STATISTICAL ANALYSIS PLAN

Title: A Phase 3, Open-Label, Single-Arm Study to Assess the Safety of Hydromorphone Hydrochloride Delivered by Intrathecal Administration

Protocol: CNS-HYD202US

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

Title:	A Phase 3, Open-Label, Single-Arm Study to Assess the Safety of Hydromorphone Hydrochloride Delivered by Intrathecal Administration
Protocol Number:	CNS-HYD202US
Author:	Social & Scientific Systems, Inc., Department of Biostatistics
Version Number:	4.0
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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
ATC	Anatomical Therapeutic Chemical
BMI	Body Mass Index
BPI	Brief Pain Inventory
BSA	Body Surface Area
COWS	Clinical Opiate Withdrawal Scale
eCRF	Electronic Case Report Form
CRO	Contract Research Organization
CSR	Clinical Study Report
CTCAE	Common Terminology Criteria for Adverse Events
ECG	Electrocardiogram
MedDRA	Medical Dictionary for Regulatory Activities
PTM	Personal Therapy Manager
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD	Standard Deviation
SOC	System Organ Class
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-HYD202US, "A Phase 3, Open-Label, Single-Arm Study To Assess The Safety Of Hydromorphone Hydrochloride Delivered By Intrathecal Administration."

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. The following documents were reviewed in preparation of this SAP:

This SAP is an amended version of the original SAP for the CNS-HYD202US trial that was finalized on 06 August 2012 as Version 1.0 and amended as:

- Version 1.1 on 26 September 2012,
- Version 1.2 on 15 April 2013,
- Version 2.0 on 28 August 2013,
- Version 3.0 on 21 March 2014,
- Version 4.0 on 16 September 2014,
- Version 5.0 on 18 December 2014,
- Version 6.0 on 24 June 2016, and
- Version 7.0 on 01 August 2016.

The following documents were reviewed in preparation of this SAP:

- Final Clinical Protocol CNS-HYD202US, Version 7.0, issued 01 August 2016
- Case report forms (CRFs) for Protocol CNS-HYD202US

2 Purpose of the Analysis

The purpose of this SAP is to outline the planned analyses to be completed to support the Clinical Study Report (CSR) for Protocol CNS-HYD202US. 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 the original plans. Piramal made a business decision to proceed with only certain analyses of the study. All subjects completed the study as planned and all data pertaining to the selected safety analyses were cleaned and queried through 08 January 2018, due to the decision to analyze only safety data. Database lock occurred on 07 February 2018. Subsequently, Piramal made the decision to go forward with the entire analysis of the study. No further cleaning of the data modules was performed. This Amended SAP described the updates in the conduct and analysis of the trial due to these decisions.

3 Study Objectives

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

Primary Objective

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

4 Study Design

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

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

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

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

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

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

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

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

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

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

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

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

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

As needed, additional intrathecal concomitant medications may be added to the therapy to optimize pain control.

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

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

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

by telephone 24 hours after initiating study medication of hydromorphone hydrochloride.

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

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

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

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

Table 1 contains the study schedule of procedures.

Table 1: Schedule Study Procedures

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

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

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

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

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

e. Informed consent for subjects entering the CSN-HYD202US trial after completion of the CNS-HYD201US trial may be obtained as early as 30 days prior to completion of the CNS-HYD201US trial.

f. For subjects entering the CNS-HYD202US trial from the CNS-HYD201US trial, medical history will be carried over from the previous trial and does not need to be repeated.

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

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. All eCRFs 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 eCRFs. Clinical monitors will also ensure that all protocol requirements, applicable FDA regulations, other requirements, and Investigator's obligations are being fulfilled.

Refer to the Data Management Plan for further details.

6 Definition of Populations

The **Safety Population** includes all subjects who receive any study medication (i.e. hydromorphone hydrochloride intrathecal treatment). All summaries of safety data will be carried out using the safety population. The **Intent-to-Treat (ITT) Population** also includes all subjects who receive any study medication. The analysis of the secondary endpoints will be carried out on the ITT Population. Inclusion in the Safety and ITT Populations will be determined programmatically from the eCRF 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. It was determined that all data from this site will be included in the analysis of safety, but should not be included in the analysis of the secondary endpoints. Since this was taken mid-way through the study, the analysis of BPI, VASPI and PGIC will be performed on two populations: **ITT Population Excluding Site 028** and on the **ITT Population**. Documentation of the site closure can be found in Appendix B.

7 Definition of Study Endpoints
7.1 Primary Safety Endpoints

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

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

7.2 Secondary Endpoints

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

- Change in the Visual Analog Scale Pain Intensity (VASPI) overtime.
- Change in the Brief Pain Inventory (BPI) overtime.
- Change in the Patient Global Impression of Change (PGIC) overtime.

8 Statistical Methods

8.1 Sample Size

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

8.2 Randomization and Masking

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

Each subject who is entered from the CNS-HYD201US study will retain their subject number from the previous study and carry that number into this trial.

Unique subjects enrolled directly into the CNS-HYD202US trial will be assigned a subject number consisting of a two-digit site number and three-digit sequential subject number (SS-XXX). This number will be used for the entire duration of the trial.

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.

Additional subjects may be enrolled as deemed necessary to reach the study submission objectives of 300 subjects completing 6 months and 100 subjects completing 12 months of intrathecal hydromorphone hydrochloride therapy.

8.4 Final Analysis and Reporting

Study submission objectives will be met when 300 subjects complete 6 months and 100 subjects complete 12 months of intrathecal hydromorphone therapy. For the purpose of the clinical study report, the analyses may occur any time after the study submission objectives are met. At the time of submission, some subjects may still be receiving study treatment. Therefore, any subsequent safety data collected on those subjects will be submitted via a safety update, unless other format is requested by Regulatory Authorities. Database lock will occur when all study submission objectives are met or subjects have completed the study (or discontinued early) and all data have been monitored. A business decision was made by Piramal to only perform the safety analysis of the study once all subjects had completed the study. Modules pertaining to the safety data were monitored, cleaned and queried, while modules pertaining to the efficacy endpoints (VASPI, BPI, PGIC) data were no longer cleaned or queried after 11 September 2017. The database was locked on 07 February 2018. Subsequently, Piramal made the business decision to move forward with the program and to complete the remaining analysis of the study. The remaining analyses will be performed under this version, Version 4.0 dated 04 February 2019 of the SAP, and will be performed on the previously locked data. No additional data cleaning will take place.

In addition, no database may be locked, or final analyses completed until the original version of the SAP had 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; 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

All missing data will remain missing and will not be imputed. Only observed data will be

summarized. The only exception is in the BPI total score as described in the corresponding section.

8.6 Interim Analysis

No formal interim analyses will be conducted. See section 8.4 of the SAP for further details regarding the timing of the analyses for study submission and the reporting of subsequent safety data.

8.7 Comments on Statistical Analysis

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

- Unless otherwise noted, tables will present summaries by formulation concentration (2 mg/mL and 10 mg/mL) and all subjects.
- Summaries will include frequency and percentages for categorical data and frequency, mean, standard deviation, median, minimum, and maximum for quantitative data.
- 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. Unless otherwise noted, all percentages will be presented to one decimal place.

9 Statistical Analyses

9.1 Subject Disposition

The number and percent of subjects in the Safety population will be summarized. The number and percent of subjects who enrolled in the study, completed the study, withdrew from the study and their reasons for withdrawal will also be tabulated. The number and percentage of subjects who rolled over from study CNS-HYD201US, subjects who were naïve to intrathecal opioids, and those who had prior opioid treatment will also be summarized. Subject disposition will be summarized using all enrolled subjects. Enrolled subjects will be those subjects who signed the informed consent form.

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 variables. 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 rounded down. 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 Complete Physical Examination

The Investigator or designee will perform a complete physical examination at screening. Results will be recorded as part of the Medical History. Assessments of height, weight, calculation of BMI, 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.

9.2.3 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 and preferred term. 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

9.2.4 Prior 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. Medications are also considered concomitant if their stop date is unknown or marked as continuing. Medications 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 and preferred term. 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 prior and concomitant medications will also be prepared.

9.2.5 Vital Signs and Electrocardiogram (ECG)

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

A safety electrocardiogram (ECG) will be recorded at Screening or at Baseline for subjects previously enrolled in study in study CNS-HYD201US. The ECG will be used to assess any cardiovascular abnormalities for the purposes of determining eligibility for this trial.

The number and percentage of subjects with normal, abnormal not clinically significant and abnormal clinically significant ECGs will be summarized. ECG results will also be listed.

9.2.6 Clinical Laboratory Assessments

Blood for chemistry, hematology, and urinalysis laboratory tests will be collected at Screening or Baseline for patients previously enrolled in study CNS-HYD201US. 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 will be listed.

Serum pregnancy tests will also be conducted at Screening, Baseline and the Final Visit for women of childbearing potential. Pregnancy test results will be listed

9.3 Study Drug Exposure, Admixtures and Compliance

Dose adjustments and pump refills will be recorded and data listed for each subject. Any admixtures (combination drugs) included into the hydromorphone hydrochloride will be recorded by combination type and dose of each component of the product in the pump and listed for each subject.

9.4 Protocol Deviations

Deviations 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

A listing of major protocol deviations that impact the evaluation of safety will be provided.

9.5 Safety Analyses

Safety will be assessed using the Safety population.

9.5.1 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.

9.5.2 Granulomas

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 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 inflammatory granuloma, as well as, the incidence and rate of confirmed granuloma will be summarized by study drug concentration and all subjects.

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

9.5.3 Vital Signs and Weight

Systolic and diastolic blood pressure (mmHg), radial pulse (beats/minute), respiratory rate (breaths/minute), weight (kg), and temperature (°C) will be obtained at baseline and each study visit and recorded on the eCRF.

All vital signs and weight measurements as well as change from Baseline for these measurements will be summarized 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. A listing of subjects with potentially clinically significant vital signs will also be presented. Table contains the criteria for identifying potentially clinically significant vital sign values.

Table 2: 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

9.5.4 Physical Examinations

The Investigator or designee will perform a complete physical examination at screening and at the final visit. The number and percentage of normal and abnormal physical exams will be summarized by body system at screening and at the final visit. Any clinically significant physical examination findings will be reported and analyzed as AEs or SAEs. Physical examination findings will also be listed.

9.6 Secondary Endpoints

9.6.1 Visual Analogue Scale of Pain Intensity (VASPI)

The VASPI will be a single question assessing how severe a subject's pain is 'right now'.

Scoring is based on the continuous visual analog scale (measured in mm) ranging from no pain at the start of the scale to unbearable pain at the end of the scale. VASPI will be assessed at Baseline and each study visit, including the final visit. The VASPI scores, as well as change from baseline, will be summarized at each visit. All assessments will be listed.

9.6.2 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.

The BPI will be assessed at Baseline, Day 28, Day 80, Day 160, Day 286, and at the final visit. The BPI scores, as well as change from baseline, will be summarized at each specified visit for the following: pain severity 'worst', pain severity 'average', calculated mean pain severity, and calculated mean pain interference with function. All assessment, including the calculated mean scores, will be listed.

9.6.3 Patient Global Impression of Change (PGIC)

The PGIC will be a single question that rates the overall change, if any, from Baseline in activity limitations, symptoms, emotions, and overall quality of life related to the subject's painful condition based on a 7-point Likert scale from 1 (no change) to 7 (a great deal better).

The PGIC will be assessed at Baseline, Day 28, Day 80, Day 160, Day 286, and at the final visit. The PGIC score will be summarized at each specified visit. All assessment will be listed.

9.7 Clinical Opiate Withdrawal Scale (COWS)

The Clinical Opiate Withdrawal Scale (COWS) assessment will assess the severity of 11 opiate withdraw 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 assessment will be performed at Baseline and the final visit to evaluate any opiate withdrawal symptoms. The COWs total scores

will be summarized at each visit and the changes from baseline to the final visit will also be summarized. Individual item scores and the total score for the COWS 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	• Changed sponsor information (MNK acquired CNS Therapeutics). • Text for study objectives, endpoints, study design, and schedule of events all updated to match protocol amendment 4.0 dated 16Sep2014 which 1] clarified aspects of the study design that were unclear due to the complicated nature of the study, particularly with regard to conversion from morphine to study drug and 2] better organized the flow of text throughout, including language with regard to endpoints – see protocol amendment change summary for individual details). • Added clarification that submission objectives would be met when 300 subjects had 6 months of exposure and 150 subjects had 12 months of exposure (reflect protocol amendment 4.0 dated 16Sep2014). • Rewrote text regarding analyses of AEs (improve section flow and better describe the analyses themselves). • Updated text for evaluation of granulomas to match protocol amendment 4.0 dated 16Sep2014 and clarified that analyses would be performed for both possible and confirmed granulomas, as well as, added text describing the evaluation of granuloma signs and symptoms (reflect protocol amendment 4.0 dated 16Sep2014). • Include definitions for clinically significant vital sign changes for systolic/diastolic blood pressure and weight (added for clarification).
3.0	• Typos corrected (clean up of document) • Clarified timing of main objective is at 12-months exposure for the 2mg/mL and 10mg/mL concentrations (based on protocol amendment 5 dated 18Dec2014). • Updated medical history text to describe the coding of terms (clarification). • Removed text that indicated latest version of MedDRA would be used for AE coding (dictionary version should remain stable to avoid constant recoding through long duration of study. • Changed protocol deviation to protocol violation (to match MNK standards).

	• Consolidated and moved description of BPI, PGIC, and VASPI into a secondary endpoints section (improve flow). • 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). • Added some description details to the PGIC, VASPI, and COWs (provided basic details on how the assessments were structured but made no changes to the original analyses). • Added Summary of Amendments to the SAP section (provide historical reference).
4.0	• Described the timeline of safety and efficacy analyses for the study • Described the exclusion of subjects from Site 028 • Clarified the analysis populations • Added Appendix A – list of Tables and Listings for output • Added Appendix B - documentation of Site 028 closure • Corrected version dates of protocol and amendments

Appendix A

The following Tables and Listings 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.

Tables		
Number	**Title**	**Analysis Population**
14.1.1	Subject Disposition	Safety
14.1.2	Demographics and Baseline Characteristics	Safety
14.1.3	Medical History	Safety
14.1.4.1	Prior Medications	Safety
14.1.4.2	Concomitant Medications	Safety
14.1.5	12-Lead Electrocardiogram	Safety
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	Overview of Adverse Events	Safety
14.3.1.2	Incidence of Adverse Events by System Organ Class and Preferred Term	Safety

14.3.1.3	Incidence of Serious Adverse Events by System Organ Class and Preferred Term	Safety
14.3.1.4	Incidence of Adverse Events by System Organ Class, Preferred Term and Severity to Study Drug	Safety
14.3.1.5	Incidence of Serious Adverse Events by System Organ Class and Preferred Term and Severity to Study Drug	Safety
14.3.1.6	Incidence of Adverse Events by System Organ Class, Preferred Term, and Relationship to Study Drug	Safety
14.3.1.7	Incidence of Serious Adverse Events by System Organ Class, Preferred Term, and Relationship to Study Drug	Safety
14.3.5.1	Vital Signs - Open Label Phase	Safety
14.3.5.2	Potentially Clinically Significant Vital Signs	Safety
14.3.5.3	Physical Examination Findings by Body System	Safety
14.3.5.4	Granuloma Assessment	All Enrolled Subjects
14.3.5.5.1	14.3.5.5.1Visual Analog Scale of Pain Intensity (VASPI)	ITT
14.3.5.5.2	Visual Analog Scale of Pain Intensity (VASPI)	ITT Excluding Site 028
14.3.5.6.1.1	Brief Pain Inventory - Pain Severity Measures	ITT
14.3.5.6.1.2	Brief Pain Inventory - Pain Severity Measures	ITT Excluding Site 028
14.3.5.6.2.1	Brief Pain Inventory - Pain Interference	ITT
14.3.5.6.2.2	Brief Pain Inventory - Pain Interference	ITT Excluding Site 028
14.3.5.7.1	Patient Global Impression of Change (PGIC)	ITT
14.3.5.7.2	Patient Global Impression of Change (PGIC)	ITT Excluding Site 028
14.3.5.8	Clinical Opiate Withdrawal Scale (COWS) Assessment	ITT
14.3.6	Study Drug Exposure Summary	Safety
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	Adverse Events	All Enrolled Subjects
16.2.7.2	Serious Adverse Events	All Enrolled Subjects

16.2.7.3	Adverse Events Leading to Discontinuation	All Enrolled Subjects
16.2.7.4	Adverse Events Leading to Death	All Enrolled Subjects
16.2.8	Oral Opioid Supplements	All Enrolled Subjects
16.2.9	Vital Signs	All Enrolled Subjects
16.2.10	Physical Examination Assessments	All Enrolled Subjects
16.2.11.1	Clinical Evaluation of Inflammatory Mass Formation	All Enrolled Subjects
16.2.11.2	Signs or Symptoms of Granuloma	All Enrolled Subjects
16.2.11.3	MRI and CT Myelogram	All Enrolled Subjects
16.2.11.4	Central Reader for MRI and CT Myelogram	All Enrolled Subjects
16.2.12.1	Visual Analog Scale of Pain Intensity (VASPI)	All Enrolled Subjects
16.2.12.2	Brief Pain Inventory (BPI)	All Enrolled Subjects
16.2.12.3	Patients' Global Impression of Change (PGIC)	All Enrolled Subjects
16.2.13	Clinical Opiate Withdrawal Scale (COWS)	All Enrolled Subjects
16.2.14.1	Exposure Summary - Dose Data	All Enrolled Subjects
16.2.14.2	Exposure Summary - Pump Information	All Enrolled Subjects
16.2.14.3	Exposure Summary – Dose Interruption	All Enrolled Subjects
16.2.14.4	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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Mallinckrodt Pharmaceuticals

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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