CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

206627Orig1s000

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

BIOPHARMACEUTICS REVIEW Office of New Drugs Quality Assessment			
Application No.:	NDA 206627	**Reviewer:** Akm Khairuzzaman, Ph.D.	
Submission Date:	04/26/2014		
Division:	Division of Anesthesia, Analgesia, and Addiction Products	**Team Leader:** Tapash Ghosh, PhD	
Sponsor:	Purdue Pharma LP One Stamford Forum, 201 Tresser Blvd, Stamford, CT 06901-3431		
Trade Name:	Not proposed	**Date Assigned:**	05/01/2014
Generic Name:	Extended-release 24-hour hydrocodone bitartrate tablets	**Date of Review:**	07/30/2014
Indication:	Pain management	**Type of Submission:** Original NDA 505(b)2	
Formulation/strengths	Tablets: 20, 30, 40, 60, 80, 100, and 120 mg		
Route of Administration	Oral		

EXECUTING SUMMARY:

Hydrocodone is a semisynthetic opoid (Scheduled II narcotic, highly soluble) derived from either of two naturally occurring opiates: codine and thebine. It is well known in the pain management treatment for a long period of time and was actually first approved by the agency on March 23rd, 1943 with a brand name of Hycodan (NDA # 005213)[1]. The developed dosage form is a 24 hr. extended release tablet formulation in seven different strengths namely: 20, 30, 40, 60, 80, 100, and 120 mg. The reference listed drug product used for this NDA is Vicoprofen Tablet (7.5 mg/200 mg), NDA 20-716 which is a fixed dose combination product of hydrocodone and ibuprofen, respectively. This new formulation is a "(b) (4)" whereby (b) (4) utilized a polyethylene oxide (PEO)-based formulation platform which is the (b) (4) excipient in the product ((b) (4) that functions in release rate-control as well as for abuse-deterrence and resistance to alcohol-induced dose dumping purposes.

The Hydrocodone Bitartrate API is very soluble (> 90 mg/mL) across the bio-relevant pH range of pH 1.2 to 8.0. Dissolution was found to be a critical quality attribute for this extended release dosage form since three different formulations (fast, slow and medium) of 20 mg prototype tablet having different dissolution rate showed direct impact on C_{max} and T_{max} from a cross-over bioavailability study. The method is capable of distinguishing significant changes in a composition or manufacturing process and show similar trend of difference between the in vitro and in vivo results.

[1] Drugs@FDA—Approval History: Hycodan. FDA. Retrieved 2006-01-07.

One of the critical process related attribute for dissolution was found to be (b) (4) can lead to dissolution failure. As a result the applicant has developed in process control for (b) (4) It is to be noted that the applicant will be using a new (b) (4)

The dissolution method and limit proposed and recommended for approval for this application are as follows:

Approved Method: Apparatus: USP apparatus 1 with 10 mesh basket
Dissolution medium: 900 ml of simulated gastric fluid (SGF) without enzyme
Paddle speed: 100 rpm
Temperature: 37 °C
Analytical method: Reversed-phase high performance liquid chromatography (HPLC) with UV detection at 230 nm

Approved Dissolution Limit:

Time Point (hr.)	Proposed Specification (Range)	
	20, 30, 40, 60, 80 and 100mg tablets	120 mg tablets
4 12 20	(b) (4)	

RECOMMENDATION

The original NDA 206627 for Extended-release 24-hour hydrocodone bitartrate tablets (20, 30, 40, 60, 80, 100, and 120 mg) is recommended for **APPROVAL** from the Biopharmaceutics perspective.

Akm Khairuzzaman, Ph.D.
Biopharmaceutics Reviewer, ONDQA

Tapash Ghosh, Ph.D.
Biopharmaceutics Team Leader, ONDQA

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/s/

AKM KHAIRUZZAMAN
07/31/2014
Recommended for APPROVAL from the Biopharmaceutics perspective.

TAPASH K GHOSH
07/31/2014

CLINICAL PHARMACOLOGY REVIEW

NDA: 206627	Submission Date(s): 4/28/2014
Brand Name	Hysingla ER
Generic Name	Hydrocodone ER Tablets
Clinical Pharmacology Reviewer	Srikanth C. Nallani, Ph.D.
Team Leader	Yun Xu, Ph.D.
OCP Division	Division of Clinical Pharmacology II
OND Division	Anesthesia, Analgesia and Addiction Products
Sponsor	Purdue Pharma LP
Relevant IND(s)	059175
Submission Type; Code	505(b)(2); New Formulation
Formulation; Strength(s)	Extended Release Tablets; 20,30, 40, 60, 80,100, 120 mg
Indication	Management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate.
Proposed Dosage Regimen	Once daily

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1 Executive Summary

1.1 Recommendation

The submission is acceptable from a Clinical Pharmacology perspective provided that a mutually satisfactory agreement can be reached between the sponsor and the Agency regarding the language in the package insert.

1.2 Phase IV Commitments

None.

1.3 Summary of Clinical Pharmacology Findings

Purdue Pharma LP (PPLP) submitted a 505(b)(2) New Drug Application (NDA) extended-release formulation of single-entity hydrocodone bitartrate tablets (HYD or Hysingla ER) for the management of moderate to severe pain when a continuous, around the-clock opioid analgesic is needed for an extended period of time.

Purdue contends the following about this hydrocodone single entity product:

a) It is formulated for once daily administration.
b) Since hydrocodone is a schedule II controlled substance they formulated the extended release with formulation ingredients to make it abuse-deterrent.
c) They also contend that the non-opioid component as in current products (Oxycontin), permitting treatment of chronic pain requiring higher total daily opioid doses.

To support the 505(b)(2) NDA Purdue is relying on Agency's previous findings of safety and efficacy from Vicoprofen NDA 020716 an immediate release product containing hydrocodone and ibuprofen. Clinical Efficacy study HYD3002: Clinical efficacy of Hysingla ER was established in this randomized withdrawal study conducted in patients with chronic pain. Clinical Safety (Open-label) study HYD3003 evaluated safety of Hysingla ER administration over a 52-week period.

From a clinical pharmacology perspective, fifteen studies were conducted.

Absorption

After a single dose administration of 20, 40, 60, 80 and 120 mg Hysingla ER tablets, Hysingla ER yields a gradual increase in plasma hydrocodone concentrations with median Tmax ranging from 14 to 18 hours after single and multiple dosing. Systemic exposure (AUC and Cmax) increased linearly with doses from 20 to 120 mg. Both Cmax and AUC increased slightly more than dose proportionally. Mean plasma concentrations of hydrocodone increased slowly after oral administration of Hysingla ER extended-release tablets and reached a maximum concentration at 14 to 16 hours post-dose at all dose levels. However, it should be noted that in some individuals peak plasma levels were noted at 24 hour or up to 30 hours following single dose of Hysingla ER administration.

Figure: Mean Plasma Concentrations of Hydrocodone Versus Time on Linear Scale.

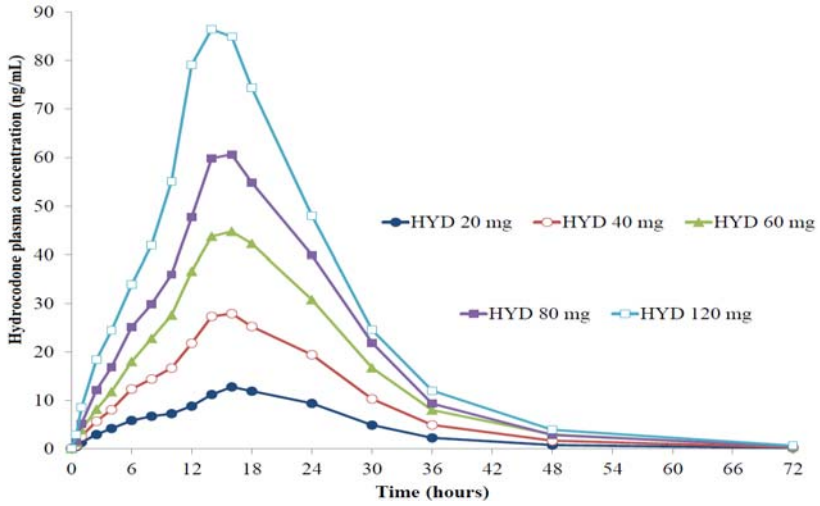
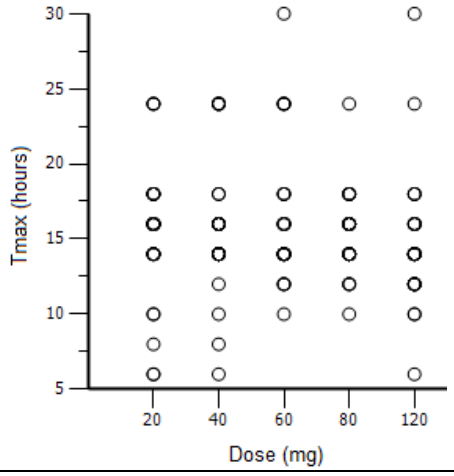


Table: Summary of Mean ± SD Plasma Hydrocodone Pharmacokinetic Metrics in Study HYD1004.

Metric (Unit)	HYD 20 mg N = 29	HYD 40 mg N = 31	HYD 60 mg N = 28	HYD 80 mg N = 30	HYD 120 mg N = 29
AUCinf (ng•h/mL)					
Mean	284.20	622.35	1009.05	1303.87	1787.17[a]
SD	127.683	251.949	294.073	375.133	678.736
%CV	44.93	40.48	29.14	28.77	37.98
Minimum, Maximum	30.56, 594.50	85.89, 1212.39	582.73, 1741.81	563.71, 2513.49	305.08, 3346.85
Cmax (ng/mL)					
Mean	14.56	33.88	53.64	69.09	109.78
SD	5.485	11.805	15.402	17.198	44.125
%CV	37.68	34.85	28.71	24.89	40.19
Minimum, Maximum	3.47, 26.20	7.60, 54.20	33.30, 83.00	39.90, 109.00	28.20, 199.00
Tmax (h)					
Mean	15.38	15.81	16.44	15.40	14.70
SD	4.476	4.422	4.660	2.580	4.359
%CV	29.10	27.97	28.36	16.76	29.65
Median	16.00	16.00	14.07	16.00	14.00
Minimum, Maximum	6.00, 24.00	6.02, 24.00	10.00, 30.00	10.00, 24.00	6.00, 30.00

Additionally, it is noteworthy that %CV in AUC and Cmax may be 40% or less for any given dose, but the range of systemic exposure it translates to is very high as the dose increases to 120 mg (Note the Minimum, Maximum value for each PK parameter as the dose increases).

Figure: The range of Tmax (hours) noted with different strengths of Hysingla ER following single dose administration in study HYD1004.



Food-effect: Hydrocodone Cmax was higher (54%) under high fat conditions relative to fasting conditions; however, hydrocodone AUC with Hysingla ER 120 mg tablets was only 20% higher when coadministered with a high fat meal. Both Cmax and AUC of hydrocodone with Hysingla ER 120 mg tablets were similar under low fat conditions relative to fasting conditions (17% and 9% higher, respectively). Upon consumption with high-fat meal the inter-individual variability (AUC %CV = 24%) of Hysingla ER Cmax and AUC decreased compared to fasting condition (AUC %CV = 37%). This observation suggests factors affecting GI transit, such as high-fat meal consumption, could affect Hysingla ER bioavailability. Four individuals (1021, 1034, 1074, 1085) had very low bioavailability under fasting condition compared to the rest of the subjects in the study, possibly due to emesis (1 subject 1021 documented and three not reported); while their plasma hydrocodone levels were higher after high-fat treatment and comparable to the rest of the subjects. Amongst these individuals, two subjects had 8-fold higher Cmax after high-fat meal compared to the low plasma levels noted under fasting condition. The magnitude of AUC increase after high-fat meal was similar to that of Cmax, and the Tmax values were delayed after high-fat meal in these four subjects, which indicates the PK changes observed were due to increased bioavailability under fed status.

Table: Summary of Plasma Pharmacokinetic Metrics of Hydrocodone (HYD1003).

Metric (Unit)	HYD 120 mg Fasted N = 51	HYD 120 mg High Fat Meal N = 51	HYD 120 mg Low Fat Meal N = 49
AUCinf (ng•h/mL)			
Mean	1639.56	1782.07	1674.86
SD	604.654	416.781	506.357
%CV	36.9	23.4	30.2
Minimum, Maximum	197.66, 2946.81	1298.50, 3169.87	310.33, 3142.86
Cmax (ng/mL)			
Mean	101.46	145.63	112.29
SD	44.894	46.748	41.358
%CV	44.2	32.1	36.8
Minimum, Maximum	17.70, 256.00	71.90, 281.00	26.00, 285.00
Tmax (h)			
Mean	14.32	14.40	13.64
SD	3.948	3.228	2.699
%CV	27.6	22.4	19.8
Median	14.00	14.00	14.00
Minimum, Maximum	4.00, 24.00	10.00, 24.07	6.00, 18.02

The controlled clinical trial HYD3002, and open-label safety study HYD3003 were conducted in patients who consumed Hysingla ER tablets without regard to food consumption. However, these clinical trials employed a 3-5 day titration period before increasing the dose. Due to the exposure increase after high-fat meal observed in some subjects mentioned in the previous paragraph, it is best if food consumption is consistent at the time of Hysingla ER administration along with the 3-5 day titration period to ensure compliance and improve safety. In addition, it is also best if patients maintain a consistent meal type only at the time of Hysingla ER consumption during maintenance dosing (after titration).

Dosage-form proportionality: In study HYD1001, there was a single-dose, 2-period, 2-way crossover design iteration/cohort that evaluated the dosage-form proportionality. AUC and Cmax of hydrocodone following the administration of a Hysingla ER 1 x 80-mg tablet and Hysingla ER 4 x 20-mg tablets were comparable.

Distribution: Following administration of hydrocodone to healthy subjects, the mean apparent volume of central compartment (Vc/F) was 402 L, suggesting extensive tissue distribution. The extent of in vivo binding of hydrocodone to human plasma proteins was minimal with a mean percent bound of 36%.

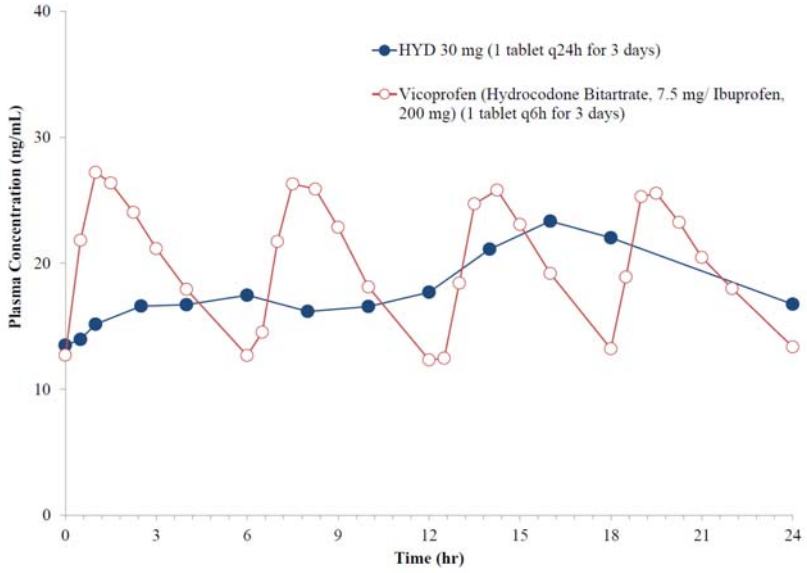
Metabolism: Hydrocodone exhibits extensive metabolism, including CYP3A4, CYP2D6 and 6-keto reduction. CYP3A4 mediated N-demethylation yields norhydrocodone (major metabolite) and CYP2D6 mediated O-demethylation yields hydromorphone (minor metabolite) and 6-keto reduction to the corresponding 6-α- and 6-β-hydroxy metabolites. Some extent of CYP2B6 and CYP2C19 involvement was also noted in the formation of norhydrocodone and hydromorphone. Taken together, multiple hepatic metabolic enzymes appear to be involved in clearing hydrocodone in to different metabolites.

Elimination: Approximately 6.5% of the administered oral dose of hydrocodone administered as HYD is excreted as unchanged hydrocodone in urine. The mean terminal half-life (t1/2) was similar for all HYD dose strengths ranging from approximately 7 to 9 hours in healthy subjects across the range of doses. Steady state of plasma hydrocodone concentrations were attained by day 2 of once-daily dosing of HYD. The extent of accumulation of systemic exposure was low (1.3 fold). The mean t1/2 at steady state was 7 hours.

Relative bioavailability to the listed drug Vicoprofen

Relative bioavailability study HYD1016 was conducted to fulfill the 505(b)(2) requirement for the NDA submission. The systemic exposure (AUC24,ss) and average plasma concentration of hydrocodone (Cavg,ss) at steady state following the administration of Hysingla ER 30 mg every 24 hours was equivalent to that following Vicoprofen (7.5 mg hydrocodone bitartrate /200 mg ibuprofen) administered every 6 hours for 3 days. The mean hydrocodone exposure (Cmaxss) following Hysingla ER 30 mg administration was lower (18%) compared to that noted with Vicoprofen 7.5 mg administered four times daily.

Figure: Mean Hydrocodone Plasma Concentration Versus Time Profiles for Hysingla ER 30-mg tablet and Vicoprofen (hydrocodone bitartrate 7.5 mg/ibuprofen 200 mg) at Steady State in Study HYD1016



Source: Adapted from CSR HYD1016, Figure 11-1.

Fluctuation in plasma levels of hydrocodone:

Fluctuation is usually used to characterize the difference between peak and trough concentration within one dosing interval at steady state. Fluctuation in plasma levels is expected even after steady-state is achieved after repeated dosing of a drug product. Percentage fluctuation and percentage swing are generally very high for immediate release product as noted with Vicoprofen IR in study HYD1016 (See table below). Controlled release products are typically developed to reduce the fluctuation and swing in plasma levels. Despite being controlled-release products, approved opioid ERLA products indicated for twice daily administration are expected to have some fluctuation in plasma concentration. However, the proposed product is indicated for once daily administration and the general expectation would be one that the product that would yield relatively stable plasma concentration over a 24 hour dosing period. Variability in plasma systemic exposure in terms of fluctuation is discussed below.

For reference, % fluctuation and % Swing were calculated as follows:
% Fluctuation The range of plasma concentration values during steady state relative to $C_{ss,avg}$: $(C_{ss,max}-C_{ss,min})$ *100 /$C_{ss,avg}$.
% Swing: The range of plasma concentration values during steady state relative to Css,min: $(C_{ss,max}-C_{ss,min})$*100/ $C_{ss,min}$

Following Hysingla ER administration for 3 days (Study HYD1016), the average % fluctuation was 60% and % swing was 88% (See Table below), lower than Vicoprofen (7.5 mg hydrocodone bitartrate/200 mg ibuprofen) dosed every 6 hour for 3 days. However, % fluctuation and % Swing for Hysingla ER 120 mg at steady-state were 98% and 286% **on average** (Study HYD1002). Although the data is from across different studies, it is still noteworthy.

Table: Summary of Day 3 Mean ± SD Plasma Pharmacokinetics of Hydrocodone in Study HYD1016.

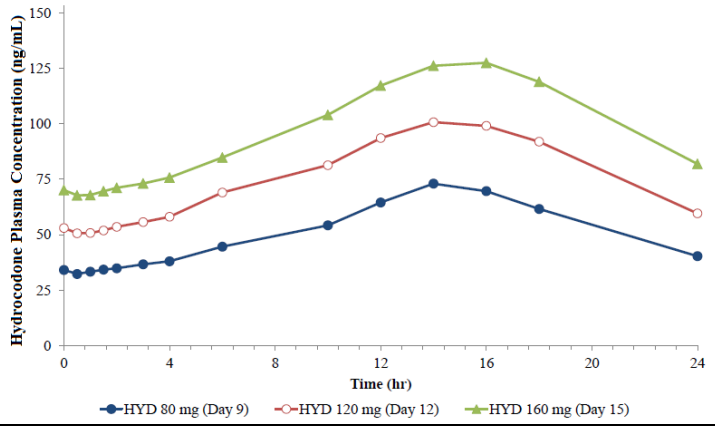
Metric (unit)	HYD (30 mg every 24h for 3 days) N = 22	Vicoprofen (every 6h for 3 days) N = 23
AUC24,ss (ng•h/mL)	443 ± 128	470 ± 111
AUCinf,ss (ng•h/mL)	602 ± 162	559 ± 141
Cmax,ss (ng/mL)	26.4 ± 7.4	31.6 ± 6.6
Tmax,ss[a] (h)	16.0 (1.0, 24.0)	1.5 (0.50, 19.5)
Cavg,ss (ng/mL)	18.4 ± 5.3	19.6 ± 4.6
Cmin,ss (ng/mL)	16.7 ± 5.2	13.4 ± 4.0
t1/2,ss (h)	8.3 ± 2.4	4.8 ± 0.64
%Fluctuation	60.5[b] ± 30.2	96.3 ± 26.8
%Swing	88.3[b] ± 85.9	148 ± 58.7

Source: CSR HYD1016, Table 11-2.
SD=standard deviation.
Note: Cmin,ss represents the concentration at 24 hours after the morning dose on Day 3.
[a] Median (minimum, maximum).
[b] N = 18.

Thorough QT (TQT) study (HYD1009) employed steady titration from Hysingla ER 20 mg to 160 mg ER over a period of 15 days. PK of hydrocodone following Hysingla ER 80 mg on Day 9, 120 mg on Day 12 and 160 mg on Day 15 each at steady-state were evaluated. Hysingla ER 80 mg showed an average %fluctuation and % swing 105% and 245%, respectively at steady-state dosing. As noted in study HYD1002, Hysingla ER 120 mg administered over three days (to steady-state) showed an average %fluctuation and % swing 102% and 220%, respectively. On an average, the PK parameters at steady-state indicate dose-proportionality between the 80 to 160 mg doses of Hysingla ER employed in the TQT study. It is noteworthy that plasma PK parameters overlap to some extent between 80 mg, 120 mg and 160 mg. In other words, some individuals taking 120 mg may experience plasma levels comparable to average plasma levels noted with 160 mg dose.

Table: Summary of Mean ± SD Plasma Hydrocodone Pharmacokinetic Metrics in TQT Study HYD1009.

	AUC0-24,ss (hr*ng/mL)	**Cmax,ss (ng/mL)**	**Tmax,ss (hr)**	**Cmin,ss (ng/mL)**	**Cavg,ss (ng/mL)**	**%Fluctuation**	**%Swing**
Hysingla ER 80 mg Day 9							
N	77	77	77	77	77	77.00	77
Mean	1252.49	82.62	14.96	28.21	52.19	105.20	245
SD	352.038	25.732	3.321	12.041	14.668	33.00	245
Median	1169.73	77.30	14.00	26.50	48.74	106.40	194
Minimum	637.51	37.50	10.00	4.05	26.56	35.65	44
Maximum	2358.64	175.00	23.92	59.90	98.28	213.80	1875
Geometric Mean	1206.66	79.03	-	25.19	50.28	99.86	193
Hysingla ER 120 mg Day 12							
N	75	75	75	75	75	75	75
Mean	1844.10	122.12	14.51	43.51	76.84	102.72	220
SD	542.945	43.259	3.945	17.479	22.623	34.31	241
Median	1763.33	115.00	14.00	41.80	73.47	102.27	176
Minimum	842.31	51.70	0.00	0.48	35.10	45.30	60
Maximum	3358.29	312.00	23.97	94.10	139.93	185.67	2073*
Geometric Mean	1771.02	115.80	-	38.02	73.79	97.06	176
Hysingla ER 160 mg Day 15							
N	73	73	73	73	73	73	73
Mean	2380.47	151.05	14.67	57.79	99.19	94.56	222.56
SD	733.371	52.393	4.169	26.261	30.557	36.69	237.21
Median	2222.37	146.00	14.00	53.30	92.60	86.93	163.61
Minimum	1282.06	66.90	0.00	7.65	53.42	29.37	33.33
Maximum	4764.17	337.00	23.92	132.00	198.51	185.20	1298.69
Geometric Mean	2280.08	142.81	.	51.44	95.00	87.41	161.45

Figure: Mean hydrocodone plasma concentration vs time following steady-state dosing of Hysingla ER 80 mg (Closed Circles), 120 mg (Open circles) and 160 mg (Triangles) in TQT study HYD1009.	

Intrinsic Factor PK Studies

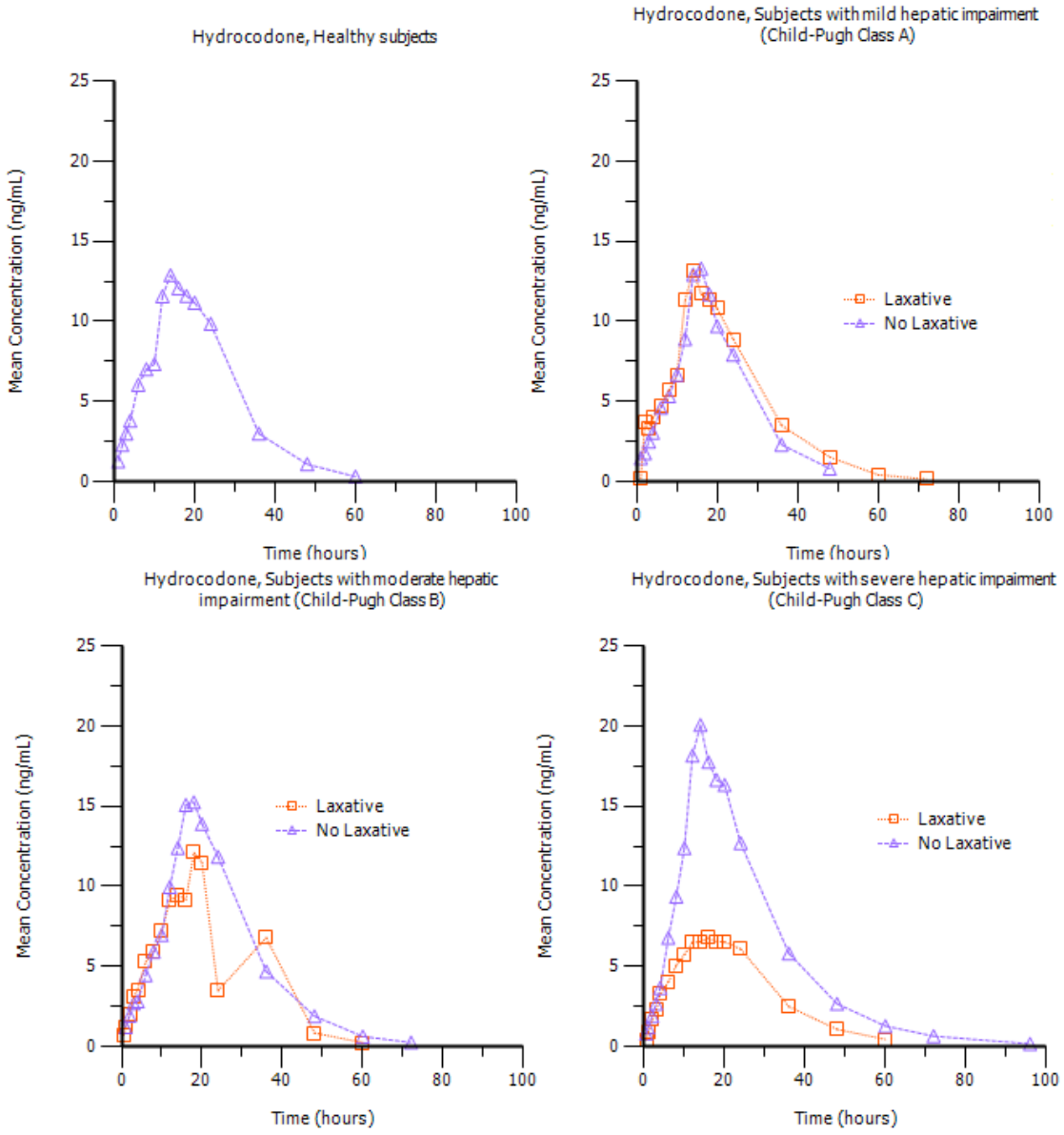
Age and Gender: The PK of hydrocodone in healthy elderly subjects (65 to 77 years old) following administration of Hysingla ER 40 mg are similar to the PK in healthy young subjects (20 to 45 years old). The slightly higher exposure to hydrocodone in elderly subjects in terms of Cmax (16%) and AUC (15%) compared to young subjects is not considered clinically meaningful. Systemic exposure to hydrocodone (Cmax and AUC) was comparable in male and female subjects.

Hepatic impairment study (HYD1007): As presented by the sponsor, data from study HYD1007 indicated that patients with mild, moderate and severe hepatic impairment did not show higher plasma concentrations (on average) than those with normal hepatic function. However, upon closer scrutiny it was observed that four out of eight patients with severe hepatic impairment had received lactulose, a strong laxative also used to manage complications of hepatic encephalopathy. In these three subjects systemic exposure of hydrocodone was lower compared to other patients with severe hepatic impairment or with respect to average healthy volunteers. Compared to subjects with normal hepatic function, hydrocodone Cmax values were lower by 6% and higher by 5% and 5% and AUC values were lower by 14%, and higher by 13% and 4% in patients with mild, moderate or severe hepatic impairment, respectively. However, after considering the potential confounding effect of strong laxative on PK Hysingla in severe HI patients, it was observed that AUC and Cmax in severe HI patients without Laxative use were higher by 50%, compared to healthy volunteers.

Table: Summary of Mean ± SD Plasma Pharmacokinetic Metrics of Hydrocodone in Healthy Subjects and Subjects with Hepatic Impairment in Study HYD1007

Variable	Treatment Group	Laxative	N	Mean	SD	Min	Median	Max
AUC0-inf	Healthy	No Laxative	8	341.55	36.83	297.34	337.97	414.19
AUC0-inf	Mild HI	Laxative	1	315.42	.	315.42	315.42	315.42
AUC0-inf	Mild HI	No Laxative	7	309.95	123.92	191.44	281.87	576.04
AUC0-inf	Moderate HI	Laxative	2	345.84	89.66	282.44	345.84	409.24
AUC0-inf	Moderate HI	No Laxative	6	404.62	66.51	329.22	398.77	528.10
AUC0-inf	Severe HI	Laxative	4	303.90	240.42	99.61	240.92	634.13
AUC0-inf	Severe HI	No Laxative	4	525.86	54.62	461.01	533.41	575.63
Cmax	Healthy	No Laxative	8	15.99	5.00	8.34	15.85	25.5
Cmax	Mild HI	Laxative	1	13.20	.	13.2	13.2	13.2
Cmax	Mild HI	No Laxative	7	15.55	5.95	8.72	14.9	25.9
Cmax	Moderate HI	Laxative	2	16.21	9.19	9.71	16.205	22.7
Cmax	Moderate HI	No Laxative	6	17.32	5.57	11.1	16.85	24.4
Cmax	Severe HI	Laxative	4	12.39	6.81	5.92	11.165	21.3
Cmax	Severe HI	No Laxative	4	24.35	7.13	13.9	27.15	29.2
Tmax	Healthy	No Laxative	8	18	4.54	12	18	24
Tmax	Mild HI	Laxative	1	14	-	14	14	14
Tmax	Mild HI	No Laxative	7	14.6	1.51	12	14	16
Tmax	Moderate HI	Laxative	2	19	7.07	14	19	24
Tmax	Moderate HI	No Laxative	6	17.3	3.72	14	17	24
Tmax	Severe HI	Laxative	4	15.5	7	8	15	24
Tmax	Severe HI	No Laxative	4	15.5	3	14	14	20

Figure: Hydrocodone (Geometric mean) Plasma Concentration over Time in Healthy Subjects and Patients with Mild, Moderate or Severe Hepatic Impairment with Concomitant Administration of a Laxative (Square).



Taken together, patients with severe hepatic impairment requiring concomitant use of Hysingla with lactulose for the management of constipation or hepatic encephalopathysymptoms, may have lower exposure to hydrocodone.

Renal impairment study (HYD1008):
Patients with renal impairment have higher plasma concentrations (AUC) than those with normal renal function. Low initial dose of Hysingla ER should be used in patients with renal impairment and patients should be monitored closely for adverse events such as respiratory depression. Compared to subjects with normal renal function, hydrocodone Cmax values were higher by 14%, 23%, 11% and lower by 13% and AUC values were higher by 13%, 61%, 57% and 4% in patients with mild, moderate or severe renal impairment or end stage renal disease, respectively.

Table: Summary of Mean ± SD Plasma Hydrocodone Pharmacokinetic Metrics in Renal Impairment Study HYD1008

		Subjects with Renal Impairment				
Metric (Unit)	**Healthy N = 8[a]**	**Mild N = 9**	**Moderate N = 6**	**Severe N = 8**	**ESRD w/dialysis N = 8**	**ESRD w/o dialysis N = 6**
AUCt (h•ng/mL)	738 ± 138	938 ± 388	1217 ± 305	1209 ± 394	922 ± 466	1085 ± 264
AUCinf (h•ng/mL)	754 ± 155	942 ± 389	1222 ± 306	1220 ± 397	932 ± 471	–
AUC0-72 (h•ng/mL)	735 ± 135	–	–	–	–	1085 ± 264
Cmax (ng/mL)	39.6 ± 6.8	49.7 ± 21.9	50.8 ± 18.2	45.5 ± 15.3	38.4 ± 16.6	50.6 ± 19.1
Tmax (h)[b]	19.0 (14, 24)	14.0 (10, 24)	17.0 (14, 24)	20.0 (14, 48)	16.0 (6, 24)	18.0 (12, 20)
t1/2 (h)	8.0 ± 3.6	14.5 ± 17.5	14.4 ± 15.0	34.2 ± 11.6	27.0 ± 13.0	–
CL/F (L/h)	82.7 ± 18.3	89.4 ± 83.2	51.8 ± 12.8	54.9 ± 21.6	104 ± 98.8	–
Vd/F (L)	916 ± 328	1604 ± 1724	1175 ± 1463	2854 ± 1833	3692 ± 3685	–

Source: CSR study HYD1008, Table 11-2.
ESRD=end-stage renal disease; w/=with; w/o=without.
[a] N = 6 for AUCinf, t1/2, CL/F, and Vd/F.
[b] median (minimum, maximum).

Extrinsic Factor Studies:

CYP3A4 interaction study: Hydrocodone exposure increased 2-fold when coadministered with strong CYP3A4 ketoconazole (study HYD1012). Dose reduction or monitoring patient for adverse events is needed as appropriate when patients on already on CYP3A4 inhibitors need Hysingla ER or patients on Hysingla ER need to take CYP3A4 inhibitors.

CYP2D6 Interaction study: Hydrocodone exposure did not change significantly when coadministered with strong CYP2D6 inhibitor paroxetine (HYD1005). From a pharmacokinetic perspective, dose adjustment may not be needed when coadministration of Hysingla ER is considered with CYP2D6 inhibitors. However, other clinical safety considerations may be required when coadministering two centrally acting agents.

In vitro CYP inhibition drug interaction potential study (HCDDR-02-073-0) revealed that hydrocodone does not inhibit major CYP enzymes.

There was no in vitro evidence of rapid or unexpectedly high rate of hydrocodone release for both 20 and 120 mg Hysingla ER tablets in the presence of ethanol. Therefore, in vivo alcohol interaction study was not conducted.

Pharmacodynamic Studies:
Thorough QTc study (HYD1009)

There was no evident exposure-response relationship for change in QTcI based on hydrocodone concentration. However, it seems there are positive trends in exposure-response relationships for change in QTcI based on HYD metabolite norhydrocodone or hydromorphone concentration.

Table: The Point Estimates and the 90% CIs Corresponding to the Largest Upper Bounds for HYD (80mg, 120 mg and 160 mg) and the Largest Lower Bound for Moxifloxacin (FDA Analysis)

Treatment Group	Time (hour)	ΔΔQTcI (ms)	90% CI (ms)
HYD 80 mg (Day 9)	24	5.6	(2.7, 8.5)
HYD 120 mg (Day 12)	24	6.9	(3.6, 10.2)
HYD 160 mg (Day 15)	10	9.9	(7.1, 12.7)
Moxifloxacin 400 mg (Day 9)*	3	11.6	(8.8, 14.5)
Moxifloxacin 400 mg (Day 12)*	3	9.7	(6.2, 13.2)
Moxifloxacin 400 mg (Day 15)*	4	8.7	(5.5, 11.8)

* Multiple endpoint adjustment was not applied. The largest lower bound after Bonferroni adjustment for 4 time points are 7.7 ms, 4.9 ms, and 4.3 ms on Days 9, 12 and 15; respectively.

Pharmacodynamic studies evaluating performance of Hysingla under conditions of misuse and abuse: clinical abuse potential/liability studies

Extended release characteristics of Hysingla ER tablet are defeated upon chewing, crushing (milling) following oral administration, and after crushing followed by intranasal administration. However, systemic absorption of hydrocodone is low following intranasal abuse compared to hydrocodone powder.

Oral abuse potential study HYD1013 in opioid non-dependent recreational users

Study HYD1013 evaluated the abuse potential, pharmacokinetics, and safety oral milled, chewed and Intact Hysingla ER tablets in recreational opioid users. Mean Cmax of hydrocodone was highest following the hydrocodone solution (127 ng/mL). Cmax values were lower following milled Hysingla ER (81.0 ng/mL) and chewed Hysingla ER (67.3 ng/mL) and lowest following intact Hysingla ER (48.4 ng/mL). Median Tmax of hydrocodone was 1.1 hours following the hydrocodone solution, was observed later following milled Hysingla ER (1.6 hours) and chewed Hysingla ER (8.0 hours) and latest following intact Hysingla ER (15.1 hours). This clearly indicates that extended-release characteristics of Hysingla ER tablets are defeated after chewing and crushing followed by oral consumption; however, Hysingla ER product may offer some resistance chewing related opioid abuse. Nevertheless, the product does not deter aggressive methods of crushing the product for oral abuse.
Corresponding with the pharmacokinetics of hydrocodone, highest "at the moment" drug liking effects were noted following administration of hydrocodone solution followed by milled, chewed and intact Hysingla ER products administered orally; the time to peak drug liking VAS was a median value of 1 hr, 1.5 hr, 3 hr, and 3 hr, respectively.

Figure: Mean Hydrocodone Plasma Concentrations Versus Time (Oral Administration) in Study HYD1013.

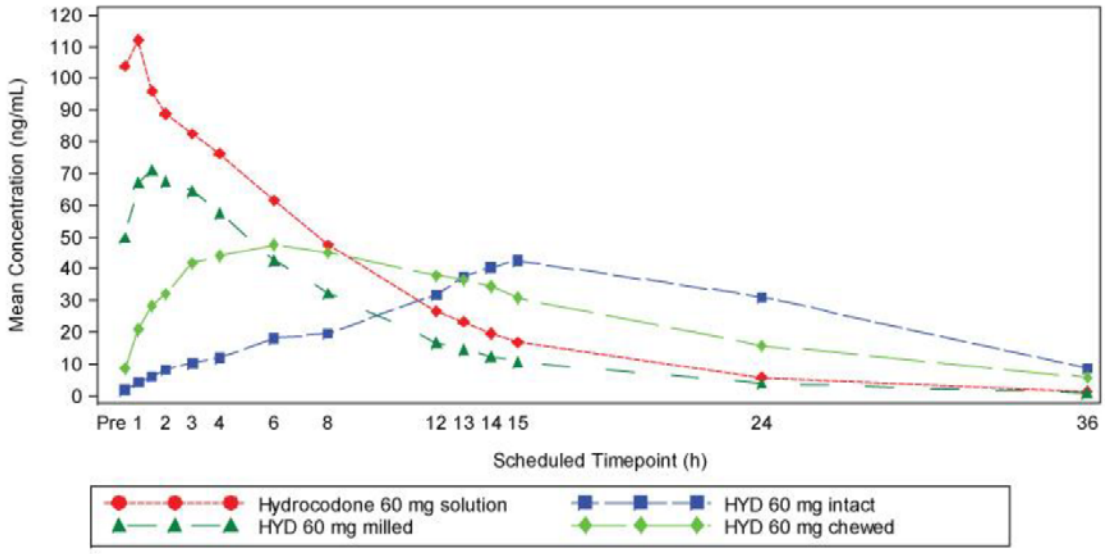
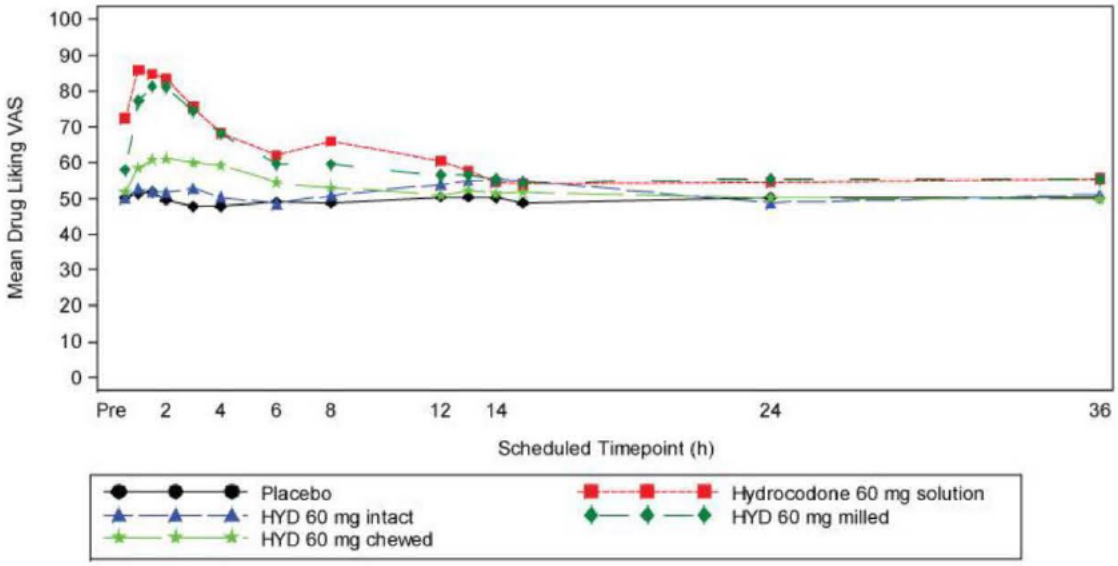


Figure: Mean Scores Over Time for Drug Liking VAS (Oral Administration, Chewed, Milled and Intact) in Study HYD1013.

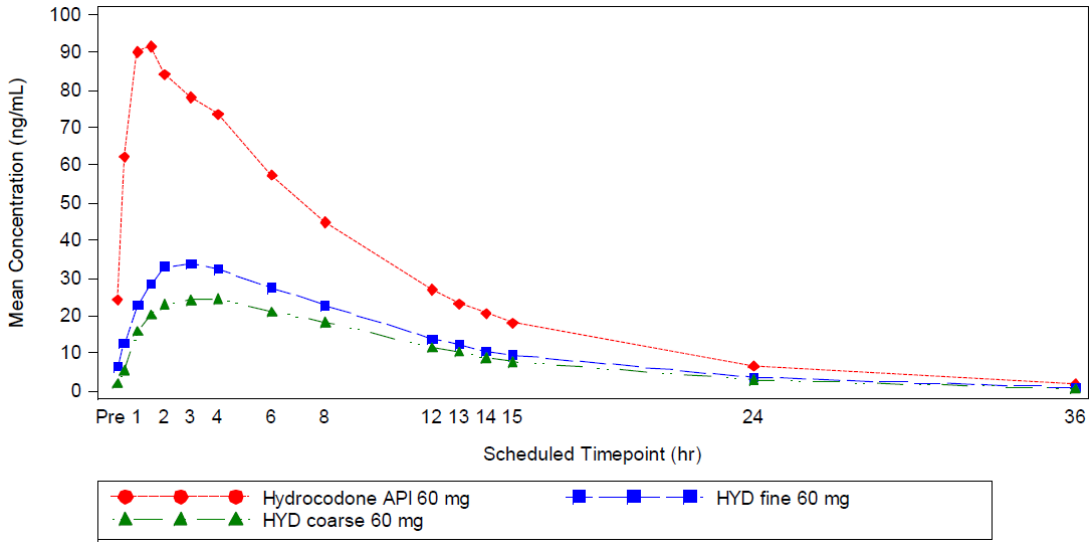


Intranasal abuse potential study HYD1014

Study hyd1014 evaluated abuse potential, pharmacokinetics, and safety study of crushed (fine or coarse) and intranasally administered Hysingla ER tablets in recreational opioid users with a history of intranasal abuse. Mean Cmax values of hydrocodone were considerably lower following Hysingla ER fine (36.5 ng/mL) and Hysingla ER coarse (27.5 ng/mL) than following hydrocodone powder (106 ng/mL), which may be related to the lower percentage of the dose observed to have been inhaled for Hysingla ER fine and Hysingla ER coarse than for hydrocodone API powder. Additionally, median Tmax was also observed later following Hysingla ER fine (3.1 hours) and Hysingla ER coarse (4.1 hours) than following hydrocodone API powder (1.6 hours).

The mean AUC_{last} value of hydrocodone was slightly higher following Hysingla ER fine (411.7 h*ng/mL) than following Hysingla ER coarse (317.9 h*ng/mL), but the standard deviations were large (205.65 and 292.66 h*ng/mL, respectively), indicating large variation between subjects. The mean AUC_{last} values following Hysingla ER fine and Hysingla ER coarse were considerably lower than the AUC_{last} value for hydrocodone powder (902.3 h*ng/mL). The results were similar for AUC_{inf}. Median t½ was approximately 6 hours following all 3 treatments.

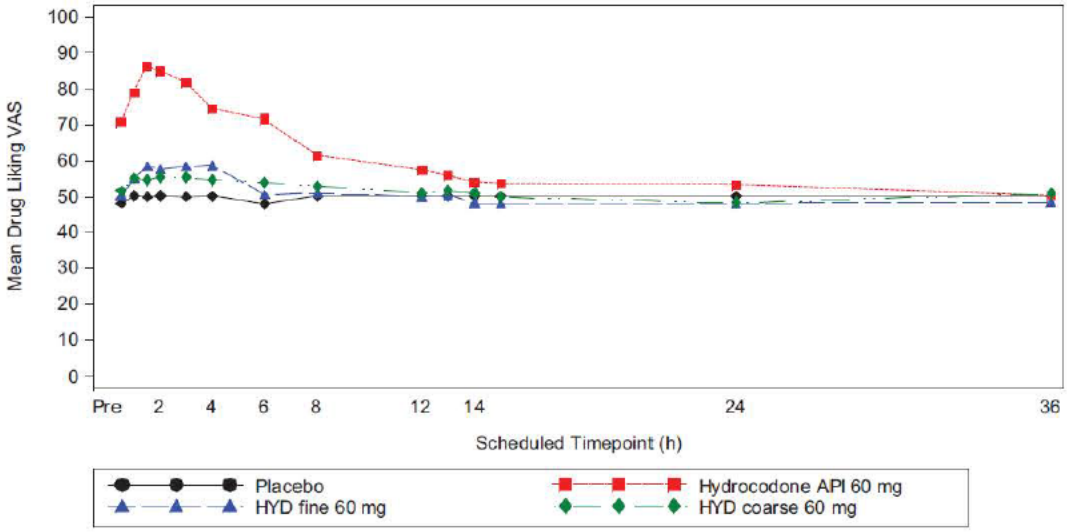
Figure: Mean Hydrocodone Plasma Concentrations Versus Time following Intranasal Administration of Hysingla ER fine powder (Squares), coarse powder (Triangles) compared to hydrocodone powder (Circles) in Study HYD1014



There were statistically significant differences between placebo and hydrocodone powder for the primary measures of Drug Liking VAS. Relative to hydrocodone API powder, Hysingla ER coarse particle size and Hysingla ER fine particle size were associated with significantly lower effects on all subjective and objective measures, including both primary endpoints, and both Hysingla ER treatments were associated with greater intranasal effects, especially measures of nasal congestion and irritation. Crushed Hysingla ER fine particle size appeared to be associated with greater nasal congestion compared to Hysingla ER coarse particle size, but on most other outcome measures, the 2 treatments were not statistically different. The majority of subjects (>50%) showed at least a 30% reduction in Drug Liking VAS scores (responders) following administration

of Hysingla ER coarse particle size and at least a 40% reduction in Drug Liking VAS scores following administration of Hysingla ER fine particle size.

Figure: Mean Scores Over Time for Drug Liking VAS following Intranasal Administration of Fine Hysingla ER (Triangle) and Coarse Particle Size Hysingla ER (Diamond) compared to hydrocodone powder (Squares) and placebo (Circles) in Study HYD1014.



Labeling:

Physicians and patients should be aware that the peak plasma levels of hydrocodone may result after 14 – 16 hours (Range 6 – 30 hours) following Hysingla ER tablet administration. Patients should know that blood levels of hydrocodone, in some patients, may be high enough beyond the 24 hours after use to impair activities that require alertness, including driving. Patients should pay adequate attention to take Hysingla ER at a consistent time every day to maintain a once every twenty four hour dosing.

Patients should adhere to the physician prescribed titration regimen. If patients experience breakthrough pain during maintenance therapy, patients **must not** attempt dosage adjustment (increase) with Hysingla ER alone, as it may not alleviate the pain immediately. In case of breakthrough pain, patients may require rescue medication with an immediate-release opioid or non-opioid analgesic as prescribed by the physician.

Patients with renal impairment have higher plasma concentrations (AUC) than those with normal renal function. Low initial dose of Hysingla ER should be used in patients with renal impairment and patients should be monitored closely for adverse events such as respiratory depression.

Patients with mild, moderate hepatic impairment did not show higher plasma concentrations (on average) than those with normal hepatic function. Patients with severe hepatic impairment may have higher plasma concentrations than those with normal hepatic function. No adjustment in starting dose with HYSINGLA ER is required in patients with mild or moderate hepatic impairment. Use a low initial dose of HYSINGLA ER in patients with severe hepatic impairment and monitor closely for adverse events such as respiratory depression.

Hydrocodone exposure increased 2-fold when coadministered with strong CYP3A4 inhibitor ketoconazole. Dose reduction and or monitoring patient for adverse events is needed as appropriate when patients already on CYP3A4 inhibitors need Hysingla ER or patients on Hysingla ER need to take CYP3A4 inhibitors.

Based on a discussion held at the Required Inter-divisional Level Clinical Pharmacology briefing on 7/21/2014, it was decided that the effect of lactulose on Hysingla ER PK should be described in the product label, in lieu of any further investigation. Concomitant use of Hysingla ER with strong laxatives or drugs that rapidly increase GI motility may decrease hydrocodone absorption resulting in decreased plasma levels. If adequate pain relief is not achieved, rescue medication (opioid/non-opioid) may be necessary before the next dose of Hysingla ER.

2 QBR

2.1 General Attributes

Regulatory Background.

Purdue Pharma LP (PPLP) submitted a 505(b)(2) New Drug Application (NDA) for extended-release (ER) formulation of single-entity hydrocodone bitartrate tablets (Hysingla ER) for the management of moderate to severe pain when a continuous, around the-clock opioid analgesic is needed for an extended period of time. To support the 5050(b)(2) NDA Purdue is relying on Agency's previous findings of safety and efficacy from Vicoprofen NDA 020716 an immediate release product containing hydrocodone and ibuprofen.

This has not been approved anywhere else in the world.

What are the proposed mechanism of action and therapeutic indication?

Hydrocodone is a semi-synthetic opioid analgesic with anti-tussive properties. Hysingla ER is indicated for the management of moderate to severe pain when a continuous, around the-clock opioid analgesic is needed for an extended period of time. Hydrocodone is a μ-opioid receptor agonist in brain and spinal cord. Other pharmacological effects of hydrocodone include euphoria, respiratory depression and physiological dependence.

What are the highlights of the chemistry and physical-chemical properties of the drug substance, and the formulation of the drug product?

Hysingla ER contains polyethylene oxide used in other opioid extended release long acting (ERLA) products such as OxyContin, proposed to allow for controlled release of hydrocodone. Hysingla ER tablet formulation strengths proposed for marketing include 20, 30, 40, 60, 80, 100, and 120 mg. Additionally, several *in vitro* manipulation and extraction studies, and two clinical abuse liability studies were conducted to support claims of abuse deterrence via intravenous, intranasal abuse of their opioid ERLA product.

What are the proposed dosage and route of administration?

Hysingla ER tablets are proposed to be used once daily following oral administration. This is the first NDA with a proposal to market a hydrocodone product as a single entity with once daily dosing regimen. The reference drug Vicoprofen or other drug product such as Vicodin are a combination product of hydrocodone and ibuprofen (Vicoprofen) or hydrocodone and acetaminophen (Vicodin) to be administered four to six times daily as needed. The highest dose of hydrocodone with the combination products is usually limited by the dosing limitation/restriction of the NSAID.

2.2 General Clinical Pharmacology

Because Hysingla ER is a single entity hydrocodone product with once daily administration regimen, clinical efficacy study was conducted (HYD3002) and additional safety was also evaluated in study HYD3003 for about one year. Clinical efficacy was established in a randomized withdrawal study HYD3002 reviewed by medical officer Dr. Jackie Spaulding. To support the 505(b)(2) NDA Purdue is relying on Agency's previous findings of safety and efficacy from Vicoprofen NDA 020716 an immediate release product containing hydrocodone and ibuprofen. From a clinical pharmacology perspective, fifteen studies were conducted.

Two clinical abuse potential/liability studies

1. Oral abuse potential study HYD1013
2. Intranasal abuse potential study HYD1014

Bioavailability Studies

3. A study comparing relative BA of Hysingla ER with Vicoprofen® immediate release (study HYD1016).
4. Multiple dose PK study (HYD1002),
5. Dose proportionality study (HYD1004),
6. Study of relative BA of different formulations and strengths (HYD1001)
7. Food-effect study (study HYD1003)

Intrinsic Factor PK Studies:

8. Study evaluating effect of age and gender (HYD1006),
9. Hepatic impairment study (HYD1007),
10. Renal impairment study (HYD1008),

Extrinsic Factor Studies:

11. HCDDR-02-102-0: In vitro Study for Identification Of Cytochrome P450 Isoforms Responsible For Hydrocodone Bitartarate Metabolism In Human Liver Microsomes
12. HCDDR-02-073-0: In vitro CYP inhibition drug interaction potential study
13. Drug-drug interaction study CYP2D6 inhibitor paroxetine (HYD1005); and
14. Drug-drug interaction study CYP3A4 inhibitor ketoconazole (study HYD1012),

Other Studies

15. Thorough QTc study (HYD1009),

The Population PK analysis included Phase 1 studies along with sparse PK sampling data from Phase 3 study HYD3003. However, population PK analysis was not reviewed as most conclusions can be drawn from the single dose PK studies designed to evaluate effect of intrinsic and extrinsic factors on PK of hydrocodone. Besides, the sparse sampling utilized in Phase 3 safety study HYD3003 collected limited number of pre-dose blood samples from a limited number of subjects recruited in the study and did not help with arriving at any robust conclusions as to the contributing factors to the variability, if any, in PK of hydrocodone. However, pre-dose concentrations of hydrocodone were examined for dose-proportionality at steady-state.

1. What is the relative bioavailability of hydrocodone following administration of Hysingla ER compared to Vicoprofen IR?

The systemic exposure (AUC24,ss) and average plasma concentration of hydrocodone (Cavg,ss) at steady state following the administration of Hysingla ER 30 mg every 24 hours was equivalent to that following Vicoprofen (7.5 mg hydrocodone bitartrate /200 mg ibuprofen) administered every 6 hours for 3 days. The mean hydrocodone exposure (Cmaxss) following Hysingla ER 30 mg administration was lower (18%) compared to that noted with Vicoprofen 7.5 mg administered four times daily.

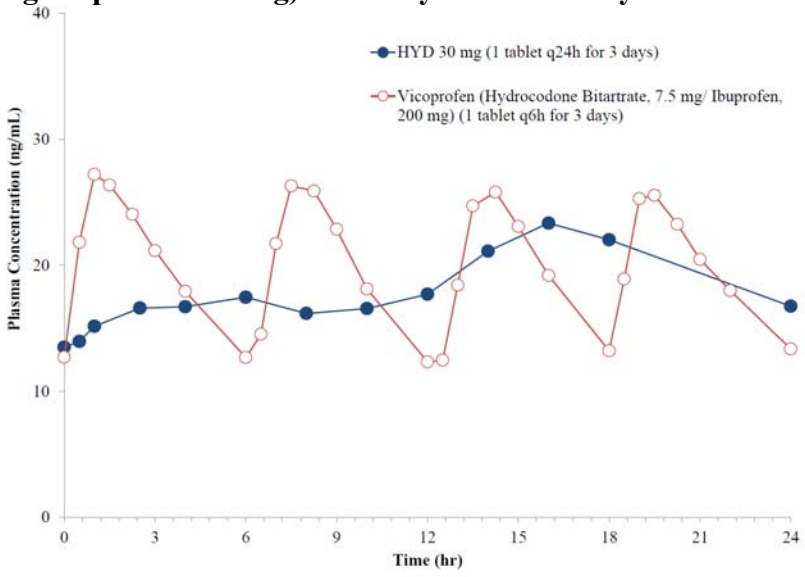
Study HYD1016 evaluated Relative BA of hydrocodone following Hysingla ER administration every 24 hours for 3 days and Vicoprofen 7.5 mg/ibuprofen 200 mg administered every 6 hours for 3 days in healthy volunteers (n=23). Naltrexone HCl 50-mg tablet was administered every 12 hours (q12h) from 12 hours predose through 36 hours post-dose on days 3 and 12 (morning dose for Vicoprofen) to minimize opioid-related AEs. Naloxone challenge test was performed prior to the first dose of naltrexone HCl to ensure the subjects were not opioid-dependent.

Table: Statistical Analysis of Plasma Pharmacokinetic Metrics of Hydrocodone in Study HYD1016

	LS Geometric Mean[a]			
Metric (unit)	**HYD (30 mg every 24h for 3 days) (test, N=22)**	**Vicoprofen® (every 6h for 3 days) (reference, N=23)**	**Estimated mean ratio (%)[b] (Test/Reference)**	**90% CI for Ratio[c]**
AUC24,ss (ng•h/mL)	427	458	93.2	(85.7, 101.4)
Cavg,ss (ng/mL)	17.8	19.1	93.2	(85.7, 101.4)
Cmax,ss (ng/mL)	25.4	31.0	81.7	(74.9, 89.2)

Source: CSR HYD1016, Table 11-3.
CI=confidence interval; LS=least squares.
[a] Least squares mean from analysis of variance. Natural log (ln) metric means were calculated by transforming the ln means back to the linear scale, ie, geometric means.
[b] Ratio of metric means for ln-transformed metrics (expressed as a percentage). Ln-transformed ratio was transformed back to linear scale.
[c] The 90% CI for ratio of metric means (expressed as a percentage). Ln-transformed confidence limits were transformed back to linear scale.

Figure: Mean Hydrocodone Plasma Concentration Versus Time Profiles for Hysingla ER 30-mg tablet and Vicoprofen (hydrocodone bitartrate 7.5 mg/ibuprofen 200 mg) at Steady State in Study HYD1016.



Source: Adapted from CSR HYD1016, Figure 11-1.

2. What are the PK characteristics of the drug and its major metabolite after intact use?

What are the single dose and multiple dose PK parameters?

Although dose-proportionality was observed in the 20 – 120 mg range of Hysingla ER doses, higher variability in plasma levels were noted with the 120 mg dose. Following multiple dose administration, on average, minimal accumulation was noted at a given dose level. However, fluctuation in Cmin to Cmax levels was observed to be significant.

Single Dose PK

Pharmacokinetics and dose proportionality of Hysingla ER tablets in healthy subjects was evaluated under naltrexone blockade in study HYD1004. Each subject was administered 4 of the 5 treatments (20, 40, 60, 80 or 120 mg) in the fasted state according to the randomization schedule. Mean plasma concentrations of hydrocodone increased slowly after oral administration of Hysingla ER extended-release tablets and reached a maximum concentration at 14 to 16 hours post-dose at all dose levels.

Figure: Mean Plasma Concentrations of Hydrocodone Versus Time on Linear Scale.

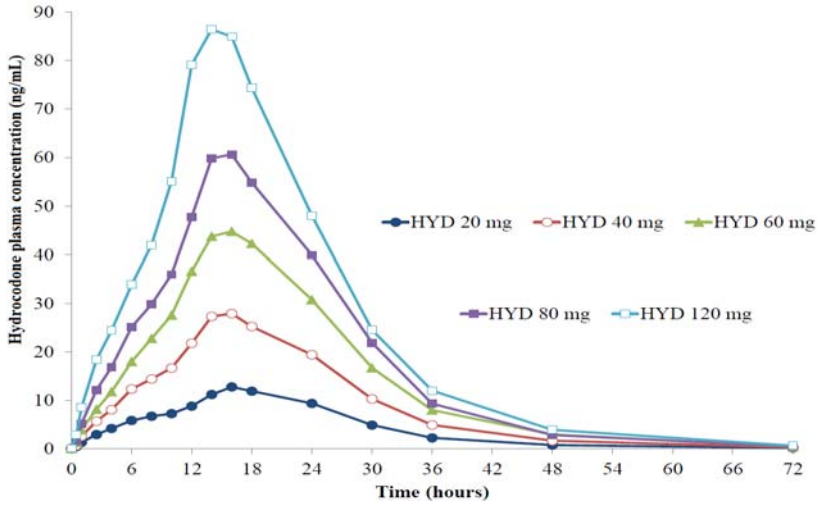


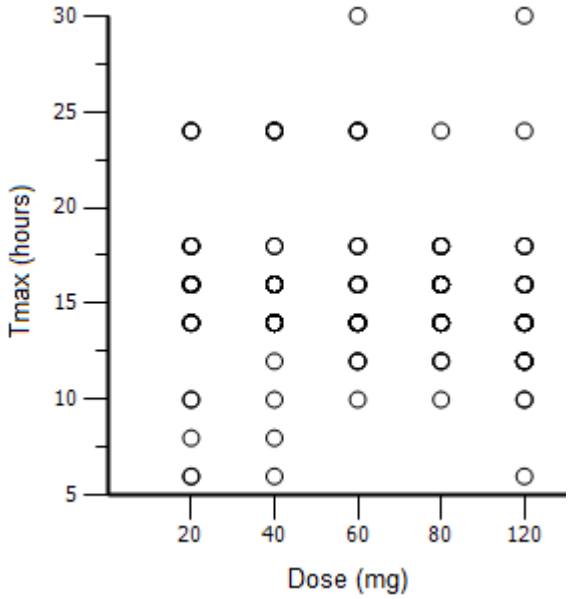
Table: Summary of Mean ± SD Plasma Hydrocodone Pharmacokinetic Metrics in Study HYD1004.

Metric (Unit)	HYD 20 mg N = 29	HYD 40 mg N = 31	HYD 60 mg N = 28	HYD 80 mg N = 30	HYD 120 mg N = 29
AUCt (ng•h/mL)	281 ± 127	618 ± 250	1004 ± 292	1298 ± 373	1759 ± 671
AUCinf (ng•h/mL)	284 ± 128	622 ± 252	1009 ± 294	1304 ± 375	1787[a] ± 679
Cmax (ng/mL)	14.6 ± 5.5	33.9 ± 11.8	53.6 ± 15.4	69.1 ± 17.2	110 ± 44.1
Tmax (h)[b]	16.0 (6.0, 24.0)	16.0 (6.0, 24.0)	14.1 (10.0, 30.0)	16.0 (10.0, 24.0)	14.0 (6.0, 30.0)
t1/2 (h)	7.6 ± 2.6	7.7 ± 2.1	8.1 ± 2.4	8.2 ± 2.4	8.7[a] ± 3.5

Source: CSR study HYD1004, Table 11-2.
HYD=extended-release tablet containing hydrocodone bitartrate.
[a] n = 28.
[b] median (minimum, maximum).

It should be noted that in some individuals peak plasma levels were noted at 24 hour or up to 30 hours following Hysingla ER administration. Plasma levels declined and remained detectable for more than 72 hours post-dose in most subjects at the dose level of 40 mg and above. The mean $t_{1/2}$ was similar for all dose levels and ranged from 7.6 to 8.7 hours.

Figure: The range of Tmax (hours) noted with different strengths of Hysingla ER following single dose administration in study HYD1004.



The results of a statistical power model analysis (Table below) showed that the slope for the power model on logarithmic scale for AUCinf was 1.11 with a 90% CI of (1.02, 1.20), which overlaps the dose proportionality limits of (0.88, 1.12). This indicates minimal deviation from dose proportionality. Similar results were observed for Cmax. The mean slope for Cmax of hydrocodone was approximately 1.16 and the 90% CI for the slope was (1.08, 1.24).

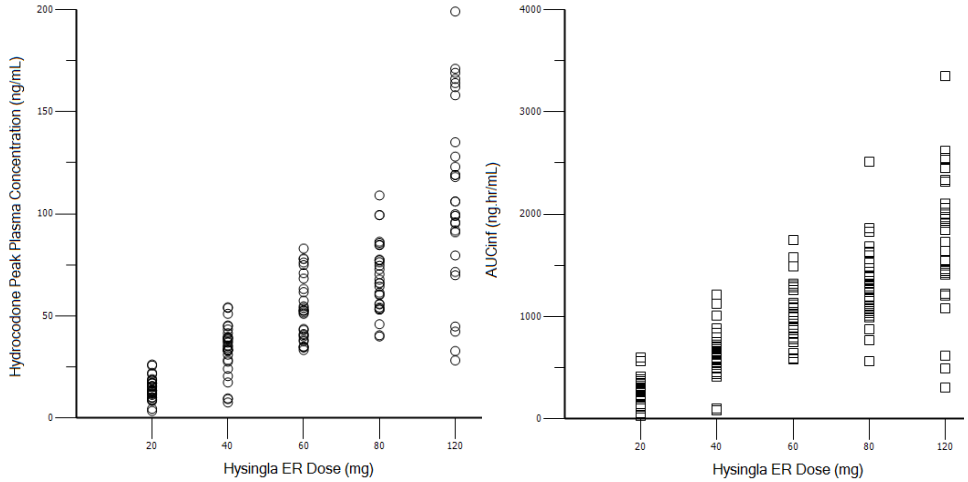
Table: Statistical Analysis of Dose Proportionality of Hydrocodone in Study HYD1004

Metric (Unit)	Estimated Slope	Standard Error	Lower 90% CI	Upper 90% CI	Intra-Subject %CV
AUCt (ng•h/mL)	1.11	0.0546	1.03	1.20	39.9
AUCinf (ng•h/mL)	1.11	0.0549	1.02	1.20	39.9
Cmax (ng/mL)	1.16	0.0484	1.08	1.24	35.0

Source: CSR study HYD1004, Table 11-3.
CI=confidence interval; %CV=coefficient of variation.
Note: The power model, log(parameter) = intercept + β × log(dose) + period + sequence + subject(sequence) + error, was used to estimate the slope and corresponding 90% CIs. Dose proportionality was concluded if the 90% CIs were entirely within (0.875, 1.125).

Upon closer examination of individual data, it was observed that subjects receiving 120 mg tablet of Hysingla ER had higher variability with respect to both Cmax (Range 28.2 – 199 ng/mL) and AUC_{inf} (305 – 3347 ng.hr/mL). Hence, the impact of the noted variability on multiple dose PK is discussed in the next section with specific attention to fluctuation in plasma levels following multiple dose administration of all available strengths.

Figure: Plot of individual PK parameters (Cmax in the left figure, AUC inf in the right figure).



Multiple dose PK

Multiple dose PK of Hysingla ER were evaluated for 30 mg dose (HYD1016) and 120 mg strength (HYD1002). In addition, steady-state PK of hydrocodone were evaluated in healthy volunteers following titration to 80 mg, 120 mg and 160 mg dose.

Multiple dose, pharmacokinetic study of Hysingla ER 120-mg tablets in healthy subjects (n=27) under naltrexone blockade was evaluated in study HYD1002. Twenty-seven opioid-nondependent subjects were administered once daily Hysingla ER 120 mg for 5 days. PK of hydrocodone following first day was compared with PK on day 5.

The mean Cmax values for day 1 and day 5 (steady state) were 128 and 135 ng/mL, respectively. The mean area under the plasma concentration-time curve during the dosing interval (AUCtau) values for day 1 and day 5 (steady state) were 1541 and 1938 ng*h/mL, respectively. Median Tmax values were 14.0 hours on both day 1 and day 5 (steady state). Mean accumulation ratios for AUCtau, Cmax, and Cmin were 1.3, 1.1, and 1.1, respectively, indicating minimal accumulation following multiple, once daily Hysingla ER dosing for 5 days.

Figure: Mean Concentration Versus Time Profile for Hydrocodone after administration of Hysingla ER 120 mg Once-daily for 5 Days in Study HYD1002.

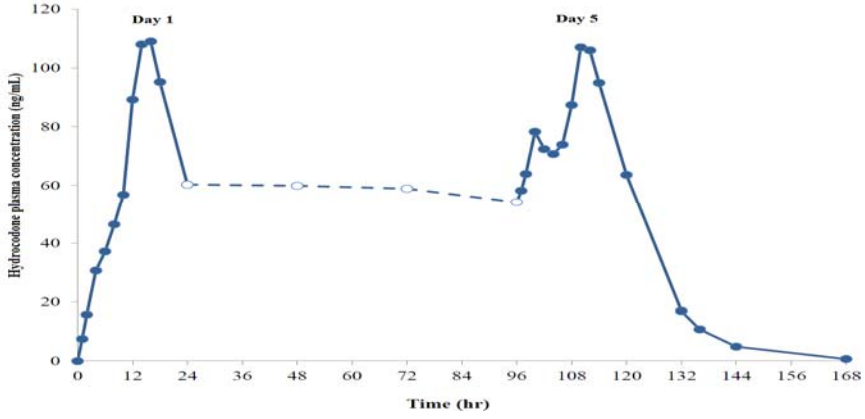


Table: Summary of Mean ± SD Plasma Hydrocodone Pharmacokinetic Metrics in Study HYD1002.

	HYD 120-mg Tablet		
Metric (Unit)	**Day 1 N=24**	**Day 5 (steady state) N=25**	**Accumulation Ratio N=23**
AUCtau (ng*h/mL)	1541 ± 332	1938 ± 729	1.3 ± 0.5
AUCss,inf (ng*h/mL)	--	2615 ± 1086	--
Cmax (ng/mL)	128 ± 29.6	135 ± 49.5	1.1 ± 0.3
Cmin (ng/mL)	60.3 ± 27.6	63.6 ± 29.4	1.1 ± 0.6
Tmax (h)[a]	14.0 (12.0, 23.9)	110 (98.0, 120)[b]	--
Tlag (h)[a]	0.00 (0.00, 0.00)	--	--
t1/2 (h)	--	7.17±1.89	--
		Steady State N= 24	
Cavg,ss (ng/mL)		80.8 ± 30.4 (N=25)	
%Fluctuation		97.9 ± 60.8	
%Swing		286 ± 542	

Source: CSR study HYD1002, Table 13.
[a] median (minimum, maximum).
[b] hours after first dose, 14 (2.0, 24) hours after last dose.

For reference, % fluctuation and % Swing were calculated as follows:
% Fluctuation The range of plasma concentration values during steady state relative to $C_{ss,avg}$: $(C_{ss,max}-C_{ss,min})$ *100 /$C_{ss,avg}$.
% Swing: The range of plasma concentration values during steady state relative to Css,min: $(C_{ss,max}-C_{ss,min})$*100/ $C_{ss,min}$

Following Hysingla ER administration for 3 days (Study HYD1016), the average % fluctuation was 60% and % swing was 88% (See Table below). However, % fluctuation numbers for Hysingla ER 120 mg at steady-state were 98% and 286% **on average**. Although the data is from across different studies, it is still noteworthy.

Table: Summary of Day 3 Mean ± SD Plasma Pharmacokinetics of Hydrocodone in Study HYD1016.

	HYD (30 mg every 24h for 3 days)	**Vicoprofen (every 6h for 3 days)**
Metric (unit)	**N = 22**	**N = 23**
AUC24,ss (ng•h/mL)	443 ± 128	470 ± 111
AUCinf,ss (ng•h/mL)	602 ± 162	559 ± 141
Cmax,ss (ng/mL)	26.4 ± 7.4	31.6 ± 6.6
Tmax,ss[a] (h)	16.0 (1.0, 24.0)	1.5 (0.50, 19.5)
Cavg,ss (ng/mL)	18.4 ± 5.3	19.6 ± 4.6
Cmin,ss (ng/mL)	16.7 ± 5.2	13.4 ± 4.0
t1/2,ss (h)	8.3 ± 2.4	4.8 ± 0.64
%Fluctuation	60.5[b] ± 30.2	96.3 ± 26.8
%Swing	88.3[b] ± 85.9	148 ± 58.7

Source: CSR HYD1016, Table 11-2.
SD=standard deviation.
Note: Cmin,ss represents the concentration at 24 hours after the morning dose on Day 3.
[a] Median (minimum, maximum).
[b] N = 18.

Fluctuation in plasma levels is expected even after steady-state is achieved after repeated dosing of a drug product. Percentage fluctuation and percentage swing are generally very high for immediate release product as noted with Vicoprofen IR in study HYD1016 (See table above). Controlled release products are typically developed to reduce the fluctuation and swing in plasma levels. Despite being controlled-release products, approved opioid ERLA products indicated for twice daily administration are expected to have some fluctuation in plasma concentration. However, the proposed product is indicated for once daily administration and the general expectation would be one that the product that would yield steady plasma concentration over a 24 hour period.

Thorough QT (TQT) study (HYD1009) employed steady titration from Hysingla ER 20 mg to 160 mg ER over a period of 15 days. PK of hydrocodone following Hysingla ER 80 mg on Day 9, 120 mg on Day 12 and 160 mg on Day 15 each at steady-state were evaluated.

As noted in study HYD1002, Hysingla ER 120 mg administered over three days to steady-state showed an average %fluctuation and % swing 102% and 220%, respectively. Hysingla ER 80 mg showed an average %fluctuation and % swing 105% and 245%, respectively at steady-state dosing.

Table: Summary of Mean ± SD Plasma Hydrocodone Pharmacokinetic Metrics in TQT Study HYD1009.

	AUC0-24,ss (hr*ng/mL)	Cmax,ss (ng/mL)	Tmax,ss (hr)	Cmin,ss (ng/mL)	Cavg,ss (ng/mL)	%Fluctuation	%Swing
Hysingla ER 80 mg Day 9							
N	77	77	77	77	77	77.00	77
Mean	1252.49	82.62	14.96	28.21	52.19	105.20	245
SD	352.038	25.732	3.321	12.041	14.668	33.00	245
Median	1169.73	77.30	14.00	26.50	48.74	106.40	194
Minimum	637.51	37.50	10.00	4.05	26.56	35.65	44
Maximum	2358.64	175.00	23.92	59.90	98.28	213.80	1875
Geometric Mean	1206.66	79.03	-	25.19	50.28	99.86	193
Hysingla ER 120 mg Day 12							
N	75	75	75	75	75	75	75
Mean	1844.10	122.12	14.51	43.51	76.84	102.72	220
SD	542.945	43.259	3.945	17.479	22.623	34.31	241
Median	1763.33	115.00	14.00	41.80	73.47	102.27	176
Minimum	842.31	51.70	0.00	0.48	35.10	45.30	60
Maximum	3358.29	312.00	23.97	94.10	139.93	185.67	2073*
Geometric Mean	1771.02	115.80	-	38.02	73.79	97.06	176
Hysingla ER 160 mg Day 15							
N	73	73	73	73	73	73	73
Mean	2380.47	151.05	14.67	57.79	99.19	94.56	222.56
SD	733.371	52.393	4.169	26.261	30.557	36.69	237.21

Median	2222.37	146.00	14.00	53.30	92.60	86.93	163.61
Minimum	1282.06	66.90	0.00	7.65	53.42	29.37	33.33
Maximum	4764.17	337.00	23.92	132.00	198.51	185.20	1298.69
Geometric Mean	2280.08	142.81	.	51.44	95.00	87.41	161.45

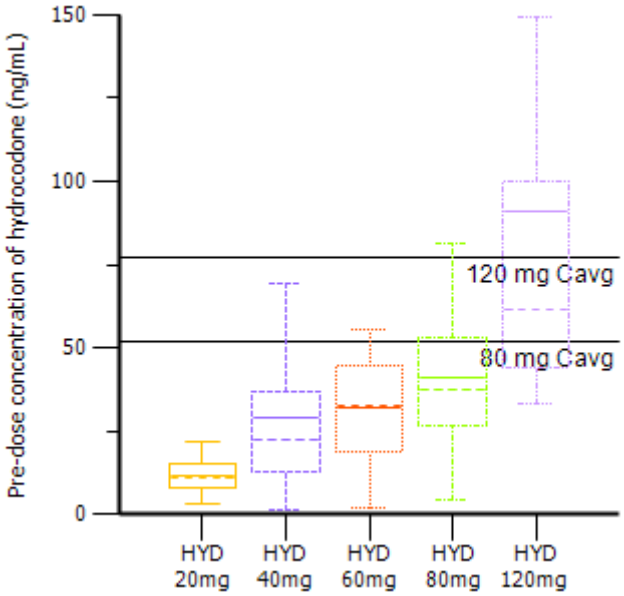
* Data from subject 1177 was excluded up on noting abnormally low initial plasma concentrations following HYD 80 mg and HYD120 mg (Potentially a compliance problem). Data for HYD160 mg is unavailable for this subject as the subject experienced vomiting.

On an average, the PK parameters at steady-state indicate dose-proportionality between the 80 to 160 mg doses of Hysingla ER employed in the TQT study.

How does the PK of the drug and its major active metabolites in healthy volunteers compare to that in patients?

The pre-dose plasma concentrations of hydrocodone following steady-state dosing appears to be consistent with that noted in healthy volunteers. A dose related increase in pre-dose plasma concentrations were observed. Higher variability in pre-dose plasma hydrocodone concentration was noted as the subjects may not have been compliant due to adverse events during one of the four visits during maintenance treatment period.

Figure: Average pre-dose plasma hydrocodone concentrations over dose during the maintenance treatment period (average of visits 4, 5, 6, and 7).



What are the characteristics of drug distribution? [Include protein binding]

Following administration of hydrocodone to healthy subjects, the mean apparent volume of central compartment (Vc/F) was 402 L, suggesting extensive tissue distribution. The extent of in vivo binding of hydrocodone to human plasma proteins was minimal with a mean percent bound of 36%.

What are the characteristics of drug metabolism?

Hydrocodone is extensively metabolized by hepatic enzymes, including CYP3A4, CYP2D6 and 6-keto reduction. Purdue conducted in vitro studies to identify specific CYP involvement in the clearance of hydrocodone into norhydrocodone and hydromorphone. Based on an old publication it appears clearance of hydrocodone is also mediated by 6-keto reduction to the corresponding 6-α- and 6-β-hydroxy metabolites (Cone, EJ et. al. Biomed. Mass Spec (5):291-295 (1978)).

Norhydrocodone and hydromorphone are the primary oxidative metabolites of hydrocodone. The rate of hydromorphone formation is approximately 14- times slower than the rate of norhydrocodone formation *in vitro,* suggesting that hydromorphone appear to be a minor metabolite. A small amount of 6β-hydroxydihydrocodeine (6β-DHCD) was detected when hydrocodone was incubated with both rat and human liver S9 or cytosolic fractions in the presence of NADPH or NADH. In humans, a marked inter-individual variation in norhydrocodone and hydromorphone was observed. The results from correlation analysis study, CYP-specific chemical inhibition study and incubations with recombinant CYP-isoforms showed that there are multiple CYP isoforms involved in hydrocodone metabolism. However, CYP3A4 and CYP2D6 are the major CYP isoforms responsible for norhydrocodone and hydromorphone formation, respectively. The major contribution to hydromorphone formation appears to be due to CYP2D6 in this study. In hydrocodone metabolism, CYP3A4 appear to be a "low-affinity" and "high-capacity" enzyme, and CYP2D6 appear to be a "high-affinity" and "low-capacity" enzyme. Inhibition studies have shown that quinidine (potent inhibitor of CYP2D6) and ketoconazole (potent inhibitor of CYP3A4) inhibited the formation of hydromorphone and norhydrocodone, respectively, and hence may alter their levels in plasma. Based on cDNA expressed CYP metabolism studies, formation of norhydrocodone and hydromorphone were noted when hydrocodone was incubated with CYP2B6 and CYP2C19 enzymes also. Taken together, multiple hepatic metabolic enzymes appear to exist in clearing hydrocodone into different metabolites.

See Appendix for in vitro study synopsis HCDDR-02-102-0: Identification Of Cytochrome P450 Isoforms Responsible For Hydrocodone Bitartarate Metabolism In Human Liver Microsomes.

What are the characteristics of drug excretion?

Approximately 6.5% of the administered oral dose of hydrocodone administered as Hysingla ER is excreted as unchanged hydrocodone in urine. Additional information on renal excretion may be found in the renal impairment study discussion below.

How do the PK parameters change with time following chronic dosing? [Include-time to steady-state; single dose prediction of multiple dose PK; accumulation ratio]

As discussed above, steady state of plasma hydrocodone concentrations was attained by day 2 of once-daily dosing of Hysingla ER. The extent of accumulation of systemic exposure was low (1.3 fold). The mean t1/2 at steady state was 7 hours.

2.3 Intrinsic Factors

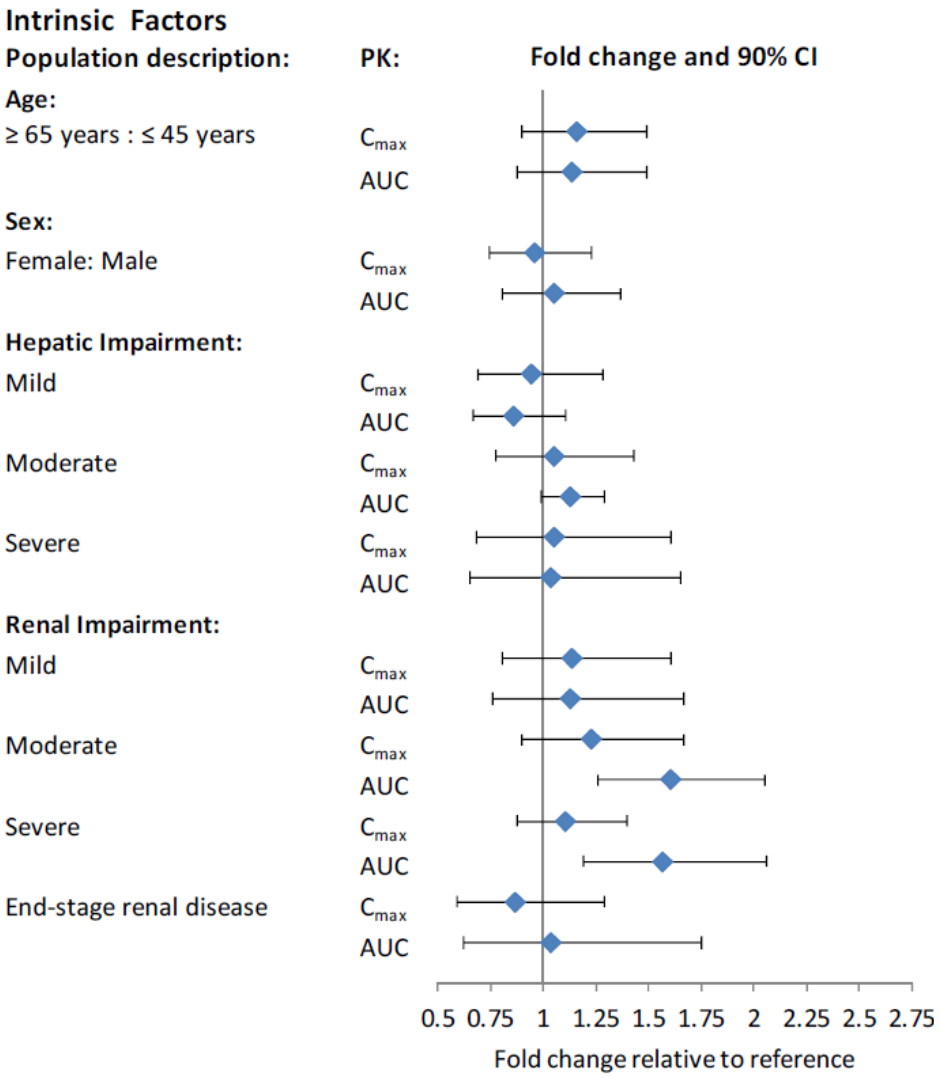
Purdue conducted dedicated PK studies to evaluate the effect of age, gender, organ function (hepatic and renal) on PK of hydrocodone following Hysingla ER administration.

Age and Gender: The PK of hydrocodone in healthy elderly subjects (65 to 77 years old) following administration of Hysingla ER 40 mg are similar to the PK in healthy young subjects (20 to 45 years old). The slightly higher exposure to hydrocodone in elderly subjects in terms of Cmax (16%) and AUC (15%) compared to young subjects is not considered clinically meaningful. Systemic exposure to hydrocodone (Cmax and AUC) was comparable in male and female subjects.

Renal Impairment: Patients with renal impairment have higher plasma concentrations (AUC) than those with normal renal function. Low initial dose of Hysingla ER should be used in patients with renal impairment and patients should be monitored closely for opioid adverse events such as respiratory depression.

Patients with mild, moderate and severe hepatic impairment did not show higher plasma concentrations (on average) than those with normal hepatic function. Patients with severe hepatic impairment may have higher plasma concentrations than those with normal hepatic function. No adjustment in starting dose with HYSINGLA ER is required in patients with mild or moderate hepatic impairment. Use a low initial dose of HYSINGLA ER in patients with severe hepatic impairment and monitor closely for adverse events such as respiratory depression.

Since hydrocodone is metabolized by CYP2D6 the sponsor was contacted to explain the potential impact of CYP2D6 genotypes on the PK variability of hydrocodone with Hysingla ER use. The sponsor indicated that blood samples were collected for exploratory pharmacogenomics analysis; however, no specific samples were evaluated to understand the impact of CYP2D6 polymorphisms on PK of hydrocodone with Hysingla ER use.


Intrinsic Factors
Population description:
PK:
Fold change and 90% CI
Age:
≥ 65 years : ≤ 45 years
Cmax
AUC
Sex:
Female: Male
Cmax
AUC
Hepatic Impairment:
Mild
Cmax
AUC
Moderate
Cmax
AUC
Severe
Cmax
AUC
Renal Impairment:
Mild
Cmax
AUC
Moderate
Cmax
AUC
Severe
Cmax
AUC
End-stage renal disease
Cmax
AUC
0.5 0.75 1 1.25 1.5 1.75 2 2.25 2.5 2.75
Fold change relative to reference

Age and Gender

HYD 1006 was a single-center, open-label, parallel-group, single-dose study in 4 cohorts: young healthy adult (aged 18 to 45 years) female and male subjects and elderly (aged 65 to 80 years) female and male subjects. Each subject was administered a single Hysingla ER 40-mg tablet and naltrexone HCl 50-mg tablet was administered at –12, 0, 12, 24 and 36 hours, relative to Hysingla ER administration to minimize opioid-related adverse events.

Table: Mean (± SD) Plasma Concentrations of Hydrocodone Versus Time by age (Left), and gender (right).

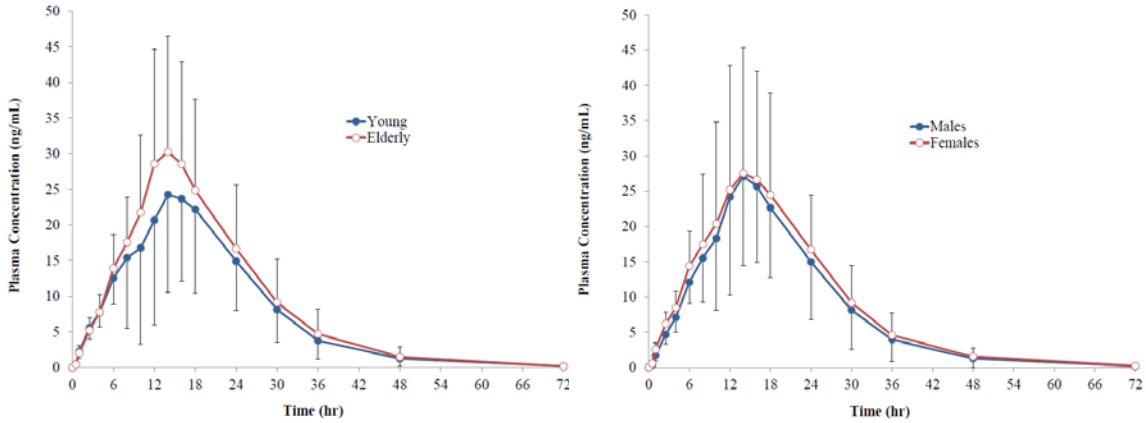


Table: Summary of Mean ± SD Plasma Hydrocodone Pharmacokinetic Metrics by Age and Gender in Study HYD1006.

	HYD 40 mg			
	Young	Elderly	Female	Male
Metric (Unit)	N = 24	N = 25	N = 24	N = 25
AUCt (ng•h/mL)	533 ± 193	628 ± 253	612 ± 246	553 ± 211
AUCinf (ng•h/mL)	539 ± 194	632 ± 254	618 ± 246	557 ± 213
Cmax (ng/mL)	31.4 ± 16.2	35.7 ± 14.8	34.7 ± 18.6	32.6 ± 12.0
Tmax (h)[a]	16.0 (6.1, 24.0)	14.0 (4.0, 24.2)	16.0 (4.0, 24.2)	14.0 (8.0, 24.0)
t1/2 (h)	8.3 ± 3.27	6.9 ± 1.8	7.6 ± 2.8	7.5 ± 2.6

Source: CSR study HYD1006, Table 11-2.
[a] median (minimum, maximum).

Race

The effect of race on Hysingla ER PK has not been studied.

Renal Impairment

Study HYD1008 was a Phase 1, multicenter, nonrandomized, open-label, parallel-group, single-dose study. The group of healthy subjects was matched, to the extent possible, to the group of subjects with renal impairment on the basis of gender, mean age, mean body mass index, and smoking habits. After a single dose of 60 mg Hysingla ER in 40 patients with normal renal function, mild, moderate, or severe renal impairment based on Cockcroft-Gault criteria and end stage renal disease patients, mean hydrocodone Cmax values were 39.6, 49.7, 50.8, 45.5, and 38.4 ng/mL, respectively. Mean hydrocodone AUCinf values were 754, 942, 1222, 1220, and 932 h*ng/mL for subjects with normal renal function, mild, moderate or severe renal impairment and ESRD, respectively. Compared to subjects with normal renal function, hydrocodone Cmax values were higher by 14%, 23%, 11% and lower by 13% and AUC values were higher by 13%, 61%, 57% and 4% in patients with mild, moderate or severe renal impairment or end stage renal disease, respectively.

Table: Summary of Mean ± SD Plasma Hydrocodone Pharmacokinetic Metrics in Renal Impairment Study HYD1008

		Subjects with Renal Impairment				
Metric (Unit)	**Healthy** N = 8[a]	**Mild** N = 9	**Moderate** N = 6	**Severe** N = 8	**ESRD w/dialysis** N = 8	**ESRD w/o dialysis** N = 6
AUCt (h•ng/mL)	738 ± 138	938 ± 388	1217 ± 305	1209 ± 394	922 ± 466	1085 ± 264
AUCinf (h•ng/mL)	754 ± 155	942 ± 389	1222 ± 306	1220 ± 397	932 ± 471	–
AUC0-72 (h•ng/mL)	735 ± 135	–	–	–	–	1085 ± 264
Cmax (ng/mL)	39.6 ± 6.8	49.7 ± 21.9	50.8 ± 18.2	45.5 ± 15.3	38.4 ± 16.6	50.6 ± 19.1
Tmax (h)[b]	19.0 (14, 24)	14.0 (10, 24)	17.0 (14, 24)	20.0 (14, 48)	16.0 (6, 24)	18.0 (12, 20)
t1/2 (h)	8.0 ± 3.6	14.5 ± 17.5	14.4 ± 15.0	34.2 ± 11.6	27.0 ± 13.0	–
CL/F (L/h)	82.7 ± 18.3	89.4 ± 83.2	51.8 ± 12.8	54.9 ± 21.6	104 ± 98.8	–
Vd/F (L)	916 ± 328	1604 ± 1724	1175 ± 1463	2854 ± 1833	3692 ± 3685	–

Source: CSR study HYD1008, Table 11-2.
ESRD=end-stage renal disease; w/=with; w/o=without.
[a] N = 6 for AUCinf, t1/2, CL/F, and Vd/F.
[b] median (minimum, maximum).

Mean hydrocodone plasma concentrations versus time are presented by subjects with normal renal function (group A) and subjects with mild, moderate and severe renal impairment (groups B, C, and D, respectively) in Figure below (left) and by subjects with normal renal function (group A) and subjects with ESRD (group E) in Figure below (right).

Figure: Mean Plasma Concentrations of Hydrocodone Versus Time in Healthy Subjects and patients

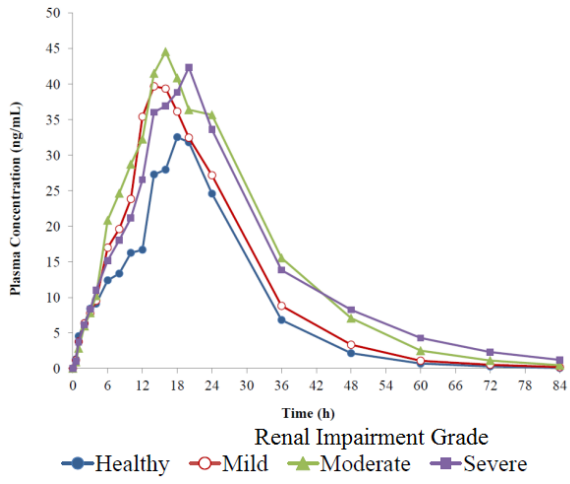
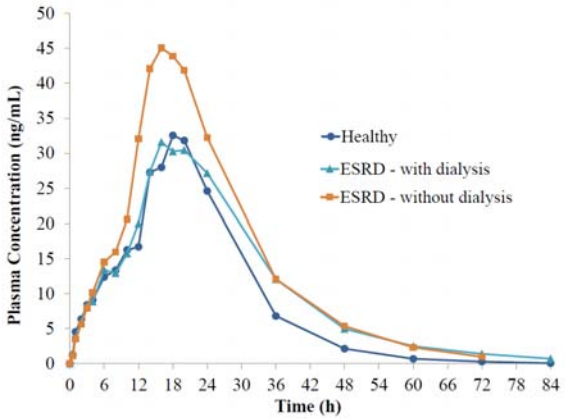
Patients with mild, moderate, or severe renal impairment or	**Patients with end-stage renal disease with or without dialysis.**
	

Table: Mean (%CV) Hydrocodone Clearance and Percent Amount Excreted Hydrocodone Pharmacokinetic Metrics in Study HYD1008

		Subjects with Renal Impairment				
					ESRD	
	Healthy	Mild	Moderate	Severe	w/ dialysis	w/o dialysis
PK Metric (unit)	(N=8)[a]	(N=9)	(N=6)	(N=8)	(N=8)[b]	(N=4)
% Ae	6.5 (13)	5.0 (40)	4.8 (22)	2.3 (56)	0.05 (134)	0.16 (155)
CL/F (L/h)	83 (22)	89 (93)	52 (25)	55 (39)	104 (95)	-
CLr (L/h)	5.3 (27)	3.2 (31)	2.5 (35)	1.2 (45)	0.07 (172)	–
CLd (L/h)	-	-	-	-	9.3 (28)	

Source: CSR study HYD1008, Table 11-2, Table 11-5, and Table 11-8.
CL/F=apparent systemic clearance; CLr=renal clearance; CLd=dialyzer clearance; ESRD=end-stage renal disease; %Ae=percent excreted unchanged in urine; %CV=coefficient of variation.
a N= 6 for CL/F and CLr
b N=4 for %Ae and CLr

As seen from the table above, hydrocodone is not substantially (only 6.5% of orally administered) eliminated by renal excretion in healthy subjects. Nevertheless, the amount of hydrocodone excreted is reduced further in patients with renal impairment.

Dialysate

In subjects with ESRD, during the approximately 4-hour hemodialysis period, 0.55% of the Hysingla ER 60-mg dose was removed as hydrocodone. The amounts of norhydrocodone and hydromorphone removed during the same 4-hour hemodialysis period were less than 0.1 mg. In comparison, the mean hydrocodone %Ae in urine during the time intervals 0 to 4 and 4 to 8 hours for subjects with normal renal function were 0.20% and 0.44% of the dose, respectively. During hemodialysis in subjects with ESRD, hydrocodone CLd was 9.3 L/h in contrast to CLr (5.3 L/h) in subjects with normal renal function.

Hepatic Impairment

Effect of Hepatic Impairment on the Single-dose (20 mg) Pharmacokinetics and Safety of Hysingla ER was evaluated in study HYD1007.

This was a Phase 1, multicenter, nonrandomized, open-label, parallel-group, single-dose study. At screening, subjects were assigned to a study group based on the degree of hepatic impairment as defined by the Child-Pugh classification system as follows:

- Group A: 8 subjects with mild hepatic impairment (Child-Pugh Class A)
- Group B: 8 subjects with moderate hepatic impairment (Child-Pugh Class B)
- Group C: 8 subjects with severe hepatic impairment (Child-Pugh Class C)
- Group D: 8 healthy subjects (normal hepatic function)

As presented by the sponsor, data from study HYD1007 indicated that after a single dose of 20 mg Hysingla ER in 32 patients with normal hepatic function, mild, moderate or severe hepatic impairment based on Child-Pugh classifications, mean hydrocodone Cmax values were 16.0, 15.3, 17.0, and 18.4 ng/mL, respectively. Mean hydrocodone AUCinf values were 342, 310, 390, and 415 h*ng/mL for subjects with normal hepatic function, mild, moderate or severe hepatic impairment, respectively. Compared to subjects with normal hepatic function, hydrocodone Cmax values were lower by 6%, and higher by 5% and 5% and AUC values were lower by 14%, and higher by 13% and 4% in patients with mild, moderate or severe hepatic impairment, respectively. Patients with mild, moderate and severe hepatic impairment did not show higher plasma concentrations (on average) than those with normal hepatic function.

However, upon closer scrutiny it was observed that four out of eight patients with severe hepatic impairment had received lactulose, a strong laxative also used to manage complications of hepatic encephalopathy. In these three subjects systemic exposure of hydrocodone was lower compared to other patients with severe hepatic impairment or with respect to average healthy volunteers. After considering the confounding effect of laxative on PK Hysingla in severe HI patients it was observed that AUC and Cmax in this group were higher by 50%, compared to healthy volunteers.

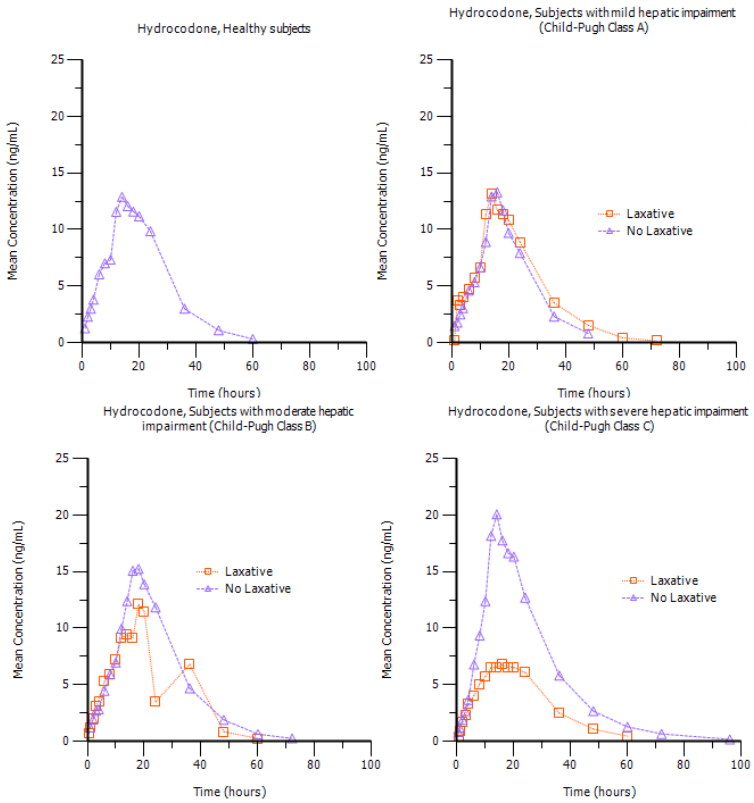
Two patients out of eight with moderate hepatic impairment had received lactulose; where only one of the two patients had lower exposure. One subject in mild hepatic impairment received a relatively mild laxative (Metamucil) and did not show any difference in PK. None of the healthy subjects received a laxative.

Therefore, pharmacokinetics of hydrocodone were recalculated to decipher the potential confounding effect of Lactulose.

Table: Summary of Mean ± SD Plasma Pharmacokinetic Metrics of Hydrocodone in Healthy Subjects and Subjects with Hepatic Impairment in Study HYD1007

Variable	Treatment Group	Laxative	N	Mean	SD	Geometric Mean	Min	Median	Max
AUC0-inf	Healthy	No Laxative	8	341.55	36.83	339.89	297.34	337.97	414.19
AUC0-inf	Mild HI	Laxative	1	315.42	.	315.42	315.42	315.42	315.42
AUC0-inf	Mild HI	No Laxative	7	309.95	123.92	293.53	191.44	281.87	576.04
AUC0-inf	Moderate HI	Laxative	2	345.84	89.66	339.98	282.44	345.84	409.24
AUC0-inf	Moderate HI	No Laxative	6	404.62	66.51	400.43	329.22	398.77	528.10
AUC0-inf	Severe HI	Laxative	4	303.90	240.42	237.89	99.61	240.92	634.13
AUC0-inf	Severe HI	No Laxative	4	525.86	54.62	523.70	461.01	533.41	575.63
Cmax	Healthy	No Laxative	8	15.99	5.00	15.30	8.34	15.85	25.5
Cmax	Mild HI	Laxative	1	13.20	.	13.20	13.2	13.2	13.2
Cmax	Mild HI	No Laxative	7	15.55	5.95	14.59	8.72	14.9	25.9
Cmax	Moderate HI	Laxative	2	16.21	9.19	14.85	9.71	16.205	22.7
Cmax	Moderate HI	No Laxative	6	17.32	5.57	16.56	11.1	16.85	24.4
Cmax	Severe HI	Laxative	4	12.39	6.81	11.03	5.92	11.165	21.3
Cmax	Severe HI	No Laxative	4	24.35	7.13	23.37	13.9	27.15	29.2
Tmax	Healthy	No Laxative	8	18	4.54	17.50	12	18	24
Tmax	Mild HI	Laxative	1	14	-	14	14	14	14
Tmax	Mild HI	No Laxative	7	14.6	1.51	14.50	12	14	16
Tmax	Moderate HI	Laxative	2	19	7.07	18.33	14	19	24
Tmax	Moderate HI	No Laxative	6	17.3	3.72	17.03	14	17	24
Tmax	Severe HI	Laxative	4	15.5	7	14.27	8	15	24
Tmax	Severe HI	No Laxative	4	15.5	3	15.31	14	14	20

Figure: Hydrocodone (Geometric mean) Plasma Concentration over Time in Healthy Subjects and Patients with Mild, Moderate or Severe Hepatic Impairment with Concomitant Administration of a Laxative (Square).



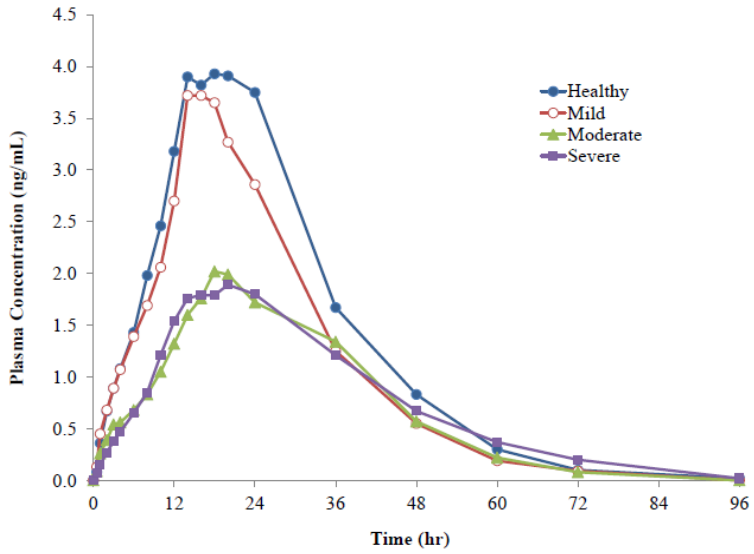
Taken together, patients with severe hepatic impairment requiring concomitant use of Hysingla with lactulose for the management of constipation or hepatic encephalopathy symptoms may have lower exposure to hydrocodone.

The mean plasma protein binding (% bound) of hydrocodone in subjects with normal hepatic function and mild, moderate, and severe hepatic impairment was low and similar at 36%, 37%, 33%, and 34%, respectively. So there is no reason to suspect that free hydrocodone plasma levels will be different in hepatic impairment.

Norhydrocodone:

Mean AUC and Cmax values of norhydrocodone in subjects with mild hepatic function were similar to those in subjects with normal hepatic function. Mean AUCinf decreased by 46% and 41%, and mean Cmax decreased by 51% and 53%, in subjects with moderate and severe hepatic impairment, respectively.

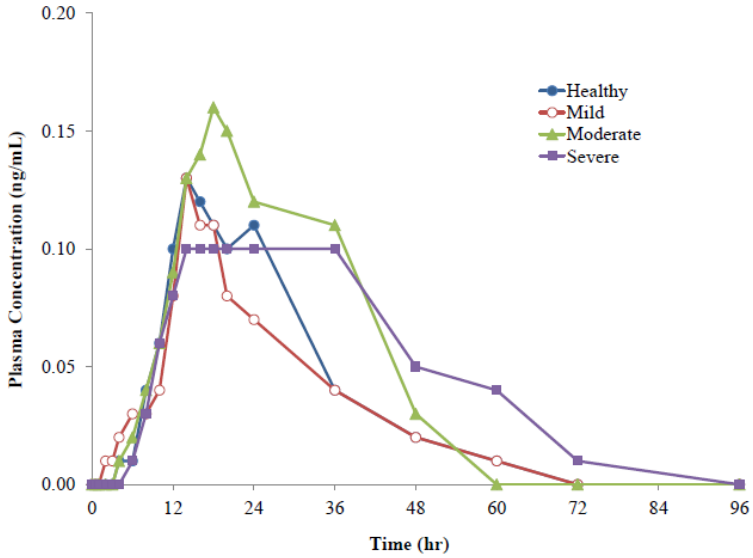
Figure: Mean Plasma Concentrations of norhydrocodone Versus Time in Subjects with Hepatic Impairment in Study HYD1007.



Hydromorphone:

The AUC and Cmax of hydromorphone, which is a minor (representing up to 3% systemic exposure of hydrocodone) active metabolite, had high within-group variability, resulting in very wide CIs of the estimated mean ratios. The mean AUCt values in subjects with mild, moderate, and severe hepatic impairment were 7% lower, 42% higher, and 49% higher, respectively, than in subjects with normal hepatic function. The corresponding mean Cmax values were 19% lower, 6% higher, and 12% lower, respectively.

Table: Mean Plasma Concentrations of Hydromorphone Versus Time in Subjects with Hepatic Impairment on Linear and Semi-logarithmic Scales in Study HYD1007.



Use in Nursing Mothers

Data for hydrocodone content in human milk are reported in literature for 32 mothers receiving hydrocodone, with hydrocodone concentrations of 2 to 100 ng/mL reported for 30 mothers receiving hydrocodone 44 to 423 mcg/kg/day and hydrocodone concentrations of 3.1 to 8.6 mcg/kg/day reported for 2 mothers receiving hydrocodone 5 to 10 mg as needed. Excretion of the metabolite hydromorphone into milk has been reported at concentrations of 0.2 to 86.7 ng/mL, with detectable concentrations obtained in 12 of 30 mothers. However, these observations are not relevant to Hysingla ER administration and hence lactating mothers should be informed that safety of Hysingla ER has not been established with regard to possible adverse effects on infants. [Anderson PO, Sauberan J, Lane JR, Rossi SS. Hydrocodone excretion into breastmilk: the first two reported cases. Breastfeed Med 2007; 2:10 – 14.
Sauberan JB, Anderson PO, Lane JR, Rafi e S, Nguyen N, Rossi SS, Stellwagen LM. Breast milk hydrocodone and hydromorphone levels in mothers using hydrocodone for postpartum pain. Obstet Gynecol 2011; 117:611 – 617.].

2.4 Extrinsic Factors

Hydrocodone exposure increased 2-fold when coadministered with strong CYP3A4 ketoconazole. Dose reduction or monitoring patient for adverse events is needed as appropriate when patients already on CYP3A4 inhibitors need Hysingla ER or patients on Hysingla ER need to take CYP3A4 inhibitors.

Hydrocodone exposure did not change significantly when coadministered with strong CYP2D6 inhibitor paroxetine. From a pharmacokinetic perspective, dose adjustment may not be needed when coadministration of Hysingla ER is considered with CYP2D6 inhibitors. However, other clinical safety considerations may be required when coadministering two centrally acting agents.

Hydrocodone does not inhibit major CYP enzymes.

There was no in vitro evidence of rapid or unexpectedly high rate of hydrocodone release for both 20 and 120 mg Hysingla ER tablets in the presence of ethanol.

Purdue conducted in vitro studies to identify specific CYP involvement in the clearance of hydrocodone into norhydrocodone and hydromorphone. Based on publications it appears clearance of hydrocodone is also mediated by 6-keto reduction to the corresponding 6-α- and 6-β-hydroxy metabolites.

The results from correlation analysis study, CYP-specific chemical inhibition study and incubations with recombinant CYP-isoforms showed that there are multiple CYP isoforms involved in hydrocodone metabolism. However, CYP3A4 and CYP2D6 are the major CYP isoforms responsible for norhydrocodone and hydromorphone formation, respectively.

The major contribution to hydromorphone formation appears to be due to CYP2D6 in this study. In hydrocodone metabolism, CYP3A4 appear to be a "low-affinity" and "high-capacity" enzyme, and CYP2D6 appear to be a "high-affinity" and "low-capacity" enzyme. Inhibition studies have shown that quinidine (potent inhibitor of CYP2D6) and ketoconazole (potent inhibitor of CYP3A4) inhibited the formation of hydromorphone and norhydrocodone, respectively, and hence may alter their levels in plasma.

At various increasing concentrations used, HCD (0-400 ng/mL), did not inhibit EROD (CYP1A2), coumarin hydroxylase (CYP2A6), S-mephenytoin hydroxylase (CYP2C19), bufuralol 1'-hydroxylase (CYP2D6), chlorzaxazone hydroxylase (CYP2E1) and testosterone 6 -hydroxylase (CYP3A4) marker activities. These results suggest that in vivo, the drug-drug interaction potential of HCD with other drugs that are metabolized by major CYP isoforms appear to be very minimal to none.

Influence of Co-administration of Alcohol

The potential of dose dumping by concomitant ingestion of alcohol was evaluated for HYD using an in vitro drug release test to determine the effect of alcohol (ethanol) at concentrations of up to and including the 40% concentration (v/v) on the dissolution profiles of HYD 20 and 120 mg in simulated gastric fluid without enzymes. Complete details of the in vitro study may be found in Dr. Akm Khairuzamman's review.

CYP3A4 drug-drug interaction study

Study HYD1012 evaluated effect of co-administration of Hysingla ER and Ketoconazole, a CYP3A4 Inhibitor, in Healthy Subjects (n=30). Subjects were administered Hysingla ER 20 mg tablet with ketoconazole 200 mg or Hysingla ER 20 mg tablet with placebo. Ketoconazole (200-mg tablet) or placebo was administered every 12 hours for 6 days in each period. A single Hysingla ER 20-mg tablet was administered once in the fasted state in each study period (on days 5 and 24). There was a 14-day washout period between treatments.

Higher hydrocodone AUC and Cmax values were observed in the presence of ketoconazole compared with placebo. Median Tmax of hydrocodone was observed at 18 hours in the presence of ketoconazole compared to 16 hours in the absence of ketoconazole. Mean t1/2 of hydrocodone ranged from 8 to 9 hours across the treatments. Hydrocodone AUCt and AUCinf in the presence of ketoconazole were 135% and 133% higher, respectively, than in the absence of ketoconazole. Hydrocodone Cmax was 78% higher due to ketoconazole.

Lower norhydrocodone AUC and Cmax values were observed in the presence of ketoconazole compared with placebo. Mean t1/2 of norhydrocodone ranged from 8 to 11 hours across the treatments. Norhydrocodone AUCt and AUCinf in the presence of ketoconazole were 36% and 34% lower, respectively, than in the absence of ketoconazole. Norhydrocodone Cmax was 52% lower due to ketoconazole.

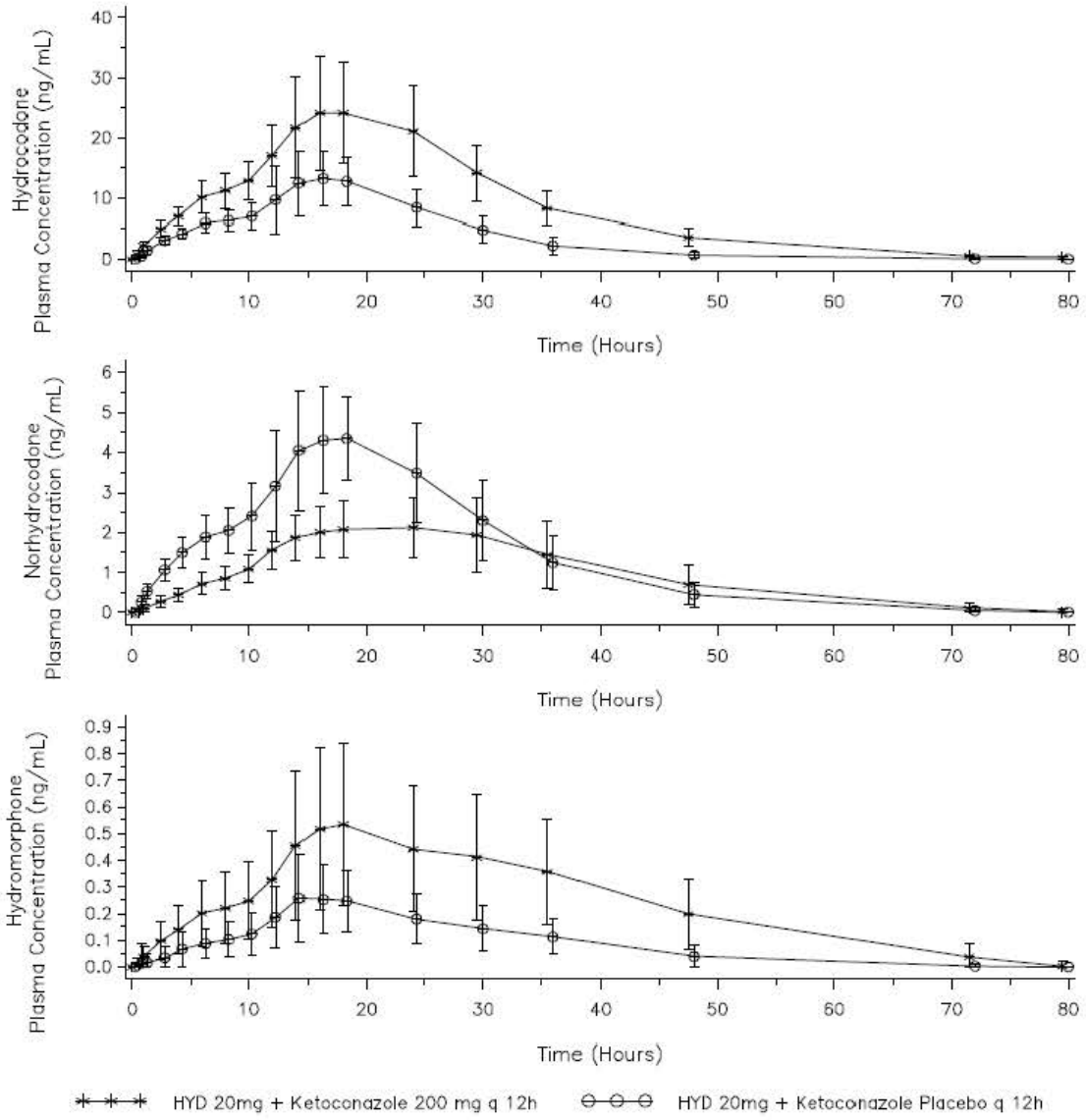
Higher hydromorphone AUC and Cmax values were observed in the presence of ketoconazole compared with placebo. Mean t1/2 ranged from 13 to 14 hours across the treatments. Hydromorphone AUCt and AUCinf in the presence of ketoconazole were 195% and 178% higher, respectively, than in the absence of ketoconazole. Hydromorphone Cmax was 95% higher due to ketoconazole.

Table: Summary of Mean ± SD Plasma Pharmacokinetic Metrics of Hydrocodone, Norhydrocodone, and Hydromorphone in Study HYD1012

Analyte Metric (Unit)	HYD 20 mg + Ketoconazole 200 mg q12h N = 25[b]	HYD 20 mg + Placebo q12h N = 27[c]
Hydrocodone		
AUCt (ng•h/mL)	674 ± 164	285 ± 71.1
AUCinf (ng•h/mL)	678 ± 165	288 ± 70.8
Cmax (ng/mL)	27.8 ± 8.4	15.4 ± 4.9
Tmax (h)[a]	18.0 (12.0, 30.0)	16.0 (12.0, 24.1)
t1/2 (h)	8.8 ± 1.6	8.2 ± 3.3
Norhydrocodone		
AUCt (ng•h/mL)	75.2 ± 32.4	109 ± 31.1
AUCinf (ng•h/mL)	78.8 ± 31.9	112 ± 31.3
Cmax (ng/mL)	2.4 ± 0.84	4.9 ± 1.2
Tmax (h)[a]	18.0 (12.0, 30.0)	16.0 (12.0, 30.0)
t1/2 (h)	10.5 ± 1.5	7.8 ± 2.6
Hydromorphone		
AUCt (ng•h/mL)	18.0 ± 10.5	6.3 ± 3.4
AUCinf (ng•h/mL)	24.4 ± 8.9	8.9 ± 2.7
Cmax (ng/mL)	0.59 ± 0.31	0.31 ± 0.15
Tmax (h)[a]	16.0 (14.0, 36.0)	16.0 (0.50, 24.0)
t1/2 (h)	14.4 ± 2.9	13.0 ± 4.0

Source: CSR study HYD1012, Table 11-2, Table 11-3, and Table 11-4.
[a] median (minimum, maximum).
[b] For hydromorphone, N = 25 for AUCt and Cmax; N = 18 for AUCinf and t1/2; N = 24 for Tmax.
[c] For hydromorphone, N = 27 for AUCt, Cmax, and Tmax; N = 18 for AUCinf and t1/2.

Figure: HYD1012 Ketoconazole drug interaction Study - Mean (± SD) Plasma Concentrations of Hydrocodone (Top Panel), Norhydrocodone (Middle Panel), and Hydromorphone (Bottom Panel) Versus Time (Linear Scale)



Abbreviations: HYD, hydrocodone bitartrate; q12h, every 12 hours.
Source: Figure 14.2.1.4.

Table: Statistical Analysis of Ketoconazole Effect on Hydrocodone, Norhydrocodone, and Hydromorphone Pharmacokinetic Metrics in Study HYD1012

Analyte Metric (Unit)	Geometric LS Mean N	HYD 20 mg + Ketoconazole 200 mg q12h	N	HYD 20 mg + Placebo q12h	Ratio of Geometric LS Mean (%)[a]	90% CI for Ratio
Hydrocodone						
AUCt (ng•h/mL)	25	651	27	277	235	(218, 252)
AUCinf (ng•h/mL)	25	655	27	281	233	(217, 251)
Cmax (ng/mL)	25	26.4	27	14.8	178	(162, 196)
Norhydrocodone						
AUCt (ng•h/mL)	25	68.0	27	106	64.3	(56.8, 72.7)
AUCinf (ng•h/mL)	25	72.1	27	109	66.3	(59.1, 74.3)
Cmax (ng/mL)	25	2.3	27	4.8	47.6	(42.2, 53.6)
Hydromorphone						
AUCt (ng•h/mL)	24	13.8	27	4.7	295	(273, 319)
AUCinf (ng•h/mL)	18	22.4	18	8.1	278	(250, 310)
Cmax (ng/mL)	24	0.51	27	0.26	195	(175, 218)

Source: CSR study HYD1012, Table 11-5, Table 11-6, and Table 11-7.
CI=confidence interval; LS=least squares; q12h=every 12 hours.
[a] An analysis of variance was performed on the natural logarithms of the pharmacokinetic metrics. The model included treatment, period, and sequence as fixed effects and subject within sequence as a random effect.

CYP2D6 drug-drug interaction study

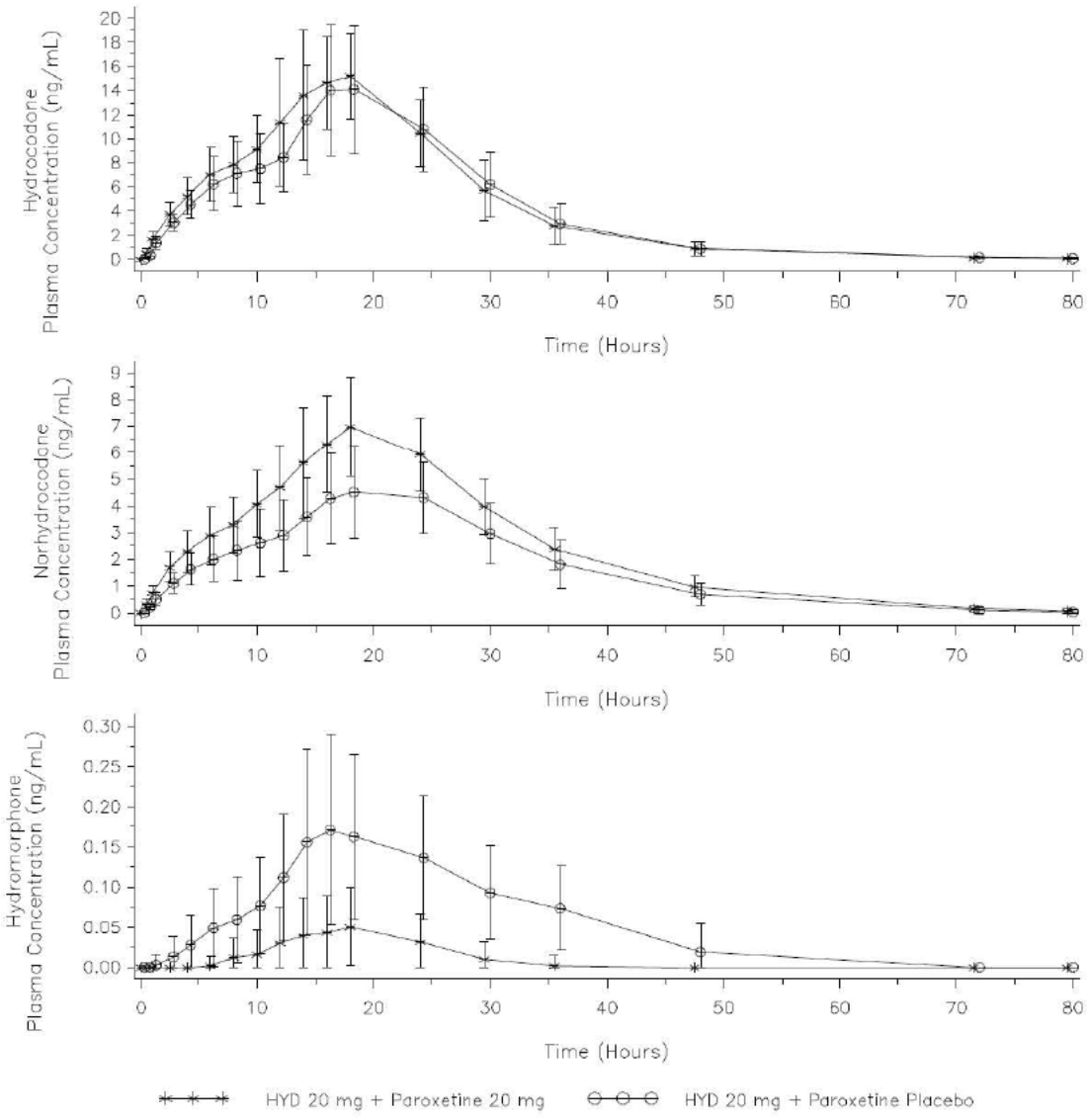
Study HYD1005 evaluated effect of co-administration of Hysingla ER and Paroxetine, a CYP2D6 Inhibitor, in Healthy Subjects (n=24). Subjects were administered Hysingla ER 20 mg (Lot number CB-2011-39) with paroxetine 20 mg or Hysingla ER 20 mg with paroxetine placebo. Paroxetine (20-mg tablet) or placebo was administered once daily for 12 days in each period. A single Hysingla ER 20-mg tablet was administered once in the fasted state in each study period (on days 10 and 23). Adequate study drug washout periods were built into the study design.

Administration of Hysingla with and without multiple doses of paroxetine, a strong CYP2D6 inhibitor, resulted in similar hydrocodone systemic exposures (See Figure below). The 90% confidence intervals (CIs) for the geometric least squares mean ratio of hydrocodone AUC and Cmax were within the 80% to 125% limits, indicating that paroxetine had no effect on hydrocodone exposures.

However, AUC and Cmax of hydromorphone, a minor (less than 3% of the parent compound) active metabolite, were lower in the presence of paroxetine. Systemic

exposure of norhydrocodone (inactive metabolite) was increased by 50% in the presence of paroxetine.

Figure: HYD1005 Paroxetine drug interaction study - Mean (± SD) Plasma Concentrations of Hydrocodone (Top Panel), Norhydrocodone (Middle Panel), and Hydromorphone (Bottom Panel) Versus Time (Linear Scale)



Abbreviation: HYD, hydrocodone bitartrate.
Note: Lower standard deviation bars were removed from some of the data points because they were partly on the negative side of the y-axis.
Source: Figure 14.2.1.4.

What are the pharmacokinetics and pharmacodynamic characteristics of hydrocodone when Hysingla ER tablets are administered in conditions of abuse?

Extended release characteristics of Hysingla ER tablet are defeated upon chewing, crushing (milling) following oral administration, and after crushing followed by intranasal administration. However, systemic absorption of hydrocodone is low following intranasal abuse compared to hydrocodone powder.

Purdue conducted two clinical abuse liability (Tier 3) PK-PD studies to evaluated the abuse potential of Hysingla ER following oral and intranasal routes.

1. Oral abuse potential study HYD1013
2. Intranasal abuse potential study HYD1014

Study HYD1013 evaluated the abuse potential, pharmacokinetics, and safety oral milled, chewed and Intact Hysingla ER tablets in recreational opioid users. This was a single-center, double-blind/quadruple-dummy, randomized, placebo-controlled and active-controlled, 5-period crossover study in healthy nondependent recreational drug users with moderate experience with opioids (n=40).

The study consisted of 4 phases: screening, qualification, treatment, and follow-up. The screening phase included 2 visits: a screening visit (visit 1) and a naloxone challenge visit (visit 2). All subjects completed the naloxone challenge test at least 12 hours prior to drug administration in the qualification phase, to confirm that subjects were not opioid dependent.

During the treatment phase, subjects received each of the following 5 treatments according to the randomization schedule:

- Hysingla ER 60-mg tablet, intact (Lot number: CB-2011-41)
- Hysingla ER 60-mg tablet, milled (Lot number: CB-2011-41)
- Hysingla ER 60-mg tablet, chewed(Lot number: CB-2011-41)
- Hydrocodone API 60-mg solution (Lot number: CB-2012-063)
- Placebo (Lot number: CB-2011-45)

There was a 5 to 7 day washout period between study drug administrations.

The primary PD measures were “at the moment“ Drug Liking visual analog scale (VAS) on a bipolar scale, where 0-50 mm measure not liking the drug and 50 -100 mm measure liking the drug. Standard PK parameters were calculated for hydrocodone and hydromorphone and summarized using descriptive statistics.

Mean Cmax of hydrocodone was highest following the hydrocodone solution (127 ng/mL). Cmax values were lower following milled Hysingla ER (81.0 ng/mL) and chewed Hysingla ER (67.3 ng/mL) and lowest following intact Hysingla ER (48.4 ng/mL). Median Tmax of hydrocodone was 1.1 hours following the hydrocodone solution, was observed later following milled Hysingla ER (1.6 hours) and chewed Hysingla ER (8.0 hours) and latest following intact Hysingla ER (15.1 hours). This clearly indicates that extended-release characteristics of Hysingla ER tablets are defeated after chewing and crushing followed by oral consumption.

Figure: Mean Hydrocodone Plasma Concentrations Versus Time (Oral Administration) in Study HYD1013.

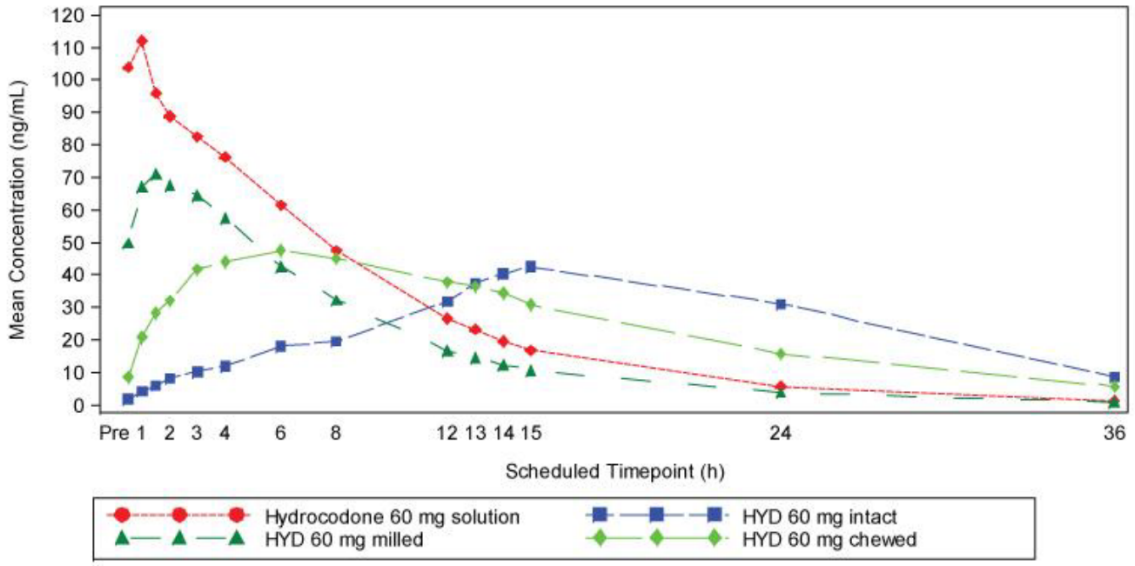
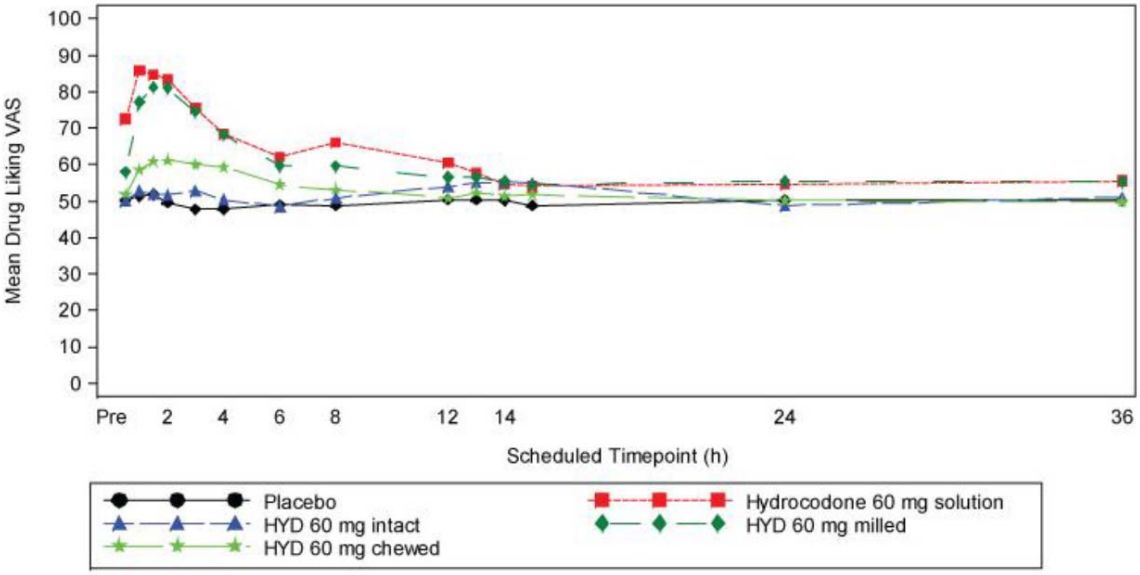


Figure: Mean Scores Over Time for Drug Liking VAS (Oral Administration, Chewed, Milled and Intact) in Study HYD1013.



Corresponding with the pharmacokinetics of hydrocodone, highest "at the moment" drug liking effects were noted following administration of hydrocodone solution followed by milled, chewed and intact Hysingla ER products administered orally; the time to peak drug liking VAS was a median value of 1 hr, 1.5 hr, 3 hr, and 3 hr, respectively.

Intact and chewed Hysingla ER treatments were associated with significantly lower effects for most subjective measures, with a delayed onset of effects relative to hydrocodone solution.

Table: Summary of Mean Hydrocodone Pharmacokinetic Parameters following Hysingla ER tablet (intact, milled, chewed) or hydrocodone solution oral administration.

Parameter	Statistic	Hydrocodone 60 mg solution (N=39[a])	HYD 60 mg intact (N=36[b])	HYD 60 mg milled (N=37)	HYD 60 mg chewed (N=36[c])
C_{max} (ng/mL)	Mean (SD)	127.1 (36.404)	48.38 (14.320)	81.00 (23.709)	67.26 (24.550)
	Median	127.0	49.80	73.70	67.60
	Range	49.0–218	22.7–76.0	49.3–169	27.2–125
	Geo Mean (%CV)	121.7 (31.45)	46.18 (32.56)	78.27 (25.93)	62.75 (40.28)
T_{max} (h)	Median	1.050	15.050	1.550	8.042
	Range	0.53–6.07	13.03–24.08	0.53–4.07	1.07–36.03
$t_{1/2}$ (h)	Median	5.413	7.055	5.380	5.611
	Range	3.72–7.14	4.62–9.15	4.20–7.56	4.41–7.55
AUC_{last} (h*ng/mL)	Mean (SD)	951.4 (238.05)	885.7 (208.03)	647.8 (201.17)	913.4 (217.94)
	Median	941.2	857.0	604.8	945.4
	Range	519–1439	536–1297	361–1299	486–1370
	Geo Mean (%CV)	921.2 (26.68)	861.4 (24.58)	621.6 (29.05)	885.9 (26.25)
AUC_{inf} (h*ng/mL)	Mean (SD)	971.4 (243.98)	1059 (265.97)	655.8 (206.40)	942.5 (243.94)
	Median	961.4	1139	614.4	946.9
	Range	521–1457	614–1402	363–1326	493–1398
	Geo Mean (%CV)	940.2 (26.93)	1026 (27.88)	628.7 (29.44)	909.7 (28.44)

Table: Summary of Maximum (Emax) Scores on Primary Endpoints and Measures of Balance of Effects Following Oral Administration of Hysingla ER (Chewed, Milled and Intact) in Recreational Opioid Users in Study HYD1013.

Parameter	Statistic	Placebo (N=35)	Hydrocodone 60 mg solution (N=35)	HYD 60 mg intact (N=35)	HYD 60 mg milled (N=35)	HYD 60 mg chewed (N=35)
E_{max}	Mean (SD)	52.3 (7.14)	94.0 (10.2)	63.3 (16.0)	89.2 (14.0)	69.0 (17.5)
	Median	51.0	100.0	58.0	93.0	66.0
	Range	50–87	51–100	50–100	50–100	50–100
TE_{max} (h)	Median	0.50	1.00	3.00	1.50	3.00
	Range	0.48–23.98	0.48–6.00	0.47–36.00	0.48–36.00	0.48–36.00
E_{min}	Mean (SD)	45.7 (14.0)	43.1 (18.9)	44.8 (13.1)	46.7 (20.5)	37.9 (19.1)
	Median	50.0	50.0	50.0	50.0	50.0
	Range	0–50	0–98	0–50	0–100	0–50
TE_{min} (h)	Median	0.50	6.00	0.50	3.00	1.98
	Range	0.48–14.98	0.48–24.00	0.48–36.00	0.48–36.00	0.48–36.00
TA_AUE	Mean (SD)	49.7 (2.55)	59.4 (13.0)	51.3 (8.65)	58.3 (15.0)	52.1 (11.0)
	Median	50.0	56.9	50.4	54.2	50.9
	Range	37.3–53.9	41.4–99.8	24.2–85.9	32.9–100.0	11.5–78.3

Source: Table 14.2.3.1.2

E_{max}=maximum effect; E_{min}=minimum effect; HYD=hydrocodone bitartrate q24h film coated tablet; Hydrocodone 60 mg solution=hydrocodone bitartrate, USP powder, administered as a 240 mL oral solution; PD=pharmacodynamic; SD=standard deviation; TA_AUE=time-averaged area under the effect curve; $TE_{max/min}$=time to peak effect; VAS=visual analog scale

Intranasal Abuse Study HYD1014

Study hyd1014 evaluated abuse potential, pharmacokinetics, and safety study of crushed and intranasally administered Hysingla ER tablets in recreational opioid users with a history of intranasal abuse. This was a single-center, double-blind, randomized, placebo-controlled and active-controlled, 4-period crossover study in non-dependent recreational drug users with moderate experience with opioids with a history of intranasal abuse (n=32).

The study consisted of 5 phases: screening, dose selection, qualification, treatment, and follow-up. The screening phase included 2 visits: a screening visit (visit 1) and a naloxone challenge visit (visit 2). All subjects completed the naloxone challenge test at least 12 hours prior to drug administration in the dose selection or qualification phases, to confirm that subjects were not opioid dependent. The dose (40 mg) of hydrocodone used during the qualification and treatment phases was determined during a dose selection phase. During the treatment phase, subjects received each of the following 4 treatments according to the randomization schedule:

- Hydrocodone API 60 mg powder
- Hysingla ER fine particle size 60 mg
- Hysingla ER coarse particle size 60 mg
- Placebo

There was a 5 to 7 day washout period between study drug administrations. The primary PD measures were "at the moment" Drug Liking VAS. Standard PK parameters were calculated for hydrocodone and hydromorphone and summarized using descriptive statistics.

There were statistically significant differences between placebo and hydrocodone powder for the primary measures of Drug Liking VAS. Relative to hydrocodone API powder, Hysingla ER coarse particle size and Hysingla ER fine particle size were associated with significantly lower effects on all subjective and objective measures, including both primary endpoints, and both Hysingla ER treatments were associated with greater intranasal effects, especially measures of nasal congestion and irritation. Crushed Hysingla ER fine particle size appeared to be associated with greater nasal congestion compared to Hysingla ER coarse particle size, but on most other outcome measures, the 2 treatments were not statistically different. The majority of subjects (>50%) showed at least a 30% reduction in Drug Liking VAS scores (responders) following administration of Hysingla ER coarse particle size and at least a 40% reduction in Drug Liking VAS scores following administration of Hysingla ER fine particle size.

Mean Cmax values of hydrocodone were considerably lower following Hysingla ER fine (36.5 ng/mL) and Hysingla ER coarse (27.5 ng/mL) than following hydrocodone powder (106 ng/mL), which may be related to the lower percentage of the dose observed to have been inhaled for Hysingla ER fine and Hysingla ER coarse than for hydrocodone API powder. Additionally, median Tmax was also observed later following Hysingla ER fine (3.1 hours) and Hysingla ER coarse (4.1 hours) than following hydrocodone API powder (1.6 hours).

The mean AUC_{last} value of hydrocodone was slightly higher following Hysingla ER fine (411.7 h*ng/mL) than following Hysingla ER coarse (317.9 h*ng/mL), but the standard deviations were large (205.65 and 292.66 h*ng/mL, respectively), indicating large variation between subjects. The mean AUC_{last} values following Hysingla ER fine and Hysingla ER coarse were considerably lower than the AUC_{last} value for hydrocodone powder (902.3 h*ng/mL). The results were similar for AUC_{inf}. Median t½ was approximately 6 hours following all 3 treatments.

Figure: Mean Hydrocodone Plasma Concentrations Versus Time following Intranasal Administration of Hysingla ER fine powder (Squares), coarse powder (Triangles) compared to hydrocodone powder (Circles) in Study HYD1014

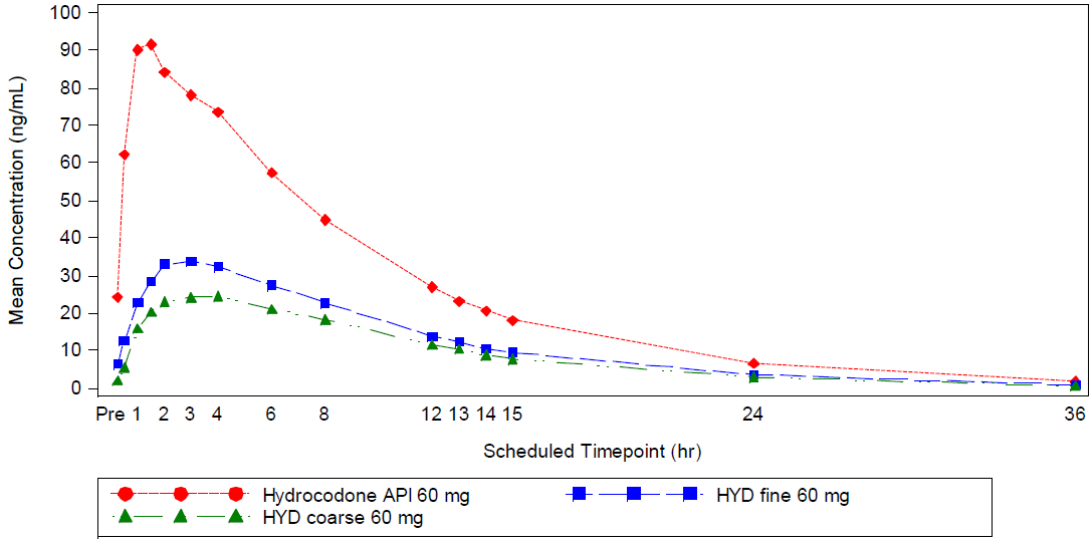


Figure: Mean Scores Over Time for Drug Liking VAS following Intranasal Administration of Fine Hysingla ER (Triangle) and Coarse Particle Size Hysingla ER (Diamond) compared to hydrocodone powder (Squares) and placebo (Circles) in Study HYD1014.

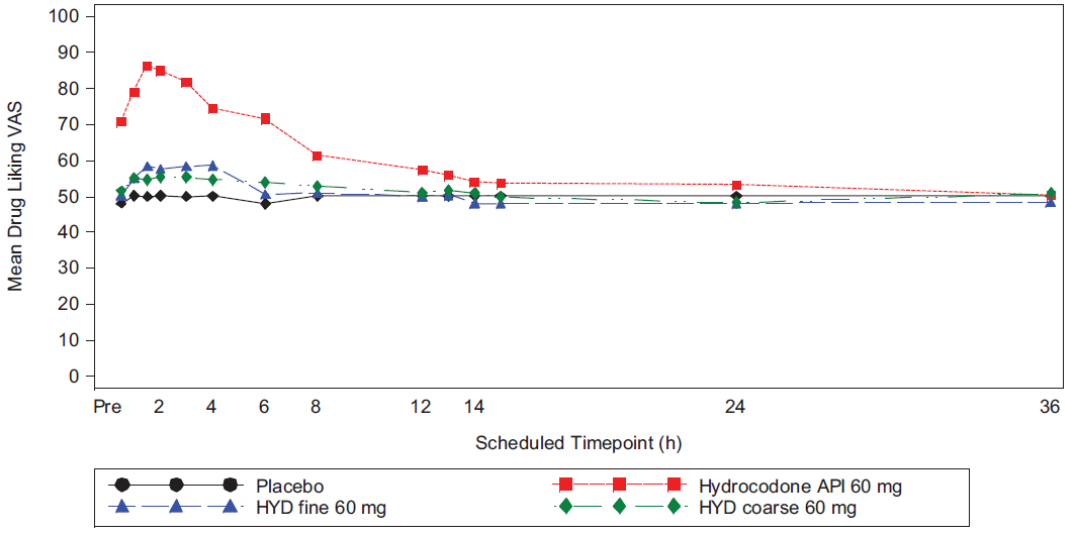


Table: Selected Descriptive Statistics of Derived Parameters for "at the moment" Drug Liking VAS.

Parameter	Statistic	Placebo (N=25)	Hydrocodone API 60 mg (N=25)	HYD fine 60 mg (N=25)	HYD coarse 60 mg (N=25)
E_{max}	Mean (SD)	50.6 (0.49)	90.4 (13.21)	66.8 (18.38)	65.4 (18.41)
	Median	51.0	100.0	61.0	56.0
	Range	50–51	51–100	50–100	50–100
T_{Emax} (h)	Median	0.98	1.00	1.98	1.00
	Range	0.48–13.98	0.48–6.00	0.48–36.00	0.50–13.00
E_{min}	Mean (SD)	45.7 (13.77)	45.2 (19.95)	45.7 (11.04)	42.4 (15.52)
	Median	50.0	50.0	50.0	50.0
	Range	0–50	0–100	0–50	0–50
T_{Emin} (h)	Median	0.50	11.98	0.52	0.50
	Range	0.47–6.00	0.48–36.00	0.48–24.02	0.48–24.00
TA_AUE	Mean (SD)	50.02 (0.66)	58.14 (10.74)	49.92 (10.32)	50.82 (3.17)
	Median	50.00	54.13	50.66	50.29
	Range	47.2–50.8	47.7–100.0	1.9–59.2	43.0–57.7

Source: Table 14.2.3.1.2

API=active pharmaceutical ingredient; E_{max}=maximum effect; E_{min}=minimum effect; HYD=hydrocodone bitartrate q24h film coated tablet; PD=pharmacodynamic; SD=standard deviation; TA_AUE=time-averaged area under the effect curve; $T_{Emax/min}$=time to peak effect; VAS=visual analog scale

Table: Summary of Mean Hydrocodone Pharmacokinetic Parameters.

Parameter	Statistic	Hydrocodone API 60 mg (N=27)	HYD fine 60 mg (N=27)	HYD coarse 60 mg (N=27)[a]
C_{max} (ng/mL)	Mean (SD)	105.8 (37.24)	36.49 (18.37)	27.49 (24.85)
	Median	97.10	37.80	22.10
	Range	29.4–173	6.69–75.5	0.165–85.3
	Geo Mean (%CV)	98.81 (41.43)	30.97 (71.06)	12.72 (441.1)
T_{max} (h)	Median	1.57	3.07	4.05
	Range	0.63–6.07	1.07–8.05	0.25–13.08
$t_{½}$ (h)	Median	5.98	5.94	5.73
	Range	4.87–7.57	4.89–8.12	4.63–7.96
AUC_{last} (h*ng/mL)	Mean (SD)	902.3 (293.78)	411.7 (205.65)	317.9 (292.66)
	Median	876.0	459.8	266.7
	Range	267–1589	61.8–802	0.248–956
	Geo Mean (%CV)	853.1 (37.00)	344.5 (76.95)	120.5 (944.0)
AUC_{inf} (h*ng/mL)	Mean (SD)	918.1 (304.23)	420.5 (211.40)	378.8 (289.10)
	Median	887.5	468.6	343.7
	Range	274–1626	63.3–815	7.28–977
	Geo Mean (%CV)	866.8 (37.33)	351.2 (77.38)	244.0 (178.5)

Sponsor indicates that when compared to placebo, both Hysingla ER treatments showed significantly higher scores on measures of balance, positive effects, sedative effects, any effects, and pupillometry. Hysingla ER treatments were also associated with greater negative effects, including intranasal effects.

Table: Summary of Select Pharmacodynamic Results

Measure	Endpoint	Treatment Effect *P* value	HCO API 60 mg - Placebo	HYD fine 60 mg - HCO API 60 mg	HYD coarse 60 mg - HCO API 60 mg	HYD fine 60 mg - Placebo	HYD coarse 60 mg - Placebo
Drug Liking VAS	E_{max}	<0.001	↑	↓	↓	↑	↑
	TA_AUE	<0.001	↑	↓	↓	↑	NS
Overall Drug Liking VAS	E_{max}	<0.001	↑	↓	↓	↑	↑
Take Drug Again VAS	E_{max}	<0.001	↑	↓	↓	↑	↑
SDV	E_{max}	<0.001	↑	↓	↓	↑	↑
High VAS	E_{max}	<0.001	↑	↓	↓	↑	↑
	TA_AUE	<0.001	↑	↓	↓	↑	↑
Good Effects VAS	E_{max}	<0.001	↑	↓	↓	↑	↑
	TA_AUE	<0.001	↑	↓	↓	↑	↑
ARCI MBG	E_{max}	<0.001	↑	↓	↓	↑	↑
	TA_AUE	<0.001	↑	↓	↓	↑	↑
Bad Effects VAS	E_{max}	0.018	↑	↓	NS	NS	NS
	TA_AUE	0.005	↑	↓	NS	NS	NS
Subject-Rated Assessment of Intranasal Effects							
Burning	E_{max}	0.006	↑	NS	NS	↑	↑
Need to Blow Nose	E_{max}	<0.001	↑	↑	↑	↑	↑
Runny Nose / Nasal Discharge	E_{max}	<0.001	NS	↑	↑	↑	↑
Facial Pain/Pressure	E_{max}	0.001	NS	↑	↑	NS	↑
Nasal Congestion	E_{max}	<0.001	↑	↑	↑	↑	↑
Observer-Rated Assessment of Intranasal Effects							
Nasal Congestion	E_{max}	<0.001	NS	↑	↑	↑	↑

Measure	Endpoint	Treatment Effect *P* value	HCO API 60 mg - Placebo	HYD fine 60 mg - HCO API 60 mg	HYD coarse 60 mg - HCO API 60 mg	HYD fine 60 mg - Placebo	HYD coarse 60 mg - Placebo
Nasal Irritation	E_{max}	<0.001	↑	↑	↑	↑	↑
Nasal Discharge	E_{max}	<0.001	NS	↑	↑	↑	↑
Drowsiness/ Alertness VAS	E_{min}	0.001	↓	↑	NS	NS	↓
Any Effects VAS	E_{max}	<0.001	↑	↓	↓	↑	↑
	TA_AUE	<0.001	↑	↓	↓	↑	↑
Pupillometry	MPC	<0.001	↑	↓	↓	↑	↑
	TA_PAOC	<0.001	↑	↓	↓	↑	↑

Source: Tables 14.2.3.1.3, 14.2.3.1.5, 14.2.3.2.3, 14.2.3.3.3, 14.2.3.4.3, 14.2.4.1.3, 14.2.4.1.4,14.2.4.2.3, 14.2.4.2.4, 14.2.4.3.3, 14.2.4.3.4, 14.2.5.1.3, 14.2.5.1.4, 14.2.5.3.3, 14.2.5.4.3, 14.2.5.5.3, 14.2.5.6.3,14.2.5.7.3, 14.2.8.2.3, 14.2.8.3.3, 14.2.8.4.3, 14.2.6.1.3, 14.2.7.1.3, 14.2.7.1.4, 14.2.8.1.3, and 14.2.8.1.4

↑ =significantly higher (*P*<0.05); ↓ =significantly lower (*P*<0.05); API=active pharmaceutical ingredient; ARCI MBG=Addiction Research Center Inventory Morphine-Benzedrine Group; E_{max}=maximum effect; E_{min}=minimum effect; HCO=hydrocodone; HYD=hydrocodone bitartrate q24h film coated tablet; MPC=maximum pupil constriction; NS=not statistically significant (*P*≥0.05); PD=pharmacodynamic; SDV=subjective drug value; TA_AUE=time-averaged area under the effect curve; TA_PAOC=time-averaged pupillometry area over the curve; VAS=visual analog scale

Pairwise comparisons were only presented if the treatment effect *P* value was significant. Treatment effect for Drug Liking VAS E_{min}, Overall Drug Liking VAS E_{min}, Feeling Sick VAS E_{max} and TA_AUE, and Drowsiness/Alertness TA_AUE is not included in this summary table.

Does Hysingla ER cause QT-prolongation?

There was no evident exposure-response relationship for change in QTcI based on hydrocodone concentration. However, it seems there are positive trends in exposure-response relationships for change in QTcI based on HYD metabolite norhydrocodone or hydromorphone concentration.

Integrated Review Team for QT issues reviewed the TQT Study HYD1009 and issued the following recommendation:

> *"This randomized study administrated of multiple doses (once daily for 3 days) of HYD titrated from 20 to 160 mg. A central tendency analysis of the individual corrected QT (QTcI) interval data at steady-state demonstrated that the maximum mean (90% upper confidence bound) difference in QTcI from placebo after baseline-correction was 9.9 (12.7) ms, 6.9 (10.2) ms, and 5.6 (8.5) ms at HYD 160 mg, 120 mg and 80 mg respectively. The largest 90% upper confidence bound for the mean differences at HYD 160 mg and 120 mg was above 10 ms, the threshold for regulatory concern as described in ICH E14 guidelines. The largest lower bound of the 2-sided 90% CI for the ΔΔQTcI for moxifloxacin was greater than 5 ms, and the moxifloxacin profile over time is adequately demonstrated in Figure 7, indicating that assay sensitivity was established.*
>
> *In this randomized, double-blind, placebo-and positive-controlled, multiple-dose escalation, parallel-design study, 208 subjects received HYD 80 mg, HYD 120 mg, HYD 160 mg, placebo, and moxifloxacin 400 mg. Overall summary of findings is presented in Table 1.*

Table 1: The Point Estimates and the 90% CIs Corresponding to the Largest Upper Bounds for HYD (80mg, 120 mg and 160 mg) and the Largest Lower Bound for Moxifloxacin (FDA Analysis)

Treatment Group	Time (hour)	ΔΔQTcI (ms)	90% CI (ms)
HYD 80 mg (Day 9)	24	5.6	(2.7, 8.5)
HYD 120 mg (Day 12)	24	6.9	(3.6, 10.2)
HYD 160 mg (Day 15)	10	9.9	(7.1, 12.7)
Moxifloxacin 400 mg (Day 9)*	3	11.6	(8.8, 14.5)
Moxifloxacin 400 mg (Day 12)*	3	9.7	(6.2, 13.2)
Moxifloxacin 400 mg (Day 15)*	4	8.7	(5.5, 11.8)

* Multiple endpoint adjustment was not applied. The largest lower bound after Bonferroni adjustment for 4 time points are 7.7 ms, 4.9 ms, and 4.3 ms on Days 9, 12 and 15; respectively.

The HYD dose (160 mg) produces mean steady state exposure 2-fold that of the therapeutic dose (80 mg) for both parent drug and major metabolites. There was no evident exposure-response relationship for

change in QTcI based on hydrocodone concentration. However, it seems there are positive trends in exposure-response relationships for change in QTcI based on HYD metabolite norhydrocodone or hydromorphone concentration."

Additionally the IRT-QT made labeling recommendations:

5.x QT INTERVAL PROLONGATION

QT prolongation has been observed with [TRADENAME]. [TRADENAME] should be avoided in patients with congenital long QT syndrome. In patients with congestive heart failure, bradyarrhythmias electrolyte abnormalities or who are taking medications that are known to prolong the QT interval, consider periodic monitoring with electrocardiograms and electrolytes. In patients who develop QTc prolongation, consider dose reduction [see Clinical Pharmacology (12.6)].

12.6 CARDIAC ELECTROPHYSIOLOGY

QTc interval prolongation was studied in a double-blind, placebo- and positive controlled 3-treatment parallel-group, dose-escalating study in 185 healthy subjects. A central tendency analysis of the QTcI data at steady-state demonstrated that the maximum mean (95% upper confidence bound) difference in QTcI from placebo after baseline-correction was 10 (13) ms, 7 (10) ms, and 6 (9) ms at [TRADENAME] 160 mg, 120 mg and 80 mg respectively.

Medical officer Dr. Jackie Spaulding evaluated cardiovascular safety, as it relates to QT-prolongation, of Hysingla ER with available data from clinical studies HYD3002 and HYD3003.

2.5 General Biopharmaceutics

Hysingla Extended-release hydrocodone bitartrate film coated tablets were developed to gradually release hydrocodone over a 24-hour period in the gastrointestinal tract following oral administration. The Hysingla formulation uses polyethylene oxide (PEO) as the (b) (4) excipient which provides multiple functions including release rate control, abuse-deterrence and resistance to alcohol induced dose dumping. The Hysingla ER drug product is a (b) (4) tablet. The (b) (4) .

The following USP/NF tablet compendial components are used to manufacture the product:

Polyethylene Oxide NF, Microcrystalline Cellulose NF, Hydroxypropyl Cellulose NF and Magnesium Stearate NF. The excipients were selected based on their widespread application in pharmaceutical formulations and experience gained from previous modified release products.

Prior to pivotal clinical studies the selected (b) (4) 20mg, 40 mg, 60 mg, 80 mg and 120 mg tablet formulations were modified slightly to produce tablets with film colors and strengths intended for commercial product. These formulations were used for open label clinical studies. A blinded version of the phase 3 formulations used a single color film coat for all tablet strengths and placebo.

The sponsor is also planning on marketing 30 mg and 100 mg strengths of the tablet and they have submitted a request for biowaiver which is being reviewed by Biopharmaceutics Reviewer Dr. Akm Khairuzzaman.

What is the effect of food on the bioavailability (BA) of the hydrocodone from Hysingla ER tablets? What dosing recommendation should be made, if any, regarding administration of the product in relation to meals or meal types?

Hydrocodone Cmax was higher (54%) under high fat conditions relative to fasting conditions; however, hydrocodone AUC with Hysingla ER 120 mg tablets was only 20% higher when coadministered with a high fat meal. Both Cmax and AUC of hydrocodone with Hysingla ER 120 mg tablets were similar under low fat conditions relative to fasting conditions (17% and 9% higher, respectively). The controlled clinical trial HYD3002, and open-label safety study HYD3003 were conducted in patients who consumed Hysingla ER tablets without regard to food consumption.

Study HYD1003 (Definitive Food Effect Study) evaluated food effect on PK of hydrocodone following Hysingla ER 120-mg tablet administered in fasted state and after a high fat meal and a low fat meal. This was a randomized, open-label, single-dose, single-center, 3-way crossover study in healthy female and male subjects (n=50).

Each subject was administered the following treatments according to the randomization schedule:

- Hysingla ER 120 mg tablet in the fasted state

- Hysingla ER 120 mg tablet after a low fat meal
- Hysingla ER 120 mg tablet after a high fat meal

Study drug was administered with 240 mL of water. Fasted doses were preceded by an overnight fast (ie, at least 10 hours) from food (not including water) and were followed by a 4-hour fast (not including water). For fed dosing, subjects fasted from food overnight for at least 10 hours. Subjects restricted their consumption of water for 3 hours prior to dose and for 2 hours postdose. Subjects started the standardized high fat or low fat content breakfast 30 ± 5 minutes prior to the administration of the dose. Each dose was administered 5 ± 2 minutes after completing breakfast, where the breakfast was consumed over approximately a 25-minute time interval. No food was allowed for 4 hours postdose.

Standard High Fat Meal

Menu	2 eggs fried in butter 2 strips of bacon 2 slices of toast with butter 4 ounces of hash brown potatoes fried with butter 8 ounces (240 mL) of whole milk
Total fat content	Approximately 500 to 600 calories
Total protein	Approximately 150 calories
Total carbohydrate	Approximately 250 calories

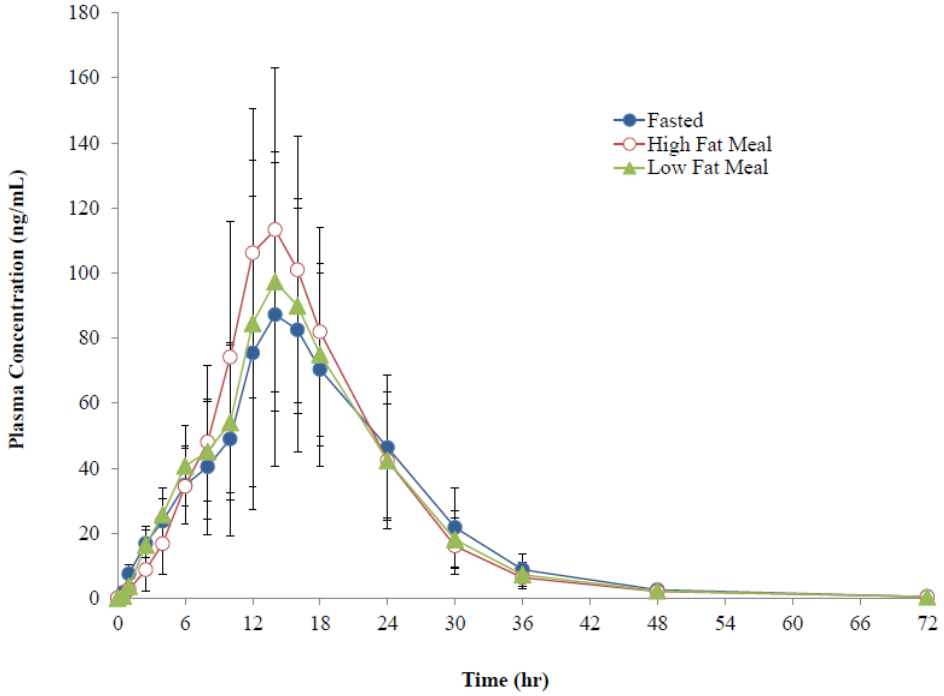
Source: CSR HYD 1003, Table 9-1.
Note: Substitutions in the content of the meal were allowed if a similar breakdown of calories was given and if meal volume and viscosity were also similar.

Low Fat Meal

Menu	2 slices bread 2 packets jelly 8 ounces (240 mL) of skim milk
Total fat content	Approximately 23 calories
Total protein	Approximately 48 calories
Total carbohydrate	Approximately 184 calories

Hydrocodone Cmax was higher (54%) under high fat conditions relative to fasting conditions; however, the AUC of Hysingla ER 120 mg tablet was only 20% higher when co-administered with a high fat meal. Hydrocodone Cmax and AUC of Hysingla ER 120 mg tablets were similar under low fat conditions relative to fasting conditions (17% and 9% higher, respectively).Estimated geometric mean hydrocodone Cmax and AUC of Hysingla ER 120 mg were 54% and 20% higher, respectively, when administered after a high fat meal relative to the values in the fasted state. Estimated geometric mean hydrocodone Cmax and AUC values obtained when Hysingla ER 120-mg was administered after a low fat meal were similar to the values obtained in the fasted state (17% and 9% higher, respectively; see Table below).

Figure: Mean Hydrocodone Plasma Concentration Versus Time Profiles following the administration of Hysingla ER 120 mg tablets Under Fasted (Closed Circle), High Fat (Open Circle), and Low Fat (Triangle) Conditions in Study HYD1003.



Source: Adapted from CSR HYD1003, Figure 1.

Table: Statistical Analysis of the Effect of Food intake on the Hydrocodone Relative Bioavailability From 120-mg HYD tablets in Study HYD1003.

Metric (unit)	LS Geometric Means[a]		Estimated mean Ratio Test/ Reference (%)[b]	90% CI of Ratio[c]
	Fed (test)	Fasted (reference)		
High fat meal treatment versus fasted treatment; 120-mg HYD				
AUCinf (h*ng/mL)	1744	1448	120	106, 137
AUCt (h*ng/mL)	1735	1441	120	106, 137
Cmax (ng/mL)	139	90.1	154	138, 173
Low fat meal treatment versus fasted treatment; 120-mg HYD				
AUCinf (h*ng/mL)	1578	1448	109	95.8, 124
AUCt (h*ng/mL)	1571	1441	109	95.8, 124
Cmax (ng/mL)	105	90.1	117	104, 131

Source: CSR HYD1003, Table 11-3.
CV=coefficient of variation; CI=confidence interval; LS=least squares.
[a] Least squares mean from analysis of variance. Natural log (ln) metric means were calculated by transforming the ln means back to the linear scale, ie, geometric means.
[b] Ratio of metric means for ln-transformed metrics (expressed as a percentage). Ln-transformed ratio was transformed back to linear scale.
[c] The 90% CI for ratio of metric means (expressed as a percentage). Ln-transformed confidence limits were transformed back to linear scale.

Note: Although average values indicate small effect of food on the Hysingla ER bioavailability of hydrocodone, significant inter-individual variability is noted as shown in the figure below. For example, %CV of 37 – 44% for AUC and Cmax in fasted subjects relates to a wide range of plasma concentration (Cmax range 17 – 256 ng/mL, AUC range 198 – 2950 ng.h/mL).

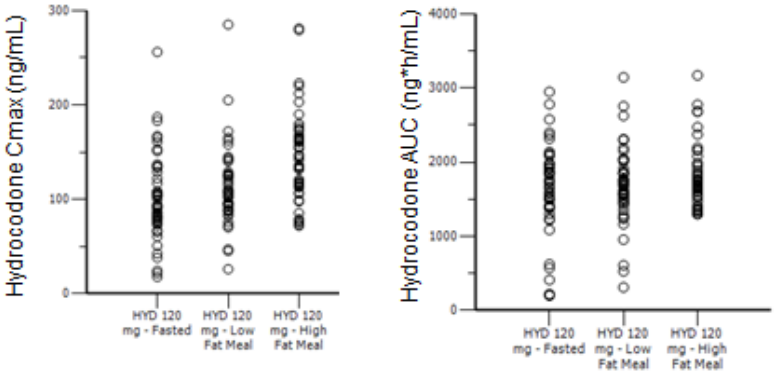
Table: Summary of Plasma Pharmacokinetic Metrics of Hydrocodone following administration of Hysingla ER tablets under fasting, high-fat meal fed, and low-fat meal fed conditions.

Metric (Unit)	HYD 120 mg Fasted N = 51	HYD 120 mg High Fat Meal N = 51	HYD 120 mg Low Fat Meal N = 49
AUCt (ng•h/mL)			
Mean	1633.03	1774.07	1667.77
SD	603.227	416.652	505.454
%CV	36.9	23.5	30.3
Minimum, Maximum	193.08, 2940.16	1295.11, 3162.67	306.98, 3134.96
AUCinf (ng•h/mL)			
Mean	1639.56	1782.07	1674.86
SD	604.654	416.781	506.357
%CV	36.9	23.4	30.2
Minimum, Maximum	197.66, 2946.81	1298.50, 3169.87	310.33, 3142.86
Cmax (ng/mL)			
Mean	101.46	145.63	112.29
SD	44.894	46.748	41.358
%CV	44.2	32.1	36.8
Minimum, Maximum	17.70, 256.00	71.90, 281.00	26.00, 285.00
Tmax (h)			
Mean	14.32	14.40	13.64
SD	3.948	3.228	2.699
%CV	27.6	22.4	19.8
Median	14.00	14.00	14.00
Minimum, Maximum	4.00, 24.00	10.00, 24.07	6.00, 18.02
t1/2 (h)			
Mean	8.57	9.14	9.03
SD	3.164	3.243	3.286
%CV	36.9	35.5	36.4
Minimum, Maximum	3.89, 21.31	4.69, 16.18	4.66, 19.62
Tlag (h)			
Mean	0.00	0.31	0.11
SD	0.000	0.349	0.234
%CV	-	114.1	208.6
Median	0.00	0.00	0.00
Minimum, Maximum	0.00, 0.00	0.00, 1.00	0.00, 1.00

Abbreviations: %CV, coefficient of variation; HYD, hydrocodone bitartrate; SD, standard deviation.
Source: Table 14.2.2.

Figure: Individual Cmax (Left) and AUC (Right) values noted in study HYD1003

- Cmax Range
- AUC Range with food-effect



Similar observation of the extent of food-effect and the variability across individuals (n=16) was noted in iteration 5 of the bioavailability study HYD1001.

In Food-effect Study HYD1003, inter-individual variability decreased under fed condition, particularly after high-fat meal consumption. It was noted that bioavailability (Cmax and or AUC) of four subjects was very low under fasting condition compared to average values in the group. Compared to their low plasma exposure under fasting condition, these subjects had up to 8-fold higher increase in Cmax and or AUC under high-fat meal fed condition. In terms of an explanation for low systemic exposure in the four individuals, one subject vomited after receiving Hysingla ER under fasting condition with the three other subjects possibly experiencing emesis (not reported). The sponsor also provided an explanation for the possible low bioavailability in terms of inter-occasion variability (See Appendix 4.2.

Does the Hysingla ER tablet formulation exhibit dosage-form proportionality or Are multiples of lower strength Hysingla ER formulations equivalent to one Hysingla ER tablet of higher strength?

AUC and Cmax of hydrocodone following the administration of a Hysingla ER 1 x 80-mg tablet and Hysingla ER 4 x 20-mg tablets were comparable.

In study HYD1001, there was a single-dose, 2-period, 2-way crossover design iteration/cohort that evaluated the dosage-form proportionality. Twenty-four subjects (14M/10F) with ages ranging from 18 to 44 years (mean: 25.7 years) were randomized and 24 subjects (100%) completed the study.

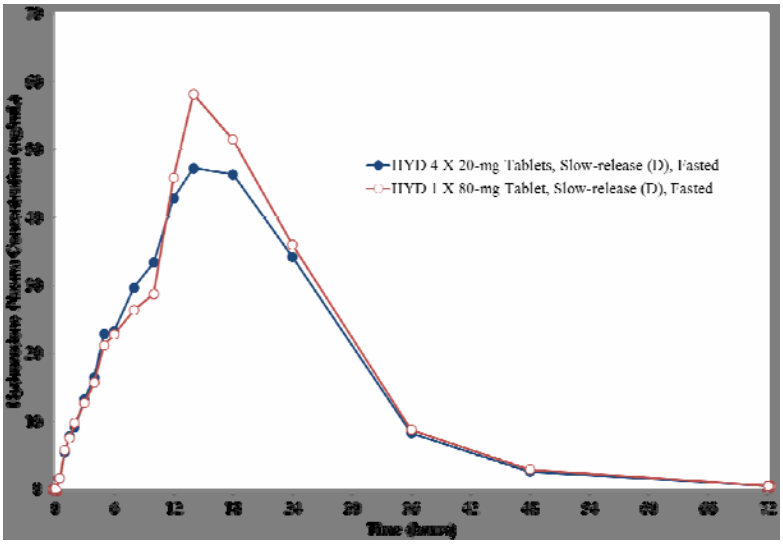
Each subject was administered the following treatments according to the randomization schedule:

- Hysingla ER 4 x 20-mg slow-release (D) tablets in the fasted state (Lot number: CB-2011-04)

• Hysingla ER 1 x 80-mg slow-release (D) tablet in the fasted state (Lot number: CB-2011-10)

According to sponsor's analysis, AUC and Cmax of hydrocodone following the administration of a Hysingla ER 1 x 80-mg tablet and Hysingla ER 4 x 20-mg tablets were comparable (differences were 9% and 18%, respectively lower, based on least squares (LS) means). Median Tmax was 14 and 18 hours following a Hysingla ER 1 x 80-mg tablet and Hysingla ER 4 x 20-mg tablets, respectively. Mean t1/2 was ~8 hours for both treatments.
During review, one subject who experienced emesis as an adverse event was noted to have low plasma hydrocodone levels in the 4 X20 mg tablet group. Excluding that individuals data improved the bioavailability comparison, although still not bioequivalent respect to Cmax.

Figure: Mean Hydrocodone Plasma Concentration Versus Time Profiles Following 80-mg Hydrocodone Bitartrate, Administered as 4 Hysingla ER 20 mg Tablets and as 1 Hysingla ER 80-mg Tablet, Formulation D in Study HYD1001 Iteration 6.



Source: Adapted from CSR HYD1001, Figure 19.

Table: Statistical Analysis of the Relative Bioavailability of 20-mg and 80-mg strengths of Hysingla ER tablets in Study HYD1001 Iteration 6 (without excluding any subjects – Sponsor's analysis).

Metric (unit)	Geometric LS Means			Ratio	
	4 x 20-mg HYD (test)	1 x 80-mg HYD (reference)	CV (%)	Test/ Reference (%)	90% CI of Ratio
AUCinf (h*ng/mL)	1099	1207	20.9	91.0	82.1, 101
AUCt (h*ng/mL)	1092	1188	20.3	92.0	83.3, 102
Cmax (ng/mL)	52.6	64.3	25.8	81.8	72.1, 92.7

Source: CSR HYD1001, Table 19.
CI=confidence interval; CV=coefficient of variation; LS=least squares.
[a] Least squares mean from analysis of variance. Natural log (ln) metric means were calculated by transforming the ln means back to the linear scale, ie, geometric means.
[b] Ratio of metric means for ln-transformed metrics (expressed as a percentage). Ln-transformed ratio was transformed back to linear scale.
[c] The 90% CI for ratio of metric means (expressed as a percentage). Ln-transformed confidence limits were transformed back to linear scale.

Table: Statistical Analysis of the Relative Bioavailability of 20-mg and 80-mg strengths of Hysingla ER tablets in Study HYD1001 Iteration 6 (excluding one subject who experienced emesis).

Metric (unit)	Geometric LS Means		CV%	Ratio	
	4 X 20 mg HYD (test)	1 X 80 mg HYD (reference)		Test/ Reference (%)	90% CI of Ratio
AUCinf (ng h/mL)	1151	1172	20.8	98.3	92 – 105
AUCt (ng h/mL)	1148	1168	20.7	98.3	92 – 105
Cmax (ng/mL)	54.7	63	24.6	86.8	77.7 – 97

2.6 Analytical

Bioanalytical methods used for the analysis of plasma samples to determine concentrations of free base equivalent hydrocodone, and its metabolites norhydrocodone and hydromorphone, and paroxetine, ketoconazole and moxifloxacin from all Hysingla ER studies submitted in this New Drug Application (NDA) are summarized in this section and in the Table below.

Table: Brief Overview of Bioanalytical Methods Used for the Analysis of Plasma Samples in the Hysingla ER Clinical Development Program.

Study No	Analyte in Plasma	Method ID	Technique/ Sample Extraction	Validated Concentration Range	Bioanalytical Facility/Location	Assay Validation Report No	Bioanalytical Report No
HYD1001	Hydrocodone	TM.848	LC/ESI/MS/MS Liquid-phase	0.100 – 100 ng/mL	(b) (4)	5584.011609	5684.060109 HYD-P-013
HYD1002	Hydrocodone Hydromorphone Norhydrocodone	TM.1117	LC/ESI/MS/MS Liquid-phase	0.100 – 100 ng/mL 0.0250 – 25.0 ng/mL 0.0250 – 25.0 ng/mL		6782.012111	6770.033111 HYD-P-026
HYD1003	Hydrocodone	LCMSC 492.6 V 1.00	HPLC-MS/MS Liquid-phase	0.100 – 100 ng/mL		TVX2	(b) (4) Project EXY HYD-P-035
HYD1004	Hydrocodone	LCMSC 492 V 1.02	HPLC-MS/MS Liquid-phase	0.100 – 100 ng/mL		PYT2, PYT4	(b) (4) Project GCY HYD-P-032
HYD1005	Hydrocodone Hydromorphone Norhydrocodone	LCMSC 492.6 V 1.00	HPLC-MS/MS Liquid-phase	0.100 – 100 ng/mL 0.0500 – 50.0 ng/mL 0.100 – 100 ng/mL		TVX2	(b) (4) Project SMZ HYD-P-040
	Paroxetine	LCMS 161 V 1.04	HPLC-MS/MS Liquid-phase	0.250 – 50.0 ng/mL		YDJ	(b) (4) Project TMZ HYD-P-042
HYD1006	Hydrocodone Hydromorphone Norhydrocodone	LCMSC 492.6 V 1.00	HPLC-MS/MS Liquid-phase	0.100 – 100 ng/mL 0.0500 – 50.0 ng/mL 0.100 – 100 ng/mL		TVX2	(b) (4) Project LDY HYD-P-033
HYD1007	Hydrocodone Hydromorphone Norhydrocodone	LCMSC 492.6 V 1.00	HPLC-MS/MS Liquid-phase	0.100 – 100 ng/mL 0.0500 – 50.0 ng/mL 0.100 – 100 ng/mL		TVX2	(b) (4) Project JCZ HYD-P-36
HYD1008	Hydrocodone Hydromorphone Norhydrocodone	LCMSC 492.6 V 1.00	HPLC-MS/MS Liquid-phase	0.100 – 100 ng/mL 0.0500 – 50.0 ng/mL 0.100 – 100 ng/mL		TVX2	(b) (4) Project BEY HYD-P-37
HYD1009	Hydrocodone Hydromorphone Norhydrocodone	LCMSC 492.6 V 1.00	HPLC-MS/MS Liquid-phase	0.100 – 100 ng/mL 0.0500 – 50.0 ng/mL 0.100 – 100 ng/mL		TVX2	(b) (4) Project POZ HYD-P-044
	Moxifloxacin	LCMSB 276 V 1.02	HPLC-MS/MS Liquid-phase	25.0 – 5000 ng/mL		DJM2	HYD-P-046
HYD1012	Hydrocodone Hydromorphone Norhydrocodone	LCMSC 492.6 V 1.00	HPLC-MS/MS Liquid-phase	0.100 – 100 ng/mL 0.0500 – 50.0 ng/mL 0.100 – 100 ng/mL		TVX2	(b) (4) Project IHZ HYD-P-039
	Ketoconazole	LCMSB 202 V 3.00	HPLC-MS/MS Liquid-phase	0.100 - 20.0 µg/mL		THQ2	HYD-P-041
HYD1013	Hydrocodone Hydromorphone Norhydrocodone	TM.1117	LC/ESI/MS/MS Liquid-phase	0.100 – 100 ng/mL 0.0250 – 25.0 ng/mL 0.0250 – 25.0 ng/mL		6782.012111	HYD-P-053
HYD1014	Hydrocodone Hydromorphone Norhydrocodone	TM.1117	LC/ESI/MS/MS Liquid-phase	0.100 – 100 ng/mL 0.0250 – 25.0 ng/mL 0.0250 – 25.0 ng/mL		6782.012111	HYD-P-054
HYD1016	Hydrocodone	LCMSC 492.6 V 1.00	HPLC-MS/MS Liquid-phase	0.100 – 100 ng/mL		TVX2	(b) (4) Project RUZ HYD-P-045

Study No	Analyte in Plasma	Method ID	Technique/ Sample Extraction	Validated Concentration Range	Bioanalytical Facility/Location	Assay Validation Report No	Bioanalytical Report No
HYD3003	Hydrocodone Hydromorphone Norhydrocodone	TM.1117	LC/ESI/MS/MS Liquid-phase	0.100 – 100 ng/mL 0.0250 – 25.0 ng/mL 0.0250 – 25.0 ng/mL	(b) (4)	6782.012111	HYD-P-056

Additional methods were validated and used to measure the concentrations of hydrocodone, hydromorphone, and norhydrodocone in urine, dialysate and plasma protein binding. These methods are summarized in the tables below (matrix urine) and (other matrices) and Section 4.2.1.

Table: Brief Overview of Bioanalytical Methods Used for the Analysis of Urine Samples in the Hysingla ER Clinical Development Program

Study No	Analyte (s)	Matrix	Method ID	Technique/ Sample Extraction	Validated Conc. Range	Bioanalytical Facility/Location	Assay Validation Report No	Bioanalytical Report No
HYD1008	Hydrocodone Hydromorphone Norhydrocodone	Urine	LCMSC 492.7 V 1.00	HPLC-MS/MS Liquid-phase	10.0 – 10000 ng/mL 5.00 – 5000 ng/mL 10.0 – 10000 ng/mL	(b) (4)	QTY2	(b) (4) Project HCZ HYD-P-038

Table: Brief Overview of Other Bioanalytical Methods Used in The Clinical Development Program

Study No	Analyte (s)	Matrix	Method ID	Technique/ Sample Extraction	Validated Concentration Range	Bioanalytical Facility/Location	Assay Validation Report No	Bioanalytical Report No
HYD1007	Hydrocodone Norhydrocodone	Plasma Protein	LCMSC 616 V 1.00	HPLC-MS/MS Liquid-phase protein precipitation	0.100 – 100 ng/mL 0.100 – 100 ng/mL	(b) (4)	RTY2	(b) (4) Project KCZ HYD-P-043
HYD1008	Hydrocodone Hydromorphone Norhydrocodone	dialysate	LCMSC 616 V 1.00	HPLC-MS/MS Liquid-phase	0.0200 – 20.0 ng/mL 0.0100 – 10.0 ng/mL 0.0200 – 20.0 ng/mL		IJZ2	HYD-P-047

Each method was validated and adopted at the respective bioanalytical facility according to applicable guidelines at the time, under Good Laboratory Practice (GLP) regulations. Analyses of the samples were conducted in GLP-compliant facilities and the laboratory procedures were followed in accordance with applicable Food and Drug Administration (FDA) GLP guidelines. Quality control procedures and acceptance criteria were based on the FDA Guidance for Industry, Bioanalytical Method Validation (2001).

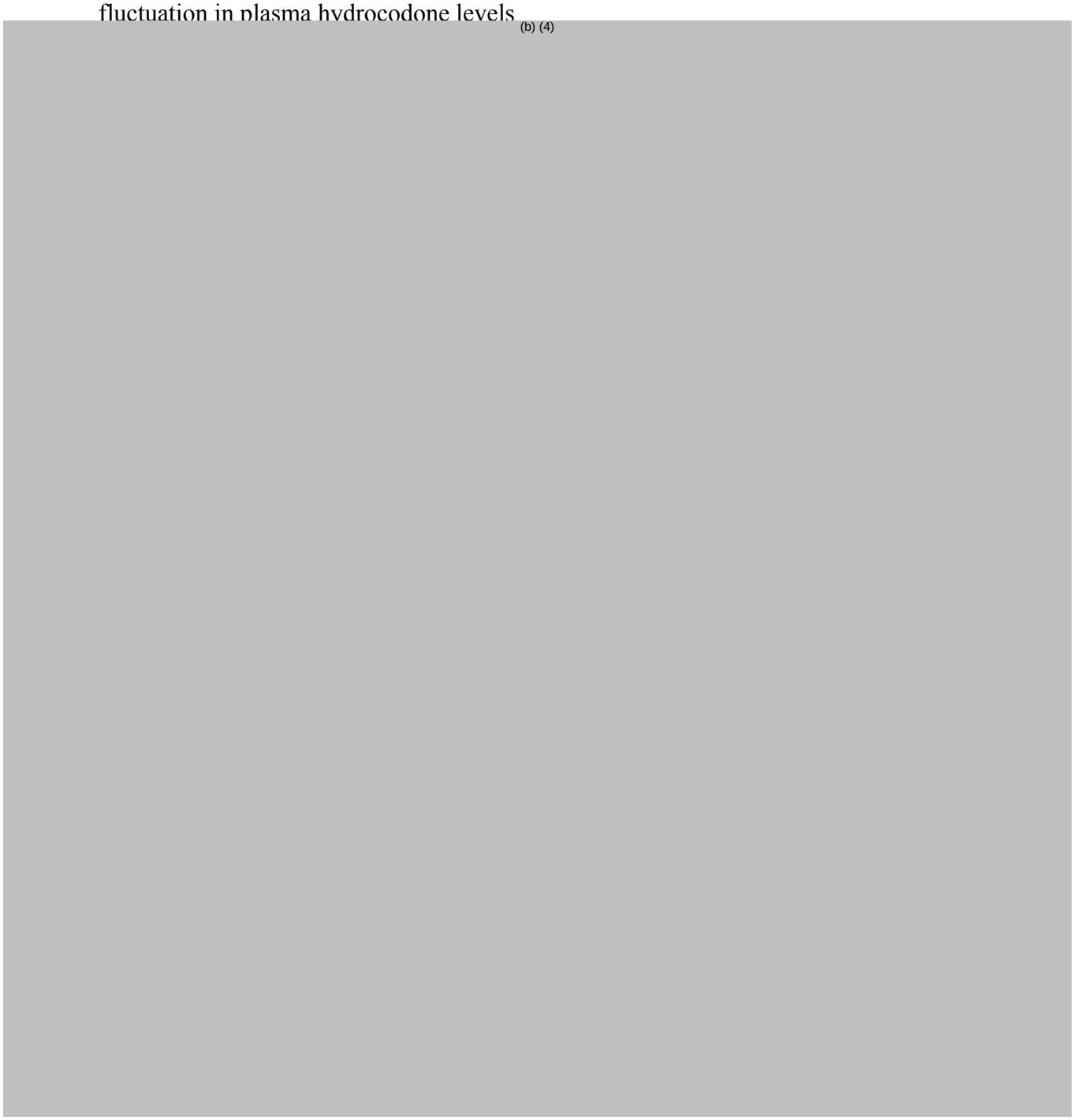
The long term stability of frozen plasma samples of hydrocodone, hydromorphone, and norhydrocodone were assessed at -20°C and -70°C after 0, 2 weeks and at 1, 3, 6, and 11 months (reference (b) (4) study number 6770-119, HCDSR04-073:1). In addition, the stability of these analytes in human plasma was evaluated for 113, 225, and 427 days at -20°C and for 113 days at -70°C ((b) (4) study number LCMSC 492 Addendum 5). The plasma samples for all listed studies were analyzed well within the established stability for the analytes.

The summaries of the 10 methods in total are presented in the tables above in the order and are described briefly in Section 4.2.1.

3 Labeling

The sponsor submitted labeling with the original submission had several references to bioavailability comparison between Hysingla ER and Vicoprofen. In an information request dated July 10th, 2014, Purdue was provided with several comments to amend the clinical pharmacology section (12.3) of the proposed product label. Comments were provided to adequately describe the pharmacokinetic characteristics of single and multiple-dose Hysingla ER administration including variability noted in terms of fluctuation in plasma hydrocodone levels

(b) (4)



4.2 Individual Study Reviews

4.2.1 Bioanalytical Assay Validation Summary

Bioanalytical methods used for the analysis of plasma samples to determine concentrations of free base equivalent hydrocodone, and its metabolites norhydrocodone and hydromorphone, and paroxetine, ketoconazole and moxifloxacin from all Hysingla ER studies submitted in this New Drug Application (NDA) were summarized in Section 2.6 in several tables.

Additional methods were validated and used to measure the concentrations of hydrocodone, hydromorphone, and norhydrodocone in urine, dialysate and plasma protein binding. These methods are summarized in the tables in Section 2.6 and below (matrix urine) and (other matrices).

Each method was validated and adopted at the respective bioanalytical facility according to applicable guidelines at the time, under Good Laboratory Practice (GLP) regulations. Analyses of the samples were conducted in GLP-compliant facilities and the laboratory procedures were followed in accordance with applicable Food and Drug Administration (FDA) GLP guidelines. Quality control procedures and acceptance criteria were based on the FDA Guidance for Industry, Bioanalytical Method Validation (2001).

The long term stability of frozen plasma samples of hydrocodone, hydromorphone, and norhydrocodone were assessed at -20°C and -70°C after 0, 2 weeks and at 1, 3, 6, and 11 months (reference (b) (4) study number 6770-119, HCDSR04-073:1). In addition, the stability of these analytes in human plasma was evaluated for 113, 225, and 427 days at -20°C and for 113 days at -70°C ((b) (4) study number LCMSC 492 Addendum 5). The plasma samples for all listed studies were analyzed well within the established stability for the analytes.

The summaries of the 10 methods in total were presented in Section 2.6 as tables above in the order and are described briefly below.

Hydrocodone Assay Method TM.848 and Validation Summary. (b) (4) (b) (4) Method Identification No. TM.848, Assay Validation Report No. 5584.011609, Issued April 2009

Hydrocodone and the IS are extracted into methyl tertiary-butyl ether in the presence of ammonium acetate. Following centrifugation, the organic layer is transferred and evaporated to dryness. An aliquot of the reconstituted extract is injected using a CTC Analytics HTS PAL automated sample injector and a Shimadzu Prominence liquid chromatograph with a Betasil silica column interfaced to a MDS Sciex API 4000 mass spectrometer with a turbo ionspray probe. Peak areas of the m/z 301 to 199 product ion of hydrocodone are measured against the m/z 303 to 199 product ion of the IS.

Quantification was performed using weighted ($1/x^2$) linear least squares regression (WLLSR) generated from calibration standards prepared immediately prior to each run. The assay was found to be linear over the 0.100 to 100 ng/mL range based on a 100-µL sample. WLLSR

analysis gave a correlation coefficient (r) of 0.9993 or better for hydrocodone during validation.

The lower limit of quantification (LLOQ) was verified by analyzing six replicates of the lowest standard calibrator (0.100 ng/mL). The absolute % deviation (%RE) was 0.700% and the CV% was 3.63% about the mean demonstrating the ruggedness of the assay at the LLOQ.

To evaluate the precision and accuracy of the assay, quality control (QC) samples were prepared from a separate set of stock solutions in low (0.3 ng/mL), mid (10 ng/mL) and high (80 ng/mL) concentrations, and were analyzed using six replicates on each day of validation. The CV% ranged from 0.763% to 1.93% while the absolute %RE ranged from 0.00% to 4.00%.

Hydrocodone QC samples were stable over five freeze/thaw cycles. Extracted QC samples were found to be stable in reconstitution solvent for up to 97 hours at approximately 4°C.

Hydrocodone, Hydromorphone and Norhydrocodone Assay Method TM.1117 and Validation Summary, (b) (4) ; Method Identification No. TM.1117, Assay Validation Report No. 6782.012111, Issued April 2011.

Hydrocodone, hydromorphone and norhydrocodone and the ISs are extracted into ethyl acetate. Following centrifugation, the organic layer is transferred and evaporated to dryness. An aliquot of the reconstituted extract is injected using a CTC Analytics HTS PAL automated sample injector and Agilent 1100 Series LC pumps with a Betasil silica column interfaced to a MDS Sciex API 4000 mass spectrometer with a turbo ionspray probe. Peak areas of the m/z 300.1 to 199.1 product ion of hydrocodoneare measured against the m/z 303.1 to 199.1 product ion of the internal standard (IS). For hydromorphone, the peak areas of the m/z 286.1 to 185.0 product ion are measured against the m/z 292.1 to 185.0 product ion of the IS, and for norhydrocodone the peak areas of the m/z 286.1 to 199.1 product ion are measured against the m/z 289.1 to 202.1 product ion of the IS.

Quantification was performed using WLLSR generated from calibration standards prepared immediately prior to each run. The assay was found to be linear from 0.100 to 100 ng/mL for hydrocodone and from 0.0250 to 25.0 ng/mL for hydromorphone and norhydrocodone, based on a 100-µL sample. WLLSR analysis gave a correlation coefficient (r) of 0.9983 or better during the five or more days of validation.

The LLOQ was verified by analyzing six replicates of the lowest standard calibrator (0.100 ng/mL for hydrocodone and 0.0250 ng/mL for hydromorphone and norhydrocodone). The absolute %RE was 6.00%, 10.8% and 5.60% for hydrocodone, hydromorphone and norhydrocodone, respectively. The CV% were 4.13%, 7.73%, and 5.64%, respectively demonstrating the ruggedness of the assay at the LLOQ.

To evaluate the precision and accuracy of the assay, QC samples were prepared from a separate set of stock solutions in concentrations of 0.3, 10, and 80 ng/mL for hydrocodone, and of 0.075, 2.5 and 20 ng/mL for hydromorphone and norhydrocodone. The QC samples

were analyzed using six replicates on each day of validation. The CV% for hydrocodone concentrations ranged from 1.32% to 3.19% while the absolute %RE ranged from 0.333% to 1.00%. The CV% for hydromorphone concentrations ranged from 1.99% to 4.79% while the absolute %RE ranged from 0.00% to 1.50%, and the CV% for norhydrocodone concentrations ranged from 2.56% to 6.42% while the absolute %RE ranged from 0.800% to 6.80%.

QC samples of all three analytes were stable over nine freeze/thaw cycles. Extracted QC samples were found to be stable in reconstitution solvent at 2 and 8°C for up to 118 hours.

Hydrocodone, Hydromorphone and Norhydrocodone Assay Method 492.6 V 1.00 and Validation Summary, (b) (4) Method Identification No. LCMSC 492.6 V 1.00, Assay Validation Report No. TVX2, Issued February 2012.

Hydrocodone, hydromorphone and norhydrocodone and the ISs are isolated through extraction and eluted with 1.6 mL of dichloromethane. The eluate is evaporated to dryness and the remaining residue is reconstituted. The final extract is analyzed via high performance liquid chromatography (HPLC) with column-switching and tandem mass spectrometry (MS/MS) detection using positive ion electrospray. Peak areas of the m/z 300.3 to 199.1 product ion of hydrocodone, are measured against the m/z 303.3 to 199.1 product ion of the ISs. For hydromorphone, the peak areas of the m/z 286.1 to 185.1 product ion are measured against the m/z 289.2 to 185.1 product ion of the IS, and for norhydrocodone the peak areas of the m/z 286.2 to 199.1 product ion are measured against the m/z 289.2 to 202.1 product ion of the IS.

Quantification was performed using WLLSR generated from calibration standards prepared immediately prior to each run. The assay was found to be linear from 0.100 to 100 ng/mL for hydrocodone and norhydrocodone, and from 0.0500 to 50.0 ng/mL for hydromorphone, based on a 100-µL sample. WLLSR analysis gave a correlation coefficient (r) of 0.9979 or better for the three analytes during the validation.

The LLOQ was verified in four runs by analyzing six replicates of the lowest standard calibrator (0.100 ng/mL for hydrocodone and for norhydrocodone, and 0.0500 ng/mL for hydromorphone). The absolute %RE across all runs was 2.83%, 5.27% and 4.22% for hydrocodone, hydromorphone and norhydrocodone, respectively. The CV% across all runs were 7.69%, 14.6%, and 10.1%, respectively demonstrating the ruggedness of the assay at the LLOQ.

To evaluate the precision and accuracy of the assay, QC samples were prepared from a separate set of stock solutions in concentrations of 0.1, 0.3, 0.8, 3, 12, and 75 ng/mL for hydrocodone and norhydrocodone, and of 0.05, 0.15, 0.4, 1.5, 6, and 37.5 ng/mL for hydromorphone. The QC samples were analyzed using six replicates on each day of validation. The CV% for hydrocodone concentrations ranged from 2.20% to 7.69% while the absolute %RE ranged from 1.51% to 6.33%. The CV% for hydromorphone concentrations ranged from 2.34% to 14.6% while the absolute %RE ranged from 0.801% to 5.27% and the CV% for norhydrocodone concentrations ranged from 2.27% to10.1% while the absolute %RE ranged from 0.103% to 5.05%.

QC samples of all three analytes were stable over five freeze/thaw cycles. Extracted QC samples were found to be stable in reconstitution solvent at 2 and 8°C for at least150 hours.

Hydrocodone and hydromorphone Method 492, V 1.02 and Validation Summary, (b) (4) (b) (4) Method Identification No. LCMSC 492 V 1.02 , Assay validation report Project code PYT4, issued September 2009.

Hydrocodone and hydromorphone and the ISs are isolated through extraction and eluted with 1.6 mL of dichloromethane. The eluate is evaporated to dryness and the remaining residue is reconstituted. The final extract is analyzed via HPLC with column-switching and MS/MS detection using positive ion electrospray. Peak areas of the m/z product ion of hydrocodone and hydromorphone are measured against the m/z product ion of the respective ISs.

Quantification was performed using WLLSR generated from calibration standards prepared immediately prior to each run.The assay was found to be linear from 0.100 to 100 ng/mL for hydrocodone and from 0.0500 to 50.0 ng/mL for hydromorphone, based on a 100-µL sample. WLLSR analysis gave a correlation coefficient (r) of 0.990 or better from one standard curve for each of the analytes.

The LLOQ was the lowest non-zero concentration level that was quantified with acceptable accuracy and precision. For this validation, the lower limit of Quantification was nominally 0.100 ng/mL for hydrocodone and 0.0500 ng/mL for hydromorphone.

To evaluate the precision and accuracy of the assay, QC samples were prepared from a separate set of stock solutions in concentrations of 0.1, 0.3, 0.8, 3, 12, and 75 ng/mL for hydrocodone, and of 0.05, 0.15, 0.4, 1.5, 6, and 37.5 ng/mL for hydromorphone. The QC samples were analyzed using two to six replicates during validation. For the single validation run, the CV% for concentrations of both analytes ranged from 1.67% to 8.39% while the absolute %RE ranged from 0.185% to 7.97%.

Paroxetine Assay Method 161 V 1.04 and Validation Summary, (b) (4) ; Method Identification No. LCMS 161 V 1.04, Assay Validation Report No. YDJ, Effective 26 March 2001, Issued 2001.

Paroxetine, and its stable, isotopically labeled IS, paroxetine-d_6, are isolated from human plasma containing sodium heparin. The eluate is evaporated to dryness and the remaining residue is reconstituted. The final extract is analyzed via HPLC with MS/MS detection. Peak areas of the m/z 330.3 to 192.6 product ion of paroxetine are measured against the m/z 336.2 to 198.5 product ion of the IS.

Quantification was performed using WLLSR regression generated from calibration standards prepared immediately prior to each run. The assay was found to be linear over the 0.250 to 50.0 ng/mL range based on a 200-µL sample. WLLSR regression gave a correlation coefficient (r) of 0.998 for the validation run.

To evaluate the precision and accuracy of the assay, QC samples were prepared from a separate set of stock solutions in concentrations of 0.5, 3.5. 25 and 40 ng/mL. The QC

samples were analyzed using 6 replicates on the day of validation. The CV% was at most 3.63% while the absolute %RE was at most 8.51%.

Analyte stability in thawed matrix was shown by allowing quality controls to thaw and remain at room temperature for up to 97 hours prior to extraction and analysis, which revealed no abnormalities.

Paroxetine QC samples were stable over three freeze/thaw cycles, and for at least 24h hours at room temperature prior to extraction. Extracted QC samples were found to be stable for approximately 91 hours at room temperature (Addendum 1). Long-term storage stability of paroxetine in frozen matrix demonstrates that paroxetine will remain stable in plasma for up to 1033 days at -20°C (Addendum 2).

Moxifloxacin Assay Method LCMSB 276 V 1.02 and Validation Summary, (b) (4) Method Identification No. LCMSB 276 V 1.02, Assay Validation Report No. DJM2, Issued December 2003.

Moxifloxacin and its stable, isotopically labeled IS, moxifloxacin-d_4, are isolated from human plasma containing K_3-EDTA by solid phase extraction (SPE) using Oasis HLB SPE cartridges. The eluate is evaporated and the remaining residue is reconstituted. An aliquot of the final extract is injected and analyzed via HPLC with MS/MS detection. Peak areas of the m/z 402.1 to 384.1 product ion of moxifloxacin are measured against the m/z 406.3 to 388.2 product ion of the IS.

Quantification was performed using WLLSR generated from calibration standards prepared immediately prior to each run. The assay was found to be linear over the 25.0 to 5000 ng/mL range based on a 50-µL sample. The LLOQ was verified by analyzing six replicates of the lowest standard calibrator (25.0 ng/mL) during three validation runs. The absolute %RE was 6.39% and the CV% was 3.37% about the mean demonstrating the ruggedness of the assay at the LLOQ.

To evaluate the precision and accuracy of the assay, QC samples were prepared from a separate set of stock solutions. Each level of QC was analyzed using at least six replicates on each day of validation. For the three days of validation, the CV% ranged from 2.28% to 3.69% while the absolute %RE ranged from 3.63% to 6.39%.

Post-preparative sample storage stability was demonstrated as well as freeze/thaw stability. Short-term and long-term analyte storage stability in frozen matrix was also demonstrated (Addendum, Method Validation Report DJM10). Human plasma samples from six different individuals as well as fortified samples were analyzed for moxifloxacin and the results demonstrated that the method has adequate specificity.

The effect of sample dilution, stability in methanolic solution, matrix suppression effects, cross-analyte interference, and the potential for carryover were evaluated and no systematic effects were demonstrated.

Ketoconazole Assay Method LCMSB 202 V 3.00 and Validation Summary, (b) (4) (b) (4) Method Identification No. LCMSB 202 V 3.00, Assay Validation Report No. THQ2, Issued June 2006.

Ketoconazole and an IS, ketoconazole-d_4, are isolated from human plasma, containing sodium heparin, by protein precipitation with acetonitrile followed by dilution. HPLC separation is achieved by reverse phase chromatography on a Waters XTerra MS C8, 5-microm column. An aliquot of the final extract is analyzed via HPLC with MS/MS detection. Peak areas of the m/z 531.2 to 489.1 product ion of ketoconazole are measured against the m/z 537.3 to 494.9 product ion of the IS.

Quantification was performed using WLLSR generated from calibration standards prepared immediately prior to each run. The assay was found to be linear over the 0.100 to 20.0 µg/mL range based on a 0.100-µL sample. The analysis gave a correlation coefficient (r) of 0.9982 or better for ketoconazole during the three days of validation (four runs). The absolute %RE ranged from 0.0195% to 4.08%.

The LLOQ was verified by analyzing six replicates of the lowest standard calibrator (0.100 µg/mL) during four validation runs. The absolute %RE was 2.72% and the CV% was 6.85% about the mean demonstrating the ruggedness of the assay at the LLOQ.

To evaluate the precision and accuracy of the assay, QC samples were prepared from a separate set of stock solutions. Each level of QC was analyzed using six replicates on each day of validation. For the three days of validation, the CV% ranged from 1.83% to 6.85% while the absolute %RE ranged from 0.796% to 2.75%.

Post-preparative extract stability was demonstrated as well as freeze thaw stability. Short-term and long-term analyte stability in frozen matrix was also demonstrated (Addendum 1, THQ3).

Hydrocodone, Hydromorphone and Norhydrocodone Assay in Urine, Method LCMSC 492.7 V 1.00 and Validation Summary. (b) (4) (b) (4) Method Identification No. LCMSC 492.7 V 1.00, Assay Validation Report No. QTY2, Issued September 2012.

Hydrocodone, hydromorphone and norhydrocodone and the ISs are isolated through supported liquid extraction and eluted with 1.0 mL of dichloromethane. The eluate is evaporated to dryness and the residue is reconstituted. The final extract is analyzed via HPLC with column-switching and MS/MS detection using positive ion electrospray. Peak areas of the m/z 300.2 to 199.0 product ion of hydrocodone, are measured against the m/z 303.2 to 199.0 product ions of the internal standards. For hydromorphone, the peak areas of the m/z 286.2 to 185.1 product ion are measured against the m/z 289.2 to 185.1 product ion of the internal standard and for norhydrocodone the peak areas of the m/z 286.2 to 199.1 product ion are measured against the m/z 289.2 to 202.1 product ion of the internal standard.

Quantification was performed using WLLSR generated from calibration standards prepared immediately prior to each run. The assay was found to be linear from 10.0 to 10,000 ng/mL

for hydrocodone and norhydrocodone and from 5.00 to 5,000 ng/mL for hydromorphone, based on a 0.25 mL sample. WLLSR analysis gave a correlation coefficient (r) of 0.9977 or better across the three analytes during the validation.

The LLOQ was verified in three runs by analyzing six replicates of the lowest standard calibrator (10.0 ng/mL for hydrocodone and norhydrocodone, and 5.00 ng/mL for hydromorphone). The absolute %RE across all runs was 3.72%, 0.561% and 4.08% for hydrocodone, hydromorphone and norhydrocodone, respectively. The CV% across all runs were 10.4%, 8.99%, and 10.8%, respectively demonstrating the ruggedness of the assay at the LLOQ.

To evaluate the precision and accuracy of the assay, QC samples were prepared from a separate set of stock solutions in concentrations of 10, 30, 80, 300, 1200, and 7500 ng/mL for hydrocodone and norhydrocodone, and of 5, 15, 40, 150, 600, and 3750 ng/mL for hydromorphone. The QC samples were analyzed using six replicates on each day of validation. The CV% for hydrocodone concentrations ranged from 3.13% to 10.4% while the absolute %RE ranged from 1.39% to 4.96%; the CV% for hydromorphone concentrations ranged from 3.09% to 8.99% while the absolute %RE ranged from 0.441% to 2.00% and the CV% for norhydrocodone concentrations ranged from 3.16% to10.8% while the absolute %RE ranged from 0.0191% to 4.08%.

QC samples of all three analytes frozen at -20°C and at -70°C were stable over five freeze/thaw cycles. Extracted QC samples were found to be stable in reconstitution solvent at 2 and 8°C for approximately 79 hours. Urine sample storage at ambient temperature for up to 25 hours, prior to addition of IS and beginning extraction did not affect the results of the measurements. Analysis of samples stored at -20°C and -70°C containing all three analytes showed that these will remain stable for at least 21days.

Hydrocodone, Hydromorphone and Norhydrocodone Assay for Protein Binding Method LCMSC 616 V 1.00 and Validation Summary, (b) (4) (b) (4) ; Method Identification No. LCMSC 616 V 1.00, Assay Validation Report No. RTY2, Issued January 2013.

A 400-µL human plasma aliquot and 600 µL of phosphate buffered saline (PBS) are placed in opposing chambers in the rapid equilibrium dialysis device. After incubation, a 100-µL sample aliquot (human plasma dialysate or buffer dialysate) is removed and diluted with PBS or human plasma blank, respectively. Human plasma calibration standards, quality controls, and matrix blanks are also diluted with PBS. This mixture is then fortified with working internal standard solution and diluted with ammonium hydroxide. Analytes are isolated through supported liquid extraction eluted with 1.6 mL of dichloromethane. The eluate is evaporated under nitrogen and the remaining residue is reconstituted. The final extract is analyzed via HPLC with column-switching and MS/MS detection using positive ion electrospray. Peak areas of the m/z 300.2 to 199.0 product ion of hydrocodone, are measured against the m/z 303.2 to 199.0 product ion of the IS. For hydromorphone, the peak areas of the m/z 286.2 to 185.1 product ion are measured against the m/z 289.2 to 185.1 product ion

of the IS and for norhydrocodone the peak areas of the m/z 286.2 to 199.1 product ion are measured against the m/z 289.2 to 202.1 product ion of the IS.

Quantification was performed using WLLSR generated from calibration standards prepared immediately prior to each run. The assay was found to be linear from 0.100 to 100 ng/mL for hydrocodone and norhydrocodone and from 0.0500 to 50.0 ng/mL for hydromorphone, based on a 0.100-mL sample. WLLSR analysis gave a correlation coefficient (r) of 0.9968 or better across the three analytes for the five or six validation runs.

The LLOQ was verified in three runs by analyzing six replicates of the lowest standard calibrator (0.100 ng/mL for hydrocodone and norhydrocodone and 0.0500 ng/mL for hydromorphone). The absolute %RE across all runs was 1.43%, 1.07% and 1.59% and for hydrocodone, hydromorphone and norhydrocodone, respectively. The CV values across all runs were 7.15%, 10.1%, and 9.44%, respectively, demonstrating the ruggedness of the assay at the LLOQ.

To evaluate the precision and accuracy of the assay, QC samples were prepared from a separate set of stock solutions in concentrations of 0.1, 0.3, 0.8, 3, 12, and 75 ng/mL for hydrocodone and norhydrocodone, and of 0.05, 0.15, 0.4, 1.5, 6, and 37.5 ng/mL for hydromorphone. Each level of QC was analyzed using six replicates on each day of validation. The CV% for hydrocodone concentrations ranged from1.65% to 7.15%while the absolute %RE ranged from 0.386% to 1.56%. The CV% for hydromorphone concentrations ranged from 1.68% to 10.1% while the absolute %RE ranged from 0.311% to 1.59%, and the CV% for norhydrocodone concentrations ranged from 1.98% to 9.44% while the absolute %RE ranged from 1.44% to 3.81%.

Freeze/thaw stability, analyte stability in thawed matrix, and analyte stability in frozen matrix were previously demonstrated under (b) (4) Method LCMSC 492.6.

Hydrocodone, Hydromorphone and Norhydrocodone Assay in Dialysis Fluid, Method LCMSC 616 V 1.00 and Validation Summary, (b) (4) (b) (4) Method Identification No. LCMSC 616 V 1.00, Assay Validation Report No. IJZ2, Issued March 2013.

A 300-µL human dialysis fluid aliquot is fortified with working IS solution and diluted with ammonium hydroxide. Analytes are isolated through supported liquid extraction and eluted with 1.6 mL of dichloromethane. The eluate is evaporated under nitrogen and the remaining residue is reconstituted.. The final extract is analyzed via HPLC with column-switching and MS/MS detection using positive ion electrospray. Peak areas of the m/z 300.0 to 199.0 product ion of hydrocodone are measured against the m/z 303.0 to 199.0 product ion of the internal standard. For hydromorphone, the peak areas of the m/z 286.3 to 185.1 product ion are measured against the m/z 289.3 to 185.0 product ion of the internal standard, and for norhydrocodone the peak areas of the m/z 286.3 to 199.1 product ion are measured against the m/z 289.3 to 202.1 product ion of the internal standard.

Quantification was performed using WLLSR generated from calibration standards prepared immediately prior to each run. The assay was found to be linear from 0.0200 to 20.0 ng/mL

for hydrocodone and norhydrocodone and from 0.0100 to 10.0 ng/mL for hydromorphone. WLLSR analysis gave a correlation coefficient (r) of 0.9972 for the three analytes for the three days of validation.

The LLOQ was verified in three runs by analyzing 6 replicates of the lowest standard calibrator (0.0200 ng/mL for hydrocodone and norhydrocodone and 0.0100 ng/mL for hydromorphone). The absolute %RE across all runs was 5.94%, 8.00% and 1.03% for hydrocodone, hydromorphone and norhydrocodone, respectively. The CV% values across all runs were 3.52%, 7.55%, and 4.68%, respectively, demonstrating the ruggedness of the assay at the LLOQ.

To evaluate the precision and accuracy of the assay, QC samples were prepared from a separate set of stock solutions in concentrations of were 0.02, 0.06, 0.15, 0.6, 2.5 and 15 ng/mL for hydrocodone and norhydrocodone, and of 0.01, 0.03, 0.075, 0.3, 1.25, and 7.5 ng/mL for hydromorphone. The QC samples were analyzed using six replicates on each day of validation. The CV% for hydrocodone concentrations of from 3.28% to 5.03% while the absolute %RE ranged from 1.96% to 6.24%. The CV% for hydromorphone concentrations ranged from 2.41% to 7.55% while the absolute %RE ranged from 5.46% to 8.00%, and the CV% for norhydrocodone concentrations ranged from 2.37% to 5.70% while the absolute %RE ranged from 0.767% to 3.76%.

Freeze/thaw stability, analyte stability in thawed matrix, and analyte stability in frozen matrix were previously demonstrated in (b) (4) Method LCMSC 492.6. Analysis of matrix samples stored for nine days at -20°C and -70°C containing hydrocodone, hydromorphone and norhydrocodone showed that these had remained stable. Analyte stability in solution under nominal storage and bench-top stress conditions was also demonstrated.

4.2.2 Study synopsis of relative bioavailability study HYD1016.

Study HYD1016

PK Profile HYD at Steady State in Comparison With That of Vicoprofen Administered Over a 24-hour Dosing Period.

Study Objective:

The primary objective was to assess the relative BA of HYD extended-release 30-mg tablets every 24 hours and Vicoprofen every 6 hours at steady state. The secondary objective of this study was to assess the safety of HYD extended-release 30-mg tablets once-daily and Vicoprofen every 6 hours in healthy subjects under naltrexone blockade.

Methods:

This was a single-center, randomized, open-label, 2-treatment, 2-period, multiple-dose, crossover study. Twenty-four subjects (12M/12F) with ages ranging from 21 to 48 years (mean: 32.7 years) were randomized and 22 subjects (91.7%) completed the study. Two subjects (8.3%) were discontinued due to AEs.

Each subject was administered the following treatments according to the randomization schedule:

- HYD 30-mg tablet once-daily for 3 days (Lot number: CB-2012-009)
- Vicoprofen (hydrocodone bitartrate 7.5 mg/ibuprofen 200 mg) tablets every 6 hours for 3 days (Lot number: 04012GY)

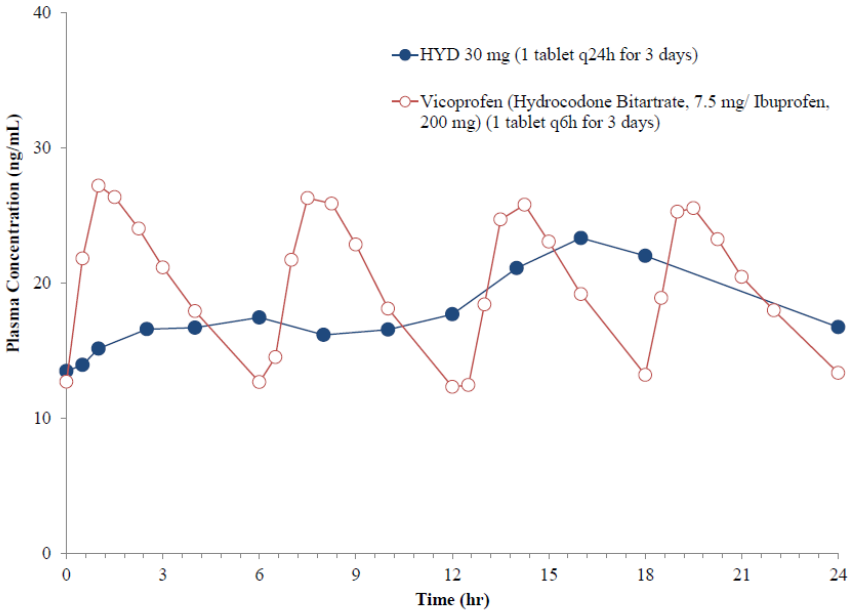
There was a minimum 7-day washout period after the HYD treatment and an approximate 6-day washout period after the Vicoprofen treatment.

Naltrexone HCl 50-mg tablet (Lot number 117OU82358) was administered every 12 hours (q12h) from 12 hours predose through 36 hours postdose on days 3 and 12 (morning dose for Vicoprofen) to minimize opioid-related AEs. A naloxone HCl (Lot number 04-317-EV) challenge test was performed prior to the first dose of naltrexone HCl.

Steady-state PK parameters were calculated for hydrocodone: AUC24,ss, AUCinf,ss, Cmin,ss, Cmax,ss, Tmax,ss, Cavg,ss, t1/2,ss, %Fluctuation (relative to Cavg,ss) and %Swing (relative to Cmin,ss). Relative hydrocodone BA of HYD (test) was assessed in comparison to that of Vicoprofen (reference). For AUC24,ss, Cavg,ss, and Cmax,ss a mixed-model ANOVA (SAS PROC MIXED) was used to compare (test versus reference) logarithmic transformed (base e) values from the test and reference treatments with fixed effects for treatment, period, and sequence, and subject nested within sequence as a random effect. The 90% CIs were estimated for the ratio (test/reference) of exponentiated LS geometric means.

Results:

Mean steady state hydrocodone plasma concentrations versus time by treatment are presented on linear scales in Figure below.



Source: Adapted from CSR HYD1016, Figure 11-1.

Figure **Mean Hydrocodone Plasma Concentration Versus Time Profiles for HYD 30-mg and Vicoprofen (hydrocodone bitartrate 7.5 mg/ibuprofen 200 mg) at Steady State in Study HYD1016**

The HYD once every 24 hours treatment exhibited lower fluctuations in the plasma concentrations of hydrocodone at steady state than did the Vicoprofen every 6 hours treatment.

Summary tables of mean (± SD) plasma hydrocodone PK metrics and statistical analysis of relative BA are presented in tables below, respectively.

Table **Summary of Day 3 Mean ± SD Plasma Pharmacokinetic Metrics of Hydrocodone in Study HYD1016**

Metric (unit)	HYD (30 mg every 24h for 3 days) N = 22	Vicoprofen (every 6h for 3 days) N = 23
AUC24,ss (ng•h/mL)	443 ± 128	470 ± 111
AUCinf,ss (ng•h/mL)	602 ± 162	559 ± 141
Cmax,ss (ng/mL)	26.4 ± 7.4	31.6 ± 6.6
Tmax,ss[a] (h)	16.0 (1.0, 24.0)	1.5 (0.50, 19.5)
Cavg,ss (ng/mL)	18.4 ± 5.3	19.6 ± 4.6
Cmin,ss (ng/mL)	16.7 ± 5.2	13.4 ± 4.0
t1/2,ss (h)	8.3 ± 2.4	4.8 ± 0.64
%Fluctuation	60.5[b] ± 30.2	96.3 ± 26.8
%Swing	88.3[b] ± 85.9	148 ± 58.7

Source: CSR HYD1016, Table 11-2.
SD=standard deviation.
Note: Cmin,ss represents the concentration at 24 hours after the morning dose on Day 3.
[a] Median (minimum, maximum).
[b] N = 18.

Table **Statistical Analysis of Plasma Pharmacokinetic Metrics of Hydrocodone in Study HYD1016**

Metric (unit)	LS Geometric Mean[a] HYD (30 mg every 24h for 3 days) (test, N=22)	LS Geometric Mean[a] Vicoprofen® (every 6h for 3 days) (reference, N=23)	Estimated mean ratio (%)[b] (Test/Reference)	90% CI for Ratio[c]
AUC24,ss (ng•h/mL)	427	458	93.2	(85.7, 101.4)
Cavg,ss (ng/mL)	17.8	19.1	93.2	(85.7, 101.4)
Cmax,ss (ng/mL)	25.4	31.0	81.7	(74.9, 89.2)

Source: CSR HYD1016, Table 11-3.
CI=confidence interval; LS=least squares.
[a] Least squares mean from analysis of variance. Natural log (ln) metric means were calculated by transforming the ln means back to the linear scale, ie, geometric means.
[b] Ratio of metric means for ln-transformed metrics (expressed as a percentage). Ln-transformed ratio was transformed back to linear scale.
[c] The 90% CI for ratio of metric means (expressed as a percentage). Ln-transformed confidence limits were transformed back to linear scale.

At steady state, total exposure (AUC24,ss) and average hydrocodone plasma concentrations (Cavg,ss) over a 24-hour period were equivalent for the 2 treatments with LS geometric mean ratios (90% CI) of 93.2% (85.7, 101.4). Steady-state peak exposure (Cmax,ss) of hydrocodone was lower for HYD every 24 hours than for Vicoprofen every 6 hours. The LS geometric mean ratio (90% CI) was 81.7% (74.9, 89.2). The percent fluctuation of hydrocodone at steady state for HYD every 24 hours (61%) was obviously less than that of Vicoprofen every 6 hours (96%). The mean t1/2,ss values were 8.3 hours and 4.8 hours for HYD every 24 hours and Vicoprofen every 6 hours, respectively.

Conclusion:

The systemic exposure (AUC24,ss) and average plasma concentration of hydrocodone (Cavg,ss) at steady state following the administration of HYD 30 mg every 24 hours was equivalent to that following Vicoprofen (7.5 mg hydrocodone bitartrate /200 mg ibuprofen) administered every 6 hours for 3 days.

4.2.3 Synopsis of multiple dose PK study HYD1002.

Name of Sponsor/Company: Purdue Pharma L.P.	**Protocol No.** HYD1002	
Name of Active Ingredient: Hydrocodone Bitartrate	**Name of Finished Product:** Not Applicable	
IND No.: 59,175		
Title of the Study: An Open-Label, Once-Daily, Multiple Dose, Pharmacokinetic Study of Hydrocodone Bitartrate (HYD) 120-mg Controlled-Release Tablets in Healthy Subjects Under Naltrexone Blockade		
Investigator, Site: Debra A. Mandarino, MD, Covance Clinical Research Unit Inc., 3402 Kinsman Blvd. Madison, Wisconsin 53704		
Publication (Reference): None.		
Study Dates: 21-Dec-2010 (First Informed Consent Form [ICF] signed) to 05-Feb-2011 (Last Subject Last Visit)	**Study Status:** Completed	**Phase of Development:** Phase 1

Objectives:

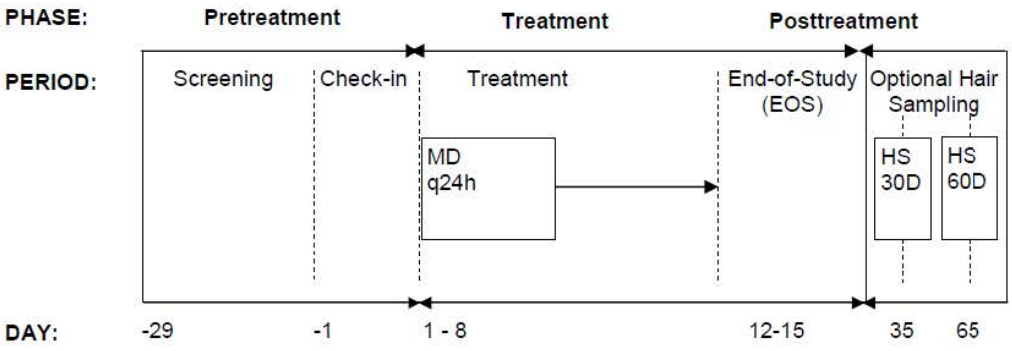
Primary:

- To characterize the multiple dose hydrocodone pharmacokinetics (PK) following the administration of one HYD 120-mg tablet q24h for 5 days.

Secondary:

- To assess the safety and tolerability of HYD 120-mg tablets q24h for 5 days under naltrexone blockade.

Study Design (Methodology): Single center, open-label, multiple-dose PK study in healthy adult male and female subjects. All subjects were administered HYD 120-mg tablets every 24 hours (q24h) for 5 days. There was an optional pharmacogenomic (PG) sampling and hair sampling portion of the study. See the Figure below.



MD = Study drug administration q24h for 5 days. D = Day post last dose of study drug. EOS = this visit took place 7 to 10 days after administration of the last dose of study drug or upon early discontinuation from the study. For subjects who consented to participate in the optional hair sampling extension after the EOS visit, there were hair sampling visits 30 (± 2) days and 60 (± 2) days post last dose of study drug.

Name of Sponsor/Company: Purdue Pharma L.P.	Protocol No. HYD1002
Name of Active Ingredient: Hydrocodone Bitartrate	Name of Finished Product: Not Applicable

Number of Subjects (Planned and Analyzed):

Planned: 27 to complete 20

Enrolled: 66

Screen failures: 37

Discontinued Prior to Study Dosing: 2

Randomized and Dosed: 27

Discontinued early: 2

Completed: 25

Indication and Main Criteria for Inclusion/Exclusion: Healthy male and female subjects aged 18 to 50 years, inclusive, with no clinically significant medical history, who were deemed suitable to take part in this clinical study by the investigator.

Test Product, Dose, Mode of Administration, and Batch Number:

Hydrocodone Bitartrate (HYD) 120-mg tablets, 1 tablet q24h x 5 doses, oral, Lot CB-2010-27

Reference Product, Dose, Mode of Administration, and Batch Number:

There was no reference product.

Concomitant Medication:

Naloxone hydrochloride (HCl) challenge test (prior to first dose of naltrexone HCl).

One Naltrexone HCl tablet (50 mg) was administered per os (PO; by mouth) every 12 hours (q12h) from approximately 12h pre first dose of HYD through 36h post last dose to minimize opioid related adverse events (AEs). At the discretion of the investigator, a naltrexone HCl dose of 25 mg could have been administered to subjects reporting intolerance to the 50 mg dose.

The use of other concomitant medications during this trial was discouraged, unless necessary to treat AEs. The use of other concomitant medications was to be approved by the sponsor (or designee) in advance, when possible.

Duration of Treatment and Study Duration:

Subjects were screened no more than 28 days prior to check-in. There was 1 treatment period. Study drug was administered q24h for 5 days. Subjects were confined to the unit the day prior to start of study drug administration and for 6 days during the treatment period. Subjects were discharged on the morning of day 7 and returned to the unit on day 8 for protocol specific procedures.

Subjects had EOS performed 7 to 10 days after last dose of study drug or upon discontinuing from the study.

Total study duration: up to approximately 44 days without the optional hair sampling portion of the study, and up to 96 days for subjects completing the optional hair sampling portion of the study.

Name of Sponsor/Company: Purdue Pharma L.P.	Protocol No. HYD1002
Name of Active Ingredient: Hydrocodone Bitartrate	Name of Finished Product: Not Applicable

Study Procedures:

Pretreatment Phase:

Screening: Subjects were screened within 28 days of check-in. Drug, alcohol, and cotinine screens, physical exam, 12-lead ECG, vital signs (systolic/diastolic blood pressure, pulse rate, respiration rate and oral temperature), pulse oximetry (SpO_2), medical and medication history, clinical laboratory testing, serum pregnancy test for females, follicle stimulating hormone (FSH) for postmenopausal women, and inclusion/exclusion criteria were evaluated.

Check-in: Subjects checked into the unit the day prior to start of dosing. Subjects received a Naloxone HCl challenge test and had biochemistry, hematology and urinalysis tests performed.

Serum pregnancy test (for women of childbearing potential), vital signs, SpO_2, alcohol, cotinine and urine drug screens were performed.

Treatment Phase:

Subjects were administered HYD 120-mg tablet with 240 mL of water q24h for 5 days. Each HYD dose was administered following an overnight fast. Subjects continued fasting from food for 2 hours following dosing. A light breakfast was served. Subjects were standing or in an upright sitting position while receiving their dose of study drug and remained in an upright position following dosing for a minimum of 4 hours.

Naltrexone HCl was administered with 240 mL of water PO q12h from approximately 12 to 11 hours pre-first dose of HYD through 36 hours post last dose of HYD.

Clinical laboratory evaluations, electrocardiogram (ECG) and vital signs (including SpO_2) measurements and blood samples for drug concentration measurements were obtained pre first dose of HYD and at prespecified times up to 168 hours post first dose of HYD.

SpO_2 was monitored continuously beginning prior to first HYD dosing and continuing through 24 hours post last dose of HYD.

Subjects participating in the optional exploratory pharmacogenomic portion of the study had samples collected relative to first dose of HYD.

End of Study Visit: This visit took place 7 to 10 days after administration of the last dose of study drug, or upon early discontinuation from the study. End of study (EOS) procedures included a physical exam, 12-lead ECG, vital signs, SpO_2, and clinical laboratory tests.

Posttreatment Phase:

Optional Hair Sampling Visits: Subjects were asked if they were interested in participating in an optional hair sampling portion of the study following their written informed consent. For subjects who consented to participate in the optional hair sampling extension after the EOS visit, there were hair sampling visits approximately 30 (± 2) days and 60 (± 2) days post last dose of study drug.

Name of Sponsor/Company: Purdue Pharma L.P.	Protocol No. HYD1002
Name of Active Ingredient: Hydrocodone Bitartrate	Name of Finished Product: Not Applicable

Criteria for Evaluation:

Pharmacokinetic Assessments

Blood samples for determining hydrocodone plasma concentrations were obtained for each subject at the following times relative to the first dose of HYD: at pre-dose and at 1, 2, 4, 6, 8, 10, 12, 14, 16, 18, 24 hours (just prior to dosing), 48 hours (just prior to dosing), 72 hours (just prior to dosing), 96 hours (just prior to dosing), and at 97, 98, 100, 102, 104, 106, 108, 110, 112, 114, 120, 132, 136, 144, and 168 hours post first dose of HYD administration.

Plasma concentrations of norhydrocodone and hydromorphone were also determined.

Pharmacokinetic Data Calculations:

Plasma concentrations of hydrocodone were analyzed to determine the following PK metrics for each treatment:

Day 1: The area under the plasma concentration-time course curve during the first dosing interval (tau=24 hours) calculated by the linear trapezoidal method (AUC_{tau}), maximum observed plasma concentration during the first dosing interval (C_{max}), time to maximum plasma concentration during the first dosing interval (T_{max}), and time to the first measurable plasma concentration value (T_{lag}).

Days 2 to 5: The minimum observed plasma concentration (C_{min}) at the end of the nth dosing interval ($C_{min,nth}$).

Day 5: The area under the plasma concentration-time course curve during a dosing interval hours at steady state ($AUC_{ss,tau}$), the area under the plasma concentration-time course curve at steady state from dosing to infinity ($AUC_{ss,inf}$), the maximum observed plasma concentration at steady state ($C_{ss,max}$), the average plasma concentration at steady state: $AUC_{ss,tau}$/dosing interval ($C_{ss,avg}$), the minimum observed plasma concentration at the end of the dosing interval at steady state ($C_{ss,min}$), time to maximum plasma concentration at steady state ($T_{ss,max}$), accumulation ratio relates steady state exposure to single dose (Dose 1) exposure (AR), the range of plasma concentration values during steady state relative to $C_{ss,avg}$ (%Fluctuation), the range of plasma concentration values during steady state relative to $C_{ss,min}$ (%Swing), and apparent terminal phase half-life ($t_{1/2}$).

Safety Assessments:

Safety was assessed using recorded AEs, clinical laboratory evaluations, vital signs, SpO_2, physical examinations, and ECGs.

Other Variable Assessments:

Optional pharmacogenomic evaluation: For subjects who consented to participate, blood samples were collected.

Optional hair sampling: The hair samples were analyzed for hydrocodone and its metabolite, hydromorphone.

Bioanalytical Methods:

Plasma concentrations of hydrocodone and its metabolites, norhydrocodone and hydromorphone, were quantified by a validated bioanalytical method (b) (4) . method TM.1117).

Name of Sponsor/Company: Purdue Pharma L.P.	Protocol No. HYD1002
Name of Active Ingredient: Hydrocodone Bitartrate	Name of Finished Product: Not Applicable

Statistical Methods for PK Data:

Listings, summaries, and figures of individual hydrocodone, norhydrocodone, and hydromorphone plasma concentrations were based on the safety population. PK analyses listings and summaries were based on the full analysis population.

Descriptive statistics were tabulated by treatment as applicable for all plasma concentrations and PK metrics.

To determine if steady state was reached, the C_{min} data for each of the study drug administrations were regressed over time sequentially for dosing intervals 1 to 5, 2 to 5, 3 to 5, or 4 to 5. A 95% confidence interval (CI) around the slope of the line was computed for each regression. The regression model was: $\ln(C_{min})$ = day + subject + random error, where $\ln(C_{min})$ was natural log-transformed prior to analysis, day was a continuous variable, and subject was a random effect. If a CI included zero, then the regression would stop and a steady state would have been reached.

Statistical Analyses of Safety Data:

All safety data (AEs, clinical laboratory results, vital signs, SpO_2, and ECGs) were listed for subjects. Subjects' AEs were categorized into preferred terms and associated system organ class using the Medical Dictionary for Regulatory Activities (MedDRA). Treatment-emergent AEs (TEAEs) were defined as AEs that started after or increased in severity after the first dose of study drug. TEAEs were summarized by presenting the incidence of AEs for each treatment group by the MedDRA preferred term, nested within System Organ Class for the safety population. Medical History was coded to MedDRA terms. Coded Medical History terms were summarized for all subjects in the safety population.

Laboratory evaluations, vital signs, and SpO_2 were summarized by time point for the safety population.

Other Variables Analysis:

The pharmacogenomic analyses, if available, will be reported separately.

The optional hair sample analyses, if available, will be reported separately.

Table **Summary of Mean ± SD Plasma Hydrocodone Pharmacokinetic Metrics in Study HYD1002 (Full Analysis for Pharmacokinetics Population)**

	HYD 120-mg Tablet		
Metric (Unit)	**Day 1 N=24**	**Day 5 (steady state) N=25**	**Accumulation Ratio N=23**
AUCtau (ng*h/mL)	1541 ± 332	1938 ± 729	1.3 ± 0.5
AUCss,inf (ng*h/mL)	--	2615 ± 1086	--
Cmax (ng/mL)	128 ± 29.6	135 ± 49.5	1.1 ± 0.3
Cmin (ng/mL)	60.3 ± 27.6	63.6 ± 29.4	1.1 ± 0.6
Tmax (h)[a]	14.0 (12.0, 23.9)	110 (98.0, 120)[b]	--
Tlag (h)[a]	0.00 (0.00, 0.00)	--	--
t1/2 (h)	--	7.17±1.89	--
		Steady State N= 24	
Cavg,ss (ng/mL)		80.8 ± 30.4 (N=25)	
%Fluctuation		97.9 ± 60.8	
%Swing		286 ± 542	

Source: CSR study HYD1002, Table 13.

[a] median (minimum, maximum).

[b] hours after first dose, 14 (2.0, 24) hours after last dose.

Name of Sponsor/Company:	Protocol No.
Purdue Pharma L.P.	HYD1002
Name of Active Ingredient:	**Name of Finished Product:**
Hydrocodone Bitartrate	Not Applicable

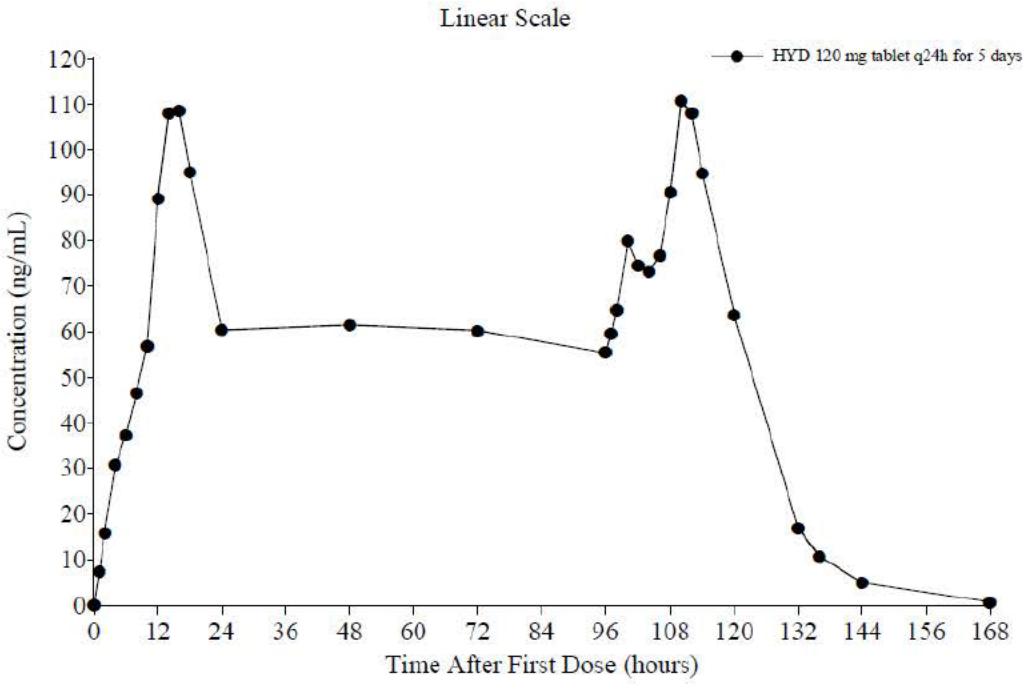
	C_{min} (ng/mL) Mean ± SD[b]					Slope from Regression[c]	
Dosing Interval	Dose 1 N=24	Dose 2 N=26	Dose 3 N=25	Dose 4 N=25	Dose 5 N=25	Estimate	95% Confidence Interval
1 to 5	60.3 ± 27.6	59.9 ± 30.0	58.9 ± 31.1	54.2 ± 38.9	63.6 ± 29.4	-0.0529	(-0.1452, 0.0395)

Note: Subject Nos. 1001, 1010, and 1033 experienced emesis within 24 hours after day 1 dosing, so the corresponding C_{min} data for the subjects were excluded from this statistical analysis. Subject No. 1033 was dosed on day 1 only and then discontinued from the study, so the day 2 C_{min} data for the subject were excluded from this statistical analysis.

[a]: Median (Min, Max)

[b]: Mean and standard deviation calculated and reported in original scale.

[c]: The slope estimate and its 95% CI were derived from a regression model: $\ln(C_{min})$ = day + subject + random error, where $\ln(C_{min})$ was natural log-transformed prior to analysis, day was a continuous variable and subject was a random effect.



Plot of Mean Plasma Hydrocodone Concentration versus Time on a Linear Scale
Study Population: Full Analysis for PK

Safety Results:

- The safety population consisted of 27 subjects, with 25 subjects completing the study.
- Two subjects discontinued from the study: 1 due to subject's choice and 1 due to AEs of headache, nausea, vomiting, and dizziness.
- There were no deaths or SAEs.
- The TEAEs reported in at least 2 subjects or with at least 2 instances consisted of nausea, vomiting, headache, dizziness, and dysgeusia.
- All TEAEs were of mild or moderate intensity; there were no subjects with severe TEAEs. All TEAEs were resolved by the EOS.
- Results of laboratory tests, vital sign and SpO_2 measurements, and ECGs raised no safety concerns for HYD 120-mg tablets.

Conclusions:

- Systemic exposure to hydrocodone was similar between day 5 (steady state) and day 1, as assessed by AUC, C_{max}, and C_{min}.
- Steady state was achieved by day 2 of once daily HYD 120-mg dosing.
- Minimal accumulation of hydrocodone was observed after multiple once daily HYD 120-mg dosing for 5 days.
- The administration of once-daily dosing of HYD 120-mg for 5 days to healthy adult subjects under naltrexone blockade was safe and well tolerated.
- The observed TEAEs were those generally associated with opioid analgesics.
- All TEAEs were of mild or moderate intensity, there were no subjects with severe TEAEs, and all TEAEs were resolved by the end of the study.

Date of Report: Final CSR, 21-Sep-2011

4.2.4 Synopsis of Food-effect study HYD1003.

Name of Sponsor/Company: Purdue Pharma L.P.	**Protocol No.** HYD1003
Name of Active Ingredient: Hydrocodone bitartrate	**Name of Finished Product**: Not applicable
US IND/EUDRACT No. 59,175	
Title of study: A Randomized, Open-Label, Single-Dose, Single-Center, Three-Way Crossover Study to Evaluate the Pharmacokinetics and Safety of Hydrocodone Bitartrate (HYD) Extended-Release 120 mg Tablets in the Fed (High Fat and Low Fat Meals) and Fasted State in Healthy Female and Male Subjects	
Investigator: Sabiha A. Mondal, MD	
Study site: PPD Phase I Clinic, 7551 Metro Center Drive, Suite 200, Austin TX 78744	
Publication (reference): None	
Studied period (years): 26-Mar-2012 (First Subject First Visit) to 08-Jun-2012 (Last Subject Last Visit)	**Phase of development**: Phase 1
Objectives: The primary objective of this study was: • To assess the pharmacokinetics of hydrocodone bitartrate (HYD) extended-release 120-mg tablets administered in the fasted state and after a high fat meal and a low fat meal. The secondary objective of this study was: • To assess the of safety and tolerability of hydrocodone bitartrate (HYD) extended-release 120-mg tablets administered in the fasted state and after a high fat meal and a low fat meal in healthy adult subjects under naltrexone blockade.	

Name of Sponsor/Company:	**Protocol No.**
Purdue Pharma L.P.	HYD1003
Name of Active Ingredient:	**Name of Finished Product**:
Hydrocodone bitartrate	Not applicable

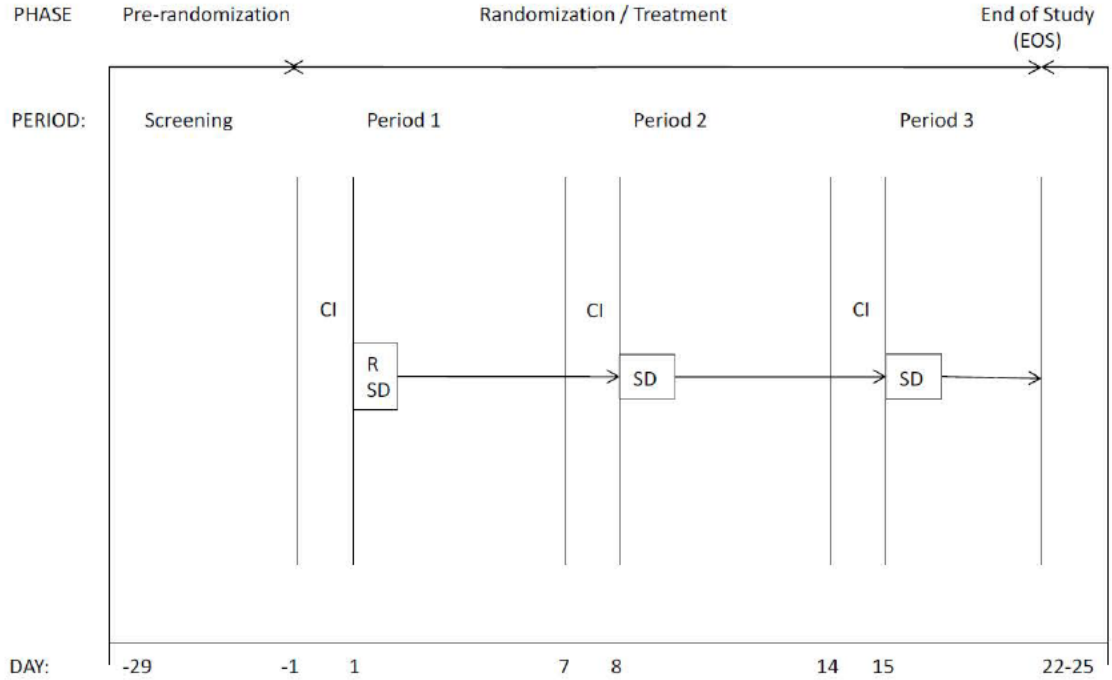
US IND/EUDRACT No.

59,175

Study Design (Methodology):

This was a randomized, open-label, single-dose, single-center, 3-way, crossover study in healthy female and male subjects.

Study Design Graphic:



CI = Check-in.
R = Randomization to treatment sequence.
SD = Study drug administration.
EOS = The end-of-study visit took place on days 22 to 25 or upon early discontinuation from the study.

Number of subjects (planned and analyzed): Based on a previous study (HYD1001), the intra-subject coefficient of variation (%CV) for the area under the plasma concentration versus time curve (AUC) and maximum observed plasma concentration (Cmax) was estimated to be approximately 25%. With this %CV, a sample size of 45 subjects was considered sufficient to conclude the absence of a food effect with 90% power when the true ratio of means equals 100%. With an estimated dropout rate of 10%, the total enrolled number of subjects was planned to be approximately 50.

Name of Sponsor/Company: Purdue Pharma L.P.	**Protocol No.** HYD1003
Name of Active Ingredient: Hydrocodone bitartrate	**Name of Finished Product**: Not applicable
US IND/EUDRACT No. 59,175	
Fifty-four subjects (26 males and 28 females) were randomly assigned to a treatment sequence in this study. Fifty subjects completed the study. Fifty-four subjects were included in the safety analyses and 52 subjects were included in the pharmacokinetic (PK) analyses. Three subjects (5.6%) were discontinued due to adverse events (AEs) and 1 subject (1.9%) was discontinued due to administrative reasons.	
Diagnosis and main criteria for inclusion: Healthy male and female subjects who met all inclusion criteria and none of the exclusion criteria who were deemed suitable to take part by the investigator.	
Test product, dose and mode of administration, batch number: HYD, single oral dose, 1 × 120-mg extended-release tablet (Lot number CB-2011-11) 1 × 120-mg HYD tablet administered after a high fat meal 1 × 120-mg HYD tablet administered after a low fat meal Study drug was defined as HYD extended-release tablets.	
Reference treatment, dose and mode of administration, batch number: HYD, single oral dose, 1 × 120-mg extended-release tablet (Lot number CB-2011-11) 1 × 120-mg HYD tablet administered in the fasted state	
Concomitant medication: Naloxone hydrochloride (HCl) challenge test (prior to first dose of naltrexone HCl). Naltrexone HCl tablets (50 mg) were administered at –12 to –11 hours, 0 (predose), 12, 24, and 36 hours relative to HYD administration to minimize opioid-related AEs. Naloxone HCl and naltrexone HCl were protocol-specified drugs, distinct from study drug. Naloxone HCl, 0.8-mg (2.0 mL) single dose; subcutaneous (Lot number 95530EV) Naltrexone HCl, 50 mg orally every 12 hours; 1 × 50-mg tablet (Lot number 116149A) The use of other concomitant medications during this trial was discouraged, unless necessary to treat AEs. The use of other concomitant medications was to be approved by the sponsor (or designee) in advance, when possible.	

Name of Sponsor/Company:	**Protocol No.**
Purdue Pharma L.P.	HYD1003
Name of Active Ingredient:	**Name of Finished Product**:
Hydrocodone bitartrate	Not applicable
US IND/EUDRACT No.	
59,175	

Duration of treatment:

Subjects were screened no more than 28 days prior to check-in of period 1. Study drug was administered in each period according to the study randomization schedule. There was a minimum 7-day washout period between study drug administrations. Subjects were confined to the study unit the day prior to study drug administration and for 72 hours following study drug administration during each period.

Subjects had end-of-study procedures performed 7 to 10 days after the last dose of study drug or upon early discontinuation.

Total study duration: up to 54 days.

Study Procedures:

Pre-Randomization Phase:

Screening: Subjects were screened within 28 days of period 1 check-in. Drug, alcohol, and cotinine screens, physical examination, 12-lead electrocardiogram (ECG), vital signs (systolic/diastolic blood pressure, pulse rate, respiratory rate, and oral temperature), pulse oximetry (SpO_2), medical and medication history, clinical laboratory testing, serum pregnancy test for female subjects, follicle-stimulating hormone test for postmenopausal women, and inclusion/exclusion criteria were evaluated.

Period 1 Check-in: Subjects checked into the study unit the day prior to period 1 dosing. Subjects received a naloxone HCl challenge test and had chemistry, hematology, and urinalysis tests performed.

Urine pregnancy test (for all female subjects), vital signs, SpO_2, alcohol, cotinine, and urine drug screens were performed.

Treatment Phase:

Periods 2 and 3 Check-in: Subjects checked into the study unit the day prior to dosing.

Subjects received protocol-specified naltrexone HCl at prespecified times with 240 mL of water.

Subjects were administered the study drug with 240 mL of water in the fasted or fed state. Subjects fasted from food for 4 hours following dosing. Subjects restricted their consumption of water for 3 hours prior to dose and for 2 hours postdose. Subjects were standing or in an upright sitting position while receiving their dose of study drug and remained in an upright position following dosing for a minimum of 4 hours.

Clinical laboratory evaluations, 12-lead ECG, and vital signs (including SpO_2)

Name of Sponsor/Company:	Protocol No.
Purdue Pharma L.P.	HYD1003
Name of Active Ingredient:	**Name of Finished Product**:
Hydrocodone bitartrate	Not applicable
US IND/EUDRACT No.	
59,175	

measurements and blood samples for drug concentration measurements were obtained at prespecified times.

Subjects participating in the optional exploratory pharmacogenomic (PG) portion of the study had samples collected at prespecified times.

All AEs and concomitant medications were recorded throughout the study.

End-of-Study Visit: This visit took place 7 to 10 days after administration of the last dose of study drug or upon early discontinuation from the study. End-of-study procedures included a physical examination, 12-lead ECG, vital signs, SpO_2, and clinical laboratory tests.

Criteria for evaluation:

Pharmacokinetics:

Blood samples for determining hydrocodone concentrations in plasma were obtained for each subject at predose and at 0.5, 1, 2.5, 4, 6, 8, 10, 12, 14, 16, 18, 24, 30, 36, 48, and 72 hours post study drug administration in each period.

Plasma concentrations of hydrocodone were quantified by a validated bioanalytical method.

Safety:

Safety was assessed using recorded AEs, clinical laboratory test results, vital signs, SpO_2, physical examinations, and 12-lead ECGs.

Other:

Optional PG evaluation: blood samples were collected predose and 72 hours postdose during period 1.

Statistical methods:

Analysis Populations:

The enrolled population consisted of all subjects who signed the informed consent form.

The randomized safety population was the group of subjects who were randomized and received at least 1 dose of study drug.

The full analysis population (FAP) was the group of subjects who were randomized, received study drug, and had at least 1 quantifiable PK metric. The PK analysis was based on the FAP. Subjects who experienced emesis within 24 hours after dosing could have

been excluded. All exclusions from any analysis set were documented in the final statistical analysis plan (SAP2).

After review of the PK data, the following subjects/profiles were excluded from the FAP:

- Subject RN030040/0001079 was excluded due to no PK samples collected after the 14-hour postdose time point in period 1 and no concentration data for periods 2 and 3.
- Subject RN030041/0001110 was excluded due to emesis after dosing in period 1 and no concentration data for periods 2 and 3.
- Subject RN030048/0001083 experienced emesis after dosing in period 1 and this profile was excluded from the PK summary and statistical analysis for period 1. However, this subject had PK data from periods 2 and 3 and was included in the FAP for those study periods.

Pharmacokinetics:

Listings and figures of individual hydrocodone plasma concentrations were based on the randomized safety population. Mean and mean (SD) plasma concentration versus time profiles were presented in figures on both linear and semi-logarithmic scales for the FAP. Spaghetti plots containing all individual subject plasma hydrocodone concentration versus time profiles for each treatment were presented on a linear scale for the FAP.

Plasma concentrations of hydrocodone were analyzed to determine the following PK metrics for each treatment by noncompartmental PK analysis (model independent approach): area under the plasma concentration versus time curve from hour 0 to the last measurable plasma concentration (AUCt), area under the plasma concentration versus time curve extrapolated to infinity (AUCinf), maximum observed plasma concentration (Cmax), time to maximum observed plasma concentration (Tmax), time prior to the first measurable (nonzero) plasma concentration (Tlag), and apparent terminal phase half-life (t1/2).

PK analyses and summaries were based on the FAP. Descriptive statistics included sample size (n), mean, standard deviation (SD), %CV, median, minimum, maximum, and geometric mean, and were tabulated by treatment as applicable for all plasma concentrations and PK metrics.

For AUCt, AUCinf, and Cmax, a mixed-model analysis of variance (SAS PROC MIXED) was used to compare (test versus reference) natural logarithmic-transformed values from the test (low fat or high fat meals) and reference (fasted state) treatments with fixed effects for treatment, period and sequence, and subject nested within sequence as a random effect.

Name of Sponsor/Company:	**Protocol No.**
Purdue Pharma L.P.	HYD1003
Name of Active Ingredient:	**Name of Finished Product**:
Hydrocodone bitartrate	Not applicable
US IND/EUDRACT No.	
59,175	

The 90% confidence intervals (CIs) were estimated for the ratio (test/reference [ie, low fat meal/fasted state and high fat meal/fasted state]) of exponentiated least squares means.

The primary comparisons of interest were as follows:

- 1 × 120-mg HYD tablet in the high fat meal state versus 1 × 120-mg HYD tablet in the fasted state.
- 1 × 120-mg HYD tablet in the low fat meal state versus 1 × 120-mg HYD tablet in the fasted state.

Safety:

All safety data (AEs, clinical laboratory results, vital signs, SpO_2, and 12-lead ECGs) were listed for subjects in the randomized safety population.

All AEs were categorized into preferred terms and associated system organ class (SOC) using the Medical Dictionary for Regulatory Activities (MedDRA) Version 15.0. Treatment-emergent AEs (TEAEs) were defined as AEs that started after or increased in intensity after the first dose of study drug. All TEAEs were summarized by presenting the incidence of AEs for each treatment by the MedDRA preferred term, nested within SOC for the randomized safety population. Medical history was coded to MedDRA terms. Coded medical history terms were summarized for all subjects in the randomized safety population.

Concomitant medication was coded using World Health Organization Drug Dictionary (WHO-DD) 01 March 2012 terms and was listed using the randomized safety population.

Laboratory evaluations, vital sign and SpO_2 measurements, and 12-lead ECG parameters were summarized overall at screening, baseline, end of study, and change from baseline for the randomized safety population. Vital sign and SpO_2 measurements were also summarized by treatment and time point.

Other:

Exploratory PG analyses will be reported separately.

RESULTS:

Pharmacokinetic results:

Mean (SD) plasma concentrations of hydrocodone versus time by treatment are presented on linear and semi-logarithmic scales in Figure 1.

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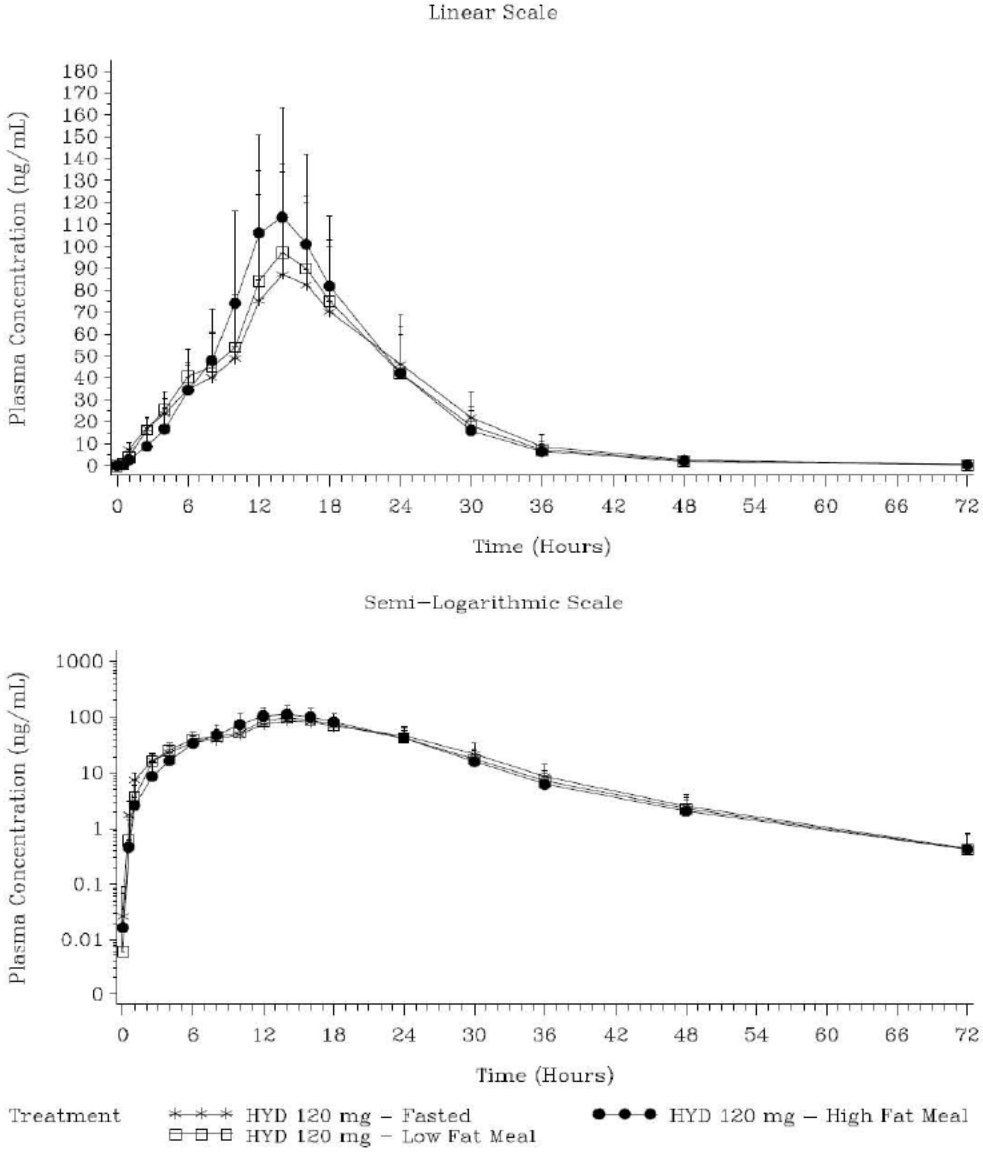

Abbreviation: HYD, hydrocodone bitartrate.

Source: Figure 14.2.3.

Figure 1: Mean (SD) Plasma Concentrations of Hydrocodone Versus Time by Treatment on Linear and Semi-logarithmic Scales (Full Analysis Population)

Name of Sponsor/Company:	**Protocol No.**
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Name of Active Ingredient:	**Name of Finished Product**:
Hydrocodone bitartrate	Not applicable
US IND/EUDRACT No.	
59,175	

Mean plasma concentrations of hydrocodone increased steadily after oral administration of a single dose of HYD 120 mg and reached a maximum concentration at approximately 14 hours postdose after all treatments (fasted, high fat meal, and low fat meal). Thereafter, plasma levels declined and remained detectable at 72 hours postdose.

The PK statistical analysis is presented in Table 1.

Table 1: Statistical Analysis of Plasma Pharmacokinetic Metrics of the Food Effect for Hydrocodone (Full Analysis Population)

Parameter (Unit)	Treatment	N	Geometric LS Means	Treatment Comparison	Ratio of Geometric LS Means (%)	90% CI for Ratio
AUCinf (ng•h/mL)	A	51	1448			
	B	51	1744	B/A	120	106, 137
	C	49	1578	C/A	109	96, 124
AUCt (ng•h/mL)	A	51	1441			
	B	51	1735	B/A	120	106, 137
	C	49	1571	C/A	109	96, 124
Cmax (ng/mL)	A	51	90			
	B	51	139	B/A	154	138, 173
	C	49	105	C/A	117	104, 131

Abbreviations: CI, confidence interval; %CV, coefficient of variation; LS, least squares.
Note: An analysis of variance was performed on the natural logarithms of the pharmacokinetic metrics. The model included treatment, period and sequence as fixed effects and subject nested within sequence as a random effect.
Treatment A = HYD 120 mg – Fasted.
Treatment B = HYD 120 mg – High Fat Meal.
Treatment C = HYD 120 mg – Low Fat Meal.
Source: Table 14.2.3.

Cmax and AUC were similar under low fat conditions relative to fasting conditions (17% and 9% higher, respectively). Cmax was higher (54%) under high fat conditions relative to fasting conditions; however, AUC of HYD 120-mg tablets was only 20% higher when coadministered with a high fat meal. Tmax, Tlag, and t1/2 were similar across all treatments (fasted, high fat meal, and low fat meal).

Safety results:

A summary of TEAEs by severity, SOC, and MedDRA preferred term that occurred in at least 2 subjects in any treatment is presented in Table 2.

Name of Sponsor/Company:	**Protocol No.**
Purdue Pharma L.P.	HYD1003
Name of Active Ingredient:	**Name of Finished Product**:
Hydrocodone bitartrate	Not applicable
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Table 2: Summary of Treatment-Emergent Adverse Events by Severity, System Organ Class, and Preferred Term (Reported by 2 or More Subjects in any Treatment) (Randomized Safety Population)

System Organ Class Preferred Term Severity[a]	HYD 120 mg Fasted (N = 51) n (%)	HYD 120 mg High Fat Meal (N = 52) n (%)	HYD 120 mg Low Fat Meal (N = 51) n (%)	Overall (N = 54) n (%)
Gastrointestinal disorders				
Abdominal discomfort				
Mild	2 (4)	1 (2)	1 (2)	3 (6)
Abdominal pain				
Mild	2 (4)	0	1 (2)	3 (6)
Diarrhoea				
Mild	2 (4)	0	1 (2)	2 (4)
Nausea				
Mild	5 (10)	3 (6)	4 (8)	6 (11)
Moderate	2 (4)	1 (2)	3 (6)	5 (9)
Vomiting				
Moderate	2 (4)	1 (2)	3 (6)	5 (9)
Musculoskeletal and connective tissue disorders				
Pain in extremity				
Mild	0	2 (4)	0	2 (4)
Nervous system disorders				
Dizziness				
Mild	3 (6)	1 (2)	3 (6)	3 (6)
Headache				
Mild	4 (8)	4 (8)	6 (12)	11 (20)
Somnolence				
Mild	3 (6)	3 (6)	3 (6)	5 (9)

Abbreviation: HYD, hydrocodone bitartrate.

Note: Percentages were based on N. Multiple occurrences of the same adverse event in 1 subject were counted only once. The Medical Dictionary for Regulatory Activities Version 15.0 was used to code adverse events. Treatment-emergent adverse events were defined as adverse events that started after or increased in intensity after the first dose of study drug.

[a] If a subject reported more than 1 occurrence of the same preferred term, the maximum severity was included in the table. Missing severities were treated as severe. Severity was taken from the severity reported on the electronic case report form by the investigator.

Source: Table 14.3.1.5.

Name of Sponsor/Company:	**Protocol No.**
Purdue Pharma L.P.	HYD1003
Name of Active Ingredient:	**Name of Finished Product**:
Hydrocodone bitartrate	Not applicable
US IND/EUDRACT No.	
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There were no deaths or serious adverse events (SAEs). Three subjects (5.6%) were discontinued from the study due to TEAEs including anxiety, a positive pregnancy test result, and a positive urine drug screen result for cannabinoids. Overall, 18 of 54 subjects (33%) experienced at least 1 TEAE. The number of treatment-related TEAEs was similar across the 3 treatments with the high fat meal treatment having the least number of TEAEs, and all of these TEAEs resolved by the end of the study.

With the exception of 12 TEAEs of moderate severity in 5 subjects, all TEAEs reported during this study were mild. Moderate TEAEs consisted of nausea and vomiting. There were no severe TEAEs. The TEAEs experienced by at least 2 subjects in any treatment consisted of headache, nausea, vomiting, somnolence, dizziness, abdominal discomfort, abdominal pain, diarrhoea, and pain in extremity.

No clinically significant changes were observed in clinical laboratory values, vital sign and SpO_2 measurements, or ECG results for any of the treatments studied.

CONCLUSIONS:

- Cmax and AUC of HYD 120-mg tablets were similar under low fat conditions relative to fasting conditions (17% and 9% higher, respectively). HYD may be taken with or without regard to low fat meals.
- Cmax was higher (54%) under high fat conditions relative to fasting conditions; however, AUC of HYD 120-mg tablets was only 20% higher when coadministered with a high fat meal.
- No dose dumping was observed with HYD 120-mg tablets in the presence of a low fat or high fat meal. Tmax of 14 hours was similar for all treatments.
- The administration of HYD 120-mg extended-release tablets at single oral doses under fasted, high fat meal, and low fat meal conditions with naltrexone blockade was safe and well tolerated.
- There were no deaths or SAEs. Three subjects were discontinued from the study due to TEAEs including anxiety, a positive pregnancy test result, and a positive urine drug screen result for cannabinoids.
- Clinical laboratory values, vital sign and SpO_2 measurements, and ECG results and changes from baseline were similar across the 3 treatments, and no apparent treatment-related trends were observed.

Date of report: 06-Nov-2012

FDA Comment

"In Food-effect Study HYD1003, we noted that inter-individual variability decreased under fed condition, particularly after high-fat meal consumption. We noted bioavailability (Cmax and or AUC) of subjects 1021, 1034, 1074, 1085 was very low under fasting condition compared to average values in the group. Under high-fat meal consumption these subjects had up to 8-fold higher increase in Cmax and or AUC. We noted that subject 1021 vomited after receiving Hysingla ER under fasting condition. Explain the experimental conditions, subject AEs or other relevant conditions that may have contributed to the low bioavailability in these subjects under fasting condition. Also, explain how you plan to address these observations in labeling.

PPLP Response:

"Explain the experimental conditions, subject AEs or other relevant conditions that may have contributed to the low bioavailability in these subjects under fasting condition."

We agree that a potential cause of the low exposures observed in the fasted state in study HYD1003 is unreported emesis. The study staff were instructed to carefully document all instances of emesis and subjects were informed that it was very important to report episodes of emesis immediately. Nevertheless, we cannot rule out the possibility of unreported emesis events. Note that subject 1021 did experience emesis following fasted administration, but not until 6 days postdose.

The four subjects cited from study HYD1003 had typical hydrocodone exposures following Hysingla ER administered in the fed state and unusually low exposures in the fasted state. The significance of the large intra-subject differences between fasted and fed dosing noted in study HYD1003 depends on whether the low exposures in the fasted state are likely to be reproducible on other occasions.

To assess the inter-occasion variability of intra-subject exposure following administration of Hysingla ER in the fasted state, we examined data from study HYD1004. Study HYD1004 was selected because Hysingla ER was given on multiple occasions in the fasted state in this study. Thus, we can determine whether low systemic exposures in the fasted state are reproducible. In this study, subjects were randomized to receive four single doses (20-120 mg) of Hysingla ER under fasting conditions, with a 7 day washout period between doses. AUCt and Cmax values were dose-normalized to facilitate comparisons following different Hysingla ER doses.

Figures 1 and 2 present the dose-normalized AUCt and Cmax values across the four study periods. Values for an individual subject are connected by line segments across periods. From Figure 1 it is evident that subjects with low dose-normalized AUCt values on a particular occasion tended not to have equally low exposures on other occasions. Figure 2 shows similar findings for dose-normalized Cmax.

Figure 1. Study HYD1004 Dose-Proportionality Study (20-120 mg) – Dose-Normalized AUCt of Hysingla ER Fasted, Single-Dose Across Study Periods

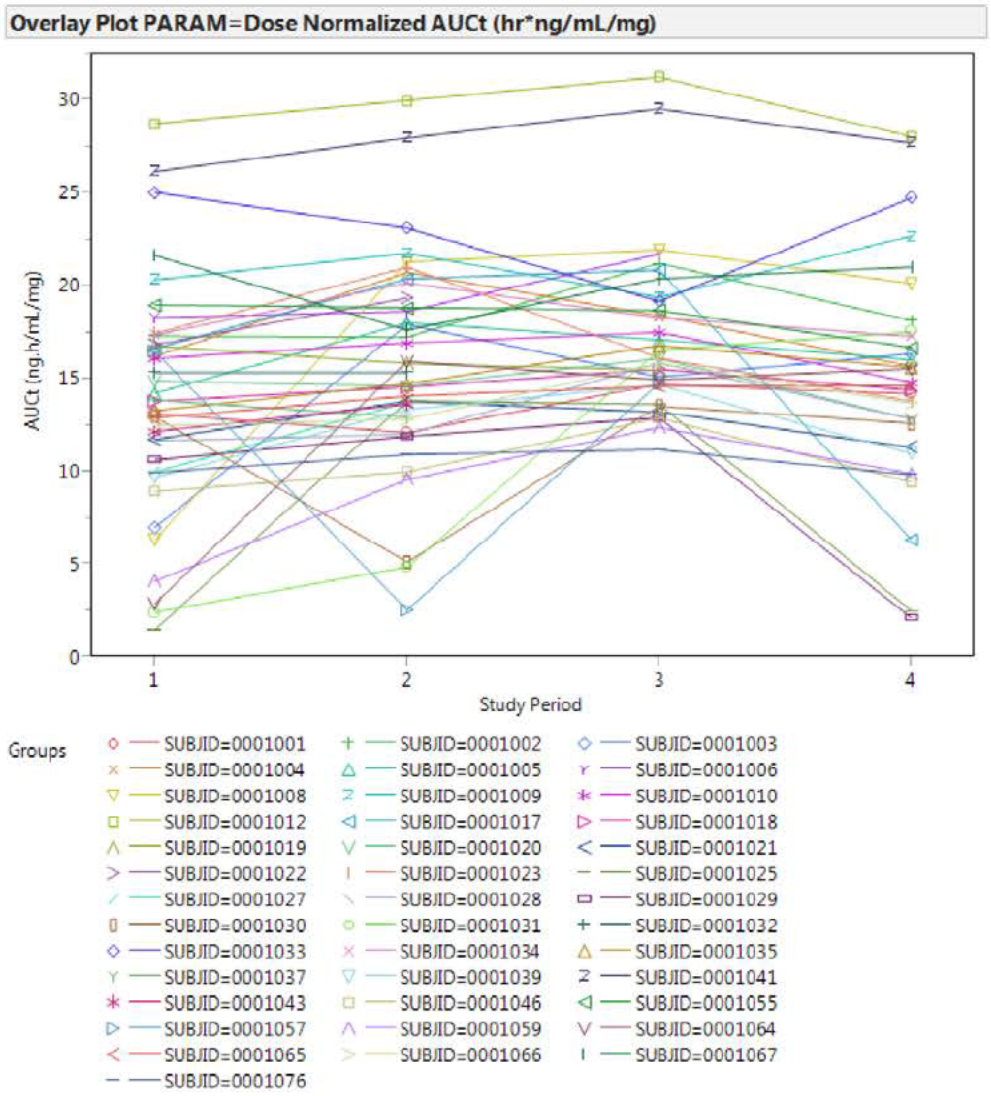
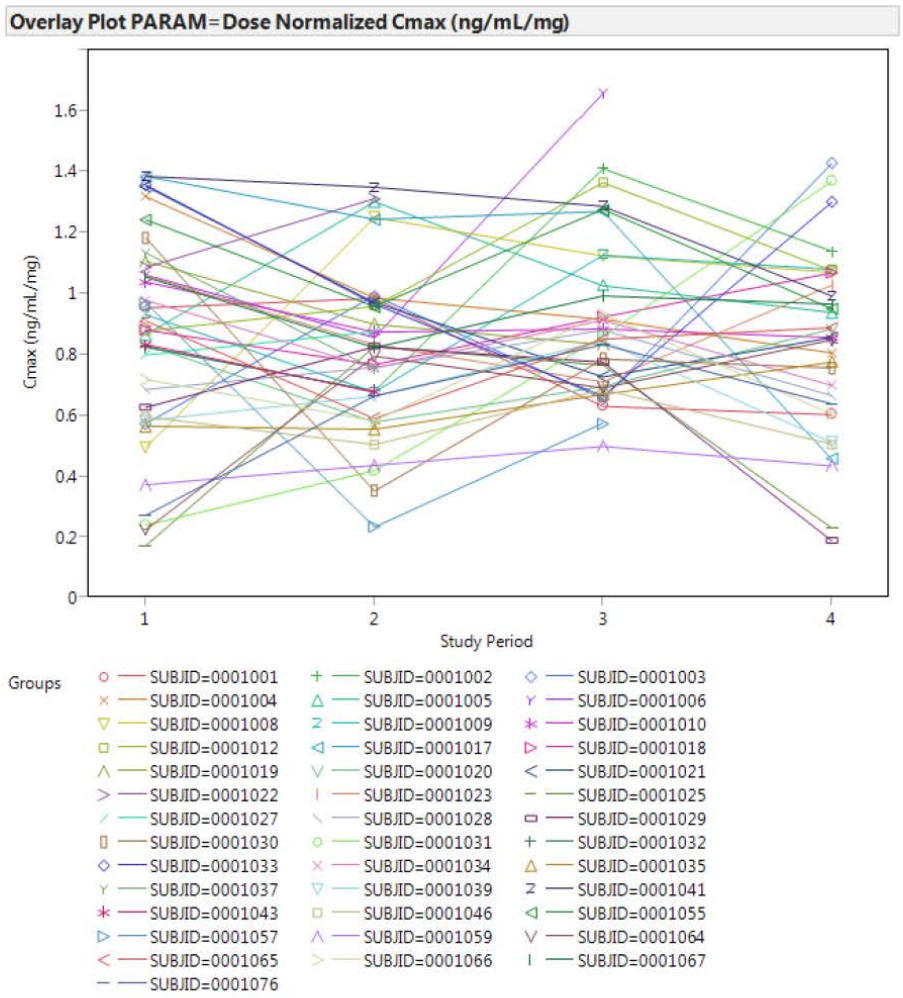


Figure 2. Study HYD1004 Dose-Proportionality Study (20-120 mg) – Dose-Normalized Cmax of Hysingla ER Fasted, Single-Dose Across Study Periods



A primary concern raised by the cited observations for study HYD1003 is the possibility that a patient titrated to an appropriate dose of Hysingla ER in the fasted state could experience a large increase in exposure if Hysingla ER was taken with a high-fat meal. Since low fasting exposure on one occasion does not reliably predict low fasting exposure on subsequent occasions, the largest observed fed versus fasting exposure differences seen in study HYD1003 are unlikely to translate into real-world dosing differences observed at steady state.

"Also, explain how you plan to address these observations in labeling"

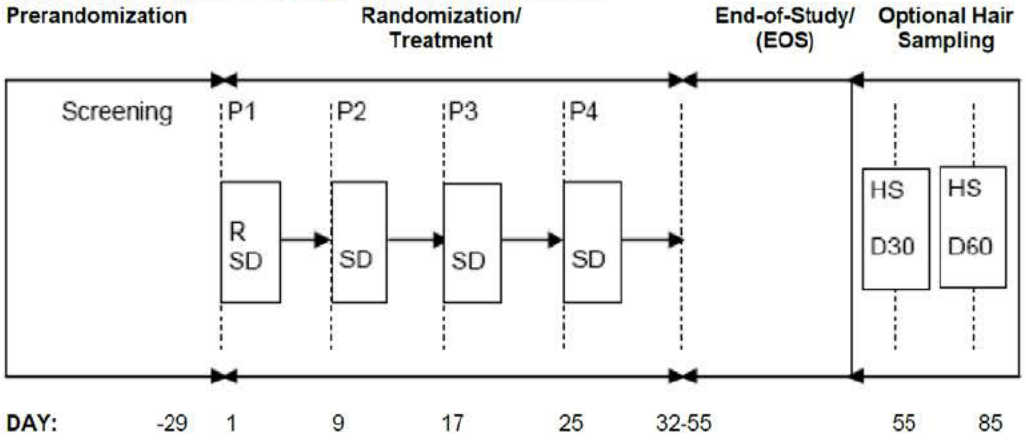
Based on our assessment of the concerns raised, we do not believe any changes in labeling are necessary. The current labeling is consistent with the findings of the food effect study HYD1003 and with the safety and efficacy results of the pivotal Phase 3 studies (HYD3002 and HYD3003) in which Hysingla ER was administered without regard to the type of meal or the timing of meal ingestion.

4.2.5 Study HYD1001: Dosage form proportionality (Iteration 6) and preliminary food-effect study (Iteration 5) synopsis.

Name of Sponsor/Company: Purdue Pharma L.P.	**Protocol No.** HYD1001	
Name of Active Ingredient: Hydrocodone Bitartrate	**Name of Finished Product:** Not Applicable	
IND No.:59,175		
Title of the Study: A randomized, open-label, crossover, pilot study in healthy subjects to assess the pharmacokinetics of hydrocodone bitartrate q24h film coated (HYD) tablets.		
Investigator, Site: Sandra K. Willsie, DO, MA, Clinical Pharmacology Center, PRA		
Publication (Reference): Not Applicable		
Study Dates:: 26-Feb-2009 (First Subject First Visit) to 29-Jul-2011 (Last Subject Last Visit)	**Study Status:** Completed	**Phase of Development:** Phase 1
Objectives: The primary objective of this study was: • To assess the relative bioavailability of hydrocodone bitartrate once daily (q24h) film-coated (HYD) tablets. The secondary objectives of this study were: • To assess the effect of food on HYD bioavailability. • To assess the safety and tolerability of HYD tablets. Note: Another secondary objective had been to assess the bioavailability of HYD tablets relative to hydrocodone 5-mg /acetaminophen 500-mg (Vicodin®) tablets in the fasted state. However, Vicodin was not included in any of the iterations.		
Study Design (Methodology): Randomized, open-label, crossover study in healthy adult male and female subjects. The study was designed to comprise a maximum of 8 iterations, with up to 8 treatments studied across a maximum of 4 periods in each iteration. An iteration was defined as a process of repeating the study design each time with a unique group of subjects undergoing a set of predefined treatments. Iterations could be run in parallel or sequentially. A total of 6 iterations were completed.		

Name of Sponsor/Company:	Protocol No.
Purdue Pharma L.P.	HYD1001
Name of Active Ingredient:	**Name of Finished Product:**
Hydrocodone Bitartrate	Not Applicable

Study Design Graphic: Example of a 4-period iteration



P1 – P4 = Periods 1 to 4 each with study drug administration. There was a minimum 8-day washout period between study drug administrations.
R = Randomization (period 1 only).
SD = Study drug administration.
HS = Hair sample(s) collection.
D = Day post last dose of study drug.
EOS = End-of-study; this visit took place 7-10 days after administration of the last dose of study drug or upon early discontinuation from the study. For subjects who consented to participate in the optional hair sampling extension after the EOS visit, there were hair sampling visits on days 30 and 60 post last dose of study drug.

Six iterations were performed. Iterations 1 and 2 each had 4 periods, iterations 3 and 4 each had 3 periods, and iterations 5 and 6 each had 2 periods, as follows:

Iteration 1:

- Cohort 1
  - HYD 20-mg, slow-release tablet (A) in the fasted state
  - HYD 20-mg, medium-release tablet (B) in the fasted state
  - HYD 20-mg, fast-release tablet (C) in the fasted state
  - HYD 20-mg, medium-release tablet (B) in the fed state
- Cohort 2
  - HYD 20-mg, slow-release tablet (A) in the fasted state
  - HYD 20-mg, medium-release tablet (B) in the fasted state

Iteration 2:

- Cohort 1
  - HYD 120-mg, slow-release tablet (A) in the fasted state
  - HYD 120-mg, medium-release tablet (B) in the fasted state
  - HYD 120-mg, fast-release tablet (C) in the fasted state
  - HYD 120-mg, medium-release tablet (B) in the fed state
- Cohort 2
  - HYD 120-mg, slow-release tablet (A) in the fasted state
  - HYD 120-mg, medium-release tablet (B) in the fasted state

Iteration 3:

- HYD 20-mg slow-release (D) tablet in the fasted state
- HYD 20-mg medium-release (E1) tablet Lot 1, in the fasted state
- HYD 20-mg fast-release (F) tablet in the fasted state

Name of Sponsor/Company:	Protocol No.
Purdue Pharma L.P.	HYD1001
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Hydrocodone Bitartrate	Not Applicable

Iteration 4:
- HYD 120-mg slow-release (D) tablet in the fasted state
- HYD 120-mg medium-release (E1) tablet, Lot 1, in the fasted state
- HYD 120-mg fast-release (F) tablet in the fasted state

Iteration 5:
- HYD 120-mg slow-release (D) tablet in the fasted state
- HYD 120-mg slow-release (D) tablet in the fed state

Iteration 6:
- HYD 4 x 20-mg slow-release (D) tablet in the fasted state
- HYD 1 x 80-mg slow-release (D) tablet in the fasted state

Number of Subjects (Planned and Analyzed):

Planned: For each iteration up to 36 subjects were to be dosed.

Enrolled: 522 subjects were enrolled (all iterations combined).

Screen failures: 317 (all iterations combined)

Not Assigned: 20

Randomized: 185 (all iterations combined)

Iteration	Randomized	Discontinued Early	Completed
Iteration 1	36	6 (adverse events [AEs]: 2; subjects choice: 4)	30
Iteration 2	37[a]	4 (AEs: 3; administrative: 1)	32
Iteration 3	36	3 (AEs: 2; administrative: 1)	33
Iteration 4	36	4 (AEs: 1; subjects choice: 3)	32
Iteration 5	16	1 (AEs: 1)	15
Iteration 6	24	0	24

a 1 subject discontinued after randomization but before treatment.

Indication and Main Criteria for Inclusion/Exclusion: Healthy male and female subjects aged 18 to 50 years, inclusive, with no clinically significant medical history, who were deemed suitable to take part in this clinical study by the Investigator.

Test Product, Dose, Mode of Administration, and Batch Number: All treatments were administered orally with 8 oz (240 mL) water.

HYD formulations/treatments varied in dose and release rate:

- HYD 20-mg, slow-release (A) tablet; batch number CB-2008-18
- HYD 20-mg, medium-release (B) tablet; batch number CB-2008-19
- HYD 20-mg, fast-release (C) tablet; batch number CB-2008-20
- HYD 120-mg, slow-release (A) tablet; batch number CB-2008-21
- HYD 120-mg, medium-release (B) tablet; batch number CB-2008-22
- HYD 120-mg, fast-release (C) tablet; batch number CB-2008-23
- HYD 20-mg slow-release (D) tablet; batch numbers CB-2010-23, CB-2011-04
- HYD 20-mg medium-release (E1) tablet Lot 1; batch number CB-2010-24
- HYD 20-mg fast-release (F) tablet; batch number CB-2010-25
- HYD 120-mg slow-release (D) tablet; batch number CB-2010-27
- HYD 120-mg medium-release (E1) tablet Lot 1; batch number CB-2010-28
- HYD 120-mg fast-release (F) tablet; batch number CB-2010-29
- HYD 80-mg slow-release (D) tablet; batch number CB-2011-10

HYD tablets were administered in the fasted or fed state, depending on the iteration methodology.

Name of Sponsor/Company:	Protocol No.
Purdue Pharma L.P.	HYD1001
Name of Active Ingredient:	**Name of Finished Product:**
Hydrocodone Bitartrate	Not Applicable

Reference Product, Dose, Mode of Administration, and Batch Number: When applicable per iteration, Vicodin (hydrocodone bitartrate 5 mg / acetaminophen 500 mg) tablets could have been administered orally (1 tablet every 6 hours for a total of 4 tablets) with 8 oz (240 mL) water in the fasted state. No Vicodin treatments were administered during the study.

Concomitant Medication (All Iterations):

Naloxone hydrochloride (HCl) challenge test (prior to first dose of naltrexone HCl).

Naltrexone HCl tablets (50 mg) were administered every 12 hours (q12h) from 12 hours predose through 36 hours postdose to minimize opioid-related AEs.

The use of other concomitant medications during this trial was discouraged, unless necessary to treat AEs. The use of other concomitant medications required approval by the sponsor (or designee) in advance, when possible.

Duration of Treatment and Study Duration: Subjects were screened no more than 28 days prior to check-in of period 1. There were up to 4 periods for each iteration. Study drug was administered in each period according to the random allocation schedule (RAS). There was a minimum 8-day washout period between study drug administration. Subjects were confined to the unit the day prior to study drug administration and for 48 hours following study drug administration during each period. Subjects returned to the unit for scheduled 72-hour procedures.

Subjects had end-of-study procedures (EOS) performed 7 to 10 days after the last dose of study drug or upon early discontinuation from the study.

Total study duration: up to approximately 64 days without the optional hair sampling, and up to approximately 114 days for subjects completing the optional hair sampling.

Treatment Schedule (Per Iteration):

Pre-Randomization Phase:

Screening: Subjects were screened within 28 days of period 1 check-in. Drug and alcohol screens, physical examination, 12-lead electrocardiogram (ECG), vital signs (systolic/diastolic blood pressure, pulse rate, respiration rate, and oral temperature), oxygen saturation by pulse oximetry (SpO_2), medical and medication history, clinical laboratory testing, and inclusion/exclusion criteria were evaluated.

Randomization Phase: For each period, subjects checked into the unit the day prior to dosing. In period 1 check-in only, subjects underwent a naloxone HCl challenge test, after a urine drug screen was reported as negative, and had biochemistry (fasting for at least 4 hours), hematology, and urinalysis tests performed.

For all periods: Urine pregnancy test (for women of childbearing potential), vital signs, SpO_2, and alcohol and urine drug screens were performed. Subjects received naltrexone HCl tablets (50 mg) with 240 mL of water 12 hours prior to study drug dosing.

Prior to study drug administration (except period 1), subjects had biochemistry (fasting for at least 4 hours), hematology, and urinalysis tests performed.

Subjects were administered the study drug and naltrexone HCl with 240 mL of water following a 10-hour overnight fast. Subjects receiving fasted treatment continued fasting from food for 4 hours following dosing. Subjects receiving fed treatment started the standard meal 30 minutes prior to administration of the study drug. Subjects were dosed 30 minutes after start of the meal, and no food was allowed for at least 4 hours postdose. Subjects were standing or in an upright sitting position while receiving their dose of study drug and remained in an upright position following dosing for a minimum of 4 hours.

Naltrexone HCl was also administered with 240 mL of water at 12, 24, and 36 hours postdose. Vital signs (including SpO_2) and blood samples for drug concentration measurements were obtained predose and at prespecified times up to 72 hours postdose.

Optional Pharmacogenomic Evaluation: Subjects were asked if they were interested in participating in an optional exploratory pharmacogenomic portion of the study following the written informed consent. Samples were collected predose and 72 hours postdose in period 1 only from subjects who gave informed consent for this portion of the study.

Name of Sponsor/Company:	Protocol No.
Purdue Pharma L.P.	HYD1001
Name of Active Ingredient:	**Name of Finished Product:**
Hydrocodone Bitartrate	Not Applicable

Continuous SpO_2 Monitoring: For subjects receiving HYD doses of 60 mg or more, SpO_2 was monitored continuously beginning prior to dosing and continuing through 24 hours postdose. Start and stop date/time were recorded in the source documents.

Subjects had biochemistry (fasting for at least 4 hours), hematology, and urinalysis tests performed 24 hours postdose.

In addition, 12-lead ECGs were performed for each subject predose and approximately 12, 24, and 48 hours postdose.

Subjects were confined to the unit from check-in to the unit on the day before dosing until the time that their 48-hour procedures were completed. The subjects returned to the unit for the 72-hour blood sample and vital signs.

AEs and concomitant medications were recorded throughout the study.

End-of-Study (E0S)Visit: This visit took place 7 to 10 days after administration of the last dose of study drug, or upon early discontinuation from the study. The EOS procedures included a physical examination, 12-lead ECG, vital signs, SpO_2, and laboratory tests.

Optional Hair Sampling Visits: Subjects were asked if they were interested in participating in an optional hair-sampling portion of the study following their written informed consent. For subjects who consented to participate in the optional hair sampling extension after the EOS visit, there were hair sampling visits on days 30 and 60 post the last dose of study drug.

Criteria and Methods for Evaluation:

Analysis Populations (Per Iteration):

The enrolled population was the group of subjects who provided informed consent.

The randomized safety population was the group of subjects who were randomized, received study drug, and had at least 1 postdose safety assessment.

The full analysis population for PK metrics was the group of subjects who were randomized, received study drug, and had at least 1 valid PK metric for that treatment. Subjects experiencing emesis within 24 hours after dosing could have been excluded from PK analysis.

Hydrocodone and Metabolite(s) Concentration Measurements:

Blood samples for determining hydrocodone plasma concentrations were collected during each of the periods for each subject. Plasma concentrations of hydrocodone metabolite(s) were not determined.

HYD Treatments: Predose and at 0.5, 1, 1.5, 2, 3, 4, 5, 6, 8, 10, 12, 14, 18, 24, 36, 48, and 72 hours postdose.

Vicodin Treatments: Not used.

Up to 5 additional postdose blood sample(s) could have been collected, or the timing of PK draws could have changed, if indicated after the analysis of blood samples from previous iteration(s). Additional blood samples were not obtained.

Bioanalytical Methods:

Plasma concentrations of hydrocodone were quantified using a validated liquid chromatography tandem mass spectrometric (LC-MS/MS) method.

Safety Assessments:

Safety was assessed using recorded AEs, clinical laboratory test results, vital signs, SpO_2, physical examinations, and ECGs.

Other Variables Assessments:

Optional pharmacogenomic evaluation: For the optional pharmacogenomic evaluation portion of the study, subjects had blood samples collected predose (day 1) and 72 hours postdose (day 4) during period 1.

Optional hair sampling: Hair samples were to be collected from subjects 2 times, 30 and 60 days after the last dose of study drug was administered. The hair samples were analyzed for hydrocodone and its metabolites.

Statistical Methods:

Name of Sponsor/Company:	Protocol No.
Purdue Pharma L.P.	HYD1001
Name of Active Ingredient:	**Name of Finished Product:**
Hydrocodone Bitartrate	Not Applicable

Pharmacokinetic Metrics: Plasma concentrations of hydrocodone were analyzed to determine the following PK metrics:

- $AUC_{(0-t)}$ – Area under the plasma concentration-time curve from hour 0 to the last measurable plasma concentration
- $AUC_{(0-inf)}$ – Area under the plasma concentration-time curve from time 0 extrapolated to infinity
- C_{max} – Maximum observed plasma concentration
- T_{max} – Time to maximum observed plasma concentration
- $t_{1/2}$ – Apparent plasma terminal phase half-life
- C_{24}/C_{max} – Ratio of observed plasma concentration at 24 hours postdose (C_{24}) divided by C_{max}. Calculated as applicable (iterations 1, 2, 3, and 4 only).

Descriptive statistics were tabulated by treatment, as applicable, for all PK metrics.

The relative bioavailability of HYD formulations/treatments were assessed.

The determination of food effect was assessed by comparing fed and fasting PK metrics.

Statistical Analyses of Safety Data:

All safety data (AEs, clinical laboratory results, vital signs, SpO_2, and ECGs) were listed for subjects in the enrolled and randomized safety populations. Results of clinical laboratory evaluations that lay outside the normal range were flagged on the listings as high or low.

Subjects' AEs were coded into preferred terms and associated system organ class (SOC) using the Medical Dictionary for Regulatory Activities (MedDRA). Treatment-emergent AEs (TEAEs) are defined as AEs that started after or increased in severity after the first dose of study drug. TEAEs were summarized by presenting the incidence of AEs for each treatment group by the MedDRA preferred term, nested within SOC for the safety population. Medical History was coded to MedDRA terms.

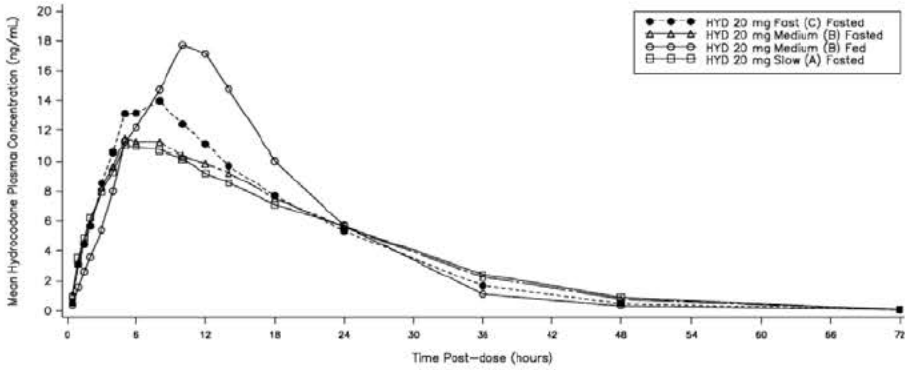
Laboratory evaluations, vital signs, and SpO_2 were summarized by time point for the safety population.

Sample Size Rationale:

No formal sample size calculations were performed. For each iteration, up to 36 subjects were randomized to provide sufficient treatment replications.

Pharmacokinetic Results:

Iteration 1:

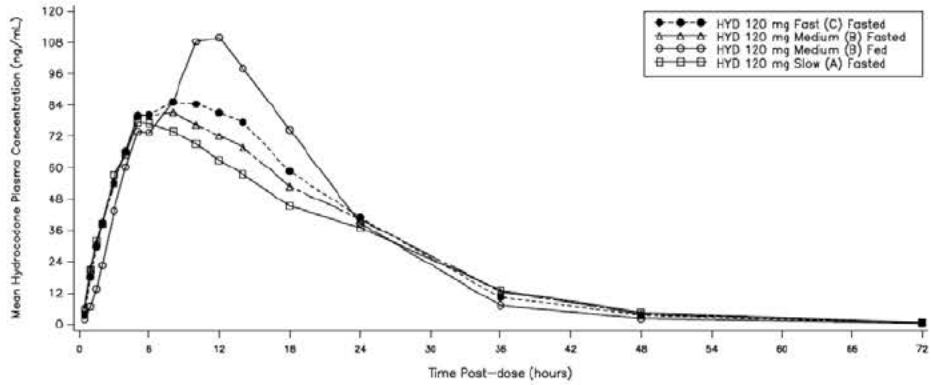


Iteration 1 - Mean Plasma Concentration-time Profiles for HYD-20 mg
Source: Table 14.2.1.1.1 and Figure 14.2.2.1.1.

Name of Sponsor/Company:	Protocol No.
Purdue Pharma L.P.	HYD1001
Name of Active Ingredient:	**Name of Finished Product:**
Hydrocodone Bitartrate	Not Applicable

- The extent of exposure (mean AUC) of HYD 20-mg was similar for the slow- (A), medium- (B) and fast-release (C) formulations.
- Mean C_{max} was slightly greater for the fast-release (C) by 16% and 22% compared to that of medium- (B) and slow-release (A) formulations, respectively.
- Median T_{max} ranged from 6 to 7 hours across the fasted formulations.
- Mean C_{24}/C_{max} ratio was 0.5 for the slow-release (A) formulation compared to 0.4 in the fast- (C) and medium-release (B) formulations.
- Mean AUC increased ~14% while mean C_{max} increased 47% for the medium-release in the presence of a high-fat meal.
- Food delayed T_{max} to a median of 10 hours for the medium-release (B) formulation.
- Based on the anticipated peak to trough performance at steady state, none of the formulations studied were selected for further development.

Iteration 2:

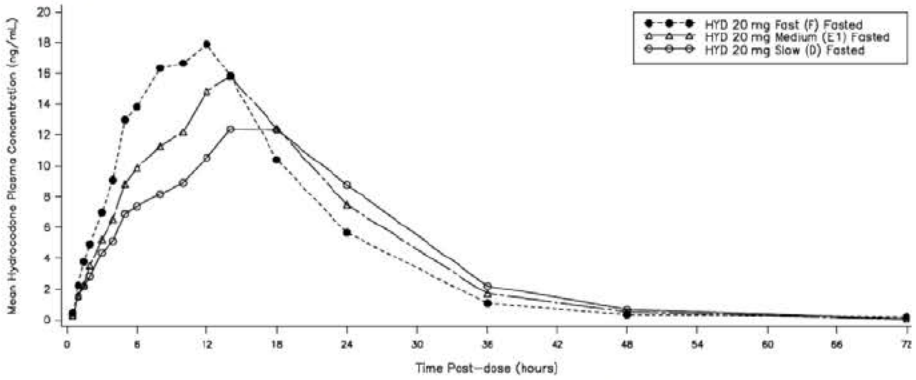


Iteration 2 - Mean Plasma Concentration-time Profiles for HYD 120
Source: Table 14.2.1.1.2 and Figure 14.2.2.1.2.

- The extent of exposure (mean AUC) of HYD 120-mg of the fast (C) formulation was slightly greater (~11%) compared to that of the slow-release (A) formulation, but similar to that of the medium-release (B) formulation.
- Mean C_{max} was slightly greater for the fast-release (C) formulation by ~16%, compared to that of slow-release (A) formulation, but similar to that of the medium-release (B) formulation.
- Median T_{max} was 6 hours in the slow-release (A) and 8 hours in the medium- (B) and fast-release (C) formulations.
- Mean C_{24}/C_{max} ratio was similar (0.4 – 0.5) between all 3 formulations in the fasted state.
- The extent of exposure (mean AUC) increased ~ 9%, while mean C_{max} was increased by ~ 33%, in the presence of a high-fat meal.
- Food delayed T_{max} to a median of ~ 10 hours for the medium-release (B) formulation.
- Based on the anticipated peak to trough performance at steady state, none of the formulations studied were selected for further development.

Name of Sponsor/Company:	Protocol No.
Purdue Pharma L.P.	HYD1001
Name of Active Ingredient:	**Name of Finished Product:**
Hydrocodone Bitartrate	Not Applicable

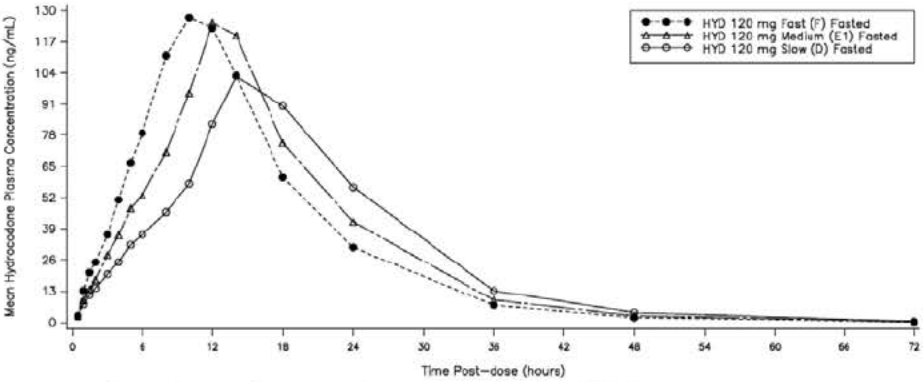
Iteration 3:



Iteration 3 - Mean Plasma Concentration-time Profiles for HYD 20 mg
Source: Table 14.2.1.1.3 and Figure 14.2.2.1.3.

- The extent of exposure (mean AUC) of HYD 20-mg of slow- (D), medium- (E1), and fast-release (F) formulations was similar.
- Mean C_{max} of the fast-release (F) formulation was greater by 20% and 40% compared to that of medium- (E1) and slow-release (D) formulations, respectively.
- Median T_{max} was 12 hours in the fast-release (F) as opposed to 14 hours in the slow- (D) and medium-release (E1) formulations.
- Mean C_{24}/C_{max} ratio was 0.6 for slow-release (D) compared to 0.5 for medium- (E1) and 0.3 for fast-release (F) formulations.
- Based on the anticipated peak to trough performance at steady state, HYD 20-mg slow-release (D) formulation was selected for further development.

Iteration 4:



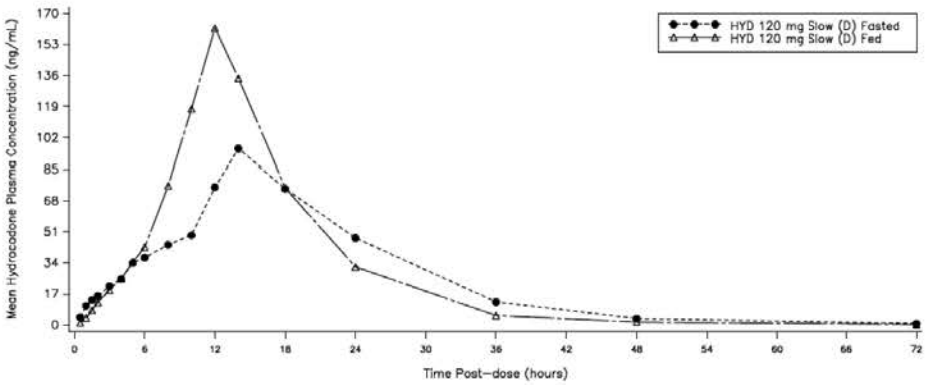
Iteration 4 - Mean Plasma Concentration-time Profiles for HYD 120 mg
Source: Table 14.2.1.1.4 and Figure 14.2.2.1.4.

- The extent of exposure (mean AUC) of HYD 120-mg was comparable between all 3 formulations.
- Mean C_{max} of the fast-release (F) formulation was greater by 20% compared to that of the slow-release (D) but similar to that of the medium-release (E1) formulation.

Name of Sponsor/Company:	Protocol No.
Purdue Pharma L.P.	HYD1001
Name of Active Ingredient:	**Name of Finished Product:**
Hydrocodone Bitartrate	Not Applicable

- Median T_{max} was 10 hours in the fast-release (F) as opposed to 14 and 12 hours in the slow- (D) and medium-release (E1) formulations, respectively.
- Mean C_{24}/C_{max} ratio was 0.5 for the slow- (D) compared to 0.3 for medium- (E1) and 0.2 for fast-release (F) formulations.
- Based on the anticipated peak to trough performance at steady state, HYD 120-mg slow-release (D) formulation was selected for further development.

Iteration 5:



Iteration 5 - Mean Plasma Concentration-time Profiles for HYD 120 mg of Slow-release Formulation D
Source: Table 14.2.1.1.5 and Figure 14.2.2.1.5.

- AUC of hydrocodone from the HYD 120-mg dose slow-release formulation was greater in the fed state (20%), while the C_{max} increased by 70% (based on the least-square means).
- Median T_{max} was 12 and 14 hours in the fed and fasted states, respectively.
- Mean $t_{1/2}$ was ~8 hours in both fed and fasted states.

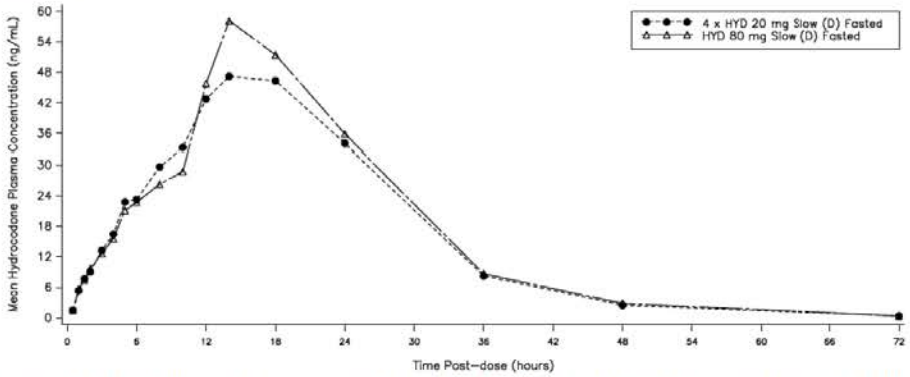
Statistical Analysis of Food Effect Bioavailability for Iteration 5 (HYD 120-mg Slow-Release) (Full Analysis for PK Metrics Population)

	Geometric LS Means			Ratio	
Metric (unit)	**Fed (test)**	**Fasted (reference)**	**CV (%)**	**Test/ Reference (%)**	**90% CI of Ratio**
$AUC_{(0\text{-}inf)}$ (hr*ng/mL)	1984	1661	31	120	(99, 145)
$AUC_{(0\text{-}tlast)}$ (hr*ng/mL)	1976	1651	31	120	(99, 145)
C_{max} (ng/mL)	162	95	33	170	(139, 208)

CV is from this model on the natural log scale and is calculated as the square root of (exp[Intra-subject Variance] - 1).
Source: Table 14.2.1.3.1.

Name of Sponsor/Company:	Protocol No.
Purdue Pharma L.P.	HYD1001
Name of Active Ingredient:	**Name of Finished Product:**
Hydrocodone Bitartrate	Not Applicable

Iteration 6:



Iteration 6 - Mean Plasma Concentration-time Profiles for Four HYD 20 mg and One HYD 80 mg Tablet of Slow-release Formulation D
Source: Table 14.2.1.1.6 and Figure 14.2.2.1.6.

- AUC and C_{max} of hydrocodone following the administration of a single 80-mg tablet and four 20 mg slow-release) tablets were comparable (9% and 18%, respectively, based on least squares mean).
- Median T_{max} was 14 and 18 hours following a HYD 1 x 80 mg tablet and HYD 4 x 20 mg tablets, respectively
- Mean $t_{1/2}$ was ~8 hours in both treatments.

Statistical Analysis of Relative Bioavailability for Iteration 6 (Full Analysis for PK Metrics Population)

	Geometric LS Means			Ratio	
Metric (unit)	4 x 20 mg (test)	1 x 80 mg (reference)	CV (%)	Test/ Reference (%)	90% CI of Ratio
$AUC_{(0\text{-}inf)}$ (hr*ng/mL)	1099	1207	21	91	(82, 101)
$AUC_{(0\text{-}tlast)}$ (hr*ng/mL)	1092	1188	20	92	(83, 102)
C_{max} (ng/mL)	53	64	26	82	(72, 93)

CV is from this model on the natural log scale and is calculated as the square root of (exp[Intra-subject Variance] - 1).
Source: Table 14.2.1.3.2.

Safety Results:

- There were no deaths or serious adverse events (SAEs) in the study. Two subjects had positive urine drug tests on study (cotinine and benzodiazepines).
- Nine subjects (4.9%) discontinued because of TEAEs (including 1 subject who was discontinued by the investigator due to positive urine drug screen). In addition to the positive drug screen, the AEs leading to discontinuation were those commonly associated with opioid analgesics (nausea, vomiting, headache, agitation, dehydration, decreased appetite, dysphoria, and restlessness) and infections unrelated to the study treatment (gastroenteritis, gastroenteritis viral, pharyngitis streptococcal, and pyrexia). These AEs did not raise any new or unexpected safety concerns regarding HYD.
- Overall, 100 subjects (54.3%) experienced TEAEs during any treatment period, and all AEs were mild to moderate in severity. In general, these AEs are expected with opioid analgesics, and the frequency or severity of all AEs or of any individual AEs did not appear related to any of the doses, formulations, or

Name of Sponsor/Company:	Protocol No.
Purdue Pharma L.P.	HYD1001
Name of Active Ingredient:	**Name of Finished Product:**
Hydrocodone Bitartrate	Not Applicable

conditions studied in any iteration.

- The most common SOCs were nervous system (35.9%) or gastrointestinal disorders (31.0%).
- The most common TEAEs were nausea (22.8%), headache (22.8%), somnolence (12.0%), and dizziness (7.1%).
- All of the TEAEs were of mild or moderate intensity and most were considered associated with study drug (unlikely, possibly, probably, or definitely related to study drug).

- Results of the laboratory tests, 12-lead ECG measurements, vital sign measurements, and SpO_2 evaluations raised no safety concerns for any of the study treatments.

Conclusions:

The primary objective of this study was to assess the relative bioavailability of HYD once daily tablets. The secondary objectives of this study were to assess the effect of food on HYD bioavailability and to assess the safety and tolerability of HYD tablets.

- HYD 20- and HYD 120-mg slow-release tablets (Formulation D) of the (b) (4) formulation satisfied the formulation criteria.
- HYD 120-mg slow-release tablets showed a C_{max} increase (~70%) in the presence of a standard high-fat meal. However, the increase (20%) in AUC was not clinically meaningful.
- Coadministration of HYD 120 mg with a standard high-fat meal did not result in dose dumping.
- Systemic hydrocodone exposures from HYD 4 x 20-mg tablets and HYD 1 x 80-mg tablet were comparable.
- The administration of HYD tablets at single oral doses up to 120 mg under naltrexone blockade was safe and well tolerated.
- There were no deaths or SAEs. Nine subjects (4.9%) discontinued because of TEAEs; the AEs leading to discontinuation were those commonly associated with opioid analgesics under naltrexone blockade or with infections unrelated to the study treatment.
- The observed TEAEs were those generally associated with opioid analgesics under naltrexone blockade. All TEAEs were of mild or moderate intensity.
- Clinical laboratory values, vital sign and SpO_2 measurements, and ECG results and changes from baseline were similar across the iterations.

Date of Draft Report: 09 Nov 2012

4.2.6 Dose-proportionality Study HYD1004 synopsis.

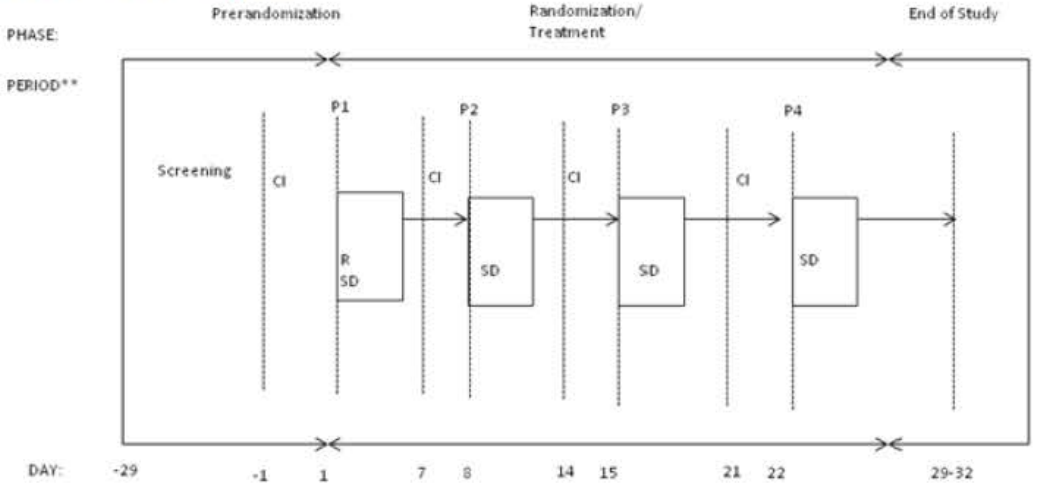
Name of Sponsor/Company: Purdue Pharma L.P.	**Protocol No.** HYD1004
Name of Active Ingredient: Hydrocodone bitartrate	**Name of Finished Product**: Not applicable
US IND/EUDRACT No. 59,175	
Title of study: Pharmacokinetics and Dose Proportionality of Hydrocodone Bitartrate (HYD) Extended-Release Tablets in Healthy Subjects Under Naltrexone Blockade	
Investigator: Aziz L. Laurent, MD	
Study site: PPD Phase I Clinic, 7551 Metro Center Drive, Suite 200, Austin TX 78744	
Publication (reference): None	
Studied period (years): 10-Oct-2011 (First Subject First Visit) to 21-Dec-2011 (Last Subject Last Visit)	**Phase of development**: Phase 1
Objectives: The primary objective of this study was: • To assess the pharmacokinetics and dose proportionality of hydrocodone bitartrate (HYD) extended-release tablets. The secondary objective of this study was: • To assess the safety and tolerability of different dosage strengths of HYD extended-release tablets in healthy adult subjects under naltrexone blockade.	

Name of Sponsor/Company:	Protocol No.
Purdue Pharma L.P.	HYD1004
Name of Active Ingredient:	**Name of Finished Product:**
Hydrocodone bitartrate	Not applicable
US IND/EUDRACT No.	
59,175	

Study Design (Methodology):

Single-center, randomized, open-label, single-dose, 5-treatment, 4-period, crossover, incomplete block study in healthy adult subjects. Treatments were separated by a minimum 7 day washout. There was an optional exploratory pharmacogenomic (PG) sampling portion of this study.

Study Design Graphic:



** P1 to P4 = Periods 1 to 4 each with study drug administration. There was a minimum 7 day washout period between study drug administrations.
CI = Check-in.
R = Randomization (period 1 only).
SD = Study drug administration.
EOS: This visit took place 7 to 10 days after administration of the last dose of study drug or upon early discontinuation from the study.

Number of subjects (planned and analyzed): No formal sample size calculations were performed. This study was planned to randomize 40 subjects to complete up to approximately 36 subjects. Subjects that completed this 4 of 5 incomplete block study would allow for approximately 28 measurements of each of the 5 treatments.

Forty subjects (22 males and 18 females) were randomly assigned to a treatment sequence in this study. Thirty-one subjects completed the study. Forty subjects were included in the safety analyses and in the pharmacokinetic (PK) analyses. Three subjects (7.5%) were discontinued due to AEs, 4 subjects (10%) were discontinued due to administrative reasons, 1 subject (2.5%) discontinued due to subject's choice, and 1 subject (2.5%) was lost to follow-up.

Name of Sponsor/Company:	**Protocol No.**
Purdue Pharma L.P.	HYD1004
Name of Active Ingredient:	**Name of Finished Product**:
Hydrocodone bitartrate	Not applicable
US IND/EUDRACT No.	
59,175	

Diagnosis and main criteria for inclusion:

Non-smoking, healthy male and female subjects aged 18 to 50 years, inclusive, with no clinically significant medical history, who were deemed suitable to take part in this clinical study by the investigator.

Test product, dose and mode of administration, batch number:

HYD, 20-mg single oral dose; 1 × 20-mg extended-release tablet
Lot number: CB-2011-04

HYD, 40-mg single oral dose; 1 × 40-mg extended-release tablet
Lot number: CB-2011-06

HYD, 60-mg single oral dose; 1 × 60-mg extended-release tablet
Lot number: CB-2011-08

HYD, 80-mg single oral dose; 1 × 80-mg extended-release tablet
Lot number: CB-2011-10

HYD, 120-mg single oral dose; 1 × 120-mg extended-release tablet
Lot number: CB-2011-11

"Study drug" in this study was defined as HYD extended-release tablets.

Bioretention samples of each strength of study drug were maintained at the site according to 21 CFR §320.28 and 21 CFR §320.63.

Reference treatment, dose and mode of administration, batch number:

There was no reference treatment in this study.

Concomitant medication:

Naloxone hydrochloride (HCl) challenge test (prior to first dose of naltrexone HCl). One naltrexone HCl tablet (50 mg) was administered at –12, 0, 12, 24 and 36 hours, relative to HYD administration to minimize opioid-related adverse events.

Naloxone HCl and naltrexone HCl were protocol-specified drugs, distinct from study drug.

Naloxone HCl, 0.8-mg (2.0 mL) single dose; subcutaneous (Lot number 94317EV)

Naltrexone HCl, 50 mg orally every 12 hours; 1 × 50-mg tablet (Lot number 34002081A)

The use of other concomitant medications during this trial was discouraged, unless necessary to treat adverse events (AEs). The use of other concomitant medications was to be approved by the sponsor (or designee) in advance, when possible.

Name of Sponsor/Company:	**Protocol No.**
Purdue Pharma L.P.	HYD1004
Name of Active Ingredient:	**Name of Finished Product**:
Hydrocodone bitartrate	Not applicable
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59,175	

Duration of treatment:

Subjects were screened no more than 28 days prior to check-in of period 1. Study drug was administered in each period according to the study randomization schedule. There was a minimum 7 day washout period between study drug administrations. Subjects were confined to the study unit the day prior to study drug administration and for 72 hours following study drug administration during each period.

Subjects had end-of-study procedures performed 7 to 10 days after last dose of study drug or upon early discontinuation from the study.

Total study duration: up to 61 days.

Study Procedures:

Pretreatment Phase:

Screening: Subjects were screened within 28 days of period 1 check-in. Drug, alcohol, and cotinine screens, physical examination, 12-lead electrocardiogram (ECG), vital signs (systolic/diastolic blood pressure, pulse rate, respiratory rate and oral temperature), pulse oximetry (SpO_2), medical and medication history, clinical laboratory testing, serum pregnancy test for females, follicle-stimulating hormone test for postmenopausal women, and inclusion/exclusion criteria were evaluated.

Check-in: Subjects checked into the study unit the day prior to start of dosing. In period 1 check-in only, subjects received a naloxone HCl challenge test and had chemistry, hematology, and urinalysis tests performed.

For all periods, serum pregnancy test (for women of child-bearing potential), vital signs, SpO_2, alcohol, cotinine, and urine drug screens were performed.

Prior to period 1 dosing, subjects were randomized to a treatment sequence according to the randomization schedule.

Treatment Phase:

Subjects were administered the study drug with 240 mL of water following a 10-hour overnight fast. Subjects fasted from food for 4 hours following dosing. Subjects were standing or in an upright sitting position while receiving their dose of study drug and remained in an upright position following dosing for a minimum of 4 hours.

One 50-mg tablet of naltrexone HCl was administered with 240 mL of water at prespecified times.

Clinical laboratory evaluations, 12-lead ECG, and vital signs (including SpO_2)

Name of Sponsor/Company:	Protocol No.
Purdue Pharma L.P.	HYD1004
Name of Active Ingredient:	**Name of Finished Product**:
Hydrocodone bitartrate	Not applicable
US IND/EUDRACT No.	
59,175	

measurements and blood samples for drug concentration measurements were obtained at prespecified times.

For subjects receiving HYD doses of 60 mg or more, SpO_2 was monitored continuously beginning prior to dosing and continuing through 24 hours postdose.

Subjects participating in the optional exploratory PG portion of the study had samples collected in period 1 only at prespecified times.

All AEs and concomitant medications were recorded throughout the study.

End-of-Study Visit: This visit took place 7 to 10 days after administration of the last dose of study drug or upon early discontinuation from the study. End-of-study procedures included a physical examination, 12-lead ECG, vital signs, SpO_2, and clinical laboratory tests.

Criteria for evaluation:

Pharmacokinetics:

Blood samples for determining hydrocodone plasma concentrations were obtained for each subject at predose and at 0.5, 1, 2.5, 4, 6, 8, 10, 12, 14, 16, 18, 24, 30, 36, 48, and 72 hours post study drug administration during each of the treatment periods.

Plasma concentrations of hydrocodone were quantified by a validated bioanalytical method.

Safety:

Safety was assessed using recorded AEs, clinical laboratory test results, vital signs, SpO_2, physical examinations, and 12-lead ECGs.

Other:

Optional PG evaluation: blood samples were collected predose and 72 hours postdose during period 1 only.

Name of Sponsor/Company:	Protocol No.
Purdue Pharma L.P.	HYD1004
Name of Active Ingredient:	**Name of Finished Product**:
Hydrocodone bitartrate	Not applicable
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Statistical methods:

Analysis Populations:

The enrolled population consisted of all subjects who signed the informed consent form.

The randomized safety population consisted of subjects who were randomized and received at least 1 dose of study drug.

The full analysis population (FAP) was the group of subjects who were randomized, received study drug, and had at least 1 valid PK metric. Subjects experiencing emesis within 24 hours after dosing could have been excluded from the PK analysis. The PK analysis was based on the FAP. As documented in the final statistical analysis plan, no subjects or profiles/metrics were excluded from the analysis set and there were no events of emesis identified that would affect the PK metrics.

Pharmacokinetics:

Listings and figures of hydrocodone plasma concentrations were based on the randomized safety population. Individual and mean plasma concentration versus time profiles were presented in figures on both linear and semi-logarithmic scales. Plasma concentration summaries were based on the FAP for PK metrics.

Plasma concentrations of hydrocodone were analyzed to determine the following PK metrics for each treatment by noncompartmental PK analysis (model independent approach): area under the plasma concentration versus time curve from hour 0 to the last measurable plasma concentration (AUCt), area under the plasma concentration versus time curve extrapolated to infinity (AUCinf), maximum observed plasma concentration (Cmax), time to maximum plasma concentration (Tmax), apparent terminal phase half-life (t1/2), and time to the first measurable plasma concentration value (Tlag). PK analyses and summaries were based on the FAP. Descriptive statistics included sample size (n), mean, standard deviation (SD), coefficient of variation (%CV), median, minimum, maximum, and geometric mean were tabulated by treatment as applicable for all plasma concentrations and PK metrics. Graphical displays of untransformed and dose-normalized AUCt, AUCinf, and Cmax were presented on both linear and log-log scales.

Dose proportionality was assessed by clinical and statistical review of the descriptive data for HYD. The power model approach was used as a sensitivity method for assessment of dose proportionality. A mixed-model approach was used to estimate the magnitude of β (slope parameter of interest) and to derive the confidence interval (CI) around the slope. Dose proportionality was concluded when the 90% CIs for β were completely contained within the critical range of (0.875, 1.125).

Name of Sponsor/Company:	**Protocol No.**
Purdue Pharma L.P.	HYD1004
Name of Active Ingredient:	**Name of Finished Product**:
Hydrocodone bitartrate	Not applicable
US IND/EUDRACT No.	
59,175	

Safety:

All safety data (AEs, clinical laboratory results, vital signs, SpO_2, physical examinations, and 12-lead ECGs) were listed for subjects in the randomized safety population.

All AEs were categorized into preferred terms and associated system organ class using the Medical Dictionary for Regulatory Activities (MedDRA) Version 14.1.
Treatment-emergent AEs (TEAEs) were defined as AEs that started after or increased in intensity after the first dose of study drug. Summaries of TEAEs were generated by treatment for subjects in the randomized safety population. The incidence of TEAEs was summarized by system organ class (SOC), preferred term, and treatment (if appropriate) by presenting the number and percentage of subjects with an AE. Separate summaries were provided for TEAEs by maximum intensity (mild, moderate, severe) and relationship (related, not related) to study drug. Medical history was coded to MedDRA terms. Coded medical history terms were summarized for all subjects in the randomized safety population.

Concomitant medication was coded using World Health Organization Drug Dictionary (WHO-DD) 01 September 2011 and was listed using the randomized safety population.

Laboratory evaluations, vital signs, and SpO_2 were summarized by treatment and time point for the randomized safety population.

Other:

Exploratory PG analyses will be reported separately.

RESULTS:

Pharmacokinetic results:

Mean plasma concentrations of hydrocodone versus time are presented on linear and semi-logarithmic scales in Figure 1.

Name of Sponsor/Company:	Protocol No.
Purdue Pharma L.P.	HYD1004
Name of Active Ingredient:	**Name of Finished Product:**
Hydrocodone bitartrate	Not applicable
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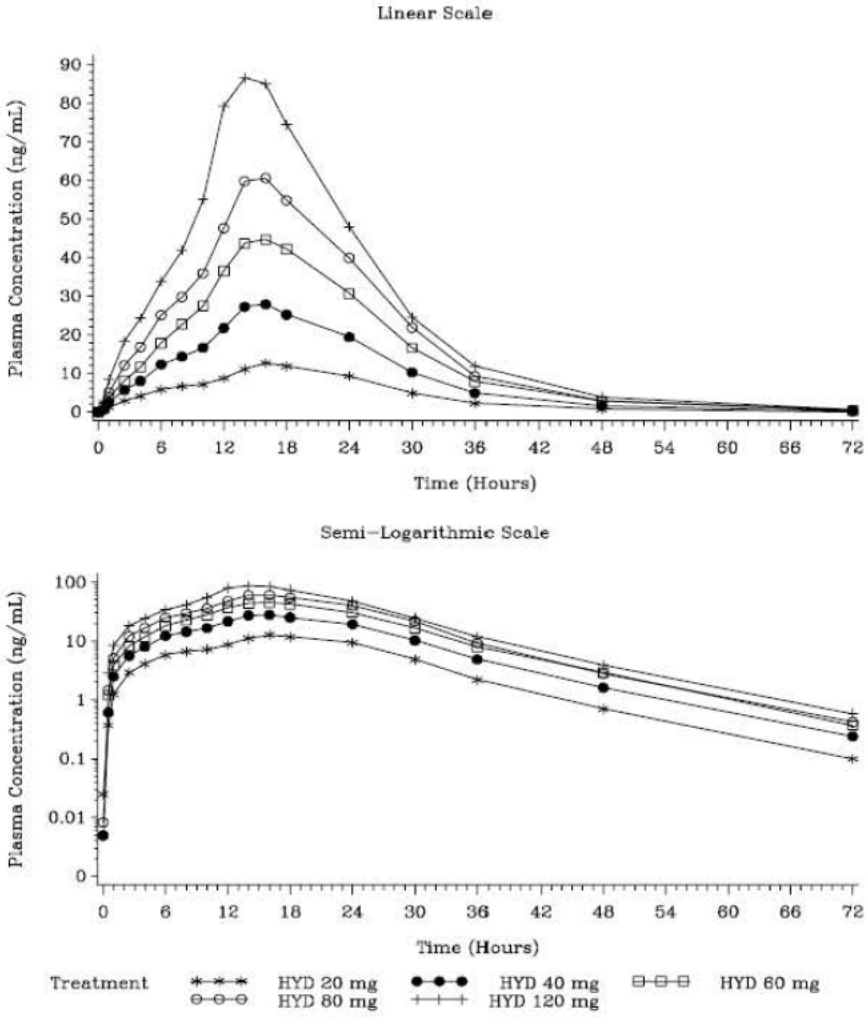
59,175	



Abbreviation: HYD, hydrocodone bitartrate.

Source: Figure 14.2.1.

Figure 1: Mean Plasma Concentrations of Hydrocodone Versus Time on Linear and Semi-logarithmic Scales (Full Analysis Population)

Mean plasma concentrations of hydrocodone increased slowly after oral administration of HYD extended-release tablets and reached a maximum concentration at 14 to 16 hours postdose. Thereafter, plasma levels declined and remained detectable for more than 72 hours postdose in most subjects at the dose level of 40 mg and above.

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A summary table of mean plasma hydrocodone PK metrics is presented in Table 1.

Table 1: Summary of Plasma Hydrocodone Pharmacokinetic Metrics (Full Analysis Population)

Metric (Unit)	HYD 20 mg N = 29	HYD 40 mg N = 31	HYD 60 mg N = 28	HYD 80 mg N = 30	HYD 120 mg N = 29
AUCt (ng•h/mL)					
Mean	280.79	617.68	1003.79	1297.66	1759.09
SD	126.914	250.377	292.104	373.110	671.404
AUCinf (ng•h/mL)					
Mean	284.20	622.35	1009.05	1303.87	1787.17[a]
SD	127.683	251.949	294.073	375.133	678.736
Cmax (ng/mL)					
Mean	14.56	33.88	53.64	69.09	109.78
SD	5.485	11.805	15.402	17.198	44.125
Tmax (h)					
Median	16.00	16.00	14.07	16.00	14.00
Minimum, Maximum	6.00, 24.00	6.02, 24.00	10.00, 30.00	10.00, 24.00	6.00, 30.00
t1/2 (h)					
Mean	7.64	7.69	8.05	8.24	8.65[a]
SD	2.588	2.121	2.352	2.396	3.463

Abbreviation: HYD, hydrocodone bitartrate.
[a] n = 28.
Source: Table 14.2.2.

A statistical power model was utilized as a sensitivity tool, and the results showed that the slope for the power model on logarithmic scale for AUCinf was 1.11 with a 90% CI of (1.02, 1.20), which overlaps the dose proportionality limits of (0.88, 1.12). This indicates minimal deviation from dose proportionality.

Similar results were observed for Cmax. The mean slope for Cmax of hydrocodone was approximately 1.16 and the 90% CI for the slope was (1.08, 1.24).

Safety results:

A summary of TEAEs by severity, SOC, and MedDRA preferred term that were reported in at least 2 subjects in any treatment is presented in Table 2.

Table: PK Parameters of hydrocodone including partial AUCs and percent partial AUC as compared to total AUC.

Variable	HYD Dose	NObs	Mean	SD	Min	Median	Max	GeometricMean	CVPercent
AUC0-3	20	29	5.15	1.17	2.41	5.20	7.01	5.00	22.72
AUC0-3	40	31	10.05	3.01	4.78	9.40	16.16	9.60	30.01
AUC0-3	60	28	14.88	5.19	1.00	14.87	29.68	13.47	34.88
AUC0-3	80	30	21.33	6.40	9.22	21.60	34.00	20.34	30.02
AUC0-3	120	29	33.31	8.28	20.68	33.13	56.96	32.36	24.86
AUC0-6	20	29	18.78	3.96	11.52	19.40	26.03	18.34	21.10
AUC0-6	40	31	37.56	9.34	18.37	36.96	58.89	36.35	24.88
AUC0-6	60	28	55.03	16.54	9.12	56.33	89.35	51.61	30.05
AUC0-6	80	30	78.45	21.18	42.92	76.80	132.63	75.61	27.00
AUC0-6	120	29	113.94	28.74	61.29	119.63	192.46	110.23	25.22
AUC0-8	20	29	31.21	6.64	17.06	32.05	46.22	30.44	21.28
AUC0-8	40	31	64.20	17.38	30.92	62.84	109.59	61.79	27.07
AUC0-8	60	28	95.69	30.08	29.95	93.90	154.00	90.47	31.43
AUC0-8	80	30	133.32	37.72	62.75	130.69	226.53	127.90	28.29
AUC0-8	120	29	189.70	56.06	85.39	187.92	321.06	181.02	29.55
AUC0-12	20	29	61.00	15.99	25.03	62.38	94.92	58.63	26.20
AUC0-12	40	31	133.50	46.30	57.90	123.27	233.19	125.75	34.68
AUC0-12	60	28	210.07	80.47	100.42	206.86	388.25	195.92	38.31
AUC0-12	80	30	282.62	84.15	128.95	267.25	456.66	270.61	29.78
AUC0-12	120	29	420.96	179.67	133.49	386.54	849.26	384.82	42.68
AUC0-14	20	29	80.89	23.86	26.46	79.20	116.72	76.83	29.50
AUC0-14	40	31	182.51	68.35	65.91	189.67	313.65	169.31	37.45
AUC0-14	60	28	290.36	109.64	145.25	280.35	517.24	270.93	37.76
AUC0-14	80	30	390.09	112.12	191.35	366.48	652.96	374.95	28.74
AUC0-14	120	29	586.60	259.99	166.19	542.93	1221.26	529.64	44.32
AUC0-16	20	29	104.75	33.40	27.44	100.89	166.07	98.43	31.88
AUC0-16	40	31	237.67	89.75	71.36	255.08	396.19	218.24	37.76
AUC0-16	60	28	378.79	135.21	173.65	370.30	660.24	355.35	35.69
AUC0-16	80	30	510.55	135.05	269.45	505.07	832.26	493.70	26.45
AUC0-16	120	29	758.06	320.27	203.19	705.67	1535.26	686.16	42.25
AUC0-20	20	29	152.15	51.84	28.82	146.59	249.50	140.48	34.07
AUC0-20	40	31	339.20	123.70	78.59	356.21	563.32	308.41	36.47
AUC0-20	60	28	546.35	170.18	264.85	520.40	891.17	520.14	31.15
AUC0-20	80	30	730.66	165.99	415.35	740.03	1104.53	712.04	22.72
AUC0-20	120	29	1057.42	402.82	274.56	1084.23	1968.93	963.22	38.09
AUC0-24	20	29	192.77	69.32	29.63	197.12	307.02	175.11	35.96
AUC0-24	40	31	424.44	149.30	82.45	448.03	695.19	383.87	35.18
AUC0-24	60	28	684.62	186.20	390.05	657.21	1065.04	660.69	27.20
AUC0-24	80	30	910.10	193.67	481.59	916.97	1276.26	888.50	21.28
AUC0-24	120	29	1284.60	470.91	286.08	1299.21	2230.26	1170.05	36.66
AUC0-30	20	29	235.23	91.67	30.03	245.50	419.22	209.58	38.97
AUC0-30	40	31	513.28	182.39	84.71	533.55	838.89	459.56	35.53
AUC0-30	60	28	826.80	203.48	524.60	752.70	1243.54	803.57	24.61
AUC0-30	80	30	1095.21	250.41	511.74	1089.37	1634.47	1065.09	22.86
AUC0-30	120	29	1502.09	546.43	295.56	1559.32	2420.76	1365.79	36.38

AUC3-6	20	29	13.63	2.98	8.05	14.35	20.52	13.29	21.84
AUC3-6	40	31	27.51	7.12	12.97	26.44	44.89	26.55	25.90
AUC3-6	60	28	40.15	12.17	8.12	39.75	61.10	37.76	30.31
AUC3-6	80	30	57.12	16.62	27.33	57.58	105.13	54.74	29.09
AUC3-6	120	29	80.63	22.75	39.33	83.13	135.50	77.13	28.21
AUC6-9	20	29	19.23	5.23	7.95	20.18	31.62	18.42	27.18
AUC6-9	40	31	41.55	15.06	18.75	37.98	80.33	39.02	36.24
AUC6-9	60	28	64.58	28.01	27.56	64.81	132.05	59.35	43.37
AUC6-9	80	30	86.18	30.21	31.76	76.30	170.83	81.24	35.06
AUC6-9	120	29	120.98	53.71	35.55	116.40	260.45	109.84	44.39
AUC9-12	20	29	23.00	8.41	4.10	24.46	37.28	21.05	36.55
AUC9-12	40	31	54.39	26.21	15.43	52.93	117.65	48.06	48.20
AUC9-12	60	28	90.46	45.44	33.85	78.81	199.65	80.61	50.23
AUC9-12	80	30	117.98	44.66	54.28	100.25	232.48	110.82	37.86
AUC9-12	120	29	186.05	109.87	36.65	155.13	441.30	155.81	59.05
AUC12-15	20	29	31.42	15.17	1.96	29.63	68.13	26.57	48.28
AUC12-15	40	31	76.44	38.02	8.89	87.98	153.13	62.75	49.73
AUC12-15	60	28	124.25	51.26	37.80	120.46	218.35	113.11	41.26
AUC12-15	80	30	167.50	50.68	100.73	165.05	293.38	160.64	30.25
AUC12-15	120	29	251.75	131.63	22.59	245.33	537.00	209.20	52.29
AUC15-18	20	29	36.88	17.41	1.22	37.32	72.58	29.56	47.20
AUC15-18	40	31	80.81	34.74	5.30	87.98	135.78	65.27	42.99
AUC15-18	60	28	131.41	46.25	36.93	118.70	232.60	122.70	35.20
AUC15-18	80	30	175.88	42.81	66.15	178.28	245.73	169.98	24.34
AUC15-18	120	29	244.71	106.40	15.99	277.28	438.78	206.86	43.48
AUC18-21	20	29	33.63	15.93	0.87	35.63	65.93	26.06	47.36
AUC18-21	40	31	71.22	30.33	3.72	72.83	122.85	56.83	42.59
AUC18-21	60	28	118.06	34.44	58.80	106.39	213.83	113.53	29.17
AUC18-21	80	30	153.26	38.37	41.64	157.43	218.03	147.16	25.04
AUC18-21	120	29	203.39	89.39	11.27	216.98	352.88	169.19	43.95
AUC21-24	20	29	29.83	15.95	0.56	32.03	67.58	21.91	53.47
AUC21-24	40	31	62.48	30.46	2.52	63.08	143.55	47.86	48.76
AUC21-24	60	28	100.83	29.46	34.80	98.70	188.48	96.39	29.22
AUC21-24	80	30	130.84	46.69	28.32	125.55	272.55	121.79	35.69
AUC21-24	120	29	163.79	82.40	8.12	178.05	337.65	131.50	50.31
AUC24-27	20	29	24.58	15.02	0.29	24.83	62.25	16.97	61.12
AUC24-27	40	31	51.26	30.08	1.38	47.27	145.35	37.08	58.68
AUC24-27	60	28	81.65	31.10	19.14	82.91	156.75	75.43	38.08
AUC24-27	80	30	106.09	53.58	18.37	96.15	315.83	94.41	50.50
AUC24-27	120	29	126.36	75.13	5.64	123.98	333.15	96.45	59.45
AUC27-30	20	29	17.88	12.37	0.10	16.98	51.23	11.69	69.16
AUC27-30	40	31	37.58	24.16	0.88	32.05	112.65	26.23	64.31
AUC27-30	60	28	60.53	30.50	11.82	57.30	148.65	53.66	50.39
AUC27-30	80	30	79.02	50.25	11.78	68.10	293.48	67.60	63.60
AUC27-30	120	29	91.12	62.15	3.84	89.85	285.45	66.64	68.20
AUCall	20	29	283.27	126.71	30.03	289.46	591.01	245.58	44.73
AUCall	40	31	619.63	249.33	85.34	624.72	1199.84	542.17	40.24
AUCall	60	28	1004.74	290.96	585.34	916.93	1724.49	966.73	28.96

AUCall	80	30	1298.60	372.28	558.98	1267.63	2500.57	1249.15	28.67
AUCall	120	29	1759.76	670.22	305.68	1838.82	3324.05	1591.70	38.09
Cmax	20	29	14.56	5.49	3.47	13.70	26.20	13.38	37.68
Cmax	40	31	33.88	11.80	7.60	35.00	54.20	30.98	34.85
Cmax	60	28	53.64	15.40	33.30	52.50	83.00	51.57	28.71
Cmax	80	30	69.09	17.20	39.90	66.95	109.00	67.03	24.89
Cmax	120	29	109.78	44.13	28.20	106.00	199.00	99.36	40.19
Tlag	20	29	0.03	0.13	0.00	0.00	0.50	.	373.93
Tlag	40	31	0.03	0.12	0.00	0.00	0.50	.	387.08
Tlag	60	28	0.04	0.13	0.00	0.00	0.50	.	367.17
Tlag	80	30	0.03	0.13	0.00	0.00	0.50	.	380.56
Tlag	120	29	0.00	0.00	0.00	0.00	0.00	.	.
Tmax	20	29	15.38	4.48	6.00	16.00	24.00	14.63	29.10
Tmax	40	31	15.81	4.42	6.00	16.00	24.00	15.18	27.98
Tmax	60	28	16.43	4.66	10.00	14.00	30.00	15.89	28.38
Tmax	80	30	15.40	2.58	10.00	16.00	24.00	15.20	16.76
Tmax	120	29	14.69	4.35	6.00	14.00	30.00	14.13	29.62
AUC0to3hAsPercentOfAUCall	20	29	2.51	2.27	1.06	1.76	11.18	2.04	90.54
AUC0to3hAsPercentOfAUCall	40	31	2.24	2.20	0.70	1.65	9.52	1.77	97.79
AUC0to3hAsPercentOfAUCall	60	28	1.54	0.51	0.11	1.53	2.59	1.39	33.32
AUC0to3hAsPercentOfAUCall	80	30	1.71	0.59	0.88	1.68	3.74	1.63	34.39
AUC0to3hAsPercentOfAUCall	120	29	2.46	2.38	1.14	1.84	13.45	2.03	96.60
AUC3to6hAsPercentOfAUCall	20	29	6.75	6.32	2.47	4.56	32.06	5.41	93.60
AUC3to6hAsPercentOfAUCall	40	31	5.86	5.05	2.18	4.36	24.20	4.90	86.15
AUC3to6hAsPercentOfAUCall	60	28	4.11	1.12	0.93	4.11	6.48	3.91	27.39
AUC3to6hAsPercentOfAUCall	80	30	4.57	1.47	2.66	4.32	9.88	4.38	32.25
AUC3to6hAsPercentOfAUCall	120	29	5.57	4.36	2.77	4.19	25.80	4.85	78.33
AUC6to9hAsPercentOfAUCall	20	29	8.74	5.87	3.20	6.76	26.46	7.50	67.21
AUC6to9hAsPercentOfAUCall	40	31	8.32	5.65	3.01	6.74	26.23	7.20	67.95
AUC6to9hAsPercentOfAUCall	60	28	6.56	2.70	3.11	5.81	16.52	6.14	41.22
AUC6to9hAsPercentOfAUCall	80	30	6.89	2.65	3.79	6.08	16.30	6.50	38.42
AUC6to9hAsPercentOfAUCall	120	29	7.85	4.76	2.98	6.41	22.26	6.90	60.63
AUC9to12hAsPercentOfAUCall	20	29	9.48	4.68	4.01	8.10	21.61	8.57	49.39
AUC9to12hAsPercentOfAUCall	40	31	9.83	4.68	3.46	8.25	23.24	8.86	47.59
AUC9to12hAsPercentOfAUCall	60	28	9.16	4.44	4.03	7.91	25.74	8.34	48.48
AUC9to12hAsPercentOfAUCall	80	30	9.48	3.73	5.21	8.16	20.13	8.87	39.37
AUC9to12hAsPercentOfAUCall	120	29	11.21	6.13	3.07	8.39	29.55	9.79	54.74
AUC12to15hAsPercentOfAUCall	20	29	11.42	3.87	6.14	10.62	20.22	10.82	33.86
AUC12to15hAsPercentOfAUCall	40	31	12.56	4.72	4.41	12.87	20.68	11.57	37.55
AUC12to15hAsPercentOfAUCall	60	28	12.60	4.49	4.07	13.01	20.62	11.70	35.61
AUC12to15hAsPercentOfAUCall	80	30	13.45	3.88	5.50	13.40	20.50	12.86	28.82
AUC12to15hAsPercentOfAUCall	120	29	14.45	5.66	4.24	15.39	23.23	13.14	39.18
AUC15to18hAsPercentOfAUCall	20	29	12.58	3.43	4.05	12.30	18.75	12.03	27.23
AUC15to18hAsPercentOfAUCall	40	31	12.78	4.00	5.46	13.77	19.95	12.04	31.27
AUC15to18hAsPercentOfAUCall	60	28	13.37	3.61	3.37	14.73	18.47	12.69	27.01
AUC15to18hAsPercentOfAUCall	80	30	13.91	2.45	4.55	14.52	17.43	13.61	17.58
AUC15to18hAsPercentOfAUCall	120	29	13.66	3.91	4.89	14.16	20.87	13.00	28.63
AUC18to21hAsPercentOfAUCall	20	29	11.22	3.15	2.89	12.18	17.14	10.61	28.09

AUC18to21hAsPercentOfAUCall	40	31	11.00	2.90	3.70	11.69	14.26	10.48	26.38
AUC18to21hAsPercentOfAUCall	60	28	12.04	2.52	6.27	12.47	16.06	11.74	20.93
AUC18to21hAsPercentOfAUCall	80	30	11.95	1.85	6.54	11.79	14.49	11.78	15.49
AUC18to21hAsPercentOfAUCall	120	29	11.17	3.23	3.69	11.71	17.04	10.63	28.87
AUC21to24hAsPercentOfAUCall	20	29	9.67	3.13	1.86	10.56	16.17	8.92	32.39
AUC21to24hAsPercentOfAUCall	40	31	9.45	2.83	2.51	9.95	14.11	8.83	30.01
AUC21to24hAsPercentOfAUCall	60	28	10.24	2.28	4.49	10.26	16.52	9.97	22.32
AUC21to24hAsPercentOfAUCall	80	30	9.93	1.76	5.07	10.31	12.14	9.75	17.70
AUC21to24hAsPercentOfAUCall	120	29	8.80	2.80	2.65	9.73	12.70	8.26	31.78
AUC24to27hAsPercentOfAUCall	20	29	7.78	2.95	0.97	8.57	12.55	6.91	37.88
AUC24to27hAsPercentOfAUCall	40	31	7.61	2.98	1.62	7.34	12.99	6.84	39.19
AUC24to27hAsPercentOfAUCall	60	28	8.19	2.46	2.47	7.81	14.72	7.80	30.08
AUC24to27hAsPercentOfAUCall	80	30	7.87	2.08	3.29	8.13	12.63	7.56	26.40
AUC24to27hAsPercentOfAUCall	120	29	6.67	2.58	1.85	7.33	10.93	6.06	38.69
AUC27to30hAsPercentOfAUCall	20	29	5.55	2.30	0.33	6.28	9.22	4.76	41.39
AUC27to30hAsPercentOfAUCall	40	31	5.50	2.39	1.03	5.03	10.69	4.84	43.35
AUC27to30hAsPercentOfAUCall	60	28	5.90	1.93	1.52	5.67	10.37	5.55	32.63
AUC27to30hAsPercentOfAUCall	80	30	5.76	1.96	2.11	5.79	11.74	5.41	34.06
AUC27to30hAsPercentOfAUCall	120	29	4.77	2.22	1.26	4.74	8.59	4.19	46.61

Table 2: Summary of Treatment-Emergent Adverse Events by Severity, System Organ Class, and Preferred Term (Reported by 2 or More Subjects in any Treatment) (Randomized Safety Population)

System Organ Class Preferred Term Severity[a]	HYD 20 mg (N = 29) n (%)	HYD 40 mg (N = 31) n (%)	HYD 60 mg (N = 28) n (%)	HYD 80 mg (N = 30) n (%)	HYD 120 mg (N = 29) n (%)	Total (N = 40) n (%)
Gastrointestinal disorders						
Abdominal pain						
Mild	0	0	2 (7)	1 (3)	2 (7)	4 (10)
Nausea						
Mild	2 (7)	1 (3)	2 (7)	2 (7)	1 (3)	7 (18)
Nervous system disorders						
Dizziness						
Mild	0	0	0	2 (7)	0	2 (5)
Headache						
Mild	2 (7)	2 (6)	0	5 (17)	0	8 (20)
Somnolence						
Mild	3 (10)	1 (3)	3 (11)	1 (3)	2 (7)	6 (15)

Abbreviations: HYD, hydrocodone bitartrate.

Note: Percentages were based on N. Multiple occurrences of the same adverse event in 1 subject were counted only once. The Medical Dictionary for Regulatory Activities Version 14.1 was used to code the adverse events. Treatment-emergent adverse events were defined as adverse events that started after or increased in intensity after the first dose of study drug. Adverse events that started more than 7 days after the last dose of study drug were not considered treatment-emergent adverse events.

[a] If a subject reported more than 1 occurrence of the same preferred term, the maximum severity was included in the table. Missing severities were treated as severe. Severity was taken from the severity reported on the electronic case report form by the investigator.

Source: Table 14.3.1.5.

There were no deaths or SAEs. Three subjects (7.5%) discontinued from the study due to the TEAEs of dyspnoea and urticaria (subject RN040034/0001027), hypoaesthesia (subject RN040037/0001032), and haematochezia (subject RN040038/0001057), respectively.

Overall, 21 of 40 subjects (53%) experienced at least 1 TEAE. The number of treatment-related TEAEs was similar across the 5 treatments. All TEAEs resolved by the end of the study.

Name of Sponsor/Company:	**Protocol No.**
Purdue Pharma L.P.	HYD1004
Name of Active Ingredient:	**Name of Finished Product**:
Hydrocodone bitartrate	Not applicable
US IND/EUDRACT No.	
59,175	

With the exception of 6 TEAEs of moderate severity in 3 subjects, all TEAEs reported during this study were mild. Moderate TEAEs consisted of nausea, vomiting, dysphagia, and dyspnoea. There were no severe TEAEs.

The TEAEs experienced by at least 2 subjects in any treatment consisted of abdominal pain, nausea, dizziness, headache, and somnolence.

No clinically significant changes were observed in clinical laboratory values, vital sign and SpO_2 measurements, or ECG results for any of the treatments studied.

CONCLUSIONS:

- AUC and Cmax increased linearly with dose from 20 to 120 mg. Both Cmax and AUC increased slightly more than dose proportionally. This deviation from dose proportionality was minimal.
- Median Tmax was between 14 and 16 hours across all dose levels.
- The administration of HYD extended-release tablets at single oral dose levels of 20, 40, 60, 80, and 120 mg under fasted conditions with naltrexone blockade was safe and well tolerated.
- There were no deaths or SAEs. Three subjects discontinued from the study due to the TEAEs of dyspnoea and urticaria, hypoaesthesia, and haematochezia, respectively.
- Clinical laboratory values, vital sign and SpO_2 measurements, and ECG results and changes from baseline were similar across the 5 treatments, and no apparent treatment-related trends were observed.

Date of report: 05-Jun-2012

4.2.7 Study HYD1006 evaluating effect of age and gender on PK synopsis.

Name of Sponsor/Company: Purdue Pharma L.P.	**Protocol No.** HYD1006
Name of Active Ingredient: Hydrocodone bitartrate	**Name of Finished Product**: Not applicable
US IND/EUDRACT No. 59,175	
Title of study: An Evaluation of the Effect of Age and Gender on the Pharmacokinetics and Safety of 40 mg Hydrocodone Bitartrate (HYD) Extended-Release Tablets in Young Female and Male Healthy Subjects and Elderly Female and Male Subjects Under Naltrexone Blockade	
Investigator: Aziz L. Laurent, MD	
Study site: PPD Phase I Clinic, 7551 Metro Center Drive, Suite 200, Austin TX 78744	
Publication (reference): None	
Studied period (years): 21-Oct-2011 (First Subject First Visit) to 14-Mar-2012 (Last Subject Last Visit)	**Phase of development**: Phase 1
Objectives: The primary objective of this study was: • To assess the effects of age and gender on the pharmacokinetics of 40 mg hydrocodone bitartrate (HYD) extended-release tablets. The secondary objective of this study was: • To assess the effects of age and gender on the safety and tolerability profile of 40 mg HYD extended-release tablets administered under naltrexone blockade.	

Name of Sponsor/Company:	**Protocol No.**
Purdue Pharma L.P.	HYD1006
Name of Active Ingredient:	**Name of Finished Product**:
Hydrocodone bitartrate	Not applicable
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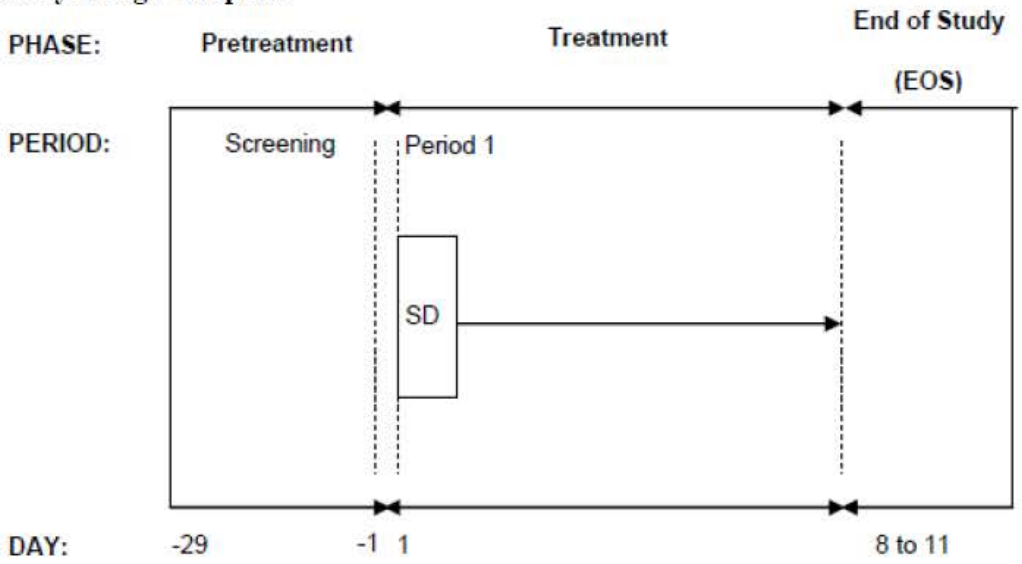
Study Design (Methodology):

Single-center, open-label, parallel-group, single-dose study in 4 cohorts: young adult healthy female and male subjects and elderly female and male subjects. There was an optional pharmacogenomic (PG) portion of the study.

Study Design Graphic:



SD = Study drug administration.
EOS: This end-of-study visit took place 7 to 10 days after administration of the study drug or upon early discontinuation from the study.

Number of subjects (planned and analyzed): The following age and gender breakdown was attempted in order to complete approximately 48 subjects: approximately 12 each female and male young healthy subjects (cohorts A and B, respectively) and 12 each female and male elderly subjects (cohorts C and D, respectively). Results of previous HYD studies suggested that the intra-subject coefficient of variation (%CV) of the maximum observed plasma concentration (Cmax) was between 25% and 30%. Given this %CV, it was estimated that 12 subjects/age and gender group would achieve a statistical power of greater than 80% in order to conclude that the female : male or elderly : young ratio of the means would fall between 0.80 and 1.25.

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One hundred thirty-three subjects were enrolled in the study. Fifty subjects received study drug and were included in the safety population (13 young females, 12 young males, 12 elderly females, and 13 elderly males). Forty-nine subjects (98%) completed the study. Fifty subjects (100%) were included in the safety and pharmacokinetic (PK) analyses. One subject (2%) discontinued due to adverse events (AEs).	
Diagnosis and main criteria for inclusion: Young (aged 18 to 45 years, inclusive) and elderly (aged 65 to 80 years, inclusive) healthy female and male subjects who met all inclusion criteria and none of the exclusion criteria who were deemed suitable to take part by the investigator.	
Test product, dose and mode of administration, batch number: HYD, 40-mg single oral dose; 1 × 40-mg extended-release tablet Lot number: CB-2011-06 "Study drug" in this study was defined as HYD extended-release tablets.	
Reference treatment, dose and mode of administration, batch number: There was no reference treatment in this study.	
Concomitant medication: Naloxone hydrochloride (HCl) challenge test was administered to subjects at check-in (prior to first dose of naltrexone HCl). One naltrexone HCl tablet (50 mg) was administered at −12, 0, 12, 24, and 36 hours relative to HYD administration to minimize opioid-related AEs. Naloxone HCl and naltrexone HCl were protocol-specified drugs, distinct from study drug. Naloxone HCl, 0.8-mg (2.0 mL) single dose; subcutaneous (Lot number 94317EV) Naltrexone HCl, 50 mg orally every 12 hours; 1 × 50-mg tablet (Lot numbers 34002081A and 316708) The use of other concomitant medications during this trial was discouraged, unless necessary to treat AEs. The use of other concomitant medications was to be approved by the sponsor (or designee) in advance, when possible.	

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Duration of treatment:

Subjects were screened no more than 28 days prior to check-in. Subjects were confined to the study unit the day prior to study drug administration and for 72 hours following study drug administration.

Subjects had end-of-study procedures performed 7 to10 days after administration of the study drug or upon early discontinuation from the study.

Total study duration for each subject: up to 40 days.

Study Procedures:

Pretreatment Phase:

Screening: Subjects were screened within 28 days of check-in. Drug, alcohol, and cotinine screens, physical examination, 12-lead electrocardiogram (ECG), vital signs (systolic/diastolic blood pressure, pulse rate, respiratory rate, and oral temperature), pulse oximetry (SpO_2), medical and medication history, clinical laboratory testing, serum pregnancy test for females, follicle-stimulating hormone test for postmenopausal women, and inclusion/exclusion criteria were evaluated.

Check-in: Subjects checked into the study unit the day prior to start of dosing. Subjects received a naloxone HCl challenge test and had chemistry, hematology, and urinalysis tests performed. Additionally, urine pregnancy test for females, vital signs, SpO_2, alcohol, cotinine, and urine drug screens were performed.

Treatment Phase:

Subjects were administered the study drug with 240 mL of water following a 10-hour overnight fast. Subjects fasted from food for 4 hours following dosing. Subjects restricted their consumption of water for 3 hours prior to dose and for 2 hours postdose (water restriction added per Protocol Amendment 2 dated 21-Oct-2011). Subjects were standing or in an upright sitting position while receiving their dose of study drug and remained in an upright position following dosing for a minimum of 4 hours.

One 50-mg tablet of naltrexone HCl was administered with 240 mL of water at prespecified times.

Vital signs (including SpO_2) measurements, 12-lead ECG, and blood samples for drug concentration measurements were obtained at prespecified times.

Subjects participating in the optional exploratory PG portion of the study had samples collected at prespecified times.

All AEs and concomitant medications were recorded throughout the study.

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End-of-Study Visit: This visit took place 7 to 10 days after administration of the study drug, or upon early discontinuation from the study. End-of-study procedures included a physical examination, 12-lead ECG, vital signs, SpO_2, clinical laboratory tests, and serum pregnancy test for females.	
Criteria for evaluation: Pharmacokinetics: Blood samples for determining hydrocodone and its metabolites, norhydrocodone (inactive metabolite) and hydromorphone (active metabolite), plasma concentrations were obtained for each subject at predose and at 0.5, 1, 2.5, 4, 6, 8, 10, 12, 14, 16, 18, 24, 30, 36, 48, and 72 hours post study drug administration. Plasma concentrations of hydrocodone and its metabolites were quantified by a validated bioanalytical method. (The hydrocodone metabolites, norhydrocodone and hydromorphone, were added to the bioanalytical analysis per Protocol Amendment 1 dated 17-Oct-2011.) Safety: Safety was assessed using recorded AEs, clinical laboratory test results, vital signs, SpO_2, physical examinations, and 12-lead ECGs. Other: Optional PG evaluation: blood samples were collected predose and 72 hours postdose.	
Statistical methods: Analysis Populations: The enrolled population consisted of all subjects who signed the informed consent form. The safety population was the group of subjects who received study drug. The full analysis population (FAP) was the group of subjects who were enrolled, received study drug, and had at least 1 quantifiable PK metric. Subjects who experienced emesis within 24 hours after dosing could have been excluded from the PK analysis. Pharmacokinetics: Listings, figures, and summaries of individual hydrocodone, and its metabolites, norhydrocodone and hydromorphone, plasma concentrations were based on the safety population. Individual, mean, and mean (± standard deviation [SD]) plasma concentration versus time profiles were presented in figures on both linear and semi-logarithmic scales. Plasma concentrations of hydrocodone and its metabolites were analyzed to determine the following PK metrics for each group by noncompartmental PK analysis (model	

independent approach): area under the plasma concentration versus time curve from hour 0 to the last measurable plasma concentration (AUCt), area under the plasma concentration versus time curve extrapolated to infinity (AUCinf), maximum observed plasma concentration (Cmax), time to maximum observed plasma concentration (Tmax), time to the first measurable plasma concentration value (Tlag), and apparent terminal phase half-life (t1/2). Mean (± SD) AUCt, AUCinf, and Cmax for hydrocodone and its metabolites were presented in figures by age, gender, and age/gender groups, respectively.

PK analyses and summaries were based on the FAP. Descriptive statistics included sample size (n), mean, SD, %CV, median, minimum, maximum, and geometric mean, and were tabulated by group as applicable for all plasma concentrations and PK metrics.

(The hydrocodone metabolites, norhydrocodone and hydromorphone, were added to the PK analysis per Protocol Amendment 1 dated 17-Oct-2011.)

Statistical analysis of the age and gender effects on hydrocodone and its metabolites pharmacokinetics was performed using an analysis of variance model (ANOVA) on the natural logarithms (LOGe) of AUCinf, AUCt, and Cmax with age, gender, and age-by-gender interaction as fixed effects. If the age-by-gender interaction was not significant at the 0.10 level of significance ($\alpha>0.10$), then the model was re-run without the age-by-gender interaction term and the comparison of young versus elderly included both males and females. If interaction was significant ($\alpha\leq0.10$), the comparison of young versus elderly was made separately for males and females. The same approach was taken for the comparison of females versus males. The 90% confidence intervals (CIs) for the ratio of the means was computed (elderly/young and female/male) from this model.

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Safety:

All safety data (AEs, clinical laboratory results, vital signs, SpO_2, and 12-lead ECGs) were listed for subjects in the safety population.

All AEs were categorized into preferred terms and associated system organ class (SOC) using the Medical Dictionary for Regulatory Activities (MedDRA) Version 14.1. Treatment-emergent AEs (TEAEs) were defined as AEs that started after or increased in intensity after the dose of study drug. TEAEs were summarized by presenting the incidence of AEs for each group by the MedDRA preferred term, nested within SOC for the safety population. Medical history was coded to MedDRA terms. Coded medical history terms were summarized for all subjects in the safety population.

Concomitant medication was coded using World Health Organization Drug Dictionary (WHO-DD) 01 September 2011 and was listed using the safety population.

Laboratory evaluations, vital signs, and SpO_2 were summarized by group and time point for the safety population.

Other:

Exploratory PG analyses will be reported separately.

RESULTS:

Pharmacokinetic results:

Mean (± SD) plasma concentrations of hydrocodone versus time are presented on linear scale by gender (female versus male) in Figure 1 and by age (elderly versus young) in Figure 2.

Mean plasma concentrations of hydrocodone increased steadily after oral administration of a single dose of HYD 40 mg and reached a maximum concentration at 14 to 16 hours postdose. Thereafter, plasma levels declined and remained detectable at 72 hours postdose in most subjects.

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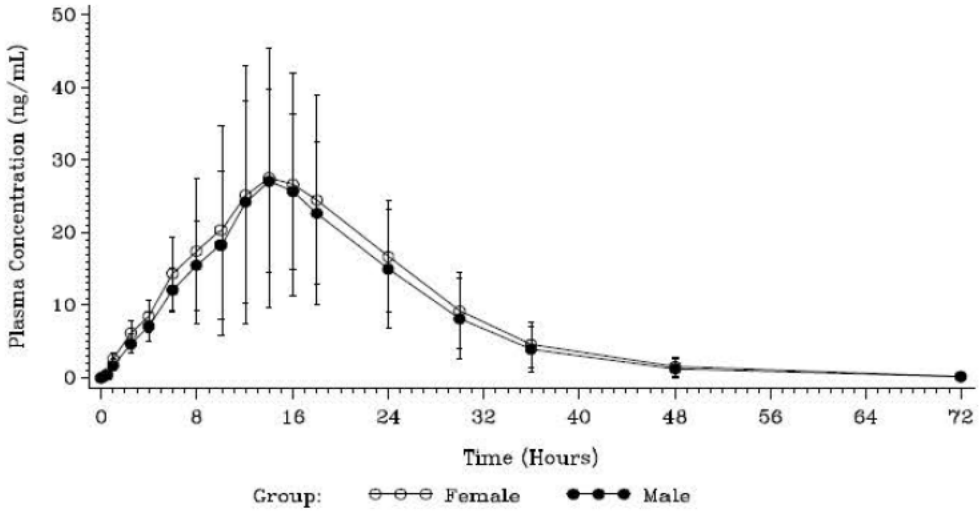
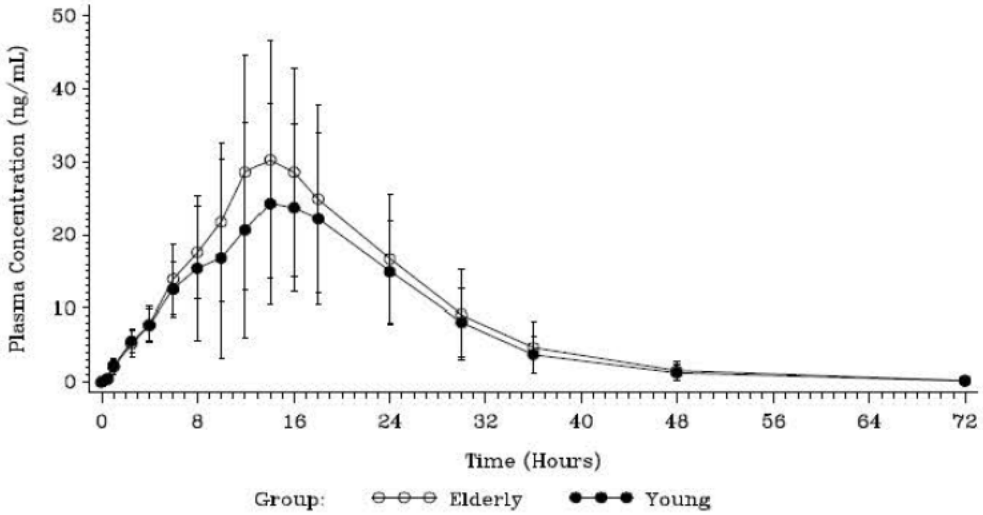


Source: Figure 14.2.1.7.

Figure 1: Mean (± SD) Plasma Concentrations of Hydrocodone Versus Time by Gender on Linear Scale (Full Analysis Population)



Source: Figure 14.2.1.4.

Figure 2: Mean (± SD) Plasma Concentrations of Hydrocodone Versus Time by Age on Linear Scale (Full Analysis Population)

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Summary tables of mean plasma hydrocodone PK metrics and PK statistical analysis are presented in Table 1 and Table 2, respectively.

Table 1: Summary of Plasma Hydrocodone Pharmacokinetic Metrics (Full Analysis Population)

	HYD 40 mg			
Metric (Unit)	**Young N = 24**	**Elderly N = 25**	**Female N = 24**	**Male N = 25**
AUCt (ng•h/mL)				
Mean	533.41	628.07	611.77	552.85
SD	193.32	252.64	245.70	211.16
AUCinf (ng•h/mL)				
Mean	539.16	632.29	617.74	556.85
SD	194.11	254.32	246.31	212.56
Cmax (ng/mL)				
Mean	31.38	35.74	34.68	32.58
SD	16.16	14.75	18.62	11.97
Tmax (h)				
Median	16.00	14.00	16.00	14.00
Minimum, Maximum	6.08, 24.00	4.00, 24.17	4.00, 24.17	8.00, 24.00
t1/2 (h)				
Mean	8.29	6.89	7.61	7.54
SD	3.27	1.76	2.80	2.61

Abbreviation: HYD, hydrocodone bitartrate.
Source: Table 14.2.10 and Table 14.2.16.

There were minimal differences in mean AUC and Cmax of hydrocodone between the elderly subjects and the young subjects and between the female subjects and the male subjects.

Median Tmax of hydrocodone ranged from 14 to 16 hours and mean t1/2 of hydrocodone ranged from 7 to 8 hours across the age and gender groups.

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Table 2: Statistical Analysis of Age and Gender Effects on Hydrocodone Pharmacokinetics (Full Analysis Population)

Parameter (unit)	Group	N	Geometric Mean	Group Comparison	Ratio (%) of Geometric Means	90% CI of the Geometric Mean Ratio (%)
AUCinf (ng•h/mL)	Elderly	25	560.980	Elderly/Young	114.10	(87.45, 148.88)
	Young	24	491.660			
	Female	24	538.672	Female/Male	105.21	(80.63, 137.27)
	Male	25	512.020			
AUCt (ng•h/mL)	Elderly	25	556.961	Elderly/Young	114.58	(87.76, 149.61)
	Young	24	486.072			
	Female	24	532.688	Female/Male	104.81	(80.28, 136.85)
	Male	25	508.221			
Cmax (ng/mL)	Elderly	25	32.086	Elderly/Young	115.76	(90.01, 148.86)
	Young	24	27.719			
	Female	24	29.197	Female/Male	95.85	(74.53, 123.26)
	Male	25	30.462			

Abbreviation: CI, confidence interval.

Note: An analysis of variance was performed on the natural logarithms of the parameters with age and gender as fixed effects in the model. Point estimates and 90% confidence intervals for differences on the log scale were exponentiated to obtain estimates for ratios of geometric means and 90% confidence intervals of the ratios on the original scale. Treatment was a single dose of 40 mg hydrocodone bitartrate extended-release tablets.

Source: Table 14.2.19.

An ANOVA was performed on the natural logarithms of AUCt, AUCinf, and Cmax of hydrocodone, norhydrocodone, and hydromorphone with age and gender as fixed effects. Statistical analysis results indicated that there was no significant age-by-gender interaction (P>0.10). Therefore, the model was re-run without the age-by-gender interaction and the results were reported using this model.

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Hydrocodone:

For the age group comparison, the geometric mean ratios (elderly/young) of AUCinf and Cmax (90% CI) were 114.10 (87.45, 148.88) and 115.76 (90.01, 148.86), respectively. These results indicate that age differences in AUCinf and Cmax of hydrocodone were 16% or less. For the gender comparison, the geometric mean ratios (females/males) of AUCinf and Cmax (90% CI) for hydrocodone were 105.21 (80.63, 137.27) and 95.85 (74.53, 123.26), respectively. These results indicate that gender differences in AUCinf and Cmax of hydrocodone were 5% or less.

Norhydrocodone:

For the age group comparison, the geometric mean ratios (elderly/young) of AUCinf and Cmax (90% CI) were 99.27 (76.21, 129.30) and 98.75 (78.15, 124.79), respectively. These results indicate that norhydrocodone exposures were similar between the elderly and young age groups. For the gender comparison, the geometric mean ratios (females/males) of AUCinf and Cmax (90% CI) for norhydrocodone were 139.13 (106.81, 181.23) and 135.15 (106.95, 170.79), respectively. These results indicate that the AUCinf and Cmax of norhydrocodone were 39% and 35% higher, respectively, in the female subjects compared with the male subjects.

Hydromorphone:

The AUCinf could not be estimated in several subjects for hydromorphone. Therefore, AUCt was used for interpretation of the results. For the age group comparison of hydromorphone, the geometric mean ratios (elderly/young) of AUCt and Cmax (90% CI) were 157.87 (85.84, 290.34) and 143.29 (98.67, 208.07), respectively. These results indicate that the AUCt and Cmax of hydromorphone were 58% and 43% higher, respectively, in the elderly age group compared with the young age group. For the gender comparison, the geometric mean ratios (females/males) of AUCt and Cmax (90% CI) for hydromorphone were 83.95 (45.65, 154.40) and 77.27 (53.21, 112.20), respectively. These results indicate that the gender difference in AUCt and Cmax of hydromorphone were 16% and 23% lower in the female subjects compared with the male subjects. Of note, hydromorphone concentrations were only 2 to 3% of the parent hydrocodone exposure and do not represent clinically meaningful levels.

Safety results:

A summary of TEAEs by severity, SOC, and MedDRA preferred term that occurred in at least 2 subjects in any group is presented in Table 3.

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Table 3: Summary of Treatment-Emergent Adverse Events by Severity, System Organ Class, and Preferred Term (Reported by 2 or More Subjects in any Group) (Safety Population)

System Organ Class Preferred Term Severity[a]	Young Female (N = 13) n (%)	Young Male (N = 12) n (%)	Elderly Female (N = 12) n (%)	Elderly Male (N = 13) n (%)	Overall (N = 50) n (%)
Gastrointestinal disorders					
Nausea					
Mild	5 (38)	0	0	2 (15)	7 (14)
Vomiting					
Moderate	1 (8)	0	1 (8)	3 (23)	5 (10)
Nervous system disorders					
Dizziness					
Mild	2 (15)	0	0	0	2 (4)
Headache					
Mild	3 (23)	0	2 (17)	3 (23)	8 (16)
Metabolism and nutrition disorders					
Decreased appetite					
Mild	0	0	0	2 (15)	2 (4)
Respiratory, thoracic, and mediastinal disorders					
Oropharyngeal pain					
Mild	0	0	0	2 (15)	2 (4)

Note: Percentages were based on N. Multiple occurrences of the same adverse event in 1 subject were counted only once. The Medical Dictionary for Regulatory Activities Version 14.1 was used to code the adverse events. Treatment-emergent adverse events were defined as adverse events that started after or increased in intensity after study drug administration. Adverse events that started more than 7 days after the last dose of study drug were not considered treatment-emergent adverse events.

[a] If a subject reported more than 1 occurrence of the same preferred term, the maximum severity was included in the table. Missing severities were treated as severe. Severity was taken from the severity reported on the electronic case report form by the investigator.

Source: Table 14.3.1.5.

Name of Sponsor/Company:	**Protocol No.**
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Hydrocodone bitartrate	Not applicable
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There were no deaths or serious adverse events (SAEs). One subject discontinued from the study due to the TEAEs of dizziness, headache, nausea, and vomiting.

Overall, 20 of 50 subjects (40%) experienced at least 1 TEAE. The number of treatment-related TEAEs was similar in the young female, elderly female, and elderly male groups. There were no treatment-related TEAEs in the young male group. All TEAEs resolved by the end of the study.

All TEAEs reported during this study were mild, with the exception of 9 TEAEs of moderate severity in 6 subjects. Moderate TEAEs consisted of nausea, vomiting, and diarrhoea. There were no severe TEAEs. The TEAEs experienced by at least 2 subjects in any age and gender group consisted of nausea, vomiting, dizziness, headache, decreased appetite, and oropharyngeal pain.

No clinically significant changes were observed in clinical laboratory values, vital sign and SpO_2 measurements, or ECG results in any of the age and gender groups.

CONCLUSIONS:

- There were no clinically meaningful increases in hydrocodone systemic exposure with regard to age (16%) and gender (5%) after administration of HYD 40 mg.
- Norhydrocodone exposures were similar between the elderly and young age groups; however, there was a gender-related systemic exposure increase of 39% in female subjects. Norhydrocodone is an inactive metabolite and this increase did not affect the overall safety profile of HYD in this study.
- There was a 58% increase in hydromorphone systemic exposure in the elderly subjects compared with the young subjects. Hydromorphone represents 2 to 3% of the parent hydrocodone exposure, and these concentrations are below clinically meaningful levels. The AUCt (16%) and Cmax (23%) of hydromorphone were similar between genders.
- HYD tablets, administered at a single oral dose of 40 mg under fasted conditions with naltrexone blockade, were safe and well tolerated in all the age and gender groups.
- There were no deaths or SAEs. One subject discontinued from the study due to the TEAEs of dizziness, headache, nausea, and vomiting.
- Clinical laboratory values, vital sign and SpO_2 measurements, and ECG results and changes from baseline were similar across the age and gender groups.

Date of report: 18-Sep-2012

4.2.8 Study HYD1007 (hepatic impairment study) synopsis.

Study HYD1007: Effect of Hepatic Impairment on the Single-dose Pharmacokinetics and Safety of HYD.

Study Objective:

The objectives of this study were to assess the PK, safety and tolerability of hydrocodone administered orally as HYD 20-mg tablet to subjects with normal hepatic function and subjects with mild, moderate, and severe hepatic impairment.

Methods:

This was a Phase 1, multicenter, nonrandomized, open-label, parallel-group, single-dose study. At screening, subjects were assigned to a study group based on the degree of hepatic impairment as defined by the Child-Pugh classification system as follows:

- Group A: 8 subjects with mild hepatic impairment (Child-Pugh Class A)
- Group B: 8 subjects with moderate hepatic impairment (Child-Pugh Class B)
- Group C: 8 subjects with severe hepatic impairment (Child-Pugh Class C)
- Group D: 8 healthy subjects (normal hepatic function)

The group of healthy subjects was matched, to the extent possible, to the group of hepatically impaired subjects (mild, moderate or severe) for gender, mean age (± 10 years), mean body mass index (± 20%), and smoking status.

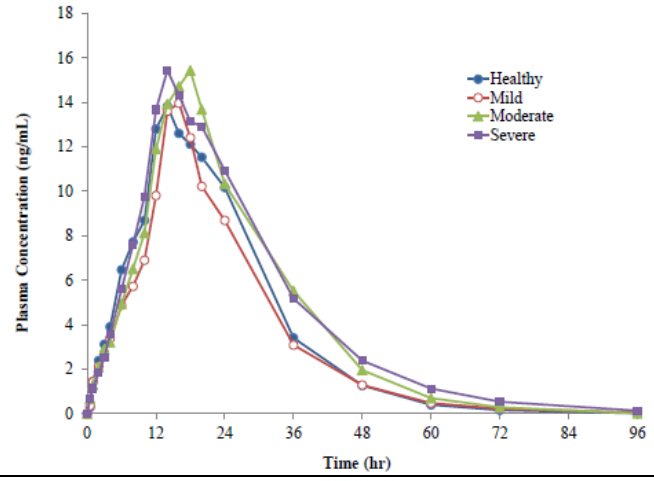
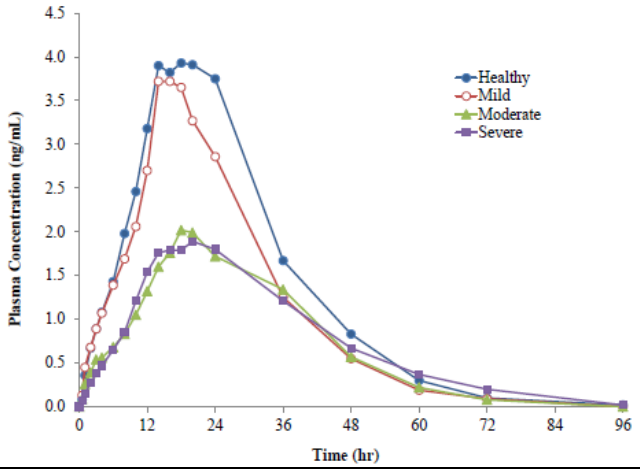
Summary of Demographic and Baseline Characteristics
Safety Population

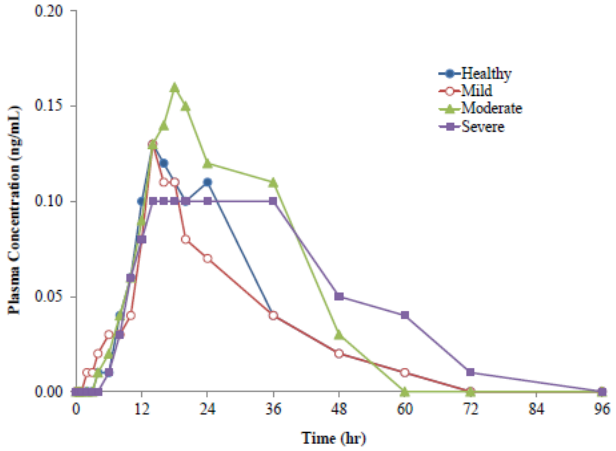
Variable	Group A (N=8)	Group B (N=8)	Group C (N=8)	Group D (N=8)	Total (N=32)
Age (years)					
n	8	8	8	8	32
Mean (SD)	52.3 (8.00)	55.3 (5.28)	56.0 (7.01)	53.1 (5.49)	54.2 (6.41)
Median	56.0	55.5	58.0	52.5	56.0
Min, Max	37, 59	47, 63	43, 64	46, 61	37, 64
Sex, n (%)					
Male	6 (75)	7 (88)	7 (88)	7 (88)	27 (84)
Female	2 (25)	1 (13)	1 (13)	1 (13)	5 (16)
Race, n (%)					
White	3 (38)	8 (100)	8 (100)	6 (75)	25 (78)
Black or African American	4 (50)	0	0	2 (25)	6 (19)
Native Hawaiian or Other Pacific Islander	0	0	0	0	0
Asian	0	0	0	0	0
American Indian or Alaska Native	0	0	0	0	0
Other	1 (13)	0	0	0	1 (3)
Ethnicity, n (%)					
Hispanic or Latino	0	0	2 (25)	0	2 (6)
Not Hispanic or Latino	8 (100)	8 (100)	6 (75)	8 (100)	30 (94)
Screening Height (cm)					
n	8	8	8	8	32
Mean (SD)	175.58 (7.785)	177.19 (8.407)	176.98 (11.546)	175.31 (7.690)	176.26 (8.591)
Median	177.15	177.45	174.75	174.95	176.50
Min, Max	161.5, 187.3	160.3, 187.5	163.5, 201.0	165.1, 186.7	160.3, 201.0
Screening Weight (kg)					
n	8	8	8	8	32
Mean (SD)	92.76 (17.077)	90.01 (16.902)	101.81 (29.362)	86.44 (11.730)	92.76 (19.736)
Median	94.85	94.90	101.10	85.25	94.00
Min, Max	64.9, 116.4	64.7, 110.3	50.7, 155.8	72.6, 103.4	50.7, 155.8
Body Mass Index (kg/m^2)					
n	8	8	8	8	32
Mean (SD)	29.94 (4.090)	28.64 (4.975)	31.93 (5.942)	27.98 (1.595)	29.62 (4.501)
Median	31.30	28.50	32.00	28.05	30.45
Min, Max	20.8, 33.2	21.2, 35.1	19.0, 38.6	25.3, 29.7	19.0, 38.6

Thirty-two subjects (27M/5F) with ages ranging from 37 to 64 years (mean: 54.2 years) were enrolled and all 32 subjects (100%) completed the study. Subjects were administered a single HYD 20-mg tablet (Lot number CB-2011-04).
Standard plasma PK parameters were calculated for hydrocodone and its metabolites, norhydrocodone and hydromorphone. Statistical analysis of the effects of hepatic impairment on the pharmacokinetics of hydrocodone and its metabolites was performed using an ANOVA on the ln of AUCt, AUCinf, Cmax, CL/F, and Vd/F with hepatic function group as a fixed effect. The point estimate and 90% CIs for the ratios of the least squares (LS) geometric means of each hepatic impairment group to the group of subjects with normal hepatic function were provided. The 90% CIs were obtained by exponentiation of the 90% CIs for the differences between the LS geometric means on the natural logarithmic scale.
Similarly, an analysis of covariance (ANCOVA) was also performed on the natural logarithms of the above parameters with hepatic function group as a fixed effect, and weight, gender, and age as covariates.

Results:

Mean hydrocodone, norhydrocodone, and hydromorphone plasma concentrations versus time profiles by hepatic function group are presented in Figure 20, Figure 21, and Figure 22, respectively.

	**Hydrocodone PK in healthy and patients with hepatic impairment.**
	**Norhydrocodone PK in healthy and patients with hepatic impairment.**



Hydromorphone PK in healthy and patients with hepatic impairment

Table 16 Summary of Mean ± SD Plasma Pharmacokinetic Metrics of Hydrocodone in Healthy Subjects and Subjects with Hepatic Impairment in Study HYD1007 (Full Analysis Population)

Metric (Unit)	Group A Mild Hepatic Impairment N = 8	Group B Moderate Hepatic Impairment N = 8	Group C Severe Hepatic Impairment N = 8	Group D Normal Hepatic Function N = 8
AUCt (ng•h/mL)	308 ± 114	387 ± 71.3	412 ± 200	339 ± 36.8
AUCinf (ng•h/mL)	310[a] ± 124	390 ± 70.9	415 ± 200	342 ± 36.8
Cmax (ng/mL)	15.3 ± 5.6	17.0 ± 5.9	18.4 ± 9.1	16.0 ± 5.0
Tmax[b] (h)	14.0 (12.0, 16.0)	17.0 (14.0, 24.0)	14.0 (8.0, 24.0)	18.0 (12.0, 24.0)
t1/2 (h)	9.0[a] ± 4.1	7.8 ± 1.9	11.9 ± 2.8	8.9 ± 3.3
CL/F (L/h)	71.2[a] ± 20.9	52.8 ± 9.6	71.9 ± 61.0	59.1 ± 6.0
Vd/F (L)	843[a] ± 167	598 ± 190	1132 ± 860	744 ± 237

Source: CSR study HYD1007, Table 11-2.
[a] N = 7.
[b] median (minimum, maximum).

Figure: AUC (Left) and Cmax (right) of hydrocodone in healthy volunteers and patients with hepatic impairment with regard to their CYP2D6 phenotype.

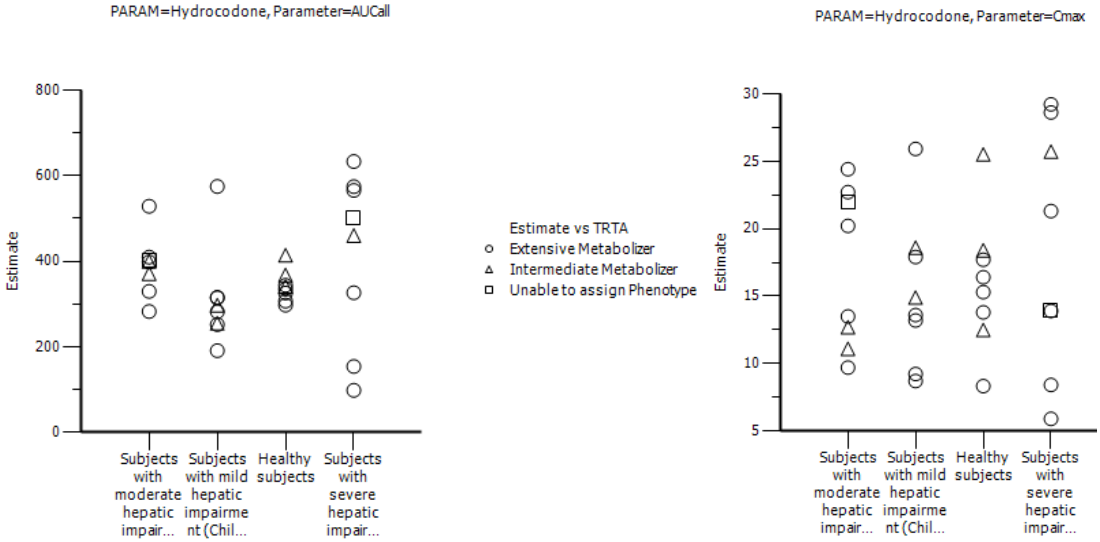


Table 17 **Statistical Analysis of Effect of Hepatic Impairment on Hydrocodone Pharmacokinetic Metrics in Study HYD1007 (Full Analysis Population)**

Metric (Unit)	Group	N	LS Geometric Mean	Group Comparison	Ratio (%) of LS Geometric Means	90% CI of the Ratio (%)
AUCt (ng•h/mL)	A	8	294	A/D	87.0	(70.0, 108)
	B	8	382	B/D	113	(98.8, 129)
	C	8	349	C/D	103	(65.0, 165)
	D	8	338			
AUCinf (ng•h/mL)	A	7	294	A/D	86.4	(67.1, 111)
	B	8	384	B/D	113	(99.0, 129)
	C	8	353	C/D	104	(65.5, 165)
	D	8	340			
Cmax (ng/mL)	A	8	14.4	A/D	94.2	(69.5, 128)
	B	8	16.1	B/D	105	(77.8, 143)
	C	8	16.0	C/D	105	(68.3, 161)
	D	8	15.3			
CL/F (L/h)	A	7	68.1	A/D	116	(90.0, 149)
	B	8	52.0	B/D	88.4	(77.5, 101)
	C	8	56.7	C/D	96.3	(60.7, 153)
	D	8	58.8			
Vd/F (L)	A	7	829	A/D	115	(93.4, 143)
	B	8	567	B/D	78.8	(59.1, 105)
	C	8	949	C/D	132	(87.7, 199)
	D	8	719			

Source: CSR study HYD1007, Table 11-5.
CI=confidence interval; %CV=coefficient of variation; LS=least squares.
Note: An analysis of variance was performed on the natural logarithms of the pharmacokinetic metrics with group as a fixed effect in the model. Point estimates and 90% CIs for differences on the log scale were exponentiated to obtain estimates for ratios of geometric means and 90% CIs of the ratios on the original scale.
Group A=Subjects with mild hepatic impairment.
Group B=Subjects with moderate hepatic impairment.
Group C=Subjects with severe hepatic impairment.
Group D=Healthy subjects.

Hydrocodone:
Mean AUC of hydrocodone in subjects with mild hepatic impairment and normal hepatic function was similar. Mean AUCinf increased by 14% and 21% for subjects with moderate and severe hepatic impairment compared with healthy subjects. Mean hydrocodone Cmax was similar across all hepatic function groups. Median Tmax of hydrocodone ranged from 14 to 18 hours and mean t1/2 ranged from 7.8 to 11.9 hours across all groups. The ANCOVA showed that neither weight nor age was a significant covariate. The mean plasma protein binding (% bound) of hydrocodone in subjects with normal hepatic function and mild, moderate, and severe hepatic impairment was low and similar at 36%, 37%, 33%, and 34%, respectively.

Norhydrocodone:
Mean AUC and Cmax values of norhydrocodone in subjects with mild hepatic function were similar to those in subjects with normal hepatic function. Mean AUCinf decreased

by 46% and 41%, and mean Cmax decreased by 51% and 53%, in subjects with moderate and severe hepatic impairment, respectively.

Hydromorphone:

The AUC and Cmax of hydromorphone, which is a minor (representing up to 3% systemic exposure of hydrocodone) active metabolite, had high within-group variability, resulting in very wide CIs of the estimated mean ratios. The mean AUCt values in subjects with mild, moderate, and severe hepatic impairment were 7% lower, 42% higher, and 49% higher, respectively, than in subjects with normal hepatic function. The corresponding mean Cmax values were 19% lower, 6% higher, and 12% lower, respectively.

Conclusions:

- Following a single 20-mg oral dose of HYD, hydrocodone exposure in subjects with mild hepatic impairment was similar to that in subjects with normal hepatic function.
- Arithmetic mean AUCinf of hydrocodone increased by 14% and 21% in subjects with moderate and severe hepatic impairment, respectively, compared to subjects with normal hepatic function. The corresponding arithmetic mean Cmax values were similar across all hepatic function groups.
- For norhydrocodone, subjects with mild hepatic impairment had similar systemic exposures as compared to subjects with normal hepatic function. Arithmetic mean
- AUCinf of norhydrocodone decreased by 46% and 41% in subjects with moderate or severe hepatic impairment, respectively, compared with normal hepatic function. The corresponding arithmetic mean Cmax values decreased by 51% and 53%, respectively.
- The AUC and Cmax of hydromorphone, which is a minor (representing up to 3% systemic exposure of hydrocodone) active metabolite, were variable across all hepatic function groups.
- There was no significant effect of age, weight, or gender on the PK of hydrocodone.
- Plasma protein binding (% bound) of hydrocodone was similar in subjects across all hepatic function groups.

4.2.9 Study 1008 (renal impairment study) synopsis.

Study HYD1008

Effect of Renal Impairment on the Single-dose Pharmacokinetics and Safety of HYD 60 mg Under Naltrexone Blockade

Study Objective:

The objectives of this study were to assess the PK and safety of HYD 60 mg under naltrexone blockade in subjects with mild, moderate, and severe renal impairment and endstage renal disease (ESRD) in comparison to subjects with normal renal function.

Methods:

This was a Phase 1, multicenter, nonrandomized, open-label, parallel-group, single-dose study. At screening, subjects were categorized based on estimated glomerular filtration rate (eGFR), calculated using the following modification of diet in renal disease formula:

eGFR (mL/min/1.73 m2) = 175 × (serum creatinine [mg/dL])–1.154 × (age)–0.203 × (0.742 if female) × (1.212 if black)

The study groups were as follows:

- Group A: healthy subjects with normal renal function (eGFR >80 mL/min/1.73 m2)
- Group B: subjects with mild renal impairment (eGFR >50 to 80 mL/min/1.73 m2)
- Group C: subjects with moderate renal impairment (eGFR >30 to 50 mL/min/1.73 m2)
- Group D: subjects with severe renal impairment (eGFR ≤ 30 mL/min/1.73 m2)
- Group E: subjects with ESRD on hemodialysis for at least 3 months preceding the initial dose of study drug in this study.
    - E1 = initiation of hemodialysis session at 90 minutes after dosing (with dialysis)
    - E2 = completion of hemodialysis session within 90 minutes before dosing (without dialysis)

The group of healthy subjects was matched, to the extent possible, to the group of subjects with renal impairment on the basis of gender, mean age (±10 years), mean body mass index (±20%), and smoking habits.

Forty-one subjects (27M/14F) with ages ranging from 27 to 77 years (mean: 57.2 years) were enrolled and all 41 subjects (100%) completed the study: 9 mild, 8 moderate, 8 severe renal impairment, and 8 ESRD, and 8 normal renal function. Two subjects experienced emesis within 24 hours after dosing and were excluded from the full analysis population. Therefore, 39 subjects were included in the PK analyses.

Following a 10-hour overnight fast, subjects (healthy, mild, moderate and severe) were administered a single HYD 60-mg tablet (Lot number CB-2011-08). Subjects with ESRD were administered HYD 60-mg tablet (Lot number CB-2011-08). on 2 occasions, once in each of 2 periods separated by a 14-day washout period; once 90 minutes before hemodialysis (E1, with dialysis) and once 90 minutes after hemodialysis (E2, without dialysis). Naltrexone HCl 50-mg tablet (Lot number 34005116A and 34007242A) was administered at –12, 0, 12, 24 and 36 hours, relative to HYD administration to minimize opioid-related adverse events. A naloxone HCl (Lot number 02-555-EU, 91-357-EU, and 95-529-EV) challenge test was performed prior to the first dose of naltrexone HCl.

Standard plasma and urine PK parameters were calculated for hydrocodone, norhydrocodone, and hydromorphone. In addition, amount of drug removed by hemodialysis during each collection interval and total amount during the period of

dialysis; percentages of the total amount of drug removed by hemodialysis and dialyzer clearance were determined.
Statistical analysis of the effects of renal impairment on the pharmacokinetics of hydrocodone and its metabolites was performed using an ANOVA. The dependent variables were the log-transformed AUCt, AUCinf, and Cmax values for hydrocodone, norhydrocodone, and hydromorphone, and the independent variable was the study group. Geometric mean ratios between renally impaired subjects (groups B, C, D, and E with dialysis) and healthy subjects (group A) and 90% CIs of the ratios for AUCt, AUCinf, and Cmax of hydrocodone, norhydrocodone, and hydromorphone were presented. The same method was used to compare AUC0-72 between Group A and Group E without dialysis.
Linear regression analysis was used to evaluate the relationships between estimated renal function (measured by eGFR) and relevant log-transformed PK metrics (AUCt, AUCinf, Cmax, CL/F [for parent only], and renal clearance [CLr]) for each analyte in order to assess the variability at normal and reduced renal function. The regression equation metrics (eg, correlation coefficient, 95% CI for the slope, P value) were presented. The plots of estimated renal function and relevant PK metrics in both log-transformed and original values were also presented for each analyte.
Results:
Mean hydrocodone plasma concentrations versus time are presented by subjects with normal renal function (group A) and subjects with mild, moderate and severe renal impairment (groups B, C, and D, respectively) and by subjects with normal renal function (group A) and subjects with ESRD (group E).

Figure: Mean Plasma Concentrations of Hydrocodone Versus Time in Healthy Subjects and patients

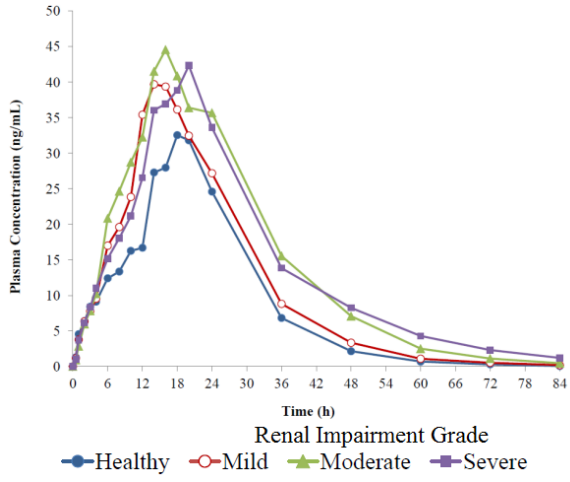
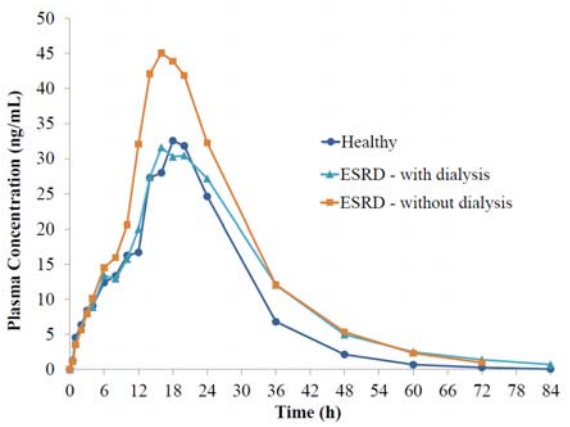
Patients with mild, moderate, or severe renal impairment or	**Patients with end-stage renal disease with or without dialysis.**
	

Table 13 Summary of Mean ± SD Plasma Hydrocodone Pharmacokinetic Metrics in Study HYD1008 (Full Analysis Population)

		Subjects with Renal Impairment				
Metric (Unit)	Healthy N = 8[a]	Mild N = 9	Moderate N = 6	Severe N = 8	ESRD w/dialysis N = 8	ESRD w/o dialysis N = 6
AUCt (h•ng/mL)	738 ± 138	938 ± 388	1217 ± 305	1209 ± 394	922 ± 466	1085 ± 264
AUCinf (h•ng/mL)	754 ± 155	942 ± 389	1222 ± 306	1220 ± 397	932 ± 471	–
AUC0-72 (h•ng/mL)	735 ± 135	–	–	–	–	1085 ± 264
Cmax (ng/mL)	39.6 ± 6.8	49.7 ± 21.9	50.8 ± 18.2	45.5 ± 15.3	38.4 ± 16.6	50.6 ± 19.1
Tmax (h)[b]	19.0 (14, 24)	14.0 (10, 24)	17.0 (14, 24)	20.0 (14, 48)	16.0 (6, 24)	18.0 (12, 20)
t1/2 (h)	8.0 ± 3.6	14.5 ± 17.5	14.4 ± 15.0	34.2 ± 11.6	27.0 ± 13.0	–
CL/F (L/h)	82.7 ± 18.3	89.4 ± 83.2	51.8 ± 12.8	54.9 ± 21.6	104 ± 98.8	–
Vd/F (L)	916 ± 328	1604 ± 1724	1175 ± 1463	2854 ± 1833	3692 ± 3685	–

Source: CSR study HYD1008, Table 11-2.
ESRD=end-stage renal disease; w/=with; w/o=without.
[a] N = 6 for AUCinf, t1/2, CL/F, and Vd/F.
[b] median (minimum, maximum).

Plasma

Hydrocodone

Subjects with mild renal impairment exhibited small increases in least squares (LS) geometric mean hydrocodone AUC (14%) and Cmax (14%) as compared to subjects with normal renal function. Subjects with moderate and severe renal impairment exhibited increases in LS geometric mean hydrocodone AUC (up to 63% and 58%) and Cmax (23% and 11%), respectively, as compared to subjects with normal renal function. For the estimated AUC ratios, the lower limits of the confidence intervals were ≥119% in subjects with moderate and severe renal impairment indicating a significant increase in exposure compared to healthy subjects.

Subjects with ESRD with dialysis exhibited a 5% increase in LS geometric mean hydrocodone AUCt and those without dialysis exhibited a 46% increase in hydrocodone AUC0-72 as compared to subjects with normal renal function. Subjects with ESRD with dialysis exhibited a 13% decrease in LS geometric mean hydrocodone Cmax and those without dialysis had a 22% increase in LS geometric mean hydrocodone Cmax as compared to subjects with normal renal function.

Mean hydrocodone terminal half-life (t1/2) was 8 hours in subjects with normal renal function compared to 14.5, 14.4, and 34.2 hours in subjects with mild, moderate, and

severe renal impairment, respectively, and 27 hours for subjects with ESRD (with dialysis). For the severe renal impairment and ESRD groups, the hydrocodone concentration levels during the terminal phase were near the lower limit of quantification and quite variable.

Table 14 Statistical Results of Effect of Renal Impairment on Hydrocodone Pharmacokinetic Metrics in Study HYD1008 (Full Analysis Population)

Metric (Unit)	Group	N	Geometric Mean	Group Comparisons	Ratio (%) of Geometric Mean	90% CI of the Ratio (%)
AUCinf (h•ng/mL)	A	6	740			
	B	9	834	B/A	113	(75.8, 167)
	C	6	1190	C/A	161	(126, 205)
	D	8	1159	D/A	157	(119, 206)
	E1	8	773	E1/A	104	(62.4, 175)
AUCt (h•ng/mL)	A	8	726			
	B	9	830	B/A	114	(77.5, 169)
	C	6	1185	C/A	163	(130, 205)
	D	8	1148	D/A	158	(122, 204)
	E1	8	764	E1/A	105	(63.2, 175)
AUC0-72 (h•ng/mL)	A	8	724			
	E2	6	1059	E2/A	146	(118, 181)
Cmax (ng/mL)	A	8	39.1			
	B	9	44.6	B/A	114	(80.8, 161)
	C	6	48.1	C/A	123	(90.2, 167)
	D	8	43.4	D/A	111	(87.6, 140)
	E1	8	34.2	E1/A	87.3	(59.2, 129)
	E2	6	47.8	E2/A	122	(89.6, 166)

Source: CSR study HYD1008, Table 11-12.
CI=confidence interval; %CV=coefficient of variation.
Note: An analysis of variance was performed on the natural logarithms of the pharmacokinetic metrics with group as a fixed effect in the model. Point estimates and 90% CIs for differences on the log scale were exponentiated to obtain estimates for ratios of geometric means and 90% CIs of the ratios on the original scale.
Group A=healthy subjects with normal renal function.
Group B=subjects with mild renal impairment.
Group C=subjects with moderate renal impairment.
Group D=subjects with severe renal impairment.
Group E=subjects with end-stage renal disease.
E1=initiation of hemodialysis session at 90 minutes after dosing (with dialysis).
E2=completion of hemodialysis session within 90 minutes before dosing (without dialysis).

Norhydrocodone

Subjects with mild, moderate, and severe renal impairment exhibited increases in LS geometric mean norhydrocodone AUC (19%, 73%, and 74%, respectively) as compared to subjects with normal renal function. Norhydrocodone Cmax was comparable across the groups.

Subjects with ESRD with dialysis exhibited a 38% increase in LS geometric mean norhydrocodone AUCt and those without dialysis had a 117% increase in geometric mean norhydrocodone AUC0-72 as compared to subjects with normal renal function. Subjects with ESRD with dialysis exhibited a 10% decrease and those without dialysis a 45% increase in norhydrocodone LS geometric mean Cmax as compared to subjects with normal renal function.

Hydromorphone
AUC and Cmax of hydromorphone, a minor (less than 3% of the parent compound) and active metabolite had high within-group variability, resulting in very wide CIs. Subjects with mild, moderate, and severe renal impairment had LS geometric mean hydromorphone AUCt values that were 45% higher, 26% lower, and 105% higher, respectively, than in subjects with normal renal function. The corresponding Cmax values were 3% higher, 48% lower, and 2% higher, respectively.
Subjects with ESRD with dialysis exhibited a 13% decrease in LS geometric mean hydromorphone AUCt and a 50% decrease in LS geometric mean hydromorphone Cmax as compared to subjects with normal renal function. Subjects with ESRD without dialysis exhibited a 22% increase in LS geometric mean hydromorphone AUC0-72 and a 27% decrease in Cmax as compared to subjects with normal renal function.

Urine
Following the administration of a single HYD 60-mg dose, total amount of unchanged hydrocodone excreted in urine (Ae) was low for all groups. The mean percentage of the administered dose excreted unchanged in urine (%Ae) was 6.5% in subjects with normal renal function, and 5.0%, 4.8%, and 2.3% in subjects with mild, moderate, and severe renal impairment, respectively (Table 15). Subjects with ESRD yielded a mean %Ae of 0.05% with dialysis and 0.16% without dialysis.

Table 15 **Mean (%CV) Hydrocodone Clearance and Percent Amount Excreted Hydrocodone Pharmacokinetic Metrics in Study HYD1008 (Full Analysis Population)**

		Subjects with Renal Impairment				
					ESRD	
	Healthy	Mild	Moderate	Severe	w/ dialysis	w/o dialysis
PK Metric (unit)	(N=8)[a]	(N=9)	(N=6)	(N=8)	(N=8)[b]	(N=4)
% Ae	6.5 (13)	5.0 (40)	4.8 (22)	2.3 (56)	0.05 (134)	0.16 (155)
CL/F (L/h)	83 (22)	89 (93)	52 (25)	55 (39)	104 (95)	-
CLr (L/h)	5.3 (27)	3.2 (31)	2.5 (35)	1.2 (45)	0.07 (172)	–
CLd (L/h)	-	-	-	-	9.3 (28)	

Source: CSR study HYD1008, Table 11-2, Table 11-5, and Table 11-8.
CL/F=apparent systemic clearance; CLr=renal clearance; CLd=dialyzer clearance; ESRD=end-stage renal disease; %Ae=percent excreted unchanged in urine; %CV=coefficient of variation.
a N= 6 for CL/F and CLr
b N=4 for %Ae and CLr

Hydrocodone mean CLr in subjects with normal renal function was 5.3 L/h. Subjects with mild, moderate, and severe renal impairment had mean CLr values of 3.2, 2.5, and 1.2 L/h, respectively. In contrast, CL/F in subjects with normal renal function and mild, moderate, and severe renal impairment were 83, 89, 52, and 55 L/h, respectively. This suggests that CLr plays a smaller role in the total contribution to systemic exposure and that nonrenal CL is the main elimination pathway.

Dialysate

In subjects with ESRD, during the approximately 4-hour hemodialysis period, 0.55% of the HYD 60-mg dose was removed as hydrocodone. The amounts of norhydrocodone and hydromorphone removed during the same 4-hour hemodialysis period were less than 0.1 mg. In comparison, the mean hydrocodone %Ae in urine during the time intervals 0 to 4 and 4 to 8 hours for subjects with normal renal function were 0.20% and 0.44% of the dose, respectively. During hemodialysis in subjects with ESRD, hydrocodone CLd was 9.3 L/h in contrast to CLr (5.3 L/h) in subjects with normal renal function.

Conclusions:

- Following a single 60-mg oral dose of HYD, hydrocodone exposure in subjects with mild renal impairment was similar to subjects with normal renal function, whereas AUC increased 63% and 58% and Cmax increased 23% and 11% in subjects with moderate and severe renal impairment, respectively, compared to subjects with normal renal function.
- Subjects with ESRD exhibited increases in hydrocodone AUC (5%) with dialysis and AUC0-72 (46%) without dialysis as compared to subjects with normal renal function.
- The corresponding Cmax was 13% lower and 22% higher, respectively.
- For norhydrocodone, AUC in subjects with mild renal impairment was similar to subjects with normal renal function, whereas AUC was increased by 73%, 74%, 38%, and 117% in subjects with moderate, severe renal impairment or ESRD with and without dialysis, respectively, compared to subjects with normal renal function. Norhydrocodone Cmax was similar across all renal function groups.
- The AUC and Cmax of hydromorphone, a minor (representing up to 3% of parent compound) active metabolite, were variable across all renal function groups.
- Following the administration of a single HYD 60-mg dose, total %Ae of unchanged hydrocodone in urine was low for all groups. The %Ae was 6.5% in subjects with normal renal function, and 5.0%, 4.8%, and 2.3% in subjects with mild, moderate, and severe renal impairment, respectively.
- CLr played a smaller role in the total contribution to systemic exposure; nonrenal CL was the main elimination pathway.

4.2.10 PK Synopsis of TQT Study HYD1009.

Study HYD1009

Dose Escalating Study of the Effect of HYD Tablets at Doses up to 160 mg on QT/QTc in Healthy Adult Subjects

Study Objective:

The primary objective of this study was to evaluate the effect of HYD tablets (HYD 80, 120, and 160 mg) on the QT/QTc interval. The secondary objectives of this study were to assess effects of moxifloxacin relative to placebo (assay sensitivity) on the QT/QTc interval and to characterize the safety of HYD at doses up to 160 mg in healthy adult subjects.

In addition, the PK was analyzed to evaluate the PK/PD relationship of HYD on the QT/QTc interval.

Methods:

This was a single-center, randomized, double-blind, placebo- and positive-controlled, multiple-dose escalation, 3-treatment parallel group study in healthy adult subjects.

Two hundred eight (208) subjects (118M/90F) with ages ranging from 19 to 50 years (mean: 33.3 years) were randomized and 196 subjects (94.2%) completed the study. Ten subjects (5%) were discontinued due to adverse events (AEs), including 7 receiving HYD, and 2 subjects (1%) discontinued due to subject‟s choice.

Subjects received one of the following 3 treatments according to the study randomization schedule:

- HYD 20, 40, 80, 120, and 160 mg (1 x 120 mg and 1 x 40 mg) (Lot numbers:
- CB-2011-39, CB-2011-40, CB-2011-42, and CB-2011-43)
- dose escalation [titration] every 24 hours for 3 days of each HYD dose
- HYD placebo (placebo control) (Lot number: CB-2011-45)
- Moxifloxacin (positive control)(Lot numbers: 5402819 and 112012AH1)

When applicable, moxifloxacin placebo (placebo control) (Lot numbers: 12E17-U01-A004294, 12A13-U03-A001586, and 032613AH1) were administered.

In order to minimize the side effects and tolerability issues for HYD, yet sufficiently characterize the effect of hydrocodone at relevant concentrations, a gradual dose titration and tapering regimen of HYD was used in this healthy subject population. The sequence of administration of active or placebo forms of HYD and moxifloxacin for each of the 3 treatments is summarized in the study design table (Table 4).

Table 4 Study Design in Study HYD1009

Treatment Group	Titration period					Taper period	
	Days 1 to 3	Days 4 to 6	Days 7 to 9[a]	Days 10 to 12[a]	Days 13 to 15[a]	Days 16 to 18	Days 19 to 21
HYD (mg)	1 × HYD 20	1 × HYD 40	1 × HYD 80	1 × HYD 120	HYD 160 (1 × HYD 120 and 1 × HYD 40)	1 × HYD 80	1 × HYD 20
			1 × PboMOX[b]	1 × PboMOX[b]	1 × PboMOX[b]		
Pbo	1 × PboHYD	1 × PboHYD	1 × PboHYD	1 × PboHYD	2 × PboHYD	1 × PboHYD	1 × PboHYD
			1 × PboMOX[b]	1 × PboMOX[b]	1 × PboMOX[b]		
MOX	1 × PboHYD	1 × PboHYD	1 × PboHYD	1 × PboHYD	2 × PboHYD	1 × PboHYD	1 × PboHYD
			1 × MOX[b]	1 × MOX[b]	1 × MOX[b]		

Source: CSR study HYD1009, Table 9-1.
[a] 24-hour digital Holter electrocardiogram recordings were collected beginning just prior to MOX/PboMOX dosing on days 9, 12, and 15.
[b] MOX/PboMOX doses were administered on the morning of days 9, 12, and 15 only.
HYD=hydrocodone bitartrate extended-release tablets administered every 24 hours.
PboHYD=matching placebo for HYD administered every 24 hours.
MOX=moxifloxacin 400 mg.
PboMOX=matching placebo for moxifloxacin.

The effects of HYD 80, 120, and 160 mg on QT and QTc (change from baseline) were examined by the IRT-QT team.

Pharmacokinetic Results

Mean concentration versus time profiles of hydrocodone are presented for HYD 80 mg (day 9), HYD 120 mg (day 12), and HYD 160 mg (day 15) on linear scale is presented in Figure 10.

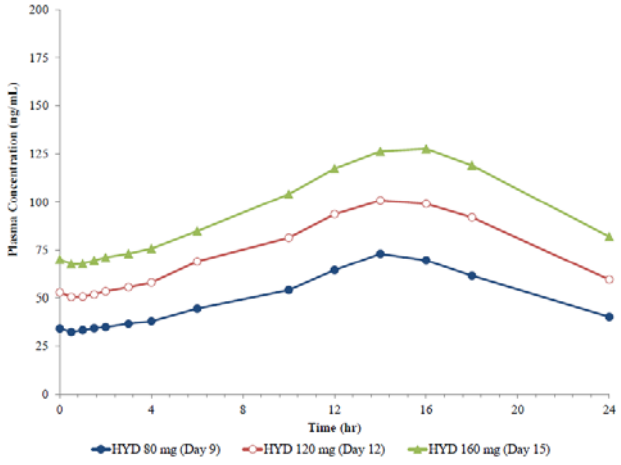


Figure 10 Mean Plasma Concentrations of Hydrocodone Versus Time on Linear Scale in Study HYD1009 (Full Analysis for Pharmacokinetic Population)

Source: Adapted from CSR study HYD1009, Figure 11-13.

As noted in study HYD1002, Hysingla ER 120 mg administered over three days to steady-state showed an average %fluctuation and % swing 102% and 220%, respectively. Hysingla ER 80 mg showed an average %fluctuation and % swing 105% and 245%, respectively at steady-state dosing.

Table: Summary of Mean ± SD Plasma Hydrocodone Pharmacokinetic Metrics in TQT Study HYD1009.

	AUC0-24,ss (hr*ng/mL)	Cmax,ss (ng/mL)	Tmax,ss (hr)	Cmin,ss (ng/mL)	Cavg,ss (ng/mL)	%Fluctuation	%Swing
Hysingla ER 80 mg Day 9							
N	77	77	77	77	77	77.00	77
Mean	1252.49	82.62	14.96	28.21	52.19	105.20	245
SD	352.038	25.732	3.321	12.041	14.668	33.00	245
Median	1169.73	77.30	14.00	26.50	48.74	106.40	194
Minimum	637.51	37.50	10.00	4.05	26.56	35.65	44
Maximum	2358.64	175.00	23.92	59.90	98.28	213.80	1875
Geometric Mean	1206.66	79.03	-	25.19	50.28	99.86	193
Hysingla ER 120 mg Day 12							
N	75	75	75	75	75	75	75
Mean	1844.10	122.12	14.51	43.51	76.84	102.72	220
SD	542.945	43.259	3.945	17.479	22.623	34.31	241
Median	1763.33	115.00	14.00	41.80	73.47	102.27	176
Minimum	842.31	51.70	0.00	0.48	35.10	45.30	60
Maximum	3358.29	312.00	23.97	94.10	139.93	185.67	2073*
Geometric Mean	1771.02	115.80	-	38.02	73.79	97.06	176
Hysingla ER 160 mg Day 15							
N	73	73	73	73	73	73	73
Mean	2380.47	151.05	14.67	57.79	99.19	94.56	222.56
SD	733.371	52.393	4.169	26.261	30.557	36.69	237.21
Median	2222.37	146.00	14.00	53.30	92.60	86.93	163.61
Minimum	1282.06	66.90	0.00	7.65	53.42	29.37	33.33
Maximum	4764.17	337.00	23.92	132.00	198.51	185.20	1298.69
Geometric Mean	2280.08	142.81	.	51.44	95.00	87.41	161.45

* Data from subject 1177 was excluded up on noting abnormally low initial plasma concentrations following HYD 80 mg and HYD120 mg (Potentially a compliance problem). Data for HYD160 mg is unavailable for this subject as the subject experienced vomiting.

On an average, the PK parameters at steady-state indicate dose-proportionality between the 80 to 160 mg doses of Hysingle ER employed in the TQT study.

4.2.11 Study HCDDR-02-102-0 Synopsis

Identification Of Cytochrome P450 Isoforms Responsible For Hydrocodone Bitartarate Metabolism In Human Liver Microsomes

Correlation analysis of hydrocodone metabolism

A bank (male = 9 and female = 7) of human liver microsomes (1 mg/ml) were individually incubated with hydrocodone (500 μM) in the presence of an NADPH-regenerating system. The microsomal bank has been characterized previously for following P450 marker activities.

CYP Isoforms	Marker Activity
CYP1A2	7-Ethoxy-resorufin dealkylase
CYP2A6	Coumarin 7-hydroxylase
CYP2C9	Tolbutamide hydroxylase
CYP2C19	*S*-Mephenytoin hydroxylase
CYP2D6	Bufuralol 1'-hydroxylase
CYP2E1	Chlorzaxazone hydroxylase
CYP3A4	Testosterone 6β-hydroxylase

The rate of NHCD formation by various individual human liver microsomes is shown in Figures BK. A significant inter-individual variation in rate of formation of NHCD was observed. One male (HLM# 117961) and one female (HLM# B13961) liver microsomes formed low and high levels of NHCD compared other microsomal samples, respectively. The rate of NHCD formation was then correlated with various P450 marker activities in a bank of human liver microsomes. The results of the correlation analysis are presented in and Table 7 A. A significant correlation was observed between the rate of NHCD formation and testosterone 6β-hydroxylase ($r^2 = 0.528$), and bufuralol 1 '-hydroxylase ($r^2 = 0.605$) activities, which are the marker activities for CYP3A4 and CYP2D6, respectively.

Tolbutamide hydroxylase (CYP2C9-dependent) activity correlated ($r^2 = 0.410$) with the rate of NHCD formation. These results suggest that NHCD formation may be catalyzed by CYP3A4 and CYP2D6. CYP2C9 may also play a minor role in NHCD formation. A minimal correlation was observed with other P450 marker activities tested, suggesting that these P450 isoforms may not be responsible for NHCD formation.

The rate of HM formation by various individual human liver microsomes was studied. A 2-3 fold variation in the rate of HM formation was noticed. The rate of HM formation was then correlated with various P450 marker activities in a bank of human liver microsomes. The results on the correlation analysis are presented in Table 7 A. A significant correlation ($r^2 = 0.482$) was observed between the rate of HM formation and CYP2D6-dependent bufuraloI1'-hydroxylase activity. As seen in Table 7A, a moderate correlation ($r^2 = 0.360$) was observed between the rate of HM formation and tolbutamide hydroxylase (CYP2C9-dependent), suggesting that CYP2C9 may play a minor role in HM formation. Other CYP isoforms (CYP1A2, 2A6, 2C19, 2E1 and 3A4) may contribute minimally for HM formation.

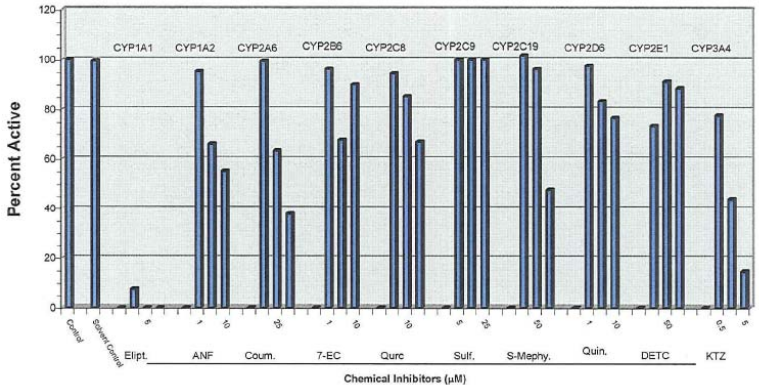
TABLE 7A. Summary of Correlation Analysis on the rate of formation of NHCD and HM, and the rate of various CYP-specific marker Activities

P450 and Marker Activities	Correlation Coefficient (r^2)	
	NHCD Formation	HM Formation
CYP1A2 7-Ethoxyresorufin O-dealkylase	0.278	0.191
CYP2A6 Coumarin hydroxylase	0.153	0.116
CYP2C9 Tolbutamide hydroxylase	0.410	0.360
CYP2C19 S-Mephenytoin hydroxylase	0.019	0.113
CYP2D6 Bufuralol 1'-hydroxylase	0.605	0.482
CYP2E1 Chlorzaxazone hydroxylase	0.032	0.081
CYP3A4 Testosterone 6β-hydroxylase	0.528	0.212

CYP-Specific Chemical Inhibition

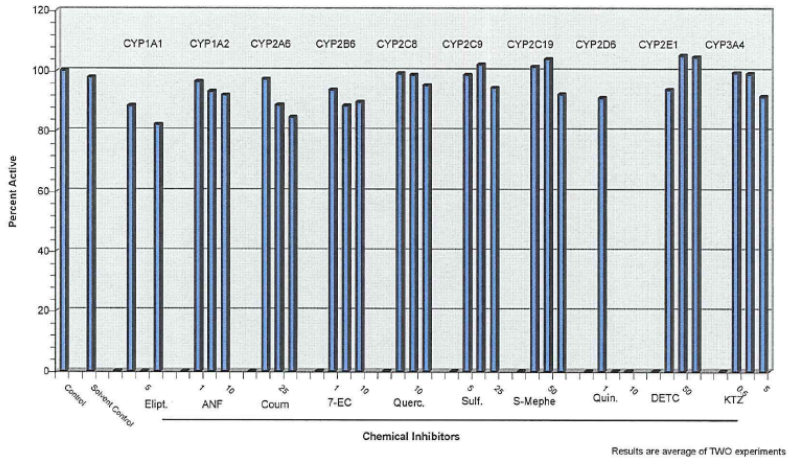
The effects of various P450 enzyme substrates/inhibitors on the rate of conversion of HCD to NHCD and HM by human liver microsomes were studied and the results are shown in Figures *8O* and 8P. Studies of this type are often difficult to interpret because the specificity of the chemical inhibitors is not well defined, in part because the specificity with which any chemical inhibits a P450 enzyme is dependent on the experimental conditions used and the results may vary from one laboratory to another. **Ketoconazole, a potent inhibitor of CYP3A4, showed significant concentration-dependent inhibition (> 80 percent inhibition at 5 µM KTZ) of NHCD formation, which is consistent with the observation that CYP3A4 is the major P450 enzyme responsible for NHCD formation.** These results suggest that in vivo, co-administration of drugs that are metabolized by CYP3A4 may alter the plasma levels of NHCD. Elipticine (an inhibitor of CYP1A1), showed nearly complete inhibition of NHCD formation at 10µM. However, CYP1A1 is expressed in extrahepatic tissues may not be responsible for NHCD formation (Ref. 6.12 - 6.14). Other chemical inhibitors such as anaphthoflavone (a potent inhibitor of CYP1A2), coumarin (inhibitor of CYP2A6) and S-mephenytoin
(inhibitor of CYP2C19) showed nearly 50 percent inhibition of NHCD formation at high concentrations. On the other hand, 7-ethoxycoumarin (inhibitor of CYP2B6 (**NOTE: this is not a recognized specific inhibitor of CYP2B6**), quercetin (inhibitor of CYP2C8), sulfaphenazole (inhibitor of CYP2C9), quinidine (inhibitor of CYP2D6), and DETC (inhibitor of CYP2E 1) showed very little or no significant inhibition of NHCD formation. These results suggest that in vivo, very minimal or no interactions are anticipated with the co-administration of drugs that are metabolized by CYP1A1/2, CYP2A6, CYP2B6, CYP2C8/19, CYP2D6 and CYP2E1 on NHCD formation.

Figure 8O. Inhibition of NHCD formation from HCD by P450-specific Chemical Inhibitors in pooled human liver microsomes



The effects of various P450 enzyme substrates/inhibitors on the rate of formation of HM by pool of human liver microsomes were studied and the results are shown in Figure 8P.

Figure 8P. Inhibition of HM formation from HCD by P450-specific Chemical Inhibitors in pooled human liver microsomes



Quinidine, a potent inhibitor of CYP2D6, showed significant concentration-dependent inhibition (complete inhibition at 5 μM quinidine) of HM formation, this is consistent with the observation that CYP2D6 is the major P450 enzyme responsible for HM formation. Other chemical inhibitors such as elipticine (an inhibitor of CYP1A1), a-naphthoflavone (a potent inhibitor of CYP1A2), coumarin (inhibitor of CYP2A6), 7-ethoxycoumarin (inhibitor of CYP2B6), quercetin (inhibitor of CYP2C8), sulfaphenazole (inhibitor of CYP2C9), S-mephenytoin (inhibitor of CYP2C 19), DETC (inhibitor of CYP2E 1) or ketoconazole (inhibitor of CYP3A4) showed very little or no inhibition of HM formation. **These results suggest that clinically co-administration of drugs that are inhibitors of CYP2D6 may alter the plasma levels of HM. Note: this observation**

was followed up with a clinical drug interaction study with paroxetine and results suggest that although formation of HM was reduced; overall, hydrocodone exposure did not increase significantly to warrant dosage changes.

Hydrocodone metabolism using cDNA-expressed human CYP Isoforms
A panel of cDNA-expressed human P450 enzymes was examined for its ability to convert HCD to NHCD and HM. The results are shown in Figures 8Q and 8R. Among the panel of recombinant P450 enzymes tested, CYP3A4 was the major enzyme responsible for the conversion of HCD to NHCD. This is consistent with the observation that ketoconazole (a potent inhibitor of CYP3A4) inhibited NHCD formation. Other CYP isoforms catalyzed the formation of NHCD are CYP1A1, CYP2B6, CYP2C8, CYP2C19, CYP2D6 and CYP3A7, and playa minor role. Of interest is the observation that cytochrome b5 increased the rate of NHCD formation by approximately 6-fold in the presence of CYP3A4. Under the experimental conditions used, CYP2C19 catalyzed the formation of NHCD only in the presence of cytochrome b5. A marked influence of cytochrome b5 was observed in the formation of NHCD and HM, when the recombinant human P450 enzymes (CYP2B6, CYP2C19, and CYP3A4) co-expressed with cytochrome b5 were incubated with HCD in the presence of NADPH. A similar stimulatory effect of cytochrome b5 was reported in the metabolism of other substrates (Ref. 6.15 and 6.16). CYP2D6 is the primary enzyme responsible for the formation of HM. This observation is consistent with the observation that quinidine, a potent inhibitor of CYP2D6 inhibited HM formation. Other CYP isoforms responsible for HM formation are CYP1A 1, CYP2A6, CYP2B6, CYP2C8/9/19, CYP2E1, CYP3A4 and CYP3A7. These results support the observation made from the correlation analysis as well as chemical inhibition results that there are multiple P450 enzymes involved in HCD metabolism, however, CYP3A4 and CYP2D6 are the major CYP isoforms responsible for the formation of NHCD and HM, respectively.

FIGURE 8Q. Formation of NHCD from HCD by various recombinant human CYP isoforms

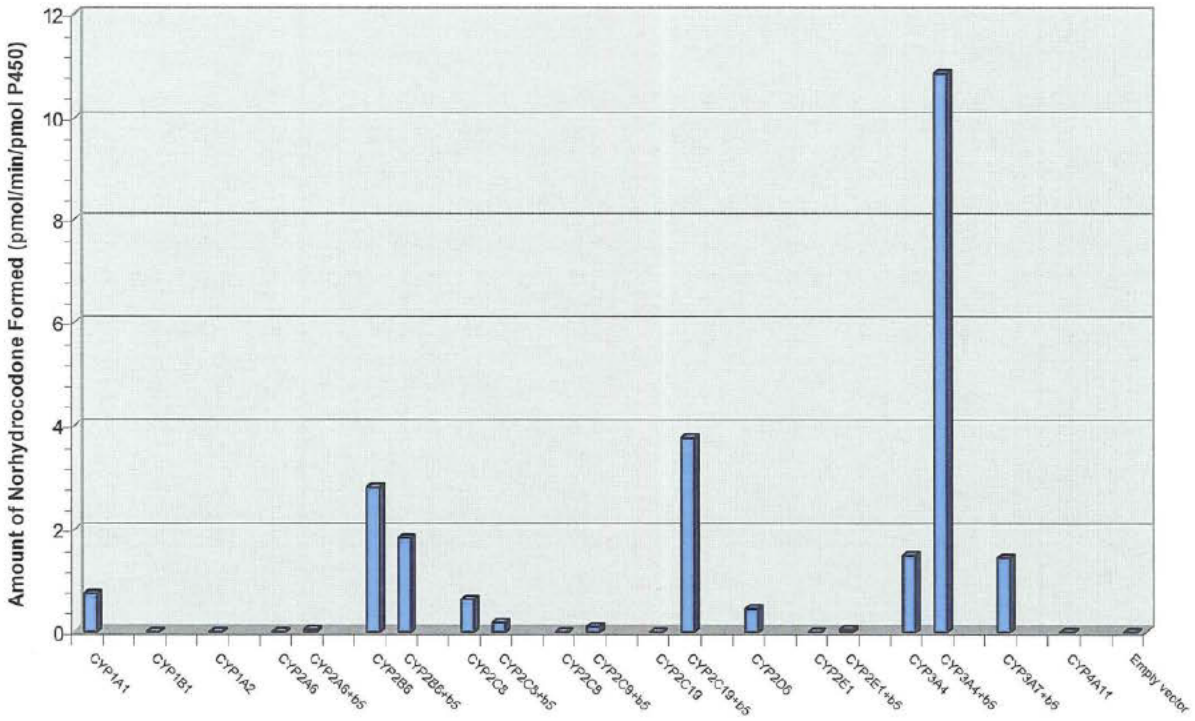
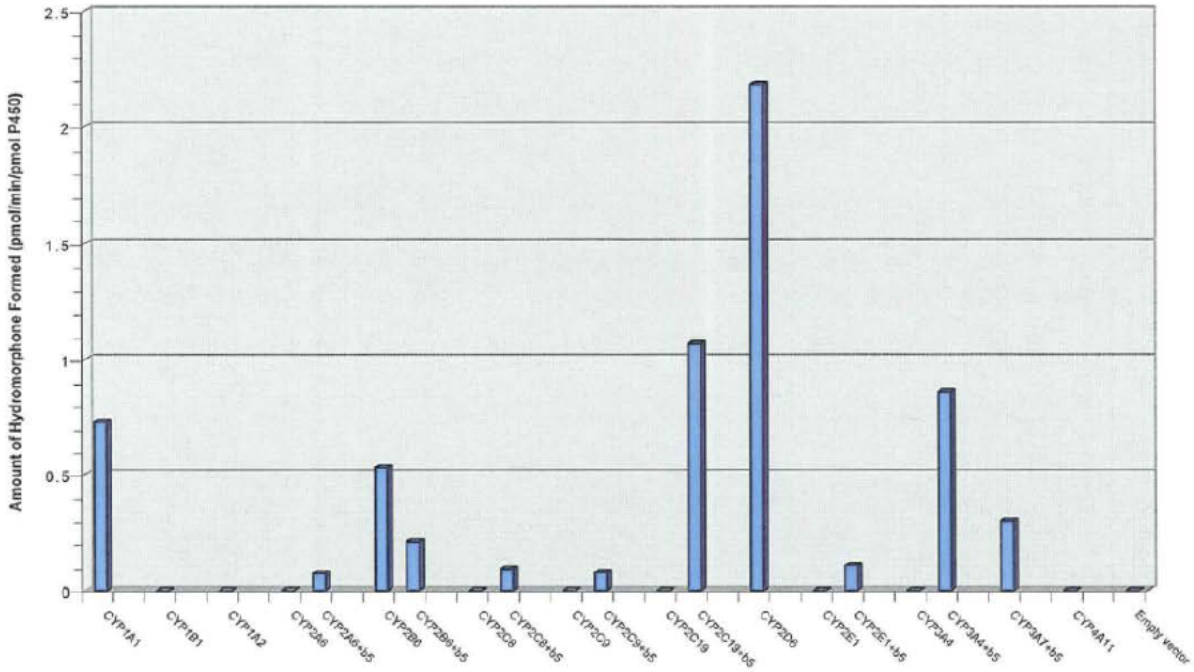


FIGURE 8R. Formation of HM from HCD by various recombinant human CYP isoforms



Conclusion
NHCD and HM are the primary oxidative metabolites of HCD. The rate of HM formation is approximately 14- times slower than the rate of NHCD formation in vitro, suggesting that HM appear to be a minor metabolite. A small amount of 6β-hydroxydihydrocodeine (6β-DHCD) was detected when HCD was incubated with both rat and human liver S9 or cytosolic fractions in the presence of NADPH or NADH. In humans, a marked inter-individual variation in NHCD and HM was observed. The results from correlation analysis study, CYP-specific chemical inhibition study and incubations with recombinant CYP-isoforms showed that there are multiple CYP isoforms involved in HCD metabolism. However, CYP3A4 and CYP2D6 are the major CYP isoforms responsible for NHCD and HM formation, respectively. The major contribution of CYP2D6 in HM formation in this study is consistent with previous observations (Ref. 6.3 and 6.4). In HCD metabolism, CYP3A4 appear to be a "low-affinity" and "high-capacity" enzyme, and CYP2D6 appear to be a "high-affinity" and "low-capacity" enzyme. Inhibition studies have shown that quinidine (potent inhibitor of CYP2D6) and ketoconazole (potent inhibitor of CYP3A4) inhibited the formation of HM and NHCD, respectively, and hence may alter their levels in plasma. Accordingly, the drug-drug interaction potential of HCD with other drugs that are metabolized by CYP2D6 and CYP3A4 may be treated with caution clinically.

Note: this observation was followed up with a clinical drug interaction study with paroxetine (HYD1005) and ketoconazole (HYD1012). Results suggest that although formation of HM was reduced when hydrocodone was coadministered with paroxetine (CYP2D6 inhibitor); overall, hydrocodone exposure did not increase significantly to warrant dosage changes.

Results suggests that formation of norhydrocodone reduced when hydrocodone was coadministered with ketoconazole (CYP3A4 inhibitor); overall, hydrocodone exposure increased by 2-fold to warrant cautionary language and dosage adjustment in the product label.

Hepatic CYP2B6 and CYP2C19 also may play some role in formation of norhydrocodone and hydromorphone.

4.2.12 CYP2D6 drug interaction Study HYD1005 Study synopsis

Study HYD1005

Co-Administration of HYD and Paroxetine, a CYP2D6 Inhibitor, in Healthy Subjects

Study Objectives:

The primary objective of this study was to assess the PK of hydrocodone and its metabolites, norhydrocodone and hydromorphone following the administration of HYD 20-mg tablets, in the presence and absence of paroxetine. The secondary objective of this study was to assess the safety of concomitant administration of HYD and paroxetine in healthy subjects.

Methods:

This was a single-center, randomized, double-blind, 2-treatment, 2-period crossover study in healthy adult subjects. Twenty-four subjects (12M/12F), with ages ranging from 21 to 49 years (mean: 36.0 years) were randomized and 23 subjects (95.8%) completed the study. One subject (4.2%) discontinued due to subject‟s choice.

Subjects were administered HYD 20 mg (Lot number CB-2011-39) with paroxetine 20 mg (Lot numbers 1ZP7708 and 082312AH1) or HYD 20 mg with paroxetine placebo (Lot numbers 2BC0611 and 082312AH2). Paroxetine (20-mg tablet) or placebo was administered once daily for 12 days in each period. A single HYD 20-mg tablet was administered once in the fasted state in each study period (on days 10 and 23). Adequate study drug washout periods were built into the study design.

Standard PK parameters were calculated for hydrocodone and its metabolites, norhydrocodone (inactive) and hydromorphone (active). For Cmax, AUCt, and AUCinf of hydrocodone and norhydrocodone, statistical analysis of the paroxetine effect on hydrocodone and norhydrocodone pharmacokinetics was performed using an analysis of variance model on the ln of the parameters with treatment, sequence, and period as fixed effects and subject within sequence as random effect. The ln-transformed Cmax, AUCt, and AUCinf values for hydrocodone and norhydrocodone in the presence of paroxetine were compared with the values in the absence of paroxetine. Geometric mean ratios and 90% CIs of the ratios for Cmax, AUCt, and AUCinf were presented.

Results:

Similar hydrocodone AUC, Cmax, and t1/2 values were observed in the presence and absence of paroxetine. The 90% CIs for the geometric least squares mean ratio of hydrocodone AUC and Cmax were fully contained within the 80% to 125% limits, indicating that there was no effect of multiple doses of paroxetine on the exposures to hydrocodone. Higher mean AUC and Cmax of norhydrocodone were observed in the presence of paroxetine compared with placebo. Mean t1/2 of norhydrocodone was approximately 9 hours across the treatments.

The geometric LS mean ratios of norhydrocodone AUC and Cmax indicate that norhydrocodone AUC and Cmax were higher in the presence of paroxetine than in the absence of paroxetine. Lower AUC and Cmax of hydromorphone were observed in the presence of paroxetine compared with placebo.

For hydromorphone, individual t1/2 and AUCinf of hydromorphone were not estimable for most of the subjects for the HYD with paroxetine treatment due to the variability of hydromorphone concentrations observed; the majority of subjects had values below or close to the lower limit of quantification (LLOQ; 0.05 ng/mL) levels across the concentration versus time profile. Hence, no statistical analysis was performed for hydromorphone.

Table 19 Statistical Results of Paroxetine Effect on Hydrocodone and Norhydrocodone Plasma Pharmacokinetic Metrics in Study HYD1005 (Full Analysis Population)

Analyte Metric (Unit)	Geometric LS Mean				Ratio of Geometric LS Mean (%)[a]	90% CI for Ratio
	N	HYD 20 mg + Paroxetine 20 mg	N	HYD 20 mg + Placebo		
Hydrocodone						
AUCt (ng•h/mL)	23	333	24	315	106	(97.7, 115)
AUCinf (ng•h/mL)	23	336	24	318	106	(97.8, 115)
Cmax (ng/mL)	23	16.1	24	15.2	106	(92.7, 121)
Norhydrocodone						
AUCt (ng•h/mL)	23	184	24	123	150	(137, 164)
AUCinf (ng•h/mL)	23	188	23	131	144	(133, 156)
Cmax (ng/mL)	23	7.0	24	4.7	149	(132, 167)

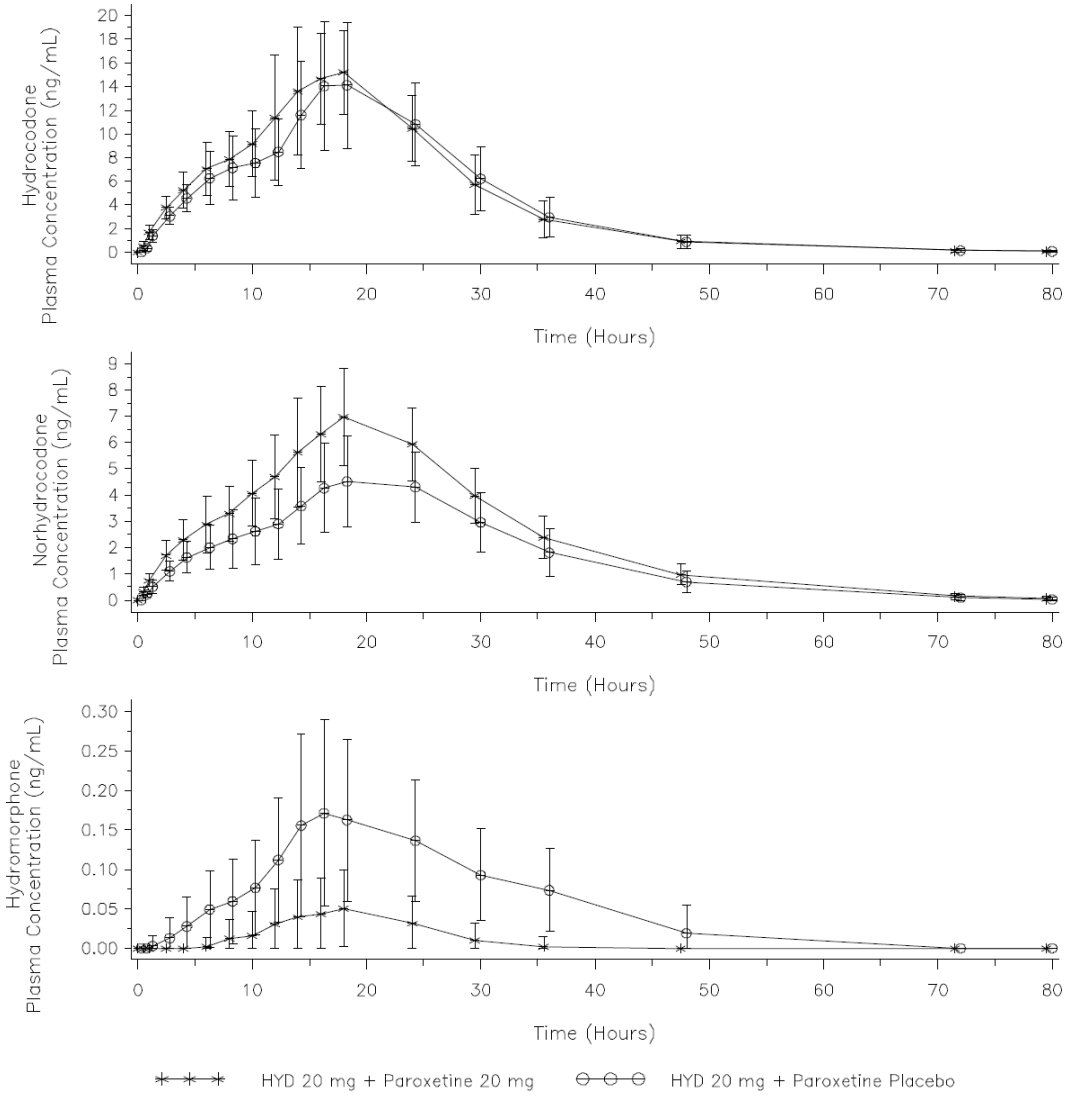
Source: CSR study HYD1005, Table 11-6 and Table 11-7.
CI=confidence interval; LS=least squares.
[a] An analysis of variance was performed on the natural logarithms of the pharmacokinetic metrics with group as a fixed effect in the model. Point estimates and 90% CIs for differences on the log scale were exponentiated to obtain estimates for ratios of geometric means and 90% CIs of the ratios on the original scale.

Table: Statistical Analysis of Ketoconazole Effect on Hydrocodone, Norhydrocodone, and Hydromorphone Pharmacokinetic Metrics in Study HYD1012

Analyte Metric (Unit)	Geometric LS Mean				Ratio of Geometric LS Mean (%)[a]	90% CI for Ratio
	N	HYD 20 mg + Ketoconazole 200 mg q12h	N	HYD 20 mg + Placebo q12h		
Hydrocodone						
AUCt (ng•h/mL)	25	651	27	277	235	(218, 252)
AUCinf (ng•h/mL)	25	655	27	281	233	(217, 251)
Cmax (ng/mL)	25	26.4	27	14.8	178	(162, 196)
Norhydrocodone						
AUCt (ng•h/mL)	25	68.0	27	106	64.3	(56.8, 72.7)
AUCinf (ng•h/mL)	25	72.1	27	109	66.3	(59.1, 74.3)
Cmax (ng/mL)	25	2.3	27	4.8	47.6	(42.2, 53.6)
Hydromorphone						
AUCt (ng•h/mL)	24	13.8	27	4.7	295	(273, 319)
AUCinf (ng•h/mL)	18	22.4	18	8.1	278	(250, 310)
Cmax (ng/mL)	24	0.51	27	0.26	195	(175, 218)

Source: CSR study HYD1012, Table 11-5, Table 11-6, and Table 11-7.
CI=confidence interval; LS=least squares; q12h=every 12 hours.
[a] An analysis of variance was performed on the natural logarithms of the pharmacokinetic metrics. The model included treatment, period, and sequence as fixed effects and subject within sequence as a random effect.

Figure: HYD1005 Paroxetine drug interaction study - Mean (± SD) Plasma Concentrations of Hydrocodone (Top Panel), Norhydrocodone (Middle Panel), and Hydromorphone (Bottom Panel) Versus Time (Linear Scale)



Conclusions:

- Mean hydrocodone AUC and Cmax were similar when a single dose of HYD extendedrelease 20-mg tablets was administered in the presence and absence of a CYP2D6 inhibitor, paroxetine.
- AUC and Cmax of norhydrocodone (inactive metabolite) were increased by 50% and 49%, respectively, in the presence of paroxetine.
- AUC and Cmax of hydromorphone, a minor (less than 3% of the parent compound) metabolite, were lower in the presence of paroxetine.

4.2.13 CYP3A4 inhibition drug interaction Study HYD1012 synopsis.

Study HYD1012

Co-Administration of HYD and Ketoconazole, a CYP3A4 Inhibitor, in Healthy Subjects.

Study Objectives:

The primary objective of this study was to assess the pharmacokinetics of hydrocodone and its metabolites, norhydrocodone and hydromorphone following the administration of HYD 20-mg tablets, in the presence and absence of ketoconazole. The secondary objective of this study was to assess the safety of concomitant administration of HYD and ketoconazole.

Methods:

This was a single-center, randomized, double-blind, 2-treatment, 2-period crossover study. Thirty subjects (13M/17F), with ages ranging from 18 to 49 years (mean: 31.5 years) were randomized and 28 subjects completed the study. Two subjects (6.7%) discontinued due to subject‟s choice.

Subjects were administered HYD 20 mg (Lot number CB-2011-39) with ketoconazole 200 mg (Lot numbers 3028816 and 072412JH5) or HYD 20 mg with placebo (Lot numbers 1AG0761 and 072412JH6). Ketoconazole (200-mg tablet) or placebo was administered every 12 hours for 6 days in each period. A single HYD 20-mg tablet was administered once in the fasted state in each study period (on days 5 and 24). There was a 14-day washout period between treatments.

Statistical analysis of the ketoconazole effect on hydrocodone, norhydrocodone, and hydromorphone pharmacokinetics was performed using an analysis of variance model on the natural logarithms of Cmax, AUCt, and AUCinf with treatment, sequence, and period as fixed effects and subject within sequence as random effect. The ln-transformed Cmax, AUCt, and AUCinf values for hydrocodone, norhydrocodone, and hydromorphone in the presence of ketoconazole (with CYP3A4 inhibition) were compared with the values in the absence of ketoconazole. Geometric mean ratios and 90% CIs of the ratios for Cmax, AUCt, and AUCinf were presented.

Results:

Mean plasma concentrations of hydrocodone and hydromorphone were considerably higher in the presence of ketoconazole than in the absence of ketoconazole. Mean plasma concentrations of norhydrocodone were lower in the presence of ketoconazole than in the absence of ketoconazole.

Summary tables of mean plasma hydrocodone, norhydrocodone, and hydromorphone PK metrics are presented in Table 20, and statistical analysis results of the ketoconazole effect on hydrocodone, norhydrocodone, and hydromorphone exposure are presented in Table 21.

Table 20 **Summary of Mean ± SD Plasma Pharmacokinetic Metrics of Hydrocodone, Norhydrocodone, and Hydromorphone in Study HYD1012 (Full Analysis Population)**

Analyte Metric (Unit)	HYD 20 mg + Ketoconazole 200 mg q12h N = 25[b]	HYD 20 mg + Placebo q12h N = 27[c]
Hydrocodone		
AUCt (ng•h/mL)	674 ± 164	285 ± 71.1
AUCinf (ng•h/mL)	678 ± 165	288 ± 70.8
Cmax (ng/mL)	27.8 ± 8.4	15.4 ± 4.9
Tmax (h)[a]	18.0 (12.0, 30.0)	16.0 (12.0, 24.1)
t1/2 (h)	8.8 ± 1.6	8.2 ± 3.3
Norhydrocodone		
AUCt (ng•h/mL)	75.2 ± 32.4	109 ± 31.1
AUCinf (ng•h/mL)	78.8 ± 31.9	112 ± 31.3
Cmax (ng/mL)	2.4 ± 0.84	4.9 ± 1.2
Tmax (h)[a]	18.0 (12.0, 30.0)	16.0 (12.0, 30.0)
t1/2 (h)	10.5 ± 1.5	7.8 ± 2.6
Hydromorphone		
AUCt (ng•h/mL)	18.0 ± 10.5	6.3 ± 3.4
AUCinf (ng•h/mL)	24.4 ± 8.9	8.9 ± 2.7
Cmax (ng/mL)	0.59 ± 0.31	0.31 ± 0.15
Tmax (h)[a]	16.0 (14.0, 36.0)	16.0 (0.50, 24.0)
t1/2 (h)	14.4 ± 2.9	13.0 ± 4.0

Source: CSR study HYD1012, Table 11-2, Table 11-3, and Table 11-4.
[a] median (minimum, maximum).
[b] For hydromorphone, N = 25 for AUCt and Cmax; N = 18 for AUCinf and t1/2; N = 24 for Tmax.
[c] For hydromorphone, N = 27 for AUCt, Cmax, and Tmax; N = 18 for AUCinf and t1/2.

Table 21 **Statistical Analysis of Ketoconazole Effect on Hydrocodone, Norhydrocodone, and Hydromorphone Pharmacokinetic Metrics in Study HYD1012 (Full Analysis Population)**

	Geometric LS Mean					
Analyte Metric (Unit)	N	HYD 20 mg + Ketoconazole 200 mg q12h	N	HYD 20 mg + Placebo q12h	Ratio of Geometric LS Mean (%)[a]	90% CI for Ratio
Hydrocodone						
AUCt (ng•h/mL)	25	651	27	277	235	(218, 252)
AUCinf (ng•h/mL)	25	655	27	281	233	(217, 251)
Cmax (ng/mL)	25	26.4	27	14.8	178	(162, 196)
Norhydrocodone						
AUCt (ng•h/mL)	25	68.0	27	106	64.3	(56.8, 72.7)
AUCinf (ng•h/mL)	25	72.1	27	109	66.3	(59.1, 74.3)
Cmax (ng/mL)	25	2.3	27	4.8	47.6	(42.2, 53.6)
Hydromorphone						
AUCt (ng•h/mL)	24	13.8	27	4.7	295	(273, 319)
AUCinf (ng•h/mL)	18	22.4	18	8.1	278	(250, 310)
Cmax (ng/mL)	24	0.51	27	0.26	195	(175, 218)

Source: CSR study HYD1012, Table 11-5, Table 11-6, and Table 11-7.
CI=confidence interval; LS=least squares; q12h=every 12 hours.
[a] An analysis of variance was performed on the natural logarithms of the pharmacokinetic metrics. The model included treatment, period, and sequence as fixed effects and subject within sequence as a random effect.

Higher hydrocodone AUC and Cmax values were observed in the presence of ketoconazole compared with placebo. Median Tmax of hydrocodone was observed at 18 hours in the presence of ketoconazole compared to 16 hours in the absence of ketoconazole. Mean t1/2 of hydrocodone ranged from 8 to 9 hours across the treatments.

Hydrocodone AUCt and AUCinf in the presence of ketoconazole were 135% and 133% higher, respectively, than in the absence of ketoconazole. Hydrocodone Cmax was 78% higher due to ketoconazole.

Lower norhydrocodone AUC and Cmax values were observed in the presence of ketoconazole compared with placebo. Mean t1/2 of norhydrocodone ranged from 8 to 11 hours across the treatments.

Norhydrocodone AUCt and AUCinf in the presence of ketoconazole were 36% and 34% lower, respectively, than in the absence of ketoconazole. Norhydrocodone Cmax was 52% lower due to ketoconazole.

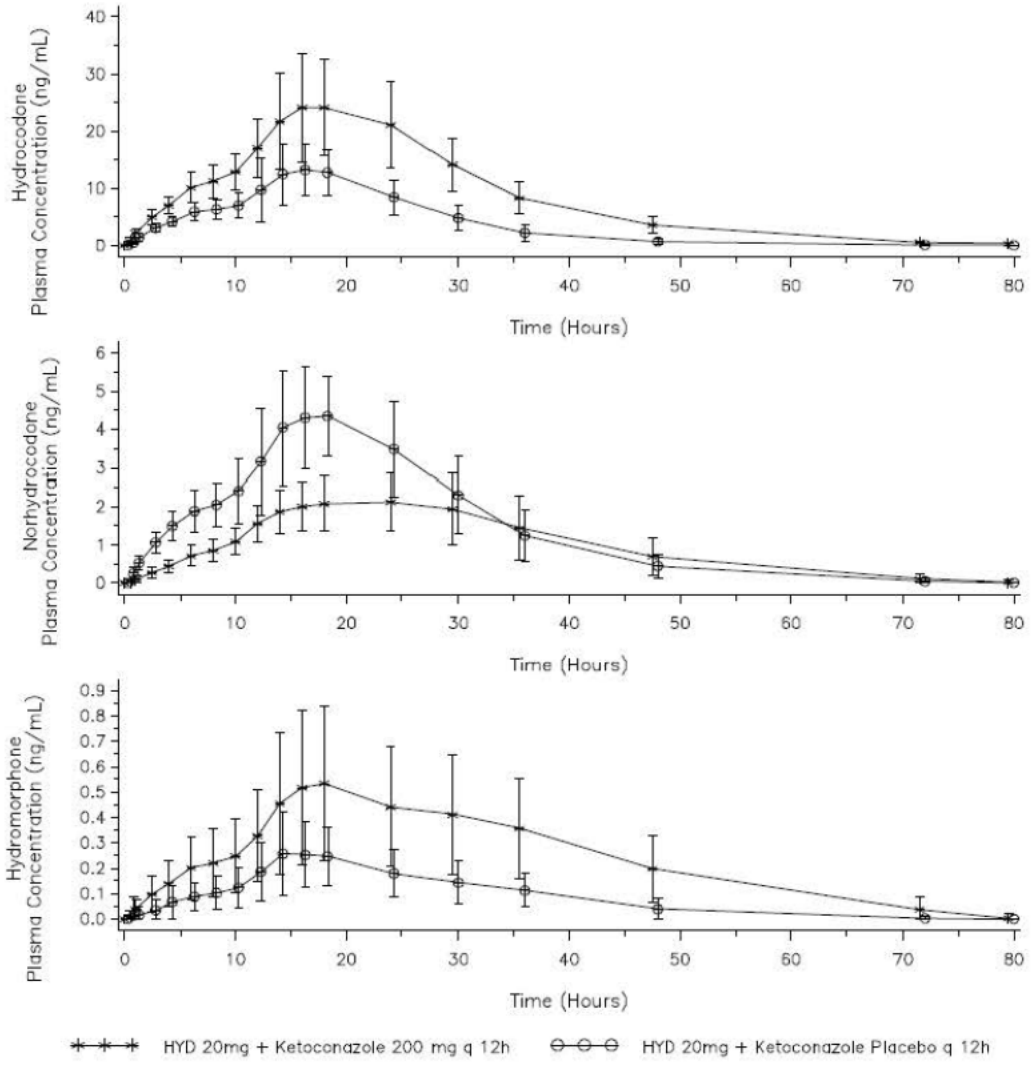
Higher hydromorphone AUC and Cmax values were observed in the presence of ketoconazole compared with placebo. Mean t1/2 ranged from 13 to 14 hours across the treatments.

Hydromorphone AUCt and AUCinf in the presence of ketoconazole were 195% and 178% higher, respectively, than in the absence of ketoconazole. Hydromorphone Cmax was 95% higher due to ketoconazole.

Conclusions:

- Co-administration of HYD with ketoconazole, a strong CYP3A4 inhibitor, increased the plasma concentrations of hydrocodone.
- In general, hydrocodone and hydromorphone exposures from a single dose of HYD 20-mg extended-release tablet after administration of ketoconazole 200 mg every 12 hours for 6 days were higher compared to exposures following placebo co-administration. At the same time, norhydrocodone exposures were lower under similar conditions.

Figure: HYD1012 Ketoconazole drug interaction Study - Mean (± SD) Plasma Concentrations of Hydrocodone (Top Panel), Norhydrocodone (Middle Panel), and Hydromorphone (Bottom Panel) Versus Time (Linear Scale)



Abbreviations: HYD, hydrocodone bitartrate; q12h, every 12 hours.
Source: Figure 14.2.1.4.

4.2.14 In vitro CYP inhibition study HCDDR-02-073:0 synopsis

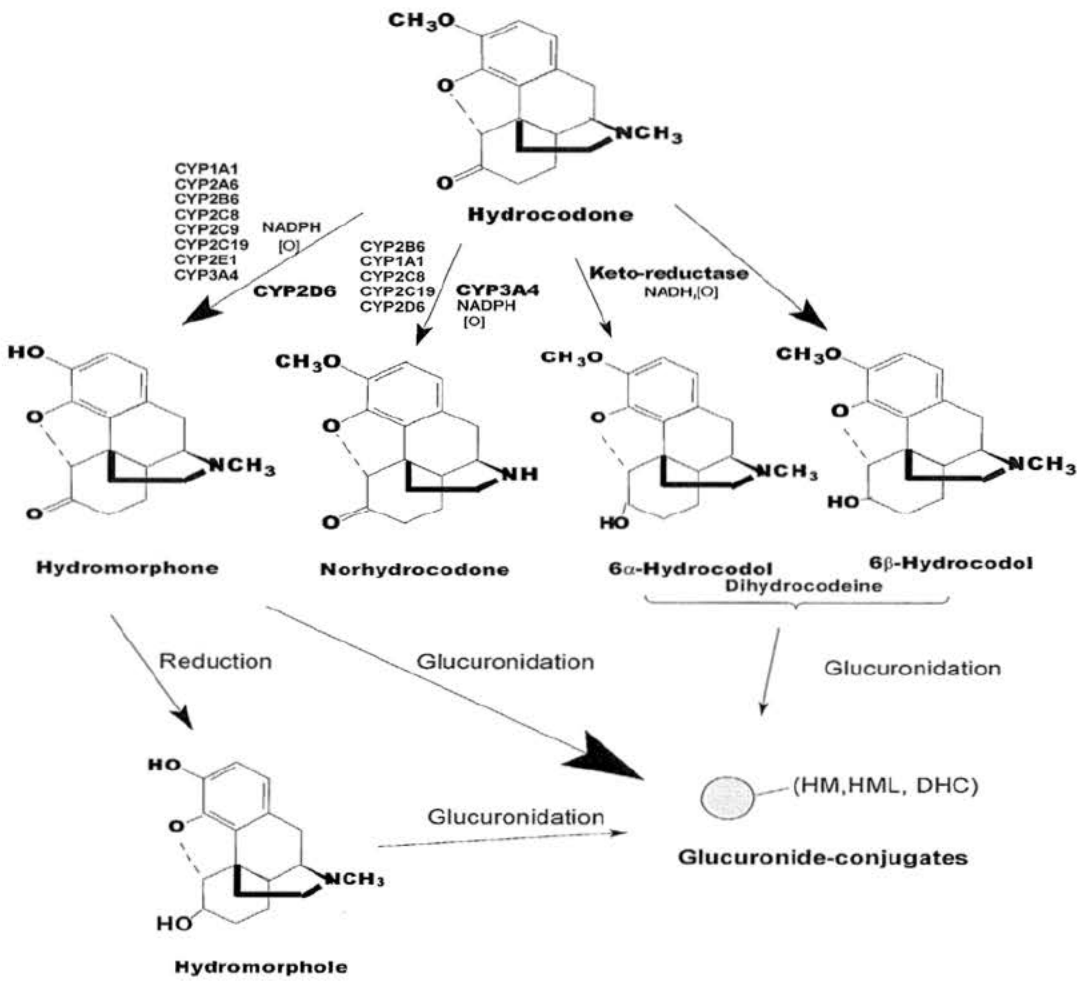
Effects of Hydrocodone, Naltrexone, Acetaminophen and their Combinations on Human Cytochrome P450 (CYP) Marker Activities. A series of in vitro incubations were carried out to evaluate, hydrocodone (HCD), naltrexone (NTX), acetaminophen (APAP) and their combinations have any drug-drug interaction potential with other CYP marker activities.

These experiments were designed such that the Cmax concentrations of HCD, NTX and APAP were used to predict the in vitro drug-drug interaction potential of individual components in HXA and their combinations with other drugs.

At various increasing concentrations used, HCD (0-400 ng/mL), NTX (0-400 pg/mL), APAP (0-30 g/mL) and HCD combinations (HCD:NTX and HCD:NTX:APAP) did not inhibit EROD (CYP1A2), coumarin hydroxylase (CYP2A6), Smephenytoin hydroxylase (CYP2C19), bufuralol 1'-hydroxylase (CYP2D6), chlorzaxazone hydroxylase (CYP2E1) and testosterone 6 -hydroxylase (CYP3A4) marker activities. These results suggest that in vivo, the drug-drug interaction potential of HCD, NTX, APAP and their combinations in HCD with other drugs that are metabolized by major CYP isoforms appear to be very minimal to none. APAP alone inhibited tolbutamide hydroxylase (CYP2C9) activity at a concentration of 30 g/mL. APAP when present in combination with HCD and NTX at a concentration of 10 or 30 g/mL, also inhibited CYP2C9 marker activity. However, HCD, NTX or their combinations (low-, mid- and high-concentrations) did not inhibit CYP2C9 marker activity . Hence, high doses of APAP in HXA may affect the metabolism of other drugs that are metabolized by CYP2C9 such as warfarin, losartan, diclofenac, sildenafil, etc.

No inhibition of CYP marker activities was observed by methanol (5 µL) or water (solvent control), which was used to dissolve HCD, NTX and APAP. A moderate to significant inhibition of various CYP marker activities was observed when known chemical inhibitors (as a positive control) such as -napthoflavone (inhibitor of CYP1A2), tranycylpromine (inhibitor of CYP2A6 and CYP2C19), sulfaphenazole (inhibitor of CYP2C9), diethylthiocarbamate (inhibitor of CYP2E1), quinidine (inhibitor of CYP2D6) and ketoconazole (inhibitor of CYP3A4), were used.

FIGURE 7A. Structure of Hydrocodone and its Metabolites



4.2.15 Oral Abuse Liability Study HYD1013 synopsis.

Name of Sponsor: Purdue Pharma L.P. **Name of Finished Product:** Hydrocodone bitartrate q24h film coated (HYD) tablets **Name of Active Ingredient:** Hydrocodone bitartrate	**Individual Study Table Referring to Part of the Dossier** Volume: Page:	*(for National Authority Use Only)*
Study Title A Single-Center, Randomized, Double-Blind, Crossover Study to Evaluate the Abuse Potential, Pharmacokinetics, and Safety of Oral Crushed and Intact Controlled Release Hydrocodone (HYD) Tablets in Recreational Opioid Users		
Investigator Pierre Geoffroy, MDCM, MSc, FCFP		
Study Center INC Research Toronto, Inc. 720 King St. W., Suite 700, Toronto, Ontario, Canada M5V 2T3		
Publication (reference) None at the time of clinical study report finalization.		
Study Period 10-Jun-2013 (first subject screened) to 25-Sep-2013 (last subject complete)	**Phase of Development** 1	
Objectives The objectives of the study were ▪ To evaluate oral abuse potential and pharmacodynamic (PD) effects of intact hydrocodone bitartrate q24h film coated (HYD) tablets, milled (crushed) HYD, and chewed HYD compared to hydrocodone oral solution and placebo in healthy, adult recreational opioid users. ▪ To evaluate the safety and tolerability of orally administered intact, milled, and chewed HYD in healthy, adult recreational opioid users. ▪ To determine the pharmacokinetic (PK) profile of orally administered intact, milled, and chewed HYD compared to hydrocodone active pharmaceutical ingredient (API) in oral solution in recreational opioid users.		
Methodology This single-center, double-blind, randomized, crossover study evaluated the abuse potential of HYD in healthy, non-dependent recreational drug users with moderate experience with opioids and examined the safety and PK profiles of hydrocodone when administered orally.		

The study consisted of 4 phases:

- Screening: visit 1 for inclusion/exclusion screening and visit 2 for a naloxone challenge to screen for symptoms of opioid withdrawal.
- Qualification: visit 3 for a randomized, crossover pharmacologic qualification (hydrocodone API 60 mg and placebo) to determine if subjects liked and could tolerate the effects of hydrocodone and could discriminate these from placebo; this visit also determined if each subject was suitable for entry into the study (ie, likely to comply with the study protocol).
- Treatment: visit 4 to visit 8, where each of the following treatments were administered:
  - HYD 60 mg tablet, intact
  - HYD 60 mg tablet, milled
  - HYD 60 mg tablet, chewed
  - Hydrocodone API 60 mg in oral solution
  - Placebo
- Follow-up: visit 9 for a safety follow-up, 3 to 7 days after the last study drug administration.

Number of Subjects (planned & analyzed)

Planned: 40 subjects were planned for randomization to the treatment phase.

Analyzed: 40 subjects were randomized and analyzed.

Subjects and Main Criteria for Inclusion

Subjects were healthy male or female recreational opioid users, 18 to 55 years of age, who were not physically dependent on opioids but had experience using opioids for non-therapeutic purposes (ie, for psychoactive effects) on at least 10 occasions within the past year and at least 3 times in the 12 weeks prior to screening visit 1. Subjects must have reported taking a dose equivalent to 60 mg hydrocodone (by any route of administration) or higher on at least 1 occasion in their lifetime. In addition, subjects must have experienced chewing an opioid medication on at least 3 occasions for the purpose of recreational abuse/misuse in the 12 months prior to screening visit 1.

Study Treatments (including dose, mode of administration, and batch numbers)

Hydrocodone bitartrate, USP powder; administered as a 240 mL oral solution ((b) (4) ; lot number: CB-2012-063)

HYD 60 mg q24h tablets (Purdue Pharmaceuticals; lot number: CB-2011-41)

Placebo to match HYD 60 mg q24h tablets (Purdue Pharmaceuticals; lot number: CB-2011-45)

Single doses of HYD, hydrocodone API, and placebo were administered as follows:

- **Treatment A:** *HYD 60 mg tablet, intact* + HYD placebo tablet, milled + HYD placebo tablet, chewed + placebo oral solution
- **Treatment B:** HYD placebo tablet, intact + *HYD 60 mg tablet, milled* + HYD placebo tablet, chewed + placebo oral solution
- **Treatment C:** HYD placebo tablet, intact + HYD placebo tablet, milled + *HYD 60 mg tablet, chewed* + placebo oral solution
- **Treatment D:** HYD placebo tablet, intact + HYD placebo tablet, milled + HYD placebo tablet, chewed + *hydrocodone API 60 mg in oral solution*

- **Treatment E:** HYD placebo tablet, intact + HYD placebo tablet, milled + HYD placebo tablet, chewed + placebo oral solution

Duration of Treatment

Subjects participated in the study for approximately 11 weeks from screening to follow-up. Single doses of study drugs in the treatment phase were separated by a washout interval of 5 to 7 days (if needed, rescheduling may have occurred up to a maximum of 14 days).

Endpoints

Pharmacodynamic:

The primary measures were the "at this moment" Drug Liking visual analog scale (VAS) and High VAS. However, conclusions regarding the abuse potential of HYD when administered via the oral route considered responses on all measures, including the following:

- Balance of effects: "at this moment" Drug Liking VAS (maximum effect [E_{max}], minimum effect [E_{min}], time-averaged area under the effect curve [TA_AUE]), Overall Drug Liking VAS (E_{max}/E_{min}), Take Drug Again VAS (E_{max}), Subjective Drug Value (SDV; E_{max})
- Positive/euphoric effects: High VAS (E_{max}, TA_AUE), Good Effects VAS (E_{max}, TA_AUE), Addiction Research Center Inventory Morphine-Benzedrine Group (ARCI MBG) scale (E_{max}, TA_AUE)
- Negative effects: Bad Effects VAS (E_{max}, TA_AUE), Feeling Sick VAS (E_{max}, TA_AUE)
- Sedative effects: Drowsiness/Alertness VAS (E_{min}, TA_AUE)
- Other effects: Any Effects VAS (E_{max}, TA_AUE)
- Objective measure: pupillometry (maximum pupil constriction [MPC], time-averaged pupillometry area over the curve [TA_PAOC])

Pharmacokinetic:

The PK endpoints for hydrocodone and its active metabolite hydromorphone were plasma concentrations over time, maximum plasma concentration (C_{max}), time to maximum plasma concentration (T_{max}), terminal elimination rate constant (λ_z), area under the plasma concentration vs time curve from time zero to last quantifiable concentration (AUC_{last}), area under the plasma concentration vs time curve extrapolated to infinity (AUC_{inf}), terminal elimination half-life ($t_{½}$), total systemic clearance (CL/F), volume of distribution (V/F), and abuse quotient (AQ).

Safety:

The following safety measures were evaluated: type, incidence and severity of adverse events (AEs); vital signs, clinical laboratory assessments; 12-lead electrocardiograms (ECG); and physical examination findings.

Statistical Methods (Data Analysis)

Pharmacodynamics:

PD data at each time point were summarized by descriptive statistics and presented graphically (where appropriate). Derived endpoints were summarized using descriptive statistics (all phases) and box plots (treatment phase, primary endpoints only). Outliers were listed by measure and parameter.

PD endpoints for the treatment phase (E_{max}, E_{min}, MPC, and/or TA_AUE/TA_PAOC, as appropriate) were analyzed using a mixed-effect model for a crossover study or a non-parametric approach (where appropriate). Time to maximum effect and time to minimum effect (TE_{max} and TE_{min}) were summarized descriptively. Means, 95% confidence intervals, and *P* values for

treatments and treatment differences were computed from each model. *P* values could be adjusted for multiplicity within a domain.

Pharmacokinetics:

Plasma concentration data for hydrocodone and hydromorphone were summarized using descriptive statistics (mean, standard deviation [SD], median, minimum, maximum, and coefficient of variation [%]) at each time point. PK parameters (C_{max}, T_{max}, λ_z, $t_{1/2}$, AUC_{last}, AUC_{inf}, CL/F, V/F, and AQ) were derived using non-compartmental methods.

Safety:

Safety data were listed and summarized using standard descriptive statistics.

Summary of Results

Pharmacodynamics:

- Overall, the results indicated that HYD intact and chewed showed significantly lower abuse potential compared to hydrocodone solution across the majority of endpoints. When HYD was milled for oral ingestion, a smaller but statistically significant reduction in abuse potential was observed for the primary endpoints; however, the differences were not statistically significant for many of the secondary endpoints.
- There were statistically significant differences between placebo and hydrocodone solution for the primary measures of Drug Liking VAS and High VAS, thereby confirming study validity. Consistent with the results of the primary measures, oral administration of hydrocodone solution resulted in statistically significant changes from placebo for the secondary measures of balance of effects, positive effects, sedative effects, any effects, and pupillometry. Hydrocodone solution was also associated with small but statistically significant negative effects compared to placebo.
- HYD intact and HYD chewed treatments were associated with significantly lower effects for most subjective measures, with a delayed onset of effects relative to hydrocodone solution. The differences were most pronounced with the HYD intact treatment, but in most cases the HYD intact and HYD chewed treatments were not statistically different. The majority of subjects (>50%) showed at least a 30% reduction in Drug Liking scores (responders) following administration of HYD chewed and at least a 50% reduction in Drug Liking scores following administration of HYD intact. Reductions in the effects of HYD milled in comparison to hydrocodone solution were less pronounced; however, HYD milled showed significantly lower effects for the primary endpoints (Drug Liking VAS E_{max} and High VAS E_{max} and TA_AUE), lower euphoric effects over time (ARCI MBG TA_AUE), and lower scores on Any Effects VAS and pupillary effects. HYD milled was associated with statistically significantly higher scores for most subjective measures relative to HYD intact and HYD chewed. There were no statistically significant effects on Drowsiness/Alertness VAS, Bad Effects VAS, Feeling Sick VAS, or pupil diameter.
- Relative to placebo, HYD intact showed significantly higher scores for positive effects and balance of effects measures (with the exception of Overall Drug Liking), greater negative effects, greater sedative effects and other effects, and statistically significant effects on pupil diameter. Effects of HYD chewed relative to placebo were similar to the HYD intact findings, with statistically significantly higher scores on positive effects and balance of effects measures (with the exception of Drug Liking TA_AUE). HYD chewed was also associated with statistically significantly greater disliking in comparison to placebo (Drug Liking E_{min}). There were statistically significant differences between placebo and HYD milled for all primary and secondary subjective measures.

- Statistically significant correlations were observed between the primary PD endpoints and PK parameters for HYD chewed only, suggesting a modest relationship between PD and PK for HYD when chewed. No other significant PK-PD correlations were observed, suggesting minimal direct relationship between PD and PK parameters.

Pharmacokinetics:

Hydrocodone

- Mean C_{max} of hydrocodone was highest following the hydrocodone solution (127.1 ng/mL). C_{max} values were lower following HYD milled (81.00 ng/mL) and HYD chewed (67.26 ng/mL) and lowest following HYD intact (48.38 ng/mL).
- Median T_{max} of hydrocodone was 1.05 hours following the hydrocodone solution, was observed later following HYD milled (1.55 hours) and HYD chewed (8.04 hours), and latest following HYD intact (15.1 hours).
- As a consequence, the mean AQ (C_{max}/T_{max}) of hydrocodone was highest following the hydrocodone solution (153.9 ng/mL/h) and lowest following HYD intact (3.1 ng/mL/h). Values following HYD milled (70.4 ng/mL/h) and HYD chewed (14.7 ng/mL/h) were intermediate, with the HYD milled results being more in line with those for the hydrocodone solution and the HYD chewed results being more in line with those for HYD intact.
- Mean AUC_{last} values of hydrocodone were similar following HYD intact (885.7 h*ng/mL), HYD chewed (913.4 h*ng/mL), and the hydrocodone solution (951.4 h*ng/mL). Mean AUC_{last} values were lower following HYD milled (647.8 h*ng/mL). The results were similar for AUC_{inf}.

Hydromorphone

- Mean C_{max} of hydromorphone was highest (1.469 ng/mL) following the hydrocodone solution. C_{max} values were lower following HYD milled (0.9759 ng/mL) and HYD chewed (0.7153 ng/mL) and lowest following HYD intact (0.5942 ng/mL).
- Median T_{max} of hydromorphone was 0.567 hours following the hydrocodone solution. T_{max} was observed later following HYD milled (1.55 hours) and HYD chewed (8.05 hours) and latest following HYD intact (15.1 hours).
- As a consequence, the mean AQ of hydromorphone was highest following the hydrocodone solution (2.3 ng/mL/h) and lowest following HYD intact (0.038 ng/mL/h). The values following HYD milled (1.0 ng/mL/h) and HYD chewed (0.14 ng/mL/h) were intermediate, with the HYD milled results being more in line with those for the hydrocodone solution and the HYD chewed results being more in line with those for HYD intact.
- Mean AUC_{last} values of hydromorphone were similar following HYD intact (11.41 h*ng/mL), HYD chewed (11.88 h*ng/mL), and the hydrocodone solution (12.39 h*ng/mL), and mean AUC_{last} values were lower following HYD milled (9.394 h*ng/mL). The results were similar for AUC_{inf} values.

Safety:

- No deaths or SAEs occurred during this study. One subject was withdrawn from the study due to a TEAE of abnormal ECG P waves following placebo administration.
- Overall, the highest incidence of TEAEs was observed after administration of hydrocodone solution (97.4%), followed by HYD milled (94.6%), HYD chewed (75.0%), HYD intact (69.4%), and placebo (34.2%).
- Most subjects had TEAEs that were mild in severity. Three subjects experienced TEAEs of moderate severity: 1 episode of presyncope following administration of HYD milled, 1 episode of sinus bradycardia following administration of hydrocodone solution, and 1 episode of

headache following HYD intact dosing. ▪ The majority of TEAEs were possibly or probably related to study drug. ▪ Euphoric mood was the most common TEAE; its incidence was highest following administration of hydrocodone solution (79.5%), followed by HYD milled (67.6%), HYD chewed (38.9%), HYD intact (33.3%), and placebo (5.3%). ▪ Of the skin and subcutaneous tissue disorders, pruritus was the most common TEAE. The incidence of pruritus was the highest after administration of HYD milled (64.9%), followed by hydrocodone solution (64.1%), HYD intact, and HYD chewed (41.7% each). No TEAE of pruritus was reported after placebo administration. ▪ Somnolence, headache, feeling hot, nausea, dizziness, pruritus generalized, and vomiting were also reported in more than 2 subjects for at least one of the treatments. ▪ All mean laboratory values were within the normal ranges at baseline and follow-up, and no notable changes from baseline were observed. Some individual subjects had out-of-range values; however, none of the abnormalities was considered clinically significant. ▪ There were no clinically meaningful changes in vital signs and mean 12-lead ECG parameters from baseline to follow-up.	
Conclusions Overall, the HYD product demonstrated significantly lower subjective and physiologic effects compared to hydrocodone solution when administered by the oral route as intact, chewed, or milled tablets. While substantial reductions in abuse potential were observed with intact and chewed HYD, the differences were less pronounced when the product was taken to its limit (ie, HYD milled), although statistically significant decreases were observed for the primary endpoints. Therefore, the results of the study indicate that HYD may have lower oral abuse potential compared to non-abuse-deterrent opioid products.	
Date of Report	03-Mar-2014

4.2.16 Intranasal Abuse Liability Study HYD1014synopsis.

Name of Sponsor: Purdue Pharma L.P. **Name of Finished Product:** Hydrocodone bitartrate q24h film coated (HYD) tablets **Name of Active Ingredient:** Hydrocodone bitartrate	**Individual Study Table Referring to Part of the Dossier** Volume: Page:	*(for National Authority Use Only)*
Study Title A Single-Center, Randomized, Double-Blind, Crossover Study to Evaluate the Abuse Potential, Pharmacokinetics, and Safety of Crushed and Intranasally Administered Controlled Release Hydrocodone in Recreational Opioid Users		
Investigator Pierre Geoffroy, MDCM, MSc, FCFP		
Study Center INC Research Toronto, Inc. 720 King St. W., Suite 700, Toronto, Ontario, Canada, M5V 2T3		
Publication (reference) None at the time of clinical study report finalization		
Study Period 07-Jun-2013 (first subject screened) to 22-Oct-2013 (last subject complete)		**Phase of Development** 1
Objectives The objectives of this study were ▪ To evaluate intranasal abuse potential and pharmacodynamic (PD) effects of intranasally administered HYD compared to hydrocodone active pharmaceutical ingredient (hydrocodone API) and placebo in recreational opioid users with a history of intranasal abuse. ▪ To evaluate the safety and tolerability of intranasally administered fine and coarse HYD powder in recreational opioid users with a history of intranasal abuse. ▪ To determine the pharmacokinetic (PK) profile of intranasally administered fine and coarse HYD powder compared to hydrocodone API in recreational opioid users with a history of intranasal abuse.		
Methodology This single-center, double-blind, placebo-controlled, randomized, 4-way crossover study evaluated the abuse potential, PD, PK, and safety profile of intranasally administered HYD (fine and coarse powder) compared to hydrocodone API and placebo in recreational opioid users with a history of intranasal abuse.		

Name of Sponsor: Purdue Pharma L.P. **Name of Finished Product:** Hydrocodone bitartrate q24h film coated (HYD) tablets **Name of Active Ingredient:** Hydrocodone bitartrate	**Individual Study Table Referring to Part of the Dossier** Volume: Page:	*(for National Authority Use Only)*

The study consisted of 5 phases:

- Screening: visit 1 for inclusion/exclusion screening and visit 2 for a naloxone challenge test to screen for symptoms of opioid withdrawal.
- Dose Selection: visit 3a for a randomized, double-blind, crossover dose selection phase to determine the dose of hydrocodone to be used during the qualification and treatment phases. An initial dose of 40 mg hydrocodone API was administered intranasally to 4 eligible subjects. If the initial dose was considered too high based on PD and safety data, a dose of 20 mg was to be tested in an additional cohort of 4 new subjects. Similarly, if the 40 mg dose was deemed insufficient, the dose was to be escalated to 60 mg, 80 mg, 100 mg, and 120 mg in up to 4 additional cohorts of 4 new subjects each, as needed. Following each cohort, unblinded safety and PD data were reviewed by the investigator (or designee) and sponsor prior to the next cohort. Based on the evidence, both the investigator and sponsor agreed that 60 mg hydrocodone API was safe and well tolerated and that subjects showed sufficient discrimination between 60 mg hydrocodone API and placebo.
- Qualification: visit 3b for a randomized, crossover pharmacologic qualification (60 mg hydrocodone API and placebo) involving a new set of eligible subjects to determine if subjects liked and could tolerate the effects of hydrocodone and could discriminate these from placebo; this visit also determined if each subject was suitable for entry into the study (ie, likely to comply with the study protocol).
- Treatment: visit 4 to visit 7, where the following treatments were received:
  - 60 mg hydrocodone API
  - 60 mg HYD, fine particle size
  - 60 mg HYD, coarse particle size
  - Placebo (lactose powder)
- Follow-up: visit 8 for a safety follow-up, 3 to 7 days after the last study drug administration.

Number of Subjects (planned & analyzed)

Planned: 32 subjects were planned for randomization to the treatment phase.

Analyzed: 32 subjects were randomized and 31 subjects were analyzed.

Subjects and Main Criteria for Inclusion

Subjects were healthy male or female recreational opioid users, 18 to 55 years of age (inclusive), who were not physically dependent on opioids, but had moderate experience using opioids for non-therapeutic purposes (ie, for psychoactive effects) on at least 10 occasions within the past year and at least 3 times in the 12 weeks prior to screening visit 1. Subjects must have experienced at least 3 occasions of intranasal opioid use for the purpose of recreational

abuse/misuse in the last 12 months prior to screening visit 1. Subjects must have reported taking a dose equivalent to 40 mg hydrocodone (by any route of administration) or higher on at least 1 occasion in the past year prior to screening visit 1.

Study Treatments (including dose, mode of administration, and batch numbers)

Hydrocodone bitartrate, USP powder ((b) (4) lot number: CB-2012-063)

HYD 60 mg tablets (Purdue Pharmaceuticals; lot number: CB-2011-41)

Placebo (lactose powder) to match hydrocodone API ((b) (4) lot number: 12080049)

Dose Selection Phase

- Cohort 1: 40 mg hydrocodone API powder (intranasal)
- Cohorts 2 and 3: 60 mg hydrocodone API powder (intranasal)

Qualification Phase

- 60 mg hydrocodone API powder (intranasal)
- Placebo (lactose powder; intranasal)

Treatment Phase

Single intranasal doses of:

- Treatment A: 60 mg hydrocodone API powder
- Treatment B: 60 mg HYD, fine particle size
- Treatment C: 60 mg HYD, coarse particle size
- Treatment D: Placebo (lactose powder)

Duration of Treatment

Dose Selection Phase

Subjects participated in the dose selection phase for approximately 5 weeks starting from the screening visit. Subjects were discharged approximately 23 hours after receiving the second dose of study drug.

Treatment Phase

Subjects participated in the study for approximately 8 weeks, from screening to follow-up. Single doses of study drugs in the treatment phase were separated by a washout interval of 5 to 7 days (if needed, rescheduling may have occurred up to a maximum of 14 days).

Name of Sponsor:	Individual Study Table Referring to Part of the Dossier	*(for National Authority Use Only)*
Purdue Pharma L.P. **Name of Finished Product:** Hydrocodone bitartrate q24h film coated (HYD) tablets **Name of Active Ingredient:** Hydrocodone bitartrate	Volume: Page:	

Endpoints

Pharmacodynamic

The primary measures were the "at this moment" Drug Liking visual analog scale (VAS) and High VAS.

- Balance of effects: Drug Liking VAS ("at this moment") (maximum effect [E_{max}], minimum effect [E_{min}], time-averaged area under the effect curve [TA_AUE]), Overall Drug Liking VAS (E_{max}, E_{min}), Take Drug Again VAS (E_{max}), Subjective Drug Value (SDV; E_{max})
- Positive/euphoric subjective effects: High VAS (E_{max}, TA_AUE), Good Effects VAS (E_{max}, TA_AUE), Addiction Research Center Inventory (ARCI) Morphine Benzedrine Group (MBG) scale (E_{max}, TA_AUE)
- Negative subjective effects: Bad Effects VAS (E_{max}, TA_AUE), Feeling Sick VAS (E_{max}, TA_AUE), subject-rated assessment of intranasal irritation (SRAII) (E_{max} for burning, need to blow nose, runny nose / nasal discharge, facial pain/pressure, and nasal congestion)
- Subjective sedative effects: Drowsiness/Alertness VAS (E_{min}, TA_AUE)
- Other subjective effects: Any Effects VAS (E_{max}, TA_AUE)
- Objective measures: Pupillometry (maximum pupil constriction [MPC], time-averaged pupillometry area over the curve [TA_PAOC]), endoscopy with intranasal photography (both nostrils) assessed using the observer-rated assessment of intranasal irritation (ORAII) (E_{max} for nasal congestion, irritation, and discharge)

Pharmacokinetic

The PK endpoints for hydrocodone and its metabolite hydromorphone were plasma concentrations over time, maximum plasma concentration (C_{max}), time to maximum plasma concentration (T_{max}), area under the plasma concentration vs time curve from time zero to last quantifiable concentration (AUC_{last}), area under the plasma concentration vs time curve extrapolated to infinity (AUC_{inf}), terminal elimination half-life ($t_{½}$), total systemic clearance (CL/F), volume of distribution (V/F), and abuse quotient ($AQ=C_{max}/T_{max}$).

Safety

The safety measures evaluated were type, incidence, and severity of adverse events (AEs); vital signs; clinical laboratory tests; 12-lead electrocardiogram (ECG); and physical examination.

Statistical Methods (Data Analysis)

Pharmacodynamic

PD data at each time point were summarized by descriptive statistics and presented graphically (where appropriate). Derived endpoints were summarized using descriptive statistics (all phases) and box plots (treatment phase only). Outliers were listed by measure and parameter.

Name of Sponsor: Purdue Pharma L.P. **Name of Finished Product:** Hydrocodone bitartrate q24h film coated (HYD) tablets **Name of Active Ingredient:** Hydrocodone bitartrate	**Individual Study Table Referring to Part of the Dossier** Volume: Page:	*(for National Authority Use Only)*

PD endpoints for the treatment phase (E_{max}, E_{min}, MPC, and/or TA_AUE/TA_PAOC, as appropriate) were analyzed using a mixed-effect model for a crossover study. Time to maximum effect and time to minimum effect (T_{Emax} and T_{Emin}) were summarized descriptively. Means, 95% confidence intervals, and *P* values for treatments and treatment differences were computed from each model. *P* values could be adjusted for multiplicity within a domain. Only the *P* values from the contrasts or comparisons were included in the Benjamini and Hochberg adjustment. Non-parametric methods were used for some endpoints, as appropriate.

Pharmacokinetic

Plasma concentration data for hydrocodone and hydromorphone were summarized using descriptive statistics (mean, standard deviation [SD], median, minimum, maximum, and coefficient of variation [%]) at each time point. PK parameters (C_{max}, T_{max}, λ_z, $t_{½}$, AUC_{last}, AUC_{inf}, CL/F, V/F, and AQ) were derived using non-compartmental methods.

Safety

Safety data were listed and summarized using standard descriptive statistics.

Summary of Results

Pharmacodynamic

- There were statistically significant differences between placebo and hydrocodone API for the primary measures of Drug Liking VAS and High VAS, thereby confirming study validity. Consistent with the results of the primary measures, intranasal administration of hydrocodone API resulted in statistically significant changes from placebo on the secondary measures of balance, positive effects, sedative effects, any effects, and pupillometry. Hydrocodone API was also associated with small but statistically significant negative effects, including increased nasal irritation and congestion in comparison to placebo.
- Relative to hydrocodone API, HYD coarse and HYD fine were associated with significantly lower effects on all subjective and objective measures, including both primary endpoints, and both HYD treatments were associated with greater intranasal effects, especially measures of nasal congestion and irritation. HYD fine appeared to be associated with greater nasal congestion compared to HYD coarse, but on most other outcome measures, the two treatments were not statistically different. The majority of subjects (>50%) showed at least a 30% reduction in Drug Liking VAS scores (responders) following administration of HYD coarse and at least a 40% reduction in Drug Liking VAS scores following administration of HYD fine.
- Compared to placebo, both HYD treatments showed significantly higher scores on measures of balance, positive effects, sedative effects, any effects, and pupillometry. HYD treatments were also associated with greater negative effects, including intranasal effects.

Pharmacokinetic

Name of Sponsor:	Individual Study Table Referring to Part of the Dossier	*(for National Authority Use Only)*
Purdue Pharma L.P. **Name of Finished Product:** Hydrocodone bitartrate q24h film coated (HYD) tablets **Name of Active Ingredient:** Hydrocodone bitartrate	Volume: Page:	

Hydrocodone

- Mean C_{max} values of hydrocodone were considerably lower following HYD fine (36.49 ng/mL) and HYD coarse (27.49 ng/mL) than following hydrocodone API (105.8 ng/mL), which may be related to the lower percentage of the dose observed to have been inhaled for HYD fine and HYD coarse than for hydrocodone API. Additionally, median T_{max} was also observed later following HYD fine (3.07 hours) and HYD coarse (4.05 hours) than following hydrocodone API (1.57 hours).
- As a consequence of the lower C_{max} and higher T_{max} values, the mean AQ (C_{max}/T_{max}) of hydrocodone following HYD fine (13.40 ng/mL/h) and HYD coarse (9.51 ng/mL/h) were lower than that following hydrocodone API (81.97 ng/mL/h).
- The mean AUC_{last} value of hydrocodone was slightly higher following HYD fine (411.7 h*ng/mL) than following HYD coarse (317.9 h*ng/mL), but the standard deviations were large (205.65 h*ng/mL and 292.66 h*ng/mL, respectively) indicating much variation between subjects. The mean AUC_{last} values following HYD fine and HYD coarse were considerably lower than the AUC_{last} value for hydrocodone API (902.3 h*ng/mL). The results were similar for AUC_{inf}.

Hydromorphone

- Mean C_{max} values of hydromorphone were similar following HYD fine (0.1832 ng/mL) and HYD coarse (0.1856 ng/mL) and considerably lower than following hydrocodone API (0.8010 ng/mL). This may be partly due to the lower percentage of the dose observed to have been inhaled for HYD fine and HYD coarse than for hydrocodone API. Median T_{max} was also considerably delayed following HYD fine and HYD coarse (6.05 hours) compared to hydrocodone API (1.57 hours).
- As a consequence of the lower C_{max} and higher T_{max} values, the mean AQ (C_{max}/T_{max}) values of hydromorphone following HYD fine (0.03839 ng/mL/h) and HYD coarse (0.09545 ng/mL/h) were lower than that following hydrocodone API (0.5611 ng/mL/h).
- The mean AUC_{last} value of hydromorphone was slightly higher following HYD fine (3.438 h*ng/mL) than following HYD coarse (2.910 h*ng/mL), but the standard deviations were large (2.5006 h*ng/mL and 3.1502 h*ng/mL, respectively), indicating much variation between subjects. The mean AUC_{last} values following HYD fine and HYD coarse were considerably lower than the AUC_{last} value for hydrocodone API (8.410 h*ng/mL).
- AUC_{inf} values following HYD fine (5.926 h*ng/mL) and HYD coarse (6.123 h*ng/mL) appeared to be closer to that following hydrocodone API (7.603 h*ng/mL) than observed for the AUC_{last} values. However, AUC_{inf} could only be estimated in a small subset of subjects and should therefore be interpreted with caution.

Pharmacokinetic–Pharmacodynamic

- Statistically significant correlations were observed between High VAS and PK parameters for

both HYD treatments (fine and coarse), suggesting a moderate to strong relationship between measures of general drug effect and PK measures for HYD when milled into fine particles or cut into coarse particles for intranasal insufflation. Almost no relationship was found between Drug Liking VAS and PK parameters, suggesting a minimal direct relationship between hydrocodone exposure and measures of "liking."

Safety

- No deaths or SAEs occurred during the study. One subject was withdrawn from the study due to a TEAE of ventricular tachycardia following administration of HYD coarse.
- Overall, the highest incidence of TEAEs was observed after administration of hydrocodone API (96.3%), followed by HYD fine (78.6%), HYD coarse (64.3%), and placebo (7.4%).
- Almost all TEAEs were mild in severity. There was 1 moderate severity TEAE of physical assault that was considered unrelated to study treatment.
- The majority of TEAEs were possibly or probably related to study drug.
- Euphoric mood was the most common TEAE; the incidence was highest following administration of hydrocodone API (88.9%), while the incidence was much lower following HYD fine (32.1%) and HYD coarse (25.0%). Euphoric mood was not reported after placebo administration.
- Pruritus was the second most common TEAE. The incidence of pruritus was highest after administration of hydrocodone API (55.6%), followed by HYD fine (14.3%). No TEAE of pruritus was reported after administration of HYD coarse or placebo.
- Of the respiratory, thoracic, and mediastinal TEAEs, nasal congestion was the most commonly reported. The incidence was highest following administration of HYD fine (50.0%), followed by HYD coarse (28.6%) and hydrocodone API (7.4%). No TEAE of nasal congestion was reported after placebo administration.
- Dizziness, headache, somnolence, nasal discomfort, nasal obstruction, rhinorrhea, nausea, and fatigue were also reported by 5% of subjects or more for at least 1 treatment.
- All mean laboratory values were within the normal range at baseline and follow-up, and no notable changes from baseline were observed. Some individual subjects had out-of-range values; however, none of the abnormalities were considered clinically significant.
- There were no clinically meaningful changes in vital signs or mean 12-lead ECG parameters from baseline to follow-up.

Conclusions

The HYD product, when administered via the intranasal route as a fine or coarse powder, demonstrated significantly lower subjective and physiologic effects and greater intranasal irritation compared to hydrocodone API administered intranasally. Furthermore, the product was associated with greater negative effects when taken to its effective limit (ie, with the HYD fine particle size). The results of the study indicate that HYD may have lower intranasal abuse potential compared to non–abuse-deterrent opioid products.

Date of Report	14-Mar-2014

4.2.17 Synopsis of Clinical Safety Study HYD3003.

Study HYD3003 was an open-label multicenter study to assess the long-term safety of HYD tablets 20 to 120 mg once daily in subjects with moderate to severe nonmalignant and nonneuropathic pain. Subjects included in this study were male and female adults, 18 years of age or older, with moderate to severe chronic nonmalignant and nonneuropathic pain that was either uncontrolled by a stable opioid analgesic regimen equivalent to 0 to 100 mg/day of oxycodone or controlled by a stable opioid analgesic regimen equivalent to 0 to 120 mg/day of oxycodone, and also including any opioid-naïve subjects who were taking nonopioid analgesics only or a nonopioid analgesic regimen plus intermittent opioid analgesics equivalent to < 5 mg/day oxycodone. These subjects were deemed by the investigator to be appropriate for around-the-clock opioid treatment for an extended period of time.

The study consisted of a core study and a 24-week open-label extension period. The core study consisted of a screening period, a dose-titration period, and a 52-week open-label post-titration (maintenance) period. Subjects were converted to HYD at the beginning of the open-label dose-titration period, and if the subjects did not achieve satisfactory analgesia with the initial HYD dose, they had their doses titrated to an individual optimal dosage. Subjects who achieved satisfactory analgesia with tolerable adverse effects entered the maintenance period.

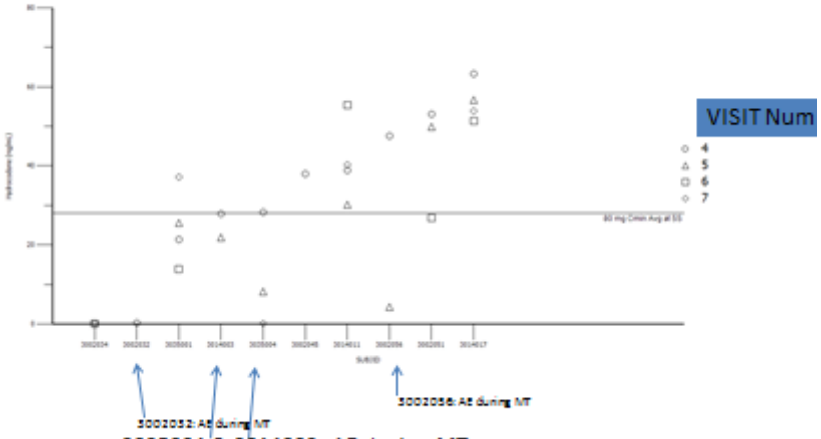
Any supplemental analgesic medications except for long-acting /extended-release opioids were permitted throughout the study if deemed appropriate by the investigator. Subjects who completed treatment in the open-label maintenance period were eligible to enter the 24-week extension period.

The sponsor indicates that the protocol for HYD3003 allowed for recruitment of completers from study HYD3002; however, none were recruited. The demographic characteristics in study HYD3002 were generally similar to those for the population of subjects in study HYD3003 who entered the maintenance period, with mean (SD) ages across both studies ranging from approximately 49 (13) to 52 (12) years and approximately 56% to 57% of subjects being female. Compared with subjects in study HYD3003 who entered the maintenance period, there was a higher proportion of black subjects (20% *v* 15%) and a smaller proportion of white subjects (68% *v* 83%) in the FAP in study HYD3002.

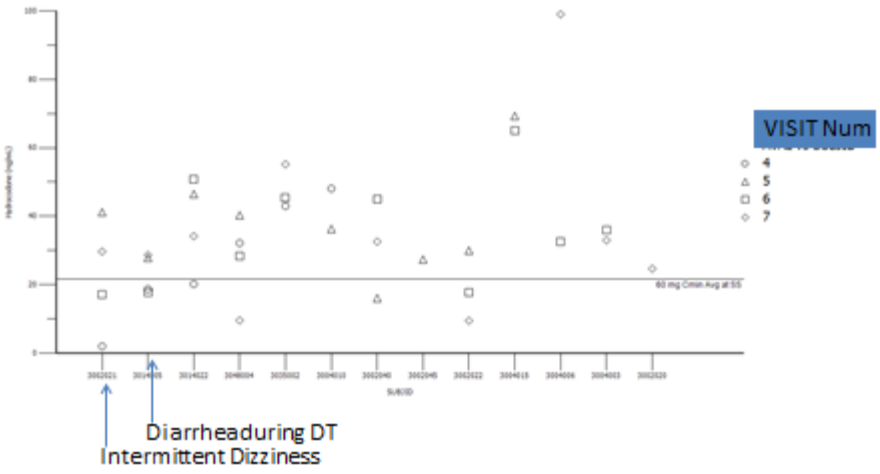
Mean (SD) average pain scores over the last 14 days prior to baseline were somewhat higher in the full analysis population of study HYD3002 (7.2 [1.21] *v* 6.5 [1.67]) compared with subjects who entered the maintenance period of study HYD3003, as were mean (SD) average pain scores over the last 24 hours prior to entry into the run-in/dose titration period (7.4 [1.16] *v* 6.4 [1.57]). This was an expected difference as study HYD3003 enrolled subjects whose pain had been controlled. Subjects who entered the maintenance period in study HYD3003 had a somewhat longer mean (SD) time since the first diagnosis of their pain condition compared with the full analysis population in study HYD3002 (129.5 [117.42] *v* 114.3 [107.40] months). More subjects who entered the maintenance period in study HYD3003 were opioid experienced (65% *v* 44%).

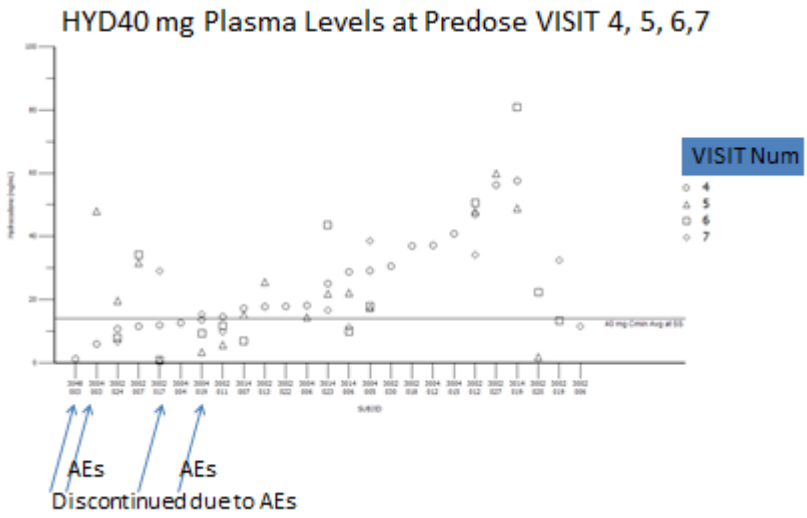
From a clinical pharmacology perspective, pharmacokinetic blood sampling was collected during maintenance treatment period at Visits 4, 5, 6, and 7. However, upon closer examination it was noted that several samples were note collected as per plan. Additionally, several subjects had very low plasma concentrations possibly due to a recent adverse event related lack of compliance.

HYD80 mg Plasma Levels at Pre-dose (Visit 4, 5, 6, or 7)



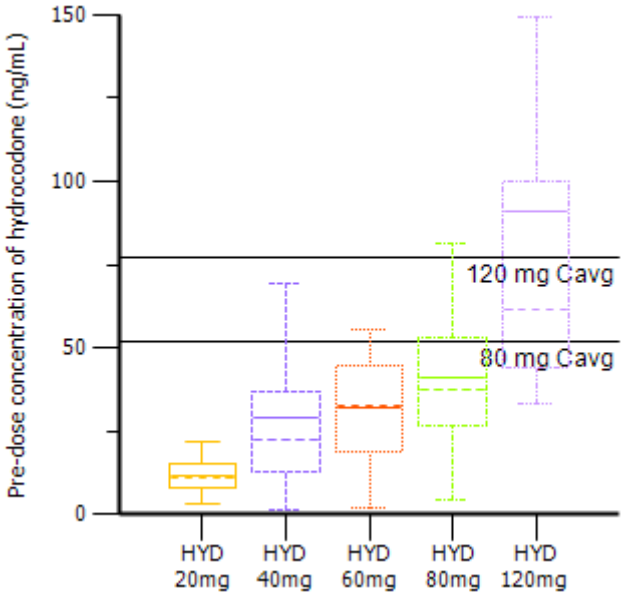
HYD60 mg Plasma Levels at Pre-dose (Visit 4, 5, 6, or 7)





The pre-dose plasma concentrations of hydrocodone following steady-state dosing appears to be consistent with that noted in healthy volunteers. A dose related increase in pre-dose plasma concentrations were observed. Higher variability in pre-dose plasma hydrocodone concentration was noted as the subjects may not have been compliant due to adverse events during on of the four visits during maintenance treatment period.

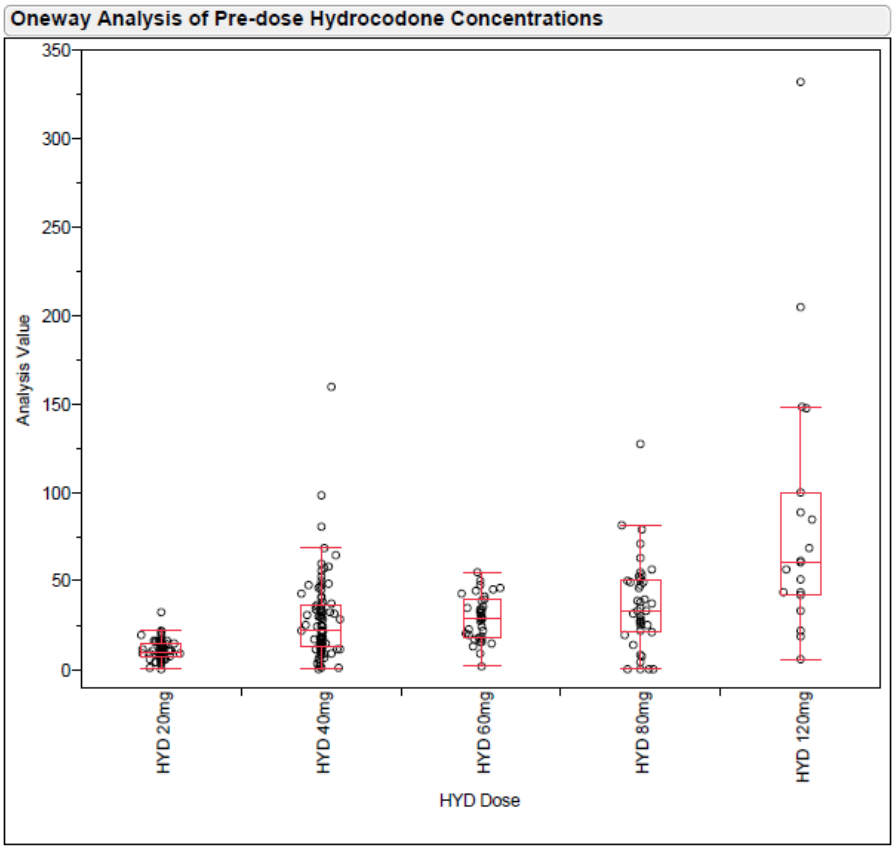
Figure: Average pre-dose plasma hydrocodone concentrations over dose during the maintenance treatment period (average of visits 4, 5, 6, and 7 discussed above).



The sponsor submitted additional discussion on the impact of laxative use with Hysingla ER pre-dose hydrocodone plasma levels. Pre-dose plasma hydrocodone concentrations were available from some patients who received Hysingla ER, including some who received concomitant laxative treatment. The outputs shown Figure 1 (below) present the distributions and descriptive statistics for the untransformed predose concentration values collected on one or more occasions by daily Hysingla ER dose. Note that some subjects

provided multiple pre-dose concentration values. Figure 1, Part A presents these for the composite groups by Hysingla ER dose, irrespective of concomitant laxative use.

Figure1, Part A



Missing Rows 17

Quantiles

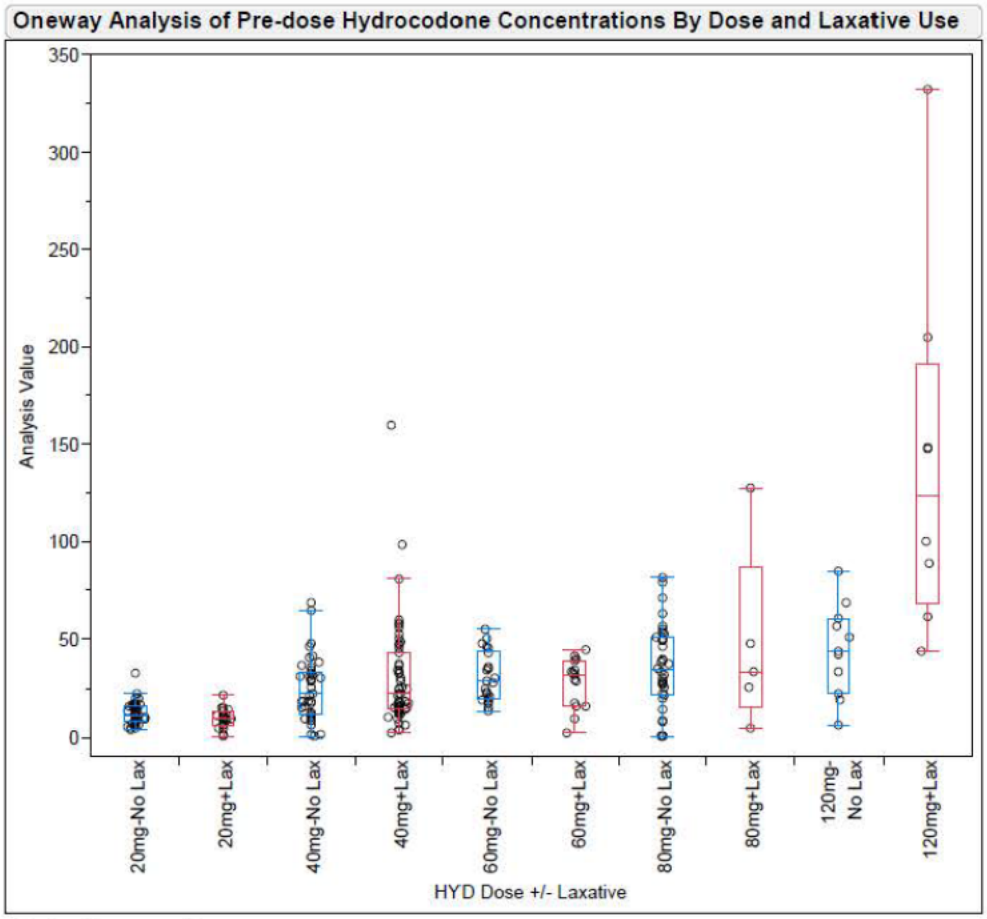
Level	Minimum	10%	25%	Median	75%	90%	Maximum
HYD 20mg	0.461	4.7	7.65	10.45	15.025	17.25	32.5
HYD 40mg	0.78	7.656	13.7	21.9	36.6	54.14	160
HYD 60mg	2.03	14.74	18.35	29.7	39.65	46.82	55.2
HYD 80mg	0.143	1.1188	21.65	33.5	50.7	69.46	128
HYD 120mg	6.51	19.1	42	60.8	100	205	332

Means and Std Deviations

Level	Number	Mean	Std Dev	Std Err Mean	Lower 95%	Upper 95%
HYD 20mg	64	11.2057	5.5488	0.694	9.820	12.59
HYD 40mg	95	27.9223	22.9304	2.353	23.251	32.59
HYD 60mg	37	29.5014	12.6440	2.079	25.286	33.72
HYD 80mg	41	36.9551	25.6213	4.001	28.868	45.04
HYD 120mg	19	85.2321	77.9354	17.880	47.668	122.80

Figure 1, Part B splits each Hysingla ER dose grouping into subgroups with and without concomitant laxative use. Review of the distributions and associated descriptive statistics in Figure 1, Part B suggests that concomitant laxative use was not associated with any clinically meaningful effect on pre-dose plasma hydrocodone concentrations.

Figure1, Part B



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Quantiles

Level	Minimum	10%	25%	Median	75%	90%	Maximum
20mg-No Lax	3.39	5.44	7.88	10.75	16.13	19.07	32.50
20mg+Lax	0.46	2.02	5.88	9.20	13.58	15.10	21.80
40mg-No Lax	0.78	6.24	11.70	21.90	33.83	45.76	69.30
40mg+Lax	1.89	8.35	14.50	21.90	43.50	57.88	160.00
60mg-No Lax	13.30	15.88	19.83	28.30	43.58	49.99	55.20
60mg+Lax	2.03	6.58	16.10	32.20	39.00	42.72	45.00
80mg-No Lax	0.14	0.27	21.53	34.25	51.00	65.61	81.50
80mg+Lax	4.33	4.33	14.72	33.50	87.80	128.00	128.00
120mg-No Lax	6.51	9.03	22.40	44.10	60.80	82.14	85.40
120mg+Lax	44.00	44.00	68.48	124.00	191.00	332.00	332.00

Means and Std Deviations

Level	Number	Mean	Std Dev	Std Err Mean	Lower 95%	Upper 95%
20mg-No Lax	42	12.05	5.71	0.88	10.27	13.83
20mg+Lax	22	9.60	4.96	1.06	7.40	11.80
40mg-No Lax	40	24.57	16.09	2.54	19.43	29.72
40mg+Lax	55	30.36	26.72	3.60	23.13	37.58
60mg-No Lax	22	30.68	12.73	2.71	25.04	36.32
60mg+Lax	15	27.77	12.76	3.29	20.70	34.84
80mg-No Lax	36	35.46	21.75	3.63	28.10	42.82
80mg+Lax	5	47.71	47.54	21.26	-11.33	106.74
120mg-No Lax	11	44.61	23.33	7.03	28.94	60.28
120mg+Lax	8	141.09	93.18	32.94	63.19	218.99

In addition, the sponsor evaluated the use of rescue medication in clinical study HYD3003 following laxative use and compared it to subjects that did not receive a laxative for the management of constipation.

Short-acting (SA) prescription opioid medications were allowed in study HYD3003 to supplement Hysingla ER treatment. The total daily dose of these medications were converted to oxycodone equivalent (mg/day) and analyzed by laxative use. The use of SA opioid medications was limited during Hysingla ER treatment and not meaningfully different between laxative users and nonusers. These data do not suggest a reduced exposure to hydrocodone (from Hysingla ER).

Non-Study Opioid Medication Use in Average Oxycodone Equivalent Daily Dose (mg/day) by Laxatives Use: HYD3003 Safety Population.

Study Period Statistics	Overall HYD Non-laxative Users (N=726)	Overall HYD Laxative Users (N=196)
Incoming to the study		
n	724	195
Mean (SD)	20.15 (26.682)	18.91 (24.895)
Median	9.82	9.00
Min, Max	0.0, 120.0	0.0, 120.0
End of Titration Period		
n	724	195
Mean (SD)	4.20 (12.510)	3.12 (10.815)
Median	0.00	0.00
Min, Max	0.0, 90.0	0.0, 72.5
Overall Maintenance Average		
n	550	177
Mean (SD)	3.42 (9.833)	2.20 (8.279)
Median	0.00	0.00
Min, Max	0.0, 80.0	0.0, 72.5

The sponsor also discussed the extent of laxative use in clinical trial HYD3002 and the impact on rescue medication used. The laxatives are classified as strong, or mild laxatives based on Goodman and Gilman's textbook of pharmacological basis of therapeutics.

Subjects identified as "laxative users" were further classified into those using "strong" laxative and those using "mild" laxatives, and the analysis of rescue use in studies HYD3002 and HYD3003 was repeated using this classification. The analyses are presented in the tables below. Rescue use was not different among users of strong laxatives and mild laxatives. These data do not suggest reduced exposure to hydrocodone (from Hysingla ER) with concurrent use of laxatives.

Summary of Mean Daily Number of Immediate-release 5 mg Oxycodone HCI Tablets Used by Laxative Classification during the Run-in Period: HYD3002 Safety Population – Laxative Users.

Summary of Mean Daily Number of Immediate-release oxycodone HCI Tablets Used During the Double-blind Period by Treatment Group in HYD3002 Full Analysis

Population	Placebo* (N=292)				HYD (N=296)			
Mean daily number of tablets for all subjects	Laxative User (N=35)	Strong Laxative User (N=24)	Mild Laxative User (N=11)	Non-laxative User (N=257)	Laxative User (N=34)	Strong Laxative User (N=20)	Mild Laxative User (n=14)	Non-laxative User (N=262)
Week 1								
Mean (SD)	1.00 (1.153)	0.86 (0.961)	1.30 (1.500)	0.63 (1.036)	0.76 (0.919)	0.65 (0.880)	0.92 (0.983)	0.56 (1.036)
Median	0.71	0.64	1.00	0.14	0.43	0.21	0.43	0.00
Min, Max	0.0, 4.7	0.0, 4.0	0.0, 4.7	0.0, 6.0	0.0, 3.1	0.0, 3.1	0.0, 3.0	0.0, 5.6
95% CI for Mean	(0.62, 1.38)	(0.48, 1.25)	(0.41, 2.19)	(0.50, 0.76)	(0.45, 1.07)	(0.26, 1.04)	(0.40, 1.43)	(0.43, 0.68)
Week 2								
Mean (SD)	1.23 (1.627)	0.98 (1.338)	1.78 (2.096)	0.83 (1.218)	0.92 (1.124)	0.76 (1.105)	1.14 (1.154)	0.57 (1.050)
Median	0.57	0.43	0.71	0.14	0.36	0.07	0.50	0.00
Min, Max	0.0, 6.1	0.0, 5.4	0.0, 6.1	0.0, 6.6	0.0, 3.1	0.0, 3.1	0.0, 3.1	0.0, 5.7
95% CI for Mean	(0.69, 1.77)	(0.44, 1.51)	(0.54, 3.02)	(0.68, 0.98)	(0.54, 1.30)	(0.28, 1.25)	(0.54, 1.75)	(0.45, 0.70)
Weeks 3-12								
Mean (SD)	0.99 (1.405)	0.96 (1.351)	1.05 (1.583)	0.72 (1.092)	0.70 (0.951)	0.63 (0.907)	0.80 (1.037)	0.56 (1.040)
Median	0.36	0.31	0.36	0.13	0.24	0.16	0.35	0.06
Min, Max	0.0, 5.3	0.0, 5.0	0.0, 5.3	0.0, 5.7	0.0, 3.3	0.0, 3.3	0.0, 3.2	0.0, 5.7
95% CI for Mean	(0.52, 1.45)	(0.42, 1.50)	(0.12, 1.99)	(0.58, 0.85)	(0.38, 1.02)	(0.23, 1.03)	(0.26, 1.35)	(0.43, 0.69)
Overall (Weeks 1-12)								
Mean (SD)	1.36 (1.412)	1.27 (1.264)	1.55 (1.745)	0.84 (1.179)	0.78 (0.919)	0.65 (0.893)	0.98 (0.954)	0.66 (1.124)
Median	1.00	0.90	1.10	0.25	0.34	0.17	0.76	0.10
Min, Max	0.0, 5.4	0.0, 4.7	0.0, 5.4	0.0, 5.8	0.0, 3.3	0.0, 3.3	0.0, 2.8	0.0, 5.6
95% CI for Mean	(0.89, 1.82)	(0.76, 1.77)	(0.52, 2.58)	(0.70, 0.99)	(0.47, 1.09)	(0.25, 1.04)	(0.48, 1.48)	(0.52, 0.79)

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/s/

SRIKANTH C NALLANI
07/31/2014

YUN XU
07/31/2014

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

Office of Clinical Pharmacology

New Drug Application Filing and Review Form

General Information About the Submission

	Information		Information
NDA/BLA Number	**206627**	**Brand Name**	**Hysingla ER or (b) (4) ER**
OCP Division (I, II, III, IV, V)	**OCP Division 2**	**Generic Name**	**Hydrocodone Extended Release Tablets**
Medical Division	**DAAAP**	**Drug Class**	**Opioid**
OCP Reviewer	**Srikanth C. Nallani, Ph.D.**	**Indication(s)**	**Chronic Pain**
OCP Team Leader	**Yun, Xu, Ph.D.**	**Dosage Form**	**Tablet**
Pharmacometrics Reviewer	**-**	**Dosing Regimen**	**Once Daily**
Date of Submission	**4/26/2014**	**Route of Administration**	**Oral**
Estimated Due Date of OCP Review	**7/28/2014**	**Sponsor**	**Purdue Pharma LP**
Medical Division Due Date	**08/11/2014**	**Priority Classification**	**Priority**
PDUFA Due Date	**10/28/2014**		

Clin. Pharm. and Biopharm. Information

	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	**X**			
Tabular Listing of All Human Studies	**X**			
HPK Summary	**X**			
Labeling	**X**			
Reference Bioanalytical and Analytical Methods	**X**			
I. Clinical Pharmacology				
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:	**X**	**1**		
multiple dose:	**X**	**2**		
Patients-				
single dose:				
multiple dose:				
Dose proportionality -				
fasting / non-fasting single dose:	**X**	**1**		
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				
In-vivo effects on primary drug:	**X**	**2**		
In-vivo effects of primary drug:				
In-vitro:				
Subpopulation studies -				
ethnicity:				
gender:	**X**	**1**		

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS
FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

pediatrics:				
geriatrics:	**X**	**1**		
renal impairment:	**X**	**1**		
hepatic impairment:	**X**	**1**		
PD -				
Phase 2:				
Phase 3:				
PK/PD -				
Phase 1 and/or 2, proof of concept:	**X**	**2**		**One Oral Drug Liking Study Intranasal Drug Liking Study**
Phase 3 clinical trial:				
Population Analyses -				
Data rich:		**1**		
Data sparse:				
II. Biopharmaceutics				
Absolute bioavailability				
Relative bioavailability -				
solution as reference:				
alternate formulation as reference:	**X**	**1**		**Vicoprofen was used a listed drug for relative BA study**
Bioequivalence studies -				
traditional design; single / multi dose:				
replicate design; single / multi dose:				
Food-drug interaction studies	**X**	**1**		
Bio-waiver request based on BCS				
BCS class				
Dissolution study to evaluate alcohol induced dose-dumping				
III. Other CPB Studies				
Genotype/phenotype studies				
Chronopharmacokinetics				
Pediatric development plan	**X**	**1**		
Literature References				
Total Number of Studies		**13**		

On **initial** review of the NDA/BLA application for filing:

	Content Parameter	Yes	No	N/A	Comment
Criteria for Refusal to File (RTF)					
1	Has the applicant submitted bioequivalence data comparing to-be-marketed product(s) and those used in the pivotal clinical trials?			X	
2	Has the applicant provided metabolism and drug-drug interaction information?	X			
3	Has the sponsor submitted bioavailability data satisfying the CFR requirements?	X			
4	Did the sponsor submit data to allow the evaluation of the validity of the analytical assay?	X			
5	Has a rationale for dose selection been submitted?	X			
6	Is the clinical pharmacology and biopharmaceutics section of the NDA organized, indexed and paginated in a manner to allow substantive review to begin?	X			
7	Is the clinical pharmacology and biopharmaceutics section of the NDA legible so that a substantive review can begin?	X			
8	Is the electronic submission searchable, does it have appropriate	X			

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

	hyperlinks and do the hyperlinks work?				
Criteria for Assessing Quality of an NDA (Preliminary Assessment of Quality)					
	Data				
9	Are the data sets, as requested during pre-submission discussions, submitted in the appropriate format (e.g., CDISC)?	X			
10	If applicable, are the pharmacogenomic data sets submitted in the appropriate format?			X	
	Studies and Analyses				
11	Is the appropriate pharmacokinetic information submitted?	X			
12	Has the applicant made an appropriate attempt to determine reasonable dose individualization strategies for this product (i.e., appropriately designed and analyzed dose-ranging or pivotal studies)?	X			
13	Are the appropriate exposure-response (for desired and undesired effects) analyses conducted and submitted as described in the Exposure-Response guidance?			X	
14	Is there an adequate attempt by the applicant to use exposure-response relationships in order to assess the need for dose adjustments for intrinsic/extrinsic factors that might affect the pharmacokinetic or pharmacodynamics?			X	
15	Are the pediatric exclusivity studies adequately designed to demonstrate effectiveness, if the drug is indeed effective?			X	
16	Did the applicant submit all the pediatric exclusivity data, as described in the WR?			X	
17	Is there adequate information on the pharmacokinetics and exposure-response in the clinical pharmacology section of the label?	X			
	General				
18	Are the clinical pharmacology and biopharmaceutics studies of appropriate design and breadth of investigation to meet basic requirements for approvability of this product?	X			
19	Was the translation (of study reports or other study information) from another language needed and provided in this submission?			X	

IS THE CLINICAL PHARMACOLOGY SECTION OF THE APPLICATION FILEABLE?
__YES_____

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.
None Identified

Purdue Pharma LP submitted NDA 206627 for marketing Hysingla ER or (b) (4) ER (hydrocodone extended release tablet) for the management of pain severe enough to require daily around the clock use. This is another single entity hydrocodone product under Agency's consideration after the recently approved Zohydro. The sponsor developed this extended-release long acting opioid product with some abuse deterrence characteristics. Several *in vitro* and *in vivo* studies were conducted to demonstrate the abuse deterrence characteristics.

The sponsor conducted two clinical trials HYD3002 and HYD3003 to demonstrate efficacy of Hysingla ER in patients with chronic pain (low back pain and nonmalignant pain). The clinical pharmacology program was designed to bridge the proposed product's safety information from previously approved

immediate release hydrocodone product, Vicoprofen (NDA 020716) with a relative bioavailability study. In addition, the sponsor conducted food-effect (HYD1003), multiple-dose (HYD1002), dose-proportionality studies (HYD1004). The sponsor conducted dedicated PK studies to address the need for dose-adjustment in special populations (age, gender), drug interactions (paroxetine, ketoconazole), renal impairment, and hepatic impairment. The sponsor conducted a TQT study to evaluate the potential for hydrocodone to cause QT-prolongation.

As mentioned before, several *in vitro* studies were conducted to evaluate the abuse deterrence characteristics of this ERLA product. The sponsor conducted two drug liking studies evaluating the potential for abuse of Hysingla ER by oral route (HYD1013) and intranasal route (HYD1014).

The sponsor conducted *in vitro* alcohol interaction study and on the basis of results suggesting that no dose dumping was observed an *in vivo* alcohol interaction study was not conducted.

See attached tabular list of all clinical studies and their design overview.

Srikanth C. Nallani, Ph.D.

Reviewing Clinical Pharmacologist Date

Yun Xu, Ph.D.

Team Leader/Supervisor Date

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

Attachment: Tabular List of All Clinical Studies

Table 1. Listing of Clinical Studies

Type of study	Study identifier	Location of study report	Objective(s) of the study	Study design and type of control/ concomitant analgesia	Test product(s)/ dosage regimen/ route of administration	Number of subjects (randomized/ dosed/ completed)	Healthy subjects or diagnosis of patients	Duration of treatment	Study status/ type of report
BA	HYD1003	5.3.1.1	Assess food effect (fasted, high-fat and low-fat meals)	OL, R, SD, 3-period XO, PK in fed and fasted state/ naltrexone blockade	HYD 120 mg/ SD/ PO	54/54/50	Healthy subjects	3 doses	Complete/ full
BA	HYD1016	5.3.1.2	Relative BA of HYD *v* Vicoprofen at steady state	OL, R, MD, 2-period XO, PK, BA comparison/ naltrexone blockade	HYD 30 mg/ MD, qd/ PO Vicoprofen 7.5 mg + 200 mg/ MD, q6h/ PO	24/24/22	Healthy subjects	3 days 3 days	Complete/ full
PK	HYD1002	5.3.3.1	Characterize HYD steady-state PK	OL, MD, PK/ naltrexone blockade	HYD 120 mg/ MD, qd/ PO	27/27/25	Healthy subjects	5 days	Complete/ full
PK	HYD1004	5.3.3.1	Assess dose proportionality of HYD tablets, in various strengths	OL, R, SD, 4-period XO, PK, incomplete block/ naltrexone blockade	HYD 20, 40, 60, 80, 120 mg/ SD/ PO	40/40/31	Healthy subjects	4 doses	Complete/ full
PK	HYD1006	5.3.3.3	Assess the effects of age and sex on the PK of hydrocodone, administered as HYD tablets	OL, SD, PG, PK/ naltrexone blockade	HYD 40 mg/ SD/ PO	50/50/49	Healthy subjects	1 dose	Complete/ full
PK	HYD1007	5.3.3.3	Assess the effects of hepatic impairment on the PK of hydrocodone, administered as HYD tablets	OL, SD, PG, PK/ none	HYD 20 mg/ SD/ PO	32/32/32	Healthy subjects and hepatically impaired (mild, moderate, and severe) subjects	1 dose	Complete/ full
PK	HYD1008	5.3.3.3	Assess the effects of renal impairment on the PK of hydrocodone, administered as HYD tablets	OL, SD, PG, PK/ naltrexone blockade	HYD 60 mg/ SD/ PO	41/41/41	Healthy, renally impaired (mild, moderate, severe), and ESRD subjects	2 doses (subjects on dialysis) 1 dose (all other subjects)	Complete/ full
PK	HYD1005	5.3.3.4	Assess the effects of paroxetine (a CYP2D6 inhibitor) co-administration with HYD on the PK of hydrocodone, norhydrocodone, and hydromorphone	DB, R, SD, 2-period XO, PK/ none	HYD 20 mg/ SD/ PO and paroxetine 20 mg/ MD, qd/ PO HYD 20 mg/ SD/ PO and placebo/ MD, qd/ PO	24/24/23	Healthy subjects	2 doses (HYD)/ 12 days each of paroxetine or placebo	Complete/ full
PK	HYD1012	5.3.3.4	Assess the effects of of ketoconazole (a CYP3A4 inhibitor) co-administration with HYD on the PK of hydrocodone, norhydrocodone, and hydromorphone	DB, R, SD, 2-period XO, drug-drug effect of ketoconazole on HYD PK/ none	HYD 20 mg/ SD/ PO and ketoconazole 200 mg/ MD, q12h/ PO HYD 20 mg/ SD/ PO and placebo/ MD, q12h/ PO	30/30/28	Healthy subjects	2 doses (HYD)/ 6 days each of ketoconazole or placebo	Complete/ full

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

Type of study	Study identifier	Location of study report	Objective(s) of the study	Study design and type of control/ concomitant analgesia	Test product(s)/ dosage regimen/ route of administration	Number of subjects (randomized/ dosed/ completed)	Healthy subjects or diagnosis of patients	Duration of treatment	Study status/ type of report
PK/PD	HYD1009	5.3.5.1	Evaluate the effect of multiple doses (once daily for 3 days each of HYD 80, 120, and 160 mg tablets) on the QT/QTc interval	DB, R, PC, AC, MD, PG, PK/ none	HYD Group HYD 20, 40, 80, 120, and 160 mg/ MD, qd/ PO and moxifloxacin placebo/ SD on days 9, 12, and 15/ PO	80/80/73	Healthy subjects	21 days (HYD)/ 3 doses (moxifloxacin placebo)	Complete/ full
					Moxifloxacin Group HYD placebo/ MD, qd/ PO and moxifloxacin 400 mg/ SD on days 9, 12, and 15/ PO	64/64/62		21 days (HYD placebo)/ 3 doses (moxifloxacin)	
					HYD placebo Group HYD placebo/ MD, qd/ PO and moxifloxacin placebo/ SD on days 9, 12, and 15/ PO	64/64/61		21 days (HYD placebo)/ 3 doses (moxifloxacin placebo)	
Efficacy	HYD3002	5.3.5.1	Evaluate analgesic efficacy and safety of HYD 20-120 mg compared with placebo	OL RI (HYD 20-120 mg daily titrated to effect), R, DB, PC, PG/ OxyIR (supplemental analgesia) during OL RI and DB	HYD 20-120 mg/ MD, qd/ PO Placebo/ MD, qd/ PO	296/296/229 292/292/210	Chronic low back pain	≤ 45 days (RI); 84 days (DB)	Complete/ full
Efficacy	HYD3003	5.3.5.2	Characterize long-term safety and analgesic effectiveness of HYD 20-120 mg	OL titration (HYD 20-120 mg daily titrated to effect), 12-month OL MT period, OTP/ stable nonopioid or short-acting opioid (supplemental analgesia) during titration and 12-month OL MT period	HYD 20-120 mg/ MD, qd/ PO	922 (treated)/ 728 (MT)/ 410	Chronic nonmalignant and non-neuropathic pain	≤ 45 days (DT); 364 days (MT); ≤ 14 days (OTP)	Complete/ full

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

Type of study	Study identifier	Location of study report	Objective(s) of the study	Study design and type of control/ concomitant analgesia	Test product(s)/ dosage regimen/ route of administration	Number of subjects (randomized/ dosed/ completed)	Healthy subjects or diagnosis of patients	Duration of treatment	Study status/ type of report
PK/PD	HYD1013	5.3.5.4	Evaluate oral abuse potential, PD, PK, and safety of intact HYD tablets, milled HYD, and chewed HYD compared with hydrocodone API oral solution and placebo	DB, R, PC, 5-period XO, PD, PK, safety/ none	HYD 60 mg/ SD/ PO HYD 60 mg milled/ SD/ PO HYD 60 mg chewed/ SD/ PO Hydrocodone API oral solution 60 mg/ SD/ PO Placebo/ SD/ PO	40/40/35	Healthy subjects nondependent recreational drug users with moderate experience with opioids	1 dose 1 dose 1 dose 1 dose 1 dose	Complete/ full
PK/PD	HYD1014	5.3.5.4	Evaluate intranasal abuse potential PD, PK, and safety profile of intranasally administered HYD (fine and coarse powder) compared with hydrocodone API and placebo	DB, R, PC, 4-period XO, PD, PK, safety/ none	HYD 60 mg fine particle size/ SD/ IN HYD 60 mg coarse particle size/ SD/ IN Hydrocodone API 60 mg/ SD/ IN Placebo/ SD/ IN	32/31/25	Healthy subjects recreational opioid users with a history of intranasal abuse	1 dose 1 dose 1 dose 1 dose	Complete/ full

AC=active control; API=active pharmaceutical ingredient; BA=bioavailability; CYP=cytochrome P450; DB=double-blind; DT=dose titration; ESRD=end-stage renal disease; I=interview; IN=intranasal; IR=immediate-release; MD=multiple dose; mg=milligrams; MT=maintenance treatment; NA=Not applicable; NI=nonintervention; OL=open-label; OTP=optional taper period; Oxy=oxycodone; PC=placebo-controlled; PD=pharmacodynamic; PG=parallel group; PK=pharmacokinetics; PO=by mouth; qd=once daily; q6h=every 6 hours; q12h=every 12 hours; QTc=corrected QT interval; R=randomized; RI=run-in; SD=single dose; XO=crossover.

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/s/

SRIKANTH C NALLANI
06/03/2014

YUN XU
06/03/2014

BIOPHARMACEUTICS FILING REVIEW Office of New Drugs Quality Assessment			
Application No.:	NDA 206627	**Reviewer:** Akm Khairuzzaman, Ph.D.	
Submission Date:	04/26/2014		
Division:	Division of Anesthesia, Analgesia, and Addiction Products	**Team Leader:** Tapash Ghosh, PhD	
Sponsor:	Purdue Pharma LP One Stamford Forum, 201 Tresser Blvd, Stamford, CT 06901-3431		
Trade Name:	Not proposed	**Date Assigned:**	05/01/2014
Generic Name:	Extended-release 24-hour hydrocodone bitartrate tablets	**Date of Review:**	05/07/2014
Indication:	Pain management	**Type of Submission:** Original NDA 505(b)2	
Formulation/strengths	Tablets: 20, 30, 40, 60, 80, 100, and 120 mg		
Route of Administration	Oral		

SUBMISSION: This NDA is submitted under the Section 505(b)(2) of the Food, Drug and Cosmetic Act for extended-release hydrocodone bitartrate q24h film coated (HYD) tablets. The drug, hydrocodone is a semisynthetic opoid (Scheduled II narcotic) derived from either of two naturally occurring opiates: codine and thebine. It is well known in the pain management treatment for a long period of time and was actually first approved by the agency on March 23rd, 1943 with a brand name of Hycodan (NDA # 005213)[1]. The NDA was submitted using the electronic common technical (eCTD) format. The reference listed drug product used under this NDA is Vicoprofen Tablet (7.5 mg/200 mg), NDA 20-716 which is a fixed dose combination product of hydrocodone and ibuprofen, respectively. Another product, Zohydro ER (also a sustained release formulation but it is in capsule dosage form, NDA- 202880, 10 mg, 15 mg, 20 mg, 40 mg and 50 mg) was also recently approved (10/25/2013) by the agency. It is to be noted that although this drug is in the market for long, but they exist as a combination drug product with another drug in the formulation.

BRIEF DESCRYPTION OF THE FORMULAITON:

The drug product developed by this applicant utilized a polyethylene oxide (PEO)-based formulation platform which is the (b) (4) excipient in the product ((b) (4) that functions as release rate-control, abuse-deterrence and resistance to alcohol-induced dose dumping. This formulation is compositionally similar to reformulated OxyContin® Tablets (approved by FDA in 2010). The final weight of the tablet is 735 mg across all the strength where (b) (4) The drug product is manufactured by utilizing a unique technique which is known as (b) (4) ". Basically (b) (4)

[1] Drugs@FDA—Approval History: Hycodan. FDA. Retrieved 2006-01-07.

(b) (4)

BIOPHARMACEUTIC INFORMATION: In support of approval, this NDA includes the following biopharmaceutics data for review and evaluation:

- Proposed dissolution method (Method # TM-0053) and acceptance criteria, with justification
- Dissolution method development report
- Dissolution method (Method # TM-0053) validation report
- Dissolution data of all clinical and registration stability batches
- Drug release kinetics study using linear regression analysis with JMP software (equation used $M_t/M_\infty = kt^n$)
- Drug product stability data (dissolution), including multi-point sampling data.
- In vitro alcohol dose dumping potential study
- Dissolution of physically manipulated tablets in simulated gastric fluid and ethanol for the assessment of *In Vitro* abuse deterrence
- PK data to support extended release claim
- Biowaiver for the additional two strengths: 30 mg and 100 mg tablets
- Selection of formulation at product development stage based on relative bioavailability study (HYD1001)
- Study HYD1016 evaluating the relative bioavailability of HYD to the reference drug, Vicoprofen. (to be reviewed by OCP)

A check list of all biopharmaceutics related information is provided in the appendix A.

RECOMMENDATION: From a biopharmaceutics perspective, the NDA is considered fileable. There is sufficient biopharmaceutics data to permit a substantive review. Information request letter requesting additional dissolution information will follow.

74 DA

(b) (4)

1.

2.

3.

4. In your submitted dissolution method development report, we could not locate information for the method's discriminating capability that can distinguish a "bad batch". You either provide exact location in the application where this information can be found or provide such study report that demonstrates the method's capability to detect any faulty batch as a result for extreme variation in either material attributes (such as (b) (4) [redacted] or manufacturing process deviation or combination of both.

Akm Khairuzzaman, Ph.D.
Biopharmaceutics Reviewer, ONDQA

Tapash Ghosh, Ph.D.
Biopharmaceutics Team Lead, ONDQA

ONDQA-BIOPHARMACEUTICS **A. INITIAL** OVERVIEW OF THE NDA APPLICATION FOR FILING				
	PARAMETER	**YES**	**NO**	**COMMENT**
1.	Does the application contain dissolution data?	X		
2.	Is the dissolution test part of the DP specifications?	X		
3.	Does the application contain the dissolution method development report?	X		
4.	Is there a validation package for the analytical method and dissolution methodology?	X		
5.	Does the application include a biowaiver request?	X		For 30 mg and 100 mg tablets
6.	Does the application include an IVIVC model?		X	
7.	Is information such as BCS classification mentioned, and supportive data provided?		X	
8.	Is information on mixing the product with foods or liquids included?		X	
9.	Is there any in *vivo* BA or BE information in the submission?	X		Study HYD1016 evaluating the relative bioavailability of HYD to the reference drug, Vicoprofen. Selection of formulation at product development stage based on relative bioavailability study (HYD1001). Dose proportionality PK studies were also conducted. These studies will be reviewed by OCP.
10.	Is there a modified-release claim? If yes, address the following: a.) Is there information submitted to support the claim in accordance with 320.25(f)? b.) Is there information on the potential for alcohol-induced dose dumping?	X X		
B. FILING CONCLUSION				
	Parameter	**Yes**	**No**	**Comment**
11.	**IS THE BIOPHARMACEUTICS SECTIONS OF THE APPLICATION FILEABLE?**	X		

ONDQA-BIOPHARMACEUTICS **A. INITIAL** OVERVIEW OF THE NDA APPLICATION FOR FILING				
	PARAMETER	**YES**	**NO**	**COMMENT**
12.	If the NDA is not fileable from the product quality-biopharmaceutics perspective, state the reasons and provide **filing** comments to be sent to the Applicant.			Not applicable.
13.	Are there any **potential review** issues to be forwarded to the Applicant for the 74-day letter?	X		Please convey the Applicant in the 74-Day letter the comments listed in pages 2 of this filing review.

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/s/

AKM KHAIRUZZAMAN

05/07/2014

Fileable from the product quality-biopharmaceutics perspective. 74 day letter comments need to be sent out.

TAPASH K GHOSH

05/07/2014