CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER

NDA 21-044

Medical Review(s)

FDA CENTER FOR DRUG EVALUATION AND RESEARCH
DIVISION OF ANESTHETIC, CRITICAL CARE, AND ADDICTION DRUG PRODUCTS
HFD-170, Room 9B-45, 5600 Fishers Lane, Rockville MD 20857 (301)827-7410

Medical Officer Review of Safety Update

NDA number:	21-044
Drug Name (Generic):	Palladone ™ (hydromorphone hydrochloride extended-release) Capsules
Sponsor:	Purdue Pharma, L.P.
Indication:	For the management of persistent, moderate to severe pain in patients requiring continuous, around-the-clock analgesia with a high potency opioid for an extended period of time (weeks to months) or longer.
Type of Submission:	Safety Update and a Minor Clinical Amendment (BM)
Date of Submission:	August 24, September 10, and September 14, 2004
Date of Review:	September 23, 2004
Reviewer:	Rigoberto Roca, M.D. Deputy Director Division of Anesthetic, Critical Care, and Addiction Drug Products
Project Manager:	Sara Stradley

Background

Purdue Pharma L.P. submitted a safety update for the time period of September 30, 2001 to July 20, 2004. It covered the time period since the previous safety update, which was included in their March 12, 2002 amendment. The applicant indicates that three studies that were previously identified as ongoing studies are now completed. Two additional clinical studies have been initiated since the previous safety update was submitted by the applicant. The studies are listed in the table below.

Study Number	Subject/Patient population	Number of Subjects/Patients	Study Status
HD98-0504	Healthy subjects with and without gallbladders (assessing enterohepatic circulation)	12	Completed
HMP3003	Acute post-operative pain	254	Completed
HD95-0801M	Cancer-related pain (comparison of immediate-release formulation and extended-release formulation)	35	Completed
HMP4005	Non-malignant pain (comparison of extended-release formulation and Duragesic ®)	464 (entered)	Ongoing
HMP3801	Moderate to severe pain (comparison of extended-release formulation and MS Contin ® tablets in patients with cancer and non-cancer pain)	139 (entered)	Ongoing (non-IND study being conducted in Australia)

The August 24th submission contained summary tables identifying the serious adverse events that have been reported in the studies. Treatment assignment for the ongoing studies is currently unknown since the study blind has not been broken. Several patient case report forms were requested from the applicant for a more detailed reviewed.

Review

The incidence and types of adverse events reported in the studies summarized in the safety update were consistent with the adverse event profile of opioid analgesics. With respect to serious adverse events (SAEs), Study HD98-0504 reported no deaths or SAEs.

Study HMP 3003 reported 11 subjects with SAEs (4 Placebo, 7 hydromorphone treatment arm); Study HD95-0801 reported 3 SAEs (2 in the hydromorphone treatment arm); Study HMP 4005 reported 16 SAEs in 15 patients (blind not broken); and Study 3801 reported 10 SAEs in 9 patients (blind not broken).

Case report forms were requested from the applicant for further evaluation of the SAEs (five of the seven hydromorphone patients from Study HMP 3003, three from Study HMP 4005 and two from Study HMP 3801). These case report forms were reviewed to assess whether the SAEs reported were consistent with what had previously been reported for hydromorphone.

Conclusions

Review of the case report forms did not reveal any information that was inconsistent with what has been previously reported for hydromorphone.

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/s/

Rigoberto Roca
9/23/04 06:08:34 PM
MEDICAL OFFICER

FDA CENTER FOR DRUG EVALUATION AND RESEARCH
DIVISION OF ANESTHETIC, CRITICAL CARE, AND ADDICTION DRUG PRODUCTS

Medical Officer Review Addendum

Review Date:	**September 19, 2002**
Drug Name:	**Palladone (Hydromorphone HCl, Extended-Release Capsules, 12mg, 16 mg, 24 mg, 32 mg)**
NDA #:	**21-044**
Sponsor:	**Purdue Pharma**
Type of Submission:	**Response to an Approvable Letter – 3/12/02**
Project Manager:	**Sara Shepherd**
Medical Reviewer:	**Michael J. Sevka, M.D.**

Review Addendum Purpose: The purpose of this addendum is to include the methods used in the assessment of the data integrity of the updated ISS in the response to the approvable letter and to include corrections for the reviews of three death narratives.

1) Methods Used in Assessing Data Integrity

Overall numbers of patients exposed to the various study treatments across the NDA was examined by comparing treatment-groupings listed in post-text Table A.7 to the numbers from various groupings using the electronic JMP dataset, DRUGASSGN.xpt. There was acceptable correlation between the two.

The appropriateness of coding adverse events was examined using the JMP dataset, CO-ADR.xpt. The verbatim adverse event term was compared to the *English* term and then to the COSTART term. Overall, the new coding from verbatim terms to COSTART terms and subsequently to body system appeared to be appropriate. Additionally, to assess the appropriateness of the recoding of adverse event terms submitted in the original NDA, the old COSTART terms were compared to the new COSTART terms and then to body system. The coding to the new COSTART term appeared appropriate. In comparing the old and new COSTART terms, reexamination of the original safety database and recoding appeared to capture additional events for some COSTART terms, in particular for terms such as nausea, vomiting, somnolence, dizziness, and pruritus.

For all subjects exposed to active treatment who died (Appendix C.1-page 3497 of the ISS) the content of narratives was compared to the information in the electronic case report forms and the line listings (Appendices B.1-page 585 of the ISS). Comparisons were made for subject identity number, age, gender, and cause of death. Acceptable correlation was observed between all three data formats except: 1) for subject 11 (HD990201-2083) who had *progression of skin cancer* instead of *progression of cervical cancer* listed as the cause of death, 2) the absence of line listings for approximately 10 subjects compared to the overall number of death narratives, and 3) the death event, date of death or both could not be confirmed in the case report forms for approximately 6 subjects.

For subjects who experienced a serious adverse event exposed to active treatment (Appendix C.2.4-page 3546 of the ISS), the content of narratives was compared to the information on the electronic case report forms. Comparisons were made for subject identity number, age, gender, and serious adverse event. This was done for the reports of serious adverse events on active treatment included in the current NDA Amendment for the following phase 3 studies: HD95-0801, HD95-0802, HMP3005, and HMP3006. Acceptable correlation was observed between the content in the narratives and in the case report forms. Some narratives contained additional serious adverse event information that was not contained in case report forms that I have viewed as follow-up information.

Narratives (Appendix C.4- page 3597 of the ISS) were also compared to the case report forms for subjects who discontinued due to an adverse reaction. Comparisons were made for subject identity number, age, gender, and adverse event leading to discontinuation. This was done for subjects on active treatment in the phase 3 studies in the current NDA Amendment (HD99-0201, HD95-0803, HMP-3005, HMP-3006). Acceptable correlation was observed between the content in the narratives to that in the case report forms.

2) Corrections to Death Narrative Reviews

Background: During the review of the death narratives for the updated ISS an incorrect assessment was inadvertently included for 3 narratives regarding possible attribution of death to study treatment. The corrections are made below. These corrections do not change the conclusions drawn from those concluded from the review of the updated ISS.

For narrative #16, the last sentence was accidentally included that should not have been included. The corrected narrative below omits that last statement.

16) 22002: HD95-0803 61-year-old male with metastatic adenocarcinoma of the lung. He entered the continuation study (HD95-0803) on 18-Dec-1996 after completing the primary study (HD95-0802). His initial dose of HHER on the continuation study was 12 mg qd; although dosing records are incomplete, they show that the patient continued on this dose until his death on [ ], with increasing use of 2-mg and then 4-mg HHIR rescue medication. The patient was hospitalized on [ ] because of

cachexia, anorexia, edema, ascites, and progressive disease, all reported as adverse events unrelated to the study drug. While hospitalized, he was diagnosed with early hepatorenal syndrome. During hospitalization he developed an unsteady gait and dysphagia. The unsteady gait was characterized as a "disability" and judged possibly related to the study drug. A data clarification after the database closed resulted in recategorizing this event as "not serious." The patient's dysphagia was attributed to his underlying disease and judged unrelated to study medication. During the hospitalization the patient continued to take HHER; his last dose of HHER was on [ ] the day before he died. The patient's death was considered unrelated to study medication. Although the patient's malignancy is the likely proximal cause of death, it is not possible to exclude study medication as a contributory factor because he continued on medication until death.

For narrative #17 the last sentence mis-states the length of time from the last dose of study medication to the time of death. The corrected narrative below states the length of time to be 6 days and not 2 weeks.

17) 16001: HD95-0801 49-year-old male receiving chemotherapy for metastatic lung cancer. He entered the open-label titration period of the study on 30-Jan-1997 at prescribed doses of 24-mg HHER qd and rescue doses of 4-mg HHIR. The dosages were gradually increased to 84 mg and 14 mg with satisfactory pain control. On [ ] during the open-label period the patient was observed to be anemic; he was hospitalized for 1 day for transfusions. While hospitalized for anemia, the patient also experienced headaches and fever/chills and underwent observation to rule out brain metastases. He entered the double-blind period on [ ] and completed the last day of double-blind period 2 on [ ] He died of progressive disease on [ ] 6 days after the last dose of study medication. In the judgment of the investigator, neither the anemia nor the progressive disease was related to the study drug. Considering the length of time from the last dose of study medication (approximately 6 days), it is very unlikely that the study medication contributed to the proximal cause of death.

For narrative #26, the correct attribution statement, the last sentence, replaces the incorrect statement.

26) 16024: HD95-0803 73-year-old female with metastatic breast cancer. She participated in the HD95-0801 trial and took her last dose of HD95-0801 medication on 15-Sep-1997. She entered the HD95-0803 study on the following day at a prescribed dose of 24-mg of HHER qd. She completed the 56-day study on [ ] at a dose of HHER 48 mg qd. She continued to take HHER, 48 mg qd, through 24 days of an extension period, taking her final dose on [ ] the day of her death. She was hospitalized only once during the study and extension period. She was admitted to the hospital on [ ] because of dizziness, a fall, and increased chest pain. While hospitalized, she was managed for increased left shoulder pain and a humerus fracture. The patient died of progressive disease on [ ], reported as an adverse event unrelated to the study drug. The dizziness and fall were judged possibly related to the

study medication. Although the patient's malignancy is the likely proximal cause of death, it is not possible to exclude study medication as a proximal contributory factor because the patient continued on medication until death.

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/s/

Michael Sevka
9/20/02 12:36:37 PM
MEDICAL OFFICER

Bob Rappaport
9/23/02 06:13:43 PM
MEDICAL OFFICER

FDA CENTER FOR DRUG EVALUATION AND RESEARCH

DIVISION OF ANESTHETIC, CRITICAL CARE, AND ADDICTION DRUG PRODUCTS

Medical Officer Review

Review Date:	**September 13, 2002**
Drug Name:	**Palladone (Hydromorphone HCl, Extended-Release Capsules, 12mg, 16 mg, 24 mg, 32 mg)**
NDA #:	**21-044**
Sponsor:	**Purdue Pharma**
Type of Submission:	**Updated Integrated Summary of Safety**
Project Manager:	**Sara Shepherd**

Background:

In response to a nonapprovable letter issued on October 4, 2001, the sponsor has submitted a new efficacy trial and reanalysis of the ISS, in addition to multiple CMC responses. Dr. Michael Sevka, the primary medical reviewer for this application, has completed a separate review of the efficacy and safety data provided on the new trial, Study HMP3006. This review will address only the new data, and comparisons with old data, submitted as an update to the ISS of the original application. The review has been performed by the following team members: Shaun Comfort, M.D.; Gerald Dal Pan, M.D.; Sharon Hertz, M.D.; Michael Sevka, M.D.; and Bob Rappaport, M.D.

The sponsor summarizes the structure of the submission in the comments extracted from their submission and reproduced below:

> This summary presents safety data that were submitted in the Original NDA submission (28-Dec-1998) and integrated safety data from all Phase 3 studies, including 2 placebo-controlled studies. The data are presented in different ways to allow tracking of key Phase 3 safety data across the different submissions: (1) Phase 3 safety information is presented as it was in the Original 1998 NDA submission; (2) Phase 3 safety information from the Original NDA submission is also presented based on a recoding process (detailed in Section 9.7 and Appendices E, F, and G) that makes it consistent with new Phase 3 safety data; (3) all new Phase 3 safety data, integrated with the recoded data from the Original NDA submission, are presented; (4) safety data from 2 Phase 3 placebo-controlled trials (HMP3005 and HMP3006) are presented; and (5) all Updated Phase 3 safety data are presented by malignant and nonmalignant pain subgroups (because of expected differences in these subpopulations due to underlying disease load in subjects with malignant pain).
>
> [page 10.; Summary of safety document; update file; 2002-03-12 file]

Methodology Used to Present Integrated Adverse Event Data:

Safety data, including adverse event data, are presented in different ways in the current NDA amendment. These various ways include:

- Phase 3 safety data is presented as it was in the original 1998 NDA submission.
- Phase 3 safety data from the original 1998 NDA submission is presented based on a recoding process, described below, to make it consistent with the new Phase 3 safety data.
- All new Phase 3 safety data integrated with the recoded safety data from the original NDA submission
- Safety data from 2 Phase 3 placebo-controlled studies (HMP3005 and HMP3006)
- All updated Phase 3 safety data are presented by malignant and non-malignant pain subgroups, because of the expected differences in these two patient populations due to underlying disease load in subjects with malignant pain).

The recoding process involved a review of the original NDA safety database and other associated clinical data from the component studies to insure that data from those studies were presented in a way that was consistent with the presentation of safety data from the more recent studies. The methodology used to integrate the data is presented in Section 9.7 of the Safety Update in the NDA amendment, as well as in Appendices E and F to that update. The major features of this process include:

A comprehensive review of previous Phase 3 studies to identify potentially serious safety information, including serious adverse events, medically significant adverse events, and premature termination due to adverse events. Data sources from these studies that were used to identify this information included:

- Subject listings of intercurrent diseases and conditions
- Subjects listings of adverse events
- Subject listings of completions and discontinuations
- Comment fields in subject listings for adverse events, subject completion/discontinuation, and intercurrent diseases and conditions

Intercurrent illnesses or conditions that were associated with a new hospitalization, prolonged hospitalization, and/or surgery were added to the database, provided that they were not already reported in the original database part of another SAE that was already in the original database. In any case, all serious or medically significant adverse events were added to the appropriate narrative. Intercurrent illnesses or conditions that were not associated with a new hospitalization, prolonged a hospitalization, and/or surgery, but

were nonetheless serious or medically significant adverse events were also added to the database, provided that they were not already in the original database, or, that they represented a worsening of a preexisting illness, if they were consistent with a preexisting illness. Adverse events identified in the comments field of CRFs were also integrated into the safety database, provided that they were not already in the safety database, or in the listings of intercurrent illnesses or conditions. In many cases complete information on the adverse event, such as start date, stop date, severity, or judged relationship to study drug was not available, and was thus not added to the safety database.

Adverse events for all Phase 3 studies were reclassified according to standardized terminology using the modified COSTART (Coding Symbols for Thesaurus of Adverse Reaction Terms, 5th edition).

In studies HD95-0801 and HD95-0802 in the original NDA, all subjects completed a 4-day open-label treatment with Hydromorphone HCl Extended-Release [HHER], prior to a randomized, double-blind crossover treatment sequence (Hydromorphone HCl Immediate-Release [HHIR] followed by HHER, or HHER followed by HHIR). There were no washout periods between the open label phase and the double-blind phase, or between the two periods of the double-blind phase. Some subjects who completed either of these two studies entered an open-label extension period, during which they received HHER. In the original NDA, adverse events were attributed to either HHER or HHIR depending on when they occurred. For this safety update, the Sponsor has developed a new algorithm for determining the incidence of adverse events in subjects receiving HHER. Specifically, any adverse events that began or worsened in severity after the start of open-label HHER in studies HD95-0801 or HD95-0802 were categorized as occurring during HHER treatment.

Subject Distribution:

The following table, copied from the sponsor's Table 9.9.1, page 24 of the Safety Update Document, summarizes the patient distribution from the original and the updated ISS:

Table 1.

Subject Disposition (Original 1998 NDA and Current NDA Amendment) – Phase 3 Studies: Safety Population

	Phase 3 Studies in Original 1998 NDA[a]		Updated Phase 3 Studies Original 1998 NDA[a]	Phase 3 Studies in Current NDA Amendment[b]		
	HHIR	HHER	HHER	MS Contin	HHER	Placebo
Category	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Exposed	209 (100.0)	343 (100.0)	343 (100)	38 (100)	568 (100.0)	191 (100.0)
Discontinued	12 (5.7)	162 (47.2)	174 (50.7)	11 (29.0)	279 (49.1)	37 (19.4)
Reason for premature discontinuation[c]						
Adverse events[d]	8 (3.8)	72 (21.0)	102 (29.7)	9 (23.7)	158 (27.8)	12 (6.3)
Ineffective treatment[e]	2 (1.0)	44 (12.8)	46 (13.4)	0 (0)	66 (11.6)	23 (12.0)
Death[f]	1 (0.5)	6 (1.7)	7 (2.0)	0 (0)	14 (2.5)	0 (0)
Lost to follow-up	0 (0)	2 (0.6)	2 (0.6)	0 (0)	3 (0.5)	1 (0.5)
Protocol violation	1 (0.5)	15 (4.4)	16 (4.7)	2 (5.3)	20 (3.5)	0 (0)
Other	0 (0)	23 (6.7)	23 (6.7)	0 (0)	46 (8.1)	1 (0.5)

[a] Includes data from studies HD95-0801, HD95-0802, and 77 subjects from HD95-0803. All discontinuations in the Updated Original NDA are attributed to HHER.
[b] Includes data from studies HD95-0801, HD95-0802, HD95-0803, HD99-0201, HMP3005, and HMP3006.
[c] Includes primary and secondary reasons for discontinuations; therefore, the sum of the percentages across all reasons may not add to the total percentage of discontinuations.
[d] Illness not due to drug was a category used in studies HD95-0801, HD95-0802, and HD95-0803. For the purpose of comparison with the current submission, illness not due to drug has been added to adverse events to reflect the total incidence of adverse events.
[e] Subjects in study HMP3006 identified as discontinued due to Ineffective Treatment are considered completers because they met the study end point of Emergence of Inadequate Analgesia. Exception: 4 subjects identified as discontinued due to Ineffective Treatment and to Adverse Event are included as discontinued prematurely due to adverse events.
[f] Deaths as reported on discontinuation page of CRF. In addition to the deaths noted on the CRF Discontinuation form, an additional 33 deaths were recorded, many occurring after subject discontinuation of the study due to an adverse event. All 47 deaths are listed and discussed in Section 9.13.
Cross-references: Original 1998 NDA ISS, Table 8.11.16.1.3B and Table 8.11.16.1.4; Current NDA Amendment, Tables A.3.1 and A.31

The frequency of discontinuations was similar in the original, the updated and the current NDA. The most frequent reason for discontinuation was AE in all three analyses. The sponsor concludes that the relatively low frequency of discontinuation for HHIR subjects is due to their shorter duration of exposure compared to HHER subjects (3-7 days per protocol vs. estimated mean exposure of 20.4 days). They also conclude that the frequency of discontinuation was higher for the HHER subjects compared to placebo-treated subjects due to the inclusion of patients with malignant pain in the HHER long-term extension study HD95-0803. These patients had a far higher incidence of deaths (5% vs. 0) and AEs leading to discontinuation (41% vs. 14%) than the non-malignant pain patients (from sponsor's Table 9.9.3, page 26, Safety Update Document).

The overall incidence of premature discontinuation was similar for the HHER-treated patients vs. the placebo-treated subjects in the placebo-controlled clinical trials as seen below in the sponsor's Table 9.9.2, reproduced from page 25 of the Safety Update Document.

Table 2.

Subject Disposition – Phase 3 Placebo-controlled Studies, by Treatment (Current NDA Amendment): Safety Population

	Phase 3 Placebo-controlled Studies[a]	
	Placebo (N = 191)	HHER (N = 190)
Category	n (%)	n (%)
Exposed	191 (100.0)	190 (100.0)
Discontinued	37 (19.4)	35 (18.4)
Reason for premature discontinuation[b]		
Adverse events	12 (6.3)	19 (10.0)
Ineffective treatment[c]	23 (12.0)	11 (5.8)
Death	0 (0)	0 (0)
Lost to follow-up	1 (0.5)	1 (0.5)
Protocol violation	0 (0)	1 (0.5)
Other	1 (0.5)	3 (1.6)

[a]Studies HMP3005 and HMP3006.
[b]Includes primary and secondary reasons for discontinuations; therefore, the sum of the percentages across all reasons may not add to the total percentage of discontinuations.
[c]Subjects in study HMP3006 identified as discontinued due to Ineffective Treatment are considered completers because they met the study end point of Emergence of Inadequate Analgesia. Exception: 4 subjects identified as discontinued due to Ineffective Treatment and to Adverse Event are included as discontinued prematurely due to adverse events.
Cross-reference: Current NDA Amendment, Table A 3.1

Demographics:

There was a somewhat higher percentage of older patients (greater than 65 years) in the Phase 3 studies in the original submission compared to the current application (33% vs. 25%). The sponsor attributes this to the greater number of patients with non-malignant pain in the new compared to the original ISS. (See sponsor's Table 9.10.1, page 28, Safety Update Document) The demographic data otherwise appears to be similar

between the original and the current submissions, and there are no clinically relevant imbalances.

Exposure:

The sponsor's Tables 9.11.1B and 9.11.2, pages 31 and 32, Safety Update Document, summarize the dose-by-time exposure for all subjects exposed to HHER in Phase 2 and 3 studies, and only subjects exposed to HHER in Phase 3 placebo-controlled trials, based on the current submission, and are reproduced below:

Table 3.

Number of Subjects Exposed to HHER, by Duration of Exposure and Average Daily Dose – Phase 3 Studies (Current NDA Amendment): Safety Population

	Phase 3 Studies[a] HHER Average Daily Dose (mg/d)[b]					
Duration of Exposure[c,d]	12 n (%)[e]	>12-16 n (%)	>16-24 n (%)	>24-32 n (%)	>32 n (%)	Total n (%)[f]
Any	259 (45.6)	20 (3.5)	63 (11.1)	47 (8.3)	179 (31.5)	568 (100)
≥1 week	202 (42.7)	20 (4.2)	48 (10.1)	39 (8.2)	164 (34.7)	473 (83.3)
≥2 weeks	161 (42.8)	15 (4.0)	33 (8.8)	30 (8.0)	137 (36.4)	376 (66.2)
≥3 weeks	149 (51.6)	14 (4.8)	17 (5.9)	18 (6.2)	91 (31.5)	289 (50.9)
≥4 weeks	131 (53.9)	13 (5.3)	15 (6.2)	15 (6.2)	69 (28.4)	243 (42.8)
≥8 weeks	18 (17.3)	10 (9.6)	13 (12.5)	13 (12.5)	50 (48.1)	104 (18.3)
≥12 weeks	2 (4.3)	3 (6.5)	5 (10.9)	7 (15.2)	29 (63.0)	46 (8.1)
≥24 weeks	1 (4.8)	1 (4.8)	2 (9.5)	5 (23.8)	12 (57.1)	21 (3.7)
≥52 weeks	0 (0)	0 (0)	0 (0)	1 (25.0)	3 (75.0)	4 (0.7)

[a]Studies HD95-0801, HD95-0802, HD95-0803, HD99-0201, HMP3005, and HMP3006.
[b]Average daily dose = total dose in mg divided by the total number of days of exposure to ≥1 dose of study drug.
[c]Duration of exposure = (date of last dose – date of first dose) + 1.
[d]In Protocol HD95-0803, subjects were allowed to stop dosing for ≤14 days. This dosing hiatus is not included in the calculation of duration of exposure.
[e]Row percentages reflect the percent of subjects with specified average daily dose of HHER given the indicated duration of exposure.
[f]Percentages in the Total column reflect percent of subjects with specified duration of exposure.
Cross-reference: Current NDA Amendment, Table A.8.2.

Table 4.

Number of Subjects Exposed by Duration of Treatment – Phase 3 Placebo-controlled Studies (Current NDA Amendment): Safety Population

Duration of Exposure[b]	Phase 3 Placebo-controlled Studies[a]	
	Placebo	HHER
Any	191 (100.0)	190 (100.0)
≥1 week	113 (59.2)	152 (80.0)
≥2 weeks	92 (48.2)	130 (68.4)
≥3 weeks	78 (40.8)	124 (65.3)
≥4 weeks	71 (37.2)	110 (57.9)

[a]Studies HMP3005 and HMP3006.
[b]Duration of exposure = (date of last dose – Date of first dose) + 1.
Cross-reference: Current NDA Amendment Table A.8.4.

In addition there was a total of 173 subjects exposed to HHER/HHIR in the Phase1 clinical pharmacology studies, the vast majority of whom received a single dose of study drug.

Deaths:

The sponsor has provided information on deaths from across all completed studies and ongoing studies. A total of 48 deaths are reported in the current NDA Amendment – 3 subjects exposed to MS Contin and 45 exposed to HHER. All deaths occurred in patients exposed to treatment for malignant pain in studies HD95-801, HD95-802, HD95-803 (open-label extension for the 2 previous studies), and HD99-0201. All of these studies were to enroll subjects with malignant and non-malignant pain. Below is a table showing the number and types of malignancies for the 45 subjects who died following exposure to HHER.

Table 5.

Types of Malignancy Stated in Subject Narrative	Number of Subjects
Lung	15 (2 subjects also had bladder)
Cervical	4
Prostate	4
Colon/Colorectal	4
Breast	3
Non-Small Cell Lung	2 (1 subject also had bladder)
Pancreatic	2
Unknown Primary	2
Bladder	1
Uterine Leiomyosarcoma	1
Squamous Cell Lung	1
Esophageal	1
Renal Cell	1
Melanoma	1
Carcinomatosis	1
Multiple Myeloma	1
Small Cell Lung	1
Total	45

Deaths from Studies in the Original NDA:

1) 33011: HD95-0801 55 year-old male with metastatic bladder cancer. Admitted to study on 4/8/98. Treated with doses of study medication up to 48-mg HHER and 8-mg rescue medication. Admitted to hospital on [redacted] for hypercalcemia. Although randomized to be treated in a double-blind treatment sequence, he was mistakenly treated in open-label and his dose was decreased to 36 mg qd. During the hospitalization he suffered a pulmonary embolus. Patient died on [redacted] This death was unlikely to be related to study medication.

Deaths from Updated Studies from the Original NDA:

2) 16006: HD95-0801 84 year-old male with metastatic cancer of lung and liver. Entered open-label period on 4-Apr-1997. Treated with doses of study medication up to 24-mg HHER and 2 mg of rescue (increased from 12 mg/2 mg on[ ] Admitted to hospital on [ ] with anorexia, nausea, vomiting, dehydration, hypovolemia, hypotension, and neutropenia. Beginning on [ ] the patient experienced left acute renal insufficiency, hypocalcemia, and volume depletion/dehydration. The patient became more hypotensive and died on [ ] While it possible that this patient's demise was directly related to progression of his underlying disease, it is not possible to ascertain whether the increased dose of study medication played a direct or indirect role in his death.

3) 16040: HD95-0801 70 year-old male with metastatic lung cancer. Other medical problems included treated hypertension and a history of cardiac arrhythmias for which he took daily prophylactic medication. He began the open-label titration period of the study on 06-Mar-1998, with a prescribed dose of 12-mg HHER qd and rescue doses of 2-mg HHIR, and completed the open-label period on 13-Mar-1998 using doses of 24 mg and 4 mg, respectively. He entered double-blind period 1 on [ ] The following morning, [ ] he had chest pain and took rescue medication but did not take any of the blinded medication. He was admitted to hospital through the ER and given morphine. On the morning of [ ] while in the hospital, he re-entered double-blind period 1 at the same doses. Chest pains did not resolve but were satisfactorily controlled with study medication. While hospitalized, the patient experienced elevated prothrombin time, shortness of breath, abdominal pain, decreased hemoglobin/hematocrit, disease progression, and cardiac dysrythmia. After his third dose (over 4 days) of blinded medication he underwent colonoscopy and Demerol was given prior to the procedure. The patient was removed from the study because of protocol violation. Discharge was never possible and the patient died on [ ] due to disease progression, — days after the last dose of study drug. Considering the length of time from the last dose of study medication , it is unlikely that this extended-release study medication contributed to the proximal cause of death in this patient.

4) 16041: HD95-0801 62 year-old female undergoing chemotherapy and irradiation for lung cancer. Past medical history significant for hypertension and emphysema. She began open-label on 13-Mar-1998 with a daily dose of 24-mg HHER and 4-mg rescue. On [ ] she complained of unsteadiness. On [ ] she was seen by her physician for a swollen left arm and admitted to hospital for management of a deep vein thrombosis in the left subclavian vein. Radiography showed no relationship between the thrombosis and injuries sustained from a fall on [ ] During hospitalization she experienced dehydration, anemia, low magnesium, and neutropenia. Her hospitalization was complicated by respiratory problems related to emphysema and progressive cancer and distrust of medical intervention. She left the hospital against medical advice on [ ] Pain control was adequate on 24-mg HHER and did not require rescue medicine. She entered and completed double-blind

period 1 on [ ] She entered double-blind period 2 on [ ] but took 24-mg HHER left over from the open-label period on the first day instead of double-blind mediation for period 2. Later that day her husband found her pulseless. Resuscitation was not attempted. Although the patient's malignancy and malignancy complications are the likely proximal cause of death particularly since she had tolerated 24-mg HHER daily for several weeks, it is not possible to completely exclude this extended-release study medication as an indirect or direct proximal contributory factor to this patient's demise because the patient continued on medication until the day of death.

5) 17008: HD95-0801 42 year-old female undergoing chemotherapy for metastatic lung cancer. She entered the open-label titration period of the study on 11-Jan-1997 with prescribed doses of 24-mg HHER qd and rescue doses of 4-mg HHIR. The initial doses provided satisfactory pain control. Drug doses and pain levels could never be confirmed, however, because the patient's family disposed of the study diary and unused medication after the patient died. The patient took the prescribed dose of HHER on 16-Jan-1997 and required a single rescue dose of HHIR. Drug exposure on 17-Jan-1997 is unknown. The patient was admitted to the hospital on [ ] with complaints of abdominal pain and hematemesis and was ultimately found to have an abdominal infarction. While hospitalized, the patient experienced a gastrointestinal bleed, pancreatitis, thrombocytopenia, bibasilar atelectasis pneumonia, and erosive duodenitis. She died of small bowel infarction on [ ] Though it is difficult to say that study medication did not contribute to the patient's sustaining a bowel infarction because of its effects on GI function, it is not possible to speculate what role study medication may have played in the proximal cause of death.

6) 33005: HD95-0801 51 year-old female with metastatic uterine leiomyosarcoma. At the time of study entry, the patient had a history of intermittent vomiting. She entered the open-label titration period on 22-Jan-1998 at a prescribed dose of 36-mg HHER qd with rescue doses of 6-mg HHIR. After [redacted] days, the doses were reduced to 24 mg and 4 mg because of drowsiness. On [ ] she was admitted to the hospital for management of nausea, vomiting, and dehydration. Oral intolerance continued during the hospitalization, and the patient was ultimately found to have a complete small bowel obstruction due to progressive intra-abdominal cancer. While hospitalized, the patient also experienced anemia and pancytopenia. The patient ultimately discontinued from the study on [ ] due to the bowel obstruction. She died of progressive disease on [ ] days after her last dose of study medication, while still in the hospital. Though it is difficult to say that study medication did not contribute to the patient's sustaining a bowel infarction because of its effects on GI function, it is unlikely that study medication may have contributed to the proximal cause of death because the last dose administered was [redacted] days before death.

7) 33012: HD95-0801 64 year-old male with metastatic lung cancer. He entered the open-label titration period on 08-Apr-1998 at a prescribed dose of 36-mg HHER qd with rescue doses of 6-mg HHIR and did not change his doses during [redacted] days of treatment with HHER. On [ ] he was admitted to the hospital for management of severe nausea judged possibly related to the study medication. While hospitalized, the patient

experienced low blood pressure, low oxygen saturation, and pneumonia. He continued his HHER medication while in the hospital until increasing problems with pain control, attributed to rapid disease progression caused the managing physicians to discontinue the study and substitute intravenous morphine on [ ]. The patient died of progressive disease on [ ] without ever leaving the hospital. The problems that appeared during the hospitalization and resulted in the patient's death were: hypoxia, pneumonia, and disease progression. Study medication may have contributed to the patient's nausea and low blood pressure, but the more proximal causes of death appear to be pneumonia, hypoxia, and disease progression.

8) 23006: HD95-0802 43 year-old female with visceral pain due to non–small-cell lung cancer. She entered the open-label titration period of the study on 01-Feb-1997 with a prescribed dose of 24-mg of HHER qd and rescue doses of 4-mg HHIR. During the study, her dose of HHER was increased to a maximum of 60 mg qd on 14-Feb-1997. The use of rescue doses diminished after 14-Feb-1997 and HHER was reduced to 48 mg on 17-Feb-1997. The patient was hospitalized from [ ] because of dyspnea/hypoxia with chest pain (increased pleural effusion). The patient also experienced disease progression beginning [ ] After discharge, she had worsening respiratory failure manifested by dyspnea and somnolence and died on [ ]. Death was due to respiratory failure secondary to progression of malignancy. The investigator attributed the patient's terminal somnolence to hypercarbia secondary to progression of lung cancer, rather than to opioid analgesics, because the somnolence progressed in spite of opioid dose reductions. Although the patient's disease was progressing and the dose of study medication reduced from previously tolerated levels, some possible contribution of study medication to the proximal cause of death can not be completely ruled out.

9) 27006: HD95-0802 80 year-old male with prostate cancer metastatic to bone. He entered the open-label titration period of the study on 01-Apr-1997 with prescribed doses of 12-mg HHER qd and rescue doses of 2-mg HHIR. The doses were increased to 24 mg and 4 mg, respectively, on 06-Apr-1997. Throughout the study, the patient complained of inadequate pain control. Although only a few doses of rescue medication were recorded in the diary, the counts of returned medication suggested the patient took larger or more frequent doses than he recorded. Because pain control was unsatisfactory and protocol compliance was poor, the patient was discontinued from the study on [ ] In the early morning hours of [ ], the patient took a total of 12-mg HHIR. Later that day, he was evaluated in the emergency room because of somnolence, progressive weakness, and vomiting; he was admitted to the hospital for management of dehydration. After intravenous rehydration the vomiting resolved and the patient became more alert. Beginning on [ ] the patient was also noted to have anorexia and urinary retention. On the morning of the third hospital day [ ] the patient was found dead in bed. Although the last dose of study medication appears to have been 2 days before his death, and the dose appears to be larger for HHIR than the patient might have been able to tolerate, it is likely the problems that brought the patient to the emergency room were partly dueto the study medication. However the study drug is less

likely to have contributed significantly to his proximal cause of death because his condition initially improved following hospital admission.

10) 29015: HD95-080 52 year-old male with a history of complicated gastrointestinal disease including inflammatory bowel disease (ulcerative colitis), sclerosing cholangitis, diverticulosis, and peptic ulcers. He required opioid analgesics for metastatic colon cancer. He entered the open-label titration period on 12-Feb-1998 with a prescribed dose of 12-mg HHER qd and rescue doses of 2-mg HHIR. After his doses were increased to 24 mg and 4 mg, respectively, he completed the open-label period on 25-Feb-1998. He completed the double-blind periods between 26-Feb-1998 and 11-Mar-1998. On [redacted], he was admitted to the hospital for management of nausea and jaundice related to cholangitis (complications from sclerosing cholangitis). The patient ultimately died on [redacted] It is not possible to judge what contribution study medication made to the proximal cause of death because it is unclear when the last dose was administered. It may have been [redacted] from the day of death.

11) 12010: HD95-0803 52-year-old male who required opioid pain medication because of metastatic esophageal carcinoma. He entered the open-label titration period of the study on 11-Apr-1997 at prescribed doses of 60-mg HHER qd and rescue doses of 10-mg HHIR. The initial doses provided satisfactory pain control and the patient entered the double-blind period on 16-Apr-1997. On [redacted] the patient was diagnosed with aspiration pneumonia and hospitalized. The study was not interrupted and the patient completed the last day of double-blind period 2 on [redacted] while in the hospital. He entered the continuation study (HD95-0803) on [redacted] and took 64-mg of HHER on that morning. While hospitalized, the patient's pneumonia worsened. He took no study medication after [redacted] he died of respiratory failure secondary to pneumonia on [redacted] This patient appears to have died — hours after his last dose of study medication and tolerated the dose for about 2 weeks, but a remote or proximal contributory effect of study medication can not be ruled out. The study medication may have exacerbated the progress of the pneumonia through respiratory depression or may have contributed to the initiation of the aspiration.

12) 16010: HD95-0803 72-year-old male with both lung and prostate cancer. He completed HD95-0801 on 10-Jun-1997 and entered the continuation study, HD95-0803, on 11-Jun-1997. He participated in the study until [redacted] when difficulty swallowing (due primarily to radiation-resistant spinal cord metastases) made it impossible for him to use oral pain medications. His dose of HHER during the study was 72 mg qd. Adverse events recorded during the study include cough and lethargy (neither judged serious). The lethargy contributed to the swallowing problems and he was withdrawn from study on [redacted]. After study withdrawal his health continued to deteriorate. He died on [redacted] days after his last dose of study medication. Considering the length of time from the last dose of study medication (approximately — days), it is very unlikely that this extended-release study medication contributed to the proximal cause of death in this patient.

13) 16022: HD95-0803 56-year-old male receiving chemotherapy for metastatic renal cell carcinoma. He entered the continuation study (HD95-0803) on 16-Aug-1997 after completing the primary study (HD95-0801). His initial dose of HHER on the continuation study was 24 mg qd. On [ ], he was hospitalized for management of nausea/vomiting attributed to his chemotherapy. Because the nausea and vomiting were difficult to control, the managing physician put the patient on leave from the study from [ ]. The patient also experienced a fluid volume deficit of varying severity, secondary to the nausea/vomiting caused by chemotherapy treatment. The patient was evaluated on [ ] for leukocytosis, with changing severity, secondary to disease progression. The patient resumed HHER on 30-Sep-1997 and continued on the 24 mg qd dose through 20-Oct-1997. He underwent a brief hospitalization for evaluation of light-headedness and symptoms related to disease progression beginning on [ ] He then was discharged and readmitted on [ ] with chest pain due to disease progression. While hospitalized, the patient experienced fever and failure to thrive. Day — of the HD95-0803 study was reached on [ ], the patient's continued enrollment in the study and use of study medication resulted from a misunderstanding about the counting of days during the leave of absence. At the time of the third admission [ ], the patient discontinued HHER because of the complicated nature of the required medical management, because the 24-mg dose was no longer effective, and because the investigator believed the end date for study participation had been reached at last. After admission on [ ], the patient had a progressive downhill course and died of complications of malignancy on [ ] The episodes of nausea and vomiting and the chest pain associated with effusions were reported as intercurrent diseases. The episode of light-headedness and patient's death due to carcinoma were reported as serious adverse events unrelated to study drug. Considering the length of time from the last dose of study medication (approximately —weeks), it is very unlikely that the study medication contributed to the proximal cause of death.

14) 21001: HD95-0803 82-year-old male with metastatic lung cancer. He participated in HD95-0802 and completed double-blind period 2 on 16-Dec-1996. He entered the continuation study (HD95-0803) on 17-Dec-1996, taking a prescribed dose of 12-mg HHER qd and occasional rescue doses of 2-mg HHIR. His dose of HHER was increased on 19-Jan-1997 to 24 mg, with no change made in the HHIR rescue dose. The patient was admitted to inpatient hospice care due to cancer progression from [ ] because caring for his needs had exhausted his wife, the primary home caregiver. He continued on the study medication during and after the period of hospice care. On [ ]week after his discharge, he died of respiratory arrest due to progressive disease. The events leading to inpatient hospice care and the fatal adverse event (respiratory arrest) were judged unrelated to the study medication. Although the patient's malignancy is the likely proximal cause of death, it is not possible to exclude study medication as a contributory factor because he continued on medication until death and died of respiratory arrest.

15) 21002: HD95-0803 59-year-old male with metastatic prostate cancer. He participated in HD95-0802 and completed double-blind period 2 on 06-Mar-1997. He

entered the continuation study (HD95-0803) on 08-Mar-1997, taking a prescribed dose of 24-mg HHER qd and occasional rescue doses of 2-mg HHIR. On [ ] he was admitted to inpatient hospice care because of disease progression and associated difficulty with swallowing, weakness, confusion, and thrombocytopenia with bleeding. He was discontinued from the study on that day and died of progressive disease – days later. The events leading to inpatient hospice care and death were judged unrelated to the study medication. It is unlikely that study medication contributed to the proximal cause of death because of the remoteness of the last dose.

16) 22002: HD95-0803 61-year-old male with metastatic adenocarcinoma of the lung. He entered the continuation study (HD95-0803) on 18-Dec-1996 after completing the primary study (HD95-0802). His initial dose of HHER on the continuation study was 12 mg qd; although dosing records are incomplete, they show that the patient continued on this dose until his death on [ ] with increasing use of 2-mg and then 4-mg HHIR rescue medication. The patient was hospitalized on [ ] because of cachexia, anorexia, edema, ascites, and progressive disease, all reported as adverse events unrelated to the study drug. While hospitalized, he was diagnosed with early hepatorenal syndrome. During hospitalization he developed an unsteady gait and dysphagia. The unsteady gait was characterized as a "disability" and judged possibly related to the study drug. A data clarification after the database closed resulted in recategorizing this event as "not serious." The patient's dysphagia was attributed to his underlying disease and judged unrelated to study medication. During the hospitalization the patient continued to take HHER; his last dose of HHER was on [ ] the day before he died. The patient's death was considered unrelated to study medication. Although the patient's malignancy is the likely proximal cause of death, it is not possible to exclude study medication as a contributory factor because he continued on medication until death.
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17) 16001: HD95-0801 49-year-old male receiving chemotherapy for metastatic lung cancer. He entered the open-label titration period of the study on 30-Jan-1997 at prescribed doses of 24-mg HHER qd and rescue doses of 4-mg HHIR. The dosages were gradually increased to 84 mg and 14 mg with satisfactory pain control. On [ ] during the open-label period the patient was observed to be anemic; he was hospitalized for 1 day for transfusions. While hospitalized for anemia, the patient also experienced headaches and fever/chills and underwent observation to rule out brain metastases. He entered the double-blind period on [ ] and completed the last day of double-blind period 2 on [ ] He died of progressive disease on [ ] days after the last dose of study medication. In the judgment of the investigator, neither the anemia nor the progressive disease was related to the study drug. Considering the length of time from the last dose of study medication (approximately [ ], it is very unlikely that the study medication contributed to the proximal cause of death.

18) 16007: HD95-0801 73-year-old female with colon cancer metastatic to the liver. She entered the open-label titration period of the study on 11-Apr-1997at a

prescribed dose of 12-mg HHER qd and rescue doses of 2-mg HHIR. Dosages were gradually increased to 36 mg and 6 mg, respectively. She completed the open-label period on 18-Apr-1997 and entered double-blind period 1 on 19-Apr-1997. On [ ] she was hospitalized for management of Clostridium difficile diarrhea. While hospitalized, the patient also experienced hypotension secondary to dehydration. She completed double-blind period 1 [ ] and entered double-blind period 2 [ ] She completed double-blind period 2 on [ ] although the hospital staff mistakenly administered 1 dose of blinded medication on the morning of [ ] The patient was discharged from the hospital on [ ] She died on [ ] days after the last dose of study medication. Considering the length of time from the last dose of study medication (approximately –days), it is very unlikely that the study medication contributed to the proximal cause of death.

19) 22011: HD95-0802 64-year-old male who required opioid pain medication because of squamous cell cancer of the lung. At the time of study entry his lung cancer was believed to be stable. In addition to his primary malignancy, the patient's health problems included a long-standing seizure disorder managed with Dilantin and chronic anemia due to cryoglobulinemia. He entered the open-label titration period on 31-Oct-1997 with a prescribed dose of 24-mg HHER and rescue doses of 4-mg HHIR. On study day 3 (02-Nov-1997) his doses were increased to 48 mg and 8 mg, respectively. Doses were reduced to 36 mg and 6 mg for study days 4, 5, and 6 (03-Nov-1997, 04-Nov-1997,05-Nov-1997). On [ ] the patient complained of severe chest pain and shortness of breath and had chronic seizures from epilepsy. He was transferred from an outpatient hospice and hospitalized for progression of lung cancer. By the time he was examined in the hospital, he was unresponsive to voice or pain. He was discontinued from the study on [ ] due to progression of lung cancer and managed with supportive care including intravenous Dilaudid and intravenous Dilantin. He died on [ ] The managing physicians attributed his death to progression of lung cancer and judged it unrelated to the study medication. Without more information around the time of death, it is not possible to judge what part study medication may contributed to this patient's proximal cause of death.

20) 23003: HD95-0803 58-year-old male undergoing chemotherapy for metastatic pancreatic carcinoma. He entered the open-label titration period on 28-Nov-1996 at a prescribed dose of 12-mg HHER qd and rescue doses of 2-mg HHIR. Dosages were increased to maximum values of 36-mg HHER qd and 6-mg HHIR. On [ ] the patient developed oral candidiasis and esophagitis, commonly observed adverse effects of myelosuppressive chemotherapy, unrelated to the study drug. The mucositis worsened and by [ ] the patient was unable to swallow oral medications. Parenteral pain management was required and the patient was discontinued from the study on [ ] due to the esophagitis. On [ ] days after the last dose of study medication, the patient died of progressive malignancy. Considering the length of time from the last dose of study medication (approximately – days), it is very unlikely that the study medication contributed to the proximal cause of death.

21) 16003: HD95-0803 62-year-old male with multiple medical problems who required morphine for pain control of metastatic adenocarcinoma of presumed lung origin. He entered the open-label titration phase of HD95-0801 on 05-Mar-1997 and completed that study on 26-Mar-1997. He entered the continuation study (HD95-0803) on 27-Mar-1997 with prescribed doses of 48-mg HHER qd and prescribed rescue doses of 8-mg HHIR. On 29-Mar-1997, 31-Mar-1997, and 01-Apr-1997, the dosages were increased to 60 mg and 10 mg, respectively, because of inadequate pain control at the lower doses. Somnolence was noted at the higher doses. On [ ] the patient was evaluated by his oncologist for a left flank soft tissue abnormality. The oncologist noted weakness, a wide unsteady gait, severe mental confusion, and leukocytosis in addition to the new flank mass. Decreased breath sounds were noted [ ] The patient was hospitalized from [ ], during which time he was on leave from the study and took no study medications. While hospitalized, the patient experienced a deep vein thrombosis, malignant pleural effusion, malignant ascites, progressive liver metastases, an anterior mediastinal mass, and a stage I decubitus to his coccyx. He was discharged to hospice care at home and taken off the study on [ ] He died of progressive disease on [ ] Among the problems that led to hospitalization, the managing physician judged the mental status changes probably related to the study medication. The other problems at admission and the patient's ultimate death were judged unrelated to the study drug. Considering the length of time from the last dose of study medication (approximately [redacted] days), it is very unlikely that the study medication contributed to the proximal cause of death.

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22) 12007: HD95-0803 71-year-old male with lung cancer. He participated in HD95-0801 and received his last dose of study medication on 10-Mar-1997. He entered the continuation study (HD95-0803) on 11-Mar-1997 taking a prescribed dose of 72-mg HHER qd and rescue doses of 12-mg HHIR. He completed the 8-week study, taking his final study dose of HHER (72 mg) on 06-May-1997. The only serious adverse event during the core study period was disease progression. In the extension period the patient continued to take HHER through [ ] and took study rescue medication through [ ]'. During the extension HHER was 72 mg per day except when decreased twice (once for 2 days and once for 1 day) to 48 mg per day due to sedation. HHER doses were initially held due to difficulty swallowing on the last 2 days of the study and were never resumed. During and after the 8-week study, the patient became progressively debilitated. He died of disease progression on [ ] ays after his last dose of study drug and 16 days after ending the study extension. Considering the length of time from the last dose of hydromorphone (approximately [redacted] days; [redacted] days after end of study extension), it is very unlikely that the study medication contributed to the proximal cause of death.

23) 12008: HD95-0803 68-year-old female with metastatic breast cancer. She participated in HD95-0801 and took her last dose of study medication on 17-Mar-1997. She entered the continuation study (HD95-0803) on 18-Mar-1997 taking a prescribed dose of 48-HHER qd and rescue doses of 8-mg HHIR. She completed the 8-week study,

taking her final study dose of HHER (48 mg) on 13-May-1997. She entered the first study extension period on 14-May-1997 and continued to take 48-mg/day of HHER until [ ]. when she was admitted to the hospital for management of a pathologic humerus fracture. After a study leave of absence, she resumed HHER on [ ] She took her last dose of HHER and discontinued her participation in the study on [ ] due to disease progression. On [ ] she entered a hospice program where she died of progressive disease. Progressive disease was reported as an adverse event, on [ ] days after the last dose of HHER. Considering the length of time from the last dose of study medication (approximately ~ days), it is very unlikely that the study medication contributed to the proximal cause of death.

24) 16002: HD95-0803 44-year-old woman who required opioid pain medication because of metastatic breast cancer. She participated in HD95-0801 and entered the continuation study (HD95-0803) on 26-Mar-1997 taking 72-mg per day of HHER and occasional doses of 12-mg HHIR for breakthrough pain. On [ ] she was seen in her physician's office with a complaint of leg pain. An MRI demonstrated L4-L5 cord compression related to progressive disease, and the patient was hospitalized and treated with radiation therapy. She continued on the study during her hospitalization and completed the study on [ ] She entered the study extension on 23-May-1997. [ ] she was hospitalized for management of severe thrombocytopenia and hypertension. The events were recorded as intercurrent illnesses related to her cancer and unrelated to the study medication. During the hospitalization and after discharge, she took daily doses of HHER. She took her last dose of HHER on [ ] and died at home of complications of cancer on [ ] Although the patient's malignancy is the likely proximal cause of death, it is not possible to exclude study medication as a proximal contributory factor because the patient continued on medication until death.

25) 16012: HD95-0803 57 year-old female with metastatic lung cancer. She completed the double-blind periods of the HD95-0801 trial on 16-Jun-1997. She entered the HD95-0803 study on 17-Jun-1997 at a prescribed dose of 12-mg of HHER qd and increased this dose to 24 mg qd on 22-Sep-1997 through day 56 of the core study period and until 29-Sep-1997. No hospitalizations or serious adverse events were reported during the core study period. On [ ] the patient was admitted to the hospital for management of nausea, vomiting, and problems related to disease progression. While hospitalized, the patient experienced epidermitis bacteremia staphylococcus, a urinary tract infection, and decreased pulmonary capacity The patient was placed on leave from the study at the time of hospital admission and was discontinued from the study due to disease progression without ever resuming the study medication. She was discharged from the hospital on [ ] and died [ ] days after her last dose of HHER. Considering the length of time from the last dose of study medication (approximately ~ days), it is very unlikely that the study medication contributed to the proximal cause of death.

26) 16024: HD95-0803 73-year-old female with metastatic breast cancer. She participated in the HD95-0801 trial and took her last dose of HD95-0801 medication on

15-Sep-1997. She entered the HD95-0803 study on the following day at a prescribed dose of 24-mg of HHER qd. She completed the 56-day study on [ ] at a dose of HHER 48 mg qd. She continued to take HHER, 48 mg qd, through 24 days of an extension period, taking her final dose on [ ] the day of her death. She was hospitalized only once during the study and extension period. She was admitted to the hospital on [ ] because of dizziness, a fall, and increased chest pain. While hospitalized, she was managed for increased left shoulder pain and a humerus fracture. The patient died of progressive disease on [ ] reported as an adverse event unrelated to the study drug. The dizziness and fall were judged possibly related to the study medication. [ ]

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27) 16037: HD95-0803 63-year-old male with metastatic prostate cancer. He completed the double-blind periods of the HD95-0801 trial on 02-Mar-1998. He entered the HD95-0803 study at a prescribed dose of 60-mg of HHER qd with rescue doses of HHIR 10 mg. His daily dose of HHER was increased to 84 mg qd but was restored to 72 mg on the final day of the core study period. The patient continued to take HHER through 4 extension periods with doses as high as 240 mg. He took his last dose of HHER on [ ] the day of his death. He was hospitalized 5 times during the study: first for severe abdominal pain, possible cord compression, dehydration, bloody stools, bloody urine, hemorrhoids, and radiation-induced proctitis/enteritis; second for orthostatic hypotension, constipation, and a fecal impaction; third for suspected spinal cord compression, difficulty urinating, and anemia; fourth for management of rectal bleeding and anemia; fifth for antibiotic therapy for a foot infection. He died on [ ] progressive malignancy. Although the patient's malignancy is the likely proximal cause of death, it is not possible to exclude study medication as a proximal contributory factor because the patient continued on medication until death.

28) 16042: HD95-0803 46-year-old male with metastatic malignant melanoma. He began the open-label titration period of the study on 2-Mar-1998, with a prescribed dose of 24-mg HHER qd and rescue doses of 4-mg HHIR. His dosages were gradually increased to 60 mg and 12 mg, respectively. On 13-Apr-1998 he entered study HD95-0803 on a prescribed dose of 60-mg of HHER qd. Later it was increased to 72 mg qd on 18-Apr-1998 and continued on this dose until 27-Apr-1998, after which he was discontinued because of inability to swallow oral medications. He was hospitalized twice for chemotherapy. He died at home on [ ] from complications due to his primary melanoma. Although the patient's malignancy is the likely proximal cause of death, it is not possible to exclude study medication as a possible proximal contributory factor because it appears that the patient continued on medication until — hours before death.

29) 16044: HD95-0803 75-year-old white male with a past medical history significant for metastatic prostate cancer, borderline MUGA (ejection fraction 40%), vomiting, constipation, diverticulosis, thoracic and lumbar scoliosis, weight loss, anxiety, depression, diminished urinary flow rate, and somnolence. He was enrolled in study

HD95-0803 on 04-May-1998. Disease progression, including difficulty swallowing, was the patient's ongoing condition at the time of study participation. The patient received the first dose of HHER (36 mg) on 05-May-1998. The patient was receiving HHER (60 mg) at the time of discontinuation from the trial on [redacted] and was referred to hospice due to deteriorating condition. He died post-study on [redacted] due to an unknown cause. Considering the length of time from the last dose of study medication (approximately [redacted] weeks), it is very unlikely that the study medication contributed to the proximal cause of death.

30) 16045: HD95-0803 The patient was a 72-year-old male with metastatic cancer of both lung and bladder. He completed the double-blind periods of the HD95-0801 trial on 08-May-1998. He entered the HD95-0803 study at a prescribed dose of 60-mg of HHER qd and continued on this dose through [redacted] when he was admitted to the hospital because of increasing pain, shortness of breath, and hemoptysis. After admission he never resumed taking the study medication. He died suddenly of a myocardial infarction or stroke on [redacted]. Considering the length of time from the last dose of study medication (approximately [redacted] days), it is very unlikely that the study medication contributed to the proximal cause of death.

31) 22012: HD95-0803 49-year-old male with adenocarcinoma metastatic to the liver from an unknown primary site. He participated in HD95-0802 and took his last dose of study medication on 07-Apr-1998. He entered the continuation study (HD95-0803) on 08-Apr-1998 taking a prescribed dose of 48-mg HHER qd and rescue doses of 8 mg HHIR. On 16-Apr-1998, his dose of HHER was increased to 64-mg qd. He completed the study on 03-Jun-1998. The patient was hospitalized twice during the study: once for transfusion due to anemia, and another for management of abdominal pain, jaundice, neutropenia, fever,and dehydration attributed to progressive liver metastases. By [redacted] he could no longer swallow medications and was withdrawn from the study. He died of progressive malignancy on [redacted] days after his last dose of HHER. Although the patient's malignancy is the likely proximal cause of death, it is not possible to exclude study medication as a proximal contributory factor because the patient continued on medication until approximately [redacted] hours before death.

32) 23005: HD95-0803 68-year-old male with visceral pain due to pancreatic carcinoma. He entered the open-label portion of the trial on 01-Feb-1997 at a dose of 36-mg of HHER qd, with rescue doses of 6-mg HHIR. During the open-label phase, he was hospitalized for disorientation, unsteady gait, and altered affect, which subsequently resolved and he resumed study participation. His dose was increased to 48 mg qd and completed the study on 18-Feb-1997. The patient entered the continuation study (HD95-0803) on a prescribed dose of 48-mg HHER qd and rescue doses of 8 mg HHIR. On [redacted] he was hospitalized for chemotherapy and experienced deep vein thrombosis. He completed the 56-day study and then entered the study extension period taking daily doses of HHER between 56 and 80 mg/d. On [redacted] he was hospitalized for fever, shortness of breath, pleuritic chest pains, dehydration, coagulopathy, congestive heart failure with pulmonary edema, and peripheral venous collapse. The subject died on [redacted] as a result of the bilateral pneumonia . Although the patient's pneumonia is the

likely proximal cause of death, it is not possible to completely exclude this extended-release study medication as a proximal contributory factor because the patient continued on medication until — hours of death.

33) 25003: HD95-0803 60-year-old male with a known history of coronary artery disease who required opioid pain medications because of lung cancer. He participated in HD95-0802 and the entered the continuation study (HD95-0803) taking a prescribed dose of 32-mg HHER qd and rescue doses of 6-mg HHIR. His dose of HHER was gradually increased to 64 mg qd by13-May-1998. He continued taking HHER on a study extension until his death on [ ] Medications and drug dose diary were not returned to the study coordinator after the patient died, and so the CRF does not contain information about the patient's use of HHER after the formal conclusion of the 8-week study period [ ]. The patient died at home, and the managing physicians attributed his death to disease progression or to cardiac arrest. Without more information about events around the time of death and confirmation that the patient was actually was swallowing the study medication, it is not possible to judge if study medication may have contributed to this patient's proximal cause of death.

34) 29014: HD95-0803 63-year-old white female with a past medical history significant for metastatic colorectal cancer, rectal bleeding, nausea, vomiting, bowel obstruction, constipation, diarrhea, gastritis, palpitations, arrhythmia, rheumatic heart disease, atrial fibrillation, congestive heart failure, hypertension, cardiomegaly, uterine fibroids, weight loss, anemia, chronic coagulopathy, left leg neuropathy, depression, anxiety, hot flashes, sarcoidosis, edema of the legs, fatigue, fibrosis, dizziness, progressive TIT B, alopecia, hearing loss, sinus problem, chronic obstructive pulmonary disease, pneumonia, and bronchitis. She was enrolled in study HD95-0803 on 03-Mar-1998. Pneumonia and progressive colon cancer disease were the patient's ongoing conditions at the time of study participation. The patient received the first dose of HHER (48 mg) on 04-Mar-1998. The patient received the last dose of HHER (48 mg) on [ ] discontinued the trial on [ ] and was admitted to hospice due to deteriorating condition. Death occurred poststudy on [ ] due to an unknown cause. Considering the length of time from the last dose of study medication (approximately —veeks), it is very unlikely that this extended-release study medication contributed to the proximal cause of death in this patient.

35) 33009: HD95-0803 66-year-old female with metastatic lung cancer who completed the double-blind periods of the HD95-0801 trial on 17-Apr-1998. She entered the HD95-0803 study on the prescribed dose of 12-mg of HHER qd and continued on this dose through day 56 of the core study period and until 05-Aug-1998 when her dose was increased to 24 mg qd. She took HHER 24 mg qd on 05-Aug-1998 and 06-Aug-1998 and then withdrew from the study because the HHER was no longer controlling the pain of her progressive cancer. During the study she took from 0 to 4 doses (2-4 mg each) of HHIR daily for breakthrough pain. No serious adverse events or hospitalizations occurred during the core study period. On [ ], the patient was evaluated in an emergency room for aphasia, tachycardia, and facial nerve palsy. A CT scan revealed brain metastases, diagnosed as metastatic disease with associated cerebral edema (disease

progression). She was admitted to the hospital and the intracranial cancer was treated with irradiation. The patient ultimately died of disease progression on [redacted] approximately [redacted] weeks after her last dose of study medication. Considering the length of time from the last dose of study medication (approximately [redacted] weeks), it is very unlikely that this extended-release study medication contributed to the proximal cause of death.

36) 33010: HD95-0803 58-year-old male with multiple myeloma and a history of testicular cancer who completed the double-blind periods of the HD95-0801 trial on 20-Apr-1998. He entered the HD95-0803 study on 21-Apr-1998 at a prescribed dose of 72-mg of HHER qd and continued on this dose until hospital admission [redacted] when he was discontinued from the study. During the study he took from 0 to 4 daily doses (8-16 mg each) of HHIR for breakthrough pain. On [redacted] he was admitted to the hospital for management of respiratory depression/narcotic intoxication and associated paranoia, psychosis, hallucinations, dysphagia, and myoclonus. During the hospitalization urinary tract infection and progressive renal failure related to his primary diagnosis were found. The study drug was discontinued primarily due to psychosis at the time of the third admission. The patient's disease progressed during the hospitalization causing renal failure and death on [redacted]. He had 2 prior hospitalizations: once for scheduled chemotherapy and another time for infection, weight loss, dehydration and malnutrition, and hyponatremia. Considering the length of time from the last dose of study medication (approximately [redacted] days), it is very unlikely that this extended-release study medication contributed to the proximal cause of death in this patient but was very likely the cause of hospital admission.

37) 40005: HD95-0803 83-year-old male with both bladder cancer and non–small cell lung cancer. He participated in HD95-0802 and took his last dose of study medication on [redacted] He entered the continuation study (HD95-0803) on 31-Mar-1998, taking a prescribed dose of 24-mg HHER qd and rescue doses of 8-mg HHIR; by 30-Apr-1998 he had increased his dose of HHER to 48 mg. He completed the 8-week study period on 26-May-1998 and entered an extension period on the following day. During the extension period he increased his dose of HHER to 96 mg per day. He continued to take HHER until [redacted] On [redacted] he died at home. No hospitalizations occurred during the [redacted] week study or the extension period, and no serious adverse events were reported other than disease progression. The managing physician attributed the patient's death to progressive cancer and judged it unrelated to the study medication. While it possible that this patient's demise was directly related to progression of his underlying disease, it is not possible to determine whether the increased dose of study medication played a direct or indirect role in the cause of death.

38) 41008: HD95-0803 45-year-old female with metastatic cervical carcinoma. She participated in HD95-0802 and took her last dose of study medication on 02-Feb-1998. She entered the continuation study (HD95-0803) on 03-Feb-1998 taking a prescribed dose of 72-mg HHER qd and rescue doses of 12-mg HHIR. She completed day 56 of the core study on 30-Mar-1998 and entered an extension on 31-Mar-1998. During the course of the 8-week core study, her daily dose of HHER was increased to 176 mg. No hospitalizations or serious adverse events occurred during the 8-week study. On [redacted]

] the patient was admitted to the hospital with signs of small bowel obstruction (nausea, vomiting, abdominal pain). The obstruction was attributed to progression of her primary disease. The patient took her last dose of study medication on the day of hospitalization; she died on [ ] days after the end of the study. Considering the length of time from the last dose of study medication (approximately month), it is very unlikely that this extended-release study medication contributed to the proximal cause of death in this patient.

39) 44005: HD95-0803 73-year-old male with metastatic colon cancer who completed the double-blind periods of the HD95-0802 trial on 02-Jan-1998. He entered the HD95-0803 study on the following morning taking 48 mg qd of HHER. His dose of HHER was reduced to 24 mg qd on 09-Jan-1998, and he continued this daily regimen until 07-Feb-1998 when his dose was increased again to 48 mg qd. He took his last dose of HHER on [ ]. On [ ] he developed inability to swallow and was discontinued from the study. He died of this progressive malignancy on [ ] While it possible that this patient's demise was directly related to progression of his underlying disease, it is not possible to determine whether the increased dose of study medication played a direct or indirect role in the cause of death.

40) 11: HD99-0201 41-year-old black female who had a history of pneumonia, constipation, pyelonephritis, hyponatremia, iron deficiency anemia, left ovarian cyst, stage 2B squamous cell cervical carcinoma, vesicovaginal-rectal fistula, and insomnia. The subject received her first dose of HHER on 28-Jul-1999, at 0900 and her last dose on [ ] at an unrecorded time. Study medication was discontinued because the subject was unable to swallow. The subject suffered disease progression of her squamous cell carcinoma. She died on [ ] Although the patient's malignancy is the likely proximal cause of death, it is not possible to completely exclude this extended-release study medication as an indirect or direct proximal contributory factor to this patient's demise because the patient continued on medication until — hours of death.

41) 16011: HD95-0803 37-year-old male who required narcotic pain medications because of small-cell lung cancer with metastases to the bone and brain. He entered the open-label titration period on 17-May-1997 at a prescribed dose of 36-mg HHER qd and rescue doses of 6-mg HHIR. On [ ] the patient had gastrointestinal and active oral bleeding related to severe thrombocytopenia resulting from recent chemotherapy. He was hospitalized from [ ] for administration of platelets. Pain control was satisfactory at the initial dosages and the patient entered the double-blind period on 24-May-1997; he took the last dose of study medication on 02-June-1997 and completed the study on 03-Jun-1997. He entered study HD95-0803 on 03-Jun-1997 at a prescribed dose of 36-mg of HHER qd, increased his daily dose to 48 mg on 01-Jul-1997, and to 60 mg on 15-Jul-1997. He completed 58 days of the core study on 30-Jul-1997 and continued taking HHER at this dose until [ ]. During the core study and extension period the patient took occasional doses of 6-10 mg HHIR for breakthrough pain. The patient was admitted to the hospital on [ ] because of a stumbling gait, falling, and confusion, which were eventually attributed to cancer metastatic to the brain. The patient was discharged home on [ ] and died at home on [ ]

— , 3 days after completing extension 1 of the study. Although the patient's malignancy is the likely proximal cause of death, it is not possible to completely exclude this extended-release study medication as an indirect or direct proximal contributory factor to this patient's demise because the patient continued on medication until approximately — hours of death.

42) 29010: HD95-0803 67-year-old female with metastatic lung cancer. At the time of study entry, she also had a history of chronic obstructive lung disease and recurrent episodes of bronchitis. She entered the open-label titration period of study on 02-Jan-1998 with a prescribed dose of 24-mg HHER qd and used first 2-mg HHIR and then 4-mg HHIR for breakthrough pain. Her doses were increased on 04-Jan-1998 to 36 mg and 6 mg, respectively, and she completed the open-label period on 08-Jan-1998 using those doses. She completed double-blind period 1 from 09-Jan-1998 through 12-Jan-1998 and double-blind period 2 between 13-Jan-1998 and 19-Jan-1998. She took her last dose of study medication on 19-Jan-1998 and entered the continuation study (HD95-0803) on the following day, taking a prescribed dose of 36-mg HHER qd and rescue doses of 6-mg HHIR. She was hospitalized from [ ] (during study HD95-0802) to [ ] (during study HD95-0803) because of complications of pneumonia 1 reported as a concomitant illness at the time of study entry. On [ ] she was hospitalized again because of difficulty breathing and other manifestations of progressive malignancy. While hospitalized, the patient experienced atrial fibrillation, electrolyte imbalance, Clostridium difficile colitis, and a bronchial obstruction that resolved on [ ] The patient took the last dose of study medication on [ ] and died of respiratory failure due to progressive malignancy on [ ] days after the last dose of study medication. Considering the length of time from the last dose of study medication (approximately days), it is very unlikely that this extended-release study medication contributed to the proximal cause of death in this patient.

43) 41009: HD95-0803 33-year-old female undergoing radiation and chemotherapy for a recurrent cervical carcinoma. She participated in HD95-0802 and took her last dose of study medication on 22-Mar-1998. She entered the continuation study (HD95- 0803) on 23-Mar-1998, taking a prescribed dose of 72-mg HHER qd. During the study she was treated for anemia. She continued to take HHER until [ ] when she was hospitalized for management of dehydration ultimately attributed to a rectal/vaginal fistula. Her last dose of study medication was on 24-Apr-1998 and she discontinued from the trial on [ ]. She died on [ ] weeks after her last dose of study medication. The managing physician attributed the patient's hospitalization and death to progressive cancer and judged them unrelated to the study medication. Considering the length of time from the last dose of study medication (approximately — weeks), it is very unlikely that this extended-release study medication contributed to the proximal cause of death in this patient.

44) 36 HD99-0201: 47-year-old black female who had a history of pulmonary embolism with left pleural effusion and shortness of breath; right lower extremity deep-vein thrombosis; peritoneal carcinomatosis with psoas muscle, liver, spleen, and retroperitoneal metastases; constipation; gastric upset; microcytic anemia; and

thrombocytosis. The subject received her first dose of study medication on 05-Aug-1999 at 0800 and her last dose on 09-Aug-1999 at 2000. On [ ], during a routine office visit, it was determined that the subject had a pleural effusion and a thoracentesis was scheduled for the following morning. At [ ] the subject complained of shortness of breath and extreme anxiety. She was hospitalized that day, and a thoracentesis was performed with resolution of the shortness of breath. Study medication was discontinued by the investigator, who determined that the subject's disease was rapidly progressing. Morphine sulfate was subsequently used for pain management. The event resolved by [ ] The shortness of breath was rated as serious, moderate in severity, and unrelated to study medication. A telephone contact on [ ] revealed that subject expired on [ ] secondary to ovarian cancer. This patient's death is not likely to have been related to study drug.

Deaths from Ongoing Studies:

45) 30: HD95-0801 51-year-old female who required daily oral opioid analgesia to control visceral pain caused by her metastatic cervical cancer. She met all the study inclusion and exclusion criteria and began the open-label titration period on 23-Nov-1999, taking doses of 48-mg of HHER each morning and rescue doses of 8-mg HHIR from 2 to 5 times daily. On 29-Nov-1999 her doses of HHER and HHIR were increased to 60 mg and 10 mg, respectively. She achieved satisfactory pain control at these doses and completed the open-label phase of the study on [ ]. She entered double-blind period 1 on 09-Dec-1999 and took her final doses of study medication on [ ]. After her second dose of study drug on [ ] the patient took an afternoon nap and died in her sleep. While it possible that this patient's demise was directly related to progression of his underlying disease, it is not possible to ascertain whether the increased dose of study medication played a direct or even indirect role in her death.

Comments:

The deaths in the patients exposed to HHER or HHIR all occurred in the setting of terminal malignancy. While many of these events may have been directly or indirectly related to study drug exposure, these AEs are expected with high dose opiate therapy.

Adverse Events Leading to Study Discontinuation:

The disposition of subjects in phase 3 trials is presented in Table 5. The sponsor notes that patients were only exposed to HHIR for a period of 3 to 7 days according to the protocols with such an arm. In comparison, exposure to HHER could last much longer due to the open label extension exposure in HD05-0803. The exposure to MS Contin was limited to one study, HD99-0201. Death as a reason for study discontinuation was not routinely coded on the CRFs, and will not be explored further here.

There were no discontinuations due to adverse events reported for the Phase 1 studies. There were 3 discontinuations due to adverse events in Phase 2 studies, one each in placebo, HHER, and HHIR groups.

Table 6. Subject Disposition, Phase 3 Trials

	Phase 3 Studies in Original 1998 NDA[a]		Updated Ph 3 Studies Original 1998 NDA[a]	Phase 3 Studies in Current NDA Amendment[b]		
	HHIR	HHER	HHER	MS Contin	HHER	Placebo
Category	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Exposed	209 (100.0)	343 (100.0)	343 (100)	38 (100)	568 (100.0)	191 (100.0)
Discontinued	12 (5.7)	162 (47.2)	174 (50.7)	11 (29.0)	279 (49.1)	37 (19.4)
Reason for premature discontinuation[c]						
Adverse events[d]	8 (3.8)	72 (21.0)	102 (29.7)	9 (23.7)	158 (27.8)	12 (6.3)
Ineff. treatment[e]	2 (1.0)	44 (12.8)	46 (13.4)	0 (0)	66 (11.6)	23 (12.0)
Death[f]	1 (0.5)	6 (1.7)	7 (2.0)	0 (0)	14 (2.5)	0 (0)
Lost to follow-up	0 (0)	2 (0.6)	2 (0.6)	0 (0)	3 (0.5)	1 (0.5)
Protocol violation	1 (0.5)	15 (4.4)	16 (4.7)	2 (5.3)	20 (3.5)	0 (0)
Other	0 (0)	23 (6.7)	23 (6.7)	0 (0)	46 (8.1)	1 (0.5)

a Includes data from studies HD95-0801, HD95-0802, and 77 subjects from HD95-0803. All discontinuations in the Updated Original NDA are attributed to HHER.
b Includes data from studies HD95-0801, HD95-0802, HD95-0803, HD99-0201, HMP3005, and MP3006.
c Includes 1° and 2° reasons for d/c; therefore, the sum of the percentages across all reasons may not add to the total percentage of discontinuations.
d Illness not due to drug was a category used in studies HD95-0801, HD95-0802, and HD95-0803. For the purpose of comparison with the current submission, illness not due to drug has been added to AEs to reflect the total incidence of AEs.
e In study HMP3006: 4 subjects identified as discontinued due to Ineffective Treatment and to AE are included as discontinued prematurely due to AEs.
f Deaths as reported on discontinuation page of CRF. An additional 33 deaths were recorded, many occurring after subject d/c of the study due to an adverse event. All 47 deaths are listed and discussed in Section 9.13.
Source: Table 9.9.1, P. 24 Summary of Safety, 3-12-02

The adverse events leading to study discontinuation are presented in Table 6 for those events recorded in at least one percent of patients. Nausea and somnolence were the two most common events occurring in 4.9% and 3.7% of patients receiving HHER, respectively. "Aggravation reaction" was also relatively common, reported by 3.7% of patients discontinuing early. These were followed by vomiting (2.1%), confusion (1.6%), and constipation (1.4%). Except for aggravation reaction, the events noted in Table 7 are known adverse events for opioids, and that these adverse events resulted in study discontinuation is not unexpected. This is supported by comparable findings in the MS Contin group.

Table 7.

Incidence of Adverse Events Leading to Discontinuation in ≥1% of Subjects Receiving HHER in Phase 3 Studies in the Updated Original 1998 NDA and the Current NDA Amendment (Safety Population)

	Updated Phase 3 Studies Original NDA[a]	Phase 3 Studies Current NDA Amendment[b]		
	HHER (N = 343)	MS Contin (N = 38)	HHER (N = 568)	Placebo (N = 191)
	n (%)	n (%)	n (%)	n (%)
Any adverse event	102 (29.7)	9 (23.7)	157[c] (27.6)	12 (6.3)
Body system/adverse event				
Body as a whole	**31 (9.0)**	**1 (2.6)**	**46 (8.1)**	**4 (2.1)**
Aggravation reaction	12 (3.5)	0 (0)	21 (3.7)	0 (0)
Asthenia	4 (1.2)	0 (0)	5 (0.9)	0 (0)
Digestive	**35 (10.2)**	**3 (7.9)**	**58 (10.2)**	**5 (2.6)**
Nausea	16 (4.7)	2 (5.3)	28 (4.9)	4 (2.1)
Vomiting	6 (1.8)	0 (0)	12 (2.1)	2 (1.1)
Constipation	5 (1.5)	0 (0)	8 (1.4)	2 (1.1)
Dysphagia	2 (0.6)	0 (0)	6 (1.1)	0 (0)
Metabolic/nutritional	**6 (1.8)**	**1 (2.6)**	**7 (1.2)**	**1 (0.5)**
Dehydration	4 (1.2)	1 (2.6)	4 (0.7)	0 (0)
Nervous	**38 (11.1)**	**5 (13.2)**	**51 (9.0)**	**6 (3.1)**
Somnolence	15 (4.4)	2 (5.3)	21 (3.7)	0 (0)
Confusion	8 (2.3)	3 (7.9)	9 (1.6)	0 (0)
Dizziness	6 (1.8)	0 (0)	7 (1.2)	1 (0.5)
Anxiety	4 (1.2)	0 (0)	6 (1.1)	0 (0)
Nervousness	5 (1.5)	0 (0)	6 (1.1)	2 (1.1)
Thinking abnormal	4 (1.2)	0 (0)	4 (0.7)	0 (0)
Hallucinations	4 (1.2)	0 (0)	5 (0.9)	0 (0)

a Updated adverse events from HD95-0801, HD95-0802, and 77 subjects from HD95-0803.
b Studies HD95-0801, HD95-0802, HD95-0803, HD99-0201, HMP3005, and HMP3006.
c Does not include subject 41006 (HD95-0803). As recorded on the CRF, this subject discontinued early from the study due to an AE; however, no AE collected on the AE page of the CRF was designated as leading to study d/c.
Source: Table 9.15.1, P. 52, Summary of Safety, 3-12-02

The narratives for early discontinuation due to adverse events were reviewed in Appendices C.3.1 - C.3.4, C.1.1-C.1.4, and C.2.1-C.2.4. All but two narratives were found and reviewed. Patient 15006 from study site 1488 in Study HD950801 had no narrative, but the CRF was reviewed. This subject withdrew due to nausea during the titration period. Patient 41006 from study site 1789 in study HD950803 withdrew due to an adverse event, but no event was specified on the CRF. Below are samples excerpted from the narratives demonstrating the type of events that led to study discontinuation.

Patient 33007 (HD95-0801, Site 1804): The patient was a 59-year-old female with metastatic lung cancer who was wheelchair bound at the time of study entry. She entered the open-label titration period on 04-Mar-1998 at a prescribed dose of 12-mg HHER qd

with rescue doses of 2-mg HHIR. During 13 days of study participation the doses were gradually increased to 36 mg and 6 mg, respectively. On [redacted] the patient was attempting to stand and toppled over. In the emergency room she was found to have a pathologic hip fracture. She was admitted to the hospital and discontinued from the study. In the assessment of the examining physician, the fall was not due to sedation and was unrelated to the study drug. The adverse event was reported as serious because it resulted in hospitalization. While a fall on opioids may be related under some circumstances, it appears to have been unrelated in this instance.

Patient 16005 (HD95-0801, Site 1635): The patient was a 69-year-old white male with past surgical and medical histories significant for needle biopsy of the prostate and orchiectomy ([redacted]) TURP for obstructive symptoms ([redacted] and for metastatic prostate cancer ([redacted] metastases to the distal humerus, ischial portion of the pubic ramus, and the pubic symphysis, hypertension, hematuria, occasional urinary urgency, diabetes, and anemia. The patient was enrolled into study HD95-0801 on [redacted] with bone pain. The patient received the first dose of HHER (12 mg) on 2-Apr-1997. Four rescue medication doses (HHIR 2 mg x 4 doses) were also administered on 1-Apr-1997. On [redacted] during the Titration Period, the patient was hospitalized for nausea, vomiting, dehydration and constipation. On [redacted] the patient was discontinued from the trial. It is possible that the study drug was responsible for, or at least contributed to these adverse events. These events are considered known and expected adverse events for hydromorphone.

Patient 16031 (HD95-0801, Site 1635): The patient was a 77-year-old female who required opioid analgesic pain control because of metastatic cancer of the uterus. She entered the open-label period of the study on 26-Nov-1997 with a prescribed dose of 12-mg HHER qd and rescue doses of 2-mg HHIR. Because of intolerable bilateral arm pain, her dosages were increased to 24 mg and 4 mg (27-Nov-1997) and then 36 mg and 6 mg (29-Nov-1997). On [redacted] and [redacted], she was evaluated in the emergency room for cervical spine metastases, worsening neck pain, confusion, sedation, and decreased urine output. Due to confusion and sedation the patient had not been eating and drinking which resulted in dehydration. She was admitted to the hospital and concomitantly found to have progressive disease involving the cervical spine (accounting for the arm pain) and a urinary tract infection. Because of the sedation and confusion, her dosages of study medication were reduced to 24 mg and 4 mg (03-Dec-1997) and then 12 mg and 2 mg (09-Dec-1997). Sedation and confusion persisted and the patient was taken off all long-acting narcotics on 11-Dec-1997. Within a few days her confusion and sedation resolved. The investigator attributed the mental status changes to the study medication. This adverse event is not unexpected and is likely due to study medication in this instance.

Patient 29022 (HD95-0802, Site 1265): The patient was a 71-year-old male who required opioid analgesics for metastatic adenocarcinoma with an unknown primary site. At the time of study entry his medical history included Crohn's disease and abdominal metastases with ascites. He entered the open-label titration period on 30-Apr-1998 with a prescribed dose of 12-mg HHER and rescue doses of 2-mg HHIR. He had adequate pain

control with these doses through 07-May-1998, his last day of study participation. On [ ] he had episodes of vomiting; on [ ] he was admitted to the hospital for management of a small bowel obstruction. The bowel obstruction was judged an intercurrent illness unrelated to the study medication. The study was discontinued at the time of hospital admission on [ ] and never resumed. While vomiting is an expected adverse event associated with hydromorphone, in this instance it appears to have been related to underlying disease.

Patient 25001 (HD95-0803, Site 1752): The patient was a 41-year-old male receiving chemotherapy for metastatic lung cancer. His medical history prior to study entry was remarkable for childhood Wilms' tumor and a myocardial infarction at age 39. He entered the open-label titration period on 19-Aug-1997 at prescribed doses of 24-mg HHER qd and rescue doses of 4-mg HHIR, and satisfactory pain control. He received blinded HHER with HHIR rescues from 29-Aug-1997 through 31-Aug-1997. On [ ] the patient was seen in the emergency room with complaints of chest pain. He was discontinued from the investigational study on [ ] and admitted to the hospital for management of a myocardial infarction. Myocardial infarction would be considered an unexpected adverse event, but in this instance, with a known history of coronary artery disease, is unlikely related to study drug.

In summary, the spectrum of the adverse events leading to study discontinuation was for the most part within the known and expected adverse events for hydromorphone. Those events that would not be considered expected for hydromorphone were attributable to other causes.

Serious Adverse Events:

Non-fatal SAEs were recorded and combined as part of an updated Integrated Summary of Safety (ISS) for the current submission. Safety data was compiled from several different studies presented by several categories. SAEs were recorded from:

1) Phase 3 studies in the Original 1998 NDA and the Current NDA Amendment (incidence).
2) Phase 3 placebo-controlled studies in the Current NDA Amendment (incidence and rate).
3) Phase 3 studies in the Current NDA Amendment by subgroup: malignant vs. nonmalignant pain (incidence and rate).
4) All clinical studies (Phases 1, 2, and 3).
5) SAEs – Ongoing Studies.

No serious adverse events (SAEs) occurred in the Phase 1 studies. The following SAE Safety Review will examine the Sponsor's Safety Data for SAEs as outlined in the above categories.

Incidence of SAEs – Phase III Studies (Original 1998 NDA and Current NDA Amendment):

The Safety Analysis of Phase 3 Study Findings from the Original 1998 NDA submission was re-evaluated. The result is that there is an increase in the incident of SAEs due mostly to inclusion of events from Intercurrent Illness CRFs, comments on the Discontinuation CRF, or other CRF comments not included in the original database. In addition, the updated analysis of the SAEs now includes events originally attributed to HHIR in the 1998 NDA.

The Sponsor summarized the incidence of SAEs in ≥ 1% of HHER subjects in Table 9.14.1, which is reproduced here. Examination of the table illustrates the change in incidence noted for HHER subjects from the original NDA Phase III trials, when more conservative criteria are used. The updated analysis results in 82/343 (23.9%) HHER exposed subjects having SAEs compared to 40/343 (11.7%) reported previously. Note that the results appear to be crude incidence rates, and are not adjusted for person-time exposed. The HHER subjects appear to have roughly similar crude SAE incidences of 23.9% (1998 NDA) and 22.9% (current NDA). This contrasts with lower "any SAE" incidence values for MS Contin™ (6/38 or 15.8%), HHIR (3/209 or 1.4%), and Placebo (6/191 or 3.1%).

Table 8.

TABLE 9.14.1.

Incidence of Serious Adverse Events ≥1% of Subjects Receiving HHER in the Original 1998 NDA and the Current NDA Amendment: Safety Population

	Phase 3 Studies Original 1998 NDA[a]		Updated Phase 3 Studies Original 1998 NDA[b]	Phase 3 Studies Current NDA Amendment[c]		
	HHIR (N = 209)	HHER (N = 343)	HHER (N = 343)	MS Contin (N = 38)	HHER (N = 568)	Placebo (N = 191)
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Any serious adverse event	3 (1.4)	40 (11.7)	82 (23.9)	6 (15.8)	130 (22.9)	6 (3.1)
Body system/adverse event (COSTART term)						
Body as a whole	2 (1.0)	16 (4.7)	37 (10.8)	1 (2.6)	64 (11.3)	0 (0)
Aggravation reaction	0 (0)	0 (0)	7 (2.0)	0 (0)	10 (1.8)	0 (0)
Accidental injury	0 (0)	3 (0.9)	5 (1.5)	0 (0)	9 (1.6)	0 (0)
Asthenia	0 (0)	4 (1.2)	7 (2.0)	1 (2.6)	9 (1.6)	0 (0)
Fever	0 (0)	4 (1.2)	6 (1.8)	0 (0)	9 (1.6)	0 (0)
Abdominal pain	1 (0.5)	3 (0.9)	5 (1.5)	0 (0)	8 (1.4)	0 (0)
Carcinoma	0 (0)	1 (0.3)	2 (0.6)	0 (0)	6 (1.1)	0 (0)
Digestive	0 (0)	11 (3.2)	18 (5.3)	0 (0)	30 (5.3)	0 (0)
Nausea	0 (0)	4 (1.2)	5 (1.5)	0 (0)	8 (1.4)	0 (0)
Nausea/Vomiting	0 (0)	3 (0.9)	4 (1.2)	0 (0)	4 (0.7)	0 (0)
Hematic/Lymphatic	0 (0)	5 (1.5)	12 (3.5)	0 (0)	19 (3.4)	0 (0)
Leukopenia	0 (0)	1 (0.3)	4 (1.2)	0 (0)	8 (1.4)	0 (0)
Anemia	0 (0)	2 (0.6)	6 (1.8)	0 (0)	7 (1.2)	0 (0)
Metabolic and nutritional	0 (0)	10 (2.9)	15 (4.4)	0 (0)	21 (3.7)	0 (0)
Dehydration	0 (0)	7 (2.0)	10 (2.9)	0 (0)	15 (2.6)	0 (0)
Nervous	0 (0)	16 (4.7)	18 (5.3)	3 (7.9)	30 (5.3)	3 (1.6)
Confusion	0 (0)	5 (1.5)	5 (1.5)	1 (2.6)	8 (1.4)	0 (0)
Somnolence	0 (0)	6 (1.7)	5 (1.5)	2 (5.3)	6 (1.1)	0 (0)
Respiratory	1 (0.5)	7 (2.0)	18 (5.3)	3 (7.9)	33 (5.8)	0 (0)
Pneumonia	0 (0)	0 (0)	7 (2.0)	0 (0)	12 (2.1)	0 (0)
Carcinoma of lung	1 (0.5)	0 (0)	4 (1.2)	0 (0)	9 (1.6)	0 (0)
Dyspnea	0 (0)	1 (0.3)	2 (0.6)	0 (0)	7 (1.2)	0 (0)

[a]Studies HD95-0801, HD95-0802, and 77 subjects from HD95-0803.
[b]Updated serious adverse events from studies HD95-0801, HD95-0802, and 77 subjects from HD95-0803.
[c]Studies HD95-0801, HD95-0802, HD95-0803, HD99-0201, HMP3005, and HMP3006.
Cross-references: Original NDA, ISS Table 8.11.18.1.5.4, Current NDA Amendment, Tables A.13.2 and A.29.

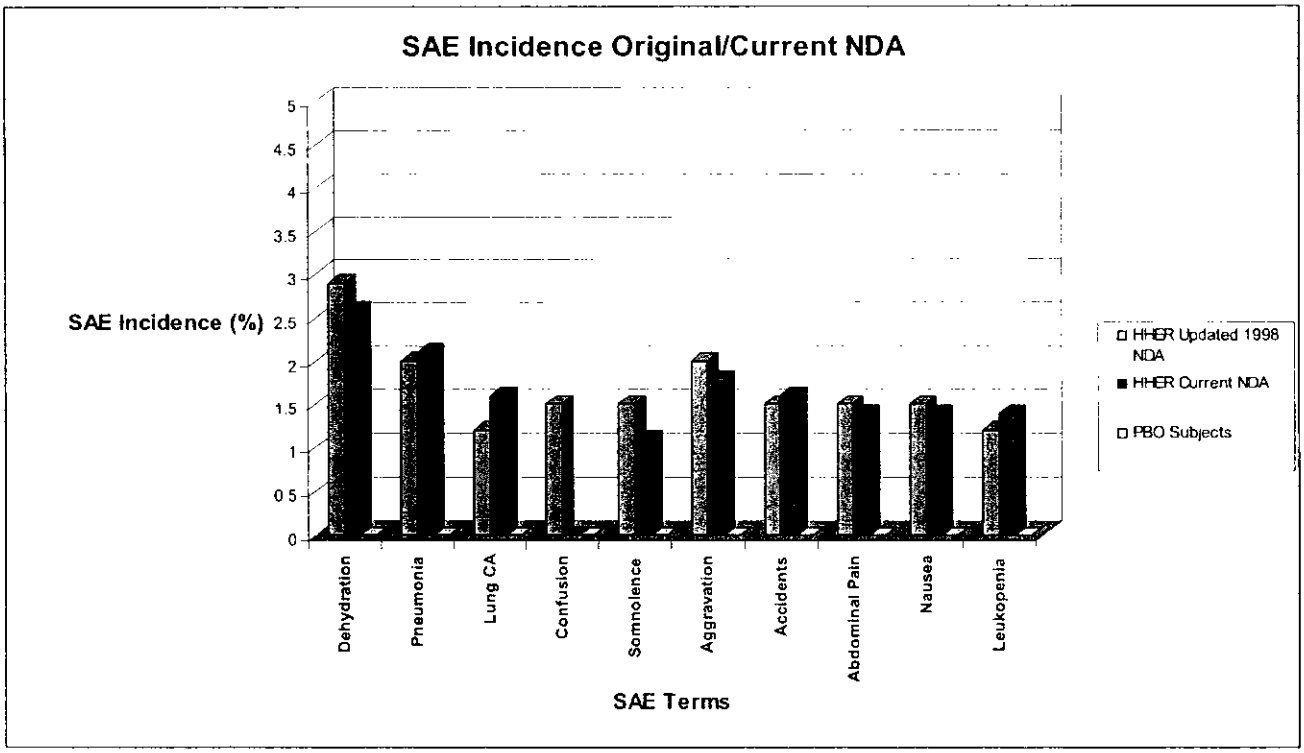
The Sponsor states that these differences can be explained by examination of the underlying study populations and the exposure times. In particular, they state that the HHIR subjects reported low frequencies of SAEs due to short exposure times of 3-7 days, in contrast to the HHER group duration of 20.4 days (average).

They note that the Placebo subjects in the current NDA studies report lower SAE frequencies due to a shorter duration of exposure compared to the HHER subjects in the long-term open-label trials. Moreover, the Sponsor notes that the HHER subjects with malignant pain had a much greater incidence of SAEs compared to those with non-malignant pain. This contributes to the greater frequency of HHER subject SAEs

compared to Placebo. The Sponsor notes that the low incidence of SAEs in the MS-Contin group was due to the small sample size and the fact that this group had either malignant or non-malignant pain from a single short-term study (HD99-0201).

The most common SAE by Body System was for "Body as a Whole" (64/568 or 11.3%) for the current NDA HHER subjects and (37/343 or 10.8%) for the Updated 1998 HHER NDA subjects. The most frequently reported serious adverse event in HHER-treated subjects in the original 1998 NDA was dehydration (2.0%). It was also the most frequently reported serious adverse event in the Updated Original 1998 NDA (2.9%) and the Current NDA Amendment (2.6%). These results are illustrated in the figure below.

Figure 1.



Evaluation of Individual Patient Narratives:

This section briefly illustrates selected patient narratives from the original/updated Phase III 1998 Safety Population. All narratives were scanned by the reviewer for possible relationship to the study drug. Only SAE narratives deemed "possibly related" by this reviewer, are shown here.

Table 9. Selected SAE Narratives from the Original & Updated Phase 3 1998 NDA

Study / Patient ID	Treatment	Descriptive Terms	Narrative / Reviewer Assessment of SAE-Study Drug Relationship
HD95-0801, #33007	HHER	FALL, PATHOLOGIC HIP FX	59 F w/ Metastatic Lung CA, WC bound. Started OLP w/ 12 mg HHER and ↑ to 36 mg HHER and 6 mg HHIR for rescue. Pt. fell while attempting to stand and was Dx'd with Pathologic Hip Fx. Fall not due to sedation? SAE / Study Drug Relationship *UNCLEAR.*
HD95-0801, #12004	HHER	ABDOMINAL PAIN	67 F with Lung CA Mets to Abdomen w/ ↑ Abdominal pain, N, V after entering the DBP. Was admitted from study and D/C'd study med 4 days after starting. Pain resolved. ?pain due to opioids or abdominal metastases. SAE / Study Drug Relationship *POSSIBLE.*
HD95-0801, #16005	HHER	DEHYDRATION NAUSEA, VOMITING	69 WM with Met. Prostate CA. Pt. started on 12 mg HHER w/ 2 mg HHIR rescue during OLP of trial. Subject hosp. For N, V, Dehydration later and D/C'd from trial. SAE / Study Drug Relationship *PROBABLE.*
HD95-0801, #16017	HHER	SOMNOLENCE	61 m WITH Met. Colon CA admitted for somnolence, ascites, RF. Was in OLP of trial for 2 days at 24 mg HHER/ 4m HHIR respectively. Investigator deemed event due to progression of primary disease, but somnolence contributed to hospitalization. SAE / Study Drug Relationship *PROBABLE.*
HD95-0803, #16018	HHER	NAUSEA, VOM., CONSTIPATION NEUTROPENIA	51 F receiving Chemo Rx for Met. Ovarian CA was enrolled in OLP. Required ↑ doses of HHER (108 mg) with rescue of 16 mg HHIR. Subject hosp. For N, V, Constipation associated with Chemo Rx treatment. Neurotopenia during hospital stay delayed D/C. *N,V, CONSTIPATION SAE / Study Drug Relationship POSSIBLE. NEUTROPENIA SAE / Study Drug Relationship UNLIKELY*
HD95-0803, #16027	HHER	WEAKNESS, DIZZINESS, WITHDRAWAL	60 M on Chemo Rx for tonsillar CA. Completed HD95-0801 study and entered continuation study at 60 mg HHER/ 8 mg HHIR. Subject hosp. 4 times during study for various symptoms including weakness, tremor, dizziness, anemia, etc… On 12/19/97 (4 days after last dose) Investigator judged that subject to have some signs of Narcotic Withdrawal. *SAE / Study Drug Relationship PROBABLE.*
HD95-0801, #16031	HHER	CONFUSION, SEDATION, DEHYDRATION	77 F w/ Met. Uterine CA. Subject w/ B. Arm Pain requiring ↑ doses of HHER to 36 mg w/ 6 mg HHIR rescue. Subject had not been eating/drinking due to sedation and confusion and was dehydrated when admitted for worsening neck pain, sedation, cystitis. Sujbect later taken off narcotic meds and all confusion/sedation resolved. *SAE / Study Drug Relationship PROBABLE.*
HD95-0801, #17017	HHER	NAUSEA, DEHYDRATION	66 F w/ Met. Colon CA. On OLP titration at 24 mg/4 mg of HHER/HHIR respectively. Developed N/Dehydration and was admitted for Rx. Unclear if disease progression also contributed to problems. *SAE / Study Drug Relationship POSSIBLE.*
HD95-0803, #22008	HHER	CONFUSION	75 F w/ MMyeloma taking 36 mg HHER qd, ↑ pain, confusion, which improved after study drug D/C'd. *SAE / Study Drug Relationship PROBABLE.*

Study / Patient ID	Treatment	Descriptive Terms	Narrative / Reviewer Assessment of SAE-Study Drug Relationship
HD95-0802, #29022	HHER	SMALL BOWEL OBSTRUCTION, VOMITING	71 M w/ Met. AdenoCA was taking 12 mg/ 2 mg HHER/HHIR respectively admitted for SBO & Vomiting which resolved after D/C Study drug. *SAE / Study Drug Relationship PROBABLE.*
HD95-0802, #41007	HHER	DEHYDRATION CONFUSION	76 M w/ Met. Prostate CA on 24 mg HHER qd. Admitted for ↑ dehydration and confusion, after starting 1st of DBP of trial. *SAE / Study Drug Relationship PROBABLE.*
HD95-0802, #45005	HHER	DEHYDRATION WEAKNESS	55 F w/ ChemoRx for Breast CA on 84 mg/14 mg HHER/HHIR respectively withdrew due to inadequate pain control. 4 days after last dose was admitted for IV fluids and dehydration. *SAE / Study Drug Relationship UNLIKELY*

Source: Appendix C.2.2 Narratives for Phase 3 Original 1998 NDA, pg. 3526.
OLP = Open-Label Phase, DBP = Double-Blind Phase

Examination of the selected SAEs shows that the majority occurred in subjects with serious underlying malignant medical conditions. In multiple episodes of dehydration and confusion, the study drug appeared to have a possible/probable relationship. However, many of the listed cases could be seen as being also due to progression of the severe underlying medical conditions. Many other case narratives did not appear to have any significant relationship to the study drugs. These narratives were not individually discussed here. For completeness, examples of these "not-included" events included new diagnoses of spinal cord compression, new liver metastases, pulmonary edema and effusions from metastatic lung cancer, etc... Overall, there does not appear to be any particular distinguishing feature or "signal" in the SAEs that suggests Palladone™ has a substantially different safety profile from other opioids.

Selected SAE narratives for the current Phase III NDA Active Controlled studies are evaluated in the following table.

Table 10. Selected SAE Narratives from the Phase III Studies In the Current NDA Amendment

Study / Patient ID	Treatment	Descriptive Terms	Narrative / Reviewer Assessment of SAE-Study Drug Relationship
HD99-0201, #51	HHER	NAUSEA, VOMITING	77 M w/ Met. Hepatic adenocarcinoma, colon CA. Took initial doses of HHER and developed severe N/V, which required hospitalization and IV fluids. *SAE / Study Drug Relationship PROBABLE.*
HD95-0803, #16013	HHER	WEAKNESS, FALLING, FATIGUE	70 F w/ Lung CA. Complete 8-week study at 48 mg/8 mg HHER/HHIR and entered continuation study. Admitted for falling & fatigue ~ 1 mo later and was DX'd w/ Brain and Adrenal Mets. Study drug may have contributed. *SAE / Study Drug Relationship POSSIBLE.*
HD95-0803, #16035	HHER	DIZZY, DEHYDRATION	46 M w/ Met. Lung CA completed DBP and entered continuation study at 72 mg qd. Hospitalized 3 times during study and extension phase. One admission for dizziness and dehydration thought related to study med. Later D/C'd meds due to insufficient analgesia. *SAE / Study Drug Relationship POSSIBLE.*
HD95-0803, #22003	HHER	URINARY RETENTION, CONSTIPATION	75 M w/ Met. Prostate CA completed primary study and then D/C'd due to paranoia. During hosp. Was noted to have Urinary retention, had another episode w/ hosp for abdominal pain and distention ? bowel obstruction. Laxatives used successfully to resolve symptoms. *SAE / Study Drug Relationship POSSIBLE.*
HD95-0803, #22010	HHER	CONFUSION, DEHYDRATION	67 M w/ Met. Malignant Fibrous Histiocytoma. Did well on study medications during active-control & OLP study. Subject admitted for dehydration, disorientation, and progression of RLL histiocytoma, while still taking HHER 48 mg qd. *SAE / Study Drug Relationship POSSIBLE.*
HD95-0803, #27019	HHER	CONFUSION, HALLUCINATE.	62 F w/ Met. Breast CA in continuation study at 36 mg HHER/6 mg HHIR. Pt. admitted for confusion, SOB, hallucinations and DX'd w/ Brain Mets, Pneumonia, Bil Pleural Effusion. *SAE / Study Drug Relationship UNCLEAR TO POSSIBLE.*
HD95-0803, #31004	HHER	NAUSEA, VOMITING	50 F w/ Met. Breast CA in continuation study at 12 mg HHER & 2 mg HHIR rescue. Subject admitted for N,V associated w/ recent ChemoRx. Study drug D/C'd. N,V is associated with opioid medications. *SAE / Study Drug Relationship UNCLEAR TO POSSIBLE.*
HD95-0803, #33018	HHER	RECTAL BLEEDING, HEMORRHOID	70 F w/ ALL enter OLP at 12 mg HHER & 2 mg HHIR. Subject admitted for rectal bleeding due to prolapsed hemorrhoids and received blood transfusion. *SAE / Study Drug Relationship POSSIBLE.*
HD95-0803, #45004	HHER	FALL, HIP FX	77 M w/ Met. Lung CA on 16 mg HHER and c/o inadequate pain relief to his physician after 10 days in study. Subject was D/C'd from study and given alternate analgesia. Pt. fell and FX hip later the same day and was DX'd w/ boney mets. *SAE / Study Drug Relationship POSSIBLE.*

Source: Appendix C.2.4 Narratives for Phase 3 Studies in Current NDA Amendment, pg. 3546.
OLP = Open-Label Phase, DBP = Double-Blind Phase

Inspection of the narratives suggests that the study drug is a possible contributing factor, but does not appear to be a significant determinant in the narratives. There appears to be a predominance of SAEs that could be due to the underlying severity and progression of disease. Note that subjects on MS Contin and Placebo are not included in this individual narrative review. Inspection of these narratives (along with other narratives not shown above) reveals similar SAEs including episodes of angina, seizure (on placebo), chest pain, confusion, pleural effusions, metastatic progression, etc... In conclusion, there appears to be no significant pattern of study drug SAEs that appear different from what one might expect for opioid medications.

Incidence and Rate of SAEs – Phase III Placebo-Controlled Studies:

The safety results in this section cover the subjects enrolled in studies HMP3005 and HMP3006, under the current NDA amendment.

Incidence of SAEs:

The overall incidence of SAEs was 6/191 (3.1%) in the Placebo group and 5/190 (2.6%) in the HHER group. There were 12 total reports for 11 subjects. The following table was reproduced from the Sponsor's ISS listing, and is arranged by treatment group and then subgrouped by study.

Inspection of the SAE listings shows that 4 subjects had serious cardiovascular-related events (2 each in the Placebo and HHER groups). Examination of the corresponding narratives described below does not indicate any obvious study-drug/SAE relationship. Several SAEs including MI (#9132), PTCA (#2143), and Seizures (#3003) occurred in the Placebo group and these narratives were not examined by the reviewer.

Table 11.

TABLE 9.14.2.1B.

Listing of Serious Adverse Events – Phase 3 Placebo-controlled Studies[a]: Safety Population

Study/ Subject No.	Age/ Gender	Days to Onset[b]	Investigator Term	COSTART Term	Body System	Outcome
Placebo (N = 191)						
HMP3006						
12084	48/M	8	Worsening depression	Depression	Nervous	Recovered
9132	64/M	20	Myocardial infarction	Myocardial infarction	Cardiovascular	Recovered
25248	40/F	16	Substance abuse	Drug dependence	Nervous	Recovered
32280	41/F	28	Urolithiasis	Urolithiasis	Urogenital	Recovered
HMP3005						
2143	63/F	7	Percutaneous coronary intervention	Coronary artery disorder	Cardiovascular	Recovered
3003	82/M	2	Seizure disorder	Convulsions	Nervous	Recovered
HHER (N = 190)						
HMP3006						
12083	59/F	6	Atypical chest pain	Chest pain	Body as a whole	Recovered
32277	53/F	9	Cholecystitis	Cholecystitis	Digestive	Recovered
35353	50/M	-1[d]	Recurrence of mycosis fungoides	Lymphoma-like reaction	Hematic/Lymphatic	Continuing
35357	70/F	5	Bilateral lower extremity ischemia	Peripheral vascular disorder	Cardiovascular	Recovered
		10	Gangrene of the left foot	Peripheral gangrene	Cardiovascular	Recovered
HMP3005						
16139	53/M	18	Esophageal cancer	Carcinoma	Body as a whole	Continuing[c]

[a]Studies HMP3005 and HMP3006.
[b]Number of days from start of double-blind study medication.
[c]See subject narrative in Appendix C for follow-up information.
[d]Recurrence of mycosis fungoides was noted prior to randomization and confirmed after randomization.
Cross-reference: Current NDA Amendment Listing B.2.2.

Appears This Way
On Original

Table 12. Selected SAE Narratives from the Current Phase III Placebo Studies

Study / Patient ID	Treatment	Descriptive Terms	Narrative / Reviewer Assessment of SAE-Study Drug Relationship
HMP3006, #12083	HHER	Atypical CP	59 opioid experienced WF experienced CP. Had h/o CAD, Angioplasty, Stable Angina, Bil LExt Edema, Osteoporis, etc... Was hosp. ~ after stopping HHER for Atypical CP. Event resolved the following day. SAE / Study Drug Relationship *UNLIKELY.*
HMP 3005, #35357	HHER	Bil LExt Ischemia, L Foot Gangrene	70 opioid-experience WF with chronic pain 2° RA, Osteo, Hypothyroid, Intermittent Claudication, and bil foot PVD. Subject started HHER on 3/14/01 and D/C'd HHER on ~ – admitted for LExt Ischemia. Underwent fem-fem bypass on ~ and L foot partial amputation. SAE / Study Drug Relationship *UNLIKELY.*
HMP-3006, #32277	HHER	Abdominal Pain, Cholecystitis	53 F w/ chronic pain, GERD, HTN, Liver Cirrhosis, SLE, DM, Chronic Constipation developed LFT abnls and abdominal pain after completing run-in and randomization to HHER. Subject had ↑ pain and moderate cholecystitis noted. Study drug D/C'd ~ 4 days later. Pain continued to ↑ in f/u period and subject underwent outpatient cholecystectomy, after which the Sxs resolved. *SAE / Study Drug Relationship POSSIBLE to PROBABLE.*

Source: Table 9.14.2.1 and Patient Narrative Sections C2.4, pg. 3546.

Rate of SAEs:

The incidence rate (IR) of SAEs by treatment group for the Phase III studies was determined by calculating the person-time for the groups. The following table was reproduced from the sponsor's Table 9.14.2.2. The reviewer also calculated the IR in terms of Events/year.

Table 13. SAE Incidence Rate Calculation Results

Treatment	# Exposed Subjects	# Event Reports	Subject Days of Exposure	IR (#/Day)	IR (#/100 patient-yrs)
Placebo	191	6	2892	0.002	75.7
HHER	190	6	4002	0.001	54.7

Source: NDA 21,044 ISS Update, Table 9.14.3.2., pg. 50.

Note that the IR rate per day gives the impression that the Placebo incidence rate is twice that of the HHER treated subjects. Increasing the projected person-time to 100 person-years shows that the PBO rate is indeed greater, but not by a factor of 2 as was suggested by the #/day rate. These rates calculated above do not suggest an obvious "safety signal" associated with the study drug.

SAE Incidence and Rate by Subgroup for Malignant and Chronic Nonmalignant Pain:

The Sponsor has performed a separate analysis of the safety occurrences of SAEs in two subgroups. These two sections will examine the results by crude incidence and then incidence rate.

Incidence of SAEs by Subgroup - Malignant and Chronic Nonmalignant Pain:

The current NDA was separated into "malignant pain" and "non-malignant pain" subgroups, in order to examine the crude incidence of SAEs. The following table was reproduced from the Sponsor's data (Table 9.14.3.1, ISS Update, pg. 49) and illustrates these results.

Table 14.

TABLE 9.14.3.1.

Incidence of Serious Adverse Events ≥2% in HHER-treated Subjects in Malignant and Chronic Nonmalignant Pain Subgroups – Phase 3 Studies: Safety Population

	Malignant Pain[a] (N = 289)	Chronic Nonmalignant Pain[b] (N = 279)
	HHER	HHER
	n (%)	n (%)
Any serious adverse event	124 (42.9)	6 (2.2)
Body system/adverse event (COSTART term)		
Body as a whole	62 (21.5)	2 (0.7)
Aggravation reaction	10 (3.5)	0 (0)
Accidental injury	9 (3.1)	0 (0)
Asthenia	9 (3.1)	0 (0)
Fever	9 (3.1)	0 (0)
Abdominal pain	8 (2.8)	0 (0)
Digestive	29 (10.0)	1 (0.4)
Nausea	8 (2.8)	0 (0)
Hematic and lymphatic	18 (6.2)	1 (0.4)
Leukopenia	8 (2.8)	0 (0)
Anemia	7 (2.4)	0 (0)
Metabolic and nutritional	21 (7.3)	0 (0)
Dehydration	15 (5.2)	0 (0)
Nervous	29 (10.0)	1 (0.4)
Confusion	8 (2.8)	0 (0)
Somnolence	6 (2.1)	0 (0)
Respiratory	33 (11.4)	0 (0)
Pneumonia	12 (4.2)	0 (0)
Carcinoma of lung	9 (3.1)	0 (0)
Dyspnea	7 (2.4)	0 (0)

[a]Includes subjects from studies HD96-0801, HD96-0802, HD96-0803, and HD99-0201.
[b]Includes subjects from studies HD96-0801, HD96-0802, HD99-0201, HMP3005, and HMP3006.
Cross-reference: NDA Amendment, Table A.24

Inspection shows a significantly greater crude incidence of "any" SAEs in the malignant pain group (124/289 or 42.9 %) vs. (6/279 or 2.2%) in the non-malignant pain group. All

the listed body group categories also show a greater predominance of SAEs in the malignant pain group. The most frequent body categories for the malignant group were "Body as a Whole" (21.5%), "Respiratory" (11.4%), "Nervous" (10%), "Digestive" (10%), Metabolic (7.3%), and "Heme/Lymphatic" (6.2%), respectively. Within these categories the two most frequent COSTART terms were Dehydration (5.2%) and Pneumonia (4.2%), respectively.

Rate of SAEs by Subgroup - Malignant and Chronic Nonmalignant Pain:

Calculation of the incidence rate (IR) allows a comparison of the frequency of SAEs along with adjustment for exposure. Again, the reviewer expanded the calculation to show the event rate per 100 patient-years.

Table 15. SAE Incidence Rate Calculation Results

Study Group	Treatment	# Exposed Subjects	# Event Reports	Subject Days of Exposure	IR (#/Day)	IR (#/100 patient-yrs)
Malignant	HHER	289	360	15,223	0.024	863.2
Chronic Non-Malig	HHER	279	7	5309	0.001	48.1
Total in Phase III	HHER	568	367	20,532	0.018	652.4

Source: NDA 21,044 ISS Update, Table 9.14.3.2., pg. 50.

Inspection of the table demonstrates a difference between the malignant and non-malignant groups that is greater than an order of magnitude (factor of 10). The malignant pain rate of 863 events per 100 patient-years studied suggests that the underlying medical condition of these subjects may account for this result. Note that another interpretation is also possible. It is possible that subjects with malignancies are taking higher doses than those in other pain categories. This is difficult to quantify as the Sponsor has not show a distribution of dosages for the two groups. This reviewer was unable to interrogate the electronic data base to assess whether there was a difference between the two groups.

SAEs – All Clinical Studies:

The Sponsor calculated the crude incidence for all SAEs in subjects receiving HHER. The overall frequency was 16.6%. The following table was constructed from the Sponsor's data in Table A.13.1. on page 226 of the Safety Update document. Note that individual patient narratives are discussed in prior sections and this table will highlight findings for the group as a whole.

Each body system is shown with the two most frequent associated SAE terms. The individual body systems are arranged in decreasing order of frequency of SAE occurrence. Note the "N" in the table does not necessarily equal the sum of individual SAE reports. This is because several studies had subjects titrated on HHER and then randomized to double-blink cross-over treatment with either HHER/HHIR or HHIR/HHER with no wash-out period. In some of these cases the SAEs during the periods of exposure to HHIR are attributed to HHER. Moreover subjects enrolled in two

studies (HD95-0801 or HD95-0802) and who rolled over to extension study HD95-0803 are counted only as one subject.

Table 16.

Body System	SAE Term	N/785 Exposed	Incidence (%)[a,b]
Total	**Overall**	**130**	**16.6**
Body as Whole	**Overall**	**64**	**8.15**
	Aggravation Reaction	10	1.27
	Accidental Injury	9	1.15
Respiratory	**Overall**	**33**	**4.20**
	Pneumonia	12	1.53
	Carcinoma of Lung	9	1.15
Nervous	**Overall**	**30**	**3.82**
	Confusion	8	1.02
	Somnolence	6	0.76
Digestive	**Overall**	**30**	**3.82**
	Nausea	8	1.02
	Vomiting	5	0.64
Metab/Nutrition	**Overall**	**21**	**2.68**
	Dehydration	15	1.91
	Peripheral Edema	3	0.38
Cardiovascular	**Overall**	**20**	**2.55**
	DVT	5	0.64
	Syncope	3	0.38
Heme/Lymphatic	**Overall**	**19**	**2.42**
	Leukopenia	8	1.02
	Anemia	7	0.89
Urogenital	**Overall**	**13**	**1.66**
	Hematuria	3	0.38
	Breast CA	2	0.25
Musculoskeletal	**Overall**	**3**	**0.38**
	Arthralgia	2	0.25

[a] N = # subjects reporting ≥ 1 SAE while exposed to HHER, % = N/# subjects valid for safety and exposed to HHER. Note exceptions to counting SAEs described in the introductory paragraphs of this section.

[b] subjects enrolled in HD95-0801 or HD95-0802, and who rolled over to extension study HD95-0803 are counted only as 1 subject.

SAEs – Ongoing Studies:

Complete safety data are not available for the 3 ongoing studies, HD95-0801M, HD98-0504, and HMP3003. However, serious adverse events reported in these studies have been reviewed and assessed and are discussed below. Selected narrative reviews for subjects with other serious adverse events in ongoing studies are also provided. Deaths are discussed in another section.

Table 17. Selected SAE Narratives from the Ongoing Studies

Study / Patient ID	Treatment	Descriptive Terms	Narrative / Reviewer Assessment of SAE-Study Drug Relationship
HMP3003, #1042	HHER	Confusion, Hypoxia	70 F on HHER 24 mg (+ PCA?) developed episode of confusion & hypoxia during hospitalization. Subject DX'd w/ CO_2 retention and was given 1 ampule naloxone, O_2, and was transferred to the ICU for observation. Subject returned to baseline over the next day. SAE / Study Drug Relationship *PROBABLE.*
HMP 3003, #1176	HHER?	Hypoxia, Not Arousable	86 F w/ hypoxia and not arousable was on study medication, in addition to 32 mg MSO4 via PCA. Subject had ↓ O2 sats to 54-68%. Subject Rx'd w/ O2, airway, and packed RBC transfusion. Blind not broken and study drug unknown at this time. Subject recovered by next morning. SAE / Study Drug Relationship *PROBABLE.*
HMP-3003, #2092	HHER?	Post Operative Ileus	56 W M w/ ileus following surgery. Started ~ post-op w/ vomiting & diarrhea. Blind not broken and Sx's resolved. SAE / Study Drug Relationship *POSSIBLE.*
HD98-0504, #04	HHER	Vomiting	47 F on 12 mg HHER and had 1.5 mg IV dose of hydromorphone 15 mins after oral dosing. Subject experienced nausea and vomiting with 14 mins of IV infusion. Subject was treated in ER w/ IV fluids and Sxs had resolved 12.5 hours after dosing. Subject released to clinic and finished remainder of study w/o further emetic episodes. SAE / Study Drug Relationship *PROBABLE.*

Source: Table 9.14.2.1 and Patient Narrative Sections C2.4, pg. 3546.

In two of the selected narratives, the study blind was not broken and the actual study drug (HHER vs. Placebo) is not known. The reviewer selected these cases because they appeared to have some possible association with the study drug. Other cases not shown here included surgical wound infections, post-op fever, atrial fibrillation, etc... did not appear to be significantly related to the study drug. Inspection of these cases again suggests SAEs typical of opioid medications such as decreased bowel motility (ileus) and respiratory suppression (hypoxia and not arousable). Note that the "not arousable" patient appeared to also be on Morphine PCA and had received a significant dose of morphine prior to the onset of symptoms.

Comments:

In summary the review of SAE narratives and tables suggests that subjects taking HHER have a much greater incidence of events than either the MS Contin, Placebo, and HHIR groups. The individual events appear to be typical of those associated with opioid treatment. Moreover, the vast majority of SAEs appear to occur in subjects with severe underlying disease such as metastatic cancer. No obvious worrisome "signal" of unusual events was observed.

The frequency of SAE reports across the differenct treatment groups differed considerably. The HHER subjects had significantly higher SAE frequency and incidence rate than any other treatment groups. The Sponsor argues that both the MS Contin, HHIR, and Placebo groups had significantly less exposure than the HHER groups. They also demonstrate that the HHER rate of SAEs in the malignant-pain group (863.2 SAEs/100 Pt-Years) is much greater than that for non-malignant group (48.1 SAEs/100 Pt-Years). Another complicating factor is that in the Updated 1998 NDA studies some events associated with HHIR were assigned to the HHER group (due to crossover from one drug to another). These three factors may indeed account for much of the difference in HHER frequency and incidence of SAEs compared to the other treatment groups. However, another hypothesis is that some of the higher incidence in the malignant pain group may be due to generally greater doses of HHER used in this group, compared to the non-malignant pain group.

Overall Adverse Event Profile

Appropriateness of Adverse Event Categorization and Preferred Terms:

The Sponsor has provided a dictionary of all investigator verbatim adverse event terms and their corresponding COSTART preferred terms in Appendix B. In general, the coding assignments appear appropriate, clinically reasonable, and internally consistent.

Some preferred terms, however, comprise a wide variety of investigator verbatim terms, making the preferred term itself rather vague. For example, the preferred term "asthenia" is used both for relatively non-specific verbatim terms such as "weak" and "tired" as well as for more specific terms such as "weakness of right hand". The preferred term "infection" refers to a variety of infections, such as those of the ear, hand, foot, sinuses, throat, and other body sites. The preferred term "pain" is used to describe a wide variety of generalized and focal pain conditions. The preferred term "arthralgia" refers to joint pain in a variety of joint sites. It is not clear why there are two preferred terms ("hallucination" and hallucinations") that are used to encode the same set of investigator verbatim terms. The preferred term "reaction unevaluable" is used to refer to a variety of apparently clinically diverse events such as "23-hour chemotherapy hold", "blocked biliary stent", "cont., infusion of chemotherapy for 1 wk", "debridement left neck", "left nodular densities", and "replacement damaged picc lines".

The preferred terms "hypesthesia" and paresthesia" are both used for various reports of numbness. The preferred terms "nervousness" and "tremor" are both used for various reports of "shaking" or "shaky". The reason for these inconsistencies is not clear.

Frequent Adverse Events in Phase 3 Clinical Studies:

The Sponsor has prepared in Table 9.12.1 (reproduced below) the incidence of adverse events occurring in 10% or more of subjects receiving HHER. This review will focus on

the data for the current NDA amendment. Review of Table 9.12.1 is notable for the following:

- Most of the common adverse events are those typically associated with opioid use (ie, headache, nausea, constipation, vomiting, somnolence, dizziness, nervousness, confusion, and pruritus).
- All of the common adverse events occurred in a subtantially higher proportion of HHER-treated patients than in placebo-treated patients. In fact, all of the adverse events that occurred in 10% or more of HHER-treated patients occurred in less than 7% of placebo-treated patients.
- For nearly all common adverse events, the frequency is notably higher in HHER-treated patients than in MS Contin-treated patients. The reason for this difference is not clear from Table 9.12.1, but may be related to the low number of subject treated with MS Contin (38) compared to the larger number treated with HHER (568). Difference in patients population, underlying disease, doses received, and duration of treatment may also account for the observed differences in frequency. The Sponsor, however, has not provided any analyses to explain these differences.
- Certain adverse events, which are not typically associated with opioid use, occurred with notably higher frequency in HHER-treated patients than in either MS Contin-treated patients or placebo-treated patients. For example, the adverse event "pain" (preferred term) was reported in 2/38 (5.3%) of HHER-treated patients, and in 1/191 (0.5%) of placebo-treated patients. The reason for this observation is not clear. If the "pain" events had been mainly due to ineffective treatment, a much higher rate in the placebo group would be expected. A higher rate of "abdominal pain" (preferred term) is also noted in the HHER-treated group than in the placebo-treated group.

Table 18.

Sponsor Table 9.12.1

Incidence of Adverse Events ≥10% of Subjects Receiving HHER (Original 1998 NDA and Current NDA Amendment): Safety Population

	Phase 3 Studies Original 1998 NDA[a]		Updated Phase 3 Studies Original 1998 NDA[a]	Phase 3 Studies Current NDA Amendment[c]		
	HHIR	HHER	HHER	MS Contin	HHER	Placebo
	(N = 209)	(N = 343)	(N = 343)	(N = 38)	(N = 568)	(N = 191)
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Any adverse event	194 (92.8)	326 (95.0)	334 (97.4)	30 (78.9)	453 (79.8)	67 (35.1)
Body system/adverse event (COSTART term)						
Body as a whole	54 (25.8)	188 (54.8)	219 (63.8)	12 (31.6)	295 (51.9)	30 (15.7)
Headache	21 (10.0)	87 (25.4)	93 (27.1)	6 (15.8)	119 (21.0)	4 (2.1)
Asthenia	12 (5.7)	61 (17.8)	78 (22.7)	2 (5.3)	110 (19.4)	1 (0.5)
Pain	6 (2.9)	44 (12.8)	46 (13.4)	2 (5.3)	73 (12.9)	1 (0.5)
Abdominal pain	6 (2.9)	45 (13.1)	51 (14.9)	0 (0)	67 (11.8)	6 (3.1)
Digestive	146 (69.9)	272 (79.3)	280 (81.6)	14 (36.8)	349 (61.4)	25 (13.1)
Nausea	97 (46.4)	194 (56.6)	203 (59.2)	6 (15.8)	238 (41.9)	12 (6.3)
Constipation	88 (42.1)	169 (49.3)	179 (52.2)	0 (0)	220 (38.7)	2 (1.0)
Vomiting	42 (20.1)	105 (30.6)	114 (33.2)	4 (10.5)	142 (25.0)	3 (1.6)
Diarrhea	8 (3.8)	50 (14.6)	54 (15.7)	0 (0)	72 (12.7)	10 (5.2)
Dyspepsia	10 (4.8)	43 (12.5)	47 (13.7)	2 (5.3)	58 (10.2)	4 (2.1)
Metabolic and nutritional	17 (8.1)	61 (17.8)	70 (20.4)	3 (7.9)	101 (17.8)	4 (2.1)
Peripheral edema	6 (2.9)	35 (10.2)	39 (11.4)	2 (5.3)	57 (10.0)	4 (2.1)
Nervous	158 (75.6)	275 (80.2)	291 (84.8)	15 (39.5)	323 (56.9)	25 (13.1)
Somnolence	149 (71.3)	218 (63.6)	239 (69.7)	5 (13.2)	250 (44.0)	3 (1.6)
Dizziness	68 (32.5)	125 (36.4)	143 (41.7)	3 (7.9)	159 (28.0)	6 (3.1)
Nervousness	5 (2.4)	43 (12.5)	43 (12.5)	0 (0)	59 (10.4)	7 (3.7)
Confusion	8 (3.8)	34 (9.9)	35 (10.2)	4 (10.5)	52 (9.2)	0 (0)
Skin and appendages	65 (31.1)	115 (33.5)	134 (39.1)	6 (15.8)	155 (27.3)	10 (5.2)
Pruritus	57 (27.3)	76 (22.2)	99 (28.9)	2 (5.3)	106 (18.7)	2 (1.0)
Sweating	10(4.8)	42 (12.2)	46 (13.4)	2 (5.3)	58 (10.2)	4 (2.1)

[a]Studies HD95-0801, HD95-0802, and 77 subjects from HD95-0803.
[b]Updated adverse events from HD95-0801, HD95-0802, and 77 subjects from HD95-0803.
[c]Studies HD95-0801, HD95-0802, HD95-0803, HD99-0201, HMP3005, and HMP3006.
Cross-references: Original NDA ISS Table 8.11.18.1.5.4; Current NDA Amendment Tables A.9.2, A.11, A.28.

The Sponsor has also examined all adverse event occurring in 2% or more of HHER-treated subjects in placebo-controlled studies. These data are provided in Table 9.12.2.1, which is reproduced below. Review of this table is notable for the fact that most of the adverse events commonly observed in opioid-treated subjects occurred with a higher frequency in HHER-treated subjects than in placebo-treated subjects. Infection, which is not an adverse event typically associated with opioid use, occurred with nearly equal frequencies between the two groups.

Table 19.

Sponsor Table 9.12.2.1.				
Incidence of Adverse Events in ≥2% of Subjects Receiving HHER – Phase 3 Placebo-controlled Studies: Safety Population				
	Phase 3 Placebo-controlled Studies[a]			
	Placebo (N = 191)		HHER 12 mg (N = 190)	
	n	(%)	n	(%)
Any adverse event	67	(35.1)	94	(49.5)
Body system/adverse event				
(COSTART term)				
Body as a whole	30	(15.7)	35	(18.4)
Infection	11	(5.8)	10	(5.3)
Headache	4	(2.1)	9	(4.7)
Asthenia	1	(0.5)	6	(3.2)
Digestive	25	(13.1)	53	(27.9)
Constipation	2	(1.0)	30	(15.8)
Nausea	12	(6.3)	20	(10.5)
Vomiting	3	(1.6)	6	(3.2)
Nervous	25	(13.1)	22	(11.6)
Somnolence	3	(1.6)	9	(4.7)
Skin and appendages	10	(5.2)	9	(4.7)
Pruritus	2	(1.0)	5	(2.6)
[a]Studies HMP3005 and HMP3006.				
Cross-reference: Current NDA Amendment, Table A.11.				

In Table 9.12.2.2, reproduced below, the Sponsor has calculated adverse event rates per day, using a person-time methodology. The rates are similar between the placebo-treated group (0.050 per day) and the HHER-treated group (0.047 per day).

Table 20.

TABLE 9.12.2.2.			
Rate of Adverse Events – Phase 3 Placebo-controlled Studies[a]: Safety Population			
No. of Subjects Treatment Exposed	No. of Reports of Event[b]	Subject Days of Exposure[c]	Event Rate (per Day)[d]
Placebo 191	144	2892	0.050
HHER 190	190	4002	0.047
[a]Studies HMP3005 and HMP3006.			
[b]Total number of reports by the subjects with at least 1 adverse event.			
[c]Sum of exposures to treatment for all treated subjects. Exposure is calculated as (stop date – start date) + 1.			
[d]Calculated as (b) divided by (c).			
Cross-reference: Current NDA Amendment, Table A.12.			

The Sponsor has examined the adverse event frequency for patients with malignant pain and for patients with non-malignant pain for adverse events occurring in 10% or more of HHER-treated subjects. These data are presented in Table 9.12.3.1, reproduced below. For all these adverse events, the frequencies were notably higher in patients with

malignant pain. The Sponsor attributes this observation to the effect of underlying disease. However, other factors, such as HHER dose and duration of treatment, were not examined.

Table 21.

Sponsor Table 9.12.3.1.

Incidence of Adverse Events ≥10% in HHER-treated Subjects for Malignant and Chronic Nonmalignant Pain Subgroups – Phase 3 Studies (Current NDA Amendment): Safety Population

	Malignant Pain[a] HHER (N = 289)		Nonmalignant Pain[b] HHER (N = 279)	
	n	(%)	n	(%)
Any adverse event	279	(96.5)	174	(62.4)
Body system/adverse event (COSTART term)				
Body as a whole	207	(71.6)	88	(31.5)
Asthenia	91	(31.5)	19	(6.8)
Headache	70	(24.2)	49	(17.6)
Pain	69	(23.9)	4	(1.4)
Abdominal pain	55	(19.0)	12	(4.3)
Fever	40	(13.8)	7	(2.5)
Accidental injury	32	(11.1)	4	(1.4)
Digestive	233	(80.6)	116	(41.6)
Nausea	183	(63.3)	55	(19.7)
Constipation	154	(53.3)	66	(23.7)
Vomiting	123	(42.6)	19	(6.8)
Diarrhea	58	(20.1)	14	(5.0)
Dyspepsia	48	(16.6)	10	(3.6)
Anorexia	43	(14.9)	4	(1.4)
Metabolic and nutritional	89	(30.8)	12	(4.3)
Peripheral edema	48	(16.6)	9	(3.2)
Nervous	237	(82.0)	86	(30.8)
Somnolence	192	(66.4)	58	(20.8)
Dizziness	124	(42.9)	35	(12.5)
Confusion	47	(16.3)	5	(1.8)
Nervousness	42	(14.5)	17	(6.1)
Anxiety	31	(10.7)	3	(1.1)
Respiratory	97	(33.6)	21	(7.5)
Dyspnea	38	(13.1)	8	(2.9)
Cough increased	30	(10.4)	2	(0.7)
Skin and appendages	116	(40.1)	39	(14.0)
Pruritus	84	(29.1)	22	(7.9)
Sweating	42	(14.5)	16	(5.7)

[a]Includes subjects from studies HD95-0801, HD95-0802, HD95-0803, and HD99-0201.
[b]Includes subjects from studies HD95-0801, HD95-0802, HD99-0201, HMP3005, and HMP3006.
Cross-reference: NDA Amendment, Table A.23.

To examine the potential influence of duration of treatment on the observed differences in frequencies of adverse events between HHER-treated subject with malignant pain and those with non-malignant pain, the Sponsor has calculated adverse event rates per day, using a person-time methodology. These data are presented in Table 9.12.2.2, reproduced below. The rate is higher for the HHER-treated group (0.355 per day) compared to the placebo-treated group (0.167 per day). Thus, within the limits of the conclusions that can be made on the basis of person-time methodology, duration of therapy does not completely account for the higher frequency of adverse events in HHER-treated subjects with malignant pain.

Table 22.

Sponsor Table 9.12.3.2.

Rate of Adverse Events for Subjects Receiving HHER for Malignant and Chronic Nonmalignant Pain Subgroups – Phase 3 Studies[a]: Safety Population

Study Group	Treatment	No. of Subjects Exposed	No. of Reports of Event[b]	Subject Days of Exposure[c]	Event Rate (per Day)[d]
Malignant pain	HHER	289	5406	15,223	0.355
Chronic nonmalignant pain	HHER	279	885	5,309	0.167
Total in Phase 3 studies	HHER	568	6291	20,532	0.306

[a]Studies HD95-0801, HD95-0802, HD95-0803, HD99-0201, HMP3005, and HMP3006.

[b]Total number of reports by the subjects with at least 1 adverse event.

[c]Sum of exposures to treatment for all treated subjects. Exposure is calculated as (stop date – start date) + 1.

[d]Calculated as (b) divided by (c).

Cross-references: Current NDA Amendment, Tables A.10 and A.26.

Comments: Adverse Events in All Clinical Studies:

The current submission has focused on adverse events in the Phase 3 clinical studies. The Sponsor has also provided, in Table A9.1, adverse event frequencies for all clinical studies, which included 785 subjects. The most frequently reported adverse events associated with HHER- treatment were nausea (36.8%), somnolence (34.3%), and constipation (31.2%). Overall, the adverse event profile for all clinical studies was consistent with the adverse event profile for the Phase 3 studies. In his review of safety from the original NDA submission, Dr. Monte Scheinbaum described the adverse events in Phase 1 studies. The common adverse events in the Phase 1 studies were consistent with the known side effect profile of opioids.

Conclusions:

The overall adverse event profile for this drug product is similar to and as expected for an extended-release, potent opiate, oral formulation. There were no unexpected findings in review of the deaths, serious adverse events, and adverse events leading to subject discontinuation. While the sponsor attempts to attribute the higher incidence of many adverse events in the malignant pain population compared to the non-malignant pain population to the patients' underlying disease, it is also possible that the increased frequency of events is related to the significantly higher doses seen in the terminal cancer patients. The sponsor's contention that the higher incidence of adverse events associated with HHER vs. HHIR exposure is due to length of treatment is not fully supported by analysis of the data.

Recommendations:

Approval of this product is supported by this review.

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/s/

Bob Rappaport
9/13/02 04:12:25 PM
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9/13/02 04:54:52 PM
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Review and Evaluation of Clinical Data [redacted]

NDA: 21-044

Product: Palladone™ (hydromorphone hydrochloride extended- release) 12 mg Capsules

Sponsor: Purdue Pharma L.P.

Amendment Submission Date: March 12, 2002

Material Reviewed: Electronic Submission of Clinical Study HMP-3006

Medical Reviewer: Michael J. Sevka, M.D.

Review Date: September 6, 2002

Executive Summary for Product: Palladone™ (hydromorphone hydrochloride extended- release) 12 mg, 16 mg, 24 mg, and 32 mg Capsules

Hydromorphone is an opiate analgesic first marketed in 1926 and approved for marketing in the United States prior to 1968. It is marketed as an injectable and as oral tablets in 2 mg, 4 mg and 8 mg strengths. The usual oral dose in nonopioid-tollerent patients is 2 to 4 mg every 4 to 6 hours followed by graduate dose increase until adequate analgesia is obtained with dosage individualized based on patient response and tolerance. In chronic pain it is administered around the clock.

Palladone™ (hydromorphone hydrochloride extended- release) capsules are a once-a-day, extended-release formulations indicated [

]

This formulation has been developed to deliver the total daily dose of hydromorphone over a 24-hour period to allow for the convenience of once-a-day dosing. This formulation is not intended to be used on a prn basis or as the first opioid product prescribed for a patient. The formulation must be swallowed whole or sprinkled on a small amount of soft food because chewing, dissolving or crushing the contents leads to rapid absorption of a potentially fatal dose. All strengths are reserved for patients already being treated with opiates.

Overall the sponsor submitted the results of six clinical trials in support of an efficacy claim for management of moderate to severe chronic pain. Only trial, HMP-3006 the object of this review, was successful in demonstrating efficacy in the management of non-malignant pain. All other trials in malignant, non-malignant, and post-operative pain were unsuccessful in demonstrating efficacy.

Study HMP-3006 was a multiple-dose, double-blind, randomized, parallel-group, multi-center, placebo-controlled study assessing the efficacy and safety of HHER dosed once daily in moderate to sever chronic non-malignant pain. The study consisted of 2 phases:

2 period baseline phase (i.e. screening period and open-label titration period) and double-blind phase. The study treatment for the open-label, run-in period was hydromorphone 2-mg immediate-release tablets (HHIR) as needed every 4 to 6 hours titrated daily for up to 10 days up to a maximum of 16 mg/day. Subjects were continued into double-blind phase if their pain was controlled at 1-2 level (none to mild) on a 5-point pain scale and their daily dose was within 8-16 mg per day of HHIR. The treatment for double-blind phase was one capsule of hydromorphone extended-release capsule 12 mg once daily for up to 28 ± 2 days.

The primary efficacy variable was to be time in days from the first dose of study medication in the double-blind phase to Emergence of Inadequate Analgesia (EIA).
The secondary efficacy variables were:
1) the Subject Global Assessment of Pain Medication conducted at each visit and phone contact from Day 0 to 28 of double-blind phase and at early study completion/discontinuation, in response to the question, "How would you rate your medicine for pain?" subjects were to rate their pain medication on a 5-point categorical scale, where 1 = poor, 2 = fair, 3 = good, 4 = very good, and 5 = excellent.
2) The Pain Control Questionnaire administered on Day 14 and Day 28 of double-blind phase and at early study completion/discontinuation, in response to the question, "How good is your pain control around-the-clock?" subjects rated their 24-hour pain control on a 4-point categorical scale, where 0 = usually poor, 1 = effective some of the time, 2 = effective most of the time, and 3 = usually effective around-the-clock.
Study Results:
The mean time from the first dose of study medication in the double-blind phase to the Emergence of Inadequate Analgesia was 18.7 days for subjects randomized to HHER vs 9.0 days (p value = 0.0001) for subjects randomized to placebo.

The Global assessment was significantly higher for subjects treated with HHER than with placebo (P<0.0001); Mean ±SEM 2.6 ± 13 vs 1.8 ± 0.11.

For the Pain Control Questionnaire (Rated on Days 14 and 28),subjects randomized to HHER rated pain control "effective most of the time" or "usually effective around the clock" (Scores = 2 or 3, respectively) vs 21% for placebo. The majority of subjects in the placebo group (59%) reported pain control as "usually poor" (Score = 0).

The safety profile of HHER was similar to other drugs in this class of drugs. The incidence of adverse events that were reported during the double-blind phase in >2% of subjects and reported at approximately 3-fold or greater incidence in the HHER-treated subjects compared to placebo-treated subjects were: headache, asthenia, fever, constipation, arthralgia, somnolence, bronchitis, and pruritus. Sinusitis was reported only in the HHER group. Vomiting, diarrhea, dizziness, and nervousness, were reported at approximately 2-fold greater incidence in the placebo group compared to the HHER group. Sweating and peripheral edema were reported only in the placebo group. Interpretation of these incidence rates should take into account that the HHER group was exposed to treatment approximately twice as long as the placebo group. Similar events occur with other opiate administration or discontinuation and in general do not appear to

be occurring at a greater rate than expected with other opiates. These events occurred at the 12 mg per day dose and may increase in frequency at higher doses.

The results of this trial support the efficacy and safety of Palladone™Capsules in the management of chronic pain.

1.0 Introduction and Background

NDA 21-044 was originally submitted to FDA on 12/29/98. Final review of this original application concluded that the sponsor had not demonstrated the effectiveness of hydromorphone hydrochloride 12, 16, 24, and 32 mg extended-release capsules (HHER). This conclusion was based on the review of three clinical trials, HD96-0505, HD95-0801, and HD95-0802. Subsequently, it was required that the sponsor perform one well-controlled study demonstrating effectiveness of Palladone™ over placebo or a dose control, particularly at the lowest proposed dose.

According to the medical officer review (MOR) by Dr M Scheinbaum, HD96-0505 was the only placebo-controlled trial; it was a placebo-controlled, randomized, double-blind, parallel, single-dose, double-dummy, single-center trial, in the immediate postoperative period following orthopedic surgery. This study compared extended-release capsules (HHER 2 X 12 mg) to immediate release (HHIR) and placebo. The primary efficacy variable was the amount of rescue fentanyl administered as patient-controlled analgesia during each of four time intervals – 0-3, 3-6, 6-12, and 12-24 hours. According to the final review, statistical significance was lost when an appropriate statistical assumption was used other than the assumption selected by the sponsor.

According to the MOR by Dr M Scheinbaum, studies HD95-0801and HD95-0802 were two period crossover trials of identical design comparing extended-release to immediate-release hydromorphone hydrochloride in subjects with cancer-related or chronic non-malignant pain. Subjects requiring at least 12 mg of opioid equivalent per day were enrolled into a non-randomized, open-label titration period of 4 to 21 days duration with HHER to achieve stable pain control for at least 48 hours. Those subjects who achieved stable pain control were randomized into the double-blind period of treatment with their stable dose of HHER administered as either HHER or HHIR for a period of 3-7 days, followed by 3-7 days of treatment with the other formulation. The primary endpoint was the patient-rated pain intensity scores for each treatment averaged over the last 2 days of each double-blind period using an 11-point intensity scale. The results from the ITT and efficacy populations showed no statistically significant difference. Because these trials had no placebo arm or internal measure of assay sensitivity they were not deemed as evidence that either treatment was truly effective.

Because the original NDA was deemed approvable if additional positive data were available, the sponsor conducted Study HPM 3005 in subjects with moderate to severe pain due to osteoarthritis requiring between 8-14 mg hydromorphone equivalent opioid for adequate pain control. Study HMP-3005 was a parallel-group, placebo-controlled, double-blind, randomized trial in three phases – screening, open-label titration with

HHIR for up to 14 days, and a double-blind 28±2 day phase. The primary endpoint was the average pain intensity over the previous 24 hours during each of the 2 days preceding each of the 2 week and 4 week clinic visits (i.e. Days 12, 13, 26 and 27). Because study HMP-3005 also failed to demonstrate efficacy a non-approvable letter was issued. Subsequently, the sponsor elected to conduct another study, HMP-3006, that currently forms the basis for demonstration of efficacy of this NDA amendment.

1.1 Review Purpose
The purpose of this review is evaluate the adequacy of efficacy and safety data from clinical trial, HMP-3006, to support approval of Palladone™ as an oral extended-release analgesic product for single daily dosing.

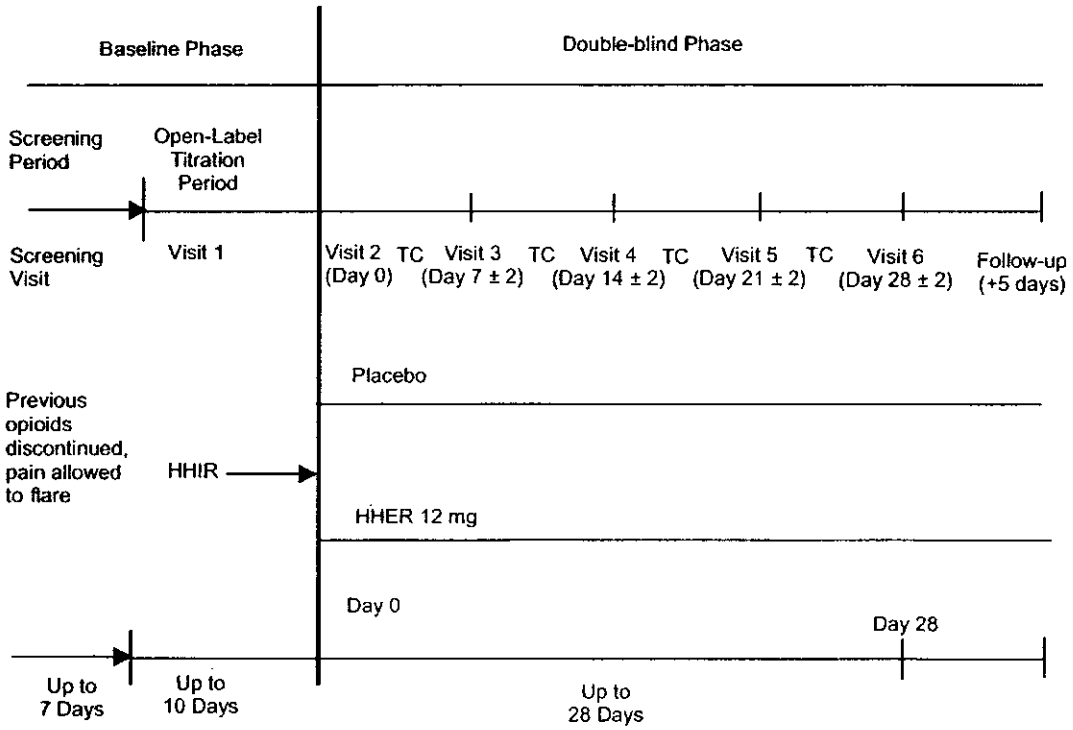
1.3 Study Dates - 10/30/00 to 4/18/01

2.0 Significant Findings from Chemistry, Animal Pharmacology, and Toxicology
There is nothing new to report.

3.0 Human Pharmacokinetics and Pharmacodynamics
There is nothing new to report.

4.0 Description of Clinical Data and Sources
In addition to the trials previously submitted and described under Section 1.0 of this review, the sponsor has submitted one additional trial, HMP-3006, entitled "*A Study of the Efficacy and Safety of Hydromorphone Hydrochloride Extended-Release (HHER) Compared to Placebo in Patients with Chronic Pain.* The objective of this study was to compare the efficacy and safety of HHER12-mg capsules taken once every 24 hours versus that of placebo in subjects with chronic pain who require an opioid medication for control of their pain."

4.1 Study Design
This study was to be a multiple-dose, double-blind, randomized, parallel-group, multi-center, placebo-controlled study assessing the efficacy and safety of HHER dosed once daily. The sponsor indicates that the study was to consist of 2 phases: 2 period baseline phase (i.e. screening period and open-label period) and double-blind phase. Reproduced below is Figure 9.1 that is the sponsor's schematic representation of the basic study design reproduced from page 22 of the sponsor's clinical study report (CSR).



TC = Telephone Contact (occurred approximately 72 hours after each visit).

Screening Period

During screening, subjects were to be discontinued from current opioid therapy and their pain was to be permitted to flare. Subjects were to be instructed to assess their pain daily based on a Pain on Average Scale from 0 = No Pain, 1=Mild Pain, 2=Moderate Pain, 3=Moderately Severe Pain, 4 = Severe Pain.

Open-label, Run-in Period

Subjects were to be eligible for entry into the open-label run-in period if they rated Pain on Average as moderately severe or severe (pain rating of 3 or 4) for at least one day during the screening period. During the open-label, run-in period, all subjects were to receive hydromorphone hydrochloride immediate-release (HHIR) 2-mg tablets every 4-6 hours in ascending doses titrated once every 24 hours for up to 10 days until they achieved adequate analgesia as determined by the investigator. Rescue medication was not to be permitted. Pain on Average score was to be collected daily by telephone contact.

Double-Blind Treatment Phase

Subjects were to be eligible for entry into the double-blind phase if they met five criteria:

(1) were on a target dose of HHIR 12 mg per day (range 8 to 16 mg per day) for at least 3 consecutive days;

(2) rated Pain on Average as none or mild (score of 0 or 1 on the 5-point Pain on Average Scale) on the last day of the time period when their total daily dose had stabilized within the target 8 to 16 mg range;

(3) had tolerable adverse events;

(4) returned unused HHIR; and

(5) immediately prior to randomization in the double-blind phase, rated their pain medication as "Good," "Very Good," or "Excellent" (score of 3 to 5) on the 5-point Subject Global Assessment of Pain Medication scale.

During the double-blind phase, subjects were to receive either one 12-mg HHER capsule or one placebo capsule in the clinic on Day 0, and subsequently were to take study medication every 24 ± 2 hours for up to 28 ± 2 days. The double-blind study medication was not to be titrated.

Occasional use of rescue medication, ≤2 doses of a short-acting analgesic per week) was to be permitted for the treatment of acute pain.

Other permitted medications were to include the following:

Analgesics (aspirin and acetaminophen) could be permitted for reasons other than analgesia for chronic pain (e.g., to treat headache, fever, and for cardioprotection).

Concomitant use of NSAIDs, aspirin, COX-2 Inhibitors, and acetaminophen could be permitted if the dose had been stable for at least 1 month and continued at the same dose level for the duration of the study

Antidiarrheal agents containing the weak opioid diphenoxylate hydrochloride could be permitted.

Oral corticosteroids could be permitted if doses had been stable for at least 6 weeks prior to screening.

Concomitant use of glucosamine and/or chondroitin sulfate could be permitted if the dose had been stable for at least 2 months prior to screening and continued at the same dose level for the duration of the study.

Chemotherapy and radiation could be permitted if the treatment, in the opinion of the investigator, was not expected to substantially alter the subject's analgesic requirement.

Adjuvant analgesics, such as antidepressants (i.e., amitriptyline, desipramine, nortriptyline, selective serotonin reuptake inhibitors) and anti-convulsant medications (i.e., gabapentin, lamotrigine) could be permitted if doses had been stable for at least 1 month prior to the screening visit and continued at the same dose level for the duration of the study.

Medications that were to be prohibited included:

Pre-study opioid medications were to be discontinued during the screening period, and all opioid analgesics other than those supplied for the study were to be prohibited

throughout the study. An exception was made for short-acting opioid analgesics, which could be given no more than twice a week for acute pain.

Intraarticular, epidural, or other corticosteroid injections were not to be permitted for 6 weeks prior to screening or during the study.

No new analgesic therapy was to be permitted during the course of the study, except as noted below.

Subjects were to have contact with the site at least twice a week, either by telephone or office visit. Subjects were to be considered to have Emergence of Inadequate Analgesia if they had unacceptable pain control in the judgment of the investigator, determined by:

(1) a rating of 1 (poor) or 2 (fair) on the 5-point categorical Subject Global Assessment of Pain Medication scale; or

(2) unacceptable pain control (i.e., subjects rated Pain on Average for the previous 24 hours as moderate to severe); or

(3) subjects took more than two doses of rescue medication in one week; or

(4) subjects discontinued study medication due to lack of efficacy.

Subjects completed the study either on Day 28, or when they reached the study endpoint of Emergence of Inadequate Analgesia.

4.2 Study Treatments

Open-Label, Run-in Period - HHIR 2-mg tablets as needed every 4 to 6 hours up to a maximum of 16 mg/day, for up to 10 days.

Double-Blind phase - HHER 12-mg capsule or matching placebo capsule dosed once daily for up to 28 ± 2 days.

4.3 Schedule of Visits and Procedures

Below is Table 9.5.1 that displays the schedule of visits and procedures reproduced from page 30 of the sponsor's CSR. It summarizes the activities and measurements to be collected across the entire course of the study.

Schedule of Visits and Procedures

	Baseline Phase				Double-blind Phase									
	Screening Period		Open-label, Run-in Period											
	Screening Visit	Screening Period[a]	Visit 1	Titrate (Up to 10 days)	Visit 2 (Day 0)	Tel. Contact	Visit 3 (Day 7 ± 2)	Tel. Contact	Visit 4 (Day 14 ± 2)	Tel. Contact	Visit 5 (Day 21 ± 2)	Tel. Contact	Visit 6 (Day 28 ± 2)[b]	5-Day Follow-up
Consent form	X													
Inclusion/ exclusion	X													
Demography	X													
Medical history	X													
Physical exam	X												X	
Serum or urine pregnancy test	X													
Vital signs	X				X[d]		X[d]		X[d]		X[d]		X	
Pain on Average	X		X	X	X	X	X	X	X	X	X	X	X	
Labs	X												X	
Discontinue all pain meds for flare-up		X												
HHIR accountability					X									
Qualifying criteria	X				X									
HHIR dosing				X										
HHER dosing					X		X		X		X		X	
Pain Control Questionnaire									X				X[e]	
Subject Global Assessment					X	X	X	X	X	X	X	X	X	
Compliance						X	X	X	X	X	X	X	X	X
Prior and concom. medications	X		X		X	X	X	X	X	X	X	X	X	X
Adverse events			X	X	X	X	X	X	X	X	X	X	X	X
Symptom Rating Scale													X	
Dosage determination			X	X										
Completion/ discontinuation													X	

[a]Screening Period: Up to 7 days.
[b]Or at completion due to Emergence of Inadequate Analgesia, or at early discontinuation
[c]Amendment 1: Removed Surgical History from Schema.
[d]Amendment 3: Vital Signs were to be collected at visits 2, 3, 4, and 5 in addition to screening, and visit 6.
[e]Pain Control Questionnaire was performed at the early completion/discontinuation visit only if it occurred prior to visit 4.

4.4 Inclusion Criteria

Males or non-pregnant females, 18 years or older, with chronic pain of at least 1 month's duration who were currently taking up to 60 mg/day of oxycodone or opioid equivalents for control of their chronic pain (see Appendix F of the protocol in Appendix 16.1.1).

Using concomitant NSAIDs, aspirin, COX-2 inhibitors, and acetaminophen only if the dose had been stable for at least 1 month and was expected to continue at the same dose for the duration of the study.

Could be currently be treated with chemotherapy or radiation only if this therapy, in the opinion of the investigator, was not expected to substantially alter the subject's analgesic requirements.

Willing to discontinue their pre-study opioid medication and willing to accept the possibility of receiving placebo during the double-blind phase.

Suffering from coexisting disease states only if the condition was stable, had been present for at least 1 week, and was expected to remain stable during the study. Subjects could be receiving medication for the condition only if the medication had been at a stable dose for at least 1 week prior to Screening and was expected to remain stable during the study.

Able to swallow capsules whole.

Able to be contacted by telephone at the specified times.

Willing to be compliant, capable of subjective evaluation, and able to read, understand, and sign the written consent statement.

4.5 Exclusion Criteria

Subjects were to be excluded from the study if they:

Were already receiving opioid medication at an average total daily dose greater than 60 mg of oxycodone or opioid equivalents during the last week prior to study entry.

Were pregnant, nursing, or unwilling to use a medically recognized method of birth control (a pregnancy test was performed at the screening visit).

Were allergic to hydromorphone or who had a history of allergies to other opioids. This did not include subjects who experienced common opioid side effects (e.g., nausea, constipation).

Were scheduled to undergo elective surgery during the study period including dental and local procedures.

Had an unstable, coexisting disease.

Had a glycosylated hemoglobin level (Hb A1c) of 10% or greater.

Had a life expectancy of less than 6 months.

Had a past (within 5 years) or present history of substance abuse or alcohol abuse.

Had any lab value, which in the impression of the investigator might have subjected the subject to increased risk by being exposed to the medication.

Had a history of opioid withdrawal symptoms upon discontinuation of opioids.

Were taking, or who had taken, an investigational new drug within 30 days prior to study entry.

Were involved in active litigation over disability compensation or damages.

Had received intraarticular, intramuscular, or epidural corticosteroid injections within 6 weeks prior to the screening visit.

Had an increase in their dose of oral corticosteroids within 6 weeks prior to the screening visit.

Had clinically significant organ dysfunction or serious unstable disease or hospitalized for a mental illness or suicide attempt.

Had any condition that the investigator believed could cause the subject increased risk by being exposed to the medication in this study or which could have confounded the interpretation of this investigation.

Were receiving methadone for the treatment of their chronic pain (per Amendment

4.6 Primary Efficacy Variable
The primary efficacy variable was to be time in days from the first dose of study medication in the double-blind phase to Emergence of Inadequate Analgesia.

During the double-blind phase subjects were to report to the clinic once a week for assessment of pain and for determination of the Emergence of Inadequate Analgesia (EIA). Subjects would be also contacted by telephone once weekly, approximately 72 hours after each office visit. One scheduled on-site assessment could be conducted by telephone; but this option applied only to Visits 3 (Day 7), 4 (Day 14) and 5 (Day 21).

Subjects with unacceptable pain control were to be considered by the investigator to have the Emergence of Inadequate Analgesia. Criteria for the Emergence of Inadequate Analgesia were to include:
1) A rating of 1 or 2 on the Subject Global Assessment of Pain Medication 5-point categorical scale, in response to the question, "How would you rate your medicine for pain?" Subjects rated their medicine 1 = poor, 2 = fair, 3 = good, 4 = very good, or 5 = excellent.
OR
2) Unacceptable pain control defined as subjects rating Pain on Average for the previous 24 hours as moderate to severe. Pain on average was defined as 0=None, 1= Mild, 2=Moderate, 3=Moderately Severe, 4=Severe
OR
3) The subject took more than 2 doses per week of a short-acting analgesic for acute pain
OR
4) The subject discontinued double-blind study medication due to lack of efficacy.

4.6 Secondary Efficacy Variables

1) The Subject Global Assessment of Pain Medication

The Subject Global Assessment of Pain Medication was to be conducted at each visit and phone contact from Day 0 to 28 of double-blind phase and at early study completion/discontinuation. In response to the question, "How would you rate your medicine for pain?" subjects were to rate their pain medication on a 5-point categorical scale, where 1 = poor, 2 = fair, 3 = good, 4 = very good, and 5 = excellent.

2) The Pain Control Questionnaire

The Pain Control Questionnaire was to be administered on Day 14 and Day 28 of double-blind phase and at early study completion/discontinuation. In response to the question, "How good is your pain control around-the-clock?" subjects rated their 24-hour pain control on a 4-point categorical scale, where 0 = usually poor, 1 = effective some of the time, 2 = effective most of the time, and 3 = usually effective around-the-clock.

4.8 Assessment of Opioid Withdrawal Symptoms on Primary Endpoint

At the final study visit, the investigator was to rate the subjects for withdrawal symptoms on a 4 point categorical scale (0-3) for each of the following symptoms: yawning, itching, lacrimating, sluggish, runny nose, restlessness. Subjects were to be evaluated in a blinded manner at the time of Emergence of Inadequate Analgesia, or at 28 days, or at premature discontinuation. The investigator was to respond to the following, "Please comment on the level or magnitude of the following physical and behavioral characteristics in the subject." The investigator to rate each symptom on a 4-point categorical scale, where 0 = none at all; 1 = relatively unnoticeable but perceivable on close observation; 2 = fairly obvious (i.e., does not need close observation to notice); 3 = very obvious (i.e., is a persistent feature or appears bothersome to the subject).

An exploratory analysis was planned to assess whether possible opioid withdrawal in subjects randomized to receive placebo in the double-blind phase could have confounded the primary efficacy results for the Emergence of Inadequate Analgesia. The objective was to assess whether subjects randomized to placebo were able to assess their pain intensity accurately or whether the possible onset of withdrawal symptoms had confounded their pain assessment.

4.9 Safety Variables

Safety assessments were to consist of

1) monitoring of vital signs at each clinic visit;
2) clinical laboratory measurements at screening and final clinic visit (hemoglobin, hematocrit, WBC, glycosylated hemoglobin, alkaline phosphatase, AST, ALT, total bilirubin, GGT, BUN, creatinine, glucose);
3) pregnancy testing at screening.

No ECG monitoring was planned.

Study Completion vs Study Discontinuation: Subjects were to be considered to have completed he study if they reached the study endpoint of the Emergence of Inadequate Analgesia, or if they maintained adequate analgesia for the 28-Day double-blind phase. Subjects who discontinued for any reason other than inadequate analgesia were to be considered to have discontinued from the study.

5.0 Clinical Review Methods and Data Integrity

5.1 Overview of Materials Consulted in Review

The materials consulted in the review consisted of previous FDA reviews conducted medical officers and statisticians and the sponsor's electronic clinical study report for study HMP-3006.

5.2 Methods Used to Evaluate Data Quality and Integrity

For efficacy, the following were examined for study HMP-3006: study design including inclusion and exclusion criteria, appropriateness of the primary efficacy endpoint,

description of study conduct and methods of endpoint analyses. Additionally, the adverse event database was examined for the number of subjects exhibiting withdrawal signs and symptoms both as verbatim terms and COSTART terms This analysis was undertaken to support the separation from placebo was not an artifact of opiate withdrawal. This is discussed in greater detail under section 6.3 of this review.

For safety, the data on the available case report forms were compared to the line listings in the JMP database and in-text tables for subjects who withdrew do to adverse events, experienced serious adverse events, and experienced withdrawal symptoms. There was good correlation between these sources for patient age and gender, and investigator verbatim except for 4 subjects in the placebo group in the population that withdrew do to non-serious adverse events. The final visit of the case report form listed loss of efficacy for these 4 subjects. Further the disposition numbers of randomized patients provided in the in-text disposition table were examined using the A_DISCO JMP spread sheet; there was good agreement between these sources except for 2-3 placebo-treated subjects who dropped out due to insufficient analgesia. It is doubtful that these few discrepancies would substantially effect the outcome of safety or efficacy. Additionally the adverse event dictionary was examined for appropriate adverse event classification to COSTART preferred term and body systems; these classifications appeared appropriate.

5.3 Financial Information

The sponsor provides the following information in the "other" folder of the 3/12/02 submission regarding financial interests or arrangements "In this section is a completed Form FDA 3454, Certification: Financial Interests and Arrangements of Clinical Investigators, All the investigators who participated in HMP-3006 had no financial interests or arrangements as certified on the completed form."

6.0 Integrated Review of Efficacy

6.1 Efficacy Results – Primary Endpoint

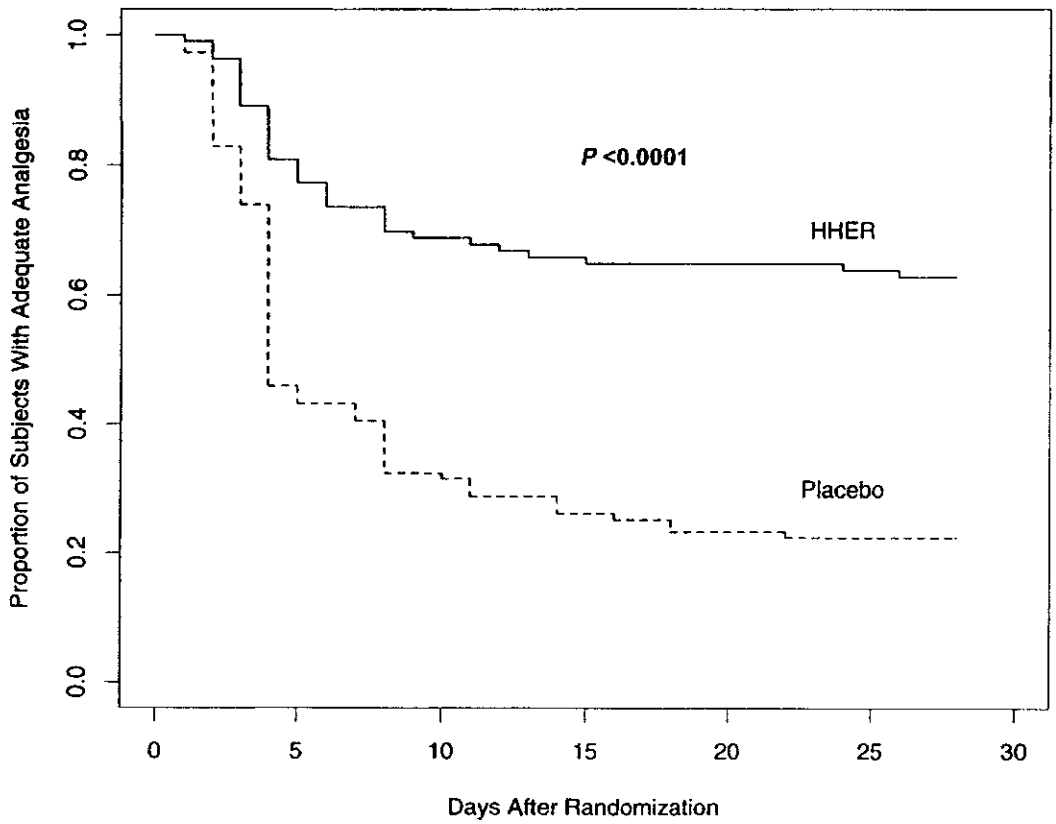
According to the sponsor the time to the Emergence of Inadequate Analgesia was derived using the Kaplan-Meier estimator. The results for the two treatment groups were compared using the log-rank test. For subjects who had adequate analgesia at the time of discontinuation, or who withdrew consent, or were lost to follow-up, the time to Emergence of Inadequate Analgesia was censored at the time of last study dose. For subjects who remained in the study for the entire double-blind phase, the time to Emergence of Inadequate Analgesia was censored at the end of the study. Any subject who took study medication after Day 28 in the double-blind phase was censored at Day 28.

Reproduced below is in-text Table 11.1.1 from pages 48-49 of the CSR. It displays the summary statistics for the time in days from the first dose of double-blind study medication to the Emergence of Inadequate Analgesia of the ITT population. The mean time from the first dose of study medication in the double-blind phase to the Emergence of Inadequate Analgesia was 18.7 days for subjects randomized to HHER vs 9.0 days (p

value = 0.0001) for subjects randomized to placebo. The median time to Emergence of Inadequate Analgesia was >28-days for subjects randomized to HHER vs 4 days for subjects randomized to placebo.

Summary Statistics[a] for Time (Days) from the First Dose of Double Bind Medication to the Emergence of Inadequate Analgesia: ITT Population		
	Placebo	**HHER**
	(N = 111)	**(N = 110)**
Time (Days) to Endpoint (Emergence of Inadequate Analgesia)		
Mean ± SEM	9.0 ± 0.75	18.7 ± 0.97
Median	4.0	>28.0
Min, max	1, >28	1, >28
Quartiles		
75%	18	>28
50%	4	>28
25%	3	6
[a] The summary statistics are estimated using the Kaplan-Meier Estimator.		
For censored subjects, the day of censoring was used in the Kaplan-Meier Estimator.		
Cross-reference: Table 14.2.1 and Appendix 16.1.9.3.		

Reproduced below is in-text Figure 11.1.1 from page 50 of the CSR. It displays the results for the time from the first dose of study medication in the double-blind phase to the Emergence of Inadequate Analgesia for the ITT population. The time from the first dose of double-blind study medication to the Emergence of Inadequate Analgesia was estimated using Kaplan-Meier Estimator, and the results for the two treatment groups were compared using the long-rank test. The time from the first dose of double-blind study medication to the Emergence of Inadequate Analgesia was significantly longer in the HHER group compared with the placebo group (P<0.0001)



6.2 Efficacy Results – Secondary Endpoints

According to the sponsor results of both the Subject Global Assessment of Pain Medication and Pain Control Questionnaire were analyzed using an analysis of variance (ANOVA) model, including the main effects of treatment and center.

Subject Global Assessment of Pain Medication
(Rated on Days 0, 3, 7, 10, 14, 17, 21, 24, 28)
Reproduced below is in-text Table 11.2.1 and in-text Figure 11.2.1A from page 53 of the CSR. For the ITT population they present the mean ± standard error of the mean [SEM]) Subject Global Assessment of Pain Medication rating at Day 14 or discontinuation, whichever came first. The Global assessment was significantly higher for subjects treated with HHER than with placebo (P<0.0001); and the median rating was "good" for subjects randomized to HHER, compared with "poor" for subjects randomized to placebo.

Mean (±SEM) Scores, Subject Global Assessment of Pain Medication: ITT Population			
Global Assessment of Pain Medication[a]	**Placebo (N = 110)[b]**	**HHER (N = 110)**	***P* Value[c]**
Mean ±SEM	1.8 ± 0.11	2.6 ± 13	*P*<0.0001
Median	1.0	3.0	
Min, max	1, 5	1, 5	

[a] 1 = poor; 2 = fair; 3 = good; 4 = very good; 5 = excellent.
[b] One subject (2162/32274 [placebo]) did not complete a Global Assessment of Pain Medication.
[c] *P* value for comparing 2 treatments at day 14 or discontinuation (whichever occurred first) was obtained from an ANOVA including the main effects if treatment and center.
Cross-reference: Table 14.2.2.1 and Appendix 16.1.9.3.

Pain Control Questionnaire (Rated on Days 14 and 28)
Reproduced below is in-text Table 11.2.2 and in-text Figure 11.2.2A from page 54 of the CSR. For the ITT, 56% of subjects randomized to HHER rated pain control "effective most of the time" or "usually effective around the clock" (Scores = 2 or 3, respectively) vs 21% for placebo. The majority of subjects in the placebo group (59%) reported pain control as "usually poor" (Score = 0).

Mean (± SEM) Scores, Pain Control Questionnaire: ITT Population			
	Placebo	**HHER**	
Pain Control Questionnaire[a]	**(N = 109[b])**	**(N = 107[b])**	***P* Value[c]**
Mean ± SEM	0.7 ± 0.1	1.5 ± 0.1	<0.0001
Median	0.0	2.0	
Min, max	0, 3	0, 3	
[a] 0 = usually poor; 1 = effective some of the time; 2 = effective most of the time; 3 = usually effective around-the-clock.			
[b] Two subjects in the placebo group and three subjects in the HHER group did not complete the Pain Control Questionnaire.			
[c] *P* value for comparing 2 treatments was obtained from an ANOVA, including effects of treatment and center.			
Cross-reference: Table 14.2.2.2.			

6.3 Evaluation of Subjective Signs and Symptoms of Opioid Withdrawal
In-text Table 11.2.3A is reproduced below. It shows the mean of the sum of opioid withdrawal symptom ratings was 0.5 for HHER and placebo. The sum of the six withdrawal symptom ratings was compared between treatment groups using a two-sample (two-sided) t-test. There was no significant difference (at a level of α= 0.05) between the two treatment groups. Therefore, as stated in the Statistical Analysis Plan, no further assessment of opioid withdrawal on the primary endpoint was performed.

Mean (±SEM) of the Sum of Six Withdrawal Symptom Ratings: ITT Population			
	Placebo	**HHER**	
Symptom Ratings Scale[a]	**(N = 110[b])**	**(N = 108[b])**	***P* Value[c]**
Mean ± SEM	0.5 ± 0.11	0.5 ± 0.12	0.6207
Median	0	0	
Min, max	0, 6	0, 7	
[a] Six symptoms rated by the investigator on a 4-point scale (0 = none at all; 1 = relatively unnoticeable; 2 = fairly obvious; 3=very obvious; for a maximum possible score of 18			
[b] One subject in the placebo group and two subjects in the HHER group did not complete			

evaluations for opioid withdrawal Symptoms			
[c] P value for comparing 2 treatments was obtained from a two-sample (two-sided) t-test.			
Cross-reference: Table 14.2.3.			

In addition, the sponsor conducted an unplanned-blinded evaluation of adverse events for subjective signs and symptoms consistent with opioid withdrawal. Using the terms listed below, the sponsor examined, the verbatim reported terms and their temporal characteristics relative to study treatment administration. They identified 9 subjects whose adverse events were consistent with withdrawal. These 9 subjects are listed in in-text Table 11.2.3B reproduced below. Subjects were considered to have **definite** withdrawal if a diagnosis was made by the Principal Investigator and could be substantiated from the subjective assessment of signs and symptoms. Subjects were considered to have **probable** withdrawal if a cluster of symptoms (2-3 or more) consistent with opioid withdrawal occurred near the start of the double-blind treatment phase, without a definite intercurrent or concurrent illness of more probable etiology. Subjects were considered to have **possible** withdrawal if at least 1 symptom consistent with opioid withdrawal occurred near the start of the double-blind treatment, and the symptoms resolved in 3-5 days.

Characteristic of opioid agonist activity	Characteristic of opioid agonist activity and opioid withdrawal	Characteristic of opioid withdrawal
Bradycardia	Agitation/hyperactivity	Craving
Constipation	Anorexia	Anger/irritability/ Nervousness
Dizziness	Apathy/anhedonia	Hyperalgesia
Drowsiness, sleepiness	Disordered temperature perception	Hyper-responsiveness
Flushing	Fatigue/asthenia/myasthesia	Diarrhea
Garrulousness	Insomnia	Abdominal cramping
Peripheral edema	Mood lability/dysphoria	Hypertension
Pupillary constriction	Nausea	Tachycardia
Pruritus	Restlessness	Myalgia (multiple sites)
Relaxation	Sexual dysfunction	Chills
Sedation	Vomiting	Piloerection
Somnolence		Frank chills
		Sweating/Cold sweats
		Yawning
		Rhinitis
		Nasal congestion (URI/FLU/Cold)
		Tremulousness,
		Shaking/nervousness

Subjects with Adverse Events Consistent with Withdrawal Signs and Symptoms: ITT Population			
Investigator/ Subject No.	**Symptoms**	**Treatment**	**Completion Status[d]**
Definite opioid withdrawal signs or symptoms[a]			
1820/9007	Shaking, sweating, anxiety, diarrhea, myalgia	Placebo	EIA[e]
1820/9216	Diarrhea, runny nose, chills	Placebo	EIA
Probable opioid withdrawal signs or symptoms[b]			
2149/8177	Diarrhea, nausea, abdominal cramps	Placebo	EIA
2151/26060	Nausea, vomiting, fever, chills	Placebo	EIA
2169/27092	Diarrhea, vomiting, sweating	Placebo	EIA
Possible opioid withdrawal signs or symptoms[c]			
1820/9132	"Cold" symptoms	Placebo	28-days
1892/12050	Stomach cramping	Placebo	EIA
1892/12293	Cold sweats, nervousness, dyspnea	Placebo	EIA
2168/20123	Stomach cramps, cold sweats	Placebo	EIA
[a] Diagnosed as opioid withdrawal by the investigator and reported as an adverse event.			
[b] 2 – 3 opioid withdrawal signs or symptoms.			
[c] 1– 2 opioid withdrawal signs or symptoms.			
[d] Subjects completed either when they reached the endpoint of Emergence of Inadequate Analgesia, or at the completion of the 28-day double-blind phase			
[e] Emergence of Inadequate Analgesia.			
Cross-reference: Table 14.3.2.2, Appendices 16.2.1 and 16.2.7.1.			

All 9 subjects were assigned to placebo. One subject assigned to placebo completed the 28-day treatment period, while 8 subjects completed the study when they reached the end point of Emergence of Inadequate Analgesia. These 8 subjects were counted as having completed the 28-day double-blind phase, and the mean time from the first dose of study medication to the Emergence of Inadequate Analgesia was recalculated. Results showed that the mean time from the first dose of study medication in the double-blind phase to the Emergence of Inadequate Analgesia was still significantly longer for HHER compared with placebo (P=0.0001) (Table 14.2.1 and Appendix 16.1.9.3).

All subjects entering the trial were to have had at least 30 days of prior opiate use. So that no subject could be considered opiate-naïve. To be certain that any potential subject who dropped out were in fact not dropping out due withdrawal, I checked the JMP database, A_ADVCF, and examined the verbatim terms and COSTART terms for adverse events suggestive of withdrawal. I examined the data for subjects who discontinued during each of the first 2 weeks of the trial. The table below shows the results that twice as many subjects on placebo dropped out during the first week compared to active treatment. I discussed this finding with the statistician, Thomas Permutt, Ph.D. His opinion was that even the most conservative treatment of these data by treating all the placebo subjects as having had adequate pain relief would not change

the separation from of active treatment from placebo and that the finding of efficacy would be upheld. Considering that the half-of HHIR is brief necessitating administration every 6 hours, this many this excess of adverse events suggestive of opioid withdrawal is not necessarily surprising during the first week following randomization to placebo

Number of Subjects Exhibiting At Least One Symptom Of Withdrawal		
	Placebo	Palladone
> 0 ≤7 Days	18*	8
>7 ≤14 Days	4	5
>14 ≤21 Days	0	2
>21 Days	0	3
Total	22	18
* Includes two patients identified as having an AE described by the investigator as *withdrawal*		

7.0 Integrated Review of Safety

7.1 Subject Exposure

The sponsor reports that 390 subjects were screened of which 326 were enrolled in the open-label phase. Of the 326 subjects, 221 met the criteria for randomization. Reproduced below is in-text Table 10.5 from page 49 of the CSR. It displays the overall treatment exposure of the ITT population. During the double-blind phase, 110 subjects were exposed to HHER 12 mg and 111 subjects were exposed to placebo. The mean number of days of exposure for HHER was 19.8, compared with 10.5 for placebo. The median number of days of exposure for HHER was 28, compared with 4 for placebo. Sixty percent of subjects randomized to HHER received study treatment for 22 days or longer vs 22.5% of subjects randomized to placebo. Thirty percent of subjects randomized to HHER received study treatment for 7 days or less compared with 62% of subjects randomized to placebo.

Summary of Subject Exposure to Double-Blind Study Medication: ITT Population				
	Placebo		**HHER**	
	(N = 111)		**(N = 110)**	
Days of exposure				
Mean ± SD	10.5 ± 10.75		19.8 ±11.96	
Median	4		28	
Range	1 to 35		1 to 33	
Days	n (%)		n (%)	
0 to 3	33	(29.7)	14	(12.7)
4 to 7	36	(32.4)	19	(17.3)
8 to 14	14	(12.6)	10	(9.1)
15 to 21	3	(2.7)	1	(0.9)

22 or longer	25	(22.5)	66	(60.0)
Cross-references: Appendices 16.2.1 and 16.2.5.3.				

7.2 Subject Baseline Demographics

Reproduced below is in-text Table 10.4 from page 48 of the CSR. It displays the baseline demographics of the ITT population. It shows that similar proportions of each gender were randomized to each treatment but that approximately twice as many females were randomized to each treatment compared to males. It also shows a similar enrollment of white subjects to each treatment group but 6 to 8 fold greater enrollments than all other racial groups combined. With regard to age groups there was a similar proportion of subjects enrolled to each treatment by age groups with a small preponderance randomized to placebo in the 35-49 year old group and a small preponderance randomized to HHER in the 50-64 year old group; similarly the mean±SEM and range of age were virtually identical. Comparative demographics between treatments for height and weight statistically mimic those for age. Regarding type of pain, all subjects randomized were classified, as having non-malignant pain with the exception of 1 patient whose pain type was not recorded.

Subject Demographics: ITT Population						
	Placebo		**HHER**		**TOTAL**	
	(N = 111)		**(N = 110)**		**(N = 221)**	
Characteristic	n (%)		n (%)		n (%)	
Gender						
Male	35	(31.5)	38	(34.5)	73	(33.0)
Female	76	(68.5)	72	(65.5)	148	(67.0)
Race						
White	96	(86.5)	98	(89.1)	194	(87.8)
Black	9	(8.1)	6	(5.5)	15	(6.8)
Hispanic	6	(5.4)	5	(4.5)	11	(5.0)
Asian	0	(0.0)	0	(0.0)	0	(0.0)
American Indian	0	(0.0)	1	(0.9)	1	(0.5)
Age						
18–34	9	(8.1)	8	(7.3)	17	(7.7)
35–49	56	(50.5)	43	(39.1)	99	(44.8)
50–64	28	(25.2)	42	(38.2)	70	(31.7)
65–74	12	(10.8)	11	(10.0)	23	(10.4)
>74	6	(5.4)	6	(5.5)	12	(5.4)
Age (y)Mean ± SEM	50.1 ± 1.22		51.3 ± 1.16		50.7 ± 0.84	
Age Range	21–81		21–80		21–81	
Height (cm)Mean ± SEM	168.05 ± 0.94		169.03 ± 0.98		168.53 ± 0.68	
Height Range	146.0–194.9		144.8–198.1		144.8–198.1	
Weight (kg)[a] Mean	82.62 ± 2.24		87.55 ± 2.30		85.07 ± 1.61	

± SEM						
Weight Range	45.8–193.2		40.8–154.2		40.8–193.2	
Type of pain						
Malignant	0	(0.0%)	0	(0.0%)	0	(0.0%)
Non-malignant	111	(100.0%)	109	(99.1%)[b]	220	(99.5%)
[a]Subject 2188/34347 in the HHER group did not have weight recorded at baseline.						
[b]Subject 1285/1075 in the HHER group did not have "Type of Pain" recorded at baseline.						
Cross-reference: Table 14.1.3.						

7.3 Subject Disposition

In-text Table 10.1 from page 44 of the CSR is reproduced below. It presents the disposition of these 221 randomized subjects. Approximately 3 times as many subjects treated with HHER 12 mg compared to placebo-treated subjects completed 28-days of study; whereas approximately 2 times as many subjects treated with placebo compared to HHER-treated subjects completed study due to Emergence of Inadequate Analgesia.

Study Results Subject Disposition: ITT Population			
	Treatment Groups		
Category	**Placebo**	**HHER 12 mg**	**Overall Total**
	n (%)	n (%)	n (%)
Randomized	111 (100.0)	110 (100.0)	221(100.0)
Completed	109 (98.2)	103 (93.6)	212 (95.9)
28-days (i.e., End of the Study)	23 (20.7)	63 (57.3)	86 (38.9)
Emergence of Inadequate Analgesia[a, b, c]	86 (77.5)	40 (36.4)	126 (57.0)
Discontinued	5 (4.5)	9 (8.2)	14 (6.3)
Reason for discontinuation:			
Adverse Event[b]	4 (3.6)	7 (6.4)	11 (5.0)
Death	0	0	0
Lost to Follow-up	1 (0.9)	0	1 (0.5)
Protocol Violation	0	0	0
Other[c, d]	0	2 (1.8)	2 (0.9)
[a] These subjects are identified as "Discontinued due to ineffective treatment" in the CRFs but are considered complete because they met the study endpoint of Emergence of Inadequate Analgesia.			
[b] Four subjects (Subjects 1892/12083 [HHER], 2149/8177 [placebo], 2154/14107 [placebo], and 2165/25248 [placebo]) were categorized by the investigator both as discontinuing due to an adverse event and as meeting the study endpoint of Emergence of Inadequate Analgesia. These subjects are counted in both categories.			
[c] One subject (Subject 2162/32229 [HHER]) was categorized by the investigator both as discontinuing due to withdrawal of consent and as meeting the study endpoint of Emergence of Inadequate Analgesia. This subject is counted in both categories.			
[d] One subject (Subject 2164/23103 [HHER]) was non-compliant with treatment and pill count.			

C0ross-reference: Table 14.1.1.

7.4 Safety Results – Deaths
No deaths were reported for study HMP-3006

7.5 Safety Results – Serious Adverse Events
The sponsor has identified 8 subjects, 4 from each treatment group, and has provided narratives for each that are summarized below. No overdoses were reported. All these subjects were opioid-experienced. All these subjects appear to have had SAEs that could be related to preexisting conditions with the possible exception of subjects #3 and #6 who were randomized to placebo and subsequently self-admitted themselves for depression and substance abuse rehabilitation that might be viewed as responses to lack of opioid. No causal association of study treatment, active or placebo, to these events can be asserted for any of these subjects because of their medical histories and other risk factors that are more likely etiologies for these events.

1) Subject 1820-9132: 65-year-old opioid-experienced white male with a history of chronic pain of the hip and knee was hospitalized due to a **myocardial infarction** (MI) 20 days after randomization to **placebo**, recovered and completed the study. His prior medical history included lactose intolerance, hypertension, high cholesterol, skin cancer, loss of hearing, ulcer, frequent urination, arthroscopic surgery on left and right knees, severe degenerative disease of the left hip, degenerative disease of both knees, herniated disc of the neck, finger numbness and tingling, chronic obstructive pulmonary disease (COPD), allergy to aspirin, and environmental allergies. At screening medication history consisted of atenolol for hypertension, potassium chloride for dietary supplement, atorvastatin for high cholesterol, omeprazole for ulcer, oxycodone/acetaminophen for pain of the hip and knees, and flu shot for flu prevention. Treatment with study drug was interrupted for 1 day on 8-Jan-01. **Assessment**: the past medical history is significant for hypertension and a lipid disorder that are risk factors for MI. It is doubtful that exposure to study treatment precipitated his MI.

2) Subject 1892-12083: This 59-year-old opioid-experienced white female with a history of chronic pain discontinued **HHER** 1 day after randomization because of the emergence of inadequate analgesia and was hospitalized [redacted] days after randomization because of **atypical chest pain** The past medical history included tinnitus, intermittent sinus congestion, seasonal allergies, myopia/hyperopia, angioplasty, coronary artery disease, stable angina, heart attack, migraine headaches, shortness of breath with exertion, bilateral lower extremity edema, intermittent constipation, intermittent diarrhea, 18-inch bowel resection secondary to blocked bowels, acid reflux disease, cholecystectomy, endometriosis, hysterectomy, contact dermatitis, vaginal reconstruction, removal of a benign cyst in the right breast, degenerative disc disease, osteoporosis, broken back, hypothyroidism, removal of thyroid goiter, laminectomy, carpal tunnel surgery, ankle fracture, and anxiety. At the time of entry into the study the medication history included propoxyphene/acetaminophen and oxaprozin for chronic pain, levothyroxine for hypothyroidism, furosemide for fluid retention, simvastatin for hypercholesterolemia,

alprazolam for anxiety, conjugated estrogen for hormone replacement therapy, nitgroglycerin and baby aspirin for cardiac prophylaxis, and metoprolol for coronary artery disease and symptoms including angina. **Assessment**: the past medical history is highly complex including acid reflux disease, significant cardiovascular disease and use of multiple medications that confound interpretation. Clear causal association of study treatment to the event is confounded by medical history..

3) Subject 1892-12084: This 48-year-old opioid-experienced white male with a history of chronic pain experienced the emergence of inadequate analgesia 3 days after randomization to **placebo** and self- admitted himself to hospital [redacted] days after his last dose for **worsening depression**. His past medical history included occasional nasal congestion, 85% hearing loss and tinnitus of the right ear, loss of smell and taste, myopia and hyperopia, occasional dry mouth, degenerative arthritis in both knees, right and left knee arthoscopic surgery, edema of the lower extremity, tension headaches, occasional skin rash, shortness of breath with exertion, nausea and dyspepsia secondary to gastric reflux, blood in urine due to kidney stones, nocturia, occasional impotence, right fourth and fifth metacarpal numbness, chronic fatigue syndrome, amputation of right leg below the knee with subsequent removal of neuroma, occasional dizziness, short-term memory loss secondary to a car accident, insomnia, night sweats, depression, anxiety, and occasional agitation. At the time of entry into the study, he was receiving oxycodone, rofecoxib, and gabapentin for chronic pain, doxycycline for chronic fatigue syndrome, lansoprazole for gastric reflux, bupropion for depression, clonazepam for anxiety, and zolpidem for insomnia. **Assessment**: the subject was on multiple other medications and his past medical included depression, anxiety, and occasional agitation, all of which confound interpretation. No causal association of study treatment to the event is likely because of his past medical history.

4) Subject 2162-32277: This 53-year-old opioid-experienced white female with a history of chronic pain and randomized to **HHER** but discontinued after 5 days due to emergence of inadequate analgesia and 3 days after moderate cholecystitis was noted and required a **cholecystectomy** during the 5-day follow-up period. Her past medical history included asthma, hypertension, gastroesophageal reflux disease, mild liver cirrhosis, lupus, subacute right shoulder bursitis, right shoulder surgery, diabetes, anxiety, insomnia, intermittent lower extremity edema, chronic constipation, hysterectomy, allergy to penicillin, allergy to EES, allergy to pentazocine, allergy to ketorolac, allergy to meperidine, lower extremity neuropathy, migraines, and chronic abdominal pain. At screening, the subject was taking omeprazole for gastroesophageal reflux disease; nifedipine for hypertension; alprazolam for anxiety; amitriptyline, and gabapentin for lower extremity neuropathy; ursodiol for mild liver cirrhosis; acetaminophen/hydrocodone for pain; hydroxychloroquine for lupus; rizatripan benzoate for migraines; docusate/casanthranol for constipation; albuterol and triamcinolone for asthma; conjugated estrogens for hormone replacement; ibuprofen for shoulder pain; Refresh PM® for lack of tears secondary to lupus; furosemide for edema; insulin regular and insulin, isophane suspension, for diabetes; and seraquil for insomnia. In addition, at screening, the subject was noted with a clinically notable WBC value of 2.2 x10 9 /L (range for clinically notable: 3 to 15 x10 9 /L) and a clinically notable alkaline

phosphatase value of 398 U/L (range for clinically notable, 0 to 280 U/L). On the day following randomization the subject reported moderate abdominal pain and on the second day following randomization the onset of moderate cholecystitis was noted. At the end of the study an alkaline phosphatase value of 295 U/L was still noted. During the follow-up period, the severity of the cholecystitis increased from moderate to severe, and the subject underwent an outpatient cholecystectomy with resolution of the abdominal pain. **Assessment**: given this subject's medical history that includes chronic abdominal pain and an elevation of alkaline phosphatase at screening, it is unlikely that the cholecyctitis is associated with study treatment administration.

5) Subject 2162-32280: This 41-year-old opioid-experienced white female with a history of chronic pain was randomized to **placebo** and hospitalized one day before her last dose with a diagnosis of **urolithiasis** that required surgical intervention. The subject had a history of hypertension, depression, hypercholesterolemia, GERD, insomnia, angina, constipation, osteonecrosis, difficulty breathing, and history of kidney stones and lupus. At the time of entry into the study, she was receiving lisinopril for hypertension, paroxetine for depression, nortriptyline for insomnia, albuterol for difficulty breathing, hydroxychloroquine for lupus, atorvastatin for hypercholesterolemia, lansoprazole for GERD, hydrocodone/acetaminophen and rofecoxib for pain, calcium+D for nutritional supplement, and nitroglycerine for angina. **Assessment**: the past medical history is complex including a history of kidney stones and use of multiple medications that confound interpretation. This patient's history of kidney stones is more likely to be a contributing factor for this event..

6) Subject 2165-25248: This 40-year-old opioid-experienced white female with a history of chronic pain due to lumbar radiculopathy and randomized to **placebo was self-admitted to a substance abuse rehabilitation center** during the study. In addition to lumbar radiculopathy, the subject had a history of frequent bronchitis, reflux, and asthma. At the time of study entry, she was receiving oxycodone/acetaminophen for lumbar radiculopathy, carisoprodol for muscle spasm, and amitriptyline for insomnia. Screening vital signs were unremarkable. Screening nonfasting chemistry GGT value was more than 5 times the upper limit of normal, judged not clinically significant by the investigator. The subject received placebo for 16 days before presenting to a rehabilitation center for substance abuse. The investigator discontinued the subject due to substance abuse. **Assessment**: The case report form indicates that the subject discontinued due to the adverse event of substance abuse, not returning her HHIR and also overtaking her double-blind treatment. No causal association of double-blind study treatment to the event should be asserted.

7) Subject 2187-35353: This 50-year-old opioid-experienced Hispanic male had a history of mycosis fungoides, ankylosing spondylitis, gastric ulcer, seasonal allergies, and depression. A mycosis fungoides lesion was treated with radiation therapy in 1996, and resolved. The subject was notified of recurrence of **mycosis fungoides** 5 days after randomization to **HHER** based upon a biopsy obtained the day before randomization during a routine check-up. He completed the study. At the time of entry to the study, the subject was receiving hydrocodone/acetaminophen, celecoxib, and prednisone for

ankylosing spondylitis, omeprazole for prevention of gastric ulcer recurrence, fluoxetine for depression, and loratadine for seasonal allergies. **Assessment**: given the subjects past medical history of mycosis fungoides and recurrence based on a biopsy obtained before exposure to double-blind study treatment, exposure to double-blind HHIR can not be associated with recurrence.

8) Subject 2187-35357: This 70-year-old opioid-experienced white female with a history of chronic pain due to rheumatoid arthritis was randomized to **HHER** – days before **hospitalization for bilateral lower extremity ischemia** that was treated femoral-femoral bypass and partial amputation of the left foot because of gangrene. The subject had a history of osteoporosis, hypothyroidism, hysterectomy, allergy to penicillin, allergy to tetanus vaccine, intermittent claudication, hyperlipidemia, and peripheral vascular disease of the left and right feet. At the time of entering the study, she was receiving hydrocodone/acetaminophen for rheumatoid arthritis pain, rofecoxib for rheumatoid arthritis, aspirin for cardiac prophylaxis, and levothyroxine for hypothyroidism. Screening vital signs were unremarkable. At the time of database lock, she remained hospitalized for rehabilitation. **Assessment**: given this subject's past medical history of peripheral vascular disease of the feet, intermittent claudication, and hyperlipidemia, exposure to double-blind study treatment can not be associated with adverse event.

7.6 Safety Results – Dropouts Due to Adverse Events

Reproduced below is in-text Table 12.2.3.1 from page 85 of the CSR. It lists the subjects who discontinued from the study due to adverse events. Five subjects on HHER and 7 on placebo. Two subjects (#3 and #4) had AEs that were characteristic of withdrawal and were classified also as probable withdrawal. Nausea was the most common term among the AEs leading to discontinuation in 4 placebo-treated subjects and 3 HHER-treated subjects. Four of the HHER-treated subjects had AEs characteristic of opioid side effects. All subjects were considered to have recovered except subject #5 who experienced a URT infection. Similar events are associated with other opiate administration or discontinuation, with the exception of collapse of the lateral arch in subject # 12. It is important to recognize these events occurred at the 12 mg per day dose and may increase in frequency at higher doses.

Non-serious Adverse Events That Resulted in Discontinuation of Study Medication or Study Participation: ITT Population					
Treatment Group/ Subject	**Age/ Gender**	**Days to Onset[a]**	**Investigator Term**	**COSTART**	**Outcome**
Placebo					
1) 1944/19317	42/M	13	Constipation	Constipation	Recovered
		13	Decreased appetite	Anorexia	Recovered
		13	Nausea	Nausea	Recovered
		13	Vomiting	Vomiting	Recovered
2) 2036/24115	47/F	2	Restless	Nervousness	Recovered
			Difficulty	Insomnia	Recovered

			falling asleep		
3) 2149/8177	56/F	2	Headache	Headache	Recovered
		4	Abdominal cramps	Abdominal pain	Recovered
		4	Diarrhea	Diarrhea	Recovered
		4	Nausea	Nausea	Recovered
4) 2151/26060[b]	39/M	2	Nausea	Nausea	Recovered
		2	Vomiting	Vomiting	Recovered
		2	Chills	Chills	Recovered
		2	Fever	Fever	Recovered
5) 2154/14107	47/M	6	URT infection	Pharyngitis	Continuing
6) 2164/23104	81/F	1	Nausea	Nausea	Recovered
		1	Nervousness, shaking	Nervousness	Recovered
7) 2165/25246	62/M	4	Twitching of extremities	Twitching	Recovered
		5	Constipation	Constipation	Recovered
HHER					
8) 1944/19318	64/F	4	Drowsiness	Somnolence	Recovered
			Nausea	Nausea	Recovered
9) 2154/14109	77/M	26	Constipation	Constipation	Continuing
10) 2154/14234	48/F	8	Nausea	Nausea	Recovered
11) 2154/14235	34/F	4	Nausea	Nausea	Recovered
12) 2169/27282[c]	53/F	6	Left arch pain	Collapse of lateral arch, left foot	Recovered

[a] Number of days from start of double-blind study medication.

[b] Table 14.3.2.2 notes that study medication was discontinued due to these adverse events. According to the CRF, no action was taken. Section 9.8.3 notes the database error

[c] Subject discontinued due to an adverse event that began in the screening period.

Cross-reference: Table 14.3.2.2.

7.7 Safety Results – Withdrawal Symptoms as Adverse Events

Reproduced below is in-text Table 12.2.3.3 from page 65 of the CSR. It lists the subjects considered by the investigator to have withdrawal syndrome as were rated at the last visit according to a symptom rating scale. These 2 placebo-treated subjects were considered to have definite withdrawal symptoms by the investigator and occur with other opiates as well. It is important to recognize these events occurred at the 12 mg per day dose.

Subjects With Opioid Withdrawal Symptoms

Subject (Age/Gender)	Study Medication/ Days on Study Medication	Days to Onset[a]	Investigator Term	COSTART	Outcome
1820/9007 (42/male)	Placebo/3 days	2 days	Withdrawal Syndrome[b]	Withdrawal Syndrome	Recovered
1820/9216 (58/male)	Placebo/4 days	2 days	Withdrawal Syndrome[c]	Withdrawal Syndrome	Recovered
[a] Days to onset indicates number of days following the start of double-blind treatment.					
[b] Sluggishness, runny nose, and restlessness; symptoms were rated as "relatively unnoticeable, but perceivable on close observation" (rating=1).					
[c] Restlessness; symptoms were rated "fairly obvious, and did not need close observation" (rating = 2).					
Cross-references: Table 14.3.2.2 and Appendix 16.2.6.5.					

7.8 Safety Results – Common Adverse Events

Examination of the adverse event dictionary shows that verbatim events were reasonably subsumed to COSTART terms. Reproduced below is in-text Table 12.1.3 from page 59 of the CSR. It displays the incidence of adverse events that were reported during the double-blind phase in >2% of subjects. Events reported at approximately 3-fold or greater incidence in the HHER-treated subjects compared to placebo-treated subjects were: headache, asthenia, fever, constipation, arthralgia, somnolence, bronchitis, and pruritus. Sinusitis was reported only in the HHER group. Vomiting, diarrhea, dizziness, and nervousness, were reported at approximately 2-fold greater incidence in the placebo group compared to the HHER group. Sweating and peripheral edema were reported only in the placebo group. Interpretation of these incidence rates should take into account that the HHER group was exposed to treatment approximately twice as long as the placebo group. Similar events occur with other opiate administration or discontinuation and in general do not appear to be occurring at a greater rate than expected with other opiates. These events occurred at the 12 mg per day dose and may increase in frequency at higher doses.

Incidence of Adverse Events >2% in Any Treatment Group, Double-Blind Phase: ITT Population		
	HHER	**Placebo**
	(N = 110)	**(N = 111)**
	Double-Blind	**Double-Blind**
	n (%)	n (%)
Total number subjects with adverse events (incidence)	56 (50.9)	38 (34.2)
Body System/ COSTART Term		
Body as a whole	25 (22.7)	14 (12.6)
Headache	7 (6.4)	1 (0.9)
Asthenia	4 (3.6)	1 (0.9)
Abdominal pain	3 (2.7)	5 (4.5)
Infection	3 (2.7)	4 (3.6)

Fever	3 (2.7)	1 (0.9)
Digestive	30 (27.3)	15 (13.5)
Constipation	14 (12.7)	2 (1.8)
Nausea	11 (10.0)	9 (8.1)
Vomiting	2 (1.8)	4 (3.6)
Diarrhea	2 (1.8)	4 (3.6)
Metabolic and Nutritional	2 (1.8)	3 (2.7)
Peripheral edema	0	3 (2.7)
Musculoskeletal	4 (3.6)	3 (2.7)
Arthralgia	3 (2.7)	1 (0.9)
Nervous	11 (10.0)	16 (14.4)
Somnolence	4 (3.6)	1 (0.9)
Dizziness	2 (1.8)	4 (3.6)
Nervousness	2 (1.8)	5 (4.5)
Respiratory	15 (13.6)	7 (6.3)
Pharyngitis	6 (5.5)	4 (3.6)
Bronchitis	3 (2.7)	1 (0.9)
Sinusitis	3 (2.7)	0
Skin	5 (4.5)	6 (5.4)
Pruritus	3 (2.7)	1 (0.9)
Sweating	0	4 (3.6)
Total number of subjects with adverse events corrected for duration of exposure to double-blind medication		
Subject days of double-blind treatment	2176	1164
Total number of subjects with adverse events	56	38
Number of subjects with adverse events per subject day	0.03	0.03
Cross-reference: Table 14.3.1.1 and 14.3.1.7.		

7.9 Safety Results – ECGs

No 1ECGs measurements were planned or reported.

7.10 **Safety Results – Vital Signs**

Vital signs were taken at screening and at each clinic visit. Below are the criteria used for Determining notable changes in vital signs.

Systolic blood pressure	≥180 mm Hg	Increase of ≥20 mm Hg
	≤90 mm Hg	Decrease of ≥20 mm Hg
Diastolic blood pressure	≥105 mm Hg	Increase of ≥15mm Hg
	≤50 mm Hg	Decrease of ≥15 mm Hg
Heart rate	≥120 bpm	Increase of ≥15 bpm
	≤50 bpm	Decrease of ≥15 bpm
Respiratory rate	≤12 breaths per minute	---

≥20 breaths per minute —

Below in-text Table 12.4.1.3 is reproduced. It lists the two subjects that the sponsor identified with notable values. One subject in the HHER group experienced a reduction in diastolic blood pressure at Visits 2 and 4 that increased slightly at the last Visit. Another subject in the HHER group experienced at the end of the study. All the other vital signs remained stable for both subjects. These events are not of such magnitude at the 12mg per day dose to be of great clinical concern and are also associated with other other opiates.

Clinically Notable Vital Sign Results: ITT Population

			Blood Pressure			
	Treatment	Visit	Systolic (mm Hg)	Diastolic (mm Hg)	Pulse (bpm)	Respiration (brth/min)
Subject 1892/12054	HHER	Screening	98	70	78	18
		Visit 2	90	[50]	60	16
		Visit 4	84	[50]	68	18
		End of study	98	56	68	18
Subject	HHER	Screening	138	70	72	16
1905/10065		End of study	130	70	[50]	16

[ ] Indicates clinically notable result.

Cross-reference: Appendix 16.2.9.2.

7.11 Safety Results – Laboratory Results

Lab measurements were obtained at screening and study end. Table 12.3.4 lists the subjects with clinically notable lab abnormalities

The most common notable values are glucose in both treatment groups (6 – HHER; 4 – placebo). Two of the subjects in the HHER group had diabetes and another, with the highest value at study end (420 mg/dL) also had the highest elevated HgAc1 of 9.7%. Of the other 3 subjects, one had an elevated glucose at baseline that remained elevated at study end, one had a level just under the upper limit at baseline that became notable at study end, and one had a normal level at baseline that increased by approximately 115 units. Since the protocol did not specify that blood samples had to be drawn under fasting conditions it is difficult to attribute these findings to study treatment since some these fluctuations may be associated with other factors such as stress, diet, hydration status, and concomitant medications.

With regard to renal function results in the HHER group, 1 subject had an elevated BUN level at baseline that decreased by study end and an elevated creatinine at baseline that remained elevated but stable at study end. One other subject had a borderline BUN at

baseline that crossed the upper limit by 3 units. With regard to alkaline phosphatase results in the HHER group, one subject had an elevated level at baseline that improved by approximately 100 units by study end. These laboratory results do not support an association with active study treatment.

Clinically Notable Laboratory Abnormalities: ITT Population						
			Ranges Used to Identify Clinically Notable Results			
Study Group Subject	**Age/ Gender**	**Test**	**Lower**	**Upper**	**Screening**	**End of Study**
Hematology						
HHER						
1892/12054[a]	46/F	Hemoglobin (g/dL)	<10	>20	11.6	9.6
		Hematocrit (%)	<30	>60	33.4	27.8
2169/27283	41/F	WBC ($\square 10^9$/L)	<3.0	>15.0	9.4	16.4
Blood						
Chemistry						
Placebo						
1820/9129[b]	69/M	Blood glucose (mg/dL)	<50	>200	203	280
1842/15140	47/F	Blood glucose (mg/dL)	<50	>200	114	221
1905/10286	74/F	Blood glucose (mg/dL)	<50	>200	277	348
1944/19023[c]	48/M	SGOT (AST) (U/L)	0	>100	32	109[c, d]
2148/2250	78/M	BUN (mg/dL)	<2	>40	38	45
		Creatinine (mg/dL)	<0.2	>2.5	2.4	2.7
2154/14107		Blood glucose (mg/dL)	<50	>200	439	242
HHER						
1820/9004[a]	52/M	Blood glucose (mg/dL)	<50	>200	190	420
1820/9131	67/M	BUN (mg/dL)	<2	>40	39	43
1944/19019	71/F	Blood glucose (mg/dL)	<50	>200	211	235
2154/14110	79/M	BUN (mg/dL)	<2	>40	52	43
		Creatinine (mg/dL)	<0.2	>2.5	3.0	3.2
2154/14239	80/F	Blood glucose (mg/dL)	<50	>200	225	214
2162/32227	61/F	Blood glucose (mg/dL)	<50	>200	371[d]	308

2162/32277	53/F	Alkaline phos. (U/L)	0	>280	398	295
2162/32279	48/M	Blood glucose (mg/dL)	<50	>200	192	262
2163/21172	59/M	Blood glucose (mg/dL)	<50	>200	116	231
[a] Laboratory abnormality was recorded as an adverse event.						
[b] The medical history indicates this patient had diabetic neuropathy. The source documentation at the site confirmed that the patient had a history of diabetes mellitus.						
[c] Subject 1944/19023 had mildly elevated SGOT value at end-of-study (51 U/L) and a clinically notable elevated SGOT at the follow-up visit (109U/.L).						
[d] Denotes repeat value.						
Cross-references: Table 14.3.4.1 and Appendix 16.2.8.2.						

9.0 Conclusions and Recommendation

This study appears to support efficacy and safety of the test drug product with an adverse event profile similar to other opiates in patients with chronic pain that are 18 years of age and older in doses of 12 mg per day. However, it is important to recognize that the safety and efficacy profile demonstrated in study, HMP-3006 was at the 12 mg per day dose and can be expected to change with any increase in daily dosage.

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/s/

Michael Sevka
9/11/02 11:05:30 AM
MEDICAL OFFICER

Bob Rappaport
9/11/02 12:45:16 PM
MEDICAL OFFICER
I concur with Dr. Sevka's conclusions and recommendation.

Review and Evaluation of Clinical Data

NDA: 21-044

Product: Palladone™ (hydromorphone hydrochloride extended-release) 12 mg Capsules

Sponsor: Purdue Pharma L.P.

Submission Date: March 30, 2001

Material Reviewed: Clinical Trial - HMP3005

Medical Reviewer: Michael J. Sevka, M.D.

Review Date: September 20, 2001

1.0 Background

NDA 21-044 was originally submitted to FDA on 12/29/98. Final review of this original application concluded that the sponsor had not demonstrated the effectiveness of hydromorphone hydrochloride 12, 16, 24, and 32 mg extended-release capsules. This conclusion was based on the review of three clinical trials, HD96-0505, HD95-0801, and HD95-0802. Subsequently, it was required that the sponsor perform one well controlled study demonstrating effectiveness of Palladone™ over placebo or a dose control, particularly at the lowest proposed dose.

HD96-0505 was the only placebo-controlled trial; it was placebo-controlled, randomized, double-blind, parallel, single dose, double-dummy, single center, in the immediate postoperative period following orthopedic surgery. This study compared extended-release capsules (2 X 12 mg) to immediate release and placebo. The primary efficacy variable was the amount of rescue fentanyl administered as patient-controlled analgesia during each of four time intervals – 0-3, 3-6, 6-12, and 12-24 hours. According to final review, statistical significance was lost when an alternate assumption was used other than the assumption used by the sponsor.

Studies HD95-0801and HD95-0802 were two period crossover trials comparing extended-release to immediate release hyromorphone hydrochloride in patients with cancer-related or chronic non-malignant pain.

2.0 Review Purpose

The purpose of this review is to evaluate the adequacy of efficacy and safety data from clinical trial, HMP3005, as support for approval of Palladone™ as an oral extended-release analgesic product for single daily dosing.

3.0 Study Title - *Double-Blind, Randomized, Parallel-group, Placebo-controlled Trial to Evaluate the Efficacy and Safety of Hydromorphone Hydrochloride Extended-release 12 mg Capsules Compared to Placebo in Subjects with Osteoarthritis Who Have Moderate to Severe Pain*

4.0 Study Dates - 7/19/00 to 11/6/00

5.0 Study Objectives

"To compare the efficacy and safety of hydromorphone hydrochloride extended-release (HHER) 12 mg capsules versus placebo in the treatment of moderate to severe pain due to osteoarthritis (OA), in subjects requiring opioid analgesia."

6.0 Study Design

6.1 The basic study design is:

--parallel-group,
--double-blind,
--placebo-controlled,
--randomized,
--three phases:

a) screening,
b) open-label phase for up to 14 days with daily patient contact by phone for determining the need for additional hydromorphone hydrochloride immediate release (HHIR) titration,
c) double-blind phase for 28±2 days with phone contact on each of the two days before Week 2 and Week 4 visits to insure proper data collection for the assessment of efficacy and 72 hour follow-up after the final study visit.

Subjects meeting inclusion and exclusion criteria at the screening clinic visit were entered into the open-label phase. The open-label phase was to identify patients who required, responded to, and tolerated on average 12 mg of hydromorphone immediate-release (HHIR) per day. During open-label patients were titrated for up to 14 days to analgesic doses between ≥8 mg and ≤14 mg per day of immediate-release hydromorphone. Patients were to assess and report their Average Pain Intensity of their affected joint over the previous twenty four hours once daily by a phone call to an interactive phone diary system. From the study report it is not clear how data was stored, electronically or reduced to writing by study personnel; and the case report forms do not have space designated for recording Average Pain Intensity scores for the double-blind period. The time of daily assessment and diary reporting was not specified by the protocol. Patients were randomized to double-blind treatment if they reported not more than mild pain for 48 consecutive hours while taking between ≥8 mg and ≤14 mg of HHIR. Ancillary treatments (TENS, biofeedback, physical therapy, and relaxation therapy) and oral corticosteroids were not allowed for the duration of the study. Intra-articular, epidural, or other corticosteriod injections were not allowed for 6 weeks before or during the study. NSAID, aspirin, acetaminophen, or COX 2 inhibitors were permitted if the dose regimen was stable for 1 month before study entry and would remain stable during the study.

6.2 Study Treatments

Open-label phase:

Hydromorphone Hydrochloride Immediate-release Tablets (HHIR) 2 mg as Dilaudid® - titrated for up to 14 days to analgesic doses between 8 mg and 14 mg per day

Double-blind phase:

Hydromorphone hydrochloride Extended-release Capsules (HHER) 12 mg each day at 8AM±2 hours for 28±2days

or

Matching Placebo Capsules one capsule each day at 8AM±2 hours for 28±2days

6.3 Patient Inclusion Criteria for Open-Label Phase

- Male or female 18 years of age or older with at least a 3 month history of OA as defined by the protocol and documented by 1) the patient's primary care physician referral with a narrative documenting OA OR 2) a history and physical exam completed by the principle investigator and radiologic evidence of OA within the previous 2 years

- Taking up to 45 mg of oral oxycodone or an equivalent amount of oral opioid medication per day for OA pain OR requires oral opioid medication in the opinion of the investigator for control of OA pain

- On current medication experiencing moderate to sever pain due to OA defined as ≥2 on a 0 to 4 scale (0 = no pain; 1= mild pain; 2= moderate pain; 3= moderate to severe pain; 4= severe pain)

- Using concomitant NSAIDs, COX-2 inhibitors, aspirin or acetaminophen only if the dose had been stable for ≥ 1 month prior to study entry and would be continued at the same dose for the duration of the study

- Using concomitant glucosamine and/or chondroitin sulfate only if the dose had been stable for ≥ 2 months prior to study entry and would be continued at the same dose for the duration of the study

- Not pregnant, documented by negative urine pregnancy test within 7 days prior to baseline, and practicing medically recognized method of contraception

- Willing to discontinue prestudy opioid prior to entering open-label phase and accept the possibility of receiving placebo during double-blind phase

- Willing to comply with the study protocol, capable of subjective evaluation, able to read, understand, and sign a written informed consent

- Able to swallow capsules

- Able to be contacted by phone

- Suffering from a coexisting illness only if the condition had been present for at least 1 week and expected to remain stable during the study; receiving medication for coexisting illness only if the medication dose was stable for at least 1 week and was expected to remain stable during the study

6.4 Patient Inclusion Criteria for Double-Blind Phase

Had completed open-label phase and

- Completed an interactive telephone diary daily for up to 14 days, and achieved a pain score of none to mild (0 to 1) for 48 consecutive hours

- Reported Average Pain Intensity over 24 hours between 0 (no pain) and 1 (mild pain) on a daily dose of ≥ 8 mg and ≤ 14mg HHIR
- Not developed symptoms of opioid withdrawal during the open-label phase of the study
- Returned their unused HHIR tablets to the study clinic

6.5 Patient Exclusion Criteria

- Were taking an average total daily dose >45 mg of oxycodone or opioid equivalents during the last week prior to study entry
- Pregnant or nursing
- Allergic to hydromorphone or had a history of allergies to other opioids
- Planning to participate in elective surgical procedures, including dental and local procedures
- Suffering from a coexisting unstable illness
- Suffering from a coexisting complex regional pain syndrome, neuropathy, fibromyalgia, or any other pain syndrome that might confound the assessments of the study
- Had active cancer within the past 5 years, excluding basal cell carcinoma
- Had a past (≤ 5 years) or present history of substance abuse or alcohol abuse, or had evidence on history or examination of opioid withdrawal symptoms
- Had a history of or active severe organ dysfunction, a physical or psychological disease (hospitalization for suicide attempt or other major psychiatric diseases) that might subject the subject to increased risk of being exposed to the medication in this study or that might confound the interpretation of this investigation
- Had any laboratory value, which in the judgment of the investigator, might subject the patient to increased risk by being exposed to the study medication
- Had received an investigational drug within 30 days prior to entry
- Were receiving workmen's compensation and/or were involved in litigation
- Had received intra-articular, intramuscular, or epidural steroid injections within 6 weeks of Screening or during the study
- Had received intra-articular injections of Hylagan® or Synvisc® within the previous 6 weeks

6.6 Primary Efficacy Measurements

Subject Average Pain Intensity assessment of pain over the previous 24 hours according to a categorical rating scale – no pain, mild pain, moderate pain, moderately severe pain, severe pain. For statistical analysis numerical values were assigned from 0-4, 0 for no pain and 4 for severe pain. The primary efficacy endpoint was defined as the mean score of Average Pain Intensity assessments from a total of 4 days, the 2 days preceding each of Week 2 and Week 4 visits.

6.7 Secondary Efficacy Measurements

a) Mean of scores at Week 2 and Week 4 visits of subject global assessment of pain medication on a descriptive categorical scale: poor =1, fair =2, good =3, very good=4, and excellent=5. Patients were asked "How would you rate your medicine for pain?"
b) Time to discontinuation due to lack of efficacy defined as the number of days from day of initial dose of test medication after randomization to discontinuation due to inadequate pain control.

6.8 Safety Measurements

Physical examination was conducted at screening and at study end. Vital sign measurements and clinical laboratory data were obtained at screening and study end. No ECGs were obtained. Adverse events were recorded at each clinic visit following spontaneous reporting and following direct/indirect questioning. Serious adverse events that occurred during the trial and within 30 days of last dose were included in the database.

6.9 Assessment of Opioid Withdrawal Symptoms

At the end of the study (Week 4) a withdrawal symptom rating scale was used by the investigator to assess possible opioid withdrawal signs and symptoms – yawning, itching, lacrimating, sluggishness, runny nose and restlessness. The categorical scale was 0 = none at all, 1 = relatively unnoticeable but perceivable on close observation, 2 = fairly obvious-do not need close observation to notice, 3 = very obvious-is a persistent feature or appears bothersome to the subject. Collection of these data was planned for an exploratory analysis to evaluate whether withdrawal may have influenced patient evaluation of Average Pain Intensity.

7.0 Study Results

7.1 Patient Accounting

Screened 281
Entering Open-label 238
Total Randomized 160

From the table below the most common reason for discontinuation from placebo was ineffectiveness at a rate 2.1 times that of HHER 12 mg. For discontinuation from HHER 12 mg, the most common reason for discontinuation was an adverse event at a rate 2.8 times that of placebo.

Patient Accounting			
	Placebo	HHER 12 mg	Total
Randomized	80	80	160
Completed	52 (65.0%)	55 (68.8%)	107 (66.9%)
Reason for Discontinuation			
Ineffective Treatment	23 (28.8%)	11 (13.8%)	34 (21.3%)
Lost to Follow-up	0 (0%)	1 (1.3%)	1 (0.6%)
Protocol Violation	0 (0%)	1 (1.3%)	1 (0.6%)
Adverse Event	4 (5%)	11 (13.8%)	15 9.4(%)
Other	1 (1.3%)	1 (1.3%)	2 (1.3%)
Source – In-text Table 10.1			

7.2 Subject Baseline Demographics

Baseline subject demographics are similar between treatment groups except there are slightly more males in the placebo group compared to the active treatment group and there is a slightly larger mean weight with a broader weight range in the placebo group.

Baseline Demographics of ITT Population	Placebo	HHER 12 mg
Male	28 (35%)	20 (25%)
Female	52 (65%)	60 (75%)
White Race	70 (87.5%)	71 (88.8%)
Black Race	7 (8.8%)	7 (8.8%)
Hispanic	2 (2.5%)	2 (2.5%)
18-34 Years	2 (2.5%)	0 (0%)
35-49 Years	20 (25%)	23 (28.8%)
50-64 Years	39 (48.8%)	40 (50%)
65-74 Years	17 (21.3%)	14 (17.5%)
≥ 75 Years	2 (2.5%)	3 (3.8%)
Mean Age ± SE (Yrs)	55.9± 1.2	56.4±1.1
Age Range (Yrs)	23-82	40-80
Mean Height ± SE (cm)	168.2±1.2 (N=78)	167.0±1.1 (N=76)
Height Range (cm)	152-193	151-188
Mean Weight ± SE (kg)	97.7±2.8 (N=78)	92.9±2.1 (N=76)
Weight Range (cm)	44.5-185.9	57.7-135
Source – post-text Table 14.1.3		

7.3 Subject Exposure

The tables below display patient exposure. It appears that three times as many subjects (9 vs 3) in the placebo group discontinued during the first 3 days of the double-blind period than in the active treatment group. By my estimate there are15915 person-days of exposure to placebo and 17125 person-days of exposure to HHER 12 mg leaving a difference of 1210 more person-days on HHER. This calculation was conducted by multiplying the number of persons exposed for each exposure interval by one-half the time in each exposure interval and summing the interval products for each treatment.

Subject Exposure	Placebo (N=80)	HHER 12 mg (N=80)
Days	n (%)	n (%)
0-3	9 (11.25%)	3 (3.75%)
4-7	6 (7.5%)	8 (10.0%)
8-14	7 (8.75%)	6 (7.5%)
15-21	5 (6.25%)	5 (6.25%)
22-30	53 (66.5%)	58 (72.5%)
Source – In-text Table 10.5		

Person-Days of Exposure					
Subject Exposure	Exposure Interval Mean	Placebo (N=80)	Placebo Person-Days	HHER 12 mg (N=80)	HHER 12mg Person-Days
Days		n (%)		n (%)	
0-3	1.5	9 (11.25%)	13.5	3 (3.75%)	4.5
4-7	5.5	6 (7.5%)	33	8 (10.0%)	44
8-14	11	7 (8.75%)	77	6 (7.5%)	66
15-21	18	5 (6.25%)	90	5 (6.25%)	90
22-30	26	53 (66.5%)	1378	58 (72.5%)	1508
Total Person-Days			15915		17125

7.4 Efficacy Results - Primary Endpoint

The primary efficacy variable was the Average Pain Intensity reported on Days 12 and 13 of Week 2 and Days 26 and 27 of Week 4. The results from the sponsor's repeated measures analysis of covariance with terms for treatment, center, and baseline Average Pain Intensity are reproduced below. Baseline Average Pain Intensity was the mean from 2 consecutive days before randomization. The results show a small but statistically significant difference between placebo and active treatment at Weeks 2 and 4.

Mean Average Pain Intensity Score – ITT Population		
	Placebo	HHER 12 mg
	N=79 Mean ± SE	N=79 Mean ± SE
Baseline (open-label)	0.87 ± 0.04	0.85 ± 0.04
Week 2 (Days 12 & 13)	1.97 ± 0.14	1.68 ± 0.12
Week 4 (Days 26 & 27)	2.15 ± 0.14	1.83 ± 0.12
		P value – 0.0259
0 = no pain; 1 = mild pain; 2 = moderate pain; 3 = moderately severe pain; 4 = severe pain		
From post-text Table 14.2.1.1		

Exploratory Evaluation of the Effect of Withdrawal Symptoms on Average Pain Intensity:
Plans for the collection of these data were included as an amendment after the study had started so that only 32 patients were assessed. Withdrawal symptoms were evaluated by the investigator at study end or at early termination. The sum of 6 symptoms was for a total possible score of 18 was compared between treatments using a 2-sample t-test. The results are summarized below. The sponsor indicates that since no significant difference was observed at the alpha level of 0.05, no further assessment of withdrawal effect on the primary end-point was conducted. The in-text reference table reports the values below as SD while the post-text table reports SE.

Mean Withdrawal Symptom Rating – ITT Population			
Summed Symptom Rating	Placebo N=32	HHER N=32	P value
Mean ± SE	0.28±0.09	1.00±0.43	
Range	0 – 2	0 – 10	
			0.1102
Withdrawal symptoms – yawning, itching, lacrimating, sluggishness, runny nose, restlessness			
From post-text Table 14.2.4			

7.5 Efficacy Results - Secondary Endpoints

1) Subject global assessment of pain medication on a descriptive categorical scale:
At study visits during Weeks 2 and 4 of double-blind, patients were asked, "How would you rate your medicine for pain?" The sponsor conducted a repeated measures analysis of covariance with terms for treatment and center. The results below show that active treatment had a more favorable score that is statistically significant. The in-text reference table reports the values below as SD while the post-text table reports SE.

Subject Global Assessment of Pain Medication – ITT Population			
	Placebo Mean ± SE (N)	HHER Mean ± SE (N)	P value
Week 2	1.87±0.18 (N=79)	2.62±0.18 (N=77)	
Week 4	1.87±0.18 (N=79)	2.56±0.18 (N=79)	
			0.0011
Poor =1, fair =2, good =3, very good=4, excellent=5			
From post-text Table 14.2.2			

2) Time to discontinuation due to lack of efficacy:
The time to discontinuation was defined as the number of days from day of initial dose of test medication after randomization to discontinuation due to inadequate pain control. The results below show that active treatment had a more favorable score that is statistically significant. The in-text reference table reports the values below as SD while the post-text table reports SE.

Time (days) to Discontinuation Due to Lack of Efficacy – ITT Population			
	Placebo Mean ± SE (N)	HHER Mean ± SE (N)	P value
Subjects who discontinued due to lack of efficacy	7.96±1.07 (N=23)	9.73±2.05 (N=11)	
All subjects	20.98±1.14 (N=80)	22.24±1.02 (N=80)	
			0.0247
From post-text Table 14.2.3.2			

7.6 Safety Results - Deaths

No deaths were reported during the conduct of this study.

7.7 Safety Results – Withdrawal Symptoms

Four HHER subjects had withdrawal symptom scores of >1 following completion or discontinuation after 24 days of double-blind treatment. No patients in the placebo group had withdrawal symptom scores >1.

Only 1 subject (2139-14028), 50 yo F was judged by the investigator to have withdrawal symptoms 1 day after dropping out of the study and after her last dose of HHER on Day 14. These symptoms consisted of nausea, insomnia, tingling under skin, hot/cold sensations, and loss of appetite. She was treated with hyoscyamine and loratadine with her symptoms completely resolving 6 days after her last dose of HHER.

The sponsor also examined the adverse event data and found 3 subjects who had more than one AE consistent with possible opioid withdrawal – 1 in the HHER group, who is described above, and 2 in the placebo group.

7.8 Safety Results – Non-Death Serious Adverse Events

Three non-death serious adverse events were reported.

Patient 100-3003 – 82yo M – experienced new onset seizure disorder 1 day after randomization to placebo and recovered.

Patient 1121-2143 – 63yo F – was hospitalized for percutaneous coronary intervention for coronary artery disease 6 days after randomization to placebo and recovered.

Patient 2070-16139 – 53yo M – was diagnosed with esophageal cancer 3 days after completing the study.

7.9 Safety Results - Dropouts Due to Adverse Events

A total of 15 patients dropped out from the double-blind phase due to adverse events – 11 on HHER and 4 on placebo.

The following AEs were the COSTART reasons subjects discontinued:

For HHER:

(4) somnolence all within 4 days;
(3) nausea all within 6 days – in 1 subject the nausea preceded the double-blind phase;
(1) vomiting within Day 22;
(1) dream abnormality (nightmares) on Day 1;
(1) headache on Day 1;
(1) hyperkinesia (restless legs) on Day 22.

For placebo:

(1) convulsions on Day 1;
(1) abdominal pain on Day 11;
(1) dizziness, speech disorder (slurred speech), and euphoria on Day 0;
(1) peripheral edema and pruritus on Day 1.

7.9 Safety Results - Common Adverse Events

The table below displays treatment emergent adverse events occurring during double-blind phase at approximately twice the placebo rate in the HHER group.

Treatment Emergent Adverse Events Occurring During Double Blind Phase		
COSTART TERM	Placebo N=80 n (%)	HHER N=80 n (%)
Asthenia	0 (0%)	2 (2.5%)
Constipation	0 (0%)	15 (18.8%)
Nausea	4 (5.0%)	7 (8.8%)
Vomiting	0 (0%)	4 (5.0%)
Somnolence	2 (2.5%)	6 (7.5%)
Abnormal Dreams	0 (0%)	2 (2.5%)
Hypertonia	0 (0%)	2 (2.5%)
Sweating	0 (0%)	2 (2.5%)
From in-text Table12.1		

7.10 Safety Results - Vital Signs

Examination of vital sign data shows no clinically important changes between treatments in mean values from screening to study end for systolic blood pressure, diastolic blood pressure, heart rate, and respiratory rate (in-text Table 12.4.1.2). The sponsor reported no shift or outlier analyses.

7.11 Safety Results - ECGs

No ECG assessments were conducted for this study.

7.12 Safety Results - Clinical Laboratory Values

Examination of clinical chemistry and hematology laboratory values shows no clinically important changes between treatments in mean values from screening to study end (in-text Tables 12.3.2A, 12.3.2B, 12.3.2.C) or numbers of subjects with shifts from screening (in-text Table 12.3.3). Two patients in each treatment group had at least one clinically significant value. For the HHER group a 62 yo M had an elevated ALT (49U/L – nl <48) and GGT (438U/L – nl <65) at screening which remained elevated at study end 65U/L and 369U/L, respectively. The other HHER patient was a78 yo F who had normal BUN and creatinine at screening but elevated to 37 mg/dL (nl 7-30) and 1.8mg/dL (nl 0.5 –1.4), respectively. For both of these patients these lab values were not classified as clinically significant by the investigator.

8.0 Data Audit Results

Given the apparent negative outcome for the primary efficacy endpoint (see conclusion below), no formal data audit was conducted by the Division. However, it was noted that typographical errors were common. The report of data auditing from the site inspection by the Division of Scientific Investigations (DSI) is pending at this time.

9.0 Conclusion

Study HMP3005 generally appears to fulfill the requirements for a well controlled clinical trial. The study objectives are clearly stated; and the study subjects are well defined by inclusion and exclusion criteria. The study was placebo-controlled and double-blinded with random assignment to study treatments. The methods for observation, recording, quantification and evaluation of data are described with the exception of data for the primary endpoint. A significant detraction from the reliability of this study stems from the use of an interactive telephone voice system for data collection for the predetermined primary end-point without adequately describing the system and how these data were recorded and processed. It is clear that these data were not recorded on the case report forms so that verification of primary source data is complicated and further complicated by use of vendors for collection and processing of primary endpoint data. The lack of an adequate description of a prospective plan for gathering and processing these data for the primary endpoint lends significant doubt to the integrity of the data and the reliability of subsequent analyses. DSI has been asked to specifically examine this issue regarding data collection and processing for the primary endpoint during their inspection of the sponsor's facilities; a final DSI report is pending at this time.

The results of this study do not adequately support efficacy of this formulation of hydromorphone hydrochloride as an oral extended-release analgesic product for single daily dosing. Although the pre-determined primary efficacy endpoint demonstrates a statistically significant difference between study treatments in favor of the active treatment, this absolute difference between treatments at Weeks 2 and 4 is only 7.25% (0.29/4) and 8.0% (0.32/4), respectively and is difficult to view as clinically significant. Furthermore the worsening of pain control between baseline and Weeks 2 and 4 as manifested as a doubling of pain scores within treatments for both placebo and HHER (HHER - 0.85 ±SE 0.04 to 1.68 ±SE 0.12 and 1.83 ±SE 0.12; Placebo - 0.87 ±SE 0.04 to 1.97 ±SE 0.14 and 2.15 ±SE 0.14) does not sustain the assertion that this study supports efficacy of HHER and does not support product approval. The sponsor provides no statistical analysis of this doubling of pain scores from baseline within each treatment.

Additionally, the results of this study do not adequately support efficacy of this formulation of hydromorphone hydrochloride because the apparent difference between treatments can be attributed to the imputation of higher scores in the placebo group. Approximately half of the subject discontinuations for all causes occurred by the end of the first week of double-blind (Placebo – 15/28 = 54%; HHER – 11/25 – 44%) which means a large number of observations were carried forward for the imputed statistical analysis. Further, the majority of discontinuations over the entire study in the placebo group were due to ineffective treatment (23/28 = 82%) while the majority discontinuations in the HHER group were equally split between ineffective treatment (11/25 = 44%) and adverse events (11/25 = 44%). The statistical reviewer, Thomas Permutt, Ph.D., reports in his review the results of his analysis of observed data and imputed data and noted that the results from the observed data were similar between the two treatments for all four days comprising the primary endpoint (Days 12/13 and 26/27) but that the imputed data were different. It could be viewed that patients who dropped out due to either ineffective treatment or adverse events were overall treatment failures leaving patients who remained in the study until completion benefiting no more on HHER than on placebo.

Additionally, the results of this study might be in question due to certain post-hoc choices of statistical methods. The statistical reviewer points out that the protocol specified statistical analysis planned for inclusion of baseline, treatment, center, and treatment-by-center interaction; but the reported analysis did not contain an interaction term. Because some of the centers had few patients an adjustment was needed. Although the statistical reviewer points out that dropping the interaction term was reasonable, dropping the center effect from the model was also

reasonable; but by also dropping the center effect the p-value for the primary endpoint changes from 0.03 as reported in the clinical study report to 0.08 as calculated by the statistical reviewer who indicates that no justification for the choices made were provided in the study report.

Finally, this study does not support efficacy of this formulation as a once-a-day product because there is no demonstration of end-of-dosing interval efficacy. Average Pain Intensity scores were recorded once daily with no requirement for score recording at the time of the end of the dosing interval to demonstrate continued efficacy at that point in time.

10.0 Recommendation

Study HMP3005 should not be accepted as a positive trial in support of efficacy of Palladone™ 12 mg capsules as an oral extended-release analgesic product for single daily dosing. This response to an approvable letter should be deemed not approved.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Michael Sevka
9/21/01 06:16:46 PM
MEDICAL OFFICER

Bob Rappaport
9/21/01 06:21:47 PM
MEDICAL OFFICER

DEC 2 3 1999

FDA CENTER FOR DRUG EVALUATION AND RESEARCH
DIVISION OF ANESTHETIC, CRITICAL CARE, AND ADDICTION DRUG PRODUCTS
HFD-170, Room 9B-45, 5600 Fishers Lane, Rockville MD 20857 Tel:(301)443-3741

MEMORANDUM

DATE: December 23, 1999

TO: File, NDA 21-044

FROM: Bob A. Rappaport, M.D.
Deputy Director, DACCADP
Team Leader, Anesthetic Drug Group

RE: Supervisory Review of Effectiveness for NDA 21-044, Palladone (Hydromorphone HCl Extended Release) 12 mg, 16 mg, 24 mg and 32 mg Capsules

BACKGROUND:

NDA 21-044, Palladone (hydromorphone HCl extended release), was submitted by Purdue Pharma L.P. on December 29, 1998. Hydromorphone is a semisynthetic opioid analgesic that has been in clinical use since 1926. It is a pure opioid agonist which is currently marketed in oral, injectable and suppository formulations for the management of moderate to severe pain. The sponsor has developed an extended release formulation of hydromorphone hydrochloride for the treatment of chronic pain on a once daily basis. The original IND (38,424) for this product was filed on December 2, 1991.

This application is based on the available results for 3 controlled clinical trials and 10 clinical pharmacology studies. The clinical studies of the effectiveness and safety of this new formulation have been reviewed [submitted December 9, 1999] by Monte Scheinbaum, Ph.D., M.D. The application has also been reviewed by Thomas Permutt, Ph.D. (biostatistics), Shinja R. Kim, Ph.D. (clinical pharmacology and biopharmaceutics), Kathleen A. Haberny, Ph.D. (pharmacology/toxicology), and Pramoda Maturu, Ph.D. (chemistry). Cynthia McCormick, M.D., Division Director, will be contributing a

supervisory review of clinical safety. In this memo, I will briefly review the effectiveness data summarized in the primary clinical review and make appropriate recommendations for action on the NDA.

EFFECTIVENESS:

Evidence of efficacy has been submitted two active-controlled trials [HD95-0801 and HD95-0802] and one active and placebo-controlled trial [HD96-0505].

Study HD95-0801 [801]:

This was a randomized, double-blind, crossover, multicenter study which compared hydromorphone HCl extended release [HHER] to hydromorphone HCl immediate release [HHIR] for cancer related or chronic nonmalignant pain in patients who already required opiate therapy. Patients were initially enrolled in an open-label stabilization period which lasted from 4 to 21 days. They were switched from their other opiate medications to HHER at a dose of 1 mg/day for each 8 mg/day of oral morphine or an equipotent dose for opiates other than morphine. The HHER dose was adjusted as necessary over the 4 to 21 days. Rescue was provided as necessary with HHIR 2 mg q 4 to 6 hours. When a stable dose had been achieved, patients were randomized to either HHER 1 qd or HHIR tablets qid, using a double-dummy blinding technique. Patients remained on this treatment for 3 to 7 days[1] and then were crossed over to the other treatment for another 3 to 7 days. HHIR 2 mg tablets were used for rescue.

In the Protocol Summary section of the protocol, the specified primary efficacy parameters were:

1. Mean of average pain intensity ratings over the last two days of each double-blind period before the PK/PD day[2]
2. Current pain intensity rating at the time of phlebotomy
3. Subject "drug effect" rating at the time of each phlebotomy
4. Plasma hydromorphone concentration at the time of each phlebotomy (actual and dose-adjusted concentrations)

However, in the Statistical Analysis section of the protocol, the specified primary efficacy parameters were:

1. Mean of average pain intensity ratings over the last two days of each double-blind period before the PK/PD day.

---

[1] The protocol does not clearly define how the length of treatment was chosen for an individual patient

[2] The Pharmacokinetic/Pharmacodynamic [PK/PD] days were Day 3, 4, 5, 6 or 7. On PK/PD days blood samples were collected and plasma levels were correlated with "current pain intensity" and "subject 'drug effect'."

2. Plasma hydromorphone concentration, current pain intensity and subjective "drug effect" ratings at the time of each blood draw.

The efficacy analysis was based on the Intent to Treat [ITT] population and an analysis on the Evaluable population was also performed.

Secondary efficacy parameters listed in the protocol for this study included:

1. Average pain intensity ratings on each of the last 2 days of each double-blind period before the PK/PD day
2. Mean of average pain intensity ratings for each double-blind study day
3. Current pain intensity ratings on each of the last 2 days of each double-blind period before the PK/PD day
4. Mean of current pain intensity ratings for each double-blind study day
5. Minimum and maximum plasma hydromorphone concentrations observed
6. Plasma hydromorphone concentration and pharmacodynamic effect (current pain and patient "drug effect") at each phlebotomy time point
7. Relationship between plasma concentration and current pain intensity and relationship between plasma concentration and patient "drug effect"
8. Time to stable pain control during the open-label period (includes number [%] of patients successfully titrated to stable pain and number [%] of patients who required a change from the conversion dose level
9. Total daily dose (mg) of hydromorphone (test or reference treatment with and without rescue) during the double-blind periods
10. Amount of rescue per day (number of doses and mg amount)during the double-blind periods; this includes amount of rescue dose as a percentage of total daily dose of test or reference treatment
11. Times at which rescue was administered during the double-blind periods
12. Number of patients who required rescue during the double-blind periods

Results:

Two patients were randomized but discontinued prior to receiving study medication. The total ITT population consisted of 104 patients. Three patients did not receive HHER during the double-blind study period. Six patients did not receive HHIR during the double-blind period. The sponsor excluded 22 patients from their Evaluable population due to the following protocol violations: unstable concomitant analgesic adjuvant and non-opioid use; insufficient number of doses in the last 2 days before PK/PD evaluations; found to have been ineligible for randomization; and, violation of another opioid use criterion.

Primary Efficacy Analyses:

1. The mean and standard errors for the average pain intensity over the last 2 days before each PK/PD Day of the double-blind periods were:

Table 1.

	HHER	HHIR	Difference	90% CI of the Difference
EVALUABLE	2.48 (0.07)	2.42 (0.07)	0.06	[-0.11, 0.23]
ITT	2.79 (0.08)	2.62 (0.08)	0.17	[-0.01, 0.35]

[based on Dr. Scheinbaum's review, page 23, and Dr. Permutt's review, Table 8.10.4E, page 2]

The confidence intervals were well within the sponsor's prespecified range of –2 and 2.

2. The following table, based on Dr. Scheinbaum's Table 4, page 24 of his review, summarizes the "current patient-rated pain intensity scores for each combined treatment group assessed immediately before each phlebotomy at Visits 3 and 4" [Evaluable population]:

Table 2.

Time (hr)	**0**	**1**	**2**	**3**	**5-6**	**22-24**
HHER						
N	62	61	61	60	60	14
Mean Pain Intensity	2.87	2.16	1.85	1.88	2.02	2.57
(SE)	0.28	0.24	0.21	0.22	0.23	0.78
HHIR						
N	59	61	61	61	60	14
Mean Pain Intensity	2.95	2.20	1.93	1.82	2.20	2.00
(SE)	0.23	0.22	0.21	0.21	0.24	0.41

[The results of the ITT analysis showed even less of a difference between the groups.]

3. The mean drug effect ratings immediately prior to phlebotomies were similar for both treatment groups. The scores ranged from 0.73 to 1.24 on a 0 to 10 point scale [see Dr. Scheinbaum's review, page 24].

4. The mean dose-adjusted plasma hydromorphone concentrations at Visits 3 and 4 are summarized in the following table, modified from Dr. Scheinbaum's Table 6, page 25 of his review:

Table 3.

Time (hr)	0	1	2	3	5-6	22-24
HHER						
N	56	56	57	56	56	13
Mean conc.	4.38	5.97	6.92	7.08	6.92	3.94
(SE)	0.45	0.55	0.67	0.68	0.67	0.71
HHIR						
N	52	55	55	54	55	13
Mean Conc.	4.11	10.3	8.34	7.04	4.74	3.33
(SE)	0.69	0.94	0.79	0.73	0.49	0.41

Secondary Efficacy Analyses:

These analyses were performed on the Evaluable population.

Average pain intensity ratings on each of the last 2 days of each double-blind period before the PK/PD day

The average pain intensity scores over the last 2 days before the PK/PD evaluation days were similar for the two formulations. [see Dr. Scheinbaum's Table 7, page 25 of his review]

Mean of average pain intensity ratings for each double-blind study day

The average pain intensity scores on each day of the double-blind periods were generally similar for the two formulations. [see Dr. Scheinbaum's Table 8, page 26 of his review]

Current pain intensity ratings on each of the last 2 days of each double-blind period before the PK/PD day

The current pain intensity scores on each of the last 2 days before the PK/PD evaluation days were similar for the two formulations. [see Dr. Scheinbaum's Table 9, page 26 of his review]

Mean of current pain intensity ratings for each double-blind study day

The average current pain intensity scores on each day of the double-blind periods were similar for both treatments except on Day 5 when the HHIR score was 0.72 higher than the HHER score. [see Dr. Scheinbaum's Table 10, page 26 of his review]

Minimum and maximum plasma hydromorphone concentrations observed

In general, patients treated with HHER had significantly higher mean C_{min} results than patients treated with HHIR [see Dr. Scheinbaum's review, page 27].

Plasma hydromorphone concentration and pharmacodynamic effect (current pain and patient "drug effect") at each phlebotomy time point. Relationship between plasma concentration and current pain intensity and relationship between plasma concentration and patient "drug effect"

As per Dr. Scheinbaum [his review, page 27], "Generally, there appeared to be no clear relationship between plasma concentration and effect (pain intensity or 'drug effect'), and no treatment differences were detected."

Time to stable pain control during the open-label period (includes number [%] of patients successfully titrated to stable pain and number [%] of patients who required a change from the conversion dose level

Sixty-nine percent of the patients who took HHER and entered the titration period were considered to have been successful in titrating to stable pain control. Of those successful patients, 39% were able to achieve stable pain control while maintaining the initial conversion dose. The mean time to stable pain control was 4.2 days for the successful patients.

Total daily dose (mg) of hydromorphone (test or reference treatment with and without rescue) during the double-blind periods

The total daily dose of hydromorphone during the double-blind periods was similar for patients when treated with HHER or HHIR [see Dr. Scheinbaum's review, page 28].

Amount of rescue per day (number of doses and mg amount) during the double-blind periods; this includes amount of rescue dose as a percentage of total daily dose of test or reference treatment

The amount of rescue medication per day was similar for patients when treated with HHER or HHIR [see Dr. Scheinbaum's review, page 28-29].

Times at which rescue was administered during the double-blind periods

The following table [modified from Dr. Scheinbaum's Table 13, page 29 of his review] summarizes the timing of rescue doses for the two treatment groups:

Table 4. Number and Times of Rescue Dosing Averaged over Last 2 Days prior to PK/PD

	HHER				HHIR			
Time of Day	**Morning**	**Afternoon**	**Evening**	**Night**	**Morning**	**Afternoon**	**Evening**	**Night**
N	67	67	67	67	66	66	66	66
Mean	0.24	0.43	0.34	0.37	0.32	0.35	0.25	0.43
SE	0.05	0.06	0.05	0.06	0.05	0.06	0.04	0.08

Number of patients who required rescue during the double-blind periods

For the Evaluable population, 73% of the HHER and 75% of the HHIR patients required rescue medication. For the ITT population, 77% of the HHER and 79% of the HHIR patients required rescue medication.

Study HD95-0802 [802]:

The study design, efficacy assessments and analysis plan for Study 802 were identical to those for Study 801.

Results:

One patient was randomized but discontinued prior to receiving study medication. The total ITT population consisted of 113 patients. Five patients did not receive HHER during the double-blind study period. One patient did not receive HHIR during the double-blind period. The sponsor excluded 22 patients from their Evaluable population due to the following protocol violations: unstable concomitant analgesic adjuvant and non-opioid use; insufficient pain ratings during the last 2 days before PK/PD evaluations; found to have been ineligible for randomization; early discontinuation; and, violation of another opioid use criterion.

Primary Efficacy Analyses:

1. The mean and standard errors for the average pain intensity over the last 2 days before each PK/PD Day of the double-blind periods were:

Table 5.

	HHER	HHIR	Difference	90% CI of the Difference
EVALUABLE	2.59 (0.08)	2.58 (0.08)	0.01	[-0.17, 0.19]
ITT	2.67 (0.08)	2.60 (0.08)	0.07	[-0.12, 0.26]

[based on Dr. Scheinbaum's review, page 38, and Dr. Permutt's review, Table 8.10.4E, page 2]

The confidence intervals were well within the sponsor's prespecified range of –2 and 2.

2. The following table, based on Dr. Scheinbaum's Table 14, page 39 of his review, summarizes the "current patient-rated pain intensity scores for each combined treatment group assessed immediately before each phlebotomy at Visits 3 and 4" [Evaluable population]:

Table 6.

Time (hr)	0	1	2	3	5-6	22-24
HHER						
N	45	45	45	45	45	10
Mean Pain Intensity	2.69	2.24	2.16	2.47	2.40	3.20
(SE)	0.25	0.21	0.23	0.30	0.28	0.57
HHIR						
N	38	38	38	38	38	9
Mean Pain Intensity	3.16	2.68	2.58	2.63	3.03	4.00
(SE)	0.42	0.41	0.39	0.42	0.43	0.47

[The results of the ITT analysis showed even less of a difference between the groups.]

3. The mean drug effect ratings immediately prior to phlebotomies were similar for both treatment groups. The scores ranged from 0.92 to 2.11 on a 0 to 10 point scale [see Dr. Scheinbaum's review, page 40]. While the scores for the HHIR patients were higher than those in the HHER population at all time points except 22 to 24 hours, per Dr. Scheinbaum they were not significantly different and the results from the ITT analysis showed even less difference between the groups.

4. The mean dose-adjusted plasma hydromorphone concentrations at Visits 3 and 4 are summarized in the following table, modified from Dr. Scheinbaum's Table 16, page 40 of his review:

Table 7.

Time (hr)	0	1	2	3	5-6	22-24
HHER						
N	46	46	47	47	46	11
Mean conc.	2.63	3.35	4.09	4.26	4.35	1.87
(SE)	0.18	0.20	0.27	0.29	0.33	0.34
HHIR						
N	58	58	58	57	58	12
Mean Conc.	2.92	5.34	4.74	3.96	2.97	1.91
(SE)	0.46	0.50	0.47	0.41	0.33	0.36

Secondary Efficacy Analyses:

These analyses were performed on the Evaluable population.

Average pain intensity ratings on each of the last 2 days of each double-blind period before the PK/PD day

The average pain intensity scores over the last 2 days before the PK/PD evaluation days were similar for the two formulations. [see Dr. Scheinbaum's Table 17, page 41 of his review]

Mean of average pain intensity ratings for each double-blind study day

The average pain intensity scores on each day of the double-blind periods were generally similar for the two formulations. [see Dr. Scheinbaum's Table 18, page 41 of his review]

Current pain intensity ratings on each of the last 2 days of each double-blind period before the PK/PD day

The current pain intensity scores on each of the last 2 days before the PK/PD evaluation days were similar for the two formulations. [see Dr. Scheinbaum's Table 19, page 41 of his review]

Mean of current pain intensity ratings for each double-blind study day

The average current pain intensity scores on each day of the double-blind periods were similar for both treatments. [see Dr. Scheinbaum's Table 20, page 42 of his review]

Minimum and maximum plasma hydromorphone concentrations observed

In general, patients treated with HHER had significantly higher mean C_{min} results than patients treated with HHIR [see Dr. Scheinbaum's review, page 42].

Plasma hydromorphone concentration and pharmacodynamic effect (current pain and patient "drug effect") at each phlebotomy time point. Relationship between plasma concentration and current pain intensity and relationship between plasma concentration and patient "drug effect"

As per Dr. Scheinbaum [his review, page 42], "Generally, there appeared to be no clear relationship between plasma concentration and effect (pain intensity or 'drug effect'), and no treatment differences were detected."

Time to stable pain control during the open-label period (includes number [%] of patients successfully titrated to stable pain and number [%] of patients who required a change from the conversion dose level

Seventy-two percent of the patients who took HHER and entered the titration period were considered to have been successful in titrating to stable pain control. Of those successful patients, 42% were able to achieve stable pain control while maintaining the initial conversion dose. The mean time to stable pain control was 6.25 days for the successful patients.

Total daily dose (mg) of hydromorphone (test or reference treatment with and without rescue) during the double-blind periods

The total daily dose of hydromorphone during the double-blind periods was similar for patients when treated with HHER or HHIR [see Dr. Scheinbaum's review, page 43].

Amount of rescue per day (number of doses and mg amount) during the double-blind periods; this includes amount of rescue dose as a percentage of total daily dose of test or reference treatment

The amount of rescue medication per day was similar for patients when treated with HHER or HHIR [see Dr. Scheinbaum's review, page 44].

Times at which rescue was administered during the double-blind periods

The following table [modified from Dr. Scheinbaum's Table 13, page 29 of his review] summarizes the timing of rescue doses for the two treatment groups:

Table 8. Number and Times of Rescue Dosing Averaged over Last 2 Days prior to PK/PD

	HHER				HHIR			
Time of Day	**Morning**	**Afternoon**	**Evening**	**Night**	**Morning**	**Afternoon**	**Evening**	**Night**
N	91	91	91	91	91	91	91	91
Mean	0.24	0.34	0.30	0.37	0.26	0.37	0.25	0.33
SE	0.04	0.04	0.04	0.06	0.04	0.04	0.04	0.06

Number of patients who required rescue during the double-blind periods

For the Evaluable population, 76% of the HHER and 73% of the HHIR patients required rescue medication. For the ITT population, 78% of the HHER and 74% of the HHIR patients required rescue medication.

Study HD96-0505 [505]:

This was a randomized, double-blind, parallel group, double-dummy, single center study which compared hydromorphone HCl extended release [HHER] to hydromorphone HCl immediate release [HHIR] and to placebo for postoperative orthopedic surgery pain. Patients were initially titrated to acceptable pain control with PCA fentanyl (25-mcg boluses with a 5 minute lockout period). Patients were then randomized and, when there pain intensity was rated as moderate to severe, they were given a single dose of 24 mg of HHER (2 x 12-mg capsules) or Dilaudid 6 mg (3 x 2-mg tablets) or placebo. PCA fentanyl was used as rescue medication.

The primary efficacy variable was the amount of rescue medication for each of four time intervals: 0 to 3, 3 to 6, 6 to 12, and 12 to 24 hours.

A secondary efficacy variable was pain intensity over a 24 hour period measured on an 11 point scale with 0 equal to "no pain" and 10 equal to "pain as bad as you can imagine."

Results:

A total of 132 patients were randomized and eligible for the safety and ITT analyses. Five patients were discontinued prior to completing the study: 3 (one from each treatment group) for adverse events; 1 on placebo for a protocol violation; and, 1 on HHER at the patient's request (to smoke). Five more patients were excluded from the sponsor's Evaluable analysis because of protocol violations (3 on placebo and 2 on HHER).

Efficacy Analyses:

The mean total fentanyl use over 24 hours for the ITT population was:

HHER	1004 mcg
HHIR	986 mcg
Placebo	1187 mcg

While the HHER and HHIR groups were reported by the sponsor to be statistically significantly different from placebo ($p = 0.0086$ and 0.0029, respectively), the two hydromorphone groups were not statistically significantly different from each other ($p = 0.7126$). However, Dr. Permutt found confusion regarding the sponsor's proposed analysis plan and errors in the actual analysis they performed. The sponsor performed a generalized least squares test as part of a mixed-effects, repeated measures analysis of variance. Dr. Permutt describes that analysis as, "...not especially advantageous for testing treatment effects in a parallel-group study because the treatment effect is a between subjects factor...It has been incorrectly applied in this case; the standard errors of the estimated treatment effects have been grossly underestimated; and the significance levels have therefore been dramatically overstated." [page 8 of his Appendix to the Statistical Review and Evaluation]

Based on Dr. Permutt's analysis, the standard errors of the mean fentanyl consumption were:

HHER	89 mcg
HHIR	96 mcg
Placebo	121 mcg

When those values are compared using a two-sample t-test, the p-values are as follows:

HHER to placebo	0.23
HHIR to placebo	0.20

Dr. Permutt also repeated the sponsor's analysis, correcting errors found in that analysis (see page 9 of his Appendix), and documented no statistically significant differences in any of the comparisons, supporting his results from the new analysis discussed above.

The differences between the treatment groups for mean pain intensity were small and not statistically significantly, even by the sponsor's own analysis. [See Dr. Permutt's Table 11.1.2, page 6 of his review.]

COMMENTS:

The sponsor has submitted three trials to document the effectiveness of their product. Two of those studies [801 and 802] were active-controlled trials comparing HHER against HHIR. Both trials documented similar levels of effectiveness for the two treatment arms. However, without a placebo control, or another internal measure of assay sensitivity, these trials lack the necessary controls to establish that either of the treatments was truly effective in the setting of the studies.

The sponsor's third study [505] was an active and placebo-controlled trial which, unfortunately, failed to show that the HHER product was more effective than either the HHIR product or placebo for both primary measures of effectiveness. While clinical experience with the immediate release formulations of hydromorphone would lead us to believe that this extended release formulation is likely to be effective to some degree, the actual efficacy profile of the product has not been established from the studies submitted. The choice of postoperative pain for the single adequate and well-controlled study submitted in this application may well have been inappropriate for this extended release formulation. I concur with Dr. Scheinbaum's comments that, in this clinical setting, the use of a formulation with an earlier onset of adequate analgesic effect would be more appropriate, and that the extended release formulation should be tested in the setting of chronic pain with multiple dosing.

RECOMMENDATIONS:

I recommend that, in regard to effectiveness, this application is approvable pending the submission of two adequate and well-controlled trials documenting that the product is effective in an appropriate clinical setting.

Bob A. Rappaport, M.D.

December 23, 1999

Cc: Original NDA 21-044
HFD-170: Division File
HFD-170:
McCormick
Rappaport
Scheinbaum
Kim
Haberny
Maturu
Fong

CENTER FOR DRUG EVALUATION AND RESEARCH
DIVISION OF ANESTHETIC, CRITICAL CARE & ADDICTION DRUG PRODUCTS

REVIEW AND EVALUATION OF CLINICAL DATA
Application Information

NDA #: 21-044

Sponsor: Purdue Pharma L.P.

Clock Date: Received 12/29/98

Drug Name

Generic Name: Hydromorphone Hydrochloride Controlled Release

Trade Name: Palladone

Drug Categorization

Pharmacological Class: Opioid Analgesic

Proposed Indication: Moderate to Severe Pain

NDA Classification: 3S

Dosage Forms: 12 mg, 16 mg, 24 mg and 32 mg Capsules

Route: Oral

Reviewer Information

Clinical Reviewer: Monte L. Scheinbaum PhD, MD

Completion Date: December 9, 1999

TABLE OF CONTENTS

1.0 Background

Hydromorphone is a well known, morphine-like, semisynthetic opioid analgesic. It has been in clinical use as the hydrochloride salt since 1926. It is a pure opioid agonist with no ceiling effects as seen with partial antagonists. The brand name, Dilaudid (Knoll), and generic hydromorphone hydrochloride products are currently marketed in oral, injectable and suppository formulations for the management of moderate to severe pain. A controlled-release formulation of hydromorphone hydrochloride (Palladone — has been developed by Purdue Pharma for the treatment of chronic pain on a once-daily basis and studied under IND 38,424, filed on December 2, 1991. This NDA presents data intended to support approval for marketing of 12, 16, 24 and 32 mg capsules of this formulation. The 24 and 32 mg capsules are intended for use in opioid-tolerant patients. There is no foreign marketing history for this formulation.

2.0 Material Reviewed

2.1 Hard Copy:

Volume	Contents
1.1	Draft Labeling
1.2	Application Summary; Summaries of chemistry, pharmacology and PK Integrated summaries of efficacy, safety and risk/benefit Proposed Phase IV study
65	Overview of Clinical Investigations, Clinical Pharmacology
66-68 106	Integrated Summary of Effectiveness
69, 109	Integrated Summary of Safety
73	Drug Abuse, Integrated Summary of Benefits and Risks
74-75	HD96-0505
76-86	HD95-0801
87-95	HD95-0802
96-99	HD95-0803 Interim
100	Protocols for planned studies
101-104	Publications
145-178	CRF Tabulations

2.2 Electronic Data: Electronic Data mounted by EDR on acrobat (Text files with pdf and SAS transport files (latter converted to 54 Jump files) and CDROM with 14 MS Word 97 text files.

2.3 Data Quality and Completeness: Case Report Forms from six selected patients (16-041, 21-001, 22-010, 22-011, 23-006 and 33-011) were compared with electronic data listings for quality assurance. Two sites with large enrollments (Dr. Woodson for HD95-0801 and Dr. Stambaugh of HD95-0802) in the pivotal trials were audited by the Office of Compliance. No major discrepancies were found.

3.0 Chemistry

3.1 Drug Substance Quality

Hydromorphone hydrochloride is a white, crystalline powder that is a semisynthetic congener of the opium alkaloid, morphine. Hydromorphone differs from morphine by substitution of the 6-hydroxyl with a ketone group and by saturation of the 7-8 double-bond. The chemical name is 4,5a-epoxy-3-hydroxy-17-methylmorphinan-6-one hydrochloride. Hydromorphone is a weak base with two ionization constants, a plasma protein binding of 7.7%, a blood/plasma partition ratio of 1.5 and an octanol/water partition coefficient of 0.32. The hydrochloride is soluble in water and sparingly soluble in alcohol. The product is made of encapsulated pellets containing homogeneous hydromorphone multiparticulates developed by extrusion melt technology. It is intended to provide controlled delivery over 24 hours.

3.2 How supplied

Palladone ™ is supplied as 12, 16, 24 and 32 mg capsules. The 12-mg capsules are cinnamon-colored and are imprinted with the terms "P-XL" and "12 mg". The 16-mg capsules are pink and are imprinted with the terms "P-XL" and "16 mg". The 24-mg capsules are blue pink and are imprinted with the terms "P-XL" and "24 mg". The 32-mg capsules are white and are imprinted with the terms "P-XL" and "32 mg". Each strength is supplied in a plastic, child-resistant bottle of 100 and as unit dose packaging with 25 numbered capsules per card: one card per glue-end carton.

4.0 Animal Pharmacology

Hydromorphone is a selective mu-opioid receptor agonist with pharmacological properties similar to morphine. It is a more potent in binding to mu receptors (10-30 fold) and a more potent analgesic (4-10 fold) than morphine in animal models. Like morphine, its respiratory depressant effects are similar to its analgesic potency, but it is less potent than morphine in emetogenic effects. It is 4-10 times more potent than morphine in inducing constipation. Like other mu-agonists, hydromorphone has antitussive properties. As with morphine and other narcotics, tolerance develops to its opioid effects. Reproductive toxicity studies revealed no evidence of teratology in rats or rabbits, although high doses resulted in fetotoxicity in rabbits. Acute toxicity studies of hydromorphone hydrochloride reveal LD_{50}'s of 84-120 mg/kg in mice and 51 mg/kg in rats following subcutaneous administration. LD_{50} for intravenous administration in mice was 51 to 104 mg/kg. Respiratory depression, convulsions, analgesia and excitation are observed at high doses.

5.0 Proposed Indication, Strengths, Route of Administration, and Directions for Use

5.1 Proposed Indication: Moderate to Severe Pain

5.2 Dosage Form: Controlled-Release Capsule

5.3 Strengths: 12 mg, 16 mg, 24 mg and 32 mg

5.4 Route of Administration: Oral

5.5 Proposed Directions for Use: Palladone — capsules are to be swallowed whole or the entire contents sprinkled on soft food such as apple sauce. They are not to be chewed or crushed, since this could lead to the rapid release and absorption of a potentially toxic dose of hydromorphone. The 24 and 32 mg capsules are for use only in opioid tolerant patients requiring daily hydromorphone equivalent of 24 mg or greater. Patients should be instructed to prevent use by individuals other than for whom it was prescribed.
Palladone — is intended for the management of moderate to severe pain in patients who require treatment with an oral opioid analgesic (minimum of hydromorphone equivalent of 12 mg daily) for more than a few days. It should be administered every 24 hours at the lowest dosage that will achieve adequate analgesia and be tolerated. The dose must be individually adjusted according to severity of pain, patient response, patient size, prior analgesic usage, patient's medical condition and side effects.

6.0 Description of Clinical Data Sources

There were 203 unique healthy subjects enrolled in ten Phase I trials (Table 1, from Sponsor's Table 8.1.2, Vol 105 pp11-14)). There were also four other earlier Phase I developmental pilot studies that involved experimental formulations other than Palladone — (HC87-0108, HS90-0707, HS92-1003 and HS92-1004). These latter studies are not included in the clinical review. There were 132 postoperative patients (44 received Palladone —) in Study HD96-0505. The two pivotal trials (HD95-0801 and HD95-0802) enrolled 344 patients, all of which received at least one dose of Palladone — During double-blind periods, 209 patients received Palladone — and 209 received immediate release hydromorphone. The extension study (HD95-0803) enrolled 78 patients (one of which did not receive medication). Table 2 summarizes the efficacy and safety studies (Sponsor's Table 8.7.1 Vol 105, p.99). There were 43 publications relating to the clinical pharmacology, efficacy and safety of the drug substance, hydromorphone, included in the NDA submission. References to those 25 publications dealing with clinical matters are listed in Section 6.1.

TABLE 1 PHASE I STUDIES

Report No./ Investigator/ Publication/ Location	Design	Treatment, Doses	No. Received/ No. Evaluable Each Treatment	Duration of Drug Treatment
HD95-0105 (Vol. 19, p. 1)	OL, AB, R, 5-way XO, 1 dose	Dilaudid® 8mg[d] HHCR Form. A 8mg[d] HHCR Form. B 8mg[d] HHCR Form. A 8mg[e] HHCR Form. B 8mg[e]	12/11 12/11 11/11 12/11 12/11	single dose of each treatment
HD95-0106 (Vol. 20, p. 1)	OL, AB, R, 3-way XO, 1 dose	Dilaudid® 8mg[d] HHCR Form. C 8mg[c] HHCR Form. C 8mg[d]	11/11 11/11 11/11	single dose of each treatment
HD95-0303 (Vol. 21, p. 1)	OL, AB, R, 2-way XO, RD	Dilaudid® 4mg q6h[d] Dilaudid® 4mg q6h[e] HHCR 2×8mg q24h[d] HHCR 2×8mg q24h[e]	6/6 6/6 6/6 6/6	4 days Multiple-dose
HD95-0701 (Vol. 22, p. 1)	OL, AB, R, 4-way XO, 1 dose	Dilaudid® 8mg[d] HHCR 24mg[e] HHCR 24mg[d] HHCR 12mg[d]	24/24 24/24 24/24 24/24	single dose of each treatment
HD95-0805 (Vol. 24, p. 1)	OL, AB, R, 2-way XO, 1 dose	3×12mg+Nx 2×50mg[d] 1×32mg+Nx 2×50mg[d]	26/26 26/26	single dose of each treatment
HD96-1101 Poster APS 11/98 (Vol. 26, p. 1)	OL, AB, R, 2-way XO, 1 dose	HHCR 24mg capsule[d] HHCR 24mg sprinkle[f]	25/24 25/24	single dose of each treatment
HD96-1206 (Vol. 27, p. 1)	OL, AB, R, 3-way XO, 1 dose	24mg Lot 5L[d] 24mg Lot CB25-34A[d] 24mg Lot CB25-34B[d]	23/23 24/23 24/23	single dose of each treatment
HD97-0502 (Vol. 29, p. 1)	OL, AB, R, 4-way XO, 1 dose	24mg Lot 4L[d] 24mg Lot CB26-15[d] 24mg Lot CB26-16[d] 24mg Lot 4L-B[d]	12/10 10/10 11/10 11/10	single dose of each treatment
HD98-0505 (Vol. 31, p. 1)	OL, AB, R, 2-way XO, 1 dose	Dilaudid® 3×2mg[d] HHIR 3×2mg[d]	36/36 36/36	single dose of each treatment
HD95-0702 Poster RCPS 9/98 (Vol. 32, p. 1)	OL, AB, R, 2-way XO, RD	HHIR 3mg q6h[d] HHCR 12mg q24h[d]	26/26 26/26	5 days

Note: AB=analytically blinded, AE=adverse event, B=black, CRF=case report forms, DC=discontinuation, F=female, Form.=formulation, G=geriatric (≥65 yrs), HHCR=hydromorphone hydrochloride controlled-release capsule, M=male, Nx=naltrexone hydrochloride, O=other race; OL=open label, Ped=pediatric (<18 yrs), R=randomized, RD=repeated dose, W=white, XO=crossover. **Formulations A, B, and C represent formulations of melt-extrusion multi-particulate technology with types and proportions of ingredients similar to those utilized in the final formulation. Formulation B is the final formulation utilized in definitive Phase I, II and III studies.

[a]All of the studies in the HHCR NDA were conducted in the U.S. unless otherwise noted. [b]Received at least one dose. [c]Evaluable for pharmacokinetic analysis. [d]Fasted. [e]Fed.

Note: AB=analytically blinded, AE=adverse event, APS=American Pain Society, B=black, CRF=case report forms, DC=discontinuation, F=female, G=geriatric (≥65 yrs), HHCR= hydromorphone hydrochloride controlled-release capsules, HHIR=hydromorphone hydrochloride immediate-release tablets (Purdue), M=male, O=other race, OL=open label, Ped=pediatric (<18 yrs), R=randomized, RCPS=Royal College of Physicians and Surgeons, RD=repeated dose, W=white, XO=crossover.

[a]All of the studies in the HHCR NDA were conducted in the U.S. unless otherwise noted. [b]Received at least one dose. [c]Evaluable for pharmacokinetic analysis. [d]Fasted. [f]Administered with one teaspoon applesauce (subjects were fasted except for this).

TABLE 2 EFFICACY AND SAFETY TRIALS

Report No./ Investigator/ Publication/ Location	Design	Treatment, Doses	No. Received[b]/ No. Evaluable[c] Each Treatment	Duration of Drug Treatment
HD96-0505 New Zealand (Vol. 74, p. 1; Vol. 114, p. 1)	DB, AB, R, P, 3-treatment, 1 dose Postop pain	HHIR 2×3mg+fent. HHCR 2×12mg+fent. Placebo+fent.	44/41 44/41 44/40	single dose of each treatment
HD95-0801 Multiple Investigators (Vol. 76, p. 1; Vol. 116, p. 1)	DB, AB, R, 2-way XO, RD cancer and nonmalignant chronic pain	HHCR 12mg≤84mg HHIR 12mg≤84mg	174/67 97/67	≤35 days
HD95-0802 Multiple Investigators (Vol. 87, p. 1; Vol. 127, p. 1)	DB, AB, R, 2-way XO, RD cancer and nonmalignant chronic pain	HHCR 12mg≤84mg HHIR 12mg≤84mg	169/91 112/91	≤35 days
HD95-0803 Multiple Investigators (Vol. 96, p. 1; Vol. 136, p. 1)	OL extension of HD95-0801 & HD95-0802, RD Cancer pain	HHCR ≥ 12 mg	77/77	≤58 days

Note: AB=analytically blinded, AE=adverse event, B=black, CRF=case report forms, DB=double-blind, DC=discontinuation, F=female, fent.=fentanyl, G=geriatric (≥65 yrs), HHCR= hydromorphone hydrochloride controlled-release, HHIR=hydromorphone hydrochloride immediate-release tablets (Purdue), M=male, O=other race; OL=open label, P=parallel, Ped=pediatric (<18 yrs), R=randomized, RD=repeated dose, W=white, XO=crossover.

[a]All of the studies in the HHCR NDA were conducted in the U.S. unless otherwise noted. [b]Received at least one dose. [c]Evaluable for pharmacokinetic and efficacy analysis (HD96-0505), DB efficacy (HD95-0801, HD95-0802), safety (HD95-0803) or pharmacokinetic (HC87-0108) analysis. [d]Fasted. [e]Patients completed in November 1998; final study report in preparation.

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7.0 Human Pharmacokinetics

7.1 Absorption

Absorption of a single dose of Palladone —is biphasic, with an initial rapid peak followed by a second broader peak with therapeutic plasma concentrations maintained over 24 hours. The bioavailability of Palladone — is said to be similar to that of immediate-release oral hydromorphone, which is 51-62% bioavailable relative to a parenteral dose. Palladone — 12 mg given every 24 hours was equivalent to immediate-release oral hydromorphone 3 mg given every 6 hours in AUC.. There was dose proportionality from 12 to 32 mg for Pallidone — with respect to absorption. There were dose-proportional increases in steady-state concentrations of hydromorphone over the 12 to 84 mg daily dose range. There was no significant effect of food resulting on the absorption of hydromorphone from Palladone — Absorption of hydromorphone from 24-mg capsules sprinkled over applesauce was bioequivalent to that from the intact capsule.

7.2 Distribution

The volume of distribution for intravenous-administered hydromorphone (terminal half-life 3 hours) was 295 L or 4 L/kg, and clearance was 1.66 L/hr. There is plasma protein binding. Although distribution was not studied, it is expected to be similar to that for other opioids, which would include distribution to skeletal muscle, liver, intestinal tract, lungs, spleen, brain and breast milk.

7.3 Pharmacokinetics

Peak plasma concentrations were observed at approximately 1.5 hours. The apparent terminal half-life was 18.8 hours (mean residence time was 27.6 hours).

7.4 Metabolism

Metabolism occurs by direct conjugation or by 6-keto reduction followed by conjugation. Following absorption, hydromorphone is metabolized primarily to hydromorphone-3-glucuronide, hydromorphone-3-glucoside and dihydroisomorphone-6-glucuronide. Lesser metabolites include dihydroisomorphone-6-glucoside, dihydromorphine and dihydroisomorphine. Possibly because of the multiple metabolic pathways available to eliminate the drug, interactions with drugs such as H_2 blockers and proton pump inhibitors appear to be unimportant.

7.5 Elimination

Excretion occurs in the urine and feces, but mass balance studies have not been done. Hepatic or renal impairment is associated with increased plasma drug concentrations. Elderly patients (>65 years) may have increased sensitivity associated with increased plasma levels. Pediatric populations under 16 years have not been studied. Gender and race effects appear to be absent.

8.0 Efficacy Findings

8.1 Overview of Efficacy

Two double-blind, controlled pivotal trials (HD95-0801 and HD95-0802) of identical design were carried out to demonstrate efficacy of the sustained-release tablets as compared to the immediate release formulation of hydromorphone hydrochloride in patients with chronic pain.
HD96-0505 was a double-blind, randomized, parallel-group, single-dose, placebo-controlled study in the treatment of moderate to severe post-operative pain carried out in Australia and New Zealand under the U.S. IND. This study provides supportive evidence of the analgesic efficacy of Palladone — versus placebo and immediate-release hydromorphone hydrochloride.

8.2 Adequate and Well-Controlled Trials Pertinent to Efficacy Claims

8.21 Study HD95-0801 (Vols 76-86)

Double-Blind, Randomized, Two-Period Crossover Study Comparing the Efficacy, Safety and Pharmacokinetic and Pharmacodynamic Profiles of Oral Administration of Hydromorphone Hydrochloride Controlled-Release Capsules (qAM) and Hydromorphone Hydrochloride Immediate-Release Tablets (qid) for
Cancer-Related or Chronic Nonmalignant Pain

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8.212 Plan

8.2121 Objective

The study was primarily intended to determine the efficacy, safety, plasma concentration, and pharmacodynamic effect of oral administration of Palladone — (hydromorphone hydrochloride controlled-release capsules) qd as compared with hydromorphone hydrochloride immediate-release (HMIR) tablets qid in the treatment of cancer-related or chronic nonmalignant pain. A secondary objective (Amendment 1) was to determine if patients with chronic pain could discriminate between a lower dose of oral hydromorphone (or placebo) and the dose of hydromorphone that previously provided stable pain control.

8.2122 Population

Patients with chronic pain of cancer origin were eligible for entry if : 10 years of age or older and required treatment of chronic cancer-related pain with opioid analgesics; or, were 18 years of age or older and required treatment of chronic nonmalignant pain (e.g., osteoarthritis, rheumatoid arthritis, intervertebral disc disease, spondylolisthesis, nerve root entrapment) with opioid analgesics. Patients with pain under stable control with Palladone — qd during the Open-Label Period could be randomized into the Double-Blind Period. The daily opioid analgesic dose required must have been equivalent to at least 12 mg of oral hydromorphone hydrochloride, and opioid treatment should have been taking place for at least 2 weeks before study entry.

Nonopioid analgesics or nonopioid medications with analgesic properties, if used, were to be dosed on a stable regimen (not prn) for at least two days before study entry. Patients must have been able to be contacted by telephone. Any co-existing disease state and related therapy had to be stable for at least the week before study entry. Patients were to be willing and able to participate in all aspects of the study, such as take oral medications, complete diaries, and undergo subjective evaluations and phlebotomy.

The following criteria had to be met before the patient could be randomized to the first of the two double-blind periods: Palladone — had been administered for at least 4 days during the Open-Label Period with tolerability and stabilization of pain intensity, study medication dosage and use of rescue medication. Adverse events, if any, were to be tolerable, and the dose, frequency and route of administration of any nonopioid analgesics or adjuvant medications with analgesic properties were to be stable for the 48-hour period preceding entry to the first double-blind period.

Patients were excluded from the study if they met any of the following criteria: allergy to hydromorphone hydrochloride; contraindication to opioid therapy, including paralytic ileus or severe pulmonary disease; required a total daily dose of oral hydromorphone greater than 72 mg; were pregnant or a nursing female; were female of childbearing potential who did not agree to use a medically recognized method of contraception throughout the study; were unable to swallow solid, oral dosage forms; were scheduled for surgery or other procedures during the 35 days following screening that would have prevented completion of the study; were participating in another study of an IND investigational drug or device; had medical condition(s) that might have increased the risk associated with exposure to the test medications or that might have confounded or obscured efficacy assessments; were administered strontium-89 chloride within 30 days before the study; had history of substance abuse (in chronic nonmalignant pain population); or were currently involved in any litigation or arbitration that is related to his/her chronic nonmalignant pain and/or injury; or underwent intra-articular or intramuscular steroid injections to the site of chronic nonmalignant pain assessment within 6 weeks prior to baseline visit.

Patients with cancer pain who were at least 18 years old and completed both double-blind periods could be enrolled into the Amendment 1 Study.

8.2123 Design

This was a randomized, double-blind, double-dummy, active-controlled, multi-center two-period crossover comparing efficacy, safety and pharmacokinetic and pharmacodynamic profiles of oral administration of Palladone — (hydromorphone hydrochloride controlled-release capsules) given qam and hydromorphone hydrochloride immediate-release tablets (HMIR) given qid to outpatients on opioid analgesics with cancer-related or chronic non-malignant pain. The maximum daily dosage of hydromorphone hydrochloride administered was 84 mg.

8.21231 Open-Label Titration Periods.

Patients were enrolled into a nonrandomized, open-label titration period (4 to 21 days in duration), prior opioid treatment was discontinued and Palladone — capsules qd (at approximately 8 am) was administered with 2 mg HMIR tablets q4-6h prn as rescue medication. Rescue doses were intended to be 1/8 to 1/6 that of the intended daily dose to be administered q4-6h as needed for incident or breakthrough pain. It was recommended that a rescue dose be taken approximately 1 hour before expected incident pain. The initial daily dose of Palladone — was selected by using the conversion table (Table 3A from sponsor's Table 9.4.5A, Vol 76 p.28)) and round-off table (Table 3B from sponsor's Table 9.4.5B, Vol 76 p.28)) below along with consideration of the investigator's judgment of recent pain and tolerability of opioid-related side effects. The prestudy opioid daily dose was thereby converted to a multiple of 12 mg hydromorphone, the strength of the Palladone — capsule. If the calculated oral hydromorphone daily dose was less than 10 mg, the investigator assessed whether the patient's pain might require treatment with 12 mg of oral hydromorphone per day. The Palladone — daily dose was titrated to achieve stable pain control, defined as pain control with the same dose for at least 48 hours. Dosage of nonopioid analgesia should have also been stabilized for at least 48 hours. After pain was controlled for at least 48 hours and all other criteria for double-blind randomization were met, the patients were randomized to the double-blind, crossover of two treatment periods (each 3 to 7 days in duration).

8.21232 Double-Blind Crossover Periods. During the double-blind periods, the stable hydromorphone daily dose established in the open-label period was administered daily. Crossover periods were 3 to 7 days in duration. Patients were randomized to either Palladone — capsules qd or HMIR tablets qid (0800 H, 1300 H, 1800 H, and bedtime) in the first double-blind period and then crossed over to the alternate treatment in the second double-blind period. The two treatments were blinded using a double-dummy technique, and 2 mg HMIR tablets were used as rescue for both treatments. Efficacy, safety, plasma hydromorphone concentration, and pharmacodynamic effects were assessed during double-blind periods 1 and 2. Visits 3 and 4 (the last days of Double-Blind Periods 1 and 2, respectively) could occur on Days 3, 4, 5, 6, or 7 of the respective double-blind period at the discretion of the principal investigator. Patients were required to stay at the study site for approximately 6 hours at Visit 3 and again at Visit 4. PK/PD observations were made at these visits. Rescue was given the same way as in the open-label titration, 1/8 to 1/6 of the established, end-of-titration given as 2 mg immediate-release oxycodone tablets q4-6h as needed to manage pain. To ensure evaluability of PK/PD data, patients were asked to refrain from using rescue medication between midnight, the evening before each PK/PD evaluation (Visits 3 and 4), and the 0 hour PK/PD evaluation the following morning. The use of rescue medication was prohibited between the 0 hour and 5-6 hour PK/PD evaluations. At Visit 3, if an optional22-24 hour PK/PD evaluation was done, it was to be done before the next 0800 hours dose.

Table 3A Prior Opioid Conversion to Hydromorphone Hydrochloride

Prestudy Opioid	Oral	Parenteral*
Codeine	0.0375	-
Hydrocodone	0.225	-
Hydromorphone	1	5
Levorphanol	1.875	3.75
Meperidine	0.025	0.1
Methadone	0.375	0.75
Morphine	0.125	0.75
Oxycodone	0.25	-
		Transdermal
Fentanyl (µg/hr)		0.225

*For patients receiving high dose parenteral opioids, a more conservative conversion was warranted. For example, for high dose parenteral morphine 0.375 was used instead of 0.75 as a multiplication factor.

Table 3B Palladone — Rounding-Off Table

Dose Level	Calculated Total Daily Oral Hydromorphone Dose (mg)	Rounded Total Daily Oral Hydromorphone Dose (mg)	Number of HMIR Capsules qd
1	10-20	12	1
2	21-32	24	2
3	33-42	36	3
4	43-54	48	4
5	55-66	60	5
6	67-78	72	6

8.21233 Protocol Amendment Number 1

An amendment to the protocol (dated January 16, 1998) added an extension to the trial involving patients at 6 study sites who completed Double-Blind Periods 1 and 2. It involved an exploratory method for internal validation of active control analgesic studies recommended by an FDA medical reviewer. The method is based on comparing the established treatment dose with a low dose (or placebo) control within patients. The objective was to determine if patients could discriminate between a lower dose of oral hydromorphone (or placebo) and a dose of hydromorphone that previously provided stable pain control. Each patient was randomized to one of two treatment sequences: same dose -> low dose or low dose -> same dose of the same treatment (test or reference) that the patient received during Double-Blind Period 2. The rescue dose was the same as in Double-Blind Periods 1 and 2 (1/6th of the scheduled daily dose, with allowance to be as low as 1/8th); the patients were supplied with 6 rescue doses per day. Each period (A and B) lasted 3 days. The double-dummy technique, double-blind, and rescue medication doses utilized in double-blind Periods 1 and 2 were retained in Periods A and B. For the same-dose arm, each patient received the same daily dose of scheduled hydromorphone hydrochloride as in Double-Blind Periods 1 and 2. For the low-dose arm, the daily dose was calculated by reducing the "same dose" by increasing multiples of 12 mg such that it was reduced by at least 50% and as much as 100% for 12 mg total daily dose. (Multiples of 12 mg were required so that placebo could be substituted for unit daily doses: 12 mg Palladone — qd or 3 mg HMIR qid.) The low-dose treatment was blinded from the same-dose treatment by replacing the appropriate number of active drug capsules/tablets with matching placebo. The unblinded sponsor's staff generated the randomization code and packaged the medication. They informed the study site staff which box of study medication to dispense to the patient based on the patient's assigned treatment for Period 2 of the core trial, and they assigned dose treatment sequences for Amendment I Periods A and B. Investigators and site staff, patients, clinical monitors, and all others of the sponsor's staff were blinded to the double-blind treatment. Since only 7 patients were enrolled in this study, no efficacy evaluations were attempted. Safety related data from this extension study was added to the safety data base. This substudy itself afforded no useful conclusions.

8.21234 Concomitant Medication

Opioids other than the hydromorphone hydrochloride test drugs supplied, including opioid cough medicines, were prohibited throughout the study except for antidiarrhea agents, e.g., Lomotil ®. Nonopioid analgesics and analgesic adjuvant medications, e.g., corticosteroids and tricyclics, were permitted, and their dosages could be adjusted during the open-label titration, but were to be stable for 2 days prior to randomization and to continue unchanged during the double-blind periods. Intra-articular or intramuscular steroid injections to the assessment site of the chronic nonmalignant pain, all other investigational drugs and devices, and use of strontium-89 were prohibited throughout the study. Medication needed for other treatment, e.g., chemotherapy, was permitted.

8.2124 Assessments

Efficacy Variables
Current and Average (averaged since the last rating) pain intensities were rated by patients immediately before each dose and immediately before each phlebotomy during Visit 3 (end of period 1) and Visit 4 (end of period 2) during the double-blind periods. An 11-point scale was used: 0 = No Pain, ...,10 = Pain As Bad As You Can Imagine.
"Drug effect" (feeling any effect(s) of the drug "right now") was rated by the patient immediately before each phlebotomy during Visits 3 and 4 using an 11-point scale: 0 = Not At All, ...,10 = An Awful Lot.
Patient ratings for current pain intensity and drug effect followed immediately by phlebotomies for drug plasma level determination were carried out at time of morning dosing, and at 1, 2, 3, 5-6 and 22-24 hours (each +/- 10 minutes) following morning dosing.

The primary efficacy variables were designated by the sponsor as:

a) the mean of average pain intensity ratings by the patient over the last 2 days of each double-blind period before Visits 3 and 4 (the PK/PD days).

b) current pain intensity rating by patient immediately before each phlebotomy at Visits 3 and 4.

c) "drug effect" patient-rating immediately prior to phlebotomies at Visits 3 and 4. Although this rating relates more to drug tolerability than to efficacy, results for this variable will be briefly discussed.

d) plasma hydromorphone concentration (actual and dose-adjusted) at the time of each phlebotomy at Visits 3 and 4. Although these measurements relate more to pharmacokinetics than to efficacy, results will be briefly discussed.

Secondary efficacy variables weredesignated by the sponsor as:

a) average pain intensity ratings on each of the last 2 days of each double-blind period before the PK/PD day.

b) mean of average pain intensity ratings for each double-blind study day.

c) current pain intensity ratings on each of the last 2 days of each double-blind period before the PK/PD day.

d) mean of current pain intensity ratings for each double-blind study day.

e) minimum and maximum plasma hydromorphone concentrations observed

f) plasma hydromorphone concentration and pharmacodynamic effect (current pain and patient "drug effect") at each phlebotomy time point.

g) relationship between plasma concentration and current pain intensity and relationship between plasma concentration and patient "drug effect."

h) time to stable pain control during the Open-Label Period (includes number [%] of patients successfully titrated to stable pain and number [%] of patients who required a change from the conversion dose level.

i) total daily dose (mg) of hydromorphone (test or reference treatment with and without rescue) during the double-blind periods.

j) amount of rescue per day (number of doses and mg amount) during the double-blind periods. This includes amount of rescue dose as a percentage of total daily dose of test or reference treatment.

k) times at which rescue was administered during the double-blind periods.

l) number of patients who required rescue during the double-blind periods.

8.2125 Analysis Plan

All statistical tests were two-sided with a significance level of 0.05. Interaction and carryover effects were conducted at a significance level of 0.10. The standard crossover analysis of variance (ANOVA) model included treatment (double-blind), sequence, period, and patient nested within sequence. All patients receiving study medication were analyzed for safety. The intent-to-treat population received at least one dose of double-blind drug. The sponsor's "efficacy" population completed the double-blind study and complied with the protocol. Some of the latter also completed PK studies (PK/PD population).

8.21251 Primary Efficacy Analyses

a. The mean of the eight average pain intensity ratings over the last 2 days of the double-blind period before the PK/PD day was analyzed using the crossover ANOVA model. Schuirmann's two one-sided hypotheses (α=0.05) was tested for the mean average pain intensity over the last two days of each double-blind period before PK/PD day by constructing a 90% confidence interval for the difference between Palladone — and HMIR means. Based on clinical consideration, the equivalence limits were chosen as (-2, 2), which reflects a 20% change in the 11-point (0 to 10) numeric scale. The two drugs were considered equivalent in pain control if the 90% confidence interval was contained within this interval (-2, 2).

b. Graphical representations of current pain intensity, patient "drug effect," and plasma hydromorphone concentration over the time points were produced (including the ratings of these variables at the time of the optional blood draw at 22 to 24 hours postdose). Repeated-measures ANOVA was used to evaluate treatment differences at the timepoints (up to 5–6 hours postdose) for current pain intensity, patient "drug effect," and plasma hydromorphone concentration (dose-adjusted to 36 mg) with time of blood draw as the repeated factor.

8.21252 Secondary Efficacy Analyses

a. Repeated-measures ANOVA was used to evaluate the diurnal treatment differences for the four current pain intensity scores over the last 2 days of the double-blind period (before the PK/PD day) with time of day as the repeated factor.

b. The mean of average pain intensity on the last day before the PK/PD day was analyzed using the crossover ANOVA model, and a 90% confidence interval for the difference in mean of average pain intensity was constructed.

c. A graphical representation of plasma hydromorphone concentration was produced for all time points (0, 1, 2, 3, 5–6, and optional 22–24 hour). Observed minimum values of plasma hydromorphone concentration were evaluated using the standard crossover ANOVA model.

d. The relationship between actual plasma hydromorphone concentration and the pharmacodynamic effect (current pain intensity and patient "drug effect") at each time point was assessed graphically, and if there was a relationship, it was to be evaluated using a mixed effects model.

e. The time (days) to stable pain in the open-label phase was determined and tabulated. Tabulations for the number (and percentage) of patients who attained stable pain control and the number (and percentage) of patients who required titration were produced.

f. The total daily dose (mg) of the test or reference treatment was tabulated along with the scheduled daily dose (mg) of the treatment plus the dose (mg) of the rescue used.

g. The amount of rescue per day (number of doses and mg), time of day of rescue, number of patients requiring rescue, and amount (mg) of rescue doses as a percent of the total daily dose of hydromorphone (scheduled drug and rescue) were tabulated by treatment and period.

8.213 Study Conduct/Outcome

8.2131 Patient Disposition

The planned enrollment was approximately 130 patients to ensure that 80 would complete. A total of 174 patients were enrolled and included in the safety analysis. There were 22 patients (13%) in the open-label Palladone — titration period who discontinued because of adverse events, and 24 (14%) patients who discontinued because of lack of efficacy during this period. Also, seven patients discontinued due to intercurrent illnesses and two patients died in the open-label period. Fourteen more patients discontinued prior to randomization for protocol violations or other reasons.

There were 106 patients randomized into the double-blind period; since there were no pain scores for two randomized patients, only 104 were included in the intent-to-treat population; 89 completed and 67 were included in the sponsor's main efficacy analysis. Of these, 30 received Palladone — prior to getting HMIR, and 37 were administered the opposite sequence.
During the double-blind periods, five patients who started on HMIR discontinued prior to crossing over to Palladone — thus, there were 101 patients who received Palladone — in the double-blind crossover. Ten of these patients discontinued while on double-blind Palladone — Five of these patients discontinued due to adverse events, one due to ineffective treatment, one because of intercurrent illness and three others for protocol violations or other reasons.

During the double-blind periods, because eight patients who started on Palladone — discontinued prior to crossing over to HMIR, there were only 98 patients treated with HMIR. While on double-blind HMIR, six patients discontinued. Two patients discontinued due to adverse events, and one died. Two discontinued because of ineffective treatment, and one for protocol violation.

Although it was anticipated that as many as 26 patients could complete the Amendment No. 1 exploratory study, only 7 patients were enrolled. All 7 completed and were included in the efficacy and safety analyses.

Summary of Disposition of Patients in Study HD95-0801
(from Sponsor's Tables 14.1.1, 14.1.2 and 14.1.3 Vol 76 pp123-136)

Patients Enrolled = 174
Patients Evaluable for Safety = 174 (100%)
Early (Open-Label) Discontinuations = 68 (39%)
Open-Label Discontinuations for AE's, Intercurrent Illness or Death = 33 (19%)
for Lack of Efficacy = 24 (14%)
for Protocol Violations = 7 (4%)
for Other Reasons = 7 (4%)
Patients Randomized to Double-Blind Crossover = 106
Patients Randomized but without Pain Scores = 2
Patients Included in the ITT Analysis = 104
Patients who did not receive Palladone in the double-blind period = 3
Patients who received Palladone in the Crossover = 101
Patients who discontinued while on Palladone in the Crossover = 10 (10%)
Patients discontinuing on Double-Blind Palladone
for AE's, Death or Intercurrent Illness = 6 (6%)
for Lack of Efficacy = 1 (1%)
for Protocol Violation = 1 (1%)
for Other Reasons = 2 (2%)
Patients who did not receive HMIR in the double-blind period = 6
Patients who received HMIR in the Crossover = 98
Patients discontinuing on Double-Blind HMIR in the Crossover = 6 (6%)
Patients discontinuing on Double-Blind HMIR
for AE's, Death or Intercurrent Illness = 3 (3%)
for Lack of Efficacy = 2 (2%)
for Protocol Violation = 1 (1%)
for Other Reasons = 0 (0%)
Patients Excluded by Sponsor for "Efficacy" Analysis Population = 22 (21%)
Excluded from "Efficacy" (some patients had more than one cause for exclusion)
for unstable nonopioid analgesic or adjuvant use = 8
for having been found ineligibile for randomization = 4
for both of the above protocol violations = 2
for insuffficient dosing during last 2 days prior to PK/PD = 6
for use of other opioids = 1
for insuffficient pain ratings during last 2 days prior to PK/PD = 6
Patients in "Efficacy" Population = 68
Patients in Reviewer's Integrated Efficacy Population
(Patients with efficacy data for both legs of the crossover) = 88

8.2132 Demographics

The demographic and baseline characteristics of the total population (n=174) enrolled and evaluable for safety analysis were as follows: There were 83 men and 91 women; there were 147 white, 19 black and 5 Hispanic and 3 Asian and "other" patients. Mean age was 58 years (range 22 to 84); mean weight was 77 kg (range 37 to 145), and mean height was 169 cm (range 141 to 190). There were 145 patients with cancer pain and 29 with nonmalignant pain. All patients had prior opioid experience.

The demographic and baseline characteristics of the 104 intent-to-treat patients were as follows: There were 51 men and 53 women; there were 91 white, 10 black and 3 Hispanic patients. Mean age was 59 years (range 29 to 79); mean weight was 74 kg (range 45 to 135), and mean height was 169 cm (range 143 to 189). There were 91 patients with cancer pain and 13 with nonmalignant pain.

The demographic and baseline characteristics of the 67 patients considered evaluable for efficacy were as follows: There were 34 men and 33 women; there were 59 white, 6 black and 2 Hispanic patients. Mean age was 60 years (range 34 to 79); mean weight was 66 kg (range 45 to 135), and mean height was 168 cm (range 143 to 189). Predominant pain sites were bone (n=38), nerve (n=6), viscera (n=8), and soft tissue (n=15).

8.2133 Open-Label Pain Scores and Dosing

There were 172 patients currently receiving opioid treatment for chronic cancer-related or nonmalignant pain that entered the open-label titration period of the study. The mean pain score was 5.16 (on a scale of 0 to 10). Mean pain score for this population at the end of titration was 3.38 (this value includes scores for patients who discontinued the titration phase prematurely and may not have reached stable pain control).

The 104 patients randomized into the double-blind treatment periods (intent-to-treat population) had mean pain score 4.88 at the beginning of the study and 2.38 on the last day of the titration period. The mean daily dose level of Palladone— was 36.4 mg at the end of the open-label titration. There were 25 patients on 12 mg/d, 22 on 24 mg/d, 21 on 36 mg/d, 15 on 48 mg/d, 9 on 60 mg/d, 6 on 72 mg/d and 6 on 84 mg/d.

The 67 patients were considered eligible for the sponsor's efficacy evaluation mean pain score 5.10 at the beginning of the study and 2.26 on the last day of the titration period. They were receiving mean daily dose level of 38 mg (range 12 to 84 mg, median 36 mg) of Palladone — at the end of open-label titration. There were 16 patients on 12 mg/d, 14 on 24 mg/d, 10 on 36 mg/d, 11 on 48 mg/d, 6 on 60 mg/d, 6 on 72 mg/d and 4 on 84 mg/d.

8.214 Efficacy Results

8.2141 Primary Efficacy Variables

a. Average Pain Intensity: The means (and SE's) of patient-rated pain intensity scores for each treatment averaged over the last 2 days of each double-blind period before Visits 3 and 4 (the PK/PD assessment days) for the sponsor's efficacy population (data from both double-blind periods combined; sponsor's Table 11.4.1.1A, Vol 76, p.57) were as follows:

The Palladone — group had mean pain intensity rating 2.48 (0.07)

The HMIR treatment group had mean pain intensity rating 2.42 (0.07)

The difference in the least squares means was 0.06 and the 90% confidence interval for the difference was [-0.11, 0.23]. Analyses of sequence effect and period effect on these pain scores revealed no statistically significant (p= 0.58 and p= 0.10, respectively) differences.

The means (and SE's) of patient-rated pain intensity scores for each treatment averaged over the last 2 days of each double-blind period before Visits 3 and 4 (the PK/PD assessment days) for the intent-to-treat population (data from both double-blind periods were combined; sponsor's Table 11.4.1.1B p.57) were as follows:

The Palladone — group had mean pain intensity rating 2.79 (0.08)

The HMIR treatment group had mean pain intensity rating 2.62 (0.08)

The difference in the least squares means was 0.17 and the 90% confidence interval for the difference was [-0.01, 0.35]. Thus, results from the intent-to-treat population were similar to those from the efficacy population, with no significant differences between treatments observed.

b. Current Pain Intensity Ratings before Phlebotomies: The current patient-rated pain intensity scores for each combined treatment group (from PK/PD population) assessed immediately before each phlebotomy at Visits 3 and 4 are tabulated in Table 4 (from sponsor's Fig 11.4.1.1A and Table 14.2.15.G Vol 76 p.58) according to time of phlebotomy. Mean current pain intensity ratings prior to phlebotomies were similar during Palladone — and HMIR treatments, with pain ratings for the former slightly lower than for HMIR at most of the time points. The largest difference was at Hours 22 to 24 when the mean current pain intensity was 2.57 for Palladone — treatment compared with 2.00 for HMIR treatment; however, the number of patients was small at this time point. Results for the intent-to-treat population showed less differences between treatments.

Table 4 Mean Current Pain Intensity Prior Immediately Prior to Each Phlebotomy
Sponsor's PK/PD Population **Pain Intensity (SE)**

Time(hr)	0	1	2	3	5-6	22-24
Palladone —						
N	62	61	61	60	60	14
Mean Pain Intensity	2.87	2.16	1.85	1.88	2.02	2.57
(SE)	0.28	0.24	0.21	0.22	0.23	0.78
HMIR						
N	59	61	61	61	60	14
Mean Pain Intensity	2.95	2.20	1.93	1.82	2.20	2.00
(SE)	0.23	0.22	0.21	0.21	0.24	0.41

c. "Drug Effect" Ratings before each Phlebotomy at Visits 3 and 4: The mean drug effect ratings immediately prior to phlebotomies were similar for both treatments in the PK/PD population. The scores from Visits 3 and 4 combined are tabulated according to formulation and times of phlebotomy in Table 5 (from sponsor's Fig 11.4.1.1B and Table 14.2.1.5G Vol 76 p.35). The effects detected were low, ranging from 0.73 to 1.24 on a 0-10 point scale.

Table 5 Drug Effect Immediately Prior to Phlebotomies

Time(hr)	0	1	2	3	5-6	22-24
Palladone —						
N	62	61	61	60	60	14
Mean	1.24	1.03	0.85	1.00	0.88	0.79
(SE)	0.24	0.22	0.20	0.24	0.21	0.54
HMIR						
N	59	61	61	61	60	14
Mean	1.17	0.95	0.97	0.82	0.73	0.86
(SE)	0.27	0.22	0.21	0.20	0.20	0.31

d. Plasma Hydromorphone Concentrations: Plasma hydromorphone concentrations (dose-adjusted to 36 mg Palladone — at Visits 3 and 4 are tabulated in Table 6 (from sponsor's Fig 11.4.1.1.C and Table 14.2.1.5 G Vol 76 p.60) according to time of each phlebotomy and formulation for the PK/PD population. Mean dose-adjusted plasma levels were similar for both treatments at 0, 3 and 22-24 hours. Mean plasma concentrations were higher for HMIR at one and two hours, particularly at one hour, and higher for Palladone — at 5-6 hours. Plasma levels from HMIR tended to peak at one hour and return to morning baseline levels at 5-6 hours, while Palladone —had levels somewhat elevated relative to baseline, but relatively constant from one hour to 5-6 hours.

Table 6 Mean Dose-Adjusted Plasma Hydromorphone Concentrations

Time(hr)	0	1	2	3	5-6	22-24
Palladone —						
n	56	56	57	56	56	13
Mean	4.38	5.97	6.92	7.08	6.92	3.94
(SE)	0.45	0.55	0.67	0.68	0.67	0.71
HMIR						
n	52	55	55	54	55	13
Mean	4.11	10.3	8.34	7.04	4.74	3.33
(SE)	0.69	0.94	0.79	0.73	0.49	0.41

8.2142 Secondary Efficacy Variables

a. *Average Pain Intensity for Each of Last 2 Days before the PK/PD Day:* Average pain intensity means (and SE's) for the last two days before the PK/PD phlebotomies from combined periods are tabulated for the efficacy population according to treatment in Table 7 (from sponsor's Table 11.4.1.1.C Vol 76 p.60). Results are similar for each formulation.

Table 7 Average Pain Intensity for each of the 2 Days Before Each PK/PD Day

	Palladone —	**Immediate Release**
Time	Mean PI	Mean PI
Mean Day -2	2.47	2.44
Mean Day -1	2.48	2.39

b. Mean Average Pain Intensity on Each Double-Blind Study Day: Average pain intensity means (and SE's) for each day) of combined double-blind periods are shown in Table 8 (from sponsor's Table 11.4.2.1.7A Vol 76 p.61) for each treatment (efficacy population). Although most days had similar means for the two formulations, the controlled-release formulation appeared to result in slightly lower mean pain intensities in the last days of the double-blind periods, particularly at Days 5 and 6.

Table 8 Means of Average Pain Intensity by Day for Days 6 and 7

Treatment	Palladone — Mean (SE), n	HMIR Mean (SE), n
Day 1	2.54 (0.17), n=67	2.39 (0.19), n=67
Day 2	2.60 (0.18), n=67	2.45 (0.18), n=67
Day 3	2.42 (0.17), n=66	2.46 (0.18), n=67
Day 4	2.34 (0.19), n=49	2.58 (0.24), n=51
Day 5	2.19 (0.21), n=36	2.85 (0.30), n=30
Day 6	2.08 (0.26), n=25	2.67 (0.25), n=27
Day 7	2.30 (0.32). n=17	2.65 (0.28), n=19

c. Current Pain Intensity on Each of Last 2 Days before the PK/PD Day
Current pain intensity means at each time point averaged over the last two days before the PK/PD phlebotomies of the combined double-blind periods are tabulated according to treatment in Table 9 (from sponsor's Table 11.4.1.1D Vol 76 p.63) for the efficacy population. Results are similar for both formulations.

Table 9 Mean Current Pain Intensity for the 2-Days Prior to Each Phlebotomy

Time	0800	1300	1800	Bedtime
Palladone	2.60	2.10	2.48	2.44
HMIR	2.56	2.41	2.37	2.34

d. *Mean Current Pain Intensity on Each Double-Blind Study Day:* Current pain intensity means on each double-blind day of combined periods were similar for both treatments with the exception of Day 5 when current pain intensity was lower for Palladone — than for HMIR as seen in Table 10 (from sponsor's Table 14.2.1.7B Vol 76 p.241).

Table 10 Mean Current Pain Intensity for each Double-Blind Day

Treatment	Palladone —	HMIR
	CurrentPainIntensity (SE), n	CurrentPainIntensity (SE), n
Day 1	2.65 (0.17), 99	2.47 (0.17), 97
Day 2	2.85 (0.17), 99	2.59 (0.16), 97
Day 3	2.81 (0.17), 99	2.80 (0.17), 97
Day 4	2.72 (0.18), 86	2.91 (0.20), 87
Day 5	2.41 (0.22), 62	3.13 (0.23), 59

Day 6	2.72 (0.23), 53	3.09 (0.26), 42
Day 7	3.07 (0.35), 32	2.77 (0.27), 37

e. Plasma Hydromorphone Concentrations: Minimum and maximum dose adjusted plasma hydromorphone concentrations are summarized in the sponsor's Table 14.2.1.10. Per protocol, only the minimum dose-adjusted plasma hydromorphone concentration levels (Cmin) were analyzed. Patients treated with Palladone — had a significantly higher mean Cmin than patients treated with HMIR in the Intent-to-treat population (4.64 ng/mL versus 3.76 ng/mL, respectively; p=0.0016). The Cmin for the PK/PD population was 4.13 ng/mL in the Palladone —treatment and 3.54 ng/mL in the HMIR treatment (p=0.071). Results for the log10 transformed Cmin were similar. Mean plasma concentrations were higher for HMIR for the first two hours (t_{max} at 1 hour) than for the controlled-release treatment. At 5-6 hours, mean plasma concentration for HMIR fell below that of Palladone —

f. *PK/PD: Plasma Levels vs. Current Pain and "Drug Effect" Relationships:* Mean current pain intensities and patient "drug effect" ratings at the time of each phlebotomy appeared relatively constant and similar for each treatment when plotted on the same graphs as plasma hydromorphone concentration over time (see for example the Sponsor's Figure 14.2.1.31.2.G on p.89 of Volume 77). Generally, there appeared to be no clear relationship between plasma concentration and effect (pain intensity or "drug effect"), and no treatment differences were detected.

g. Time to Stable Pain Control during Open-Label Period : A total of 174 patients took Palladone — and went into the Titration Period. There were 120 (69.0%) of 174 patients considered to be successful in titrating to stable pain as defined by protocol. Forty-seven (47) of these 120 successful patients (39.2%) were able to achieve stable pain while maintaining the initially calculated dose (conversion dose) from when they entered the study.
The mean time to stable pain control for the 120 successful patients was 4.2 days and the median was 3.0 days.

h. Total Daily Dose (mg) of Hydromorphone during Double-Blind Periods:
The number (and percent) of patients (efficacy population) at each total daily dose (mg) of controlled-release hydromorphone at the end of titration is summarized in Table 11(from sponsor's Table 14.2.1.2.A Vol 76, p.176). The mean daily dose of hydromorphone at the end of titration in the efficacy population was 38.0 mg for patients randomized to the Palladone — to HMIR sequence and 38.0 mg for patients randomized to the opposite sequence. The mean daily dose of hydromorphone taken by patients while administered Palladone — (combined treatment periods) ranged from 31.9 mg (Day 6) to 38.0 mg (Days 1, 2, and 3) for this population. The mean daily dose of hydromorphone taken by patients during their participation in the HMIR arm ranged from 25.7 mg (Day 7) to 38.0 mg (Day 3). For the ITT population, the mean daily dose of hydromorphone taken during the Palladone — arm (combined treatment periods) ranged from 33.78 mg (Day 5) to 37.60 mg (Day 7). This can be compared with mean daily doses taken while on HMIR, which ranged from 26.69 mg (Day 7) to 36.60 mg (Day 3). Since patients could complete a double-blind treatment period after Day 3, changes in mean daily dose were affected by reductions in the number of patients still receiving treatment.

Table 11 Hydromorphone (Palladone —) Dose at End of Titration

Dose (mg)	12	24	36	48	60	72	84
N	16	14	10	11	6	6	4

i. Rescue Medication (# Doses and mg Amount) during Double-Blind Periods:
The mean amounts (mg) of rescue medication used by patients in the efficacy population by study day are presented in Table 12 (from sponsor's Table 14.2.1.13.1.A Vol 76 p.267) according to treatment for the combined treatment periods. The mean daily dose of rescue medication ranged from 7.86 mg to 10.81 mg and 6.84 mg to 10.52 mg for the Palladone —. and HMIR treatments, respectively. Values for each study day were similar for both treatments. The mean daily dose of rescue medication used by the ITT population ranged from 7.81 mg to 9.96 mg and 6.29 mg to 10.04 mg for the Palladone — and HMIR treatments, respectively. The amounts of rescue medication as percentages of the total daily dose of hydromorphone taken by the efficacy population for the last two days prior to the PK/PD day of each double-blind treatment period were 14.43% (Day –2) and 17.57% (Day –1) during Palladone — treatment, compared with 10.82% (Day –2) and 20.57% (Day –1) during HMIR treatment. The values were similar for both treatments. The mean percentages of the total daily dose of hydromorphone taken as rescue medication by the ITT population were similar.

Table 12 Mean Amount in mg (SE) Rescue Medication by Day

Day	1	2	3	4	5	6	7
Palladone –	8.84 (1.51) n=67	10.81 (1.68) n=67	9.19 (1.56) n=67	9.84 (1.54) n=50	9.28 (1.79) n=39	7.86 (1.51) n=28	10.22 3.17 n=18
HMIR	6.84 (1.32) n=67	9.13 (1.56) n=67	10.39 (1.70) n=67	10.04 (1.66) n=53	10.48 (1.89) n=33	10.52 (2.34) n=27	8.30 (2.45) n=20

j. Times of Rescue Medication Administration during Double-Blind Periods: The mean numbers of rescue doses used by patients in the PK/PD population during the combined treatments by time of day and averaged over the last 2 days prior to each of the PK/PD days are summarized in Table 13 (from sponsor's Table 14.2.1.14.2.A Vol 76 p. 299). The timing of rescue doses was similar between treatments. except that Palladone – administration seemed associated with less rescue in the morning and the most rescue in the afternoon, while the immediate release treatment tended to need the least rescue in the afternoon and the most at night. Nevertheless, there were no clinically significant differences between treatments in the number of rescue doses taken across time intervals.

Table 13 Number and Times of Rescue Dosing Averaged over Last 2 Days prior to PK/PD

	Palladone –				HMIR			
Time of Day	**Morning**	**Afternoon**	**Evening**	**Night**	**Morning**	**Afternoon**	**Evening**	**Night**
N	67	67	67	67	66	66	66	66
Mean	0.24	0.43	0.34	0.37	0.32	0.35	0.25	0.43
SE	0.05	0.06	0.05	0.06	0.05	0.06	0.04	0.08

k. Number of Patients Requiring Rescue Medication in Double-Blind Periods: The number and percentage of patients who used rescue medication during the combined double-blind periods were 49 of 67 patients on Palladone – (73%) and 50 of 67 patients on HMIR (75%) for the efficacy population. The corresponding results for the intent-to-treat population were 77% for Palladone – and 79% for HMIR.

8.2143 Reviewer's Integrated Analysis of Pain Intensity and Escape Medication Usage: The reviewer examined individual patient data for the 88 patients who completed both crossover arms of the study and for whom data was available for both rescue use and average pain intensity for the last two days prior to PK/PD assessments in each double-blind period. The mean amounts of rescue medication for these patients were 9.19 mg for Palladone [redacted] and 9.13 mg for HMIR. The objectives of the reviewer's integrated analysis was to judge whether each patient's pain and need for rescue medication appeared to be managed better while on one formulation or the other or whether no decision favoring a particular treatment could be made. The rules for evaluating "superiority" of one formulation over another for each evaluable patient were as follows:

a. The "superior" formulation may be associated with at least 20% less average pain intensity for the last two days prior to PK/PD assessment than the other formulation. The use of rescue medication (mg) on Day –1 prior to PK/PD assessment for the "superior" formulation must be unchanged or reduced relative to that of the other formulation in this situation.

b. The "superior" formulation can be associated with at least 20% less use of rescue medicine (mg) for Day –1 prior to PK/PD assessment than the other formulation. Average pain intensity for the last two days prior to PK/PD assessment for the "superior" formulation must be unchanged or reduced or less than 20% increased relative to that of the other formulation in this situation.

c. Neither formulation may be deemed "superior" if both pain intensity and rescue usage are within +/- 20 % of each other.

d. Neither formulation may be deemed "superior" if pain intensity or rescue use increases in one by at least 20% while the other variable decreases by at least 20% in the other formulation.

Results: There were 24 of the 88 patients (27%) for which no formulation could be judged "superior" according to the rules above. The immediate release formulation was deemed "superior" for 34 patients (39%), and Palladone [redacted] was favored for 30 patients (34%). These values are consistent with similar efficacy for the two treatments; however, there may be a trend favoring the immediate release formulation.

8.215 Efficacy Conclusions for Study HD95-0801

a. Average Pain Intensity
The primary efficacy variable as defined by the sponsor was the mean patient-rated pain intensity scores for each treatment averaged over the last two days of each double-blind period prior to Visits 3 and 4 (the PK/PD assessment days). When data from both double-blind periods were combined for the sponsor's efficacy population, mean pain intensity ratings (and standard errors) for Palladone — and the immediate-release treatments were 2.48 (0.07) and 2.42 (0.07), respectively. There were no significant differences between treatments. Similar results were obtained from the intent-to-treat population. Evaluation of secondary efficacy variables involving average pain intensity confirmed these findings. These included the average pain intensity means for the last two days before the PK/PD phlebotomies and average pain intensity means for each day of the combined double-blind periods.

b. Current Pain Intensity
Current patient-rated pain intensity scores for each combined treatment group assessed immediately before each phlebotomy at Visits 3 and 4 were also considered primary variables by the sponsor. Palladone — and the immediate-release treatments had similar ratings at most of the time points for the efficacy population. Results from the intent-to-treat population showed still more similarity between treatments. Results from evaluating secondary efficacy variables involving current pain intensity were in accord with these findings. These included current pain intensity means at each time point for each of the last two days of the combined double-blind periods prior to PK/PD phlebotomies and current pain intensity means on each double-blind day of combined periods.

c. Drug Effects, PK and PK/PD
The sponsor also included "drug effect" ratings and plasma hydromorphone concentrations as primary efficacy variables, although subjective opioid drug effects might better be associated with tolerability and drug levels with pharmacokinetics than with efficacy. Very minimal effects were detectable for "drug effect" ratings with no differences between treatments. Mean plasma concentrations were higher for the immediate-release formulation at one and two hours, particularly at one hour, but higher for Palladone — at 5-6 hours. Plasma levels from HMIR tended to peak at one hour and return to morning baseline levels at 5-6 hours, while Palladone— had levels somewhat elevated relative to baseline, but relatively constant from one hour to 5-6 hours. Generally, Palladone — maintained higher minimum concentrations than did the other formulation. There were no relationships detected between plasma concentrations and current pain intensities or patient "drug effect" ratings, since the latter variables were relatively constant over time and seemed independent of plasma levels.

d. Time to Stable Pain Control and Hydromorphone Dose
The mean time to stable pain control for the 120 patients who successfully titrated to control with Palladone ~ in the open-label period was 4.2 days and the median was 3.0 days. The mean daily dose of hydromorphone at the end of titration in the efficacy population was 38.0 mg for patients randomized to the Palladone ~ to HMIR sequence and 38.0 mg for patients randomized to the HMIR to Palladone ~ sequence. The mean daily dose of hydromorphone taken by patients while administered Palladone ~ combined treatment periods) ranged from 31.9 mg (Day 6) to 38.0 mg (Days 1, 2, and 3) for this population. Values were similar for the intent-to-treat population.

e. Rescue Medication
The mean daily dose of rescue medication for the efficacy population ranged from 7.86 mg to 10.81 mg and 6.84 mg to 10.52 mg for the Palladone ~ and immediate-release treatments, respectively. Values for the ITT population were similar. Rescue medication as percentages of the total daily dose of hydromorphone taken by the efficacy population for the last two days prior to the PK/PD day of each double-blind treatment period were 14.43% and 17.57% during Palladone ~ treatment and 10.82% and 20.57% during immediate-release treatment, for Days –2 and –1, respectively. The values were similar for both treatments, and findings from the intent-to-treat population were also similar. The timing of rescue doses was similar for the treatments, with no clinically significant differences between treatments in the number of rescue doses taken across time intervals.
Rescue medication was used during the combined double-blind periods by 73% and 75% of patients from the efficacy population on Palladone ~ and HMIR, respectively. The corresponding results for the intent-to-treat population were similar.

f. Integration of Pain Intensity and Rescue Medication
The reviewer's integrated analysis of pain intensity and rescue medication usage found 27% for which no formulation could be judged "superior" according to the rules above. The immediate release formulation was deemed "superior" 39% of patients, and Palladone — was favored for 34% patients.

g. Overall Conclusion for the Study

The results are consistent with similar analgesic efficacy for both formulations in the treatment of moderate to severe chronic pain. The study serves as a positive clinical trial supporting Palladone — as an effective once-daily opioid analgesic.

8.22 Study HD95-0802

Double-Blind, Randomized, Two-Period Crossover Study Comparing the Efficacy, Safety and Pharmacokinetic and Pharmacodynamic Profiles of Oral Administration of Hydromorphone Hydrochloride Controlled-Release Capsules (qAM) and Hydromorphone Hydrochloride Immediate-Release Tablets (qid) for Cancer-Related or Chronic Nonmalignant Pain

8.221 Investigators/Location (from Sponsor's Table 6A Vol 87 pp.20-22)

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8.222 Plan

8.2221 Objective

The study was intended to determine the efficacy, safety, plasma concentration, and pharmacodynamic effect of oral administration of Palladone — (hydromorphone hydrochloride controlled-release capsules) qd as compared with hydromorphone hydrochloride immediate-release (HMIR) tablets qid in the treatment of cancer-related or chronic nonmalignant pain. This study was identical in design to that HD95-0801 except that the latter study also contained an exploratory trial referred to as Amendment 1.

8.2222 Population

The inclusion and exclusion criteria for this study are the same as that for HD95-0801 (cf. Section 8.2122).

8.2223 Design

Except for the Amendment 1 extension substudy in HD95-0801, the design of study HD95-0802 is identical to that of HD95-0801. Details of design and methodology are found in the 8.2123, 8.21232 and 8.21234 subsections of Section 8.2123, including dosing guideline Tables 3A and 3B.

8.2224 Assessments

Efficacy assessments, including primary and secondary efficacy variables were the same as in HD95-0801 (cf. Section 8.2124).

8.2225 Analysis Plan

The plan of analysis was the same as for HD95-0801 (cf. Section 8.2125, including subsections 8.21251 and 8.21252).

8.223 Study Conduct/Outcome

8.2231 Patient Disposition

The enrollment was planned to enter enough patients to obtain at least 80 evaluable patients. One hundred seventy patients were enrolled and entered the open-label titration period. All but one (169) received at least one dose of study medication and were analyzed for safety. Of these, 113 patients completed the open-label phase and were randomized to receive double-blind treatment with either the sustained release formulation, Palladone — followed by immediate-release hydromorphone (HMIR) or HMIR followed by Palladone —. All 113 were included in the evaluation of safety for the double-blind period. There were 106 patients who completed both double-blind treatment periods, and seven patients who were discontinued at some time during the double-blind period. There were 91 patients considered evaluable for efficacy in the sponsor's efficacy analysis.

There were 57 patients who discontinued during the open-label phase and prior to the double-blind period. Of these, 20 discontinued because of adverse events, 16 because of ineffective treatment, 8 because of intercurrent illness, one who died, three due to protocol violations and 9 for other reasons.

There were 108 patients who received Palladone — in the double-blind crossover (Five patients who started on HMIR discontinued prior to the crossover). There were 112 patients who received HMIR in the double-blind crossover (One patient who started on Palladone — discontinued prior to the crossover). Of the seven patients who discontinued during the double-blind phase prior to completion of both crossover periods, two were taking Palladone — at the time (one had intercurrent illness, the other was a protocol violator). The other five were on HMIR (one discontinued because of an adverse event, the other four because of intercurrent illness). No patient discontinued double-blind treatment because of lack of efficacy.

Three patients were excluded from the sponsor's efficacy analysis because their prestudy opioid usage and/or disease status were not sufficiently stabilized prior to randomization. Three other patients were excluded because of rescue medication usage and/or pain scores in excess of protocol limitations. There were nine more patients excluded because of protocol violations with respect to concomitant nonopioid analgesic usage.

Summary of Disposition of Patients in Study HD95-0802
(from Sponsor's Tables 14.1.1, 14.1.2 and 14.1.3 Vol 87 pp 18-32)

Patients Enrolled = 170
Patients Evaluable for Safety = 169 (99%)
Early (Open-Label) Discontinuations = 57 (34%)
Open-Label Discontinuations for AE's, Intercurrent Illness or Death = 29 (17%)
for Lack of Efficacy = 16 (9%)
for Protocol Violations = 3 (2%)
for Other Reasons = 9 (5%)
Patients Randomized to Double-Blind Crossover = 113
Patients Included in the ITT Analysis = 113
Patients who did not receive Palladone — in the double-blind period = 5
Patients who received Palladone in the Crossover = 108
Patients who discontinued while on Palladone in the Crossover = 2 (2%)
Patients discontinuing on Double-Blind Palladone
for AE or Intercurrent Illness = 1 (1%)
for Protocol Violation = 1 (1%)
Patients who did not receive HMIR in the double-blind period = 1
Patients who received HMIR in the Crossover = 112
Patients discontinuing on Double-Blind HMIR in the Crossover = 5 (5%)
Patients discontinuing on Double-Blind HMIR
for AE's or Intercurrent Illness = 5 (5%)
Patients Excluded by Sponsor for "Efficacy" Analysis Population = 22 (21%)
Excluded from "Efficacy" (patients may have more than one cause for exclusion)

a) for unstable nonopioid analgesic or adjuvant use = 8
b) for having been found ineligibile for randomization = 6
c) for insuffficient pain ratings during last 2 days prior to PK/PD = 1
d) for insuffficient dosing during last 2 days prior to PK/PD = 1
e) for use of other opioids = 0
f) for early discontinuation = 7

Patients in "Efficacy" Population = 91
Patients in Reviewer's Integrated Efficacy Population
(Patients with efficacy data for both legs of the crossover = 106

8.2232 Demographics

The demographic and baseline characteristics of the total population (n=170) enrolled in the study were as follows: There were 86 men and 84 women; there were 153 white, 13 black and 3 Hispanic patients and one Asian patient. Mean age was 57.9 years (range 24 to 85); mean weight was 76.8 kg (range 46 to 193), and mean height was 169.5 cm (range 140 to 196). There were 128 patients with cancer pain and 42 with nonmalignant pain. All patients had prior opioid experience.

The intent-to-treat patients or those who received any double-blind treatment (n=113) were 53.8% female, and 91.2% were white. Approximately 90% of patients were between the ages of 35 and 80 (overall range 24 to 85 years); the mean age was 57.9 years. Mean weight was 78.3 kg and mean height was 168.9 cm. The percentage of females in the Palladone — → HMIR sequence was higher (61.5%) than in the reverse sequence (48.1%). There were otherwise no notable differences in the demographic characteristics of the two treatment sequences. Of the 113 patients randomized to receive double-blind treatment, 83 had cancer, and 30 had a nonmalignant condition causing pain.

The demographics of the sponsor's "efficacy" population (n=91) were as follows: 39 received Palladone — prior to HMIR in the double-blind phase; 52 received the opposite treatment. There were 42 males (46%) and 49 females (54%). This population was 91% white, 7% black, 1% Hispanic and 1% Asian. Mean age was 57.6 years (range 24 to 85). Mean weight was 79.1 kg (range 46 to 193 kg) and mean height 169 cm (range 140 to 196).

8.2233 Open-Label Pain Scores and Dosing

Patients currently receiving opioid treatment for chronic cancer-related or nonmalignant pain (N = 169) entered the open-label titration period of this study with a mean pain score of 5.42 on a scale of 0 to 10. Mean pain score for this population at the end of titration was 3.39 (includes scores for patients who discontinued the titration phase prematurely and may not have reached stable pain control).

The mean scores for patients randomized into the double-blind treatment periods (intent-to-treat population, N = 113), were 5.19 at the beginning of the study and 2.58 on the last day of the titration period: Daily doses of hydromorphone hydrochloride were as follows: There were 38 patients on 12 mg, 24 on 24 mg, 16 on 36 mg, 15 on 48 mg, 7 on 60 mg, 9 on 72 mg and 4 on 84 mg.

The corresponding means for the sponsor's efficacy population (n=91) were 5.09 at baseline and 2.56 at the end of titration. Daily doses of hydromorphone hydrochloride were as follows: There were 28 patients on 12 mg, 21 on 24 mg, 12 on 36 mg, 13 on 48 mg, 5 on 60 mg, 9 on 72 mg and 3 on 84 mg.

8.224 Efficacy Results

8.2241 Primary Efficacy Variables

a. Average Pain Intensity
The means (and SE's) of patient-rated pain intensity scores for each treatment averaged over the last 2 days of each double-blind period before Visits 3 and 4 (the PK/PD assessment days) for the sponsor's efficacy population (data from both double-blind periods were combined) were as follows (cf. sponsor's Table 11.4.1.1A Vol 87 p.55_:

The Palladone ™ group had mean pain intensity rating 2.59 (0.08)

The HMIR treatment group had mean pain intensity rating 2.58 (0.08)

The difference in the least squares means was 0.01 and the 90% confidence interval for the difference was [-0.17, 0.19].

The means (and SE's) of patient-rated pain intensity scores for each treatment averaged over the last 2 days of each double-blind period before Visits 3 and 4 (the PK/PD assessment days) for the intent-to-treat population (data from both double-blind periods were combined) were as follows(cf. sponsor's Table 11.4.1.1B Vol 87 p.55):

The Palladone ™ group had mean pain intensity rating 2.67 (0.08)

The HMIR treatment group had mean pain intensity rating 2.60 (0.08)

The difference in the least squares means was 0.07 and the 90% confidence interval for the difference was [-0.12, 0.26]. Thus, results from the intent-to-treat population were similar to those from the efficacy population, with no significant differences between treatments observed.

b. Current Pain Intensity Ratings before Phlebotomies
The current patient-rated pain intensity scores for each combined treatment group (from the sponsor's PK/PD population) assessed immediately before each phlebotomy at Visits 3 and 4 are tabulated in Table 14 (adapted from sponsor's Table 14.2.1.3A Vol 87 p.174) according to time of phlebotomy. Mean current pain intensity ratings prior to phlebotomies were generally slightly higher during HMIR than Palladone ™ treatments; however, there were on significant differences between treatments. Results for the two treatments were more similar to each other in the intent-to-treat population as seen in Table 14A (frm sponsor's Table 14.2.1.4.1A Vol 87 p.176).

Table 14 Mean Current Pain Intensity Immediately Prior to Each Phlebotomy
Sponsor's PK/PD Population **Pain Intensity (SE)**

Time(hr)	0	1	2	3	5-6	22-24
Palladone –						
N	45	45	45	45	45	10
Mean Pain Intensity	2.69	2.24	2.16	2.47	2.40	3.20
(SE)	0.25	0.21	0.23	0.30	0.28	0.57
HMIR						
N	38	38	38	38	38	9
Mean Pain Intensity	3.16	2.68	2.58	2.63	3.03	4.00
(SE)	0.42	0.41	0.39	0.42	0.43	0.47

Table 14A Mean Current Pain Intensity Immediately Prior to Each Phlebotomy
Intent-to-Treat Population **Pain Intensity (SE)**

Time(hr)	0	1	2	3	5-6	22-24
Palladone –						
N	83	83	83	83	83	19
Mean Pain Intensity	2.70	2.22	2.05	2.31	2.40	3.42
(SE)	0.21	0.19	0.19	0.21	0.21	0.47
HMIR						
N	83	83	83	83	83	21
Mean Pain Intensity	3.12	2.43	2.28	2.33	2.73	3.67
(SE)	0.24	0.22	0.22	0.24	0.26	0.31

c. "Drug Effect" Ratings before each Phlebotomy at Visits 3 and 4.

The mean drug effect ratings immediately prior to phlebotomies were similar for both treatments in the PK/PD population. The scores from Visits 3 and 4 combined are tabulated according to formulation and times of phlebotomy in Table 15 (from sponsor's Fig 11.4.1.1.B and Table 14.2.1.5G Vol 87 p.57). The effects detected were minimal, ranging from 0.92 to 2.11 on a 0-10-point scale. Generally, values for HMIR were slightly higher than for Palladone – except at 22-24 hours; however, there were no significant differences between treatments, and results for the two treatments from the intent-to-treat population were more similar to each other.

TABLE 15 Drug Effect Immediately Prior to Phlebotomies

Time(hr)	0	1	2	3	5-6	22-24
Palladone — N	38	38	38	38	38	9
Mean	1.50	1.47	1.24	1.21	1.13	1.67
(SE)	0.34	0.32	0.36	0.30	0.26	0.62
HMIR N	44	61	61	61	60	14
Mean	2.11	1.73	1.84	1.59	1.34	0.92
(SE)	0.35	0.32	0.35	0.30	0.31	0.40

d. Plasma Hydromorphone Concentrations: Plasma hydromorphone concentrations (dose-adjusted to 36 mg Palladone — at Visits 3 and 4 are tabulated in Table 16 (from sponsor's Fig 11.4.1.1C and Table 14.2.1.5G Vol 87 p.59) for the PK/PD population, according to time of each phlebotomy and formulation. Mean dose-adjusted plasma levels were similar for both treatments at 0, 3 and 22-24 hours. Mean plasma concentrations were higher for HMIR at one and two hours, particularly at one hour, and higher for Palladone — at 5-6 hours. Plasma levels from HMIR tended to peak at one hour and return to morning baseline levels at 5-6 hours, while Palladone — had levels somewhat elevated relative to baseline, but relatively constant from one hour to 5-6 hours.

TABLE 16 Mean Dose-Adjusted Plasma Hydromorphone Concentrations Intent-to-Treat Population Adjusted to 24-mg ng/ml

Time(hr)	0	1	2	3	5-6	22-24
Palladone —						
n	46	46	47	47	46	11
Mean	2.63	3.35	4.09	4.26	4.35	1.87
(SE)	0.18	0.20	0.27	0.29	0.33	0.34
HMIR						
n	58	58	58	57	58	12
Mean	2.92	5.34	4.74	3.96	2.97	1.91
(SE)	0.46	0.50	0.47	0.41	0.33	0.36

8.2242 Secondary Efficacy Variables

a. Average Pain Intensity for Each of Last 2 Days before the PK/PD Day
Average pain intensity means (and SE's) for the last two days before the PK/PD phlebotomies from combined periods are tabulated for the intent-to-treat population according to treatment in Table 17(from sponsor's Table 14.2.1.6.1B Vol 87 p.204). Results are similar for each formulation.

TABLE 17 Average Pain Intensity for each of the 2 Days Before Each PK/PD Day

	Palladone —	Immediate Release
Time	Mean PI	Mean PI
Mean Day -2	2.75	2.56
Mean Day -1	2.57	2.65

b. Mean Average Pain Intensity on Each Double-Blind Study Day
Average pain intensity means (and SE's) for each day) of combined double-blind periods (efficacy population) are shown in Table 18 (from sponsor's Table 14.2.1.9.2A Vol 87 p.275) for each treatment. Most days had similar means for the two formulations. The immediate-release formulation appeared to result in slightly lower mean pain intensities in Days 5 and 6, but the n's were smaller in these last days of double-blind treatment.

TABLE 18 Means of Average Pain Intensity by Day

Treatment	Palladone — Mean (SE), n	HMIR Mean (SE), n
Day 1	2.54 (0.15), n=91	2.43 (0.16), n=91
Day 2	2.65 (0.15), n=91	2.47 (0.16), n=91
Day 3	2.55 (0.15), n=91	2.63 (0.17), n=91
Day 4	2.64 (0.18), n=77	2.58 (0.22), n=69
Day 5	2.56 (0.22), n=44	2.43 (0.30), n=40
Day 6	2.93 (0.27), n=23	2.37 (0.31), n=28
Day 7	2.73 (0.34). n=13	2.11 (0.36), n=18

c. Current Pain Intensity on Each of Last 2 Days before the PK/PD Day
Current pain intensity means at each time point averaged over the last two days before the PK/PD phlebotomies of the combined double-blind periods are tabulated according to treatment in Table 19 (adaptred from sponsor's Table 14.2.1.9.1A Vol 87, p.270) for the efficacy population. Results are similar for both formulations.

TABLE 19 Mean Current Pain Intensity for the 2-Days Prior to Each Phlebotomy

Time	0800	1300	1800	Bedtime
Palladone —	2.49	2.72	2.60	2.58
HMIR	2.43	2.52	2.59	2.77

e. *Mean Current Pain Intensity on Each Double-Blind Study Day*
Current pain intensity means on each double-blind day of combined periods (efficacy population) were similar for both treatments as seen in Table 20 (from sponswor's Table 14.2.1.9.2B Vol 87 p.275).

TABLE 20 Mean Current Pain Intensity for each Double-Blind Day

Treatment	Palladone —	HMIR
	CurrentPainIntensity (SE), n	CurrentPainIntensity (SE), n
Day 1	2.64 (0.15), 91	2.47 (0.17), 91
Day 2	2.64 (0.16), 91	2.51 (0.17), 91
Day 3	2.48 (0.16), 91	2.59 (0.17), 91
Day 4	2.65 (0.18), 88	2.81 (0.19), 85
Day 5	2.72 (0.22), 63	2.58 (0.24), 59
Day 6	2.80 (0.26), 32	2.37 (0.31), 35
Day 7	2.88 (0.33), 19	2.48 (0.32), 26

f. Plasma Hydromorphone Concentrations: Mean plasma minimum hydromorphone concentration (Cmin) was significantly higher (p=0.0001) for patients treated with Palladone — (2.60 ng/ml for the PK/PD population and 2.82 ng/ml for the intent-to-treat population) than with HMIR (2.02 ng/ml for the PK/PD population and 2.26 ng/ml for the intent-to-treat population). Mean dose-adjusted plasma concentrations for the PK/PD population at the time of each phlebotomy in ng/ml are tabulated in Table 21 (FROM SPONSOR'S Table 14.2.1.22A Vol 88 p.363). Palladone — plasma levels were relatively constant from 1 to 6 hours, while HMIR levels peaked in the first hour and declined to near baseline by hours 5-6.

TABLE 21 Mean Dose-Adjusted Plasma Concentrations at the Time of Each Phlebotomy in ng/ml

Time	(hours)	0	1	2	3	5-6	22-24
Palladone —	N	82	82	81	82	81	19
	Mean	2.70	3.31	3.81	4.08	4.15	2.12
	SE	0.16	0.17	0.21	0.24	0.26	0.25
HMIR	N	82	82	82	81	82	22
	Mean	2.27	4.94	4.31	3.59	2.57	1.81
	SE	0.14	0.29	0.27	0.23	0.18	0.24

g. PK/PD: Plasma Levels vs. Current Pain and "Drug Effect" Relationships
Mean current pain intensities and patient "drug effect" ratings at the time of each phlebotomy appeared relatively constant and similar for each treatment when plotted on the same graphs as plasma hydromorphone concentration over time (see for example the Sponsor's Figures 14.2.1.24.2.G on p.367 and 14.2.1.25.1.G of Volume 88). Generally, there appeared to be no clear relationship between plasma concentration and effect (pain intensity or "drug effect") and no treatment differences were detected.

h. *Time to Stable Pain Control during Open-Label Period:*
A total of 169 patients took Palladone — and went into the Titration Period. There were 122 (72%) of these patients considered to be successful in titrating to stable pain as defined by protocol. Fifty-one (51) of these 122 successful patients (42%) were able to achieve stable pain while maintaining the initially calculated dose (conversion dose) from when they entered the study.
The mean time to stable pain control for the 122 successful patients was 6.25 days and the median was 4.0 days.

i. Total Daily Dose (mg) of Hydromorphone during Double-Blind Periods
The number (and percent) of patients at each total daily dose (mg) of controlled-release hydromorphone at the end of titration is summarized in Table 22. The mean daily dose of hydromorphone prescribed at the end of titration in the efficacy population was 34.5 mg for patients randomized from the Palladone — to the HMIR sequence and 33.7 mg for patients randomized from the HMIR to the Palladone – sequence. The mean daily dose of hydromorphone taken by patients while administered Palladone – and HMIR (combined treatment periods) is tabulated by in Table 23 (adapted from sponsor's Table 14.2.1.15.2A Vol 87 p.302) for the efficacy population. Since patients could complete a double-blind treatment period after Day 3, changes in mean daily dose were affected by reductions in the number of patients still receiving treatment. Nevertheless, daily doses were similar for both treatments, and values for the intent-to-treat population were also similar.

TABLE 22 Hydromorphone (Palladone –)
Dose at End of Titration (efficacy population)

Dose (mg)	12	24	36	48	60	72	84
N	28	21	12	13	5	9	3

TABLE 23 Hydromorphone Dose by Day in Combined Double Periods (mg)

DAY	1	2	3	4	5	6	7
Palladone —							
N	91	91	91	78	44	23	14
Mean	34.0	34.0	34.0	34.8	34.6	34.4	36.0
SE	2.27	2.27	2.27	2.54	3.29	4.79	6.89
HMIR							
N	91	91	91	70	41	28	18
Mean	33.6	33.9	33.7	33.5	34.3	35.5	38.8
SE	2.25	2.26	2.27	2.61	3.67	4.66	5.67

j. *Rescue Medication (# Doses and mg Amount) during Double-Blind Periods:* The mean amounts (mg) of rescue medication used by patients in the efficacy population by study day are presented in Table 24 (from sponsor's Table 14.2.1.14.1.A Vol 87 p.289) according to treatment for the combined treatment periods. The mean daily dose of rescue medication ranged from 6.51 to 9.86 mg and 5.43 mg to 11.89 mg for the Palladone — and HMIR treatments, respectively. Values for each study day were similar for both treatments. The mean daily doses of rescue medication used by the Intent-to-Treat population were also similar. The amounts of rescue medication as percentages of the total daily dose of hydromorphone taken by the efficacy population for the last two days prior to the PK/PD day of each double-blind treatment period were calculated. These values were 13.0% on Day -2 and 15.9% on Day –1 during Palladone — treatment, compared with 13.2% and 14.6% during HMIR treatment. The values were similar for both treatments.

TABLE 24 Mean Amount in mg (SE) Rescue Medication by Day

Day	1	2	3	4	5	6	7
Palladone —	6.51 (1.01) n=91	9.49 (1.49) n=91	8.46 (1.26) n=91	8.46 (1.33) n=79	8.33 (1.60) n=44	9.17 (2.41) n=24	9.86 (3.92 n=14
HMIR	5.43 (0.91) n=91	8.02 (1.38) n=91	8.44 (1.28) n=91	8.29 (1.47) n=70	8.62 (2.17) n=45	9.31 (2.26) n=29	11.89 (3.83) n=19

k. Times of Rescue Medication Administration during Double-Blind Periods: The mean numbers of rescue doses used by patients in the efficacy population during the combined treatments by time of day and averaged over the last 2 days prior to each of the PK/PD days are summarized in Table 25 (from sponsor's Table 14.2.1.13.2A). The timing of rescue doses was similar between the Palladone — and HMIR treatments. The values for the intent-to-treat population were also similar for both formulations.

TABLE 25 Number and Times of Rescue Dosing Averaged over Last 2 Days prior to PK/PD

	Palladone				HMIR			
Time of Day	**Morning**	**Afternoon**	**Evening**	**Night**	**Morning**	**Afternoon**	**Evening**	**Night**
N	91	91	91	91	91	91	91	91
Mean	0.24	0.34	0.30	0.37	0.26	0.37	0.25	0.33
SE	0.04	0.04	0.04	0.06	0.04	0.04	0.04	0.06

l. Number of Patients Requiring Rescue Medication in Double-Blind Periods The number and percentage of patients who used rescue medication during the combined double-blind periods were 69 of 91 patients on Palladone — (76%) and 66 of 91 patients on HMIR (73%) for the efficacy population. The corresponding results for the intent-to-treat population were 78% for Palladone — and 74% for HMIR.

8.2243 Reviewer's Integrated Analysis of Pain Intensity and Escape Medication Usage

The reviewer examined individual patient data for the 106 patients who completed both crossover arms of the study and for whom data was available for both rescue use and average pain intensity for the last two days prior to PK/PD assessments in each double-blind period. The mean amounts of rescue medication for these patients were 8.64 mg for Palladone — and 8.28 mg for HMIR. The objectives of the reviewer's integrated analysis was to judge whether each patient's pain and need for rescue medication appeared to be managed better while on one formulation or the other or whether no decision favoring a particular treatment could be made. The rules for evaluating "superiority" of one formulation over another for each evaluable patient were as follows:

a. The "superior" formulation can be associated with at least 20% less average pain intensity than with the other formulation for the last two days prior to PK/PD assessment. The use of rescue medication (mg) on Day –1 prior to PK/PD assessment for the "superior" formulation must be unchanged or reduced relative to that of the other formulation in this situation.

b. The "superior" formulation can be associated with at least 20% less use of rescue medicine (mg) for Day –1 prior to PK/PD assessment than the other formulation. Average pain intensity for the last two days prior to PK/PD assessment for the "superior" formulation must be unchanged or reduced or less than 20% increased relative to that of the other formulation in this situation.

c. Neither formulation may be deemed "superior" if pain intensity and rescue usage are both within +/- 20 % of each other.

d. Neither formulation may be deemed "superior" if pain intensity or rescue use increases in one by at least 20% while the other variable decreases by at least 20% in the other formulation.

Results: There were 33 of the 106 patients (31%) for which no formulation could be judged "superior" according to the rules above. The immediate release formulation was deemed "superior" for 39 patients (37%), and Palladone — was favored for 34 patients (32%). These values are consistent with similar efficacy for the two treatments; however, there may be a trend favoring the immediate release formulation.

8.225 Efficacy Conclusions for Study HD95-802

a. Average Pain Intensity

The primary efficacy variable as defined by the sponsor was the mean patient-rated pain intensity scores for each treatment averaged over the last two days of each double-blind period prior to Visits 3 and 4 (the PK/PD assessment days). When data from both double-blind periods were combined for the sponsor's efficacy population, mean pain intensity ratings (and standard errors) for Palladone — and the immediate-release treatments were 2.59 (0.08) and 2.58 (0.08), respectively. There were no significant differences between treatments. Similar results were obtained from the intent-to-treat population. Evaluation of secondary efficacy variables involving average pain intensity confirmed these findings. These included the average pain intensity means for the last two days before the PK/PD phlebotomies and average pain intensity means for each day of the combined double-blind periods.

b. Current Pain Intensity

Current patient-rated pain intensity scores for each combined treatment group assessed immediately before each phlebotomy at Visits 3 and 4 were also considered primary variables by the sponsor. Palladone — and the immediate-release treatments had similar ratings at most time points for the efficacy population. Results from the intent-to-treat population showed still more similarity between treatments. Results from evaluating secondary efficacy variables involving current pain intensity were in accord with these findings. These included current pain intensity means at each time point for each of the last two days of the combined double-blind periods prior to PK/PD phlebotomies and current pain intensity means on each double-blind day of combined periods.

c. Drug Effects, PK and PK/PD

The sponsor also included "drug effect" ratings and plasma hydromorphone concentrations as primary efficacy variables, although subjective opioid drug effects might better be associated with tolerability and drug levels with pharmaokinetics than with efficacy. Very minimal effects were detectable for "drug effect" ratings with no differences between treatments. Palladone — maintained significantly higher minimum concentrations than did the HMIR formulation. Palladone — plasma levels were relatively constant from 1 to 6 hours, while HMIR levels peaked in the first hour and declined to near baseline by hours 5-6. There were no relationships detected between plasma concentrations and current pain intensities or patient "drug effect" ratings, since the latter variables were relatively constant over time and seemed independent of plasma levels.

d. Time to Stable Pain Control and Hydromorphone Dose

The mean time to stable pain control for the 122 patients who successfully titrated to control with Palladone — in the open-label period was 6.25 days and the median was 4.0 days. The mean daily dose of hydromorphone at the end of titration in the efficacy population was 34.5 mg for patients randomized to the Palladone — to the HMIR sequence and 33.7 mg for patients randomized from the HMIR to the Palladone — sequence. The mean daily dose of hydromorphone taken by patients while administered Palladone — (combined treatment periods) ranged from 34.0 mg (Days 1 to 3) to 36.0 mg (Day 7) for this population. Corresponding ranges for patients while on HMIR were 33.6 mg (Day 1) to 38.8 mg (Day 2). Values were similar for the intent-to-treat population.

e. Rescue Medication

The mean daily dose of rescue medication for the efficacy population ranged from 6.51 mg to 9.86 mg and 5.43 mg to 11.89 mg for the Palladone — and immediate-release treatments, respectively. Values for the ITT population were similar. Rescue medication as percentages of the total daily dose of hydromorphone taken by the efficacy population for the last two days prior to the PK/PD day of each double-blind treatment period were 13.0% and 13.2% on Day -2 and 15.9% and 14.6% during Palladone — and immediate-release treatments, respectively. The values were similar for both treatments, and findings from the intent-to-treat population were also similar. The timing of rescue doses was similar for the treatments, with no clinically significant differences between treatments in the number of rescue doses taken across time intervals. Rescue medication was used during the combined double-blind periods by 76% and 73% of patients from the efficacy population while on Palladone — and HMIR, respectively. The corresponding results for the intent-to-treat population were similar.

f. Integration of Pain Intensity and Rescue Medication

The reviewer's integrated analysis of pain intensity and rescue medication usage found 31% for which no formulation could be judged "superior". The immediate release formulation was deemed "superior" for 37% of patients, and Palladone — was favored for 32% patients.

g. Overall Conclusion for the Study

The results are consistent with similar analgesic efficacy for both formulations in the treatment of moderate to severe chronic pain. The study serves as a positive clinical trial supporting Palladone — as an effective once-daily opioid analgesic.

8.3 Supportive Studies

8.31 HD95-0803 Open-Label Extension Study (Interim Data)

8.311 Summary of Methodology:
This was a multicenter, open-label study to be conducted at 32 study centers. The daily dose of hydromorphone hydrochloride controlled release (Palladone — capsules, administered once daily, was titrated to obtain and maintain effective stable pain control. Rescue medication (hydromorphone hydrochloride immediate release 2 mg tablets) was provided for the treatment of breakthrough or incident pain.

The study population comprised 142 patients who were enrolled from two prior double-blind studies, HD95-0801 or HD95-0802. All patients had cancer and required treatment of chronic cancer-related pain with opioid analgesics. Of the 142 patients enrolled in the study, 78 had completed the 8-week study period or had discontinued by the cut-off date (January 31, 1998) for the interim report.

Each patient was enrolled for a maximum of 8 weeks (56 ± 2 days). Temporary leave from the study was permitted for up to 14 days; however, any days on temporary leave were included within the 8-week study period. Patient visits to the study site were scheduled at Baseline and at 14, 28, 42, and 56 days (± 2 days) after the start of dosing for assessments of effectiveness, pharmacodynamic variables, and safety. On Days 14 and 42 (± 2 days), blood samples were collected for pharmacokinetic evaluation. Rescue dosing, average weekly pain intensity, adverse events, and concomitant treatments were recorded by patients in a daily diary and also monitored by telephone contact at least weekly between scheduled visits. Upon completion of the 8-week study, subjects had the option to continue dosing with Palladone — for one 2-month extension period, followed by an additional 4-month extension period. Subjects were to have demonstrated satisfactory pain control and safety findings for eligibility to continue at each extension phase.

8.312 Interim Findings:
a. Demographics: Efficacy data was to be fully analyzed at completion of the study. At the interim time of submission, there were 77 cancer patients who received study drug and whose data are included in the integrated safety analysis. There were 43 (55.8%) male and 34 (44.2%) female. The majority was white (88.3%) and weighed between 60-89 kg (62.4%). Approximately 95% of patients were between the ages of 35 and 80. The mean age of the safety population was 58.3 (± 1.6) years. Although patients between the ages of 10 and 17 were allowed to enter the study, no pediatric patients were enrolled. There were 51 patients (66%) who completed the 8-week study. Reasons for discontinuation for the 27 patients not completing the study are listed in Table 26 (from sponsor's Table 10.1B Vol 96 p.15).

TABLE 26 Reasons for Discontinuation HD95-0803

Reason for Discontinuation	HHCR (N=78)	
	N	%
Adverse Event	4	5.1
Ineffective Treatment	3	3.8
Intercurrent Illness NOT Due to Drug	6	7.7
Death	3	3.8
Lost to Follow-Up	2	2.6
Protocol Violator	3	3.8
Other Reason*	6	7.7
Totals	27	34.6

b. Dosing: Overall weekly average total daily doses were 48.7 mg (± 0.67) for Palladone — and rescue combined, 38.4 mg (± 0.53) for Palladone — alone, and 10.2 mg (± 0.34) for rescue alone. Rescue medication thus accounted for an overall weekly average of 16.3% (± 0.52) of the average of the mean total daily dose of hydromorphone hydrochloride (Palladone — and rescue combined). Across study weeks, the mean percentage of the total daily dose of hydromorphone given as rescue remained relatively constant (range 14.5% to 19.3%). The majority of patients (77.4% to 88.3%) took rescue medication at some point, and most took rescue doses on 5 to 7 days a week. The percent of patients needing no rescue increased from 11.7 to 15.6% during Weeks 1 to 6, to 17.5% during Week 7, and 22.6% during Week 8, probably reflecting increased overall Palladone — dose by the end of the study (from 37.6 mg/day to 41.1 mg/day). Need for rescue medication would be expected to diminish as patients titrate upward. The majority of rescue doses were taken during the first 16 hours of the day. Patients required less rescue medication during the night, even though a sizeable proportion (27%) of patients reported (at Baseline) that their worst pain typically occurred at night. Most patients (63.6%) did not require a change in Palladone — dose from the dose they were receiving at entry; however, 32.5% had an increase, and 3.9% had a decrease. In these patients, the average increase in Palladone — dose (initial to final) was 73.7%, and the average decrease was 44.4%.

8.313 Conclusions Regarding Interim Findings from HD95-0803:
The study is open-label and not expected to provide more than soft data. Nevertheless it is reassuring that the majority of patients had reasonably controlled pain to permit completion of the 8-week study.

Only 3.8% discontinued for lack of efficacy.
Approximately one third of patients had increases in the Palladone — dose.
The majority of patients required rescue medication, and the percentage of total hydromorphone dose as rescue medication increased to 23% at Week 8, either because of increased disease progress associated with more pain or development of tolerance.

8.32 Study HD96-0505

Randomized, Double-Blind, Single Dose, Parallel Group Study to Determine Analgesic Efficacy of Hydromorphone Hydrochloride Controlled-Release Capsules, Hydromorphone Hydrochloride Immediate-Release Tablets and Placebo in Patients with Post-Operative Orthopedic Surgery Pain

8.321 Investigator/Location

[redacted], New South Wales
2107

8.322 Plan

8.3221 Objective

The study was primarily intended to determine the efficacy and safety of single-dose, oral administration of Palladone — (hydromorphone hydrochloride controlled-release capsules, 12 mg x 2) as compared with hydromorphone hydrochloride immediate-release (Dilaudid) tablets (2 mg x 3) and placebo in the treatment of moderate to severe pain following surgery. Secondary objectives were to characterize the plasma hydromorphone time-concentration profile and the time- and concentration-effect relationships.

8.3222 Population

Patients 18 years of age or older with moderate to severe pain following orthopedic surgery. Female patients were to be nonnursing and nonpregnant. Concomitant analgesia (except APAP for headache or fever or one aspirin 162 mg) or other medication or other medical conditions that would interfere with the study were excluded. Enrollment was planned as 120 patients.

8.3223 Design

This was a randomized, double-blind, double-dummy, placebo- and active-controlled, single-center, parallel-group trial comparing acute analgesic efficacy, safety and pharmacokinetic and pharmacodynamic profiles of oral administration of Palladone — (hydromorphone hydrochloride controlled-release capsules) and hydromorphone hydrochloride immediate-release tablets (Dilaudid) in orthopedic postoperative patients with moderate to severe pain.

8.3224 Methodology
Patient-controlled analgesia (PCA) fentanyl (25 mcg boluses with a 5-minute lockout period) was used following surgery to titrate patients' pain to comfortable intensity and without intolerable adverse effects. Patients were randomized, and PCA was discontinued. When pain intensity became moderate (score 5-6) to severe (score 7-10), a single-dose of 24 mg Palladone — (two 12 mg capsules) or Dilaudid 6 mg (three 2 mg tablets) or placebo was administered in double-blind, double-dummy fashion. PCA fentanyl was used as rescue medication to maintain pain at a comfortable intensity.

8.3225 Assessments
The primary efficacy variables was the amount of rescue medication by time intervals (analyzed by ANOVA for both intent-to-treat and protocol-compliant, efficacy populations with intervals at 0-3 hours, 3-6 hours, 6-12 hours and 12-24 hours). Secondary variables were pain intensity measured on an 11-point scale (0 = no pain, 10 = pain as bad as you can imagine) during a 24-hour evaluation period. Efficacy assessments and plasma sampling for pharmacokinetics were performed at 0, 0.5, and 1 hour and hourly until 12 hours, and at 14, 16, 20 and 24 hours postdosing. Safety assessments included adverse events, vital signs, and oxygen saturation. This section of the review will be focused on efficacy.

8.323 Study Conduct/Outcome

8.3231 Patient Disposition
The planned enrollment was 120 patients (40 per group). There were 132 randomized, enrolled and eligible for intent-to-treat and safety analyses. There were 127 patients who completed the study. Five were discontinued; three (one on each treatment) for adverse events, one on placebo for a protocol violation, and one on Palladone — at the patient's request (in order to smoke). Five more patients were excluded from the sponsor's efficacy analysis because of protocol violations (three on placebo and two on Palladone —. There were 122 patients considered eligible for the sponsor's efficacy and pharmacokinetic analyses.

8.3232 Demographics
The demographic and baseline characteristics of the total population (n=132) enrolled and evaluable for intent-to-treat and safety analyses were as follows: There were 86 (65%) men and 46 (35%) women; there were 123 (93%) white, 9 (7%) of other races. Mean age was 59.1 years. The primary orthopedic procedures involved hip in 54 (41%) and knee in 36 (27%). There were no statistical differences between treatment groups in age, height, weight, sex, race, time to first rescue dose of prebaseline PCA fentanyl or duration of prebaseline period.

8.324 Efficacy Results

8.3241 Primary Efficacy Variable (Rescue Medication): The mean total amount of rescue fentanyl over 24 hours for the ITT population was 1004.0, 985.8, and 1186.9 mcg in the Palladone ™ (n=44), Dilaudid (n=44), and placebo groups (n=44), respectively (cf. sponsor's Table 11.1.1 Vol 114 p.31). The Palladone ™ and Dilaudid treatment groups used 15.4% and 16.9% less fentanyl, respectively, than did the placebo group. According to the sponsor, there was no statistically significant difference between the Palladone ™ and Dilaudid treatment groups (p = 0.7126), but Palladone ™ was significantly different from placebo (p = 0.0086), and Dilaudid was significantly different from placebo (p = 0.0029). Results for the sponsor's efficacy population were similar. The FDA statistician also analyzed these data, but found no statistical differences between either of the active drugs and placebo. Based on the large standard errors, the p values (2-sided) were: for Palladone to placebo, 0.23, and for Dilaudid to placebo, 0.20. It should be noted that over 90% of patients required rescue medication within the first hour for all three treatments (91% each for Palladone ™ and placebo and 96% for Dilaudid). The mean numbers of rescue doses taken over the first three hours were 7.75 for Palladone ™ 7.55 for Dilaudid and 8.36 for placebo. For the first six hours, the mean numbers were respectively 13.66, 13.18 and 15.68. The differences from placebo were increased at hours 6-12: 10.14, 9.73 and 12.35, respectively. There was no meaningful difference between treatment groups in the mean microgram amount of fentanyl use prior to Hour 1 or after Hour 17. However, between Hour 1 and Hour 17, the placebo treatment group seemed to require more fentanyl than the Palladone ™ and Dilaudid treatment groups. However, no statistical statements were made in this connection.

8.3242 Secondary Efficacy Variable (Pain Intensity): The mean pain intensities of the ITT population at baseline and at 24 hours and the overall mean pain intensity over the 24 hour period are tabulated in Table 27 below for each treatment group (from sponsor's Table 11.1.2 Vol 114 p.33). The study was intended for patients to titrate with rescue medication to similar, modest pain intensities. Also, as time passed over the 24 hour period, acute postoperative pain would be expected to lessen. Differences between treatments were generally small, and no significant differences were detected.

TABLE 27 Mean Pain Intensities HD96-0505

Time	Palladone ™	Dilaudid	Placebo
Baseline	5.68	5.55	5.55
24 hours	1.40	1.72	1.83
Overall	2.48	2.78	2.69

8.3243 Plasma Levels: As might be anticipated, Cmax was lower for the controlled-release than for the immediate-release formulation (1.09 vs. 1.47 ng/ml), and tmax was greater for the controlled-release than for the immediate-release formulation (9.36 vs. 3.86 hours). There did not seem to be an attempt to make correlations of pharmacokinetics with pharmacodynamics.

8.325 Conclusions Regarding Efficacy from HD96-0505
Both Palladone — and the immediate-release hydromorphone (Dilaudid) seemed to lower PCA fentanyl needs relative to placebo in this postoperative study. It would not be surprising that hydromorphone formulations would make further opioid contributions to the analgesic effect of another opioid. It is remarkable that a single dose of 6 mg of immediate release agent (Dilaudid) did at least as well as 24 mg of Palladone — over each time interval. This may be a function of the temporal relationship of postoperative pain intensity, which would be expected to lessen over the period of observation. It is very likely that fentanyl, which is a powerful opiate, largely overwhelmed any significant distinctions between the three treatments. There is also a question of what clinical benefit there might be for the use of oral hydromorphone in this capacity and with this type of pain. The results of the study do suggest that Palladone — may not be ideally suitable for use in postoperative or other acute pain syndromes. Treatments for acute pain conditions should show early onset of analgesic effect. The active drugs in this trial did not differ in effect from placebo during the first hour following administration, even according to the sponsor's analysis. Even over the first three hours, differences in PCA rescue medication between active drugs and placebo were slight. The results are consistent with slow onset of activity that would be unacceptable for the indication of treating acute pain.

According to the FDA statistician, both active drugs failed to separate from placebo when the primary variable of fentanyl usage was analyzed. The trial has to be considered a failed study. This may not have been the best pain model to demonstrate analgesia relative to placebo. A repeated dose (e.g., a one-week) study using a weaker, escape medication, in a chronic pain population, might have been more likely to show separations from placebo.

8.4 Efficacy Conclusions

8.41 Discussion of Efficacy:

The sponsor chose pain intensity measurements as primary efficacy variables. These included mean patient-rated pain intensity scores for each treatment averaged over the last two days of each double-blind period prior to Visits 3 and 4 (the PK/PD assessment days). These also included current patient-rated pain intensity scores for each combined treatment group assessed immediately before each phlebotomy at Visits 3 and 4. On this basis, there were no significant differences found between the two formulations in either of the two pivotal trials. The sponsor included as secondary efficacy variables average pain intensity means for each of the last two days before the PK/PD phlebotomies and average pain intensity means for each day of the combined double-blind periods. Results for these variables from both pivotal studies were in accord with similar efficacy for the two formulations.

The sponsor relegated aspects of rescue medication usage to serve as secondary efficacy variables in the pivotal chronic pain trials. Rescue or escape medication usage should logically be of at least equal importance to pain intensity measurements. If pain intensity is reduced at the expense of increased rescue analgesic administration, then the relief pain is not necessarily attributable to analgesic effects of the drug being tested. The converse (reduced rescue medication and increased pain) also makes conclusions regarding efficacy difficult. It may even be argued that rescue medication usage can have more reliability for comparisons than pain measurements. The sponsor in fact used rescue, rather than pain as the primary variable in the postoperative acute pain study, since the intent of the trial was for patients to titrate to acceptable pain levels. Chronic pain trials allowing escape medication should also tend to result in tolerable pain intensities in order to keep the patient from dropping out. The patient might be expected to titrate pain to similar levels, depending upon the individual's tolerability thresholds, in both legs of a crossover. Thus, results based on comparison of pain assessments alone are not definitive.

The sponsor escape medication usage data included mean daily dose of rescue medication, percentages of total daily dose of hydromorphone as rescue medication during the last two days prior to the PK/PD assessments, timing of rescue medication and percentages of patients who ever took rescue analgesia. Results were similar for both formulations.

The placebo-controlled postoperative study failed to demonstrate that either formulation of hydromorphone had more analgesic activity than placebo.

The reviewer carried out an integrated assessment of the 194 patients completing both legs of the study. The mean rescue dosages for this population was slightly higher for Palladone — (8.89 mg vs. 8.66 mg for HMIR), but mean pain intensity at these assessment times was also slightly higher than for the immediate-release formulation (2.89 vs. 2.63). The integrated pain intensity resulted in 57 (29%) of patients for whom no treatment was superior. There were 73 (38%) for whom the immediate-release was superior and 64 (33%) who did better on the controlled-release formulation. Thus, there was a weak suggestion from this data that Palladone — may be slightly less effective than an equivalent dosing of the conventional-release hydromorphone. An integrated analysis by the FDA statistician concluded that these differences were not significant.

8.42 Overall Efficacy Conclusions:

The postoperative study failed to clearly demonstrate analgesic activity relative to placebo, probably because fentanyl was too potent as escape medication.

Efficacy conclusions from the pivotal studies are limited by the concomitant use of immediate-release hydromorphone, the relatively brief duration of the double-blind periods and the potential for crossover effects. These studies may only be capable of identifying prominent differences between formulations. Within the limits of their capabilities, the pivotal studies, HD95-0801 and HD95-0802, did demonstrate similar efficacy for Palladone — administered once-daily and immediate-release hydromorphone hydrochloride administered q6h for the treatment of moderate to severe chronic pain. The study finds no differences in pain intensity or escape medication assessments for the two formulations; however, the study was not intended to show equivalence of the two formulations. The controlled-release formulation would be expected to provide convenience of dosing.

9.0 Safety Findings

9.01 Primary Source Data Reviewed for Safety

The following sources were used in the review of safety:

Volume	Contents
69, 109	Integrated Summary of Safety
74	Drug Abuse, Integrated Summary of Benefits and Risks
74-76	HD96-0505
76-87	HD95-0801
87-96	HD95-0802
97-99	HD95-0803 Interim
145-179	Case Report Forms from discontinued patients

Electronic Data mounted by EDR on acrobat
CDROM with SAS transport files converted to 16 Jump files
Other Electronic Data: CDROM with 14 MS Word 97 text files

9.011 Clinical Studies and Foreign Marketing Experience: Table I in Section 6.0 lists clinical pharmacology (Phase I) studies, and Table 2 describes efficacy and safety studies in terms of design, treatments and patient numbers. Palladone — is a new sustained-release formulation of hydromorphone hydrochloride with no previous marketing experience in any country.

9.02 Demographics

This NDA included 560 unique individuals who received Palladone — (The cut-off was 1/31/98, but no new individuals were reported in the 120-day update). These consisted of 173 healthy volunteers in Phase I trials (Table 8.11.18.1.3C in the ISS, Vollume 109, p.124), 44 postoperative patients in Study HD96-0505, and 343 patients in the two pivotal crossover trials (HD95-0801and HD95-0802) *(Volume 2, p.156).*

9.021 Gender: This NDA included more males, n = 343; 61% (147 healthy volunteers and 196 patients) exposed to Palladone — than females, n = 217; 39%) There were roughly equal populations of men (49%) and women (51%) enrolled in the chronic pain trials (422 patients).

9.022 Age: The mean age of the 560 subjects enrolled subjects was 51 years. The mean age for chronic pain patients was 58 years, with 33% of these patients at least 65 years old. The mean age was 32 years for Phase I studies and 59 years for postoperative studies. No pediatric patients were exposed. Age ranges for chronic pain patients and all patients exposed are as follows:

Age Range	0-18 yrs	18-24 yrs	25-44 yrs	45-64 yrs	=/>65 yrs	=/>75 yrs
Chronic Pain Patients	0	2	58	172	112	34
All exposed subjects	0	53	245	266	199	46

9.023 Race: There were more whites (n = 449; 80%) in the total population enrolled than other races. There were 57 (10%) black and 54 (10%) other races. Chronic pain patients were mostly white (n=300, 87%).

9.024 Weight: The mean weight was 77.7 (SE=0.6) kg for all exposed subjects, and 76.7 (SE=1.1) kg for chronic pain patients.

9.025 Disease: Most of the chronic pain patients (79%) had cancer; the primary cancer sites involved the thorax, digestive system, and breast in 65% of the patients. There was renal impairment (estimated creatinine clearance less than 80 ml/min) in 36% and hepatic impairment in 9%. Hepatic impairment was defined by the sponsor as involving two or more of the following six abnormalities: SGOT (AST) concentration >1.5 x upper limit of normal, SGPT (ALT) concentration >1.5 x upper limit of normal, prothrombin time prolonged at least 2 seconds beyond the upper limit of normal (in patients not being treated with warfarin), albumin concentration greater than 15% below the lower limit of normal, total bilirubin concentration above the upper limit of normal, and GGT concentration above the upper limit of normal.

9.026 Prior and Concomitant Medications: All patients in the chronic pain studies had received opioids prior to participating in the studies. The most common concomitant analgesic medication was ibuprofen. The most common adjuvant therapies were steroids, antidepressants and anxiolytics. The most common nonanalgesic concomitant medications were laxatives, antiemetics, H2-receptor antagonist and/or gastric acid pump inhibitors, antihistamines, coumadin and chemotherapy.

9.03 Extent of Exposure: The total exposure to Palladone — in this NDA included 560 unique individuals. In response to the reviewer's request, the sponsor estimated in February 1999, a total of 8702 patient exposure days for the Palladone — formulation. This NDA consisted of:

a. Ten completed pharmacokinetics and bioavailability studies involving 173 of these subjects on Palladone — (536 subject exposure days).
b. Two completed efficacy crossover trials (HD95-0801 and HD95-0802) comparing immediate-release and sustained-release formulations in 343 patients with chronic pain who received Palladone —
c. An open-label safety study (HD95-0803) involving 78 patients (up to 3 months) previously exposed in the crossover trials. (The total exposure for chronic pain patients (studies HD95-0801, HD95-0802 and HD95-0803) was 8122 patient days.
d. A placebo-controlled study (HD96-0505) in which 44 postoperative patients received single doses of Palladone — (44 patient exposure days).

Table 28 (adapted from the sponsor's Table 8.11.18.1.3C on page 124 of the ISS Appendix) tabulates numbers of subjects receiving Palladone — from all studies according to dose of Palladone — and duration of treatment range. Table 28A (adapted from the sponsor's Table 8.11.18.1.3C on page 125 of the ISS Appendix) tabulates numbers of chronic pain patients treated for over one week (286 patients) according to duration of treatment range and the range of combined hydromorphone hydrochloride dose of Palladone — and the immediate-release formulation.

TABLE 28 Duration of Exposure

Number of Subjects (%) at each Palladone dose range and duration range

Therapy Duration	0-18 mg/day	>18-30 mg/day	>30-66 mg/day	>66-102 mg/day	>102 mg/day	Total
< 1 week	83 (15%)	145(36%)	33 (8%)	5 (1%)		276 (49%)
8-14 days	37 (7%)	23 (4%)	40 (7%)	6 (1%)		106 (18%)
15-21 days	12 (2%)	21 (4%)	44 (8%)	6 (1%)		83 (15%)
22-30 days	5 (1%)	7 (1%)	14 (3%)	1 (0%)	1 (0%)	28 (5%)
31-60 days	4 (1%)	3 (1%)	7 (1%)	1 (0%)		15 (3%)
61-90 days	14 (3%)	9 (2%)	20 (4%)	9 (2%)		52 (9%)
Total	155 (28%)	208 (37%)	108 (30%)	28 (5%)	1 (0%)	560 (100%)

TABLE 28A Duration of Exposure (Palladone — and HMIR Combined)

Numbers of Chronic Pain Patients (%) treated for > 1 week (n = 286) at each combined hydromorphone hydrochloride dose range and duration range

Therapy Duration	0-18 mg/day	>18-30 mg/day	>30-66 mg/day	>66-102 mg/day	>102 mg/day	Total
8-14 days	17 (6%)	11 (4%)	23 (8%)	6 (2%)	5 (2%)	62 (22%)
15-21 days	22 (8%)	13 (5%)	37 (13%)	15 (5%)	3 (1%)	90 (31%)
22-30 days	7 (2%)	10 (3%)	25 (9%)	12 (4%)	2 (1%)	56 (20%)
31-60 days	6 (2%)	2 (1%)	7 (2%)	8 (3%)	1 (0.3%)	24 (8%)
61-90 days	15 (5%)	5 (2%)	24 (8%)	6 (2%)	3 (1%)	53 (19%)
>90 days					1 (0.3%)	1 (0.3%)
Total	67 (23%)	41 (14%)	116 (41%)	47 (16%)	15 (5%)	286(100%)

9.1 Deaths

There were 28 cancer patients (including patients reported in the 120-day safety update) who died. Essentially all of these deaths were likely to have at least some relationship to the progression of the malignant disease. None of these deaths were considered related to study drug by the investigators, although fourteen of these patients died as a result of problems reported as adverse events. None of the adverse events leading to death was judged related to the study medication by the investigators; however, there were cases worthy of discussion. Patient 27-006 had drug-related nausea and vomiting, causing dehydration requiring hospitalization. The patient was found dead three days later of "cardiac events" to which dehydration may have rendered him vulnerable. There were three cases of respiratory failure to which opioids could contribute; however, all three cases involved patients with advanced pulmonary cancer, and one of them also had pneumonia. Opioid-dependent patients are expected to be minimally susceptible to the respiratory depressive effects of oral narcotics, except in overdose situations. Doses of study medication for these three patients were not increased prior to the respiratory symptoms or death.

Seven of the deaths were associated with the open-label period, and thirteen were from the open-label extension study.

There were seven deaths associated with the double-blind period, three in which Palladone — was the last double-blind drug taken and four when the immediate-release formulation was the last double-blind. Comparisons between treatments are made difficult by the concomitant use of immediate-release hydromorphone as escape medication. In any case, no differences in frequency of deaths in double-blind periods are evident between treatments.

There were no deaths in non-cancer patients or healthy volunteers.

Table 29 (developed from sponsor's Vol 76, pp 89-90 and pp 94-96, Vol 87, pp 83-84 and 88-89, Vol 96 pp 30-33, Vols 168-170 and 120-Day Safety Update Vol 9.1, pp 18-19 and p. 22) lists patients who died and causes of death.

The reviewer generally viewed serious events involving typical opiate types of adverse events as possibly drug-related, but generally agreed with the invesigators that the deaths reported below were unlikely to be related to study drug.

TABLE 29 DEATHS

Study	Pt ID	Sex Age	Last Study Rx Taken	Analgesic used after dc during last days of life	Day of Death in Relation to Last Dose Study Drug	Cause of Death	Days on Study Rx
801	33-012	M 64	IR (DB)	MS drip		Pneumonia and progressive lung CA. Patient was discontinued since not experiencing effective pain control due to rapid disease progression.	11
801/803	12-010	M 52	Pal	N/A	1	Patient with esophageal CA had pneumonia with apnea thought unrelated to treatment by investigator. Patient also experienced dysphagia and stomatitis in the last days prior to death.	21
801	16-006	M 84	Pal (OL)	N/A		Progressive lung CA with liver metastases and renal insufficiency considered unrelated to treatment by investigator	20
801	17-008	F 42	Pal (OL)	meperidine and fentanyl		Progressive lung CA, small bowel infarction considered unrelated to treatment by investigator.	6
801	33-011	M 55	Pal (DB)	N/A		Patient with bladder CA and hypercalcemia had a pulmonary embolus	18
801	16-001	M 49	Pal (DB)	Not reported		Progressive lung CA.	33
801	16-007	F 73	Pal (DB)	Not reported		Progessive colon CA with C.difficile diarrhea	17
801	16-041	F 62	IR (DB)	N/A		Respiratory failure considered secondary to progressive lung CA by the investigator.	16
801	33-005	F 51	Pal (OL)	dilaudid drip		Bowel obstruction considered secondary to progressive uterine CA. Had to discontinue because of need for npo	22
801	16-040	M 70	IR (DB)	Not reported		Progressive Lung CA, Patient dc'd due to possibly drug-related abdominal pain.	12
801	16-030	M 73	IR (DB)	Not reported		Patient dc'd for dysphagia. Progressive prostate CA,	18
802	23-006	F 43	Pal (OL)	N/A		Respiratory failure considered secondary to progressive small-cell lung CA by investigator	17
802	27-006	M 80	Pal (OL)	IV dilaudid		Patient with prostate CA found dead by nurse, thought by investigator to have been from "cardiac events" unrelated to treatment. Patient was hospitalized and dc'd owing to dehydration from drug-related vomiting	7
802	22-011	M 64	Pal (OL)	IV dilaudid		Progressive lung CA and exacerbation of underlying epilepsy thought unrelated to study drug by investigator.	7
802	23-003	M 58	Pal (OL)	Duragesic		Progressive pancreatic CA Was unable to keep down po medication.	6
803	16-003	M 62	Pal	Not reported		Progressive lung adenocarcinoma,	34
803	16-022	M 56	Pal	Not reported		Progressive renal CA; pleural & pericardial effusions Dc'd due to dysphagia thought unrelated to study drug by investigator.	57
803	21-002	M 59	Pal	Not reported		Progressive prostate CA with thrombocytopenia and bleeding. Dc'd due to dysphagia thought unrelated to study drug by investigator.	46
803	21-001	M 82	Pal	N/A		Respiratory failure in patient with progressive lung CA thought unrelated to study drug by investigator.	47
803	16-010	M 72	Pal	Not reported		Progressive lung & prostate CA; dc'd due to dysphagia thought unrelated to study drug by investigator.	77
803	16-037	M 63	Pal	N/A		Progressive prostate cancer	8 mos
803	16-042	M 46	Pal	Not reported		Progressive melanoma. Patient dc'd for stomatitis and dysphagia not considered drug-related	25
803	16-045	M 72	Pal	Cervical epidural block		Patient with advanced melanoma had either myocardial infarction or CVA; had been having dyspnea & rales	54
803	22-002	M 61	Pal	N/A		Progressive lung CA, with ascites	47
803	22-012	M 50	Pal	Not reported		Patient with metastatic hepatic cancer had hepatic failure not thought to be drug-related by investigator	68
803	29-010	F 69	Pal	Not reported		Progressive lung CA	31
803	33-010	M 59	Pal	Dilaudid iv		Progressive CA (unknown primary), renal failure and wasting	90
803	44-005	M 73	Pal	N/A		Progressive colon CA	45

9.2 Overdose and Drug Interactions

9.21 Overdose: No adverse events were reported as "overdose" during the controlled clinical trials; however, there were cases of patients taking higher doses than prescribed during the open-label, titration periods of studies HD95-0801 and HD95-0802. There were six patients in HD95-0801 who took more than prescribed (three accidentally and three who took second daily doses of medication due to increased pain. At least three of the four cases in HD95-0802 who took more than prescribed were inadvertent; the fourth case was of unclear nature. One of these accidental overprescribings was due to investigator miscalculation of the conversion dose, and this was the only case of significant dosing deviation resulting in a prolonged adverse event. The patient (44-003 enrolled in HD95-0802) experienced headache, an episode of vomiting, and developed mild ankle swelling and moderate confusion persisting over nine days. None of the other cases referred to above resulted in severe or prolonged adverse events. There was one patient (27-013) in the open-label study HD95-0803 who took a second dose of Palladone — 48 mg on one day of the study. No adverse events were recorded following the second dose, but the patient was discontinued from the study the following day due to intercurrent illness said to be unrelated to study drug. (See Vol 76 pp 107-108, Vol 87 pp101-102, and Vol 96 pp.38-39).

9.22 Drug Interactions: A total of 56 patients received lorazepam in Studies HD95-0801 and HD95-0802 (Vol 76 p.109 and Vol 87 p.102-3). A patient required hospitalization for mental status and gait changes considered by the investigator to be attributable to additive effects of lorazepam and Palladone — after a single dose of lorazepam 1 mg.. There were two cases of somnolence (16-001 and 23-006) attributed by the investigators to concomitant use of lorazepam in addition to Palladone — There was one case of insomnia (41-006) associated with a single dose of lorazepam by the investigator. Benzodiazepines are well known to have additive effects when given with opiates.

9.3 Nonfatal Serious Adverse Events

Serious adverse event discussion has been separated according to the type of subject and exposure. These include healthy volunteers (Phase I), postoperative patients and chronic pain patients. Serious adverse events with the latter are further divided into double-blind periods so as to attempt serious adverse event comparisons between extended-release and immediate-release treatments, open-label titration periods and events occurring in longer term (extention study) exposure.

9.31 Serious Phase I Events: There were no serious adverse events reported among the 173 subjects who received Palladone — in the healthy volunteer studies.

9.32 Serious Postoperative Events: There was only one serious event reported for study HD96-0505, a vagal episode during fentanyl stabilization and prior to randomization to Palladone — for one patient.

9.33 Serious Adverse Events during the Double-Blind Periods of HD95-0801 and HD95-0802: Eight patients had serious adverse events while taking Palladone — and six while taking HMIR during the double-blind periods of the chronic pain, crossover studies. Table 30 (adapted from sponsor's Table 12.3.1.1B in Vol 76, p. 91 and Vol 87, p.86) identifies these patients, their double-blind treatment and serious events and the reviewer's judgment on relationship to treatment. The reviewer considered those events typical for opiates as possibly related to study drug. Although comparisons between formulations are complicated by the concomitant use of HMIR as rescue medication and the small number of subjects having serious adverse events during the double-blind period, there appears to be no obvious difference between treatments in this regard.

TABLE 30 Serious Adverse Events in the Double-Blind Periods of Chronic Pain Studies

Palladone — Patient ID	**Serious Adverse Events**	**Relationship to Drug**
12-004	Nausea	Possibly
17-004	Confusion, somnolence	Possibly
17-017	Nausea, dehydration	Possibly
33-013	UTI, hypokalemia, anemia, hypertension	Unlikely
16-033	Respiratory distress	Possibly
27-014	Neutropenic fever	Unlikely
27-015	Confusion, dehydration	Possibly
29-015	Cholangitis	Unlikely
HMIR Patient ID		
31-003	Chest pain, pain	Unlikely
33-018	Rectal bleeding	Unlikely
16-040	Abdominal pain	Possibly
25-001	Myocardial infarction	Unlikely
25-005	Mental status changes	Possibly
25-019	Pneumonia	Unlikely
41-007	Dehydration, confusion	Possibly
29-010	Pneumonia	Unlikely

9.34 Serious Adverse Events during the Open-Label Titration Periods of Chronic Pain Studies: Forty-six patients had serious adverse events while taking Palladone — in the open-label periods of studies HD95-801 and HD95-802 (Sponsor's Table 12.3.1.2A in Vol 76, p.90 and Vol 87, p.85). The patients with serious adverse events, the type of events and the reviewer's estimate of possible relationship to Palladone — treatment are described below. Adverse events known to be typically associated with opiate use were considered possibly drug-related by the reviewer. (Note that some patients had more than one serious event).

Six patients had gastrointestinal problems and/or dehydration, such as abdominal pain, bowel obstruction, fecal impaction, nausea, vomiting and dehydration, requiring hospitalization. There were three cases of serious diarrhea resulting in hospitalization, two induced by chemotherapy and one thought possibly to be from C.dificile infection.

Eight patients had CNS related events, such as sedation, somnolence confusion, hallucinations, psychotic mental changes and depression, that resulted in hospitalization. Concomitant benzodiazepines and steroids may have been contributory to some of these events. One patient had a fall, leading to hip fracture, that may have been related to CNS effects of study drug.

Five patients had pulmonary-related adverse events, such as hypoxia, hypoventilation, dyspnea and respiratory insufficiency, requiring hospitalization. Some of these events may have been of possible relationship to Palladone — and/or concomitant benzodiazepine treatment. Also requiring hospitalization, were seven cases of pneumonia and other respiratory infections and two cases of pleural effusion.

Cardiovascular, renal, hepatic or hematological events included thrombocytopenia, anemia and melena, atrial fibrillation, SV, neutropenia, deep vein thrombosis, blood clot, chest pain, hepatic failure and renal insufficiency. There were also hospitalizations for increased pain and progression of disease and fever.

9.35 Serious Adverse Events in the Open-Label Extension Study (HD95-0803): Thirty-nine patients had serious adverse events while taking Palladone — in the open-label, longterm, extension study, HD95-0803 (Sponsor's Table 12.3.1.2 in Vol 96, p.29 and Table 9.2.6.3.2A in the 120 Day Safety Update Vol 9.1, p.85). The numbers of patients with serious adverse and the type of events are described below. Adverse events known to be typically associated with opiate use were considered possibly drug-related by the reviewer. (Note that some patients had more than one serious event).

Six patients had gastrointestinal problems and/or dehydration requiring hospitalization and of possible relationship to Palladone — treatment, including abdominal pain, constipation, fecal impaction, nausea, vomiting and dehydration. There was also a case of chemotherapy-induced diarrhea.

Nine patients had CNS problems, such as dizziness, weakness and falling, asthenia, hypesthesia, headache, confusion, confusion, hallucinations, agitation, disorientation, anorexia and convulsions, that resulted in hospitalization and were possibly related to study drug.

Five patients had dyspnea requiring hospitalization; one of these patients had both pneumonia and pulmonary embolism. Fifteen patients had various adverse events leading to hospitalization, such as disease progression, cord compression, adenopathy, abscess, ascites, cachexia, peripheral edema, fever, bronchitis, melena, leucocytosis, hematuria, anemia, tinnitus, hypotension, hypertension, hypokalemia, deep vein thrombosis, stomatitis and increased pain.

9.4 Discontinuations for Adverse Events
Discontinuation for adverse events is a measure of drug tolerability. These are grouped according to subject type, namely healthy volunteers, postoperative or chronic pain patients. The latter group is separated to events in the double-blind periods so as to compare tolerability of extended and immediate release treatments, events in the titration periods and those in longterm treatment.

9.41 Phase I Discontinuations for Adverse Events: There were no discontinuations for adverse events in the Phase I trials.

9.42 Study HD96-0505 Discontinuations for Adverse Events: There were three patients discontinued for adverse events: one patient receiving Dilaudid, and one taking Palladone, each had nausea and vomiting. A patient on placebo had dizziness.

9.43 Discontinuations for Adverse Events in the Double-Blind Periods of Studies HD95-801 and HD95-802: There were eight patients who discontinued because of adverse events in the double-blind phases of the chronic pain crossover trials. Five were receiving Palladone — and three received HMIR at the time of discontinuation (Sponsor's Table 12.3.1.3A , Vol 76 p.93 and Vol 87 p.87). Table 31 summarizes the events and patients involved. Nausea seemed to be the most prevalent cause for the discontinuations tabulated below. Although comparisons between treatments are complicated by the concomitant use of immediate-release formulation as escape medication and the small number of discontinuations, there are no obvious differences between treatments in the frequency of dropouts for adverse events.

TABLE 31 Adverse Events Leading to Discontinuation in the Double-Blind Periods of Studies HD95-801 and HD95-802

Palladone ~ Patient ID	*Adverse Event*	*HMIR Patient ID*	*Adverse Event*
13-001	Nausea	16-030	Dysphagia
16-021	Nausea/ Vomiting	18-008	Dizziness Constipation
17-002	Nausea	42-002	Nausea
17-004	Confusion		
50-006	Constipation, Dysuria		

9.43 Discontinuations for Adverse Events in the Open-Label Titration Periods of Studies HD95-801 and HD95-802: Forty-two patients, approximately 29% of the 343 patients who received Palladone [redacted] discontinued from the study because of adverse events during the open-label titration periods of the chronic pain studies (Sponsor's Table 12.3.1.3A Vol 76 p.93 and Vol 87 p.87). Note that some patients had more than one event contributing to discontinuation. The counts of each adverse events leading to discontinuation were as follows: Somnolence (10), nausea (7), anxiety/nervousness (6), vomiting (5), confusion/abnormal thinking (5), dizziness (3), constipation (2), headache (2), hallucination (2), dehydration (2), abdominal pain (1), rash (1), dry mouth (1), insomnia (1), malaise (1), sweating (1), peripheral edema (1), accidental bone fracture (1), pruritus (1), fever (1) and infection (1).

9.44 Discontinuations for Adverse Events in the Open-Label Extension Study HD95-803: Ten patients discontinued Study HD95-803 because of adverse events (Sponsor's Table 12.3.1.3 in Volume 96 p. 30 and Table 9.2.6.3.3A of the 120 Day Safety Update Vol 9.1, p.21). The most common reason for discontinuation in the extension study was dysphagia, for which there were three cases. Two patients were discontinued due to nausea and/or vomiting. One patient had confusion, paranoia, agitation and lethargy, considered to be of possible drug relationship. One patient had somnolence, and one had leg weakness and paresthesia. There was also a case of stomatitis and another of disease progression.

9.5 Common Adverse Events

9.51 Adverse Events in All Studies: Table 32 (Developed from Sponsor's Table 8.11.5B ISS Vol 109 pp. 26-29) lists commonly reported (at least 5% of patients) adverse events and the number (and percentage) of patients or subjects reporting the event for all 560 people exposed to Palladone — in the NDA regardless of relationship to drug. Nausea and somnolence were the most frequently reported adverse events, followed by constipation, dizziness, headache, vomiting and pruritus.

TABLE 32 Common Adverse Events in All Studies for 560 Patients on Palladone —

ADVERSE EVENT	N (%) Patients Reporting AE's
Nausea	240 (42%)
Somnolence	227 (41%)
Constipation	178 (32%)
Dizziness	146 (26%)
Headache	139 (25%)
Vomiting	127 (23%)
Pruritus	99 (18%)
Asthenia	74 (13%)
Abdominal Pain	55 (10%)
Pain	48 (9%)
Sweating	47 (8%)
Diarrhea	50 (9%)
Confusion	36 (6%)
Fever	47 (8%)
Dyspepsia	48 (9%)
Nervousness	44 (8%)
Dry Mouth	30 (5%)
Peripheral Edema	35 (6%)
Anorexia	30 (5%)
Insomnia	29 (5%)

9.52 Adverse Events in Phase I Studies: There were adverse events reported for 58% of the 173 subjects who received Palladone — in the Phase I trials. All but 1.7% of these events were considered mild or moderate in severity, and no event was considered serious. Events that were thought to be drug-related were reported by 53% of subjects taking Palladone — The most common event was headache in 26% of volunteers. (Headache is often the most common complaint in Phase I clinical trials even in subjects receiving placebo.) Other common events reported by subjects in the Phase I studies include nausea (15%), dizziness (12%), pruritus (11%), asthenia (8%), vomiting (7%), abdominal pain and constipation (5% each) and somnolence (5%). See Sponsor's Table 8.11.5E ISS Vol 69, p.33.

9.53 Adverse Events in Study HD96-0505: There were adverse events reported for 82% of the 44 postoperative patients who received Palladone — (along with fentanyl) in the HD96-0505 trial. The most common adverse events were nausea (41%), vomiting (23%), fever (14%), hypoxia (11%), headache (9%) and pruritus (7%). Hypoxia was reversed with oxygenation. See Sponsor's Table 8.11.5F, ISS Vol 69, p. 35.

9.54 Adverse Events in the Chronic Pain Patient Population for all Studies: The summary of all adverse events for all study periods of HD95-0801, HD95-0802 and HD95-0803 indicates that 95% of the 343 patients receiving Palladone — reported at least one adverse event. The Sponsor's Table 8.11.5G, ISS Vol 69 pp 37-38) lists the most common (at least 5%) adverse events and their incidences irrespective of drug relationship. The most frequently reported events were somnolence (64%), nausea (57%), constipation (49%), dizziness (36%) and vomiting (31%). The Sponsor's Table 9.2.6.1.1.A of the 120-Day Update Vol 9.1 p 9. lists the most common adverse events and their incidences irrespective of drug relationship for the 143 patients involved in the extension trial, Study HD95-0803. Somnolence (52%), nausea (49%), constipation (47%), dizziness (34%) and vomiting (33%) remained the most frequent adverse events reported.

9.55 Comparison of Adverse Events for Palladone — and Immediate-Release Hydromorphone in Chronic Pain Patients in the Double-Blind Periods of the Pivotal Studies: Table 33 (developed from Sponsor's Table 8.11.18.1.9.1 ISS Vol. 110 pp. 462-474) is a listing of numbers of patients (and percentages) experiencing the more common adverse events without regard to drug relationship while on either Palladone — or HMIR in the double-blind periods of studies HD95-0801 and HD95-0802. The most frequent event was somnolence, reported by 66.5 % of patients on Palladone — and by 71.3 % on HMIR. This difference may not be significant. Other common events (nausea, constipation, dizziness, pruritus and vomiting) were very similar in frequencies for both formulations. At least one adverse event was reported by 90.9% of the 101 patients who received Palladone — in the double-blind phase of HD95-0801 and by 95.9% of the 97 patients who received HMIR . At least one adverse event was reported by 89.8% of the 108 patients who received Palladone — in the double-blind phase of HD95-0802 and by 90.2% of the 112 patients who received HMIR.

TABLE 33 COMPARISON OF FREQUENCY OF PATIENTS REPORTING COMMON (>1%) ADVERSE EVENTS WHILE TAKING PALLADONE — (n = 209) OR IMMEDIATE-RELEASE HYDROMORPHONE (n = 209) IN DOUBLE-BLIND PERIODS OF STUDIES HD95-0801 AND HD95-0802

ADVERSE EVENT	# Patients on Palladone —	% Patients on Palladone —	# Patients on HMIR	% Patients on HMIR
Somnolence	139	66.5 %	149	71.3 %
Nausea	91	43.5 %	96	45.9 %
Constipation	88	42.1 %	88	42.1 %
Dizziness	62	29.7 %	68	32.5 %
Pruritus	46	22.0 %	57	27.3 %
Vomiting	32	15.3 %	42	20.1 %
Asthenia	15	7.2 %	12	5.7 %
Diarrhea	15	7.2 %	7	3.3 %
Headache	13	6.2 %	21	10.0 %
Sweating	12	5.7 %	10	4.8 %
Dyspepsia	11	5.3 %	10	4.8 %
Abdominal Pain	10	4.8 %	6	2.9 %
Peripheral Edema	10	4.8 %	6	2.9 %
Confusion	9	4.3 %	8	3.8 %
Fever	9	4.3 %	7	3.3 %
Pain	8	3.8 %	6	2.9 %
Dry Mouth	8	3.8 %	9	4.3 %
Insomnia	6	2.9 %	8	3.8 %
Arthralgia	6	2.9 %	12	2.9 %
Depression	5	2.4 %	5	2.4 %
Nervousness	5	2.4 %	5	2.4 %
Chest Pain	4	1.9 %	10	4.8 %
Anorexia	4	1.9 %	6	2.9 %
Hallucination	4	1.9%	1	0.5 %
Flatulence	3	1.4 %	3	1.4 %
Nausea&Vomiting	3	1.4 %	3	1.4 %
Hypokalemia	3	1.4 %	1	0.5 %
Hypertonia	3	1.4 %	5	2.4 %
Paresthesia	3	1.4 %	1	0.5 %
Cough Increased	3	1.4 %	3	1.4 %
Dyspnea	3	1.4 %	6	2.9 %
Rhinitis	3	1.4 %	2	1.0 %
Rash	3	1.4 %	4	1.9 %
Dysgeusia	3	1.4 %	2	1.0 %
Polyuria	3	1.4 %	1	0.5 %

9.6 Results of Subgroup Analyses of Adverse Events

9.61 Effects of Age: The sponsor analyzed the overall incidence of adverse experiences with Palladone —in the three chronic pain studies according to three age groups. The age group of 18-64 years (n=231) had an 87.4% of adverse events and a 2.2 % incidence of serious adverse events. The 65 years or older group (n=112) had a 92.0% incidence of adverse events and a 7.1% incidence of serious events. The third group, 75 years or older (n=34), may have been too small to make reliable comparisons with the other groups, but some of the more frequent adverse events, nausea, somnolence, confusion and pruritus appeared to be more prevalent than in the younger groups.

9.62 Effects of Gender: There were 169 men and 174 women enrolled in the chronic pain studies. The overall incidences of adverse events reported were 87.6% for men and 90.2% for women. Incidences of serious adverse events reported were 4.7% for men and 2.9% for women. Nausea (54.6% vs. 33.1%) and pruritus (25.3% vs. 14.8%) appeared to be more frequently reported by women.

9.63 Effects of Race: The study population was overwhelmingly Caucasian (n = 299), with 32 black patients and 12 patients of other races, making comparisons unreliable. Overall incidences of adverse events were 89.6% for white and 78.1% for black patients.

9.64 Effects of Renal Function: Serum creatinine and blood urea nitrogen (BUN) were measured at baseline and at the conclusion of studies HD95-0801, HD95-0802 and HD95-0803. Creatinine clearance (CCl) in mL/min was calculated for men as 140 – serum creatinine in mg/dL x (age in years x weight in kilos)/72 . The same formula with the result multiplied by 0.85 was used for the CCl of women. Normal renal function was defined as CCl at least 80 mL/min. Mild renal dysfunction was defined as CCl less than 80, but greater than or equal to 60 mL/min. Moderate renal dysfunction was defined as CCl less than 60, but greater than or equal to 30 mL/min. Less than 30 mL/min would be severe renal dysfunction. Patients were divided into those with normal renal function or mild dysfunction (n = 293) and those with moderate to severe renal dysfunction (n = 46). The incidence of patients with adverse events was a little higher in the moderate to severe renal dysfunction group (91.3% vs. 88.7%), but the incidence of patients with serious adverse events was more than twice as high (8.7% vs. 3.1%) for this group. Nausea (63.0% vs. 48.1%), vomiting (37.0% vs. 19.8%), confusion (19.6% vs. 6.1%) and pruritus (32.6% vs. 18.1%) were in particular more frequently reported by patients in the more renal-impaired group.

9.65 Effects of Hepatic Function: Serum albumin, SGOT (AST), SGPT (ALT), GGT, total serum bilirubin and prothrombin time (PT) were assessed at baseline. A patient was designated as having hepatic dysfunction when two or more of the following six abnormalities were present: AST or ALT > 1.5 x upper limit of normal, PT prolonged by at least 2 seconds beyond the upper limit of normal in patients not taking warfarin, albumin greater than 15% the lower limit of normal, total serum bilirubin or GGT above the upper limit of normal. On this basis, there were 310 patients classified as having normal hepatic function and 31 patients considered to have hepatic dysfunction. There appeared to be increased incidences of patients with adverse events (96.8% vs. 88.4%) and serious adverse events (6.5% vs. 3.5%) in patients with hepatic dysfunction. Constipation (58.1% vs. 45.5%) and somnolence (64.5% vs. 54.2%) were slightly more prevalent in patients designated as having hepatic dysfunction. Headache was reported more frequently (16.8% vs. 6.5%) in patients with normal hepatic function. The small number of patients considered to have hepatic impairment limits the reliability of these comparisons.

9.66 Effects of Gastric Acid Suppressing Agents: The sponsor separated patients into those who took (n =232) concomitant H2-receptor antagonists (cimetidine, ranitidine, nizatidine or famotidine) or gastric pump inhibitors (lamsoprazole and omeprazole) and those who did not take these agents concomitantly (n = 111). There were no meaningful differences between the two groups in the incidences of patients with either adverse events (86.5% who took vs. 90.1% who did not take) nor serious adverse events (2.7% who took vs. 4.3% who did not take these agents).

9.67 Effects of Non-opioid Analgesics: The sponsor separated patients into those who took (n = 86) and those who did not take (n = 257) concomitant non-opioid analgesics. The incidences of patients reporting adverse events (91.9% for those taking and 87.9% for those not taking such medications) and serious adverse events (3.5% vs. 3.9%, respectively) were similar for both groups. Pruritus was reported more often (23.3% vs. 10.5%) by patients not taking concomitant non-opioid analgesics.

9.68 Effects of Analgesic Adjuvants: The sponsor separated patients into those who took (n = 76) and those who did not take (n = 267) concomitant analgesic adjuvants, e.g., antidepressants and steroids. The frequencies of patients reporting adverse events (88.2% for those taking and 89.1% for those not taking such medications) were similar. Serious event reporting appeared to be a little higher in the group taking analgesic adjuvants (6.6% vs. 3.0%). Insomnia was reported by a higher percentage of patients (13.2% vs. 2.2%) taking concomitant analgesic adjuvants. Since the group taking such concomitant medications was small, these comparisons may not be reliable.

9.69 Effects of Pain Type (Cancer vs. Non-malignant Pain): There were 272 patients with pain secondary to cancer and 71 patients with chronic non-malignant pain. The frequency of patients reporting adverse events was similar for both cancer pain (87.9%) and non-cancer pain (93.0%) groups, but serious adverse events were only reported in the cancer patient population (4.8% vs. 0%). Headache (43.7% vs. 8.5%), nervousness (18.3% vs. 4.8%) and insomnia (14.1% vs. 2.2%) were reported more in the non-malignant patient population, while vomiting (24.6% vs. 12.7%) was more prevalent in the cancer patients. The small number of patients in the non-cancer group limits reliability of these comparisons.

9.7 Other Safety Data

9.71 Physical Examinations, Vital Signs and EKG: There were no post-treatment physical examination, vital sign or EKG findings reported in the chronic studies except in connection with adverse events. There were small decreases in mean blood pressures and heart rates noted in two of the Phase I studies (HD96-1101 and HD95-0805). The latter study also detected a small decrease in mean respiratory rate. There were small but statistically significant vital sign changes found in the postoperative study (HD96-0505) in which patients also took PCA fentanyl. These included decreases in mean systolic blood pressure and increases in both heart rate and mean diastolic pressure. There were no clinically significant differences across treatment groups (including the placebo group).

9.72 Laboratory Evaluations

9.721 Phase I Lab Abnormalities: There were four subjects (2 in HD95-0701 and HD95-0702) in the healthy volunteer studies with decreases in hemoglobin described as clinically significant, probably owing to repeated blood sampling. There were three cases of white count lowering: a subject in HD95-0702 had WBC fall from 3.8 to 3.3, and another in HD95-0805 WBC fell from 3.8 to 3.0. A subjects in HD970502 with normal absolute neutrophil count (4403 /cumm) was found to have become neutropenic (430/cumm and 342 cumm) when removed from the study for positive blood alcohol. The subject had normal WBC throughout. Opioid analgesics are not thought to be associated with neutropenia, but drug-relationship cannot be ruled out in this case.

There were four subjects (one in HD95-0106 and three in HD96-1206) with normal liver function tests at baselines that had post-study elevations of ALT and/or AST to greater than twice upper-limit-of-normal values (highest was ALT 155U/L and AST 135 IU/L). Drug relationship is uncertain.

There were only trivial abnormalities detected in the post-treatment urinalyses.

9.722 Study HD96-0505 Labs: The only laboratory studies reported in the postoperative trial were oxygen saturation assessments. There were seven patients on Palladone —, three on Dilaudid and three on placebo with at least one episode of oxygen saturation below 90%. The investigator described five of the patients with Palladone — as having hypoxia. All cases of desaturation responded to supplemental oxygen. It should be noted that the amount of hydromorphone delivered as Palladone — was 24 mg, the Dilaudid dose was 6 mg, and all patients were on concomitant fentanyl. The larger amount of hydromorphone taken by the patients on Palladone — may have contributed to an increased respiratory depressing effect relative to the other groups. This relative effect on oxygen saturation, coupled with the fentanyl-sparing activity of Palladone — not separating from placebo, again recommends against the use of Palladone — in post-operative analgesia.

9.723 Studies HD95-0801 and HD95-0802 Labs:

a. Significant Renal Abnormalities: Fifteen patients had BUN and/or creatinine abnormalities deemed clinically significant. One had transient elevated values along with an episode of cellulitis. Three were attributed to dehydration. Three had previous chemotherapy-induced renal damage. Four had known renal metastases. Four others had known renal insufficiency with elevated levels at baseline. None of these were considered study drug related.

b. Significant Hepatic Abnormalities: Six patients had low albumin levels considered clinically significant (five attributed to malnutrition and one to cancer). There were 25 patients with abnormalities of serum bilirubin, liver enzymes or prothrombin time (other than anticoagulant-induced changes) considered clinically significant. Twelve patients (11 thought to have liver malignancy) had clinically significant elevations at baseline and no follow-up values. Ten of thirteen patients with post-treatment significant abnormalities were attributed to metastatic or primary hepatic cancer. One patient (33-002) had acetaminophen toxicity; another was thought to have elevations in association with hypercalcemia (33-011), and a third (17-008) had elevations of PT and GGT that decreased to normal on follow-up. None of these hepatic function abnormalities were considered drug-related.

9.724 Study HD95-0803 Labs: Neither the interim report in the original submission nor the 120-Day Safety Update contained laboratory data from the long-term, open-label study.

9.73 Drug Abuse Potential

9.731 Opioid Dependence: Hydromorphone hydrochloride is a pure agonist opioid and a Schedule II controlled substance which has been used by drug abusers, including drug addicts. Palladone — a new formulation of hydromorphine hydrochloride would also be expected to have abuse liability.

Drug addiction involves psychological dependence with or without physical dependence and tolerance. It is characterized by a preoccupation with the procurement, hoarding, and abuse or misuse of drugs for non-medicinal purposes. Opioid addiction can often occur in combination with abuse of other psychoactive substances. Drug seeking behavior for other than analgesic uses with opioids is an earmark of addiction, but can be confused with the patient's need for more analgesia to control increasing pain. This may be due to progression of the patient's disease or the development of tolerance, which occurs in patients treated with chronic opioid therapy. Tolerance and physical dependence in pain patients are not necessarily signs of psychological dependence. Preoccupation with achieving adequate pain relief can be appropriate behavior in a patient with poor pain control. Chronic pain patients usually limit their intake of opioids to achieve a balance between the benefits of the drug and dose-limiting side effects. The incidence of iatrogenic addiction (with the development of psychological dependence) to opioids legitimately used in the management of pain is unknown, but thought to be very rare. It is more likely to occur in patients with previous histories of substance abuse. Drug dependence is treatable, but relapse is common.

9.732 Drug Abuse/Misuse in the Clinical Trials: There were three patients in the chronic pain trials for whom the sponsor described as having possible inappropriate drug seeking behavior or diversion of drug supplies (50-002, 31-008 and 12-002). There were two others (12-002 and 16-027) that appeared to be suspect in this regard. There were a number of other patients with discrepancies in study drug usage, but without clear evidence of abuse or misuse.

Patient 50-002, in study HD95-0801, was a 44 year-old woman with chronic nonmalignant pain secondary to spondylolisthesis who had been on MS Contin 30 mg bid, Vicodin one tablet qd and Dilaudid 2 mg qid at baseline. The patient claimed to have dropped 10 of the HMIR escape medication tablets down the sink on the first day of the open-label period. The investigator contacted one of her previous physicians regarding suspicious behavior and then discontinued her for possible drug abuse behavior.

Patient 31-008, in study HD95-0801, a 60 year-old woman with chronic pain from metastatic lung cancer with no history of drug abuse, began the open-label period on 12 mg Palladone — She was hospitalized on the fifth day of the study for gram negative sepsis. It was noted that both her controlled- and immediate-release medication bottles were empty; there were 26 Palladone — 12 mg capsules and 41 HMIR 2 mg tablets unaccounted for by the patient or family. A social worker consult was requested to investigate the home situation, and the patient was discontinued.

Patient 12-002, a 42 year-old woman with metastatic colon cancer while in the open-label titration period of Study HD95-0801, claimed that there were 10 less tablets of HMIR than reportedly packaged to explain a discrepancy. She completed the trial and entered Study HD95-0803. The patient returned three less capsules of Palladone — and 43 less HMIR 2 mg tablets than could be accounted for by dosing records. She claimed to have possibly dropped the three capsules, but had no explanation for the tablet discrepancy.

Patient 16-027 was said to have lost a bottle of Palladone — during the open-label titration phase of Study HD95-0801 and that there was a discrepancy count of 10 less HMIR tablets than reportedly packaged. The patient was randomized and completed the trial, but there were also questions regarding compliance during the double-blind periods.

A suspicious case was that of Patient 17-016 who reported keeping 6 or 7 capsules of Palladone — at home; however, the patient did not account for 27 missing 12 mg capsules of Palladone —

There were no clear reasons for discrepancies for four patients from Study HD95-0801 and two patients from HD95-0802: Patient 13-002 had 40 HMIR tablets unaccounted for; Patient 12-013 had 18, Patient 51-008 had 10 and Patient 50-001 had 15 tablets unaccounted for. Patient 63-011 had 21 Palladone — capsules and Patient 41-007 had 14 HMIR tablets unaccounted for.

Discrepancies in returning HMIR tablets were noted in a number of patients for which there was no overt evidence of abuse. Discrepancies in four patients (16-016, 13-003, 17-015 and 33-002) in HD95-0801 and six patients in HD95-0802 (Patients 27-009, 27-011, 23-011, 22-001, 45-003 and 29-019) were thought to be due to questionable reliability of their rescue dose usage recordings. Also Patients 33-002 and 27-011 (the latter from HD95-0802) had claimed to spill the medication and may not have retrieved all of it. The caregiver for Patient 23-011 from HD95-0802 discarded the medication.

Two patients in HD95-0801 (52-003 and 18-007) were reported to have flushed all remaining study drug down the toilet on discontinuing the study. Patient 27-012 in HD95-0802 inadvertently had medication sent to a nursing home (where it was lost) at the end of the study. The family of patient 17-008 in HD95-0801 disposed of study drug after the patient expired. Two patients in HD95-0802 (20-003 and 22-011) expired before accountability was performed, so that discrepancies were not explained.

9.733 Conclusions Regarding Abuse Potential: There were at least five of the 343 chronic pain patients (1.5%) that were treated with Palladone — in which inappropriate drug seeking behavior, hoarding or diversion of study drug supplies may have occurred. There were a number of others where the suspicion of such activity is less, but where drug abuse or misuse cannot be ruled out.

9.74 Human Reproduction Data

9.741 Pregnancy, Labor and Delivery

Hydromorphone hydrochloride is classified as Category C in the labeling for Dilaudid. It is known to be teratogenic in hamsters when given doses 600 times that of human dosage. No adequate and well-controlled were reported. The labeling allowed usage in pregnant women only if potential benefits outweigh risks to the fetus. Physical dependence and withdrawal effects that may be seen in neonates born to women taking opioids prior to delivery are considered nonteratogenic effects. These withdrawal effects include irritability, excessive crying, tremors, hyperactive reflexes, increased respiratory rate, increased stools, sneezing, yawning, vomiting and fever. Severity of symptoms may not correlate with duration or amount of maternal usage. Treatment with chlorpromazine 0.7-1.0 mg/kg q6h, phenobarbital 2 mg/kg q6h and paregoric 2-4 drops/kg q4h have been used to treat symptoms for periods of 4 to 28 days, with decreasing doses as tolerated. When opioids are used for women in labor, respiratory depression can occur in the neonate.

The sponsor carried out four animal reproductive toxicology studies with Palladone — There were slight increases in reduced ossification of hyoid bone and thoracic centrum variants in rats at 10 mg/kg/d. These effects were not observed at lower doses (5-10 mg/kg/d is roughly 2-4 x human dose). There was increased frequency of minor skeletal variations at 25-50 mg/kg/d and increased frequency of visceral and external variations and fetotoxicity at 50 mg/kg/d (approximately 10 x human dose) in rabbits. The Ames Test, Mouse Micronucleus Assay and inactivated Mouse Lymphoma Forward Mutation Assay were negative. Hydromorphone was positive at 200-1000 mcg/ml in the presence of metabolic activation in the Mouse Lymphoma Forward Mutation Assay, indicating slight risk of genotoxicity in humans.

9.742 Nursing

Labeling for Dilaudid products state that it is unknown whether hydromorphone appears in breast milk, but opioids have been detected in breast milk. There is also a statement that a decision should be made whether to discontinue nursing or discontinue the drug.

9.8 Pediatric Exposure

Safety and effectiveness of any hydromorphone product have not been established. No pediatric patients were studied in this NDA.

9.9 Conclusions Regarding Safety

The most frequent adverse events reported by chronic pain patients on Palladone — were somnolence, nausea, constipation, dizziness, vomiting, headache and pruritus. At least one adverse event was reported by 95% of patients in the three chronic pain trials.

There were 42 patients (29% of those who received study medication) who discontinued Palladone — because of adverse effects during the open-label phases of the crossover studies, indicating that Palladone — was not well tolerated by all cancer pain patients. There were 12 patients (3% of those who received study medication) on Palladone — with serious adverse events of possible drug relationship, occurring in the open-label titration phase of the pivotal studies. These resulted in hospitalizations and usually involved mental status changes or gastrointestinal effects.

There were 28 deaths, all in cancer patients, and all considered unlikely to be study drug-related by both investigators and the reviewer. There were 43 patients (13% of those receiving study medication) in the pivotal trials hospitalized for serious events; often these involved aspects of cancer progression. Serious adverse events were reported only in cancer patients. The incidences of serious events appeared to be higher in older patients and those with renal or hepatic impairment.

The overall incidence of adverse events occurring during the double-blind periods of the chronic pain trials was not significantly different between the two formulations (90.4% of the 209 patients on Palladone — and 92.8% of the 209 patients on immediate-release hydromorphone hydrochloride). Nor were there any clear cut differences noted with respect to incidence of types of events. No differences between the two formulations during the double-blind periods were evident with regard to deaths, serious adverse events or discontinuations for adverse events. It should be noted that conclusions regarding comparisons between formulations are limited by the relatively brief exposures during double-blind periods, the concomitant use of immediate-release hydromorphone and the potential for crossover effects.

Laboratory and other safety findings revealed no evident differences between the two formulations. There was more hypoxia or oxygen desaturation with Palladone — than with immediate-release hydromorphone hydrochloride in the postoperative study, but the difference in dosages used (24 mg of Palladone — and 6 mg of the other formulation) can account for this finding.

Although development of psychological abuse is infrequent in patients treated with opioids for analgesic purposes, there were five cases (1.5%) of possible inappropriate drug seeking behavior or diversion of drug supplies. There were a number of cases of discrepancies in returning drug supplies where there was no evidence of abuse.

Teratogenicity in animals at high doses has been observed for hydromorphone. There are no cases of pregnant or nursing women receiving Palladone — There has been no pediatric exposure for Palladone —

In conclusion, there were no evident differences in safety between Palladone — and immediate-release hydromorphone hydrochloride.

10.0 Labeling Review

The draft labeling submitted with the NDA was reviewed. Two adjustments of clinical nature are addressed below:

Effects of hepatic and renal impairment, gender, age and disease should be reworded, since effects have been observed in the clinical trials.

Dosage Section: Opioid-naïve patients should be started on immediate-release hydromorphone hydrochloride, rather than Palladone — since there is no data supporting safety of directly initiating opioid-naïve patients with Palladone —

11.0 Conclusions

Palladone — (12, 16, 24 and 32 mg) capsules when given every 24 hours and supplemented with escape medication (immediate-release hydromorphone hydrochloride) as needed was essentially equivalent in efficacy to immediate release hydromorphone (2 mg) tablets given every six hours and supplemented in the same way. The sustained release formulation was also similar to the immediate release formulation with respect to safety. Neither objective advantages or disadvantages of one formulation over the other could be clearly defined in terms of safety or efficacy.

The placebo-controlled, postoperative pain study intended to demonstrate analgesic efficacy of both sustained and immediate release formulations relative to placebo failed in this objective.

12.0 Recommendations

12.1 Approvability: Palladone — is approvable for the treatment of moderate to severe chronic pain in patients who need opioid analgesia.

12.2 Phase IV: No postmarketing trials were proposed by the sponsor. Studies should be carried out in populations of patients younger than 18 to define appropriate pediatric usage.

12.3

12.4 Demonstration of Efficacy relative to Placebo: *If the agency decides that a placebo-controlled demonstration of analgesic efficacy is needed for approval, it is recommended that such a study be carried out as a multiple dose trial in patients with chronic pain, with primary efficacy variable being use of an appropriate standardized rescue medication.*