CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

207975Orig1s000

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

CLINICAL PHARMACOLOGY REVIEW ADDENDUM

NDA: 207975SDN1,4,5,21	Submission Date(s): 12/23/14, 2/6, 2/10, 7/21/2015
Brand Name	Vantrela ER Tablets
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	Teva Branded Pharmaceuticals Products
Submission Type; Code	Original NDA 505(b)(1)
Formulation; Strength(s)	Tablet; 15, 30, 45, 60, and 90 mg
Indication	Management of pain severe enough to require daily, around-the-clock, long-term opioid treatment.
Proposed Dosage Regimen	Titrate to effect with a twice daily administration.

This is an addendum to the clinical pharmacology review on 9/17/2015. Originally submitted as 505(b)(2) application, TEVA decided to change the application to a 505(b)(1) application during the NDA review cycle. Hydrocodone is a well-known drug substance with extensive previous findings on its safety and effectiveness, and it has been approved under multiple NDAs. However, as a 505 (b)(1) application, the Sponsor cannot rely on the Agency's previous findings on safety and effectiveness; they can only use their own data to support this NDA. The submitted NDA does not provide independent data to address safety issues such as 1) drug interactions between CYP3A4 inhibitors and Vantrela ER tablets, and 2) systemic exposure in patients with mild and severe hepatic impairment, and 3) Risk of QT-prolongation potential of hydrocodone. Hence, to support a 505(b)1 application, the following Post-marketing requirements (PMRs) pertaining to FDAAA required safety study/clinical trial should be required from Teva Branded Pharmaceutical Products:

a) A clinical study evaluating pharmacokinetic drug interaction between CYP3A4 strong inhibitor and Vantrela ER tablets.

b) A clinical study evaluating pharmacokinetics of Vantrela ER tablets in patients with mild and severe hepatic impairment.

c) A Thorough-QT (TQT) study evaluating the QT-prolongation potential of Vantrela ER tablets.

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/s/

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09/23/2015

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CLINICAL PHARMACOLOGY REVIEW

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1 Executive Summary

1.1 Recommendation

Originally submitted as 505(b)(2) application, the Sponsor decided to change it to a 505(b)(1) application during the review cycle. Due to its complicated regulatory background, the decision on this NDA is still pending; it is likely that post-marketing requirements (PMR) will be recommended. An addendum will be documented in Darrts.

1.2 Phase IV Commitments

The need for specific PMR's will be decided soon and an addendum to this review will be submitted.

1.3 Summary of Clinical Pharmacology Findings

Teva Branded Pharmaceutical Products submitted NDA 207975 for the use of Vantrela ER tablet or hydrocodone bitartrate extended-release (CEP-33237), abuse deterrent, oral tablets in 15, 30, 45, 60, and 90 mg strengths. The proposed indication is for the management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate. This is a conversion to a 505(b)(1) application which was originally a 505(b)(2) NDA submission (See General Attributes section 2.1). The Sponsor originally planned to submit this NDA under a 505(b)(2) pathway using Vicoprofen as the listed drug. However, during the NDA review stage, the Sponsor obtained right of reference to use data in the NDA package of Vicoprofen. Therefore, the clinical pharmacology findings in the Vicoprofen label can be used to support this NDA, if appropriate.

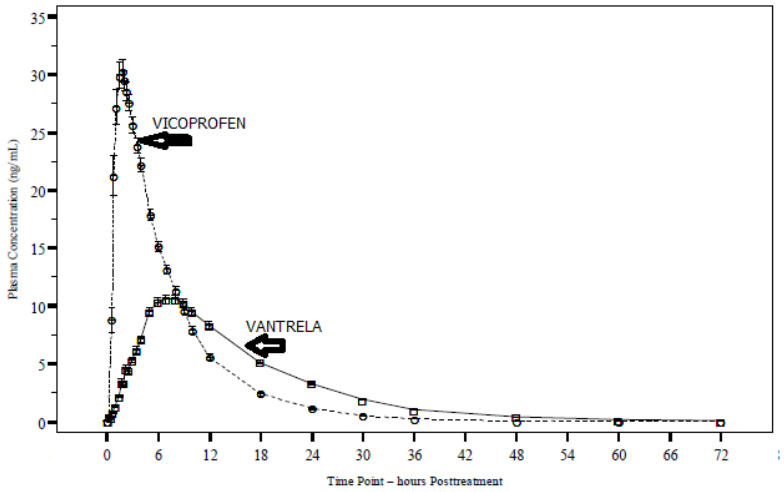
Hydrocodone bitartrate is a semi-synthetic opioid that is available in combination with acetaminiophen (Vicodin or other generics) or ibuprofen (Vicoprofen) and as a single entity opioid ER product (Zohydro). It is a Schedule II controlled substance with known potential for abuse and diversion. Teva developed this single entity extended release tablet, Vantrela ER, using a proprietary abuse deterrent technology that is intended to control misuse and abuse if the formulation is manipulated or misused.

To support the safety and efficacy of their product, the sponsor submitted Clinical Pharmacology Studies includes data on the pharmacokinetics and pharmacodynamics (PD)s of hydrocodone from 19 studies of hydrocodone ER. The majority (16) of these studies were conducted in healthy subjects who also received naltrexone hydrochloride (hereafter referred to as naltrexone) to block opioid receptors and minimize opioid-related adverse events. The sponsor conducted two well controlled clinical trials to support the safety and efficacy of Vantrela ER tablet (Study 3079 and Study 3103).

The pharmacokinetics of hydrocodone and its metabolite hydromorphone have been well characterized in healthy subjects following administration of single doses of Vantrela ER tablet (hydrocodone ER tablet) in the dose range of 15 to 90 mg and multiple doses of 45 and 90 mg of hydrocodone ER administered every 12 hours for 5.5 days. Following oral administration of intact product, a steady rise in systemic exposure is noted with the extended release product compared to immediate release product which shows a relatively rapid appearance of peak plasma concentrations. Median peak plasma

concentrations are noted after 8.5 hours after single dose administration. Since the Sponsor originally planned to submitted the NDA uncder a 505(b)(2) pathway using Vicoprofen as the listed drug, a relative BA study with Vicoprofen was conducted. While the overall exposure of hydrocodone (AUC) was similar between Vantrela ER tablet 15 mg and Vicoprofen (two tablets of 7.5 mg hydrocodone/200 mg Ibuprofen), peak plasma levels with Vantrela ER tablet 15 mg were 1/3 that noted with IR Vicoprofen (Study 1079).

Figure: **Mean (±SE) Plasma Concentration versus Time Profiles for Hydrocodone Over 72 Hours Following Administration of a Single Dose of Hydrocodone ER (Dose Normalized to 15 mg) and a Single 15 mg Dose of Hydrocodone within VICOPROFEN in Healthy Subjects (Pharmacokinetic Analysis Set, Bioavailability Subset)**



SOURCE: Pharmacokinetic Analysis Set, Bioavailability Subset, Figure 3.1, Summary 10.1

The systemic exposure of hydrocodone increased dose-proportionally over the range of 15 through 90 mg doses of Vantrela ER tablet (Study 1082). The absolute bioavailability of orally administered hydrocodone is unknown.

Figure: **Mean (Standard Error) Plasma Concentration by Time Profiles for Hydrocodone in Healthy Subjects Administered a Single 15-, 30-, 45-, 60-, or 90-mg Dose of the Hydrocodone Bitartrate Extended-Release Tablet**

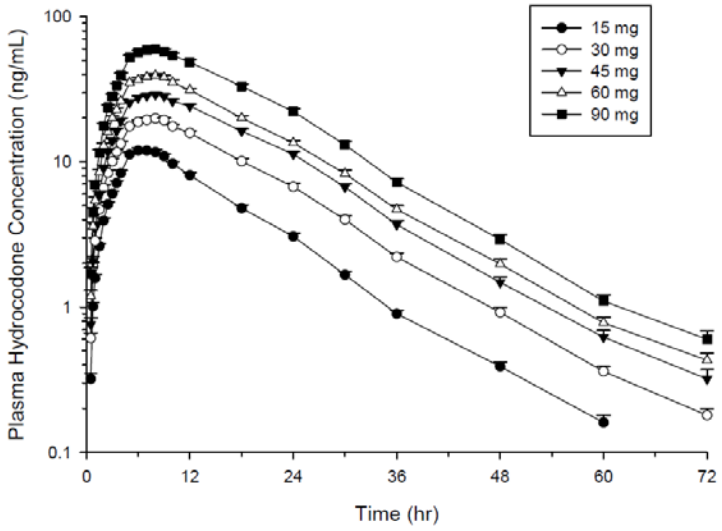


Table: Mean (Standard Deviation) Pharmacokinetic Parameters for Hydrocodone Following Oral Administration of Vantrela ER tablet (Study 1082).

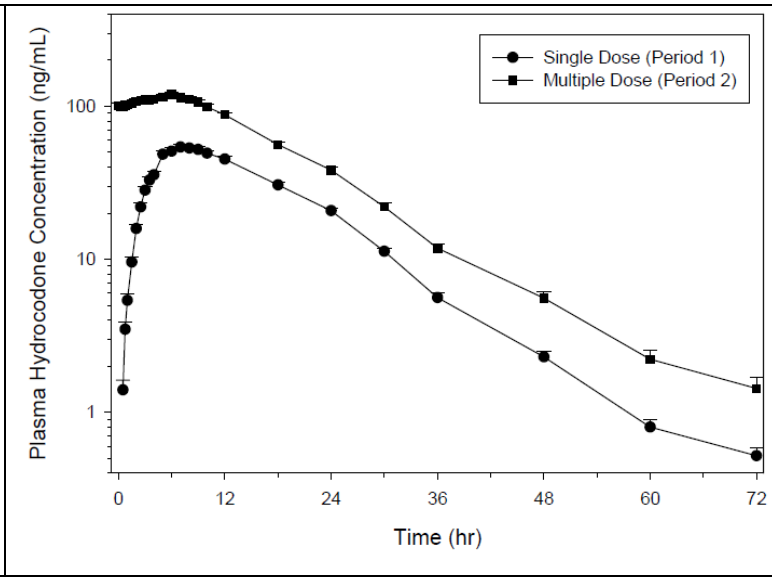
Variable	A 15 mg (N=60)	B 30 mg (N=60)	C 45 mg (N=60)	D 60 mg (N=60)	E 90 mg (N=60)
C_{max} (ng/mL)	12.6 (3.50)	20.7 (5.47)	30.3 (7.48)	41.2 (10.11)	62.5 (16.19)
$AUC_{0-\infty}$ (ng·h/mL)	198.8 (60.37)	381.6 (117.78)	592.3 (167.20)	765.7 (193.98)	1189.0 (341.31)
AUC_{0-t} (ng·h/mL)	195.8 (60.09)	377.6 (116.47)	585.8 (163.68)	757.2 (190.82)	1178.8 (335.97)
AUC_{0-72} (ng·h/mL)	196.7 (59.98)	378.1 (116.31)	586.0 (163.48)	757.3 (190.66)	1178.8 (335.94)
AUC_{0-12} (ng·h/mL)	99.9 (27.40)	169.5 (45.31)	247.1 (62.94)	334.2 (78.09)	505.6 (129.73)
t_{max} (h)	7.0 (5.0, 9.0)	8.0 (5.0, 12.0)	8.0 (5.0, 12.1)	8.0 (5.0, 12.0)	8.0 (5.0, 12.0)
$t_{1/2}$ (h)	10.4 (4.05)	10.6 (4.06)	10.2 (3.64)	10.8 (4.13)	10.0 (2.94)
Percentage extrapolation (%)	1.4 (0.85)	1.0 (0.72)	1.0 (1.19)	1.1 (1.06)	0.8 (0.83)
λ_z (1/h)	0.08 (0.027)	0.07 (0.024)	0.08 (0.025)	0.07 (0.025)	0.08 (0.020)
V/F	1233.9 (588.91)	1323.4 (797.07)	1206.3 (543.84)	1289.5 (575.27)	1196.2 (584.14)
CL/F	83.4 (29.14)	85.7 (25.31)	81.6 (21.54)	83.0 (19.66)	82.2 (24.93)

SOURCE: Adhoc Summary 15.9.1, Listing 16.2.8.23.
NOTE: Median (range) is presented for t_{max}

With regard to food-effect, overall exposure (both AUC_{0-t} and $AUC_{0-\infty}$) including specific emphasis on first 8 hours (AUC0-8, median t_{max} in the fasted state) met the bioequivalence criteria within the range of (0.800, 1.250), mean C_{max} was approximately 34% to 45% higher (Studies 1076, 1090, and 10024) following administration of a single 90-mg dose of hydrocodone ER with a high-fat meal as compared to when administered in a fasted state (See General Biopharmaceutics section 2.6).

Unlike single dose administration, peak plasma concentrations are noted earlier (Median Tmax ~4.5 hours) with repeated administration. Following twice-daily administration of 90-mg doses (Study 1091) of the Vantrela ER tablet, accumulation of hydrocodone in plasma was observed. The steady-state plasma concentrations are 3-fold higher than that observed with single dose or mean observed accumulation ratio (R_{obs}) was 2.8. Similar observation of accumulation was also made after multiple dose administration of 45 mg Vantrela ER tablet (Study 1081).

Figure: Mean (SE) Plasma Profiles of Hydrocodone in Healthy Subjects Administered Single and Twice daily 90 mg Doses of Vantrela ER Tablet.



Source: Figure 2, Study C33237/1091 study report.

Hydrocodone appears to be well distributed beyond the vascular system with a V_z/F of approximately 1300 to 1400 L following administration of the hydrocodone ER tablet (integrated single and multiple-dose PK analysis set Study 1081 and 1091). The extent of protein binding of hydrocodone in human plasma has not been determined.

As described in Vicoprofen product label, hydrocodone exhibits a complex pattern of metabolism, including O-demethylation, N-demethylation, and 6-keto reduction to the corresponding 6-α-an d 6-β-hydroxymetabolites. Hydromorphone, a potent opioid, is formed from the O-demethylation of hydrocodone and contributes to the total analgesic effect of hydrocodone. The O-and N-demethylation processes are mediated by separate P-450 isoenzymes: CYP2D6 and CYP3A4, respectively.

Given the partial involvement of CYP2D6 in the metabolism of hydrocodone, the impact of metabolism status (eg, poor or extensive CYP2D6 metabolism) on systemic exposure to hydrocodone and hydromorphone following administration of hydrocodone ER was assessed using the pooled clinical pharmacology database. The results of the subgroup analyses suggest that the mean hydrocodone exposure (as assessed by C_{max} and $AUC_{0-\infty}$) is slightly higher in CYP2D6 poor metabolizers as compared to the rest of the population. A corresponding decrease in exposure (as assessed by C_{max}) to hydromorphone was observed in the poor metabolizers (Section 2.3 Intrinsic factors). However, given the small differences observed, the negligible levels of hydromorphone following administration of hydrocodone ER, and the fact that hydrocodone ER is titrated to a therapeutic dose for the same subject, it is unlikely that these differences in systemic exposure would produce significant differences in safety or efficacy.

Decline from peak plasma concentrations generally occurs in a biphasic manner with a mean half-life of approximately 11 to 12 hours (integrated single- and multiple-dose PK analysis set). Mean apparent total plasma clearance following administration of hydrocodone ER is approximately 70 to 90 L/h.

There is no known information on effect of age, race, sex, BMI, or CYP2D6 metabolizer status on the pharmacokinetics of hydrocodone from Vicoprofen product label. However, the sponsor utilized the single dose PK data (C_{max} and $AUC_{0-\infty}$ data) and generally compared PK of hydrocodone across the following demographic groups and indicates that no major impact is observed:

- Age subgroups (18 to 45 years (n=474), 46 to 65 years (n=14), and >65 years (n=5)).
- White (n=349) vs. Non-white (all other races combined to n=144)
- Male (n=325) vs. female (n=168)
- BMI $\leq$25 kg/m^2 vs. >25 kg/m^2
- CYP2D6 poor metabolizers (n=21), intermediate metabolizers (n=225) and extensive metabolizers (n=225). Impact of CYP2D6 polymorphisms on hydromorphone, metabolite of hydrocodone, was also evaluated and noted to be significant but may not be clinically relevant because hydromorphone is formed in very small quantities.

Impact of renal impairment on hydrocodone PK following Vantrela ER 45 mg tablet administration was evaluated in Study 1088. Mild renal impairment had little impact on hydrocodone exposure. Although the mean increase in C_{max} was approximately 50% in the moderately impaired, there was no consistent trend toward an increase in C_{max} with increasing severity of renal impairment. Overall systemic exposure to hydrocodone (as assessed by $AUC_{0-\infty}$) in subjects with moderate or severe renal impairment was, on average, up to approximately 70% higher than that in subjects with normal renal function. Subjects with ESRD undergoing dialysis displayed similar exposure as subjects with normal renal function or mild renal impairment indicating possible impact of dialysis on hydrocodone elimination.

Table: PK Parameters for Hydrocodone Following Administration of the 45-mg Bitartrate Extended-Release Tablet to Subjects With Normal Renal Function and Subjects With Moderate Renal Impairment (Study 1088).

Parameter	Normal renal function (N=13)	Mild renal impairment (N=8)	Moderate renal impairment (N=9)	Severe renal impairment (N=9)	ESRD (N=9)
C_{max} (ng/mL)	28.60 (5.6704)	33.42 (9.7765)	42.44 (11.5942)	36.48 (12.4442)	31.58 (6.8311)
$AUC_{0-\infty}$ (ng·h/mL)	565 (163.5)	660 (204.8)	973 (227.7)	983 (390.8)	638 (106.1)
AUC_{0-144} (ng·h/mL)	563 (161.5)	658 (204.2)	971 (229.0)	979 (390.1)	634 (108.0)
AUC_{0-t} (ng·h/mL)	561 (161.6)	656 (204.3)	969 (227.9)	975 (390.7)	632 (106.9)
AUC_{0-12} (ng·h/mL)	232 (42.1)	272 (81.7)	345 (111.1)	304 (111.1)	252 (58.4)
t_{max} (h)	8.0 (6.0, 10.0)	6.5 (5.0, 12.0)	10.0 (8.0, 12.0)	9.0 (5.0, 12.1)	8.0 (6.0, 12.0)
$t_{1/2}$ (h)	14.2 (11.08)	17.4 (12.84)	16.1 (9.83)	18.3 (9.92)	22.6 (13.71)
V_z/F	1694 (1370.22)	1729 (1156.07)	1199 (981.06)	1411 (990.13)	2452 (1730.90)
CL/F	85.3 (22.66)	76.0 (29.38)	48.7 (12.41)	53.0 (21.77)	72.4 (13.09)

SOURCE: Summary 15.9, Summary 15.10, and Listing 16.2.8.25.
NOTE: Median (range) is presented for t_{max}.
ESRD=end-stage renal disease; C_{max}=maximum observed plasma drug concentration; $AUC_{0-\infty}$=area under

Pharmacokinetics of hydrocodone following a single dose administration of Vantrela ER 15 mg tablet was evaluated in patients with moderate hepatic impairment and compared to subjects with normal hepatic function in study 1089. Mean C_{max} was approximately 30% higher and mean $AUC_{0-\infty}$ was approximately 70% higher in subjects with moderate hepatic impairment than in subjects with normal hepatic function. **PK of hydrocodone is unknown in patients with mild or severe hepatic impairment after receiving Vantrela ER tablet.**

No clinical drug-drug interaction studies have been performed for hydrocodone ER.

Based on Vicoprofen label, the pharmacokinetics of hydrocodone may be affected by inhibitors and inducers of CYP3A4, with a possible impact on safety and efficacy. To a lesser extent inhibitors of CYP2D6 may have an impact on efficacy in some individual patients. In addition, pharmacodynamic interactions with CNS depressants (e.g., alcohol, benzodiazepines, barbiturates, hypnotics, and muscle relaxants), anticholinergics, mixed/partial agonist opioids, MAO inhibitors and anticholinergics are possible. The use

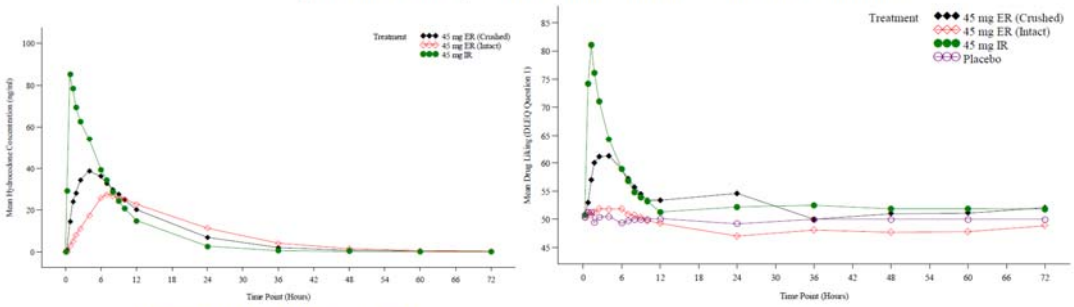
of careful titration and monitoring for adverse effects, especially respiratory depression, is warranted when concomitantly administering CEP-33237 with these substances and/or changing concomitant therapies.

Teva conducted in vitro alcohol interaction study to evaluate the potential for dose-dumping with up to 90 mg Vantrela ER tablet. The sponsor indicates that the dose released within the first two hours of the dissolution test did not suggest dose-dumping with Vantrela ER tablet. The clinical alcohol interaction study 1076 evaluated PK of Vantrela ER 15 mg tablet (higher doses not evaluated) since 15 mg strength showed the most potential of alcohol dose dumping based on *in vitro* data and did not reveal a significant change in systemic exposure following coadministration with 20% or 40% alcohol compared to drug taken without alcohol under fasting condition. Cmax and AUC of hydrocodone were bioequivalent following alcohol treatment (20% and 40%) compared to fasted treatment Vantrela ER 15 mg tablet.

Teva evaluated relative abuse potential of the Vantrela ER tablet when finely crushed and ingested orally or after intranasal administration in nondependent recreational opioid users.

The abuse liability study 1085 compared PK and PD (drug liking) of Vantrela ER tablet crushed with intact tablet, crushed IR tablet and Placebo. In this study, intact Vantrela ER 45 mg tablet systemic exposure was comparable to that noted in other single dose PK studies. Cmax and AUC0-inf were 29 ng/mL & 568 ng.h/mL in study 1081. Mean drug liking for intact Vantrela ER tablet was low (~50 or neither like nor dislike) followed by crushed Vantrela ER tablet and most drug liking noted with crushed IR tablet.

Figure : Mean Plasma Concentration-Time Profiles and Mean Drug Liking (DLEQ Question 1) Over Time in Healthy, Nondependent, Recreational Opioid Users Administered Single Doses of Hydrocodone Extended-Release Tablets (Crushed or Intact) or an Immediate-Release Formulation or Placebo



SOURCE: Section 15, Figure 1.1.1.A, Adhoc Figure 1.1.0.A.
ER=hydrocodone bitartrate extended-release tablet; IR=immediate-release hydrocodone; DLEQ=Drug Liking and Effects Questionnaire.

Based on BE analysis, crushed Vantrela ER 45 mg tablet and IR hydrocodone had 42% and 313% higher Cmax compared to intact Vantrela ER 45 mg tablet.

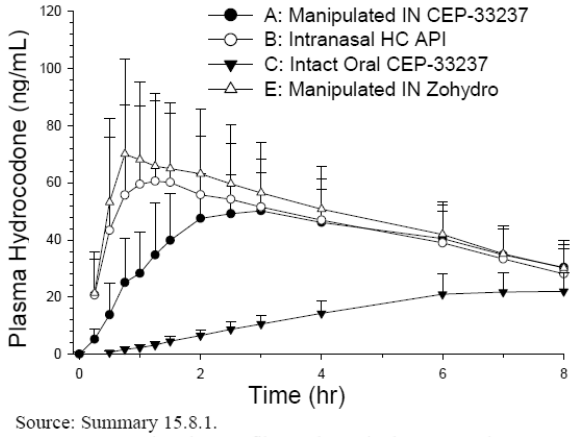
Table : Mean (Standard Deviation) Pharmacokinetic Parameters for Hydrocodone After Administration of Immediate- and Extended-Release Hydrocodone (Pharmacokinetic Analysis Set)

Variable	45-mg IR (N=39)	45-mg ER crushed (N=41)	45-mg ER intact (N=40)
C_{max} (ng/mL)	91.46 (16.817)	40.78 (10.204)	28.77 (6.088)
t_{max} (h)	0.8 (0.3, 4.1)	4.0 (1.8, 7.0)	7.1 (6.1, 12.0)
$AUC_{0-\infty}$ (ng·h/mL)	625 (137.3)	586 (138.5)	584 (124.8)
$AUC_{0-0.75}$ (ng·h/mL)	29 (13.5)	3 (1.7)	1 (0.3)
AUC_{0-4} (ng·h/mL)	246 (42.9)	103 (25.0)	34 (9.0)
AUC_{0-7} (ng·h/mL)	377 (60.2)	212 (47.1)	104 (22.6)
AUC_{0-t} (ng·h/mL)	623 (135.5)	584 (138.6)	581 (124.5)
Extrapolation (%)	0.26 (0.098)	0.40 (0.200)	0.61 (0.497)
λ_z (1/h)	0.1384 (0.02176)	0.0933 (0.02519)	0.0929 (0.02671)
$t_{1/2}$ (h)	5.13 (0.804)	7.97 (2.132)	8.04 (2.194)
AQ (ng/mL/h)	108.59 (58.789)	10.97 (3.997)	3.88 (1.056)

SOURCE: Summary 15.9.1, Listing 16.2.5.03.

Intranasal abuse of crushed Vantrela ER tablet was evaluated in abuse liability study 10032. PK and PD of intranasal crushed Vantrela ER 45 mg tablet, intranasal crushed Zohydro 45 mg tablet, intranasal hydrocodone powder 45 mg were compared with intact Vantrela ER 45 mg or Placebo. The peak plasma concentrations of hydrocodone and maximum drug liking were highest and achieved rapidly (Tmax 1.5 hrs) following intranasal administration of API and crushed Zohydro. As noted in the oral abuse liability study, mean drug liking for intact Vantrela ER tablet was low (~50 or neither like nor dislike). A two-fold increase in systemic exposure is noted following intranasal administration of Vantrela ER tablet which was associated with significant increase in drug liking (See bottom right figure).

Mean hydrocodone PK profile following intranasal abuse of different hydrocodone preparations (45 mg) vs. intact oral Vantrela ER 45 mg tablet.



Source: Summary 15.8.1.
Note: Concentration-time profile to 8 hours is shown as an inset.

Mean drug liking (question 1) vs. time following intranasal abuse of different hydrocodone preparations (45 mg) vs intact oral Vantrela ER 45 mg tablet.

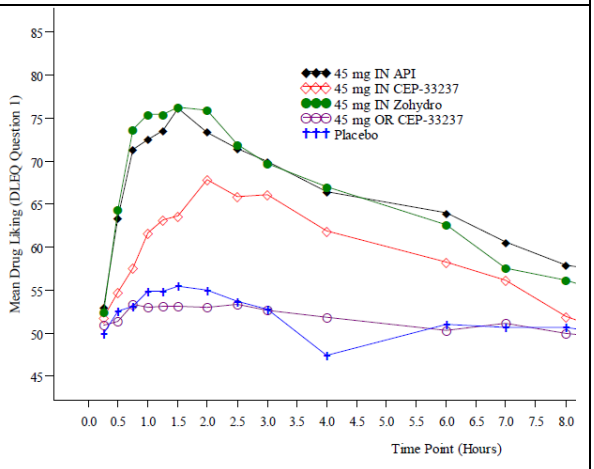


Table: Mean (Standard Deviation) Pharmacokinetic Parameters for Hydrocodone After Intranasal Administration of Crushed Vantrela ER (IN CEP-33237), Hydrocodone API or Crushed Zohydro™, or Oral Administration of Intact Vantrela ER (OR CEP-33237) at 45 mg Dose (Study 10032).

Variable	45 mg IN API (N=38)	45 mg IN Zohydro™ (N=39)	45 mg IN CEP-33237 (N=41)	45 mg OR CEP-33237 (N=38)
C_{max} (ng/mL)	71.28 (30.48)	80.27 (29.29)	56.84 (15.07)	25.05 (7.18)
t_{max} (h)	1.38 (0.60, 7.07)	1.12 (0.55, 6.17)	2.62 (1.33, 7.02)	9.11 (4.10, 12.12)
$AUC_{0-\infty}$ (ng·h/mL)	579 (163)	639 (179)	572 (150)	568 (172)
AUC_{0-t} (ng·h/mL)	576 (161)	637 (178)	568 (149)	531 (152)
$AUC_{0\text{-}tmax,\ API}$ (ng·h/mL)	57.5 (28.3)	66.5 (28.3)	24.9 (13.4)	1.9 (0.8)
$AUC_{0\text{-}tmax,\ CEP\ (IN)}$ (ng·h/mL)	125.9 (51.8)	142.4 (51.5)	78.5 (28.6)	9.4 (2.7)
$AUC_{0\text{-}tmax,\ CEP\ (Oral)}$ (ng·h/mL)	380.0 (112.3)	416.3 (108.8)	336.4 (75.1)	127.5 (34.9)
$AUC_{0\text{-}tmax,\ Zohydro}$ (ng·h/mL)	39.3 (20.9)	46.4 (21.2)	15.1 (8.7)	1.0 (0.5)
Extrapolation (%)	0.60 (0.94)	0.38 (0.24)	0.73 (0.72)	6.04 (3.94)
λ_z (1/h)	0.124 (0.023)	0.127 (0.021)	0.114 (0.015)	0.076 (0.024)
$t_{1/2}$ (h)	5.78 (1.06)	5.58 (0.86)	6.16 (0.76)	9.96 (3.03)
AQ (ng/mL/h)	59.6 (55.2)	75.4 (54.0)	22.6 (12.2)	3.1 (1.2)

Source: Summary 15.9.1.
API=active pharmaceutical ingredient; AQ=abuse quotient (C_{max}/t_{max})

PK of hydrocodone in single dose studies with and without naltrexone:

As such most of the single dose PK or PK/PD studies, except food-effect studies, recruited either healthy volunteers who received naltrexone to block opioid effects of Vantrela ER tablet or opioid-experienced, non-dependent subjects without naltrexone-block. A cross study comparison was made to generally evaluate hydrocodone systemic exposure following Vantrela ER tablet administration in fasting healthy volunteers. There was no data available from drug liking studies where Vantrela ER tablet was given with food. As shown in the table below, Cmax and AUC values appear to be similar across different studies. Mean peak plasma concentrations were in the range of 25 – 30 ng/mL, AUCinf was in the range of 565 – 592 ng.hr/mL, and median Tmax was 8 hours (5 -12 hours). Hence, it appears that there is no major difference in hydrocodone PK in different studies that were conducted while fasting with or without naltrexone.

Table: Pharmacokinetics (mean (SD))of hydrocodone following administration of intact Vantrela ER 45 mg tablet to healthy volunteers under fasting condition with or without naltrexone block.

	Study 1082	Study 1081	Study 1088	Study 1085	Study 10032
Parameter (unit)	**Vantrela ER 45 mg (N=60)**	**Vantrela ER 45 mg (N=36)**	**Normal Renal function Arm 45 mg (N=13)**	**Intact Vantrela ER 45 mg Arm (N=40)**	**Intact Vantrela ER 45 mg Arm (N=38)**
	Fasting Arm with Naltrexone-Block			**Fasting Arm without Naltrexone-Block**	
Cmax (ng/mL)	30.3 (7.5)	29 (8.16)	28.60 (5.67)	28.77 (6.088)	25.05 (7.18)
AUC0-∞ (ng·h/mL)	592 (167)	568.3 (142.52)	565 (164)	584 (124.8)	568 (172)
AUC0-t (ng·h/mL)	586 (164)	561.2 (140)	561 (162)	581 (124.5)	531 (152)
Tmax (h)[a]	8.0 (5.0, 12.1)	8.5 (5, 12)	8.0 (6, 10)	7.1 (6.1, 12.0)	9.11 (4.10, 12.12)
t½ (h)	10.2 (3.6)	11.1 (2.97)	14.2 (11.1)	8.04 (2.194)	9.96 (3.03)
λz (1/h)	0.08 (0.025)	0.07 (0.21)	0.0719 (0.0363)	0.0929 (0.02671)	0.076 (0.024)

[a] Median value and range.

Conclusion: Clinical pharmacology studies support use of Vantrela ER tablet in most of the special populations except mild, severe hepatic impairment and drug-drug interactions with CYP3A4 inhibitors. Additionally, potential for hydrocodone to cause QT-prolongation needs to be evaluated.

2 QBR

2.1 General Attributes

2.1.1 Regulatory background:

Teva Branded Pharmaceutical Products submitted NDA 207975 for the use of Vantrela ER tablet or hydrocodone bitartrate extended-release (CEP-33237), abuse deterrent, oral tablets in 15, 30, 45, 60, and 90 mg strengths. The proposed indication is for the management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate. Originally, the submission was a 505(b)(2) NDA with reference to Agency's findings of safety and efficacy from Vicoprofen NDA 020716 which is a combination product containing hydrocodone (7.5 mg) and ibuprofen (200 mg). However, on July 21st, 2015, the sponsor revised their 505(b)(2) application to a 505(b)(1) application based on the fact that Teva obtained the right of reference to the Vicoprofen NDA 020716 from AbbVie, Inc. Therefore, the clinical pharmacology findings in the Vicoprofen label can be used to support this NDA, if appropriate.

2.1.2 What are the highlights of chemistry and physico-chemical properties of drug substance, and the formulation as it relates to clinical pharmacology review?

Hydrocodone bitartrate is a semi-synthetic opioid that is available in combination with acetaminiophen (Vicodin or other generics) or ibuprofen (Vicoprofen) and as a single entity opioid ER product (Zohydro). It is a Schedule II controlled substance with known potential for abuse and diversion. Teva developed this single entity extended release tablet, Vantrela ER, using a proprietary abuse deterrent technology that is intended to control misuse and abuse if the formulation is manipulated or misused.

Table: Composition of Vantrela, Hydrocodone Bitartrate, Extended Release Tablets

Component	Reference to Standard	15 mg (Light Red)	30 mg (Yellow)	45 mg (White)	60 mg (Light Blue)	90 mg (Light Green)
		mg/tablet	mg/tablet	mg/tablet	mg/tablet	mg/tablet
Hydrocodone bitartrate[a]	USP	15.00	30.00	45.00	60.00	90.00
(b) (4) lactose monohydrate	NF	(b) (4)				
Ethyl cellulose, (b) (4)	NF					
Hypromellose (b) (4)	USP					
Glyceryl behenate	NF					
Magnesium stearate, (b) (4)	NF					
Red ferric oxide	NF					
Yellow ferric oxide	NF					
FD&C Blue #2 aluminum lake	FD&C					
(b) (4)	USP/NF					
Total Weight / Tablet		575	575	575	1150	1150

2.1.3 What are the proposed mechanism(s) of action and therapeutic indication(s)?

Hydrocodone is a semi-synthetic opioid agonist with relative selectivity for the mu-opioid (μ) receptor, although it can interact with other opioid receptors at higher doses. Hydrocodone acts as an agonist binding to and activating opioid receptors in the brain and the spinal cord to produce analgesia. The analgesia, as well as the euphoriant, respiratory depressant and physiologic-dependence properties are believed to be primarily mediated via μ opioid receptors.

2.1.4 What are the proposed dosage(s) and route(s) of administration?

Vantrela ER tablet is available as 15, 30, 45, 60 and 90 mg extended-release tablets intended for oral route of administration with a twice daily dosing regimen (every 12 hours).

2.2 General Clinical Pharmacology

2.2.1 What are the design features of the clinical pharmacology and clinical studies used to support dosing or claims?

The sponsor submitted Clinical Pharmacology data on the pharmacokinetics and pharmacodynamics (PD)s of hydrocodone from 19 studies of Vantrela ER tablet (hydrocodone ER tablet). The majority (16) of these studies were conducted in healthy subjects who also received naltrexone hydrochloride (hereafter referred to as naltrexone) to block opioid receptors and minimize opioid-related adverse events. The clinical pharmacology program included studies to characterize the pharmacokinetics of hydrocodone following administration of single and multiple doses of hydrocodone ER in the fed and fasted states. In addition, studies were conducted to characterize the pharmacokinetics in subjects with varying degrees of renal function and in subjects with normal hepatic function versus those with moderate hepatic impairment.

The sponsor conducted two Phase 3 studies to support the clinical safety and efficacy of Vantrela ER tablet:

1. Study C33237/3079 (hereafter referred to as Study 3079) was a double-blind, placebo-controlled study in patients with moderate to severe pain associated with osteoarthritis (OA) or low back pain who required opioid treatment for an extended period of time.

2. Study C33237/3103 (hereafter referred to as Study 3103) was a double-blind, placebo-controlled study in patients with moderate to severe chronic low back pain who required continuous opioid treatment for an extended period of time.

A tabular list of all clinical pharmacology studies supporting the NDA are presented below. Some of the bioavailability studies supporting manufacturing site changes are being reviewed by the biopharmaceutics reviewer Dr. Assad Noory and Dr. Fang Wu.

Most of the bioavailability studies above were conducted using intact product. In addition, the pharmacokinetics and/or pharmacodynamics of hydrocodone were characterized following administration of a manipulated hydrocodone ER tablet either orally (Studies 1079 and 1085) or intranasally (Study 10032).

Table: Hydrocodone ER Clinical Pharmacology Studies Discussed in the Summary

Bioavailability/ bioequivalence studies	Studies contributing to the PK profile	Studies of special populations	Extrinsic factor studies	Clinical abuse potential studies
C33237/1071[a]	C33237/1071[a]	C33237/1088	C33237/1076	C33237/1085
C33237/1079[b]	C33237/1081	CC33237/1089	C33237/1079[b]	C33237-AP-10032
C33237/1090[c]	C33237/1082		C33237/1085[d]	
C33237/1095	C33237/1091		C33237/1090	
C33237/1096			C33237-PK-10024	
C33237/1097			C33237-AP-10032[e]	
C33237/1098				
C33237/1099				
C33237/1104				
C33237/1106				

[a] Objectives in Study 1071 included PK characterization of several prototypes as well as relative bioavailability to NORCO®, Watson Pharmaceuticals.
[b] Objectives in Study 1079 included characterization of pharmacokinetics when crushed and ingested orally as well as relative bioavailability to VICOPROFEN®, Abbott Laboratories.
[c] Objectives in Study 1090 included evaluation of the effect of food on pharmacokinetics as well as relative bioavailability to VICOPROFEN.
[d] The primary objective in Study 1085 was to assess the relative abuse potential (oral study). Characterization of the pharmacokinetics of the manipulated hydrocodone ER tablet was a secondary objective.
[e] The primary objective in Study 10032 was to assess the relative abuse potential (intranasal study). Characterization of the pharmacokinetics of the manipulated hydrocodone ER tablet was a secondary objective.
ER=extended-release; PK=pharmacokinetic.

2.2.2 Does this drug prolong the QT or QTc interval?

No studies were conducted to characterize the QT-prolongation potential of hydrocodone/Vantrela ER tablet.

2.2.3 What are the PK characteristics of the drug and its major metabolite?

a) What are the single dose and multiple dose PK parameters?

The pharmacokinetics of hydrocodone and hydromorphone have been well characterized in healthy subjects following administration of single doses of hydrocodone ER up to 90 mg and multiple doses of 45 and 90 mg of hydrocodone ER administered every 12 hours for 5.5 days. Data from a total of 69 healthy subjects participating in 2 Phase 1 studies (Studies 1081 and 1091) were integrated and used to describe the single- and multiple-dose PK profile.

Following oral administration of intact product, a steady rise in systemic exposure is noted with the extended release product compared to immediate release product which shows a relatively rapid appearance of peak plasma concentrations. Peak plasma concentrations are noted after 7 - 8.5 hours after single dose administration. While the overall exposure of hydrocodone (AUC) was similar between Vantrela ER tablet 15 mg and Vicoprofen (two tablets of 7.5 mg hydrocodone/200 mg Ibuprofen), peak plasma levels with Vantrela ER tablet 15 mg were 1/3 that noted with IR Vicoprofen (Study 1079).

Figure: Hydrocodone PK profile following oral administration of Vantrela ER 15 mg Tablet compared to two tablets of Vicoprofen. (Log-plot shown here Vs. Linear plot in summary CP findings)

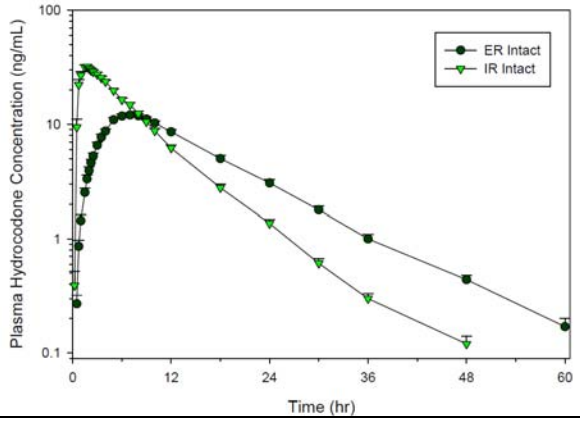


Table: Mean (SD) PK parameters of hydrocodone following oral administration of Vantrela ER 15 mg Tablet compared to two tablets of Vicoprofen.

Variable	VANTRELA ER TABLET 15 mg A (N=27)	VICOPROFEN Two Tablets C (N=28)
C_{max} (ng/mL)	12.4 (2.54)	36.1 (8.15)
t_{max} (h)	7.0 (5.0, 9.0)	1.8 (0.8, 4.0)
$AUC_{0-\infty}$ (ng·h/mL)	203.6 (50.75)	253.6 (50.67)
AUC_{0-t} (ng·h/mL)	200.6 (50.55)	251.8 (50.33)
AUC_{0-72} (ng·h/mL)	201.7 (50.36)	253.0 (50.70)
AUC_{0-12} (ng·h/mL)	100.9 (20.85)	201.0 (35.47)
AUC_{0-tmax} (ng·h/mL)	2.1 (1.1)	33.8 (11.6)
$t_{1/2}$ (h)	10.2 (3.34)	9.0 (5.11)
Percentage extrapolation (%)	1.5 (0.85)	0.8 (0.36)
λ_z (1/h)	0.0763 (0.02706)	0.0958 (0.03941)
Abuse quotient (ng/mL/h)	1.8 (0.61)	24.8 (14.53)

SOURCE: Adhoc Summary 1, Summary 15.10, Adhoc Listing 1, Listing 16.2.8.24. NOTE: Median (range) is presented for t_{max}.

Table: Comparison of Mean Pharmacokinetic Parameter Values for Hydrocodone Following Administration of a Single Dose of Hydrocodone ER (Dose Normalized to 15 mg) and a Single 15 mg Dose of Hydrocodone within VICOPROFEN in Healthy Subjects (Pharmacokinetic Analysis Set, Bioavailability Subset)

Parameter (unit)	VICOPROFEN (N=60)	Hydrocodone ER (N=60)	Ratio of Hydrocodone ER:VICOPROFEN	90% CI
C_{max} (ng/mL)	34.0 (8.33)	10.8 (2.72)	0.319	0.297, 0.342
$AUC_{0-\infty}$ (ng·h/mL)	227 (53.45)	190.8 (48.11)	0.840	0.783, 0.902

SOURCE: Pharmacokinetic Analysis, Bioavailability Subset, Summary 11.1
NOTE: Values for C_{max} and $AUC_{0-\infty}$ are geometric mean (standard error of the mean).
CI=Confidence Interval; C_{max}=maximum observed plasma drug; $AUC_{0-\infty}$=area under the plasma drug concentration versus time curve (AUC) from time zero to infinity.

Since the Sponsor originally planned to submitted the NDA under a 505(b)(2) pathway using Vicoprofen as the listed drug, a relative BA study with Vicoprofen was conducted. Relative bioavailability of 90 mg dose of Vantrela ER tablet was assessed (Study 1090) in comparison to Vicoprofen (two tablets).

Table: Hydrocodone PK parameters (mean (SD)) following administration of Vantrela ER tablets (2 X 45 mg) fasted (Treatment A), fed (Treatment B) and two Vicoprofen (7.5/200 mg) fasted (Study 1090).

Parameter	Two Vantrela ER 45 mg tablets Fasted (A)	Two Vantrela ER 45 mg Tablets Fed (B)	Two Vicoprofen Tablets Fasted (C) (15 mg Hydrocodone)
	n=36	n=35	n=36
C_{max} (ng/mL)	60.6 (14.5)	86.11 (22.67)	33.2 (8.4)
$AUC_{0-\infty}$ (ng·h/mL)	1135 (275.1)	1262 (269.0)	215 (47.2)
AUC_{0-t} (ng·h/mL)	1126 (272.6)	1255 (268.7)	214 (46.9)
t_{max} (h)	8.0 (5.0, 10.0)	9.0 (6.0, 12.0)	1.6 (0.8, 3.5)
$t_{1/2}$ (h)	10.0 (3.69)	9.4 (2.7)	7.5 (5.53)
λ_z (1/h)	0.078 (0.027)	0.08 (0.23)	0.115 (0.04)

As noted above, following administration of the hydrocodone/ibuprofen immediate-release product (VICOPROFEN, treatment C), Cmax was approximately 3 times higher than the dose-normalized Cmax for the hydrocodone bitartrate extended-release tablet (treatment A). Total systemic exposure to hydrocodone following administration of the hydrocodone bitartrate extended-release tablet as assessed by (dose-normalized AUC) was equivalent to that following administration of the immediate-release product.

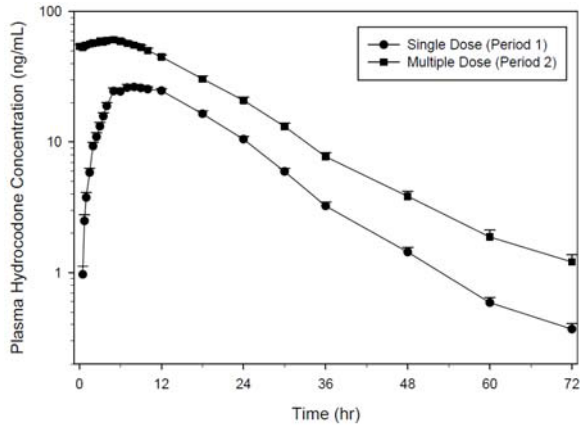
Table: Comparison of Pharmacokinetic Parameters Following Administration of Vantrela ER Tablet (Dose-Normalized to 15 mg) and the Immediate-Release Hydrocodone/ Ibuprofen Product (VICOPROFEN) in Study 1090.

Variable Statistic	A (dose normalized to 15 mg) (N=36)	C (N=36)	C/A ratio	90% CI
C_{max} (ng/mL)	9.8 (0.40)	32.3 (1.40)	3.253	3.061, 3.458
$AUC_{0-\infty}$ (ng·h/mL)	184.3 (7.64)	210.6 (7.87)	1.143	1.087, 1.201
AUC_{0-t} (ng·h/mL)	182.9 (7.57)	209.0 (7.82)	1.143	1.088, 1.201

SOURCE: Summary 15.11.2, Listing 16.2.8.23.
NOTE: Values presented are geometric mean (standard error of the mean).

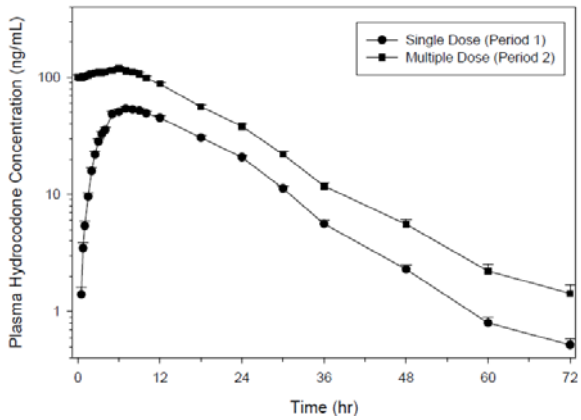
Multiple dose pharmacokinetics of Vantrela ER: Unlike single dose administration, peak plasma concentrations are noted earlier (Median Tmax ~4.5 hours) with repeated administration. Following twice-daily administration of 90-mg doses (Study 1091) of the Vantrela ER tablet, accumulation of hydrocodone in plasma was observed. The steady-state plasma concentrations are 3-fold higher than that observed with single dose or mean observed accumulation ratio (R_{obs}) was 2.8. Similar observation of accumulation was also made after multiple dose administration of 45 mg Vantrela ER tablet (Study 1081).

Figure: Mean PK Profile of Vantrela 45 mg following single and multiple dose administration (5.5 days) (Study 1081)



Source: Study 1081 report.

Figure: Mean PK Profile of Vantrela 90 mg following single and multiple dose administration (5.5 days) (Study 1091)



Source: Figure 2, Study C33237/1091 study report.

Table: Hydrocodone PK parameters (mean (SD)) following single dose (Left) and multiple dose (Right - 5.5 days) administration of Vantrela ER 45 mg tablet (Study 1081).

Variable	Single-dose period (N=36)
C_{max} (ng/mL)	29.0 (8.16)
t_{max} (hr)[a]	8.5 (5.0, 12.0)
AUC_{0-12} (ng·hr/mL)	234.0 (64.31)
AUC_{0-72} (ng·hr/mL)	561.5 (139.64)
AUC_{0-t} (ng·hr/mL)	561.2 (140.04)
$AUC_{0-\infty}$ (ng·hr/mL)	568.3 (142.52)
λ_z (1/hr)	0.07 (0.021)
$t_{½}$ (hr)	11.1 (2.97)
CL/F (L/hr)	86.1 (31.69)
V/F (L)	1337.5 (456.35)
Extrapolation (%)	1.2 (0.81)
R_{pred}	2.5

SOURCE: Summary 15.10.1 and Listing 16.2.8.23.
[a] Median (range) is provided for t_{max}.

Variable	Multiple-dose period (N=36)
C_{max} (ng/mL)	63.8 (13.14)
t_{max} (hr)[a]	4.5 (1. 0, 7.0)
AUC_{τ} (ng·hr/mL)	662.5 (140.56)
AUC_{0-72} (ng·hr/mL)	1330.1 (345.83)
AUC_{0-t} (ng·hr/mL)	1330.1 (345.85)
λ_z (1/hr)	0.06 (0.023)
$t_{½}$ (hr)	13.2 (4.96)
CL/F (L/hr)	71.3 (16.85)
V/F (L)	1375.7 (715.34)
R_{obs}	2.9
R_{ss}	1.2

SOURCE: Summary 15.10.1 and Listing 16.2.8.23.
[a] Median (range) is provided for t_{max}.

Table: Hydrocodone PK parameters (mean (SD)) following single dose (Left) and multiple dose (Right - 5.5 days) administration of Vantrela ER 90 mg tablet (Study 1091).

Variable	Single 90-mg dose (N=33)
C_{max} (ng/mL)	56.40 (13.6428)
$AUC_{0-\infty}$ (ng·h/mL)	1073 (218.5)
AUC_{0-t} (ng·h/mL)	1064 (215.4)
AUC_{0-12} (ng·h/mL)	462 (105.8)
t_{max} (h)	7.0 (5.0, 12.0)
$t_{1/2}$ (h)	9.9 (2.80)
Percentage extrapolation (%)	0.8 (0.66)
λ_z (1/h)	0.0758 (0.02411)
CL/F (L/h)	87.9 (21.68)
V_z/F (L)	1230 (347.21)
R_{pred}	2.4

SOURCE: Summary 15.10.1, Listing 16.2.8.23.
NOTE: Median (range) is presented for t_{max}.

Variable	Twice daily 90-mg doses (N=33)
C_{max} (ng/mL)	123.07 (25.1417)
C_{avg} (ng/mL)	106.8 (21.60)
C_{min} (ng/mL)	86.45 (17.403)
AUC_{0-t} (ng·h/mL)	2453 (518.3)
AUC_{τ} (ng·h/mL)	1282 (259.3)
t_{max} (h)	5.0 (0.0, 9.1)
$t_{1/2}$ (h)	10.7 (4.05)
λ_z (1/h)	0.0729 (0.02464)
R_{obs}	2.8
R_{ss}	1.2
Fluctuation (%)	33.94 (11.106)
Swing (%)	43.45 (21.504)

SOURCE: Summary 15.10.1,
NOTE: Median (range) is presented for t_{max}.

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

Pharmacokinetics of hydrocodone following Vantrela ER tablet administration in pain population have not been determined. However, difference in PK of hydrocodone is not expected in pain patients compared to healthy volunteers (see intrinsic factors).

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

Hydrocodone appears to be well distributed beyond the vascular system with a V_z/F of approximately 1300 to 1400 L following administration of the hydrocodone ER tablet (integrated single and multiple-dose PK analysis set Study 1081 and 1091). The extent of protein binding of hydrocodone in human plasma has not been determined.

d) Does the mass balance study suggest renal or hepatic as the major route of elimination?

Based on Vicoprofen label, hydrocodone exhibits a complex pattern of metabolism in liver, including O-demethylation, N-demethylation, and 6-keto reduction to the corresponding 6-α-and 6-β-hydroxy metabolites. Hydrocodone and its metabolites are eliminated primarily in the kidneys, with a mean plasma half-life of 4.5 hours.

f) What are the characteristics of drug metabolism?

As described in Vicoprofen product label, hydrocodone exhibits a complex pattern of metabolism, including O-demethylation, N-demethylation, and 6-keto reduction to the corresponding 6-α-an d 6-β-hydroxymetabolites. Following administration of Vantrela ER tablet, hydromorphone plasma concentrations are approximately 1% to 2% of those of the parent drug. Hydromorphone, a potent opioid, is formed from the O-demethylation of hydrocodone and contributes to the total analgesic effect of hydrocodone. The O-and N-demethylation processes are mediated by separate P-450 isoenzymes: CYP2D6 and CYP3A4, respectively.

g) What are the characteristics of drug excretion?

Based on Vicoprofen label, hydrocodone and its metabolites are eliminated primarily in the kidneys, with a mean plasma half-life of 4.5 hours.

h) Based on PK parameters, what is the degree of linearity or nonlinearity in the dose-concentration relationship?

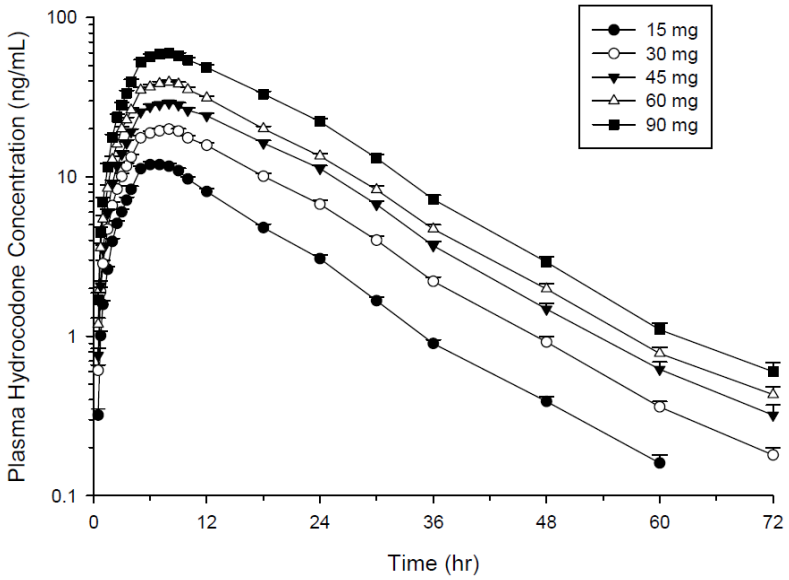
The systemic exposure of hydrocodone increased dose-proportionally over the range of 15 through 90 mg doses of Vantrela ER tablet (Study 1082).

Note: PK study was conducted in naltrexone-blocked subjects while fasting. The 90 mg dose was administered as two 45 mg Vantrela ER tablets. The absolute bioavailability of orally administered hydrocodone is unknown.

As noted in the single dose PK results described above, peak plasma hydrocodone concentrations were noted approximately 8 hours after Vantrela ER tablet administration.

Unlike immediate release hydrocodone, elimination half-life of hydrocodone following intact oral administration of Vantrela ER tablet was approximately 10 hours. Volume of distribution was approximately ~1250 mL

Figure: Mean (Standard Error) Plasma Concentration by Time Profiles for Hydrocodone in Healthy Subjects Administered a Single 15-, 30-, 45-, 60-, or 90-mg Dose of the Hydrocodone Bitartrate Extended-Release Tablet



Source: Study 1082, Figure 2.

Table: Mean (Standard Deviation) Pharmacokinetic Parameters for Hydrocodone Following Oral Administration of Vantrela ER tablet (Study 1082).

Variable	A 15 mg (N=60)	B 30 mg (N=60)	C 45 mg (N=60)	D 60 mg (N=60)	E 90 mg (N=60)
C_{max} (ng/mL)	12.6 (3.50)	20.7 (5.47)	30.3 (7.48)	41.2 (10.11)	62.5 (16.19)
$AUC_{0-\infty}$ (ng·h/mL)	198.8 (60.37)	381.6 (117.78)	592.3 (167.20)	765.7 (193.98)	1189.0 (341.31)
AUC_{0-t} (ng·h/mL)	195.8 (60.09)	377.6 (116.47)	585.8 (163.68)	757.2 (190.82)	1178.8 (335.97)
AUC_{0-72} (ng·h/mL)	196.7 (59.98)	378.1 (116.31)	586.0 (163.48)	757.3 (190.66)	1178.8 (335.94)
AUC_{0-12} (ng·h/mL)	99.9 (27.40)	169.5 (45.31)	247.1 (62.94)	334.2 (78.09)	505.6 (129.73)
t_{max} (h)	7.0 (5.0, 9.0)	8.0 (5.0, 12.0)	8.0 (5.0, 12.1)	8.0 (5.0, 12.0)	8.0 (5.0, 12.0)
$t_{1/2}$ (h)	10.4 (4.05)	10.6 (4.06)	10.2 (3.64)	10.8 (4.13)	10.0 (2.94)
Percentage extrapolation (%)	1.4 (0.85)	1.0 (0.72)	1.0 (1.19)	1.1 (1.06)	0.8 (0.83)
λ_z (1/h)	0.08 (0.027)	0.07 (0.024)	0.08 (0.025)	0.07 (0.025)	0.08 (0.020)
V/F	1233.9 (588.91)	1323.4 (797.07)	1206.3 (543.84)	1289.5 (575.27)	1196.2 (584.14)
CL/F	83.4 (29.14)	85.7 (25.31)	81.6 (21.54)	83.0 (19.66)	82.2 (24.93)

SOURCE: Adhoc Summary 15.9.1, Listing 16.2.8.23.
NOTE: Median (range) is presented for t_{max}

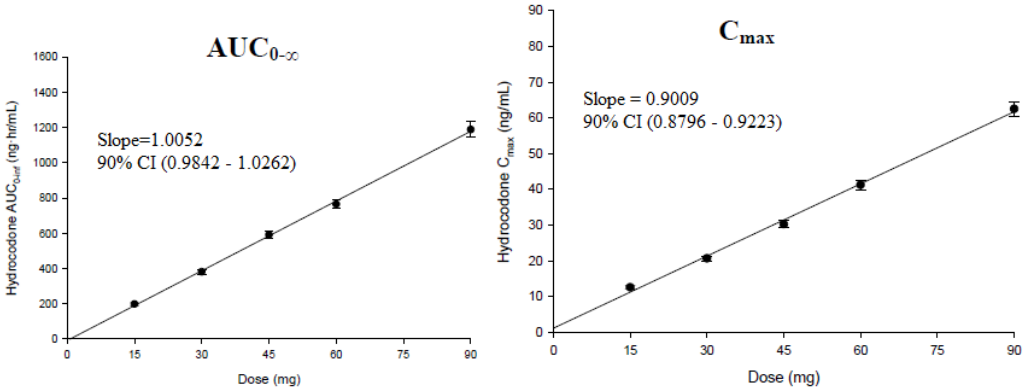
The designated primary pharmacokinetic variables for evaluating the dose proportionality of the hydrocodone bitartrate extended-release tablet over the dose range of 15 through 90 mg were $AUC_{0-\infty}$ and C_{max} of hydrocodone. The primary pharmacokinetic analyses included only the subjects who had pharmacokinetic data from each of the 5 periods.

Dose proportionality was measured by the slope, β, of the regression line as follows:
$\ln(PK) = \alpha + \beta\ln(dose) + \varepsilon$

The error term ε was modeled to account for both intrasubject and intersubject variation.

A mixed-effects model was used to provide a 90% confidence interval (CI) on the fixed effect of β. Dose proportionality would be concluded if the CI fell completely within the limits (0.875 to 1.125).

Figure: Mean (Standard Error) AUC0-inf and Mean Observed Peak Plasma Concentration of Hydrocodone as a Function of Dose Following a Single 15-, 30-, 45, 60-, or 90-mg Dose of the Vantrela ER Tablet.



SOURCE: Drug Safety and Disposition Department at Cephalon, Inc.
$AUC_{0-\infty}$=area under the plasma drug concentration by time curve from time 0 to infinity; C_{max}=maximum observed plasma drug concentration.

2.3 Intrinsic Factors

No clinical studies have been performed to assess the effect of age, race, sex, or BMI on the pharmacokinetics of hydrocodone following administration of hydrocodone ER. Where possible, Teva attempted to evaluate the potential impact of these covariates is based on subgroup analyses using the single-dose integrated demographics database from Phase 1 studies (see table below). In addition, the effect of CYP2D6 metabolism status on the pharmacokinetics of hydrocodone was also evaluated using the integrated database.

Table: Summary demographic characteristics of subjects recruited to all PK studies.

Variable Statistic	Healthy Subjects Men (N=313)	Healthy Subjects Women (N=159)	Healthy Subjects Total (N=472)	Normal Organ Function Men (N=12)	Normal Organ Function Women (N=9)	Normal Organ Function Total (N=21)
Age (years)						
n	313	159	472	12	9	21
Mean	29.7	30.1	29.8	58.8	52.3	56.0
SD	7.09	7.37	7.18	10.36	6.22	9.24
SE	0.40	0.58	0.33	2.99	2.07	2.02
Median	28.0	28.0	28.0	60.5	50.0	56.0
Min, max	18.0, 45.0	18.0, 45.0	18.0, 45.0	41.0, 70.0	42.0, 60.0	41.0, 70.0
Age group (years)						
20 - 45	313 (100)	159 (100)	472 (100)	1 (8)	1 (11)	2 (10)
46 - 65	0	0	0	6 (50)	8 (89)	14 (67)
>65	0	0	0	5 (42)	0	5 (24)
Sex, n (%)						
Male	313 (100)	0	313 (66)	12 (100)	0	12 (57)
Female	0	159 (100)	159 (34)	0	9 (100)	9 (43)
Race, n (%)						
White	211 (67)	123 (77)	334 (71)	9 (75)	6 (67)	15 (71)
Black	89 (28)	33 (21)	122 (26)	3 (25)	2 (22)	5 (24)
Asian	5 (2)	2 (1)	7 (1)	0	0	0
American Indian or Alaskan Native	3 (<1)	0	3 (<1)	0	0	0
Pacific Islander	2 (<1)	0	2 (<1)	0	0	0
Other	3 (<1)	1 (<1)	4 (<1)	0	1 (11)	1 (5)
Race group, n (%)						
White	211 (67)	123 (77)	334 (71)	9 (75)	6 (67)	15 (71)
Non-white	102 (33)	36 (23)	138 (29)	3 (25)	3 (33)	6 (29)
Weight (kg)						
n	313	159	472	12	9	21
Mean	79.7	66.7	75.3	85.4	75.5	81.2
SD	9.69	8.67	11.20	12.45	8.42	11.78
SE	0.55	0.69	0.52	3.59	2.81	2.57
Median	80.5	67.4	75.2	87.0	73.9	81.0
Min, max	55.0, 103.8	46.6, 89.7	46.6, 103.8	67.1, 102.1	64.6, 88.8	64.6, 102.1
Height (cm)						
n	313	159	472	12	9	21
Mean	174.7	162.5	170.6	175.3	166.9	171.7
SD	6.89	6.61	8.91	7.03	3.07	7.00
SE	0.39	0.52	0.41	2.03	1.02	1.53
Median	175.0	162.1	171.0	176.9	166.0	171.0
Min, max	153.7, 198.0	143.5, 179.9	143.5, 198.0	163.8, 182.9	163.0, 172.0	163.0, 182.9
BMI (kg/m^2)						
n	313	159	472	12	9	21
Mean	26.1	25.2	25.8	27.7	27.1	27.4
SD	2.61	2.62	2.65	2.78	3.09	2.85
SE	0.15	0.21	0.12	0.80	1.03	0.62
Median	26.6	25.1	26.1	28.0	27.4	27.6
Min, max	20.2, 30.0	20.2, 29.9	20.2, 30.0	21.5, 30.9	23.4, 32.9	21.5, 32.9
BMI group						
<=25	110 (35)	75 (47)	185 (39)	2 (17)	2 (22)	4 (19)
> 25	203 (65)	84 (53)	287 (61)	10 (83)	7 (78)	17 (81)
CYP2D6 Metabolism						
Poor metabolizer	13 (4)	8 (5)	21 (4)	0	0	0
Not poor	219 (70)	120 (75)	339 (72)	12 (100)	9 (100)	21 (100)
Unknown	81 (26)	31 (19)	112 (24)	0	0	0

Dedicated studies to assess the impact of renal (1088) or hepatic impairment (1089) on the pharmacokinetics of hydrocodone following administration of hydrocodone ER were performed.

2.3.1 Effect of Age:

There is appears to be no known effect of age on the pharmacokinetics of hydrocodone possibly confounded by the limited number of elderly subjects >65 yrs age. Cmax and AUC0-∞ data (dose normalized to 15 mg) from the single-dose integrated demographics database are presented by age subgroup (18 to 45 years, 46 to 65 years, and >65 years).

Figure: Box plot of Cmax and AUC (dose-normalized to 15 mg) following administration of Vantrela ER tablets in healthy subjects by Age group.

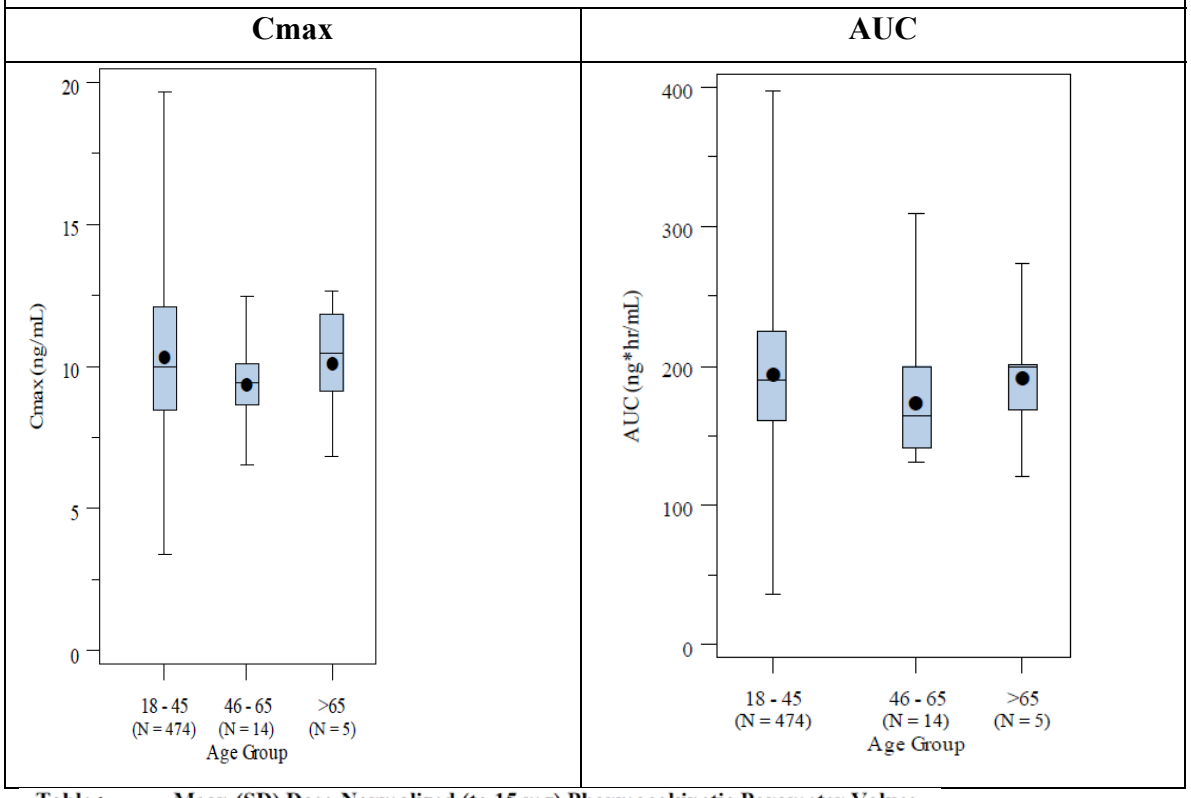


Table : Mean (SD) Dose-Normalized (to 15 mg) Pharmacokinetic Parameter Values for Hydrocodone Following Administration of a Single Dose of Hydrocodone ER in Healthy Subjects by Age Group (Pharmacokinetic Analysis Set, Integrated Demographic Subset)

Parameter (unit)	18-45 years (N=474)	46-65 years (N=14)	>65 years (N=5)
C_{max} (ng/mL)	10.43 (2.71)	9.47(1.47)	10.19 (2.99)
$AUC_{0-\infty}$ (ng·h/mL)	195.5 (50.6)	174.5 (47.8)	192.7 (55.1)
AUC_{0-t} (ng·h/mL)	193.3 (49.7)	172.4 (47.3)	191.3 (55.3)
t_{max} (h)[a]	8.0 (5.0, 13.0)	7.0 (5.0, 9.0)	8.0 (6.0, 10.0)
$t_{½}$ (h)	10.4 (3.2)	11.6 (5.8)	14.4 (15.2)
λ_z (1/h)	0.0741 (0.0234)	0.0700 (0.0262)	0.0780 (0.0371)

Source: Pharmacokinetic Analysis Set, Integrated Demographic Subset, Summary 9.1.

[a] Median (range) is presented for t_{max}.

$AUC_{0-\infty}$=area under the plasma drug concentration versus time curve (AUC) from time zero to infinite time; AUC_{0-t}=AUC from time 0 to last measurable concentration; C_{max}=maximum observed plasma drug concentration; ER=extended-release; SD=standard deviation; t_{max}=time to maximum observed plasma drug concentration; $t_{½}$=elimination half-life; λ_z=apparent plasma terminal elimination rate constant.

2.3.2 Effect of Race:

There is no known effect of race on the pharmacokinetics of hydrocodone. Given the small numbers of subjects of the other races (eg, Asian 7 [1%], American Indian or Alaskan Natives 3 [<1%], Pacific Islanders 2 [<1%], Other 5 [1%]), Teva grouped all the above races together with black subjects for this subgroup analysis. Such an approach is not optimal for understanding racial differences in PK of hydrocodone. Nevertheless, the mean dose-normalized PK parameters for hydrocodone following single dose administration from different studies tabulated below suggest similar PK in whites compared to non-white subjects.

Table : Mean (SD) Dose-Normalized (to 15 mg) Pharmacokinetic Parameter Values for Hydrocodone Following Administration of a Single Dose of Hydrocodone ER in Healthy Subjects by Race (Integrated Single-Dose Pharmacokinetic Analysis Set)

Parameter (unit)	White (N=349)	Non-white (N=144)
C_{max} (ng/mL)	10.49 (2.72)	10.18 (2.59)
$AUC_{0-\infty}$ (ng·h/mL)	195 (48)	194 (56)
AUC_{0-t} (ng·h/mL)	194 (48)	191 (54)
t_{max} (h)[a]	8.0 (5.0, 12.0)	8.0 (5.0, 13.0)
$t_{½}$ (h)	9.5 (2.9)	12.9 (4.0)
λ_z (1/h)	0.0806 (0.0234)	0.0582 (0.0152)

Source: Integrated Single Dose Pharmacokinetic Analysis Set, Summary 6.1.

[a] Median (range) is presented for t_{max}.

$AUC_{0-\infty}$=area under the plasma drug concentration versus time curve (AUC) from time zero to infinite time AUC_{0-t}=AUC from time 0 to last measurable concentration; C_{max}=maximum observed plasma drug concentration; ER=extended-release; SD=standard deviation; t_{max}=time to maximum observed plasma drug concentration; $t_{½}$=elimination half-life; λ_z=apparent plasma terminal elimination rate constant.

2.3.3 Effect of Sex:

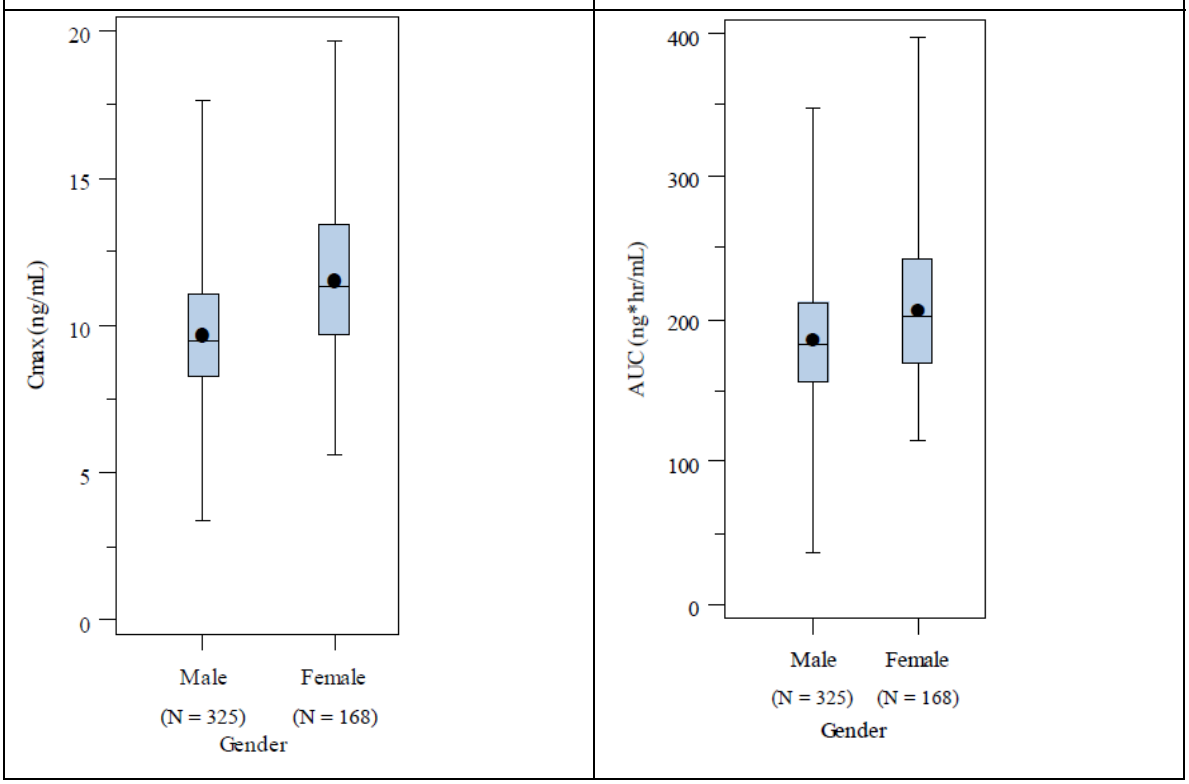
Overall, exposure was generally comparable between men and women. These data support a lack of effect of sex on the pharmacokinetics of hydrocodone following administration of hydrocodone ER.

Table : Mean (SD) Dose-Normalized (to 15 mg) Pharmacokinetic Parameter Values for Hydrocodone Following Administration of a Single Dose of Hydrocodone ER in Healthy Subjects by Sex (Pharmacokinetic Analysis Set, Integrated Demographic Subset)

Parameter (unit)	Male (N=325)	Female (N=168)
C_{max} (ng/mL)	9.77 (2.25)	11.60 (3.04)
$AUC_{0-\infty}$ (ng·h/mL)	188 (48)	209 (52)
AUC_{0-t} (ng·h/mL)	186 (47)	206 (52)
t_{max} (h)a	8.0 (5.0, 13.0)	7.4 (5.0. 12.0)
$t_{½}$ (h)	10.1 (3.4)	11.2 (3.8)
λ_z (1/h)	0.0761 (0.0230)	0.0700 (0.0243)

Source: Pharmacokinetic Analysis Set, Integrated Demographic Subset, Summary 5.1.
[a] Median (range) is presented for t_{max}.

Figure: Box plot of Cmax and AUC (dose-normalized to 15 mg) following administration of Vantrela ER tablets in healthy subjects by Age group.



2.3.4 Effect of Body Mass Index:

No meaningful difference in exposure was observed between subjects ≤25 mg/m2 and subjects >25 kg/m2. These data support the lack of effect of BMI on the pharmacokinetics of hydrocodone following administration of hydrocodone ER within the relatively limited range of BMI of the subjects participating in the clinical pharmacology studies.

Table: Mean (SD) Dose-Normalized (to 15 mg) PK Parameters for Hydrocodone Following Vantrela ER Tablet administration in Healthy Subjects by BMI Group.

Parameter	≤25 kg/m^2 (N=189)	>25 kg/m^2 (N=304)
C_{max} (ng/mL)	10.66 (2.88)	10.24 (2.54)
$AUC_{0-\infty}$ (ng·h/mL)	197 (51)	194 (50)
AUC_{0-t} (ng·h/mL)	194 (50)	192 (49)
t_{max} (h)[a]	8.0 (5.0, 12.0)	8.0 (5.0, 13.0)
$t_{½}$ (h)	10.8 (3.3)	10.3 (3.8)
λ_z (1/h)	0.0714 (0.0229)	0.0757 (0.0239)

Source: Pharmacokinetic Analysis Set, Integrated Demographic Subset, Table 8.1.

[a] Median (range) is presented for t_{max}. $AUC_{0-\infty}$=area under the plasma drug concentration versus time curve (AUC)

2.3.5 Effect of CYP2D6 Metabolism Status:

Hydrocodone systemic exposure was not altered in patients with different CYP2D6 metabolism status. Hydromorphone, a potent opioid, is formed from the O-demethylation of hydrocodone, mediated by polymorphic enzyme CYP2D6, and contributes to the total analgesic effect of hydrocodone. As shown below, CYP2D6 poor metabolizers have very low hydromorphone levels followed with intermediate and extensive metabolizers showing most systemic exposure of hydromorphone. However, following administration of Vantrela ER tablet, hydromorphone plasma concentrations are approximately 1% to 2% of those of the parent drug. Hence, impact of CYP2D6 metabolism status is limited.

Table : Mean (SD) Dose-Normalized (to 15 mg) Pharmacokinetic Parameters for Hydrocodone Following Administration of a Single Dose of Hydrocodone ER in Healthy Subjects by CYP2D6 Metabolizer Status (Pharmacokinetic Analysis Set, Integrated Demographic Subset)

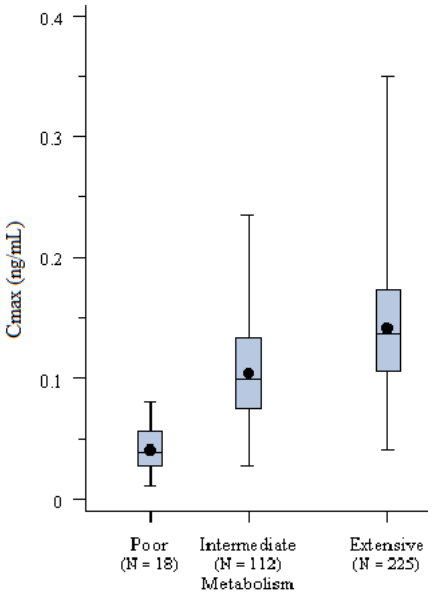
Parameter (unit)	Poor metabolizers (N=21)	Intermediate metabolizers (N=114)	Extensive metabolizers (N=225)
C_{max} (ng/mL)	12.02 (2.78)	10.91 (2.75)	10.22 (2.66)
$AUC_{0-\infty}$ (ng·h/mL)	213 (58)	207 (52)	189 (47)
AUC_{0-t} (ng·h/mL)	212 (58)	205 (51)	187 (47)
t_{max} (h)[a]	8.0 (5.0,10.5)	8.0 (5, 13)	8.0 (5, 12.5)
$t_{½}$ (h)	9.6 (3.4)	10.2 (3.1)	10.4 (3.1)
λ_z (1/h)	0.0804 (0.0245)	0.0756 (0.0244)	0.0737 (0.0233)

Source: Ad Hoc Summary 1.

[a] Median (range) is presented for t_{max}.

$AUC_{0-\infty}$=area under the plasma drug concentration versus time curve (AUC) from time zero to infinite time; AUC_{0-t}=AUC from time 0 to last measurable concentration; C_{max}=maximum observed plasma drug concentration; CYP2D6=cytochrome P450 2D6 enzyme; ER=extended-release; SD=standard deviation; t_{max}=time to maximum observed plasma drug concentration; $t_{½}$=elimination half-life; λ_z=apparent plasma terminal elimination rate constant.

Figure: Box-Plot of Hydromorphone Cmax (Dose Normalized to 15 mg) Following Administration of Single Dose of Vantrela ER Tablet by CYP2D6 metabolism status.



2.3.6 Effect of Renal Impairment:

Mild renal impairment had little impact on hydrocodone exposure. Although the mean increase in Cmax was approximately 50% in the moderately impaired, there was no consistent trend toward an increase in Cmax with increasing severity of renal impairment. Overall systemic exposure to hydrocodone (as assessed by AUC0-∞) in subjects with moderate or severe renal impairment was, on average, up to approximately 70% higher than that in subjects with normal renal function. Subjects with ESRD displayed similar exposure as subjects with normal renal function.

Table summarizing PK parameters of hydrocodone in patients with renal impairment was presented above in the summary of clinical pharmacology findings. Comparison of systemic exposure in terms of statistical analysis is presented in the table below.

Table: Comparison of Primary Pharmacokinetic Parameter Values for Hydrocodone Following Administration of a Single 45-mg Dose of Hydrocodone ER in Subjects With Varying Degrees of Renal Function (Study-Specific Pharmacokinetic Analysis Set)

Parameter	Normal renal function (N=13)	Mild renal impairment (N=8)	Mild/normal ratio	90% CI
C_{max} (ng/mL)	28.07	32.10	1.144	0.9400,1.3920
$AUC_{0-\infty}$ (ng·h/mL)	545	628	1.151	0.9180, 1.4420
	Normal renal function (N=13)	**Moderate renal impairment (N=9)**	**Moderate/normal ratio**	**90% CI**
C_{max} (ng/mL)	28.07	40.99	1.461	1.2080, 1.7660
$AUC_{0-\infty}$ (ng·h/mL)	545	949	1.739	1.3990, 2.1620
	Normal renal function (N=13)	**Severe renal impairment (N=9)**	**Severe/normal ratio**	**90% CI**
C_{max} (ng/mL)	28.07	34.87	1.243	1.0280, 1.5020
$AUC_{0-\infty}$ (ng·h/mL)	545	914	1.675	1.3470, 2.0830
	Normal renal function (N=13)	**ESRD (N=9)**	**ESRD/normal ratio**	**90% CI**
C_{max} (ng/mL)	28.07	30.98	1.104	0.9130, 1.3340
$AUC_{0-\infty}$ (ng·h/mL)	545	630	1.155	0.9290, 1.4370

Source: Study 1088, Summary 15.9.

$AUC_{0-\infty}$=area under the plasma drug concentration by time curve from time 0 to infinity; CI=confidence interval; C_{max}=maximum observed plasma drug concentration; ER=extended-release; ESRD=end-stage renal disease.Normal renal function=estimated creatinine clearance >80 mL/min; mild renal impairment=creatinine clearance >50-80 mL/min; moderate renal impairment=creatinine clearance of 30-50 mL/min, inclusive; severe renal impairment=creatinine clearance <30 mL/min; ESRD=hemodialysis.

Note: Values represent the geometric mean.

Table: Mean (Standard Deviation) Pharmacokinetic Parameters for Hydromorphone Following Administration of the 45-mg Bitartrate Extended-Release Tablet to Subjects With Varying Degrees of Renal Function

Parameter	Normal renal function (N=13)	Mild renal impairment (N=8)	Moderate renal impairment (N=9)	Severe renal impairment (N=9)	ESRD (N=9)
C_{max} (ng/mL)	0.305 (0.1308)	0.338 (0.1224)	0.312 (0.1272)	0.443 (0.3037)	0.290 (0.2134)
t_{max} (h)	10.0 (7.0, 18.0)	11.0 (5.0, 12.0)	12.0 (9.0, 18.0)	14.0 (5.0, 24.0)	9.0 (6.0, 18.0)

SOURCE: Summary 15.11 and Listing 16.2.8.26.

NOTE: Median (range) is presented for t_{max}.

ESRD=end-stage renal disease; C_{max}=maximum observed plasma drug concentration; t_{max}=time to maximum observed plasma drug concentration by inspection.

AUC could not be calculated because of incomplete hydromorphone profiles.

As noted in the tables above, hydromorphone concentrations were approximately 1 to 2% of those of hydrocodone in each group.

Table: Recovery of Hydrocodone in Urine in Patients with Different Degree of Renal Impairment or Healthy subjects.

Variable Statistic	Normal (N=13)	Mild (N=8)	Moderate (N=9)	Severe (N=9)	ESRD (N=9)
Renal clearance (L/hr)					
n	13	8	9	9	6
Mean	4.76	3.30	1.57	1.36	0.23
Geometric mean	4.32	3.22	1.52	1.27	0.09
SD	2.672	0.763	0.414	0.538	0.263
SE of mean	0.741	0.270	0.138	0.179	0.107
CV	56.12200	23.10588	26.33656	39.64273	113.36723
Median	4.33	3.20	1.61	1.24	0.12
Min, max	2.53, 12.86	2.20, 4.51	1.06, 2.39	0.72, 2.35	0.01, 0.60
Cumulative % dose recovered in urine (%)					
n	13	8	9	9	6
Mean	5.94	4.61	3.37	2.70	0.30
Geometric mean	5.22	4.49	3.20	2.57	0.14
SD	3.757	1.132	1.092	0.843	0.316
SE of mean	1.042	0.400	0.364	0.281	0.129
CV	63.26233	24.55228	32.38432	31.22776	106.52254
Median	5.42	4.56	3.43	2.90	0.18
Min, max	2.23, 17.31	3.30, 5.96	1.51, 5.60	1.33, 3.66	0.02, 0.77
Cumulative amount recovered in urine (mcg)					
n	13	8	9	9	6
Mean	2672.53	2074.21	1517.94	1215.78	133.76
Geometric mean	2348.50	2018.80	1442.52	1155.00	64.93
SD	1690.237	509.508	491.454	379.741	142.670
SE of mean	468.787	180.138	163.818	126.580	58.245
CV	63.24472	24.56393	32.37633	31.23441	106.66534
Median	2438.90	2049.47	1543.10	1306.95	79.46
Min, max	1003.39, 7788.38	1485.66, 2680.25	681.22, 2520.63	598.20, 1646.99	9.49, 347.47

2.3.7 Effect of Hepatic Impairment:

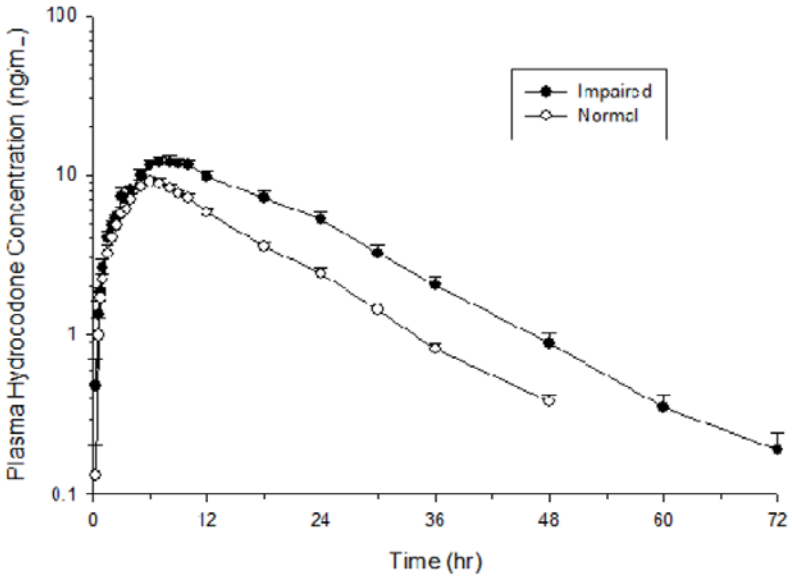
Mean Cmax was approximately 30% higher and mean AUC0-∞ was approximately 70% higher in subjects with moderate hepatic impairment than in subjects with normal hepatic function. Teva has not evaluated the impact of mild and severe hepatic impairment on Vantrela ER tablet PK.

Table : Comparison of Primary Pharmacokinetic Parameter Values Following Administration of the 15-mg Hydrocodone ER Tablet to Subjects With Normal Hepatic Function and Subjects With Moderate Hepatic Impairment (Study-Specific Pharmacokinetic Analysis Set)

Parameter (unit)	Normal hepatic function (N=8)	Moderate hepatic impairment (N=8)	Moderate/normal ratio	90% CI
C_{max} (ng/mL)	9.96	12.73	1.277	1.077, 1.515
$AUC_{0-\infty}$ (ng·h/mL)	153	261	1.704	1.415, 2.052

Source: Study 1089, Table 9.
$AUC_{0-\infty}$=area under the plasma drug concentration by time curve from time 0 to infinity; CI=confidence interval; C_{max}=maximum observed plasma drug concentration; ER=extended-release; SR=standard error.
Note: Values presented are geometric mean (SE of the mean).

Figure: PK profile of hydrocodone in healthy and moderate hepatic impaired subjects following Vantrela ER administration (15 mg).



Source: Study 1089, Figure 2.
ER=extended-release; SE=standard error.
Subjects were considered to have moderate hepatic impairment if they had a Child-Pugh Classification score of 7-9 points (moderate) and exhibited physical signs consistent with 1 or more of the following characteristic clinical manifestations of liver cirrhosis: liver firmness to palpation, splenic enlargement, spider angiomas, palmar erythema, parotid hypertrophy, testicular atrophy, ascites (accumulation of fluid in the abdominal cavity), or gynecomastia.

2.4 Extrinsic Factors

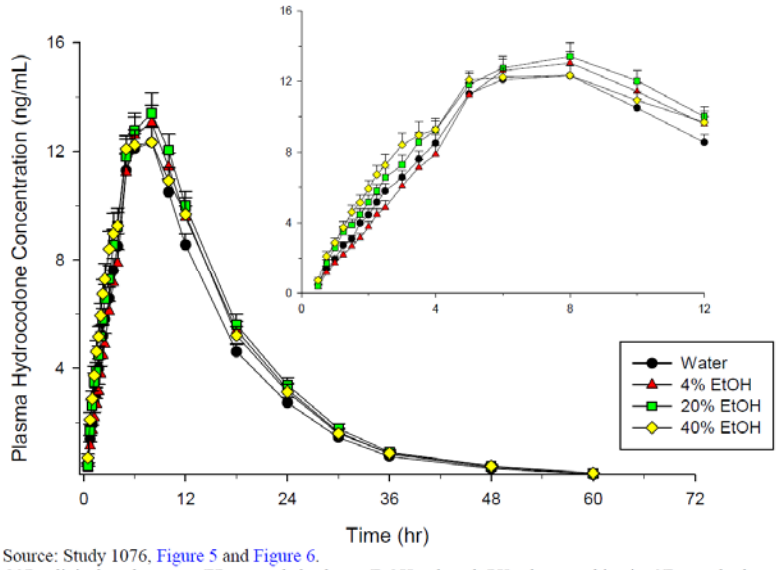
a) Drug-Drug Interactions: No clinical drug-drug interaction studies have been performed for hydrocodone ER.

Hydrocodone is metabolized by CYP3A4 and CYP2D6. The pharmacokinetics of hydrocodone may be affected by inhibitors and inducers of CYP3A4, with a possible impact on safety and efficacy. To a lesser extent inhibitors of CYP2D6 may have an impact on efficacy in some individual patients. However, role of CYP2D6 may be limited.

2.4.1 Alcohol Interaction:

Cmax and AUC of hydrocodone were bioequivalent following alcohol treatment (20% and 40%) compared to fasted treatment Vantrela ER 15 mg tablet. Teva conducted in vitro alcohol interaction study to evaluate the potential for dose-dumping with up to 90 mg Vantrela ER tablet. The sponsor indicates that the dose released within the first two hours of the dissolution test did not suggest dose-dumping with Vantrela ER tablet. The clinical alcohol interaction study 1076 evaluated PK of Vantrela ER 15 mg tablet (higher doses were not evaluated) and did not reveal a significant change in systemic exposure following coadministration with 20% or 40% alcohol compared to drug taken without alcohol under fasting condition.

Figure : **Mean (+SE) Plasma Concentration versus Time Profiles for Hydrocodone Over 72 Hours and 12 Hours (Inset) Following Administration of A Single 15-mg Dose of Hydrocodone ER Fasting With Water and Fasting With Varying Strengths of Alcohol in Healthy Subjects (Study-Specific Pharmacokinetic Analysis Set)**



Source: Study 1076, Figure 5 and Figure 6.
CSR=clinical study report; ER=extended-release; EtOH=ethanol; PK=pharmacokinetic; SE=standard error.
Note: The y-axis for this plot and inset have been modified to a linear scale (source is presented as log scale).
Although PK sampling was performed over 72 hours, plasma hydrocodone concentrations were primarily below the lower limit of quantification of the assay at the 72-hour time point, resulting in no mean value being presented for this time point.

Table : Mean (Standard Deviation) Plasma Hydrocodone Pharmacokinetic Parameters by Treatment (Pharmacokinetic Analysis Set)

Variable	Treatment A (N=30)	Treatment B (N=29)	Treatment C (N=30)	Treatment D (N=27)	Treatment E (N=24)
C_{max} (ng/mL)	12.8 (3.21)	19.0 (4.65)	13.6 (3.58)	14.0 (3.85)	13.6 (2.89)
t_{max} (hr)[a]	8.0 (5.0,10.0)	6.00 (3.00, 10.00)	8.00 (5.00, 12.00)	8.00 (4.00, 10.00)	6.00 (3.50, 12.00)
AUC_{0-t} (ng·hr/mL)	195.2 (53.56)	214.6 (51.25)	211.4 (52.68)	225.6 (63.44)	216.5 (58.59)
AUC_{0-72} (ng·hr/mL)	196.4 (53.48)	216.0 (51.38)	212.7 (52.80)	226.5 (63.25)	217.5 (58.26)
AUC_{0-2} (ng·hr/mL)	4.0 (1.56)	2.4 (1.98)	3.3 (1.53)	4.8 (1.85)	5.5 (2.22)
AUC_{0-12} (ng·hr/mL)	105.1 (26.70)	125.1 (24.54)	107.9 (27.31)	116.1 (29.23)	113.0 (22.69)
$AUC_{0-\infty}$ (ng·hr/mL)	198.2 (53.76)	216.7 (51.44)	214.3 (53.24)	228.2 (63.52)	219.7 (58.69)
Extrapolation (%)	1.5 (0.85)	1.0 (0.37)	1.3 (0.67)	1.2 (0.66)	1.5 (1.03)
λ_z (1/hr)	0.077 (0.0303)	0.091 (0.0305)	0.080 (0.0287)	0.073 (0.0221)	0.069 (0.0282)
$t_{½}$ (hr)	10.8 (5.30)	8.6 (3.55)	9.9 (3.89)	10.5 (3.89)	11.8 (4.90)

SOURCE: Summary 15.9.1and Listing 16.2.8.19.
[a] Median (range) are presented for t_{max}.

A=One 15-mg hydrocodone bitartrate extended-release tablet with 240 mL of water in a fasted state;
B=One 15-mg hydrocodone bitartrate extended-release tablet with 240 mL of water in a fed state;
C=One 15-mg hydrocodone bitartrate extended-release tablet with 240 mL of 4% volume/volume (v/v) alcohol in a fasted state; D=One 15-mg hydrocodone bitartrate extended-release tablet with 240 mL of 20% v/v alcohol in a fasted state;
E=One 15-mg hydrocodone bitartrate extended-release tablet with 240 mL of 40% v/v alcohol in a fasted state.

Table : Effect of Alcohol on Hydrocodone Exposure (Pharmacokinetic Analysis Set)

Parameter	Treatment C (n=30)	Treatment A (n=30)	Ratio C/A	95% CI
C_{max} (ng/mL)	13.2	12.4	1.050	0.992, 1.112
$AUC_{0-\infty}$ (ng·hr/mL)	207.6	191.3	1.068	1.013, 1.125
	Treatment D (n=27)	**Treatment A (n=27)**	**Ratio D/A**	**95% CI**
C_{max} (ng/mL)	13.5	12.3	1.085	1.025, 1.147
$AUC_{0-\infty}$ (ng·hr/mL)	219.7	192.8	1.129	1.060, 1.203
	Treatment E (n=24)	**Treatment A (n=24)**	**Ratio E/A**	**95% CI**
C_{max} (ng/mL)	13.3	11.8	1.144	1.077, 1.216
$AUC_{0-\infty}$ (ng·hr/mL)[a]	212.9	186.3	1.170	1.110, 1.234

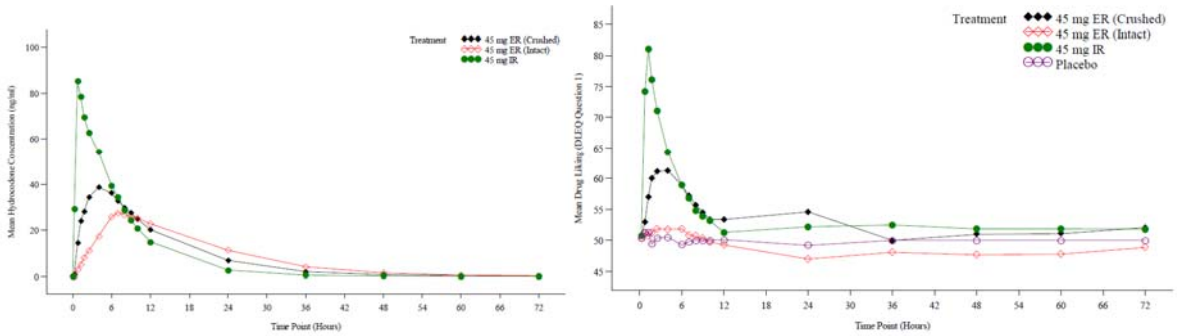
SOURCE: Summary 15.11.1, Summary 15.12.1, Summary 15.13.1, Listing 16.2.8.19.
A=One 15-mg hydrocodone bitartrate extended-release tablet with 240 mL of water in a fasted state;
C=One 15-mg hydrocodone bitartrate extended-release tablet with 240 mL of 4% volume/volume (v/v) alcohol in a fasted state; D=One 15-mg hydrocodone bitartrate extended-release tablet with 240 mL of 20% alcohol in a fasted state; E=One 15-mg hydrocodone bitartrate extended-release tablet with 240 mL of 40% alcohol in a fasted state.
NOTE: Values are geometric means; CI=confidence interval.

2.4.2 Oral and Intranasal Abuse after crushing:

Teva evaluated relative abuse potential of the Vantrela ER tablet when finely crushed and ingested orally or after intranasal administration in nondependent recreational opioid users.

The abuse liability study 1085 compared PK and PD (drug liking) of Vantrela ER tablet crushed with intact tablet, crushed IR tablet and Placebo. In this study, intact Vantrela ER 45 mg tablet systemic exposure was comparable to that noted in other single dose PK studies. Cmax and AUC0-inf were 29 ng/mL & 568 ng.h/mL in study 1081. Mean drug liking for intact Vantrela ER tablet was low (~50 or neither like nor dislike) followed by crushed Vantrela ER tablet and most drug liking noted with crushed IR tablet.

Figure : Mean Plasma Concentration-Time Profiles and Mean Drug Liking (DLEQ Question 1) Over Time in Healthy, Nondependent, Recreational Opioid Users Administered Single Doses of Hydrocodone Extended-Release Tablets (Crushed or Intact) or an Immediate-Release Formulation or Placebo



SOURCE: Section 15, Figure 1.1.1.A, Adhoc Figure 1.1.0.A.
ER=hydrocodone bitartrate extended-release tablet; IR=immediate-release hydrocodone; DLEQ=Drug Liking and Effects Questionnaire.

Based on BE analysis, crushed Vantrela ER 45 mg tablet and IR hydrocodone had 42% and 313% higher Cmax compared to intact Vantrela ER 45 mg tablet.

Table : Mean (Standard Deviation) Pharmacokinetic Parameters for Hydrocodone After Administration of Immediate- and Extended-Release Hydrocodone (Pharmacokinetic Analysis Set)

Variable	45-mg IR (N=39)	45-mg ER crushed (N=41)	45-mg ER intact (N=40)
C_{max} (ng/mL)	91.46 (16.817)	40.78 (10.204)	28.77 (6.088)
t_{max} (h)	0.8 (0.3, 4.1)	4.0 (1.8, 7.0)	7.1 (6.1, 12.0)
$AUC_{0-\infty}$ (ng·h/mL)	625 (137.3)	586 (138.5)	584 (124.8)
$AUC_{0-0.75}$ (ng·h/mL)	29 (13.5)	3 (1.7)	1 (0.3)
AUC_{0-4} (ng·h/mL)	246 (42.9)	103 (25.0)	34 (9.0)
AUC_{0-7} (ng·h/mL)	377 (60.2)	212 (47.1)	104 (22.6)
AUC_{0-t} (ng·h/mL)	623 (135.5)	584 (138.6)	581 (124.5)
Extrapolation (%)	0.26 (0.098)	0.40 (0.200)	0.61 (0.497)
λ_z (1/h)	0.1384 (0.02176)	0.0933 (0.02519)	0.0929 (0.02671)
$t_{1/2}$ (h)	5.13 (0.804)	7.97 (2.132)	8.04 (2.194)
AQ (ng/mL/h)	108.59 (58.789)	10.97 (3.997)	3.88 (1.056)

SOURCE: Summary 15.9.1, Listing 16.2.5.03.

Intranasal abuse of crushed Vantrela ER tablet was evaluated in abuse liability study 10032. PK and PD of intranasal crushed Vantrela ER 45 mg tablet, intranasal crushed Zohydro 45 mg tablet, intranasal hydrocodone powder 45 mg were compared with intact Vantrela ER 45 mg or Placebo. The peak plasma concentrations of hydrocodone and maximum drug liking were highest and achieved rapidly (Tmax 1.5 hrs) following intranasal administration of API and crushed Zohydro. As noted in the oral abuse liability study, mean drug liking for intact Vantrela ER tablet was low (~50 or neither like nor dislike). A two-fold increase in systemic exposure is noted following intranasal administration of Vantrela ER tablet which was associated with significant increase in drug liking (See bottom right figure).

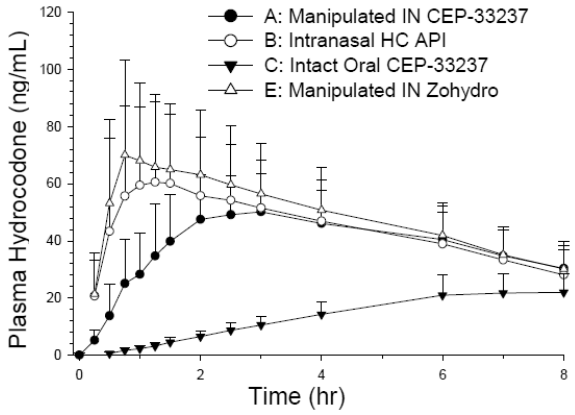
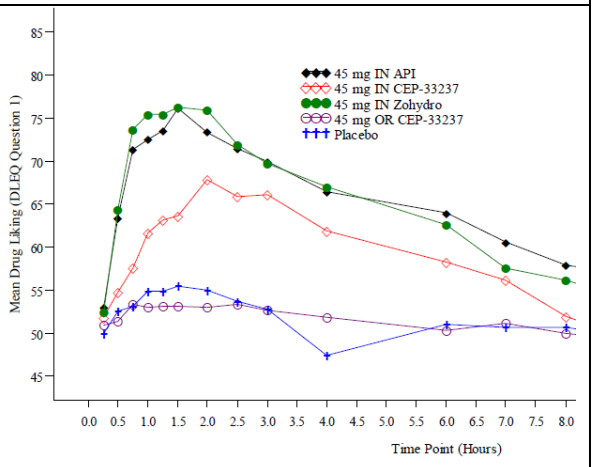
Mean hydrocodone PK profile following intranasal abuse of different hydrocodone preparations (45 mg) vs. intact oral Vantrela ER 45 mg tablet.	**Mean drug liking (question 1) vs. time following intranasal abuse of different hydrocodone preparations (45 mg) vs intact oral Vantrela ER 45 mg tablet.**
 Source: Summary 15.8.1. Note: Concentration-time profile to 8 hours is shown as an inset.	

Table: Mean (Standard Deviation) Pharmacokinetic Parameters for Hydrocodone After Intranasal Administration of Crushed Vantrela ER (IN CEP-33237), Hydrocodone API or Crushed Zohydro™, or Oral Administration of Intact Vantrela ER (OR CEP-33237) at 45 mg Dose.

Variable	45 mg IN API (N=38)	45 mg IN Zohydro™ (N=39)	45 mg IN CEP-33237 (N=41)	45 mg OR CEP-33237 (N=38)
C_{max} (ng/mL)	71.28 (30.48)	80.27 (29.29)	56.84 (15.07)	25.05 (7.18)
t_{max} (h)	1.38 (0.60, 7.07)	1.12 (0.55, 6.17)	2.62 (1.33, 7.02)	9.11 (4.10, 12.12)
$AUC_{0-\infty}$ (ng·h/mL)	579 (163)	639 (179)	572 (150)	568 (172)
AUC_{0-t} (ng·h/mL)	576 (161)	637 (178)	568 (149)	531 (152)
$AUC_{0\text{-}tmax,\ API}$ (ng·h/mL)	57.5 (28.3)	66.5 (28.3)	24.9 (13.4)	1.9 (0.8)
$AUC_{0\text{-}tmax,\ CEP\ (IN)}$ (ng·h/mL)	125.9 (51.8)	142.4 (51.5)	78.5 (28.6)	9.4 (2.7)
$AUC_{0\text{-}tmax,\ CEP\ (Oral)}$ (ng·h/mL)	380.0 (112.3)	416.3 (108.8)	336.4 (75.1)	127.5 (34.9)
$AUC_{0\text{-}tmax,\ Zohydro}$ (ng·h/mL)	39.3 (20.9)	46.4 (21.2)	15.1 (8.7)	1.0 (0.5)
Extrapolation (%)	0.60 (0.94)	0.38 (0.24)	0.73 (0.72)	6.04 (3.94)
λ_z (1/h)	0.124 (0.023)	0.127 (0.021)	0.114 (0.015)	0.076 (0.024)
$t_{1/2}$ (h)	5.78 (1.06)	5.58 (0.86)	6.16 (0.76)	9.96 (3.03)
AQ (ng/mL/h)	59.6 (55.2)	75.4 (54.0)	22.6 (12.2)	3.1 (1.2)

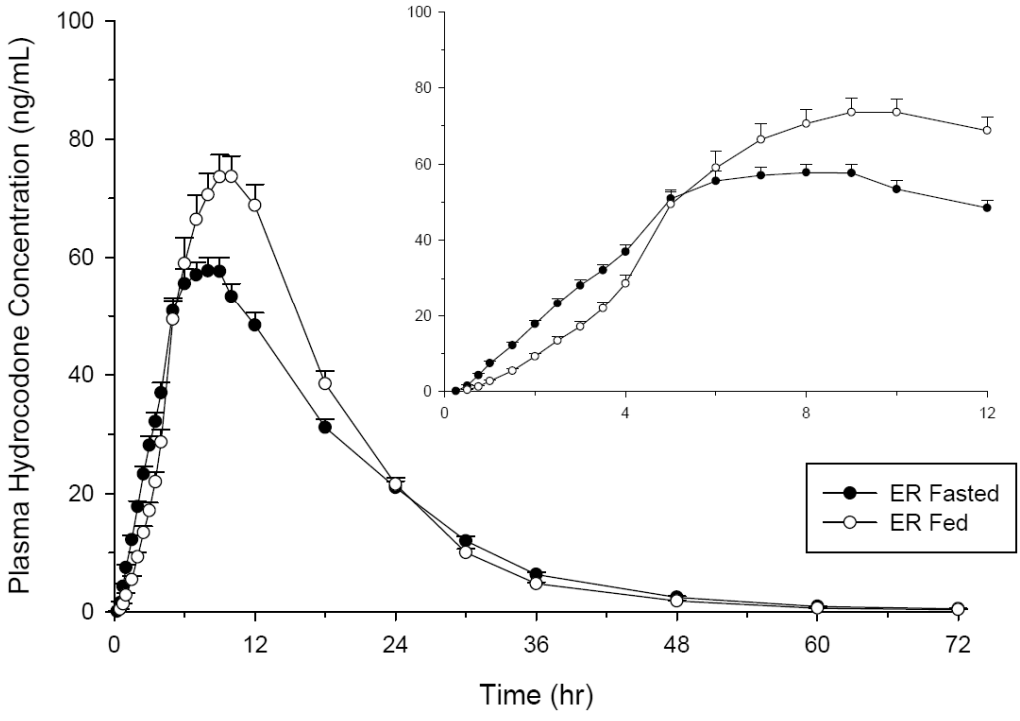
Source: Summary 15.9.1.
API=active pharmaceutical ingredient; AQ=abuse quotient (C_{max}/t_{max})

2.5 General Biopharmaceutics

2.5.1 What is the extent of food-effect on Vantrela ER tablet PK?

Although overall exposure (as assessed based by AUC0-t and AUC0-∞) as well as AUC up to 8 hours (median tmax in the fasted state) met criteria to conclude bioequivalence (0.800, 1.250), mean Cmax was approximately 34% to 45% higher (Studies 1076, 1090, and 10024) following administration of a single 90-mg dose of hydrocodone ER with a high-fat meal as compared to when administered in a fasted state. The maximum observed increase in the presence of food (approximately 118%) is consistent with the maximum intra-individual difference observed under fasting conditions in studies in which bioequivalence was tested and demonstrated.

Figure : Mean (+SE) Plasma Concentration versus Time Profiles for Hydrocodone in Healthy Subjects Over 72 Hours and Over 12 Hours (Inset) Following Administration of a Single 90-mg Dose of Hydrocodone ER Under Fasted and Fed Conditions
(Study 1090)



Source: Study 1090, Figure 2 and Figure 3.
ER=extended-release; SE=standard error.
Note: The y-axis for this plot and inset have been modified to a linear scale (source is presented as log scale).

2.6 Analytical

2.6.1 Are the active moieties in the plasma (or other biological fluid) appropriately identified and measured to assess pharmacokinetic parameters

Quantification of hydrocodone and hydromorphone in human plasma containing dipotassium EDTA was conducted via a validated HPLC method with MS/MS detection at (b) (4) (DP-2009-084). This analytical method was used across the full clinical program. Plasma samples were kept frozen at approximately -20°C prior to analysis. A 100-µL human plasma aliquot was fortified with 25 µL of 25 ng/mL internal standard working solution at approximately -20°C prior to analysis. Analytes were isolated through supported liquid extraction using Isolute® SLE+, 200 mg, 96-well SPE plates (Biotage, Charlotte, NC, USA) and eluted with 1.6 mL of dichloromethane. The eluate was evaporated under a nitrogen stream at approximately 45°C, and the remaining residue was reconstituted with 250 µL of 100:0.025 acetonitrile/trifluoroacetic acid, v/v. The final extract was analyzed via HPLC with column-switching with MS/MS detection using positive ion electrospray.

The method has a nominal range of 0.100 to 100 ng/mL for hydrocodone and 0.0500 to 50.0 ng/mL for hydromorphone. Precision and accuracy of the method were within acceptable ranges according to (b) (4) SOPs using quality control (QC) samples prepared at concentrations of 0.100, 0.300, 0.800, 3.00, 12.0, and 75.0 ng/mL for hydrocodone and 0.0500, 0.150, 0.400, 1.50, 6.00, and 37.5 ng/mL for hydromorphone. Inter-assay precision for hydrocodone, as measured by the coefficient of variation percent (CV%), was less than or equal to 5.13%, and inter-assay bias ranging from -5.49% to 3.19% from nominal. Inter-assay precision for hydromorphone, as measured by the CV%, was less than or equal to 10.8%, and inter-assay bias ranging from -8.42% to -1.46% from nominal was also acceptable. Stability studies, including stability of hydrocodone and hydromorphone in processed sample, matrix (plasma), blood, and solution provided acceptable results and are summarized in Table 5 (DP-2009-084).

Method performance in lipemic (DP-2014-131) and hemolyzed plasma, and in the presence of common over-the-counter medications, including acetaminophen, ibuprofen, naproxen, caffeine, ethanol, acetylsalicylic acid, and salicylic acid, was tested and found to be acceptable. (DP-2009-084) Method performance was also tested and found to be acceptable in the presence of naltrexone and its metabolite 6β-naltrexol. The validity of the method was supported by incurred sample reanalysis (ISR).

Table : Stability of Hydrocodone and Hydromorphone in Matrix and Solutions[a]

		Hydrocodone	Hydromorphone
Stability in matrix	Room temperature	24 hours	24 hours
	Freeze/Thaw (–20°C)	6 cycles	6 cycles
	Freezer (–20°C)	1069 days	1069 days
	Freezer (–70°C)	371 days	371 days
Stability in extracted matrix	2 to 8°C	181 hours	181 hours
Stability in whole blood [a]	Room temperature	1 hour	1 hour
	On wet ice	1 hour	1 hour
Stability in solution	Stock solutions at 4°C (0.1 mg/mL)		28 days
	Stock solutions at room temperature (0.1 mg/mL)		7 hours

[a] From DP-2014-131

3 Labeling

Recommend the following changes to the clinical pharmacology section of the product label.

Highlights:

Dosage and Administration:

[redacted]. Monitor closely. (2.4 8.6)

. [redacted].
Monitor closely. (2.5, 8.7)

USE IN SPECIFIC POPULATIONS:

· Severe Hepatic Impairment: Use not recommended.

[redacted]

8.5 [redacted]

…

Hydrocodone is known to be substantially secreted by the kidney [redacted] the risk of [redacted] reactions may be greater in patients with impaired renal function [redacted] Because elderly patients are more likely to have decreased renal function, care should be taken in dosage selection, and it may be useful to monitor renal function.

8.6 Hepatic Impairment

Patients with [redacted] hepatic impairment ~~may~~ have higher plasma concentrations of hydrocodone than those with normal function. [redacted]

(b) (4)

(b) (4) Monitor these patients closely for adverse events such as respiratory depression *[see Clinical Pharmacology (12.3)]*. (b) (4)

8.7. Renal Impairment

(b) (4) No adjustment in starting dose with VANTRELA ER is required for patients with mild renal impairment (b) (4) **Patients with moderate or severe renal impairment or end stage renal disease have higher plasma concentrations than those with normal renal function.** (b) (4) Monitor all patients closely for adverse events such as respiratory depression *[see Clinical Pharmacology (12.3)]*.

12.3 Pharmacokinetics

(b) (4)

(b) (4) *Populations*

(b) (4)

(b) (4)

Systemic exposure of hydrocodone (Cmax and AUC) was similar between males and females

(b) (4)

Race

(b) (4)

(b) (4) -Systemic exposure (as assessed by AUC and Cmax) was comparable in Caucasian subjects (n=349) and in subjects of other races (n=144).

Hepatic Impairment
In subjects with moderate hepatic impairment (n=8; Child-Pugh classification (CPC) score of 7-9 points), overall systemic exposure to hydrocodone (as assessed by AUC) was approximately 70% higher and Cmax was approximately 30% higher following a single dose of VANTRELA ER as compared to subjects with normal hepatic function (n=8). Subjects with severe hepatic impairment were not studied.

Renal Impairment
Pharmacokinetics of VANTRELA ER were evaluated in healthy subjects with normal renal function (n=13 subjects with normal renal function [creatinine clearance >80 mL/min]) and compared with patients with mild (n=8; creatinine clearance >50-80 mL/min), moderate (n=9; Creatinine clearance 30-50 mL/min**)**, and severe renal impairment (n=9 Creatinine clearance <30 mL/min**)** or patients with end-stage renal disease (ESRD) undergoing hemodialysis. Patients with mild renal impairment did not show significant difference in Cmax and AUC of hydrocodone compared to healthy subjects. Overall systemic exposure to hydrocodone (as assessed by AUC) was up to approximately 70% higher following administration of a single dose of VANTRELA ER to subjects with moderate or severe renal impairment as compared to healthy subjects , . Mean peak concentrations were approximately 25% and 50% higher in patients with moderate and severe renal impairment, respectively compared to healthy subjects. Patients with ESRD undergoing hemodialysis after Vantrela ER administration had similar exposure compared to healthy subjects.

(b) (4)

4 Appendix

37 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

4.2 Individual Study Reviews

4.2.1 Study # 1071 Synopsis (Relative Bioavailability study)

Name of Sponsor/Company: Cephalon, Inc.	**Individual study table referring to part of dossier in which the individual study or study table is presented** **Volume:** **Reference:**	(For National Authority Use Only)
Name of Finished Product: Hydrocodone bitartrate extended-release tablet		
Name of Active Ingredient: Hydrocodone bitartrate (CEP-33237)		

Title of Study: A Randomized, Open-Label, 4-Period Crossover Study to Characterize the Pharmacokinetics and Safety of Hydrocodone Bitartrate From 3 Extended-Release Prototypes (45-mg Tablet) and From a Commercially Available Immediate-Release Hydrocodone/Acetaminophen Product (10-mg/325-mg Tablet) in Healthy Subjects

Investigators and Study Centers: Matthew Medlock, MD, PPD Development, LP, 7551 Metro Center Drive, Suite 200, Austin, Texas 78744 USA

Publication (reference): Results from this study have not been published at the time of approval of this report.

Study Period: 7 January 2010 to 25 February 2010 **Phase of Development:** 1

Primary Objective: The primary objective of the study was to characterize the pharmacokinetic profiles of 3 hydrocodone bitartrate extended-release prototypes (CEP-33237) and commercially available hydrocodone bitartrate immediate-release tablets in healthy subjects.

Secondary Objectives: The secondary objective of the study was to assess the safety of each treatment in healthy subjects who were not tolerant to opioids and who had been administered naltrexone hydrochloride by evaluating the following:

- occurrence of adverse events throughout the study
- clinical laboratory (serum chemistry, hematology, and urinalysis) test results at final assessment or early withdrawal
- vital signs measurements (blood pressure, pulse, and respiratory rate) throughout the study
- 12-lead electrocardiogram (ECG) findings at final assessment or early withdrawal
- physical examination findings at final assessment or early withdrawal
- oxyhemoglobin saturation (SpO_2) monitoring throughout the study
- concomitant medication usage throughout the study

Number of Subjects (Planned and Analyzed): For this study, 40 subjects were planned to be enrolled; data from 39 subjects were analyzed for safety and data from 36 patients were analyzed for pharmacokinetics.

Main Criteria for Inclusion: Subjects were included in the study if all of the following main criteria were met (not all inclusive):

- The subject was a man or woman 18 through 45 years of age, with a body mass index (BMI) between 20 and 30 kg/m^2, inclusive.
- The subject was in good health as determined by a medical and psychiatric history, physical examination, ECG, serum chemistry, hematology, urinalysis, and serology.

Main Criteria for Exclusion: Subjects were excluded from participating in this study if 1 or more of the following main criteria were met (not all inclusive):

- The subject had any clinically significant uncontrolled medical conditions (treated or untreated).
- The subject had a clinically significant deviation from normal in clinical laboratory values, or ECG or physical examination findings, as determined by the investigator or the medical monitor.

Study Drug Dose, Mode of Administration, Administration Rate, and Batch Number: Treatment A was a 45-mg hydrocodone bitartrate extended-release tablet with a [redacted] (b) (4) (lot number 200917),

treatment B was a 45-mg hydrocodone bitartrate extended-release tablet with a [redacted] (b) (4) (lot number 200916), and treatment C was a 45-mg hydrocodone bitartrate extended-release tablet with a [redacted] (b) (4) (lot number 200915). All 3 prototype tablets had the same [redacted] (b) (4) matrix. Study drug was orally administered to subjects at approximately 0800 (±2 hours) on the 1st day of each period.

Reference Therapy Dose, Mode of Administration, and Administration Rate: Treatment D was one 10-mg/325-mg hydrocodone bitartrate and acetaminophen immediate-release tablet (commercially available NORCO® [Watson Pharmaceuticals], lot number 217162A) administered orally every 6 hours until 4 tablets had been administered.

Method of Blinding: This was an open-label study with no blinding.

Duration of Treatment: Subjects were expected to participate in this study for approximately 45 days.

General Design and Methodology: Subjects were randomly assigned to 1 of the 4 following treatment sequences: ABCD, BCDA, CDAB, or DABC. The study consisted of a screening visit within 21 days before the 1st dose of study drug, followed by 4 open-label treatment periods, a final assessment at the last discharge or early withdrawal, and a follow-up visit. There was a minimum 5-day washout between the last administration of hydrocodone in 1 period and the 1st administration of hydrocodone in the next period. Subjects received all 4 treatments during the study. Subjects received one 50-mg tablet of naltrexone hydrochloride with 240 mL of water to block opioid receptors and minimize opioid-related adverse events approximately 15 and 3 hours before and approximately 9 and 21 hours after study drug administration (at 0800±2 hours) in each treatment period. For each of the 4 treatment periods, venous blood samples were collected immediately before and over 72 hours after study drug administration at 0800±2 hours for pharmacokinetic analyses. Subjects remained in the study center throughout each pharmacokinetic sampling period. Safety was also assessed throughout the study by monitoring the occurrence of adverse events, clinical laboratory test results, vital signs measurements, 12-lead ECG findings, physical examination findings, SpO_2 monitoring, and use of concomitant medications. Subjects who completed all scheduled visits had final procedures and assessments performed prior to discharge in administration period 4 (visit 5). Subjects who withdrew from the study before the completion of all scheduled assessments had final procedures and assessments performed prior to discharge in their last study drug administration period. All subjects were asked to return for a follow-up visit to occur 48 to 72 hours after their final discharge from the center. Safety parameters were evaluated at that time.

Pharmacokinetic Measures and Endpoints: During each administration period, blood samples (3 mL) were collected by venipuncture or indwelling catheter. Samples were collected immediately (within approximately 5 minutes) before and at specified time points through 72 hours after study drug administration at 0800 (±2 hours).

The following pharmacokinetic parameters were calculated for hydrocodone and its metabolite hydromorphone, when possible, for each extended-release formulation of hydrocodone:

- maximum observed plasma drug concentration (C_{max}) by inspection (without interpolation)
- time to maximum observed plasma drug concentration (t_{max}) by inspection
- area under the plasma drug concentration by time curve (AUC) from time 0 to infinity ($AUC_{0-\infty}$)
- AUC from time 0 to 72 hours after study drug administration (AUC_{0-72})

- AUC from time 0 to 24 hours after study drug administration (AUC_{0-24})
- AUC from time 0 to 12 hours after study drug administration (AUC_{0-12})
- AUC from time 0 to 2 hours after study drug administration (AUC_{0-2})
- AUC from time 0 to the time of the last measurable plasma drug concentration (AUC_{0-t})
- percentage extrapolation, $100x(AUC_{0-\infty}–AUC_{0-t})/AUC_{0-\infty}$
- apparent plasma terminal elimination rate constant (λ_z) and associated elimination half-life ($t_{½}$)

The following pharmacokinetic parameters were calculated for hydrocodone and its metabolite hydromorphone, when possible, following the 1st and last doses of the immediate-release tablet:

- C_{max} by inspection (without interpolation)
- t_{max} by inspection (NOTE: T_{max} was calculated both relative to the first dose administered [t_{max1}] and to the most recent dose [t_{max2}]).
- $AUC_{0-\infty}$
- AUC_{0-12}
- AUC from time 0 to 6 hours after study drug administration (AUC_{0-6})
- AUC_{0-2}
- AUC from 18 to 24 hours after study drug administration (AUC_{18-24})
- percentage extrapolation
- λ_z and associated $t_{½}$

Safety Variables: Safety was assessed during the study by evaluating adverse events, clinical laboratory test results (chemistry, hematology, and urinalysis), vital signs measurements, ECG and physical examination findings, SpO_2, and concomitant medication usage.

Statistical Considerations: Up to 40 healthy subjects were planned to be enrolled in this study, with the intent that approximately 30 subjects would complete the study. This sample size estimate was not based on statistical considerations. The set of randomized subjects includes all subjects who were randomly assigned to a treatment sequence, regardless of whether or not a subject received any study drug. The safety analysis set includes those subjects in the set of randomized subjects who received at least 1 dose of study drug. The pharmacokinetic analysis set includes those subjects in the safety analysis set who had sufficient data to calculate the pharmacokinetic parameters for treatment periods relevant to the planned comparisons. Demographic and baseline characteristics were summarized using descriptive statistics. Pharmacokinetic parameters were summarized with descriptive statistics including the geometric mean (if appropriate), coefficient of variation, and 95% confidence interval. Comparisons between treatments are descriptive. No formal statistical testing was performed. Summaries were presented for all subjects in the safety analysis set (ie, total) except summaries of adverse events and vital signs. Adverse events are presented overall and by treatment, whereas vital signs are presented by treatment only.

Summary of Results

Subject Disposition and Demography: In this study, 40 healthy subjects were enrolled and randomly assigned to a treatment sequence. Of the 40 subjects enrolled, 39 (98%) subjects received at least 1 dose of study drug and were evaluable for safety; 37 (93%) subjects were evaluable for pharmacokinetics and completed the study. One subject did not have a full pharmacokinetic dataset and the data were therefore removed from the pharmacokinetic analyses; therefore, data from 36 (90%) subjects were included in the

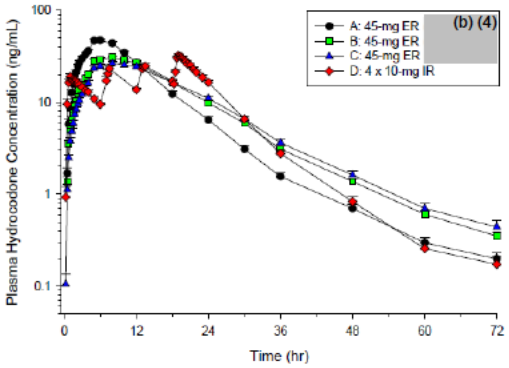
pharmacokinetic analyses presented in this report. The average age of the subjects was 32.6 years (range 23 to 44 years). The majority (77%) of subjects were men and approximately two-thirds (64%) were white.

Pharmacokinetics Results: Following administration of each of the 3 prototypes of the hydrocodone bitartrate extended-release tablet, plasma concentrations of hydrocodone rose gradually, with the median t_{max} ranging from 5.9 hours after study drug administration for the prototype with the lowest coating level to 8.5 hours after study drug administration for the prototype with the highest coating level. Mean maximum concentration values ranged from 28.4 to 49.2 ng/mL and were inversely related to coating level. Plasma concentrations declined from peak in an apparent biphasic manner. Half-life was comparable across each of the prototypes (ranging from 11.3 to 11.7 hours). All 3 prototypes exhibited extended-release characteristics with plasma concentrations maintained over the intended 12-hour dosing interval. The active metabolite, hydromorphone, was detected following administration of each of the extended-release prototypes and the immediate-release product. Systemic exposure to hydromorphone is approximately 1% to 2% of that to hydrocodone following administration of the hydrocodone bitartrate extended-release prototypes. The pharmacokinetic profile observed following administration of the immediate-release product in this study is comparable to the established profile for immediate-release hydrocodone. Following administration of the first dose of the hydrocodone bitartrate immediate-release tablet, plasma concentrations of hydrocodone rose rapidly to a mean C_{max} of 22.6 ng/mL. Dose normalization was performed for C_{max} in order to allow for an assessment of relative bioavailability between extended- and immediate-release products. Dose normalized to a 45-mg dose, C_{max} for the immediate-release product is 101.7 ng/mL. Median t_{max} occurred 1 hour after study drug administration. The mean half-life was 9.1 hours.

Safety Results: The safety data indicate that single 45-mg doses of the hydrocodone bitartrate extended-release tablet were generally well tolerated in the healthy subjects concurrently receiving naltrexone in this study. The safety profile observed was comparable to that of the immediate-release product and that of opioid products in general. No deaths or other serious adverse events occurred in this study. One subject withdrew due to an adverse event (dyspnea) after being enrolled, but prior to receiving the first dose of study drug or naltrexone. It was subsequently noted that this subject had a medical history of dypsnea that had not been reported at the screening visit. In addition, 1 subject withdrew due to an adverse event (depressed mood) after receiving at least 1 dose of study drug. The most frequently occurring adverse event overall was headache (26%). Other frequently occurring adverse events (those occurring in 10% or more of subjects overall were nausea (18%), abdominal pain (10%), and vomiting (10%). Overall, no clinically significant changes in hematology, chemistry, urinalysis, systolic and diastolic blood pressure, pulse, or ECG results were reported during the course of the study. Clinically significant decreases in respiratory rate were reported both prior to and after study drug administration. No clinically significant decreases in oxygen saturation (below 90%) were reported during the study.

Conclusions: The pharmacokinetic profiles of all 3 prototypes exhibited extended-release characteristics with plasma concentrations maintained over the intended 12-hour interval. Treatment C (b) (4) (b) (4) was selected as the prototype to be used for the clinical program because it is anticipated to provide the most protection against dose dumping if the tablet is crushed. The single 45-mg doses of the hydrocodone bitartrate extended-release tablet were generally well tolerated in the healthy subjects concurrently receiving naltrexone in this study.

Figure: Mean (+Standard Error) Plasma Concentration By Time Profiles Through 72 Hours for Hydrocodone in Healthy Subjects Administered Single 45-mg Doses of the 3 Prototypes of the Hydrocodone Bitartrate Extended-Release Tablet or Four 10-mg Doses of the Immediate-Release Product.



SOURCE: Department of Drug Safety and Disposition at Cephalon.
ER=extended-release; IR=immediate release.

Table : Mean (Standard Deviation) Pharmacokinetic Parameters for 3 Prototypes of the Hydrocodone Bitartrate Extended-Release Tablet

Parameter	Treatment A	Treatment B	Treatment C (b) (4)	Treatment D 40 mg (10 mg q6h)
	(n=36)	(n=36)	(n=36)	(n=36)
C_{max} (ng/mL)	49.2 (13.60)	32.6 (7.72)	28.4 (7.48)	22.6 (6.02)
t_{max} (h)	5.9 (5.0, 8.0)	8.0 (5.0, 11.9)	8.5 (5.0, 11.9)	1.0 (0.5, 3.5)
$AUC_{0-\infty}$ (ng·hr/mL)	640.0 (186.64)	600.3 (164.57)	577.8 (188.01)	580.6 (167.08)
AUC_{0-t} (ng·h/mL)	635.3 (185.19)	593.4 (163.76)	568.4 (181.48)	576.8 (165.35)
AUC_{0-12} (ng·hr/mL)	397.3 (97.99)	268.4 (65.93)	228.8 (62.83)	
% extrapolation	0.7 (0.50)	1.2 (0.83)	1.5 (1.17)	0.6 (0.50)
λ_z (1//h)	0.0706 (0.0327)	0.0672 (0.0241)	0.0690 (0.0247)	
$t_{1/2}$ (h)	11.7 (4.52)	11.4 (3.43)	11.3 (3.95)	9.1 (3.99)

SOURCE: Adhoc Summary 15.9.1, Listing 16.2.8.20, and Study 2009-090.

NOTE: Median (range) is presented for t_{max}.

A=one 45-mg hydrocodone bitartrate extended-release tablet (b) (4)); B=one 45-mg dose of the hydrocodone bitartrate extended-release tablet (b) (4)); C=one 45-mg dose of the hydrocodone bitartrate extended-release tablet (b) (4)).

C_{max}=maximum observed plasma drug concentration by inspection (without interpolation); t_{max}=time to maximum observed plasma drug concentration by inspection; $AUC_{0-\infty}$=area under the plasma drug concentration by time curve (AUC) from time 0 to infinity; AUC_{0-t}=AUC from time 0 to time of the last measurable plasma drug concentration; AUC_{0-12}=AUC from time 0 to 12 hours after study drug administration; % extrapolation=100($AUC_{0-\infty}$-AUC_{0-t})/ $AUC_{0-\infty}$; λ_z=terminal elimination rate constant; $t_{1/2}$=elimination half-life.

Treatment D=one 10-mg/325-mg hydrocodone bitartrate and acetaminophen immediate-release tablet (commercially available NORCO) every 6 hours until 4 tablets were administered; q6h=administered every 6 hours.

4.2.2 Study # 1081 Synopsis (Single and multiple dose PK study).

Name of Sponsor/Company: Cephalon, Inc.	**Individual study table referring to part of dossier in which the individual study or study table is presented** **Volume:** **Reference:**	(For National Authority Use Only)
Name of Finished Product: Hydrocodone bitartrate extended-release tablet		
Name of Active Ingredient: Hydrocodone bitartrate (CEP-33237)		

Title of Study: An Open-Label Study to Assess the Pharmacokinetics of Single and Multiple Doses of the Hydrocodone Bitartrate Extended-Release Tablet (45 mg) in Healthy Subjects

Investigators and Study Centers: Aziz L. Laurent, MD, PPD Development, LP, 7551 Metro Center Drive, Suite 200, Austin, Texas 78744 USA

Publication (reference): Results from this study have not been published at the time of approval of this report.

Study Period: 16 June 2010 to 26 July 2010 **Phase of Development:** 1

Primary Objective: The objective of the study was to characterize the pharmacokinetic profiles following single and multiple 45-mg doses of the hydrocodone bitartrate extended-release tablet in healthy subjects by assessing plasma concentration data over 72 hours following study drug administration.

Secondary Objectives: The secondary objective of the study was to assess the safety of single- and multiple-dose treatment in healthy subjects who were not tolerant to opioids and who had been administered naltrexone hydrochloride by evaluating the following:

- occurrence of adverse events throughout the study
- clinical laboratory (serum chemistry, hematology, and urinalysis) test results at final assessment or early withdrawal
- vital signs measurements (blood pressure, pulse, and respiratory rate) throughout the study
- 12-lead electrocardiogram (ECG) findings at final assessment or early withdrawal
- physical examination findings at final assessment or early withdrawal
- oxyhemoglobin saturation (SpO_2) monitoring throughout the study
- concomitant medication usage throughout the study

Number of Subjects (Planned and Analyzed): For this study, 40 subjects were planned to be enrolled; data from all 40 subjects were analyzed for safety and data from 36 patients were analyzed for pharmacokinetics.

Main Criteria for Inclusion: Subjects were included in the study if all of the following main criteria were met (not all inclusive):

- The subject was a man or woman 18 through 45 years of age, with a body mass index (BMI) between 20 and 30 kg/m^2, inclusive.
- The subject was in good health as determined by a medical and psychiatric history, physical examination, ECG, serum chemistry, hematology, urinalysis, and serology.

Main Criteria for Exclusion: Subjects were excluded from participating in this study if 1 or more of the following main criteria were met (not all inclusive):

- The subject had any clinically significant uncontrolled medical conditions (treated or untreated).
- The subject had a clinically significant deviation from normal in clinical laboratory values, or ECG or physical examination findings, as determined by the investigator or the medical monitor.

Study Drug Dose, Mode of Administration, Administration Rate, and Batch Number: Subjects received a single 45-mg dose of the hydrocodone bitartrate extended-release tablet (CEP-33237) on day 1 of period 1 and multiple (twice daily) 45-mg doses of the hydrocodone bitartrate extended-release tablet from the morning of day 1 through the morning of day 6 of period 2. For this study, 45-mg hydrocodone

bitartrate extended-release tablets were provided with a [redacted] (b) (4) (lot number 09AA001A501). Tablets were 0.275" x 0.625" convex, capsule-shaped, white (with no debossing), and were 575 mg in total weight. Hydrocodone bitartrate extended-release tablets were packaged in 100-cc round, white, high-density polyethylene (HDPE) bottles with 38-mm child-resistant caps and stored at a controlled room temperature (20°C to 25°C [68°F to 77°F]). Each bottle was foil-induction sealed and contained [redacted] (b) (4) tablets.

Reference Therapy Dose, Mode of Administration, and Administration Rate: Not applicable

Method of Blinding: This was an open-label study with no blinding.

Duration of Treatment: Subjects were expected to participate in this study for approximately 35 days.

General Design and Methodology: The study consisted of a screening visit within 21 days before the 1st dose of study drug, followed by a single-dose administration period, a 72-hour pharmacokinetic sampling period, an optional washout period, a multiple-dose administration period, a 72-hour pharmacokinetic sampling period, a final assessment on day 9 of period 2 or upon early withdrawal, and a follow-up visit 48 to 72 hours after discharge from the study center after the last dose of study drug. Subjects received a single 45-mg dose of the hydrocodone bitartrate extended-release tablet on day 1. Subjects received one 50-mg tablet of naltrexone hydrochloride with 240 mL of water to block opioid receptors and minimize opioid-related adverse events approximately 15 and 3 hours before and approximately 9 and 21 hours after study drug administration (at 0800±2 hours). Blood samples were collected just before study drug administration and over a 72-hour period after study drug administration to determine the pharmacokinetics of hydrocodone and its primary metabolite, hydromorphone, after single-dose administration. Following completion of period 1, subjects continued directly into the multiple-dose treatment period (period 2) or were discharged from the study center and returned for period 2. There were no more than 7 days between administration of the 1st dose in period 2 and the single dose in period 1. In the multiple-dose treatment period, from the morning of day 1 of period 2 through the morning of day 6 of period 2, subjects received twice daily 45-mg doses of the hydrocodone bitartrate extended-release tablet at approximately 0800±2 hours and 2000±2 hours. Subjects received one 50-mg tablet of naltrexone hydrochloride with 240 mL of water to block opioid receptors and minimize opioid-related adverse events approximately 15 and 3 hours before the 1st dose of study drug, 9 hours after the 1st dose of study drug, and every 12 hours thereafter through 21 hours after the last dose of study drug in period 2. During period 2, blood samples were collected prior to study drug administration and at 4 and 8 hours after study drug administration on the evening of day 4, the morning and evening of day 5, and the morning of day 6 to determine plasma concentrations of hydrocodone and its active metabolite, hydromorphone. Blood samples were also collected over a 72-hour period after administration of the last dose of study drug to determine the pharmacokinetics after multiple-dose administration. Final assessment procedures were performed before discharge from the study center.

Pharmacokinetic Measures and Endpoints: During each treatment period, blood samples (4 mL) were collected by venipuncture or indwelling catheter for measurement of concentration of hydrocodone and its metabolite hydromorphone. Samples were collected immediately before and at time points through 72 hours after single-dose administration in period 1. For the multiple-dose treatment period (period 2), samples were collected immediately before and at time points through 72 hours after administration of the last dose of study drug on day 6. In addition, during treatment period 2, concentrations of hydrocodone and its metabolite hydromorphone were measured from blood samples obtained prior to and approximately

4 hours after study drug administration on the evening of day 4, and the morning and evening of day 5. Trough samples obtained on days 4 and 5 of treatment period 2 were used to ensure subjects had concentrations reflective of steady state. The following pharmacokinetic parameters were calculated for hydrocodone and its metabolite hydromorphone, when possible, after administration of a single dose of study drug: maximum observed plasma drug concentration (C_{max}) by inspection (without interpolation), time to maximum observed plasma drug concentration (t_{max}) by inspection, area under the plasma drug concentration by time curve (AUC) from time 0 to 12 hours after study drug administration (AUC_{0-12}), AUC from time 0 to 72 hours after study drug administration (AUC_{0-72}), AUC from time 0 to the time of the last measurable drug concentration (AUC_{0-t}), AUC from time 0 to infinite time ($AUC_{0-\infty}$), percentage extrapolation calculated as ($AUC_{0-\infty}$-AUC_{0-t})/($AUC_{0-\infty}$)x100, apparent plasma terminal elimination rate constant (λ_z) and associated elimination half-life ($t_{½}$), apparent total plasma clearance, normalized for systemic bioavailability (CL/F; hydrocodone only), apparent volume of distribution, normalized for systemic bioavailability (V/F; of hydrocodone only), and predicted accumulation ratio (R_{pred}); R_{pred}=$AUC_{0-\infty}$(day 1, period 1)/AUC_{0-12} (day 1, period 1). Following multiple-dose administration, the following pharmacokinetic parameters for hydrocodone and its metabolite hydromorphone (if appropriate) were calculated, when possible: C_{max}, t_{max}, AUC_{0-12}, AUC_{0-72}, AUC_{0-t}, AUC over 1 dosing interval ($AUC_{0-\tau}$) (also considered as AUC_{0-12}), λ_z and $t_{½}$, CL/F (hydrocodone only), V/F (hydrocodone only), observed accumulation ratio (R_{obs}); R_{obs}=$AUC_{0-\tau}$ (day 6, period 2)/AUC_{0-12} (day 1, period 1), and steady-state accumulation ratio (R_{ss}); R_{ss}=$AUC_{0-\tau}$ (day 6, period 2)/$AUC_{0-\infty}$ (day 1, period 1).

Safety Variables: Safety was assessed during the study by evaluating adverse events, clinical laboratory test results (chemistry, hematology, and urinalysis), vital signs measurements, ECG and physical examination findings, SpO_2, and concomitant medication usage.

Statistical Considerations: Up to 40 healthy subjects were planned to be enrolled in this study, with the intent that approximately 30 subjects would complete the study. This sample size estimate was not based on statistical considerations. The set of enrolled subjects includes all subjects who were enrolled into the study, regardless of whether or not a subject took any study drug. The safety analysis set includes those subjects in the set of enrolled subjects who took at least 1 dose of study drug. The pharmacokinetic analysis set includes those subjects in the safety analysis set who completed both the single- and multiple-dose treatment periods. Demographic and baseline characteristics were summarized using descriptive statistics. All pharmacokinetic parameters were summarized by treatment period using descriptive statistics, including number (n), mean, standard deviation (SD), standard error (SE), geometric mean (if appropriate), coefficient of variation (if appropriate), median, minimum, and maximum. Adverse events are presented by treatment period and for all subjects, whereas vital signs are presented by treatment period only.

Summary of Results

Subject Disposition and Demography: In this study, 40 healthy subjects were enrolled; all 40 (100%) subjects received at least 1 dose of study drug and were evaluable for safety and 36 (90%) subjects completed the study. The average age of the subjects was 29.8 years (range 20 to 45 years). The majority (65%) of subjects were white. Approximately two-thirds (68%) of subjects were men.

Pharmacokinetics Results: Following administration of one 45-mg hydrocodone bitartrate extended-release tablet, plasma concentrations of hydrocodone rose gradually to a mean C_{max} of

29.0 ng/mL with a median t_{max} of 8.5 hours. Plasma concentrations declined from peak in an apparent biphasic manner. Mean half-life was 11.1 hours. Following administration of 90 mg/day (45 mg twice daily), peak plasma concentrations of 63.8 ng/mL were attained at a median t_{max} of 4.5 hours. Plasma concentrations declined from peak in an apparent biphasic manner. Mean half-life was approximately 13 hours. Trough concentrations obtained prior to study drug administration suggest that steady state was attained within 5 days of twice-daily administration. However, there did appear to be some diurnal variation in the hydrocodone plasma concentrations. The pharmacokinetic profile of hydrocodone following multiple-dose administration of the hydrocodone bitartrate extended-release tablet was qualitatively similar to that following single-dose administration. However, median t_{max} occurred earlier (at approximately 4.5 hours) than after a single-dose. The observed accumulation ratio (2.9) was slightly higher than that predicted from the single-dose data (2.5). The mean steady-state accumulation ratio (R_{ss}) was 1.2. Systemic exposure to hydromorphone was approximately 1% to 2% of that to hydrocodone.

Safety Results: The safety data indicate that single and multiple 45-mg doses (twice daily for 5.5 days) of the hydrocodone bitartrate extended-release tablet were generally well tolerated in the healthy subjects concurrently receiving naltrexone in this study. No deaths or other serious adverse events occurred in this study. Four subjects withdrew from the study due to adverse events; 3 of these events began after at least 1 dose of hydrocodone had been administered. The numbers of subjects who had adverse events were comparable in the single- and multiple-dose periods (33% of subjects in the single-dose period and 29% of subjects in the multiple-dose period). The most frequently reported (≥5%, occurring in at least 2 subjects) adverse events in the single-dose period were nausea, headache, dizziness, abdominal pain, vomiting, and somnolence. The most frequently reported adverse events in the multiple-dose period were headache, nausea, dizziness, and abdominal pain. Most of the adverse events occurred after administration of study drug that were assessed as related to treatment by the investigator were mild in severity and generally associated with opioid use. Most of the adverse events during the study were mild to moderate in severity; 1 adverse event was severe (syncope). All adverse events resolved before the end of the study. No clinically significant changes in serum chemistry, hematology, or ECG findings were reported during the course of the study. Two subjects had clinically significant changes in urinalysis values at the final assessment, but neither of these was associated with an adverse event. There was no evidence of any trends in changes in pulse, blood pressure, or respiratory rate values over time. Clinically significant decreases in respiratory rate were reported both prior to and after study drug administration. No correlation was detected between these low respiratory rates, oxygen saturation levels, or hydrocodone plasma concentrations. No clinically significant decreases in oxygen saturation (below 90%) were reported during the course of the study and none of the clinically significant decreases in respiratory rates were reported as adverse events.

Conclusions: The concentration-time profile of hydrocodone following multiple-dose administration was qualitatively similar to that following administration of a single dose. Exposure at steady state is slightly greater than would be expected based on single-dose data. Trough plasma concentrations of hydrocodone indicate that, consistent with the half-life of hydrocodone, steady state is attained within 5 days of twice daily administration. The safety data indicate that single and multiple 45-mg doses of the hydrocodone bitartrate extended-release tablet were generally well tolerated in the healthy subjects concurrently receiving naltrexone in this study.

Table : Mean (Standard Deviation) Trough Plasma Concentrations (ng/mL) of Hydrocodone (Pharmacokinetic Analysis Set)

Time of dose	Day	Predose hydrocodone concentration (N=36)	4 hours post dose (N=36)	8 hours post dose (N=36)
Evening dose	4	43.4 (11.31)	54.2 (12.67)	58.4 (15.01)
	5	46.3 (9.34)	57.3 (12.12)	52.6 (10.86)
Morning dose	5	52.4 (13.66)	58.0 (13.41)	60.6 (13.56)
	6	53.8 (12.60)	59.9 (12.66)	55.0 (12.35)

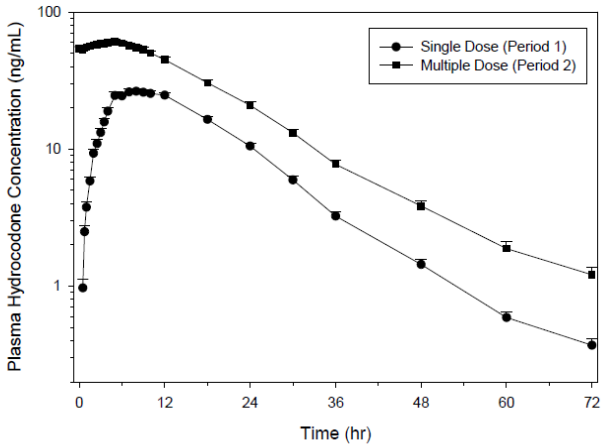
SOURCE: Summary 15.8.1 and Summary 15.9.1.

Table : Mean (Standard Deviation) Plasma Hydrocodone Pharmacokinetic Parameters by Period

Variable	Single-dose period (A) (N=36)	Multiple-dose period (B) (N=36)
C_{max} (ng/mL)	29.0 (8.16)	63.8 (13.14)
t_{max} (hr)[a]	8.5 (5.0, 12.0)	4.5 (1. 0, 7.0)
AUC_{0-12} (ng·hr/mL)	234.0 (64.31)	NA
AUC_{τ} (ng·hr/mL)	NA	662.5 (140.56
AUC_{0-t} (ng·hr/mL)	561.2 (140.04)	1330.1 (345.85)
$AUC_{0-\infty}$ (ng·hr/mL)	568.3 (142.52)	NA
R_{pred}	2.5	NA
R_{obs}	NA	2.9
R_{ss}	NA	1.2

SOURCE: Summary 15.10.1 and Listing 16.2.8.23.
[a] Median (range) is provided for t_{max}.
A=single dose of hydrocodone bitartrate extended-release tablet; B=twice daily administration of the hydrocodone bitartrate extended-release tablet for 5.5 days; AUC_{0-12}=area under the plasma drug concentration–by-time curve (AUC) from time 0 to 12 hours; AUCτ=AUC over 1 dose administration interval; AUC_{0-t}=AUC from time 0 to last measurable concentration; $AUC_{0-\infty}$=AUC from time 0 to infinity; R_{pred}=predicted accumulation ratio; R_{obs}=observed accumulation ratio; R_{ss}=steady-state accumulation ratio.

Figure : Mean (Plus Standard Error) Plasma Concentration By Time Profiles for Hydrocodone Following Administration of a Single 45-mg Dose or Administration of 90 mg per day of the Hydrocodone Bitartrate Extended-Release Tablet (45 mg Twice Daily) for 5.5 Days in Healthy Subjects



SOURCE: Drug Safety and Disposition.

Table: Plasma hydromorphone pharmacokinetic parameters by period.

Variable Statistic	Period 1 (N=36)	Period 2 (N=36)
Cmax (ng/mL)		
n	36	36
Mean	0.3	0.9
Geometric mean	0.3	0.8
SD	0.16	0.36
SE of mean	0.03	0.06
CV	49.84	40.03
Median	0.3	0.9
Min, max	0.0, 0.6	0.1, 1.6
95% C.I for mean	0.3, 0.4	0.8, 1.0
tmax (hr)		
n	35	36
Mean	10.1	4.0
Geometric mean	9.5	2.6
SD	3.80	4.22
SE of mean	0.64	0.70
CV	37.44	105.15
Median	10.0	1.8
Min, max	5.0, 24.0	0.0, 12.0
95% C.I for mean	8.8, 11.5	2.6, 5.4

Notes: Period 1=single dose hydrocodone bitartrate extended-release (ER) tablet. Period 2=hydrocodone bitartrate ER bid for 5.5 days.
Cmax=maximum observed plasma drug concentration (PDC); tmax=time to Cmax;

4.2.3 Study # 1082 Synopsis (Dose-proportionality Study).

Name of Sponsor/Company: Cephalon, Inc.	**Individual study table referring to part of dossier in which the individual study or study table is presented**	(For National Authority Use Only)
Name of Finished Product: Hydrocodone bitartrate extended-release tablet		
Name of Active Ingredient: Hydrocodone bitartrate (CEP-33237)	**Volume:** **Reference:**	

Title of Study: A Randomized, Open-Label, 5-Period Crossover Study to Evaluate the Dose Proportionality of the Hydrocodone Bitartrate Extended-Release Tablet Over the Dose Range of 15 Through 90 mg in Healthy Subjects

Investigators and Study Centers: Aziz L. Laurent, MD, PPD Development, LP, 7551 Metro Center Drive, Suite 200, Austin, Texas 78744 USA

Publication (reference): Results from this study have not been published at the time of approval of this report.

Study Period: 30 November 2010 to 22 March 2011 **Phase of Development:** 1

Primary Objective: The primary objective of the study was to assess dose proportionality of the hydrocodone bitartrate extended-release tablet over the dose range of 15 through 90 mg using the following pharmacokinetic parameters for hydrocodone:

- maximum observed plasma drug concentration (C_{max}) by inspection, without interpolation
- area under the plasma concentration by time curve (AUC) from time 0 to infinity ($AUC_{0-\infty}$)

NOTE: If it was not possible to calculate $AUC_{0-\infty}$ for at least 75% of subjects in the pharmacokinetic analysis set, AUC up to the time point at which at least 75% of the subjects within each dose group had a measurable plasma concentration ($AUC_{0-t'}$) was to be used in the assessment of dose proportionality.

Secondary Objectives: The secondary objective of the study was to assess the safety of single doses of the hydrocodone bitartrate extended-release tablet over the dose range of 15 through 90 mg in healthy subjects who were not tolerant to opioids and who had been administered naltrexone hydrochloride, by evaluating the following:

- occurrence of adverse events throughout the study
- clinical laboratory (serum chemistry, hematology, and urinalysis) test results at final assessment or early withdrawal
- vital signs measurements (blood pressure, pulse, and respiratory rate) throughout the study
- 12-lead electrocardiogram (ECG) findings at final assessment or early withdrawal
- physical examination findings at final assessment or early withdrawal
- oxyhemoglobin saturation (SpO2) monitoring throughout the study
- concomitant medication usage throughout the study

Number of Subjects (Planned and Analyzed): For this study, up to 80 subjects were planned to be enrolled; data from 78 subjects were analyzed for safety and data from 61 subjects were analyzed for pharmacokinetics. However, 1 subject was excluded from the pharmacokinetic analysis set because of a dose administration error that was discovered during the study close-out visit.

Main Criteria for Inclusion: Subjects were included in the study if all of the following main criteria were met (not all inclusive):

- The subject was a man or woman 18 through 45 years of age, with a body mass index (BMI) between 20 and 30 kg/m^2, inclusive.
- The subject was in good health as determined by a medical and psychiatric history, physical examination, ECG, serum chemistry, hematology, urinalysis, and serology.

Main Criteria for Exclusion: Subjects were excluded from participating in this study if 1 or more of the following main criteria were met (not all inclusive):

- The subject had any clinically significant uncontrolled medical conditions (treated or untreated).
- The subject had a clinically significant deviation from normal in clinical laboratory values, or ECG or physical examination findings, as determined by the investigator or the medical monitor.

Study Drug Dose, Mode of Administration, Administration Rate, and Batch Number: The hydrocodone bitartrate extended-release tablets were administered to healthy subjects at dose levels of 15 (A), 30 (B), 45 (C), 60 (D), and 90 mg (E). Qualified subjects were randomly assigned to 1 of the 5 following treatment sequences: ABCDE, BCDEA, CDEAB, DEABC, or EABCD. Each subject received 1 dose of hydrocodone during each of the 5 administration periods. Subjects received all 5 doses during the study. Each administration of hydrocodone was separated by a minimum of 14 days. Each dose was orally administered to subjects, while they were seated, at 0800±2 hours on the 1st day of each administration period. Hydrocodone bitartrate extended-release tablets were provided at dose strengths of 15 (lot number 10-000943), 30 (lot number 10-000944), and 45 mg (lot number 10-000945). The 60-mg dose was administered as two 30-mg tablets and the 90-mg dose was administered as two 45-mg tablets. Tablets were 0.275" x 0.625" convex, capsule-shaped, and are 575 mg in total weight. The 15-mg tablets were light red, 30-mg tablets were yellow, and the 45-mg tablets were white.

Reference Therapy Dose, Mode of Administration, and Administration Rate: Not applicable

Method of Blinding: This was an open-label study with no blinding.

Duration of Treatment: This study consisted of 5 single-dose administration periods. Each dose of the hydrocodone bitartrate extended-release tablet was separated by a minimum of 14 days.

General Design and Methodology: This was a Phase 1, randomized, open-label, 5-period crossover study to assess the dose proportionality of the hydrocodone bitartrate extended-release tablet over a dose range of 15 through 90 mg in healthy subjects. The study consisted of a screening visit within 21 days before the 1st dose of study drug (visit 1), followed by 5 single-dose administration periods, each including a 72-hour pharmacokinetic sampling period (visits 2 through 6), a final assessment after the final pharmacokinetic sample was collected in the last period or upon early withdrawal, and a follow-up visit 48 to 72 hours after the last discharge from the study center (visit 7). Each study drug administration was separated by a minimum of 14 days. After the screening assessments were completed, eligible subjects checked in to the study center on day –1. Subjects who continued to meet the criteria for enrollment were randomized to receive the hydrocodone bitartrate extended-release tablet in 1 of 5 treatment sequences: ABCDE, BCDEA, CDEAB, DEABC, or EABCD, whereby A, B, C, D, and E were the dose levels from lowest to highest (15, 30, 45, 60, and 90 mg). Each subject received a single dose of the hydrocodone bitartrate extended-release tablet according to their assigned randomization on the first day of each administration period. Subjects received one 50-mg tablet of naltrexone hydrochloride with 240 mL of water to block opioid receptors and minimize opioid-related adverse events approximately 15 and 3 hours before and approximately 9 and 21 hours after each study drug administration at 0800±2 hours. Blood samples were collected just before each study drug administration and over a 72-hour period after each study drug administration. In each administration period, subjects were permitted to leave the study center after collection of the 72-hour pharmacokinetic sample and completion of discharge or final assessment procedures (as appropriate). Safety was assessed throughout the study by monitoring the occurrence of adverse events, clinical laboratory test results, vital signs measurements, 12-lead ECG findings, physical examination findings, SpO_2 findings, and use of concomitant medications. Subjects who completed all scheduled visits had final procedures and assessments performed prior to discharge in administration period 5. Subjects who withdrew from the study before the completion of all scheduled assessments had final procedures and assessments performed prior to discharge in their last administration period. All subjects were asked to return for a follow-up visit 48 to 72 hours after their last discharge from the study center.

Primary Pharmacokinetic Measure(s) and Endpoint(s): The following primary pharmacokinetic parameters were calculated for hydrocodone: C_{max} by inspection (without interpolation) and $AUC_{0-\infty}$. NOTE: If it had not been possible to calculate $AUC_{0-\infty}$ for at least 75% of subjects in the pharmacokinetic analysis set, $AUC_{0-t'}$ would have been used in the assessment of dose proportionality.

Secondary Pharmacokinetic Measures and Endpoints: The following secondary pharmacokinetic parameters were calculated for the active metabolite of hydrocodone, hydromorphone (if appropriate): C_{max} by inspection (without interpolation) and $AUC_{0-\infty}$. The following secondary pharmacokinetic parameters

were calculated for hydrocodone and its active metabolite, hydromorphone (if appropriate): AUC from time 0 to the time of the last measurable drug concentration (AUC_{0-t}), AUC from time 0 to 72 hours after study drug administration (AUC_{0-72}), AUC from time 0 to 12 hours after study drug administration (AUC_{0-12}), time to maximum observed plasma drug concentration (t_{max}) by inspection, percentage extrapolation, $100 \times (AUC_{0-\infty} - AUC_{0-t})/AUC_{0-\infty}$, apparent plasma terminal elimination rate constant (λ_z) and associated elimination half-life ($t_{½}$), apparent volume of distribution, normalized for systemic bioavailability (V/F; hydrocodone only), apparent total plasma clearance, normalized for systemic bioavailability (CL/F; hydrocodone only)

Safety Variables: Safety was assessed during the study by evaluating adverse events, clinical laboratory test results (chemistry, hematology, and urinalysis), vital signs measurements, 12-lead ECG and physical examination findings, SpO_2 measurements, and concomitant medication usage.

Statistical Considerations: An estimated withdrawal rate of 30% was assumed. As a result, up to approximately 80 subjects were to be randomly assigned to a treatment sequence with the intent that a minimum of 55 subjects would complete all administration periods. The set of randomized subjects includes all subjects who were randomly assigned to a treatment sequence, regardless of whether or not a subject received any study drug. The safety analysis set includes those subjects in the set of randomized subjects who received at least 1 dose of the hydrocodone bitartrate extended-release tablet (15, 30, 45, 60, or 90 mg). The pharmacokinetic analysis set includes those subjects in the safety analysis set who had sufficient data to calculate the pharmacokinetic parameters C_{max} or $AUC_{0-\infty}$ for all administration periods. The set of randomized subjects was used for all study population summaries unless otherwise noted. Summaries were presented by sequence and for all subjects. Subject disposition and baseline safety assessments were summarized using descriptive statistics for the set of randomized subjects. All prior and concomitant medications were coded according to WHO Drug. The incidence of prior and concomitant medications was summarized using descriptive statistics by therapeutic class and preferred term. Prior medications included all medications taken prior to the first day of study drug treatment and concomitant medications included all medications taken while the subject takes study drug. ECG and physical examination findings (normal, abnormal, and missing) at baseline were summarized using descriptive statistics. The pharmacokinetic analysis set was used for all pharmacokinetic analyses. For each subject, pharmacokinetic parameters were only summarized if they could be calculated for all 5 administration periods. Summaries are presented by dose. For each dose, pharmacokinetic parameters for hydrocodone and its active metabolite, hydromorphone, were calculated. The primary pharmacokinetic variables for evaluating dose proportionality over the dose range of 15 through 90 mg were $AUC_{0-\infty}$ and C_{max}. The primary pharmacokinetic analyses included only the subjects who had pharmacokinetic data from each of the 5 periods. Dose proportionality was measured by the slope, β, of the regression line as follows: $\ln(PK) = \alpha + \beta\ln(dose) + \varepsilon$ The error term ε was modeled to account for both intrasubject and intersubject variation. A mixed-effects model was used to provide a 90% confidence interval (CI) on the fixed effect of β. Dose proportionality would be concluded if the CI fell completely within the limits (0.875 to 1.125). All pharmacokinetic parameters were summarized by dose using descriptive statistics, including n, mean, standard deviation (SD), standard error (SE), geometric mean (if appropriate), coefficient of variation (if appropriate), median, minimum, and maximum. The safety analysis set was used for all safety analyses unless otherwise noted. Summaries were presented for all subjects (ie, total) except summaries of adverse events, vital signs, and SpO_2 measurements. Adverse events were summarized by dose and for all subjects, whereas vital signs and SpO_2 results were presented by dose only. For continuous variables, descriptive statistics are provided for actual values and changes from baseline to each visit. For categorical variables, subject counts and percentages are provided. Descriptive summaries of subjects with serious adverse events, subjects who withdrew from the study because of adverse events, and subjects with clinically significant abnormal laboratory or vital signs values on the basis of predefined criteria are also provided. All adverse events were coded according to the MedDRA dictionary. Summaries are provided for all adverse events (overall and by severity), adverse events determined by the investigator to be treatment related (overall and by severity), serious adverse events, nonserious adverse events, and adverse events causing discontinuation from the study. Adverse events were attributed to the treatment period corresponding to the last dose administered. In addition, adverse events after the 1st dose of naltrexone but before the 1st dose of the study drug are presented for all subjects who received the 1st dose of naltrexone in

the set of randomized subjects. Summary statistics for chemistry, hematology, and urinalysis laboratory tests are presented at baseline and endpoint. Actual values and changes from baseline to endpoint were summarized using descriptive statistics. The incidence of clinically significant abnormal values was summarized for laboratory data using descriptive statistics. Summary statistics for body weight and temperature are presented at baseline and endpoint for all subjects. Actual values and changes from baseline in body weight and temperature were summarized using descriptive statistics. Summary statistics for vital signs are presented for all specified time points. Actual values and changes from pretreatment to each time point were summarized using descriptive statistics. The incidence of clinically significant abnormal values was summarized for selected vital signs using descriptive statistics. Shifts (normal and abnormal) from baseline to endpoint were summarized using subject counts. Summary statistics for ECG variables were presented at baseline and endpoint. Actual values and changes from baseline to endpoint were summarized using descriptive statistics. Shifts (normal and abnormal) from baseline to endpoint were summarized using subject counts for each physical examination category. Summary statistics for SpO_2 are presented for all specified following time points. Actual values and changes from pretreatment to each time point were summarized using descriptive statistics. The incidence of clinically significant abnormal values was summarized for SpO_2 using descriptive statistics. SpO_2 values of less than 90% were identified as clinically significant abnormal. A listing for clinically significant abnormal SpO_2 is presented.

Summary of Results

Subject Disposition and Demography: In this study, 80 healthy men and women were randomly assigned to a treatment sequence; 78 (98%) subjects received at least 1 dose of study drug and were evaluable for safety; 61 (76%) subjects were evaluable for pharmacokinetics and completed the study. However, 1 subject was excluded from the pharmacokinetic analysis set because of a dose administration error that was discovered during the study close-out visit. The average age of the subjects was 30.3 years (range 19 to 45 years). The majority (80%) of subjects were white and approximately two-thirds (66%) were men.

Pharmacokinetic Results: Maximum plasma concentrations of hydrocodone were typically attained approximately 7 to 8 hours following administration of the hydrocodone bitartrate extended-release tablets. Decline from peak plasma concentrations generally occurred in a biphasic manner with a mean half-life of approximately 10 to 11 hours. Hydromorphone concentrations were approximately 100-fold lower than concentrations of hydrocodone. The 90% CIs for both $AUC_{0-\infty}$ and C_{max} fell within the protocol-specified limits (0.875 to 1.125), indicating that systemic exposure to hydrocodone increases in a dose-proportional manner over the range of 15 through 90 mg.

Safety Results: The safety data indicate that single doses of the hydrocodone bitartrate extended-release tablet (15, 30, 45, 60, and 90 mg) were generally well tolerated in the healthy subjects concurrently receiving naltrexone in this study. No deaths or other serious adverse events occurred in this study. A total of 8 subjects withdrew from the study due to adverse events; 1 of these subjects withdrew after receiving naltrexone but before receiving a dose of hydrocodone. The most common adverse event leading to withdrawal was vomiting (6 subjects). The incidence of adverse events did not increase with increasing dose. The most frequently occurring adverse events overall (occurring in ≥5% of subjects following any treatment) were nausea (42%), headache (37%), dizziness (23%), abdominal pain (19%), vomiting (15%), somnolence (10%), diarrhea (8%), fatigue (8%), abdominal distension (6%), tremor (6%), catheter site pain (5%), cough (5%), feeling drunk (5%), flatulence (5%), oropharyngeal pain (5%), and pain in extremity (5%). All adverse events were mild to moderate in severity. Most of the adverse events occurred after administration of study drug that were assessed as related to treatment by the investigator were mild in severity and are consistent with those generally associated with opioid use. All adverse events resolved before the end of the study. Overall, no clinically significant changes in hematology, chemistry, or ECG results were reported during the course of the study. Clinically significant decreases in respiratory rate and in oxygen saturation were reported both prior to and after study drug administration. No correlation was detected between these low respiratory rates, oxygen desaturation and plasma hydrocodone concentrations.

Conclusions: $AUC_{0-\infty}$ and C_{max} increased in a dose-proportional manner across the range of 15 to 90 mg of the hydrocodone bitartrate extended-release tablet. The hydrocodone bitartrate extended-release tablet was generally well tolerated across the entire dose range evaluated (15 to 90 mg) in the healthy subjects who were concurrently receiving naltrexone in this study.

Figure : Mean (Standard Error) Plasma Concentration by Time Profiles for Hydromorphone in Healthy Subjects Administered a Single 15-, 30-, 45 60-, or 90-mg Dose of the Hydrocodone Bitartrate Extended-Release Tablet (Pharmacokinetic Analysis Set [Excluding Subject 001162])

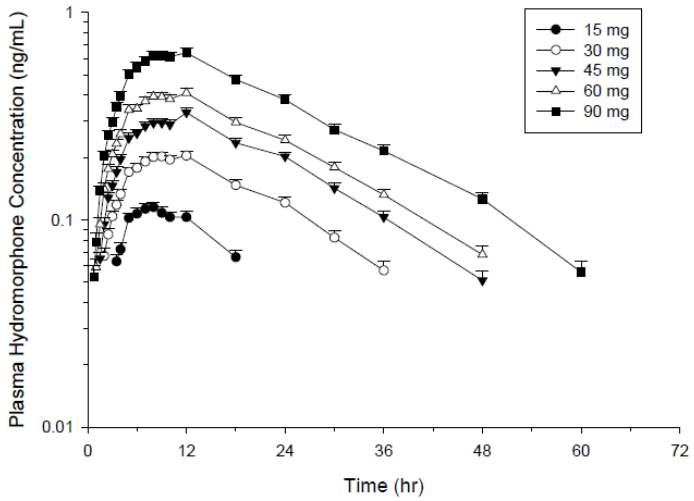


Table : Mean (Standard Deviation) Pharmacokinetic Parameters for Hydrocodone Following Administration of Hydrocodone Bitartrate Extended-Release by Treatment

Variable	A 15 mg (N=60)	B 30 mg (N=60)	C 45 mg (N=60)	D 60 mg (N=60)	E 90 mg (N=60)
C_{max} (ng/mL)	12.6 (3.50)	20.7 (5.47)	30.3 (7.48)	41.2 (10.11)	62.5 (16.19)
$AUC_{0-\infty}$ (ng·h/mL)	198.8 (60.37)	381.6 (117.78)	592.3 (167.20)	765.7 (193.98)	1189.0 (341.31)
AUC_{0-t} (ng·h/mL)	195.8 (60.09)	377.6 (116.47)	585.8 (163.68)	757.2 (190.82)	1178.8 (335.97)
AUC_{0-72} (ng·h/mL)	196.7 (59.98)	378.1 (116.31)	586.0 (163.48)	757.3 (190.66)	1178.8 (335.94)
AUC_{0-12} (ng·h/mL)	99.9 (27.40)	169.5 (45.31)	247.1 (62.94)	334.2 (78.09)	505.6 (129.73)
t_{max} (h)	7.0 (5.0, 9.0)	8.0 (5.0, 12.0)	8.0 (5.0, 12.1)	8.0 (5.0, 12.0)	8.0 (5.0, 12.0)
$t_{1/2}$ (h)	10.4 (4.05)	10.6 (4.06)	10.2 (3.64)	10.8 (4.13)	10.0 (2.94)
Percentage extrapolation (%)	1.4 (0.85)	1.0 (0.72)	1.0 (1.19)	1.1 (1.06)	0.8 (0.83)
λ_z (1/h)	0.08 (0.027)	0.07 (0.024)	0.08 (0.025)	0.07 (0.025)	0.08 (0.020)
V/F	1233.9 (588.91)	1323.4 (797.07)	1206.3 (543.84)	1289.5 (575.27)	1196.2 (584.14)
CL/F	83.4 (29.14)	85.7 (25.31)	81.6 (21.54)	83.0 (19.66)	82.2 (24.93)

SOURCE: Adhoc Summary 15.9.1, Listing 16.2.8.23.
NOTE: Median (range) is presented for t_{max}

Table : Mean (Standard Deviation) Pharmacokinetic Parameters for Hydromorphone Following Administration of Hydrocodone Bitartrate Extended-Release by Treatment (Pharmacokinetic Analysis Set [Excluding Subject 001162])

Variable	A 15 mg (N=60)	B 30 mg (N=60)	C 45 mg (N=60)	D 60 mg (N=60)	E 90 mg (N=60)
C_{max} (ng/mL)	0.1 (0.06)	0.2 (0.08)	0.3 (0.14)	0.4 (0.16)	0.7 (0.26)
t_{max} (min)	8.0 (4.0, 24.0)	9.0 (5.0, 30.0)	12.0 (5.0, 24.0)	9.5 (5.0, 12.1)	10.0 (4.0, 12.0)

SOURCE: Adhoc Summary 15.9.1, Listing 16.2.8.23.
NOTE: Median (range) is presented for t_{max}
C_{max}=maximum observed plasma drug concentration; t_{max}=time to maximum observed plasma drug concentration by inspection.
A=a single 15-mg dose of the hydrocodone bitartrate extended-release tablet; B=a single 30-mg dose of the hydrocodone bitartrate extended-release tablet; C=a single 45-mg dose of the hydrocodone bitartrate extended-release tablet; D=a single 60-mg dose of the hydrocodone bitartrate extended-release tablet; E=a single 90-mg dose of the hydrocodone bitartrate extended-release tablet.

Hydromorphone concentrations were approximately 100-fold lower than concentrations of hydrocodone.

4.2.4 Study # 1085 Synopsis (Oral Drug Liking Study)

Name of Sponsor/Company: Teva Branded Pharmaceutical Products, R&D, Inc.	**Individual study table referring to part of dossier in which the individual study or study table is presented**	(For National Authority Use Only)
Name of Finished Product: Hydrocodone bitartrate extended-release tablet	**Volume:**	
Name of Active Ingredient: Hydrocodone bitartrate (CEP-33237)	**Reference:**	

Title of Study: A Randomized, Double-Blind, Placebo-Controlled, Crossover Study to Assess the Abuse Potential of the Hydrocodone Bitartrate Extended-Release Tablet in Healthy, Nondependent, Recreational Opioid Users

Investigators and Study Centers: Lynn R. Webster, MD, Lifetree Clinical Research, 3838 South 700 East, Suite 202, Salt Lake City, Utah 84106 USA.

Publication (reference): Bond, M, Yang R, Darwish M. Evaluation of the abuse potential of an extended-release hydrocodone bitartrate tablet formulated with OraGaurd™ technology in non-dependent, recreational opioid users [poster abstract]. Presented at the 32nd Annual Scientific Meeting of the Americal Pain Society (APS); May 8-11, 2013; New Orleans, Louisiana, USA.

Darwish M, Bond M, Robertson P, Tracewell W. Evaluation of the abuse potential of an extended release hydrocodone bitartrate tablet formulated with OraGuard™ technology in non-dependent, recreational opioid users [abstract 395]. J Pain 2013;14(4 Suppl):S74.

Study Period: 24 January 2012 to 16 May 2012 **Phase of Development:** 1

Primary Objective: The primary objectives of this study were as follows:

- to assess the relative abuse potential of the hydrocodone bitartrate extended-release tablet (crushed) as compared with that of immediate-release hydrocodone bitartrate based on the maximum effect (E_{max}) of drug liking assessed using question 1 of the Drug Liking and Effects Questionnaire (DLEQ)
- to assess the relative abuse potential of the hydrocodone bitartrate extended-release tablet (intact) as compared with that of immediate-release hydrocodone bitartrate based on the E_{max} of drug liking assessed using question 1 of the DLEQ

Secondary Objectives: The secondary objectives of the study were as follows:

- to assess the relative abuse potential of the hydrocodone bitartrate extended-release tablet (crushed) as compared with that of immediate-release hydrocodone bitartrate as assessed by all secondary pharmacodynamic variables
- to assess the relative abuse potential of the hydrocodone bitartrate extended-release tablet (intact) as compared with that of immediate-release hydrocodone bitartrate as assessed by all secondary pharmacodynamic variables
- to assess the relative abuse potential of the hydrocodone bitartrate extended-release tablet (crushed) as compared with that of the hydrocodone bitartrate extended-release tablet (intact) as assessed by the primary and secondary pharmacodynamic variables
- to characterize the pharmacokinetics of the hydrocodone bitartrate extended-release tablet (crushed and intact) and immediate-release hydrocodone bitartrate by assessing plasma concentration data over 72 hours following study drug administration
- to assess the pharmacokinetic/pharmacodynamic relationships of the hydrocodone bitartrate extended-release tablet (crushed and intact) and immediate-release hydrocodone bitartrate
- to evaluate the safety of the hydrocodone bitartrate extended-release tablet (crushed and intact) and immediate-release hydrocodone bitartrate by evaluating the following:
  - occurrence of adverse events throughout the study

- clinical laboratory (serum chemistry, hematology, and urinalysis) test results throughout the study
- vital signs (blood pressure, respiratory rate, and pulse) measurements throughout the study
- resting 12-lead electrocardiogram (ECG) findings throughout the study
- physical examination findings throughout the study
- oxyhemoglobin saturation (SpO2) monitoring throughout the study
- concomitant medication usage throughout the study

Number of Subjects (Planned and Analyzed): For this study, 100 subjects were planned to be and were enrolled. In phase B, data from 97 subjects were analyzed for safety and 92 subjects completed the phase. In phase C, data for 49 subjects were analyzed for safety, data for 45 subjects were analyzed for pharmacodynamics, and data for 43 subjects were analyzed for pharmacokinetics.

Diagnosis and Main Criteria for Inclusion: Subjects were included in the study if all of the following main criteria were met (not all inclusive):

- The subject was not physically dependent on opioids as demonstrated by successful completion of a naloxone challenge; ie, subject did not exhibit signs or symptoms of opioid withdrawal (as assessed b a Clinical Opiate Withdrawal Scale [COWS] score of <5) following administration of intravenous naloxone in the Naloxone Challenge.
- The subject had a history of recreational opioid use to achieve a "high" at least 10 times in the last ye and at least on 1 occasion within the 12 weeks before screening. Subjects who abused multiple drugs were to express a preference for opioids.
- The subject was aged 18 through 50 years with a minimum body weight of 50 kg and a body mass index (BMI) of 18.0 through 32.0 kg/m^2.

Main Criteria for Exclusion: Patients were excluded from participating in this study if 1 or more of the following main criteria were met (not all inclusive):

- The subject had any clinically significant uncontrolled medical conditions (treated or untreated).
- The subject had a clinically significant deviation from normal in the clinical laboratory values or ECG or physical examination findings, as determined by the investigator or the medical monitor.
- The subject was a poor metabolizer of cytochrome P450 (CYP)2D6 substrates based on genotyping performed at screening.

Study Drug Dose, Mode of Administration, Administration Rate, and Batch Number: The following 2 treatment sequences were used for phase B of this study: XY and YX, whereby treatment X was 60 mL of a noncarbonated flavored beverage and treatment Y was hydrocodone bitartrate powder at a dose strength of 45 mg reconstituted in 60 mL of a noncarbonated flavored beverage.

Each subject received 1 treatment during each administration period. Subjects received each of the 2 treatments once. Subjects were required to consume all 60 mL of solution within 2 minutes. After the reconstituted product or matching placebo was consumed by the subject, as specified in the protocol, the empty drinking cup was refilled with at least 60 mL (but no more than 240 mL) of water, and the rinse water was also consumed by the subject. There was a minimum 48-hour washout period between each study drug administration in phase B. Treatments were orally administered to subjects, while they were seated, at approximately 0800 (±2 hours) on the first day of each administration period.

Immediately (within approximately 5 minutes) before study drug administration in phase C, subjects consumed 60 mL of the same type of noncarbonated flavored beverage that was used in each treatment.

The following 4 treatment sequences were used for phase C of this study: ABDC, BCAD, CDBA, and DACB. Treatments were as follows:

- Treatment A consisted of 1 intact placebo tablet (matching the 45-mg hydrocodone bitartrate extended-release tablet), 60 mL of a noncarbonated flavored beverage, and 1 crushed 45-mg hydrocodone bitartrate extended-release tablet.

- Treatment B consisted of 1 intact placebo tablet (matching the 45-mg hydrocodone bitartrate extended-release tablet), hydrocodone bitartrate powder at a dose strength of 45 mg reconstituted in 60 mL of a noncarbonated flavored beverage, and 1 crushed placebo tablet (matching the 45-mg hydrocodone bitartrate extended-release tablet).
- Treatment C consisted of 1 intact 45-mg hydrocodone bitartrate extended-release tablet, 60 mL of a noncarbonated flavored beverage, and 1 crushed placebo tablet (matching the 45-mg hydrocodone bitartrate extended-release tablet).
- Treatment D consisted of 1 intact placebo tablet (matching the 45-mg hydrocodone bitartrate extended-release tablet), 60 mL of a noncarbonated flavored beverage, and 1 crushed placebo tablet (matching the 45-mg hydrocodone bitartrate extended-release tablet).

Each subject received 1 treatment during each administration period. Subjects consumed both tablets (crushed and intact) together with the 60 mL of juice containing the immediate-release product or matching placebo. The juice and both tablets were consumed within 2 minutes. After the reconstituted product or matching placebo was consumed by the subject, as specified in the protocol, the empty drinking cup was refilled with at least 60 mL (but no more than 240 mL) of water, and the rinse water was also consumed by the subject. Up to 240 mL of water (including the rinse) was permitted for consumption of the intact and crushed tablets, if needed. Subjects received each of the 4 treatments once. There was a minimum 14-day washout period between each administration of study drug in phase C. Treatments were orally administered to subjects, while subjects were seated, at approximately 0800 (±2 hours) on the first day of each administration period.

Investigational Product: Hydrocodone bitartrate extended-release tablets (lot number 10-000833) were packaged in 60-cc round, white, high-density polyethylene (HDPE) bottles with 38-mm child-resistant caps. Each bottle contained 1 canister of desiccant. Each bottle was foil-induction sealed and contained (b) (4) tablets.

Placebo: Placebo tablets (lot number 11-00165) to match the 45-mg hydrocodone bitartrate extended-release tablets were provided and were packaged in the same manner as the hydrocodone bitartrate extended-release tablets. Placebo to match the immediate-release product consisted of 60 mL of Ocean Spray Diet Cranberry Grape Juice Drink.

Comparison Drug: The immediate-release product was hydrocodone bitartrate powder (lot number 11-003279) for reconstitution provided at a dose strength of 45 mg. Each powder for reconstitution dosage unit was packaged in a green, round, 75-mL (b) (4) bottle closed with a (b) (4) screw cap.

Reference Therapy Dose, Mode of Administration, and Administration Rate: Not applicable

Method of Blinding: Subjects, the investigator, and all study center personnel involved in conducting study-related procedures (other than preparation of study drug) remained blinded to the identity of the treatment administered to each subject while that subject was participating in phase B and during each treatment period during phase C. In addition, pupillometry assessments were to be performed by specified study center staff members who performed only pupillometry assessments during the study. These staff members were not to be involved in other study assessments. Source data for pupillometry measurements were maintained in a separate area from other source documents, which study center staff responsible for performing other study-related procedures were not able to access. Pharmacokinetic samples were assayed after the last subject completed the study but before unblinding of the treatment codes. Therefore, for a given subject, those responsible for sample bioanalysis knew which periods the subject had received hydrocodone in and which period the subject had received placebo in prior to database lock. However, bioanalytical staff did not have access to any clinical data and other staff did not have access to any bioanalytical data until at or after the time of database lock.

Duration of Treatment: Subjects were to participate in the study for up to approximately 12 weeks.

General Design and Methodology: The study consisted of 3 phases. Phase A of the study was the screening period during which subjects were evaluated to determine if they met criteria for inclusion in the study up to 28 days before the first study drug administration in phase B. Subjects who satisfactorily

completed this phase were eligible to continue into phase B. Phase B of the study (qualification phase) was designed to ensure that the subject could tolerate a 45-mg dose of hydrocodone (eg, no emesis within 2.5 hours of dose administration) and that the subject could discriminate between the effect of hydrocodone and the effect of placebo. Phase B was the randomized, double-blind, placebo-controlled, 2-treatment, 2-period crossover portion of the study. Subjects arrived at the study center on the day before the first study drug administration and remained at the study center for a minimum of 24 hours after the second study drug administration in phase B. After a review of the inclusion/exclusion criteria and check-in procedures (including a Naloxone Challenge), eligible subjects were randomly assigned to a treatment sequence.

Pharmacodynamic assessments were performed at specified time points throughout 72 hours after the start of each study drug administration. Subjects checked out of the study center after the procedures required 24 hours after the second dose in phase B had been completed. Safety was assessed during phase B by monitoring adverse events, concomitant medication usage, clinical laboratory test results, vital signs measurements, ECG and physical examination findings, and SpO_2 measurements.

To be eligible to continue into phase C, subjects must have tolerated a 45-mg dose of hydrocodone bitartrate (eg, no emesis within 2.5 hours of dose administration), must have had a response to hydrocodone bitartrate greater than that to placebo (ie, a peak score of at least 15 points greater on drug liking as assessed by question 1 of the DLEQ and on overall drug liking as assessed by the Overall Drug Liking VAS), and must have demonstrated behaviors consistent with an ability to complete the study. For subjects who qualified to continue into phase C, there was a minimum 7-day washout period between the second dose in phase B and the first dose in phase C.

Phase C (treatment phase) was the randomized, double-blind, triple-dummy, placebo-controlled, 4-period crossover portion of the study. Eligible subjects were randomly assigned to 1 of 4 treatment sequences. Each treatment in phase C was separated by a minimum 14-day washout period. Subjects arrived at the study center the day before each study drug administration in phase C. Subjects fasted from approximately 2200 the evening before each study drug administration until 4 hours after each study drug administration. Before each study drug administration, a blood sample for pharmacokinetics was obtained and specified pharmacodynamic assessments were performed. Each subject then received the study drug (and additional placebo for blinding purposes) identified in the randomization schedule for that treatment period. Pharmacokinetic, pharmacodynamic, and safety assessments were performed before and at specified time points through 72 hours after the start of administration of the study drug in each period. Subjects who participated in all scheduled visits had final procedures and assessments performed before discharge in administration period 4 of phase C. Subjects who withdrew from the study before the completion of all scheduled assessments had final procedures and assessments performed before discharge in their last study drug administration period. All subjects (including those who withdrew from the study) were asked to return to the study center for a follow-up visit approximately 48 to 72 hours after discharge from the study center following their final dose of study drug.

Pharmacodynamic Measures and Endpoints

Phase B

The overall drug liking visual analog scale (VAS), the Take Drug Again VAS, and Price Value Assessment Questionnaire (PVAQ) Assessment were completed 24 hours after the start of administration of study drug in each period of phase B. The Drug Liking and Effects Questionnaire (DLEQ) was completed at 0.25, 0.75, 1.25, 1.75, 2.5, 4, 6, 7, 8, 9, 10, 12, and 24 hours after the start of administration of study drug in each period of phase B. Pupil diameter measurements were completed prior to study drug administration and at 0.25, 0.75, 1.25, 1.75, 2.5, 4, 6, 7, 8, 9, 10, 12, and 24 hours after the start of administration of study drug in each period of phase B. Questions from the Addiction Research Center Inventory (ARCI) that comprise the following subscales were completed prior to study drug administration and at 0.25, 0.75, 1.25, 1.75, 2.5, 4, 6, 8, 12, and 24 hours after the start of administration of study drug in each period of phase B:

- Morphine Benzedrine Group (MBG)
- Lysergic Acid Diethylamide (LSD)

- Pentobarbital Chlorpromazine Alcohol Group (PCAG)

Pharmacodynamic requirements to qualify for phase C of the study were as follows:

- The subject must have had a peak score in response to the immediate-release product of at least 15 points greater than that of placebo on drug liking as assessed by question 1 of the DLEQ and on overall drug liking as assessed by the Overall Drug Liking VAS.
- The subject must have had an acceptable placebo and hydrocodone response on all other measures (as judged by the investigator and/or designee).

Phase C

The overall drug liking VAS, the Take Drug Again Assessment (TDAA), and the PVAQ assessment were completed 24 hours after the start of administration of study drug in each period of phase C. The DLEQ was completed at 0.25, 0.75, 1.25, 1.75, 2.5, 4, 6, 7, 8, 9, 10, 12, 24, 36, 48, 60, and 72 hours after the start of administration of study drug in each period of phase C. Pupil diameter measurements were completed prior to study drug administration and at 0.25, 0.75, 1.25, 1.75, 2.5, 4, 6, 7, 8, 9, 10, 12, 24, 36, 48, 60, and 72 hours after the start of administration of study drug in each period of phase C. Questions from the ARC that comprise the MBG, LSD, and PCAG subscales were completed prior to study drug administration and at 0.25, 0.75, 1.25, 1.75, 2.5, 4, 6, 8, 12, 24, 36, 48, 60, and 72 hours after the start of administration of study drug in each period of phase C.

Primary Pharmacodynamic Measures and Endpoints

The primary pharmacodynamic measures and endpoints for assessment of relative abuse potential in phase C of the study include the following:

- Maximum effect (E_{max}) of drug liking assessed using question 1 of the DLEQ

Secondary Pharmacodynamic Measures and Endpoints

The secondary pharmacodynamic measures and endpoints for assessment of relative abuse potential in phase C of the study included measures of balance of drug effects, positive drug effects, negative drug effects, sedative effects, and other drug effects as follows:

- Overall drug liking VAS score
- Measures of balance of effects:
  - Minimum score (E_{min}) and area under the effect curve (AUEC) for drug liking assessed using question 1 of the DLEQ
  - TDAA score
  - PVAQ score
- Measures of positive effects:
  - E_{max} and AUEC for good effects using question 3 of the DLEQ
  - E_{max} and AUEC for the MBG subscale of the ARCI
- Measures of negative effects:
  - E_{max} and AUEC for bad effects using question 4 of the DLEQ
  - E_{max} and AUEC for the LSD subscale of the ARCI
  - E_{max} and AUEC for nausea using question 5 of the DLEQ
- Measures of sedative effects:
  - E_{max} and AUEC for the PCAG subscale of the ARCI
  - E_{min} and AUEC for Alertness/Drowsiness using question 2 of the DLEQ
- Measures of other drug effects:
  - E_{max} and AUEC for any effects using question 6 of the DLEQ
  - E_{min} for pupillometry

Time to maximum effect for each pharmacodynamic measure was also assessed.

Pharmacokinetics: In each administration period of phase C, blood samples (3-4 mL) were collected by venipuncture or indwelling catheter. Blood samples were collected immediately (within approximately 30 minutes) before each study drug administration and 0.25, 0.75, 1.25, 1.75, 2.5, 4, 6, 7, 8, 9, 10, 12, 24, 36, 48, 60, and 72 hours after the start of each study drug administration. The following pharmacokinetic parameters for hydrocodone and its metabolite, hydromorphone, were calculated for each subject, when possible, for each treatment:

- maximum observed plasma drug concentration (C_{max}) by inspection (without interpolation)
- time to maximum observed drug concentration (t_{max}) by inspection
- area under the plasma concentration by time curve (AUC) from time zero to 0.75 hours after study drug administration ($AUC_{0-0.75}$)
- AUC from time 0 to 4 hours after study drug administration (AUC_{0-4})
- AUC from time 0 to 7 hours after study drug administration (AUC_{0-7})
- AUC from time 0 to the time of the last measurable drug concentration (AUC_{0-t})
- AUC from time 0 to infinity ($AUC_{0-\infty}$)
- percentage extrapolation, calculated as $(AUC_{0-\infty}-AUC_{0-t})/(AUC_{0-\infty})x100$
- apparent plasma terminal elimination rate constant (λ_z) and associated elimination half-life ($t_{½}$)
- abuse quotient calculated as C_{max}/t_{max}

Safety Variables: In this study, safety was assessed by evaluating the following: adverse events, clinical laboratory test results (chemistry, hematology, and urinalysis), vital signs measurements, ECG and physical examination findings, SpO_2 monitoring, and concomitant medication usage.

Statistical Considerations: The set of enrolled subjects includes all subjects who were randomly assigned to a treatment sequence in phase B, regardless of whether a subject took any study drug. The phase B safety analysis set includes all subjects who received 1 or more doses of study drug in phase B. The set of randomized subjects includes all subjects who were randomly assigned to a treatment sequence in phase C, regardless of whether a subject took any study drug. The phase C safety analysis set includes all subjects who received 1 or more doses of study drug in phase C. The pharmacokinetic analysis set includes those subjects in the phase C safety analysis set who have adequate pharmacokinetic data to contribute to at least 1 planned comparison. The pharmacodynamic analysis set includes subjects who have adequate pharmacodynamic data from phase C to contribute data to at least 1 planned comparison. Phase B pharmacodynamic data are listed for individual subjects. Continuous and ordinal categorical pharmacodynamic parameters were analyzed using a mixed effects analysis of variance (ANOVA) model that includes study drug, treatment sequence, and period as fixed effects, and subject as a random effect. Comparisons between pairs of treatments were made using the least squares means that were estimated from the ANOVA. Pharmacodynamic assessments were also summarized by time point. The comparison between treatments B and D was assessed first to ensure the validity of the measure. If the treatment difference was significant at an alpha level of 0.05, the comparison between treatments B and C was made. If that treatment difference was also significant at an alpha level of 0.05, the comparison between treatments B and A was made. The same mixed model used for the primary endpoint was used to assess treatment differences (treatment B vs other treatments) for each of the above endpoints. Time to maximum effect for each pharmacodynamic measure was also summarized descriptively. The plasma concentration data and individual pharmacokinetic parameters were summarized by treatment. All pharmacokinetic variables were summarized by treatment using n, mean, standard deviation (SD), standard error (SE) of mean, geometric mean (if appropriate), median, minimum, and maximum. Exploratory analyses were undertaken to describe the relationship between plasma concentration and the effect of hydrocodone treatment on pharmacodynamic variables over time using graphics. With the exception of adverse events, vital signs, and SpO_2 measurements, summaries were presented for all subjects (ie, total). Adverse events and vital signs were summarized by treatment group and for all subjects, whereas SpO_2 measurements are presented by treatment group only. This study was to enroll up to 100 subjects into phase B with the intent that at least 50 subjects would be enrolled into the double-blind crossover phase (phase C) and at least 32 evaluable subjects would complete the study. To be evaluable for the abuse potential evaluation, the subjects were required to have adequate pharmacodynamic data from phase C to contribute data to at least

Summary of Results

Subject Disposition and Demography: In this study, 100 subjects were enrolled and randomly assigned to a treatment sequence in phase B; 97 (97%) subjects received at least 1 dose of study drug in phase B, and 92 (92%) subjects completed phase B. Of the 92 subjects who completed phase B, 43 were ineligible for enrollment into phase C, primarily due to drug discrimination failure (n=40). Forty-nine (49%) subjects were randomly assigned to a treatment sequence, received at least 1 dose of study drug, and were evaluable for safety in phase C; 45 (45%) subjects were evaluable for pharmacodynamics; 43 (43%) subjects were evaluable for pharmacokinetics; and 35 (35%) subjects completed the study.

The average age of the subjects was 24.5 years (range, 18 to 43 years) and 24.3 years (range, 18 to 43 years) for those enrolled in phase B and phase C, respectively. The majority of subjects were white and non-Hispanic or Latino (89% and 94% for subjects enrolled in phases B and C, respectively). The majority of subjects were men (79% and 80% for subjects enrolled in phases B and C, respectively). Mean BMI was 24.5 kg/m^2 for subjects enrolled in both phases B and C.

Pharmacokinetics Results: Consistent with the known pharmacokinetic profile of immediate-release hydrocodone, mean C_{max} of hydrocodone was attained approximately 1 hour following administration. Decline from peak plasma concentrations generally occurred in a monophasic manner with a mean $t_{1/2}$ of approximately 5 hours.

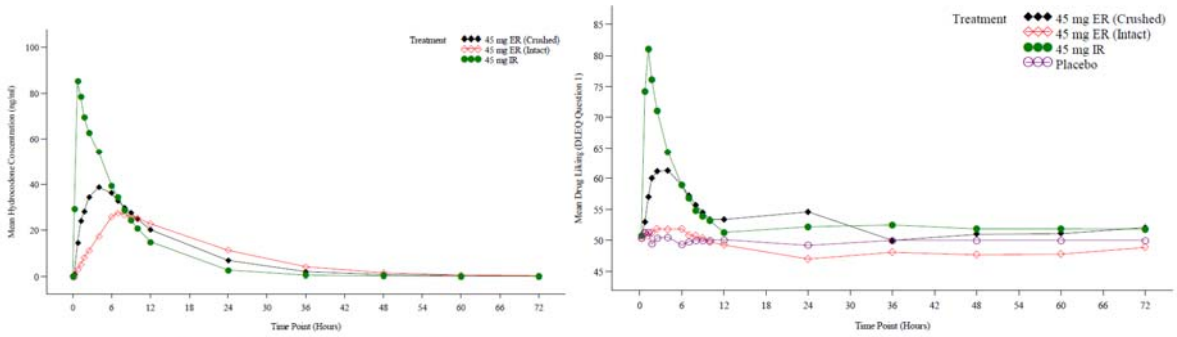
Likewise, the pharmacokinetic profiles of the extended-release tablet (crushed and intact) observed in this study are consistent with that observed in previous studies. Mean maximum plasma concentrations of hydrocodone were attained 7 and 4 hours following administration of the hydrocodone bitartrate extended-release tablet intact or crushed, respectively. Decline from peak plasma concentrations generally occurred in a monophasic manner with a mean $t_{1/2}$ of approximately 8 hours for both the crushed and intact tablets.

Statistical comparisons indicate that overall systemic exposure (as assessed by $AUC_{0-\infty}$) is comparable among treatments. However, C_{max} and early exposure (as assessed by AUC_{0-7} [reflects approximate t_{max} for the extended-release tablet intact]) to hydrocodone were approximately 70% lower following administration of the intact extended-release tablet, as compared with that following administration of the immediate-release product. Similarly, early exposure (as assessed by $AUC_{0-0.75}$ [reflects approximate t_{max} for immediate-release hydrocodone]) to hydrocodone was approximately 97% lower following administration of the intact extended-release tablet as compared with that following administration of the immediate-release product. Consistent with these findings, the abuse quotient was approximately 95% lower for the intact extended-release tablet than for the immediate-release product.

In this study, C_{max} and early exposure (as assessed by AUC_{0-4} [reflects approximate t_{max} for the extended-release tablet crushed]) were approximately 55% to 60% lower following administration of the crushed extended-release tablet, as compared with that following administration of the immediate-release product. Similarly, early exposure (as assessed by $AUC_{0-0.75}$) to hydrocodone was approximately 86% lower following administration of the crushed extended-release tablet, as compared with that following administration of the immediate-release product. The abuse quotient was approximately 85% lower for the crushed extended-release tablet than for the immediate-release product.

Furthermore, C_{max} is approximately 30% lower and early exposure (as assessed by AUC_{0-7}) is approximately 50% lower following administration of the intact extended-release tablet, as compared with that following administration of the crushed extended-release tablet. Similarly, early exposure (as assessed by AUC_{0-4}) to hydrocodone was approximately 66% lower following administration of the intact extended-release tablet as compared with that following administration of the immediate-release product. The abuse quotient was approximately 60% lower for the intact extended-release tablet than for the crushed extended-release tablet.

Figure : Mean Plasma Concentration-Time Profiles and Mean Drug Liking (DLEQ Question 1) Over Time in Healthy, Nondependent, Recreational Opioid Users Administered Single Doses of Hydrocodone Extended-Release Tablets (Crushed or Intact) or an Immediate-Release Formulation or Placebo



SOURCE: Section 15, Figure 1.1.1.A, Adhoc Figure 1.1.0.A.
ER=hydrocodone bitartrate extended-release tablet; IR=immediate-release hydrocodone; DLEQ=Drug Liking and Effects Questionnaire.

Table : Mean (Standard Deviation) Pharmacokinetic Parameters for Hydrocodone After Intranasal Administration of CEP-33237, Hydrocodone API or Zohydro™, or Oral Administration of Intact CEP-33237 (Pharmacokinetic Analysis Set)

Variable	45 mg IN API (N=38)	45 mg IN Zohydro™ (N=39)	45 mg IN CEP-33237 (N=41)	45 mg OR CEP-33237 (N=38)
C_{max} (ng/mL)	71.28 (30.48)	80.27 (29.29)	56.84 (15.07)	25.05 (7.18)
t_{max} (h)	1.38 (0.60, 7.07)	1.12 (0.55, 6.17)	2.62 (1.33, 7.02)	9.11 (4.10, 12.12)
$AUC_{0-\infty}$ (ng·h/mL)	579 (163)	639 (179)	572 (150)	568 (172)
AUC_{0-t} (ng·h/mL)	576 (161)	637 (178)	568 (149)	531 (152)
$AUC_{0\text{-}tmax,\ API}$ (ng·h/mL)	57.5 (28.3)	66.5 (28.3)	24.9 (13.4)	1.9 (0.8)
$AUC_{0\text{-}tmax,\ CEP\ (IN)}$ (ng·h/mL)	125.9 (51.8)	142.4 (51.5)	78.5 (28.6)	9.4 (2.7)
$AUC_{0\text{-}tmax,\ CEP\ (Oral)}$ (ng·h/mL)	380.0 (112.3)	416.3 (108.8)	336.4 (75.1)	127.5 (34.9)
$AUC_{0\text{-}tmax,\ Zohydro}$ (ng·h/mL)	39.3 (20.9)	46.4 (21.2)	15.1 (8.7)	1.0 (0.5)
Extrapolation (%)	0.60 (0.94)	0.38 (0.24)	0.73 (0.72)	6.04 (3.94)
λ_z (1/h)	0.124 (0.023)	0.127 (0.021)	0.114 (0.015)	0.076 (0.024)
$t_{1/2}$ (h)	5.78 (1.06)	5.58 (0.86)	6.16 (0.76)	9.96 (3.03)
AQ (ng/mL/h)	59.6 (55.2)	75.4 (54.0)	22.6 (12.2)	3.1 (1.2)

Source: Summary 15.9.1.
API=active pharmaceutical ingredient; AQ=abuse quotient (C_{max}/t_{max}); $AUC_{0-\infty}$=area under the plasma drug concentration by time curve (AUC) from time 0 to infinity; AUC_{0-t}=AUC from time 0 to the time of the last measurable drug concentration; $AUC_{0\text{-}tmax,\ API}$= AUC from time 0 to the median t_{max} for intranasal hydrocodone API; $AUC_{0\text{-}Tmax,\ CEP\ (IN)}$=AUC from time 0 to the median t_{max} for CEP-33237 when manipulated and administered intranasally; $AUC_{0\text{-}Tmax,\ CEP\ (oral)}$=AUC from time 0 to the median t_{max} for CEP-33237 when administered orally

Table : Statistical Comparison of Intranasal Zohydro™ and Intranasal CEP-33237 (Pharmacokinetic Analysis Set)

Variable	45 mg IN Zohydro™ (N=38)	45 mg IN CEP-33237 (N=41)	Mean % difference[a]	90% CI
C_{max} (ng/mL)	80.27	56.84	-22.01	-29.00, -15.03
$AUC_{0-\infty}$ (ng·h/mL)	639	572	-7.59	-13.31, -1.87
AUC_{0-t} (ng·h/mL)	637	568	-7.81	-13.51, -2.12
$AUC_{0\text{-}tmax,\ Zoh\ (IN)}$ (ng·h/mL)	46.4	15.1	-62.75	-68.39, -57.11
$AUC_{0\text{-}tmax,\ CEP\ (IN)}$ (ng·h/mL)	142.4	78.5	-38.58	-45.56, -31.60
AQ (ng/mL/h)	75.4	22.6	-42.39	-60.72, -24.07

Source: Summary 15.9.1.
[a] Values represent the mean of individual subject differences.
API=active pharmaceutical ingredient; AQ=abuse quotient (calculated as C_{max}/t_{max}); $AUC_{0-\infty}$=area under the plasma concentration by time curve from time 0 to infinity; AUC_{0-t}=AUC from time 0 to the time of the last measurable drug concentration; $AUC_{0\text{-}tmax,\ Zoh\ (IN)}$= AUC from time 0 to the median t_{max} for Zohydro™ when manipulated and administered intranasally; $AUC_{0\text{-}Tmax,\ CEP\ (IN)}$=AUC from time 0 to the median t_{max} for CEP-33237 when manipulated and administered intranasally; CI=confidence interval; C_{max}=maximum observed plasma drug concentration; IN=intranasal; OR=oral.

4.2.5 Study # 1088 Synopsis (Renal Impairment Study)

Name of Sponsor/Company: Teva Branded Pharmaceutical Products R&D, Inc.	**Individual study table referring to part of dossier in which the individual study or study table is presented**	(For National Authority Use Only)
Name of Finished Product: Hydrocodone bitartrate extended-release tablet	**Volume:**	
Name of Active Ingredient: Hydrocodone bitartrate (CEP-33237)	**Reference:**	

Title of Study: An Open-Label, Single-Dose Study to Assess the Pharmacokinetics of the Hydrocodone Bitartrate Extended-Release Tablet (45 mg) in Subjects With Normal Renal Function and Subjects With Varying Degrees of Renal Impairment

Investigators and Study Centers: The study was conducted at 4 centers in the United States by 4 investigators. A complete list of investigators and their affiliations is included in the clinical study report.

Publication (reference): Results from this study have not been published at the time of approval of this report.

Study Period: 09 March 2011 to 02 October 2011 **Phase of Development:** 1

Primary Objective: The primary objective of this study was to assess the effect of renal impairment on the pharmacokinetics of the hydrocodone bitartrate extended-release tablet (45 mg) in subjects with varying degrees of renal impairment as compared with subjects with normal renal function using the following pharmacokinetic parameters for hydrocodone:

- maximum observed plasma drug concentration (C_{max})
- area under the plasma concentration by time curve (AUC) from time 0 to infinity ($AUC_{0-\infty}$)

Secondary Objectives: The secondary objective of the study was to assess the safety of a single 45-mg dose of the hydrocodone bitartrate extended-release tablet in subjects with normal renal function and subjects with varying degrees of renal impairment who were not tolerant to opioids and who were administered naltrexone hydrochloride by evaluating the following:

- occurrence of adverse events throughout the study
- clinical laboratory (serum chemistry, hematology, and urinalysis) test results at final assessment or early withdrawal
- vital signs measurements (blood pressure, pulse, and respiratory rate) throughout the study
- 12-lead electrocardiogram (ECG) findings at final assessment or early withdrawal
- physical examination findings at final assessment or early withdrawal
- oxyhemoglobin saturation (SpO_2) monitoring throughout the study
- concomitant medication usage throughout the study

Number of Subjects (Planned and Analyzed): This study planned to enroll an adequate number of subjects (up to 12 subjects enrolled in each of 4 renal impairment groups and up to 16 subjects with normal renal function) to achieve the targeted minimum of 8 subjects in each renal impairment group and 10 subjects with normal renal function completing the study. Fourteen subjects with normal renal function, 8 subjects with mild renal impairment, 9 subjects with moderate renal impairment, 9 subjects with severe renal impairment, and 9 subjects with ESRD received the dose of the hydrocodone bitartrate extended-release tablet and were evaluable for safety. Thirteen subjects with normal renal function, 8 subjects with mild renal impairment, 9 subjects with moderate renal impairment, 9 subjects with severe renal impairment, and 9 subjects with ESRD were evaluable for pharmacokinetics and completed the study.

Main Criteria for Inclusion: Subjects were included in the study if all of the following main criteria were met (not all inclusive):

All subjects

- The subject was a man or woman at least 18 years of age, with a body mass index (BMI) of 20 kg/m^2 or more.

Subjects with normal renal function

- The subject had an estimated creatinine clearance >80 mL/min.

Subjects with renal impairment

- The subject was renally impaired as defined by 1 of the following categories:
  - — subjects with ESRD were on hemodialysis for at least 6 months prior to enrollment and were receiving standard in-center thrice weekly treatments
  - — subjects with severe renal impairment had an estimated creatinine clearance of less than 30 mL/min
  - — subjects with moderate renal impairment had an estimated creatinine clearance of 30-50 mL/mir
  - — subjects with mild renal impairment had an estimated creatinine clearance of >50-80 mL/min

Main Criteria for Exclusion: Subjects were excluded from participating in this study if 1 or more of the following main criteria were met (not all inclusive):

All subjects

- The subject was a poor metabolizer of cytochrome P450 (CYP) 2D6 substrates based on genotyping performed at screening.
- The subject had any disorder that could have interferred with drug absorption, distribution, metabolism, or excretion (including gastrointestinal surgery, excluding appendectomy).
  NOTE: Cholecystectomy performed 2 years or more prior to enrollment was permitted.

Subjects with normal renal function

- The subject had any clinically significant, uncontrolled medical condition (treated or untreated).

Subjects with renal impairment

- The subject had a condition that, in the opinion of the investigator or protocol-specified contact for medical issues, would have introduced an additional risk factor or interfered with the study objectives and procedures.
- The subject had evidence of an unstable clinically important medical condition other than impaired renal function.
- The subject had an acute exacerbation or unstable renal function, as indicated by worsening of clinical and/or laboratory signs of renal impairment, within the 4 weeks before study drug administration.
- The subject had an acute renal disease caused by infection or drug toxicity.

Study Drug Dose, Mode of Administration, Administration Rate, and Batch Number: Subjects with normal renal function and subjects with varying degrees of renal impairment received a single 45-mg dose of the hydrocodone bitartrate extended-release tablet. The dose was orally administered to subjects, while they were seated, at 0800±2 hours on day 1 of the administration period. Hydrocodone bitartrate extended-release tablets (CEP-33237) were provided at a dose strength of 45 mg (lot number 11-000065). Tablets were white, 0.275" x 0.625" convex, capsule-shaped, and were 575 mg in total weight. Hydrocodone bitartrate extended-release tablets were packaged in 60-cc round, white, high-density polyethylene (HDPE) bottles with 38-mm child-resistant caps. Each bottle contained 1 canister of desiccant. Each bottle was foil-induction sealed and contained 20 tablets.

Reference Therapy Dose, Mode of Administration, and Administration Rate: Not applicable

Method of Blinding: This was an open-label study with no blinding.

Duration of Treatment: This study will consist of a 28-day screening period, a single-dose, open-label administration period including a 6-day pharmacokinetic sampling period, and a follow-up visit 48 to 72 hours after discharge from the study center. Subjects are expected to participate in this study for up to approximately 30 days.

Subjects with ESRD underwent hemodialysis treatment according to their prescribed regimen. A single dialysate sample was collected during hemodialysis on day –1 and hourly dialysate samples were obtained during each hemodialysis treatment following study drug administration. NOTE: In the event that a post-study drug hemodialysis

treatment started or ended within 5 minutes of a scheduled time point at which a blood sample for pharmacokinetic analysis was required, 1 sample was collected to satisfy the requirement for the scheduled time point as well as the pre- or post-hemodialysis blood sample for pharmacokinetics.

General Design and Methodology: This was a multicenter, open-label, pharmacokinetic and safety study to assess the effect of renal impairment on the pharmacokinetics of the hydrocodone bitartrate extended-release tablet at a single dose of 45 mg in adults with varying degrees of renal impairment (mild, moderate, severe, and ESRD) as compared with subjects with normal renal function. The study consisted of a screening visit within 28 days before the dose of study drug (visit 1), followed by a single-dose administration period including a 144-hour pharmacokinetic sampling period (visit 2), a final assessment after the final pharmacokinetic sample is collected or upon early withdrawal, and a follow-up visit 48 to 72 hours after discharge from the study center (visit 3). Subjects were categorized into either the control group or 1 of the impaired renal function groups (mild, moderate, severe, or ESRD). Up to 12 subjects in each of 4 renal impairment groups and up to 16 subjects with normal renal function groups were scheduled to be included in the study. An attempt was made to match the groups according to age, sex, race, weight, and smoking status. To facilitate this, an effort was made to ensure that a minimum of 1 subject with ESRD was enrolled prior to enrolling each subject with mild renal impairment and an effort was made to ensure that a minimum of 1 subject with severe renal impairment was enrolled prior to enrolling each subject with moderate renal impairment. Subjects with normal renal function were enrolled after all renally impaired subjects had completed the study. After the screening assessments were completed, eligible subjects checked into the study center on day –1. Subjects who continued to meet the criteria for enrollment received a single dose of the hydrocodone bitartrate extended-release tablet on day 1. Subjects received one 50-mg tablet of naltrexone hydrochloride with 240 mL of water to block opioid receptors and minimize opioid-related adverse events approximately 15 and 3 hours before and approximately 9 and 21 hours after study drug administration at 0800±2 hours. Blood samples were collected just before study drug administration and at specified time points over a 144-hour period after study drug administration. Subjects were permitted to leave the study center after collection of the 144-hour pharmacokinetic sample. Safety was assessed throughout the study by monitoring the occurrence of adverse events, clinical laboratory test results, vital signs measurements, 12-lead ECG findings, physical examination findings, SpO_2 findings, and use of concomitant medications. Subjects who completed all scheduled visits had final procedures and assessments performed prior to discharge from the study center after pharmacokinetic sampling completed. Subjects who withdrew from the study before the completion of all scheduled assessments had final procedures and assessments performed prior to discharge. All subjects were asked to return for a follow-up visit 48 to 72 hours after discharge from the study center.

Pharmacokinetic Measures and Endpoints: During the administration period, blood samples (3 mL) were collected by venipuncture or indwelling catheter. Samples were collected immediately (within approximately 5 minutes) before and 15, 30, and 45 minutes, and 1, 1.5, 2, 2.5, 3, 3.5, 4, 5, 6, 7, 8, 9, 10, 12, 18, 24, 30, 36, 48, 60, 72, 96, 120, and 144 hours after study drug administration. For subjects with ESRD, blood samples for pharmacokinetics were also collected immediately prior to and following each hemodialysis treatment that occured after administration of study drug. NOTE: In the event that a post-study drug hemodialysis treatment started or ended within 5 minutes of a scheduled time point at which a blood sample for pharmacokinetic analysis was required, 1 sample could be collected to satisfy the requirement for the scheduled time point as well as the pre- or post-hemodialysis blood sample for pharmacokinetics. In addition, urine samples were collected prior to study drug administration and over the following intervals after study drug administration: 0 to 4 hours, 4 to 8 hours, 8 to 12 hours, 12 to 24 hours, 24 to 48 hours, 48 to 72 hours, 72 to 96 hours, 96 to 120 hours, and 120 to 144 hours. For subjects with ESRD, a single dialysate sample was obtained on day –1 and hourly dialysate samples were obtained during each hemodialysis treatment that occured following administration of study drug. NOTE: The first post-dose hemodialysis treatment was scheduled no sooner than 26 hours (±2 hours) following administration of study drug. Subsequent hemodialysis treatments were scheduled to occur at intervals of no less than 48 hours. The following pharmacokinetic parameters for hydrocodone and its metabolite hydromorphone were calculated, if appropriate: C_{max} by inspection (without interpolation), $AUC_{0-\infty}$, area under the plasma drug concentration by time curve from time 0 to the time of the last measurable drug concentration (AUC_{0-t}), area under the plasma drug concentration by time curve from time 0 to 144 hours after study drug administration (AUC_{0-144}), area under the plasma drug concentration by time curve from time 0 to 12 hours after study drug administration (AUC_{0-12}), time to maximum observed plasma drug

concentration (t_{max}) by inspection, percentage extrapolation, 100 x ($AUC_{0-\infty} - AUC_{0-t}$)/$AUC_{0-\infty}$, terminal elimination rate constant (λ_z) and associated elimination half-life ($t_{½}$), apparent oral volume of distribution (V_z/F) [hydrocodone only]), apparent total oral clearance (CL/F [hydrocodone only]), apparent renal clearance (CL_R [hydrocodone only]), percentage of dose excreted renally as unchanged drug, and percentage of dose excreted unchanged in the dialysate (subjects with ESRD only).

Safety Variables: In this study, safety was assessed by evaluating the following: reported adverse events, clinical laboratory test results, vital signs measurements, 12-lead ECG findings, physical examination findings, SpO_2 measurements, and concomitant medication usage.

Statistical Considerations: The set of enrolled subjects included all subjects who were enrolled in the study, regardless of whether or not a subject took study drug. The safety analysis set included those subjects in the set of enrolled subjects who received study drug. The pharmacokinetic analysis set included those subjects in the safety analysis set for whom at least 1 pharmacokinetic parameter could be calculated. Subject disposition and demographic characteristics were summarized using descriptive statistics. In addition, medical history, ECG, and physical examination findings at baseline were summarized using descriptive statistics. Protocol violations for each category were summarized using descriptive statistics. The pharmacokinetic analysis set was used for all pharmacokinetic analyses. The primary plasma pharmacokinetic parameters $AUC_{0-\infty}$ and C_{max} were compared between subjects in each renal impairment group and subjects in the normal renal function group using the ratio of geometric means and its 90% confidence interval (CI). Concentration for hydrocodone and hydromorphone (if appropriate) in plasma and urine and their pharmacokinetic parameters are summarized by renal function group using n, mean, standard deviation (SD), geometric mean (if appropriate), median, minimum, and maximum. In addition, listing of concentrations of hydrocodone and hydromorphone (if appropriate) from hemodialysis are also presented. The safety analysis set was used for all safety analyses unless otherwise noted. Summaries are presented by renal function group. For continuous variables, descriptive statistics (n, mean, SD, median, minimum, and maximum) are provided for actual values and changes from baseline to each visit. For categorical variables, subject counts and percentages are provided. Descriptive summaries of subjects with serious adverse events, subjects who withdrew from the study because of adverse events, and subjects with clinically significant abnormal laboratory, vital signs, or SpO_2 values. The determination of sample size was not made on the basis of power calculations. Data from 8 subjects in each of the 5 renal function groups were considered adequate to assess the effect of renal impairment on the pharmacokinetics of hydrocodone.

Summary of Results

Subject Disposition and Demography: In this study, 55 subjects (14 with normal renal function, 9 with mild renal impairment, 12 with moderate renal impairment, 10 with severe renal impairment, and 10 with ESRD) were enrolled. Fourteen subjects with normal renal function, 8 subjects with mild renal impairment, 9 subjects with moderate renal impairment, 9 subjects with severe renal impairment, and 9 subjects with ESRD received the dose of the hydrocodone bitartrate extended-release tablet and were evaluable for safety. Thirteen subjects with normal renal function, 8 subjects with mild renal impairment, 9 subjects with moderate renal impairment, 9 subjects with severe renal impairment, and 9 subjects with ESRD were evaluable for pharmacokinetics and completed the study. For subjects with normal renal function, mild, moderate, and severe renal impairment, and ESRD, the average age was 59.5, 66.9, 66.6, 62.7, and 49.3 years respectively. The majority of subjects with normal renal function and mild, moderate, or severe renal impairment were white (71%, 89%, 83%, and 80%, respectively) and the majority of subjects with ESRD were black (70%). The majority of subjects with normal renal function and moderate and severe renal impairment and ESRD were men (57%, 58%, 80%, and 70%, respectively) and the majority of subjects with mild renal function were women (67%).

Pharmacokinetics Results: The pharmacokinetic profile observed in subjects with normal renal function in this study is qualitatively similar to that observed in previous studies of the hydrocodone bitartrate extended-release tablet. While an increase in C_{max} was noted in the mild to moderate renal impairment groups, this trend was not consistent in the severe renal impairrment group. Overall systemic exposure (as assessed by AUC) was higher in subjects with moderate and severe renal impairment as compared to that in

subjects in the other renal function groups. The higher exposure in the subjects with moderate or severe renal impairment is due to decreased clearance of hydrocodone while the comparable exposure in ESRD subjects is due to clearance of the drug via dialysis. Of note, since smokers were permitted to participate in the study and because some concomitant medications were permitted, subgroup analyses were performed to determine if any differences in pharmacokinetics were observed in subjects who were smokers or in those concomitantly receiving a weak CYP3A4 or CYP2D6 inhibitor or inducer. These limited data suggest that there is no consistent trend toward decreased exposure in smokers or in subjects who were taking a weak inducer of CYP3A4 or CYP2D6. Likewise, no consistent trend towards an increase in exposure was observed in subjects who were taking an inhibitor of CYP3A4 or CYP2D6. Hydromorphone concentrations were approximately 1 to 2% of those of hydrocodone in each group.

Safety Results: In this study, the following was observed in nonopioid tolerant subjects with varying degrees of renal function who were concurrently receiving naltrexone and who were not poor CYP2D6 metabolizers, following a single, oral 45-mg oral dose of extended-release hydrocodone bitartrate:

- There were no deaths or serious adverse events. One subject was withdrawn from this study due to an adverse event of vomiting (per protocol requirements).
- Overall, the adverse events reported were generally similar across renal function groups. Most of the adverse events were confined to gastrointestinal and nervous system disorders were mild or moderate in severity and resolved. One severe adverse event of orthostatic hypotension was reported; this event began 5 days after study drug administration and resolved without residual effect.
- There appears to be little correlation between hydrocodone levels and overall adverse event frequency in this study.
- There were no clinically meaningful changes in clinical laboratory tests, vital signs, oxygen saturation, physical examinations, ECGs, or concomitant medication use across renal function groups.

Conclusions: Although there was no consistent trend toward an increase in C_{max} with increasing severity of renal impairment, overall systemic exposure to hydrocodone (as assessed by AUC) in subjects with moderate or severe renal impairment was, on average, up to approximately 70% higher than that in subjects in the other renal function groups. Prescribing physicians should be aware of the higher systemic exposure when titrating the dose of the hydrocodone bitartrate extended-release tablet for subjects with moderate to severe renal impairment to an effective dose. In this study, in nonopioid tolerant subjects with varying degrees of renal function who were concurrently receiving naltrexone and who were not poor CYP2D6 metabolizers, there were no new adverse events of interest or safety concerns or signals, following a single, oral 45-mg oral dose of extended-release hydrocodone bitartrate. The safety profile demonstrated in this study was consistent with the known safety profile of hydrocodone.

Plasma Hydromorphone Pharmacokinetic Parameters by Renal Function Group
Pharmacokinetic Analysis Set

Variable Statistic	Normal (N=13)	Mild (N=8)	Moderate (N=9)	Severe (N=9)	ESRD (N=9)
Cmax (ng/mL)					
n	13	8	8	8	9
Mean	0.305	0.338	0.312	0.443	0.290
Geometric mean	0.282	0.319	0.290	0.323	0.240
SD	0.1308	0.1224	0.1272	0.3037	0.2134
SE of mean	0.0363	0.0433	0.0450	0.1074	0.0711
CV	42.8	36.2	40.8	68.6	73.5
Median	0.251	0.310	0.301	0.469	0.183
Min, max	0.146, 0.558	0.207, 0.538	0.168, 0.548	0.084, 0.827	0.117, 0.721
tmax (hr)					
n	13	8	8	8	9
Mean	10.3	10.3	12.1	14.9	9.9
Geometric mean	10.0	9.9	11.9	12.4	9.3
SD	2.98	2.43	2.64	8.56	3.76
SE of mean	0.83	0.86	0.93	3.03	1.25
CV	28.9	23.8	21.8	57.5	38.0
Median	10.0	11.0	12.0	14.0	9.0
Min, max	7.0, 18.0	5.0, 12.0	9.0, 18.0	5.0, 24.0	6.0, 18.0

4.2.6 Study # 1089 Synopsis (Hepatic Impairment Study):

Name of Sponsor/Company: Cephalon, Inc.	**Individual study table referring to part of dossier in which the individual study or study table is presented**	(For National Authority Use Only)
Name of Finished Product: Hydrocodone bitartrate extended-release tablet		
Name of Active Ingredient: Hydrocodone bitartrate (CEP-33237)	**Volume:** **Reference:**	

Title of Study: An Open-Label, Single-Dose, Parallel-Group Study to Assess the Pharmacokinetics of the Hydrocodone Bitartrate Extended Release Tablet (15 mg) in Subjects With Normal Hepatic Function and Subjects With Moderate Hepatic Impairment

Investigators and Study Centers: Thomas C. Marbury, MD, Orlando Clinical Research Center, 5055 South Orange Avenue, Orlando, FL 32809 USA

Publication (reference): Results from this study have not been published at the time of approval of this report.

Study Period: 25 April 2011 to 8 August 2011 **Phase of Development:** 1

Primary Objective: The primary objective of this study was to assess the effect of hepatic impairment on the pharmacokinetics of the hydrocodone bitartrate extended-release tablet (15 mg) in subjects with moderate hepatic impairment as compared with subjects with normal hepatic function using the following pharmacokinetic parameters for hydrocodone:

- maximum observed plasma drug concentration (C_{max})
- area under the plasma drug concentration by time curve (AUC) from time 0 to infinity ($AUC_{0-\infty}$)

Secondary Objectives: The secondary objective of the study was to evaluate the safety of hydrocodone bitartrate extended-release tablet treatment by evaluation of the following:

- occurrence of adverse events throughout the study
- clinical laboratory (serum chemistry, hematology, blood coagulation, and urinalysis) test results at the final assessment or early withdrawal
- vital signs (blood pressure, pulse, and respiratory rate) measurements throughout the study
- electrocardiogram (ECG) findings at the final assessment or early withdrawal
- physical examination findings at the final assessment or early withdrawal
- oxyhemoglobin saturation (SpO2) monitoring throughout the study
- concomitant medication usage throughout the study

Number of Patients (Planned and Analyzed): Up to approximately 12 men and women per hepatic function group were planned to be included in this study, with the intent that a minimum of 8 subjects in each group would complete the study. In this study, 16 subjects (8 with normal hepatic function and 8 with moderate hepatic impairment) were enrolled; all 16 (100%) subjects received the dose of the hydrocodone bitartrate extended-release tablet, were evaluable for safety and pharmacokinetics, and completed the study.

Main Criteria for Inclusion: Subjects were included in the study if all of the following main criteria were met (not all inclusive):

- For all subjects: the subject was a man or woman at least 18 years of age, with a body mass index (BMI) of 20 kg/m^2 or more
- For subjects with normal hepatic function: the subject was in generally good health as determined by medical and psychiatric history, physical examination, ECG, serum chemistry, hematology, coagulation, urinalysis, and serology.
- For subjects with moderate hepatic impairment: the subject had case record notes demonstrating stable biochemistry within 3 months before screening and at baseline; was otherwise clinically stable as determined by medical history, physical examination, ECG, serum chemistry, hematology, coagulation parameters, urinalysis, and serology except for those signs and symptoms attributable to liver disease;

and had case record notes demonstrating physical signs consistent with 1 or more of the following characteristic clinical manifestations of liver cirrhosis: liver firmness to palpation, splenic enlargement, spider angiomas, palmar erythema, parotid hypertrophy, testicular atrophy, ascites (accumulation of fluid in the abdominal cavity), or gynecomastia.

Main Criteria for Exclusion: Subjects were excluded from participating in this study if 1 or more of the following main criteria were met (not all inclusive):

- For all subjects: The subject had any clinically significant, uncontrolled medical condition (treated or untreated)
- For subjects with normal hepatic function: the subject had a clinically significant deviation from normal in ECG or physical examination findings, as determined by the investigator or the medical monitor
- For subjects with moderate hepatic impairment: the subject had a condition that, in the opinion of the investigator or medical monitor, would introduce an additional risk factor or interfere with the study objectives and procedures.

Study Drug Dose, Mode of Administration, Administration Rate, and Batch Number:

Investigational Product: Hydrocodone bitartrate extended release tablets (CEP 33237) were provided at a dose strength of 15 mg. Tablets were light red, 0.275" x 0.625" convex, capsule shaped, and were 575 mg in total weight.

Reference Therapy Dose, Mode of Administration, and Administration Rate: Not applicable

Method of Blinding: This was an open-label study with no blinding.

Duration of Treatment: The study consisted of a screening visit within 28 days before study drug administration (visit 1), followed by a single dose administration period including a 144 hour pharmacokinetic sampling period (visit 2) with a final assessment after the final pharmacokinetic sample was collected or upon early withdrawal, and a follow up visit 48 to 72 hours after discharge from the study center (visit 3).

General Design and Methodology: Subjects were categorized into either the control group with normal hepatic function or the group of subjects with moderate hepatic impairment. Up to 12 subjects per hepatic function group were enrolled with the intent that a minimum of 8 subjects in each group would complete the study. An attempt was made to match the groups according to age, sex, weight, and smoking status. In addition, an effort was made to ensure that a minimum of 1 subject with moderate hepatic impairment was enrolled prior to enrolling each subject with normal hepatic function. Screening efforts focused on meeting these criteria. The sponsor was notified and provided approval prior to enrollment of each subject to maintain balance across study groups. Qualified subjects were considered for inclusion into the study in an order other than that specified above only after discussion with, and agreement by, the medical monitor. After the screening assessments were completed, eligible subjects checked in to the study center on day –1. Subjects who continued to meet the criteria for enrollment received a single dose of the hydrocodone bitartrate extended release tablet on day 1. Blood samples were collected just before study drug administration and over a 144 hour period after study drug administration. Subjects were permitted to leave the study center after final assessment procedures were performed following collection of the 144-hour pharmacokinetic sample. Safety was assessed throughout the study by monitoring the occurrence of adverse events, clinical laboratory test results, vital signs measurements, 12 lead ECG findings, physical examination findings, SpO2 findings, and use of concomitant medications. Subjects who completed all scheduled visits had final procedures and assessments performed prior to discharge from the study center after pharmacokinetic sampling was completed. Subjects who withdrew from the study before the completion of all scheduled assessments had final procedures and assessments performed prior to discharge. All subjects were asked to return for a follow up visit 48 to 72 hours after discharge from the study center.

Pharmacokinetic Measures and Endpoints: During the administration period, blood samples (3 mL) for pharmacokinetic analysis were collected by venipuncture or indwelling catheter. Samples were collected immediately (within approximately 5 minutes) before and 15, 30, and 45 minutes, and 1, 1.5, 2, 2.5, 3, 3.5, 4, 5, 6, 7, 8, 9, 10, 12, 18, 24, 30, 36, 48, 60, 72, 96, 120, and 144 hours after study drug administration. The following pharmacokinetic parameters were calculated for hydrocodone and its active metabolite, hydromorphone (if appropriate): C_{max} by inspection (without interpolation), $AUC_{0-\infty}$, area under the plasma

drug concentration by time curve from time 0 to 144 hours after study drug administration (AUC_{0-144}), area under the plasma drug concentration-by-time curve from time 0 to the time of the last measurable drug concentration (AUC_{0-t}), area under the plasma drug concentration by time curve from time 0 to 12 hours after study drug administration (AUC_{0-12}), time to maximum observed drug concentration (t_{max}), percentage extrapolation, terminal elimination rate constant (λz) and associated elimination half life ($t_{½}$), oral volume of distribution (V_z/F [hydrocodone only]), apparent total plasma drug clearance of hydrocodone (CL/F [hydrocodone only])

Safety Variables: Safety was assessed by evaluating the following: reported adverse events, clinical laboratory test results, vital signs measurements, 12 lead ECG findings, physical examination findings, SpO2 measurements, and concomitant medication usage. For each safety parameter, all findings (whether normal or abnormal) were recorded in the CRF. The investigator judged the clinical significance of any abnormalities, and abnormalities were described in detail.

Statistical Considerations: The set of enrolled subjects includes all subjects who were enrolled in the study, regardless of whether or not a subject received any study drug. The safety analysis set includes those subjects in the set of enrolled subjects who received study drug. The pharmacokinetic analysis set includes those subjects in the safety analysis set for whom at least 1 pharmacokinetic parameter was calculated. Subject disposition and demographic characteristics were summarized using descriptive statistics. In addition, medical history, ECG, and physical examination findings at baseline were summarized using descriptive statistics. Protocol violations for each category were summarized using descriptive statistics. All prior medications were coded according to World Health Organization (WHO) drug dictionary. The incidence of prior medications was summarized using descriptive statistics by therapeutic class and preferred term. Summaries are presented by hepatic function groups. The pharmacokinetic analysis set was used for all pharmacokinetic analyses. The primary pharmacokinetic parameters, $AUC_{0-\infty}$ and C_{max}, were compared between subjects with moderate hepatic impairment and subjects with normal hepatic function. The ratio of geometric means and its 90% confidence interval are provided. All pharmacokinetic parameters are summarized by hepatic function group (normal or moderately impaired) using n, mean, standard deviation (SD), geometric mean (if appropriate), median, minimum, and maximum.

Summary of Results

Patient Disposition and Demography: In this study, 16 subjects (8 with normal hepatic function and 8 with moderate hepatic impairment) were enrolled in the study. All 16 (100%) subjects received the dose of the hydrocodone bitartrate extended-release tablet, were evaluable for safety and pharmacokinetics, and completed the study. The average age of subjects with normal hepatic function was 49.9 years (range 41 to 59 years) and the average age of subjects with moderate hepatic impairment was 55.1 years (range 47 to 60 years). The majority of subjects (75% with normal hepatic function and 88% with moderate hepatic impairment) were white. The percentages of men and women were the same in both hepatic function groups (63% men and 38% women).

Pharmacokinetics Results: Systemic exposure was higher in subjects with moderate hepatic impairment as compared with subjects with normal hepatic function. Decline from peak plasma concentrations occurred in a monophasic manner with comparable $t_{1/2}$ in subjects with moderate hepatic impairment and subjects with normal hepatic function. Following administration of the 15 mg hydrocodone extended release tablet, AUC0-∞ was approximately 70% higher and C_{max} was approximately 28% higher in subjects with moderate hepatic impairment than in subjects with normal hepatic function. Hydromorphone concentrations were approximately 1 to 2% of those of hydrocodone in subjects with normal hepatic function and subjects with moderate hepatic impairment.

Safety Results: A single 15-mg dose of the hydrocodone bitartrate extended release tablet was generally well tolerated by the subjects with normal hepatic function and subjects with moderate hepatic impairment. No deaths or serious adverse events occurred in this study and no subjects withdrew from this study due to adverse events. The incidence of adverse events that occurred following the administration of hydrocodone extended release tablets to subjects with normal hepatic function and subjects with moderate hepatic impairment was comparable, and all of the adverse events reported were mild or moderate in severity. These findings indicate that the higher systemic exposure in subjects with hepatic impairment was not associated with an increase in adverse events. No clinically significant changes in urinalysis results, ECG

findings, respiratory rate, or SpO_2 measurements were reported during the course of study. None of the clinically significant changes in heart rate or blood pressure that occurred following administration of hydrocodone bitartrate extended release tablet were reported as an adverse event, nor were they temporally associated with other adverse events. There was no apparent correlation between plasma concentration of hydrocodone and clinically significant changes in heart rate or blood pressure.

Conclusions: Following administration of the 15 mg hydrocodone bitartrate extended release tablet, overall systemic exposure to hydrocodone was approximately 70% higher in subjects with moderate hepatic impairment than that in subjects with normal hepatic function. Mean C_{max} was also higher (approximately 30%) in subjects with moderate hepatic impairment. Prescribing physicians should be mindful of the higher systemic exposure when titrating hepatically impaired individuals to an effective dose. A single 15 mg dose of the hydrocodone bitartrate extended release tablet was generally well tolerated in subjects with moderate hepatic impairment and subjects with normal hepatic function, indicating that the higher systemic exposure in subjects with hepatic impairment was not associated with an increase in adverse events or other safety related events.

Table: Hydrocodone Pharmacokinetic Parameters Following Administration of the Vantrela Extended-Release 15 mg Tablet to Subjects With Normal Hepatic Function and Subjects With Moderate Hepatic Impairment

Parameter	Normal hepatic function (N=8)	Moderate hepatic impairment (N=8)	Moderate/normal ratio	90% CI
$AUC_{0-\infty}$ (ng·h/mL)	153 (8.9)	261 (24.0)	1.704	1.415, 2.052
C_{max} (ng/mL)	9.96 (0.5848)	12.73 (1.0914)	1.277	1.077, 1.515

SOURCE: Summary 15.9 and Listing 16.2.8.25.
NOTE: Values presented are geometric mean (standard error of the mean).
$AUC_{0-\infty}$=area under the plasma drug concentration by time curve (AUC) from time 0 to infinity;
C_{max}=maximum observed plasma drug concentration; CI=confidence interval.

Table: Mean (Standard Deviation) Pharmacokinetic Parameters for Hydromorphone Following Administration of the 15-mg Vantrela Extended-Release Tablet to Subjects With Normal Hepatic Function and Subjects With Moderate Hepatic Impairment

Parameter	Normal hepatic function (N=8)	Moderate hepatic impairment (N=8)
AUC_{0-t} (ng·h/mL)	2.35 (2.419)	2.23 (1.861)
t_{max} (h)	7.5 (2.79)	8.8 (2.60)
C_{max} (ng/mL)	0.160 (0.1139)	0.138 (0.0595)

SOURCE: Summary 15.11 and Listing 16.2.8.26.
AUC_{0-t}=AUC from time 0 to the time of the last measurable drug concentration; C_{max}=maximum observed plasma drug concentration; t_{max}=time to maximum observed plasma drug concentration by inspection.

Hydromorphone concentrations were approximately 1 to 2% of those of hydrocodone in subjects with normal hepatic function and subjects with moderate hepatic impairment.

4.2.7 Study # 1076 Synopsis (Alcohol Interaction study):

Name of Sponsor/Company: Cephalon, Inc.	**Individual study table referring to part of dossier in which the individual study or study table is presented**	(For National Authority Use Only)
Name of Finished Product: Hydrocodone bitartrate extended-release tablet	**Volume:**	
Name of Active Ingredient: Hydrocodone bitartrate (CEP-33237)	**Reference:**	

Title of Study: A Randomized, Open-Label, 5-Period Crossover Study to Assess the Effect of Food and the Effect of Alcohol on the Pharmacokinetics of Hydrocodone Bitartrate From an Extended-Release Prototype (15-mg Tablet) in Healthy Subjects

Investigators and Study Centers: Aziz L. Laurent, MD, PPD Development, LP, 7551 Metro Center Drive, Suite 200, Austin, Texas 78744 USA.

Publication (reference): Results from this study have not been published at the time of approval of this report.

Study Period: 25 January 2010 to 30 April 2010 **Phase of Development:** 1

Primary Objective: The primary objective of the study was to characterize the pharmacokinetic profiles of hydrocodone bitartrate through the 72 hours following administration of a 15-mg dose of a hydrocodone bitartrate extended-release prototype (CEP-33237 [(b) (4) with water in a fasted state, with water in a fed state, and with varying strengths of alcohol in a fasted state.

Secondary Objectives: The secondary objective of the study was to assess the safety of hydrocodone bitartrate following administration of a hydrocodone bitartrate extended-release prototype (CEP-33237 (b) (4) with water in a fasted state, with water in a fed state, and with varying strengths of alcohol in a fasted state by evaluation of the following:

- occurrence of adverse events throughout the study
- clinical laboratory test results at the final assessment (or early withdrawal)
- vital signs measurements throughout the study
- 12-lead electrocardiogram (ECG) findings at the final assessment (or early withdrawal)
- physical examination findings, including body weight measurements, at the final assessment (or early withdrawal)
- oxyhemoglobin saturation (SpO_2) monitoring on the day of each study drug administration, at the final assessment (or early withdrawal), and at follow-up
- concomitant medication usage throughout the study

Number of Subjects (Planned and Analyzed): For this study, 40 subjects were planned to be enrolled. From the 40 subjects enrolled, data from 39 subjects were analyzed for safety and data from 30 subjects were analyzed for pharmacokinetics.

Main Criteria for Inclusion: Subjects were included in the study if all of the following main criteria were met (not all inclusive):

- The subject was a man or woman 21 through 45 years of age, with a body mass index (BMI) between 20 and 30 kg/m^2, inclusive.
- The subject was in good health as determined by a medical and psychiatric history, physical examination, ECG, serum chemistry, hematology, urinalysis, and serology.

Main Criteria for Exclusion: Subjects were excluded from participating in this study if 1 or more of the following main criteria were met (not all inclusive):

- The subject had any clinically significant uncontrolled medical conditions (treated or untreated).
- The subject had habitually consumed, within the past 2 years, more than 21 units of alcohol per week, or had a history of alcohol, narcotic, or any other substance abuse as defined by the Diagnostic and

Study Drug Dose, Mode of Administration, Administration Rate, and Batch Number: Hydrocodone bitartrate extended-release tablets (lot number 200923) were provided at a dose of 15 mg and a [(b) (4)]. Tablets are 0.275″ x 0.625″ convex, capsule-shaped, light red, and are 575 mg in total weight. Subjects were randomly assigned to 1 of the following 5 treatment sequences: ABCDE, BCDEA, CDEAB, DEABC, and EABCD. Each of the 5 treatments was a single 15-mg hydrocodone bitartrate extended-release tablet (CEP-33237 [(b) (4)]). The tablet was administered either with water (fed or fasted) or with alcohol (fasted), as follows: treatment A was with 240 mL of water in a fasted state; treatment B was with 240 mL of water in a fed state; treatment C was with 4% volume per volume (v/v) ethanol in orange juice (total volume 240 mL) in a fasted state; treatment D was with 20% v/v ethanol in orange juice (total volume 240 mL) in a fasted state; and treatment E was with 40% v/v ethanol in orange juice (total volume 240 mL) in a fasted state. Subjects had to consume all water or alcohol within 20 minutes of study drug administration. Each subject received 1 treatment during each administration period. Subjects received each of the 5 treatments once. There was a minimum 5-day washout period separating successive administrations of study drug. Treatments were orally administered to subjects, while they were seated, at approximately 0800 (±2 hours) on the first day of each administration period.

Reference Therapy Dose, Mode of Administration, and Administration Rate: Not applicable

Method of Blinding: This was an open-label study with no blinding.

Duration of Treatment: Subjects received 5 single doses, each separated by a minimum 5-day washout period. Subjects participated in the study for approximately 50 days.

General Design and Methodology: This was a single-center, randomized, open-label, 5-period crossover study to characterize the pharmacokinetics of hydrocodone bitartrate following administration of a hydrocodone bitartrate extended-release prototype (CEP-33237 [(b) (4)]) with water in a fasted state, with water in a fed state, and with varying amounts of alcohol in a fasted state. Subjects were randomly assigned to 1 of the 5 treatment sequences. The study consisted of a screening visit within 21 days before the first dose of study drug, followed by 5 open-label single-dose administration periods, and a follow-up visit. Subjects received one 50-mg tablet of naltrexone hydrochloride with 240 mL of water to block opioid receptors and minimize opioid-related adverse events approximately 15 hours and 3 hours before and approximately 9 hours and 21 hours after each study drug administration. For each of the 5 treatment periods, venous blood samples for pharmacokinetic analyses were collected immediately before and over 72 hours after study drug administration. Blood samples were obtained for quantitative measurement of blood alcohol concentrations immediately before and 1 hour after each study drug administration. Subjects remained in the study center throughout each pharmacokinetic sampling period. Safety was assessed throughout the study by monitoring the occurrence of adverse events, clinical laboratory test results, vital signs measurements, 12-lead ECG findings, physical examination findings, SpO_2 monitoring, and use of concomitant medications. Safety was assessed prior to each subject's discharge from the last administration period that subject participated in. All subjects were asked to return to the study center for a follow-up visit to occur 48 to 72 hours after their last discharge from the center. Safety parameters were evaluated at that time.

Pharmacokinetic Measure(s) and Endpoint(s): For each of the 5 treatment periods, blood samples (3 mL) for pharmacokinetic analyses were collected immediately before and over the 72 hours following study drug administration by venipuncture or indwelling catheter. In addition, blood samples (3.5 mL) were collected for quantitative blood alcohol concentration measurements immediately before and 1 hour after study drug administration at each treatment period. The following pharmacokinetic parameters of hydrocodone and its metabolite hydromorphone were calculated, when possible: maximum observed plasma drug concentration (C_{max}) by inspection (without interpolation), time to maximum observed plasma drug concentration (t_{max}) by inspection, area under the plasma drug concentration versus time curve (AUC) from time 0 to the time of the last measurable drug concentration (AUC_{0-t}), AUC from time 0 to 72 hours after hydrocodone administration (AUC_{0-72}), AUC from time 0 to 12 hours after hydrocodone administration (AUC_{0-12}), AUC from time 0 to 2 hours after hydrocodone administration (AUC_{0-2}), AUC from time 0 to infinity ($AUC_{0-\infty}$), percentage extrapolation $100x(AUC_{0-\infty}-AUC_{0-t})/AUC_{0-\infty}$), and apparent plasma terminal elimination rate constant (λ_z) and associated elimination half-life ($t_{½}$).

Safety Variables: In this study, safety was assessed by evaluating the following: reported adverse events, clinical laboratory test results, vital signs measurements, 12-lead ECG findings, physical examination findings, SpO_2 monitoring, and concomitant medication usage. For each safety parameter, all findings (whether normal or abnormal) were recorded in the case report form (CRF). The investigator judged the clinical significance of any abnormalities, and abnormalities were described in detail.

Statistical Considerations: Up to 40 healthy subjects were planned to be enrolled in this study, with the intent that approximately 30 subjects would complete the study. This sample size was anticipated to provide at least 80% power to detect bioequivalence if the intrasubject standard deviation of a natural-log transformed pharmacokinetic parameter was 0.283 or lower. Pharmacokinetic parameters were summarized with descriptive statistics including the geometric mean (if appropriate), coefficient of variation, and 95% confidence interval (CI). Comparisons between treatments were descriptive. In addition, the effect of food on the pharmacokinetics of hydrocodone was assessed by comparing C_{max}, AUC_{0-t}, and $AUC_{0-\infty}$ of treatment B with those of treatment A. Each parameter was analyzed using the analysis of variance model (ANOVA). The ANOVA included treatment, treatment sequence, and period as the fixed effects and subject as a random effect. The 2-sided 90% CI for the log-transformed treatment difference was obtained from the ANOVA for treatment B versus A. Treatment B was to be considered bioequivalent to treatment A if the 90% CI fell completely within the limits of 0.8 to 1.25 for all 3 pharmacokinetic parameters. Equivalence between treatment B and A was to be considered as no food effect. If equivalence was not achieved, ie, the 90% CI was outside of the limits of 0.8 to 1.25, the 2-sided 95% CI from the same ANOVA model was to be provided along with the effect estimate. The effect of alcohol on the pharmacokinetics of hydrocodone was assessed by descriptively comparing systemic exposure as measured by $AUC_{0-\infty}$ and C_{max} following treatments C, D, and E to that following treatment A. The 2-sided 95% CI for the log-transformed treatment differences of treatments C versus A, D versus A, and E versus A from the same ANOVA model is provided along with the effect estimates. In addition to the analysis described in the protocol, the above analysis was also performed on the metabolite hydromorphone. For the safety analyses, continuous variables, descriptive statistics (n, mean, standard deviation, standard error of the mean median, minimum and maximum) are provided for actual values and changes from baseline to endpoint. For categorical variables, subject counts and percentages are provided.

Summary of Results

Subject Disposition and Demography: In this study, 40 healthy subjects were enrolled and randomly assigned to a treatment sequence. Of the 40 subjects enrolled, 39 (98%) subjects received at least 1 dose of study drug and were evaluable for safety; 30 (75%) subjects were evaluable for pharmacokinetics, and 31 (78%) subjects completed the study. The average age of the subjects was 30.3 years (range 21 to 44 years). The majority (90%) of subjects were men and 34 (87%) were white.

Pharmacokinetics Results: Following administration of one 15-mg hydrocodone bitartrate extended-release tablet with 240 mL of water in a fasted state (treatment A), plasma concentrations of hydrocodone rose gradually, with a median t_{max} of 8.0 hours. Plasma concentrations declined from peak in an apparent biphasic manner. Mean $t_{1/2}$ was 10.8 hours. There was a notable increase in C_{max} when the hydrocodone bitartrate extended-release tablet was administered with food as compared to when it was administered in a fasted state (approximately 40% higher C_{max}). While the CI for the ratio of treatment B (fed) to treatment A (fasted) for C_{max} did not meet the criteria for bioequivalence (1.354, 1.548), the CIs for AUC did (1.041, 1.117 for AUC_{0-t} and 1.035, 1.111 for $AUC_{0-\infty}$). Systemic exposure to hydrocodone, as assessed by AUC and C_{max}, was comparable when the hydrocodone bitartrate extended-release tablets were administered with alcohol as compared to when administered with water.

Safety Results: No deaths or other serious adverse events occurred in this study. One subject withdrew from the study due to an adverse event before receiving a dose of study drug but after receiving naltrexone. The most frequently reported adverse events overall included nausea, headache, vomiting, feeling drunk, dizziness, paresthesia, abdominal pain, fatigue, somnolence, dyspepsia, and pain in extremity. The reported treatment-related adverse events were generally similar among the treatment groups and were generally consistent with the known pharmacologic activity of opioids. The overall frequency of adverse events was approximately the same with administration of treatment B or C as with treatment A. The frequency of adverse events overall increased with the administration of increasing strengths of alcohol with treatments D and E as compared with treatment C or A. Several of the adverse events reported following administration of treatments C, D, and E are events that are generally accepted to be associated with alcohol ingestion (eg, feeling drunk, dizziness). The increased frequency of adverse events reported with treatments D and E most likely represents additive toxicity of increasing strengths of alcohol administered in combination with hydrocodone. No clinically significant changes in hematology, serum chemistry, urinalysis, systolic and diastolic blood pressure, pulse, or ECG findings were reported during the study. Clinically significant decreases in respiratory rate were reported both prior to and after study drug administration. No clinically significant decreases in oxygen saturation were reported during the study.

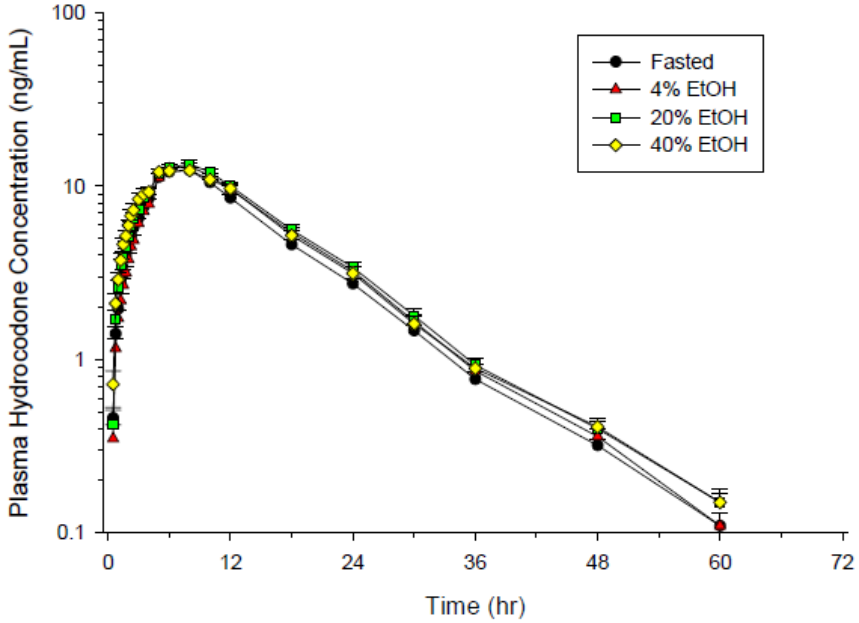
Conclusions: There was a notable increase in C_{max} when the hydrocodone bitartrate extended-release tablet was administered with food as compared to when it was administered in a fasted state (approximately 40% higher C_{max}). While the CI for the ratio of fed versus fasted treatments for C_{max} did not meet the criteria for bioequivalence, the CIs for AUC did. Administration of the hydrocodone bitartrate extended-release tablet with 4%, 20%, or 40% v/v alcohol solutions did not have a notable effect as assessed by AUC and C_{max} on systemic exposure to hydrocodone as compared with administration with water. The safety data indicate that single 15-mg doses of the hydrocodone bitartrate extended-release tablet administered with and without food and with varying concentrations of alcohol were generally well tolerated in the healthy subjects concurrently receiving naltrexone in this study.

Table: Effect of Food on Hydrocodone Exposure.

Parameter	Treatment B (n=29)	Treatment A (n=29)	Ratio B/A	90% CI
C_{max} (ng/mL)	18.5	12.5	1.448	1.354, 1.548
AUC_{0-t} (ng·hr/mL)	208.7	190.5	1.078	1.041, 1.117
$AUC_{0-\infty}$ (ng·hr/mL)	210.8	193.5	1.072	1.035, 1.111

SOURCE: Summary 15.10.1, Listing 16.2.8.19.
A=One 15-mg hydrocodone bitartrate extended-release tablet with 240 mL of water in a fasted state.
B=One 15-mg hydrocodone bitartrate extended-release tablet with 240 mL of water in a fed state.
NOTE: Values are geometric means; CI=confidence interval.

Figure: Mean (+Standard Error) Plasma Concentration-By-Time Profiles Through 72 Hours for Hydrocodone in Healthy Subjects Administered a Single 15-mg Dose of the Hydrocodone Bitartrate Extended-Release Tablet Fasting With Water or Fasting With 4%, 20%, or 40% Volume/Volume Alcohol Solutions.



SOURCE: Drug Safety and Disposition.

Table : Effect of Alcohol on Hydrocodone Exposure (Pharmacokinetic Analysis Set)

Parameter	Treatment C (n=30)	Treatment A (n=30)	Ratio C/A	95% CI
C_{max} (ng/mL)	13.2	12.4	1.050	0.992, 1.112
$AUC_{0-\infty}$ (ng·hr/mL)	207.6	191.3	1.068	1.013, 1.125
	Treatment D (n=27)	**Treatment A (n=27)**	**Ratio D/A**	**95% CI**
C_{max} (ng/mL)	13.5	12.3	1.085	1.025, 1.147
$AUC_{0-\infty}$ (ng·hr/mL)	219.7	192.8	1.129	1.060, 1.203
	Treatment E (n=24)	**Treatment A (n=24)**	**Ratio E/A**	**95% CI**
C_{max} (ng/mL)	13.3	11.8	1.144	1.077, 1.216
$AUC_{0-\infty}$ (ng·hr/mL)[a]	212.9	186.3	1.170	1.110, 1.234

SOURCE: Summary 15.11.1, Summary 15.12.1, Summary 15.13.1, Listing 16.2.8.19.
A=One 15-mg hydrocodone bitartrate extended-release tablet with 240 mL of water in a fasted state; C=One 15-mg hydrocodone bitartrate extended-release tablet with 240 mL of 4% volume/volume (v/v) alcohol in a fasted state; D=One 15-mg hydrocodone bitartrate extended-release tablet with 240 mL of 20% alcohol in a fasted state; E=One 15-mg hydrocodone bitartrate extended-release tablet with 240 mL of 40% alcohol in a fasted state.
NOTE: Values are geometric means; CI=confidence interval.

Plasma Hydromorphone Pharmacokinetic Parameters by Treatment
Pharmacokinetic Analysis Set

Variable Statistic	A (N=30)	B (N=29)	C (N=30)	D (N=27)	E (N=24)
Cmax (ng/mL)					
n	30	29	30	27	24
Mean	0.1	0.2	0.1	0.1	0.1
Geometric mean	0.1	0.2	0.1	0.1	0.1
SD	0.08	0.12	0.08	0.08	0.08
SE of mean	0.01	0.02	0.02	0.02	0.02
Median	0.1	0.2	0.1	0.1	0.1
Min, max	0.0, 0.4	0.0, 0.7	0.0, 0.5	0.0, 0.4	0.0, 0.3
95% C.I for mean	0.1, 0.2	0.2, 0.2	0.1, 0.2	0.1, 0.2	0.1, 0.1
Tmax (hr)					
n	29	28	29	26	20
Mean	11.93	6.98	10.32	10.41	11.23
Geometric mean	10.13	6.58	10.02	10.13	10.76
SD	11.798	2.532	2.287	2.174	2.922
SE of mean	2.191	0.479	0.425	0.426	0.653
Median	10.00	6.00	12.00	12.00	12.00
Min, max	5.00, 72.00	3.00, 12.00	5.00, 12.12	5.00, 12.10	5.00, 18.00
95% C.I for mean	7.445, 16.420	6.001, 7.965	9.445, 11.186	9.528, 11.284	9.861, 12.597
AUC[0-t] (ng*hr/mL)					
n	30	29	30	27	24
Mean	2.0	2.5	2.2	2.1	1.6
Geometric mean	1.5	2.1	1.6	1.7	1.4
SD	1.70	1.59	1.81	1.53	1.53
SE of mean	0.31	0.30	0.33	0.29	0.31
Median	2.0	2.5	1.8	2.0	1.4
Min, max	0.0, 8.3	0.0, 7.2	0.0, 8.2	0.0, 6.8	0.0, 6.0
95% C.I for mean	1.4, 2.7	1.9, 3.1	1.6, 2.9	1.5, 2.7	1.0, 2.3
AUC[0-inf] (ng*hr/mL)					
n	12	19	19	17	12
Mean	3.8	4.3	4.3	4.0	3.9
Geometric mean	3.6	4.1	4.0	3.8	3.6
SD	1.14	1.60	1.70	1.54	1.53
SE of mean	0.33	0.37	0.39	0.37	0.44
Median	3.5	4.0	4.4	3.8	3.7
Min, max	2.2, 6.3	2.0, 9.2	1.9, 8.9	2.4, 7.9	1.5, 6.9
95% C.I for mean	3.1, 4.5	3.6, 5.1	3.5, 5.2	3.2, 4.8	2.9, 4.8

Treatment	How administered
A	With 240 mL of water in fasted state
B	With 240 mL of water in fed state
C	With 240 mL of 4% (v/v) ethanol in a fasted state
D	With 240 mL of 20% (v/v) ethanol in a fasted state
E	With 240 mL of 40% (v/v) ethanol in a fasted state

NOTE: Each treatment included administration of a single 15-mg hydrocodone bitartrate extended-release tablet (CEP-33237 [42.5% coating level]).

4.2.8 Study # 10024 Synopsis (Food-effect after single dose and multiple dose).

Name of Sponsor/Company: Teva Pharmaceutical Industries, Limited	**Individual study table referring to part of dossier in which the individual study or study table is presented**	(For National Authority Use Only)
Name of Finished Product: Hydrocodone Bitartrate Extended-Release Tablet	**Volume:**	
Name of Active Ingredient: Hydrocodone	**Reference:**	

Title of Study: A Randomized, Open-Label, 2-Period Crossover Study to Assess the Effect of Food on the Pharmacokinetics of the Hydrocodone Bitartrate Extended-Release Tablet at Steady-State

Investigator and Study Center: Aziz L. Laurent, MD, PPD, Suite 200, 7551 Metro Center Drive, Austin, Texas 78744, USA

Publication (reference): Results from this study have not been published at the time of approval of this report.

Study Period: 29 January 2014 to 09 March 2014 Phase of Development: 1

Primary Objective: The primary objective of the study was to characterize the steady-state pharmacokinetics of hydrocodone bitartrate following administration of multiple 90-mg doses of the hydrocodone bitartrate extended-release tablet administered to healthy subjects in fed and fasted states.

Secondary Objectives: The secondary objective of the study was to characterize the safety of hydrocodone bitartrate following administration of multiple doses of the hydrocodone bitartrate extended-release tablet in a fed and fasted state to naltrexone-blocked subjects by evaluating the following:

- occurrence of adverse events throughout the study
- clinical laboratory test results throughout the study
- vital signs measurements throughout the study
- 12-lead electrocardiogram (ECG) findings at the final assessment (or early withdrawal)
- physical examination findings at the final assessment (or early withdrawal)
- oxyhemoglobin saturation (SpO_2) monitoring throughout the study
- suicidality assessments throughout the study
- concomitant medication usage throughout the study.

Number of Subjects (Planned and Analyzed): For this study, 44 subjects were planned to be enrolled. Data from 30 subjects were analyzed for pharmacokinetics and data from 43 subjects were analyzed for safety.

Diagnosis and Main Criteria for Inclusion: Subjects were included in the study if all of the following main criteria were fulfilled (not all inclusive):

- The subject was a man or woman 18 through 45 years of age, with a body mass index of 20.0 to 30.0 kg/m^2, inclusive, at screening.
- The subject was in good health as determined by medical and psychiatric history, suicidality assessment, physical examination, ECG, serum chemistry, hematology, urinalysis, and serology.
- Women must have been surgically sterile, 2 years postmenopausal, or, if of childbearing potential, used an acceptable method of contraception, and agreed to continued use of this method for the duration of the study and for 30 days after discontinuation of study drug.
- The subject had a negative alcohol test and urine drug screen.

Main Criteria for Exclusion: Subjects were excluded from participating in this study if one or more of the following main criteria were met (not all inclusive):

- The subject had any clinically significant uncontrolled medical conditions (treated or untreated).
- The subject had a clinically significant deviation from normal in ECG or physical examination findings, as determined by the investigator or the medical monitor.
- The subject was a poor metabolizer of cytochrome P450 2D6 substrates based on genotyping performed at screening or documented prior testing.
- The subject had any procedure or any disorder that may have interfered with drug absorption, distribution, metabolism, or excretion (including gastrointestinal surgery; a history of appendectomy was allowed).
- The subject had habitually consumed, within the past 2 years, more than 21 units of alcohol per week, or had a history of alcohol, narcotic, or any other substance abuse as defined by the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision (DSM-IV-TR, American Psychiatric Association 2000).
- The subject had a known sensitivity or idiosyncratic reaction to hydrocodone or hydromorphone, their related compounds, or to any metabolites, or naltrexone, or any compound listed as being present in a study formulation.
- The subject had 1 or more clinical laboratory test value(s) outside the following specified range, or any other clinically significant laboratory abnormality as determined by the investigator or medical monitor: hemoglobin value of less than 12.0 g/dL, aspartate aminotransferase or alanine aminotransferase value more than 1.5× the upper limit of the normal range, or total bilirubin value of more than 25.7 µmol/L (1.5 mg/dL).
- The subject had, after resting for 5 minutes, oxygen saturation less than 95%. (Only 2 rechecks of the subject's SpO_2 were permitted for eligibility purposes.)

Study Drug Dose, Mode of Administration, Administration Rate, and Batch Number:

Investigational Product: hydrocodone bitartrate extended-release tablets, provided at dose strengths of 30 mg (lot numbers 13-000785, 14-000015, and 13-000800) and 45 mg (lot numbers 13-000786, 14-000016, and 13-000802) of hydrocodone bitartrate; administered orally, titrated to a 90-mg dose twice daily.

Reference Therapy Dose, Mode of Administration, and Administration Rate: Not applicable.

Concomitant Therapy Dose, Mode of Administration, and Administration Rate: Naltrexone hydrochloride tablets, administered orally (before and after hydrocodone administration to block opioid receptors and minimize opioid-related adverse events); subjects received one 50-mg tablet every 12 hours starting 15 hours before the first dose of study drug and continuing through 33 hours after the last dose of study drug; lot number 117OU82358.

Method of Blinding: This was an open-label study with no blinding.

Duration of Treatment: 24 days (12 days in each of 2 periods, separated by a minimum 14-day washout period).

General Design and Methodology: This was a Phase 1, single-center, randomized, open-label, 2-period, crossover study to assess the effect of food on the steady-state pharmacokinetics of the hydrocodone bitartrate extended-release tablet in healthy subjects aged 18 to 45 years, inclusive. Subjects were randomly assigned to receive treatments in one of the following regimen sequences: AB or BA, where A was multiple doses of study drug administered in a fasted state and B was multiple doses of study drug administered in a fed state.

The first dose of study drug was followed by 2 open-label multiple-dose administration periods (periods 1 and 2), each of which was 12 days long, and a follow-up visit. There was a minimum 14-day washout between the last dose of study drug in period 1 and the first dose of study drug in period 2. Both periods were conducted on an inpatient basis.

In each period, study drug was titrated to a 90-mg dose of the hydrocodone bitartrate extended-release tablet twice daily as follows:

- day 1: a single 90-mg dose in the morning
- days 2 and 3: 45-mg dose twice daily
- days 4 and 5: 60-mg dose twice daily
- days 6 to 10: 90-mg dose twice daily
- day 11: a single 90-mg dose in the morning.

Doses were administered with subjects randomly assigned to either a fed or fasted state. In each period, subjects received one 50-mg tablet of naltrexone hydrochloride with 240 mL of water, to block opioid receptors and minimize opioid-related adverse events, every 12 hours starting 15 hours before the first dose and continuing through 33 hours after the last dose.

In each period, blood samples to determine plasma concentrations of hydrocodone and its active metabolite, hydromorphone, were collected before and over a 12-hour period following the morning dose on day 1 and before

each study drug administration on days 9 and 10. Blood samples were also collected before and over a 12-hour period after administration of the last dose of study drug on the morning of day 11. Subjects remained in the study center from the day before administration of the first dose of study drug through administration of the final dose of naltrexone (day –1 to the evening of day 12 in each period).

Efficacy Measure(s) and Endpoint(s): Not applicable.

Safety Variables: Safety was assessed throughout the study by monitoring the occurrence of adverse events (including deaths, serious adverse events, and withdrawals due to adverse events), clinical laboratory tests (serum chemistry, hematology, and urinalysis), vital signs measurements, 12-lead ECG findings, physical examination findings, SpO_2 monitoring, suicidality assessments, and use of concomitant medications.

Primary Pharmacokinetic Measures and Endpoints: The primary pharmacokinetic variables for this study were as follows:

- The maximum observed plasma drug concentration (C_{max}) and the area under the plasma drug concentration by time curve for 1 dosing interval of a multiple-dose regimen calculated by linear trapezoidal method (AUC_{τ}) for hydrocodone at steady-state (day 11) with fasted and fed regimens

Secondary Pharmacokinetic Measures and Endpoints: The secondary pharmacokinetic variables for this study were as follows:

- C_{max} for hydrocodone after a single dose (day 1) with fasted and fed regimens
- C_{max} of hydromorphone and time to maximum observed drug concentration (t_{max}) and area under the plasma drug concentration by time curve from time 0 to 12 hours after study drug administration calculated by linear trapezoidal method (AUC_{0-12}) of hydrocodone and hydromorphone following a single dose (day 1) for fasted and fed regimens
- C_{max} and AUC_{τ} of hydromorphone and t_{max} and the observed accumulation ratio (R_{obs}) of hydrocodone and hydromorphone at steady-state (day 11) for fasted and fed regimens

Statistical Considerations: All data were processed and summarized by the use of SAS® Version 9.2 (SAS Institute Inc, Cary, North Carolina) or higher. Baseline was defined as the last observed data before the first dose of study drug. Endpoint for analyses and summaries was defined as the last observed postbaseline data.

Descriptive statistics for continuous variables included number, mean, SD, standard error (SE) of the mean, median, minimum, and maximum. If inferential statistics were computed, least squares (LS) mean and SE of the LS mean were also included. Descriptive statistics for categorical variables included subject counts and percentages.

All disorders recorded in the medical history data were coded using the Medical Dictionary for Regulatory Activities (MedDRA) Version 16.1. All prior medications were coded using WHO Drug Version 01 March 2013.

Fasted regimen A (90 mg, reference) and fed regimen B (90 mg, test) were assessed by comparing C_{max} and AUC_{τ} of hydrocodone at steady-state. The natural log-transformed values of each parameter were analyzed using a linear mixed-effect model, which included treatment, regimen sequence, and period as the fixed effects and subject nested within sequence as a random effect. The 2-sided 90% confidence interval (CI) for the geometric LS mean ratio

between regimen B and regimen A was provided through this model. Regimen B was considered to be bioequivalen to regimen A if the 90% CI of the geometric LS mean ratio fell completely within the limits of 0.8 to 1.25 for both C_{max} and AUC_{τ} at steady-state. The effect of food on C_{max} following the first dose of study drug was assessed in the same manner.

The secondary pharmacokinetic parameters were summarized by fasted or fed status using descriptive statistics (number, mean, SD, SE, median, minimum, and maximum for all parameters and geometric mean and coefficient of variation for AUCs and C_{max}).

All adverse events were coded using MedDRA Version 16.1. Summaries were presented for all adverse events (overall and by severity), adverse events determined by the investigator to be treatment related (overall and by severity), serious adverse events, adverse events causing discontinuation from the study, and nonserious adverse events. Adverse events were attributed to the treatment regimen corresponding to the last study drug administered. In addition, adverse events after the first dose of naltrexone but before the first dose of hydrocodone bitartrate extended-release tablet were presented for all subjects (randomly assigned not treated, treated, and total) who received the first dose of naltrexone in the set of randomly assigned subjects.

The incidences of potentially clinically significant abnormal results were summarized for laboratory data, selected vital signs, and SpO_2 using descriptive statistics. Oxyhemoglobin saturation less than 90% was identified as potentially clinically significant abnormal.

All concomitant medications were coded using WHO Drug Version 01 March 2013. The incidence of concomitant medications was summarized using descriptive statistics by therapeutic class and preferred term.

Summary of Results

Subject Disposition and Demography: A total of 106 subjects were screened for enrollment into this study, of which 43 subjects were considered eligible and were randomly assigned (21 subjects in the AB sequence group and 22 subjects in the BA sequence group); 43 (100%) subjects received at least 1 dose of study drug and were evaluable for safety; and 30 (69.8%) subjects completed the study. A total of 13 of 43 (30.2%) subjects discontinued from the study due to adverse events (9 [20.9%] subjects, of which 8 [18.6%] subjects experienced emesis following administration of study drug and were withdrawn from the study per the protocol), protocol violations (2 [4.7%] subjects), and other reasons (2 [4.7%] subjects).

The mean age of the subjects was 31.5 years (range 19 to 42 years); 56% of subjects were men and 58% of subjects were white. Mean weight was 74.7 kg.

Efficacy Results: Not applicable.

Safety Results: There were no deaths reported in the study and no subjects had a serious adverse event. Overall, 29 of 43 (67.4%) subjects reported at least 1 adverse event after receiving study drug in the fed and/or fasted state, and the incidence of subjects who reported at least 1 adverse event was comparable for subjects in the fasted (19 [51.4%] subjects) and fed (21 [53.8%] subjects) state. There was a higher incidence of adverse events considered by the investigator to be treatment related (reasonable possibility of being related to study drug) for subjects in the fed state (19 [48.7%] subjects) as compared with the fasted state (13 [35.1%] subjects). Nine (20.9%) subjects were discontinued from the study because of adverse events (7 [17.9%] subjects in the fed state and 2 [5.4%] subjects in the fasted state). Consistent with the protocol requirement that any subject

experiencing emesis at any time following administration of study drug in either period be withdrawn from the study, the most common adverse event leading to discontinuation was vomiting (7 [17.9%] subjects in the fed state and 1 [2.7%] subject in the fasted state). One (2.7%) subject was withdrawn due to influenza-like illness and oropharyngeal pain in the fasted state.

Moderate adverse events occurred at a higher frequency in subjects in the fed state: 6 (15.4%) subjects had moderate vomiting (4 of whom also had moderate nausea) as compared with 1 (2.7%) subject with moderate nausea and vomiting in the fasted state.

Five of 43 (11.6%) subjects reported at least 1 adverse event after the first dose of naltrexone and before the first administration of study drug, including nausea (3 [7.0%] subjects), fatigue (2 [4.7%] subjects), and abdominal pain, feeling of body temperature change, vision blurred, somnolence, dyspnoea, and night sweats (1 [2.3%] subject each).

The most frequently occurring adverse events overall were headache (12 [27.9%] subjects) and events which were gastrointestinal in nature (infrequent bowel movements, nausea, vomiting, constipation, abdominal distension, and abdominal pain). Infrequent bowel movements and constipation were more commonly reported following study drug administration in the fasted state, whereas nausea and vomiting were reported more frequently in the fed state.

The overall incidence of adverse events reported was highest on the first day of dosing in each state (fed or fasted). On that day, the incidence of adverse events was higher in the fed state (10 events for 5 subjects) as compared with the fasted state (4 events for 2 subjects). The incidence of adverse events during the multiple-dosing period was comparable in both states (19 subjects experienced 50 adverse events starting after the first day of dosing in the fasted state as compared with 19 subjects experiencing 53 events in the fed state).

All adverse events were reported as mild or moderate in severity, regardless of fed or fasted state. A total of 7 (16.3%) subjects experienced adverse events of moderate severity (all of which were nausea or vomiting), more commonly in the fed state (6 [15.4%] subjects) as compared with the fasted state (1 [2.7%] subject).
Six (15.4%) subjects experienced moderate vomiting (4 of whom also had moderate nausea) in the fed state, and a further 1 (2.7%) subject had moderate nausea and vomiting in the fasted state. All other adverse events were considered mild in severity.

There were no clinically meaningful trends observed for any clinical laboratory variables, vital signs measurements, SpO_2 measurements, ECG findings, or physical examination findings. Three SpO_2 measurements <90% in 3 subjects are considered by the investigator to have been documented erroneously: the 3 subjects would have been clearly symptomatic and shown obvious signs of respiratory distress if these pulse oximetry values had been legitimate. There were no associated adverse events reported by any of these 3 subjects. There were no clinically meaningful trends in mean changes from baseline for any clinical laboratory parameter. Per predefined criteria, several subjects had potentially clinically significant laboratory abnormalities while on treatment, including high alanine aminotransferase, aspartate aminotransferase, and lactate dehydrogenase (1 subject); eosinophils/leukocytes ≥10% (1 subject); and a ≥2 unit increase in ketones and/or blood in the urine (3 subjects). No suicidal ideation or suicide attempts were reported.

Pharmacokinetics Results:

Hydrocodone Pharmacokinetics

Single-Dose Administration in a Fasted State

Following a single 90-mg dose of hydrocodone bitartrate extended-release tablet in the fasted state (regimen A), plasma concentrations of hydrocodone rose gradually, with a median t_{max} of 9.0 hours.

Multiple-Dose Administration in a Fasted State

Following multiple-dose administration of hydrocodone bitartrate extended-release tablets, mean morning predose concentrations for days 9, 10, and 11 were relatively consistent under fasted conditions, ranging from approximately 90 to 100 ng/mL, as were those under fed conditions (approximately 114 to 122 ng/mL) (see following table). Similarly, the mean evening predose concentrations for days 9 and 10 and the 12-hour postdose concentration for day 11 were consistent across days under fasted conditions and under fed conditions. These findings confirm that pharmacokinetic steady-state had been attained prior to pharmacokinetic sampling on day 11. A small degree of diurnal variation was observed in the mean hydrocodone trough concentrations (see following table), with trough concentrations prior to evening doses being approximately 7% to 19% lower than those prior to morning doses in the fasted state and 13% to 25% lower than trough concentrations prior to morning doses in the fed state.

Plasma Hydrocodone Predose Trough Concentrations (ng/mL) Following Multiple Doses of 90 mg Hydrocodone Extended-Release Tablets under Fasted or Fed Conditions (Pharmacokinetic Analysis Set)

	Regimen A (Fasted) (n=30)						Regimen B (Fed) (n=30)					
	Day 9		Day 10		Day 11		Day 9		Day 10		Day 11	
	AM	PM	AM	PM	AM	12h	AM	PM	AM	PM	AM	12h
Mean	99.81	81.09	90.38	82.42	91.13	84.85	121.62	98.29	113.68	99.11	117.78	92.89
SD	32.26	26.07	25.99	29.17	28.43	27.35	34.49	28.17	32.60	29.12	36.57	30.91
CV%	32.3	32.2	28.8	35.4	31.2	32.2	28.4	28.7	28.7	29.4	31.0	33.3

Food Effect - Single-Dose Administration

As observed previously, plasma concentrations of hydrocodone in the fed state remained lower than those in the fasted state over the first several hours after dosing. After that time, plasma concentrations rose to higher levels in the fed state, producing a higher peak with food as compared with a fasted state.

The following table presents the mean pharmacokinetic parameters for hydrocodone following a single dose of the hydrocodone bitartrate extended-release tablet in the fed and fasted states.

Mean (± SD) Plasma Hydrocodone Pharmacokinetic Parameters in Healthy Volunteers Administered 90-mg Hydrocodone Extended-Release Tablet as a Single Dose (Day 1) under Fasted or Fed Conditions (Pharmacokinetic Analysis Set)

Parameter	Regimen A (Fasted) (n=30)	Regimen B (Fed) (n=30)
C_{max} (ng/mL)	49.73 ± 12.16	66.90 ± 16.52
t_{max}[a] (hr)	9.0 [6.0 to 12.0]	6.0 [5.0 to 12.0]
AUC_{0-12} (ng•hr/mL)	398 ± 97.14	489 ± 97.22

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The median time to peak plasma concentrations in the fed state was reported as 6 hours, approximately 3 hours earlier than observed in the fasted state. However, the range of t_{max} values between regimens is comparable and the plasma concentration-time curve for both regimens is essentially flat over the period from 6 to 10 hours after dosing.

The following table presents the statistical comparisons of AUC and C_{max} for hydrocodone following administration of a single dose of the hydrocodone bitartrate extended-release tablet in the fed and fasted states.

Statistical Analysis of Hydrocodone Exposure Following Single-Dose Administration (Pharmacokinetic Analysis Set)

Parameter	Geometric LS Means		Ratio B/A	90% CI for the Ratio (B/A)
	Regimen B (Fed) (n=30)	Regimen A (Fasted) (n=30)		
AUC_{0-12} (ng•hr/mL)	479.467	385.659	1.243	1.189, 1.300
C_{max} (ng/mL)	64.833	48.314	1.342	1.282, 1.404

There was a notable increase in systemic exposure when administered with food as compared with administration in the fasted state (AUC_{0-12} and C_{max} were approximately 23% and 35% higher, respectively). The CIs for the ratio of geometric means between regimen B (fed) and regimen A (fasted) for AUC_{0-12} (1.189, 1.300) and C_{max} (1.282, 1.404) did not meet the criteria for bioequivalence (0.8 to 1.25) following single-dose administration.

Of note, a small number of subjects had a more pronounced food effect. In particular, Subjects 12214040, 12214049, and 12214070 had C_{max} values that were 65.4%, 70.7%, and 70.8%, respectively, higher in the fed state as compared with the fasted state on day 1.

Food Effect - Multiple-Dose Administration

The following table presents the mean pharmacokinetic parameters for hydrocodone following multiple doses of the hydrocodone bitartrate extended-release tablet in the fed and fasted states.

Mean (± SD) Plasma Hydrocodone Pharmacokinetic Parameters in Healthy Volunteers Administered 90-mg Hydrocodone Extended-Release Tablets at Steady-State (Day 11) under Fasted or Fed Conditions (Pharmacokinetic Analysis Set)

Parameter	Regimen A (Fasted) (n=30)	Regimen B (Fed) (n=30)
C_{max} (ng/mL)	115.19 ± 31.86	131.20 ± 35.89
t_{max}[a] (hr)	6.0 [0.5 to 9.0]	6.0 [0.0 to 8.0]
AUC_{τ} (ng•hr/mL)	1205 ± 329	1334 ± 355
R_{obs}	3.08 ± 0.68	2.75 ± 0.53

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AUC_{τ} for day 1 = AUC_{0-12} for day 1.

The mean hydrocodone C_{max} under fed conditions was approximately 14% greater than that under fasted conditions (131.20 vs. 115.19 ng/mL, respectively) and mean systemic exposure (AUC_{τ}) was approximately 11% greater when hydrocodone was administered following a meal relative to in the fasted state (1334 vs. 1205 ng•hr/mL, respectively). The time to C_{max} (t_{max}) was comparable between fed and fasted states (median of 6.0 hours for each treatment). The observed accumulation ratio is comparable in the fasted and fed states: 3.1 and 2.8, respectively.

The following table presents the statistical comparisons of AUC and C_{max} for hydrocodone following administration of multiple doses of the hydrocodone bitartrate extended-release tablet in the fed and fasted states.

Statistical Analysis of Hydrocodone Exposure Following Doses of 90-mg Hydrocodone Extended-Release Tablets (Pharmacokinetic Analysis Set)

Parameter	Geometric LS Means		Ratio B/A	90% CI for the Ratio (B/A)
	Regimen B (Fed) (n=30)	Regimen A (Fasted) (n=30)		
AUC_{τ} (ng•hr/mL)	1288.693	1164.976	1.106	1.042, 1.174
C_{max} (ng/mL)	126.553	111.330	1.137	1.071, 1.206

AUC_{τ} for day 1 = AUC_{0-12} for day 1.

The CIs for the ratio of geometric means between regimen B (fed) and regimen A (fasted) for AUC_{τ} (1.042, 1.174) and C_{max} (1.071, 1.206) met the criteria for bioequivalence (0.8 to 1.25) following multiple-dose administration.

As observed following single-dose administration in this study and in previous studies, there was considerable variability in the effect of food on the pharmacokinetics of hydrocodone following multiple doses of hydrocodone bitartrate extended-release tablet. In particular, for Subjects 12214017, 12214040, and 12214085, C_{max} values were 66.2%, 71.2%, and 89.9%, respectively, higher in the fed state as compared with the fasted state on day 11.

Hydromorphone Pharmacokinetics

The active metabolite, hydromorphone, was detected following both single- and multiple-dose administration. Under all conditions studied, systemic exposure to hydromorphone was approximately 1% to 2% to that of hydrocodone (see the following table).

Mean (± SD) Plasma Hydromorphone Pharmacokinetic Parameters in Healthy Volunteers Administered 90-mg Hydrocodone Extended-Release Tablets as a Single Dose (Day 1) or at Steady-State (Day 11) under Fasted or Fed Conditions (Pharmacokinetic Analysis Set)

Parameter	Regimen A (Fasted) (n=30)		Regimen B (Fed) (n=30)	
	Day 1	Day 11	Day 1	Day 11
C_{max} (ng/mL)	0.641 ± 0.256	1.735 ± 0.800	0.868 ± 0.453	2.114 ± 0.851
AUC_{τ} (ng•hr/mL)	4.7 ± 1.86	15.9 ± 6.09	6.1 ± 2.72	19.3 ± 7.19
t_{max}[a] (hr)	12.0 [5.0 to 12.0]	5.50 [0.0 to 12.0]	8.0 [5.0 to 12.0]	0.5 [0.0 to 9.0]

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AUC_{τ} for day 1 = $AUC_{0\text{-}12}$ for day 1.

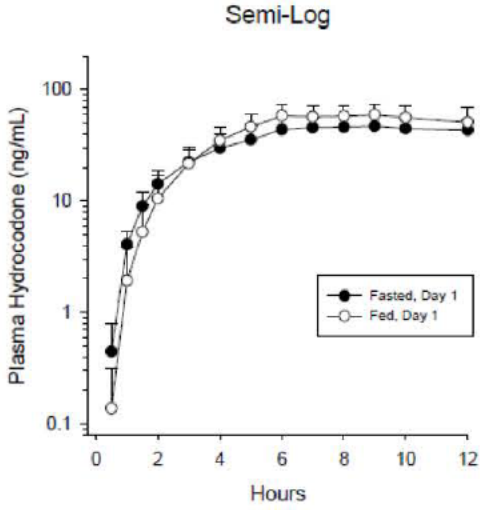
Conclusions:

- Administration of a single 90-mg hydrocodone bitartrate extended-release tablet in the fed state resulted in a notable increase in hydrocodone peak (35%) and total systemic (23%) exposures than administration of the same formulation and dose in the fasted state. The CIs for the ratio of geometric means (fed:fasted) for C_{max} (1.282, 1.404) and $AUC_{0\text{-}12}$ (1.189, 1.300) did not meet the criteria for bioequivalence (0.8 to 1.25) following single-dose administration.

- At steady-state the effect of food was less pronounced, with C_{max} increasing by 14% and AUC_{τ} increasing by 11% as compared with administration in the fasted state. The CIs for the ratio of geometric means (fed:fasted) for C_{max} (1.071, 1.206) and AUC_{τ} (1.042, 1.174) met the criteria for bioequivalence following multiple-dose administration.

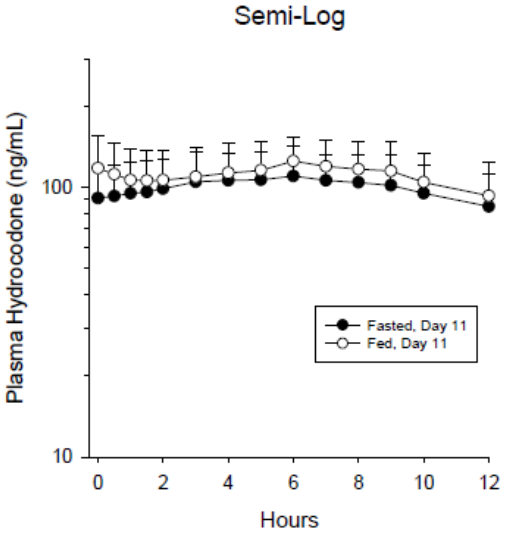
- Administration of hydrocodone bitartrate extended-release tablets titrated to a 90-mg dose twice daily was generally well tolerated by healthy naltrexone-blocked subjects in either the fasted or fed state.

Figure : **Mean (+SD) Plasma Hydrocodone Concentration by Time Profiles in Healthy Volunteers Administered 90-mg Hydrocodone Extended-Release Tablets as a Single Dose (Day 1) under Fasted or Fed Conditions (Semilogarithmic Scale) (Pharmacokinetic Analysis Set)**



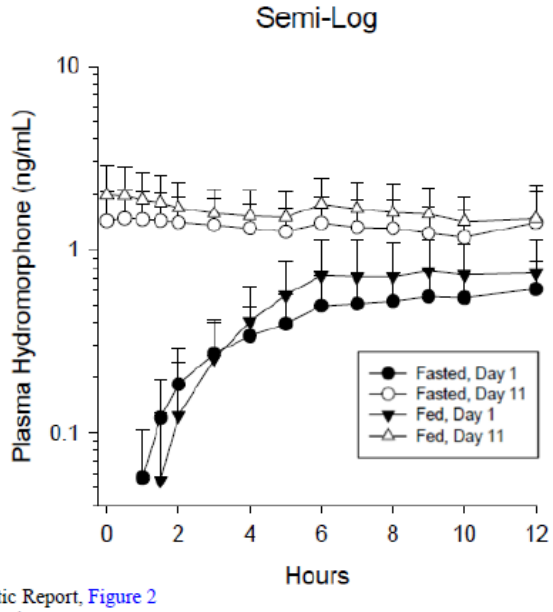
Semi-log=semilogarithmic.

Figure : **Mean (+SD) Plasma Hydrocodone Concentration-by-Time Profiles in Healthy Volunteers Administered 90-mg Hydrocodone Extended-Release Tablets at Steady-State (Day 11) under Fasted or Fed Conditions (Semilogarithmic Scale) (Pharmacokinetic Analysis Set)**



Semi-log=semilogarithmic

Figure : **Mean (+SD) Plasma Hydromorphone Concentration-by-Time Profiles in Healthy Volunteers Administered 90-mg Hydrocodone Extended-Release Tablets as a Single Dose (Day 1) or at Steady-State (Day 11) under Fasted or Fed Conditions (Semilogarithmic Scale)**



Source: Pharmacokinetic Report, Figure 2
Semi-log=semilogarithmic.

4.2.9 Study # 1079 Synopsis (relative BA study)

Name of Sponsor/Company: Teva Branded Pharmaceutical Products R&D, Inc.	**Individual study table referring to part of dossier in which the individual study or study table is presented**	(For National Authority Use Only)
Name of Finished Product: Hydrocodone bitartrate extended-release tablet		
Name of Active Ingredient: Hydrocodone bitartrate (CEP-33237)	**Volume:** **Reference:**	

Title of Study: A Randomized, Open-Label, 4-Period Crossover Study to Assess the Pharmacokinetics of a Single 15-mg Dose of the Hydrocodone Bitartrate Extended-Release Tablet (Crushed and Intact) and a Single 15-mg/400-mg Dose of a Commercially Available Immediate-Release Hydrocodone/Ibuprofen Tablet (Crushed and Intact) in Healthy Subjects

Investigators and Study Centers: Aziz L. Laurent, MD, PPD Development, LP, 7551 Metro Center Drive, Suite 200, Austin, Texas 78744, USA

Publication (reference): Results from this study have not been published at the time of approval of this report.

Study Period: 22 June 2011 to 14 September 2011 **Phase of Development:** 1

Primary Objective: The primary objective of the study was to characterize the pharmacokinetics of hydrocodone bitartrate following administration of a 15-mg dose of the hydrocodone bitartrate extended-release tablet (a single 15-mg tablet) crushed and intact and a 15-mg dose of hydrocodone within an immediate-release hydrocodone combination product, VICOPROFEN (two 7.5-mg hydrocodone/200-mg ibuprofen tablets) crushed and intact.

Secondary Objectives: The secondary objectives of the study were to assess the relative bioavailability of the hydrocodone bitartrate extended-release tablet and VICOPROFEN and to characterize the safety of hydrocodone bitartrate following administration of the hydrocodone bitartrate extended-release tablet and VICOPROFEN in healthy subjects who were concurrently receiving naltrexone by evaluating the following:

- occurrence of adverse events throughout the study
- clinical laboratory test results at the final assessment (or early withdrawal)
- vital signs measurements throughout the study
- 12-lead electrocardiogram (ECG) findings at the final assessment (or early withdrawal)
- physical examination findings, including body weight measurements, at the final assessment (or early withdrawal)
- oxyhemoglobin saturation (SpO_2) monitoring on the day of each study drug administration, at the final assessment (or early withdrawal), and at follow-up
- concomitant medication usage throughout the study

Number of Subjects (Planned and Analyzed): For this study, up to 40 subjects were planned to be enrolled; 38 subjects were enrolled and randomly assigned to a treatment sequence; data from 35 subjects were analyzed for safety and data from 31 subjects were analyzed for pharmacokinetics.

Main Criteria for Inclusion: Subjects were included in the study if all of the following main criteria were met (not all inclusive):

- The subject was a man or woman 18 through 45 years of age, with a body mass index (BMI) of 20 to 30 kg/m^2, inclusive.
- The subject was in good health as determined by medical and psychiatric history, physical examination, ECG, serum chemistry, hematology, urinalysis, and serology.

Main Criteria for Exclusion: Subjects were excluded from participating in this study if 1 or more of the following main criteria were met (not all inclusive):

- The subject had any clinically significant uncontrolled medical conditions (treated or untreated).
- The subject had a clinically significant deviation from normal in ECG or physical examination findings, as determined by the investigator or the medical monitor.

Study Drug Dose, Mode of Administration, Administration Rate, and Batch Number: Subjects were randomly assigned to 1 of the following 4 treatment sequences: ABDC, BCAD, CDBA, or DACB. Each subject received 1 treatment during each administration period. Subjects received each of the 4 treatments once. There was a minimum 14-day washout period between the 4 administrations of study drug. Treatments were orally administered to subjects, while they were seated, with 240 mL of water, at approximately 0800 (±2 hours) on the 1st day of each administration period.

Investigational Product: Hydrocodone bitartrate extended-release tablets (CEP-33237) were provided at a dose strength of 15 mg (treatments A and B, administered intact and crushed, respectively [lot number C62913]). Tablets were light red, 0.275" x 0.625" convex, capsule-shaped, and were 575 mg in total weight.

Comparison Drug: Treatments C and D were a 15-mg dose of hydrocodone within an immediate-release hydrocodone combination product, VICOPROFEN (two 7.5-mg hydrocodone/200-mg ibuprofen tablets), administered intact and crushed, respectively.

Reference Therapy Dose, Mode of Administration, and Administration Rate: Not applicable

Method of Blinding: This was an open-label study with no blinding.

Duration of Treatment: Subjects received 4 single doses of study drug, each separated by a minimum 14-day washout period. Subjects were expected to participate in this study for up to approximately 70 days.

General Design and Methodology: The study consisted of a screening visit (visit 1) within 21 days before the first dose of study drug, followed by 4 open-label single-dose administration periods (periods 1 through 4 [visits 2 through 5]) and a follow-up visit (visit 6). There was a minimum 14-day washout between successive administrations of study drug. Subjects received each of the 4 treatments once. Subjects received one 50-mg tablet of naltrexone hydrochloride with 240 mL of water to block opioid receptors and minimize opioid-related adverse events approximately 15 hours and 3 hours before each study drug administration and approximately 9 hours and 21 hours after each study drug administration. In each administration period, venous blood samples for pharmacokinetic analyses were collected immediately before and over 72 hours after study drug administration. Subjects remained in the study center throughout each pharmacokinetic sampling period. Safety was also assessed throughout the study by monitoring the occurrence of adverse events, clinical laboratory test results, vital signs measurements, 12-lead ECG findings, physical examination findings, SpO_2 monitoring, and use of concomitant medications. Subjects who participated in all scheduled visits had final procedures and assessments performed prior to discharge in administration period 4 (visit 5). Subjects who withdrew from the study before the completion of all scheduled assessments had final procedures and assessments performed prior to discharge in their last period. All subjects were asked to return to the study center for a follow-up visit occurring 48 to 72 hours after their last discharge from the center. Safety parameters were evaluated at that time.

Pharmacokinetic Measures and Endpoints: In each administration period, blood samples (3 mL) were collected by venipuncture or indwelling catheter. Blood samples were collected immediately (within approximately 5 minutes) before study drug administration and 15, 30, and 45 minutes, and 1, 1.5, 1.75, 2, 2.25, 2.5, 3, 3.5, 4, 5, 6, 7, 8, 9, 10, 12, 18, 24, 30, 36, 48, 60, and 72 hours after study drug administration. The following pharmacokinetic parameters for hydrocodone and its metabolite, hydromorphone, were calculated, when possible, for each treatment:

- maximum observed plasma drug concentration (C_{max}) by inspection (without interpolation)
- time to maximum observed plasma drug concentration (t_{max}) by inspection
- area under the plasma drug concentration by time curve (AUC) from time 0 to infinity ($AUC_{0-\infty}$)
- AUC from time 0 to 72 hours after hydrocodone administration (AUC_{0-72})
- AUC from time 0 to the time of the last measurable drug concentration (AUC_{0-t})
- percentage extrapolation, $100x(AUC_{0-\infty}-AUC_{0-t})/AUC_{0-\infty}$)
- apparent plasma terminal elimination rate constant (λ_z) and associated elimination half-life ($t_{½}$)

- $AUC_{0\text{-}tmax'}$ where $t_{max'}$ is the median tmax of treatment C (intact VICOPRFEN)
- Abuse Quotient (calculated as C_{max}/t_{max})

Safety Variables: Safety was assessed during the study by evaluating adverse events, clinical laboratory test results (chemistry, hematology, and urinalysis), vital signs measurements, ECG and physical examination findings, SpO_2 monitoring, and concomitant medication usage.

Statistical Considerations: The set of randomized subjects includes all subjects who were randomly assigned to a treatment sequence, regardless of whether or not a subject received any study drug. The safety analysis set includes those subjects in the set of randomized subjects who received at least 1 dose of either the hydrocodone bitartrate extended-release tablet or the commercially available immediate-release hydrocodone/ibuprofen product. The pharmacokinetic analysis set includes those subjects in the safety analysis set who had sufficient data to calculate the pharmacokinetic parameters for administration periods to be used for at least 1 of the planned comparisons. Subject disposition and demographic characteristics were summarized using descriptive statistics. In addition, medical history, ECG, and physical examination findings at baseline were summarized using descriptive statistics. Protocol violations for each category were summarized using descriptive statistics. The pharmacokinetic analysis set was used for all pharmacokinetic analyses. Summaries are presented by treatment. Plasma concentration data of hydrocodone and its metabolite hydromorphone were summarized at each time point using descriptive statistics. Pharmacokinetic parameters of hydrocodone and its metabolite hydromorphone were summarized using descriptive statistics, including the geometric mean and coefficient of variation. Parameters characterizing the pharmacokinetic profile took into account the actual dose administered. The difference between the pharmacokinetics of hydrocodone bitartrate from crushed and intact hydrocodone bitartrate extended-release tablets (treatments B and A, respectively) was assessed by comparing C_{max}, $AUC_{0\text{-}\infty}$, and $AUC_{0\text{-}t}$ following treatment B with the same parameters for treatment A. Natural log-transformed values of each parameter were analyzed using the analysis of variance (ANOVA). The ANOVA model included sequence, treatment, and period as the fixed effects and subject as a random effect. The 2-sided 95% and 90% confidence intervals (CIs) for the ratio were obtained from the ANOVA for B vs A by anti-log transformation. The differences between the pharmacokinetics of the following treatments were assessed in the same manner:

- treatment A versus treatment C
- treatment B versus treatment C
- treatment B versus treatment D
- treatment D versus treatment C

The safety analysis set was used for all safety analyses. With the exception of adverse events, vital signs, and SpO_2 summaries were presented for all subjects (ie, total). Adverse events are presented by treatment, for the hydrocodone bitartrate extended-release tablets treatments combined, and for all subjects, whereas vital signs and SpO_2 are presented by treatment only. Up to 40 healthy subjects were planned to be enrolled in this study, with the intent that at least 28 subjects would complete the study. This sample size estimate was not based on statistical considerations.

Summary of Results

Subject Disposition and Demography: In this study, 38 subjects were randomly assigned to a treatment sequence; 35 (92%) subjects received at least 1 dose of study drug and were evaluable for safety; 31 (82%) subjects were evaluable for pharmacokinetics; and 25 (66%) subjects completed the study. The average age of the subjects was 28.8 years (range 18 to 45 years). Approximately half (53%) of the subjects were white and the majority (76%) of subjects were men. Mean BMI was 25.4 kg/m^2 (range 20.7 to 30.0 kg/m^2).

Pharmacokinetics Results: Following administration of the hydrocodone bitartrate extended-release tablet intact, mean maximum plasma concentrations of hydrocodone were attained approximately 7 hours following administration. Decline from peak plasma concentrations generally occurred in a monophasic manner with a mean half-life of approximately 10 hours. Following administration of the immediate-release product (VICOPROFEN) intact, mean maximum plasma concentrations of hydrocodone were attained approximately 2 hours following administration. Decline from peak plasma concentrations generally occurred in a monophasic manner with a mean half-life of approximately 9 hours. These profiles

are comparable to those previously observed for these products. Statistical comparisons indicate that maximum plasma concentration of hydrocodone is approximately 65% lower and early systemic exposure (as assessed by $AUC_{0\text{-}tmax'}$) is approximately 93% lower following administration of the hydrocodone bitartrate extended-release tablet intact, compared with that following administration of the immediate-release product intact. Consistent with these findings, the abuse quotient (a measure of concentration over time), was much higher for the immediate-release product (approximately 14-fold) than for the extended-release tablet. As expected, the profiles of the immediate-release product (VICOPROFEN) intact and crushed are nearly identical. Hydromorphone concentrations were approximately 1% of those of hydrocodone following administration of each treatment. Following administration of a crushed 15-mg hydrocodone bitartrate extended-release tablet, maximum plasma concentrations are reached earlier than those following administration of the hydrocodone bitartrate extended-release tablet intact (median t_{max} of 2.5 and 7.0 hours, respectively). Half-life is comparable between treatments. Statistical comparisons indicate that overall systemic exposure is comparable between treatments. However, the maximum plasma concentration of hydrocodone is approximately 40% lower and early exposure (as assessed by $AUC_{0\text{-}tmax'}$) is approximately 85% lower following administration of the intact extended-release tablet as compared with that following administration of the crushed extended-release tablet. Consistent with these findings, the abuse quotient was higher for the crushed tablet than for the intact tablet (approximately 5-fold). Following administration of VICOPROFEN intact, maximum plasma concentrations are reached slightly earlier than those following administration of the hydrocodone bitartrate extended-release tablet crushed (median t_{max} of 1.8 and 2.5 hours, respectively). Half-life is comparable between treatments. Statistical comparisons indicate that maximum plasma concentration following administration of the hydrocodone bitartrate extended-release tablet crushed are approximately 40% lower and early systemic exposure (as assessed by $AUC_{0\text{-}tmax'}$) is approximately 50% lower than that following administration of VICOPROFEN intact.

Safety Results: The safety data indicate that single 15-mg doses of the hydrocodone bitartrate extended-release tablet (intact or crushed) and the immediate-release product VICOPROFEN (intact or crushed) were generally well tolerated in the healthy subjects concurrently receiving naltrexone in this study. No deaths or other serious adverse events occurred in this study. Two subjects withdrew from the study due to adverse events. One subject withdrew prior to receiving the first dose of study drug due to an adverse event of asthenia and 1 subject withdrew after receiving all 4 doses of study drug due to an unrelated adverse event of vomiting. All adverse events were mild to moderate in severity and resolved before the end of the study. The overall incidence of adverse events and treatment-related adverse events was comparable across treatments. The most frequently occurring adverse events overall (≥5% of subjects following any treatment) were nausea, dizziness, vomiting, headache, and diarrhea. Treatment-related adverse events were generally consistent with the known pharmacologic activity of opioids. Clinically significant respiratory rate values were reported both prior to and after administration of the extended-release and the immediate-release tablets in this study. No correlation was detected between these low respiratory rates, oxygen desaturation, and plasma concentrations of hydrocodone or hydromorphone. Overall, mean vital signs values remained within the normal range throughout the study. None of the clinically significant changes in blood pressure or heart rate were reported as adverse events and no correlation was detected between clinically significant changes in blood pressure or heart rate and plasma concentrations. No clinically meaningful changes in laboratory values, ECG, or SpO_2 results were reported during the course of the study.

Conclusions: Overall systemic exposure, as assessed by AUC, is comparable following administration of the extended-release tablet crushed or intact. Mean C_{max} after administration of the intact extended-release tablet is approximately 40% lower than that after administration of the crushed extended-release tablet. Comparisons to the immediate-release product (at the same dose level) demonstrate that mean C_{max} for the crushed extended-release tablet is approximately 40% lower and mean C_{max} for the intact extended-release tablet is approximately 65% lower. The hydrocodone bitartrate extended-release tablet and VICOPROFEN, administered intact or crushed, were generally well tolerated in the healthy subjects who were concurrently receiving naltrexone in this study.

Figure: Mean (Standard Error) Plasma Concentration by Time Profiles for Hydrocodone in Healthy Subjects Administered a 15-mg Dose of Hydrocodone Within the Hydrocodone Bitartrate Extended-Release Tablet and VICOPROFEN (Intact).

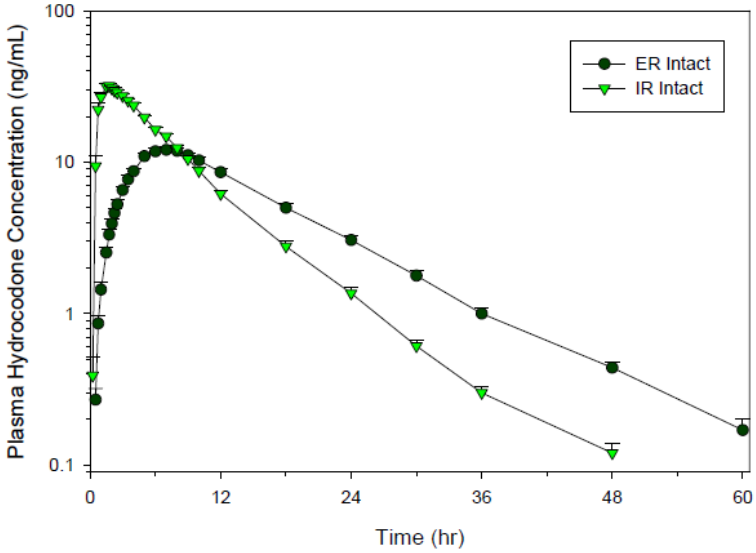


Table : Mean (Standard Deviation) Pharmacokinetic Parameters for Hydrocodone Following a 15-mg Dose of the Hydrocodone Bitartrate Extended-Release Tablet and VICOPROFEN (Intact) (Pharmacokinetic Analysis Set)

Variable	A (N=27)	C (N=28)
C_{max} (ng/mL)	12.4 (2.54)	36.1 (8.15)
t_{max} (h)	7.0 (5.0, 9.0)	1.8 (0.8, 4.0)
$AUC_{0-\infty}$ (ng·h/mL)	203.6 (50.75)	253.6 (50.67)
AUC_{0-t} (ng·h/mL)	200.6 (50.55)	251.8 (50.33)
AUC_{0-72} (ng·h/mL)	201.7 (50.36)	253.0 (50.70)
AUC_{0-12} (ng·h/mL)	100.9 (20.85)	201.0 (35.47)
$AUC_{0-tmax'}$ (ng·h/mL)	2.1 (1.1)	33.8 (11.6)
$t_{1/2}$ (h)	10.2 (3.34)	9.0 (5.11)
Percentage extrapolation (%)	1.5 (0.85)	0.8 (0.36)
λ_z (1/h)	0.0763 (0.02706)	0.0958 (0.03941)
Abuse quotient (ng/mL/h)	1.8 (0.61)	24.8 (14.53)

SOURCE: Adhoc Summary 1, Summary 15.10, Adhoc Listing 1, Listing 16.2.8.24.
NOTE: Median (range) is presented for t_{max}.
C_{max}=maximum observed plasma drug concentration; $AUC_{0-\infty}$=area under the plasma drug concentration by time curve (AUC) from time 0 to infinity; AUC_{0-t}=AUC from time 0 to the time of the last measurable drug concentration; AUC_{0-72}=AUC from time 0 to 72 hours after study drug administration; AUC_{0-12}=AUC from time 0 to 12 hours after study drug administration; AUC_{0-tmax}=AUC from time 0 to $t_{max'}$, where $t_{max'}$ is the median t_{max} of treatment C; t_{max}=time to maximum observed plasma drug concentration; $t_{1/2}$=elimination half-life; percentage extrapolation=$100\cdot(AUC_{0-\infty}-AUC_{0-t})/AUC_{0-\infty}$; λ_z=apparent plasma terminal elimination rate constant; abuse quotient=C_{max}/t_{max}.
A=15-mg hydrocodone bitartrate extended-release tablet administered intact; C=two 7.5-mg hydrocodone/200-mg ibuprofen tablets of VICOPROFEN administered intact.

Figure: Mean (Standard Error) Plasma Concentration by Time Profiles Through

60 Hours for Hydrocodone in Healthy Subjects Administered a 15-mg Dose of Hydrocodone In the Hydrocodone Bitartrate Extended-Release Tablet (Intact and Crushed) and VICOPROFEN (Intact and Crushed)

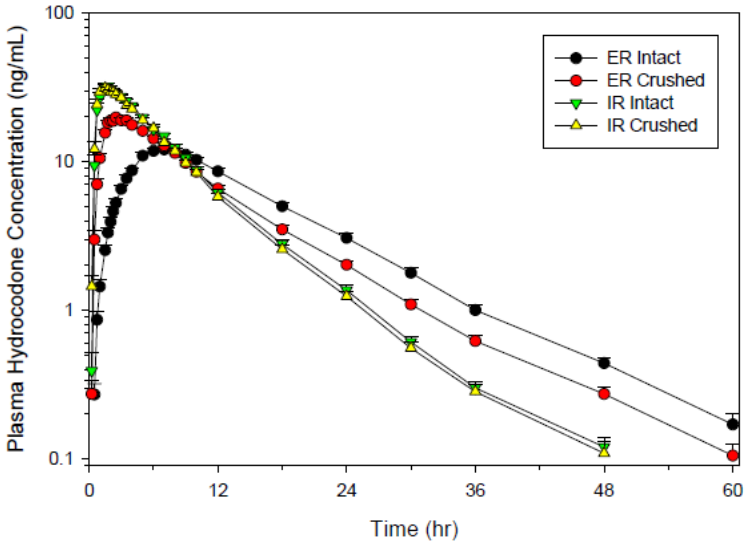


Table: Mean (SD) PK Parameters for Hydrocodone Following Administration of a 15 mg Dose of Vantrela ER tablet intact and crushed.

Variable	A (N=27)	B (N=29)
C_{max} (ng/mL)	12.44 (2.541)	21.4 (4.41)[a]
t_{max} (h)	7.0 (5.0, 9.0)	2.5 (1.5, 6.0)
$AUC_{0-\infty}$ (ng·h/mL)	203.6 (50.75)	220.9 (50.48)[a]
AUC_{0-t} (ng·h/mL)	200.6 (50.55)	218.4 (50.25)[a]
AUC_{0-72} (ng·h/mL)	201.7 (50.36)	219.6 (50.05)[a]
AUC_{0-12} (ng·h/mL)	100.9 (20.85)	142.6 (29.09)[a]
$AUC_{0-max'}$ (ng·h/mL)	2.1 (1.1)	14.6 (4.41)[a]
$t_{1/2}$ (h)	10.2 (3.34)	10.1 (3.77)
Percentage extrapolation (%)	1.5 (0.85)	1.1 (0.42)
λ_z (1/h)	0.0763 (0.02706)	0.0783 (0.02877)
Abuse quotient (ng/mL/h)	1.8 (0.61)	8.9 (2.99)

SOURCE: Adhoc Summary 1, Summary 15.10, Adhoc Listing 1, Listing 16.2.8.24.

[a] Values are dose-normalized to a 15-mg dose.

NOTE: Median (range) is presented for t_{max}.

C_{max}=maximum observed plasma drug concentration; $AUC_{0-\infty}$=area under the plasma drug concentration by time curve (AUC) from time 0 to infinity; AUC_{0-t}=AUC from time 0 to the time of the last measurable drug concentration; AUC_{0-72}=AUC from time 0 to 72 hours after study drug administration; AUC_{0-12}=AUC from time 0 to 12 hours after study drug administration; $AUC_{0-max'}$=AUC from time 0 to $t_{max'}$, where $t_{max'}$ is the median t_{max} of treatment C; t_{max}=time to maximum observed plasma drug concentration; $t_{1/2}$=elimination half-life; percentage extrapolation=100x($AUC_{0-\infty}$-AUC_{0-t})/ $AUC_{0-\infty}$; λ_z=apparent plasma terminal elimination rate constant; abuse quotient=C_{max}/t_{max}.

A=15-mg hydrocodone bitartrate extended-release tablet administered intact; B=15-mg hydrocodone bitartrate extended-release tablet administered crushed.

4.2.10 Study # 1090 Synopsis (Relative BA, Food-effect study):

Name of Sponsor/Company: Cephalon, Inc.	**Individual study table referring to part of dossier in which the individual study or study table is presented** **Volume:** **Reference:**	(For National Authority Use Only)
Name of Finished Product: Hydrocodone bitartrate extended-release tablet		
Name of Active Ingredient: Hydrocodone bitartrate (CEP-33237)		

Title of Study: A Randomized, Open-Label, 4-Period Study to Assess the Effect of Food on the Pharmacokinetics of a Single 90-mg Dose of the Hydrocodone Bitartrate Extended-Release Tablet and to Assess Its Relative Bioavailability to the Commercially Available Immediate-Release Hydrocodone/Ibuprofen Tablet in Healthy Subjects

Investigators and Study Centers: Aziz L. Laurent, MD, PPD Development, LP, 7551 Metro Center Drive, Suite 200, Austin, Texas 78744 USA

Publication (reference): Results from this study have not been published at the time of approval of this report.

Study Period: 17 March 2011 to 10 May 2011 **Phase of Development:** 1

Primary Objective: The primary objective of the study was to characterize the pharmacokinetics of hydrocodone bitartrate following administration of a 90-mg dose of the hydrocodone bitartrate extended-release tablet administered with water (fed and fasted) and to assess the relative bioavailability of the hydrocodone bitartrate extended-release tablet to VICOPROFEN, an immediate-release formulation of hydrocodone and ibuprofen (fasted with water).

Secondary Objectives: The secondary objective of the study was to characterize the following in healthy subjects who were concurrently receiving naltrexone:

- safety parameters over time following administration of placebo
- safety of a 90-mg dose of the hydrocodone bitartrate extended-release tablet administered with water (fed and fasted)
- safety of an immediate-release product, VICOPROFEN (fasted with water)

Safety was assessed by evaluation of the following:

- occurrence of adverse events throughout the study
- clinical laboratory test results at the final assessment (or early withdrawal)
- vital signs measurements throughout the study
- 12-lead electrocardiogram (ECG) findings at the final assessment (or early withdrawal)
- physical examination findings, including body weight measurements, at the final assessment (or early withdrawal)
- oxyhemoglobin saturation (SpO_2) monitoring on the day of each study drug administration, at the final assessment (or early withdrawal), and at follow-up
- concomitant medication usage throughout the study

Number of Subjects (Planned and Analyzed): Forty healthy men and women were planned to be enrolled and were randomly assigned to a treatment sequence. All 40 subjects received at least 1 dose of study drug and were evaluable for safety, 36 (90%) subjects were evaluable for pharmacokinetics, and 35 (88%) subjects completed the study.

Main Criteria for Inclusion: Subjects were included in the study if all of the following main criteria were met (not all inclusive):

- The subject was a man or woman 18 through 45 years of age, with a body mass index (BMI) of 20 to 30 kg/m_2, inclusive.

- The subject was in good health as determined by a medical and psychiatric history, physical examination, ECG, serum chemistry, hematology, urinalysis, and serology

Main Criteria for Exclusion: Subjects were excluded from participating in this study if 1 or more of the following main criteria were met (not all inclusive):

- The subject had any clinically significant uncontrolled medical conditions (treated or untreated).
- The subject had a clinically significant deviation from normal in ECG or physical examination findings, as determined by the investigator or the medical monitor.
- The subject was a pregnant or lactating woman. (If a woman had become pregnant during the study, she would have been withdrawn from the study.)
- The subject had any disorder that may have interfered with drug absorption, distribution, metabolism, or excretion (including gastrointestinal surgery; a history of appendectomy was allowed).

Study Drug Dose, Mode of Administration, Administration Rate, and Batch Number: Subjects were randomly assigned to 1 of the following 3 treatment sequences in which treatment D was always administered in period 4: ABCD, BCAD, or CABD. Treatments were administered orally on the first day of each administration period. There was a minimum 14-day washout between successive administrations of study drug. Subjects received each of the 4 treatments once.

Investigational Product: Hydrocodone bitartrate extended-release tablets (CEP-33237) were provided at a dose strength of 45 mg (treatments A and B, lot number 10AA013A501). Tablets were white, 0.275" x 0.625" convex, capsule-shaped, and were 575 mg in total weight.

Placebo: Placebo (treatment D, lot number 10AA004A501) matched the 45-mg hydrocodone bitartrate extended-release tablets and was packaged in the same manner as the hydrocodone bitartrate extended-release tablets.

Reference Therapy Dose, Mode of Administration, and Administration Rate: Treatment C was two 7.5-mg/200-mg hydrocodone bitartrate and ibuprofen immediate-release tablets (commercially available VICOPROFEN, lot number 00PROF1001).

Method of Blinding: This was an open-label study with no blinding.

Duration of Treatment: This study consisted of 4 single-dose administration periods. Each treatment was separated by a minimum of 14 days.

General Design and Methodology: Subjects were randomly assigned to 1 of the following 3 treatment sequences in which treatment D was always administered in period 4: ABCD, BCAD, or CABD. The study consisted of a screening visit within 21 days before the first dose of study drug, followed by 4 open-label single-dose administration periods, and a follow-up visit. There was a minimum 14-day washout between successive administrations of study drug. Subjects received each of the 4 treatments once. Subjects received one 50-mg tablet of naltrexone hydrochloride with 240 mL of water to block opioid receptors and minimize opioid-related adverse events approximately 15 and 3 hours before each study drug administration and approximately 9 and 21 hours after each study drug administration. In each administration period, venous blood samples for pharmacokinetic analyses were collected immediately before and over 72 hours after study drug administration. Subjects remained in the study center throughout each pharmacokinetic sampling period. Safety was assessed throughout the study by monitoring the occurrence of adverse events, clinical laboratory test results, vital signs measurements, 12-lead ECG and physical examination findings, SpO_2 monitoring, and use of concomitant medications. Subjects who participated in all scheduled visits had final procedures and assessments performed prior to discharge in administration period 4 (visit 5). Subjects who withdrew from the study before the completion of all scheduled assessments had final procedures and assessments performed prior to discharge in their last administration period. All subjects were asked to return to the study center for a follow-up visit to occur 48 to 72 hours after their last discharge from the center. Safety parameters were evaluated at that time.

Pharmacokinetic Measures and Endpoints: In each administration period, blood samples for pharmacokinetic analyses were collected over the 72 hours following study drug administration by venipuncture or indwelling catheter. The following pharmacokinetic parameters of hydrocodone and its metabolite hydromorphone were calculated for each treatment, when possible: maximum observed plasma drug concentration (C_{max}) by inspection (without interpolation), time to maximum observed plasma drug concentration (t_{max}) by inspection, area under the plasma drug concentration versus time curve (AUC) from

time 0 to infinity ($AUC_{0-\infty}$), AUC from time 0 to 72 hours after hydrocodone administration (AUC_{0-72}), AUC from time 0 to the time of the last measurable drug concentration (AUC_{0-t}), percentage extrapolation, $100x(AUC_{0-\infty}-AUC_{0-t})/AUC_{0-\infty})$, and apparent plasma terminal elimination rate constant (λ_z) and associated elimination half-life ($t_{½}$).

Safety Variables: Safety was assessed during the study by evaluating adverse events, clinical laboratory test results (chemistry, hematology, and urinalysis), vital signs measurements, ECG and physical examination findings, SpO_2 monitoring, and concomitant medication usage. For each safety parameter, all findings (whether normal or abnormal) were recorded in the CRF. The investigator judged the clinical significance of any abnormalities, and abnormalities were described in detail.

Statistical Considerations: An estimated withdrawal rate of 25% was assumed. As a result, approximately 40 subjects were to be randomly assigned to a treatment sequence with the intent that a minimum of 30 subjects complete the first 3 periods. The set of randomized subjects includes all subjects who were randomly assigned to a treatment sequence, regardless of whether or not a subject received any study drug. The safety analysis set includes those subjects in the set of randomly assigned subjects who received at least 1 dose of study drug. The pharmacokinetic analysis set includes those subjects in the safety analysis set who had sufficient data to calculate the pharmacokinetic parameters for administration periods to be used for the planned comparisons. The set of randomized subjects was used for all study population summaries unless otherwise noted. Summaries were presented by treatment sequence and for all subjects. Subject disposition and baseline safety assessments were summarized using descriptive statistics for the set of randomized subjects. All prior and concomitant medications were coded according to WHO Drug. The incidence of prior and concomitant medications was summarized using descriptive statistics by therapeutic class and preferred term. The pharmacokinetic analysis set was used for all pharmacokinetic analyses. Summaries are presented by treatment. All pharmacokinetic parameters from treatments A, B, and C were summarized by treatment using descriptive statistics, including number (n), mean, standard deviation (SD), standard error (SE), geometric mean (if appropriate), median, minimum, and maximum. The effect of food on the pharmacokinetics of hydrocodone was assessed by comparing C_{max} and $AUC_{0-\infty}$ following treatment B with those for treatment A. Natural log-transformed values of each parameter were analyzed using the analysis of variance (ANOVA) model. The ANOVA model included sequence, treatment, and period as the fixed effects and subject as a random effect. The 2-sided 90% and 95% confidence intervals (CIs) for the ratio of geometric means were obtained from the ANOVA for B versus A by anti-log transformation. Treatment B was to be considered to be bioequivalent to treatment A if the 90% CI fell completely within the limits of 0.8 to 1.25 for both parameters. The equivalence between treatments B and A would be considered as no food effect. Only the subjects with data from both treatments were entered into the model. AUC_{0-t} was analyzed in the same manner. The difference between the pharmacokinetics of immediate- and extended-release hydrocodone bitartrate (treatments C and A, respectively) was assessed by comparing dose-normalized C_{max} and $AUC_{0-\infty}$ following treatment A with those for treatment C. Natural log-transformed values of each parameter were analyzed using the ANOVA. The ANOVA model included sequence, treatment, and period as the fixed effects and subject as a random effect. The 2-sided 90% and 95% CIs for the ratio were obtained from the ANOVA for A versus C by anti-log transformation. Only the subjects with data from both treatments were entered into the model. AUC_{0-t} was analyzed in the same manner. The safety analysis set was used for all safety analyses unless otherwise noted. Summaries were presented for all subjects (ie, total) except summaries of adverse events, vital signs, and SpO_2. Summaries of adverse events, vital signs, and SpO_2 findings were presented by treatment only. All adverse events were coded using MedDRA. Summaries are provided for all adverse events (overall and by severity), adverse events determined by the investigator to be treatment related (overall and by severity), serious adverse events, nonserious adverse events, and adverse events causing withdrawal from the study. Listings for deaths, serious adverse events, adverse events leading to discontinuation, and adverse event preferred terms by subject number are presented. Summary statistics for chemistry, hematology, and urinalysis laboratory tests are provided at baseline and endpoint. Summary statistics for vital signs (including pulse, systolic and diastolic blood pressure, manual and machine-read respiratory rate) are provided for each time point. Actual values and changes from pretreatment to each time point were summarized using descriptive statistics. Shifts from baseline to endpoint in ECG and physical examination findings were summarized using subject counts. Summary statistics for ECG variables are presented at baseline and endpoint. Summary statistics for SpO_2 are provided for each time point.

Summary of Results

Subject Disposition and Demography: In this study, 40 healthy men and women were randomly assigned to a treatment sequence. All 40 subjects received at least 1 dose of study drug and were evaluable for safety; 36 (90%) subjects were evaluable for pharmacokinetics, and 35 (88%) subjects completed the study. The average age of the subjects was 30.1 years (range 19 to 44 years). The majority (65%) of subjects were white and 75% were men.

Pharmacokinetics Results: Mean C_{max} values were observed approximately 8 to 9 hours after administration of the hydrocodone bitartrate extended-release tablet under fed and fasting conditions. Decline from peak plasma concentrations occurred in a biphasic manner with a mean $t_{1/2}$ of 9 to 10 hours. The CIs for AUC met the protocol-specified criteria to conclude bioequivalence (0.8, 1.25) in the fed and fasted states (1.058, 1.164 for AUC_{0-t} and 1.055, 1.161 for $AUC_{0-\infty}$) while those for C_{max} did not (1.306, 1.509). The C_{max} was approximately 40% higher following administration of the hydrocodone bitartrate extended-release tablet under fed conditions. Despite the higher C_{max} in the fed state, exposure up to the time of C_{max} ($AUC_{0-tmax'}$) is equivalent to that in the fasted state. The mean C_{max} value was higher and occurred earlier after administration of the immediate-release product as compared to the extended-release tablet. Decline from peak plasma concentrations generally occurred in a biphasic manner with a mean $t_{1/2}$ of 10 and 7.5 hours for the extended-release and immediate-release products, respectively. Following administration of the hydrocodone/ibuprofen immediate-release product (VICOPROFEN, treatment C), C_{max} was approximately 3 times higher than the dose-normalized C_{max} for the hydrocodone bitartrate extended-release tablet (treatment A). Total systemic exposure to hydrocodone following administration of the hydrocodone bitartrate extended-release tablet as assessed by (dose-normalized AUC) was equivalent to that following administration of the immediate-release product.

Safety Results: The hydrocodone bitartrate extended-release tablet was generally well tolerated following administration in the fed and fasted states to healthy subjects who were concurrently receiving naltrexone. No deaths or other serious adverse events occurred during the study. One subject withdrew from the study because of an adverse event (vomiting) after receiving the hydrocodone bitartrate extended-release tablet in a fed state. The incidence of adverse events following administration of the hydrocodone bitartrate extended-release tablet in the fasted state was comparable to that observed following administration of the immediate-release product and was higher than that in the fed state. Adverse events that occurred in 5% or more of subjects following any treatment were dizziness (11% following administration of the hydrocodone bitartrate extended-release tablet in the fasted state) and nausea and headache (5% each following administration of the immediate-release product). All adverse events were mild to moderate in severity. Most of the adverse events that occurred after administration of study drug were assessed as related to treatment by the investigator, were mild in severity, and are consistent with those generally associated with opioid use. All adverse events resolved before the end of the study. Overall, no clinically meaningful changes in chemistry, hematology, or urinalysis results; ECG or physical examination findings; or SpO_2 measurements were reported during the course of the study. Clinically significant decreases in blood pressure and respiratory rate were reported with comparable incidence both prior to and after administration of the hydrocodone bitartrate extended-release tablet, the immediate-release product, and placebo. No correlation was detected between these low respiratory rates and SpO_2 measurements and no correlation was detected between plasma hydrocodone concentrations and clinically significant respiratory rates or blood pressure values. The observed values for respiratory rates are believed to be reflective of the range of normal resting respiratory rates for healthy subjects. None of decreases in respiratory rate or blood pressure were reported as adverse events.

Conclusions: Systemic exposure to hydrocodone (as assessed by dose-normalized AUC) was equivalent for subjects in the fed and fasted states. Although C_{max} was approximately 40% higher when administered with food, exposure through the time of C_{max} ($AUC_{0-tmax'}$) was equivalent for that observed for subjects in the fasted state. Following administration of the hydrocodone/ibuprofen immediate-release product (VICOPROFEN, fasted), C_{max} was approximately 3 times higher than the dose-normalized C_{max} for the hydrocodone bitartrate extended-release tablet following administration in a fasted state. The hydrocodone bitartrate extended-release tablet was generally well tolerated in this study following administration in the fed and fasted states to healthy subjects who were concurrently receiving naltrexone. VICOPROFEN, an immediate-release formulation of hydrocodone and ibuprofen was also generally well tolerated in the healthy subjects who were concurrently receiving naltrexone in this study.

4.2.11 Study # 10032 Synopsis (Intranasal Drug Liking Study):

2. SYNOPSIS

Name of Sponsor/Company: Teva Global Branded Products R&D, Inc.	**Individual study table referring to part of dossier in which the individual study or study table is presented**	(For National Authority Use Only)
Name of Finished Product: Hydrocodone bitartrate extended-release tablet (CEP-33237)	**Volume:**	
Name of Active Ingredient: Hydrocodone bitartrate	**Reference:**	

Title of Study: A Single-Dose, Double-Blind, Randomized Crossover Study to Assess the Intranasal Pharmacokinetics, Abuse Potential and Safety of CEP-33237 in Healthy, Nondependent, Recreational Opioid Users

Investigator and Study Center: Shawn Searle, MD, CRI Lifetree, 3838 South 700 East, Suite 202, Salt Lake City, UT 84106.

Publication (reference): Results from this study have not been published at the time of approval of this report.

Study Period: 16 May 2014 to 24 July 2014 **Phase of Development:** 1

Primary Objective: The primary objective of the study was to assess the relative abuse potential of manipulated intranasal CEP-33237 as compared to that of intranasal hydrocodone active pharmaceutical ingredient (API), based on the peak score (E_{max}) of the Drug Liking visual analog scale (VAS) and Overall Drug Liking VAS E_{max}.

Secondary Objectives: The secondary objectives of the study were as follows:

- to assess the relative abuse potential of manipulated intranasal CEP-33237 as compared to that of intranasal hydrocodone API, as assessed by all secondary pharmacodynamic variables
- to assess the relative abuse potential of manipulated intranasal CEP-33237 as compared to that of intact oral CEP-33237, as assessed by the primary and secondary pharmacodynamic variables
- to assess the relative abuse potential of manipulated intranasal CEP-33237 as compared with that of manipulated intranasal Zohydro™ (commercially available hydrocodone extended-release capsules), as assessed by the primary and secondary pharmacodynamic variables
- to assess the relative abuse potential of manipulated intranasal Zohydro™ as compared with that of intranasal hydrocodone API, as assessed by the primary and secondary pharmacodynamic variables
- to assess the abuse potential of manipulated intranasal CEP-33237, manipulated intranasal Zohydro™ and intranasal hydrocodone API as compared with that of placebo, as assessed by the primary and secondary pharmacodynamic variables
- to characterize the pharmacokinetics of CEP-33237 (manipulated intranasal and intact oral), manipulated intranasal Zohydro™, and intranasal hydrocodone API

- to assess the pharmacokinetic/pharmacodynamic relationships of CEP-33237 (manipulated intranasal and intact oral), manipulated intranasal Zohydro™, and intranasal hydrocodone API using plasma concentrations and select pharmacodynamic variables over time

- to evaluate the safety of CEP-33237 (manipulated intranasal and intact oral), manipulated intranasal Zohydro™, and intranasal hydrocodone API by evaluating the following:

  - occurrence of adverse events
  - clinical laboratory (serum chemistry, hematology, and urinalysis) test results
  - vital signs (blood pressure, respiratory rate, and pulse) measurements
  - resting 12-lead electrocardiogram (ECG) findings
  - oxyhemoglobin saturation (SpO_2) monitoring
  - suicidality assessments
  - concomitant medication usage

Number of Subjects (Planned and Analyzed): Up to approximately 115 subjects were planned to be enrolled into phase B of the study (drug discrimination phase), and up to 45 subjects were planned to be assigned to a treatment sequence in phase C (treatment phase). A total of 73 subjects were enrolled in phase B and 45 subjects were randomized in phase C; data from 34 subjects were analyzed for pharmacodynamics, data from 42 subjects were analyzed for pharmacokinetics and data from 45 subjects were analyzed for safety.

Diagnosis and Main Criteria for Inclusion: Subjects were included in the study if all of the following main inclusion criteria were met (not all inclusive):

- The subject was not physically dependent on opioids as demonstrated by successful completion of a Naloxone Challenge; ie, subject did not exhibit signs or symptoms of opioid withdrawal (as assessed by a Clinical Opiate Withdrawal Scale [COWS] score of <5) following administration of intravenous naloxone in the Naloxone Challenge.

- The subject had a history of recreational opioid use to achieve a "high" at least 10 times in the last year and at least on 1 occasion within the 12 weeks before screening. Subjects who abused multiple drugs must have expressed a preference for opioids.

- The subject had experience with intranasal use of opioids on at least 3 occasions in the year prior to screening.

- The subject was a man or woman 18 through 55 years of age with a minimum body weight of 50 kg and a body mass index (BMI) of 18.0 through 32.0 kg/m2.

Main Criteria for Exclusion: Subjects were excluded from participating in this study if 1 or more of the following main exclusion criteria were met (not all inclusive):

- The subject had any clinically significant medical condition (treated or untreated).

- The subject had a clinically significant deviation from normal in the physical examination, clinical laboratory tests, 12-lead electrocardiogram (ECG) or vital signs.

- The subject was a poor metabolizer of CYP2D6 substrates based on genotyping performed at screening.

- The subject had participated in, was currently participating in, or was seeking treatment for substance-related disorders (excluding nicotine).

Study Drug Dose, Mode of Administration, Administration Rate, and Batch Number: The following 2 treatment sequences were used for phase B of this study: XY and YX, whereby treatment X was placebo powder, and treatment Y was hydrocodone API at a dose strength of 45 mg. Each subject received 1 treatment during each administration period. To prevent material loss due to the small volume of powder, hydrocodone API was blended 50/50 with lactose for a total weight of ~90 mg. Approximately 90 mg of lactose was used as the placebo (treatment Y), thus, subjects insufflated ~90 mg of powder in each drug administration period. Subjects received each of the 2 treatments once.

Treatment randomization in phase C utilized two 5x5 Williams squares to achieve balance with respect to first order carry over effect. Eligible subjects were randomized to 1 of the following 10 treatment sequences: ABECD, BCADE, CDBEA, DECAB, EADBC, DCEBA, EDACB, AEBDC, BACED, or CBDAE, based on treatments defined as follows:

- A (intranasal CEP 33237 45 mg): ~90 mg of manipulated 45-mg CEP-33237 tablet (container 1), ~158 mg of manipulated 45-mg CEP-33237 tablet (container 2) and ~327 mg of manipulated 45 mg CEP-33237 tablet (container 3) administered intranasally, and 1 intact CEP-33237 placebo tablet administered orally.

- B (intranasal hydrocodone API 45 mg): ~45 mg hydrocodone API plus ~45 mg lactose (container 1), ~158 mg crushed sugar spheres (container 2) and ~327 mg lactose (container 3) administered intranasally, and 1 intact CEP-33237 placebo tablet administered orally.

- C (oral CEP-33237 45 mg): ~90 mg crushed sugar spheres (container 1), ~158 mg lactose (container 2) and ~327 mg crushed sugar spheres (container 3) administered intranasally, and 1 intact 45 mg CEP-33237 tablet administered orally.

- D (placebo): ~90 mg manipulated CEP-33237 placebo tablet (container 1), ~158 mg manipulated CEP-33237 placebo tablet (container 2) and ~327 mg manipulated CEP-33237 placebo tablet (container 3) administered intranasally, and 1 intact CEP-33237 placebo tablet administered orally.

- E (intranasal Zohydro™ 45 mg): ~90 mg of manipulated contents of 2 hydrocodone extended-release capsules (1 15-mg and 1 30-mg capsule) (container 1), ~158 mg of manipulated contents of 2 hydrocodone extended-release capsules (1 15-mg and 1 30-mg capsule) (container 2) and ~327 mg lactose (container 3) administered intranasally, and 1 intact CEP-33237 placebo tablet administered orally.

Subjects received each of the treatments once. There was a minimum 7 day washout period between each administration of study drug in phase C. In each period, subjects ingested the oral tablet with ~240 mL of non-carbonated room temperature water. Each subject then received ~575 mg of intranasal material to insufflate. Subjects were required to intranasally administer the study drugs within 5 minutes of oral administration. Intranasal treatments in phase C was administered sequentially from 3 containers with straws preinserted to facilitate administration. To ensure blinding given the difference in weights and particle size distribution between the API (~90 mg), Zohydro™ (~247.9 mg), and CEP-33237 (~575 mg), intranasal treatments were administered sequentially in 3 containers. Container 1 was always administered first so that administration of the primary active control was not be compromised in subjects who had difficulty managing the higher volume of container 2 and 3. Subjects used one nostril to administer container 1 and the other nostril to administer containers 2 and 3. If the contents of container 3 could not be administered in the same nostril, the subject returned to the first nostril to complete administration. To ensure blinding, 3 different placebos were used; one to match CEP-33237 (manipulated CEP-33237 placebo tablet), one to match hydrocodone API (lactose) and one to match Zohydro™ (manipulated sugar spheres). To ensure complete blinding of Treatment A (intranasal CEP-33237), Treatment D (placebo) comprised 3 containers of manipulated CEP-33237 placebo tablet. To ensure blinding of hydrocodone API and Zohydro™, a combination of crushed sugar spheres and lactose placebo was administered in these periods, as well as the Treatment C (oral CEP-33237) period. Since manipulated CEP-33237 placebo could have affected the absorption of hydrocodone API and Zohydro™ and/or induced nasal irritation (i.e., during these periods, as well as the oral intact CEP 33237 period), thereby compromising study validity, it was not administered in any periods other than Treatment D. Intranasal administration was performed over a tray or piece of paper. The containers were inspected following intranasal administration by the subject. If any material remained in the bottle, the subject was asked to re-attempt administration. If any material inadvertently dropped (i.e., from the container, straw or subject's nose) during administration, it was collected, returned to the container and the subject was asked to re-attempt administration. If administration failed following the second attempt or if the subject refused to re-attempt administration, the remaining drug was carefully collected and returned to the container. The container was weighed before and after administration. Subjects were not allowed to blow their nose for at least 1 hour postdose. Any events of sneezing within 1 hour post-dose were recorded. Drug administration was performed under blue lighting to further mask any visual differences in study drugs/placebos, in case any drug inadvertently fell onto the tray/paper during dosing.

Investigational Product: Hydrocodone bitartrate extended-release tablets (CEP-33237) were provided at a dose strength of 45 mg (lot number 13-000786). Tablets were white, 0.275" x 0.625" convex, capsule shaped, and were 575 mg in total weight. CEP-33237 tablets were packaged in 60 cc round, white, high-density polyethylene (HDPE) bottles with 38-mm child resistant caps. Each bottle contained 1 canister of desiccant and was foil induction sealed and contained 20 tablets.

Placebos: Placebo tablets to match the 45 mg CEP-33237 tablets were provided and were packaged in the same manner as the CEP-33237 tablets (lot number 201402). Lactose monohydrate, NF (lot number 340007027) was used as the placebo powder to match hydrocodone API. Sugar spheres 25/30 NF (lot number 340008207) alone were used as a placebo to match Zohydro™.

Reference Therapy Dose, Mode of Administration, and Administration Rate: The primary comparator was hydrocodone bitartrate API powder administered at a dose strength of 45 mg. Due to the small volume and potential for material loss, hydrocodone API was blended 50/50 with lactose monohydrate, NF (lot number 340007027) for intranasal administration (for a total weight of ~90 mg). Zohydro™ ER (hydrocodone bitartrate) extended-release capsules were hard gelatin capsules for oral administration (lot number 13P171 for 15 mg and lot number 13P168

for 30 mg). The manipulated contents of one 15 mg capsule and one 30 mg capsule were used for intranasal drug administration (dose strength of 45 mg). Among other inactive ingredients, Zohydro™ contains sugar spheres.

Method of Blinding: Subjects, the investigator, and all study center personnel involved in conducting study-related procedures (other than preparation of study drug) remained blinded to the identity of the treatment administered in each treatment period. The pharmacist at the study center who prepared the study drug knew the treatment given to each subject. In addition, other individuals from the study center knew the treatment assignments in order to provide quality assurance, oversight for preparation of study drug for each day of study drug administration, and supervision of the subjects during intranasal administration of the drugs. None of the individuals involved in the preparation of the study drug or supervision of study drug administration were involved in the conduct of any study procedures or assessment of any adverse events. In addition, pupillometry assessments were performed by specified study center staff members who were not permitted to be involved in other study assessments. Measurements were made in a well-controlled, dimly lit (mesopic) room that was separate from the area where other study procedures were performed. The staff engaged in bioanalysis and/or pharmacokinetic parameter calculation did not have access to any clinical data. In order to maintain the treatment blinding, no plasma concentration data or pharmacokinetic parameters were provided to other staff members until the time of database lock.

Duration of Treatment: Subjects were expected to participate in this study for up to approximately 10 weeks (including screening and follow-up).

General Design and Methodology: This was a single-dose, randomized, double-blind, quadruple-dummy, active- and placebo- controlled crossover study designed to assess the abuse potential of manipulated intranasal CEP-33237 in healthy, nondependent recreational opioid users. The study consisted of 3 phases. Phase A was the screening period during which subjects were evaluated to determine if they met criteria for inclusion in the study up to 28 days before the first study drug administration in phase B. Subjects who satisfactorily completed this phase were eligible to continue into phase B. Phase B was the randomized, double-blind, placebo-controlled, 2-treatment, 2-period crossover drug discrimination phase to ensure that the subjects could tolerate a 45-mg intranasal dose of hydrocodone API and that the subjects could discriminate between the effects of intranasal hydrocodone and placebo. Subjects also underwent a Naloxone Challenge at least 12 hours prior to first drug administration in phase B, to ensure that they were not physically dependent on opioids. Subjects arrived at the study center on the day prior to the first study drug administration and remained at the study center for a minimum of 24 hours after the second study drug administration. There was a minimum 48-hour washout between treatments; subjects were permitted to leave the study center after the 24-hour procedures were completed following the second treatment. For subjects who qualified to continue into phase C, there was a minimum 7-day washout period between the second dose in phase B and the first dose in phase C. Pharmacodynamic assessments, including some or all of the following were performed prior to and at specified time points over 24 hours after the start of administration of each treatment: Drug Liking VAS and other scales from the Drug Liking and Effects Questionnaire (DLEQ), Overall Drug Liking VAS, Take Drug Again VAS, Price Value Assessment Questionnaire (PVAQ), specified subscales of the Addiction Research Center Inventory (ARCI), and pupillometry.

To be eligible for phase C, the subject must have had a peak score (E_{max}) in response to hydrocodone API of at least 15 points greater than that of placebo on the Drug Liking VAS and the Overall Drug Liking VAS, with a minimum score of 65 points with hydrocodone API for both measures, within 3 hours after study drug administration (for Drug Liking VAS). The subject must also have had an acceptable placebo response (between 40 and 60, inclusive, for Drug Liking VAS and Overall Drug Liking VAS) and acceptable hydrocodone API response on all measures. Subjects must also have been able to tolerate the 45 mg intranasal hydrocodone API dose, as assessed by no emesis

within 2 hours following dosing, ability to insufflate the entire volume of manipulated treatments (without sneezing or attempting to blow their nose within 1 hour of administration), and as otherwise judged by the investigator or designee, and have had general behavior suggesting that the subject could successfully complete the study. For subjects who qualified to continue into phase C, there was a minimum 7 day washout period between the second dose in phase B and the first dose in phase C.

Phase C was the randomized, double-blind, quadruple-dummy, placebo-controlled, 5-period crossover treatment phase. Subjects arrived at the study center the day prior to each study drug administration in phase C. Subjects fasted from approximately 8 hours prior to each study drug administration until approximately 4 hours after each study drug administration. Subjects who participated in all scheduled visits had final assessment procedures performed prior to leaving the study center in period 5 of phase C. Subjects who withdrew from the study before the completion of all scheduled assessments had final assessment procedures performed prior to leaving the study center in their last study drug administration period. All subjects (including those who withdrew from the study at any point during the study) were asked to return to the study center for a follow-up visit approximately 48 to 72 hours after discharge from the study center following their final dose of study drug. Pharmacodynamic assessments included some or all of the following at each specified time point: Drug Liking VAS and other scales from the DLEQ, Overall Drug Liking VAS, Take Drug Again VAS, PVAQ, specified subscales of the ARCI, assessments of intranasal effects (subject-rated assessment of intranasal irritation [SRAII] and Ease of Snorting VAS), and pupillometry.

Pharmacodynamic Measures and Endpoints

Phase B

The DLEQ was completed at 0.25, 0.5, 1, 1.5, 2, 4, 6, 8 and 24 hours after the start of administration of study drug in each period. Scales not referring to drug were also administered prior to study drug administration. The Overall Drug Liking VAS, the Take Drug Again VAS, and PVAQ were completed at 8 and 24 hours after the start of administration of study drug in each period. Pupil diameter measurements were completed prior to study drug administration and at 0.25, 0.5, 1, 1.5, 2, 4, 6, 8 and 24 hours after the start of administration of study drug in each period. Questions from the ARCI (Morphine Benzedrine Group [MBG], Lysergic Acid Diethylamide [LSD], and Pentobarbital Chlorpromazine Alcohol Group [PCAG]) were completed prior to study drug administration and at 1, 3, 6 and 24 hours after the start of administration of study drug in each period of phase B.

Phase C

The DLEQ was completed at 0.25, 0.5, 0.75, 1, 1.25, 1.5, 2, 2.5, 3, 4, 6, 7, 8, 9, 10, 12, 24, 36, and 48 hours after the start of administration of study drug in each period of phase C. Scales not referring to drug were also administered prior to study drug administration. The Overall Drug Liking VAS, the Take Drug Again VAS, and the PVAQ assessment were completed at 12 and 24 hours after the start of administration of study drug in each period of phase C. Ease of Snorting VAS was performed once drug administration was completed (approximately 5 minutes after the start of administration of study drug in each period of phase C). The SRAII were completed prior to study drug administration and at 0.25, 0.5, 1, 1.5, 2, 4, 6 and 8 hours after the start of administration of study drug in each period. Pupil diameter measurements were completed prior to study drug administration and at 0.25, 0.5, 0.75, 1, 1.25, 1.5, 2, 2.5, 3, 4, 6, 7, 8, 9, 10, 12, 24, 36, and 48 hours after the start of administration of study drug in each period of phase C. Questions from the ARCI that comprise the MBG, LSD, and PCAG subscales were completed prior to study drug administration and at 1, 2, 3, 6, 12, and 24 hours after the start of administration of study drug in each period of phase C.

Primary Pharmacodynamic Measures and Endpoints:

The primary pharmacodynamic measures and endpoints for assessment of relative abuse potential in phase C of the study included the following:

- E_{max} of Drug Liking VAS (question 1 of the DLEQ) and E_{max} of Overall Drug Liking VAS.

Secondary Pharmacodynamic Measures and Endpoints: The secondary pharmacodynamic measures and endpoints for assessment of relative abuse potential in phase C of the study included measures of balance of drug effects, positive drug effects, negative drug effects, sedative effects, and other drug effects as follows:

- Measures of balance of effects:
  - Peak minimum score (E_{min}) and area under the effect curve (AUEC) for Drug Liking VAS
  - E_{min} for Overall Drug Liking VAS
  - E_{max} for Take Drug Again VAS
  - E_{max} for the PVAQ
- Measures of positive effects:
  - E_{max} and AUEC for Good Effects VAS (question 3 from the DLEQ)
  - E_{max} and AUEC for ARCI Morphine Benzedrine Group (MBG)
- Measures of negative effects:
  - E_{max} and AUEC for Bad Effects VAS (question 4 of the DLEQ)
  - E_{max} and AUEC for ARCI Lysergic Acid Diethylamide (LSD)
  - E_{max} and AUEC for Nausea VAS (question 5 of the DLEQ)
- Measures of nasal effects:
  - E_{max} and AUEC for SRAII
  - Score for Ease of Snorting VAS
- Measures of sedative effects:
  - E_{max} and AUEC for ARCI Pentobarbital Chlorpromazine Alcohol Group (PCAG)
  - E_{min} and AUEC for Alertness/Drowsiness VAS (question 2 of the DLEQ)

- Measures of other drug effects:
  - E_{max} and AUEC for Any Effects VAS (question 6 of the DLEQ)
  - E_{min} (minimum pupil diameter) and area over the effect curve (AOEC) for pupillometry
- Time to maximum (and/or minimum) effect ($TE_{max/min}$) for each pharmacodynamic measure

Pharmacokinetic Measures and Endpoints: Blood samples were obtained for measurement of plasma concentrations of hydrocodone and hydromorphone prior to study drug administration (ie, within approximately 60 minutes) and 0.25, 0.5, 0.75, 1, 1.25, 1.5, 2, 2.5, 3, 4, 6, 7, 8, 9, 10, 12, 24, 36, and 48 hours after the start of administration of the study drug. The following pharmacokinetic parameters for hydrocodone and its metabolite hydromorphone were calculated for each subject, when possible, from plasma concentrations obtained after each treatment:

- Maximum observed plasma drug concentration (C_{max}) by inspection (without interpolation)
- Time to maximum observed drug concentration (t_{max}) by inspection
- Area under the plasma concentration-time curve (AUC) from time 0 to the median t_{max} for intranasal hydrocodone API ($AUC_{0\text{-}tmax,API}$)
- AUC from time 0 to the median t_{max} for CEP-33237 when manipulated and administered intranasally ($AUC_{0\text{–}tmax,\ CEP(IN)}$)
- AUC from time 0 to the median t_{max} for CEP-33237 when administered orally (intact; $AUC_{0\text{–}tmax,\ CEP(oral)}$)
- AUC from time 0 to the median t_{max} for Zohydro™ when administered intranasally ($AUC_{0\text{–}tmax,\ Zoh(IN)}$)
- AUC from time 0 to the time of the last measurable drug concentration ($AUC_{0\text{–}t}$)
- AUC from time 0 to infinity ($AUC_{0\text{–}\infty}$)
- Percentage extrapolation calculated as $(AUC_{0\text{-}\infty}\text{-}AUC_{0\text{-}t})/(AUC_{0\text{-}\infty}) \times 100$
- Apparent plasma terminal elimination rate constant (λ_z) and associated elimination half-life ($t_{1/2}$)
- Abuse quotient (AQ) calculated as C_{max}/t_{max}
- AUC and C_{max} ratios (CEP-33237 intranasal vs CEP-33237 oral, hydrocodone API intranasal and Zohydro™ intranasal; and Zohydro™ intranasal vs hydrocodone API)

Safety Variables: Safety was assessed by evaluating the following: reported adverse events, suicidality assessments, clinical laboratory test results, vital signs measurements, ECG findings, SpO_2 monitoring, and concomitant medication usage.

Statistical Considerations: The enrolled population included all subjects who were randomly assigned to a treatment sequence in phase B, regardless of whether or not a subject took any study drug. The phase B safety population (hereafter referred to as the phase B safety analysis set) included all subjects who received 1 or more doses of study drug in phase B. The randomized population included all subjects who were randomly assigned to a treatment sequence in phase C, regardless of whether or not a subject took any study drug.

The phase C safety population (hereafter referred to as the phase C safety analysis set) included all subjects who received 1 or more doses of study drug in phase C. The pharmacokinetic population included those subjects in the phase C safety analysis set who had sufficient pharmacokinetic data to contribute to at least 1 planned comparison. The pharmacodynamic population (hereafter referred to as the pharmacodynamic analysis set) included subjects who received all 5 treatments in phase C. Continuous and ordinal categorical pharmacodynamic parameters were analyzed using a mixed effects model. The model included: treatment, period, and randomized treatment sequence as fixed effects; baseline (predose) measurement as covariate where applicable; and subject nested within sequence as a random effect. The first order carryover effect was included in the model as fixed effect and was to be dropped if not statistically significant at the 25% significance level. The residuals from the mixed-effect model were investigated for normality using the Shapiro-Wilk W-test. Parameters were analyzed as having a normal distribution if the probability value was $\geq$0.05. Parameters that did not meet this criterion were analyzed non-parametrically. Overall treatment effect was assessed using Friedman's test; pairwise treatment comparisons were assessed using the Wilcoxon sign-rank test on the within-subject differences. The comparison of intranasal CEP-33237 vs intranasal hydrocodone API was performed only if statistical significant difference was observed between intranasal hydrocodone API vs placebo for both primary endpoints. In order to claim less abuse liability for intranasal CEP-33237 compared to intranasal hydrocodone API, statistical significant treatment difference had to be observed for both primary endpoint in favor of intranasal CEP-33237. Adjusted means, SE, and 95% confidence intervals (CIs) for treatments and treatment differences were presented (unless non-parametric testing was required). For each of the contrasts or pairwise comparisons, the null hypothesis was: there is no treatment effect difference between the tested pair, and the alternative hypothesis was: there is a treatment effect difference between the tested pair. A 5% Type-I error rate with a p-value less than 0.05 was considered as statistically significant for all individual hypothesis tests. All statistical tests were performed using two-tailed significance criteria. A responder analysis of the primary pharmacodynamic variables was also performed. All pharmacokinetic variables were summarized by treatment using number (n), mean, standard deviation (SD), geometric mean (if appropriate), median, minimum, and maximum. Exploratory analyses may have been undertaken to describe the relationship between plasma concentration and the effect of hydrocodone treatment on select pharmacodynamic variables over time. If the data allowed, an attempt may have been made to characterize the relationship using modeling. Safety variables that were evaluated included the incidence of adverse events, suicidality assessments, clinical laboratory test results (chemistry, hematology, and urinalysis), vital signs measurements, ECG, SpO_2 monitoring, and concomitant medication usage. All adverse events were coded using the Medical Dictionary for Regulatory Activities (MedDRA). Each subject was counted only once in each preferred term or system organ class category for the analyses of safety. Summaries are presented for all adverse events (overall and by severity), adverse events determined by the investigator to be related to study treatment (overall and by severity), serious adverse events, and adverse events causing withdrawal from the study. Summaries were presented by treatment group and for all subjects. Subject listings of serious adverse events and adverse events leading to withdrawal were presented. Changes in laboratory and vital signs measurement data were summarized descriptively. All values were compared with prespecified boundaries to identify potentially clinically significant changes or values. The use of concomitant medications was summarized by therapeutic class using descriptive statistics. Concomitant medications included all medications taken while the subject was treated with study drug.

Summary of Results

Subject Disposition and Demography: In this study, 73 subjects were enrolled and received at least 1 study treatment in phase B. Two subjects (3%) received 1 study treatment in phase B but were discontinued from the study; 71 (97%) subjects completed phase B. Of the 71 subjects who completed phase B, 26 subjects were ineligible for enrollment into phase C, primarily due failure to discriminate between hydrocodone and placebo. Forty-five (62%) subjects were randomly assigned to a treatment sequence in phase C, received at least 1 study treatment, and were included in the phase C safety analysis set. Thirty-four (47%) subjects were evaluable for pharmacodynamics and 42 (58%) subjects were evaluable for pharmacokinetics in phase C. Thirty-four (47%) subjects completed the study.

For subjects enrolled in phase B, the mean age was 27.5 years (range, 18.0 to 52.0 years); 71% of subjects were men and 90% were white. Mean BMI was 23.8 kg/m^2 (range, 18.2 to 31.2 kg/m^2). For subjects randomized in phase C, the mean age was 27.8 years (range, 19.0 to 52.0 years); 73% of subjects were men and 87% were white. Mean BMI was 23.6 kg/m^2 (range, 18.4 to 30.4 kg/m^2).

Pharmacokinetic Results: Following administration of intranasal hydrocodone API, mean C_{max} was achieved at approximately 1.4 hours. Decline from peak plasma hydrocodone concentrations generally occurred in a monophasic manner, with a mean $t_{1/2}$ of approximately 5.8 hours. Administration of intranasal Zohydro™ resulted in a comparable mean C_{max} at approximately 1 hour postdose with a mean $t_{1/2}$ of approximately 5.6 hours. In contrast, administration of intranasal CEP-33237 resulted in a lower and delayed mean C_{max} (t_{max} ~2.6 hours). Decline from peak plasma hydrocodone concentrations generally occurred in a monophasic manner, with a mean $t_{1/2}$ of approximately 6.2 hours. As expected, based on the known profile from previous studies, the rise to peak plasma hydrocodone concentrations was slowest following administration of oral intact CEP-33237, with a mean C_{max} achieved at approximately 9 hours postdose. Oral intact CEP-33237 was also associated with a longer $t_{1/2}$ compared to the other treatments (~10 hours).

Statistical comparisons indicate that overall systemic exposure (as assessed by $AUC_{0-\infty}$ and AUC_{0-t}) was comparable following administration of intranasal hydrocodone API and intranasal CEP-33237. However, C_{max} was approximately 12% lower following administration of intranasal CEP-33237 compared to intranasal hydrocodone API. Due to the lower later peak value, early exposure, as assessed by $AUC_{0\text{-}tmax,API}$ and $AUC_{0\text{-}tmax,\ CEP\ (IN)}$, to hydrocodone was notably lower for intranasal CEP-33237 (~51% and ~30%, respectively) compared with that

following administration of intranasal hydrocodone API. Consistent with these findings, the AQ was, on average, approximately 17% lower for intranasal CEP-33237 compared to intranasal hydrocodone API.

Statistical comparisons indicate that overall systemic exposure (as assessed by $AUC_{0-\infty}$ and AUC_{0-t}) was comparable, but slightly lower following administration of intranasal CEP-33237 compared to intranasal Zohydro™. However, C_{max} was approximately 22% lower following intranasal CEP-33237 compared to intranasal Zohydro™, consistent with the lower early exposure, as assessed by $AUC_{0\text{-}tmax,\ Zoh\ (IN)}$ and $AUC_{0\text{-}tmax,\ CEP\ (IN)}$, which showed a reduction of approximately 63% and 39%, respectively following intranasal CEP-33237. Consistent with these findings, the AQ was approximately 42% lower for intranasal CEP-33237 compared to intranasal Zohydro™.

Overall systemic exposure was similar following administration of oral intact CEP-33237 and intranasal CEP-33237. However, C_{max} was approximately 134% higher following administration of intranasal CEP-33237, which is consistent with the controlled-release profile of hydrocodone following oral administration of intact CEP-33237. Early systemic exposure, as measured $AUC_{0\text{-}tmax,\ CEP\ (IN)}$, was ~796% higher following intranasal CEP-33237 as compared with oral intact CEP-33237. Evaluation of exposure up to the t_{max} of oral intact CEP-33237 also showed higher exposure to hydrocodone following intranasal CEP-33237 compared to oral intact CEP-33237 (~173%). Comparison of AQ demonstrated a higher AQ for the intranasal CEP-33237 treatment.

Overall systemic exposure and peak (C_{max}) exposure were comparable, but slightly higher following intranasal administration of Zohydro™ compared with intranasal hydrocodone API. Consistent with these findings, early exposure, as assessed by $AUC_{0\text{-}tmax,\ API}$ and $AUC_{0\text{-}tmax,\ Zoh\ (IN)}$, was higher (~22% and 26%, respectively) following intranasal Zohydro™ as compared with that of intranasal hydrocodone API. The AQ was also approximately 105% higher for intranasal Zohydro™ relative to intranasal hydrocodone API.

Conclusions: Consistent with the observed differences in pharmacokinetics across treatments, intranasal CEP 33237 demonstrated significantly lower subjective effects compared to intranasal hydrocodone API and Zohydro™, with a markedly different timecourse profile of slower onset and rate of rise, lower peak and shorter duration of effects. While not evaluated statistically, oral intact CEP-33237 showed a similar pharmacodynamic profile to placebo. Overall, the pharmacodynamic and pharmacokinetic results demonstrate that CEP 33237 may have lower abuse potential compared to non-abuse deterrent opioid products, including Zohydro™.

In this study, intranasal or oral intact CEP-33237, intranasal hydrocodone API and intranasal Zohydro™ demonstrated an adverse event profile consistent with other opioids in healthy nondependent recreational opioid users. However, intranasal administration of CEP-33237, hydrocodone API and Zohydro™ were associated with a higher incidence of adverse events when compared to oral administration of CEP-33237 or placebo.

4.2.12 Study # 1095 Synopsis (dosage form proportionality).

Name of Sponsor/Company: Cephalon, Inc.	**Individual study table referring to part of dossier in which the individual study or study table is presented**	(For National Authority Use Only)
Name of Finished Product: Hydrocodone bitartrate extended-release tablet	**Volume:**	
Name of Active Ingredient: Hydrocodone bitartrate (CEP-33237)	**Reference:**	

Title of Study: A Randomized, Open-Label, 2-Period, Crossover Study to Assess the Bioequivalence of Two 30-mg Hydrocodone Bitartrate Extended-Release Tablets Versus One 60-mg Hydrocodone Bitartrate Extended-Release Tablet

Investigators and Study Centers: Aziz L. Laurent, MD, PPD Development, LP, 7551 Metro Center Drive, Suite 200, Austin, Texas 78744, USA

Publication (reference): Results from this study have not been published at the time of approval of this report.

Study Period: 18 April 2011 to 1 June 2011 **Phase of Development:** 1

Primary Objective: The primary objective of this study was to assess the bioequivalence of two 30-mg hydrocodone bitartrate extended-release tablets versus one 60-mg hydrocodone bitartrate extended-release tablet as assessed by the area under the plasma drug concentration by time curve from time 0 to infinity ($AUC_{0-\infty}$) and the maximum observed plasma drug concentration (C_{max}).

Secondary Objectives: The secondary objective of the study was to characterize the safety of hydrocodone bitartrate following administration of the hydrocodone bitartrate extended-release tablet by evaluating the following:

- occurrence of adverse events throughout the study
- clinical laboratory test results at the final assessment (or early withdrawal)
- vital signs measurements throughout the study
- 12-lead electrocardiogram (ECG) findings at the final assessment (or early withdrawal)
- physical examination findings, including body weight measurements, at the final assessment (or early withdrawal)
- oxyhemoglobin saturation (SpO_2) monitoring on the day of each study drug administration, at the final assessment (or early withdrawal), and at follow-up
- concomitant medication usage throughout the study

Number of Subjects (Planned and Analyzed): For this study, approximately 38 subjects were planned to be and were enrolled. Of these, 36 subjects received at least 1 dose of study drug and were evaluated for safety and 28 (74%) subjects were evaluated for pharmacokinetics in the study.

Main Criteria for Inclusion: Subjects were included in the study if all of the following main criteria were met (not all inclusive):

- The subject was a man or woman 18 through 45 years of age, with a body mass index (BMI) of 20 to 30 kg/m^2, inclusive.
- The subject was in good health as determined by medical and psychiatric history, physical examination, ECG, serum chemistry, hematology, urinalysis, and serology.

Main Criteria for Exclusion: Subjects were excluded from participating in this study if 1 or more of the following main criteria were met (not all inclusive):

- The subject had any clinically significant uncontrolled medical conditions (treated or untreated).
- The subject had a clinically significant deviation from normal in ECG or physical examination findings, as determined by the investigator or the medical monitor.

Study Drug Dose, Mode of Administration, Administration Rate, and Batch Number: Subjects were randomly assigned to 1 of the following 2 treatment sequences: AB or BA, whereby A was two 30-mg hydrocodone bitartrate extended-release tablets and B was a single 60-mg hydrocodone bitartrate extended-release tablet. Each subject received 1 treatment during each administration period. Subjects received each of the 2 treatments once. There was a minimum 14-day washout period between the 2 administrations of study drug. Treatments were orally administered to subjects, while they were seated, at approximately 0800 (±2 hours) on the 1st day of each administration period. Hydrocodone bitartrate extended-release tablets were provided at dose strengths of 30 and 60 mg. Tablets are 0.275" x 0.625" convex, capsule shaped, and are 575 mg in total weight. The 30-mg tablets are yellow and the 60-mg tablets are blue. The 30-mg hydrocodone bitartrate extended-release tablets (treatment A, lot number C62021) were packaged in 60-cc round, white, high-density polyethylene (HDPE) bottles with 38-mm child-resistant caps. Each bottle contained 1 canister of desiccant. Each bottle was foil-induction sealed and contains 20 tablets. The 60-mg hydrocodone bitartrate extended-release tablets (treatment B, lot number C63781) were packaged in 90-cc square, white, HDPE bottles with 38-mm child-resistant caps. Each bottle contained 1 canister of desiccant. Each bottle was foil-induction sealed and contains 30 tablets.

Reference Therapy Dose, Mode of Administration, and Administration Rate: Not applicable

Method of Blinding: This was an open-label study with no blinding.

Duration of Treatment: Subjects received 2 single doses during the study, each separated by a 14-day washout period.

General Design and Methodology: Subjects were randomly assigned to receive treatments in 1 of the following treatment sequences: AB or BA, whereby A was two 30-mg tablets and B was a single 60-mg tablet. The study consisted of a screening visit (visit 1) within 21 days before the first dose of study drug followed by 2 open-label single-dose administration periods (periods 1 and 2 [visits 2 and 3]) and a follow-up visit (visit 4). There was a minimum 14-day washout between each dose of study drug. Subjects received each treatment once. Subjects received one 50-mg tablet of naltrexone hydrochloride with 240 mL of water to block opioid receptors and minimize opioid-related adverse events approximately 15 hours and 3 hours before each study drug administration and approximately 9 hours and 21 hours after each study drug administration. In each administration period, venous blood samples for pharmacokinetic analyses were collected immediately before and over 72 hours after study drug administration. Subjects remained in the study center throughout each pharmacokinetic sampling period. Safety was assessed throughout the study by monitoring the occurrence of adverse events, clinical laboratory test results, vital signs measurements, 12-lead ECG findings, physical examination findings, SpO_2 monitoring, and use of concomitant medications. Subjects who participated in all scheduled visits had final procedures and assessments performed prior to discharge in administration period 2 (visit 3). Subjects who withdrew from the study before the completion of all scheduled assessments had final procedures and assessments performed prior to discharge in their last study drug administration period. All subjects were asked to return to the study center for a follow-up visit to occur 48 to 72 hours after their last discharge from the center. Safety parameters were evaluated at that time.

Primary Pharmacokinetic Measure(s) and Endpoint(s): In each administration period, blood samples (3 mL) were collected by venipuncture or indwelling catheter. During each administration period, blood samples were collected immediately (within approximately 5 minutes) before study drug administration and 15, 30, and 45 minutes, and 1, 1.5, 2, 2.5, 3, 3.5, 4, 5, 6, 7, 8, 9, 10, 12, 18, 24, 30, 36, 48, 60, and 72 hours after study drug administration. The bioequivalence of treatment A (two 30-mg tablets) and treatment B (one 60-mg tablet) was assessed by comparing the following 2 primary pharmacokinetic parameters:

- C_{max}
- $AUC_{0-\infty}$

Secondary Pharmacokinetic Measures and Endpoints: The following additional pharmacokinetic parameters of hydrocodone were calculated from plasma concentrations collected at specified time points through 72 hours after study drug administration, when possible:

- time to maximum observed plasma drug concentration (t_{max}) by inspection
- AUC from time 0 to 72 hours after study drug administration (AUC_{0-72})

- AUC from time 0 to the time of the last measurable drug concentration (AUC_{0-t})
- percentage extrapolation, $100x(AUC_{0-\infty}-AUC_{0-t})/AUC_{0-\infty}$)
- apparent plasma terminal elimination rate constant (λ_z) and associated elimination half-life ($t_{½}$)

Pharmacokinetic parameters (primary and secondary) were also calculated, when possible, for the active metabolite of hydrocodone (hydromorphone).

Safety Variables: Safety was assessed during the study by evaluating adverse events, clinical laboratory test results (chemistry, hematology, and urinalysis), vital signs measurements, ECG and physical examination findings, SpO_2 monitoring, and concomitant medication usage.

Statistical Considerations: The set of randomized subjects includes all subjects who were randomly assigned to a treatment sequence, regardless of whether or not a subject received any study drug. The safety analysis set includes those in the set of randomized subjects who received at least 1 dose of the hydrocodone bitartrate extended-release tablet. The pharmacokinetic analysis set includes those in the safety analysis set who had sufficient data to calculate the pharmacokinetic parameters C_{max} and $AUC_{0-\infty}$ for both administration periods. Subject disposition and demographic characteristics were summarized using descriptive statistics. In addition, medical history, ECG, and physical examination findings at baseline were summarized using descriptive statistics. Protocol violations for each category were summarized using descriptive statistics. The pharmacokinetic analysis set was used for all pharmacokinetic analyses. Summaries are presented by treatment group (two 30-mg tablets versus one 60-mg tablet). For each treatment of the hydrocodone bitartrate extended-release tablets, pharmacokinetic parameters for hydrocodone and its metabolite hydromorphone were calculated, if appropriate. The bioequivalence of treatment A (two 30-mg tablets) and treatment B (one 60-mg tablet) was assessed by comparing C_{max} and $AUC_{0-\infty}$ for each treatment. The natural-log transformed values of each parameter were analyzed using a mixed-effect model. The mixed-effect model included treatment, treatment sequence, and period as the fixed effects and subject as a random effect. The 2-sided 90% and 95% confidence intervals (CIs) for the treatment ratio were provided through this model. Treatment B was considered to be bioequivalent to treatment A if the 90% CI fell completely within the limits of 0.8 to 1.25 for both pharmacokinetic parameters. All pharmacokinetic parameters were summarized by treatment group using descriptive statistics, including number (n), mean, standard deviation (SD), standard error (SE), geometric mean (if appropriate), coefficient of variation (if appropriate), median, minimum, and maximum. The safety analysis set was used for all safety analyses. With the exception of adverse events and vital signs and SpO_2 measurements, summaries were presented for all subjects (ie, total). Adverse events were summarized by treatment group and for all subjects, whereas vital signs and SpO_2 measurements were summarized by treatment group only.

Summary of Results

Subject Disposition and Demography: In this study, 38 healthy men and women were randomly assigned to a treatment sequence; 36 (95%) subjects received at least 1 dose of study drug and were evaluable for safety; 28 (74%) subjects were evaluable for pharmacokinetics and completed the study. The average age of the subjects was 28.5 years (range 19 to 45 years). Approximately two-thirds (68%) of subjects were white and 61% were women.

Pharmacokinetic Results: Mean maximum plasma concentrations of hydrocodone were attained approximately 8 hours following administration for both treatments. Decline from peak plasma concentrations generally occurred in a monophasic manner with a mean $t_{1/2}$ of approximately 10 to 11 hours. Hydrocodone concentrations were approximately 100-fold higher than concentrations of hydromorphone. The assessment of bioequivalence indicates that while the CI for the ratio of treatment B (one 60-mg tablet) to treatment A (two 30-mg tablets) for AUC met the criteria for bioequivalence (within 0.8, 1.25), the CI for the ratio for C_{max} did not (0.769, 0.869).

Safety Results: The safety data indicate that two 30-mg tablets and one 60-mg tablet of the hydrocodone bitartrate extended-release tablet were generally well tolerated in the healthy subjects concurrently receiving naltrexone in this study. No deaths or other serious adverse events occurred in this study. A total of 7 subjects withdrew from the study due to adverse events; 1 of these subjects withdrew due to an adverse event that began after receiving naltrexone but before receiving a dose of hydrocodone. All adverse events leading to withdrawal were vomiting. All adverse events were mild to moderate in severity and had

resolved before the end of the study. The overall incidence of adverse events or treatment-related adverse events following administration of treatment A was comparable to that following administration of treatment B. The most frequently occurring adverse events overall (≥5% of subjects following any treatment) were nausea (31%), vomiting (17%), dizziness (17%), diarrhea (8%), abdominal pain (6%), and dry mouth (6%). Treatment-related adverse events were generally consistent with the known pharmacologic activity of opioids. There was no apparent correlation between plasma concentration and incidence of treatment-related events of vomiting because the mean maximum plasma concentration of hydrocodone following administration of treatment B was lower than that following treatment A and because plasma concentrations of subjects with treatment-related adverse events of vomiting following administration of treatment B were comparable to those in other subjects receiving treatment B. Clinically significant respiratory rate values were reported both prior to and after administration of the hydrocodone bitartrate extended-release tablet in this study. No correlation was detected between these low respiratory rates, oxygen desaturation, and plasma hydrocodone concentrations. Overall, mean vital signs values remained within normal ranges throughout the study. None of clinically significant changes in blood pressure or pulse were reported as adverse events and no correlation was detected between clinically significant changes in blood pressure or pulse and plasma hydrocodone concentrations. No clinically significant changes in hematology, chemistry, ECG, or SpO_2 results were reported during the course of the study.

Conclusions: The assessment of bioequivalence indicates that while the CI for the ratio of treatment B (one 60-mg tablet) to treatment A (two 30-mg tablets) for AUC met the criteria for bioequivalence (within 0.8, 1.25), the CI (0.769, 0.869) for the ratio for C_{max} did not. The hydrocodone bitartrate extended-release tablet (administered as two 30-mg tablets or one 60-mg tablet) was generally well tolerated in the healthy subjects who were concurrently receiving naltrexone in this study.

Table : Mean (Standard Deviation) Pharmacokinetic Parameters for Hydrocodone Following Administration of Hydrocodone Bitartrate Extended-Release by Treatment (Pharmacokinetic Analysis Set)

Variable	A (N=28)	B (N=28)
C_{max} (ng/mL)	46.140 (11.6470)	38.059 (11.9596)
$AUC_{0-\infty}$ (ng·h/mL)	863 (241.2)	803 (248.5)
AUC_{0-t} (ng·h/mL)	857 (239.9)	790 (243.5)
AUC_{0-72} (ng·h/mL)	857 (239.7)	790 (243.4)
t_{max} (h)	8.5 (5.0, 10.0)	8.0 (5.0, 12.1)
$t_{1/2}$ (h)	10.0 (2.72)	11.1 (3.57)
Percentage extrapolation (%)	0.8 (0.50)	1.7 (1.55)
λ_z (1/h)	0.0739 (0.01889)	0.0689 (0.02125)

SOURCE: Summary 15.9.1, Listing 16.2.5.02.
NOTE: Median (range) is presented for t_{max}
C_{max}=maximum observed plasma drug concentration; $AUC_{0-\infty}$=area under the plasma drug concentration versus time curve (AUC) from time zero to infinity; AUC_{0-t}=AUC from time zero to the time of the last measurable drug concentration; AUC_{0-72}=AUC from time zero to 72 hours; t_{max}=time to maximum observed plasma drug concentration by inspection; $t_{1/2}$=elimination half-life;
% extrapolation=100x($AUC_{0-\infty}$-AUC_{0-t})/$AUC_{0-\infty}$; λ_z=apparent plasma terminal elimination rate constant.
A=two 30-mg hydrocodone bitartrate extended-release tablets, B=one 60-mg hydrocodone bitartrate extended-release tablet.

Table : Statistical Comparison of Two 30-mg Tablets and One 60-mg Hydrocodone Bitartrate Extended-Release Tablet (Pharmacokinetic Analysis Set)

Variable	A (N=28)	B (N=28)	B/A ratio	90% CI
C_{max} (ng/mL)	44.6 (2.20)	36.4 (2.26)	0.818	0.769, 0.869
$AUC_{0-\infty}$ (ng·h/mL)	830.0 (45.58)	767.5 (46.97)	0.927	0.893, 0.961

SOURCE: Summary 15.10, Listing 16.2.5.02.
NOTE: Values for C_{max} and $AUC_{0-\infty}$ are geometric mean (standard error of the mean).
C_{max}=maximum observed plasma drug concentration; $AUC_{0-\infty}$=area under the plasma concentration by time curve from time 0 to infinity.
A=two 30-mg hydrocodone bitartrate extended-release tablets; B=one 60-mg hydrocodone bitartrate extended-release tablet.

4.2.13 Study # 1096 Synopsis (Dosage form proportionality study)

Name of Sponsor/Company: Cephalon, Inc.	**Individual study table referring to part of dossier in which the individual study or study table is presented**	(For National Authority Use Only)
Name of Finished Product: Hydrocodone bitartrate extended-release tablet	**Volume:**	
Name of Active Ingredient: Hydrocodone bitartrate (CEP-33237)	**Reference:**	

Title of Study: A Randomized, Open-Label, 2-Period, Crossover Study to Assess the Bioequivalence of Two 45-mg Hydrocodone Bitartrate Extended-Release Tablets Versus One 90-mg Hydrocodone Bitartrate Extended-Release Tablet

Investigators and Study Centers: Aziz L. Laurent, MD, PPD Development, LP, 7551 Metro Center Drive, Suite 200, Austin, Texas 78744 USA

Publication (reference): Results from this study have not been published at the time of approval of this report.

Study Period: 13 May 2011 to 24 June 2011 **Phase of Development:** 1

Primary Objective: The primary objective was to assess the bioequivalence of two 45-mg hydrocodone bitartrate extended-release tablets versus one 90-mg hydrocodone bitartrate extended-release tablet as assessed by the area under the plasma drug concentration by time curve from time 0 to infinity ($AUC_{0-\infty}$) and the maximum observed plasma drug concentration (C_{max}) of hydrocodone.

Secondary Objectives: The secondary objective of the study was to characterize the safety of hydrocodone bitartrate following administration of the hydrocodone bitartrate extended-release tablet by evaluating the following:

- occurrence of adverse events throughout the study
- clinical laboratory test results at the final assessment (or early withdrawal)
- vital signs measurements throughout the study
- 12-lead electrocardiogram (ECG) findings at the final assessment (or early withdrawal)
- physical examination findings, including body weight measurements, at the final assessment (or early withdrawal)
- oxyhemoglobin saturation (SpO_2) monitoring on the day of each study drug administration, at the final assessment (or early withdrawal), and at follow-up
- concomitant medication usage throughout the study

Number of Subjects (Planned and Analyzed): For this study, up to approximately 38 subjects were planned to be and were enrolled. Thirty-five subjects were enrolled, 33 (94%) received at least 1 dose of study drug and were evaluated for safety, 29 (83%) subjects were evaluated for pharmacokinetics, and 28 (80%) subjects completed the study.

Main Criteria for Inclusion: Subjects were included in the study if all of the following main criteria were met (not all inclusive):

- The subject was a man or woman 18 through 45 years of age, with a body mass index (BMI) of 20 to 30 kg/m^2, inclusive.
- The subject was in good health as determined by medical and psychiatric history, physical examination, ECG, serum chemistry, hematology, urinalysis, and serology.

Main Criteria for Exclusion: Subjects were excluded from participating in this study if 1 or more of the following main criteria were met (not all inclusive):

- The subject had any clinically significant uncontrolled medical conditions (treated or untreated).

- The subject had a clinically significant deviation from normal in ECG or physical examination findings, as determined by the investigator or the medical monitor.

Study Drug Dose, Mode of Administration, Administration Rate, and Batch Number: Subjects were randomly assigned to 1 of the following 2 treatment sequences: AB or BA, whereby A was two 45-mg hydrocodone bitartrate extended-release tablets and B was a single 90-mg hydrocodone bitartrate extended-release tablet. Each subject received 1 treatment during each administration period. Subjects received each of the 2 treatments once. There was a minimum 14-day washout period between the 2 administrations of study drug. Treatments were orally administered to subjects, while they were seated, at approximately 0800 (±2 hours) on the 1st day of each administration period. Hydrocodone bitartrate extended-release tablets were provided at dose strengths of 40 and 90 mg. Tablets are 0.275" x 0.625" convex, capsule shaped, and are 575 mg in total weight. The 45-mg tablets are white and the 90-mg tablets are green. The 45-mg hydrocodone bitartrate extended-release tablets (treatment A, lot number 11-000564) were packaged in 60-cc round, white, high-density polyethylene (HDPE) bottles with 38-mm child-resistant caps. Each bottle contained 1 canister of desiccant. Each bottle was foil-induction sealed and contained 20 tablets. The 90-mg hydrocodone bitartrate extended-release tablets (treatment B, lot number 11-000563) were packaged in 90-cc square, white, HDPE bottles with 38-mm child-resistant caps. Each bottle contained 1 canister of desiccant. Each bottle was foil-induction sealed and contained 30 tablets.

Reference Therapy Dose, Mode of Administration, and Administration Rate: Not applicable

Method of Blinding: This was an open-label study with no blinding.

Duration of Treatment: Subjects received 2 single doses during the study, each separated by a 14-day washout period.

General Design and Methodology: Subjects were randomly assigned to receive treatments in 1 of the following treatment sequences: AB or BA, on a 1:1 basis, whereby A was two 45-mg tablets and B was a single 90-mg tablet. The study consisted of a screening visit (visit 1) within 21 days before the first dose of study drug followed by 2 open-label single-dose administration periods (periods 1 and 2 [visits 2 and 3]) and a follow-up visit (visit 4). There was a minimum 14-day washout between each dose of study drug. Subjects received each treatment once. Subjects received one 50-mg tablet of naltrexone hydrochloride with 240 mL of water to block opioid receptors and minimize opioid-related adverse events approximately 15 hours and 3 hours before each study drug administration and approximately 9 hours and 21 hours after each study drug administration. In each administration period, venous blood samples for pharmacokinetic analyses were collected immediately before and over 72 hours after study drug administration. Subjects remained in the study center throughout each pharmacokinetic sampling period. Safety were assessed throughout the study by monitoring the occurrence of adverse events, clinical laboratory test results, vital signs measurements, 12-lead ECG findings, physical examination findings, SpO_2 monitoring, and use of concomitant medications. Subjects who participated in all scheduled visits had final procedures and assessments performed prior to discharge in administration period 2 (visit 3). Subjects who withdrew from the study before the completion of all scheduled assessments had final procedures and assessments performed prior to discharge in their last study drug administration period. All subjects were asked to return to the study center for a follow-up visit to occur 48 to 72 hours after their last discharge from the center. Safety parameters were evaluated at that time.

Primary Pharmacokinetic Measure(s) and Endpoint(s): In each administration period, blood samples (3 mL) were collected by venipuncture or indwelling catheter. During each administration period, blood samples were collected immediately (within approximately 5 minutes) before study drug administration and 15, 30, and 45 minutes, and 1, 1.5, 2, 2.5, 3, 3.5, 4, 5, 6, 7, 8, 9, 10, 12, 18, 24, 30, 36, 48, 60, and 72 hours after study drug administration. The bioequivalence of treatment A (two 45-mg tablets) and treatment B (one 90-mg tablet) was assessed by comparing the following 2 primary pharmacokinetic parameters:

- C_{max}
- $AUC_{0-\infty}$

Secondary Pharmacokinetic Measures and Endpoints: The following additional pharmacokinetic parameters of hydrocodone were calculated from plasma concentrations collected at specified time points through 72 hours after study drug administration, when possible:

- time to maximum observed plasma drug concentration (t_{max}) by inspection
- AUC from time 0 to 72 hours after study drug administration (AUC_{0-72})
- AUC from time 0 to the time of the last measurable drug concentration (AUC_{0-t})
- percentage extrapolation, $100(AUC_{0-\infty}-AUC_{0-t})/AUC_{0-\infty}$)
- apparent plasma terminal elimination rate constant (λ_z) and associated elimination half life ($t_{½}$)

Pharmacokinetic parameters (primary and secondary) were also calculated, when possible, for the active metabolite of hydrocodone (hydromorphone).

Safety Variables: Safety was assessed during the study by evaluating adverse events, clinical laboratory test results (chemistry, hematology, and urinalysis), vital signs measurements, ECG and physical examination findings, SpO_2 monitoring, and concomitant medication usage.

Statistical Considerations: The set of randomized subjects includes all subjects who were randomly assigned to a treatment sequence, regardless of whether or not a subject received any study drug. The safety analysis set includes those in the set of randomized subjects who received at least 1 dose of the hydrocodone bitartrate extended-release tablet. The pharmacokinetic analysis set includes those in the safety analysis set who had sufficient data to calculate the pharmacokinetic parameters C_{max} and $AUC_{0-\infty}$ for both administration periods. Subject disposition and demographic characteristics were summarized using descriptive statistics. In addition, medical history, ECG, and physical examination findings at baseline were summarized using descriptive statistics. Protocol violations for each category were summarized using descriptive statistics. The pharmacokinetic analysis set was used for all pharmacokinetic analyses. Summaries are presented by treatment group (two 45-mg tablets versus one 90-mg tablet). For each treatment of the hydrocodone bitartrate extended-release tablets, pharmacokinetic parameters for hydrocodone and its metabolite hydromorphone were calculated, if appropriate. The bioequivalence of treatment A (two 45-mg tablets) and treatment B (one 90-mg tablet) was assessed by comparing C_{max} and $AUC_{0-\infty}$ for each treatment. The natural-log transformed values of each parameter were analyzed using a mixed-effect model. The mixed-effect model included treatment, treatment sequence, and period as the fixed effects and subject as a random effect. The 2-sided 90% and 95% confidence intervals (CIs) for the treatment ratio were provided through this model. Treatment B was considered to be bioequivalent to treatment A if the 90% CI fell completely within the limits of 0.8 to 1.25 for both pharmacokinetic parameters. All pharmacokinetic parameters were summarized by treatment group using descriptive statistics, including n, mean, standard deviation (SD), standard error (SE), geometric mean (if appropriate), coefficient of variation (if appropriate), median, minimum, and maximum. The safety analysis set was used for all safety analyses. With the exception of adverse events and vital signs, summaries were presented for all subjects (ie, total). Adverse events were summarized by treatment group and for all subjects, whereas vital signs were summarized by treatment group only.

Summary of Results

Subject Disposition and Demography: In this study, 35 healthy men and women were randomly assigned to a treatment sequence; 33 (94%) subjects received at least 1 dose of study drug and were evaluable for safety; 29 (83%) subjects were evaluable for pharmacokinetics, and 28 (80%) subjects completed the study. The average age of the subjects was 27.9 years (range 19 to 44 years). Approximately three-quarters (74%) of subjects were white and 63% were women.

Pharmacokinetics Results: Mean maximum plasma concentrations of hydrocodone were attained approximately 7 and 9 hours following administration for treatments A and B, respectively. Decline from peak plasma concentrations generally occurred in a monophasic manner with a mean half-life of approximately 11 hours for both treatments. Hydromorphone concentrations were approximately 1% to 2% of those of hydrocodone. The assessment of bioequivalence indicates that while the 90% CI for the ratio of treatment B (one 90-mg tablet) to treatment A (two 45-mg tablets) for AUC met the criteria for bioequivalence (0.946, 1.043), the 90% CI for the ratio for C_{max} did not (0.776, 0.877).

Safety Results: The safety data indicate that two 45-mg tablets and one 90-mg tablet of the hydrocodone bitartrate extended-release tablet were generally well tolerated in the healthy subjects concurrently

receiving naltrexone in this study. No deaths or other serious adverse events occurred in this study. A total of 3 subjects withdrew from the study due to adverse events of vomiting; 1 of these subjects withdrew due to an adverse event that began after receiving naltrexone but before receiving a dose of hydrocodone.

All adverse events were mild to moderate in severity and resolved before the end of the study. The incidence of adverse events of nausea, headache, and dizziness was higher following treatment A than treatment B. The incidence of other adverse events was comparable between treatments. Treatment-related adverse events which were reported were generally consistent with the known pharmacologic activity of opioids. There was no apparent correlation between plasma concentration and the most frequently reported treatment-related adverse. Overall, no clinically meaningful changes in hematology, chemistry, urinalysis, ECG, or SpO_2 results were reported during the course of the study. Clinically significant decreases in respiratory rate were reported both prior to and after study drug administration. No correlation was detected between these low respiratory rates, oxygen desaturation, and plasma hydrocodone concentrations. None of clinically significant changes in blood pressure or pulse were reported as adverse events and no correlation was detected between these clinically significant changes in blood pressure or pulse and plasma hydrocodone concentrations.

Conclusions: The assessment of bioequivalence indicates that while the 90% CI for the ratio of treatment B (one 90-mg tablet) to treatment A (two 45-mg tablets) for AUC met the criteria for bioequivalence (0.946, 1.043), the 90% CI for the ratio for C_{max} did not (0.776, 0.877). The hydrocodone bitartrate extended-release tablet (administered as two 45-mg tablets or one 90-mg tablet) was generally well tolerated in the healthy subjects who were concurrently receiving naltrexone in this study.

Table : Mean (Standard Deviation) Pharmacokinetic Parameters for Hydrocodone Following Administration of Hydrocodone Bitartrate Extended-Release by Treatment (Pharmacokinetic Analysis Set)

Variable	A (N=29)	B (N=29)
C_{max} (ng/mL)	64.79 (18.901)	53.40 (16.338)
$AUC_{0-\infty}$ (ng·h/mL)	1180 (262.0)	1172 (262.4)
AUC_{0-t} (ng·h/mL)	1167 (258.3)	1155 (258.3)
AUC_{0-72} (ng·h/mL)	1167 (258.3)	1155 (258.1)
t_{max} (h)	7.0 (5.0, 12.0)	9.0 (5.0, 12.0)
$t_{1/2}$ (h)	11.4 (2.84)	11.1 (2.81)
Percentage extrapolation (%)	1.1 (0.76)	1.5 (0.95)
λ_z (1/h)	0.0649 (0.01656)	0.0667 (0.01823)

SOURCE: Summary 15.9.1, Listing 16.2.5.02.
NOTE: Median (range) is presented for t_{max}
C_{max}=maximum observed plasma drug concentration; $AUC_{0-\infty}$=area under the plasma drug concentration versus time curve (AUC) from time zero to infinity; AUC_{0-t}=AUC from time zero to the time of the last measurable drug concentration; AUC_{0-72}=AUC from time zero to 72 hours; t_{max}=time to maximum observed plasma drug concentration by inspection; $t_{1/2}$=elimination half-life;
% extrapolation=100x($AUC_{0-\infty}$-AUC_{0-t})/$AUC_{0-\infty}$; λ_z=apparent plasma terminal elimination rate constant.
A=two 45-mg hydrocodone bitartrate extended-release tablets, B=one 90-mg hydrocodone bitartrate extended-release tablet.

Table : Statistical Comparison of Two 45-mg Tablets and One 90-mg Hydrocodone Bitartrate Extended-Release Tablet (Pharmacokinetic Analysis Set)

Variable	A (N=29)	B (N=29)	B/A ratio	90% CI
C_{max} (ng/mL)	62.51 (3.510)	51.25 (3.034)	0.825	0.776, 0.877
$AUC_{0-\infty}$ (ng·h/mL)	1151.66 (48.661)	1144 (48.7)	0.993	0.946, 1.043

SOURCE: Summary 15.10, Listing 16.2.5.02.
NOTE: Values for C_{max} and $AUC_{0-\infty}$ are geometric mean (standard error of the mean).
C_{max}=maximum observed plasma drug concentration; $AUC_{0-\infty}$=area under the plasma concentration by time curve from time 0 to infinity.
A=two 45-mg hydrocodone bitartrate extended-release tablets; B=one 90-mg hydrocodone bitartrate extended-release tablet.

4.2.14 Clinical Pharmacology Filing Form (completed).

CLINICAL PHARMACOLOGY FILING FORM

Application Information			
NDA/BLA Number	207975	**SDN**	1, 4, 5
Applicant	Teva Branded Pharmaceutical Products R & D Inc	**Submission Date**	12/23/14, 2/6/15, 2/10/15
Generic Name	Hydrocodone Bitartarate Extended Release Tablets	**Brand Name**	Vantrela ER Tablets
Drug Class	Opioid Analgesic		
Indication	Chronic Pain Management		
Dosage Regimen	Twice Daily		
Dosage Form	Tablet	**Route of Administration**	Oral
OCP Division	DCP2	**OND Division**	DAAAP
OCP Review Team	**Primary Reviewer(s)**	**Secondary Reviewer/ Team Leader**	
Division	Srikanth C. Nallani, Ph.D.	Yun Xu, Ph.D.	
Pharmacometrics	NA	NA	
Genomics	NA	NA	
Review Classification	☑ Standard ☐ Priority ☐ Expedited		
Filing Date	12/23/2015	**74-Day Letter Date**	2/20/2015
Review Due Date	9/18/2015	**PDUFA Goal Date**	10/23/2015

Application Fileability

Is the Clinical Pharmacology section of the application fileable?

☑ Yes

☐ No

If no list reason(s)

Are there any potential review issues/ comments to be forwarded to the Applicant in the 74-day letter?

☐ Yes

☑ No

If yes list comment(s)

Is there a need for clinical trial(s) inspection?

☐ Yes

☑ No

If yes explain			
Clinical Pharmacology Package			
Tabular Listing of All Human Studies	☑ Yes ☐ No	Clinical Pharmacology Summary	☑ Yes ☐ No
Bioanalytical and Analytical Methods	☑ Yes ☐ No	Labeling	☑ Yes ☐ No

Clinical Pharmacology Studies			
Study Type		**Count**	**Comment(s)**
In Vitro Studies			
☐ Metabolism Characterization			
☐ Transporter Characterization			
☐ Distribution			
☐ Drug-Drug Interaction			
In Vivo Studies			
Biopharmaceutics			
☐ Absolute Bioavailability			
☑ Relative Bioavailability		2	Reference Drug VICOPROFEN, Abbott Labs (1079) Reference Drug NORCO, Watson Pharma (1071)
☐ Bioequivalence			
☑ Food Effect		2	Study 10024 food-effect multiple dose (bid) study. Study 1090 food-effect SD and relative BA study (IR comparator).
☐ Other			
Human Pharmacokinetics			
Healthy Subjects	☑ Single Dose	1	1082 Dose-proportionality. 1095 dosage form proportionality (2X30 mg to 1 X60 mg) 1106 same as 1095 but with final formulation to previous bridge 1096 dosage form proportionality (2X45 mg to 1 X90 mg) 1099 same as 1096 but with final formulation to previous bridge Other bridging type biopharmaceutics studies 1097, 1098, 1099, 1104, and 1106 will be reviewed by ONDQA Biopharm reviewer Dr. Assad Noory.
	☑ Multiple Dose	2	1081 SAD and MAD study. 1091 MAD study on 90 mg dose bid.
Patients	☐ Single Dose		

☐ Multiple Dose		
☐ Mass Balance Study		
☐ Other (e.g. dose proportionality)		
Intrinsic Factors		
☐ Race		
☐ Sex		
☐ Geriatrics		
☐ Pediatrics		
☑ Hepatic Impairment	1	1089
☑ Renal Impairment	1	1088
☐ Genetics		In studies where subjects were not blocked with naltrexone or where there was the potential for notably higher exposure to hydrocodone due to the dosing regimen or the population under study (Studies 1085, 1088, 1089, 1091, 10024, and 10032), blood samples were obtained at screening to genotype for cytochrome P450 2D6 (CYP2D6) enzyme metabolism status. Poor metabolizers of CYP2D6 substrates were excluded from these studies (VP029-00 Validation Report CYP2D6-16, AVP068-00-01 Gel Based Genotyping Validation Report, AVP02-00-00 Multiplex PCR Validation Report). In Studies 1079, 1090, 1095, 1096, 1097, 1098, 1099, 1104, and 1106, blood samples were obtained at baseline to genotype for CYP2D6 metabolism status. Subjects were permitted to participate in these studies irrespective of metabolism status. (AVP029-00 Validation Report CYP2D6-16, AVP068-00-01 Gel Based Genotyping Validation Report, AVP02-00-00 Multiplex PCR Validation Report). No labeling changes are proposed based on the exploratory analysis and hence a consult to Genomics Group is not needed.
Extrinsic Factors		
☑ Effects on Primary Drug	1	1076 alcohol interaction study (in vivo)
☑ Effects of Primary Drug	1	Publications discussing drug-drug interaction potential on hydrocodone PK. **(Note: The white paper submitted discusses lack of publications to show CYP drug interactions).**
Pharmacodynamics		
☐ Healthy Subjects		

☐ Patients		
Pharmacokinetics/Pharmacodynamics		
☑ Healthy Subjects	2	Clinical abuse liability studies: oral abuse 1085, intranasal abuse 10032.
☐ Patients		
☐ QT		
Pharmacometrics		
☐ Population Pharmacokinetics		
☐ Exposure-Efficacy		
☐ Exposure-Safety		

Total Number of Studies	**In Vitro**		**In Vivo**	20
Total Number of Studies to be Reviewed				13

Criteria for Refusal to File (RTF)		
RTF Parameter	**Assessment**	**Comments**
1. Did the applicant submit bioequivalence data comparing to-be-marketed product(s) and those used in the pivotal clinical trials?	☑Yes ☐No ☐N/A	
2. Did the applicant provide metabolism and drug-drug interaction information? (Note: RTF only if there is complete lack of information)	☑Yes ☐No ☐N/A	**Addressed based on reference drug reliance and also publications indicating lack of data.**
3. Did the applicant submit pharmacokinetic studies to characterize the drug product, or submit a waiver request?	☑Yes ☐No ☐N/A	
4. Did the applicant submit comparative bioavailability data between proposed drug product and reference product for a 505(b)(2) application?	☑Yes ☐No ☐N/A	
5. Did the applicant submit data to allow the evaluation of the validity of the analytical assay for the moieties of interest?	☑Yes ☐No ☐N/A	
6. Did the applicant submit study reports/rationale to support dose/dosing interval and dose adjustment?	☑Yes ☐No ☐N/A	
7. Does the submission contain PK and PD analysis datasets and PK and PD parameter datasets for each primary study that supports items 1 to 6 above (in .xpt format if data are submitted electronically)?	☑Yes ☐No ☐N/A	
8. Did the applicant submit the module 2 summaries (e.g. summary-clin-pharm, summary-biopharm, pharmkin-written-summary)?	☑Yes ☐No ☐N/A	
9. Is the clinical pharmacology and biopharmaceutics section of the submission legible, organized, indexed and paginated in a manner to allow substantive review to begin? If provided as an electronic submission, is the electronic submission searchable, does it have	☑Yes ☐No ☐N/A	

appropriate hyperlinks and do the hyperlinks work leading to appropriate sections, reports, and appendices?		
Complete Application **10.** Did the applicant submit studies including study reports, analysis datasets, source code, input files and key analysis output, or justification for not conducting studies, as agreed to at the pre-NDA or pre-BLA meeting? If the answer is 'No', has the sponsor submitted a justification that was previously agreed to before the NDA submission?	☑Yes ☐No ☐N/A	
Criteria for Assessing Quality of an NDA (Preliminary Assessment of Quality) Checklist		
Data		
1. Are the data sets, as requested during pre-submission discussions, submitted in the appropriate format (e.g., CDISC)?	☑Yes ☐No ☐N/A	
2. If applicable, are the pharmacogenomic data sets submitted in the appropriate format?	☐Yes ☐No ☑N/A	
Studies and Analysis		
3. Is the appropriate pharmacokinetic information submitted?	☑Yes ☐No ☐N/A	
4. 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)?	☑Yes ☐No ☐N/A	
5. Are the appropriate exposure-response (for desired and undesired effects) analyses conducted and submitted as described in the Exposure-Response guidance?	☐Yes ☐No ☑N/A	
6. 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?	☐Yes ☐No ☑N/A	Dedicated PK studies conducted. See above.

7. Are the pediatric exclusivity studies adequately designed to demonstrate effectiveness, if the drug is indeed effective?	☐Yes ☐No ☑N/A	
General		
8. Are the clinical pharmacology and biopharmaceutics studies of appropriate design and breadth of investigation to meet basic requirements for approvability of this product?	☑Yes ☐No ☐N/A	
9. Was the translation (of study reports or other study information) from another language needed and provided in this submission?	☐Yes ☐No ☑N/A	

Filing Memo
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/s/

SRIKANTH C NALLANI
09/17/2015

YUN XU
09/17/2015

CLINICAL PHARMACOLOGY FILING FORM

Application Information

NDA/BLA Number	207975	**SDN**	1, 4, 5
Applicant	Teva Branded Pharmaceutical Products R & D Inc	**Submission Date**	12/23/14, 2/6/15, 2/10/15
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Drug Class	Opioid Analgesic		
Indication	Chronic Pain Management		
Dosage Regimen	Twice Daily		
Dosage Form	Tablet	**Route of Administration**	Oral
OCP Division	DCP2	**OND Division**	DAAAP
OCP Review Team	**Primary Reviewer(s)**	**Secondary Reviewer/ Team Leader**	
Division	Srikanth C. Nallani, Ph.D.	Yun Xu, Ph.D.	
Pharmacometrics	NA	NA	
Genomics	NA	NA	
Review Classification	☑ Standard ☐ Priority ☐ Expedited		
Filing Date	12/23/2015	**74-Day Letter Date**	2/20/2015
Review Due Date	9/18/2015	**PDUFA Goal Date**	10/23/2015

Application Fileability

Is the Clinical Pharmacology section of the application fileable?

☑ Yes

☐ No

If no list reason(s)

Are there any potential review issues/ comments to be forwarded to the Applicant in the 74-day letter?

☐ Yes

☑ No

If yes list comment(s)

Is there a need for clinical trial(s) inspection?

☐ Yes

☑ No

If yes explain

Clinical Pharmacology Package

Tabular Listing of All Human Studies	☑ Yes ☐ No	Clinical Pharmacology Summary	☑ Yes ☐ No
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Clinical Pharmacology Studies

Study Type	Count	Comment(s)
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General		
8. Are the clinical pharmacology and biopharmaceutics studies of appropriate design and breadth of investigation to meet basic requirements for approvability of this product?	☑Yes ☐No ☐N/A	
9. Was the translation (of study reports or other study information) from another language needed and provided in this submission?	☐Yes ☐No ☑N/A	

Filing Memo
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/s/

SRIKANTH C NALLANI
02/13/2015

YUN XU
02/13/2015