STATISTICAL ANALYSIS PLAN

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

Protocol: CNS-HYD201US

Sponsor: Piramal Critical Care, Ltd.
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Statistical Analysis Plan Approval

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Protocol Number:	CNS-HYD201US
Author:	Social & Scientific Systems, Inc., Department of Biostatistics
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The undersigned have reviewed this document and find that it meets the requirements with respect to the protocol.

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GLOSSARY OF TERMS

Abbreviation	Definition
AE	Adverse Event
ANCOVA	Analysis of covariance
ATC	Anatomical Therapeutic Chemical
BMI	Body Mass Index
BPI	Brief Pain Inventory
BSA	Body Surface Area
CMH	Cochran-Mantel-Haenszel
COWS	Clinical Opiate Withdrawal Scale
CRO	Contract Research Organization
CSR	Clinical Study Report
CTCAE	Common Terminology Criteria for Adverse Events
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
HEENT	Head, eyes, ears, nose, and throat
ITT	Intent-to-Teat
IWRS	Interactive Web-based Randomization System
MedDRA	Medical Dictionary for Regulatory Activities
MITT	Modified intent-to-treat
PK	Pharmacokinetics
PGIC	Patient Global Impression of Change
PTM	Personal Therapy Manager
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD	Standard Deviation
SF-MPQ	Short-Form McGill Pain Questionnaire
SOC	System Organ Class
SOWS	Subjective Opiate Withdrawal Scale
TEAE	Treatment Emergent Adverse Event
TESAE	Treatment Emergent Serious Adverse Event
VASPI	Visual Analog Scale of Pain Intensity
WHO-DD	World Health Organization Drug Dictionary

1 Introduction

This Statistical Analysis Plan (SAP) describes the planned statistical analyses to be performed for the analysis of data from Protocol CNS-HYD201US, "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."

The structure and content of this SAP provides sufficient detail to meet the requirements identified by the FDA and International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH): Guidance on Statistical Principles in Clinical Trials.

This SAP is an amended version of the original SAP written for the CNS-HYD201US protocol that was finalized on 25 September 2012 as Version 1.1 and as amended as:

1. Version 2.0 on 15 November 2012,
2. Version 2.1 on 20 December 2012
3. Version 2.2 on 30 July 2013
4. Version 2.3 on 11 March 2014
5. Version 3.0 on 18 December 2014,
6. Version 4.0 on 24 June 2016, and
7. Version 5.0 on 01 August 2016

The following documents were reviewed in preparation of this SAP:

- Final Clinical Protocol CNS-HYD201US, Version 5.0, issued 01 August 2016
- Current case report forms for Protocol CNS-HYD201US

2 Purpose of the Analyses

The purpose of this SAP is to outline the planned analyses to be completed to support the Clinical Study Report (CSR) for Protocol CNS-HYD201US. The planned analyses identified in this SAP will be included in regulatory submissions and/or future manuscripts. Also, exploratory analyses not necessarily identified in this SAP may be performed to support the clinical development program. Any post-hoc or unplanned analyses not identified in this SAP will be clearly identified in the CSR.

Additionally, the purpose of this Amended SAP is to clarify the analyses to be performed as well as the timing of various analyses. During the course of the trial, the Sponsor changed from Mallinckrodt Pharmaceuticals, Inc. (MNK) to Piramal Critical Care, Ltd. (Piramal). As occurs with such changes, the priorities for the study differed from original plans. Piramal made a business decision to proceed with only the safety portion of the study. All subjects completed the study as planned and all data modules pertaining to the safety analysis were cleaned and queried. Efficacy data modules were cleaned and queried up to

11 September 2017, when the decision was made to analyze safety data only. Database lock occurred on 18 October 2017. Subsequently, Piramal made the decision to go forward with the entire analysis of the study. As the study was already unblinded, no further cleaning of the efficacy data modules was permitted. The efficacy analyses will be completed on the locked database, with no changes to the data, unless obvious date errors (i.e., incorrect year resulting in a record incompatible with the study timeline). This Amended SAP describes the updates in conduct and analysis of the trial due to these changes.

3 Study Objectives

The purpose of this clinical study is to demonstrate the efficacy and safety of a 2mg/mL and 10mg/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.

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.

Secondary Objective

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

4 Study Design

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.

Subjects entering the trial on a stable 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 ≤ 30 mg IT morphine and tolerating therapy well	1 : 6 [1]
Dose > 30 mg IT morphine or subject has significant side effects on morphine	1 : 12 [2]

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

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

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 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 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 (i.e. direct conversion from previous treatment with hydromorphone, or a 1:6 conversion from a therapeutic dose of morphine) will start the study on Day 1. 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	50 %
> 0.5 mg	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 subject 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 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 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 day of 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 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 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 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 weaned off any oral supplement of opioid or other prescription medications prior to randomization. For those subjects randomized to be withdrawn from hydromorphone therapy on Day 84, the pump speed will be adjusted to decrease the total daily 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 continuous 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 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 medications or non-pharmacologic interventions being used for pain are allowed from Days 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 of 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.

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 (i.e. rescue), or
3. A 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 oral prescription pain medications or non-pharmacologic treatments being administered to manage 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 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 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.

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). 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. Subjects who do not experience adequate benefit or cannot tolerate intrathecal hydromorphone hydrochloride during the 12-week chronic dosing period will not enter the randomized withdrawal period of the trial, and thus not be eligible for the long term treatment protocol. Subjects who experience a drug related adverse event that requires discontinuation after randomization will also 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.

Table 1 and Table 2 contain the study schedule of assessments.

Table 1: Schedule of Study Procedures: Screening and Chronic Dosing Phase to Day 56

Study Procedure	Screening	Baseline	Titration	Visit Schedule (Days 1 to 56)						
Study Day[a]	**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									
Compete physical exam	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[j]	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

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. 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.
b. Screening period is 14 days. Baseline, Screening and Initiation of Dosing (i.e. Optional Titration Day or Day 1) visits may be combined.
c. 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.
d. 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.
e. 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.
f. ECG is to be performed in triplicate for all measurements at Screening and Baseline period.
g. Blood samples are to be obtained during screening. Includes RBC morphology, reticulocyte count, and standard urinalysis.
h. 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.
i. If there are clinical signs of an inflammatory granuloma as defined in **Section 3.3 (of the protocol)**, 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 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**							
Study Day[a]	**Day 77**	**Day 84**	**Day 91**	**Day 98**	**Day 105**	**Day 112**	**Day 119[e]**	**Final Visit[f]**
Compete physical exam		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**		
Hydromophone 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, 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 subjects 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 **Section3.3 (of the protocol)**, 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

5 Data Management

Data management, including database design, development of the data dictionary, and coding of adverse events and medications will be performed at Social and Scientific Services (S-3), the CRO managing data base entry and cleaning. Data will be entered into electronic case report forms (eCRFs) at the study sites. Logic and consistency checks will be performed on all data entered into the eCRFs to ensure accuracy and completeness. Refer to the Data Management Plan for further details. An ePRO device will also be used to collect VASPI measurements from Day 77 to 119.

A paper CRF page will be used by the Unblinded Pump Operator to record dose administration information during Days 84 to 119. The protocol indicates that 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 actual practice being followed is that the unblinded site representative sends this CRF page to the unblinded Clinical Research Associate for monitoring. These CRFs will be collected at the end of the study and sent in for manual entry into the database.

6 Definition of Populations

The intent-to-treat (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 group to which they were randomized.

The Safety population includes all subjects who have study medication loaded into their intrathecal pump (i.e. 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 (i.e., randomized withdrawal or same dose hydromorphone continuation). Subjects who do not reach the point of randomization will be included in the overall column only.

Inclusion in the ITT and Safety populations will be determined programmatically from the CRF data.

Exclusion of Subjects from Site 028

During the execution of the study, it came to the attention of the Sponsor and SSS that the integrity of the data from Site 028 (Dr. Minkowitz, Advanced Invasive Pain Management, Houston, TX) may have been compromised due to documentation shortcomings, errors and oversights on the part of the investigator. After careful review of the data integrity and regulatory implications of this situation, the Sponsor made the decision to terminate the Investigator from the study and to close the study site for enrollment. No Case Report Form reported data queries would be generated from that point forward. However, it was

determined that all data from this site would be included in the analyses of safety, but should not be included in the analysis of efficacy.

Since this decision was taken mid-way through the study, efficacy analyses will be performed on two populations, excluding or including subjects from Site 028. The primary efficacy analysis will be performed on the population: **ITT/Randomized Subjects Excluding Site 028.** Additionally, selected analyses will be performed on the population **All ITT/ Randomized Subjects** as a sensitivity analysis. Documentation of the site closure can be found in Appendix B.

7 Definition of Study Endpoints

7.1 Primary Efficacy Endpoint

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

VASPI Calculation Algorithm

VASPI scores will routinely be collected twice each day. The daily VASPI score from Day 77 to 119 will be computed as follows:

- As the average of the two scores when both of the twice-daily VASPI measures are present.
- If only one score is present, then the daily score will be equal to that non-missing value.

- If both scores are missing, then the daily score will be missing.

The 5-day baseline (Days 77-83) average VASPI will be computed as follows:

- If the daily score is present on days 79, 80, 81, 82, and 83, then the 5-day average is the average of days 79-83.
- If one of the daily scores from days 79-83 is missing, then the day 78 value (if present) will be included in the 5 daily scores to be averaged. If the day 78 value is also missing, then the day 77 value will instead be used.
- If two of the daily scores from days 79-83 are missing, then the day 78 and day 77 values (if present) will be included in the 5 daily scores to be averaged.

During the double-blind randomized withdrawal period, the 5-day average will be calculated as follows:

- If the daily score is present on all 5 consecutive days, then the 5-day average will be calculated using the data from these days.
- If any of the daily scores are missing, then the 5-day average will be based on the most recent 5 days for which daily scores are available.
- If 5 post-randomization daily scores are not available, then the average of the subject's available scores will be used.

In the event that a subject rescues for intolerable pain a self-initiated VASPI will be obtained, if possible. In this event, it is possible that more than one VASPI score may be obtained in the AM or PM time periods. In the event of more than one VASPI score recorded in the AM (12:01 am to 12:00 noon) or in the PM (12:01 noon to 12:00), the AM or PM values will be averaged to obtain a single AM or PM score for pain that will then be used in the algorithm above.

7.2 Secondary Endpoints

Secondary endpoints include:

- The most important secondary endpoint is safety of intrathecal hydromorphone as assessed through collection of adverse events (AEs) and serious adverse events (SAEs) during the conduct of the trial. Particular attention will be paid to:
  - Rate of confirmed granulomas that are verified by MRI, CT Myelogram or by surgery.
  - Rate of possible granulomas

Other secondary endpoints include:

- Short-Form McGill Pain Questionnaire (SF-MPQ)
- Time to Rescue after Randomization
- Oral Opioid Supplement Consumption
- Brief Pain Inventory (BPI)
- Patient Global Impression of Change (PGIC)

7.2.1 Short-form McGill Pain Questionnaire (SF-MPQ)

The SF-MPQ consists of a 15 item pain rating index. The severity of each item will be scored as None (0), Mild (1), Moderate (2), or Severe (3). The total SF-MPQ score is the sum of the severity scores for each item. The total score can range from 0 to 45. During the double-blind treatment period, the SF-MPQ will be collected on Days 84, 98, 112, and 119.

7.2.2 Time to Rescue after Randomization

If at any time a subject experiences intolerable pain, the subject will be allowed to 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.

The number of days to rescue will be calculated by calculating the number of hours between the time of randomization and the time of rescue. The number of hours will then be divided by 24 to obtain the number of days.

7.2.3 Oral Opioid Supplement Consumption

The total number of milligrams consumed of any oral opioid product from Day 84 through the end of study will be calculated for each subject. Opioid consumption was to be recorded via subject diaries throughout the study. As a rule, subject diaries are not queried for data clarification purposes. Occasionally, a subject would report opioid consumption that was not recorded on the subject diary. This data was then recorded on the concomitant medication CRF page by the study site staff. In order to calculate the total opioid consumption during the randomized phase of the trial, both CRF modules will be utilized. Medications recorded as concomitant medications, with ATC3 text equal to “OPIOIDS” and with a start date on or after the randomization date will be combined with records from the Opioid Products Administered CRF.

7.2.4 Brief Pain Inventory (BPI)

The BPI will consist of two domains, pain severity and pain interference with functioning.

Pain severity will be evaluated by rating pain on a scale from 0 (no pain) to 10 (pain as bad as you can imagine) for the 'worst', 'least', and 'average' pain experienced in the past 24 hours, as well as, the pain experienced 'now'. In addition, a calculated mean pain severity score will be based on the sum of all 4 of the pain scores divided by 4. If any of the 4 questions are missing, then the calculated mean pain severity score will be considered missing.

Pain interference with daily functioning will be evaluated by rating interference on a scale from 0 (does not interfere) to 10 (completely interferes) for 'general activity', 'mood', 'walking ability', 'normal work', 'relation with other people', 'sleep', and 'enjoyment of life'. A calculated mean pain interference will be based on the sum of non-missing interference questions answered divided by the number of questions answered. The mean should be set to missing if fewer than 4 pain interference questions are answered.

During the double-blind treatment period, the BPI will be collected on Days 84, 98, 112, and 119.

7.2.5 Patient Global Impression of Change (PGIC)

The PGIC rating represents observed changes (if any) from the subject's Baseline Visit in activity limitations, symptoms, emotions, and overall quality of life, related to the subject's painful condition. Change is rated on a 7-point Likert-type scale from 1 (no change) through 7 (a great deal better). During the double-blind treatment period, the PGIC will be collected on Days 84, 98, 112, and 119.

7.3 Pharmacokinetic Outcomes

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 as four samples over the course of the study. Each PK sample will be a 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 approximately 1.5 mL aliquots and frozen to < -20°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 (i.e. other oral opioids permitted in the protocol) on Day 14, Day 56, 77 and Day 84.

8 Statistical Methods

8.1 Sample Size

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 (i.e. > 50 mm on a 0 to 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% (i.e., the control group who will have their dose titrated downward has a failure rate of 55%).

8.2 Randomization and Masking

Each subject who is entered into the trial 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) by the interactive web based randomization system. 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 via an interactive web-based randomization system (IWRS). The subject will then be randomized to either remain on the current dose of intrathecal hydromorphone or be titrated off therapy starting on Day 84 with a 1:1 ratio. The unblinded pump technician at the site will have access to the patient treatment assignment through accessing a separate page of the EDC on line. The unblinded pump technician will have a unique user name and password to allow them to access the treatment assignment.

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 lowest pump setting. An unblinded technician or nurse at the site will be assigned (i.e. 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.

8.3 Subject Discontinuation and Replacement of Subjects

Subjects may withdraw from the study at any time. Subjects may be discontinued from study treatment or the study at the request of the Investigator or Sponsor. Subjects who drop out of the study after randomization will not be replaced.

8.4 Final Analyses and Reporting

In addition, no database may be locked, randomization code unblinded, or final analyses completed until this SAP has been approved. The final analyses outlined in the protocol and in this SAP will be carried out after:

- The SAP has been approved;
- The study database has been authorized by the sponsor clinical team as complete and final;
- All analysis populations are determined; and
- Protocol violations have been identified.

Further exploratory analyses not necessarily identified in this SAP may be performed to support the clinical development program. Any post-hoc or unplanned analyses performed and not identified in this SAP will be clearly identified in the CSR.

8.5 Handling of Missing Data

Unless otherwise noted, missing data will not be imputed.

A subject who does not provide data sufficient to evaluate his/her treatment failure status during the double-blind period will **not** be considered to be a treatment failure. This includes subjects who drop out of the study during this period for any reason other than treatment failure. This methodology is aligned with 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 (National Research Council, 2010, pages 33-34).

For all secondary efficacy endpoints (other than the time to rescue after randomization and oral opioid supplement consumption), last observation carried forward imputation (LOCF) will be used for missing data when performing an analysis at Day 119 or the last study visit.

Partially Answered Questionnaires:

When calculating the total score for the SF-MPQ, the Clinical Opiate Withdrawal Scale (COWS), and the Subjective Opiate Withdrawal Scale (SOWS), the 20% imputation rule will be used for partially answered questionnaires. If more than 20% of the items for the total

score are missing, then the total score will be set to missing. If 20% or less of the items for the total score are missing, then the total score will be calculated as:

(total of items present) ÷ (maximum possible total of items present)
× (maximum possible total of all items).

For the BPI, follow the rules for missing information discussed in the BPI section. Since the PGIC is a single question questionnaire, no imputation will be used.

8.6 Comments on Statistical Analysis

The following general comments apply to all statistical analyses and data presentations:

Summaries will include frequency and percentages for categorical data and frequency, mean, standard deviation, median, minimum, and maximum for quantitative data.

- Where appropriate and unless otherwise specified, analyses will be presented by randomized treatment arm: hydromorphone arm or titrated down (control) arm.

- Duration variables will be calculated using the general formula: Duration = (end date – start date) + 1.

- Individual subject listings of all data represented on the eCRFs will be provided to facilitate the investigation of tabulated values and to allow for the clinical review of all data.

- Version 9.1 or greater of SAS statistical software package will be used to provide all summaries, listings, and graphs described in this document.

- All raw data will be presented to the original number of data places. The means and medians will be presented to one more decimal place than the raw data. The standard deviations will be presented to two more decimal places than the raw data. For averages of averages, the means and medians will also be presented to one more decimal place than the raw data and the standard deviations will also be presented to two more decimals places than the raw data.

- Generally, the denominator for percentages will be based on the number of subjects in the study population. However, for cases where appropriate, the denominator for percentages will be based on the number of subjects with non-missing data appropriate for summary purposes. Unless otherwise noted, all percentages will be presented to one decimal place.

- There are approximately 10-30 study sites in this study. Due to the large number of study sites and the small numbers of subjects per site, the analysis of efficacy endpoints will not include adjustments for study site. However, descriptive summaries of the primary endpoint will be provided by site.

- Analyses for the randomization phase, Day 84 through Day 119, will be calculated for the period defined as randomization date through end of study date, as study day of randomization and Day 119 visit may not always occur on the scheduled study days (84 and 119) due to various circumstances.

9 Statistical Analyses

9.1 Subject Disposition

The number and percent of subjects in each of the analysis populations (i.e., ITT, Safety) will be summarized by treatment arm and overall. The number and percent of subjects who enrolled in the study, completed the study, who withdrew from the study and their reasons for withdrawal will be tabulated by treatment arm and overall. Subject disposition will be summarized using all enrolled subjects. Enrolled subjects are those subjects who signed the informed consent form and receive intrathecal hydromorphone supplied by MNK as GMP product for this study.

A listing summarizing whether subjects completed or discontinued from the study will also be presented and the primary reason for discontinuation will be provided for those subjects who withdrew.

9.2 Screening and Baseline Characteristics

9.2.1 Demographics and Baseline Characteristics

Descriptive statistics will be used to summarize demographic and baseline characteristics by treatment arm and for both treatment arms combined. Subject demographics include sex, age, ethnicity, race, height, weight, and body mass index (BMI). Age (in years) will be calculated from the date of birth to the date of informed consent. Age will be reported as an integer. BMI will be calculated using the following formula: BMI (kg/m^2) = weight (kg)/(height (m))^2.

All demographic and baseline characteristics will also be listed.

9.2.2 Medical History

Medical history information will be collected at the Screening visit.

Medical history will be coded using the Medical Dictionary for Regulatory Activities (MedDRA); the dictionary version will be noted in the CSR. Medical history will be summarized by system organ class, preferred term, and treatment arm. Medical history verbatim terms and coded terms will be listed.

Listings will also be provided with the following information:

- History of intractable pain
- Implantation of intrathecal pump and prior opioid use prior to pump implantation
- Surgical intervention(s) for treatment of intractable pain

9.2.2 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. Medications are also considered concomitant if their stop date is unknown or marked as continuing. Medications will with missing start dates will be considered ongoing on the first day of study drug administration except where positive confirmation is available that the medication was stopped before study drug administration.

The World Health Organization Drug Dictionary (WHO-DD) will be used to classify prior and concomitant medications by therapeutic class and preferred term. The WHO-DD version will be noted in the CSR. The number and percentage of subjects receiving concomitant medications will be summarized by Anatomical Therapeutic Chemical (ATC) level 3, preferred term, and treatment arm. Subjects will be counted only once for an ATC class and preferred term, even if the subject took the same medication on multiple occasions. Prior medications will be summarized in a similar manner.

A listing of medications will be prepared.

9.2.1 12-Lead Electrocardiogram (ECG)

A safety ECG will be performed at screening to assess any cardiovascular abnormalities for the purpose of determining eligibility for this trial. The number and percentage of subjects with normal, abnormal not clinically significant and abnormal clinically significant ECGs at Screening and Baseline will be summarized.

ECG results will also be listed.

9.2.2 Laboratory Assessments

Blood for chemistry, hematology, and urinalysis laboratory tests will be collected at Screening. The results will be used to determine the subject's eligibility for the study. If abnormal, the investigator will describe the abnormality in the eCRF. Individual laboratory results will not be entered into the eCRF. Abnormal laboratory results (i.e. investigator description of abnormalities) will be listed.

Urine pregnancy tests will also be conducted at Screening and/or Baseline for women of childbearing potential. Pregnancy test results will be listed.

9.3 Study Drug Exposure and Compliance

A listing containing the date and time the current product was removed from the pump, drug concentration, lot number, volume refilled, whether dose adjustments were made, date and time of dose changes, the original and changed daily doses, and whether there were any problems with the pump refill will be listed.

A dosing summary by treatment arm will be presented for the ITT and Safety populations.

9.4 Protocol Violations

Violations of the protocol will be recorded appropriately. Examples might include, but not necessarily limited to, the following categories:

- Inclusion/exclusion criteria violation
- Prohibited medication use
- Incorrect treatment or dose
- Treatment non-compliance
- Procedure non-compliance
- Safety observation

Classification of violations from the protocol as minor or major will be decided on a case-by-case basis without knowledge of the treatment assigned and before database lock. A listing of major protocol violations that impact the evaluation of efficacy will be provided.

9.5 Efficacy Analyses

All efficacy endpoints identified in Section 7.1 will be summarized using descriptive statistics by treatment arm (and by visit for secondary efficacy endpoints, where applicable). All summaries of efficacy data will be carried out in the ITT population. All efficacy endpoints will also be listed.

9.5.1 Primary Efficacy Analysis

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

The number and percentage of subjects with treatment failure during the double-blind period will be summarized by treatment group. Differences in treatment group failure rates will be test using a Pearson's chi-square (two-sided) test at the 5% level of significance. The corresponding 95% confidence interval for failure rate will be provided.

9.5.2 Secondary Efficacy Analyses

Safety is the most important secondary endpoint. Other secondary endpoints include quality of life / pain scale assessments.

For the purpose of efficacy analyses, 'baseline' will be Day 84.

The change from baseline) to Day 119 in the BPI (pain severity 'worst', pain severity 'average', calculated mean pain severity, and calculated mean pain interference with function.) will be analyzed using an ANCOVA model with treatment group as a factor and the baseline BPI as a covariate. The change from baseline to Day 119 in the SF-MPQ and in oral opioid supplement consumption 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. Subjects who do not receive rescue medication will be censored at their date of last follow-up. The two groups will be compared using the log rank test.

The PGIC on Day 119 (or at the time of rescue) 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.

9.6 Safety Analyses

Safety will be assessed using the Safety population. Safety data will be presented using

summary tables and subject data listings. Safety will primarily be addressed through examination of the incidence and severity of adverse events, as well as, the rate of possible granulomas and the rate of confirmed granulomas. Other safety assessments include vital signs.

9.6.1 Adverse Events

Unless otherwise noted, analyses will be based on treatment-emergent adverse events (TEAEs), defined as those events that begin or worsen in severity after the first treatment with study drug at Baseline. For AEs with missing start dates, the AE will be considered treatment-emergent unless there is additional information indicating that the AE started prior to the first study drug treatment.

Adverse events will be coded to system organ class and preferred term using MedDRA; the dictionary version will be noted in the CSR. AE severity will be assessed and summarized using the Common Terminology Criteria for Adverse Events (CTCAE) v 4.03.

AE incidence tables will include the number and percentage of subject reporting at least one AE, as well as, the number and percentage of AEs summarized by MedDRA system organ class and preferred term. Subjects with two or more AEs in the same system organ class will be counted once for that system organ class; likewise for preferred term. For 'by severity' and 'by relationship to study treatment' tables, subjects will be counted once at the maximum severity and at the strongest causal relationship, respectively. Summaries of treatment-related AEs will include those events classified by the investigator as having a possible or probable relationship to study drug (or unknown relationship). Tables will be produced for the following: TEAEs, treatment-related TEAEs, TEAEs by strongest relationship, TEAEs by maximum severity, treatment-emergent serious adverse events (TESAEs), TESAEs by strongest relationship, treatment-related SAEs, and TESAEs by maximum severity. An overall AE summary table will provide top level subject counts for all the AE analyses noted. In addition, the AE summary table will include the number and percentage of subjects reporting any AE (including non TEAEs), the number and percentage of subjects with an AE that led to withdraw of study drug, and the number and percentage of subjects with an AE with outcome of death.

Complete listings of all AEs will be provided (non TEAEs will be flagged with a '*'). In addition, data listings of all SAEs, AEs leading to discontinuation, and AEs leading to death will also be provided.

9.6.2 Vital Signs and Weight

Systolic and diastolic blood pressure (mmHg), radial pulse (beats/minute), breathing rate (breaths/minute), and temperature (°C) will be obtained at Baseline and each study visit. Weight (kg) will be collected at screening and each study visit.

All vital signs and weight measurements as well as change from Baseline for these measurements will be summarized by treatment arm at each visit. A listing of weight and vital signs will also be provided.

The number and percentage of subjects with potentially clinically significant vital signs will be summarized at each visit by vital sign and treatment arm. A listing of subjects with potentially clinically significant vital signs will also be presented. Table 3 contains the criteria for identifying potentially clinically significant vital sign values.

Table 3: Criteria for Identifying Potentially Clinically Significant Vital Sign Values

Vital Sign Parameter	Criteria
Systolic Blood Pressure (mmHg)	>160 mmHg or increase of ≥20 mmHg from baseline
Systolic Blood Pressure (mmHg)	<95 mmHg or decrease of ≥20 mmHg from baseline
Diastolic Blood Pressure (mmHg)	>110 mmHg or increase of ≥15 mmHg from baseline
Diastolic Blood Pressure (mmHg)	<50 mmHg or decrease of ≥15 mmHg from baseline
Heart Rate (bpm*)	>100 bpm or increase of ≥15 bpm from baseline
Heart Rate (bpm*)	<50 bpm or decrease of ≥15 bpm from baseline
Weight (kg) Gain	>10% weight increase
Weight (kg) Loss	>10% weight decrease

*bpm = Beats per minute

9.6.3 Physical Examinations

A complete physical examination will be conducted at Screening, Day 84, Day 119, and at the Final Visit. The number and percentage of normal and abnormal physical examinations will be summarized by body system and treatment arm at each visit. Any clinically significant physical examination findings will be reported as AEs or SAEs. Physical examination findings will also be listed for each visit.

9.6.4 Granulomas

A clinical evaluation for mass formation will be conducted at baseline, Days 1, 7, 14, 21, 28, 42, 56, 77, 84, 91, 98, 105, 112, 119, and the Final Visit. However, at any time that clinical signs and symptoms warrant, an evaluation for the potential for a granuloma will be conducted.

Signs and symptoms of an inflammatory granuloma, including radicular pain, sudden loss of drug efficacy that is not attributed to other assignable causes, and spinal cord compression at the level of the catheter tip will be monitored. If there are signs or symptoms identified which may indicate an inflammatory mass formation, an MRI (with and without contrast) or

CT scan will be performed (with consent of the subject) 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.

All data captured with regard to possible or confirmed inflammatory granulomas will be listed, including the date of clinical evaluation for an inflammatory mass, signs and/or symptoms of the granuloma, and all MRI or CT scan results. The incidence and rate of possible granuloma, as well as, the incidence and rate of confirmed granuloma will be summarized by treatment group.

The method of inflammatory granuloma assessment will be summarized by the number and percentage of subjects in the following categories:

- Subjects with clinical signs and symptoms of a granuloma
- Subjects with clinical signs and symptoms of granuloma, but MRI/CT not performed
- Subjects with clinical signs and symptoms of granuloma, MRI/CT performed
- Subjects with confirmed granuloma by MRI/CT via independent radiologist or surgery

All signs and symptoms data related to mass formation including MRI or CT information will be listed.

9.6.5 Subgroup Analysis

A supportive exploratory subgroup analysis by site will be done for the primary endpoint of treatment failure. Due to the potential for having sites with very small enrollment numbers, only descriptive statistics will be presented.

9.7 Clinical and Subjective Opiate Withdrawal Scales

The COWS assessment will assess the severity of 11 opiate withdrawal symptoms. Each symptom severity score ranges from 0 (asymptomatic) to a maximum of 3, 4, or 5 (severe based on criteria for the individual symptom). A total score is calculated based on the sum of the individual symptoms scores.

The SOWS assessment will assess the severity of 18 subjective symptoms associated with opiate withdrawal. Each symptom severity score ranges from 0 (Not at All) to 4 (Extreme). A total score is calculated based on the sum of the individual symptoms scores.

During the double-blind treatment period, the COWS and SOWS assessments will be performed at Days 84, 91, 98, 105, 112, and 119 to assess any withdrawal symptoms. The COWs and SOWs total scores will be summarized at each visit and the changes from baseline (i.e. Day 84) to each visit will also be summarized by treatment arm. Individual item scores and the total score for the COWS and SOWS will also be listed.

10 Summary of Amendments to the SAP

After the initial SAP approval (version 1.0), all major or minor amendments will be summarized in the table below.

Version	Change (Reason)
2.0	• Section 4 text regarding catheter line aspiration deleted (to be consistent with protocol text amendment as version 2.2 dated 02Jul 2013). • Text in sections 4, 7.1, and 9.7.1 regarding treatment failure criteria updated to further clarify interventions meeting failure criteria and to clarify that subjects who discontinue prematurely after randomization without sufficient info to evaluate failure will be deemed a failure (to be consistent with protocol text which was amended). • Reference to interim analysis deleted in section 8.4 (no interim analysis planned). • Section 9.8 moved to be section 9.6.5 (improve flow).
3.0	• Ownership reference to CNS changed to be MNK (updated to acknowledge MNKs acquirement of the intrathecal hydromorphone product from CNS). • Objectives and general study design updates to be consistent with protocol amendment 2.3 dated 11March2014). • Text in sections 4, 7.1, and 9.7.1 regarding treatment failure criteria updated to further clarify that subjects with a COW>12 cannot be counted as a failure and subjects who discontinue prematurely after randomization without sufficient info to evaluate failure will be deemed a non-failure instead of failure (to be consistent with protocol text which was amended, note this was partly due to FDA feedback regarding failure definition and their particular concerns with true failure being undistinguishable from opiate withdrawal). • Sample size changed from 150 randomized to 80 randomized and power calculations updated (to match amended protocol, note the initial sample size estimates were likely based on underestimated predicted treatment differences in failure rates. Internal decision for adjustment was made based on group and executive approval. Enrollment was vas limited at the time of adjustment and no study data were used for assessments.) • Section 9.5.2 COWS > 12 sensitivity analyses dropped (not applicable given that the failure definition was updated to exclude subjects with COWS > 12 as failures).

4.0	• Typos corrected and clarification text added throughout document (cleanup of document) • Updated study information in sections 1 to 4 and section 7.2 (very minor updates to match exact language within the protocol) • Section 5 updated regarding process used for the dose CRF on Days 84 to 119 (clarified that the unblinded site representative sends this CRF page to the unblinded CRA for monitoring rather than this CRF remaining on site until the subject completes the study, note: this actual process does not impact blinding). • Updated throughout 'Time to Rescue after Randomized Withdraw' to be 'Time to Rescue after Randomization' (improved terminology but no change in intent) and updated start time of randomization (time of randomization on Day 84 more appropriate than dose time on Day 84). • Updated analyses of BPI (analysis was updated to conventional published description whereby the BPI is assessed based on 2 domains separately: pain severity and interference with daily function). • Deleted section 7.2.6 (unnecessary repeat of safety endpoints). • In section 8.3, deleted text regarding subjects re-entering the study (this text does not belong in the SAP) and clarified that subjects who drop out *after randomization* are not replaced (clarified because subjects dropping out prior to randomization are replaced). • Updated section 8.5 to clarify missing data rules for secondary endpoints (updated to indicate missing data rule is different for BPI vs other secondary endpoint measures). • BSA calculations dropped from section 9.2.1 (not applicable in this setting per Medical Monitor). • Updated medical history text to describe coding of terms (clarification). • Removed analyses of ECG and laboratory data (ECG and lab measures are not collected however text added that abnormality text recorded on the CRF by the investigator will be listed). • Changed protocol deviation to protocol violation (to match MNK standards). • In section 9.5, 'by center' primary efficacy exploratory analyses moved to subgroups section 9.6.5 and dropped for secondary endpoints (sample size previously reduced to 80 randomized subjects so 'by center' not as meaningful for all efficacy endpoints). • Added analyses text for primary endpoint to section 9.5.1 (methodology comparing active vs titrated treatment arms described in sample size section but not in current section).

	• In section 9.5.2, 'baseline' clarified as randomization/Day 84 for efficacy (clarification added but intent was always to use randomization day as baseline for efficacy) and dropped repeated measures analyses (sample size previously reduced to 80 subjects and likely hood for intermittent missing questionnaires make analysis less meaningful). • Adverse events text (section 9.6.1), Vitals text (section 9.6.2), and Granuloma text (section 9.6.4) updated (to improve flow and match language within the companion safety study HYD202). • Subgroup analyses by PTM vs continuous and pump/catheter replacement vs non- replacement dropped and exploratory 'by study site' exploratory analyses of primary efficacy endpoint moved to this section from another section (sample size previously reduced to 80 randomized subjects so subgroup analyses anticipated to be too small to be meaningful). • In section 9.7 additional text added regarding COWS and SOWS (informational addition only) and 'baseline' clarified as randomization/Day 84 (clarification added but intent was always to use randomization day as baseline for efficacy). • Added Summary of Amendments section to the SAP (provide historical reference)
5.0	• Described the timeline of safety and efficacy analyses • Added ITT, Excluding Subjects from Site 028 Population • Added Appendix A – list of Tables, Listings and Figures for output • Added Appendix B - documentation of Site 028 closure • Clarified calculations of opioid consumption. • Clarified the randomization period as the time from date of randomization through end of study, rather than Day 84 through Day 119.

Appendix A

The following Tables, Listings and Figures are anticipated to be produced to display the results of the statistical analyses. Additions or deletions to this list may be made in order to produce the analyses described in this SAP.

Number	Title	Analysis Population
Tables		
14.1.1	Subject Disposition	All Enrolled Subjects
14.1.2	Analysis Populations	All Enrolled Subjects
14.1.3	Demographics and Baseline Characteristics	All Enrolled Subjects
14.1.4	Medical History	All Enrolled Subjects
14.1.5.1	Prior Medications	All Enrolled Subjects
14.1.5.2	Concomitant Medications	All Enrolled Subjects
14.1.6	12-Lead Electrocardiogram	All Enrolled Subjects
14.2.1.1.1	Treatment Failure Rate	ITT
14.2.1.1.2	Treatment Failure Rate	ITT Excluding Site 028
14.2.1.2	Treatment Failure Rate by Site	ITT
14.2.2.1	Time to Rescue after Randomization	ITT
14.2.2.2	Time to Rescue after Randomization	ITT Excluding Site 028
14.2.3.1.1	Pain Indicators Summary	ITT
14.2.3.1.2	Pain Indicators Summary	ITT Excluding Site 028
14.2.3.1.3	Oral Opioid Supplement Consumption	ITT
14.2.3.1.4	Oral Opioid Supplement Consumption	ITT Excluding Site 028
14.2.3.1.5	Patient Global Impression of Change Summary	ITT
14.2.3.1.6	Patient Global Impression of Change Summary	ITT Excluding Site 028
14.2.3.2.1	Brief Pain Inventory - Pain Severity Measures	ITT
14.2.3.2.2	Brief Pain Inventory - Pain Severity Measures	ITT Excluding Site 028
14.2.3.3.1	Brief Pain Inventory - Pain Interference	ITT
14.2.3.3.2	Brief Pain Inventory - Pain Interference	ITT Excluding Site 028
14.2.3.4.1	Patient Global Impression of Change (PGIC)	ITT
14.2.3.4.2	Patient Global Impression of Change (PGIC)	ITT Excluding Site 028
14.2.3.5.1	Short-form McGill Pain Questionnaire (SF-MPQ)	ITT
14.2.3.5.2	Short-form McGill Pain Questionnaire (SF-MPQ)	ITT Excluding Site 028
14.2.3.6.1	Visual Analog Scale of Pain Intensity (VASPI)	ITT
14.2.3.6.2	Visual Analog Scale of Pain Intensity (VASPI)	ITT Excluding Site 028
14.3.1.1.1	Overview of Adverse Events - Open Label Phase	Safety
14.3.1.1.2	Overview of Adverse Events - Randomized Phase	Safety

14.3.1.1.3	Overview of Adverse Events - Overall	Safety
14.3.1.2.1	Incidence of Adverse Events by System Organ Class and Preferred Term - Open Label Phase	Safety
14.3.1.2.2	Incidence of Adverse Events by System Organ Class and Preferred Term - Randomized Phase	Safety
14.3.1.2.3	Incidence of Adverse Events by System Organ Class and Preferred Term - Overall	Safety
14.3.1.3.1	Incidence of Serious Adverse Events by System Organ Class and Preferred Term - Open Label Phase	Safety
14.3.1.3.2	Incidence of Serious Adverse Events by System Organ Class and Preferred Term - Randomized Phase	Safety
14.3.1.3.3	Incidence of Serious Adverse Events by System Organ Class and Preferred Term - Overall	Safety
14.3.1.4.1	Incidence of Adverse Events by System Organ Class, Preferred Term and Severity to Study Drug - Open Label Phase	Safety
14.3.1.4.2	Incidence of Adverse Events by System Organ Class, Preferred Term and Severity to Study Drug - Randomized Phase	Safety
14.3.1.4.3	Incidence of Adverse Events by System Organ Class , Preferred Term and Severity to Study Drug - Overall	Safety
14.3.1.5.1	Incidence of Serious Adverse Events by System Organ Class and Preferred Term and Severity to Study Drug - Open Label Phase	Safety
14.3.1.5.2	Incidence of Serious Adverse Events by System Organ Class and Preferred Term and Severity to Study Drug- Randomized Phase	Safety
14.3.1.5.3	Incidence of Serious Adverse Events by System Organ Class and Preferred Term and Severity to Study Drug - Overall	Safety
14.3.1.6.1	Incidence of Adverse Events by System Organ Class, Preferred Term, and Relationship to Study Drug - Open Label Phase	Safety
14.3.1.6.2	Incidence of Adverse Events by System Organ Class, Preferred Term, and Relationship to Study Drug - Randomized Phase	Safety
14.3.1.6.3	Incidence of Adverse Events by System Organ Class, Preferred Term, and Relationship to Study Drug - Overall	Safety
14.3.1.7.1	Incidence of Serious Adverse Events by System Organ Class, Preferred Term, and Relationship to Study Drug - Open Label Phase	Safety
14.3.1.7.2	Incidence of Serious Adverse Events by System Organ Class, Preferred Term, and Relationship to Study Drug - Randomized Phase	Safety

14.3.1.7.3	Incidence of Serious Adverse Events by System Organ Class, Preferred Term, and Relationship to Study Drug - Overall	Safety
14.3.5.1.1	Vital Signs - Open Label Phase	Safety
14.3.5.1.2	Vital Signs - Randomized Phase	ITT
14.3.5.2.1	Potentially Clinically Significant Vital Signs - Open Label Phase	Safety
14.3.5.2.2	Potentially Clinically Significant Vital Signs - Randomized Phase	ITT
14.3.5.3.1	Physical Examination Findings by Body System - Open Label Phase	Safety
14.3.5.3.2	Physical Examination Findings by Body System - Randomized Phase	ITT
14.3.5.4	Granuloma Assessment	All Enrolled Subjects
14.3.6.1	Study Drug Exposure Summary - Open Label Phase	Safety
14.3.6.2	Study Drug Exposure Summary - Randomized Phase	Safety
14.3.6.3	Study Drug Exposure Summary - Overall	Safety
14.4.1.1	Clinical Opiate Withdrawal Scale (COWS) Assessment	ITT
14.4.1.2	Clinical Opiate Withdrawal Scale (COWS) Assessment	ITT Excluding Site 028
14.4.2.1	Subjective Opiate Withdrawal Scale (SOWS) Assessment	ITT
14.4.2.2	Subjective Opiate Withdrawal Scale (SOWS) Assessment	ITT Excluding Site 028
Figures		
14.2.2.1	Kaplan-Meier Curve for Time to Rescue	ITT
14.2.2.2	Kaplan-Meier Curve for Time to Rescue	ITT Excluding Site 028
Listings		
16.2.1	Subject Disposition	All Enrolled Subjects
16.2.2	Subject Demographics	All Enrolled Subjects
16.2.3.1	Medical History	All Enrolled Subjects
16.2.3.2	History of Intractable Pain	All Enrolled Subjects
16.2.3.3	Implantation of Intrathecal Pump	All Enrolled Subjects
16.2.3.4	Surgical Intervention for Intractable Pain	All Enrolled Subjects
16.2.4	Prior and Concomitant Medication	All Enrolled Subjects
16.2.5.1	12-Lead ECG	All Enrolled Subjects
16.2.5.2	Laboratory Summary	All Enrolled Subjects
16.2.5.3	Laboratory Results - Pregnancy	All Enrolled Subjects
16.2.6	Protocol Deviations	All Enrolled Subjects
16.2.7.1	Intolerable Pain Assessment - Rescue	All Enrolled Subjects
16.2.7.2	Visual Analog Scale of Pain Intensity (VASPI)	All Enrolled Subjects

16.2.7.3	Brief Pain Inventory (BPI)	All Enrolled Subjects
16.2.7.4	Patients' Global Impression of Change (PGIC)	All Enrolled Subjects
16.2.7.5	Short-Form McGill Pain Questionnaire (SF-MPQ)	All Enrolled Subjects
16.2.8.1	Adverse Events	All Enrolled Subjects
16.2.8.2	Serious Adverse Events	All Enrolled Subjects
16.2.8.3	Adverse Events Leading to Discontinuation	All Enrolled Subjects
16.2.8.4	Adverse Events Leading to Death	All Enrolled Subjects
16.2.9	Non-Pharmaceutical Intervention	All Enrolled Subjects
16.2.10	Oral Opioid Supplements	All Enrolled Subjects
16.2.11	Vital Signs	All Enrolled Subjects
16.2.12	Physical Examination Assessments	All Enrolled Subjects
16.2.13.1	Clinical Evaluation of Inflammatory Mass Formation	All Enrolled Subjects
16.2.13.2	Signs or Symptoms of Granuloma	All Enrolled Subjects
16.2.13.3	MRI and CT Myelogram	All Enrolled Subjects
16.2.13.4	Central Reader for MRI and CT Myelogram	All Enrolled Subjects
16.2.14.1	Clinical Opiate Withdrawal Scale (COWS)	All Enrolled Subjects
16.2.14.2	Subjective Opiate Withdrawal Scale (SOWS)	All Enrolled Subjects
16.2.15.1	Exposure Summary - Dose Data	All Enrolled Subjects
16.2.15.2	Exposure Summary - Pump Information	All Enrolled Subjects
16.2.15.3	Exposure Summary - Dose Conversion	All Enrolled Subjects

Appendix B

The following two Memos-to-File document the closure of Site 028.

Mallinckrodt Pharmaceuticals

June 3, 2015

Harold Minkowitz, M.D.
Research Concepts
Advanced Invasive Pain Management
308 West Parkwood Avenue, Suite 106
Friendswood, TX 77546

SUBJECT: CNS-HYD201US and CNS-HYD202US
Study Site Non-Compliance with Good Clinical Practice ("GCP")

Dear Dr. Minkowitz:

Between May 20 and 22, 2015, Mallinckrodt Inc. ("Mallinckrodt") conducted a "for cause" audit of your study site for CNS-HYD201US and CNS-HYD202US after receiving reports of GCP non-compliance from your study monitor. Our colleague, Victoria Camaione, completed an in-depth inspection of study-related records and documents and conducted interviews with you, the sub-investigator, and several study staff members. The audit revealed a lack of adequately trained and qualified study staff members, insufficient investigator oversight and poor documentation practices.

Based upon these findings, Mallinckrodt has decided to discontinue, effective immediately, conducting both CNS-HYD201US and CNS-HYD202US at your study site. For each study, we ask that you take the following steps *as soon as possible*:

- Schedule all active study participants for final study visits as described in each study protocol;
- Create an action plan that ensures the study drug is removed from the implanted pumps of study participants and replaced with non-study drug; and
- Complete a study close-out with your Institutional Review Board ("IRB").

Your study monitor, Karim Mohammed, will work with you and your staff to ensure that the final study visits are completed in a timely manner and all study documents are completed appropriately. For each study, Mallinckrodt then will schedule a close-out visit to collect final study documents and facilitate return of study drug.

Your study monitor will remain your primary point-of-contact for routine, study-related questions. However, please contact Lisa Sisk at 314-654-3524 or Amy Crary at 314-654-6414 in the event you have concerns about the contents of this letter.

Sincerely,

James L. Young
Vice President, Clinical Affairs and Program Management

cc: Victoria Camaione – Clinical Quality Assurance (Mallinckrodt)

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23 November 2015

Sharon Hertz, MD
Director, Division of Anesthesia, Analgesia and Addiction Products (DAAAP)
Food and Drug Administration
Center for Drug Evaluation and Research
Central Document Room
5901-B Ammendale Road
Beltsville, MD 20705-1266

RE: IND 114,373: Hydromorphone Hydrochloride Injection for Intrathecal Use
Serial No. 0027
General Correspondence: Updated Investigator Information for clinical trials CNS-HYD201US and CNS-HYD202US

Dear Dr. Hertz,

Reference is made to Mallinckrodt Inc.'s ("Mallinckrodt") ongoing IND 114,373 under which clinical trials CNS-HYD201US and CNS-HYD202US are being conducted. The purpose of CNS-HYD201US is to evaluate the safety and efficacy of intrathecal hydromorphone and the purpose of CNS-HYD202US is to evaluate the long-term safety of intrathecal hydromorphone. In both studies, hydromorphone is administered by an implanted intrathecal pump.

Mallinckrodt has terminated the participation of an investigator, Dr. Harold Minkowitz, Site 28 in clinical trials CNS-HYD201US and CNS-HYD202US. Mallinckrodt has notified Dr. Minkowitz of termination of his participation in clinical trials CNS-HYD201US and CNS-HYD202US due to noncompliance. It was determined that Dr. Minkowitz has not provided adequate oversight or supervision of the site (Research Concepts) staff to who he has delegated responsibilities.

Mallinckrodt has discontinued the participation of Dr. Minkowitz in the CNS-HYD201US and CNS-HYD202US trials to ensure the integrity of the clinical trial study data. Safety data, but not efficacy data from Site 28 will be included and an explanation of events will be provided the Clinical Study Report.

The following actions have been taken by Mallinckrodt to terminate the investigational site:

- Notification of termination has been sent to Dr. Minkowitz,
- Hydromorphone study drug has been removed from the reservoir of all subject's intrathecal pumps and all subjects have completed final study visits as described in each study protocol,

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- Investigational drug shipments to the site have been discontinued and investigational product has been removed from the site and destroyed or returned to stock,
- The Subjects' Case Report Forms are being finalized, and,
- Dr. Minkowitz has been instructed to complete study close-out with his Institutional Review Board.

Contact information for Dr. Minkowitz is:

Harold Minkowitz, M.D.
Research Concepts
Advanced Invasive Pain Management
308 West Parkwood Avenue, Suite 106
Friendswood, TX 77546

This submission is submitted in electronic format as eCTD SN0027 via the Electronic Submissions Gateway (approximately 1 MB). The submission has been checked and found free from virus infection using Trend Micro™ OfficeScan™ v10.6. The technical point of contact for this electronic submission is Juanito Baladad whom may be reached by telephone at (314) 654-6107, by fax at (314) 654-6496 or email at Juanito.Baladad@mallinckrodt.com.

If you have any questions or concerns regarding this submission, please contact me directly at (314) 654-3351 or e-mail at Bill.Kirkpatrick@mallinckrodt.com.

Sincerely,

Bill Kirkpatrick, PhD
Mallinckrodt Regulatory Affairs

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