. Of 7 clonidine monotherapy treatment failure, 3 added hydromorphone hydrochloride, 1 of whom failed the combination therapy. Deer et al (35) retrospectively examined intrathecal ziconotide and opioid-ziconotide therapy. Seven of 16 subjects studied received hydromorphone hydrochloride. These retrospective studies confirm the common use of hydromorphone hydrochloride alone or in combination in present-day clinical practice in intrathecal therapy despite lack of high-quality randomized clinical studies to characterize its effectiveness and safety.

Safety of Intrathecal Hydromorphone:

A major difference in the pharmacology of hydromorphone hydrochloride versus morphine is that morphine induces histamine release while hydromorphone hydrochloride does not (37, 38). This difference may be responsible for reports of decreased pruritus in subjects switched from morphine to hydromorphone hydrochloride (39). Potential improvements in other histamine-related morphine adverse events such as peripheral vasodilation and hypotension by switching to hydromorphone hydrochloride have not been investigated although a study in morphine versus fentanyl did find histamine release by morphine to be related to differences in these adverse events between these two drugs (9).

A metabolite of hydromorphone hydrochloride, hydromorphone-3-gucuronide, has been demonstrated to accumulate in chronic renal failure, perhaps producing neuropsychological effects including cognitive impairment (5, 40).

Case reports related to safety include a subject extracting hydromorphone hydrochloride from his pump (41), injection of hydromorphone hydrochloride into the subcutaneous pocket around the intrathecal pump (42), and a pontine hemorrhage following implantation of the pump and

initiation with hydromorphone hydrochloride /bupivacaine (43); the subject had a previously undiagnosed underlying metastatic lesions.

A major complication of intrathecal drug therapies is the formation of inflammatory masses at the catheter tip (granulomas) (44, 45) that, if undetected, can lead to irreversible neurological effects. Several review articles in the literature also evaluate the risk of mass formations or granulomas at the catheter tip with both morphine and hydromorphone hydrochloride (46-48). These publications describe case studies of events where a mass formation or granuloma formed during the use of an intrathecal implantable pump.

In a surveillance study Deer (49) found that the majority of cases reported in the literature were due to morphine. Among 208 subjects receiving intrathecal therapy, 3% (6/208) were found to have a significant lesion by imaging. Five were asymptomatic. No specific characteristics, such as drugs or concentrations were identified. All 6 subjects had percutaneous catheter revisions without complication. The Coffey et. al. (47) publication reviewed more than 40 cases of suspected granulomas, of which most were caused by mixtures of opioids and other agents, but some were from the use of only morphine or hydromorphone hydrochloride. Thus the risk of a granuloma exists, but given the low number of reports compared to the high utilization of intrathecal pumps to administer morphine or hydromorphone hydrochloride, the actual frequency of such events is considered extremely low

Symptoms from granulomas are motor weakness, sensory loss, changes in reflex functions, and bladder dysfunction. Other symptoms can be numbness, tingling, burning, hyperesthesia, hyperalgesia, and radicular pain at the same level as the catheter tip. A granuloma is suspected when the required amount of opioids increases for the same amount of analgesia effect and pain control (49). Precipitated drug, however, can mimic a granuloma, which are usually distinct, globular spheroid-shaped lesions best visualized on T1 MR image sequences with gadolinium contrast (46). Preliminary evidence suggests that dural mast cell degranulation and concomitant release of inflammatory mediators such as histamine may be responsible for the formation of these (48). In animal studies, however, opiates at equianalgesic doses differ in the rate of granuloma formation (50, 51).

Granulomas have been reported most commonly with morphine. Other drugs have also been implicated in causing this complication, including hydromorphone hydrochloride, fentanyl, and tramadol (8, 51, 52). Animal studies in the sheep may indicate that at equivalent daily doses (eg, 10 mg/day) hydromorphone hydrochloride has less potential to induce an inflammatory mass or granuloma than morphine (18, 30). Given that hydromorphone hydrochloride is at least five-times more potent than morphine, these observations may explain the belief of physicians that hydromorphone hydrochloride has fewer side effects and potential for granuloma in that the dose and concentration at the catheter tip during infusion is far less with hydromorphone hydrochloride than morphine. Given the daily dose and concentration are considered the primary factors that induce a granuloma the lower dose and slower infusion rate resulting in a lower

concentration in the area of the catheter tip, would be predicted based on these animal models to have a lower potential of granuloma formation than with intrathecal morphine.

In addition to the literature, Medtronic Inc. has conducted a large publicly available post-approval surveillance study for the SynchroMed® II Programmable Pump that also includes surveillance of various drug products delivered by IT administration. This study followed 4,384 subjects with implanted SynchroMed® II Programmable Pump drug delivery systems at fifty centers, with 3,101 subjects receiving various other IT medications for pain. This study also included subjects receiving intrathecal morphine (Infumorph). Medtronic's study was a careful examination of granuloma formation in subjects. A granuloma in the Medtronic surveillance study was defined as "an intradural extra medullary mass at the catheter tip that could be visualized by enhanced MRI imaging." The criteria for diagnosing such a granulomatous mass is based on several clinical signs and symptoms: a decrease of drug effect and new radicular pain and/or cord compression, MRI findings of an enhancing mass at the catheter tip on the T-1 infusion and surgical or histological confirmation.

From 2003 to 2010 six cases of confirmed or probable granuloma were noted as well as six cases of possible granuloma out of the 4,384 subjects evaluated (12/4384, 0.27%). All of these subjects were being treated with intrathecal morphine for severe, intractable pain. Literature reviews of intrathecal hydromorphone hydrochloride use have not reported significant risk of granuloma formation. While there is no well-controlled trial with hydromorphone hydrochloride that examines the risk of granuloma formation, the potential is not considered to be higher than with Infumorph. Other side effects may be improved with hydromorphone hydrochloride, including the complication of drug dependency.

Based on the literature and wide spread use of off-label hydromorphone hydrochloride, there is potential that intrathecal hydromorphone hydrochloride has a similar, if not superior, efficacy and safety profile to that of intrathecal morphine. The risks do not appear from all literature to be greater than morphine use. The most skeptical publications imply that there may be no significant difference in either safety or efficacy between intrathecal morphine and hydromorphone hydrochloride, but that having two alternatives is beneficial in allowing drug rotations that may help reduce tolerance and the need for increased doses and worsening of side effects. Thus, the rationale for a formal development program for intrathecal hydromorphone hydrochloride to establish the efficacy and safety, as well as a cGMP formulation demonstrated to be compatible in the intrathecal implantable pumps would appear to have a positive benefit risk profile based on all available information.

1.4 Study Rationale

This is a prospective, open-label, single-arm, Phase 3 clinical trial to be conducted at up to 30 clinical trial sites that are experienced with the use and management of implanted SynchroMed II pumps for intrathecal delivery of pain medications. The purpose of this study is to establish the long-term safety of a continuous intrathecal infusion of hydromorphone hydrochloride using a

programmable implantable pump in subjects with opioid resistant intractable pain. Subjects completing the CNS-HYD201US study as well as those subjects dropping out of CNS-HYD201US prior to randomization will be allowed to continue on long term follow-up therapy by enrollment in the CNS-HYD202US study. The study will also involve switching subjects from current opioid therapy per standard medical practice or titration of naïve subjects, or those weaned off intrathecal treatment, onto hydromorphone hydrochloride therapy. All subjects will be entered after signing an IRB approved informed consent. Subjects will be followed for safety for the duration of their treatment with intrathecal hydromorphone hydrochloride using the intrathecal pump or until the study is terminated after the 12-month safety evaluation.

This Phase 3 clinical trial is intended to provide safety data of a 2 mg/mL and 10 mg/mL Intrathecal hydromorphone hydrochloride given by the intrathecal route of administration for up to 12 months in subjects with intractable pain.

2.0 PURPOSE AND STUDY OBJECTIVES

2.1 Purpose

The purpose of this clinical study is to demonstrate the long term safety of a 2 mg/mL and 10 mg/mL formulation of hydromorphone hydrochloride dosed by the intrathecal route of administration in subjects with chronic pain that require continuous opioid treatment through an implantable micro-infusion pump.

2.2 Study Objectives

2.2.1 Primary Objective

To evaluate the long term (12-month) safety of a 2 mg/mL and 10 mg/mL intrathecal hydromorphone hydrochloride formulation given by the intrathecal route of administration.

3.0 STUDY DESIGN

3.1 Description of Trial Design

This is an open-label, single-arm study to evaluate the safety of hydromorphone hydrochloride given by continuous intrathecal infusion using an implantable pump device. This clinical trial will be conducted at up to 30 clinical trial sites that are experienced with the use of intrathecal opioids. This study will enroll both subjects on a current opioid (eg, morphine or hydromorphone hydrochloride) intrathecal medication as well as naïve subjects not currently on intrathecal opioid medications. Dosing regimens allowed in this study will include simple continuous, complex continuous and Personal Therapy Manager (PTM) dosing.

For subjects entering the trial already on a therapeutic dose of another intrathecal hydromorphone hydrochloride, the hydromorphone hydrochloride will be replaced by the study

drug (hydromorphone hydrochloride for intrathecal injection) on a 1:1 basis without dose adjustment or optional titration days. The subject is considered at a therapeutic dose and will start the study on Day 1.

Subjects converted from an intrathecal opioid therapy other than hydromorphone hydrochloride to the study drug will be dosed with the study drug according to the following conversion scheme:

Subject on Morphine or on another Opioid [3]	**Conversion Ratio**
Dose ≤ 30 mg IT morphine and tolerating therapy well	1 : 6 [1]
Dose > 30 mg IT morphine or subject has significant side effects on morphine	1 : 12 [2]

[1] Conversion is based on mg-morphine equivalence such that for each 6 mg morphine sulfate the dose is converted to 1 mg hydromorphone hydrochloride.

[2] Conversion is based on mg-morphine equivalence such that for each 12 mg morphine sulfate the dose is converted to 1 mg hydromorphone hydrochloride.

[3] Convert the opioid to mg-morphine equivalence dose first. Then convert to hydromorphone hydrochloride based on mg-morphine equivalent dose using the conversion scheme.

Subjects who are converted directly to the study drug based on the 1:6 morphine-equivalence ratio are, by definition, at a therapeutic dose and must start the study on Day 1 without titration. Dose adjustments may be performed at subsequent visits, based on the investigator discretion.

For subjects using 1:12 conversion ratio, due to safety considerations, the conversion will be followed by up to five (5) optional titration days (Titration Days A, B, C, D and E) to achieve a therapeutic dose that is well tolerated before starting Day 1. These optional titration days may be three (3) to fourteen (14) days apart.

In subjects receiving an intrathecal opioid in combination with another drug(s) prior to the enrollment of the study, the intrathecal opioid will be converted directly to the study medication (see the conversion scheme above) while the dose of the other drug(s) used in the combination should be kept the same.

The conversion will take place by removing the current intrathecal opioid therapy in the pump and then replacing the contents with study hydromorphone hydrochloride for intrathecal injection. At the discretion of the investigator the pump reservoir may be rinsed with preservative free sterile saline or study medication (hydromorphone hydrochloride for intrathecal injection).

Dose adjustments may occur for any subject during the study, either on scheduled visits or unscheduled visits after study Day 1, as needed based on the following scheme:

Dose of Hydromorphone Hydrochloride IT	Maximum Dose Adjustment
0.1 to 0.5 mg/day	50 %
> 0.5 mg/day	25 %

As needed, additional intrathecal concomitant medications may be added to the therapy to optimize pain control (see Section 3.6.2).

Subjects who are naïve to intrathecal analgesics will have the pumps filled initially with a 2 mg/mL hydromorphone hydrochloride for intrathecal injection. Naïve subjects will be initiated on a dose between 0.1 mg/day and 0.5 mg/day, based on their current opioid dose and the discretion of the investigator. These subjects will be allowed up to five (5) optional titration days to achieve a therapeutic dose of hydromorphone prior to starting the long term safety period on Day 1 of this study. These optional titration days may be three (3) to fourteen (14) days apart. It is suggested that prior to a dose adjustment above 1 mg/day, the pump should be drained and refilled with 10 mg/mL hydromorphone hydrochloride undiluted and pump speed adjusted to achieve the target dose. Dose adjustments may continue as needed to optimize the therapy. After achieving a therapeutic dose of hydromorphone hydrochloride, additional intrathecal concomitant medications may be added to the therapy to optimize pain control for these subjects (see Section 3.6.2).

Subjects continuing on therapy from the CNS-HYD201US trial may remain at their current dose of hydromorphone hydrochloride or may have a dose adjustment if clinically indicated, beginning at Day 1 of this study. Subjects who were titrated off of hydromorphone hydrochloride as part of the CNS-HYD201US control arm will be titrated back to a therapeutic dose using one or more optional titration days prior to Day 1 of this study.

A maximum dose 10 mg/day intrathecal hydromorphone hydrochloride is permitted at any time during this study. For subjects on PTM dosing regimens, the maximum daily dose will include the combined continuous dose and the allowed maximum PTM dose. All subjects should be contacted by telephone 24 hours after initiating study medication of hydromorphone hydrochloride.

Subjects may be given FDA approved oral supplemental opioid medication and other FDA approved non-opioid medications to help manage pain during the 12 month treatment.

Subjects will remain on therapy for a total of 12 months or until discontinuation from the study. During this continuous dosing period, dose adjustments (up or down) are permitted to manage pain or side effects provided the maximum 10 mg/day dose of hydromorphone hydrochloride is

not exceeded. All medications administered must be recorded. At no time may a contraindicated treatment (see Section 3.6.3) be administered in combination with hydromorphone hydrochloride. Subjects will be assessed for pain intensity using a VASPI instrument at each study visit.

Subjects will be evaluated for side effects and clinical complications associated with the use of intrathecal hydromorphone hydrochloride. Signs and symptoms of a suspected granuloma will be monitored; examples of these include but are not limited to radicular pain and loss of drug efficacy.

If there are signs or symptoms identified which may indicate an inflammatory mass formation, an MRI (with and without contrast) or CT myelogram will be performed (with consent of the subject) to evaluate the potential presence of a granuloma as opposed to other catheter related problems that may result in reduced delivery or clinical symptoms. Events will be classified by duration, and concentration of intrathecal hydromorphone hydrochloride. Events that may be related to a granuloma will be classified as confirmed granuloma or suspected granuloma.

3.2 Study Endpoints

3.2.1 Primary Endpoint

Safety of intrathecal hydromorphone hydrochloride as assessed through collection of AEs and SAEs during the conduct of the trial. Particular attention will be paid to:

- The rate of confirmed granulomas verified by MRI (with and without contrast), CT myelogram or by surgery.
- The rate of suspected granulomas that cannot be verified by MRI (with and without contrast), CT Myelogram or surgery.

3.2.2 Secondary Endpoints

The following secondary endpoints will be assessed. Each of these endpoints will be evaluated at each study visit.

- Change in Visual Analog Scale Pain Intensity (VASPI) over time.
- Change in the Brief Pain Inventory (BPI) (1, 2) over time.
- Change in the Patient Global Impression of Change (PGIC) (3) over time.

3.3 Diagnosis of an Inflammatory Granuloma

The use of intrathecal morphine has been associated in rare cases with a granuloma at the catheter tip that can result in serious neurological impairment, including paralysis. These events have been reported infrequently with hydromorphone hydrochloride and are more commonly associated with use of combinations of compounded drugs or high concentration formulations.

Nevertheless, the potential for a granuloma or mass will be assessed at each visit to the investigator.

Clinical signs and symptoms that may indicate a granuloma include:

- A sudden decrease in therapeutic response requiring increased daily doses that is not attributed to other assignable causes (eg, mechanical failures, catheter movement or catheter blockages).
- Change in the character, quality, or intensity of the subjects pain (ie, is less well managed).
- Unexplained pain at the dermatomal level of the catheter tip.
- Unexplained neurological deficit or dysfunction that could be caused by mass effect at the spinal level of the catheter tip.

If in the opinion of the investigator there is a reasonable probability that the subject may be experiencing a granuloma, an MRI (with and without contrast) or CT myelogram will be requested. All MRIs (with and without contrast) and CT myelograms will be assessed by a single central independent radiologist who will be blinded to the subject's history. The criteria used by the primary investigator to detect a potential granuloma will be recorded.

For the purpose of this study to establish that there is a definite granuloma, an MRI (with and without contrast) or CT myelogram must demonstrate an intradural extra-medullary mass near the catheter tip and be confirmed by an independent blinded radiologist. If only clinical signs are detected, but the granuloma or mass cannot be verified by MRI (with and without contrast) or CT myelogram, and no other cause can be determined, the event will be classified as a suspected granuloma.

3.3.1 Treatment of an Inflammatory Granuloma

If a granuloma is detected early in its clinical course, depending upon an individual subject's clinical condition, intra-spinal therapy may be continued after one of the following interventions:

- Withdraw the catheter to a level below the granuloma.
- Remove the involved catheter and replace it with a new catheter positioned below the granuloma.
- Lower the IT dose or replace with saline until the inflammatory mass resolves.
- Disconnect the involved catheter from the connector (two-piece catheter), or transect the involved catheter above the level of the lumbodorsal fascia (one-piece catheter) leaving the intra-spinal catheter segment undisturbed. Ligate the exposed end of involved catheter to prevent CSF loss. Implant a new catheter with its tip below the granuloma, and connect the new catheter to the proximal (pump) catheter segment.

Prompt open surgical removal of the granuloma or decompression of the spinal cord should

only be considered in subjects who have a significant or progressive neurological deficit.

3.4 Measures to Minimize Bias

3.4.1 Blinding

This is an open-label, single-arm safety trial. As such there is no blinding.

3.4.2 Randomization/Assignment to Study Drug

Each subject entered into the trial will be assigned a subject number consisting of a two-digit site number and three-digit sequential subject number (SS-XXX). This number will be used for the entire duration of the trial. There is no randomization in this trial.

3.5 Study Drugs

3.5.1 Rationale for Doses and Dosing Regimen

3.5.1.1 Titration to a Therapeutic Dose of Hydromorphone Hydrochloride

For subjects entering the trial already on a therapeutic dose of another intrathecal hydromorphone hydrochloride, the hydromorphone hydrochloride will be replaced by the study drug (hydromorphone hydrochloride for intrathecal injection) on a 1:1 basis without dose adjustment or optional titration days. The subject is considered at a therapeutic dose and will start the study on Day 1.

Subjects who are converted directly to the study drug based on the 1:6 morphine-equivalence ratio are, by definition, at a therapeutic dose and must start the study on Day 1 without titration Dose adjustments may be performed at subsequent visits, based on the investigator discretion (see Section 3.1).

For subjects converted using the 1:12 ratio, due to safety considerations, the conversion will be followed by up to five (5) optional titration days (Titration Days A, B, C, D and E) to achieve a therapeutic dose before starting Day 1. These optional titration days may be three (3) to fourteen (14) days apart.

The conversion will take place by removing the current intrathecal opioid therapy in the pump and then replacing the contents with study hydromorphone hydrochloride for intrathecal injection. At the discretion of the investigator the pump reservoir may be rinsed with preservative free sterile saline or study medication (hydromorphone hydrochloride for intrathecal injection).

Subjects who are naïve to intrathecal analgesics will have the pumps filled initially with a 2 mg/mL hydromorphone hydrochloride for intrathecal injection. Naïve subjects will be initiated on a dose between 0.1 mg/day and 0.5 mg/day, based on their current opioid dose and the

discretion of the investigator. These subjects will be allowed up to five (5) optional titration days to achieve a therapeutic dose of hydromorphone prior to starting the long term safety period on Day 1 of this study. These optional titration days may be three (3) to fourteen (14) days apart. Prior to a dose adjustment above 1 mg/day, the pump should be drained and refilled with 10 mg/mL hydromorphone hydrochloride undiluted and pump speed adjusted to achieve the target dose. Dose adjustments may continue as needed to optimize the therapy. After achieving a therapeutic dose of hydromorphone hydrochloride, other permitted drug products (see Section 3.6.2) may be added to the pump to optimize analgesia for these subjects if needed.

Subjects continuing on therapy from the CNS-HYD201US trial may remain at their current dose of hydromorphone hydrochloride or may have a dose adjustment if clinically indicated, beginning at Day 1 of this study. Subjects who were titrated off of hydromorphone hydrochloride as part of the CNS-HYD201US control arm will be titrated back to a therapeutic dose using one or more optional titration days prior to Day 1 of this study.

A maximum dose 10 mg/day intrathecal hydromorphone hydrochloride is permitted at any time during this study. For subjects on PTM dosing regimens, the maximum daily dose will include the combined continuous dose and the allowed maximum PTM dose. All subjects should be contacted by telephone 24 hours after initiating study medication of hydromorphone hydrochloride.

3.5.1.2 12-Month Course of Treatment

After the initial titration period, if needed, subjects will start on Day 1 of this trial and remain on therapy for an additional 365 days of hydromorphone hydrochloride treatment. After the initial titration and during the 365 day continuous dosing period run in period, dose adjustments are permitted either upward or down as deemed necessary by the investigator, provided that the maximum dose of 10 mg/day is not exceeded. During this long term evaluation period subjects will visit the clinic as outlined in the Schedule of Events (Appendix A) for evaluations, but may come back sooner if necessary to adjust the daily dose or for any safety related reason.

As needed, additional concomitant medications and intrathecal therapies may be added to the therapy to optimize pain control of the compound and dose (see Section 3.1).

3.5.2 Dose Interruption

Unscheduled dose interruptions are permitted on this clinical trial as deemed necessary by the investigator. If a dose interruption occurs this should be recorded and reason for the interruption documented. Dose interruptions are permitted up to 14 days to correct mechanical issues with the pump or catheter, as well as pump replacements if necessary. Supportive oral, intravenous or transdermal medication may be given to manage pain and withdrawal symptoms at the discretion of the investigator.

3.5.3 Pump or Catheter Replacements

Pump or catheter replacements are permitted in this trial due to mechanical malfunctions, battery failures or other related mechanical reasons. The Medical Monitor should be notified if any subject requires a surgical procedure to correct a catheter failure or requires a pump replacement.

If a subject requires a pump replacement or catheter replacement, drug interruptions for up to 14 days are permitted while the procedure is conducted and study drug can be replaced into the new pump. If the pump is removed, drug within the pump should be discarded and replaced with investigational product from a new vial(s) of hydromorphone hydrochloride. Investigational drug wasted from the pump should be documented for accurate drug accountability. After the pump or catheter replacement, at the discretion of the investigator, subjects may be restarted at their previous dose of hydromorphone hydrochloride or a reduced dose and titrated back to a therapeutic dose as part of normal standard of care for that subject after the pump or catheter replacement.

3.6 Concomitant Medications

3.6.1 Prior and Concomitant Medications

Prior medications are defined as medications that were taken within 30 days prior to initial dosing with study drug.

Concomitant medications are defined as medications taken any time after the start of dosing until the final visit.

While there is minimal published systematic experience with the use of intrathecal hydromorphone hydrochloride in combination with other medications the practice of giving combinations of products in intrathecal pumps to manage pain symptoms is common. Physiological interactions attributed to the combined use of intrathecal hydromorphone hydrochloride and other epidural analgesics may include excessive sedation, hypotension and respiratory depression.

3.6.2 Concomitant Medications Permitted to be Combined with Hydromorphone Hydrochloride in the Pump

If additional therapeutic agents are needed to achieve optimal analgesic effect, it is permissible to use a concomitant medication added to the hydromorphone hydrochloride to be used through the intrathecal route. Naïve subjects will need to be titrated to a therapeutic dose that is well tolerated prior to starting intrathecal combination therapy. All other subjects on combination therapies may maintain their combination therapy regimen upon conversion to study medication. A list of drugs commonly combined with hydromorphone hydrochloride and administered through intrathecal pumps is provided below:

- Bupivacaine
- Fentanyl
- Clonidine
- Baclofen
- Gabapentin
- Ropivacaine

Other concomitant medications should be avoided during the conduct of this study.

3.6.3 Prohibited Concomitant Medications

During treatment with intrathecal hydromorphone hydrochloride, subjects should avoid sedatives, hypnotics, phenothiazines, anesthetics, tranquilizers or other drugs that may induce hypotension or depressive effects. Subjects should be advised to avoid excessive alcohol consumption while on therapy.

Agonist/antagonist analgesics (i.e. pentazocine, nalbuphine, butorphanol, and buprenorphine) should be administered with caution to a subject who has received or is receiving a course of therapy with a pure opioid agonist analgesic such as hydromorphone hydrochloride. In this situation, mixed agonist/antagonist analgesics may reduce the analgesic effect of hydromorphone hydrochloride and/or may precipitate withdrawal symptoms in these subjects.

Opioids can interact with drugs that increase the effects of serotonin (see Section 1.3.1). These include antidepressants such as selective serotonin reuptake inhibitors (SSRIs), serotonin and norepinephrine reuptake inhibitors (SNRIs), tricyclic antidepressants (TCAs), monoamine oxidase (MAO) inhibitors, mirtazapine, and trazodone; triptans (migraine medication); 5-HT3 receptor antagonists (antiemetic drug); tramadol (analgesic drugs); linezolid (antibiotics); and intravenous methylene blue (antidote for methemoglobinemia). The interaction could cause a rare but potentially life-threatening condition called serotonin syndrome. All such medications should be administered with caution[53].

3.7 Duration of Therapy

In the absence of a granuloma or intolerable related AEs (Adverse Drug Reactions) subjects in this trial may continue on treatment for approximately 365 days after Day 1 of this trial.

3.8 Procedures for Monitoring Subject Compliance

Subjects will return to the clinic for scheduled visits and pump refills as specified in Appendix A, but pumps may be filled sooner if necessary or for scheduling purposes. Subjects who do not comply with the visit schedule will be discontinued from the study, weaned off study medication, and can receive another treatment at the discretion of the attending physician caring for the patient.

4.0 STUDY POPULATION

Male or female subjects requiring intrathecal opioid treatment to manage chronic moderate-to-severe intractable pain, 18 to 75 years of age.

4.1 Inclusion Criteria

For a subject to be eligible for this study, s/he must meet all of the following criteria:

1. Subjects must be at least 18 years of age and no more than 75 years old.
2. Clinically diagnosed with moderate-to-severe intractable pain for at least a 6-month period.
3. Subject is reasonably expected to benefit from intrathecal pain medication and has a SynchroMed II programmable intrathecal pump.
4. Subject agrees to sign a Pain Treatment Agreement (Narcotic Contract) limiting narcotic prescriptions to the study medication prescribed by the investigator.
5. Subject must be cognitively intact and, in the opinion of the investigator, capable of participation in the trial.
6. Female subjects of child-bearing potential must agree to use a medically acceptable and effective double-barrier method of birth control.
7. Subjects who can receive an MRI (with and without contrast) or CT myelogram.
8. Provides written Ethics Committee approved informed consent.
9. Willing to comply with all study procedures and requirements.

4.2 Exclusion Criteria

Subjects who meet any of the following criteria will be excluded from participation in the study:

1. Women who are pregnant or breast-feeding.
2. Subject has any known or suspected allergy to hydromorphone hydrochloride or to the materials of the infusion pump or intrathecal catheter.
3. Subject has a history of dependence and abuse of opioids, stimulants, alcohol, or benzodiazepines, as defined by DSM-IV criteria, within the past year (physical dependence on prescribed opioid analgesics is allowed but abuse of opioids according to DSM-IV is not permitted, ie, opioid addiction for recreational use).
4. Subjects who show signs of active systemic infection.
5. Subjects with a metastatic cancer to the spinal canal or a known central nervous system contraindication to intrathecal therapy.
6. Subjects have a condition requiring diathermy procedures.
7. Subject has a life expectancy of less than 12 months.
8. Subjects who are unable or unwilling to return to all of the required follow-up visits.
9. As a result of medical review and physical examination, the Investigator considers the subject unfit for the study.

5.0 SAFETY ASSESSMENTS

5.1 Collection of Adverse Events Data

Data regarding treatment-emergent AEs will be collected in this study. Treatment-emergent AEs are events that are not present at baseline, or if present at baseline, have worsened in severity. AEs will be assessed at each study visit from the time of study drug administration, during optional titration days, and for the long-term safety period starting on Study Day 1 through the final visit. AEs assessed by the Investigator as related to study drug and "ongoing" at the final scheduled study visit will be monitored by the Investigator until resolved or stabilized.

Each subject will be observed and queried by the Investigator or his/her designee at each study visit for any continuing AEs or new AEs since the previous visit. If an AE occurs between study visits, regardless of causal relationship to study drug and in the opinion of the Investigator, requires a study visit for full evaluation, the subject will be asked to return to the site for an unscheduled visit.

Any AE reported by the subject or noted by the Investigator or his/her designee will be recorded. The following information will be recorded for each AE: description of the event, date and time of onset, date and time of resolution, severity, causal relationship to study drug, outcome, action taken with the study drug and any treatment given.

All abnormal changes from baseline in physical examination findings including vital signs will be collected, graded with regards to severity or clinical significance, assessed for causal relationship, and will be recorded.

5.2 Physical Examinations and Medical History

5.2.1 Complete Physical Examination

The Investigator or designee will perform a complete physical examination at screening. Results will be recorded as part of the Medical History. Assessments of height, weight, calculation of body surface area (BSA), and vital signs will be recorded. Any underlying medical condition will be recorded as ongoing baseline events for future assessment of adverse events or serious adverse events. Only adverse changes from this baseline condition will be considered adverse events or serious adverse events.

5.2.2 Medical History

A medical history will be obtained at screening. For subjects entering the CNS-HYD202US trial from the CNS-HYD201US trial, medical history will be imported from the previous trial and does not have to be repeated.

Medical history will include demographic data (age, gender, race/ethnicity, etc.). In addition to general medical conditions, specific information relative to the underlying disease that resulted

in severe intractable pain requiring an intrathecal pump will be obtained and recorded in the CRF:

- Underlying disease, injury or condition resulting in intractable pain, date of initial diagnosis, and prior treatments.
- Date of implantation of an intrathecal SynchroMed II pump. If a previous pump was removed and a new pump has been implanted, the date of each implantation and reason for removal is requested.
- Date of surgical interventions for treatment of intractable pain.
- History of prior opioid use (oral, transdermal or intravenous) prior to implantation of the pump.
- Other significant medical history.

5.3 Vital Signs and ECG

Systolic and diastolic blood pressure, radial pulse, breathing rate and temperature will be obtained at baseline and each study visit and recorded. All vital signs will be obtained in a semi-recumbent position.

An ECG will also be obtained at screening to assess any cardiovascular abnormalities for the purposes of determining eligibility for this trial.

5.4 Documentation of Prior Concomitant Medications

Details regarding the name, indication, dose, route of administration, and frequency of all prescription medications within the past 30-days will be recorded. For subjects entering the CNS-HYD202US trial from the CNS-HYD201US trial, medical history will be imported from the previous trial and does not have to be repeated.

6.0 PHARMACOKINETICS

No pharmacokinetic assessments will be conducted during this trial.

7.0 PHARMACODYNAMICS

Other than pain evaluation, no pharmacodynamic assessments are planned during this trial.

8.0 EFFICACY

There is no efficacy endpoint in this trial given the open-label nature of the study. Subjects will be given a VASPI at scheduled time periods and generally during visits to the clinical site.

9.0 STUDY VISITS

Refer to Appendix A for the Schedule of Study Procedures.

9.1 Screening

The Investigator or his/her approved designee must explain the nature of the study protocol and associated risks to the potential study participant. The potential participant must be allowed to review the study information and to ask questions before being asked to sign the Informed Consent Form. Written informed consent must be provided by the potential study participant or legal guardian prior to initiation of any screening evaluations or other study-related procedures that are not considered standard of care assessments. The signature, date, and the name of the individual(s) who obtained the informed consent will be recorded in the subject's medical record.

Screening, baseline, and initiation of dosing (Day 1 or optional titration day) may be combined as one visit for this trial. Laboratory testing is obtained as part of the baseline status of the subject for future adverse event evaluation, however, laboratory test results are not required for entry criteria and thus the subject may be enrolled prior to results being obtained.

For subject entering this trial from the CNS-HYD201US trial, informed consent may be obtained up to 30-days prior to the transition to this study. Screening, baseline and Day 1 assessments for this trial will be conducted as part of the final visit of the CNS-HYD201US study as indicated in Appendix A. Subjects transitioning from the CNS-HYD201US trial will retain their subject number from that study for the long-term safety trial.

For all other subjects not transitioning from CNS-HYD201US, after written informed consent is obtained, the subject will be assigned a subject number (SS-XXX) by the site and will undergo the designated screening procedures listed in Appendix A within 14 days prior to initiation of weaning or start of study drug administration. The Investigator will assess the results of these screening evaluations to determine eligibility for entry into the study according to the inclusion/exclusion criteria listed in Section 4.0. Screening procedures may be combined with baseline assessments and enrollment (Day 1 or optional titration day) in this trial.

9.2 Baseline Evaluations

If the subject is determined to be eligible for participation in the study they will undergo baseline assessments prior to study drug administration. Baseline assessments will be conducted according to the procedures outlines in Appendix A.

Note that the Screening, Baseline and/or the first day of dosing (enrollment) may be combined at one visit.

Note that for randomized subjects entering the CNS-HYD202US trial from the CNS-HYD201US trial, a physical examination and vital signs will be completed on the final visit day of the CNS-HYD201US trial, which is Day -1 of the CNS-HYD202US trial. However,

those subjects dropping out of CNS-HYD201US prior to randomization will need to do all assessments and meet all subject selection criteria in the current trial. Their assessments for CNSHYD201US will not carry over.

9.3 Dose Titration Period (Optional Titration Days)

Subjects requiring dose titration onto hydromorphone hydrochloride for injection will return to the investigational site every 3 to 14 days for dose adjustments. These dose adjustment days are considered Optional Titration days in the Schedule of Study Procedures (Appendix A).

Subjects who are not participating in the CNS-HYD201US trial, and are naïve to intrathecal medications or have been weaned off current intrathecal medications, will have the pumps filled initially with a 2 mg/mL hydromorphone hydrochloride for intrathecal injection. Subjects requiring titration from a low dose will be initiated on a dose between 0.1 mg/day and 0.5 mg/day, based on their current oral opioid dose and at the discretion of the investigator. These subjects will be allowed up to five (5) Optional Titration periods to achieve a therapeutic dose of hydromorphone prior to starting the long term safety period on Day 1 of this study. Dose adjustments thereafter will be allowed at regular scheduled visits by adjusting the pump speed with a maximum dose adjustment of 50% for doses up to 0.5 mg/day and 25% for doses above 0.5 mg/day.

For subjects who are entering this study from the CNS-HYD201US trial or who are converting directly from compounded hydromorphone hydrochloride (eg, Dilaudid®), the starting dose will be based on their prior dose. For subjects who have been weaned off therapy or are at a dose below what is considered adequate to treat their chronic pain, or are on other Intrathecal opioids, will need to be switched to hydromorphone hydrochloride Intrathecal Injection first and may require one or more Optional Titration days (See Schedule of Study Events in Appendix A). Once a dose that achieves adequate pain relief is determined, the subject will start at Day 1 of this study and continue per the Schedule of Study Events. Dose adjustments thereafter will be allowed at regular scheduled visits by adjusting the pump speed with a maximum dose adjustment of 50% for doses up to 0.5 mg/day and 25% for doses above 0.5 mg/day.

Prior to a dose adjustment above 1 mg/day, the pump should be drained and refilled with 10 mg/mL hydromorphone hydrochloride undiluted and pump speed adjusted to achieve the target dose. Dose adjustments may continue as needed to optimize the therapy. It is recommended that naïve subjects that are titrated onto hydromorphone hydrochloride be maintained on a monotherapy until on a therapeutic dose of hydromorphone hydrochloride. After titration and stabilization, other drugs may be included in the intrathecal pump (see Section 3.6.2) as part of the therapy if judged necessary by the primary investigator.

Oral opioid medication may be prescribed as needed during the dose titration phase. Other FDA approved non-opioid oral pain medications are permitted during this period in accordance with their marketed product labeling.

9.4 Long-Term Follow Up Period (Day 1 to Day 365)

After the titration period (if required based on the investigators discretion) subjects will start Day 1 of this trial and remain on continuous intrathecal treatment for the next 365 days or until withdrawal from the trial. Subjects may have their dose of intrathecal hydromorphone hydrochloride adjusted upwards or downwards during this period as necessary to obtain optimal pain relief and manage side effect, provided the dose does not exceed 10 mg/day (eg, 1.0 mL/day of 10 mg/mL hydromorphone hydrochloride for injection). Oral opioid supplemental medication may be prescribed as necessary and appropriate according to the practice of medicine. As needed other intrathecal medications (see Section 3.6.2) may also be added as deemed appropriate by the investigator with the drug generic name and daily dose recorded. Other FDA approved nonopioid oral pain medications are permitted during this period in accordance with their marketed product labeling.

Study procedures and assessments during this period are conducted according to Appendix A. Pump refills during this period are conducted as needed to maintain the appropriate volume of product in the pump and maintain the subject dosing. Additional unscheduled visits for dose adjustments, titration or to assess potential complications are permitted as needed.

All visit dates during the long term follow-up period are to be conducted within 7 days of the scheduled date (ie, ± 7 days).

9.5 Final Visit

Subjects will return to the investigational site for the final visit at approximately Day 365 (12 months after long term treatment starts) or when discontinued from the study for any reason. At the final study visit subjects will be assessed for AEs and clinical signs or symptoms of a granuloma as well as other procedures according to Appendix A. At the final study visit, the investigator will remove the residual study drug from the subject's pump and will replace the study drug with standard of care medication/therapy.

10.0 PREMATURE DISCONTINUATION FROM STUDY

A subject may be involuntarily discontinued from the study for the following reasons, at the discretion of the investigator and the Sponsor:

- Noncompliance with study procedures and visits to the investigational site
- Significant safety event that does not resolve within 7 days of lowering the dose or other clinical interventions.
- Lost to follow-up after every attempt has been made to contact the subject including sending a registered letter.
- Subject withdraws consent.

The reason for the discontinuation should be recorded.

The Principal Investigator and the Institutional Review Board/Ethics Committee (IRB/EC) reserve the right to prematurely terminate the study in the interest of subject safety and welfare. The Sponsor reserves the right to prematurely terminate the study at any time for administrative reasons. If subjects are discontinued, they will be titrated off of hydromorphone hydrochloride therapy and placed on other alternative treatments at the discretion of the investigator and according to standard medical practice and manufacturer instructions for the intrathecal pump.

11.0 PREMATURE DISCONTINUATION FROM STUDY DRUG

The Investigator will continue to monitor subjects who have discontinued prematurely from study drug due to an AE (serious and non-serious) until resolution or stabilization of the AE.

The Investigator (or designee) must complete all applicable CRF pages for subjects who discontinue study drug prematurely. Final visit procedures (See Appendix A) should be conducted for any subject who discontinues study drug prematurely.

Subjects who prematurely discontinue study drug for any reason other than toxicity may be re-entered into the study after consultation between the Investigator and the Sponsor or the Sponsor's designee. Dosing of a subject who previously discontinued in the study is at the discretion of the Sponsor. However, subjects who drop out due to toxicity will not be replaced.

12.0 PRODUCT SPECIFICATIONS

12.1 Description

Hydromorphone hydrochloride for injection (intrathecal) 2 mg/mL and 10 mg/mL is provided in single use vials of 40,000 mcg per 20 mL (2,000 mcg/mL) or 200,000 mcg per 20 mL (10,000 mcg/mL) for intrathecal administration only.

The drug product is manufactured under current Good Manufacturing Practices (cGMP) at DSM Pharmaceuticals, Inc, or at Patheon Manufacturing Services LLC, contract manufacturing facilities that have undergone FDA inspection.

12.2 Formulation, Packaging, and Labeling

Hydromorphone hydrochloride for injection (intrathecal) 2 mg/mL and 10 mg/mL will be supplied in single use vials and contains hydromorphone hydrochloride and water. Vials will be packaged in boxes for shipment to the clinical sites.

Study drug vial will be affixed with a single label panel containing the following information:

> Hydromorphone Hydrochloride Injection (Intrathecal)
> 40,000 mcg/20 mL (2,000 mcg/mL) or 200,000 mcg/20 mL (10,000 mcg/mL)

Lot Number: XXXXXX
Manufacturing Date: MM-DD-YYYY
Store at Room Temperature (15 to 30℃)
Protect from light - store in package until ready to use

Caution: New Drug – Limited by U.S. Federal Law to Investigational Use
Manufactured for CNS Therapeutics, Inc.

12.3 Receipt, Storage and Stability of Hydromorphone Intrathecal

Hydromorphone hydrochloride for injection (intrathecal) 2 mg/mL and 10 mg/mL vials will be packaged in boxes for shipment to investigational sites. During shipment excursions are permitted to 4° to 30°C (39° to 86°F), and after receipt drug should be stored at 15° to 30°C (59° to 86°F) until use. Excursions from the temperature storage condition should be reported to the study monitor.

12.4 Preparation and Administration of Study Drug

There is no manipulation or preparation of study drug other than filling into the intrathecal programmable infusion pump according to the manufacturer's instructions.

12.5 Ordering and Distribution of Study Drug

Study drug may be requested by submission of a medication request form. The form may be submitted to the Sponsor or designee by facsimile or electronic mail PDF as per the instructions on the drug ordering form.

12.6 Accountability of Study Drugs

All study drugs received, dispensed, and returned must be accounted for in the study drug Dispensing Log, including:

- Subject number and initials.
- Date study drug was dispensed.
- Quantity dispensed.
- Quantity returned.
- Amount wasted (if applicable).

All study drug received and dispensed by the Investigator will be inventoried and accounted for throughout the study. The study drug must be stored in a restricted area with limited access. Contents of the study drug containers must not be combined.

The Investigator must maintain an accurate, up to date Dispensing Log for all study drugs supplied by the Sponsor. The study drug Dispensing Log and remaining drug inventory will be reviewed at each monitoring visit by the Sponsor-designated clinical monitor.

Study drug dispensed for all subjects must be recorded on subject specific Drug Accountability Log.

The study drug supplied for this study is for use only in subjects properly consented and enrolled into this protocol. Study drugs must be kept in a secure location physically separated from standard clinic or office drug supplies.

13.0 SAFETY MONITORING AND ADVERSE EVENTS

13.1 Adverse Events

Data regarding treatment-emergent AEs will be collected in this study. Treatment-emergent AEs are events that are not present at baseline, or if present at baseline, have worsened in severity.

The descriptions and grading scales found in the Common Terminology Criteria for Adverse Events (CTCAE) v 4.03 will be used for AE reporting. A copy of the CTCAE v 4.03 is provided in Appendix B.

The medical monitor and contact information for this study are presented below:

Jean T. (Toby) Barbey, MD	Medical Director, Social & Scientific Systems, Inc. Silver Spring, MD 20910	Office: 301-628-3316 Mobile: 202-251-6523	E-mail: jbarbey@s-3.com

Definition of Adverse Events and Adverse Drug Reactions:

Adverse events in the CRF will be classified according to the most recent FDA definitions and in a manner consistent with ICH guidelines. As such the following definitions will be used:

An adverse event (AE) is any unfavorable and unintended sign, symptom, or disease temporally associated with the use of an investigational (medicinal) product (IP) or other protocol-imposed intervention, regardless of attribution. An AE may include intercurrent illnesses or injuries that represent an exacerbation (increase in frequency, severity, or specificity) of pre-existing conditions (worsening of asthma). A laboratory abnormality will be reported on the "Adverse Event" case report form only if it is associated with clinical sequelae or requires therapeutic intervention. Whenever possible, it is preferable to record a diagnosis as the AE term rather than a series of symptoms relating to a diagnosis. AEs will be graded according to the NCI Common Terminology Criteria for Adverse Events (CTCAE) v 4.03.

The reporting period for AEs starts after the first administration of study drug on Day 1 and ends after discontinuation of study medication.

SAEs must be followed until resolution by the PI, even if this extends beyond the study-reporting period. Resolution is defined as the return to baseline status or stabilization of the condition with the expectation that it will remain chronic.

The investigator will assess AEs for severity, for relationship to Investigational Product (IP), and as to whether the event meets one or more of the definitions of an SAE. The investigator will determine the relationship of an AE to the IP and will record it on the source documents and AE CRF, using the categories defined below.

Table 13–1 Causality Categories for AE Descriptions

Causality Category	Description
Unlikely	A clinical event, including laboratory test abnormality, with a temporal relationship to drug administration which makes a causal relationship improbable, and in which other drugs, chemicals or underlying disease provide plausible explanations. For the purpose of this protocol, the term unlikely will be considered not related to study medication and an "Adverse Event".
Possible	A clinical event, including laboratory test abnormality, with a reasonable time sequence to administrations of the drug, but which could also be explained by concurrent disease or other drugs or chemicals. Information on drug withdrawal may be lacking or unclear. For the purpose of this protocol an event that has possible relationship to study medication will be defined as a "Suspected Adverse Drug Reaction".
Probable	A clinical event, including laboratory test abnormality, with a reasonable time sequence to administration of the drug, unlikely to be attributed to concurrent disease or other drugs or chemicals, and which follows a clinically reasonable response on withdrawal. For the purpose of this protocol an event that has probable relationship to study medication will be defined as a "Adverse Drug Reaction".

Whenever possible, it is preferable to record a diagnosis as the AE term rather than a series of symptoms relating to a diagnosis. AEs will be graded according to the NCI Common Terminology Criteria for Adverse Events (CTCAE) v4.03. The investigator will determine the severity of each AE based on CTCAE criteria and will record the grade of the event on the source documents and AE CRF.

In order to classify adverse events and diseases, preferred terms will be assigned by the sponsor or its designee to the original terms entered on the CRF, using MedDRA. CTCAE is provided in Appendix B.

Table 13–2: Severity Assessment Terminology for Reporting Adverse Events (CTCAE v4.03)

CTCAE Grade	Common Term	Description
1	Mild	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
2	Moderate	Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental Activities of Daily Living (ADL).
3	Severe	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self care Activities of Daily Living (ADL).
4	Life-Threatening	Life-threatening consequences; urgent intervention indicated.
5	Death	Outcome of AE was death

For those AEs that are not described on the CTCAE v4.03, such AEs will be graded according to the same scale as defined above.

13.2 Serious Adverse Events

According to the ICH Guidelines for Good Clinical Practice (E6), an SAE is any untoward medical occurrence during the course of a clinical investigation that is characterized by one or more of the following:

- Results in death.
- Is life-threatening.
- Requires nonscheduled (not routine or planned) in-subject hospitalization or prolongation of existing hospitalization.
- Results in persistent or significant disability/incapacity.
- Is a congenital anomaly/birth defect.
- Important medical events.

Although not a formal SAE, exposure to study drug during pregnancy, even if no AE is reported in the mother, should be reported within 24 hours as an SAE.

For subjects who are maintained in the hospital for scheduled observation or procedures related to the pump, and are not due to SAEs, the hospitalization will not be considered an SAE. Please contact the Medical Monitor with any questions on the definition of a routine event or scheduled hospitalization and if this event should be recorded as an SAE or will be considered routine standard of care.

13.2.1 Reporting Requirements for Serious Adverse Events

Initial Reporting

SAEs (based on FDA/ICH definition of an SAE) require immediate reporting to Mallinckrodt or designated representative.

For all fatal or life-threatening events, the investigator(s) or designee must report information within 24 hours to the Medical Monitor at 334-868-3111.

For all SAEs, the investigator(s) or designee must complete the SAE report form with the minimum information required by FDA and ICH and fax it to Mallinckrodt Pharmacovigilance at 314-654-5759 within 24 hours of first knowledge of the event even if the experience does not appear to be related to the study drug.

The investigator(s) or designee will receive acknowledgement of receipt of the SAE report form from Mallinckrodt.

Should the investigator(s) or designee have any difficulty in sending the SAE report, they may contact Mallinckrodt Pharmacovigilance at 1-800-778-7898 (24 hour call center) or email: globalpv@mallinckrodt.com.

If there is any doubt about whether the information constitutes an SAE, the information is to be treated as an SAE.

Follow Up Reporting

The investigator(s) or designee must complete an SAE report form for all follow-up information received and fax it to the sponsor 314-654-5759 within 24 hours of receipt of additional or updated information (eg, detailed written descriptions that include copies of relevant subject records, autopsy reports and other supporting documents). The investigator(s) or designee will receive acknowledgement of receipt for each SAE report form from Mallinckrodt.

The investigator(s) or designee is required to report immediately unexpected SAEs to the responsible IRB/IEC.

All adverse events (serious and non-serious) occurring in subjects from the time of informed consent through the completion of the follow-up telephone call will be documented as an AE in the source and in the eCRF. All fields on the AE eCRF page should be completed for each event with a full description of the event and date and time of onset and resolution. The investigator must follow up on all AEs and SAEs until the events have subsided, until values return to within the acceptable range, the investigator determines that follow-up is no longer necessary, or the subject is referred to a nonstudy physician.

The sponsor will report SAEs to the FDA and investigators according to local regulations.

Table 13-3 Reporting Requirements for Adverse Events

REPORTING REQUIREMENTS FOR ADVERSE EVENTS		
Seriousness	Reporting Time	Type of Report
ALL SERIOUS	Within 24 hours	Initial report on the SAE form Appropriate eCRF
	Within 24 hours of receipt of follow-up information	Follow up/final report on the SAE form
NON-SERIOUS	Per case report form submission procedure	Appropriate eCRF

Table 13–4: Contact Information for SAE Reporting

Contact Information For SAE Reporting	
Mallinckrodt Global Pharmacovigilance:	
Office Fax:	+1-314-654-5759
24-Hour Call Center Telephone:	+1-800-778-7898
Email:	GlobalPV@mallinckrodt.com

13.2.2 Recording of Serious Adverse Events

All SAE information must be recorded on the SAE form provided by the Sponsor. Additional follow-up information (eg, test results, autopsy, and discharge summary) may be requested to supplement the SAE report form and can be attached as de-identified records. A copy of all initial and follow-up reports must be filed with the subject's medical records.

14.0 STATISTICAL CONSIDERATIONS

14.1 Sample Size Determination

This study is planned to enroll approximately 350 subjects at up to thirty (30) investigative sites to obtain 300 subjects completing 6-months and 100 subjects completing 12-months of intrathecal hydromorphone hydrochloride therapy. Additional subjects may be enrolled as deemed necessary to reach the study completion requirements for subjects on long term intrathecal hydromorphone hydrochloride therapy.

14.2 Analysis Data Sets

Subjects who receive at least one day of hydromorphone hydrochloride intrathecal treatment will be included in the safety analyses.

14.3 Safety Analysis

Safety data will be presented as summary and descriptive statistics, and will be provided for actual values and change from baseline values for vital signs.

The incidence and severity of AEs reported during the study and their relationship to study drug will be tabulated. AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA™) and the CTCAE v 4.03, and will be presented by body system and preferred term.

The World Health Organization Drug Dictionary (WHODD) will be used to classify prior and concomitant medications by therapeutic class and preferred term. Prior and concomitant medication usage will be summarized by the number and percentage of subjects receiving each medication within each therapeutic class by dose cohort.

The incidence (number and percentage) and rate (including 95% confidence interval) of granuloma will be summarized for suspected and confirmed granulomas.

Study objectives will be met when 300 subjects complete 6 months and 100 subjects complete 12 months of intrathecal hydromorphone therapy. For the purpose of the study report, the analyses may occur any time after the study submission objectives are met. At the time of submission, some subjects may still be receiving study treatment. Therefore, any subsequent safety data collected on those subjects will be submitted via a safety update, unless a different format is requested by regulatory authorities.

15.0 DATA COLLECTION, STUDY MONITORING, AND DATA DISCLOSURE

15.1 Data Collection and Reporting

A CRF will be completed for each subject assigned a study number, ICF and receives at least one dose of study drug. All entries on the CRF must be supported by original source documentation (eg, laboratory reports, medical records) maintained at the investigational site.

The Investigator will make all safety assessments (AEs, vital signs, and results from physical examinations) on an ongoing basis. The Investigator is required to review all entries on the CRF and sign at appropriate time intervals.

15.2 Study Monitoring

All aspects of the study will be monitored carefully by the Sponsor's designees with respect to current Good Clinical Practice and Standard Operating Procedures for compliance with applicable government regulations. It is the responsibility of the Investigator to provide all study records, including source documents, CRFs, etc., for review and inspection by the clinical monitor.

All CRFs will be 100% source verified against corresponding source documentation (eg, office and clinical laboratory records) for each subject. Clinical monitors will evaluate periodically the progress of the study, including the verification of appropriate consent form procedures, review of drug accountability and preparation procedures, adherence to dosing procedures, and the verification of the accuracy and completeness of the source documents and the CRFs. Clinical monitors will also ensure that all protocol requirements, applicable FDA regulations, other requirements, and Investigator's obligations are being fulfilled.

15.3 Data Disclosure and Subject Confidentiality

Subject medical information obtained as a result of this study is considered confidential. Disclosure to third parties other than those noted below is prohibited. All reports and communications relating to subjects in this study will identify each subject only by their initials and number. Medical information resulting from a subject's participation in this study may be given to the subject's personal physician or to the appropriate medical personnel responsible for the subject's welfare. Data generated as a result of this study are to be available for inspection on request by FDA or other government regulatory agency auditors, the Sponsor clinical monitor (or designee), and the IRB/EC.

All laboratory specimens, evaluation forms, reports, and other records that leave the site will be identified by a coded number to maintain subject confidentiality. All records will be kept in a locked file cabinet. All computer entry and networking programs will be identifiable only by coded numbers. Clinical information will not be released without written permission from the

subject, except as necessary for monitoring by the IRB, the FDA, or the study Sponsor clinical monitor (or designee).

Any information, inventions, or discoveries (whether patentable or not), innovations, suggestions, ideas, and reports, made or developed by the Investigator(s) as a result of conducting this study shall be promptly disclosed to the Sponsor and shall be the sole property of the Sponsor. The Investigator agrees, upon the Sponsor's request and at the Sponsor's expense, to execute such documents and to take such other actions, as the Sponsor deems necessary or appropriate, to obtain patents in the Sponsor's name covering any of the foregoing.

The results of this study will be published under the direction of the Sponsor. Results will not be published without prior review and approval by the Sponsor.

16.0 PROTECTION OF HUMAN SUBJECTS

16.1 Declaration of Helsinki

The study will be conducted in accordance with the Declaration of Helsinki (1964) including all amendments up to and including the South Africa revision (1996).

16.2 Institutional Review Board/Ethics Committee

The Investigator agrees to provide the IRB/EC with all appropriate material, including a copy of the Informed Consent Form. The study will not be initiated until the Investigator obtains written approval of the research plan and the Informed Consent Form from the appropriate IRB/EC and copies of these documents are received by the Sponsor. Appropriate reports on the progress of this study will be made by the Investigator to the IRB/EC and Sponsor in accordance with applicable government regulations and in agreement with the policies established by the Sponsor. The Sponsor ensures that the IRB/EC complies with the requirements set forth in 21 CFR Part 56.

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Appendix A: Schedule of Study Procedures

Table A- 1: Schedule of Study Procedures

Study Procedure				Visit Schedule									
Study Day[a]	**Screening Days -14 to 1[b]**	**Baseline Days -3 to 1[b]**	**Baseline for HYD201US Subjects[b]**	**Optional Titration Days[b,c]**	**Day 1[b,d]**	**Day 28**	**Day 56**	**Day 80**	**Day 104**	**Day 160**	**Day 216**	**Day 286**	**Final Study Visit Day 365**
Signed Informed Consent	X[e]		X										
Medical History[f]	X		*										
Complete physical exam[g]	X		*										X
Vital signs and Weight[g]	X	X	*	X	X	X	X	X	X	X	X	X	X
Urine pregnancy test [g]	X	X	X										X
ECG[g]	X		X										
CBC, CMP, Urinalysis[g]	X		X										
Concomitant medication assessment	X	X	*	X	X	X	X	X	X	X	X	X	X
Adverse event assessment	X	X	*	X	X	X	X	X	X	X	X	X	X
Hydromorphone Hydrochloride Pump Dose Adjustment and Refills [h,I,l]			X	X	X	X	X	X	X	X	X	X	X[l]
Oral Opioid			X ----------→										
Clinical evaluation for Granulomas[j]	X		*		X	X	X	X	X	X	X	X	X
VASPI Assessment[k]	X	X	*	X	X	X	X	X	X	X	X	X	X
COWS Assessment[k]		X	*	X									X
BPI[k]		X	*			X		X		X		X	X
PGIC[k]		X	*			X		X		X		X	X

a. Study Day is based on Day 1 defined as the first day a subject achieves a therapeutic dose of hydromorphone therapy. There is no Day 0 in this trial. Optional titration days for subjects below therapeutic levels will not be counted towards the 365 day study period. All visit days are +/- 7 days during the long-term extension phase of the study. Additional unscheduled visits may be scheduled to make dose adjustments or prescribe oral medication to manage pain and withdrawal symptoms as deemed appropriate by the investigator.

b. Screening period is 14 days. Screening, Baseline and/or Initiation of Dosing (ie, Optional Titration Day or Day 1) visits may be combined. For subjects entering the CNS-HYD202US clinical trial that are transitioning from the CNS-HYD201US efficacy trial, these subjects will not be required to repeat Screening. For these subjects the last day of the CNS-HYD201US trial will be considered the first day (either optional titration day or Day 1) of the CNS-HYD202US trial. Baseline assessments will be completed as part of the final day (Day 119 or Treatment Failure day) and only additional activities or tests shown on the Schedule of Events (shown in table of events as "X") for these subjects are required to enter the CNS-HYD202US trial. Tests that are done as part of the final visit of the CNS-HYD201US trial and will not be repeated in this study are shown in the table with a "*".

c. Optional titration days are intended for subjects requiring titration after switching from other opioids or control arm subjects enrolling after completion of the CNS-HYD201US trial. Titration days are only if needed to achieve a therapeutic dose of hydromorphone after which subjects will start on Day 1 of the trial. Optional titration days may be scheduled from 3 to 14 days apart depending on the investigator discretion.

d. Day 1 of the trial is considered the first day of the long term extension period. All subjects should be titrated to a therapeutic dose prior to starting Day 1. Day 1 may include a dose adjustment as needed.

e. Informed consent for subjects entering the CNS-HYD202US trial after completion of the CNS-HYD201US trial may be obtained as early as 30 days prior to completion of the CNS-HYD201US trial.
f. For subjects entering the CNS-HYD202US trial from the CNS-HYD201US trial, medical history will be carried over from the previous trial and does not need to be repeated.
g. For subjects entering the CNS-HYD202US trial from the CNS-HYD201US trial, Physical Examination, will be completed on the final visit day of the CNS-HYD201US trial, which is Day -1 of the CNS-HYD202US trial.
h. Pump refills will be conducted as necessary to adjust the treatment regimen and conduct pump refills. Pump refills are not required at all visits.
i. Dose adjustments are allowed during the long-term follow up period both as an increase or decrease to optimize the dose. The maximum dose is 10 mg/day of hydromorphone hydrochloride.
j. If there are clinical signs of a granuloma as defined in Section 3.3, the Medical Monitor should be notified and an MRI (with and without contrast) or CT myelogram scheduled to confirm the pathology of the granuloma.
k. VASPI, COWS, BPI and PGIC are administered at the study site on specified visits.
l. At the final study visit, the investigator will remove the residual study drug from the subjects pump and will replace the study drug with normal standard of care medication/therapy.

Appendix B: National Cancer Institute Common Terminology Criteria for Adverse Events

Version 4.03

Publication Date: 14 June 2010

http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_8.5x11.pdf

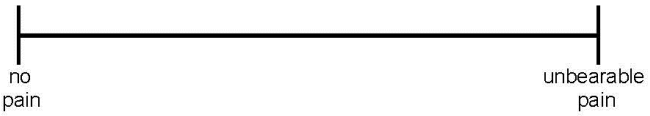
Appendix C: Visual Analog Scale of Pain Intensity (VASPI)

VISUAL ANALOGUE SCALE OF PAIN INTENSITY (VASPI)

TO BE COMPLETED BY PATIENT

Place a single vertical line on the scale that best characterizes your answer to the following question:

How severe is your pain **right now**?



Initials by the patient: _____

TO BE COMPLETED BY SITE PERSONNEL

Measurement from the inside of the left vertical line to the inside of the patient's vertical mark: __ __ __ mm

Appendix D: Clinical Opiate Withdrawal Scale (COWS)

CLINICAL OPIATE WITHDRAWAL SCALE (COWS)			
	Date/Time:	Date/Time:	Date/Time:
Resting Pulse Rate: (record beats per minute) *Measured after subject is sitting/lying for one minute.* **0** pulse rate 80 or below **1** pulse rate 81-100 **2** pulse rate 101-120 **4** pulse rate greater than 120			
Sweating: *Over past ½ hour not accounted for by room temperature or subject activity.* **0** no report of chills of flushing **1** one subjective report of chills or flushing **2** flushed or observable moistness on face **3** beads of sweat on brow or face **4** sweat streaming off face			
Restlessness: *Observation during assessment.* **0** able to sit still **1** report difficulty sitting still, but is able to do so **3** frequent shifting or extraneous movements of legs/arms **5** unable to sit still for more than a few seconds			
Pupil Size: **0** pupils pinned or normal size for room light **1** pupils possibly larger than normal for room light **2** pupils moderately dilated **5** pupils so dilated that only rim of the iris is visible			
Bone or Joint aches*: If subject was having pains previously, only the additional component attributed to opiate withdrawal is scored.* **0** not present **1** mild diffuse discomfort **2** subject reports severe diffuse aching of joints/muscles **4** subject is rubbing joints or muscles and is unable to sit still because of discomfort			
Runny nose or tearing: *Not accounted for by cold symptoms or allergies.* **0** not present **1** nasal stuffiness or unusually moist eyes **2** nose running or tearing **4** nose constantly running or tears streaming down cheeks			

CLINICAL OPIATE WITHDRAWAL SCALE (COWS) - CONTINUED			
	Date/Time	Date/Time:	Date/Time:
GI Upset: *Over last ½ hour* **0** no GI symptoms **1** stomach cramps **2** nausea or loose stools **3** vomiting or diarrhea **5** multiple episodes of diarrhea or vomiting			
Tremor: *Observation of outstretched hands* **0** no tremor **1** tremor can be felt, but not observed **2** slight tremor observable **4** gross tremor or muscle twitching			
Yawning: *Observation during assessment* **0** no yawning **1** yawning once or twice during assessment **2** yawning three or more times during assessment **4** yawning several times/minute			
Anxiety or Irritability **0** none **1** subject reports increasing irritability or anxiousness **2** subject obviously irritable, anxious **4** subject so irritable or anxious that participation in the assessment is difficult			
Gooseflesh skin **0** skin is smooth **3** piloerection of skin can be felt or hairs standing up on arms **5** prominent piloerection			
Total Score			
Observer's Initials			

SCORE: **5-12 = Mild**
13-24 = Moderate
25-36 = moderately severe
More than 36 = severe withdrawal

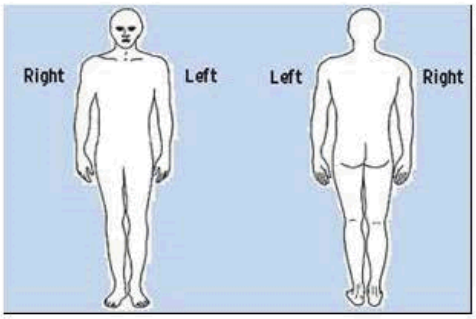
Appendix E: Brief Pain Inventory (BPI)

BRIEF PAIN INVENTORY (BPI)

1) Throughout our lives, most of us have had pain from time to time (such as minor headaches, sprains, and toothaches). Have you had pain other than these everyday kinds of pain today?

1. Yes 2. No

2) On the diagram, shade in the areas where you feel pain. Put an X on the area that hurts the most.



3) Please rate your pain by circling the one number that best describes your pain at its **WORST** in the past 24 hours.

0	1	2	3	4	5	6	7	8	9	10
No Pain										Pain as bad as you can imagine

4) Please rate your pain by circling the one number that best describes your pain at its **LEAST** in the past 24 hours.

0	1	2	3	4	5	6	7	8	9	10
No Pain										Pain as bad as you can imagine

5) Please rate your pain by circling the one number that best describes your pain on the **AVERAGE**.

0	1	2	3	4	5	6	7	8	9	10
No Pain										Pain as bad as you can imagine

BRIEF PAIN INVENTORY (BPI)

6) Please rate your pain by circling the one number that tell how much pain you have **RIGHT NOW**.

0	1	2	3	4	5	6	7	8	9	10
No Pain										Pain as bad as you can imagine

7) What treatments or medications are you receiving for your pain?

_____

8) In the past 24 hours, how much **RELIEF** have pain treatments or medications provided? Please circle the one percentage that most shows how much relief you have received.

0%	10%	20%	30%	40%	50%	60%	70%	80%	90%	100%
No Relief										Complete Relief

9) Circle the one number that describes how, during the past 24 hours. **PAIN HAS INTERFERED** with your:

A. General Activity:

0	1	2	3	4	5	6	7	8	9	10
Does not interfere										Completely interferes

B. Mood:

0	1	2	3	4	5	6	7	8	9	10
Does not interfere										Completely interferes

C. Walking Ability:

0	1	2	3	4	5	6	7	8	9	10
Does not interfere										Completely interferes

D. Normal work (includes both work outside the home and housework::

0	1	2	3	4	5	6	7	8	9	10
Does not interfere										Completely interferes

E. Relation with other people:

0	1	2	3	4	5	6	7	8	9	10
Does not interfere										Completely interferes

F. Sleep:

0	1	2	3	4	5	6	7	8	9	10
Does not interfere										Completely interferes

G. Enjoyment of life:

0	1	2	3	4	5	6	7	8	9	10
Does not interfere										Completely interferes

Appendix F: Patient Global Impression of Change (PGIC)

PATIENT'S GLOBAL IMPRESSION OF CHANGE (PGIC) SCALE

Chief Complaint (Presenting Problem): _____

Since beginning treatment at this clinic, how would you describe the change (if any) in ACTIVITY LIMITATIONS, SYMPTOMS, EMOTIONS, and OVERALL QUALITY OF LIFE, related to your painful condition? Please circle the number below, that matches your degree of change since beginning care at this clinic for the above stated chief complaint.

No change	Almost the same	A little better	Somewhat better	Moderately better	Better	A great deal better
1	2	3	4	5	6	7

Explanation:

1 = No change (or condition has got worse)
2 = Almost the same, hardly any change at all
3 = A little better, but no noticeable change
4 = Somewhat better, but the change has not made any real difference
5 = Moderately better, and a slight but noticeable change
6 = Better, and a definite improvement that has made a real and worthwhile difference
7 = A great deal better, and a considerable improvement that has made all the difference

18.0 SPONSOR SIGNATURE

My signature, in conjunction with the signature of the investigator, confirms the agreement of both parties that the clinical study will be conducted in accordance with the protocol and applicable laws and other regulations including, but not limited to, the International Conference on Harmonisation (ICH) Guideline for Good Clinical Practice (GCP), the US Code of Federal Regulations (CFR), protections for privacy, and generally accepted ethical principles for human research such as the Declaration of Helsinki.

Nothing in this document is intended to limit the authority of a physician to provide emergency medical care.

G.E. Lanza
Sponsor Signature

01 Aug 2016
Date of Signature

(DD Month YYYY)

Gus Lanjani
Sponsor Name (print)