

MALLINCKRODT PHARMACEUTICALS, INC

INVESTIGATIONAL NEW DRUG PROTOCOL

INTRATHECAL HYDROMORPHONE HCL 10 MG/ML

PROTOCOL NUMBER CNS-HYD201US

VERSION 5.0 DATED 01 AUGUST 2016

AMENDMENT REVISING PRIOR VERSION 4.0 DATED 24 JUNE 2016

**A Controlled, Two-Arm, Parallel Group, Randomized Withdrawal Study
To Assess The Safety And Efficacy Of Hydromorphone Hydrochloride
Delivered By Intrathecal Administration Using A Programmable
Implantable Pump**

SPONSOR:

MALLINCKRODT PHARMACEUTICALS INC

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CONFIDENTIAL

SUMMARY OF CHANGES FROM VERSION 4.0 TO VERSION 5.0

DATED 01 AUGUST 2016

This protocol amendment was required (1) to correctly specify a dose titration up to 10 mg/day rather than 5 mg/day and (2) to further clarify the handling of subjects who are dropped or otherwise go off study prior to the 5-week randomized withdrawal period. These and other changes are listed below:

1. Version is changed from v4.0 to v5.0 and protocol re-dated as appropriate. Title page, headers and footers are revised appropriately.
2. The Protocol Synopsis, Dosage & Regimen Section was corrected to specify a 0.1 mg/day to 10 mg/day dosage based on dose titration, rather than 0.1 mg/day to 5 mg/day.
3. The Protocol Synopsis, Study Visit Schedule Section, last paragraph, was revised to include those subjects who go off study prior to randomization, since the protocol defines treatment failures as those subjects who fail after randomization.
4. Section 1.3.3, 4th paragraph, was corrected to specify dose titration up to 10 mg/day rather than 5 mg/day.
5. Section 1.4 Study Rationale, final paragraph, is revised to include those subjects who do not enter the 5-week randomized withdrawal period.
6. Section 3.1, Description of Trial Design, third paragraph on pg 34, is revised to add text concerning those subjects who were dropped prior to randomization. These subjects will complete the study visit that they are on, go directly into CNS-HYD202US and complete scales there at the Screening and Baseline Visit, since they will not have a Day 119 or treatment failure visit that will carry over.
7. Section 3.5.1.2, 12-Week Open-Label Treatment Phase, last paragraph, was revised to clarify the situation of subjects discontinuing prior to randomization and not rolling over into the CNS-HYD202US trial.
8. Appendix Table A-2, footnote 'e' is revised to include subjects who are dropped prior to randomization.
9. Minor edits were made as necessary to correct spelling, capitalization, grammar or format errors.

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LIST OF ABBREVIATIONS

ABBREVIATION	DEFINITION
AE	Adverse event
CFR	Code of Federal Regulations
CMP	Comprehensive Metabolic Panel
cGMP	Current Good Manufacturing Practices
CSF	Cerebral Spinal Fluid
CNS	Central nervous system
COWS	Clinical Opiate Withdrawal Scale
CRF	Case report form
CRU	Clinical research unit
CTCAE	Common Terminology Criteria for Adverse Events (v. 4.03)
EC	Ethics Committee
EDC	Electronic Data Capture
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
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

ABBREVIATION	DEFINITION
MFD	Maximum Feasible Dose
mg	Milligram
mL	Milliliter
MNK	Mallinckrodt Pharmaceuticals Inc
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
SOWS	Subjective Opioid Withdrawal Scale
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, Mallinckrodt Pharmaceuticals, Inc. 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 Mallinckrodt Pharmaceuticals, Inc. The information contained herein is provided for the purpose of conducting a clinical trial for Mallinckrodt Pharmaceuticals, Inc.

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 Mallinckrodt Pharmaceuticals, Inc.

Investigator's Signature

Date

Investigator's Print Name

PROTOCOL SYNOPSIS (PAGE 1 of 7)							
Study Title	A Controlled, Two-Arm, Parallel Group, Randomized Withdrawal Study to Assess the Safety and Efficacy of Hydromorphone Hydrochloride Delivered by Intrathecal Administration Using a Programmable Implantable Pump (CNS-HYD201US)						
Sites	10 to 30						
Indication	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.						
Objectives	<p><u>Primary objective:</u> The primary objective of this clinical trial is to demonstrate the superiority of intrathecal hydromorphone hydrochloride in subjects who are on an optimal dose compared with those who have their dose titrated downward during the randomized withdrawal period as measured by treatment failure rate.</p> <p><u>Secondary objective:</u> To evaluate the safety of hydromorphone hydrochloride given by the intrathecal route of administration.</p>						
Study Design	<p>This is a controlled, prospective, randomized withdrawal trial to be conducted at 10 to 30 US clinical trial sites that are experienced with the use of intrathecal opioids. All subjects will be entered after signing an IRB approved informed consent. Subjects who currently have a SynchroMed® II Implantable Infusion Pump will be eligible to enroll in this trial. For subjects that do not have a current infusion pump implanted, they may be consented and enrolled only after pump implantation and stabilization on intrathecal morphine. Subjects who are naïve to intrathecal therapy, may be enrolled 2-weeks after pump implantation with a SynchroMed® II Implantable Infusion Pump. Subjects entering the study should have a reasonable likelihood of benefiting from intrathecal treatment with an opioid such as hydromorphone hydrochloride.</p> <p>Subjects entering the trial on a stable dose of intrathecal hydromorphone hydrochloride may be converted directly to study medication without dose adjustment.</p> <p>Subjects converted from their current intrathecal morphine therapy to intrathecal hydromorphone hydrochloride will be dosed according to the following scheme:</p> <table border="1" data-bbox="418 1291 1279 1453"> <thead> <tr> <th>Subject Status on Morphine</th> <th>Conversion Ratio</th> </tr> </thead> <tbody> <tr> <td>Dose ≤ 30 mg IT morphine <u>and</u> tolerating therapy well</td> <td>1 : 6¹</td> </tr> <tr> <td>Dose > 30 mg IT morphine <u>or</u> subject has significant side effects on morphine</td> <td>1 : 12²</td> </tr> </tbody> </table> <p>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.</p> <p>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.</p> <p>The conversion will take place by removing the current product in the pump and then replacing the contents with hydromorphone hydrochloride Intrathecal injection . At the discretion of the investigator the pump reservoir may be rinsed with preservative free sterile saline or the study medication (hydromorphone hydrochloride for intrathecal injection). The subject should be contacted by telephone 24 hours after initiating study medication. If combinations were used in the previous intrathecal therapy, oral medications permitted by the protocol may be provided to replace the intrathecal combination regimen. However, for the duration of the CNS-HYD201US trial only hydromorphone hydrochloride may be used in the intrathecal pump as monotherapy. Depending on the subjects starting dose on hydromorphone hydrochloride, either a 2 mg/mL or 10 mg/mL formulation of hydromorphone hydrochloride for intrathecal injection may be used. Dosing with the SynchroMed II Implantable</p>	Subject Status on Morphine	Conversion Ratio	Dose ≤ 30 mg IT morphine <u>and</u> tolerating therapy well	1 : 6 ¹	Dose > 30 mg IT morphine <u>or</u> subject has significant side effects on morphine	1 : 12 ²
Subject Status on Morphine	Conversion Ratio						
Dose ≤ 30 mg IT morphine <u>and</u> tolerating therapy well	1 : 6 ¹						
Dose > 30 mg IT morphine <u>or</u> subject has significant side effects on morphine	1 : 12 ²						

PROTOCOL SYNOPSIS (PAGE 2 of 7)

Study Design (Cont.)

Infusion pump may utilize simple continuous, complex continuous with or without Personal Therapy Manager (PTM) dosing. Subjects who are converted directly to a therapeutic dose of hydromorphone hydrochloride based on a 1:6 conversion morphine equivalent dose of their current opioid should start the study on Day 1 (see [Appendix A: Schedule of Study Procedures](#)). For subjects that are converted to a lower dose based on the 1:12 conversion scheme for safety reasons, up to five (5) optional study visits (Days A, B, C, D and E) are permitted to allow dose titration to a therapeutic dose that is well tolerated. These optional visit days may be from three (3) to seven (7) days apart. After the subject achieves a therapeutic dose of hydromorphone hydrochloride the procedures starting with Day 1 of the study will be followed to ensure the subject is treated for the full 12 week period at a therapeutic dose of intrathecal hydromorphone hydrochloride.

Dose adjustments thereafter will be allowed by adjusting the pump speed, with a maximum dose adjustment of no more than 50% if the current dose is 0.5 mg or less, and 25% for subjects on doses above 0.5 mg, as described in the following scheme:

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

A maximum dose of 10 mg/day intrathecal hydromorphone hydrochloride is permitted at any time during this study. For PTM dosing this maximum dose includes the subjects activated doses that are allowed by the device programming.

Subjects may be given oral supplemental medication for pain up to a maximum of 180 mg-equivalent morphine per day prior to Day 77 of treatment, however, the objective of the trial during this period is to achieve an optimal dose of intrathecal hydromorphone hydrochloride and eliminate any oral supplement. Oral supplement in excess of 180 mg-equivalent morphine per day or other interventions due to intolerable pain, is not permitted and the subject will be withdrawn from the trial and weaned off intrathecal hydromorphone hydrochloride and converted to other appropriate pain therapies. From Day 77 to Day 119 or rescue, subjects are permitted up to 60 mg-equivalent morphine per day only to manage possible withdrawal symptoms.

On Day 77 the pump should be refilled with intrathecal hydromorphone hydrochloride and any final adjustments made to the daily dose or programming. On Day 77, the subject will be given a remote monitoring device to measure VASPI scores twice daily in the morning beginning (5:30 am to 12:00 noon) and in the evening (6:00 pm to 11:45 pm). After Day 77 and during the randomized double-blind period there should be no dose adjustments to intrathecal hydromorphone hydrochloride other than those dictated by the protocol for subjects on the control arm who have their dose titrated downward. After Day 77, there should also be no changes to the pump programming for simple continuous, complex continuous or PTM dosing regimens until after the completion of the trial.

At the end of the 12 week continuous dosing period, subjects who meet criteria for randomization will be randomized in a 1:1 ratio to either remain at their current dose of hydromorphone hydrochloride or who have their dose titrated downward (control group) in a blinded fashion. The criteria for randomization is defined as an average VASPI score of 50 mm or less on a scale of 100 mm for the last 5 days with daily pain measurements prior to randomization on Day 84. After Day 77 the subject should be off any oral supplement of opioid or other prescription medications for pain prior to randomization. For those subjects randomized to be withdrawn from therapy with hydromorphone hydrochloride on Day 84, the pump speed will be adjusted to decrease the total daily dose each 7 days (\pm 1 day), starting at a dose of 75%, 50%, 25%, 12.5% and approximately 0% of the dose at the time of randomization. For PTM dosing, the base continuous dose and the PTM dose would be decreased by the specified percentages above. The total maximum dose of 10 mg/day will be the combined total of the decreased base continuous dose and PTM dose.

PROTOCOL SYNOPSIS (PAGE 3 of 7)

**Study
Design
(Cont.)**

For those subjects randomized to stay on their current dose of hydromorphone hydrochloride, they will also return to the clinic on the same schedule for assessments and for mock pump adjustments. The blind will be maintained by having an independent unblinded medical professional at the site to manage the pump infusion rate and medication provided to the subject.

Pain assessments using the VASPI scale will continue twice daily (morning and evening) from Day 77 prior to the randomization period and throughout the randomized withdrawal period. COWS and SOWS assessments will be performed at specified time points to assess any withdrawal symptoms. Subjects will be permitted a maximum of 60 mg of morphine-equivalent oral opioid per day during the randomized withdrawal period only for the purpose of managing withdrawal symptoms. This oral supplement is not intended to manage pain and should be provided only if the subject starts to experience withdrawal symptoms. No other changes to prescription pain medications or non-pharmacologic interventions being used to help manage pain are allowed from Day 84 to 119, or treatment failure. Baseline pain for the double-blind randomized withdraw period is defined as the average of the last 5 days in the last 7 days with daily pain measurements while on the optimal intrathecal dose of hydromorphone hydrochloride, between Days 77 to 83 of the open-label dosing period.

Treatment Failure Criteria: After randomization, a treatment failure will be defined by the following criteria:

1. A subject who experiences an increase of 20 mm or more above the baseline value on a 100 mm VASPI based on the average of 5 days, or
2. A subject who experiences intolerable pain that in the opinion of the investigator requires intervention (ie, rescue), or
3. Any subject who has other interventions for pain that violate the protocol from Day 84 to 119, including:
 - a. Requires oral opioid supplement in excess of 60 mg/day morphine-equivalent to manage withdrawal symptoms, or
 - b. Has a change in non-opioid oral prescription medications or non-pharmacological treatments being administered for the management of pain.

Note: A subject who does not have sufficient data for evaluation, drops out for any other reasons that are not listed above, or who experiences withdrawal syndrome as identified by COWS > 12 during the double-blind treatment phase will **not** be classified as a treatment failure in the primary efficacy analysis.

Prior to rescue medication being administered, subjects will complete Day 119 study assessments, if possible. After confirming with the investigator that it is acceptable to take rescue medication, if a subject cannot return to the study site for assessments they will be instructed to complete a VASPI score on the remote monitoring device immediately prior to taking oral rescue medication. If the subject can return to the site, rescue may be performed by either oral or IV medication being administered or by increasing the pump speed to achieve a therapeutic dose of hydromorphone hydrochloride, or both.

Subjects will be evaluated for side effects and clinical complications associated with the use of intrathecal hydromorphone hydrochloride. Signs and symptoms of an inflammatory granuloma, including radicular pain, loss of drug efficacy, and spinal cord compression will be monitored by clinical assessments. If there are clinical signs or symptoms identified which may indicate an inflammatory mass formation, an MRI with or without contrast or CT myelogram will be performed to evaluate the potential presence of an inflammatory granuloma as opposed to other catheter related problems that may result in reduced delivery or clinical symptoms. Events that may be related to an inflammatory granuloma will be classified as a confirmed granuloma, suspected granuloma, other

PROTOCOL SYNOPSIS (PAGE 4 of 7)	
Study Design (Cont.)	<p>catheter related problem (confirmed not caused by a granuloma) or other clinical event caused by the underlying disease or other non-catheter/product related event.</p> <p>Following the 5-week randomized withdrawal period, all randomized subjects may be allowed to continue on intrathecal hydromorphone hydrochloride for up to 12 months of safety evaluation by entering the open-label safety study (CNS-HYD202US) if the investigator believes that the subject meets the study selection criteria for the study and would benefit from participation in the study.</p> <p>Subjects in the control group who had their dose titrated down will be first titrated back onto intrathecal hydromorphone hydrochloride as part of the CNS-HYD202US protocol.</p> <p>A subject who is a treatment failure or is dropped from the study prior to randomization can enroll into the long term safety study (CNS-HYD202US) if the subject meets the study selection criteria for CNS-HYD202US and would benefit from study participation. Subjects who experience a drug related adverse event that requires discontinuation after randomization will not be qualified for the long-term extension study, CNS-HYD202US. Subjects will be followed for safety for the duration of their treatment with intrathecal hydromorphone hydrochloride using the SynchroMed® II Programmable Pump or until the study completion.</p>
Dosage & Regimen	0.1 mg/day to 10 mg/day based on dose titration.
Sample size	Approximately 80 randomized (40 per arm).
Study population	Subjects requiring intrathecal opioid treatment to manage chronic intractable pain, age 18 to 75 years of age.
Main Inclusion Criteria	<p>Subjects must meet <u>all</u> of the following criteria to be included:</p> <ol style="list-style-type: none"> 1. Subject must be at least 18 years of age and no more than 75 years old. 2. Clinically diagnosed with chronic pain for at least a 6-month period. 3. Subject is presently on intrathecal pain medication and has a SynchroMed II Implantable pump or meets clinical criteria for implantation of a SynchroMed II Implantable pump. Subjects who are naïve to intrathecal therapy, may be enrolled 2-weeks after pump implantation. 4. Subject agrees to sign a Pain Treatment Agreement (Narcotic Contract) limiting narcotic prescriptions to the study physician. 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 with existing SynchroMed II Implantable pumps and are reasonably expected to benefit from intrathecal opioid therapy only. 8. Subjects who are capable of receiving an MRI with or without contrast or CT myelogram, if required by the study protocol. 9. Provides written Ethics Committee approved informed consent. 10. Willing to comply with all study procedures and requirements.

PROTOCOL SYNOPSIS (PAGE 5 of 7)

<p>Main Exclusion Criteria</p>	<p>Subjects meeting <u>any</u> of the following criteria will be excluded:</p> <ol style="list-style-type: none"> 1. Women who are pregnant or are breast-feeding. 2. Subjects who have participated in an investigational drug or device trial within 4 weeks prior to enrollment. 3. Subject has any known or suspected allergy to hydromorphone or to the materials of the infusion pump or intrathecal catheter. 4. Subject is scheduled for a pump or catheter replacement within 6 months of their enrollment into the trial. 5. 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). 6. Subjects who show signs of active systemic infection. 7. Subjects with a metastatic cancer to the spinal canal or a known central nervous system contraindication to intrathecal therapy. 8. Subject has a condition requiring diathermy procedures. 9. Subject has a life expectancy of less than 12 months. 10. Subject cannot independently comprehend and participate in the required assessments, including responding to the VASPI, SF-MPQ, COWS, SOWS, BPI and PGIC measurement tools. 11. Subject is not considered to be medically or psychologically appropriate for pump implantation. 12. Subjects who are unable or unwilling to return to all of the required follow-up visits. 13. Subjects with active implanted devices such as pacemakers, defibrillators, and cochlear implants or other medical device use, if in the opinion of the investigator the device would interfere with the ability to perform an MRI or CT myelogram. 14. As a result of medical review and physical examination, the Investigator considers the subject unfit for the study. 15. Pain located above the shoulders in the head or neck region (e.g. trigeminal neuralgia), central pain syndromes or any other condition in which it is judged to be unlikely that the subject would benefit from intrathecal administration of the drug product. 16. Subjects who have previously been unresponsive to intrathecal hydromorphone therapy.
<p>Study Visit Schedule (See Appendix A: Schedule of Study Procedures)</p>	<p>Subjects will be screened and evaluated for study participation prior to administration of any study medications. Screening, baseline and subject initiation on study medication (Day 1 or optional titration day) may be conducted on a single day. After signing an informed consent, and confirming eligibility and conformance with all entry criteria, the subject will be enrolled in the trial. Subjects will have hydromorphone hydrochloride 2 mg/mL or 10 mg/mL for injection loaded into the intrathecal pump and either start directly at Day 1 of the study if at a therapeutic dose, or will be titrated to a therapeutic dose. Subjects who require titration will return to the clinic up to two times a week (each 3 to 7 days) for up to 4 weeks to have dose adjustments. The subject will continue dose adjustments to a stable dose and then remain on treatment for the chronic dosing period. Once at a stable dose, subjects will start Day 1 of the study according to the Schedule of Study Procedures (Appendix A). Dose adjustments during Days 1 to 77 are permitted as needed to optimize the therapy. A final dose adjustment may be conducted on Day 77, after which no pump programming changes or dose adjustments are permitted other than those dictated by the protocol for subjects randomized to the control arm who have their dose titrated downward as part of the randomized withdraw design.</p> <p>Subjects stabilized on intrathecal hydromorphone hydrochloride and who meet the randomization criteria, will be randomized to remain at their current IT dose or to have their dose titrated downward over a four week period. Subjects will be monitored by the physician and examined at least every week</p>

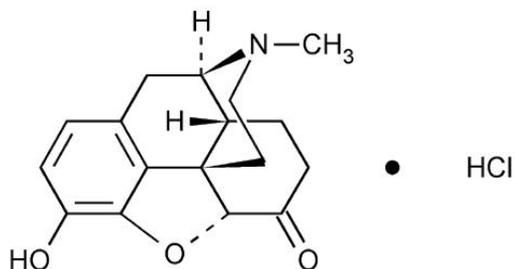
	over a 5-week period for any indications of complications with the device or clinical signs.
PROTOCOL SYNOPSIS (PAGE 6 of 7)	
Study Visit Schedule (See Appendix A: Schedule of Study Procedures)	<p>Symptoms of concern, and other study procedures. Subjects will record a VASPI score twice daily at approximately the same times each day, once in the morning (between 5:30 am and 12:00 noon) and once in the evening (between 6:00 pm and 11:45 pm).</p> <p>Subjects who complete the study or rescue due to treatment failure during the randomized withdrawal period or were dropped from the study prior to randomization will be allowed to enter the CNS-HYD202US trial and receive intrathecal hydromorphone hydrochloride treatment for 12 months for ongoing safety evaluations.</p>
Study Duration	It is planned that each subject will participate in the study for up to 24 weeks as part of this protocol with an extension for up to 12 additional months permitted at the discretion of the subject and attending physician if entered into the CNS-HYD202US long term safety trial.
Safety Analysis	<p>Clinical signs and symptoms that may indicate an inflammatory granuloma include:</p> <ul style="list-style-type: none"> • A sudden decrease in therapeutic response requiring increased daily doses that is not attributed to other assignable causes (e.g. 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. <p>For the purpose of this study, definite inflammatory granuloma is an intramural extra-medullary mass at the catheter tip that is confirmed by an MRI with or without contrast, CT myelogram, or by surgery. If only clinical signs are detected, but the inflammatory granuloma or mass cannot be verified by imaging or surgery, and no other cause can be determined, the event will be classified as a possible inflammatory granuloma. If in the opinion of the investigator there is a reasonable probability that the subject may be experiencing an inflammatory granuloma, an MRI without and with infusion of a contrast agent, or CT myelogram, will be requested. All MRIs and CT myelograms will be assessed by a single central independent radiologist who will be blinded to the subject's history. 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 details of the SAE, an assessment of severity of the event and an opinion as to the cause.</p> <p>Safety data from the study will be summarized descriptively by dose and product used. Descriptive statistics will be calculated for quantitative data and frequency counts and percentages will be provided for categorical data. The nature, frequency, and severity of drug related serious adverse events will be tabulated for all subjects combined and by treatment. Baseline, within study, end of study, and change-from-baseline values for vital signs will be summarized as appropriate.</p>
Primary Efficacy Endpoint	The primary efficacy endpoint is the proportion of subjects who are treatment failures during the double-blind randomized withdrawal period (see treatment failure criteria in Study Design section).

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Secondary Efficacy Endpoints	<ul style="list-style-type: none"> • 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: <ol style="list-style-type: none"> a. Rate of confirmed granulomas that are verified by MRI with and without contrast, CT myelogram or by surgery. b. Rate of possible granulomas. • Short-Form McGill Pain Questionnaire (SF-MPQ) (1). • Time to Rescue after Randomized-Withdrawal (2, 3). • Oral Opioid Supplement Consumption. • Brief Pain Inventory (BPI) (4, 5). • Patient Global Impression of Change (PGIC) (6).
Statistics – Primary Endpoint	<p>The primary efficacy endpoint is the proportion of subjects who are treatment failures. The primary efficacy analysis will be completed in the Intent-to-Treat population (all randomized subjects) and will be carried out using Pearson’s chi-square test at the 0.05 level of significance (two-sided).</p> <p>The true treatment failure rate in the hydromorphone hydrochloride arm is assumed to be at most 20%. Based on a two-sided, two-sample comparison of proportions at the alpha=0.05 level of significance, a sample size of 80 subjects (40 per arm) will provide greater than 90% power to detect an increase in the treatment failure rate of 35 percentage points (ie, the control group has a failure rate of 55%).</p>

1.0 INTRODUCTION

1.1 Background

Hydromorphone is a 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 (7, 8). Dilaudid was first marketed as an intravenous form of hydromorphone 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 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 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 GMP 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 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 compounding or by manipulation of Dilaudid-HP (hydromorphone 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-HYD201US) is to support the efficacy of intrathecal hydromorphone hydrochloride (referred to in this protocol as hydromorphone) monotherapy given by continuous intrathecal administration using a SynchroMed II Implantable pump. The results of this protocol will be used to support submission and approval of intrathecal hydromorphone 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% to 40%. After intramuscular administration of hydromorphone, the analgesic onset is about 10-20 minutes, the time to peak analgesic effect is roughly 30 to 60 minutes, the analgesic duration is about 3-5 hours, and the elimination half-life is roughly 2 to 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 (e.g. 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 (e.g., allodynia, myoclonus, seizures) (8).

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 (9). 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 (10).

Allen et. al. measured the full analgesic dose and the maximum tolerated dose for a variety of 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-o]-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 (11).

Histamine release

Guedes et. al. found that intravenous hydromorphone induced minimal histamine release. They compared plasma histamine concentrations, behavioral and cardiovascular parameters following intravenous administration of hydromorphone 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, 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 (12).

In conclusion, the analgesic properties and mechanism of action of intrathecal hydromorphone as a potent agonist of the mu-opioid receptor is well understood and documented in the literature (7). The analgesic potency of hydromorphone 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 (13, 14). 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 (14). 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 (15).

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 increase⁵⁷.

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. Seek medical attention if you experience symptoms of adrenal insufficiency such as nausea, vomiting, loss of appetite, fatigue, weakness, dizziness, or low blood pressure⁵⁷.

Long-term use of opioids may be associated with decreased sex hormone levels. Inform your study doctor if you experience signs or symptoms of low libido, impotence, erectile dysfunction, lack of menstruation, or infertility⁵⁷.

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 (e.g., 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 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 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 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 ($CL_{cr} = 40 - 60$ mL/min) renal impairment and 3-fold in severe ($CL_{cr} < 30$ mL/min) renal impairment compared with normal subjects ($CL_{cr} > 80$ 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 has not been evaluated in children.

Geriatric

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

Gender

Gender has little effect on the pharmacokinetics of hydromorphone. 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 use in subjects with intractable pain. These reports have also led to the common use of hydromorphone in practice, with either compounded hydromorphone 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 is discussed in an article by Lee et. al. (16) that evaluated literature in support of hydromorphone, but concludes that the risk of unlicensed use of hydromorphone 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, 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 (16-19).

A review article entitled “Hydromorphone for Acute and Chronic Pain” (19) reports data from 48 studies (3510 participants). Of these studies 5 of the 48 studies were placebo-controlled, 43 of 48 studies compared hydromorphone use with other opioids, bupivacaine and with itself with different formulations and routes of administration including intrathecal. The author concludes that hydromorphone appears to be a more potent analgesic, but that there is little difference between morphine and hydromorphone in terms of efficacy, adverse effect profile and subject preference.

Other review articles also provide important data on the of intrathecal opioids, including hydromorphone (14,15, 20-31). The use in children is also examined and provides some evidence of the effectiveness of intrathecal hydromorphone in the pediatric population (32). These articles also establish a conservatively safe starting dose for intrathecal hydromorphone 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 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 use and the efficacy in severe pain populations. The general conclusions presented were that intrathecal hydromorphone is safe and at least as effective as morphine, with the potential for some benefits.

Although there are no randomized controlled studies of hydromorphone administered intrathecally, there are retrospective and prospective studies that have specifically examined the efficacy and safety of intrathecal hydromorphone alone or in combination (32-38).

Anderson et al (39) retrospectively reviewed 37 subjects with chronic nonmalignant pain managed with intrathecal hydromorphone 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 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 in most subjects. Peripheral edema was improved by hydromorphone but tended to recur with prolonged hydromorphone exposure. Analgesic response was improved by at least 25% in six of 16 subjects who were switched to hydromorphone because of poor pain relief. Du Pen et al (17) retrospectively reviewed 24 subjects with noncancer-related chronic pain receiving hydromorphone monotherapy. Average pain scores decreased significantly ($p = 0.03$).

Dominguez et al (40) found that half of 86 subjects in a retrospective review required either a switch to hydromorphone from morphine or adjuvants were added to morphine by 18 months after initiation of intrathecal morphine therapy. Ackerman et. al. (36) retrospectively examined intrathecal clonidine and combination opioid/clonidine. Of 7 clonidine monotherapy treatment failure, 3 added hydromorphone, 1 of whom failed the combination therapy. Deer et al (38) retrospectively examined intrathecal ziconotide and opioid ziconotide therapy. Seven of 16 subjects studied received hydromorphone. These retrospective studies confirm the common use of hydromorphone 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 versus morphine is that morphine induces histamine release while hydromorphone does not (40, 41). This difference may be responsible for reports of decreased pruritus in subjects switched from morphine to hydromorphone (42). Potential improvements in other histamine-related morphine adverse events such as peripheral vasodilation and hypotension by switching to hydromorphone 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 (12).

A metabolite of hydromorphone, hydromorphone-3-gucuronide, has been demonstrated to accumulate in chronic renal failure, perhaps producing neuropsychological effects including cognitive impairment (8, 43).

Case reports related to safety include a subject extracting hydromorphone from his pump (44), injection of hydromorphone into the subcutaneous pocket around the intrathecal pump (45), and a pontine hemorrhage following implantation of the pump and initiation with hydromorphone/bupivacaine (46); 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) (47, 48) 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 (49-51). 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 (52) 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. (50) 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. 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, 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 (52). 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 (49). 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 (51). In animal studies, however, opiates at equianalgesic doses differ in the rate of granuloma formation (53, 54).

Granulomas have been reported most commonly with morphine. Other drugs have also been implicated in causing this complication, including hydromorphone, fentanyl, and tramadol (11, 54, 55). Animal studies in the sheep may indicate that at equivalent daily doses (e.g. 12 mg/day) hydromorphone has less potential to induce an inflammatory mass or granuloma than morphine (21, 33). Given that hydromorphone is at least five-times more potent than morphine, these observations may explain the belief of physicians that hydromorphone 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 than morphine. 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 inflammatory granuloma formation in subjects. An inflammatory 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 inflammatory 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 use have not reported significant risk of granuloma formation. While there is no well-controlled trial with hydromorphone 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, including the complication of drug dependency.

Based on the literature and wide spread use of off-label hydromorphone, there is potential that intrathecal hydromorphone 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, 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 to establish the efficacy and safety, as well as a GMP 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 controlled, prospective, randomized withdrawal trial to be conducted at 10 to 30 US clinical trial sites that are experienced with the use of intrathecal opioids. The primary objective of this study is to demonstrate the efficacy and safety of intrathecal hydromorphone hydrochloride.

Subjects who currently have a SynchroMed[®] II Implantable Infusion Pump will be eligible to enroll in this trial. The reason for restricting the efficacy study to one intrathecal infusion pump is to avoid confounding factors and adverse effects that may be pump related.

For subjects that do not have a current infusion pump implanted, they may be consented and enrolled after pump implantation and stabilization on intrathecal morphine. Given that the study will allow direct switching from other opioids to hydromorphone hydrochloride, and the fact that morphine is approved for administration by intrathecal infusion, titration of subjects according to the approved morphine labeling is recommended in this trial (CNS-HYD201US).

Subjects entering the study should have a reasonable likelihood of benefiting from intrathecal treatment with an opioid such as hydromorphone hydrochloride. Thus, for subjects who are already on intrathecal opioid therapy at a dose that is at or approaching an equivalent dose to 10 mg hydromorphone hydrochloride by intrathecal administration it may be questionable if they will benefit from this therapy. As such, the investigator should use their judgment in enrolling subjects to ensure that there is a good probability that the person will experience reasonable pain control and be eligible for the double-blind period (ie, can achieve a 5 day average pain intensity score of 50 mm or less on a 100 mm scale).

All subjects will be converted from their current intrathecal therapy to intrathecal hydromorphone hydrochloride according to standard medical practice in a 1:6 or 1:12 ratio based on their previous morphine dose and tolerance of intrathecal opioid therapy. If already on a stable dose of compounded hydromorphone hydrochloride, subjects may be converted directly to study medication at a 1:1 ratio. This conversion scheme is consistent with current medical practice of intrathecal pain physicians. Medical practice in switching subjects is to convert the subject based on a 1:6 ratio of hydromorphone to morphine if the subject is tolerating therapy well. Depending on the subject's dose and general condition, a safety factor of up to 50% is sometimes used but in general is not considered necessary by most practicing intrathecal pain physicians. As such, a conversion scheme of 1:6 or 1:12 is planned based on starting morphine dose and subjects tolerance to that dose. After the initial replacement of medication with hydromorphone hydrochloride, the subject should be contacted by telephone 24 hours after initiating study medication. Dose adjustments are then planned according to the protocol to achieve an optimal dose of hydromorphone hydrochloride.

For the CNS-HYD201US trial, only hydromorphone hydrochloride may be used in the infusion pump to help assess the safety and effectiveness as a monotherapy. Given many subjects are on combination intrathecal treatment, if another concomitant medication by IT is necessary, it should be given orally, if possible. If other required medications in the pump cannot be given effectively by oral administration, then the subject will not be eligible for the CNS-HYD201US trial.

Dosing with the SynchroMed II Implantable Infusion pump may be by simple continuous, complex continuous with or without use of a Personal Therapy Manager (PTM) dosing. For those subjects who are dosed using simple continuous or complex continuous dosing, the total daily dose will be considered and documented. Subjects on PTM dosing will be allowed as long as the maximum allowed dose is less than or equal to 10 mg/day. PTM dosing will be recorded as the base continuous dose and the maximum dose allowed by the PTM.

The purpose of the 12-week open label period of the trial is to titrate subjects to an optimal dose of hydromorphone hydrochloride and demonstrate the ability to maintain adequate pain relief in subjects requiring intrathecal opioid therapy. During the open label period of this trial up to Day 77, subjects may be given oral supplemental medication up to a maximum of 180 mg-equivalent morphine per day to manage pain during the titration to an optimal dose. The subject should be

weaned off this oral supplement as much as possible as the intrathecal dose of hydromorphone hydrochloride is optimized. Prior to randomization from Day 77 to 83, the goal is to demonstrate adequate pain relief without oral supplement, defined as an average VASPI score of 50 mm or less based on the last 5 days with nonmissing pain scores. During the double-blind period from Day 84 to 119, up to 60 mg per day of oral morphine-equivalence of opioid is permitted and is intended only for the purpose of managing withdrawal symptoms in subjects who may require some intervention. The 60 mg per day morphine-equivalence dose of opioid is expected to help relieve possible withdrawal effects, but is not intended to significantly impact pain. Doses of oral opioids, any change in prescription medications, or any changes to non-pharmacologic interventions intended to manage pain, will constitute treatment failure.

Given subjects on strong intrathecal opioids cannot be abruptly withdrawn, during the randomization phase one group will remain on their optimal dose of therapy, while the other control group is weaned off therapy over a 4 week period followed by 1 week at the lowest pump setting. It is anticipated that most subjects in the group whose dose of intrathecal opioids is being titrated downward will fail treatment prior to reaching a near 0% dose. The final step of the titration will be to place the pump in shipping mode, which lowers the speed to 0.005 mL/day. Subjects may rescue based on intolerable pain at any time and will be considered a treatment failure, or if their 5 day average pain intensity score is 20 mm greater than their baseline score prior to randomization they will also be considered a treatment failure.

Subjects, whether they enter the 5-week randomized withdrawal period or not, who meet the inclusion criteria for the CNS-HYD202US safety trial, and would like to participate in the 12-month extension, will be allowed to continue on intrathecal hydromorphone hydrochloride as part of that study. All subjects who were in the group whose dose of intrathecal opioids is being titrated downward may be titrated back to an effective dose of intrathecal hydromorphone hydrochloride as part of the CNS-HYD202US trial. 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 SynchroMed[®] II Programmable Pump or until the study is terminated after the 12-month safety follow up study.

2.0 PURPOSE AND STUDY OBJECTIVES

2.1 Purpose

The purpose of this clinical study is to demonstrate the efficacy and 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

The primary objective of this clinical trial is to demonstrate the superiority of intrathecal hydromorphone hydrochloride in subjects who are on an optimal dose compared with those who have their dose titrated downward during the randomized withdrawal period as measured by treatment failure rate.

2.2.2 Secondary Objective

To evaluate the safety of hydromorphone hydrochloride given by the intrathecal route of administration.

3.0 STUDY DESIGN

3.1 Description of Trial Design

This is a controlled, prospective, randomized withdrawal trial to be conducted at 10 to 30 clinical trial sites that are experienced with the use of intrathecal opioids. All subjects will be entered after signing an IRB approved informed consent. Subjects who currently have a SynchroMed[®] II Implantable Infusion Pump will be eligible to enroll in this trial. Subjects who are naïve to intrathecal therapy, may be enrolled 2-weeks after pump implantation. Subjects entering the study should have a reasonable likelihood of benefiting from intrathecal treatment with an opioid such as hydromorphone hydrochloride.

Subjects entering the trial on a therapeutic dose of intrathecal hydromorphone hydrochloride may be converted directly to study medication without dose adjustment.

Subjects who will be converted from their current intrathecal morphine therapy to intrathecal hydromorphone hydrochloride according to the following scheme:

Subject Status on Morphine	Conversion Ratio
Dose \leq 30 mg IT morphine <u>and</u> tolerating therapy well	1 : 6 ^a
Dose > 30 mg IT morphine <u>or</u> subject has significant side effects on morphine	1 : 12 ^b

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

^b Conversion is based on mg-morphine equivalence such that for each 12 mg morphine sulfate, the dose is converted to 1 mg hydromorphone hydrochloride.

The conversion will take place by removing the current product in the pump and then replacing the contents with hydromorphone hydrochloride for intrathecal injection. At the discretion of the investigator the pump reservoir may be rinsed with preservative free sterile saline or the study medication (hydromorphone hydrochloride for injection). The subject should be contacted by telephone 24 hours after initiating study medication. If combinations are used in the previous intrathecal therapy, oral medications may be provided to replace the intrathecal combination regimen. However, for the duration of the CNS-HYD201US trial only hydromorphone hydrochloride may be used in the intrathecal pump as monotherapy. Depending on the subjects starting dose on hydromorphone hydrochloride, either a 2 mg/mL or 10 mg/mL formulation of hydromorphone hydrochloride for intrathecal injection may be used. Dosing with the SynchroMed II Implantable Infusion pump may be by simple continuous, complex continuous or PTM dosing.

Dose adjustments thereafter will be allowed by adjusting the pump speed 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 %

A maximum dose of 10 mg/day intrathecal hydromorphone hydrochloride is permitted at any time during this study. For PTM dosing this maximum dose includes the patient activated doses that are allowed by the device programming. Subjects may be given oral supplemental medication up to Day 77 up to a maximum of 180 mg-equivalent morphine per day, however, the objective of the trial during this period is to achieve an optimal dose of intrathecal hydromorphone hydrochloride and reduce or eliminate any oral supplement. Oral supplement in excess of 180 mg-equivalent morphine per day or other interventions due to intolerable pain, is not permitted.

On Day 77 the pump should be refilled with intrathecal hydromorphone and any final adjustments made to the daily dose or programming. On Day 77, the subject will be given a remote monitoring device to measure VASPI scores twice daily in the morning (5:30 am to 12:00 noon) and in the evening (6:00 pm to 11:45 pm). After Day 77 and during the randomized double-blind period there should be no dose adjustments other than those dictated by the protocol for subject in the control arm whose dose of intrathecal opioids is being titrated downward. After Day 77, there should also be no changes to the pump programming for simple continuous, complex continuous or PTM dosing regimens until after the completion of the trial.

At the end of the 12 week chronic dosing period, subjects who meet criteria for randomization will be assigned to either remain at their current dose of hydromorphone hydrochloride or to have their dose titrated downward (control group) in a blinded fashion. The criteria for randomization is defined as a an average VASPI score of 50 mm or less on a scale of 100 mm for

the last 5 days with daily pain measurements prior to randomization on Day 84. After Day 77 the subject should be off all oral opioid supplements and should have no change in other prescription pain medications or non-pharmacologic interventions they are receiving for pain management. For those subjects randomized to be withdrawn from therapy with hydromorphone hydrochloride on Day 84, the pump speed will be adjusted to decrease the dose each 7 days (± 1 day), starting at a dose of 75%, 50%, 25%, 12.5% and approximately 0% of the dose at the time of randomization. For PTM dosing, the base continuous dose and the PTM dose would be decreased by the specified percentages above. The total maximum dose of 10 mg/day will be the combined total of the decreased base dose and PTM dose.

For those subjects randomized to stay on their current dose of hydromorphone hydrochloride, they will also return to the clinic on the same schedule for assessments and for mock pump adjustments. The blind will be maintained by having an independent unblinded medical professional at the site manage the pump infusion rate and medication provided to the subject.

Pain assessments using the VASPI scale will continue twice daily, once in the a.m. (between 5:30 am and 12:00 noon) and once in the p.m. (between 6:00 pm and 11:45 pm) for the 7 days prior to the randomization period and throughout the randomized withdrawal period. COWS and SOWS assessments will be performed at specified time points to assess any withdrawal symptoms. Subjects will be permitted a maximum of 60 mg of morphine-equivalence of oral opioid per day during the randomized withdrawal period (Day 84 to 119) only for the purpose of managing withdrawal symptoms. Use of oral opioids, any change in non-opioid prescription medications, or any changes to non-pharmacologic interventions intended to manage pain during the double-blind period will constitute treatment failure.

Baseline pain for the double-blind randomized withdraw period is defined as the average of the last 5 days with daily pain measurements while on an optimal intrathecal dose of hydromorphone hydrochloride, between Days 77 and 83 of the open-label dosing period.

Treatment Failure Criteria: After randomization, a treatment failure will be defined by the following criteria:

1. A subject who experience an increase of 20 mm or more above the baseline value on a 100 mm VASPI based on the average of 5 days, or
2. A subjects who experience intolerable pain that in the opinion of the investigator requires intervention (i.e. rescue), or
3. Any subject who has other interventions for pain that violate the protocol from Day 84 to 119 that includes:
 - a. Requires oral opioid supplement in excess of 60 mg/day morphine-equivalent to manage withdrawal symptoms, or
 - b. Has a change in non-opioid oral prescription medications or non-pharmacological treatments being administered for the management of pain.

Note: A subject who does not have sufficient data for evaluation, drops out for any other reasons that are not listed above or who experiences withdrawal syndrome as identified by COWS > 12 during the double-blind treatment phase will **not** be classified as a treatment failure in the primary efficacy analysis.

Prior to rescue medication being administered, subjects will complete Day 119 study assessments, if possible. After confirming with the investigator that it is acceptable to take rescue medication, if a subject cannot return to the study site for assessments they will be instructed to complete a VASPI score on the remote monitoring device immediately prior to taking oral rescue medication. If the subject can return to the site, rescue may be performed by either oral or IV medication being administered or by increasing the pump speed to achieve a therapeutic dose of hydromorphone hydrochloride, or both.

Subjects who are treatment failures or those who are dropped from the study prior to randomization under this protocol will be permitted to enroll into Mallinckrodt clinical study CNS-HYD202US if the PI believes that the subject meets the study selection criteria and would benefit from participation in the study. For any subject continuing therapy on the CNS-HYD202US trial, the Day 119 (or failure visit) assessments will be considered the last day on the CNS-HYD201US trial and the first day of CNS-HYD202US. Subjects in the CNS-HYD201US trial who were dropped prior to randomization and judged by the primary physician to benefit from participation in CNS-HYD202US will complete the study visit that they are on, go directly into CNS-HYD202US and complete scales there at the Screening and Baseline Visit. Subsequent visits, including re-titration onto hydromorphone hydrochloride if necessary, will be considered part of the CNS-HYD202 US trial.

Subjects will be evaluated for side effects and clinical complications associated with the use of intrathecal hydromorphone hydrochloride. Signs and symptoms of an inflammatory granuloma, including radicular pain, loss of drug efficacy, and spinal cord compression will be monitored by clinical assessments. If there are clinical signs or symptoms identified which may indicate an inflammatory mass formation, an MRI scan with and without contrast or CT myelogram, will be performed to evaluate the potential presence of an inflammatory granuloma as opposed to other catheter related problems that may result in reduced delivery or clinical symptoms. Events that may be related to an inflammatory granuloma will be classified as with confirmed granuloma, suspected granuloma, other catheter related problem (confirmed not caused by a granuloma) or other clinical even caused by the underlying disease or other non-catheter/product related event.

Following the 5 week randomized withdrawal period, or if a subject is rescued and completes the failure assessment visit, all subjects that entered the randomization period may be allowed to continue on intrathecal hydromorphone hydrochloride for up to 12-months of safety evaluation by entering the open-label safety study (CNS-HYD202US), with all subjects who were withdrawn from optimal therapy being titrated back onto intrathecal hydromorphone hydrochloride. A subject who is a treatment failure or who is dropped from the study prior to randomization can enroll into the long term safety study (CNS-HYD202US) if the subject meets

the inclusion/exclusion criteria for CNS-HYD202US. Subjects who cannot tolerate intrathecal hydromorphone hydrochloride during the 12-week chronic dosing period will not be eligible for the long term treatment protocol.

3.2 Study Endpoints

3.2.1 Primary Endpoint

The primary efficacy endpoint is the proportion of subjects who are treatment failures during the double-blind randomized withdrawal period.

Treatment Failure Criteria: After randomization, a treatment failure will be defined by the following criteria:

1. A subject who experience an increase of 20 mm or more above the baseline value on a 100 mm VASPI based on the average of 5 days, or
2. A subjects who experience intolerable pain that in the opinion of the investigator requires intervention (ie, rescue), or
3. Any subject who has other interventions for pain that violate the protocol from Day 84 to 119 that includes:
 - a. Requires oral opioid supplement in excess of 60 mg/day morphine-equivalent to manage withdrawal symptoms, or
 - b. Has a change in non-opioid oral prescription medications or non-pharmacological treatments being administered for the management of pain.

Note: A subject who does not have sufficient data for evaluation, drops out for any other reasons that are not listed above or who experiences withdrawal syndrome as identified by COWS > 12 during the double-blind treatment phase will **not** be classified as a treatment failure in the primary efficacy analysis.

3.2.2 Secondary Endpoints

The most important secondary endpoint is:

- 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:
 - Rate of confirmed granulomas that are verified by MRI with and without contrast, CT myelogram or by surgery.
 - Rate of possible granulomas.

Other secondary endpoints include:

- Short-Form McGill Pain Questionnaire (SF-MPQ) (1).
- Time to Rescue after Randomized-Withdrawal (2, 3).
- Oral Opioid Supplement Consumption.

- Brief Pain Inventory (BPI) (4, 5).
- Patient Global Impression of Change (PGIC) (6) .

3.3 Diagnosis of 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 (e.g. 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.

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. If only clinical signs are detected, but the granuloma or mass cannot be verified by MRI, CT myelogram or surgery, and no other cause can be determined, the event will be classified as a possible or suspected granuloma.

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 infusion of a contrast agent or a CT myelogram will be requested. All MRI or CT myelograms will be assessed by a single central independent radiologist who will be blinded to the subject's history.

3.3.1 Treatment of Granuloma

If a granuloma is detected the subject will be considered a treatment failure and discontinued from the trial. If the granuloma is confirmed early in its clinical course, depending upon an individual subject's clinical condition, intraspinal 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 intraspinal 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 a double-blind, randomized study. After randomization on Day 84, subjects will receive either intrathecal hydromorphone hydrochloride or will have their dose titrated downward over a 4 week period followed by 1 week at the minimal pump setting or shipping mode (ie, 0.005 mL/day). An unblinded technician or nurse at the site will be assigned (ie, Pump Operator) to adjust pump speeds during the 5 week double-blind period. The unblinded pump operator will not be involved in any other evaluations of the subject and will be instructed to avoid revealing any information to study personnel about the group assignment of the subject. Dosing after randomization will be done by randomization code for each subject. Subjects who utilize a PTM device will be blinded to the display screen of the PTM. The display screen will be covered with a non-transparent tamper resistant tape that will be checked at each visit. The PTM device will be able to operate normally, but the screen or any data from the PTM will not be visible to the subject.

3.4.2 Randomization/Assignment to Study Drug

Each subject who is entered into the study will be assigned an enrollment number by the site, that consists of the two digit site number (##) and a subject number consisting of three-digits (XXX). This number will be used for the entire duration of the trial.

For subjects who meet the criteria for randomization, a treatment group randomization code will be assigned to that subject number via an interactive web-based randomization system (IWRS). The subject will then be randomized to either remain on the current dose of intrathecal hydromorphone hydrochloride or will be titrated downward to a sub-therapeutic dose starting on Day 84. The unblinded pump technician will have a unique user name and password to the IXRS (ie, web based randomization system) to allow them to access the treatment assignment.

3.5 Study Drugs

3.5.1 Rationale for Doses and Dosing Regimen

3.5.1.1 Dose Conversion Period

Subjects entering the trial on a therapeutic dose of intrathecal hydromorphone hydrochloride may be converted directly to study medication without dose adjustment.

Subjects who will be converted from their current intrathecal morphine therapy to intrathecal hydromorphone hydrochloride according to the following scheme:

Subject Status on Morphine	Conversion Ratio
Dose \leq 30 mg IT morphine <u>and</u> tolerating therapy well	1 : 6 ¹
Dose $>$ 30 mg IT morphine <u>or</u> subject has significant side effects on morphine	1 : 12 ²

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

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

The subject should be contacted by telephone 24 hours after initiating study medication. If combinations are used in the previous intrathecal therapy, oral medications may be provided to replace the intrathecal combination regimen. However, for the duration of the CNS-HYD201US trial only hydromorphone hydrochloride may be used in the intrathecal pump as monotherapy. Depending on the subjects starting dose on hydromorphone hydrochloride, either a 2 mg/mL or 10 mg/mL formulation of hydromorphone hydrochloride for intrathecal injection may be used.

Subjects who are converted directly to a therapeutic dose of hydromorphone hydrochloride (ie, direct conversion from previous treatment with hydromorphone, will start the study on Day 1 (see [Appendix A: Schedule of Study Procedures](#)). For subjects that are converted to a lower dose based on the 1:12 conversion scheme for safety reasons, up to five (5) optional study visits (Days A, B, C, D and E) are permitted to allow dose titration to a therapeutic dose that is well tolerated. These optional visit days may be from three (3) to seven (7) days apart. After the subject achieves a therapeutic dose of hydromorphone hydrochloride the procedures starting with Day 1 of the study will be followed to ensure the subject is treated for the full 12 week period at a therapeutic dose of intrathecal hydromorphone hydrochloride.

3.5.1.2 12-Week Open-Label Treatment Phase

Subjects will start study Day 1 when they are determined to be at a therapeutic dose of intrathecal hydromorphone hydrochloride. Day 1 should be initiated after a direct conversion to

intrathecal hydromorphone based on a 1:6 morphine equivalence ratio, or if converted to a lower dose after a short titration period to achieve a therapeutic dose.

Dose adjustments thereafter will be allowed by adjusting the pump speed 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%

Prior to a dose adjustment above 1 mg/day, the pump will be drained and refilled with 10 mg/mL hydromorphone hydrochloride undiluted and the pump speed will be adjusted to achieve the target dose.

During the switch to hydromorphone hydrochloride, oral opioid supplement is permitted up to a dose of 180 mg-equivalent morphine per day. Dose adjustments may continue until an optimal dose of intrathecal hydromorphone is achieved and the subject can be weaned off oral supplement as much as possible.

A maximum dose of 10 mg/day intrathecal hydromorphone hydrochloride is permitted at any time during this study. For PTM dosing this maximum dose includes the patient activated doses that are allowed by the device programming. Subjects may be given oral supplemental medication up to a maximum of 180 mg-equivalent morphine per day, however, the objective of the trial during this period through Day 77 is to achieve an optimal dose of intrathecal hydromorphone hydrochloride and eliminate any oral supplement.

On Day 77 the pump should be refilled with intrathecal hydromorphone and any final adjustments made to the daily dose or programming. On Day 77, the subject will be given a remote monitoring device to measure VASPI scores twice daily in the morning (5:30 am to 12:00 noon) and in the evening (6:00 pm to 11:45 pm). After Day 77 and during the randomized double-blind period there should be no dose adjustments other than those dictated by the protocol for subject on the control arm who are weaned off therapy. After Day 77, there should also be no changes to the pump programming for simple continuous, complex continuous with or without use of a PTM dosing regimens until after the completion of the trial.

Subjects discontinuing prior to randomization and not rolling over into the CNS-HYD202US trial, will have their follow up visit approximately 2 weeks after discontinuing the trial.

3.5.1.3 5-Week Randomized Double-Blind Period

On Day 84 subjects will be randomized to one of two groups. The criteria for randomization is defined as a an average VASPI score of 50 mm or less on a scale of 100 mm for the last 5 days with daily pain measurements prior to randomization on Day 84. The active group will remain at

their optimal dose of hydromorphone hydrochloride for the duration of the 5-week double-blind period. For those subjects randomized to be withdrawn from hydromorphone hydrochloride therapy on Day 84, the pump speed will be adjusted to decrease the dose each 7 days (± 1 day), starting at a dose of 75%, 50%, 25%, 12.5% and approximately 0% of the dose at the time of randomization (See [Appendix A, Table A- 2](#)). For PTM dosing, the base continuous dose and the PTM dose would be decreased by the specified percentages above. The total maximum dose of 10 mg/day will be the combined total of the decreased base dose and PTM dose.

To preserve the blind during the 5-week double-blind period, an Unblinded Pump Operator will be assigned at the site, who is independent from the investigator or other personnel that evaluate the subject's condition. This Unblinded Pump Operator will manage all pump speed and dose adjustments. The group randomized to remain at a constant optimal dose and those randomized to the control group (titration group) will return to the site on the same schedule and receive the same treatment. Subjects, who are on the active dose group, will have mock dose adjustments. Subjects that use a PTM device will also have tamper resistant tape applied to the display screen. The tamper resistant tape will be checked at each site visit to ensure the subject has not viewed the PTM screen.

After randomization on Day 84, no further dose adjustments for intrathecal hydromorphone hydrochloride dosing, other than those dictated by the protocol for the control (titration) group, will be permitted until after the 5 week double-blind phase of this study. Subjects will be allowed up to 60 mg morphine-equivalence or oral opioid per day only for the purpose of managing withdrawal symptoms after randomization. This oral opioid supplement is not intended to manage pain and should only be prescribed for management of withdrawal symptoms, if needed. Other non-opioid medications or non-pharmacologic (ie, devices) interventions used to manage pain should be kept constant after randomization on Day 84.

Prior to rescue medication being administered, subjects will complete Day 119 study assessments, if possible. After confirming with the investigator that it is acceptable to take rescue medication, if a subject cannot return to the study site for assessments they will be instructed to complete a VASPI score using the remote monitoring device immediately prior to taking oral rescue medication. If the subject can return to the site, rescue may be performed by either oral medication being administered or by increasing the pump speed to achieve a therapeutic dose of hydromorphone hydrochloride, or both.

At the time of rescue the day, time and amount of rescue medication provided to address the intolerable pain will be recorded. Rescue may include providing oral or intravenous medication, as well as increasing the pump speed to titrate the subject back to an effective dose of intrathecal hydromorphone hydrochloride. Subjects who experience an increase on the average 5 day pain intensity score increase of 20 mm or more on a 100 mm scale over their baseline score on Days 77 to 83, will be considered a treatment failure regardless of receiving any rescue medication.

3.5.1.4 12 Month Course of Treatment

Subjects that complete the 5-week randomized, controlled portion of this trial and those who are treatment failures or were dropped from the study prior to randomization may be able to continue on intrathecal hydromorphone hydrochloride therapy for an additional 12 months to obtain safety data with long term treatment. If these subjects qualify they may enroll in the CNS-HYD202US trial that will be ongoing in parallel with this study.

For those subjects randomized to hydromorphone hydrochloride in the CNS-HYD201US trial and then enter the CNS-HYD202US trial, their dose may be maintained at the dose used during the 5-Week randomization phase of the trial, or may be adjusted.

For subjects randomized to the titration group who had a significant downward dose adjustment in the CNS-HYD201US trial and then enter the CNS-HYD202US trial, the pump will be adjusted to titrate the subject back to the optimal dose of intrathecal hydromorphone hydrochloride.

In all cases, the highest dose permitted in these trials will be 10 mg/day of intrathecal hydromorphone hydrochloride.

3.5.2 Dose Interruption

Unscheduled dose interruptions are not permitted on this clinical trial. Subjects who must experience a dose interruption will be discontinued from the trial.

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. For concomitant medications being taken during the dosing period with intrathecal hydromorphone hydrochloride and the randomized withdraw, if the medication is needed long term the medication should be recorded as a concomitant medication and maintained at a constant dose during the trial.

There is inadequate systematic experience with the use of intrathecal hydromorphone hydrochloride in combination with other medications to predict specific drug-drug interactions. Interactions attributed to the combined use of intrathecal hydromorphone hydrochloride and other epidural drugs include hypotension and respiratory depression.

3.6.2 Prohibited Concomitant Medications

During treatment with intrathecal hydromorphone hydrochloride, use of sedatives, hypnotics, phenothiazines, anesthetics, tranquilizers or other drugs that may induce CNS and respiratory depression should be assessed by the primary investigator and used with caution. For subjects who are on concomitant medications that may induce respiratory depression in combination with hydromorphone hydrochloride, the medical monitor should be consulted prior to enrollment. Subjects will be instructed to avoid excessive alcohol consumption while on therapy.

Agonist/antagonist analgesics (ie, 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 caution⁵⁷.

3.7 Nonpharmacologic Interventions

Non-pharmacologic interventions for the management of pain are permitted in the CNS-HYD201US trial. After Day 77 no changes in the subject's non-pharmacologic treatments for the management of pain are permitted until the end of the study.

3.8 Duration of Therapy

The duration of this trial is anticipated to include a 2 week screening period, an optional 5 weeks of titration, a 12 week chronic dosing period and 5 week double-blind period to assess efficacy. Thus, subjects will remain in this trial for a total of up to 24 weeks if all 5 weeks of optional titration are needed.

3.9 Procedures for Monitoring Subject Compliance

Subjects will return to the clinic for scheduled visits and pump refills as specified in [Appendix A](#). Subjects who do not comply with the visit schedule may be discontinued from the study.

4.0 STUDY POPULATION

Male or female subjects requiring intrathecal opioid treatment to manage 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. Subject must be at least 18 years of age and no more than 75 years old.
2. Clinically diagnosed with chronic pain for at least a 6-month period.
3. Subject is presently on intrathecal pain medication and has a SynchroMed II Implantable pump or meets clinical criteria for implantation of a SynchroMed II Implantable pump. Subjects who are naïve to intrathecal therapy, may be enrolled 2-weeks after pump implantation.
4. Subject agrees to sign a Pain Treatment Agreement (Narcotic Contract) limiting narcotic prescriptions to the study physician.
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 with existing SynchroMed II Implantable pumps and are reasonably expected to benefit from intrathecal opioid therapy.
8. Subjects who are capable of receiving an MRI with and without contrast or CT myelogram, if required by the study protocol.
9. Provides written Ethics Committee approved informed consent.
10. 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 are breast-feeding.
2. Subjects who have participated in an investigational drug or device trial within 4 weeks prior to enrollment.
3. Subject has any known or suspected allergy to hydromorphone or to the materials of the infusion pump or intrathecal catheter.
4. Subject is scheduled for a pump or catheter replacement within 6 months of their enrollment into the trial.
5. 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).
6. Subjects who show signs of active systemic infection.

7. Subjects with a metastatic cancer to the spinal canal or a known central nervous system contraindication to intrathecal therapy.
8. Subject has a condition requiring diathermy procedures.
9. Subject has a life expectancy of less than 12 months.
10. Subject cannot independently comprehend and participate in the required assessments, including responding to the VASPI, SF-MPQ, COWS, SOWS, BPI and PGIC measurement tools.
11. Subject is not considered to be medically or psychologically appropriate for pump implantation.
12. Subjects who are unable or unwilling to return to all of the required follow-up visits.
13. Subjects with active implanted devices such as pacemakers, defibrillators, and cochlear implants or other medical device use, if in the opinion of the investigator the device would interfere with ability to perform an MRI or CT myelogram.
14. As a result of medical review and physical examination, the Investigator considers the subject unfit for the study.
15. Pain located above the shoulders in the head or neck region (e.g. trigeminal neuralgia), central pain syndromes or any other condition in which it is judged to be unlikely that the subject would benefit from intrathecal administration of the drug product.
16. Subjects who have previously been unresponsive to intrathecal hydromorphone therapy.

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 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 the subject 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 or 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 and record a complete physical examination at screening, Day 84, Day 119 and final study visit. 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, Pump Implantation and Surgical History

A medical history will be obtained at screening. 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:

- Underlying disease, injury or condition resulting in intractable pain, date of initial diagnosis, and prior treatments.
- Date of implantation of an intrathecal 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 Clinical Laboratory Testing and ECGs

Clinical laboratory testing (CBC, CMP, and urinalysis) and ECGs are performed only at screening for the purpose of determining the subject's eligibility for the study. Results will be recorded as normal, abnormal or abnormal clinically significant. Raw data will be kept as source documents at the site and not entered into the database.

Women of childbearing potential will have urine pregnancy testing completed at screening and/or baseline results will be recorded.

5.4 Vital Signs

Systolic and diastolic blood pressure, radial pulse, breathing rate, temperature, and weight will be obtained and recorded at screening, baseline (if a different visit) and each study visit.

5.5 Documentation of Concomitant Medications

Details regarding the name, indication, dose, route of administration, and frequency of all prescription medications taken within the past 30-days or while on study will be recorded.

6.0 PHARMACOKINETICS

Blood samples for determination of the steady state plasma pharmacokinetics (PK) of hydromorphone following continuous infusion will be collected during the study. The total volume of blood drawn for PK analysis is 24 mL over the course of the study. Each PK sample will be 6 mL of blood collected into a standard plasma sample tube and centrifuged to obtain at least 3 mL of plasma. The sample will be separated into two 1.5 mL aliquots and frozen to $< -20^{\circ}\text{C}$ until shipment to the central testing facility.

Blood will be collected for analysis of hydromorphone concentration in plasma prior to dosing with any daily oral medications (ie, other oral opioids permitted in the protocol) on Day 14, Days 56, 77 and Day 84.

7.0 PHARMACODYNAMICS

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

8.0 EFFICACY

The primary efficacy endpoint is the proportion of subjects who are treatment failures during the double-blind randomized withdrawal period. The definition of a treatment failure for this trial is:

Treatment Failure Criteria: After randomization, a treatment failure will be defined by the following criteria:

1. A subject who experience an increase of 20 mm or more above the baseline value on a 100 mm VASPI based on the average of 5 days, or
2. A subjects who experience intolerable pain that in the opinion of the investigator requires intervention (ie, rescue), or
3. Any subject who has other interventions for pain that violate the protocol from Day 84 to 119 that includes:

- a. Requires oral opioid supplement in excess of 60 mg/day morphine-equivalent to manage withdrawal symptoms, or
- b. Has a change in non-opioid oral prescription medications or non-pharmacological treatments being administered for the management of pain.

Note: A subject who does not have sufficient data for evaluation, drops out for any other reasons that are not listed above or who experiences withdrawal syndrome as identified by COWS > 12 during the double-blind treatment phase will **not** be classified as a treatment failure in the primary efficacy analysis.

9.0 STUDY VISITS

Refer to [Appendix A: Schedule of Study Procedures](#)

The Schedule of Study Procedures includes two separate tables:

- [Table A- 1: Schedule of Study Procedures: Screening and Chronic Dosing Phase to Day 56.](#)
- [Table A- 2: Schedule of Study Procedures: Final 7 Days of Continuous Dosing, Randomized Withdrawal and Efficacy Evaluation Period.](#)

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. The signature date and the name of the individual at the site who obtained the informed consent will be recorded in the subject's medical record.

After written informed consent is obtained, the subject will be assigned a three-digit number screening number (SXXX) and will undergo the designated screening procedures listed in [Appendix A](#) within 14 days prior to 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](#). Subjects who delay participation in the trial for any reason or fall outside the screening window before dosing, may be rescreened and will retain their same screening number. For subjects who fail an entry criteria, rescreening may be permitted, retaining the original screening number, with the approval of the Medical Monitor prior to enrollment of the subject.

9.2 Baseline Evaluations

If a subject is determined to be eligible for participation in the study they will undergo baseline assessments prior to drug administration. Baseline assessments will be conducted according to the procedures outlined in [Appendix A: Schedule of Study Procedures](#)

Note that the Baseline, Screening and the first day of dosing may be combined at one visit.

9.3 Dose Conversion and Optional Titration Period

Subjects entering the trial on a therapeutic dose of intrathecal hydromorphone hydrochloride may be converted directly to study medication without dose adjustment.

Subjects who will be converted from their current intrathecal morphine therapy to intrathecal hydromorphone hydrochloride according to the following scheme:

Subject Status on Morphine	Conversion Ratio
Dose \leq 30 mg IT morphine <u>and</u> tolerating therapy well	1 : 6 ^a
Dose > 30 mg IT morphine <u>or</u> subject has significant side effects on morphine	1 : 12 ^b

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

^bConversion is based on mg-morphine equivalence such that for each 12 mg morphine sulfate the dose is converted to 1 mg hydromorphone hydrochloride.

The conversion will take place by removing the current product in the pump and then replacing the contents with hydromorphone hydrochloride for intrathecal injection. At the discretion of the investigator the pump reservoir may be rinsed with preservative free sterile saline or the study drug (hydromorphone hydrochloride for injection). The subject should be contacted by telephone 24 hours after initiating study medication. If combinations are used in the previous intrathecal therapy, oral medications may be provided to replace the intrathecal combination regimen. However, for the duration of the CNS-HYD201US trial only hydromorphone hydrochloride may be used in the intrathecal pump as monotherapy. Depending on the subjects starting dose on hydromorphone hydrochloride, either a 2 mg/mL or 10 mg/mL formulation of hydromorphone hydrochloride for intrathecal injection may be used.

Subjects who are converted directly to a therapeutic dose of hydromorphone hydrochloride (ie, direct conversion from previous treatment with hydromorphone, or a 1:6 conversion from a therapeutic dose of converted to a lower dose based on the 1:12 conversion scheme for safety reasons, up to five (5) optional study visits (Days A, B, C, D and E) are permitted to allow dose titration to a therapeutic dose that is well tolerated. These optional visit days may be from three (3) to seven (7) days apart. After the subject achieves a therapeutic dose of hydromorphone

hydrochloride the procedures starting with Day 1 of the study will be followed to ensure the subject is treated for the full 12 week period at a therapeutic dose of intrathecal hydromorphone hydrochloride.

9.4 Continuous Dosing Period (Day 1 to Day 83)

Once a subject is at a therapeutic dose of hydromorphone hydrochloride for intrathecal injection, study Day 1 will be initiated. This may be directly after conversion to hydromorphone hydrochloride if at a therapeutically equivalent dose to their prior therapy or after dose titration as needed to achieve a therapeutic dose.

Further dose adjustments during the 12-week continuous dosing period are permitted with each scheduled visit ([Appendix A, Table A- 2](#)) to achieve the optimal treatment of pain. Dose adjustments will be allowed by adjusting the pump speed 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 %

Unscheduled visits are permitted if deemed necessary to manage the subjects condition with notification to the study Medical Monitor.

A maximum dose of hydromorphone hydrochloride of 10 mg/day is permitted in this trial.

Subjects may be given up to 180 mg-equivalent morphine per day up to Day 77 to help manage break through pain or withdrawal until the subject is titrated to an optimal dose. Ideally, the subject should be weaned of all oral medications as the optimal dose of hydromorphone hydrochloride is achieved.

On Day 77 the pump should be refilled with intrathecal hydromorphone hydrochloride and any final adjustments made to the daily dose or programming. On Day 77, the subject will be given a remote monitoring device to measure VASPI scores twice daily in the morning (5:30 am to 12:00 noon) and in the evening (6:00 pm to 11:45 pm). After Day 77 and during the randomized double-blind period there should be no dose adjustments other than those dictated by the protocol for subject on the control arm who are weaned off therapy. After Day 77, there should also be no changes to the pump programming for simple continuous, complex continuous or PTM dosing regimens until after the completion of the trial.

During the last 7 days of the continuous dosing period (Days 77 to 83) the subject should be off any oral opioid supplement and no new or changes to prescription medications for pain, as well as no new or change in non-pharmacologic interventions for pain are allowed.

At each study interim visit subjects will be assessed for AEs and clinical signs or symptoms of an inflammatory granuloma. If an AE is reported, a targeted physical exam will be conducted to evaluate the severity and causality of the event (See [Appendix A](#)).

If interim visits more frequent than scheduled in [Appendix A, Table A- 1](#), are necessary due to the need to adjust dose to optimize the pain relief or reduce side effects, the site may schedule the extra visit, but is asked to notify the Medical Monitor.

All visit dates during the dose titration and stabilization period are to be conducted within 2 days of the scheduled date (ie, \pm 2 days).

9.5 Randomized Withdrawal and Efficacy Evaluation Period (Day 84 to Day 119)

On Day 84 subjects will be randomized to one of two groups. The active group will remain at their optimal dose of hydromorphone hydrochloride for the duration of the 5-week double-blind period. The group randomized to be withdrawn from therapy will have their dose of intrathecal hydromorphone hydrochloride titrated downward with a dose reduction each 7 days. Dose reductions will be to 75%, 50%, 25%, 12.5%, and approximately 0% (ie, minimum pump speed or shipping mode) of the initial dose on each successive dose reduction (See [Appendix A, Table A- 2](#)).

To preserve the blind during the 5-week double-blind period, a person at the site, who is independent from the investigator or other personnel that evaluate the subjects condition, will manage pump speed adjustments. Both groups randomized to remain at a constant optimal dose and those randomized to withdraw will return to the site on the same schedule and receive the same treatment. Subjects who are on the active optimal dose group, will have mock dose adjustments. Subjects who utilize a PTM device will have the display screen covered with tamper resistant tape to avoid seeing the pump refill date alarm.

After randomization on Day 84, no further dose adjustments will be permitted other than those defined by the protocol for the control (titration) group, until after the 5 week double-blind phase of this study. Subjects will be allowed up to 60 mg morphine-equivalence of oral opioid per day only for the purpose of managing withdrawal symptoms after randomization. During the 5-week period after randomization, VASPI assessments will be conducted twice each day using a remote data collection device. COWS, SOWS, BPI and PGIC assessments will be conducted at each scheduled visit.

Prior to rescue medication being administered, subjects will complete Day 119 study assessments, if possible. After confirming with the investigator that it is acceptable to take rescue medication, if a subject cannot return to the study site for assessments they will be instructed to complete the VASPI assessment on the remote monitoring device immediately prior to taking oral rescue medication. If the subject can return to the site, rescue may be performed by either oral medication being administered or by increasing the pump speed to achieve a therapeutic dose of hydromorphone hydrochloride, or both.

The day, time and amount of rescue medication provided to address the intolerable pain will be recorded. Rescue may include providing oral or intravenous medication, as well as increasing the pump speed to titrate the subject back to an effective dose of intrathecal hydromorphone hydrochloride. Subjects who experience an average 5 day pain intensity score increase of 20 mm or more on a 100 mm scale over their baseline score, will be considered a treatment failure regardless of experiencing any intolerable pain.

At each study interim visit subjects will be assessed for AEs and clinical signs or symptoms of an inflammatory granuloma. If an AE is reported, a targeted physical exam will be conducted to evaluate the severity and causality of the event (See [Appendix A](#)).

All visit dates during the randomized withdrawal period are to be conducted within 1 day of the scheduled date (ie, \pm 1 day).

9.6 Long-Term Follow Up (CNS-HYD202US Safety)

Subjects who complete the CNS-HYD201US trial are allowed to enroll in the CNS-HYD202US study and continue on hydromorphone hydrochloride therapy for an additional 12 months. A subject who is dropped from the study prior to randomization or a treatment failure during the double-blind randomized withdrawal period will be allowed to enroll in the CNS HYD202US study if the PI believes that the subject meets the study selection criteria and would benefit from participation in the study. For subjects who were stable during the double-blind randomized withdrawal period, the same infusion rate and daily dose may be maintained or a dose adjustment implemented at the discretion of the investigator. If the subject experienced significant increases in pain and required rescue medication, the subject should be re-titrated onto intrathecal hydromorphone hydrochloride and slowly withdrawn from any oral opioid medications. All subjects may have their dose of intrathecal hydromorphone hydrochloride adjusted during this period as necessary to obtain optimal pain relief, provided the dose does not exceed 10 mg/day. Oral opioid supplemental medication may be prescribed as necessary and appropriate according to the practice of medicine. Other FDA approved non-opioid oral pain medications are permitted during this period in accordance with their marketed product labeling.

Study procedures and assessments for the long term follow up safety study should be followed according to protocol CNS-HYD202US. Pump refills during this period are conducted as needed to maintain the appropriate volume of product in the pump and maintain the subject dosing.

9.7 Final Visit

Subjects who do not enter the CNS-HYD202US long-term safety trial will return to the investigational site for the final visit 2 weeks (\pm 4 days) after discontinuation from the trial. At the final study visit subjects will be assessed for AEs and clinical signs or symptoms of an inflammatory granuloma as well as other procedures according to [Appendix A, Table A- 2](#). Also during the final visit the investigator will remove all study drug from the subjects pump and will continue the subjects normal standard of care.

10.0 PREMATURE DISCONTINUATION FROM STUDY

A premature discontinuation from study will occur when a subject who signed informed consent ceases participation in this study, regardless of circumstances, prior to completion of the defined study period. Subjects can be prematurely discontinued from the study for one of the following reasons:

- Failure to meet inclusion/exclusion criteria before receiving first dose of study drug has been administered.
- Noncompliance with study procedures and visit schedules.
- Death.
- 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.

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 must complete all applicable electronic CRF pages for subjects who discontinue study drug prematurely. Final visit procedures (See [Appendix A, Table A- 2](#)) should be conducted for any subject who discontinues study drug prematurely.

If a subject is discontinued from therapy, study medication should be removed from the pump and the subject placed on standard of care therapy at the discretion of the investigator.

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 or 200,000 mcg per 20 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. Single use vials will be packaged in shipping containers 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°C)
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) vials will be packaged in boxes for shipment to investigational sites. Excursions permitted to 4° to 30°C (39° to 86 °F), and after receipt should be stored at 15° to 30°C (59° to 86°F) until use.

12.4 Preparation and Administration of Study Drug

There is no manipulation or preparation of study drug other than filling into the SynchroMed[®] II 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 by the clinical monitors. 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. Study drug dispensed for all subjects must be recorded on the Drug Accountability Form. The study drug Dispensing Log and remaining drug inventory will be verified at each monitoring visit by the Sponsor-designated clinical monitor.

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.

Please note that hydromorphone hydrochloride is a Schedule II DEA restricted drug and as such all appropriate DEA procedures for handling and accountability of the investigational drug product must be complied with during this trial. All sites must be registered and licensed to manage Schedule II drugs by the DEA. See the Investigators Brochure for more detail about management of scheduled opioid products.

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
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Definition of Adverse Events and Adverse Drug Reactions:

Adverse events 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 (e.g., 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 nonserious AEs starts after the first administration of study drug 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”.

In order to classify adverse events and diseases, preferred terms will be assigned by the sponsor or its designee to the original terms using MedDRA. CTCAE is provided in [Appendix B](#).

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

Description of Event Intensity	Grade
Mild	1
Moderate	2
Severe	3
Life-threatening or disabling*	4
Death related to AE*	5

*must be reported as an SAE

For those AEs that are not described on the CTCAE v 4.03, 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 (e.g., 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

Approximately 150 subjects will be enrolled at up to thirty (30) US investigative sites to obtain approximately 80 subjects who qualify for randomization into the double-blind period on Day 84. This enrollment is based on a combined drop out and treatment failure (ie, > 50 mm on a 100 mm VASPI score for the last 5 days with non-missing data prior to the double-blind period) rate of approximately 45%.

During the double-blind period, the true treatment failure rate in the hydromorphone hydrochloride arm is assumed to be at most 20%. Based on a two-sided, two-sample comparison

of proportions at the $\alpha = 0.05$ level of significance, a sample size of 80 subjects (40 per arm) will provide greater than 90% power to detect an increase in the treatment failure rate of 35% (ie, the control group who will have their dose titrated downward has a failure rate of 55%).

14.2 Analysis Data Sets

The ITT population includes all subjects who are randomized on Day 84 to either the active or control group in the double-blind randomized withdrawal portion of this study and receive at least one day of hydromorphone hydrochloride intrathecal treatment during the randomization period. All efficacy analyses will be carried out using the ITT population. In all efficacy analyses, subjects will be included in the group based on the treatment to which they were randomized.

The Safety population includes all subjects who have study medication loaded into their intrathecal pump (ie, any exposure to study medication). Safety analyses will be carried out using the Safety population. In all safety analyses, subjects will be included in the group based on the treatment they received (ie, randomized withdrawal or same dose hydromorphone continuation). Subjects who do not reach the point of randomization will be included in the overall column only.

14.3 Primary Efficacy Analysis

The primary efficacy endpoint is the treatment failure rate during the 5-week randomized double-blind period. After randomization, a treatment failure will be defined by the following criteria:

1. Any subject who experiences an increase of 20 mm or more above the baseline value on a 100 mm VASPI based on the average of 5 days, or
2. Any subject who experiences intolerable pain that in the opinion of the investigator requires intervention (ie, rescue), or
3. Any subject who has other interventions for pain that violate the protocol from Day 84 to 119 that includes:
 - a. Requires oral opioid supplement in excess of 60 mg/day morphine-equivalent to manage withdrawal symptoms, or
 - b. Has a change in non-opioid oral prescription medications or non-pharmacological treatments being administered for the management of pain.

Note: A subject who does not have sufficient data for evaluation, drops out for any other reasons that are not listed above or who experiences withdrawal syndrome as identified by COWS > 12 during the double-blind treatment phase will **not** be classified as a treatment failure in the primary efficacy analysis.

As discussed in the National Research Council (2010, page 24) report on missing data, the estimand is the difference in outcome improvement in tolerators. Because the primary endpoint

is defined as a failure rate, and because any subject who cannot be defined as a “failure” is a treatment “success”, the use of this endpoint in a randomized withdrawal study minimizes missing data (56).

The treatment failure rates in the hydromorphone hydrochloride and control groups will be compared using Pearson’s chi-square test (two-sided) at the $\alpha = 0.05$ level of significance.

14.4 Secondary Analyses

The change from baseline to week 5 in the BPI will be analyzed using an ANCOVA model with treatment group as a factor and the baseline BPI as a covariate. Other quantitative secondary endpoints will also be analyzed using this same type of ANCOVA model.

The distributions of time to rescue will be summarized in each treatment group using the Kaplan-Meier method. The two groups will be compared using the log rank test.

The PGIC will be analyzed using the Cochran-Mantel-Haenszel mean score test (using equally spaced scores).

All secondary analyses will be carried out using two-sided tests at the 5% level of significance.

14.5 Safety

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. Particular attention will be paid to potential or confirmed granulomas and the outcome of these events will be followed to resolution.

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.

15.0 DATA COLLECTION, STUDY MONITORING, AND DATA DISCLOSURE

15.1 Data Collection and Reporting

An electronic CRF (ie, Electronic Data Capture (EDC) system) will be completed for each subject who is assigned a study number, signs and dates the study-approved ICF, and receives at least one dose of study drug. For all entries into the EDC that are not source electronic data, the

data entries must be supported by original source documentation (e.g., laboratory reports, medical records) maintained at the investigational site.

A paper CRF page will be used by the Unblinded Pump Operator to record dose administration information during Days 84 to 119. This CRF page will be held at the site and collected after the subject has completed the trial for manual entry into the database.

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 entered into the EDC and electronically 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 EDC (CRFs), source documents, etc., for review and inspection by the clinical monitor.

All EDC (CRFs) will be 100% source verified against corresponding source documentation (e.g., 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 EDC (CRFs). Clinical monitors will also ensure that all protocol requirements, applicable FDA regulations, other requirements, and Investigator's obligations are being fulfilled.

Paper CRFs will not be monitored by the blinded clinical monitor during routine monitoring visits. The CRF pages will be reviewed and confirmed to be accurate by a central unblinded monitor not involved in the conduct of the clinical trial. This central unblinded monitor will issue any queries necessary. The blinded clinical monitor will not review paper CRF pages until the subject completed the study.

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, the Sponsor-assigned 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 maintained in lockable file cabinets. 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 representatives of the study Sponsor.

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: Screening and Chronic Dosing Phase to Day 56

Study Procedure	Screening	Baseline	Titration	Visit Schedule (Days 1 to 56)							
	Day ^b -14 to 1	Day ^c -3 to 1	Optional Days ^e	Day 1	Day 7	Day 14	Day 21	Day 28	Day 42	Day 56	
Signed informed consent	X										
Medical history	X										
Complete physical examination	X										
Vital signs, Height and Weight	X	X	X	X	X	X	X	X	X	X	
Urine pregnancy test	X	X									
ECG ^f	X										
CBC, CMP, urinalysis ^g	X										
Concomitant medication assessment	X	X		X	X	X	X	X	X	X	
Adverse event assessment	X	X		X	X	X	X	X	X	X	
Hydromorphone HCl (Pump Refill)			X^d	X^d							
Pump Dose Adjustment			X	X	----->						
Oral Opioid (180 mg morphine-eq/day max.)^h				X	----->						
Plasma concentration (PK) of Hydromorphone						X				X	
Clinical evaluation for Inflammatory Granuloma ⁱ	X			X	X	X	X	X	X	X	
VASPI ^l	X	X	X	X	X	X	X	X	X	X	
COWS ^k		X	X			X					
SOWS ^k		X	X			X					
SF-MPQ ^k		X				X		X		X	
BPI ^k		X				X		X		X	
PGIC ^k		X				X		X		X	

- Study day is based on Day 1 defined as the first day at a therapeutic dose of intrathecal hydromorphone. There is no Day 0 in this trial. Visit days are ±2 day for Optional Titration Days and Days 1, 7, 14, 21, 28, 42 56 and 77. “Unscheduled Visits” will be considered as “Optional Days” for the purpose of study assessments.
- Screening period is 14 days. Baseline, Screening and Initiation of Dosing (ie, Optional Titration Day or Day 1) visits may be combined.
- Baseline evaluations must be performed within 72 hours prior to initial dose reduction to wean subject off current opioid therapy. Baseline and Screening visit may be combined.
- Pump refills are conducted during regular visits only when necessary based on the pump alarm date, or on Day 1 and Day 77 per protocol regardless of pump alarm date.
- For subjects requiring titration to a therapeutic dose of intrathecal hydromorphone, up to five (5) additional study days are allowed for titration (Days A, B, C, D and E) each 3 to 7 days apart.
- ECG is to be performed in triplicate for all measurements at Screening and Baseline period.
- Blood samples are to be obtained during screening. Includes RBC morphology, reticulocyte count, and standard urinalysis.
- Oral supplemental opioid medications are allowed up to 180 mg-morphine equivalence per day up to Day 77. As the intrathecal dose of hydromorphone is optimized oral supplement should be reduced as much as possible.
- If there are clinical signs of an inflammatory granuloma as defined in [Section 3.3](#), the Medical Monitor should be notified and an MRI or CT myelogram scheduled to confirm the pathology of the granuloma.

- j. VASPI will be obtained in the clinic using a standardized scale.
- k. COWS, SOWS, BPI, SF-MPQ and PGIC will be conducted at each office visit as specified in the Schedule of Events. Assessments conducted per the Schedule of Events should be completed prior to any dose adjustment or providing any oral supplemental opioid medication for withdrawal symptoms or rescue, if possible.

Table A- 2: Schedule of Study Procedures: Final 7 Days of Continuous Dosing, Randomized Withdrawal and Efficacy Evaluation Period

Study Procedure	Visit Schedule ^b Days 77 to 119							
	Day 77	Day 84	Day 91	Day 98	Day 105	Day 112	Day 119 ^c	Final Visit ^f
Complete physical examination		X					X	X
Vital signs and Weight	X	X	X	X	X	X	X	X
Concomitant medication assessment	X	X	X	X	X	X	X	X
Adverse event assessment	X	X	X	X	X	X	X	X
Hydromorphone HCl (Pump Refill)	X							
Hydromorphone Titration^{c, d}		X	X	X	X	X		
Hydromorphone HCl (removal from pump)								X
Oral Opioid (60 mg morphine-eq/day max.)^g			X ----->					
Plasma concentration (PK) of Hydromorphone	X	X						
Clinical evaluation for Inflammatory Granulomas ^h	X	X	X	X	X	X	X	X
VASPI Assessment ⁱ	X ----->							
COWS Assessment ^j		X	X	X	X	X	X	
SOWS Assessment ^j		X	X	X	X	X	X	
Short-Form McGill ^j		X		X		X	X	
BPI ^j		X		X		X	X	
PGIC ^j		X		X		X	X	

- a. Study day is based on Day 1 defined as the first day at a therapeutic dose of intrathecal hydromorphone., There is no Day 0 in this trial.
- b. All visit days are +/- 1 day after Day 77 except for the final study visit.
- c. On Days 84, 91, 98, 105 and 112 all subjects will have a pump adjustment. For those subjects randomized to maintain therapy, the adjustments will be a mock change to the dose, but no change will actually be made. For control group subjects randomized to be weaned off medication, the pump will be adjusted to give a 75%, 50%, 25%, 12.5% and 0% dose on each successive dose adjustment visit.
- d. For the 0% dose, the pump will be set to the shipping mode (minimal speed possible)
- e. On Day 119, or after treatment failure, all subject will receive scheduled Day 119 assessments before rescue medication is administered, if possible. If the subject cannot come to the site prior to rescue, they will be instructed to take a final VASPI using the remote monitoring device prior to taking oral rescue medication. After completion of the randomization period or rescue due to intolerable pain, or if dropped prior to randomization, subjects may be eligible to enter the CNS-HYD202US long term safety trial for an additional 12-months of hydromorphone therapy.
- f. Subjects that discontinue or do not enter the CNS-HYD202US trial will return to the site 2 weeks after their last visit to have a final study visit This visit can be +/- 4 days of the target date.
- g. Oral opioid up to a maximum of 60 mg morphine-equivalence of oral opioid per day is allowed after Day 84 only for the purpose of managing withdrawal symptoms experienced as subject's are weaned off intrathecal medication. Doses of opioids in excess of 60 mg morphine-equivalence oral opioid per day, or other interventions to manage pain will be considered a treatment failure.
- h. If there are clinical signs of an inflammatory granuloma as defined in [Section 3.3](#), the Medical Monitor should be notified and an MRI or CT myelogram scheduled to confirm the pathology of the granuloma.
- i. VASPI assessments are performed twice daily by the subject using a remote monitoring device that can capture VASPI measurements at approximately the same times each day.
- j. COWS, SOWS, BPI, SF-MPQ and PGIC will be conducted at each office visit as specified in the Schedule of Events. Assessments conducted per the Schedule of events should be completed prior to any dose adjustment or providing any oral supplemental opioid medication for withdrawal symptoms or rescue, if possible.

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	
<p><i>Place a single vertical line on the scale that best characterizes your answer to the following question:</i></p> <p>How severe is your pain right now?</p>  <p>no pain unbearable pain</p>	
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:
<p>Resting Pulse Rate: (record beats per minute) <i>Measured after subject is sitting/lying for one minute.</i></p> <p>0 pulse rate 80 or below 1 pulse rate 81-100 2 pulse rate 101-120 4 pulse rate greater than 120</p>			
<p>Sweating: <i>Over past ½ hour not accounted for by room temperature or subject activity.</i></p> <p>0 no report of chills or 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</p>			
<p>Restlessness: <i>Observation during assessment.</i></p> <p>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</p>			
<p>Pupil Size:</p> <p>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</p>			
<p>Bone or Joint aches: <i>If subject was having pains previously, only the additional component attributed to opiate withdrawal is scored.</i></p> <p>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</p>			
<p>Runny nose or tearing: <i>Not accounted for by cold symptoms or allergies.</i></p> <p>0 not present 1 nasal stuffiness or unusually moist eyes 2 nose running or tearing 4 nose constantly running or tears streaming down cheeks</p>			

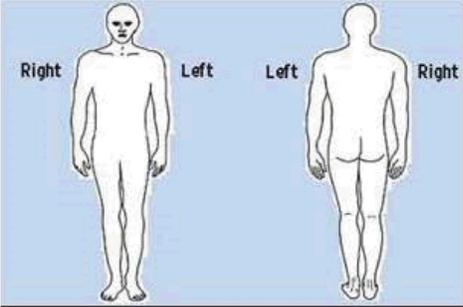
CLINICAL OPIATE WITHDRAWAL SCALE (COWS) - CONTINUED			
	Date/Time	Date/Time:	Date/Time:
GI Upset: <i>Over last 1/2 hour</i> 0 no GI symptoms 1 stomach cramps 2 nausea or loose stools 3 vomiting or diarrhea 5 multiple episodes of diarrhea or vomiting			
Tremor: <i>Observation of outstretched hands</i> 0 no tremor 1 tremor can be felt, but not observed 2 slight tremor observable 4 gross tremor or muscle twitching			
Yawning: <i>Observation during assessment</i> 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: Subjective Opiate Withdrawal Scale (SOWS)

SUBJECTIVE OPIATE WITHDRAWAL SCALE (SOWS)							
Please indicate if you are having any of the following withdrawal symptoms by rating its severity.							How long AFTER you last dose did you begin to feel this symptom?
	Symptom	Not at all	A Little	Moderate	Quite a bit	Extremely	Onset (hrs)
1	Anxious/Nervous	0	1	2	3	4	<input type="checkbox"/> 3-4 <input type="checkbox"/> 8 <input type="checkbox"/> 16 <input type="checkbox"/> 24
2	Body Aches & Pains	0	1	2	3	4	<input type="checkbox"/> 3-4 <input type="checkbox"/> 8 <input type="checkbox"/> 16 <input type="checkbox"/> 24
3	Constipation	0	1	2	3	4	<input type="checkbox"/> 3-4 <input type="checkbox"/> 8 <input type="checkbox"/> 16 <input type="checkbox"/> 24
4	Diarrhea	0	1	2	3	4	<input type="checkbox"/> 3-4 <input type="checkbox"/> 8 <input type="checkbox"/> 16 <input type="checkbox"/> 24
5	Drug Hunger/Craving	0	1	2	3	4	<input type="checkbox"/> 3-4 <input type="checkbox"/> 8 <input type="checkbox"/> 16 <input type="checkbox"/> 24
6	Goosebumps	0	1	2	3	4	<input type="checkbox"/> 3-4 <input type="checkbox"/> 8 <input type="checkbox"/> 16 <input type="checkbox"/> 24
7	Hot/Cold Flashes	0	1	2	3	4	<input type="checkbox"/> 3-4 <input type="checkbox"/> 8 <input type="checkbox"/> 16 <input type="checkbox"/> 24
8	Muscle Twitching	0	1	2	3	4	<input type="checkbox"/> 3-4 <input type="checkbox"/> 8 <input type="checkbox"/> 16 <input type="checkbox"/> 24
9	Nausea	0	1	2	3	4	<input type="checkbox"/> 3-4 <input type="checkbox"/> 8 <input type="checkbox"/> 16 <input type="checkbox"/> 24
10	Restlessness	0	1	2	3	4	<input type="checkbox"/> 3-4 <input type="checkbox"/> 8 <input type="checkbox"/> 16 <input type="checkbox"/> 24
11	Runny Nose	0	1	2	3	4	<input type="checkbox"/> 3-4 <input type="checkbox"/> 8 <input type="checkbox"/> 16 <input type="checkbox"/> 24
12	Sedation/Sleepiness	0	1	2	3	4	<input type="checkbox"/> 3-4 <input type="checkbox"/> 8 <input type="checkbox"/> 16 <input type="checkbox"/> 24
13	Shaking	0	1	2	3	4	<input type="checkbox"/> 3-4 <input type="checkbox"/> 8 <input type="checkbox"/> 16 <input type="checkbox"/> 24
14	Stomach Cramps	0	1	2	3	4	<input type="checkbox"/> 3-4 <input type="checkbox"/> 8 <input type="checkbox"/> 16 <input type="checkbox"/> 24
15	Sweating	0	1	2	3	4	<input type="checkbox"/> 3-4 <input type="checkbox"/> 8 <input type="checkbox"/> 16 <input type="checkbox"/> 24
16	Teary Eyes	0	1	2	3	4	<input type="checkbox"/> 3-4 <input type="checkbox"/> 8 <input type="checkbox"/> 16 <input type="checkbox"/> 24
17	Vomiting	0	1	2	3	4	<input type="checkbox"/> 3-4 <input type="checkbox"/> 8 <input type="checkbox"/> 16 <input type="checkbox"/> 24
18	Yawning	0	1	2	3	4	<input type="checkbox"/> 3-4 <input type="checkbox"/> 8 <input type="checkbox"/> 16 <input type="checkbox"/> 24
Total							

Appendix F: 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.																						
<table style="width: 100%; border-collapse: collapse;"> <tr> <td style="border-top: 1px solid black; border-bottom: 1px solid black; width: 10%;">0</td> <td style="border-top: 1px solid black; border-bottom: 1px solid black; width: 10%;">1</td> <td style="border-top: 1px solid black; border-bottom: 1px solid black; width: 10%;">2</td> <td style="border-top: 1px solid black; border-bottom: 1px solid black; width: 10%;">3</td> <td style="border-top: 1px solid black; border-bottom: 1px solid black; width: 10%;">4</td> <td style="border-top: 1px solid black; border-bottom: 1px solid black; width: 10%;">5</td> <td style="border-top: 1px solid black; border-bottom: 1px solid black; width: 10%;">6</td> <td style="border-top: 1px solid black; border-bottom: 1px solid black; width: 10%;">7</td> <td style="border-top: 1px solid black; border-bottom: 1px solid black; width: 10%;">8</td> <td style="border-top: 1px solid black; border-bottom: 1px solid black; width: 10%;">9</td> <td style="border-top: 1px solid black; border-bottom: 1px solid black; width: 10%;">10</td> </tr> <tr> <td style="text-align: center;">No Pain</td> <td></td> <td></td> <td></td> <td></td> <td></td> <td></td> <td></td> <td></td> <td></td> <td style="text-align: center;">Pain as bad as you can imagine</td> </tr> </table>		0	1	2	3	4	5	6	7	8	9	10	No Pain										Pain as bad as you can imagine
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.																						
<table style="width: 100%; border-collapse: collapse;"> <tr> <td style="border-top: 1px solid black; border-bottom: 1px solid black; width: 10%;">0</td> <td style="border-top: 1px solid black; border-bottom: 1px solid black; width: 10%;">1</td> <td style="border-top: 1px solid black; border-bottom: 1px solid black; width: 10%;">2</td> <td style="border-top: 1px solid black; border-bottom: 1px solid black; width: 10%;">3</td> <td style="border-top: 1px solid black; border-bottom: 1px solid black; width: 10%;">4</td> <td style="border-top: 1px solid black; border-bottom: 1px solid black; width: 10%;">5</td> <td style="border-top: 1px solid black; border-bottom: 1px solid black; width: 10%;">6</td> <td style="border-top: 1px solid black; border-bottom: 1px solid black; width: 10%;">7</td> <td style="border-top: 1px solid black; border-bottom: 1px solid black; width: 10%;">8</td> <td style="border-top: 1px solid black; border-bottom: 1px solid black; width: 10%;">9</td> <td style="border-top: 1px solid black; border-bottom: 1px solid black; width: 10%;">10</td> </tr> <tr> <td style="text-align: center;">No Pain</td> <td></td> <td></td> <td></td> <td></td> <td></td> <td></td> <td></td> <td></td> <td></td> <td style="text-align: center;">Pain as bad as you can imagine</td> </tr> </table>		0	1	2	3	4	5	6	7	8	9	10	No Pain										Pain as bad as you can imagine
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 .																						
<table style="width: 100%; border-collapse: collapse;"> <tr> <td style="border-top: 1px solid black; border-bottom: 1px solid black; width: 10%;">0</td> <td style="border-top: 1px solid black; border-bottom: 1px solid black; width: 10%;">1</td> <td style="border-top: 1px solid black; border-bottom: 1px solid black; width: 10%;">2</td> <td style="border-top: 1px solid black; border-bottom: 1px solid black; width: 10%;">3</td> <td style="border-top: 1px solid black; border-bottom: 1px solid black; width: 10%;">4</td> <td style="border-top: 1px solid black; border-bottom: 1px solid black; width: 10%;">5</td> <td style="border-top: 1px solid black; border-bottom: 1px solid black; width: 10%;">6</td> <td style="border-top: 1px solid black; border-bottom: 1px solid black; width: 10%;">7</td> <td style="border-top: 1px solid black; border-bottom: 1px solid black; width: 10%;">8</td> <td style="border-top: 1px solid black; border-bottom: 1px solid black; width: 10%;">9</td> <td style="border-top: 1px solid black; border-bottom: 1px solid black; width: 10%;">10</td> </tr> <tr> <td style="text-align: center;">No Pain</td> <td></td> <td></td> <td></td> <td></td> <td></td> <td></td> <td></td> <td></td> <td></td> <td style="text-align: center;">Pain as bad as you can imagine</td> </tr> </table>		0	1	2	3	4	5	6	7	8	9	10	No Pain										Pain as bad as you can imagine
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 G: 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)			5 = Moderately better, and a slight but noticeable change			
2 = Almost the same, hardly any change at all			6 = Better, and a definite improvement that has made a real and worthwhile difference			
3 = A little better, but no noticeable change			7 = A great deal better, and a considerable improvement that has made all the difference			
4 = Somewhat better, but the change has not made any real difference						

Appendix H: Short-Form McGill Pain Questionnaire (SF-MPQ)

SHORT-FORM MCGILL PAIN QUESTIONNAIRE (SF-MPQ)				
	<u>NONE</u>	<u>MILD</u>	<u>MODERATE</u>	<u>SEVERE</u>
THROBBING	0)_____	1)_____	2)_____	3)_____
SHOOTING	0)_____	1)_____	2)_____	3)_____
STABBING	0)_____	1)_____	2)_____	3)_____
SHARP	0)_____	1)_____	2)_____	3)_____
CRAMPING	0)_____	1)_____	2)_____	3)_____
GNAWING	0)_____	1)_____	2)_____	3)_____
HOT-BURNING	0)_____	1)_____	2)_____	3)_____
ACHING	0)_____	1)_____	2)_____	3)_____
HEAVY	0)_____	1)_____	2)_____	3)_____
TENDER	0)_____	1)_____	2)_____	3)_____
SPLITTING	0)_____	1)_____	2)_____	3)_____
TIRING-EXHAUSTING	0)_____	1)_____	2)_____	3)_____
SICKENING	0)_____	1)_____	2)_____	3)_____
FEARFUL	0)_____	1)_____	2)_____	3)_____
PUNISHING-CRUEL	0)_____	1)_____	2)_____	3)_____

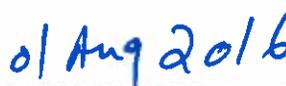
18.0 SPONSOR SIGNATURE

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.



Sponsor Signature



Date of Signature

(DD Month YYYY)



Sponsor Name (print)