2. SYNOPTIC REPORT

Name of Company: Purdue Pharma L.P.	INDIVIDUAL STUDY TABLE	(For National Authority Use Only)
Name of Finished Product: Palladone™ Capsules	Referring to Part IV of the Dossier	
Name of Active Ingredient: Hydromorphone HCl	Volume: Page:	

Title of the Study: A Double-blind, Randomized, Two-period Crossover Study Comparing the Efficacy, Safety, and Pharmacokinetic Profiles of Oral Administration of Hydromorphone Hydrochloride Extended-release[a] Capsules Sprinkled Onto Food (QAM) Vs Hydromorphone Hydrochloride Immediate-release Whole Tablets (QID) On Cancer-related Pain.

[a]Both the Protocol and Amendment 4 use the term "controlled-release" (HHCR). PPLP now uses "extended-release" (HHER).

Investigator/Center: This was a single-site study. The investigator was Dr. Silvia Allende-Perez, National Institute of Cancerology, Ave. San Fernando No. 22, Tlalpan 1400, Mexico, D.F., Mexico.

Publication (Reference): none

Study Dates:	**Study Status:**	**Phase of Development:**
15-Jul-1999 to 16-Dec-1999	Completed	Phase 3

Objectives: To determine the efficacy, safety, plasma concentration, and feasibility of oral administration of hydromorphone HCl extended-release (HHER) 12-mg capsules qAM when sprinkled onto soft palatable food, as compared with hydromorphone HCl immediate-release (HHIR) whole tablets qid for the treatment of cancer-related pain.

Methodology: This was a single center, open-label titration, randomized, double-blind, 2-period crossover study based on Amendment 4 to Protocol HD95-0801. Amendment 4 stipulated that the contents of each HHER capsule was opened and sprinkled into soft palatable food (such as applesauce) and swallowed without chewing or crushing; eliminated the pharmacodynamic assessments; required that a pharmacokinetic assessment be made at the end of the open-label titration period; and adjusted the statistical analyses to accommodate the sprinkled administration of the study drug. During the open-label titration period, subjects were administered HHER 12-mg whole capsules qAM with HHIR 2-mg whole tablets q4h-q6h prn as rescue. The HHER dose was titrated to achieve stable pain control, and this dose was administered in sprinkle form during the 2 double-blind periods. Subjects were randomized to the double-blind periods who achieved stable pain control for 48 hours (dose of HHER capsules unchanged; ≤2 doses of rescue/day; average pain intensity rated 0-4 on a 0-10 scale). However, if any 1 of the 8 average pain intensity ratings in a 48-hour period was ≥8, the pain was considered unstable. If more than 2 of the 8 average pain intensity ratings in a 48-hour period were rated as 5, 6, or 7, the pain was considered unstable. In the double-blind periods, subjects were randomized to either HHER 12-mg sprinkled capsules qAM (12 to 84 mg/day) or HHIR 3-mg whole tablets qid (12 to 84 mg/day), with HHIR 2-mg whole tablets as rescue and then crossed over to the alternate treatment in the second period.

Number of Subjects: Planned: 40 subjects. Enrolled: 45 subjects. Randomized: 40 subjects (of the 40 subjects randomized, only 38 received at least 1 dose of double-blind study drug). Completed both double-blind periods: 35 subjects. Safety population: 44 subjects. Full analysis population: 38 subjects. Discontinued: 7 subjects. (Tables 14.1.1, 14.1.2 and Appendix 16.2.3, 16.2.5.3)

Criteria for Inclusion/Exclusion: Inclusion criteria were: males or females aged 10 years or older with cancer-related pain, who required treatment of pain with opioid analgesics equivalent to 12-mg hydromorphone HCl for at least the past 2 weeks, had stable dosing for at least the past 2 days, and able to swallow soft palatable food. Excluded were subjects who had a total daily dose of oral hydromorphone greater than 72 mg.

Test Treatment, Dose, and Mode of Administration

Product	Mode	Dosage Form	Unit Strength	Batch No.	Formulation No.
HHER	Oral	Capsule	12 mg (qAM)	CB25-33	1580-0012-01:0
HHER Placebo	Oral	Capsule	12 mg	CB25-31	1580-0012-01P:0
Reference Treatment, Dose, and Mode of Administration:					
HHIR	Oral	Tablet	3 mg (qid)	CB25-37	1600-0003-01:0
HHIR Placebo	Oral	Tablet	3 mg	CB25-36	1600-003-01P:0

Cross-reference: Drug Information, Appendix 16.1.6.1; Certificate of Analysis, Appendix 16.1.6.2.

Duration of Treatment: The duration of subject participation was a maximum of 35 days: open-label period was from 4 to 21 days, and the double-blind 2-period crossover was from 3 to 7 days per period.

Criteria for Evaluation: The primary efficacy variable was the mean of average pain intensity ratings (0 = no pain to 10 = pain as bad as you can imagine) over the last 2 days of each double-blind period before PK day (4 ratings/ day). See Protocol for secondary and other efficacy variables.

Pharmacokinetic: Hydromorphone was assessed for minimum and maximum observed values (including dose-adjusted to 12 mg) of plasma concentrations at the time of each phlebotomy (Visits 3 and 4).

Safety: Safety variables assessed during the open-label and double-blind periods were the percent of subjects with treatment-emergent adverse events by body system. Serious adverse events that occurred 7 days after the last dose of study drug were included in the analysis. Laboratory test results were collected prestudy and poststudy.

Sample Size Estimation With Assumptions: Based on previous studies HD95-0801 and HD95-0802, the sample size was re-estimated for HD95-0801M in Amendment 4. The within-subject coefficient of variation (CV) for the average pain intensity was 32% and the mean difference was 6% of the reference mean. A sample size of 40 subjects was sufficient to ensure that the 90% confidence interval for the ratio of least squares means were within the default interval (75%, 125%) with 82% power.

Randomization: The randomization code and associated memoranda are contained in Appendix 16.1.7.

Bioanalytical Methods: Plasma concentrations of hydromorphone were quantified by a GC/MS-based method, PDM No.93-0224M:2 "Quantitation of Hydromorphone in Plasma Using D_3-Hydromorphone as Internal Standard by Gas Chromatography/Mass Spectrometry." The limit of quantitation was 0.1 ng/mL with the calibration curve ranging from 0.1 to 5 ng/mL (Bioanalytical Report, Appendix 16.1.13).

Statistical Methods: Statistical programming and analyses were performed using SAS® (SAS Institute, Cary, NC). All statistical tests were 2-sided with a significance level of $\alpha = 0.05$ for main effects and $\alpha = 0.10$ for interactions and sequence effects.

Primary efficacy: Efficacy analyses were performed on the full analysis population (subjects who completed the open-label period, were randomized to the double-blind periods, received at least 1 dose of study drug, and completed at least 1 day of double-blind efficacy evaluation) using a crossover ANOVA model including treatment, sequence, period, and the effect of subject within each sequence. The 2 formulations were considered equivalent in controlling pain if the 90% confidence interval was within the default interval of 75% to 125%. See Protocol for secondary and other efficacy statistical analyses.

Safety: Adverse events analyses were performed on the safety population for the open-label period, and the randomized safety population was used to analyze the double-blind periods (at least 1 dose of double-blind study drug, and had at least 1 safety measurement postrandomization). The subject incidence (%) and number of reports of adverse events were presented by body system and COSTART term. Laboratory results were presented for the safety population and analyzed for the prestudy and poststudy laboratory results as well as for clinically notable laboratory values.

Pharmacokinetics: PK was analyzed using the full analysis population (38 subjects who completed the open-label period, were randomized to the double-blind periods, received at least 1 dose of double-blind study drug, and had at least 1 full day of double-blind assessments). Minimum and maximum observed values of plasma hydromorphone concentrations were listed and concentrations dose-adjusted to 12 mg were summarized. Per Amendment 4, only the minimum concentration level (C_{min}) was statistically analyzed using a crossover ANOVA model.

Changes to the Planned Analyses in the Protocol: Amendments 1, 2, and 3 refer to Protocol HD95-0801, while Amendment 4 refers to HD95-0801M. The sample size was re-estimated for HD95-0801M based on previous studies. The protocol proposed analysis of spontaneous reports of adverse events; the statistical analysis plan (SAP) proposed analyzing treatment-emergent adverse events. The SAP added summaries of laboratory values to the safety analyses. Efficacy results were presented for the full analysis population only. Demographic variables were not statistically tested for differences between the treatment sequences. The randomized safety population was added. Only C_{min} was statistically analyzed in HD95-0801M.

Results: All efficacy variables are contained in Section 14.2, Appendix 16.1.9, and listed in Appendices 16.2.6.1 to 16.2.6.2.

Primary Efficacy: The 90% CI for the ratio (HHER/HHIR) of the least means of average pain intensity on the last 2 days of each double-blind period was (76%, 119%) which was contained within the default interval of 75% to 125%. HHER sprinkled onto soft food was considered equivalent in efficacy to HHIR whole tablets (Table 14.2.1.3, Appendix 16.1.9).

Pharmacokinetic: Results for all PK variables are contained in Table 14.2.1.10, and Appendices 16.1.9 and 16.2.5.3.

- Subjects treated with HHER had a statistically significantly higher C_{min} dose-adjusted to 12-mg than subjects treated with HHIR in the full analysis set (LSmean [SE] HHER, 0.187 [0.028]; HHIR, 0.014 [0.028]; P = .0004) (Appendix 16.1.9).

Safety: Listings of deaths, other serious events, and other significant events are contained in Tables 14.3.2.1, 14.3.2.2, and Appendix 16.2.7.1. The incidence of adverse events is contained in Tables 14.3.1.1 to 14.3.1.7. Narratives are contained in Section 14.3.3. The table below presents the incidence of deaths, other serious adverse events, and other significant events.

Incidence of Deaths, Other Serious Adverse Events, and Other Significant Events[a]: Enrolled in Study Population

	Titration	Double-blind			
		Period 1		Period 2	
	HHER (N = 44)	HHER (N = 20)	HHIR (N = 20)	HHER (N = 20)	HHIR (N = 20)
Deaths	0	0	1 (5%)	0	0
Serious adverse events	1 (2%)	1 (5%)[b]	0	0	0
Other Significant Events					
Adverse events leading to discontinuation	1 (2%)	2 (10%)[b]	0	0	0

[a]A subject may have had more than one other significant event; subjects with other significant events may have also had a serious adverse event or died. [b]Subjects No. 1 and 10 were incorrectly shown to discontinue during titration. They were randomized to HHER and therefore belong to Period 1. Cross-references: Tables 14.1.1, 14.3.2.1, 14.3.2.2; Appendices 16.2.1, 16.2.7.1.

- There was 1 death, 2 serious adverse events, and 3 other significant events (discontinuation due to adverse events) (Table 14.3.2.1, 14.3.2.2; Appendices 16.2.1, 16.2.7.1).
- The most common adverse events (>10% of subjects, combined HHER and HHIR) during open-label titration were: vomiting 43%, nausea 36%, somnolence 21%, dizziness 16%, dry mouth 11%, headache 11%, constipation 11%, and asthenia 11% (Table 14.3.1.1).
- The most common adverse events (>10%) of HHER subjects during both double-blind periods were: vomiting, 22%; asthenia, 19%; nausea, 17%; dizziness 14%, constipation 11%, and somnolence 11% (Table 14.3.1.1).
- The most common adverse events (>10%) of HHIR subjects during both double-blind periods were: nausea 19%, dizziness 14%, headache 14%, somnolence 11%, constipation 11%, and asthenia 11% (Table 14.3.1.1).

Laboratory Values: Number and percent of subjects with changes in laboratory values are contained Table 14.3.4.

Conclusions:

- In these subjects, HHER sprinkled onto soft food was considered equivalent in efficacy to HHIR whole tablets based on an equivalent daily dose (90% CI of ratio = 76% to 119%).
- Subjects treated with HHER had a statistically significantly higher mean dose-adjusted C_{min} than subjects treated with HHIR in the full analysis set (P = .0004). The higher trough plasma hydromorphone levels with HHER suggest that the efficacy would be maintained for the 24-hour duration.
- No unexpected safety concerns of HHER were identified.

Date of the Report: 15-Jan-2004