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CLINICAL STUDY PROTOCOL

An Open-Label, Safety and Pharmacokinetic Study of Hydromorphone Hydrochloride Extended-Release Tablets (Once-Daily Hydromorphone) in Opioid-Tolerant Pediatric Subjects with Chronic Pain

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Sponsor: **Mallinckrodt Pharmaceuticals**
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7 SYNOPSIS

This is a synopsis. The body of the protocol must be referenced for the complete study information.

Study Title: An Open-Label, Safety and Pharmacokinetic Study of Hydromorphone Hydrochloride Extended-Release Tablets (Once-Daily Hydromorphone) in Opioid-Tolerant Pediatric Subjects with Chronic Pain

Protocol Number	COV02520124	**Phase**	3b	**Type**	Interventional

Condition/Disease: Subjects 7 to 17 years old with chronic pain secondary to cancer and/or noncancer origins.

	Approximate		
Number of Subjects	100	**Duration of Subject Participation**	Approximately 28 days including an optional safety observation extension of up to 3 weeks.
Number of Study Centers	Up to 10	**Duration of Study**	Five years.

Rationale: This pediatric study is designed to provide safety information, dosing guidelines, and a pharmacokinetic (PK) evaluation of once-daily hydromorphone hydrochloride (HCl) extended-release (ER) tablets in children with chronic painful conditions who are "opioid-tolerant" prior to enrollment under the Pediatric Research Equity Act of 2003. Population PK techniques will be utilized in order to better understand the PK profile of once-daily hydromorphone HCl ER tablets in pediatric subjects while limiting the number and timing of sample collections.

Objectives:

Primary

The primary objective of this study is to evaluate the safety (based on vital signs, pulse oximetry, clinical laboratory assessments, and adverse events [AEs]) of once-daily dosing of hydromorphone HCl ER tablets in pediatric subjects between 7 and 17 years old with pain secondary to cancer and/or noncancer origins.

Secondary

The secondary objectives of this study are to evaluate the following parameters:

- PK data following initial and steady-state dosing in subjects between 7 and 17 years old (in even distribution of age strata, for example, age 7 to less than 12 years and age 12 to 17 years).
- Effectiveness (based on pain intensity scores) in controlling pain.
- Quality of life utilizing a validated pediatric testing instrument (Pediatric Quality of Life [PedsQL]).

Design: This is an open-label, multidose, multicenter study for safety, PK, and efficacy of hydromorphone HCl ER in an opioid tolerant pediatric population 7 to 17 years of age with chronic pain secondary to cancer and/or noncancer origins.

Subjects with continuous, around-the-clock opioid treatment with at least 6 mg of daily hydromorphone (or other opioid equivalents) for 5 or more days (ie, opioid tolerant) will be evaluated for study qualification at screening (Visit 1).

On the morning of Day 1 (Visit 2), qualified subjects will switch from their current therapy to receive the first dose of hydromorphone HCl ER at the clinic with a dose strength matching 66% of their prior opioid dosage based on the protocol-provided conversion table. Subjects will remain at the clinic for up to 24 hours for safety and efficacy assessments and blood sampling. Subjects will continue to receive once daily hydromorphone HCl ER for 7 (± 2) days. No increase or decrease in hydromorphone HCl ER dose will be allowed. In the event of uncontrolled pain, 5 mg of immediate release oxycodone can be used as rescue therapy at 1 to 2 tablets per dose up to 5 times per day depending on the strength of hydromorphone HCl ER received.

Subjects will return to the clinic on Day 7 (± 2 days) (Visit 3), take hydromorphone HCl ER in the morning, and stay for 12 hours while completing all remaining procedures and assessments before exiting the study (or proceeding to the optional safety extension).
As safety assessments, vital signs and pulse oximetry measurements will be conducted at scheduled visits and adverse events will be collected throughout the 7 (± 2) days of the treatment period. In addition, clinical laboratory evaluations will be performed at Screening (Visit 1) and study exit (Visit 3).
Sparse blood sampling of a subset of subjects for the measurement of plasma hydromorphone and hydromorphone-3-β-D glucuronide metabolite concentrations will take place on Day 1 (Visit 2) at the following time points: predose, between 4 to 6 hours, 7 to 9 hours, 14 to 18 hours, and 22 to 24 hours postdose; and on Day 7 (± 2 days) (Visit 3) at the following time points: predose and between 8 to 12 hours postdose.
Pain intensity ratings will be recorded by subject on the electronic diary at Screening (Visit 1); on Day 1 (Visit 2) at the following time points: predose (within 15 minutes of initial dosing), and 1, 2, 4, 6, and 8 hours (±15 minutes) postdose; on Days 2-6 (± 2) at the following time points: predose (within 15 minutes of dosing) and prior to bedtime; on Day 7 (± 2): predose (within 15 minutes of dosing). Age-appropriate pain scales will be used for the study, i.e. Faces Pain Scale – Revised (FPS-R) is for 7 to less than 12 years and Visual Analog Scale (VAS) is for 12 to 17 years.
A quality of life (PedsQL) questionnaire will also be completed on Day 1 (Visit 2) predose and at study exit/Day 7 (Visit 3).
Subjects who complete the 7 (± 2) days of treatment have the option to extend hydromorphone HCl ER usage for pain relief and safety observation for up to 3 additional weeks per investigator's discretion. Dose adjustment is allowed during this period. Subjects will visit the clinic weekly for continued eligibility assessment, safety evaluation, drug accountability (return and dispense), and/or dose adjustment. Subjects will visit the clinic at the end of safety observation extension for final assessment within 2 days after the last dose of hydromorphone HCl ER.
Subjects will be contacted by the site for a follow-up phone call at 7 (± 1) days after the study exit (Visit 3) or the last dose of extended hydromorphone HCl ER usage.

Inclusion Criteria: For inclusion into the study at screening (Visit 1), subjects must:

1. Be adequately informed and understand the nature and risks of the study and must be able to provide a signature and date on the informed assent form if appropriate, to participate. Parent(s)/legal guardian must provide written approval to participate.
2. Be male or female subjects aged 7 to 17 years, inclusive.
3. Be opioid-tolerant with chronic cancer or noncancer pain requiring continuous, around-the-clock oral or injectable opioid treatment. Opioid-tolerant is defined as having received a stable dose of regularly scheduled opioid or opioid combination products (including a regular rescue medication regimen) equivalent to least 6 mg of oral hydromorphone (see Table 15–1 for opioid dose conversion) per day for at least 5 days prior to first dose.
4. (Female subjects of childbearing potential) Have a negative serum pregnancy test result at screening and a negative urine pregnancy test result on Day 1 (Visit 2). Those subjects who are sexually active (as determined by the investigator or designee) must be surgically sterilized (eg, hysterectomy or bilateral tubal ligation) at least 12 months prior to screening or use 1 of the following methods of birth control at least 30 days prior to screening and for the duration of study participation: hormonal contraception, intrauterine contraceptive device, or spermicide with barrier method (condom, cervical cap, or diaphragm). Subjects should continue contraception for at least 30 days after the last dose of study drug.
5. (Male subjects with reproductive potential who are sexually active as determined by the investigator or designee) Agree to use an acceptable method of contraception for the duration of the study (vasectomy or condom with spermicide).
6. Have established a favorable response to opioid therapy in reducing pain.

7. Require a minimum dose of 4 mg (1 JURNISTA tablet) and a maximum dose of 16 mg (1 hydromorphone HCl ER tablet) after determining 66% of the converted dose of hydromorphone HCl per day from an established conversion table (Table 15–1).
8. Be able to swallow a whole tablet without breaking, crushing, chewing or dissolving.
9. Be expected to require extended opioid treatment for at least 1 week.
10. Be able to communicate effectively with study personnel.
11. (Subjects and parents/legal guardian) Be able and willing to follow all protocol requirements and study restrictions.

Exclusion Criteria: Subjects will be ineligible for the study if any of the following criteria are present:

1. Have a life expectancy of less than 4 weeks.
2. Have a history of allergy or any significant intolerance with opioid treatment or allergies to sulfites as determined by the investigator or designee.
3. Are currently managed with opioid (transcutaneous) analgesic patches.
4. Have a history of drug or alcohol dependence.
5. Have a history of renal, hepatic, cardiovascular, or respiratory conditions that would contraindicate their participation in this study as determined by the investigator or designee.
6. Plan to undergo a surgical procedure within 3 days of Day 1 and for the duration of participation in the study. Subjects undergoing minor surgical procedures (eg, central line insertion, biopsies) will be eligible for participation in the study.
7. Exhibit hemodynamic instability as determined by the investigator or designee.
8. Have dysphagia or difficulty swallowing whole tablets as determined by the investigator or designee.
9. Have narrowing of the digestive tract, often due to esophageal strictures, Short Gut Syndrome, inflammatory bowel disease, peritonitis, cystic fibrosis, Meckel's diverticulum, or past gastrointestinal surgery.
10. Have hypothyroidism, Addison's disease, asthma (including exercise induced asthma) requiring daily inhalers, an enlarged prostate, epilepsy, low blood pressure, seizure disorder, high intracranial pressure, gallbladder problems, pancreatic disease, liver disease, or kidney disease.
11. Have an ileostomy or paralytic ileus.
12. Have had a blood-product transfusion within 2 weeks prior to screening (Visit 1) or expected to require transfusion during the study.
13. Participated in a study with any pain medication in the 2 weeks prior to screening (Visit 1). Subjects participating in other investigational studies are allowed.
14. Have a known history of human immunodeficiency virus, hepatitis C virus or hepatitis B virus.

Prior and Concomitant Treatment:

Subjects will be allowed to continue taking any nonprohibited prior medication/therapy if:

- The drug was started at least 14 days prior to first dose of study drug, AND
- The dose of medication is expected to remain unchanged for the duration of study participation.

Pertinent information for any medication taken during the study will be recorded.

Investigational Product and Administration:

- EXALGO (Hydromorphone HCl ER) 8-mg, 12-mg, and 16-mg tablets.
- JURNISTA (hydromorphone HCl ER) 4-mg tablets.

Tablets to be swallowed whole and not broken, chewed, dissolved, or crushed.

Rescue Medication:

- Immediate-release oxycodone (5 mg tablets).

Safety Assessment:

1. Physical examination.
2. Clinical laboratory tests.
3. Vital sign measurements.
4. Pulse oximetry measurements.
5. AEs.

Assessments:

1. The effectiveness endpoint is pain intensity measured on a FPS-R or VAS.
2. The health outcomes endpoint is quality of life, as measured by the PedsQL.

Pharmacokinetics:

Blood samples for the determination of plasma hydromorphone and hydromorphone-3-β-D glucuronide metabolite concentrations will be collected in selected windows of time: predose, 4 to 6 hours, 7 to 9 hours, 14 to 18 hours, 22 to 24 hours postdose on Day 1 (Visit 2); and predose and 8 to 12 hours postdose on Day 7 ± 2 (Visit 3) in a subset of subjects.

Statistical Considerations:

Analysis Populations

The analysis populations include the following:

- The Safety Population will include all subjects who receive any quantity of study drug.
- The PK Population will consist of all subjects who receive at least 1 dose of study drug and have any samples collected after dosing at Visit 2 and/or Visit 3 that were analyzed for hydrocodone and hydromorphone-3-β-D glucuronide.
- The Modified Intent-To-Treat Population will consist of all subjects who receive study drug and who have at least 1 postdose pain intensity assessment.

Subject Characteristics

Demographic and baseline characteristics (including age, sex, race, ethnicity, weight, height, and medical history) will be summarized for the safety population by descriptive statistics. No statistical analyses will be performed.

Effectiveness and Health Outcomes Analysis

The endpoints below will be summarized at each assessment time point:

- Pain intensity with validated pain intensity scales FPS-R and VAS.
- Quality of life, as measured by the PedsQL.

Pharmacokinetic Analysis

A population PK dataset will be developed from the pooled pediatric and adult data from studies C-2005-013-01, C-2005-032-02 and 42801-PAI-1009 and the current study. Population PK analyses will be conducted via nonlinear mixed effect modeling using the nonlinear mixed-effects modeling software NONMEM®, Version 7 or higher (ICON Development Solutions, Hanover, MD). A covariate analysis will be undertaken to determine the contribution of demographic and disease characteristics to variability in hydromorphone PK. Individual predicted hydromorphone exposure metrics (apparent first-order terminal elimination rate constant, the apparent plasma terminal elimination half-life, the minimum plasma concentration at steady-state, the peak plasma concentration at steady-state, the average concentration at steady-state, and the area under the plasma time-concentration curve at steady-state) will be derived from estimated parameters from the final model.

Safety Analysis

Data listings will be provided for all protocol-specified safety data. The Medical Dictionary for Regulatory Activities (MedDRA Version 9.1 or higher) will be used to classify all AEs with respect to system organ class and preferred term. Numbers of subjects with treatment-emergent AEs will be summarized.

For vital signs and pulse oximetry, descriptive statistics will be provided at each scheduled time point, including study exit. Descriptive statistics will be provided on changes from baseline of these assessments at each scheduled time point after baseline. No formal statistical tests will be performed.
Ethical Considerations: The study will be conducted in compliance with applicable US Food and Drug Administration (FDA) regulations, International Council for Harmonisation (ICH) guidelines for Good Clinical Practice (GCP), and in accordance with generally accepted ethical principles for the conduct of human research such as the Declaration of Helsinki. The institutional review board (IRB) must review and approve the protocol and informed assent/consent forms before any subjects are enrolled. Before any protocol-required procedures are performed, the subject must be able to provide a signature and date on the informed assent form (IAF), if appropriate, to participate. The subject's legal guardian or parent(s) must provide written approval to participate.