CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

205777Orig1s000

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

June 26, 2014

The text below the table on page 8 in the below review has been modified to be more fact-based. Newer reviews exist that reference this review, however this change does not affect what they specifically reference or the conclusions they make. The date of the original version of this review needed to be maintained because of those newer reviews, so its content has been replaced with a corrected version. Srikanth Nallani requested this replacement on June 25, 2014. Yun Xu agreed with this replacement on June 26, 2014.

CLINICAL PHARMACOLOGY REVIEW

NDA: 205777	Submission Date(s): 9/22/2013
Brand Name	Targiniq
Generic Name	Oxycodone HCl and Naloxone HCl extended release tablets
Clinical Pharmacology Reviewer	Srikanth C. Nallani, Ph.D.
Team Leader	Yun Xu, Ph.D.
OCP Division	Division of Clinical Pharmacology II
OND Division	Anesthesia, Analgesia and Addiction Products
Sponsor	Purdue Pharma LP
Relevant IND(s)	70,851
Submission Type; Code	505(b)(2); New formulation
Formulation; Strength(s)	Tablets; 10/5, 20/10, and 40/20 mg
Indication	Management of (b) (4) pain (b) (4) (b) (4) around-the-clock (b) (4)
Proposed Dosage Regimen	Administer twice daily

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1 Executive Summary

1.1 Recommendation

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

1.2 Phase IV Commitments

None.

1.3 Summary of Clinical Pharmacology Findings

Purdue Pharma LP., submitted NDA 205777 for the approval of Targiniq (oxycodone HCl/naloxone HCl) combination extended release tablets (10/5, 20/10, and 40/20 mg) to manage (b) (4) chronic pain. For this 505(b)(2) NDA, Purdue has conducted the relative bioavailability study ONU1009, which established a pharmacokinetic (PK) bridge of each component of Targiniq (oxycodone and naloxone) to approved NDA products, OxyContin (oxycodone extended release NDA 022272 and its predecessor NDA 020553) and Narcan (Naloxone, NDA 016-636, via an ANDA generic designated as the Reference Listed Drug for Narcan since Narcan is not available on the market). Targiniq is a combination product that was developed in accordance with 21 CFR 300.50(a), "Fixed combination antagonist containing product to minimize the potential for abuse of the principal active component". Purdue developed the combination where both oxycodone and naloxone will be released from the tablet in the GI tract. Sponsor hypothesizes that naloxone is not significantly absorbed into the systemic circulation via the oral route; (b) (4) for oxycodone extended release product. Additionally the sponsor hypothesizes that if patients/users try misuse or abuse of the product by administering crushed product intranasally or intravenously, adequate naloxone is released into systemic circulation to block opioid effects of oxycodone.

The proposed product is approved under tradename Targin in Europe with an indication to control severe pain while counteracting opioid-induced constipation. Targiniq was previously developed in Europe by Mundipharma Research Limited (Mundipharma, an associated company of PPLP) and first approved in Germany under the proprietary name Targin. Targiniq has been approved in 36 European and other countries since 2006 under several proprietary names (Targin®, Targinact®, or Targiniq®) at 4 dosage strengths (5/2.5 mg, 10/5 mg, 20/10 mg and 40/20 mg) for BID dosing up to a maximum daily dose of Targiniq 80/40 mg.

For this submission, the sponsor is only claiming abuse deterrence properties for the oxycodone/naloxone product under conditions of intranasal and intravenous abuse.

A total of 23 Phase 1 clinical studies and 1 Phase 2 clinical study were conducted as part of the Targiniq clinical pharmacology program to support the Targiniq dosage regimen proposed for US registration. These studies characterized the PK and PD properties, effect of age, sex, special populations, drug interaction potential, abuse deterrence, and

GI motility effects associated with Targiniq. The results of these studies support the proposed BID dosing regimen and dosage range, within which the exposures to oxycodone from Targiniq are bioequivalent to those from the oxycodone CR marketed products including reformulated OxyContin and Oxygesic, the European marketed product. Eighteen of the clinical studies were reviewed. The main goal of the clinical pharmacology review is to focus on the clinical and clinical pharmacology studies with regard to impact of naloxone on clinical safety and efficacy.

During drug development Purdue was advised that a clinical trial demonstrating efficacy will be needed if detectable levels of naloxone in systemic circulation were noted, since naloxone is a known opioid antagonist. Systemic levels of naloxone were noted to be low but highly variable following normal use, and significantly higher naloxone levels were noted under circumstances resembling opioid drug abuse by chewing, crushing, etc. Clinical trial ONU3701 was conducted to establish efficacy of Targiniq in the target population. Despite detectable levels of naloxone noted in systemic circulation, efficacy of oxycodone in patients was demonstrated in this randomized withdrawal study. The sponsor also demonstrated that oxycodone PK (not naloxone PK) from Targiniq is dose-proportional (Study OXN 1506) and is bioequivalent to OxyContin (Study ONU1009).

Oxycodone Pharmacokinetics

Purdue Pharma conducted a randomized crossover study (ONU1009) in healthy volunteers (n=27) to assess the relative bioavailability of Targiniq (Oral Oxycodone 20 mg and Naloxone 10 mg) as compared to IV naloxone 0.4 mg and oral OxyContin 20 mg. Oxycodone Cmax and AUC were bioequivalent between Targiniq and Oxycontin. In a separate study (OXN1506) pharmacokinetics of oxycodone were observed to be dose-proportional for Targiniq strengths proposed 10/5 mg, 20/10 mg and 40/20 mg. Food-effect study (OXN1003) revealed a 25% increase in Cmax and a 17% increase in AUC for oxycodone following administration of Targiniq (40/20 mg) with high-fat meal compared to fasting. Following multiple dose administration (BID) systemic exposure of oxycodone was similar to that noted with a controlled release oxycodone (similar to OxyContin) on Day 4.

Naloxone Pharmacokinetics

Observations from the relative bioavailability study ONU1009 also provide a context for the plasma naloxone levels. Parenteral (IV, IM or SC) naloxone is commonly used in the treatment of reversing opioid overdose with a dose range from 0.4 mg to 2 mg based on Narcan label. Additionally, parenteral (0.2 to 0.6 mg IM or IV) naloxone challenge test is used to screen for subjects claiming to be recreational users of opioids. Absolute bioavailability of naloxone from Targiniq was <1% as measured by dose-normalized AUC. **The first noted plasma concentrations of naloxone (at 30 min) following IV administration were 1.26 ± 0.37 ng/mL (Range 0.725 to 2 ng/mL).**

As mentioned before, naloxone from Targiniq is meant to be released slowly over a twelve hour period, but because of low oral bioavailability plasma levels of naloxone are very low. Under normal circumstances, systemic levels of naloxone in majority of the subjects were observed to be low (<0.725 ng/mL, the lower end of the observed concentration at T= 30 min) and highly variable (See Table below). Dose-proportionality in naloxone PK is **not** noted with increased doses of Targiniq (See Table below).

With regard to naloxone, administration of Targiniq with food resulted in higher plasma levels of naloxone compared to fasted state. Four different food-effect studies were conducted where a worst case of 75% increase in plasma levels of naloxone was noted with Targiniq 40/20 mg (Study OXN1003). This observed increase in plasma naloxone levels may not be clinically significant. **Table: Peak Plasma (Cmax) levels of naloxone following administration of different strengths of Targiniq under fasted or fed condition (normal use).**

Treatment	N	Mean (ng/mL)	SD	Median (ng/mL)	Min (ng/mL)	Max (ng/mL)
Study OXN 1506 (Dose Proportionality Study)						
Targiniq 20/10 Fast	31	0.031	0.024	0.023	0.011	0.102
Targiniq 40/20 Fast	31	0.084	0.083	0.062	0.029	0.496
Targiniq 80/40 Fast	31	0.25	0.45	0.13	0.065	2.64
Study OXN 1003 (Food Effect Study)						
Targiniq 10/5 Fast	27	0.025	0.024	0.016	0	0.103
Targiniq 10/5 Fed	26	0.051	0.046	0.032	0.016	0.205
Targiniq 40/20 Fast	25	0.074	0.044	0.054	0.03	0.177
Targiniq 40/20 Fed	26	0.14	0.19	0.085	0.05	1.034
Study OXN 1505 (Food Effect Study)						
Targiniq 80/40 Fast	26	0.29	0.27	0.21	0.089	1.45
Targiniq 80/40 Fed	25	0.42	0.29	0.32	0.14	1.17
Study ONU1009 (Relative Bioavailability Study)						
Targiniq 20/10 Fast	27	0.084	0.081	0.049	0.029	0.377
Study OXN1011 (Multiple dose PK Study)						
Targiniq 40/20 BID Day 4 (Steady-state)	29	0.217	0.173	0.161	0.725	0.843

Simulations to address nonclinical review consideration of theoretical maximum daily dose:

During the course of the NDA review, nonclinical team required the sponsor to address the safety of the excipients used in the Targiniq formulation. This is typically addressed by the maximum theoretical daily dose that a patient could take and comparing it to the amount deemed to be safe in the inactive ingredients database. Currently, the sponsor proposed labeling recommends a maximum daily dose of 80/40 mg Targiniq (administered as 40/20 bid) because of the clinical experience in the study ONU3701 and in clinical database from Europe. However, nonclinical team reviews also evaluates the safety of excipients in the formulation with due consideration to the maximum theoretical daily dose. An information request was send to the Sponsor for justification of this proposed maximum daily dose based on excipient levels as follows:

> *Based on the information provided to date, you have concluded that there are insufficient data to support dosing above 80 mg oxycodone/40 mg of naloxone per day via your drug product. However, you have not provided any data to support that Targiniq ER should not be used at higher daily doses. We note that all currently approved single-entity oxycodone drug products have no maximum daily dose listed in the drug product labeling. Therefore in the absence of data to support the proposed dosing limit, we will use the maximum theoretical daily dose of 1.5 grams of oxycodone (750 mg of naloxone) per day that is applied to extended-release oxycodone products.*

However, the Sponsor responded on June 5, 2014, stating that they had difficulty to address the IR based on excipient data.

Instead of using the excipient doses, pharmacokinetic simulations utilized naloxone Cmax as a limitation to the use of higher doses of Targiniq, thus addressing the proposed maximum theoretical daily dose in patients.

Single dose pharmacokinetic data of naloxone following administration of Targiniq 80/40 mg strength (From Study OXN1505) was used in nonparametric superposition based multiple-dose PK simulations. Study OXN1505 was one of the four different food-effect studies conducted by Purdue. A European site manufactured strength of Targiniq 80/40 mg was administered in approximately 25 healthy adult volunteers with or without a high fat meal. The simulations employed each individual's PK profile data from single dose PK of naloxone and extended it to 108 hours (~4.5 days) assuming twice daily administration of Targiniq 80/40 mg tablet (i.e. total daily dose of 160/80 mg).

Simulations indicate that steady-state is noted within a few doses of twice daily administration of Targiniq 80/40 mg or twice that dose. In addition, simulations extend the observed food-effect in study OXN1505, an approximately 50% increase in Cmax, following single dose to multiple dose administration.

Figure: Simulated Naloxone PK Profile in fasted (left) and fed (right) condition following twice daily administration of Targiniq 80/40 mg strength with a total daily dose of 160/80 mg (based on data from OXN1505). Reference lines indicate the range of observed plasma concentrations at 30 minutes following IV bolus administration of IV naloxone.

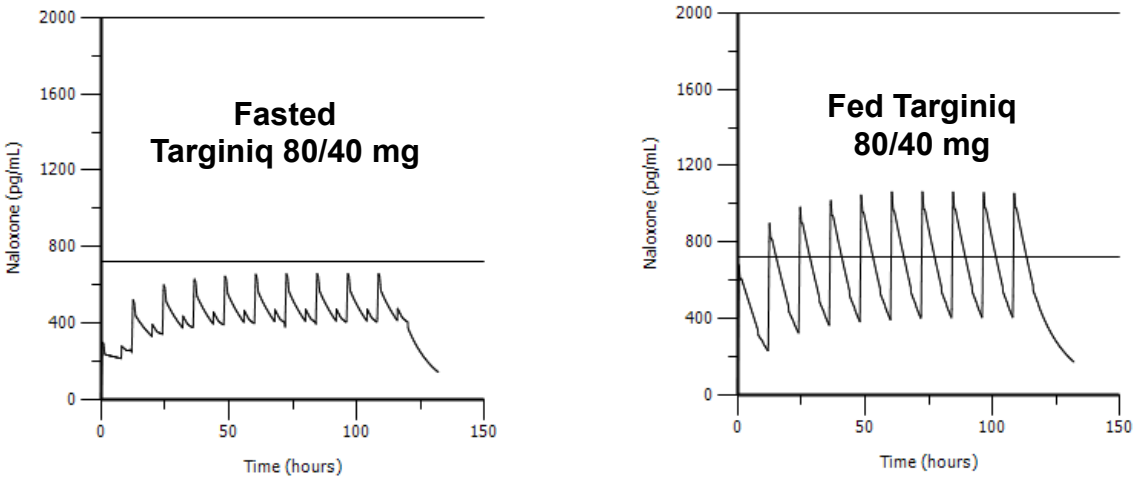


Table: Plasma naloxone Cmax at steady-state following simulation of twice daily administration of Targiniq 80/40 mg with a total daily dose of 160/80 mg (based on single dose Targiniq 80/40 mg PK data from study OXN1505).

Parameter	Treatment	N	Mean	SD	Min	Median	Max	Geometric Mean
Cmaxss	Targiniq 80/40 mg Fasted	25	727.8	602.2	181.3	393.8	2184.0	535
Cmaxss	Targiniq 80/40 mg Fed	23	1258.5	1274.7	174.0	652.6	5029.4	792

Similarly, assuming dose-proportional increase in naloxone exposure following administration of two tablets of Targiniq 80/40 mg (total dose of Targiniq 160/80 mg), simulations by the nonparametric superposition were conducted to predict naloxone PK following twice daily administration up to 108 hours.

Figure: Simulated Naloxone PK Profile in fasted (left) and fed (right) condition following twice daily administration of Targiniq 160/80 mg strength with a total daily dose of 320/160 mg (based on data from OXN1505 and assumed dose-proportional PK). Reference lines indicate the range of observed plasma concentrations at 30 minutes following IV bolus administration of IV naloxone.

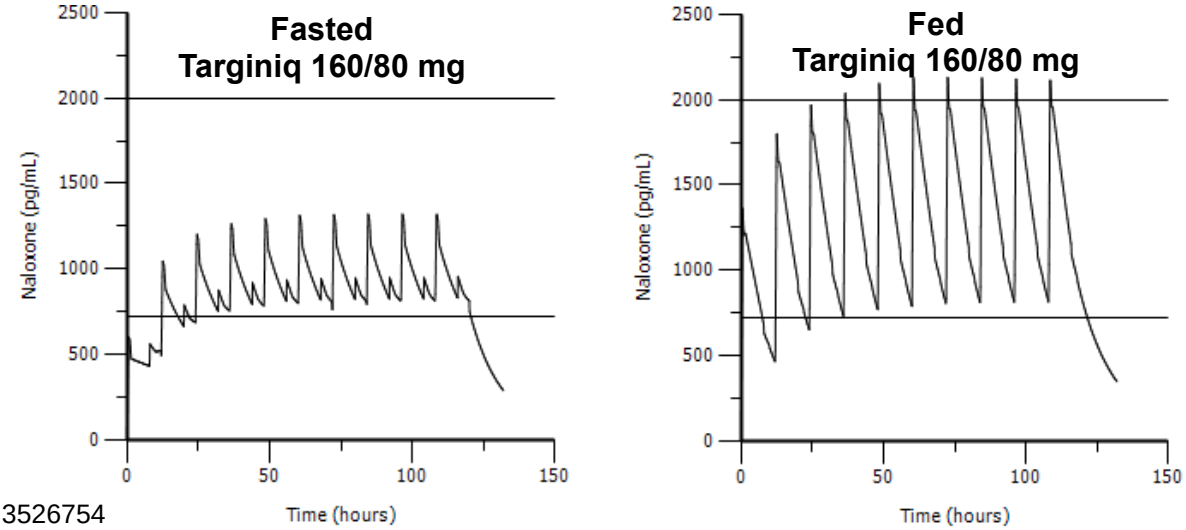


Table: Plasma naloxone Cmax at steady-state following simulation of twice daily administration of Targiniq 160/80 mg (based on single dose Targiniq 80/40 mg PK data from study OXN1505 and assumed dose-proportional PK).

Parameter	Treatment	N	Mean	SD	Min	Median	Max	Geometric Mean
Cmaxss	Targiniq 160/80 mg Fasted	25	1455.6	1204.3	362.6	787.7	4367.9	1070.0
Cmaxss	Targiniq 160/80 mg Fed	23	2517.0	2549.3	347.9	1305.1	10058.8	1584.0

As mentioned previously IM or IV injection of naloxone 0.4 mg is commonly used in the naloxone challenge test. Plasma naloxone concentrations were noted to be 1.26 ng/mL (range 0.725 – 2 ng/mL) at 30 minutes following IV bolus administration.

As indicated in the two tables above, simulated plasma naloxone levels that are more likely to produce opioid-blockade or opioid-withdrawal in dependent subjects may occur under following circumstances:

- Targiniq 160/80 mg dose administered twice daily under fasted or fed condition (total daily dose of 320/160 mg) or,
- Targiniq 80/40 mg dose administered under fed condition (high-fat meal consumption) twice daily (total daily dose of 160/80 mg under fed condition)

Targiniq pharmacokinetics and pharmacodynamics under conditions of abuse/misuse:

Purdue conducted study ONU1007 evaluating drug liking of Targiniq ER 40/20 mg following oral abuse and intranasal abuse in healthy non-dependent recreational opioid users. Purdue also conducted study ONU1003 where pharmacokinetics and pharmacodynamics of Targiniq ER 40/20 mg were evaluated following common methods/conditions of opioid ER product abuse in healthy non-dependent recreational users of opioids. In addition, drug liking studies were also conducted in methadone-dependent subjects where PK and PD of Targiniq ER was evaluated following oral abuse (Study ONU1004 and Study ONU1008).

Oral abuse following Chewing: Study ONU1007, ONU1003, ONU1004 and ONU1008 all demonstrated that Targiniq ER loses extended release characteristics following oral administration after chewing. Both naloxone and oxycodone pharmacokinetic parameters indicated significant increase immediately after oral administration of chewed product. However, the systemic concentrations of naloxone were not significant enough to block the drug liking effects of oxycodone in recreational drug users (like non-methadone maintained patients).

Figure: Mean plasma oxycodone (left) and naloxone (right) profile over time following administration of intact Targiniq ER (or ONU 40/20 mg-Circles), chewed Targiniq (Squares) and oxycodone API (oxycodone profile only- Triangles) in Study ONU1007.

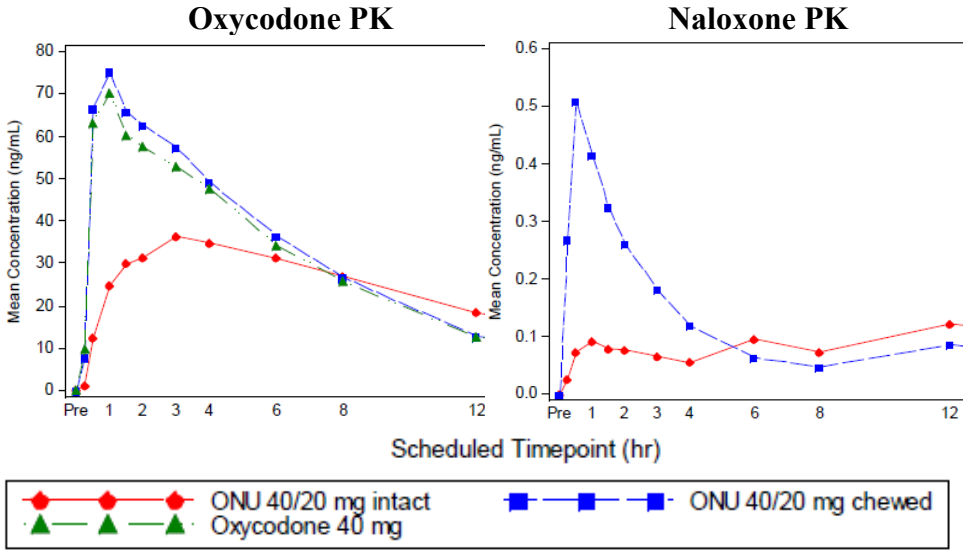


Figure: Mean drug liking profile over time following administration of intact Placebo (circles), intact Targiniq ER (or ONU 40/20 mg-Squares), chewed Targiniq (Triangles) and oxycodone API (diamond).(Group 1, Study ONU1003)

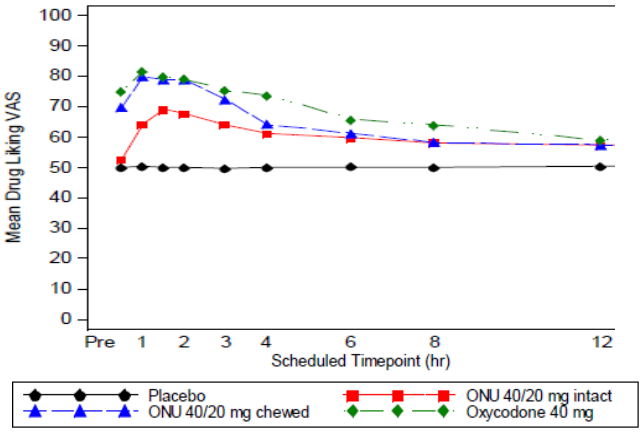


Figure: Mean Oxycodone Plasma Concentrations over Time following oral abuse (chewing) (Group 1 – PK Population Study ONU1003) compared to oxycodone oral solution.

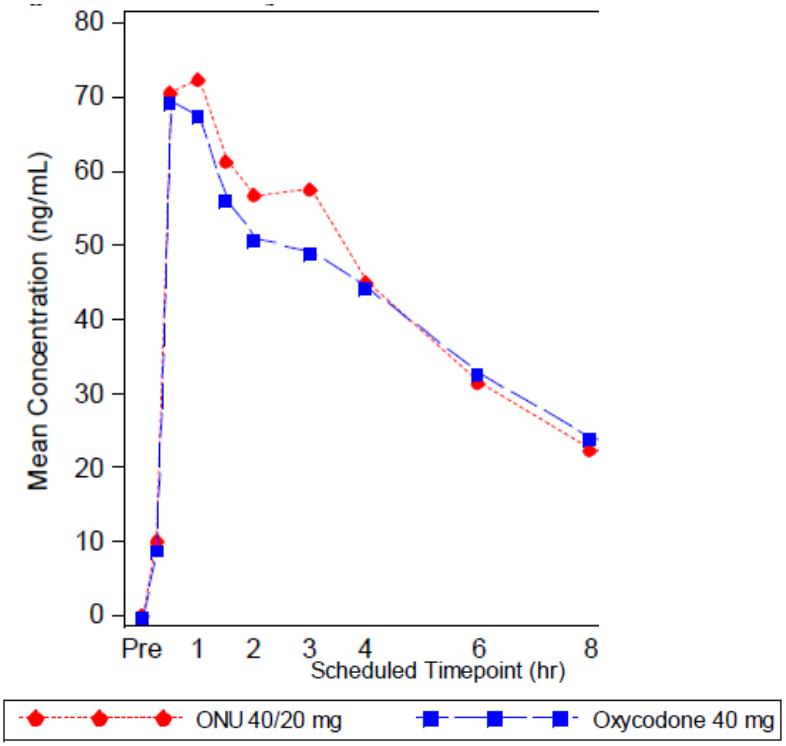
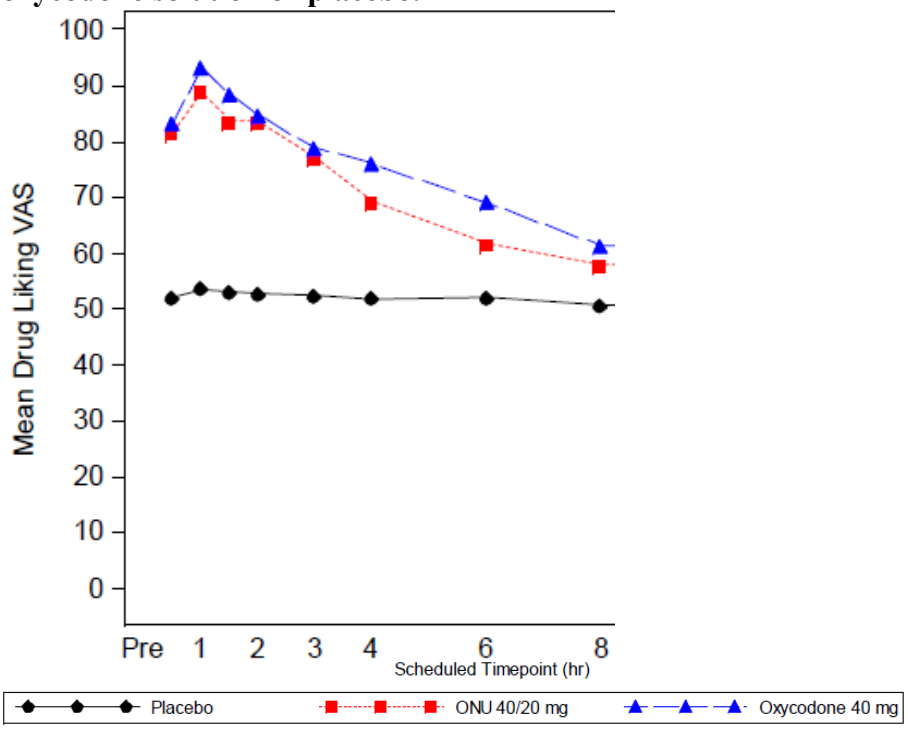
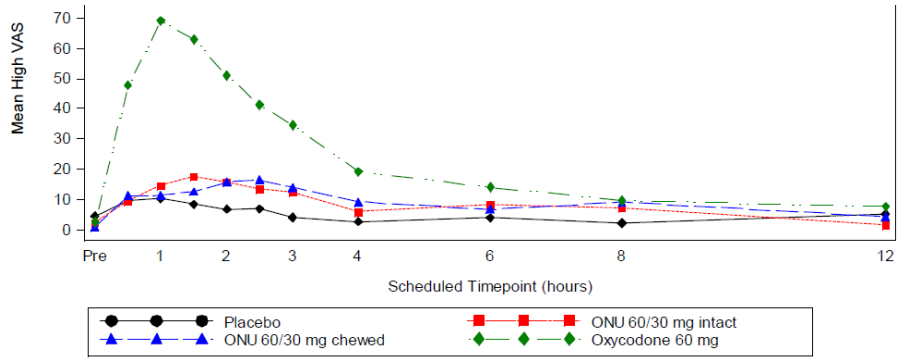


Figure: Mean Scores over Time for "At the Moment" Drug Liking VAS following oral abuse (chewing) of Targiniq (Group 1 – PD Population) compared to oxycodone solution or placebo.



Although in studies ONU1004 and ONU1008 dose dumping was observed with chewed Targiniq ER 60/30 mg, in methadone maintained patients, drug liking was not observed. This observation is significantly different from that noted in healthy non-dependent subjects where drug liking was experienced (Study ONU1003, ONU1007). In addition, there were reports of opioid withdrawal symptoms following oral consumption of chewed Targiniq ER in the methadone-maintained patients.

Figure: Mean Drug Liking (Drug high experienced) Scores over Time for High Visual Analogue Scale in Study ONU1008 ((Methadone-maintained patients)



Drug Liking VAS: "At this moment, my liking for this drug is", where values can range from 0 (strong disliking) to 100 (strong liking) and 50 is the neutral point.

Table: Descriptive statistics of Subjective Opioid Withdrawal Scale score in methadone-maintained patients after receiving different treatments (Study ONU1008).

	Placebo			ONU 60/30 mg intact			ONU 60/30 mg chewed			Oxycodone 60 mg solution		
	Emax	TEmax (h)	TA_AUE	Emax	TEmax (h)	TA_AUE	Emax	TEmax (h)	TA_AUE	Emax	TEmax (h)	TA_AUE
Summary Statistics												
n	29	29	29	29	29	29	29	29	29	28	28	28
Mean	6.8		2.43	4.4		1.55	9.3		2.13	2.7		0.98
SD	7.97		3.605	8.66		3.766	13.54		2.729	2.39		1.187
Median	6.0	1.000	1.13	2.0	1.000	0.50	4.0	1.000	1.38	2.0	1.500	0.62
Min	0	1.00	0.0	0	0.98	0.0	0	0.98	0.0	0	0.98	0.0
Max	37	12.00	17.1	44	12.00	20.3	54	12.00	14.1	9	8.00	4.3
Lower 95% CI	3.8		1.06	1.2		0.12	4.2		1.09	1.8		0.52
Upper 95% CI	9.9		3.80	7.7		2.98	14.5		3.17	3.6		1.44
Q1	1.0		0.29	0.0		0.08	2.0		0.58	1.0		0.08
Q3	9.0		3.04	4.0		1.29	6.0		3.47	4.0		1.31

Source: Page 305 of Study report ONU1008

Figure: Mean Drug Liking Visual Analog Scale Score by Time point and Treatment: Treatment Phase Pharmacodynamic Population (Study ONU1004, Methadone-maintained patients)

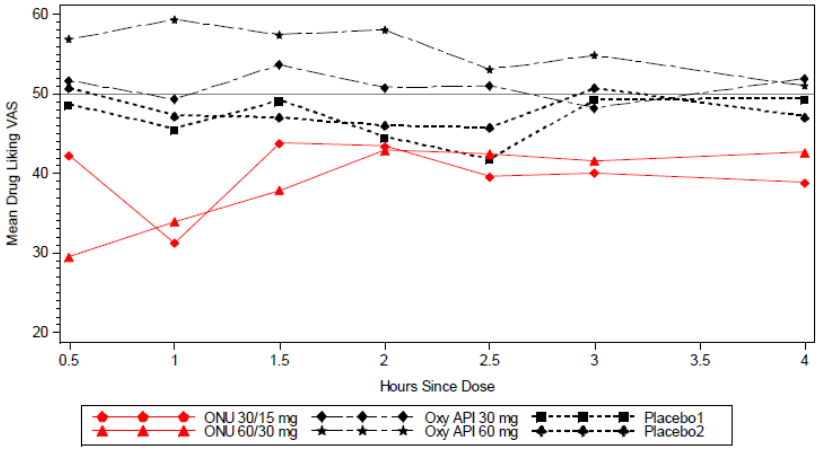
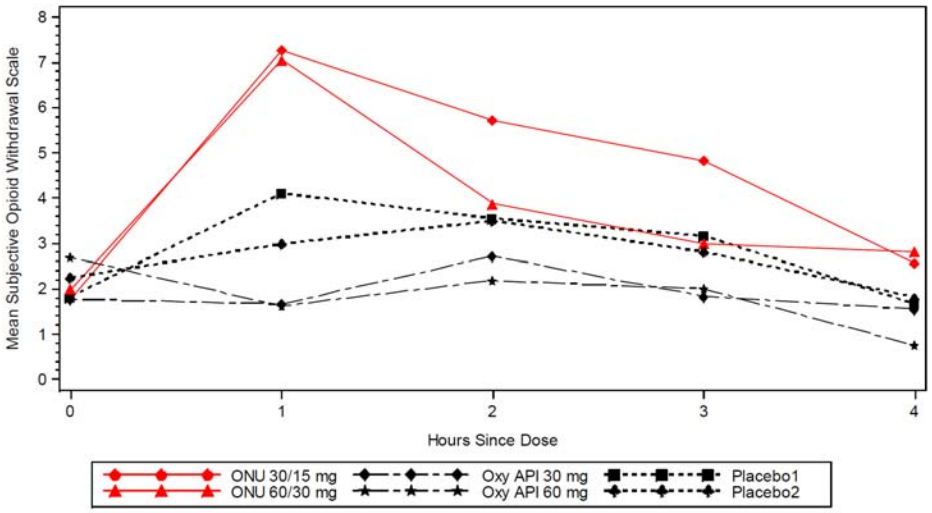
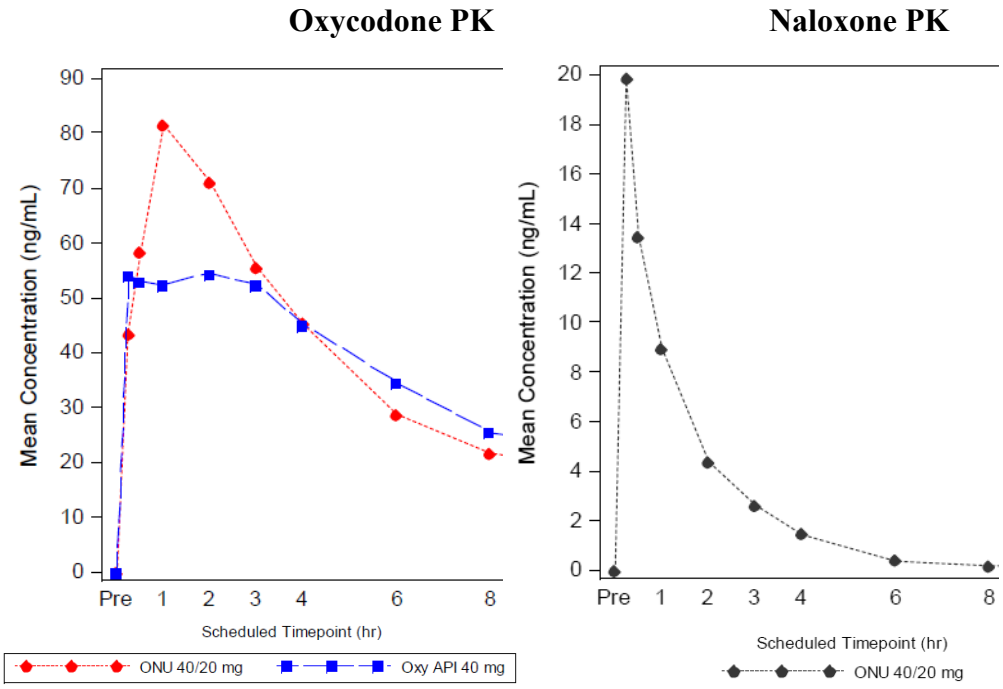


Figure: Mean SOWS by Time point and Treatment: Treatment Phase Pharmacodynamic Population (Study ONU1004, Methadone-maintained patients)



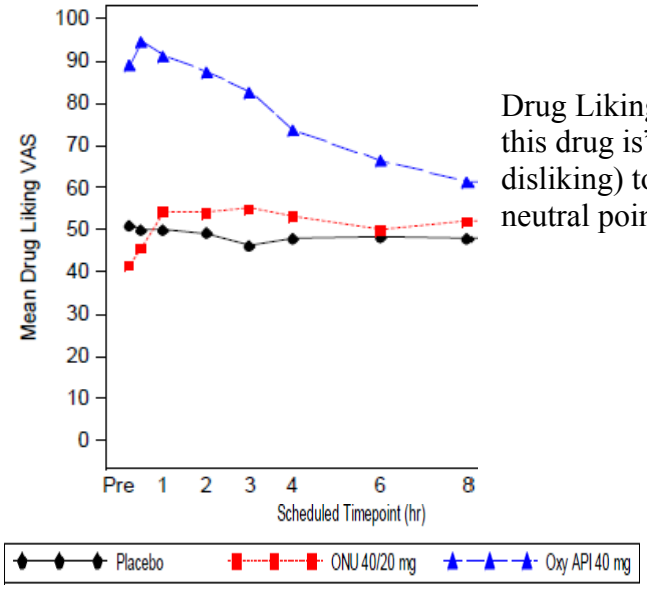
Intranasal administration of crushed product: As noted with oral abuse, extended release characteristics of oxycodone and naloxone are defeated following crushing of Targiniq ER followed by intranasal administration. However, systemic absorption of both oxycodone and naloxone is noted. Peak exposure (Cmax) of oxycodone was higher following administration of crushed OXN compared to OXY API. Total exposure to naloxone via the IN route was much higher than that observed via the oral route (Cmax: 19.3 vs. 0.336 ng/mL; AUC0-t: 27.4 vs. 1.24 hr*ng/mL).

Figure: Plasma oxycodone (left) and naloxone (right) profile following intranasal administration (Study ONU1003) of crushed Targiniq ER (Circles) and oxycodone powder (Squares, left only).



Because of the significant plasma concentrations of naloxone following intranasal administration of crushed Targiniq 40/20 mg, significant number of recreational opioid users did not experience the drug liking as compared to oxycodone powder (See Figure below).

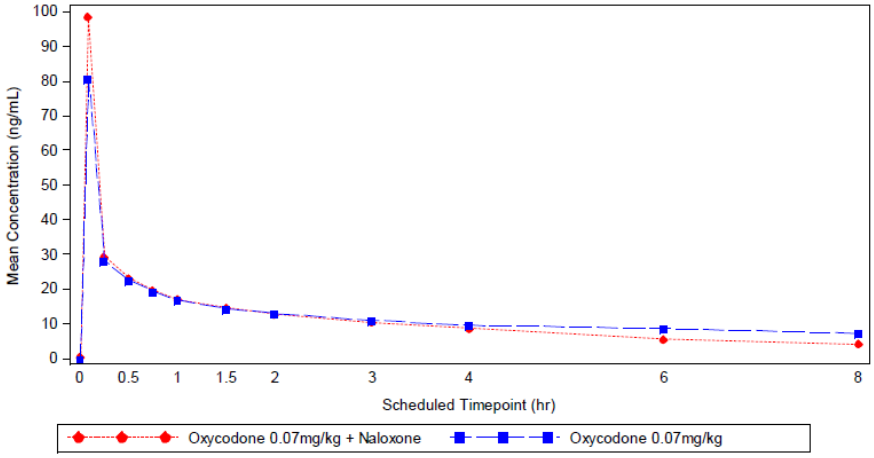
Figure: Mean "At the moment" Drug Liking Visual Analog Scale (VAS) scores over time. (Group 2 Intranasal Pharmacodynamic Population, Study ONU1003)



Drug Liking VAS: "At this moment, my liking for this drug is", where values can range from 0 (strong disliking) to 100 (strong liking) and 50 is the neutral point.

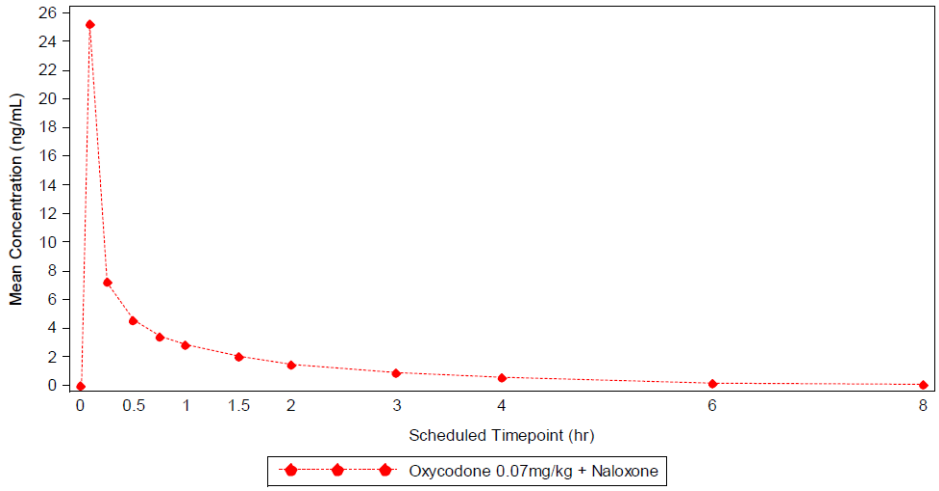
IV administration simulating parenteral abuse: Because it is unsafe to administer particulate matter intravenously, sponsor evaluated drug abuse of intravenously administered clear solution of oxycodone with and without concomitant naloxone administration. Mean plasma oxycodone concentration profiles were similar between IV doses of oxycodone with and without concomitant naloxone, as also evidenced by the almost identical AUC values of oxycodone between.

Figure: Mean Plasma Concentrations of Oxycodone vs Time in Study ONU1003 Following Intravenous Oxycodone Solution With and Without Concomitant Naloxone.



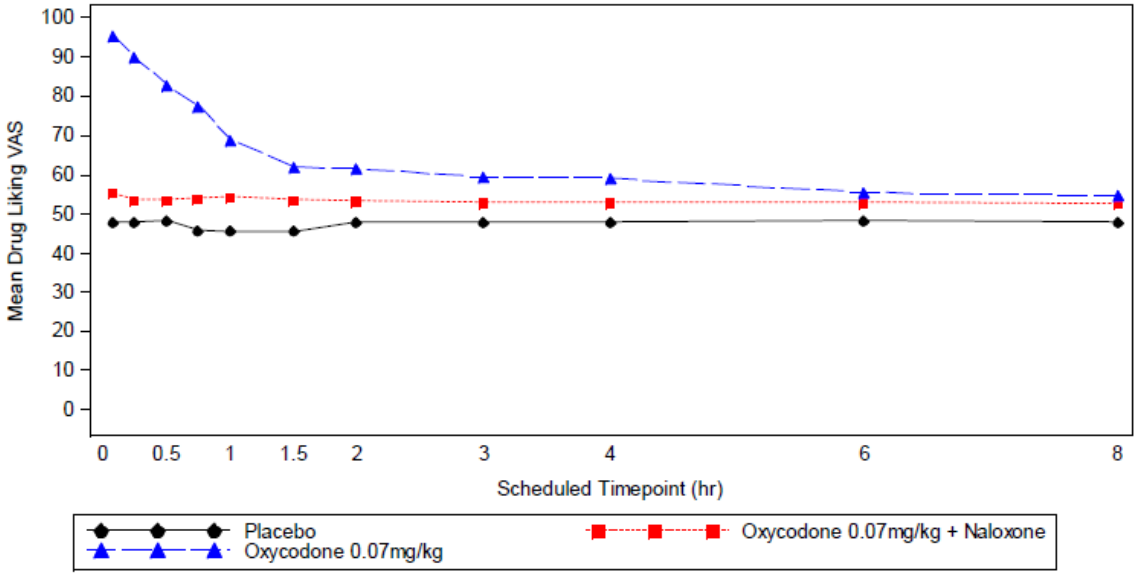
Plasma levels of naloxone were significantly higher following IV administration (0.035 mg/kg, or 2.5 mg for a 70 kg subject) compared to that following oral administration of Targiniq 40/20 mg.

Figure: Mean Plasma Concentrations of Naloxone vs Time in Study ONU1003 Following Intravenous Administration of Naloxone Solution.



Accordingly, significant blockade of opioid effects was noted with regard to drug liking.

Figure: Mean Scores over Time for "At the Moment" Drug Liking VAS in Study ONU1003 (Group 3, Intravenous Pharmacodynamic population).



Drug Liking VAS: "At this moment, my liking for this drug is", where values can range from 0 (strong disliking) to 100 (strong liking) and 50 is the neutral point.

Complete analysis of abuse liability of Targiniq as it relates to different routes of administration was conducted by Dr. James Tolliver of the Controlled Substances Staff.

Systemic Exposure of oxycodone and naloxone following different routes of abuse are described below and compare very differently from intact use of the product described on page 4.

Table: Descriptive Statistics of Oxycodone (left) and Naloxone (right) PK characteristics following different routes of abuse of Targiniq (Study ONU1003).

	Oxycodone PK				Naloxone PK			
Oral Abuse by Chewing of Targiniq 40/20 mg (Group 1)								
	Cmax (ng/mL)	AUClast (h*ng/mL)	AUCinf (h*ng/mL)	Tmax (h)	Cmax (ng/mL)	AUClast (h*ng/mL)	AUCinf (h*ng/mL)	Tmax (h)
Summary Statistics								
n	14	14	14	14	14	14	14	14
Mean	87.51	542.7	552.0		0.4004	1.350	1.548	
SD	24.968	165.56	172.24		0.25377	0.65407	0.69198	
Min	37.8	281	283	0.55	0.140	0.788	0.846	0.25
Median	90.15	549.1	556.7	0.600	0.2920	1.094	1.203	0.550
Max	132	901	922	3.05	0.994	2.74	3.02	1.05
Intranasal Abuse (Group 2)								
	Cmax (ng/mL)	AUClast (h*ng/mL)	AUCinf (h*ng/mL)	Tmax (h)	Cmax (ng/mL)	AUClast (h*ng/mL)	AUCinf (h*ng/mL)	Tmax (h)
Summary Statistics								
n	22	22	22	22	22	22	22	22
Mean	90.10	559.1	588.0		20.15	29.60	29.93	
SD	31.080	130.30	200.64		5.7145	12.507	12.471	
Min	53.9	357	358	0.57	8.48	12.7	12.9	0.28
Median	80.30	550.5	555.7	1.075	19.15	26.01	26.11	0.300
Max	182	807	1306	3.07	32.8	63.3	63.6	0.73
Simulated IV Abuse (Group 3)								
	Cmax (ng/mL)	AUClast (h*ng/mL)	AUCinf (h*ng/mL)	Tmax (h)	Cmax (ng/mL)	AUClast (h*ng/mL)	AUCinf (h*ng/mL)	Tmax (h)
Summary Statistics								
n	24	24	24	24	24	24	24	24
Mean	98.56	94.68	116.4		25.27	12.63	12.73	
SD	44.108	15.510	22.835		11.690	2.5261	2.5523	
Min	26.2	66.9	76.2	0.05	8.95	8.78	8.81	0.05
Median	96.45	91.28	107.8	0.050	24.10	13.05	13.13	0.050
Max	208	137	175	0.22	56.6	17.0	17.1	0.05

Targiniq Pharmacokinetics in Special Populations:

Because of its bioequivalence to OxyContin, Targiniq can be expected to perform similar to OxyContin in special populations with regard to oxycodone pharmacokinetics. Additionally, the impact of any potential difference, if any, in pharmacokinetics of oxycodone is very limited with regard to intrinsic factors as Targiniq is administered by titration to effect.

Nevertheless, the sponsor conducted dedicated studies to evaluate the effect of age, renal impairment and hepatic impairment on PK of oxycodone and naloxone from Targiniq. Additionally, effect of sex, bodyweight/BMI on PK of oxycodone and naloxone from Targiniq was also evaluated based on data from different biopharmaceutics studies. This review will focus on if the magnitude of exposure change is different between oxycodone and naloxone, since these two components cannot be individually adjusted.

Effect of Hepatic Impairment:

Study OXN1006 evaluated the effect of mild, moderate and severe hepatic impairment on pharmacokinetics of oxycodone and naloxone following Targiniq 10/5 mg administration compared to healthy subjects (n=6 for each category).

Oxycodone Pharmacokinetics in HI:
After a single dose of Targiniq 10/5 mg, oxycodone PK was significantly altered in subjects with moderate and severe hepatic impairment, as compared with healthy subjects. GLSM Cmax was about twice as high; GLSM AUC was about 3 times as high in subjects with moderate and severe hepatic impairment; while a much modest increase in systemic exposure was noted in patients with mild hepatic impairment compared to healthy volunteers. This observed increase in systemic exposure of oxycodone with Targiniq in patients with hepatic impairment is similar to that already noted with OxyContin and appropriately described in its product label. Dosing adjustment of Targiniq in patients with hepatic impairment requires additional consideration with regard to naloxone (see below).

Naloxone Pharmacokinetics in HI:

After a single dose of Targiniq 10/5 mg, naloxone concentrations were low in healthy volunteers as noted in different Biopharmaceutics studies. Compared to these low and variable plasma levels, plasma levels of naloxone were found to be higher by orders of magnitude in patients with mild, moderate and severe hepatic impairment (See summary table below). Utilizing the single dose PK data of naloxone from healthy subjects and patients with mild – severe hepatic impairment, simulations were conducted to understand the potential extent of systemic exposure following bid regimen. As noted in the figure below, by the hour 135 (~5.5 days), significantly high concentrations of naloxone are expected in patients with moderate to severe hepatic impairment.

Figure: Observed (left) and simulated (right) mean plasma concentrations of naloxone in healthy volunteers and patients with mild, moderate, and severe hepatic impairment.

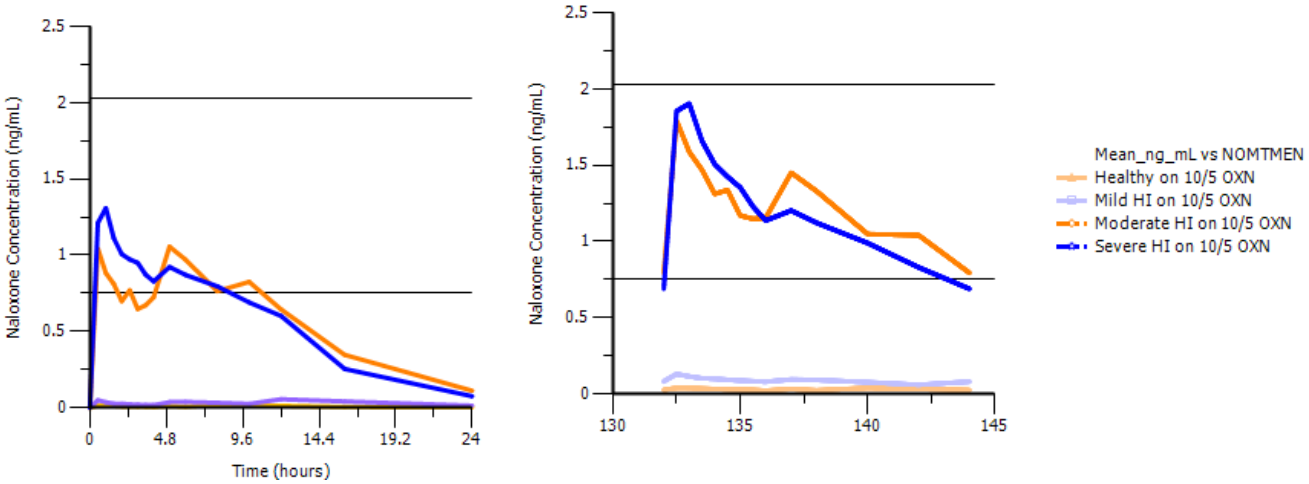


Table: Summary table indicating observed percentage change in Cmax and AUC for oxycodone and naloxone following single Targiniq 10/5 mg administration.

	Oxycodone		**Naloxone**	
	Percent Change in Cmax	**Percent Change in AUC**	**Percent Change in Cmax**	**Percent Change in AUC**
	Food Effect (Study OXN1003)			
Food Effect	↑25%	↑15%	↑75%	↑25 – 65 %
	Hepatic Impairment (HI) (Study OXN1006)			
Mild HI	↑20%	↑43%	↑93%	↑311%
Moderate HI	↑100%	↑219%	↑5192%	↑11418%
Severe HI	↑91%	↑210%	↑5152%	↑10566%
	Renal Impairment (RI) (Study OXN1007)			
Mild RI	↑10%	↑53%	↑976%	↑2750%
Moderate RI	↑35%	↑66%	↑758%	↑3910%
Severe RI	↑67%	↑124%	↑1575%	↑7512%

Effect of Renal Impairment:

Study OXN1007 evaluated the effect of mild, moderate and severe renal impairment on pharmacokinetics of oxycodone and naloxone following Targiniq 10/5 mg administration compared to healthy subjects (n=6 for each category).

Oxycodone Pharmacokinetics in RI:

Following Targiniq 10/5 mg administration, geometric least square mean (GLSM) Cmax of oxycodone was about 10%, 35%, and 67% higher and GLSM AUC of oxycodone was 53%, 66%, and 124% higher in subjects with mild, moderate, and severe renal impairment, respectively, than in subjects with normal renal function. Similar observation of increased systemic levels in patients with severe renal impairment was noted with OxyContin and appropriately described in the product label.

Naloxone Pharmacokinetics in RI:

Following Targiniq 10/5 mg administration, two out of six healthy subjects did not show measurable levels of naloxone at any of the time points evaluated over 24 hours. Similar observation of low and undetectable plasma levels in healthy volunteers has been reported in different biopharmaceutics studies involving use of Targiniq 10/5 mg administration in healthy volunteers.

Compared to healthy volunteers, plasma levels of naloxone were significantly higher in patients with mild, moderate and severe renal impairment (See summary table above).

However, given the fact that observed naloxone levels in healthy subjects were very low and variable, these noted increases do not rise to the same concern as noted with hepatic impairment. Nevertheless, caution should be exercised when administering TARGINIQ to patients with renal impairment because of the potential for precipitating withdrawal symptoms with repeated use and dose titration. Patients with severe renal impairment should start with the lowest strength and be monitored for opioid withdrawal related adverse events, particularly when increasing the dose or maintained at the highest dose.

Effect of Age, Race, Gender and Bodyweight:

Oxycodone PK

There was no significant effect of age, race and gender on pharmacokinetics of oxycodone following administration of Targiniq.

Naloxone PK

Plasma levels of naloxone were low in healthy volunteers of different age, race and gender following administration of Targiniq.

Compared to the low and variable levels of naloxone in young adults, higher steady state naloxone AUC (82% increase) was noted in elderly. The observed increase in naloxone levels is not expected to be clinically significant.

Effect of drug interactions

CYP3A4 is the major enzyme involved in clearance of oxycodone to noroxycodone formation. A drug interaction between OxyContin and ketoconazole resulting in higher exposure of oxycodone is indicated in its product label. Additionally, published report of

a study showing decreased systemic exposure of oxycodone with co-administration of rifampin is also documented in OxyContin label. Naloxone undergoes direct glucuronidation and is unlikely to be affected by CYP3A4 inhibitors and inducers.

Hence, Targiniq ER label will also reflect the noted drug interactions with CYP3A4 inhibitors and inducers.

Labeling Recommendations:

Hepatic Impairment: Lower starting dose may be recommended in patients with mild hepatic impairment with regard to oxycodone PK changes noted. This recommendation is consistent with the described caution in Section 8.6 of OxyContin label.

Use of Targiniq in patients with moderate to severe hepatic impairment should be contraindicated. This recommendation is due to the potential for high naloxone concentrations in moderate to severe renal impairment.

Renal Impairment: Patients with renal impairment (mild, moderate or severe) should be monitored and followed up by a conservative approach to dose initiation and adjust to the clinical situation. This recommendation is also consistent with that described in Section 8.7 of OxyContin label.

2 QBR

2.1 General Attributes

1. What regulatory background or history information contributes to the assessment of the clinical pharmacology and biopharmaceutics of this drug?

Purdue Pharma LLC., submitted NDA 205777 for the approval of Targiniq (oxycodone HCl/naloxone HCl) combination extended release tablets (10/5, 20/10, and 40/20 mg) to manage (b) (4) chronic pain. For this 505(b)(2) NDA, Purdue has conducted the relative bioavailability study ONU1009, which established a pharmacokinetic (PK) bridge of each component of Targiniq (oxycodone and naloxone) to approved NDA products, OxyContin (oxycodone extended release NDA 022272 and its predecessor NDA 020553) and Narcan (Naloxone, NDA 016-636, via an ANDA generic designated as the Reference Listed Drug for Narcan). Targiniq is a combination product that was developed in accordance with 21 CFR 300.50(a), "Fixed combination antagonist containing product to minimize the potential for abuse of the principal active component".

The proposed product is approved under tradename Targin in Europe with an indication to control severe pain while counteracting opioid-induced constipation. Targiniq was initially developed in Europe by Mundipharma Research Limited (Mundipharma, an associated company of PPLP) and first approved in Germany under the proprietary name Targin. Targiniq has been approved in 36 European and other countries since 2006 under several proprietary names (Targin®, Targinact®, or Targiniq®) at 4 dosage strengths (5/2.5 mg, 10/5 mg, 20/10 mg and 40/20 mg) for BID dosing up to a maximum daily dose of Targiniq 80/40 mg.

For this submission, the sponsor is only claiming abuse deterrence properties for the oxycodone naloxone product under conditions of intranasal and intravenous abuse. The sponsor is not seeking approval of an indication for use in patients with opioid-induced constipation.

2. What are the highlights of the formulation of the drug product?

Oxycodone is an μ-opioid agonist with analgesic properties.

Naloxone is a selective μ-opioid antagonist with the capacity a) to block opioid effects of oxycodone and other opioid analgesic drugs; or b) to block actions of opioid agonist type addiction management drugs.

Purdue developed this combination product where both oxycodone and naloxone will be released slowly from the tablet in the GI tract to allow for twice daily administration. Sponsor hypothesizes that naloxone is not significantly absorbed into the systemic circulation via the oral route; however, the released naloxone is adequate for local action of naloxone to improve the GI outcomes (reduced constipation) for oxycodone extended product. Additionally the sponsor hypothesizes that if patients/users try misuse or abuse of product by administering crushed product intranasally or intravenously, adequate naloxone is absorbed into systemic circulation to block opioid effects of oxycodone.

2.2 General Clinical Pharmacology

Targiniq was developed to be bioequivalent to OxyContin. Hence, pharmacokinetics, clinical efficacy of Targiniq may be similar to OxyContin. However, the additional naloxone component, a known opioid antagonist, presented a potential effect on safety and efficacy of extended-release oxycodone product.

Hence, during drug development Purdue was advised that a clinical trial will be needed if any detectable levels of naloxone in systemic circulation were noted. Although systemic levels of naloxone were noted to be low and highly variable following normal use and significantly higher naloxone levels were noted under circumstances resembling opioid drug abuse by chewing, crushing, etc.

Therefore, clinical trial ONU3701 was conducted to establish efficacy and safety of Targiniq in the target population. Despite detectable levels of naloxone in systemic circulation, efficacy of oxycodone in patients were demonstrated in this randomized withdrawal study. Medical officer review by Dr. Elizabeth Kilgore outlines the clinical efficacy of Targiniq with respect to the proposed indication of "Management of (b) (4) (b) (4) pain (b) (4), around-the-clock (b) (4) (b) (4)."

The sponsor also demonstrated that oxycodone PK (not naloxone PK) from Targiniq is dose-proportional (Study OXN 1506) and is bioequivalent to OxyContin (Study ONU1009). In addition, absolute bioavailability of naloxone released from Targiniq was evaluated compared to IV naloxone bolus injection and was found to be less than 1%.

A total of 23 Phase 1 clinical studies and 1 Phase 2 clinical study were conducted as part of the Targiniq clinical pharmacology program to support the Targiniq dosage regimen proposed for US registration. These studies characterized the PK and/or PD properties of Targiniq under normal use situations and conditions of abuse and misuse.

Conditions of normal use and the intrinsic factors such as effect of age, sex, special populations were evaluated with Targiniq.

- ONU1009: Relative bioavailability of Targiniq compared to IV naloxone, Oxycontin and Suboxone.
- OXN1003 (Pilot study Targiniq 10/5 mg, 40/20 mg), OXN1008 (Targiniq 40/20 mg), OXN1009 (Targiniq 10/5 mg) and OXN1505 (Targiniq 80/40 mg): Food-effect studies.
- OXN1506: Dose proportionality study.
- OXN1011 (Targiniq 40/20 mg) and OXN1017 (Targiniq 10/5 mg): Multiple dose PK studies.
- OXN1006: Hepatic impairment study.
- OXN1007: Renal impairment study.

Extrinsic factors such as potential for drug interaction, abuse deterrence after chewing, intranasal and IV abuse associated with Targiniq were also evaluated.

Studies in non-dependent opioid abusers:

- ONU1003: PK and PD of Targiniq following oral, intranasal and IV abuse.
- ONU1007: PK and PD of Targiniq following oral abuse.

Studies in opioid-dependent abusers:

- ONU1004: PK and PD of Targiniq following oral abuse in methadone-maintained patients.
- ONU1008: PK and PD of Targiniq following oral abuse in methadone-maintained patients.

Results of several biopharmaceutics type Phase 1 (OXN1005, OXN1008, OXN1009, OXN 1403) and Phase 2/3 (OXN2401, ONU3701) studies were also examined to understand the variability of the naloxone plasma concentrations and its clinical impact when developmental formulations/European formulations were used. A total of eighteen studies were reviewed as part of this clinical pharmacology submission.

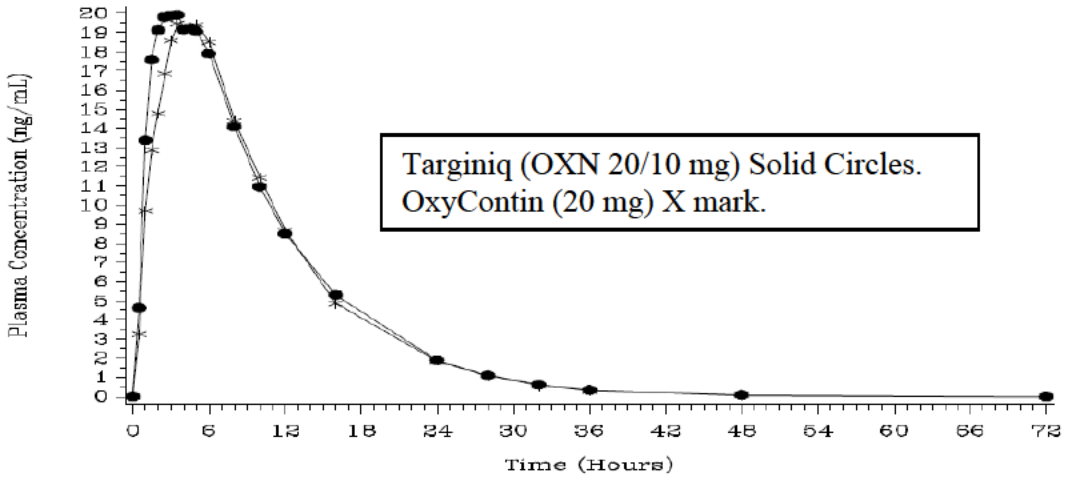
The clinical pharmacology review identifies the plasma levels of naloxone noted following Targiniq use under normal/prescribed use and conditions of abuse/misuse to address its relevance of opioid efficacy and safety with regard to opioid withdrawal effects in opioid non-dependent and opioid-dependent subjects.

The results of these studies generally support the proposed BID dosing regimen and dosage range, within which the exposure of oxycodone from Targiniq is bioequivalent to those from the oxycodone CR marketed products including reformulated OxyContin.

Is Targiniq bioequivalent to OxyContin?

With regard to oxycodone, Targiniq is bioequivalent to OxyContin. In study ONU1009 with regard to plasma concentrations of oxycodone, when comparing the oral ONU 20/10 mg treatment with the oral OxyContin 20 mg treatment, the least squares mean ratios (90% CI) of AUCt, AUCinf, and Cmax were 105.4% (101.6, 109.4), 105.5% (101.6, 109.5), and 106.1% (99.0, 113.7), respectively (See figure below).

Figure: Oxycodone pharmacokinetic profile following oral administration of Targiniq (20/10 mg) and OxyContin (20 mg) (Study ONU1009).



Additionally Study OXN1011 evaluated multiple dose PK of Targiniq 40/10 mg and a European version of OxyContin 40 mg (Oxycodone PR tablet). Targiniq 40/20 mg provided an equivalent availability of oxycodone compared to oxycodone PR tablet in terms of AUCτ, Cmaxss and Cminss, with the 90% confidence intervals for these comparisons falling within the 80-125% limits of acceptability for bioequivalence (See figure and table below). Study OXN1017 conducted to evaluate steady-state plasma oxycodone levels following multiple dose administration of Targiniq (see intrinsic factors).

Figure: Oxycodone pharmacokinetic profile following oral administration of Targiniq (40/20 mg, Closed circles) and European version of OxyContin (Oxycodone PR tablets 40 mg, Open circles Study OXN1011).

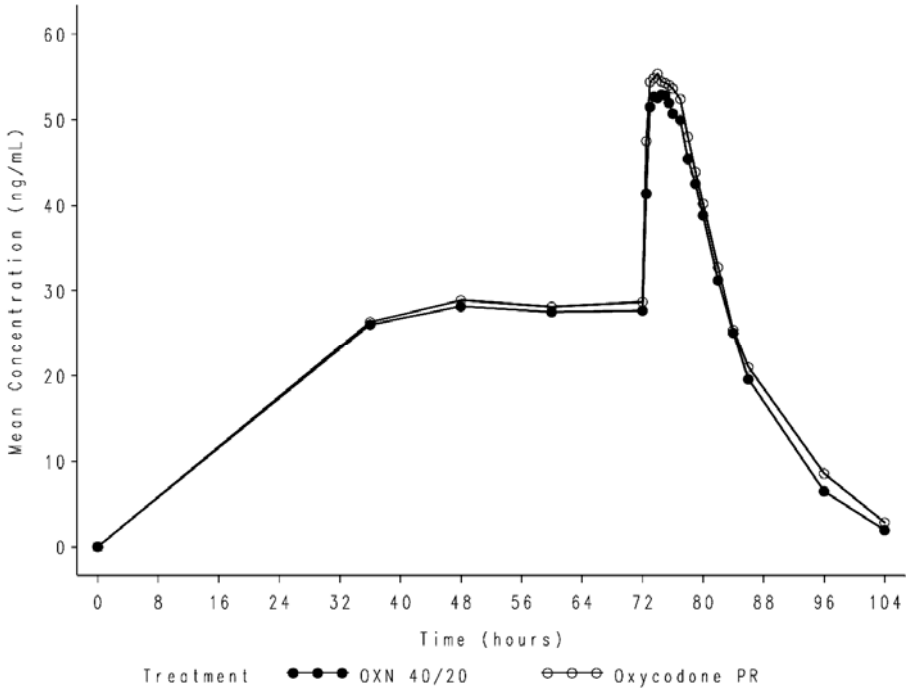


Table: Summary of Ratios for Oxycodone Pharmacokinetic Parameters in Study OXN1011.

PK Metrics	Treatment Comparison	LS Means Ratio[a]	90% Confidence Interval[a] -Lower-	-Upper-
AUCτ (ng.h/ml)	OXN 40/20 vs. Oxycodone PR	96.2	93.09	99.33
Cmaxss (ng/ml)	OXN 40/20 vs. Oxycodone PR	94.6	90.71	98.57
Cminss (ng/ml)	OXN 40/20 vs. Oxycodone PR	99.3	95.22	103.47

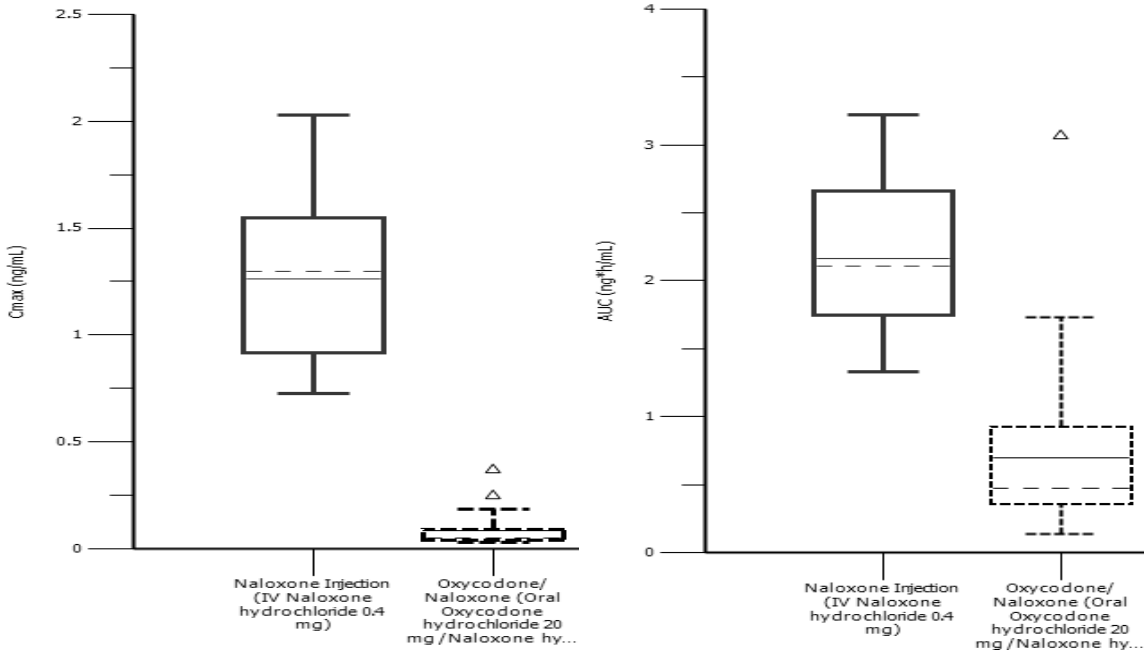
Cross-Reference: Table 14.2.3.1; Appendix 16.2.13.1

[a] Transformed back to the linear scale, expressed as a percent.

What is the absolute bioavailability of naloxone released from Targiniq compared to IV naloxone?

With regard to naloxone, the relative bioavailability of naloxone from ONU 20/10 mg was very low compared with IV naloxone treatment. For dose-normalized AUC0-t, the LS mean ratio (90% CI) for OXN 20/10 mg vs. IV naloxone was 0.765 (0.624, 0.938) %. For dose-normalized Cmax, the corresponding GLSM ratio (90% CI) was 0.134 (0.106, 0.170) %.

Figure: Boxplot indicating naloxone systemic exposure (Cmax and AUC) following IV bolus and Targiniq (20/10 mg) administration.



Agency required a relative bioavailability study ONU1009 comparing naloxone released from Targiniq to IV naloxone. But the sponsor also compared bioavailability of naloxone with a sublingual buprenorphine with naloxone (Suboxone). However, for the purpose of this NDA only results with regard to IV naloxone are being used, since the sponsor has is not seeking that Agency refer to Suboxone NDA for any reason. The relative bioavailability study was required to fulfill the 505(b)(2) requirements to bridge the pertinent safety and efficacy information from Narcan product label. Parenteral naloxone is commonly used in the treatment of reversing opioid overdose. Additionally, parenteral (0.2 to 0.6 mg IM or IV) naloxone challenge test is very commonly used to screen for subjects claiming to be recreational non-dependent users of opioids. Volunteers claiming to be non-dependent users are confirmed when they do not precipitate opioid withdrawal symptoms that include anxiety, increase in blood pressure, sweating etc. Post-dosing PK collection time points for all treatments started at 30 minutes after dose. The first noted plasma concentrations of naloxone (at 30 min) following IV administration were 1.26 ± 0.37 ng/mL (Range 0.725 to 2 ng/mL). Even though the plasma concentrations were first collected at 30 minutes post IV dose, these concentrations are still relevant considering other routes of administration, particularly intramuscular route (Dowling et. al., 2008. Ther. Drug Monit. 30(4). Population Pharmacokinetics of Naloxone).

What are the PK characteristics of naloxone?

Absorption: Naloxone from Targiniq tablets was absorbed with the median Tmax 1.3-5.3 hrs following a single oral dose administration over a range of doses from Targiniq 10/5 mg to Targiniq 80/40 mg (study OXN1506). As described above, absolute oral bioavailability of naloxone from Targiniq tablets was very low (≤ 1%; study ONU1009; Smith et al., 2012 Int J Clin Pharmacol Ther. 2012; 50:360- 367.). However, higher bioavailability was achieved when finely crushed Targiniq 40/20 mg tablets were snorted (approximately 31%; study ONU1003), presumably due to circumvention of the hepatic (and GI) first-pass effect (See Section 2.4 Extrinsic Factors).

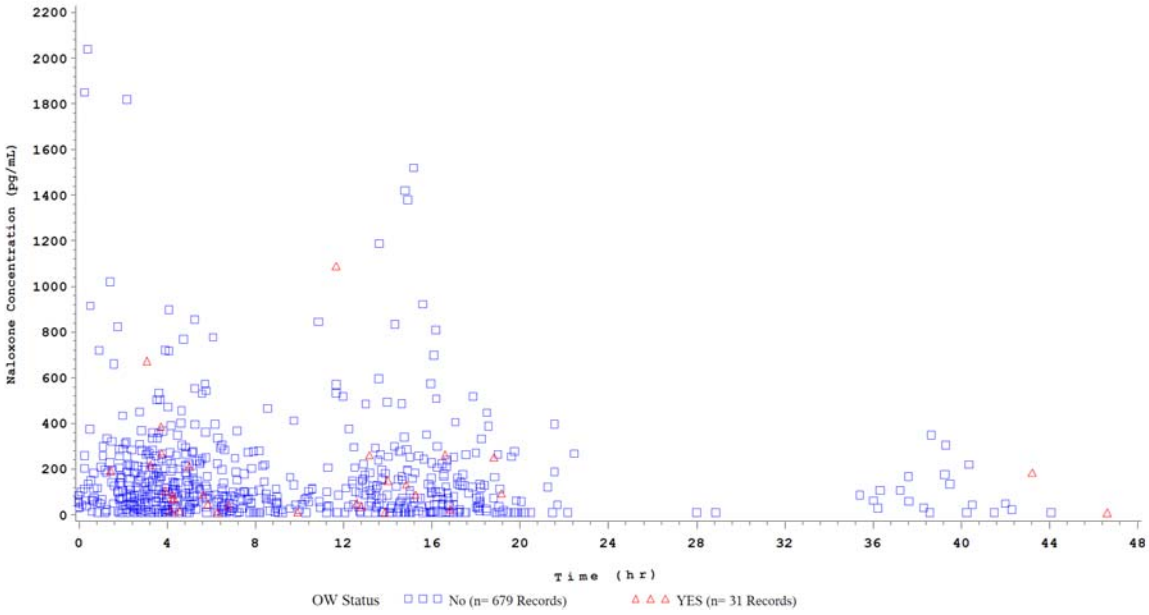
Distribution: Plasma protein binding for oxycodone, measured in the plasma samples from healthy subjects, was <24% (studies OXN1006, OXN1007). Following an IV administration, the mean volume of distribution for oxycodone (0.07 mg/kg) was 245 L, indicating extensive tissue distribution (study ONU1003). Plasma protein binding for naloxone, measured in plasma samples from healthy subjects, was <60% (studies OXN1006, OXN1007). Following an IV administration, the mean volume of distribution for naloxone (0.035mg/kg) was 378 L, indicating extensive tissue distribution (study ONU1003).

Metabolism: Naloxone metabolism is primarily mediated by hepatic and extra-hepatic UGT1A8 and UGT2B7 (Gill et al., 2012 Drug Metabolism and Disposition, 40(4):825-835). Naloxone is mainly metabolized into naloxone-3β-glucuronide, 6β-naloxol and 6β-naloxol-3β-glucuronide. The mean (SD) molar ratio of metabolite to parent (naloxone), as evaluated by AUC across proposed therapeutic doses Targiniq 10/5 mg, Targiniq 20/10 mg and Targiniq 40/20 mg, was 1459 (4206) for naloxone-3β-glucuronide (N=447), 31.5 (73.3) for 6β naloxol (N=360) and 1301 (3380) for 6β-naloxol-3β-glucuronide (N=82), respectively. All known naloxone metabolites are present in plasma at much higher concentrations than the parent drug, especially for naloxone-3β-glucuronide and 6βnaloxol-3β-glucuronide possibly due to extensive first-pass metabolism after oral administration and lower protein binding.

Elimination: Naloxone was eliminated from the body with a mean $t_{1/2}$ approximately of 4.1 to 17.2 hrs after a single oral dose administration of Targiniq in healthy subjects (OXN 10/5 mg to 80/40 mg; study OXN1506). The mean (SD) total plasma clearance was 217 (46.8) L/hr following an IV dose (0.035mg/kg) – exceeding hepatic flow; the mean renal clearance was 7.85-31.9 L/hr following an oral dose of OXN 10/5 mg (study ONU1003, study OXN1006, study OXN1007). This suggests that (first-pass and systemic) hepatic and extra-hepatic metabolism, followed by likely urinary and biliary excretion of the primary and secondary metabolites, may be the major route of elimination. Renal clearance of parent naloxone due to glomerular filtration and possible tubular secretion seems to be minor elimination pathway.

What were the observed naloxone plasma levels in clinical trial ONU3701?

The average plasma naloxone concentrations observed with the use of Targiniq 40/20 mg bid in chronic pain patients were low and highly variable. As indicated in the relative bioavailability study, plasma concentrations noted with IV naloxone (naloxone challenge test) at a 30 minute time point were 1.26 ng/mL. There were a few individuals who had plasma concentrations up to 2 ng/mL; however, these individuals did not exhibit opioid withdrawal symptoms in Study ONU3701.



OW=Opioid Withdrawal. Source: Study ONU3701

2.3 Intrinsic Factors

1. What intrinsic factors (age, gender, race, and organ dysfunction) influence exposure and/or response and what is the impact of any differences in exposure on the pharmacodynamics?

Because of its bioequivalence to OxyContin, Targiniq can be expected to perform similar to OxyContin in special populations with regard to oxycodone pharmacokinetics. Additionally, the impact of any potential difference, if any, in pharmacokinetics of oxycodone is very limited with regard to intrinsic factors as Targiniq is administered by titration to an efficacious dose.

Nevertheless, the sponsor conducted dedicated studies to evaluate the effect of age, renal impairment and hepatic impairment on PK of oxycodone and naloxone from Targiniq. Additionally, effect of sex, bodyweight/BMI on PK of oxycodone and naloxone from Targiniq was also evaluated based on data from different biopharmaceutics studies.

Effect of age

Oxycodone PK

It is generally known, from OxyContin label, that the plasma concentrations of oxycodone are only nominally affected by age, being 15% greater in elderly (greater than 65 years) as compared to young subjects (age 21-45). In Study 1017, following 10/5 mg Targiniq BID administration to steady-state oxycodone plasma concentrations were found to be slightly higher in elderly compared with young adults, but cannot be considered clinically significant. Steady-state oxycodone Cmax and AUC were 14 and 18% higher in elderly compared to young adults.

Naloxone PK

In general, plasma concentrations of naloxone were low and variable in either of the age groups following administration of 10/5 mg Targiniq BID to steady-state. However, average plasma exposure parameters such as Cmin, Cmax, and AUCtau at steady-state were higher in elderly (≥ 65 year old) compared to young adults (18 – 45 years old).

Table: Observed naloxone peak plasma levels in young adults and elderly subjects in study OXN1017.

Variable	AGE GRP	N	Mean	SD	Median	Min	Max
C_{minss}	≥65 yrs age	18	37.86	45.5	29.15	10.5	208
C_{minss}	18 - 45 yrs age	18	15.44	8.8	14.15	0	38.3
AUC_{tau}	≥65 yrs age	18	880.3	903	579.1	227.7	3346.7
AUC_{tau}	18 - 45 yrs age	18	415.7	367.13	289.8	183.3	1749.8
C_{maxss}	≥65 yrs age	18	139.14	166.4	78.4	24.4	633
C_{maxss}	18 - 45 yrs age	18	72.53	88.46	35.7	24	387

In the clinical trial ONU3701, significant number of elderly (>65 yrs old) were recruited. For any given dose administered, it was generally observed that elderly patients had higher systemic concentrations at a noted time point compared to younger patients. However, it is noteworthy that irrespective of age very few subjects exhibited any opioid withdrawal symptoms and corresponding plasma levels in any of the subjects did not seem particularly high.

Effect of Gender:

No clinically meaningful difference in systemic exposure (Cmax and AUC) of oxycodone and naloxone following Targiniq administration was observed in male subjects compared to females to warrant dose adjustment with regard to Sex/Gender of the patient.

Table: Observed plasma naloxone systemic exposure at steady-state following repeated administration of Targiniq 10/5 mg BID (Study OXN1017) in Males and Females.

Statistic	Elderly	Younger	Elderly	Younger
	Male		Female	
AUCτ (pg.h/mL)				
n	8	9	10	9
Geometric Mean	533	391	698	296
Geometric (SD/SE)	0.934/0.330	0.685/0.228	0.721/0.228	0.428/0.143
Mean	840	506	912	326
SD/SE	1048/371	488/163	826/261	174/57.9
Median	494	393	579	252
Min, Max	228, 3347	183, 1750	285, 2979	195, 726
Cmaxss (pg/mL)				
n	8	9	10	9
Geometric Mean	75.9	57.5	97.1	44.1
Geometric (SD/SE)	1.07/0.378	0.863/0.288	0.860/0.272	0.665/0.222
Mean	131	88.3	146	56.7
SD/SE	162/57.2	115/38.3	178/56.4	53.8/17.9
Median	62.8	45.5	78.4	33.7
Min, Max	24.4, 499	24.0, 387	37.3, 633	25.2, 188
Cminss (pg/mL)				
n	8	9	10	9
Geometric Mean	27.4	NA	27.2	NA
Geometric (SD/SE)	0.928/0.328	NA/NA	0.564/0.178	NA/NA
Mean	45.7	17.1	31.6	13.7
SD/SE	66.2/23.4	10.2/3.40	20.2/6.39	7.41/2.47
Median	24.0	17.8	29.2	13.1
Min, Max	10.6, 208	0, 38.3	10.5, 83.0	0, 28.4

Effect of Race:

Clinically significant difference in systemic exposure of oxycodone and naloxone was not observed with regard to race.

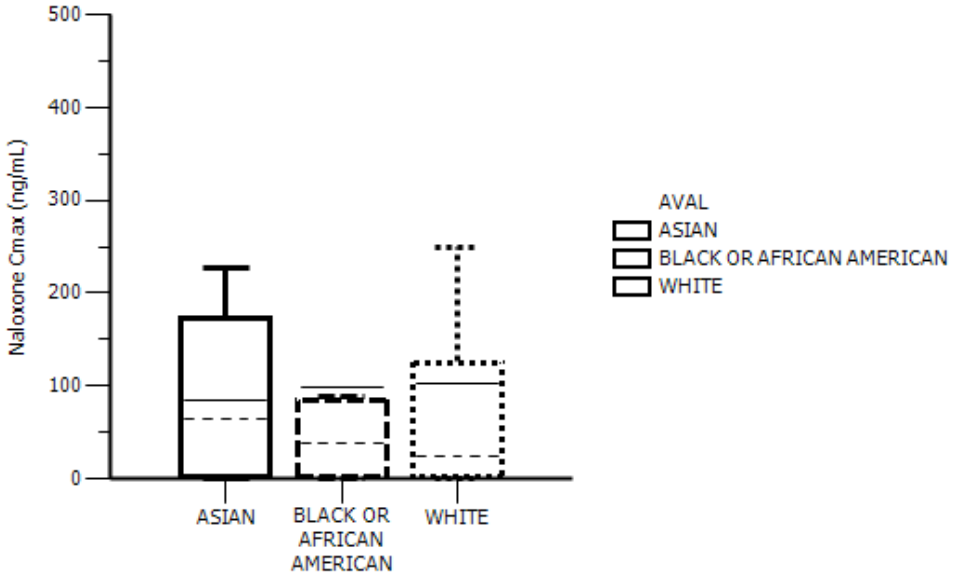
Targiniq is administered by a dose individualization strategy to maximize efficacy and also to avoid safety issues. As such OxyContin does not carry any specific dose adjustment with regard to race. Most of the clinical pharmacology studies were done predominantly in Caucasian subjects with very limited number of Asian, and Black subjects. When data was pooled across different studies no clinically significant difference in terminal elimination half -life of oxycodone was noted.

Table: Descriptive statistics of Mean Plasma Oxycodone half-life in subjects of different race (Asian, Black, Other or White).

RACE	N	Mean	SD	Geometric Mean	90%CI	90%CI
ASIAN	43	4.85	0.93	4.77	3.29	6.41
BLACK OR AFRICAN AMERICAN	49	7.98	4.13	7.09	1.05	14.9
OTHER	44	5.23	1.37	5.08	2.93	7.54
WHITE	1011	4.76	1.24	4.62	2.72	6.79

With regard to naloxone, as such plasma levels were very low and variable when Targiniq 40/20 mg was administered. When data was combined across couple of different biopharmaceutics studies evaluating single dose PK of Targiniq 40/20 mg, clinically significant difference in peak plasma naloxone levels was not observed.

Figure: Box plot showing average, median and 90% CI intervals of naloxone Cmax in Asian, Black/African American, and White subjects administered with Targiniq 40/20 mg.



Effect of Hepatic Impairment:

Study OXN1006 evaluated the effect of mild, moderate and severe hepatic impairment on pharmacokinetics of oxycodone and naloxone following Targiniq 10/5 mg administration compared to healthy subjects (n=6 for each category). Results are described in the table below.

Table: PK Parameter Values (geometric mean [%CV]) of Oxycodone, Naloxone, and Naloxone-3β-glucuronide in Subjects with Varying Degrees of Hepatic Impairment Following a Single Dose of OXN 10/5 mg, and Statistical Results by Level of Hepatic Impairment in Study OXN1006.

Analyte	Healthy, Normal Liver Function OXN 10/5 mg (n =6)			Mild Hepatic Impairment OXN 10/5 mg (n = 6)		
	C_{max} (ng/mL)	t_{max}[b] (hr)	AUC_{0-t} (hr*ng/mL)	C_{max} (ng/mL)	t_{max}[b] (hr)	AUC_{0-t} (hr*ng/mL)
Oxycodone	9.00 (22.0%)	2.0 (1.0-5.0)	96.4 (19.4%)	10.8 (17.8%)	2.8 (1.0-4.0)	138 (25.0%)
Naloxone	0.0278 (64%)	1.5 (0.5-8.0)	0.118 (265%)	0.0537 (84.9%)	0.75 (0.50-12)	0.486 (201%)
Naloxone-3β-glucuronide	22.4 (21.8%)	1.0 (0.5-2.5)	168 (39.9%)	31.4 (19.5%)	1.0 (0.5-2.0)	231 (27.1%)
	Moderate Hepatic Impairment OXN 10/5 mg (n = 6)			Severe Hepatic Impairment OXN 10/5 mg (n = 6)		
	C_{max} (ng/mL)	t_{max}[b] (hr)	AUC_{0-t} (hr*ng/mL)	C_{max} (ng/mL)	t_{max}[b] (hr)	AUC_{0-t} (hr*ng/mL)
Oxycodone	18.1 (16.9%)	3.8 (1.0-6.0)	309 (25.8%)	17.2 (19.4%)	5.0 (4.0-6.0)	300 (32.0%)
Naloxone	1.47 (34.2%)	2.8 (0.5-5.0)	13.6 (30.7%)	1.46 (31.5%)	1.0 (0.5-3.0)	12.6 (47.8%)
Naloxone-3β-glucuronide	26.4 (50.5%)	1.0 (1.0-6.0)	189 (75.5%)	21.9 (39.7%)	1.8 (1.0-2.5)	184 (66.9%)

Statistical Results		
	C_{max} GLSM Ratio (90% CI) Mild Impairment/Healthy	AUC[a] GLSM Ratio (90% CI) Mild Impairment/Healthy
Oxycodone	120 (99.0-144)%	143 (111-184)%
Naloxone	193 (115-324)%	411 (152-1112)%
Naloxone-3β-glucuronide	141 (100-197)%	157 (88.8-279)%
	C_{max} GLSM Ratio (90% CI) Moderate Impairment/Healthy	AUC[a] GLSM Ratio (90% CI) Moderate Impairment/Healthy
Oxycodone	201 (166-242)%	319 (248-411)%
Naloxone	5292 (3148-8896)%	11518 (4259-31149)%
Naloxone-3β-glucuronide	118 (84.5-166)%	128 (72.2-227)%
	C_{max} GLSM Ratio (90% CI) Severe Impairment/Healthy	AUC[a] GLSM Ratio (90% CI) Severe Impairment/Healthy
Oxycodone	191 (158-231)%	310 (241-398)%
Naloxone	5252 (3124-8830)%	10666 (3944-28847)%
Naloxone-3β-glucuronide	98.1 (70.0-138)%	125 (70.6-222)%

[a] AUC for oxycodone and naloxone-3-glucuronide, AUC_{0-t} for naloxone

[b] median (range)

Source: for C_{max} and AUC: ISCP Table D-1, ISCP Table D-2, ISCP Table D-3; for T_{max} and statistical results: OXN1006 CSR Table 10, Table 11, Table 28, Table 29, Table 32, Table 33

Oxycodone Pharmacokinetics in HI:

After a single dose of Targiniq 10/5 mg, oxycodone PK was significantly altered in subjects with moderate and severe hepatic impairment, as compared with healthy

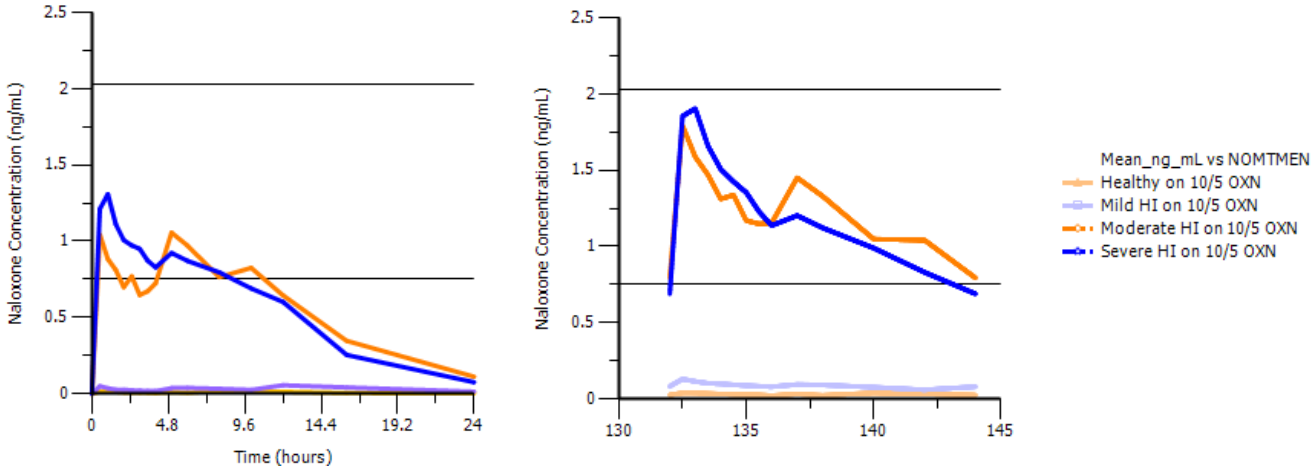
subjects. GLSM Cmax was about twice as high; GLSM AUC was about 3 times as high in subjects with moderate and severe hepatic impairment; while a much modest increase in systemic exposure was noted in patients with mild hepatic impairment compared to healthy volunteers. This observed increase in systemic exposure of oxycodone with Targiniq in patients with hepatic impairment is similar to that already noted with OxyContin and appropriately described in its product label. Dosing adjustment of Targiniq in patients with hepatic impairment requires additional consideration with regard to naloxone (see table above).

Naloxone Pharmacokinetics in HI:

After a single dose of Targiniq 10/5 mg, naloxone concentrations were low in healthy volunteers as noted in different Biopharmaceutics studies. Compared to these low and variable plasma levels, plasma levels of naloxone were found to be higher by orders of magnitude in patients with mild, moderate and severe hepatic impairment (See summary table above).

Utilizing the single dose PK data of naloxone from healthy subjects and patients with mild – severe hepatic impairment, simulations were conducted to understand the potential extent of systemic exposure following bid regimen. As noted in the figure below, by the hour 135 (~5.5 days), significantly high concentrations of naloxone are expected in patients with moderate to severe hepatic impairment.

Figure: Observed (left) and simulated (right) mean plasma concentrations of naloxone in healthy volunteers and patients with mild, moderate, and severe hepatic impairment. Horizontal reference lines are the observed range of naloxone plasma levels in the relative bioavailability study ONU1009 (0.725 – 2 ng/mL) at 30 minute time point following IV administration of naloxone.



Effect of Renal Impairment:

Study OXN1007 evaluated the effect of mild, moderate and severe renal impairment on pharmacokinetics of oxycodone and naloxone following Targiniq 10/5 mg administration compared to healthy subjects (n=6 for each category).

Oxycodone Pharmacokinetics in RI:

Following Targiniq 10/5 mg administration, geometric least square mean (GLSM) Cmax of oxycodone was about 10%, 35%, and 67% higher and GLSM AUC of oxycodone was 53%, 66%, and 124% higher in subjects with mild, moderate, and severe renal impairment, respectively, than in subjects with normal renal function. Similar observation of increased systemic levels in patients with severe renal impairment was noted with OxyContin and appropriately described in the product label.

Naloxone Pharmacokinetics in RI:

Following Targiniq 10/5 mg administration, two out of six healthy subjects did not show measurable levels of naloxone at any of the time points evaluated over 24 hours. Similar observation of low and undetectable plasma levels in healthy volunteers has been reported in different biopharmaceutics studies involving use of Targiniq 10/5 mg administration in healthy volunteers.

Compared to healthy volunteers, plasma levels of naloxone were significantly higher in patients with mild, moderate and severe renal impairment (See summary table above).

Table: Comparison of oxycodone and naloxone plasma Cmax and AUC in patients of mild, moderate and severe renal impairment with healthy volunteers.

Statistical Results		
	C_{max} GLSM Ratio (90% CI) Mild Impairment/Healthy	AUC[a] GLSM Ratio (90% CI) Mild Impairment/Healthy
Oxycodone	110 (93.7-129)%	153 (130-182)%
Naloxone	1076 (154, 7502)%	2850 (369, 22042)%
Naloxone-3β-glucuronide	148 (110-197)%	220 (148-327)%
	C_{max} GLSM Ratio (90% CI) Moderate Impairment/Healthy	AUC[a] GLSM Ratio (90% CI) Moderate Impairment/Healthy
Oxycodone	135 (115-159)%	166 (140-196)%
Naloxone	858 (123, 5981)%	3910 (506, 30243)%
Naloxone-3β-glucuronide	202 (151-271)%	370 (249-550)%
	C_{max} GLSM Ratio (90% CI) Severe Impairment/Healthy	AUC[a] GLSM Ratio (90% CI) Severe Impairment/Healthy
Oxycodone	167 (142-196)%	224 (189-265)%
Naloxone	1675 (240, 11676)%	7612 (984, 58871)%
Naloxone-3β-glucuronide	239 (179-320)%	525 (354-781)%

However, given the fact that observed naloxone levels in healthy subjects were very low and variable, these noted increases do not rise to the same concern as noted with hepatic impairment. Nevertheless, caution should be exercised when administering TARGINIQ to patients with renal impairment because of the potential for precipitating withdrawal symptoms with repeated use or when the dose is increased.

Table: Observed naloxone plasma exposure parameters in healthy subjects or patients with mild, moderate, and severe renal impairment following administration of Targiniq 10/5 mg.

Parameter	Renal Impairment Category	N	Mean (pg/mL)	SD (pg/mL)	Min (pg/mL)	Median (pg/mL)	Max (pg/mL)
Cmax	Healthy	6	34.52	52.2	0	13.85	136
Cmax	Mild	6	99.77	163.4	15.8	29.55	430
Cmax	Moderate	6	48.63	51.05	18.4	25.65	149
Cmax	Severe	6	147.08	208	17.2	41.4	547
Tmax	Healthy	4	2.62	3.61	0.5	1	8
Tmax	Mild	6	4.83	4.27	0.5	4.75	10
Tmax	Moderate	6	7.42	5.31	1	9	12
Tmax	Severe	6	8.17	3.12	5	7	12
AUCall	Healthy	6	124	168.7	0	33.92	381.2
AUCall	Mild	6	1083.7	1918.7	91.8	150.42	4925.7
AUCall	Moderate	6	503.6	281.4	228.85	362.07	864.4
AUCall	Severe	6	1165.7	1234.3	364.35	716.31	3592.7
Source: Table 25 of OXN1007 clinical study report.							

2.4 Extrinsic Factors

The sponsor evaluated various conditions of opioid misuse and abuse as relevant extrinsic factors that could affect PK of Targiniq (ONU1003, ONU1007, ONU1004, and ONU1008). In addition, the sponsor is relying on OxyContin label for describing information pertinent to oxycodone drug interactions with CYP3A4 inhibitors and CYP2D6 inhibitors. Parenteral naloxone does not have any recorded incidence of clinically relevant pharmacokinetic drug interactions. The sponsor submitted an in vitro alcohol interaction study to justify that Targiniq does not dose dump in presence of alcohol.

Targiniq pharmacokinetics and pharmacodynamics under conditions of abuse/misuse:

Targiniq loses its extended release characteristics when administered orally (chewing), intranasally or intravenous after crushing.

Purdue conducted study ONU1007 evaluating drug liking of Targiniq ER 40/20 mg following oral abuse and intranasal abuse in healthy non-dependent recreational opioid users. Purdue also conducted study ONU1003 where pharmacokinetics and pharmacodynamics of Targiniq ER 40/20 mg were evaluated following common methods/conditions of opioid ER product abuse in healthy non-dependent recreational users of opioids. In addition, a drug liking studies were also conducted in methadone-dependent subjects where PK and PD of Targiniq ER was evaluated following oral abuse (Study ONU1004 and Study ONU1008).

Oral abuse following Chewing: Study ONU1007, ONU1003, ONU1004 and ONU1008 all demonstrated Targiniq ER loses extended release characteristics following oral administration after chewing. Both naloxone and oxycodone pharmacokinetic parameters indicated significant increase immediately after oral administration of chewed

product. However, the systemic concentrations of naloxone were not significant enough to block the drug liking effects of oxycodone in recreational drug users.

Figure: Mean plasma oxycodone (left) and naloxone (right) profile over time following administration of intact Targiniq ER (or ONU 40/20 mg-Circles), chewed Targiniq (Squares) and oxycodone API (oxycodone profile only- Triangles) in Study ONU1007.

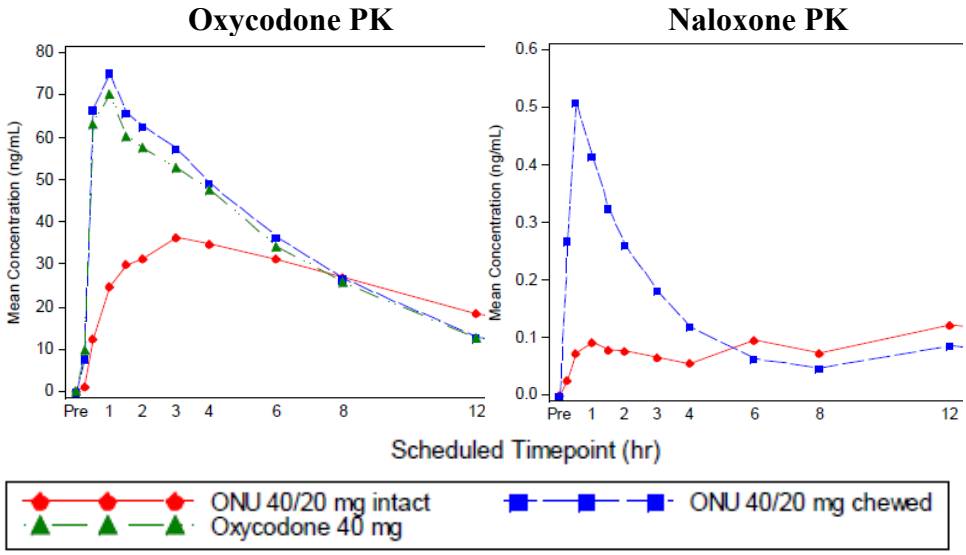


Figure: Mean drug liking profile over time following administration of intact Placebo (circles), intact Targiniq ER (or ONU 40/20 mg-Squares), chewed Targiniq (Triangles) and oxycodone API (diamond).(Group 1, Study ONU1003)

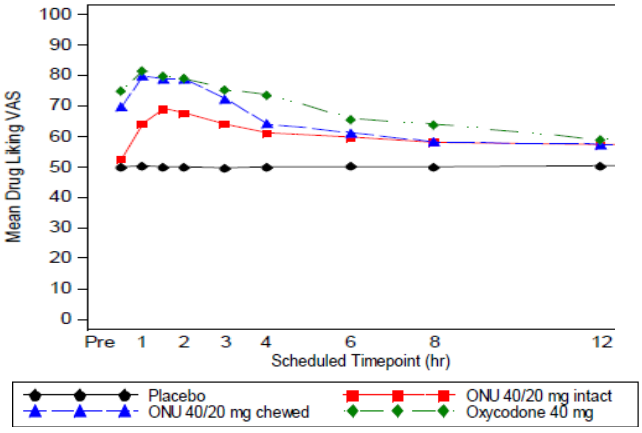


Figure: Mean Oxycodone Plasma Concentrations over Time following oral abuse (Group 1 – PK Population Study ONU1003)

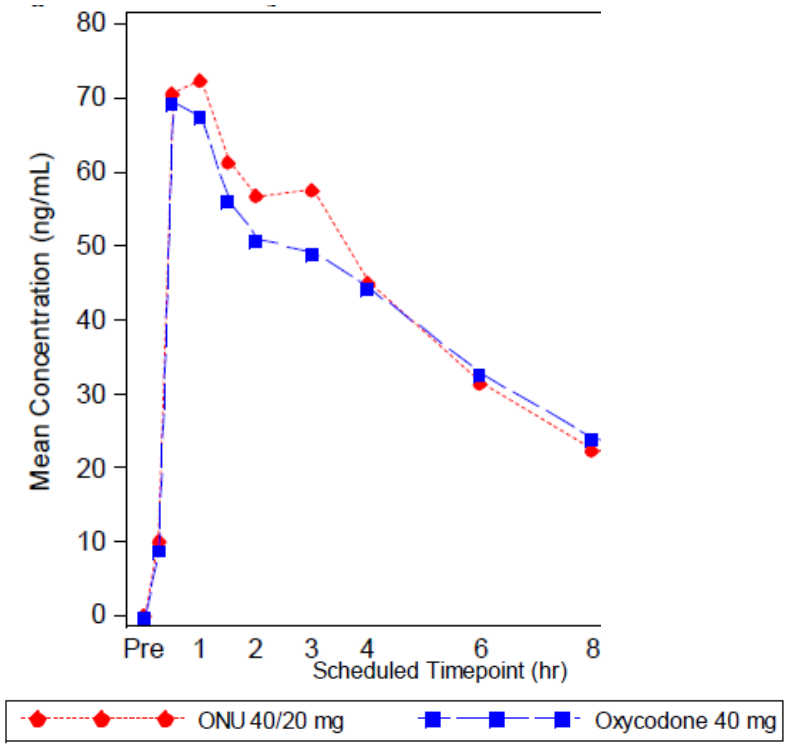
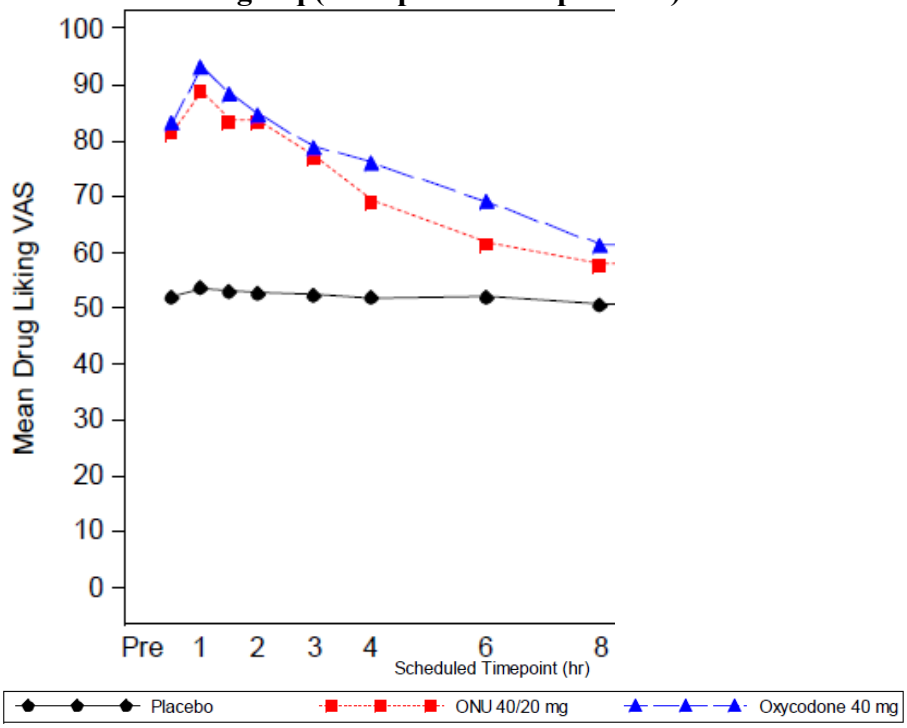
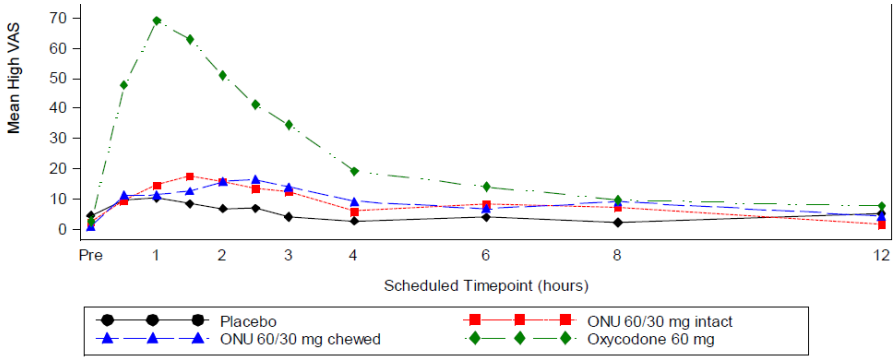


Figure: Mean Scores over Time for "At the Moment" Drug Liking VAS following oral abuse of Targiniq (Group 1 – PD Population)



Although in studies ONU1004 and ONU1008 dose dumping was observed with chewed Targiniq ER 60/30 mg, in methadone maintained patients, drug liking was not observed. This observation is significantly different from that noted in healthy non-dependent subjects where drug liking was experienced (Study ONU1003, ONU1007). In addition, there were reports of opioid withdrawal symptoms following oral consumption of chewed Targiniq ER in the methadone-maintained patients.

Figure: Mean Drug Liking (Drug high experienced) Scores over Time for High Visual Analogue Scale in Study ONU1008 ((Methadone-maintained patients)



Drug Liking VAS: "At this moment, my liking for this drug is", where values can range from 0 (strong disliking) to 100 (strong liking) and 50 is the neutral point.

Table: Descriptive statistics of Subjective Opioid Withdrawal Scale score in methadone-maintained patients after receiving different treatments (Study ONU1008).

	Placebo			ONU 60/30 mg intact			ONU 60/30 mg chewed			Oxycodone 60 mg solution		
	Emax	TEmax (h)	TA_AUE	Emax	TEmax (h)	TA_AUE	Emax	TEmax (h)	TA_AUE	Emax	TEmax (h)	TA_AUE
Summary Statistics												
n	29	29	29	29	29	29	29	29	29	28	28	28
Mean	6.8		2.43	4.4		1.55	9.3		2.13	2.7		0.98
SD	7.97		3.605	8.66		3.766	13.54		2.729	2.39		1.187
Median	6.0	1.000	1.13	2.0	1.000	0.50	4.0	1.000	1.38	2.0	1.500	0.62
Min	0	1.00	0.0	0	0.98	0.0	0	0.98	0.0	0	0.98	0.0
Max	37	12.00	17.1	44	12.00	20.3	54	12.00	14.1	9	8.00	4.3
Lower 95% CI	3.8		1.06	1.2		0.12	4.2		1.09	1.8		0.52
Upper 95% CI	9.9		3.80	7.7		2.98	14.5		3.17	3.6		1.44
Q1	1.0		0.29	0.0		0.08	2.0		0.58	1.0		0.08
Q3	9.0		3.04	4.0		1.29	6.0		3.47	4.0		1.31

Source: Page 305 of Study report ONU1008

Figure: Mean Drug Liking Visual Analog Scale Score by Time point and Treatment: Treatment Phase Pharmacodynamic Population (Study ONU1004, Methadone-maintained patients)

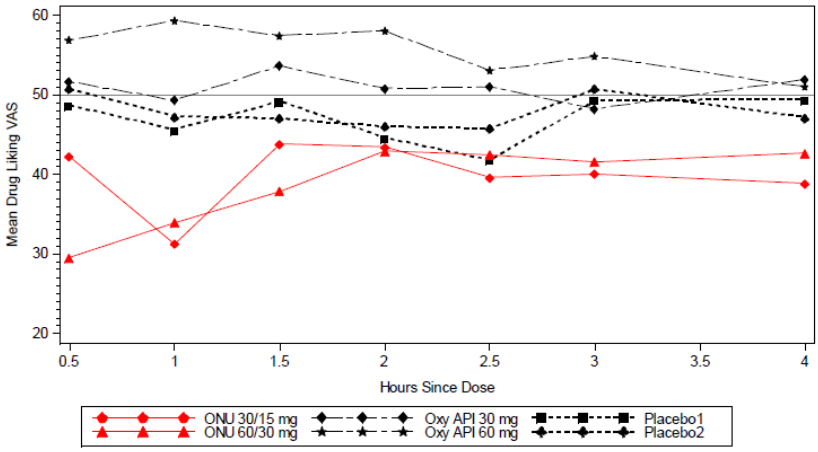
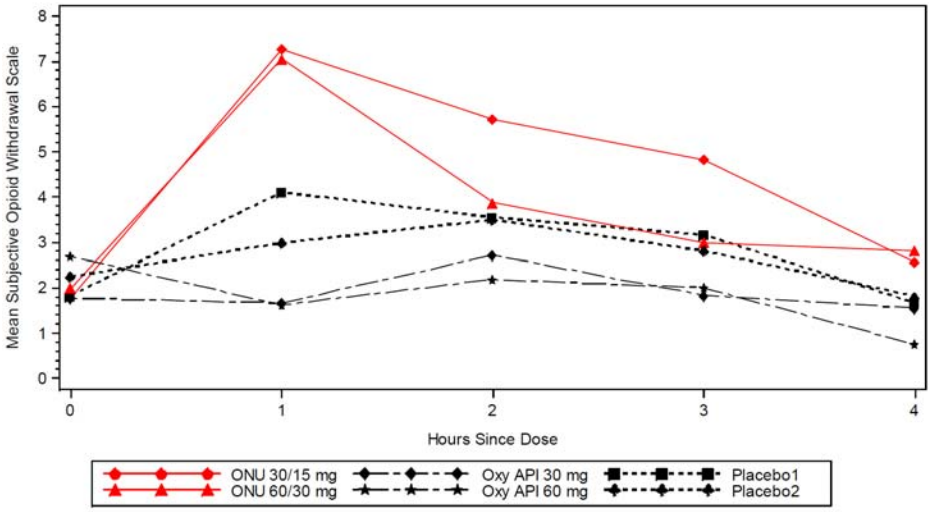
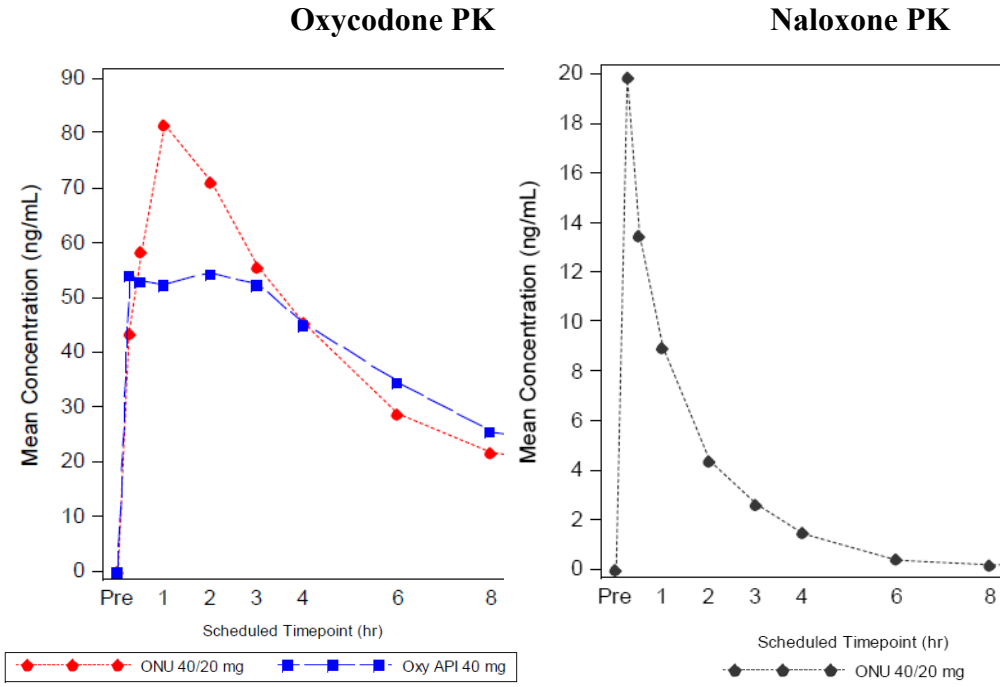


Figure: Mean SOWS by Time point and Treatment: Treatment Phase Pharmacodynamic Population (Study ONU1004, Methadone-maintained patients)



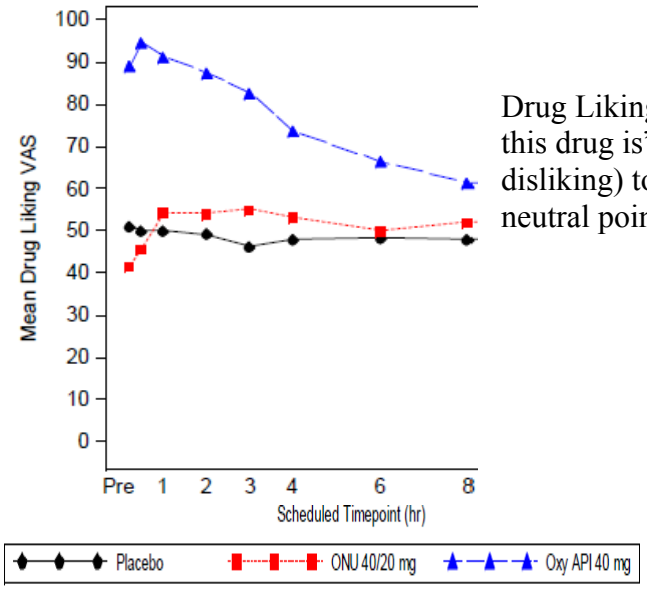
Intranasal administration of crushed product: As noted with oral abuse, extended release characteristics of oxycodone and naloxone are defeated following crushing of Targiniq ER followed by intranasal administration. However, systemic absorption of both oxycodone and naloxone is noted. Peak exposure (Cmax) of oxycodone was higher following administration of crushed OXN compared to OXY API. Total exposure to naloxone via the IN route was much higher than that observed via the oral route (Cmax: 19.3 vs. 0.336 ng/mL; AUC0-t: 27.4 vs. 1.24 hr*ng/mL).

Figure: Plasma oxycodone (left) and naloxone (right) profile following intranasal administration (Study ONU1003, Group 2) of crushed Targiniq ER (Circles) and oxycodone powder (Squares, left only).



Because of the significant plasma concentrations of naloxone following intranasal administration of crushed Targiniq 40/20 mg, significant number of recreational opioid users did not experience the drug liking as compared to oxycodone powder (See Figure below).

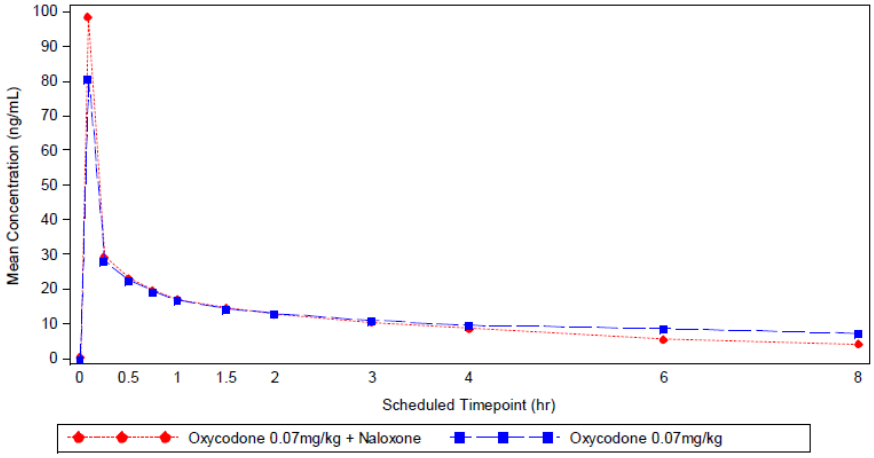
Figure: Mean "At the moment" Drug Liking Visual Analog Scale (VAS) scores over time. (Group 2 Intranasal Pharmacodynamic Population, Study ONU1003)



Drug Liking VAS: "At this moment, my liking for this drug is", where values can range from 0 (strong disliking) to 100 (strong liking) and 50 is the neutral point.

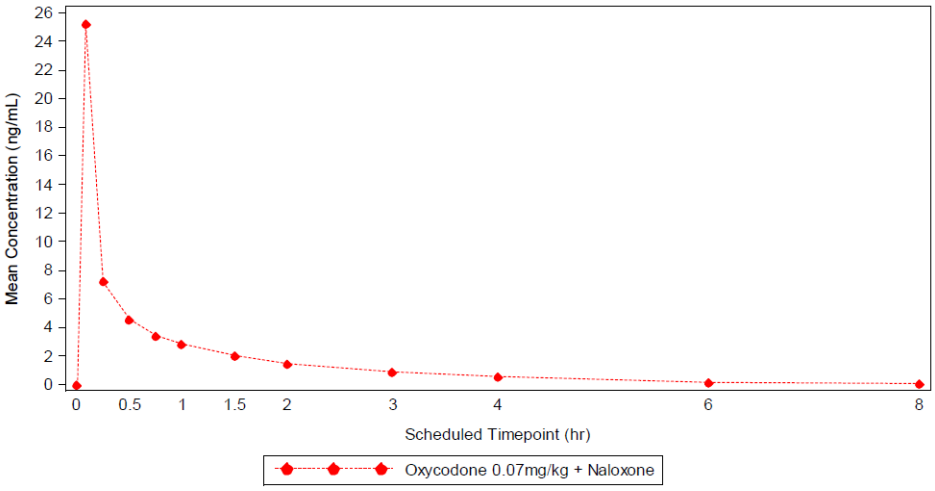
IV administration simulating parenteral abuse: Because it is unsafe to administer particulate matter intravenously, sponsor evaluated drug abuse of intravenously administered clear solution of oxycodone with and without concomitant naloxone administration. Mean plasma oxycodone concentration profiles were similar between IV doses of oxycodone with and without concomitant naloxone, as also evidenced by the almost identical AUC values of oxycodone between.

Figure: Mean Plasma Concentrations of Oxycodone vs Time in Study ONU1003 Following Intravenous Oxycodone Solution With and Without Concomitant Naloxone.

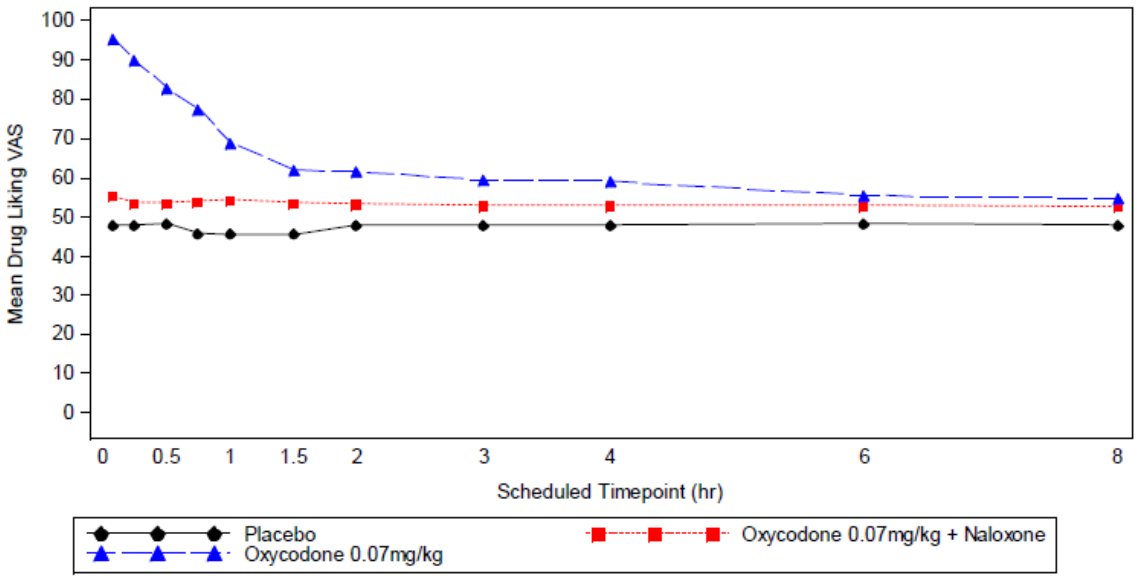


Plasma levels of naloxone were significantly higher following IV administration (0.035 mg/kg, or 2.5 mg for a 70 kg subject) compared to that following oral administration of Targiniq 40/20 mg.

Figure: Mean Plasma Concentrations of Naloxone vs Time in Study ONU1003 Following Intravenous Administration of Naloxone Solution.



Accordingly, significant blockade of opioid effects was noted with regard to drug liking.
Figure: Mean Scores Over Time for "At the Moment" Drug Liking VAS in Study ONU1003 (Group 3, Intravenous Pharmacodynamic population).



Drug Liking VAS: "At this moment, my liking for this drug is", where values can range from 0 (strong disliking) to 100 (strong liking) and 50 is the neutral point.

Complete analysis of abuse liability of Targiniq as it relates to different routes of administration was conducted by Dr. James Tolliver of the Controlled Substances Staff.

Systemic Exposure of oxycodone and naloxone following different routes of abuse are described below and compare very differently from intact use of the product described on page 4.

Table: Descriptive Statistics of Oxycodone (left) and Naloxone (right) PK characteristics following different routes of abuse of Targiniq (Study ONU1003).

	Oxycodone PK				Naloxone PK			
Oral Abuse by Chewing of Targiniq 40/20 mg (Group 1)								
	Cmax (ng/mL)	AUClast (h*ng/mL)	AUCinf (h*ng/mL)	Tmax (h)	Cmax (ng/mL)	AUClast (h*ng/mL)	AUCinf (h*ng/mL)	Tmax (h)
Summary Statistics								
n	14	14	14	14	14	14	14	14
Mean	87.51	542.7	552.0		0.4004	1.350	1.548	
SD	24.968	165.56	172.24		0.25377	0.65407	0.69198	
Min	37.8	281	283	0.55	0.140	0.788	0.846	0.25
Median	90.15	549.1	556.7	0.600	0.2920	1.094	1.203	0.550
Max	132	901	922	3.05	0.994	2.74	3.02	1.05
Intranasal Abuse (Group 2)								
	Cmax (ng/mL)	AUClast (h*ng/mL)	AUCinf (h*ng/mL)	Tmax (h)	Cmax (ng/mL)	AUClast (h*ng/mL)	AUCinf (h*ng/mL)	Tmax (h)
Summary Statistics								
n	22	22	22	22	22	22	22	22
Mean	90.10	559.1	588.0		20.15	29.60	29.93	
SD	31.080	130.30	200.64		5.7145	12.507	12.471	
Min	53.9	357	358	0.57	8.48	12.7	12.9	0.28
Median	80.30	550.5	555.7	1.075	19.15	26.01	26.11	0.300
Max	182	807	1306	3.07	32.8	63.3	63.6	0.73
Simulated IV Abuse (Group 3)								
	Cmax (ng/mL)	AUClast (h*ng/mL)	AUCinf (h*ng/mL)	Tmax (h)	Cmax (ng/mL)	AUClast (h*ng/mL)	AUCinf (h*ng/mL)	Tmax (h)
Summary Statistics								
n	24	24	24	24	24	24	24	24
Mean	98.56	94.68	116.4		25.27	12.63	12.73	
SD	44.108	15.510	22.835		11.690	2.5261	2.5523	
Min	26.2	66.9	76.2	0.05	8.95	8.78	8.81	0.05
Median	96.45	91.28	107.8	0.050	24.10	13.05	13.13	0.050
Max	208	137	175	0.22	56.6	17.0	17.1	0.05

[a] median (range).

Following oral abuse by chewing Targiniq 40/20 releases oxycodone plasma levels comparable to oxycodone solution. However, the released naloxone plasma levels are not adequate to block the opioid drug effects.

Alcohol Interaction:

There was no evidence of rapid or unexpectedly high rates of release of oxycodone or naloxone from OXN tablets in the presence of alcohol up to 40% (v/v) in the dissolution media in vitro. Therefore, there is not expected to be an issue for dose dumping when OXN tablets are taken concomitantly with alcoholic drinks (See Biopharmaceutics

review by Dr. Kareen Riviera). However, due to potential additive effects on sedation and other adverse consequences, alcohol and OXN should not be consumed together.

2.5 General Biopharmaceutics

Targiniq tablet formulations [redacted] stearyl alcohol and ethylcellulose [redacted] lactose monohydrate [redacted] povidone [redacted] Talc and magnesium stearate [redacted]

Food-effect:

Four different food effect studies (OXN1003, OXN1008, OXN1009, OXN 1505) were conducted on different formulations and strengths of Targiniq (See attached synopses). Administration of OXN with standardized high-fat meal did not meaningfully affect the extent of absorption of oxycodone, naloxone or naloxone-3β-glucuronide.

In Study OXN1008 food effect on PK of Targiniq 40/20 mg, the highest strength, was evaluated. As shown in the table below, oxycodone systemic exposure increase by 28% (Cmax) and 14% (AUC). Naloxone plasma levels were higher by 9% (Cmax) and 13% (AUC) in this study.

Table PK Parameters [geometric mean (%CV)] of Oxycodone, Naloxone and Naloxone-3β -Glucuronide and Statistical Analysis Results for Food Effect on the Bioavailability of OXN 40/20 mg Tablets (Study OXN1008)

	Treatment A (Reference) OXN 40/20 mg, Fasted (n = 26)		Treatment B (Test) OXN 40/20 mg, Fed (n = 25)	
Analyte	C_{max} (ng/mL)	AUC (hr*ng/mL)	C_{max} (ng/mL)	AUC (hr*ng/mL)
Oxycodone[a]	37.4 (24.7)	466 (38.2)	47.6 (24.3)	555 (28.8)
Naloxone[a]	0.116 (109)	1.15 (97.1)	0.125 (66.9)	1.38 (67.7)
Naloxone-3β-glucuronide[a]	80.7 (29.1)	550 (29.5)	70.6 (28.9)	568 (26.1)
Statistical Analysis Results				
	C_{max} GLSM Ratio (90% CI)		AUC[a] GLSM Ratio (90% CI)	
	Treatment B/Treatment A		Treatment B/Treatment A	
Oxycodone	128 (118-138)%		114 (109-119)%	
Naloxone	109 (84.8-140)%		113 (99.3-129)%	
Naloxone-3β- Glucuronide	88.4 (81.9-95.4)%		99.7(94.4-105)%	

Abbreviations: AUC = area under the plasma drug concentration-time curve extrapolated to infinity; C_{max} = maximum concentration of drug in plasma; CI = confidence interval; CV = coefficient of variation; GLSM = geometric least squares mean; hr = hour; mL = milliliter; n = number of subjects; ng = nanogram.
[a] AUC for oxycodone and naloxone-3β-glucuronide, AUC_{0-t} for naloxone.
Source: post-text Table D-1, post-text Table D-2, post-text Table D-3; OXN1008 CSR Table 12, Table 14.2.3.6, Table 14

Plasma naloxone levels were low and variable when given under fasting condition in other food effect studies, compared to the fasted condition higher plasma naloxone concentrations were noted when Targiniq(See synopsis of Study OXN1003, OXN1009, OXN1505). Results of food-effect study OXN1003 are described in the summary of

clinical pharmacology findings. Greater increase in systemic levels of naloxone were noted in study OXN1003 (75% increase in Cmax).

Table PK Parameters [geometric mean (% CV)] of Oxycodone, Naloxone and Naloxone-3β -Glucuronide and Statistical Analysis Results for Food Effect on the Bioavailability of OXN 10/5 and OXN 40/20 mg Tablets (Study OXN1003)

Analyte	Treatment A (Test) OXN 40/20 mg, Fed (n = 23)		Treatment B (Test) OXN 10/5 mg, Fed (n = 24)	
	C_{max} (ng/mL)	AUC_{0-t} (hr*ng/mL)	C_{max} (ng/mL)	AUC_{0-t} (hr*ng/mL)
Oxycodone	48.8 (25.0)	574 (33.6)	14.2 (22.2)	146 (33.6)
Naloxone	0.108 (79.9)	0.910 (61.2)	0.0375 (82.4)	0.102 (158)
Naloxone-3β-glucuronide	81.5 (29.5)	696 (31.5)	22.7 (39.1)	165 (38.0)
	Treatment C (Reference) OXN 40/20 mg, Fasted (n = 21)		**Treatment D (Reference)** OXN 10/5 mg, Fasted (n = 27)	
Oxycodone	38.9 (26.4)	489 (35.7)	11.7 (31.3)	130 (33.4)
Naloxone	0.0628 (61.4)	0.772 (76.9)	0.0247 (98.6)[b]	0.116 (140)[b]
Naloxone-3β-glucuronide	83.1 (27.4)	613 (29.4)	22.7 (31.3)	152 (36.5)

Statistical Analysis Results

	C_{max} GLSM Ratio (90% CI)	AUC[a] GLSM Ratio (90% CI)
	Treatment A/Treatment C	Treatment A/Treatment C
Oxycodone	124 (116-132) %	117 (113-122) %
Naloxone	175 (137-223) %	124 (92.9-166) %
Naloxone-3β-glucuronide	97.4 (88.5-107) %	110 (103-118) %
	Treatment B/Treatment D	Treatment B/Treatment D
Oxycodone	124 (117-132) %	113 (109-118) %
Naloxone	171 (134-218) %	165 (124-221) %
Naloxone-3β-glucuronide	98.9 (90.3-108) %	109 (101-117) %

Abbreviations: AUC_{0-t} = area under the plasma drug concentration-time curve from time zero to the last measurable concentration after dosing; C_{max} = maximum concentration of drug in plasma; CI = confidence interval; CV = coefficient of variation; GLSM = geometric least squares mean; hr = hour; mL = milliliter; n = number of subjects; ng = nanogram.

[a] AUC for oxycodone and naloxone-3β-glucuronide; AUC_{0-t} for naloxone.

[b] Mean (%CV)

Source: post-text Table D-1, post-text Table D-2, post-text Table D-3; OXN1003 CSR Table 10, Table 12, Table 14

However, considering the low naloxone levels under fasting condition, the impact of food may not be clinically significant.

In the phase 3 program, patients were allowed to take OXN doses with or without food. Thus, the safety of OXN taken with food has been evaluated in the large numbers of patients who participated in the US clinical studies and in the patients who need pain medications in European and other countries. Thus, collective evidence supports that oxycodone Cmax increases due to food are not clinically important.

2.6 Analytical

For purposes of the human biopharmaceutics and clinical pharmacology sections of this NDA, bioanalytical methods, assay validation results, and in-study assay performance data mainly for 3 key analytes, i.e., oxycodone, naloxone and naloxone-3β-glucuronide in plasma, are presented and summarized.

One method was used to determine concentrations of oxycodone and its 3 metabolites, noroxycodone, oxymorphone, and noroxymorphone, by LC-MS/MS following solid-phase extraction over the concentration range of 0.1 to 50 ng/mL. Another method was also used to determine the concentrations of oxymorphone and noroxymorphone by LC-MS/MS following solid-phase extraction over the concentration range of 0.1 to 10 ng/mL. A method was used to measure concentrations of naloxone and its metabolite, 6β-naloxol, by LC-MS/MS following liquid-liquid extraction over the concentration range of 10 to 1000 pg/mL. A method was used to quantify concentrations of 2 other metabolites of naloxone, naloxone-3β-glucuronide and 6β-naloxol-3β-glucuronide, by LC-MS/MS following protein precipitation over the concentration range of 100 to 10,000 pg/mL. Recently, additional methods were developed and validated to measure the concentrations of oxycodone and buprenorphine by LC-MS/MS following solid-phase extraction over a concentration range of 0.1 to 50 ng/mL for oxycodone and 0.025 to 12.5 ng/mL for buprenorphine. Each method was validated and adopted at each of 3 bioanalytical facilities according to the "then" current guidelines under GLP regulations.

Study No	Sample Matrix	Analyte	Method No	Technique/ Sample Extraction	Validated Conc. Range	Bioanalytical Facility/Location	Assay Validation Report No	Bioanalytical Report No
ONU1001	Plasma	oxycodone	TM 664	LC-MS/MS Solid-phase	0.1– 50 ng/mL	(b) (4)	3351.061505.2	ONU-P-007
		naloxone-3β-glucuronide	TM 913	LC-MS/MS Liquid-liquid phase	0.1 – 50 ng/mL		5857.042709	
ONU1002	Plasma	oxycodone	TM 664	LC-MS/MS Solid-phase	0.1– 50 ng/mL		3351.061505.2	ONU-P-008
		naloxone-3β-glucuronide	TM 913	LC-MS/MS Liquid-liquid phase	0.1 – 50 ng/mL		5857.042709	
ONU1003	Plasma	oxycodone	TM 664	LC-MS/MS Solid-phase	0.1– 50 ng/mL		3351.061505.2	ONU-P-010
		naloxone	TM 912	LC-MS/MS Solid-phase	10 – 5000 pg/mL		5856.042709	
ONU1004	Plasma	oxycodone	TM 664	LC-MS/MS Solid-phase	0.1– 50 ng/mL		3351.061505.2	ONU-P-011
		naloxone	TM 912	LC-MS/MS Solid-phase	10 – 5000 pg/mL		5856.042709	
		methadone	TM1109	Protein precipitation	0.5 – 100 ng/mL		6754.011510	
ONU1007	Plasma	oxycodone	TM 664	LC-MS/MS Solid-phase	0.1– 50 ng/mL		3351.061505.2	ONU-P-018
		naloxone	TM 912	LC-MS/MS Solid-phase	10 – 5000 pg/mL		5856.042709	
ONU1008	Plasma	oxycodone	TM 664	LC-MS/MS Solid-phase	0.1– 50 ng/mL		3351.061505.2	ONU-P-021

Study No	Sample Matrix	Analyte	Method No	Technique/ Sample Extraction	Validated Conc. Range	Bioanalytical Facility/Location	Assay Validation Report No	Bioanalytical Report No
		naloxone methadone	TM 912 TM1109	LC-MS/MS Solid-phase Protein precipitation	10 – 5000 pg/mL 0.5 – 100 ng/mL	(b) (4)	5856.042709 6754.011510	
ONU1009	Plasma	oxycodone buprenorphine naloxone 6β-naloxol naloxone-3β-glucuronide	TM 1238 TM 913	LC-MS/MS Solid-phase LC-MS/MS Liquid-Liquid Extraction	oxycodone: 0.1– 50 ng/mL buprenorphine : 0.025-12.5 ng/mL Naloxone, 6β-naloxol: 0.01-5 ng/mL naloxone-3β-glucuronide: 0.1 – 50 ng/mL		7573.022813 5857.042709	ONU-P-022
OXN1403	Plasma	oxycodone noroxycodone oxymorphone noroxymorphone naloxone 6β-naloxol naloxone-3β-glucuronide	OXYMR00-004:1 OXMMR02-123:1 NLXMR04-127:1 NLXMR04-128:1	LC-MS/MS Solid-phase LC-MS/MS Solid-phase LC-MS/MS Solid-phase LC-MS/MS Solid-phase	oxycodone, noroxycodone: 0.1– 50 ng/mL oxymorphone, noroxymorphone: 0.1– 10 ng/mL naloxone, 6β-naloxol: 0.01 – 1 ng/mL naloxone-3β-glucuronide: 0.1 – 10 ng/mL		OXYVR00-017:1 OXMVR03-040:1 NLXVR04-133:1 NLXVR04-124:1	OXNBR04-143:1
OXN1003	Plasma	oxycodone noroxycodone oxymorphone noroxymorphone naloxone 6β-naloxol naloxone-3β-glucuronide	OXYMR00-004:1 OXMMR02-123:1 NLXMR04-127:1 NLXMR04-128:1	LC-MS/MS Solid-phase LC-MS/MS Solid-phase LC-MS/MS Solid-phase LC-MS/MS Liquid-liquid	Oxycodone, noroxycodone: 0.1– 50 ng/mL oxymorphone, noroxymorphone: 0.1– 10 ng/mL		OXYVR00-017:1 OXMVR03-040:1 NLXVR04-133:1	OXNBR05-002:1
		6β-naloxol-3β-glucuronide	NLXMR04-166:1	LC-MS/MS Protein precipitation LC-MS/MS Protein precipitation	naloxone, 6β-naloxol: 0.01 – 1 ng/mL 6β-naloxol, naloxone-3β-glucuronide 6β-naloxol-3β-glucuronide: 0.1 – 10 ng/mL		NLXVR04-124:1 NLXVR04-174:2	
OXN1008	Plasma	oxycodone noroxycodone oxymorphone noroxymorphone naloxone 6β-naloxol naloxone-3β-glucuronide	TM 543 TM 544 TM 545	LC-MS/MS Solid Phase Extraction LC-MS/MS Liquid-liquid LC-MS/MS Protein precipitation	Oxycodone, noroxycodone, oxymorphone, noroxymorphone: 0.1 – 50 ng/mL Naloxone, 6β-naloxol: 10 – 1000 pg/mL naloxone-3β-glucuronide: 100 – 10000 pg/mL		OXNVR05-051:1 OXNVR05-052:1 OXYVR05-037:1 3353.063005	OXNBR06-006:1
OXN1009	Plasma	oxycodone noroxycodone oxymorphone noroxymorphone naloxone 6β-naloxol naloxone-3β-glucuronide 6β-naloxol-3β-glucuronide	TM 543 TM 544 TM 591	LC-MS/MS Solid Phase Extraction LC-MS/MS Liquid-liquid LC-MS/MS Protein precipitation	Oxycodone, Noroxycodone, oxymorphone, noroxymorphone: 0.1– 50 ng/mL naloxone, 6β-naloxol: 10 – 1000 pg/mL naloxone-3β-glucuronide, 6β-naloxol-3β-glucuronide: 100 – 10000 pg/mL		OXNVR05-051:1 OXNVR05-052:1 NLGVR06-005:1 OXYVR05-037:1	OXNBR06-018:1
OXN1004	Plasma	oxycodone noroxycodone oxymorphone	OXYMR00-004:1	LC-MS/MS Solid Phase Extraction	Oxycodone, Noroxycodone, oxymorphone,		OXYVR00-017:1	OXNBR05-009:1

Study No	Sample Matrix	Analyte	Method No	Technique/ Sample Extraction	Validated Conc. Range	Bioanalytical Facility/Location	Assay Validation Report No	Bioanalytical Report No
		noroxymorphone naloxone 6β-naloxol naloxone-3β-glucuronide 6β-naloxol-3β-glucuronide	OXMMR02-123:2 32-0333 32-0334 32-0408	LC-MS/MS Solid Phase Extraction LC-MS/MS Liquid-Liquid Extraction Protein Precipitation Protein Precipitation	noroxymorphone: 0.1–10 ng/mL Naloxone, 6β-naloxol: 10 – 1000 pg/mL naloxone-3β-glucuronide, 6β-naloxol-3β-glucuronide:100 – 10000 pg/mL	(b) (4)	OXMVR03-040:1 (b) (4) 32-0333 32-0334 32-0408	OXNBR05-031:1 OXNBR05-084:1 NLXBR06-014
OXN1016	Plasma	oxycodone noroxycodone oxymorphone noroxymorphone naloxone 6β-naloxol naloxone-3β-glucuronide 6β-naloxol-3β-glucuronide	TM 543 TM 544 TM 545	LC-MS/MS Solid Phase Extraction LC-MS/MS Liquid-Liquid Extraction LC-MS/MS Protein Precipitation	Oxycodone, Noroxycodone, oxymorphone, noroxymorphone: 0.1–50 ng/mL Naloxone, 6β-naloxol: 10 – 1000 pg/mL naloxone-3β-glucuronide, 6β-naloxol-3β-glucuronide: 100 – 10000 pg/mL		OXNVR05-051:1 OXNVR05-052:1 3353.063005	OXNBR06-008:1 OXNBR06-008:2
OXN1013	Plasma	oxycodone noroxycodone oxymorphone noroxymorphone naloxone 6β-naloxol naloxone-3β-glucuronide	TM 543 TM 544 TM 591	LC-MS/MS Solid Phase Extraction LC-MS/MS Liquid-Liquid Extraction LC-MS/MS Protein	Oxycodone, Noroxycodone, oxymorphone, noroxymorphone: 0.1–50 ng/mL Naloxone, 6β-naloxol: 10 – 1000 pg/mL		OXNVR05-051:3 OXNVR05-052:1 OXYVR05-037:1	OXN-P-028
		6β-naloxol-3β-glucuronide		Precipitation	naloxone-3β-glucuronide, 6β-naloxol-3β-glucuronide: 100 – 10000 pg/mL		NLGVR06-005:1	
OXN1005	Plasma	oxycodone naloxone naloxone-3β-glucuronide	TM 664 TM 544 TM 591	LC-MS/MS Solid Phase Extraction LC-MS/MS Liquid-Liquid Extraction LC-MS/MS Protein Precipitation	oxycodone: 0.1– 50 ng/mL naloxone: 10 – 1000 pg/mL naloxone-3β-glucuronide: 100 – 10000 pg/mL		OXNVR05-051:3 OXNVR05-052:1 NLGVR06-005:1	OXN-P-029
OXN1006	Plasma	oxycodone noroxycodone oxymorphone noroxymorphone naloxone 6β-naloxol naloxone-3β-glucuronide 6β-naloxol-3β-glucuronide	TM 543 TM 544 TM545 TM 591	LC-MS/MS Solid Phase Extraction LC-MS/MS Liquid-Liquid Extraction LC-MS/MS Protein Precipitation	Oxycodone, Noroxycodone, oxymorphone, noroxymorphone: 0.1–50 ng/mL Naloxone, 6β-naloxol: 10 – 1000 pg/mL naloxone-3β-glucuronide, 6β-naloxol-3β-glucuronide: 100 – 10000 pg/mL		OXNVR05-051:3 OXNVR05-052:1 OXYVR05-037:1 NLGVR06-005:1	OXNBR06-017:1
OXN1007	Plasma	oxycodone noroxycodone oxymorphone noroxymorphone naloxone 6β-naloxol naloxone-3β-glucuronide	TM 543 TM 544 TM545 TM 591	LC-MS/MS Solid Phase Extraction LC-MS/MS Liquid-Liquid Extraction LC-MS/MS Protein	Oxycodone, Noroxycodone, oxymorphone, noroxymorphone: 0.1–50 ng/mL naloxone 6β-naloxol: 10 – 1000		OXNVR05-051:3 OXNVR05-052:1 OXYVR05-037:1	OXNBR06-016:1

Study No	Sample Matrix	Analyte	Method No	Technique/ Sample Extraction	Validated Conc. Range	Bioanalytical Facility/Location	Assay Validation Report No	Bioanalytical Report No
		noroxycodone oxymorphone noroxymorphone naloxone naloxone-3β-glucuronide	HFL10061 6/2 HFL10061 6/3	Extraction LC-MS/MS Protein Precipitation	noroxycodone, oxymorphone, noroxymorphone 0.1–50 ng/mL naloxone: 10 – 2500 pg/mL naloxone-3β-glucuronide: 1000 - 250000 pg/mL	(b) (4)	(b) (4) 110867QB 05	
OXN1506	Plasma	oxycodone noroxycodone oxymorphone noroxymorphone naloxone naloxone-3β-glucuronide	HFL10061 6/1 HFL10061 6/2 HFL10061 6/3	LC-MS/MS Solid Phase Extraction LC-MS/MS Protein Precipitation	oxycodone: 0.1-200 ng/mL noroxycodone, oxymorphone, noroxymorphone: 0.1–50 ng/mL naloxone: 10 – 2500 pg/mL naloxone-3β-glucuronide: 1000 - 250000 pg/mL		(b) (4) 110867QB 04 110867QB 03 110867QB 05	QBR110867 QB02
ONU3701	Plasma	oxycodone naloxone naloxone-3β-glucuronide	TM 543 TM 912 TM 913	LC-MS/MS Solid Phase Extraction LC-MS/MS Solid Phase Extraction LC-MS/MS Protein Precipitation	oxycodone: 0.1– 50 ng/mL naloxone: 0.01 – 5 ng/mL naloxone-3β-glucuronide: 0.10 – 50 ng/mL		3351.061505.2 5856.042709 5857.042709 NLGVR06-005:1	ONU-P-016

Abbreviations: oxy = oxycodone; noroxy = noroxycodone; oxym = oxymorphone; noroxym = noroxymorphone; nal = naloxone; nal3 = naloxone-3β-glucuronide; nalo6 = 6β-naloxol; nalo63 = 6β-naloxol-3β-glucuronide; met = methadone; bup = buprenorphine.

3 Labeling

Sponsor proposed text is presented as regular text, reviewers edits are noted as deletions (strikethrough text) or additions (bold text) along with notes to sponsor.

(b) (4)

62 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 Synopsis of relative bioavailability study ONU1009

Title of study: A Single-Center, Randomized, Open-label, 4-Treatment, 4-Period, 4-Way Crossover Study to Assess the Relative Bioavailability of ONU (Oral Oxycodone and Naloxone) as Compared to Sublingual Naloxone, IV Naloxone and Oral Oxycodone.

Objectives:

The primary objectives of this study were:

• To assess the relative bioavailability of oral naloxone in ONU (oxycodone/naloxone) versus sublingual (SL) naloxone in Suboxone® (SL buprenorphine and naloxone) and versus intravenous (IV) naloxone.

• To assess the relative bioavailability of oxycodone in ONU (oxycodone/naloxone) versus oral oxycodone in OxyContin®.

The secondary objective of this study was:

• To assess the safety and tolerability of oral ONU, SL Suboxone, IV naloxone, and oral OxyContin.

Study Design: This was a single-center, randomized, open-label, 4-treatment, 4-period, single-dose crossover study. In each period, subjects received a single dose of study drug followed by pharmacokinetic (PK) blood sample collection up to 72 hours postdose. Treatments were separated by a minimum 7-day washout. There was an optional pharmacogenomic (PG) sampling portion of this study.

Number of subjects (planned and analyzed): No formal sample size calculations were performed.
Thirty subjects (18 males and 12 females) were randomly assigned to a treatment sequence in this study. Twenty-seven subjects completed the study. Thirty subjects were included in the safety and PK analyses. Two subjects (6.7%) were discontinued due to adverse events (AEs) and 1 subject (3.3%) was discontinued due to administrative reasons.

Test product, dose and mode of administration, batch number:
Oxycodone/Naloxone (ONU), single oral dose, 1 × 20-mg oxycodone/10-mg naloxone tablet (Purdue Pharmaceuticals L.P.; Lot number CB-2010-34) was administered orally after a 10-hour overnight fast with 8 ounces (240 mL) of water in the fasted state.

Reference treatment, dose and mode of administration, batch number:
All reference treatments were administered after a 10-hour overnight fast.
• Suboxone, single SL dose, 1 × 2-mg buprenorphine/0.5-mg naloxone SL film (Reckitt Benckiser Pharmaceuticals Inc; Lot number G12DW102)
• IV naloxone, single IV dose, 0.4-mg (1 mL) preloaded Carpuject® syringe (Hospira, Inc; Lot number 20625LL)
• OxyContin, single oral dose, 1 × 20-mg tablet (Purdue Pharmaceuticals L.P.; Lot number WLH41).

Naltrexone hydrochloride (HCl), 50 mg orally every 12 hours; 1 × 50-mg tablet (Lot number 1170U82358) was administered at –12, 0, 12, 24, and 36 hours relative to the ONU, OxyContin, and Suboxone treatments to minimize opioid-related AEs.

Criteria for evaluation:

Pharmacokinetics:

Blood samples for determining oxycodone, naloxone, naloxone-3-glucuronide, 6-β-naloxol, and buprenorphine plasma concentrations were collected during each period for each subject at predose and at 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5, 6, 8, 10, 12, 16, 24, 28, 32, 36, 48, and 72 hours postdose. Plasma concentrations of oxycodone, naloxone, naloxone-3-glucuronide, 6-β-naloxol, and buprenorphine were quantified by a validated liquid chromatography tandem mass spectrometry method.

Safety:

Safety was assessed using recorded AEs, clinical laboratory test results, vital signs, SpO2, physical examinations, and 12-lead ECGs.

Other:

Optional PG evaluation: Blood samples were collected at check-in and 72 hours postdose during period 1 only.

RESULTS:

Pharmacokinetic results:

The PK statistical analyses of relative bioavailability are presented for oxycodone and naloxone in Table 1 and Table 2, respectively.

Table 1: Statistical Analysis of Plasma Pharmacokinetic Metrics of Oxycodone (Full Analysis Population)

	LS Mean[a]				LS Mean Ratio (%) (A/D)[b]	90% CI for LS Mean Ratio[c]
Parameter (Unit)	N	ONU Treatment A	N	OxyContin Treatment D		
AUCt (ng•h/mL)	27	240.2	28	227.8	105.4	(101.6, 109.5)
AUCinf (ng•h/mL)	27	241.6	28	229.0	105.5	(101.6, 109.5)
Cmax (ng/mL)	27	21.8	28	20.5	106.1	(99.0, 113.7)

Abbreviations: CI, confidence interval; LS, least squares; ONU, oxycodone/naloxone controlled-release tablets.

Note: A linear mixed model on the natural logarithms (ln) of the pharmacokinetic metrics was performed with treatment, sequence, and period as fixed effects and subject within sequence as a random effect.

Treatment A = Oxycodone/Naloxone (oral oxycodone HCl 20 mg/naloxone HCl dehydrate 10 mg).

Treatment D = OxyContin (oral oxycodone HCl 20 mg).

[a] Least squares mean from analysis of variance. Least squares means were calculated by transforming the ln means back to linear scale, ie, geometric means.

[b] Ratio of LS means (expressed as a percentage). Ln-transformed difference was transformed back to linear scale to obtain the ratio of geometric LS means.

[c] The 90% CI for ratio of metric means (expressed as a percentage). Ln-transformed confidence limits were transformed back to linear scale.

Source: Table 14.2.3.1.

For oxycodone, when comparing the oral ONU 20/10 mg treatment with the oral OxyContin 20 mg treatment, the least squares mean ratios (90% CI) of AUCt, AUCinf, and Cmax were 105.4% (101.6, 109.4), 105.5% (101.6, 109.5), and 106.1% (99.0, 113.7), respectively. These results indicate equivalent bioavailability of oxycodone for the 2 treatments.

Table 2: Statistical Analysis of Dose-normalized Plasma Pharmacokinetic Metrics of Naloxone (Full Analysis Population)

Parameter (Unit)	N	ONU Treatment A	N	Reference Treatment C (Naloxone)		LS Mean Ratio (%) (A/C)[b]	90% CI for LS Mean Ratio[c]
AUCt/Dose (ng*h/mL/mg)	27	0.049	29	C	6.401	0.765	(0.62, 0.94)
Cmax/Dose (ng/mL/mg)	27	0.006	29	C	4.652	0.134	(0.11, 0.17)

Abbreviations: CI, confidence interval; LS, least squares; ONU, oxycodone/naloxone controlled-release tablets.

Note: A linear mixed model on the natural logarithms (ln) of the pharmacokinetic metrics was performed with treatment, sequence, and period as fixed effects and subject within sequence as a random effect.

Treatment A = Oxycodone/Naloxone (oral oxycodone HCl 20 mg/naloxone HCl dehydrate 10 mg).

Treatment C = Naloxone injection (IV naloxone HCl 0.4 mg).

[a] Least squares mean from analysis of variance. Least squares means were calculated by transforming the ln means back to linear scale, ie, geometric means.

[b] Ratio of LS means (expressed as a percentage). Ln-transformed difference was transformed back to linear scale to obtain the ratio of geometric LS means.

[c] The 90% CI for ratio of metric means (expressed as a percentage). Ln-transformed confidence limits were transformed back to linear scale.

For Treatment C, the back-extrapolated parameter C0 was used for the statistical comparisons of Cmax.

Source: Table 14.2.3.5.

The bioavailability of naloxone from ONU 20/10 mg versus IV naloxone was less than 1% as measured by dose-normalized AUCt.

4.2.2 Synopsis of Study ONU1003

Study Title

A Single-Center, Randomized, Double-Blind Study in Recreational Opioid Users to Evaluate the Abuse Potential, Pharmacokinetics, and Safety of Oxycodone/Naloxone (ONU) Tablets Administered via the Oral, Intranasal and Intravenous Routes.

Objectives

Objectives - Oral Administration (Group 1)

- To evaluate oral abuse potential and pharmacodynamic (PD) effects of chewed ONU compared to oxycodone oral solution and placebo in healthy, adult recreational opioid users with a history of oral chewing abuse/misuse
- To evaluate the safety and tolerability of orally administered chewed ONU in healthy, adult recreational opioid users with a history of oral chewing abuse/misuse
- To determine the comparative pharmacokinetic (PK) profile of orally administered chewed ONU compared to oxycodone oral solution

Objectives - Intranasal (IN) Administration (Group 2)

- To evaluate intranasal abuse potential and PD effects of crushed ONU compared to oxycodone active pharmaceutical ingredient (Oxy API) and placebo in healthy, adult recreational opioid users with a history of intranasal abuse/misuse.
- To evaluate the safety and tolerability of intranasally administered crushed ONU in healthy, adult recreational opioid users with a history of intranasal abuse/misuse.
- To determine the comparative PK profile of intranasally administered crushed ONU compared to Oxy API.

Objectives - Intravenous (IV) Administration (Group 3)

- To evaluate intravenous abuse potential and PD effects of oxycodone/naloxone compared to oxycodone alone, and placebo in healthy, adult recreational opioid users.
- To evaluate the safety and tolerability of intravenously administered oxycodone/naloxone in healthy, adult recreational opioid users.
- To determine the comparative PK profile of intravenously administered oxycodone/naloxone compared to oxycodone alone.

Methodology

This was a single-center, double-blind, parallel-group, randomized crossover study to evaluate the abuse potential of ONU in healthy non-dependent recreational drug users with moderate experience with opioids and to evaluate the safety and PK profiles of both oxycodone and naloxone, when administered orally, IN, or IV. Subjects were divided into 3 parallel groups, separated by route of administration.

The study consisted of 4 phases:

- Screening: Visit 1 for inclusion/exclusion screening and Visit 2 for a Naloxone Challenge to screen for symptoms of opiate withdrawal.
- Qualification: Visit 3 for a randomized, crossover pharmacologic qualification (oxycodone and placebo) to ensure tolerability and appropriate reporting of positive subjective effects.

- Treatment: Visit 4 to Visit 6 where each of the following single-dose treatments were administered (1 per visit), by Group:
    - Group 1: ONU 40/20 mg tablet, chewed/placebo solution, oxycodone oral solution 40 mg/placebo tablet, chewed, and placebo solution/placebo tablet, chewed
    - Group 2: ONU 40/20 mg, finely crushed, Oxy API powder 40 mg, and placebo (lactose powder)
    - Group 3: Oxycodone 0.07 mg/kg/naloxone placebo, oxycodone 0.07 mg/kg/naloxone 0.035 mg/kg, and oxycodone placebo/naloxone placebo
- Follow-up: Visit 7 for a safety follow-up, 3 to 7 days after the last Treatment Phase drug administration.

Study Treatments (including dose, mode of administration, and batch numbers)

Group 1:

ONU 40/20 mg, chewed oral (Purdue Pharmaceuticals, L.P.; lot number: CB-2010-35)
Oxycodone 40 mg, oral solution ((b) (4); lot numbers: 6CC, 19CC)
ONU placebo tablets, oral ((b) (4).; lot number: CB-2009-24)

Group 2:

ONU 40/20 mg, crushed IN (Purdue Pharmaceuticals, L.P.; lot number: CB-2010-35)
Oxy API 40 mg, IN ((b) (4); lot number: 24-10XYK)
Lactose powder, IN ((b) (4); lot number: 09050043; Purdue Pharmaceuticals, L.P.; lot number: 10100037)

Group 3:

Oxycodone 0.07 mg/kg, IV ((b) (4); lot numbers: 6CC, 19CC)
Naloxone HCl 0.035 mg/kg, IV ((b) (4); lot number: AR2903)

Endpoints

Pharmacodynamic:

The primary measures consisted of the Drug Liking ("at this moment") visual analog scale (VAS), Overall Drug Liking VAS, Addiction Research Center Inventory (ARCI) Morphine-Benzedrine Group (MBG) scale, and Subjective Drug Value (SDV). Secondary measures were included to evaluate other subjective effects including balance of effects (Take Drug Again VAS); positive effects (High VAS, Good Effects VAS); negative effects (Bad Effects VAS, Feeling Sick VAS); sedative effects (Drowsiness/Alertness VAS); other effects (Any Effects VAS); and pupillometry was used as an objective measure of opioid effects. For Group 2, subject- and observer-rated assessments of intranasal irritation, including endoscopy, were also used to evaluate negative drug effects.

Pharmacokinetic:

Plasma concentrations of oxycodone were analyzed for all treatments. Pharmacokinetic parameters were derived to examine treatment differences in exposure to oxycodone and naloxone within each group.

Safety:

The following safety measures were evaluated: adverse events (AEs), vital signs, clinical laboratory assessments, 12-lead electrocardiograms (ECGs), concomitant medications, and physical examinations.

Results: Pharmacodynamics

Group 1 (Oral)

The following conclusions are based on the results of a descriptive analysis of 14 subjects studied from a planned number of 24 subjects, evaluating the oral (chewed ONU) route of administration.

- Mean Drug Liking VAS Emax (primary) for chewed ONU and oxycodone oral solution were similar and within the "strong liking" range, and were clearly distinct from PBO, which was near neutral;
- The time course and magnitude of mean Drug Liking scores were similar for ONU when chewed prior to ingestion compared to oxycodone oral solution;
- Both oxycodone oral solution and chewed ONU showed prominent responses on the primary and secondary global measures of balance of effects (Overall Drug Liking VAS, Take Drug Again VAS, SDV) compared to PBO, but did not differ notably from each other;
- As observed with measures of balance of effects, positive, sedative and any effects of chewed ONU were similar to those reported for oxycodone oral solution, though slightly lower. Both active treatments separated from placebo;
- Overall, negative effects were minimal for all treatments;
- The miotic response to chewed ONU was slightly weaker compared to that observed with oxycodone oral solution, though both produced considerable pupil constriction.

Group 2 (Intranasal)

- 'At the moment' Drug Liking (primary) of intranasally administered Oxy API was significantly higher compared to PBO and crushed ONU. While crushed ONU was significantly liked relative to PBO, the median difference in peak Drug Liking scores was 0. In addition to lower Emax, Emin of Drug Liking for crushed ONU was significantly lower compared to Oxy API, and in the disliking range (<50);
- Administration of Oxy API resulted in a significantly higher Emax compared to PBO and crushed ONU on SDV, Take Drug Again VAS, and Overall Drug Liking VAS measures. In contrast with the 'at the moment' Drug Liking VAS results, Emax for crushed ONU were observed to be not statistically different from that of PBO for any of these global measures of balance of effects;
- On ARCI MBG, the primary measure of positive effects, Emax for Oxy API was significantly higher than PBO and crushed ONU, which did not differ from each other. For both secondary measures of positive effects, Emax for intranasally administered Oxy API and crushed ONU were significantly higher than PBO, and Emax was significantly lower for crushed ONU compared to Oxy API;
- Oxy API and crushed ONU had larger negative effects relative to PBO, but were not different from each other. Overall, negative effects were minimal and there was little intranasal irritation observed for any of the treatments, though nasal burning and congestion were observed to be higher for crushed ONU compared to PBO;
- For sedative and any effects, both Oxy API and crushed ONU had significantly greater effects compared to PBO; however, the magnitude of sedative and any effects was significantly lower for crushed ONU compared to Oxy API;

- For the objective measure of pupillometry, MPC was observed to be statistically significantly higher for both Oxy API and crushed ONU compared to PBO, but MPC was significantly lower following intranasal administration of crushed ONU versus Oxy API.

Group 3 (Intravenous)

- 'At the moment' Drug Liking VAS (primary) Emax values for both oxycodone alone and oxycodone/naloxone co-administration were significantly higher than PBO. However, the median difference between Emax of oxycodone/naloxone and PBO was 0, demonstrating that the effect of oxycodone/naloxone on Drug Liking was marginal. As expected, co-administration of naloxone significantly reduced Emax of Drug Liking for oxycodone;
- Intravenous administration of oxycodone resulted in a significantly higher Emax compared to PBO and oxycodone/naloxone on all global measures of balance of effects. Emax for oxycodone/naloxone were observed to be not statistically different from that of PBO for any of these measures;
- For ARCI MBG, Emax values for oxycodone alone were significantly higher than PBO and oxycodone/naloxone co-administration, whereas Emax for oxycodone/naloxone was not statistically different from PBO;
- For the measures of positive, sedative and any effects, peak scores for oxycodone alone were significantly higher than both PBO and oxycodone/naloxone co-administration, which did not differ from each other.
- Negative effects of all treatments were minimal and no significant main effect was observed for any of the derived parameters;
- MPC was observed to be statistically significantly higher for oxycodone alone compared to PBO and significantly lower for oxycodone/naloxone compared to oxycodone alone, whereas MPC derived for oxycodone/naloxone was not statistically different from PBO.

Pharmacokinetics

Oxycodone

Group 1 (Oral)

- Plasma oxycodone concentrations rose rapidly to a mean peak at ~0.5-1 hour post-dosing with both oxycodone oral solution and chewed ONU and declined biexponentially;
- There were few differences in exposure (eg, mean Cmax ~85-90 ng/mL, AUCinf ~520-560 h*ng/mL), time to peak exposure (Tmax), and clearance of oxycodone (CL/F), though median values were consistently higher in terms of peak and overall exposure for chewed ONU relative to oxycodone oral solution.

Group 2 (Intranasal)

- Mean peak concentrations were attained by 1 hour post-dose following intranasal administration of crushed ONU. For Oxy API, mean concentrations rose rapidly and plateaued from 0.25 to 3 hours post-dose and declined thereafter. The plateauing effect may in part be explained by the individual differences in time to peak concentrations;
- Overall, mean oxycodone PK parameters derived for both Oxy API and crushed ONU were comparable.

- There were few differences in overall exposure (AUCinf ~590 h*ng/mL), time to peak exposure (Tmax), and clearance of oxycodone (CL/F), though peak exposure (Cmax) was slightly higher following administration of crushed ONU (~90 ng/mL) compared to Oxy API (~70 ng/mL).

Group 3 (Intravenous)

- Independent of active treatment, mean plasma oxycodone concentrations were highest at 5 minutes postinfusion (ie, the first assessment time point, and then declined rapidly in a biphasic manner);
- Mean oxycodone PK parameters derived for both oxycodone alone and oxycodone/naloxone were comparable, though peak exposure (Cmax) was slightly higher following administration of oxycodone/naloxone (~99 ng/mL) compared to oxycodone alone (~83 ng/mL).

Naloxone (All Groups)

- Following oral administration (chewed ONU), mean concentrations reached a peak (0.37 ng/mL) at 0.5 hours post-dose, whereas intranasal administration of crushed ONU and intravenous administration of naloxone resulted in considerably higher mean peak concentrations (~20 ng/mL and 25 ng/mL, respectively) that were observed earlier (0.25 hours post-dose and 5 minutes post-infusion, respectively);
- Exposure to naloxone following administration of chewed ONU was very low and variable (Cmax ~0.4 ng/mL and AUCinf ~1.55h*ng/mL);
- Relative to the oral route, peak and overall exposure to naloxone following intranasal administration of crushed ONU or intravenous naloxone was higher (eg, with mean Cmax of 20.2 ng/mL and 25.3 ng/mL, respectively);

Conclusions

- Based on the overall pattern of response on the measures evaluated in this study, the intranasal and intravenous abuse potential of oxycodone is significantly reduced to near placebo-like levels when co-administered with naloxone in a 2:1 ratio.
- The oral abuse potential of chewed ONU appears to be similar to that of oxycodone solution, which is an expected result based on the extremely low oral bioavailability of naloxone.
- It can be concluded that ONU (or oxycodone/naloxone solution) has less potential for intranasal and intravenous abuse compared to Oxy API and oxycodone solution, respectively.

APHASE	Variable	SUBJGRP	TRTP	N	Mean	SD	Min	Median	Max	GeometricMean
Qualification Phase	AUE0-0.25	Group 2 (Intranasal)	Lactose placebo powder	27	6.06	1.21	0.00	6.25	6.50	
Qualification Phase	AUE0-0.5	Group 2 (Intranasal)	Lactose placebo powder	27	18.19	3.64	0.00	18.75	19.63	
Qualification Phase	AUE0-0.75	Group 2 (Intranasal)	Lactose placebo powder	27	30.31	6.06	0.00	31.31	32.56	
Qualification Phase	AUE0-1	Group 2 (Intranasal)	Lactose placebo powder	27	42.38	8.48	0.00	43.75	44.88	
Qualification Phase	AUE0-2	Group 2 (Intranasal)	Lactose placebo powder	27	90.63	18.12	0.00	94.25	95.63	
Qualification Phase	AUE0-4	Group 2 (Intranasal)	Lactose placebo powder	27	185.52	38.32	0.00	194.38	196.75	
Qualification Phase	Emax	Group 2 (Intranasal)	Lactose placebo powder	27	50.11	11.29	0.00	51.00	78.00	
Qualification Phase	Tmax	Group 2 (Intranasal)	Lactose placebo powder	27	1.51	2.00	0.25	0.50	8.00	0.73
Qualification Phase	AUE0-0.25	Group 2 (Intranasal)	Oxy API powder 40 mg	27	11.24	1.53	7.50	11.88	12.50	11.12
Qualification Phase	AUE0-0.5	Group 2 (Intranasal)	Oxy API powder 40 mg	27	34.25	4.22	23.75	35.88	37.50	33.97
Qualification Phase	AUE0-0.75	Group 2 (Intranasal)	Oxy API powder 40 mg	27	57.85	6.78	37.88	60.00	62.50	57.40
Qualification Phase	AUE0-1	Group 2 (Intranasal)	Oxy API powder 40 mg	27	81.50	9.14	53.63	85.00	87.50	80.91
Qualification Phase	AUE0-2	Group 2 (Intranasal)	Oxy API powder 40 mg	27	172.63	20.17	117.63	181.75	187.50	171.31
Qualification Phase	AUE0-4	Group 2 (Intranasal)	Oxy API powder 40 mg	27	338.59	53.33	224.13	363.50	387.50	334.05
Qualification Phase	Emax	Group 2 (Intranasal)	Oxy API powder 40 mg	27	96.96	8.05	71.00	100.00	100.00	96.59
Qualification Phase	Tmax	Group 2 (Intranasal)	Oxy API powder 40 mg	27	1.33	4.35	0.25	0.25	23.00	0.47
Qualification	AUE0-	Group 3	Oxycodone 0.07 mg/kg	24	20.41	1.02	17.17	20.83	20.83	20.39

Phase	0.25	(Intravenous)	infusion							
Qualification Phase	AUE0-0.5	Group 3 (Intravenous)	Oxycodone 0.07 mg/kg infusion	24	43.68	3.04	35.29	45.27	45.83	43.57
Qualification Phase	AUE0-0.75	Group 3 (Intravenous)	Oxycodone 0.07 mg/kg infusion	24	65.38	6.83	50.17	68.65	70.83	65.01
Qualification Phase	AUE0-1	Group 3 (Intravenous)	Oxycodone 0.07 mg/kg infusion	24	86.18	11.43	62.29	91.77	95.83	85.38
Qualification Phase	AUE0-2	Group 3 (Intravenous)	Oxycodone 0.07 mg/kg infusion	24	162.45	29.48	108.79	168.33	195.83	159.69
Qualification Phase	AUE0-4	Group 3 (Intravenous)	Oxycodone 0.07 mg/kg infusion	24	297.68	64.98	208.79	277.13	395.83	290.91
Qualification Phase	Emax	Group 3 (Intravenous)	Oxycodone 0.07 mg/kg infusion	24	98.54	3.95	84.00	100.00	100.00	98.46
Qualification Phase	Tmax	Group 3 (Intravenous)	Oxycodone 0.07 mg/kg infusion	24	0.33	1.21	0.08	0.08	6.00	0.10
Qualification Phase	AUE0-0.25	Group 1 (Oral)	Oxycodone oral solution 40 mg + matching placebo tablet, chewed	16	5.72	1.07	3.13	6.25	6.25	5.60
Qualification Phase	AUE0-0.5	Group 1 (Oral)	Oxycodone oral solution 40 mg + matching placebo tablet, chewed	16	22.89	4.28	12.50	25.00	25.00	22.39
Qualification Phase	AUE0-0.75	Group 1 (Oral)	Oxycodone oral solution 40 mg + matching placebo tablet, chewed	16	45.98	7.80	27.56	49.97	50.00	45.20
Qualification Phase	AUE0-1	Group 1 (Oral)	Oxycodone oral solution 40 mg + matching placebo tablet, chewed	16	69.48	9.86	46.50	74.88	75.00	68.71
Qualification Phase	AUE0-2	Group 1 (Oral)	Oxycodone oral solution 40 mg + matching placebo tablet, chewed	16	161.30	17.60	128.50	173.50	175.00	160.34
Qualification Phase	AUE0-4	Group 1 (Oral)	Oxycodone oral solution 40 mg + matching placebo tablet, chewed	16	321.55	55.47	232.50	338.25	375.00	316.80
Qualification Phase	Emax	Group 1 (Oral)	Oxycodone oral solution 40 mg + matching	16	97.94	5.71	81.00	100.00	100.00	97.77

			placebo tablet, chewed							
Qualification Phase	Tmax	Group 1 (Oral)	Oxycodone oral solution 40 mg + matching placebo tablet, chewed	16	0.75	0.48	0.50	0.50	2.00	0.65
Qualification Phase	AUE0-0.25	Group 1 (Oral)	Placebo solution + matching placebo tablet, chewed	16	3.08	0.86	0.19	3.16	4.63	2.73
Qualification Phase	AUE0-0.5	Group 1 (Oral)	Placebo solution + matching placebo tablet, chewed	16	12.33	3.42	0.75	12.63	18.50	10.90
Qualification Phase	AUE0-0.75	Group 1 (Oral)	Placebo solution + matching placebo tablet, chewed	16	24.83	6.19	4.44	25.38	37.13	23.32
Qualification Phase	AUE0-1	Group 1 (Oral)	Placebo solution + matching placebo tablet, chewed	16	37.67	7.76	14.00	37.88	56.00	36.62
Qualification Phase	AUE0-2	Group 1 (Oral)	Placebo solution + matching placebo tablet, chewed	16	87.66	11.30	52.00	88.00	112.50	86.83
Qualification Phase	AUE0-4	Group 1 (Oral)	Placebo solution + matching placebo tablet, chewed	16	182.09	34.21	56.00	188.38	213.50	176.38
Qualification Phase	Emax	Group 1 (Oral)	Placebo solution + matching placebo tablet, chewed	16	53.13	6.28	50.00	51.00	76.00	52.84
Qualification Phase	Tmax	Group 1 (Oral)	Placebo solution + matching placebo tablet, chewed	16	1.31	1.84	0.50	0.75	8.00	0.88
Qualification Phase	AUE0-0.25	Group 3 (Intravenous)	Saline infusion	24	10.31	0.87	6.38	10.42	11.54	10.26
Qualification Phase	AUE0-0.5	Group 3 (Intravenous)	Saline infusion	24	22.14	3.47	6.38	22.92	24.04	21.62
Qualification Phase	AUE0-0.75	Group 3 (Intravenous)	Saline infusion	24	33.74	6.52	6.38	35.42	36.54	32.39
Qualification	AUE0-1	Group 3	Saline infusion	24	45.28	9.88	6.38	47.98	49.04	42.79

Phase		(Intravenous)								
Qualification Phase	AUE0-2	Group 3 (Intravenous)	Saline infusion	24	91.40	23.93	6.38	98.25	99.54	82.47
Qualification Phase	AUE0-4	Group 3 (Intravenous)	Saline infusion	24	183.57	52.26	6.38	198.73	201.04	157.22
Qualification Phase	Emax	Group 3 (Intravenous)	Saline infusion	24	51.13	1.73	50.00	51.00	59.00	51.10
Qualification Phase	Tmax	Group 3 (Intravenous)	Saline infusion	24	0.74	1.10	0.08	0.38	4.00	0.32
Treatment Phase	AUE0-0.25	Group 2 (Intranasal)	Lactose placebo powder	25	6.40	0.52	6.13	6.25	8.88	6.38
Treatment Phase	AUE0-0.5	Group 2 (Intranasal)	Lactose placebo powder	25	19.07	2.66	12.50	18.75	30.25	18.91
Treatment Phase	AUE0-0.75	Group 2 (Intranasal)	Lactose placebo powder	25	31.59	6.22	12.50	31.31	55.25	30.95
Treatment Phase	AUE0-1	Group 2 (Intranasal)	Lactose placebo powder	25	44.12	9.81	12.50	44.00	80.25	42.78
Treatment Phase	AUE0-2	Group 2 (Intranasal)	Lactose placebo powder	25	93.80	23.22	12.50	94.00	173.25	88.75
Treatment Phase	AUE0-4	Group 2 (Intranasal)	Lactose placebo powder	25	189.10	43.72	12.50	194.00	299.25	174.93
Treatment Phase	Emax	Group 2 (Intranasal)	Lactose placebo powder	25	53.00	9.84	50.00	51.00	100.00	52.42
Treatment Phase	Tmax	Group 2 (Intranasal)	Lactose placebo powder	25	2.05	2.69	0.25	0.50	8.00	0.85
Treatment Phase	AUE0-0.25	Group 2 (Intranasal)	ONU 40/20 mg finely crushed	24	5.16	2.37	0.00	6.25	8.13	
Treatment Phase	AUE0-0.5	Group 2 (Intranasal)	ONU 40/20 mg finely crushed	24	16.23	6.72	0.00	18.75	25.00	
Treatment Phase	AUE0-0.75	Group 2 (Intranasal)	ONU 40/20 mg finely crushed	24	28.54	10.48	3.75	31.31	44.31	24.88
Treatment Phase	AUE0-1	Group 2 (Intranasal)	ONU 40/20 mg finely crushed	24	41.85	13.35	14.38	44.00	67.25	38.96
Treatment	AUE0-2	Group 2	ONU 40/20 mg finely	24	97.06	24.65	46.00	94.19	166.75	94.04

Phase		(Intranasal)	crushed							
Treatment Phase	AUE0-4	Group 2 (Intranasal)	ONU 40/20 mg finely crushed	24	205.69	43.51	136.50	195.06	366.75	202.06
Treatment Phase	Emax	Group 2 (Intranasal)	ONU 40/20 mg finely crushed	24	59.92	13.87	50.00	51.00	100.00	58.61
Treatment Phase	Tmax	Group 2 (Intranasal)	ONU 40/20 mg finely crushed	24	2.18	1.85	0.25	2.00	8.00	1.37
Treatment Phase	AUE0-0.25	Group 1 (Oral)	ONU 40/20 mg tablet, chewed + placebo solution	15	5.17	1.25	3.13	6.19	6.25	5.01
Treatment Phase	AUE0-0.5	Group 1 (Oral)	ONU 40/20 mg tablet, chewed + placebo solution	15	20.68	4.99	12.50	24.75	25.00	20.06
Treatment Phase	AUE0-0.75	Group 1 (Oral)	ONU 40/20 mg tablet, chewed + placebo solution	15	41.80	9.58	25.00	49.50	50.00	40.65
Treatment Phase	AUE0-1	Group 1 (Oral)	ONU 40/20 mg tablet, chewed + placebo solution	15	63.80	13.46	37.50	73.75	75.00	62.28
Treatment Phase	AUE0-2	Group 1 (Oral)	ONU 40/20 mg tablet, chewed + placebo solution	15	149.77	27.50	87.75	160.50	175.00	146.98
Treatment Phase	AUE0-4	Group 1 (Oral)	ONU 40/20 mg tablet, chewed + placebo solution	15	306.50	56.83	188.25	318.50	371.75	300.86
Treatment Phase	Emax	Group 1 (Oral)	ONU 40/20 mg tablet, chewed + placebo solution	15	92.87	15.14	51.00	100.00	100.00	91.38
Treatment Phase	Tmax	Group 1 (Oral)	ONU 40/20 mg tablet, chewed + placebo solution	15	1.07	0.70	0.50	1.00	3.00	0.90
Treatment Phase	AUE0-0.25	Group 2 (Intranasal)	Oxy API powder 40 mg	24	11.01	1.83	6.88	11.38	12.50	10.84
Treatment Phase	AUE0-0.5	Group 2 (Intranasal)	Oxy API powder 40 mg	24	33.68	4.95	21.38	34.94	37.50	33.28

Treatment Phase	AUE0-0.75	Group 2 (Intranasal)	Oxy API powder 40 mg	24	56.82	7.73	36.31	58.91	62.50	56.22
Treatment Phase	AUE0-1	Group 2 (Intranasal)	Oxy API powder 40 mg	24	79.57	10.64	50.63	83.00	87.50	78.77
Treatment Phase	AUE0-2	Group 2 (Intranasal)	Oxy API powder 40 mg	24	168.09	23.85	104.63	174.50	187.50	166.19
Treatment Phase	AUE0-4	Group 2 (Intranasal)	Oxy API powder 40 mg	24	329.07	54.94	217.13	336.75	387.50	324.19
Treatment Phase	Emax	Group 2 (Intranasal)	Oxy API powder 40 mg	24	93.92	11.17	61.00	100.00	100.00	93.16
Treatment Phase	Tmax	Group 2 (Intranasal)	Oxy API powder 40 mg	24	0.46	0.37	0.25	0.38	2.00	0.39
Treatment Phase	AUE0-0.25	Group 3 (Intravenous)	Oxycodone 0.07 mg/kg and naloxone 0.035 mg/kg	24	11.30	2.58	9.50	10.42	20.83	11.10
Treatment Phase	AUE0-0.5	Group 3 (Intravenous)	Oxycodone 0.07 mg/kg and naloxone 0.035 mg/kg	24	24.66	5.55	18.38	22.98	45.83	24.22
Treatment Phase	AUE0-0.75	Group 3 (Intravenous)	Oxycodone 0.07 mg/kg and naloxone 0.035 mg/kg	24	38.07	8.62	26.75	35.52	70.83	37.38
Treatment Phase	AUE0-1	Group 3 (Intravenous)	Oxycodone 0.07 mg/kg and naloxone 0.035 mg/kg	24	51.56	11.61	36.13	48.04	95.83	50.62
Treatment Phase	AUE0-2	Group 3 (Intravenous)	Oxycodone 0.07 mg/kg and naloxone 0.035 mg/kg	24	105.10	23.40	72.13	98.17	195.83	103.23
Treatment Phase	AUE0-4	Group 3 (Intravenous)	Oxycodone 0.07 mg/kg and naloxone 0.035 mg/kg	24	210.64	45.40	138.13	199.02	395.83	207.11
Treatment Phase	Emax	Group 3 (Intravenous)	Oxycodone 0.07 mg/kg and naloxone 0.035 mg/kg	24	56.08	12.86	50.00	51.00	100.00	55.04
Treatment Phase	Tmax	Group 3 (Intravenous)	Oxycodone 0.07 mg/kg and naloxone 0.035	24	1.63	2.16	0.08	0.75	8.00	0.51

			mg/kg							
Treatment Phase	AUE0-0.25	Group 3 (Intravenous)	Oxycodone 0.07 mg/kg and naloxone placebo	23	19.49	3.23	6.25	20.83	20.83	19.05
Treatment Phase	AUE0-0.5	Group 3 (Intravenous)	Oxycodone 0.07 mg/kg and naloxone placebo	23	41.23	9.00	6.25	45.83	45.83	39.10
Treatment Phase	AUE0-0.75	Group 3 (Intravenous)	Oxycodone 0.07 mg/kg and naloxone placebo	23	61.49	14.95	6.25	66.96	70.83	57.22
Treatment Phase	AUE0-1	Group 3 (Intravenous)	Oxycodone 0.07 mg/kg and naloxone placebo	23	80.00	20.51	6.25	88.33	95.83	73.52
Treatment Phase	AUE0-2	Group 3 (Intravenous)	Oxycodone 0.07 mg/kg and naloxone placebo	23	144.43	40.61	6.25	149.29	195.83	129.10
Treatment Phase	AUE0-4	Group 3 (Intravenous)	Oxycodone 0.07 mg/kg and naloxone placebo	23	263.88	82.63	6.25	249.79	395.83	228.65
Treatment Phase	Emax	Group 3 (Intravenous)	Oxycodone 0.07 mg/kg and naloxone placebo	23	96.52	10.58	50.00	100.00	100.00	95.72
Treatment Phase	Tmax	Group 3 (Intravenous)	Oxycodone 0.07 mg/kg and naloxone placebo	23	0.13	0.14	0.08	0.08	0.75	0.10
Treatment Phase	AUE0-0.25	Group 1 (Oral)	Oxycodone oral solution 40 mg + matching placebo tablet, chewed	15	5.16	1.25	3.13	5.88	6.25	5.01
Treatment Phase	AUE0-0.5	Group 1 (Oral)	Oxycodone oral solution 40 mg + matching placebo tablet, chewed	15	20.65	4.98	12.50	23.50	25.00	20.02
Treatment Phase	AUE0-0.75	Group 1 (Oral)	Oxycodone oral solution 40 mg + matching placebo tablet, chewed	15	41.89	9.08	28.13	47.38	50.00	40.89
Treatment Phase	AUE0-1	Group 1 (Oral)	Oxycodone oral solution 40 mg + matching placebo tablet, chewed	15	64.30	11.66	46.00	72.00	75.00	63.25
Treatment Phase	AUE0-2	Group 1 (Oral)	Oxycodone oral solution 40 mg + matching placebo tablet, chewed	15	151.22	23.79	106.00	156.25	175.00	149.34
Treatment Phase	AUE0-4	Group 1 (Oral)	Oxycodone oral solution 40 mg + matching placebo tablet, chewed	15	306.58	59.24	207.00	300.50	375.00	300.92

Treatment Phase	Emax	Group 1 (Oral)	Oxycodone oral solution 40 mg + matching placebo tablet, chewed	15	93.13	12.22	66.00	100.00	100.00	92.29
Treatment Phase	Tmax	Group 1 (Oral)	Oxycodone oral solution 40 mg + matching placebo tablet, chewed	15	1.00	0.89	0.50	1.00	4.00	0.82
Treatment Phase	AUE0-0.25	Group 3 (Intravenous)	Oxycodone placebo and naloxone placebo	23	10.03	2.19	0.00	10.42	10.96	
Treatment Phase	AUE0-0.5	Group 3 (Intravenous)	Oxycodone placebo and naloxone placebo	23	22.08	4.82	0.00	23.04	23.96	
Treatment Phase	AUE0-0.75	Group 3 (Intravenous)	Oxycodone placebo and naloxone placebo	23	33.86	7.50	0.00	35.54	36.83	
Treatment Phase	AUE0-1	Group 3 (Intravenous)	Oxycodone placebo and naloxone placebo	23	45.33	10.64	0.00	48.13	49.46	
Treatment Phase	AUE0-2	Group 3 (Intravenous)	Oxycodone placebo and naloxone placebo	23	91.70	21.62	0.00	98.29	99.46	
Treatment Phase	AUE0-4	Group 3 (Intravenous)	Oxycodone placebo and naloxone placebo	23	187.57	41.73	0.00	198.67	200.63	
Treatment Phase	Emax	Group 3 (Intravenous)	Oxycodone placebo and naloxone placebo	23	48.78	10.65	0.00	51.00	53.00	
Treatment Phase	Tmax	Group 3 (Intravenous)	Oxycodone placebo and naloxone placebo	23	0.58	0.87	0.08	0.25	4.00	0.28
Treatment Phase	AUE0-0.25	Group 1 (Oral)	Placebo solution + matching placebo tablet, chewed	15	3.25	0.40	3.13	3.13	4.69	3.23
Treatment Phase	AUE0-0.5	Group 1 (Oral)	Placebo solution + matching placebo tablet, chewed	15	13.00	1.60	12.50	12.50	18.75	12.93
Treatment Phase	AUE0-0.75	Group 1 (Oral)	Placebo solution + matching placebo tablet, chewed	15	26.09	3.31	24.94	25.06	38.00	25.93
Treatment Phase	AUE0-1	Group 1 (Oral)	Placebo solution + matching placebo tablet, chewed	15	39.35	5.30	37.25	37.75	58.25	39.09
Treatment	AUE0-2	Group 1	Placebo solution +	15	92.38	12.34	87.25	88.25	134.50	91.76

Phase		(Oral)	matching placebo tablet, chewed							
Treatment Phase	AUE0-4	Group 1 (Oral)	Placebo solution + matching placebo tablet, chewed	15	197.05	21.47	187.50	189.75	263.50	196.11
Treatment Phase	Emax	Group 1 (Oral)	Placebo solution + matching placebo tablet, chewed	15	54.27	8.97	50.00	51.00	83.00	53.72
Treatment Phase	Tmax	Group 1 (Oral)	Placebo solution + matching placebo tablet, chewed	15	1.27	0.78	0.50	1.00	3.00	1.06

Table: Naloxone PK Parameters following different routes of administration

SUBJGRP	TRTP	Variable	N	NMiss	NObs	Mean	SD	Min	Median	Max	GeometricMean
Group 1 (Oral)	ONU 40/20 mg tablet, chewed + placebo solution	AUCall	15	0	15	1.305	0.626	0.767	1.064	2.677	1.196
Group 1 (Oral)	ONU 40/20 mg tablet, chewed + placebo solution	AUE0-0.25	15	0	15	0.035	0.031	0.003	0.023	0.124	0.024
Group 1 (Oral)	ONU 40/20 mg tablet, chewed + placebo solution	AUE0-0.5	15	0	15	0.115	0.086	0.020	0.092	0.346	0.091
Group 1 (Oral)	ONU 40/20 mg tablet, chewed + placebo solution	AUE0-0.75	15	0	15	0.201	0.131	0.051	0.161	0.523	0.167
Group 1 (Oral)	ONU 40/20 mg tablet, chewed + placebo solution	AUE0-1	15	0	15	0.276	0.167	0.085	0.215	0.661	0.236
Group 1 (Oral)	ONU 40/20 mg tablet, chewed + placebo solution	AUE0-2	15	0	15	0.501	0.269	0.192	0.406	1.083	0.441
Group 1 (Oral)	ONU 40/20 mg tablet, chewed + placebo solution	AUE0-4	15	0	15	0.762	0.385	0.308	0.681	1.649	0.681
Group 1 (Oral)	ONU 40/20 mg tablet, chewed + placebo solution	Cmax	15	0	15	0.392	0.246	0.140	0.281	0.994	0.332
Group 1 (Oral)	ONU 40/20 mg tablet, chewed + placebo solution	Tmax	15	0	15	0.533	0.208	0.250	0.500	1.000	0.500
Group 1 (Oral)	Oxycodone oral solution 40 mg + matching placebo	AUCall	0	15	15	.	.	.	.	.	.

	tablet, chewed										
Group 1 (Oral)	Oxycodone oral solution 40 mg + matching placebo tablet, chewed	AUE0-0.25	0	15	15	.	.	.	.	.	.
Group 1 (Oral)	Oxycodone oral solution 40 mg + matching placebo tablet, chewed	AUE0-0.5	0	15	15	.	.	.	.	.	.
Group 1 (Oral)	Oxycodone oral solution 40 mg + matching placebo tablet, chewed	AUE0-0.75	0	15	15	.	.	.	.	.	.
Group 1 (Oral)	Oxycodone oral solution 40 mg + matching placebo tablet, chewed	AUE0-1	0	15	15	.	.	.	.	.	.
Group 1 (Oral)	Oxycodone oral solution 40 mg + matching placebo tablet, chewed	AUE0-2	0	15	15	.	.	.	.	.	.
Group 1 (Oral)	Oxycodone oral solution 40 mg + matching placebo tablet, chewed	AUE0-4	0	15	15	.	.	.	.	.	.
Group 1 (Oral)	Oxycodone oral solution 40 mg + matching placebo tablet, chewed	Cmax	0	15	15	.	.	.	.	.	.
Group 1 (Oral)	Oxycodone oral solution 40 mg + matching placebo tablet, chewed	Tmax	0	15	15	.	.	.	.	.	.
Group 1 (Oral)	Placebo solution + matching placebo tablet, chewed	AUCall	0	15	15	.	.	.	.	.	.
Group 1 (Oral)	Placebo solution + matching placebo tablet, chewed	AUE0-0.25	0	15	15	.	.	.	.	.	.
Group 1 (Oral)	Placebo solution + matching placebo tablet, chewed	AUE0-0.5	0	15	15	.	.	.	.	.	.
Group 1 (Oral)	Placebo solution + matching placebo tablet, chewed	AUE0-0.75	0	15	15	.	.	.	.	.	.
Group 1 (Oral)	Placebo solution + matching placebo tablet, chewed	AUE0-1	0	15	15	.	.	.	.	.	.

Group 1 (Oral)	Placebo solution + matching placebo tablet, chewed	AUE0-2	0	15	15	.	.	.	.	.	.
Group 1 (Oral)	Placebo solution + matching placebo tablet, chewed	AUE0-4	0	15	15	.	.	.	.	.	.
Group 1 (Oral)	Placebo solution + matching placebo tablet, chewed	Cmax	0	15	15	.	.	.	.	.	.
Group 1 (Oral)	Placebo solution + matching placebo tablet, chewed	Tmax	0	15	15	.	.	.	.	.	.
Group 2 (Intranasal)	Lactose placebo powder	AUCall	0	25	25	.	.	.	.	.	.
Group 2 (Intranasal)	Lactose placebo powder	AUE0-0.25	0	25	25	.	.	.	.	.	.
Group 2 (Intranasal)	Lactose placebo powder	AUE0-0.5	0	25	25	.	.	.	.	.	.
Group 2 (Intranasal)	Lactose placebo powder	AUE0-0.75	0	25	25	.	.	.	.	.	.
Group 2 (Intranasal)	Lactose placebo powder	AUE0-1	0	25	25	.	.	.	.	.	.
Group 2 (Intranasal)	Lactose placebo powder	AUE0-2	0	25	25	.	.	.	.	.	.
Group 2 (Intranasal)	Lactose placebo powder	AUE0-4	0	25	25	.	.	.	.	.	.
Group 2 (Intranasal)	Lactose placebo powder	Cmax	0	25	25	.	.	.	.	.	.
Group 2 (Intranasal)	Lactose placebo powder	Tmax	0	25	25	.	.	.	.	.	.
Group 2 (Intranasal)	ONU 40/20 mg finely crushed	AUCall	24	1	25	26.997	12.757	9.339	24.485	61.573	24.396
Group 2 (Intranasal)	ONU 40/20 mg finely crushed	AUE0-0.25	24	1	25	2.366	0.810	1.018	2.325	4.100	2.224
Group 2 (Intranasal)	ONU 40/20 mg finely crushed	AUE0-0.5	24	1	25	6.334	2.168	2.605	6.263	12.163	5.974
Group 2 (Intranasal)	ONU 40/20 mg finely crushed	AUE0-0.75	24	1	25	9.268	3.383	3.641	9.066	19.519	8.708

Group 2 (Intranasal)	ONU 40/20 mg finely crushed	AUE0-1	24	1	25	11.661	4.554	4.468	11.175	25.738	10.883
Group 2 (Intranasal)	ONU 40/20 mg finely crushed	AUE0-2	24	1	25	17.981	7.979	6.508	17.015	42.338	16.496
Group 2 (Intranasal)	ONU 40/20 mg finely crushed	AUE0-4	24	1	25	23.216	10.763	8.069	21.529	53.648	21.087
Group 2 (Intranasal)	ONU 40/20 mg finely crushed	Cmax	24	1	25	19.212	6.320	8.140	18.800	32.800	18.128
Group 2 (Intranasal)	ONU 40/20 mg finely crushed	Tmax	24	1	25	0.271	0.071	0.250	0.250	0.500	0.265
Group 2 (Intranasal)	Oxy API powder 40 mg	AUCall	1	23	24	0.017	.	0.017	0.017	0.017	0.017
Group 2 (Intranasal)	Oxy API powder 40 mg	AUE0-0.25	1	23	24	0.000	.	0.000	0.000	0.000	0.000
Group 2 (Intranasal)	Oxy API powder 40 mg	AUE0-0.5	1	23	24	0.001	.	0.001	0.001	0.001	0.001
Group 2 (Intranasal)	Oxy API powder 40 mg	AUE0-0.75	1	23	24	0.002	.	0.002	0.002	0.002	0.002
Group 2 (Intranasal)	Oxy API powder 40 mg	AUE0-1	1	23	24	0.004	.	0.004	0.004	0.004	0.004
Group 2 (Intranasal)	Oxy API powder 40 mg	AUE0-2	1	23	24	0.017	.	0.017	0.017	0.017	0.017
Group 2 (Intranasal)	Oxy API powder 40 mg	AUE0-4	0	24	24	.	.	.	.	.	.
Group 2 (Intranasal)	Oxy API powder 40 mg	Cmax	1	23	24	0.017	.	0.017	0.017	0.017	0.017
Group 2 (Intranasal)	Oxy API powder 40 mg	Tmax	1	23	24	2.000	.	2.000	2.000	2.000	2.000
Group 3 (Intravenous)	Oxycodone 0.07 mg/kg and naloxone 0.035 mg/kg	AUCall	24	0	24	11.739	2.271	8.104	12.077	15.636	11.523
Group 3 (Intravenous)	Oxycodone 0.07 mg/kg and naloxone 0.035 mg/kg	AUE0-0.25	24	0	24	3.759	1.490	1.681	3.556	7.574	3.490
Group 3 (Intravenous)	Oxycodone 0.07 mg/kg and naloxone 0.035 mg/kg	AUE0-0.5	24	0	24	5.225	1.589	3.069	4.701	8.782	5.002

Group 3 (Intravenous)	Oxycodone 0.07 mg/kg and naloxone 0.035 mg/kg	AUE0-0.75	24	0	24	6.214	1.638	4.004	5.513	9.635	6.013
Group 3 (Intravenous)	Oxycodone 0.07 mg/kg and naloxone 0.035 mg/kg	AUE0-1	24	0	24	6.986	1.659	4.681	6.549	10.315	6.800
Group 3 (Intravenous)	Oxycodone 0.07 mg/kg and naloxone 0.035 mg/kg	AUE0-2	24	0	24	9.045	1.829	6.319	9.479	12.330	8.865
Group 3 (Intravenous)	Oxycodone 0.07 mg/kg and naloxone 0.035 mg/kg	AUE0-4	24	0	24	10.894	2.089	7.831	11.315	14.257	10.696
Group 3 (Intravenous)	Oxycodone 0.07 mg/kg and naloxone 0.035 mg/kg	Cmax	24	0	24	25.273	11.690	8.950	24.100	56.600	22.771
Group 3 (Intravenous)	Oxycodone 0.07 mg/kg and naloxone 0.035 mg/kg	Tmax	24	0	24	0.083	0.000	0.083	0.083	0.083	0.083
Group 3 (Intravenous)	Oxycodone 0.07 mg/kg and naloxone placebo	AUCall	1	22	23	0.014	.	0.014	0.014	0.014	0.014
Group 3 (Intravenous)	Oxycodone 0.07 mg/kg and naloxone placebo	AUE0-0.25	1	22	23	0.001	.	0.001	0.001	0.001	0.001
Group 3 (Intravenous)	Oxycodone 0.07 mg/kg and naloxone placebo	AUE0-0.5	1	22	23	0.003	.	0.003	0.003	0.003	0.003
Group 3 (Intravenous)	Oxycodone 0.07 mg/kg and naloxone placebo	AUE0-0.75	1	22	23	0.008	.	0.008	0.008	0.008	0.008
Group 3 (Intravenous)	Oxycodone 0.07 mg/kg and naloxone placebo	AUE0-1	1	22	23	0.014	.	0.014	0.014	0.014	0.014
Group 3 (Intravenous)	Oxycodone 0.07 mg/kg and naloxone placebo	AUE0-2	0	23	23	.	.	.	.	.	.
Group 3 (Intravenous)	Oxycodone 0.07 mg/kg and naloxone placebo	AUE0-4	0	23	23	.	.	.	.	.	.
Group 3 (Intravenous)	Oxycodone 0.07 mg/kg and naloxone placebo	Cmax	1	22	23	0.028	.	0.028	0.028	0.028	0.028
Group 3 (Intravenous)	Oxycodone 0.07 mg/kg and naloxone placebo	Tmax	1	22	23	1.000	.	1.000	1.000	1.000	1.000
Group 3 (Intravenous)	Oxycodone placebo and naloxone placebo	AUCall	0	23	23	.	.	.	.	.	.
Group 3 (Intravenous)	Oxycodone placebo and naloxone placebo	AUE0-0.25	0	23	23	.	.	.	.	.	.

Group 3 (Intravenous)	Oxycodone placebo and naloxone placebo	AUE0-0.5	0	23	23	.	.	.	.	.	.
Group 3 (Intravenous)	Oxycodone placebo and naloxone placebo	AUE0-0.75	0	23	23	.	.	.	.	.	.
Group 3 (Intravenous)	Oxycodone placebo and naloxone placebo	AUE0-1	0	23	23	.	.	.	.	.	.
Group 3 (Intravenous)	Oxycodone placebo and naloxone placebo	AUE0-2	0	23	23	.	.	.	.	.	.
Group 3 (Intravenous)	Oxycodone placebo and naloxone placebo	AUE0-4	0	23	23	.	.	.	.	.	.
Group 3 (Intravenous)	Oxycodone placebo and naloxone placebo	Cmax	0	23	23	.	.	.	.	.	.
Group 3 (Intravenous)	Oxycodone placebo and naloxone placebo	Tmax	0	23	23	.	.	.	.	.	.

Table: Oxycodone PK Parameters following different routes of administration of OXN

SUBJGRP	TRTP	Variable	N	NMiss	NObs	Mean	SD	Min	Median	Max	GeometricMean
Group 1 (Oral)	ONU 40/20 mg tablet, chewed + placebo solution	AUCall	15	0	15	528.35	166.11	279.02	536.00	898.62	503.34
Group 1 (Oral)	ONU 40/20 mg tablet, chewed + placebo solution	AUE0-0.25	15	0	15	1.27	0.97	0.04	1.01	3.50	0.85
Group 1 (Oral)	ONU 40/20 mg tablet, chewed + placebo solution	AUE0-0.5	15	0	15	11.12	5.79	1.09	11.33	23.50	9.13
Group 1 (Oral)	ONU 40/20 mg tablet, chewed + placebo solution	AUE0-0.75	15	0	15	28.34	12.54	4.97	29.10	53.16	24.97
Group 1 (Oral)	ONU 40/20 mg tablet, chewed + placebo solution	AUE0-1	15	0	15	45.64	17.02	12.57	47.44	76.15	42.01
Group 1 (Oral)	ONU 40/20 mg tablet, chewed + placebo solution	AUE0-2	15	0	15	106.02	33.85	45.09	118.40	147.73	99.68
Group 1 (Oral)	ONU 40/20 mg tablet, chewed + placebo solution	AUE0-4	15	0	15	209.81	67.93	86.09	231.08	299.74	197.18
Group 1 (Oral)	ONU 40/20 mg tablet, chewed + placebo solution	Cmax	15	0	15	84.55	26.66	37.80	88.70	132.00	79.90
Group 1	ONU 40/20 mg tablet, chewed +	Tmax	15	0	15	0.93	0.73	0.50	0.50	3.00	0.76

(Oral)	placebo solution										
Group 1 (Oral)	Oxycodone oral solution 40 mg + matching placebo tablet, chewed	AUCall	15	0	15	537.79	162.44	229.93	516.91	901.80	513.69
Group 1 (Oral)	Oxycodone oral solution 40 mg + matching placebo tablet, chewed	AUE0-0.25	15	0	15	1.11	1.26	0.09	0.99	4.96	0.59
Group 1 (Oral)	Oxycodone oral solution 40 mg + matching placebo tablet, chewed	AUE0-0.5	15	0	15	10.88	5.85	2.44	10.00	20.23	9.17
Group 1 (Oral)	Oxycodone oral solution 40 mg + matching placebo tablet, chewed	AUE0-0.75	15	0	15	28.10	13.23	8.90	27.02	54.59	24.95
Group 1 (Oral)	Oxycodone oral solution 40 mg + matching placebo tablet, chewed	AUE0-1	15	0	15	45.10	18.64	17.48	43.83	83.34	41.29
Group 1 (Oral)	Oxycodone oral solution 40 mg + matching placebo tablet, chewed	AUE0-2	15	0	15	102.78	39.39	43.31	90.14	155.61	95.19
Group 1 (Oral)	Oxycodone oral solution 40 mg + matching placebo tablet, chewed	AUE0-4	15	0	15	199.53	71.78	68.76	180.80	308.56	186.04
Group 1 (Oral)	Oxycodone oral solution 40 mg + matching placebo tablet, chewed	Cmax	15	0	15	84.87	32.74	41.50	76.80	151.00	78.99
Group 1 (Oral)	Oxycodone oral solution 40 mg + matching placebo tablet, chewed	Tmax	15	0	15	0.87	0.64	0.50	0.50	3.00	0.74
Group 1 (Oral)	Placebo solution + matching placebo tablet, chewed	AUCall	0	15	15	.	.	.	.	.	.
Group 1 (Oral)	Placebo solution + matching placebo tablet, chewed	AUE0-0.25	0	15	15	.	.	.	.	.	.
Group 1 (Oral)	Placebo solution + matching placebo tablet, chewed	AUE0-0.5	0	15	15	.	.	.	.	.	.
Group 1 (Oral)	Placebo solution + matching placebo tablet, chewed	AUE0-0.75	0	15	15	.	.	.	.	.	.
Group 1 (Oral)	Placebo solution + matching placebo tablet, chewed	AUE0-1	0	15	15	.	.	.	.	.	.
Group 1 (Oral)	Placebo solution + matching placebo tablet, chewed	AUE0-2	0	15	15	.	.	.	.	.	.
Group 1 (Oral)	Placebo solution + matching placebo tablet, chewed	AUE0-4	0	15	15	.	.	.	.	.	.
Group 1	Placebo solution + matching	Cmax	0	15	15	.	.	.	.	.	.

(Oral)	placebo tablet, chewed										
Group 1 (Oral)	Placebo solution + matching placebo tablet, chewed	Tmax	0	15	15	.	.	.	.	.	.
Group 2 (Intranasal)	Lactose placebo powder	AUCall	0	25	25	.	.	.	.	.	.
Group 2 (Intranasal)	Lactose placebo powder	AUE0-0.25	0	25	25	.	.	.	.	.	.
Group 2 (Intranasal)	Lactose placebo powder	AUE0-0.5	0	25	25	.	.	.	.	.	.
Group 2 (Intranasal)	Lactose placebo powder	AUE0-0.75	0	25	25	.	.	.	.	.	.
Group 2 (Intranasal)	Lactose placebo powder	AUE0-1	0	25	25	.	.	.	.	.	.
Group 2 (Intranasal)	Lactose placebo powder	AUE0-2	0	25	25	.	.	.	.	.	.
Group 2 (Intranasal)	Lactose placebo powder	AUE0-4	0	25	25	.	.	.	.	.	.
Group 2 (Intranasal)	Lactose placebo powder	Cmax	0	25	25	.	.	.	.	.	.
Group 2 (Intranasal)	Lactose placebo powder	Tmax	0	25	25	.	.	.	.	.	.
Group 2 (Intranasal)	ONU 40/20 mg finely crushed	AUCall	24	1	25	535.46	149.95	186.75	539.17	806.35	512.25
Group 2 (Intranasal)	ONU 40/20 mg finely crushed	AUE0-0.25	24	1	25	5.23	1.65	2.14	5.08	8.95	4.97
Group 2 (Intranasal)	ONU 40/20 mg finely crushed	AUE0-0.5	24	1	25	17.53	6.59	8.94	16.61	40.65	16.57
Group 2 (Intranasal)	ONU 40/20 mg finely crushed	AUE0-0.75	24	1	25	33.01	13.40	15.11	31.29	82.71	31.02
Group 2 (Intranasal)	ONU 40/20 mg finely crushed	AUE0-1	24	1	25	51.23	19.40	21.76	48.38	117.90	48.25
Group 2 (Intranasal)	ONU 40/20 mg finely crushed	AUE0-2	24	1	25	124.47	38.15	47.81	117.73	216.90	118.75
Group 2	ONU 40/20 mg finely crushed	AUE0-4	24	1	25	233.58	61.93	87.81	224.66	349.76	224.84

(Intranasal)											
Group 2 (Intranasal)	ONU 40/20 mg finely crushed	Cmax	24	1	25	86.32	32.74	27.60	76.85	182.00	80.67
Group 2 (Intranasal)	ONU 40/20 mg finely crushed	Tmax	24	1	25	1.29	0.61	0.50	1.00	3.00	1.18
Group 2 (Intranasal)	Oxy API powder 40 mg	AUCall	24	0	24	563.45	136.62	220.58	552.12	853.69	545.28
Group 2 (Intranasal)	Oxy API powder 40 mg	AUE0-0.25	24	0	24	6.76	2.26	3.63	6.41	13.13	6.44
Group 2 (Intranasal)	Oxy API powder 40 mg	AUE0-0.5	24	0	24	20.13	6.42	10.94	18.40	40.13	19.27
Group 2 (Intranasal)	Oxy API powder 40 mg	AUE0-0.75	24	0	24	33.44	10.18	18.33	32.31	65.46	32.12
Group 2 (Intranasal)	Oxy API powder 40 mg	AUE0-1	24	0	24	46.92	13.62	25.76	46.09	85.98	45.17
Group 2 (Intranasal)	Oxy API powder 40 mg	AUE0-2	24	0	24	102.18	26.34	53.31	99.88	160.53	98.68
Group 2 (Intranasal)	Oxy API powder 40 mg	AUE0-4	24	0	24	207.45	49.76	107.51	218.45	311.63	200.94
Group 2 (Intranasal)	Oxy API powder 40 mg	Cmax	24	0	24	69.78	19.24	31.80	72.05	111.00	66.97
Group 2 (Intranasal)	Oxy API powder 40 mg	Tmax	24	0	24	1.45	1.12	0.25	1.00	4.00	1.01
Group 3 (Intravenous)	Oxycodone 0.07 mg/kg and naloxone 0.035 mg/kg	AUCall	24	0	24	91.45	15.88	64.04	87.15	137.25	90.22
Group 3 (Intravenous)	Oxycodone 0.07 mg/kg and naloxone 0.035 mg/kg	AUE0-0.25	24	0	24	14.78	5.72	5.09	14.63	28.28	13.56
Group 3 (Intravenous)	Oxycodone 0.07 mg/kg and naloxone 0.035 mg/kg	AUE0-0.5	24	0	24	21.36	6.21	10.27	21.41	34.15	20.41
Group 3 (Intravenous)	Oxycodone 0.07 mg/kg and naloxone 0.035 mg/kg	AUE0-0.75	24	0	24	26.72	6.53	14.85	27.25	38.78	25.90
Group 3 (Intravenous)	Oxycodone 0.07 mg/kg and naloxone 0.035 mg/kg	AUE0-1	24	0	24	31.31	6.75	18.89	32.15	42.78	30.57
Group 3	Oxycodone 0.07 mg/kg and	AUE0-2	24	0	24	46.11	7.77	32.49	46.40	63.82	45.48

(Intravenous)	naloxone 0.035 mg/kg										
Group 3 (Intravenous)	Oxycodone 0.07 mg/kg and naloxone 0.035 mg/kg	AUE0-4	24	0	24	67.30	10.90	50.62	66.06	98.22	66.50
Group 3 (Intravenous)	Oxycodone 0.07 mg/kg and naloxone 0.035 mg/kg	Cmax	24	0	24	98.56	44.11	26.20	96.45	208.00	87.21
Group 3 (Intravenous)	Oxycodone 0.07 mg/kg and naloxone 0.035 mg/kg	Tmax	24	0	24	0.09	0.03	0.08	0.08	0.25	0.09
Group 3 (Intravenous)	Oxycodone 0.07 mg/kg and naloxone placebo	AUCall	23	0	23	99.24	48.66	75.31	86.76	317.23	93.81
Group 3 (Intravenous)	Oxycodone 0.07 mg/kg and naloxone placebo	AUE0-0.25	23	0	23	12.45	5.18	3.22	12.60	22.99	11.24
Group 3 (Intravenous)	Oxycodone 0.07 mg/kg and naloxone placebo	AUE0-0.5	23	0	23	18.77	5.74	8.63	18.82	30.28	17.86
Group 3 (Intravenous)	Oxycodone 0.07 mg/kg and naloxone placebo	AUE0-0.75	23	0	23	24.00	6.05	13.64	24.18	36.07	23.24
Group 3 (Intravenous)	Oxycodone 0.07 mg/kg and naloxone placebo	AUE0-1	23	0	23	28.51	6.22	18.09	28.66	40.88	27.85
Group 3 (Intravenous)	Oxycodone 0.07 mg/kg and naloxone placebo	AUE0-2	23	0	23	43.11	6.65	31.31	43.64	58.29	42.62
Group 3 (Intravenous)	Oxycodone 0.07 mg/kg and naloxone placebo	AUE0-4	23	0	23	65.28	8.00	52.02	63.05	86.84	64.83
Group 3 (Intravenous)	Oxycodone 0.07 mg/kg and naloxone placebo	Cmax	23	0	23	83.08	37.60	23.00	82.10	162.00	73.31
Group 3 (Intravenous)	Oxycodone 0.07 mg/kg and naloxone placebo	Tmax	23	0	23	0.44	1.65	0.08	0.08	8.00	0.11
Group 3 (Intravenous)	Oxycodone placebo and naloxone placebo	AUCall	1	22	23	0.02	.	0.02	0.02	0.02	0.02
Group 3 (Intravenous)	Oxycodone placebo and naloxone placebo	AUE0-0.25	1	22	23	0.02	.	0.02	0.02	0.02	0.02
Group 3 (Intravenous)	Oxycodone placebo and naloxone placebo	AUE0-0.5	0	23	23	.	.	.	.	.	.
Group 3 (Intravenous)	Oxycodone placebo and naloxone placebo	AUE0-0.75	0	23	23	.	.	.	.	.	.
Group 3	Oxycodone placebo and naloxone	AUE0-1	0	23	23	.	.	.	.	.	.

(Intravenous)	placebo										
Group 3 (Intravenous)	Oxycodone placebo and naloxone placebo	AUE0-2	0	23	23	.	.	.	.	.	.
Group 3 (Intravenous)	Oxycodone placebo and naloxone placebo	AUE0-4	0	23	23	.	.	.	.	.	.
Group 3 (Intravenous)	Oxycodone placebo and naloxone placebo	Cmax	1	22	23	0.20	.	0.20	0.20	0.20	0.20
Group 3 (Intravenous)	Oxycodone placebo and naloxone placebo	Tmax	1	22	23	0.25	.	0.25	0.25	0.25	0.25

4.2.3 Synopsis of Study ONU1007

Study Title

A Single-Center, Randomized, Double-Blind Study in Recreational Opioid Users to Evaluate the Abuse Potential, Pharmacokinetics, and Safety of Oxycodone/Naloxone (ONU) Tablets when Chewed or Administered Intact via the Oral Route.

Objectives

The objectives of the study were to evaluate the following:

- The oral abuse potential and pharmacodynamic (PD) effects of chewed ONU and intact ONU compared to oxycodone oral solution and placebo (PBO) in healthy, adult, non-physically dependent recreational opioid users with a history of oral chewing abuse/misuse.
- The safety and tolerability of orally administered chewed and intact ONU in healthy, adult, non-physically dependent recreational opioid users with a history of oral chewing abuse/misuse.
- The comparative pharmacokinetic (PK) profile of orally administered chewed and intact ONU compared to oxycodone oral solution.

Methodology

This was a single-center, double-blind, randomized, crossover study to evaluate the abuse potential of ONU in healthy non-dependent recreational drug users with moderate experience with opioids and to evaluate the safety and PK profiles of both oxycodone and naloxone, when administered orally.

The study consisted of 4 phases:

- Screening: Visit 1 for inclusion/exclusion screening and Visit 2 for a naloxone challenge test to screen for symptoms of opioid withdrawal
- Qualification: Visit 3 for a randomized, crossover pharmacologic qualification (oxycodone and PBO) to ensure tolerability, appropriate reporting of positive subjective effects, and to demonstrate that subjects were able to complete the study procedures (including the chewing procedures)
- Treatment: Visit 4 to Visit 7 where each of the following single-dose treatments were administered (1 per visit): *ONU 40/20 mg tablet, intact* + ONU PBO tablet, chewed + PBO oral solution; ONU PBO tablet, intact + *ONU 40/20 mg tablet, chewed* + PBO oral solution; ONU PBO tablet, intact + ONU PBO tablet, chewed + *oxycodone oral solution*; ONU PBO tablet, intact + ONU PBO tablet, chewed + PBO oral solution
- Follow-up: Visit 8 for a safety follow-up, 3 to 7 days after the last Treatment Phase drug administration

Study Treatments (including dose, mode of administration, and batch numbers)

Oxycodone hydrochloride, USP powder; administered as a 40 mg, oral solution ((b) (4) (b) (4); lot number: 10-11XYK)

ONU 40/20 mg, oral, chewed or intact (Purdue Pharma L.P.; lot number: CB-2010-35)

ONU PBO tablets, oral, chewed or intact (Purdue Pharma L.P.; lot number: CB-2010-43)

Endpoints

Pharmacodynamic:

The primary endpoints were 'at this moment' Drug Liking visual analog scale (VAS; maximum effect [Emax], minimum effect [Emin], time-averaged area under the effect curve [TA_AUE]) and High VAS (Emax, TA_AUE).

Secondary endpoints included: Overall Drug Liking VAS (Emax/Emin, end-of-day and next day mean scores), Take Drug Again VAS (Emax, end-of-day and next day mean scores), Subjective Drug Value (SDV; Emax, end-of-day and next day mean scores), High VAS (Emax, TA_AUE), Good Effects VAS (Emax, TA_AUE), Addiction Research Center Inventory - Morphine-Benzedrine Group (ARCI MBG) scale (Emax, TA_AUE), Bad Effects VAS (Emax, TA_AUE), Feeling Sick VAS (Emax, TA_AUE), Drowsiness/Alertness VAS (Emin, TA_AUE), and Any Effects VAS (Emax, TA_AUE).

Pupillometry (maximum pupil constriction [MPC] and time-averaged pupillometry area over the curve [TA_PAOC]) was used as an objective measure of opioid effects.

Pharmacokinetic:

The PK endpoints for oxycodone and naloxone were plasma concentrations over time, maximum plasma concentration (Cmax), time to maximum plasma concentration (Tmax), area under the plasma concentration-time curve from time zero until the last quantifiable concentration (AUClast), area under the plasma concentration-time curve extrapolated to infinity (AUCinf), terminal elimination rate constant (λz), terminal elimination half-life (t1/2), total systemic clearance (CL/F), and volume of distribution (V/F).

Pharmacodynamics:

Balance of Effects

- 'At this moment' Drug Liking Emax values (primary) for Oxy API and ONU tablets (both intact and chewed) were significantly higher compared to PBO. Emax values for Oxy API and ONU chewed were both significantly higher than that for ONU intact, and no significant differences between Oxy API and ONU chewed were observed.

- For secondary global measures (Overall Drug Liking VAS, Take Drug Again VAS, and SDV), administration of Oxy API and ONU (intact and chewed) resulted in a significantly higher Emax compared to PBO on all measures. Emax values for intact ONU were significantly lower than those for Oxy API and ONU chewed, which were not significantly different from each other.

Pharmacokinetics:

Oxycodone

- Plasma oxycodone concentrations rose rapidly to a mean peak at 1 hour post-dose following both Oxy API solution and chewed ONU and declined biexponentially. Few differences in exposure (Cmax, AUCs), time to peak exposure (Tmax), and clearance of oxycodone (CL/F) were observed between Oxy API in solution and ONU chewed.

- With intact ONU, Cmax was lower than those of the other treatments and was not reached until 3 hours post-dose. T½ was also larger for intact ONU than for Oxy API and ONU chewed.

Naloxone

- Exposure to naloxone following administration of intact and chewed ONU was very low and variable.
- Following ONU chewed, mean concentrations reached a peak at 0.5 hours post-dose, whereas administration of intact ONU resulted in lower concentrations that increased slowly over the course of 12 hours.
- CL/F was rapid following oral administration of naloxone. V/F and T½ were larger for ONU intact compared to ONU chewed.

Conclusions

Based on the overall pattern of response on the measures evaluated in this study, the oral abuse potential of ONU chewed appears to be similar to that of Oxy API, which is an expected result based on the extremely low oral bioavailability of naloxone. In contrast, the abuse potential of intact ONU tablets was lower than that of Oxy API and ONU chewed, consistent with its controlled release properties.

This study confirmed that naloxone has no impact on the PD effects of oral ONU when administered intact or chewed to non-physically dependent recreational opioid users.

4.2.4 Synopsis of Study ONU1004.

Study Title

A Single-Center, Randomized, Double-Blind Crossover Study to Evaluate the Pharmacodynamics, Pharmacokinetics, and Safety of Oxycodone/Naloxone (ONU) in Opioid Dependent Subjects.

Objectives

The objectives of the study were to evaluate the following:

- The pharmacodynamic effects of chewed ONU compared to the active pharmaceutical ingredient oxycodone HCl (Oxy API) and placebo in methadone-maintained opioid-dependent subjects
- The pharmacokinetics of oxycodone and naloxone in methadone-maintained opioid-dependent subjects
- The safety and tolerability of chewed ONU in methadone-maintained opioid-dependent subjects.

Methodology

This was a single-center, double-blind, placebo-controlled, randomized, block-order crossover study to evaluate the pharmacodynamic effects (subjective, physiologic, and withdrawal), pharmacokinetics, and safety of oral ONU (chewed) compared to Oxy API in methadone-maintained opioid-dependent subjects. The study consisted of 3 phases: screening, treatment, and follow-up. The screening visit was conducted within 30 days of first study drug administration.

The Treatment Phase consisted of 2 sessions (2 blocks), each lasting 4 days (with 3 overnight stays). Subjects received study drugs according to a randomized block-order design, with each block consisting of two 3 × 3 Williams squares. In the first block, subjects received the following study drugs, each separated by an interval of approximately 24 hours: chewed 30/15 mg ONU + placebo solution, 30 mg Oxy API in solution + chewed placebo and placebo solution + chewed placebo. Following an interval of at least 3 days, subjects who completed Session 1 were randomized to the second block, where the subjects received the following study drugs: chewed 60/30 mg ONU + placebo solution, 60 mg Oxy API in solution + chewed placebo, and placebo solution + chewed placebo. The ONU 30/15 mg and ONU 60/30 mg doses were administered as one 10/5 mg tablet and one 20/10 mg tablet and as a 40/20 mg tablet and a 20/10 mg tablet respectively.

Prior to initiation of the second block, the investigator, in consultation with the sponsor, performed a documented review of safety data from the first block to determine if 60 mg was an appropriate dose for the second block. As an added safety measure, a sentinel group of 2 subjects participated in the second block (Treatment Session 2) at least 24 hours prior to dosing of the remaining subjects.

Subjects returned for a Follow-up Visit 3 to 7 days following the last study drug administration.

Number of Subjects (planned & analyzed)

Planned: 18 subjects were planned for randomization to the Treatment Phase.

Analyzed: 18 subjects were randomized and analyzed in Treatment Session 1; 16 subjects were randomized and treated in Treatment Session 2.

Study Treatments (including dose, mode of administration, and batch numbers)

Single oral doses of ONU, Oxy API, and placebo were administered in Session 1 as follows:

- Chewed 30/15 mg ONU + placebo solution: One 10/5 mg ONU tablet (Purdue Pharma, L.P.; Lot number: CB-2010-33) + one 20/10 mg ONU tablet (Purdue Pharma, L.P.; Lot number: CB- 2010-34) + 240 mL placebo solution
- 30 mg Oxy API in solution + chewed placebo: One 10/5 mg ONU placebo tablet (Purdue Pharma, L.P.; Lot number: CB-2009-22) + one 20/10 mg ONU placebo tablet (Purdue Pharma, L.P.; Lot number: CB-2009-23) + 30 mg Oxy API (oxycodone hydrochloride USP powder; (b) (4); Lot number: 24-10XYK) in a 240 mL solution
- Placebo solution + chewed placebo: One 10/5 mg ONU placebo tablet (Purdue Pharma, L.P.; Lot number: CB-2009-22) + one 20/10 mg ONU placebo tablet (Purdue Pharma, L.P.; Lot number: CB-2009-23) + 240 mL placebo solution

Single oral doses of ONU, Oxy API, and placebo were administered in Session 2 as follows:

- Chewed 60/30 mg ONU + placebo solution: One 20/10 mg ONU tablet (Purdue Pharma, L.P.; Lot number: CB-2010-34) + one 40/20 mg ONU tablet (Purdue Pharma, L.P.; Lot number: CB- 2010-35) + 240 mL placebo solution
- 60 mg Oxy API in solution + chewed placebo: One 20/10 mg ONU placebo tablet (Purdue Pharma, L.P.; Lot number: CB-2009-23) + one 40/20 mg ONU placebo tablet (Purdue Pharma, L.P.; Lot number: CB-2009-24) + 60 mg Oxy API (oxycodone hydrochloride USP powder; (b) (4); Lot number: 24-10XYK) in a 240 mL solution
- Placebo solution + chewed placebo: One 20/10 mg ONU placebo tablet (Purdue Pharma, L.P.; Lot number: CB-2009-23)+ one 40/20 mg ONU placebo tablet (Purdue Pharma, L.P.; Lot number: CB-2009-24) + 240 mL placebo solution

Subjects received their daily methadone dose at their prescribed dose level (between 20 mg/day to 40 mg/day) as methadone hydrochloride oral concentrate, USP, 10 mg/ml solution prepared in approximately 100 mL orange flavored Tang® (Metadol™; Paladin Labs, Inc.; Lot number: 449376).

Endpoints

Pharmacodynamic:

The subjective pharmacodynamic endpoints were Drug Liking visual analog scale (VAS) 'at the moment' (maximum effect [Emax], minimum effect [Emin], time-averaged area under the effect curve [TA_AUE]), Overall Drug Liking VAS (end-of-session score), Take Drug Again VAS (end-of-session score), High VAS (Emax, TA_AUE), Good Effects VAS (Emax, TA_AUE), Bad Effects VAS (Emax, TA_AUE), Feeling sick VAS (Emax, TA_AUE), Drowsiness/Alertness VAS (Emin, TA_AUE), and Any Effects VAS (Emax, TA_AUE).

The objective physiologic endpoints were pupillometry (maximum pupil constriction [MPC] and pupillometry area over the effect curve relative to baseline [PAOE]).

The withdrawal endpoints were Subjective Opiate Withdrawal Scale (SOWS) (Emax, TA_AUE) and Objective Opioid Withdrawal Scale (OOWS) (Emax, TA_AUE).

Pharmacokinetic:

The pharmacokinetic endpoints for oxycodone and naloxone were plasma concentrations over time, maximum plasma concentration (Cmax), time to maximum plasma concentration (Tmax), and area under the plasma concentration vs. time curve from time zero to last quantifiable concentration (AUClast). Plasma concentrations of methadone were also evaluated.

Summary of Results

Pharmacodynamic, Physiological, and Withdrawal Endpoints

Treatment Session 1:

 There were no significant differences between placebo and Oxy API on subjective measures; however, pupil diameter was significantly lower with Oxy API 30 mg compared to placebo.

 Effects of ONU 30/15 mg were also minimal; however, compared with placebo, ONU 30/15 mg showed significantly higher Bad Effects VAS scores over time (TA_AUE) and significantly lower Overall Drug Liking VAS (ie, overall disliking), but no effect on pupil diameter or other subjective measures.

 Relative to Oxy API 30 mg, ONU 30/15 mg showed significant greater disliking (Drug Liking VAS Emin and TA_AUE and Overall Drug Liking VAS) and less willingness to take the drug again. Bad Effects VAS scores were significantly greater with ONU 30/15 mg relative to Oxy API 30 mg.

Treatment Session 2:

 Oxy API 60 mg showed no statistically significant treatment effects on Drug Liking, Overall Drug Liking VAS or Take Drug Again VAS, but did show significant effects relative to placebo on Good Effects VAS, High VAS, and Any Effects VAS endpoints (particularly TA_AUE), as well pupil diameter. In addition, peak Feeling Sick VAS was lower with Oxy API 60 mg compared to placebo.

 There were few significant differences between ONU 60/30 mg and placebo. However, ONU 60/30mg was associated with lower Drug Liking VAS Emax, and higher negative effects (including Bad Effects VAS, Feeling Sick VAS, and SOWS). There was no effect of ONU 60/30 mg on peak pupil diameter, but over time (TA_PAOE), there was a small but significant miotic effect compared to placebo.

 Compared to Oxy API 60 mg, ONU 60/30 mg was associated with fewer balance (Drug Liking VAS, Take Drug Again VAS), positive (Good Effects VAS, High VAS),

and pupillary effects and greater negative effects (Bad Effects VAS, Feeling Sick VAS, and SOWS).

 Examination of the distribution and individual subject responses suggests that most subjects experienced little or no effect of ONU at either dose, while a small subset of subjects showed mild negative/withdrawal-like responses.

Pharmacokinetic Endpoints

 Peak and extent of exposure to oxycodone plasma were slightly lower and Tmax was delayed by 1 hour for ONU doses compared to respective Oxy API doses. Inter-subject variability in pharmacokinetic parameters was also higher with ONU (chewed) versus Oxy API (oral solution).

 Plasma naloxone concentrations with ONU 30/15 mg and 60/30 mg were low and were cleared more rapidly than oxycodone.

 Methadone concentrations were similar at pre-dose for all treatments within a session (ie, baseline methadone concentrations were similar between treatments).

Conclusions

In conclusion, ONU 30/15 mg was associated with few subjective or withdrawal effects, while ONU 60/30 mg was associated with lower abuse-related subjective effects compared to Oxy API. In addition, ONU 60/30 mg was associated with significant negative subjective effects compared to Oxy API and placebo in methadone maintained, opioid dependent subjects. In some subjects, ONU 60/30 mg was associated with mild subjective withdrawal effects and gastrointestinal TEAEs potentially related to naloxone blockade. These results demonstrate that the naloxone component reduces the abuse potential of chewed ONU in opioid-dependent individuals.

4.2.5 Synopsis of Study ONU1008.

Study Title

A Single-Center, Randomized, Double-Blind, Crossover Study to Evaluate the Pharmacodynamics, Pharmacokinetics, and Safety of Intact and Chewed Oxycodone/Naloxone (ONU) Tablets in Opioid-Dependent Subjects.

Objectives

The objectives of the study were to evaluate the following:

 The pharmacodynamic (PD) effects of intact and chewed ONU compared to the active pharmaceutical ingredient, oxycodone HCl (Oxy API), and placebo (PBO) in methadone-maintained, opioid-dependent subjects

 The pharmacokinetics (PK) of oxycodone and naloxone in methadone-maintained, opioid-dependent subjects

 The safety and tolerability of intact and chewed ONU in methadone-maintained, opioiddependent subjects.

Methodology

This was a single-center, double-blind, triple-dummy, PBO-controlled, randomized, 4-way crossover study to evaluate the PD effects (subjective, physiologic, and withdrawal), PK, and safety of oral ONU (chewed and intact) compared to Oxy API and PBO in methadone-maintained, opioid-dependent subjects.

The study consisted of 4 phases: screening, qualification, treatment, and follow-up.

 Screening: Visit 1 for inclusion/exclusion screening was conducted within 30 days prior to admission to the qualification phase.

 Qualification: 1 visit (Visit 2) lasting 3 days (2 overnight stays). On the morning of days 1 and 2, subjects were administered single doses of Oxy API 60 mg, in oral solution and PBO in a randomized fashion (washout of 24 hours) to determine if they showed an appropriate response to PBO; this visit also determined if each subject was suitable for study entry.

 Treatment: 1 inpatient session (Visit 3) lasting 9 days (with 8 overnight stays). Subjects received each of the following treatments in a randomized, double-blind, triple-dummy fashion:

– **Treatment A**: ONU 60/30 mg intact
– **Treatment B**: ONU 60/30 mg chewed
– **Treatment C**: Oxy API 60 mg, in oral solution
– **Treatment D**: PBO

 Follow-up: Visit 4 was a safety follow-up, 3 to 7 days after the last study drug administration.

Number of Subjects (planned & analyzed)

Planned: 36 subjects were planned for randomization to the treatment phase.

Analyzed: 33 subjects were randomized and 29 subjects were analyzed.

Study Treatments (including dose, mode of administration, and lot numbers)

Oxycodone hydrochloride, USP powder; administered as a 240 mL oral solution ((b) (4) (b) (4) ; Lot number: 55-11XYK)

ONU 20/10 mg tablets (Purdue Pharmaceuticals, L.P.; Lot number: CB-2010-34)

ONU 40/20 mg tablets (Purdue Pharmaceuticals, L.P.; Lot number: CB-2010-37)

PBO to match ONU 20/10 mg tablets (Purdue Pharmaceuticals, L.P.; Lot number: CB-2010-42)

PBO to match ONU 40/20 mg tablets (Purdue Pharmaceuticals, L.P.; Lot number: CB-2010-43)
Single oral doses of ONU, Oxy API, and PBO were administered as follows:
 Treatment A: *ONU 40/20 mg + ONU 20/10 mg tablets, intact* + 2 ONU PBO tablets, chewed +PBO oral solution
 Treatment B: 2 ONU PBO tablets, intact + *ONU 40/20 mg + ONU 20/10 mg tablets, chewed* +PBO oral solution
 Treatment C: 2 ONU PBO tablets, intact + 2 ONU PBO tablets, chewed + *Oxy API, 60 mg oral solution*
 Treatment D: 2 ONU PBO tablets, intact + 2 ONU PBO tablets, chewed + PBO oral solution Subjects received their daily methadone dose at their prescribed dose level (between 20 mg/day to 50 mg/day) as methadone HCl oral concentrate, USP, 10 mg/ml solution prepared in approximately 100 mL orange-flavored Tang® (Metadol; Paladin Labs Inc.; Lot number: 460107).

Endpoints

Pharmacodynamic:
 The primary endpoints were High visual analog scale (VAS; maximum effect [Emax] and time-averaged area under the effect curve [TA_AUE]).
 Secondary endpoints included: 'at this moment' Drug Liking VAS (Emax, minimum effect [Emin], TA_AUE), Overall Drug Liking VAS (end-of-session score), Take Drug Again VAS (end-of-session score), Good Effects VAS (Emax, TA_AUE), Bad Effects VAS (Emax, TA_AUE), Feeling Sick VAS (Emax, TA_AUE), Drowsiness/Alertness VAS (Emin, TA_AUE), and Any Effects VAS (Emax, TA_AUE).
 Objective physiological endpoints included: pupillometry (maximum pupil constriction [MPC] and pupillometry area over the effect curve relative to baseline [PAOE]).
 Withdrawal endpoints included: Subjective Opioid Withdrawal Scale (SOWS; Emax, TA_AUE) and Objective Opioid Withdrawal Scale (OOWS; Emax, TA_AUE).

Pharmacokinetic:
The PK endpoints for oxycodone and naloxone were plasma concentrations over time, maximum plasma concentration (Cmax), time to maximum plasma concentration (Tmax), and area under the plasma concentration vs time curve from time zero to last quantifiable concentration (AUClast).

Plasma concentrations of methadone were also evaluated.

Summary of Results

Pharmacodynamics:
 There were statistically significant differences between PBO and Oxy API 60 mg on all subjective measures with the exception of Bad Effects VAS. Pupil diameter and subjective withdrawal (SOWS) were statistically significantly lower following administration of Oxy API 60 mg.
 No statistically significant differences were observed between ONU 60/30 mg intact and PBO on measures of subjective drug effects; however, self-reported withdrawal effects were statistically significantly lower with ONU 60/30 mg intact.
There were few statistically significant differences between ONU 60/30 mg intact and ONU 60/30 mg chewed. However, ONU 60/30 mg chewed was associated with statistically significantly greater disliking (Drug Liking VAS Emin), higher scores on Bad Effects VAS, higher

Any Effects VAS Emax, and greater self-reported withdrawal effects.

 Review of the distribution and individual subject responses on the OOWS, SOWS, and negative VAS measures suggests that most subjects experienced a mild negative effect of ONU 60/30 mg chewed, with a small subset of subjects showing mild withdrawal-like responses.

Pharmacokinetics:

Oxycodone

 Plasma oxycodone concentrations for Oxy API 60 mg and ONU 60/30 mg chewed rose rapidly to mean peak at 1 and 2 hours post-dose, respectively. Plasma oxycodone concentration for ONU 60/30 mg intact rose gradually with mean peak at 3 hours post-dose.

 With ONU 60/30 mg intact, Cmax and AUClast were lower than those of the other treatments.

Few differences in exposure (Cmax and AUClast) were observed between Oxy API 60 mg and ONU 60/30 mg chewed.

Naloxone

 Exposure to naloxone following administration of intact and chewed ONU 60/30 mg was relatively low with high inter-subject variability.

 Following ONU 60/30 mg chewed, mean concentrations reached a peak at 1 hour post-dose then rapidly declined, whereas administration of ONU 60/30 mg intact resulted in lower concentrations that increased slowly over the course of 12 hours.

Methadone

 Methadone concentrations were similar at pre-dose and across time points for all treatments.

4.2.6 Synopsis of Food-effect study OXN1003 (40/20 mg and 10/20 mg)

Title of the Study: A Pilot, Open-Label, Single-Dose, 4-Treatment, 4-Period, Randomized, Crossover Study to Investigate the Effect of Food on Oxycodone and Naloxone Pharmacokinetics, When Administered as Fixed Combination Prolonged Release Tablets OXN 40/20 and 10/5, in Healthy Volunteers

Objectives: To investigate the effect of a high-fat breakfast on the bioavailability of oxycodone and naloxone-3-glucuronide when administered as a fixed combination prolonged release tablet.

Methodology: Open-label, single-dose, randomized, 4-treatment, 4-period crossover.

Number of Subjects: Planned: 28 subjects. Randomized: 28 subjects. Completed: 25 subjects.

Discontinued: 3 (SAE 1; Subject's choice 2)

Indication and Criteria for Inclusion Healthy males and females (females could not be pregnant or nursing) of any ethnic group, aged between 18 - 45 years of age, with no clinically significant medical history, and whose general practitioners (if applicable) confirmed that they were suitable to take part in clinical studies.

Test Treatment, Dose, and Mode of Administration: Oxycodone/Naloxone 40/20 (OXN 40/20) [batch number OXN 40/20-157A-04] and Oxycodone/Naloxone 10/5 (OXN 10/5) [batch number: OXN 10/5-155A-04] prolonged release tablets, a combination containing oxycodone HCl and naloxone HCl in an extruder formulation, manufactured by Mundipharma Research GmbH & Co. KG, Germany.

In the morning following a 10-hour overnight fast and after a high-fat breakfast.

Treatment A: 1 tablet of OXN 40/20 fed

Treatment B: 1 tablet of OXN 10/5 fed

Reference Treatment, Dose, and Mode of Administration In the morning following a 10 hour overnight fast.

Treatment C: 1 tablet of OXN 40/20 fasted

Treatment D: 1 tablet of OXN 10/5 fasted

Duration of Treatment: Screening within 21 days before Day 1 of Study Period 1. There were 4 study periods, with at least a 7-day washout between dosing in each study period. Pharmacokinetic blood sampling and safety monitoring continued up to 96 hours after dosing. Subjects had a poststudy evaluation 7-10 days after dosing in Study Period 4, or 7-10 days after their last dose in the case of discontinuation from the study. Duration of the study was 52 days.

Treatment Schedule: On Day 1 of each study period subjects were administered one of the 4 treatments in accordance with the random allocation schedule (RAS). No food was allowed during the 4 hours after dosing.

Criteria for Evaluation: The full analysis population for pharmacokinetic metrics included subjects who had at least one valid pharmacokinetic metric.

The safety population included subjects who had received study drug and had at least one post dose safety assessment.

Bioanalytical Methods: The plasma samples were analyzed for oxycodone, noroxycodone, oxymorphone, noroxymorphone, naloxone, 6β-naloxol, naloxone-3-glucuronide and 6β-naloxol-3-glucuronide by validated bioanalytical assays.

Sample Size: With a sample size of 24 completing subjects, a within subject standard deviation of 0.185 (on the log scale) and a true ratio of one (100%) between test(s) and references this study had an overall power of 97% to confirm the primary objective.

Clinical Pharmacology:

Pharmacokinetic Parameters:

AUCt, AUCINF, Cmax, tmax, LambdaZ and t½Z for oxycodone, noroxycodone, oxymorphone, noroxymorphone, naloxone, 6β-naloxol, naloxone-3-glucuronide and 6β-naloxol-3-glucuronide. The treatments were compared as follows:

Treatment A vs. C; Treatment B vs. D

The full analysis population for pharmacokinetic metrics was used for these analyses.

Safety: Safety assessments were based on medical review of AE reports and the results of vital sign measurements, ECGs, physical examinations, and clinical laboratory tests.

Statistical Methods: The primary outcome for the study were assessed as follows:

• The rate and extent of absorption of oxycodone from the combination formulation in the fed vs. fasted state.

• The rate and extent of absorption of naloxone-3-glucuronide from the combination formulation in the fed vs. fasted state.

All other outcomes were of secondary interest.

Pharmacokinetic parameters for all analytes were summarized descriptively by treatment. Log transformed data for AUCt, AUCINF (if available) and Cmax were analyzed using a mixed effect linear model, with fixed terms for treatment, sequence and period. Compound symmetry was assumed. Ratios of treatment difference population geometric means were estimated by exponentiating the difference (test reference) between treatment least square means, and 90% confidence intervals for the ratios were calculated.

The data for tmax, LambdaZ and t½Z were analyzed using a mixed effect linear model, with fixed terms for treatment, sequence, and period. Compound symmetry was assumed. Treatment differences and their associated 90% confidence intervals were calculated from the least square means for comparisons of interest.

Results:

Pharmacokinetic: For oxycodone, the AUCt [ng.h/mL, mean and (SD)] for OXN 40/20 Fasted, OXN 40/20 Fed, OXN 10/5 Fasted and OXN 10/5 Fed were 517.81 (176.87), 604.34 (198.84), 136.82 (41.04) and 153.26 (50.97) respectively and the Cmax (ng.mL) values were 40.16 (10.42), 50.29 (12.92), 12.16 (3.54) and 14.54 (3.27) respectively.

For naloxone-3-glucuronide the AUCt [ng.h/mL, mean and (SD)] for OXN 40/20 Fasted, OXN 40/20 Fed, OXN 10/5 Fasted and OXN 10/5 Fed were 638.86 (196.83), 728.83 (234.65), 161.18 (55.55) and 176.11 (71.59) respectively and the Cmax (ng.mL) values were 86.05 (24.39), 84.68 (23.60), 23.65 (7.01) and 24.30 (9.03) respectively.

Safety: One subject experienced SAEs of acute laryngitis and dyspnoea during his OXN 10/5 fasted period (Period 1). Study drug was stopped and the subject was discontinued but fully recovered from the events, which were not considered to be related to study drug. Nausea, fatigue and headache were the most frequently reported adverse events across the treatments, with nausea in particular occurring more often with the OXN 40/20 dose.

Table 14. PK Parameters [geometric mean (% CV)] of Oxycodone, Naloxone and Naloxone-3β -Glucuronide and Statistical Analysis Results for Food Effect on the Bioavailability of OXN 10/5 and OXN 40/20 mg Tablets (Study OXN1003)

Analyte	Treatment A (Test) OXN 40/20 mg, Fed (n = 23)		Treatment B (Test) OXN 10/5 mg, Fed (n = 24)	
	C_{max} (ng/mL)	AUC_{0-t} (hr*ng/mL)	C_{max} (ng/mL)	AUC_{0-t} (hr*ng/mL)
Oxycodone	48.8 (25.0)	574 (33.6)	14.2 (22.2)	146 (33.6)
Naloxone	0.108 (79.9)	0.910 (61.2)	0.0375 (82.4)	0.102 (158)
Naloxone-3β-glucuronide	81.5 (29.5)	696 (31.5)	22.7 (39.1)	165 (38.0)
	Treatment C (Reference) OXN 40/20 mg, Fasted (n = 21)		**Treatment D (Reference)** OXN 10/5 mg, Fasted (n = 27)	
Oxycodone	38.9 (26.4)	489 (35.7)	11.7 (31.3)	130 (33.4)
Naloxone	0.0628 (61.4)	0.772 (76.9)	0.0247 (98.6)[b]	0.116 (140)[b]
Naloxone-3β-glucuronide	83.1 (27.4)	613 (29.4)	22.7 (31.3)	152 (36.5)

Statistical Analysis Results

	C_{max} GLSM Ratio (90% CI)	AUC[a] GLSM Ratio (90% CI)
	Treatment A/Treatment C	Treatment A/Treatment C
Oxycodone	124 (116-132) %	117 (113-122) %
Naloxone	175 (137-223) %	124 (92.9-166) %
Naloxone-3β-glucuronide	97.4 (88.5-107) %	110 (103-118) %
	Treatment B/Treatment D	Treatment B/Treatment D
Oxycodone	124 (117-132) %	113 (109-118) %
Naloxone	171 (134-218) %	165 (124-221) %
Naloxone-3β-glucuronide	98.9 (90.3-108) %	109 (101-117) %

Abbreviations: AUC_{0-t} = area under the plasma drug concentration-time curve from time zero to the last measurable concentration after dosing; C_{max} = maximum concentration of drug in plasma; CI = confidence interval; CV = coefficient of variation; GLSM = geometric least squares mean; hr = hour; mL = milliliter; n = number of subjects; ng = nanogram.

[a] AUC for oxycodone and naloxone-3β-glucuronide; AUC_{0-t} for naloxone.

[b] Mean (%CV)

Source: post-text Table D-1, post-text Table D-2, post-text Table D-3; OXN1003 CSR Table 10, Table 12, Table 14

Treatment A: 1 tablet of OXN 40/20 fed, **Treatment B:** 1 tablet of OXN 10/5 fed
Treatment C: 1 tablet of OXN 40/20 fasted, **Treatment D:** 1 tablet of OXN 10/5 fasted
Conclusions:

• Administering OXN 40/20 and OXN10/5 after a high fat breakfast had no clinically significant effect on the oxycodone, naloxone or naloxone-3-glucuronide, compared with administering OXN 40/20 and OXN 10/5 in a fasted state.

• The presence of food did not alter the mean Cmax value for naloxone-3-glucuronide, slightly increased the mean Cmax value for oxycodone and 75% increase in mean Cmax value for naloxone. With regard to oxycodone, this increase was in accordance with that recorded for OxyContin®/Oxygesic® and is not considered to be of clinical importance. Further investigations on the effect of food on OXN tablets are planned.

4.2.7 Synopsis of Food-effect Study OXN1008 (Targiniq 40/20 mg)

Title of the Study: An open-label, single-dose, 3-treatment, 3-period, randomized crossover study in healthy subjects to assess the pharmacokinetics of oxycodone and naloxone after administration of OXN 40/20 in a fed and fasted state, and oxycodone hydrochloride immediate release liquid 20 mg (20 mL of 5 mg/5 mL solution) and naloxone hydrochloride liquid 10 mg (10 mL of 1mg/1mL solution) in a fasted state.

Objectives: The objectives of this study were to assess the pharmacokinetics, bioavailability and safety of OXN 40/20 administered in a fed and fasted state, and oxycodone HCl and naloxone HCl administered in a fasted state, to healthy subjects.

The primary objective was to assess the effect of food on the bioavailability of oxycodone and naloxone (or surrogate of naloxone) from OXN 40/20.

The secondary objective was to compare the pharmacokinetics of oxycodone and naloxone (or surrogate of naloxone) from OXN 40/20 with oxycodone hydrochloride immediate release liquid 20 mg & naloxone hydrochloride liquid 10 mg.

Methodology: Open-label, single-dose, 3-treatment, 3-period, randomized crossover study in healthy male and female subjects.

Number of Subjects: Planned: 28 subjects. Randomized: 29 subjects. Completed: 26 subjects.

Indication and Criteria for Inclusion:

Healthy males and females, 18 - 55 years of age, free of significant abnormal findings as determined by medical history, physical examination, vital signs and electrocardiogram (ECG).

Test Treatment, Dose, and Mode of Administration:

Oxycodone/naloxone prolonged-release (PR) tablet 40/20 mg (OXN 40/20), a PR combination tablet containing 40 mg of oxycodone HCl and 20 mg of naloxone HCl. Manufactured by Mundipharma Research GmbH & Co. KG, Germany.

The treatment was administered orally as follows:

A: One tablet of OXN 40/20 in a fasted state, B: One tablet of OXN 40/20 in a fed state

Reference Treatment, Dose, and Mode of Administration:

Oxycodone hydrochloride oral liquid (OxyNorm liquid), an immediate release liquid containing 5 mg/5 mL oxycodone HCl. Marketing Authorisation Holder is [redacted]. Naloxone hydrochloride injection 1 mg/mL, given as an oral solution. Manufactured by [redacted]. Marketing Authorisation Holder is [redacted].

The treatment was given orally in the fasted state as follows:

C: Oxycodone immediate release liquid 20 mg (20 mL of 5 mg/5mL solution) and naloxone injection 10 mg (10 mL of 1 mg/1mL injection given as an oral solution).

Naltrexone Administration

The test and reference treatments were taken under the cover of naltrexone to reduce the risk of opioid-related side effects. Naltrexone hydrochloride tablet 50 mg (Nemexin ® tablets, Bristol Myers Squibb Pharmaceuticals Limited, Germany).

1 tablet swallowed whole, with 100 mL water at -13 h Day -1.

1 tablet swallowed whole, with 100 mL water at -1 h, 11 h, and 23 h Day 1

Duration of Treatment:

Screening within 21 days before Day 1 of Study Period 1. There were three study periods, with at least a 7-day washout between Day 1 of each study period. Subjects were

administered the study treatment according to a random allocation schedule (RAS). Pharmacokinetic blood sampling and safety monitoring continued for up to 72 hours after dosing with each treatment. Subjects had a post-study medical 7-10 days after dosing of Study Period 3 or 7-10 days after last dose in case of discontinuation from the study. Total duration of the study was 42-45 days.

Treatment Schedule:

A single dose of each treatment was given to subjects according to the RAS. Each dose of study medication was given with 240 mL water to subjects in a standing position.

Criteria for Evaluation:

Analysis Populations:

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

The safety population was defined as those subjects who received one dose of study medication and had at least one subsequent safety assessment.

The full analysis population for pharmacokinetic metrics was defined as those subjects who had a valid pharmacokinetic metric.

Drug Concentration Measurements:

Blood Sampling Times: Treatments A and B: Pre-dose on Day 1 of the respective study period, and at 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 5, 6, 8, 10, 12, 16, 24, 28, 32, 36, 48 and 72 hours post-dose (21 blood samples per dosing period).

Treatment C: Pre-dose on Day 1 of the respective study period, and at 0.25, 0.5, 0.75, 1, 1.25, 1.5, 2, 2.5, 3, 3.5, 4, 5, 6, 8, 10, 12, 16, 24, 28, 32, 36, 48 and 72 hours post-dose (24 blood samples per dosing period). If subjects experienced emesis within 12 hours after OXN 40/20 dosing or within 6 hours after dosing with the oral solutions, no further pharmacokinetic blood sampling was undertaken for the rest of the study period.

Pharmacokinetic:

AUCt, AUCINF, Cmax, tmax, LambdaZ and t1/2Z for oxycodone, noroxycodone, oxymorphone and noroxymorphone, and for naloxone, 6ß-naloxol and naloxone-3-glucuronide. Areas under the plasma concentration-time curve calculated from the time of dosing to the last measurable concentration (AUCt) were determined using the linear trapezoidal method. Where possible, the terminal phase rate constants (LambdaZ) were estimated using those points determined to be in the terminal loglinear phase. Half lives (t1/2Z) were determined from the ratio of ln 2 to LambdaZ. The areas under the plasma concentration-time curve between the last measured point and infinity were calculated from the ratio of the final observed plasma concentration (Clast) to LambdaZ. This was added to the AUCt to yield the area under the plasma concentration-time curve between the time of administration and infinity (AUCINF).

Safety: Safety was assessed using adverse events, clinical laboratory results, vital signs, physical examinations, and electrocardiograms (ECGs).

Bioanalytical Methods: The plasma samples were analyzed for oxycodone, noroxycodone, oxymorphone, and noroxymorphone, and for naloxone, 6β-naloxol and naloxone-3-glucuronide by validated bioanalytical assays.

Statistical Methods:

Pharmacokinetic Analysis:

Plasma concentration data and pharmacokinetic metrics were listed for subjects in the safety population. Plasma concentration data for each analyte were summarized descriptively by time-point and treatment for subjects in the safety population. Individual

and mean plasma concentrations for each analyte were also plotted over time for each treatment. Pharmacokinetic metrics (AUCt, AUCINF, Cmax, tmax, LambdaZ and t1/2Z) for each analyte were summarized descriptively by treatment and gender for subjects in the full analysis population for pharmacokinetic metrics. To have a valid pharmacokinetic metric, subjects must not have experienced emesis within 12 hours after OXN 40/20 dosing or within 6 hours after dosing with the oral solutions. Log transformed data for oxycodone and naloxone-3-glucuronide metrics AUCt, AUCINF and Cmax were analyzed using a mixed effect linear model, with fixed terms for treatment, sequence, and period and a random effect for subject. Treatment ratios/differences and their associated 90% confidence intervals were calculated from the least square means.
The primary comparison for the treatments was as follows:
• One tablet of OXN 40/20 in a fed state vs one tablet of OXN 40/20 in a fasted state.
The secondary comparisons for the treatments were dose-adjusted and were as follows:
• One tablet of OXN 40/20 in a fasted state vs oxycodone immediate release liquid 20 mg and naloxone immediate release liquid 10 mg in a fasted state.
• One tablet of OXN 40/20 in a fed state vs oxycodone immediate release liquid 20 mg and naloxone immediate release liquid 10 mg in a fasted state.
Sample Size Rationale: OXN1003 preliminary results were used for estimating the sample size for this study. This was a pilot, open-label, single-dose, 4-treatment, 4-period, randomized, crossover study to investigate the effect of food on oxycodone and naloxone pharmacokinetics, when administered as fixed combination prolonged-release tablets OXN 40/20 and 10/5, in 28 healthy subjects.
The following table shows within subject variation of log-transformed AUCt and Cmax based upon preliminary results from OXN1003:

	AUCt	Cmax
Oxycodone	0.171	0.169
Naloxone	0.163	0.192

Assuming a within subject standard deviation of 0.2, it was expected that 24 completed subjects would provide a 90% confidence interval for the ratio of log-transformed AUCt and Cmax with a precision of 0.1 in each direction. However, 26 subjects actually completed the study.
Results:
Pharmacokinetic: The availabilities of oxycodone and naloxone-3-glucuronide from OXN 40/20, as measured by AUCINF, were not affected by food.
Food did increase the mean observed Cmax values of oxycodone from OXN 40/20 by 28%, consistent with previous data for oxycodone given as a single entity. Naloxone peak plasma levels were 9% higher under fed condition. The naloxone-3-glucuronide Cmax values remained unaffected by food.
Recognizing the different characteristics of a prolonged-release and immediate-release profile, OXN 40/20 given fasted and after a high fat meal provided an equivalent availability of oxycodone and naloxone-3-glucuronide to the oxycodone liquid & naloxone liquid.

Table 15. PK Parameters [geometric mean (%CV)] of Oxycodone, Naloxone and Naloxone-3β -Glucuronide and Statistical Analysis Results for Food Effect on the Bioavailability of OXN 40/20 mg Tablets (Study OXN1008)

	Treatment A (Reference) OXN 40/20 mg, Fasted (n = 26)		Treatment B (Test) OXN 40/20 mg, Fed (n = 25)	
Analyte	C_{max} (ng/mL)	AUC (hr*ng/mL)	C_{max} (ng/mL)	AUC (hr*ng/mL)
Oxycodone[a]	37.4 (24.7)	466 (38.2)	47.6 (24.3)	555 (28.8)
Naloxone[a]	0.116 (109)	1.15 (97.1)	0.125 (66.9)	1.38 (67.7)
Naloxone-3β-glucuronide[a]	80.7 (29.1)	550 (29.5)	70.6 (28.9)	568 (26.1)
Statistical Analysis Results				
	C_{max} GLSM Ratio (90% CI)		AUC[a] GLSM Ratio (90% CI)	
	Treatment B/Treatment A		Treatment B/Treatment A	
Oxycodone	128 (118-138)%		114 (109-119)%	
Naloxone	109 (84.8-140)%		113 (99.3-129)%	
Naloxone-3β- Glucuronide	88.4 (81.9-95.4)%		99.7(94.4-105)%	

Abbreviations: AUC = area under the plasma drug concentration-time curve extrapolated to infinity; C_{max} = maximum concentration of drug in plasma; CI = confidence interval; CV = coefficient of variation; GLSM = geometric least squares mean; hr = hour; mL = milliliter; n = number of subjects; ng = nanogram.
[a] AUC for oxycodone and naloxone-3β-glucuronide, AUC_{0-t} for naloxone.
Source: post-text Table D-1, post-text Table D-2, post-text Table D-3; OXN1008 CSR Table 12, Table 14.2.3.6, Table 14

A: One tablet of OXN 40/20 fasted state, B: One tablet of OXN 40/20 fed

Oxycodone Summary of Ratios

PK Metrics	Treatment Comparison	LS Means Ratio[a] (%)	90% Confidence Interval[a] -Lower-	-Upper-
Cmax (ng/mL)	OXN 40/20 Fed vs. OXN 40/20 Fasted	128	118.46	137.86
	OXN 40/20 Fasted vs. Solution Fasted[b]	36.6	33.95	39.50
	OXN 40/20 Fed vs. Solution Fasted[b]	46.8	43.37	50.49
AUCt (ng.h/mL)	OXN 40/20 Fed vs. OXN 40/20 Fasted	115	109.74	119.52
	OXN 40/20 Fasted vs. Solution Fasted[b]	102	98.17	106.94
	OXN 40/20 Fed vs. Solution Fasted[b]	117	112.43	122.48
AUCINF (ng.h/mL)	OXN 40/20 Fed vs. OXN 40/20 Fasted	114	109.32	119.09
	OXN 40/20 Fasted vs. Solution Fasted[b]	103	98.52	107.33
	OXN 40/20 Fed vs. Solution Fasted[b]	117	112.41	122.47

Naloxone-3-glucuronide Summary of Ratios

PK Metrics	Treatment Comparison	LS Means Ratio[a](%)	90% Confidence Interval[a] -Lower-	-Upper-
Cmax (ng/mL)	OXN 40/20 Fed vs. OXN 40/20 Fasted	88.4	81.94	95.39
	OXN 40/20 Fasted vs. Solution Fasted[b]	29.2	27.07	31.51
	OXN 40/20 Fed vs. Solution Fasted[b]	25.8	23.93	27.87
AUCt (ng.h/mL)	OXN 40/20 Fed vs. OXN 40/20 Fasted	102	96.38	107.57
	OXN 40/20 Fasted vs. Solution Fasted[b]	99.9	94.57	105.56
	OXN 40/20 Fed vs. Solution Fasted[b]	102	96.28	107.50
AUCINF (ng.h/mL)	OXN 40/20 Fed vs. OXN 40/20 Fasted	99.7	94.37	105.28
	OXN 40/20 Fasted vs. Solution Fasted[b]	102	96.15	108.41
	OXN 40/20 Fed vs. Solution Fasted[b]	102	96.04	107.82

4.2.8 Synopsis of Food-effect study OXN1009 (Targiniq 10/5 mg)

Title of the Study: An open-label, single-dose, 3-treatment, 3-period, randomised crossover study in healthy subjects to assess the pharmacokinetics of oxycodone and naloxone after administration of oxycodone/naloxone prolonged release tablets 10/5 mg (OXN 10/5) in a fed and fasted state, and oxycodone hydrochloride immediate release liquid 10 mg (10 ml of 5 mg/5 ml solution) and naloxone hydrochloride liquid 5 mg (5 ml of 1 mg/1 ml solution) in a fasted state.

Objectives: The objectives of this study were to assess the pharmacokinetics, bioavailability and safety of OXN 10/5 administered in a fed and fasted state, and oxycodone immediate release liquid and naloxone liquid administered in a fasted state, to healthy subjects.

The primary objective was to assess the effect of food on the bioavailability of oxycodone and naloxone (or surrogate of naloxone) from OXN 10/5.

The secondary objective was to compare the pharmacokinetics of oxycodone and naloxone (or surrogate of naloxone) from OXN 10/5 with oxycodone immediate release liquid 10 mg and naloxone liquid 5 mg.

Methodology: Open-label, single dose, 3-treatment, 3-period, randomised crossover study in healthy male and female subjects.

Number of Subjects: It was planned to randomise 20 subjects with the aim that 14 subjects completed the study and provided valid pharmacokinetic data. A total of 20 subjects were actually randomised and 18 subjects completed the study.

Indication and Criteria for Inclusion: Healthy males and females, 18 to 55 years of age, free of significant abnormal findings as determined by medical history, physical examination, vital signs, and electrocardiogram (ECG).

Test Treatment, Dose, and Mode of Administration: Oxycodone/naloxone prolonged release (PR) tablet 10/5 mg (OXN 10/5), a PR combination tablet containing 10 mg of oxycodone HCl and 5 mg of naloxone HCl. Manufactured by Mundipharma Research GmbH & Co. KG, Germany.

The treatment was administered orally as follows:

Treatment A: One tablet of OXN 10/5 in a fasted state

Treatment B: One tablet of OXN 10/5 in a fed state

Reference Treatment, Dose, and Mode of Administration: OxyNorm® liquid, an immediate release liquid containing 5 mg/5 ml oxycodone HCl. Marketing Authorisation Holder is [redacted] (b) (4).

Naloxone HCl injection 1 mg/ml, given as an oral solution. Manufactured by [redacted] (b) (4).

Marketing Authorisation Holder is [redacted] (b) (4).

The treatment was given orally in the fasted state as follows:

Treatment C: Oxycodone immediate release liquid 10 mg (10 ml of 5 mg/5ml solution) and naloxone injection 5 mg (5 ml of 1 mg/1ml injection given as an oral solution)

Bioanalytical Methods: The plasma samples were analysed for oxycodone, noroxycodone, oxymorphone and noroxymorphone, and for naloxone, 6β-naloxol, naloxone-3-glucuronide, and 6β-naloxol-3-glucuronide using validated bioanalytical assays.

Statistical Methods:

Pharmacokinetic Analyses: For each analyte (oxycodone, naloxone-3-glucuronide, noroxycodone, oxymorphone, noroxymorphone, naloxone, 6β-naloxol, and 6β-naloxol-3-glucuronide), natural log transformed data for the pharmacokinetic parameters AUCt, AUCINF, and Cmax were analysed using a mixed effects model. Treatment ratios and their associated 90% confidence intervals were calculated from the least squares means.
The primary comparison for the treatments was as follows:
• One tablet of OXN 10/5 in a fed state vs one tablet of OXN 10/5 in a fasted state.
The secondary comparisons for the treatments were as follows:
• One tablet of OXN 10/5 in a fasted state vs oxycodone immediate release liquid 10 mg and naloxone liquid 5 mg in a fasted state.
• One tablet of OXN 10/5 in a fed state vs oxycodone immediate release liquid 10 mg and naloxone liquid 5 mg in a fasted state.
Sample Size Rationale: OXN1003 preliminary results were used for estimating the sample size for this study. This was a pilot, open-label, single-dose, 4-treatment, 4-period, randomized, crossover study to investigate the effect of food on oxycodone and naloxone pharmacokinetics, when administered as fixed combination prolonged-release tablets OXN 40/20 and 10/5, in 28 healthy subjects.
The following table shows within subject variation of log-transformed AUCt and Cmax based upon preliminary results from OXN1003:

	AUCt	Cmax
Oxycodone	0.171	0.169
Naloxone	0.163	0.192

Assuming a within subject standard deviation of 0.2, it was expected that 24 completed subjects would provide a 90% confidence interval for the ratio of log-transformed AUCt and Cmax with a precision of 0.1 in each direction.

Results:

Pharmacokinetic:

Oxycodone results

The geometric mean AUCt, AUCINF and Cmax values for OXN 10/5 were consistent with observations from previous studies (OXN1003 and OXN1016 study of 5/2.5 mg OXN).
The availability of oxycodone from OXN 10/5 fed was around 17% higher than for OXN 10/5 fasted in terms of AUCt and AUCINF, however the fed vs fasted comparison met the conditions required for bioequivalence, with the 90% confidence intervals for these comparisons falling within the 80-125% limits.
On average the increase in Cmax following the ingestion of a high-fat breakfast was very similar to that noted in earlier studies with the OXN tablet 40/20 (OXN1008), and also in studies involving **OxyContin®** tablets (AA03901, OC87-0501, OC93-0801 and OC99-0301). Overall, when OXN 10/5 was given after a high-fat breakfast, the mean observed Cmax increased by 27%. The 90% confidence interval associated with the mean Cmax ratio was outside the upper limit of acceptability for bioequivalence. For two subjects (#01001 and #01020), OXN 10/5 administered after a high-fat breakfast was associated with increases in Cmax values of 78% and 97% compared with OXN 10/5 given after an over-night fast. However, similar outlying results have been recorded in **OxyContin®** studies (increases in Cmax of greater than 130% in OC87-0501, and an increase of greater than 88% in OC93-0801). No such outliers were observed in the OXN 40/20

study (OXN1008). Subject 01001 experienced mild somnolence approximately 2 hours after dosing with OXN 10/5 (fed), and mild dizziness and abdominal pain within 4 hours after dosing with OXN 10/5 (fasted). She also experienced mild headache, abdominal pain, feeling abnormal and somnolence, and moderate postural dizziness within a few hours of dosing with the solution. No treatment-related adverse events were experienced by Subject 01020 following the administration of OXN 10/5 with food. She did experience mild paraesthesia and somnolence and moderate vasovagal syncope within a few hours of dosing with the solution. These adverse events were similar to those experienced by other subjects in the study.
OXN 10/5 fasted and OXN 10/5 fed both provided an equivalent dose-adjusted availability of oxycodone in terms of AUCt and AUCINF to the oxycodone liquid and naloxone liquid given orally. The 90% confidence interval for the AUC comparisons fell within the 80-125% limits of acceptability for bioequivalence. OXN 10/5 fasted and OXN 10/5 fed both provided a lower dose-adjusted Cmax ratio than oxycodone liquid and naloxone liquid given orally.

The mean half-life values were similar for all three treatments.

Table 16. PK Parameters [geometric mean (%CV)] of Oxycodone, Naloxone and Naloxone-3β -Glucuronide and Statistical Analysis Results for Food Effect on the Bioavailability of OXN 10/5 mg Tablets (Study OXN1009)

Analyte	Treatment A (Reference) OXN 10/5 mg, Fasted (n = 18)		Treatment B (Test) OXN 10/5 mg, Fed (n = 16)	
	C_{max} (ng/mL)	AUC_{0-t} (hr*ng/mL)	C_{max} (ng/mL)	AUC_{0-t} (hr*ng/mL)
Oxycodone	10.6 (26.5)	117 (24.3)	13.4 (13.7)	133 (22.0)
Naloxone	0.0234 (42.0)[b]	0.0791 (199)[b]	0.0305 (78.6)	0.0806 (161)
Naloxone-3β-glucuronide	21.9 (22.8)	147 (24.0)	19.6 (21.0)	147 (22.0)
Statistical Analysis Results				
	C_{max} GLSM Ratio (90% CI)		AUC[a] GLSM Ratio (90% CI)	
	Treatment B/Treatment A		Treatment B/Treatment A	
Oxycodone	127 (114-143) %		117 (113-121) %	
Naloxone	149 (110-201) %		127 (76.4-213) %	
Naloxone-3β-glucuronide	90.0 (79.8-102) %		99.0(93.8-104) %	

Abbreviations: AUC_{0-t} = area under the plasma drug concentration-time curve from time zero to the last measurable concentration after dosing; C_{max} = maximum concentration of drug in plasma; CI = confidence interval; CV = coefficient of variation; GLSM = geometric least squares mean; hr = hour; mL = milliliter; n = number of subjects; ng = nanogram.
[a] AUC for oxycodone and naloxone-3β-glucuronide; AUC_{0-t} for naloxone.
[b] n = 14 for naloxone in Treatment A due to un measurable concentrations in some subjects.
Source: post-text Table D-1, post-text Table D-2, post-text Table D-3; OXN1009 CSR Table 11, Table 14.2.2.5, Table 13

Summary of Ratios for Oxycodone Pharmacokinetic Parameters: Full Analysis Pharmacokinetic Population

PK Parameter	Treatment comparison	LS Means Ratio[a]	90% confidence interval	
			-Lower-	-Upper-
AUCt (ng.h/ml)	OXN 10/5 Fed vs. OXN 10/5 Fasted	117	112.83	121.77
	OXN 10/5 Fasted vs. Solution Fasted	100	96.59	104.06
	OXN 10/5 Fed vs. Solution Fasted	118	113.11	122.09
AUCINF (ng.h/ml)	OXN 10/5 Fed vs. OXN 10/5 Fasted	117	112.65	121.44
	OXN 10/5 Fasted vs. Solution Fasted	100	96.85	104.21
	OXN 10/5 Fed vs. Solution Fasted	118	113.17	122.00
Cmax (ng/ml)	OXN 10/5 Fed vs. OXN 10/5 Fasted	127	113.89	142.57
	OXN 10/5 Fasted vs. Solution Fasted	43.1	38.65	48.01
	OXN 10/5 Fed vs. Solution Fasted	54.9	49.10	61.37

[a] Transformed back to the linear scale, expressed as a percent.

Naloxone-3-glucuronide results

The geometric mean AUCt, AUCINF and Cmax values for OXN 10/5 were consistent with observations from previous studies (OXN1003 and OXN1016).

OXN 10/5 fed provided an equivalent availability of naloxone-3-glucuronide to OXN 10/5 fasted in terms of AUCt and AUCINF. The 90% confidence intervals for these comparisons fell within the 80-125% limits of acceptability for bioequivalence. The mean Cmax for OXN 10/5 fed was on average 10% lower than for OXN 10/5 fasted, and this was reflected in the 90% confidence interval which was marginally outside the lower limit of acceptability for bioequivalence.

OXN 10/5 fasted and OXN 10/5 fed both provided an equivalent dose-adjusted availability of naloxone-3-glucuronide in terms of AUCt and AUCINF to the naloxone liquid and oxycodone liquid given orally. The 90% confidence intervals for the AUC comparisons fell within the 80-125% limits of acceptability for bioequivalence. OXN 10/5 fasted and OXN 10/5 fed both provided a lower dose-adjusted Cmax ratio than naloxone liquid and oxycodone liquid given orally.

Summary of Ratios for Naloxone-3-glucuronide Pharmacokinetic Parameters: Full Analysis Pharmacokinetic Population

PK Parameter	Treatment comparison	LS Means Ratio[a]	90% confidence interval	
			-Lower-	-Upper-
AUCt (ng.h/ml)	OXN 10/5 Fed vs. OXN 10/5 Fasted	101	95.25	106.06
	OXN 10/5 Fasted vs. Solution Fasted	111	105.29	116.92
	OXN 10/5 Fed vs. Solution Fasted	112	105.68	117.68
AUCINF (ng.h/ml)	OXN 10/5 Fed vs. OXN 10/5 Fasted	99.0	93.76	104.44
	OXN 10/5 Fasted vs. Solution Fasted	112	106.36	117.75
	OXN 10/5 Fed vs. Solution Fasted	111	104.42	117.45
Cmax (ng/ml)	OXN 10/5 Fed vs. OXN 10/5 Fasted	90.0	79.78	101.62
	OXN 10/5 Fasted vs. Solution Fasted	39.1	34.75	43.90
	OXN 10/5 Fed vs. Solution Fasted	35.2	31.18	39.66

[a] Transformed back to the linear scale, expressed as a percent.

4.2.9 Synopsis of food-effect study OXN1505 (OXN 80/40 mg)

Title of the Study: An open-label, single-dose, 3-treatment, 3-period, randomised crossover study in healthy subjects to assess the pharmacokinetics of oxycodone and naloxone after administration of OXN PR tablet 80 mg/40 mg in a fed and fasted state, and oxycodone hydrochloride immediate release liquid 20 mg (20 mL of mg /5 mL solution) and naloxone hydrochloride liquid 10 mg (10 mL 1 mg/1 mL solution) in a fasted state.

Objectives & Endpoints:

Primary: The primary objective was to assess the effect of food on the bioavailability of oxycodone and naloxone from OXN PR tablet 80/40 mg.

Secondary: The secondary objectives were to compare the pharmacokinetics and safety of oxycodone and naloxone from OXN PR tablet 80/40 mg with oxycodone hydrochloride immediate release (IR) liquid 20 mg and naloxone hydrochloride liquid 10 mg.

Methodology: An open-label, single-dose, 3-treatment, 3-period, randomised crossover study.

Number of Subjects: A total of 28 healthy adult, male and female subjects were randomised to receive study medication, with the aim that 24 subjects completed the study and provided valid pharmacokinetic data.

Indication and Criteria for Inclusion: Healthy males and females aged 18 to 55 years, using highly effective methods of contraception, with a body mass index between 18 and 29, with no significant medical history were enrolled into the study.

Test Treatment, Dose, and Mode of Administration:

OXN PR tablets containing 80 mg oxycodone hydrochloride and 40 mg naloxone hydrochloride (80/40 mg), were administered as a single oral dose in a fed or fasted state with 140 mL of water in a standing position.

Reference Treatment, Dose, and Mode of Administration:

Oxycodone hydrochloride liquid (20 mg) and naloxone hydrochloride liquid (10 mg) were given orally as a single dose in a fasted state with 140 mL of water.

Naltrexone Cover:

Naltrexone hydrochloride (50 mg tablet) was administered orally, with 100 mL of water in a standing position, to reduce opioid-related adverse events at -13 h (1 x 50 mg), -1 h (2 x 50 mg) and 23 h (1 x 50 mg) relative to administration of study medication.

Treatment Schedule: Subjects were administered a different treatment in each study period according to a random allocation schedule (RAS). In each study period, subjects were administered a single dose of study drug on the morning of Day 1. They then remained in the study unit for 36 hours if they were randomised to receive oxycodone/naloxone liquid 20/10 mg, or 48 hours if they were randomised to receive OXN PR tablet 80/40 mg (fed or fasted). Subjects fasted from food for at least 8 hours prior to dosing. Subjects allocated to a fed treatment consumed a high-fat breakfast in the 30 minutes before dosing.

The dose of OXN PR was fixed at 80/40 mg, and the dose of oxycodone hydrochloride liquid and naloxone hydrochloride liquid was fixed at 20 and 10 mg, respectively.

Results:

Pharmacokinetic:

Oxycodone: OXN PR 80/40 mg fed provided an equivalent availability of oxycodone to that from OXN PR 80/40 mg fasted in terms of AUCt and AUCINF (geometric mean ratios of 116.19% and 116.13%), with the 90% confidence intervals (CI) for these comparisons falling within the 80-125% limits of acceptability for bioequivalence. Administration of OXN PR 80/40 mg with a high fat meal increased Cmax in comparison to OXN PR 80/40 mg fasted, with a geometric mean ratio of 128.87%, and the upper 90% confidence interval falling outside the limit of acceptability for bioequivalence (upper CI 137.4%).

OXN PR 80/40 mg fasted provided an equivalent dose-adjusted availability of oxycodone in terms of AUCt and AUCINF to the oxycodone oral liquid given together with naloxone oral liquid (geometric mean ratios of 103.48% and 103.35% respectively). Compared with the fasted treatment however, the OXN PR 80/40 mg fed treatment provided slightly increased exposure (geometric mean ratios of 120.7% and 120.5%, upper CI of 126.9% and 126.6% for AUCt and AUCINF respectively) compared to the oxycodone/naloxone liquid treatment in a fasted state. As expected, OXN PR 80/40 mg fasted and fed both provided a lower dose-adjusted Cmax ratio than oxycodone oral liquid given together with naloxone oral liquid (geometric mean ratios of 38.97% and 51.50% for fasted and fed respectively, with lower and upper 90% CI below the 80% limit for bioequivalence).

The mean half-life for oxycodone was similar for all treatments, with a value of 4.6 hours for OXN PR 80/40 mg fasted and fed, and 3.7 hours for the IR oxycodone and naloxone solution.

The median tmax was the same for OXN PR 80/40 mg fasted and fed, at 3.5 hours, and as expected was earlier for the IR solution at 1 hour.

Naloxone: Administration of OXN PR 80/40 mg with food did not increase the oral bioavailability of naloxone, (with geometric mean ratios of 109.84% and 102.18% for AUCt and AUCINF respectively). The Cmax ratio increased to 156.83%, with an upper 90% confidence interval falling outside of the 125% limit (201.0%).

Compared to the IR oxycodone and naloxone solution, OXN PR 80/40 mg fasted and fed naloxone dose-adjusted geometric mean ratios for AUCt were 176.70% and 192.11% respectively, with upper limits for both comparisons falling outside of the 125% limit for bioequivalence (AUCINF could not be characterized for the majority of subjects following treatment with the IR solution). As anticipated, when comparing controlled release formulations with an IR formulation, the dose-adjusted Cmax was reduced, with geometric mean ratios of 43.46% and 67.86% for the fasted and fed treatments respectively.

Mean half-life for naloxone was similar for all treatments, with values of 8.5, 7.9 and 6.9 hours for OXN PR 80/40 mg fasted, fed and the IR solution respectively.

Naloxone-3-glucuronide: OXN PR 80/40 mg fed provided an equivalent availability of naloxone-3-glucuronide to OXN PR 80/40 fasted in terms of AUCt, AUCINF and Cmax ratios. The 9% confidence intervals for each bioequivalence comparison fell within the 80-125% limits of acceptability.

OXN PR 80/40 mg fasted provided an equivalent dose-adjusted availability of naloxone-3-glucuronide in terms of AUCINF to the naloxone oral liquid given together with the oxycodone oral liquid, but availability increased by approximately 20% for AUCt, with the upper 90% limit for the comparison falling above the acceptance limit (upper CI

126.4%). OXN PR 80/40 mg fed demonstrated increased availability by approximately 20%, with upper 90% confidence intervals falling slightly above the acceptance limit for both AUCt and AUCINF (upper CI 126.8% and 125.1% respectively). OXN PR 80/40 mg fasted and fed both provided a lower dose-adjusted Cmax ratio than naloxone oral liquid given together with oxycodone oral liquid (geometric mean ratios of 38.29% and 34.75% respectively).

Table 17. PK Parameters [geometric mean (SD)] of Oxycodone, Naloxone, and Naloxone-3β-Glucuronide and Statistical Analysis Results for Relative Bioavailability of OXN 80/40 mg (Study OXN1505)

Analyte	Treatment A OXN 80/40 mg Fasted (n =24)		Treatment B OXN 80/40 mg Fed (n=23)	
	C_{max} (ng/mL)	AUC_{0-t} (hr*ng/mL)	C_{max} (ng/mL)	AUC_{0-t} (hr*ng/mL)
Oxycodone	84.6 (1.24)	1032 (1.31)	110 (1.19)	1238 (1.29)
Naloxone	0.239 (1.85)	2.68 (1.64)	0.378 (1.74)	2.94 (1.50)
Naloxone-3β-glucuronide	202 (1.31)	1360 (1.24)	185 (1.23)	1381 (1.25)
Statistical Analysis Results				
	C_{max} GLSM Ratio (90% CI) Treatment A/Treatment B		AUC[a] GLSM Ratio (90% CI) Treatment A/Treatment B	
Oxycodone	129 (121-137) %		116 (110-122) %	
Naloxone	157 (122-201) %		110 (96.9-125) %	
Naloxone-3β-glucuronide	93.1 (85.5-101) %		102 (97.8-106) %	

Abbreviations: AUC_{0-t} = area under the plasma drug concentration-time curve from time zero to the last measurable concentration after dosing; C_{max} = maximum concentration of drug in plasma; CI = confidence interval; GLSM = geometric least squares mean; hr = hour; mL = milliliter; n = number of subjects; ng = nanogram; SD = standard deviation.

[a] AUC for oxycodone and naloxone-3β-glucuronide; AUC_{0-t} for naloxone.

Source: OXN1505 CSR Table 14, Table 15, Table 16, Table 17, Table 18, Table 19

4.2.10 Synopsis of dose-proportionality study OXN1506

Title of the Study: An open-label, single-dose, 7-treatment, 5-period, randomised incomplete crossover study to compare the dose proportionality of an oxycodone/naloxone prolonged release tablet at different strengths (2.5/1.25 mg, 10/5 mg, 15/7.5 mg, 30/15 mg, 40/20 mg, 60/30 mg and 80/40 mg), administered to healthy subjects in a fasted state.

Objectives and Endpoints:

Primary objective: The primary objective was to assess the pharmacokinetics and dose-proportionality of five new (2.5/1.25 mg, 15/7.5mg, 30/15 mg, 60/30mg and 80/40 mg) and two existing strengths (10/5 mg and 40/20 mg) of OXN PR tablets.

Study endpoints: The pharmacokinetic parameters that were of interest for the study included: AUCt, AUCINF and Cmax (considered as main endpoints), and tmax, LambdaZ and t.Z (considered as secondary endpoints), calculated for plasma concentrations of oxycodone, noroxycodone, oxymorphone and noroxymorphone, and for naloxone and naloxone-3-glucuronide.

Number of Subjects: It was planned that 48 healthy adult male and female subjects, were to have been randomised to receive study medication with the aim that 42 subjects would complete the study and provide valid PK data. A total of 105 subjects were enrolled into the study, 48 were randomised to receive study medication and provide PK data and 40 subjects completed.

Indication and Criteria for Inclusion:

Male or female subjects were required to have been between 18 and 55 years old and willing to use highly effective methods of contraception. Female subjects could not be pregnant or lactating. Body weight must have been between 55 and 100 kg with a body mass index (BMI) between 18 and 29 kg/m2. Subjects must have been healthy, without relevant medical history and free from significant abnormal clinical findings and willing to eat all the food supplied throughout the study. Subjects must not have taken opioid-based medications in the last 30 days or have a history of drug or alcohol abuse. Subjects must have adhered to all restrictions regarding food intake, smoking and consumption of alcoholic beverages according to the study design.

Test Treatment, Dose, and Mode of Administration: Subjects were administered oxycodone/naloxone prolonged release (OXN PR) tablets at different strengths (2.5/1.25 mg, 15/7.5 mg, 30/15 mg, 60/30 mg and 80/40 mg), in a fasted state with 140 mL water.

Reference Treatment, Dose, and Mode of Administration:

The well-characterised doses of OXN PR (10/5 mg and 40/20 mg) were administered as a reference with 140 mL water.

Naltrexone Cover, Dose and Mode of Administration:

Naltrexone cover was provided at -13 hours (1 x 50mg tablet), -1 hour (2 x 50 mg tablet) and 23 hours (1 x 50 mg tablet) relative to the test treatment, with 100 mL water.

Bioanalytical methods:

Plasma concentrations of oxycodone, noroxycodone, oxymorphone, noroxymorphone, naloxone and naloxone-3-glucuronide were quantified by validated bioanalytical methods.

Statistical Methods:

The primary objective of the study was to assess the pharmacokinetics and dose proportionality of five new (2.5/1.25 mg, 15/7.5 mg, 30/15 mg, 60/30 mg and 80/40 mg) and two existing (10/5 mg and 40/20 mg) strengths of OXN PR tablets.
It was assumed that AUCt was proportional to (b) (4) where ρ was an estimated parameter. The alternative hypothesis was that ρ had the value 1 which implied that oxycodone (or naloxone) has dose proportionality. The criterion for setting the null hypothesis was to find the values of ρ that would imply the fitted values for the extrema of the doses (80/40 mg and 2.5/1.25 mg) had a dose-adjusted ratio outside the standard bioequivalence bounds of 80% to 125%. Hence the null hypothesis was that ρ lies outside of the range (0.936, 1.064).
Log-transformed AUCt parameters were analysed using a mixed model repeated measures (MMRM) model. The principal analysis had fixed terms for log(dose), sequence, period and random terms for subject. The estimated coefficient for log(dose) was compared to the reference value of 1 as a global test of dose-proportionality. Pharmacokinetic parameters with a value of zero were excluded from the analysis. Interval estimation was performed based on a MMRM for log transformed AUCt, with fixed effects for log(dose), sequence and period, with a subject level random intercept. The null hypothesis was rejected if the 90% confidence interval (CI) for ρ lay within the range (0.936, 1.064).
In terms of secondary analyses, the primary analysis was repeated for the parameters AUCINF and Cmax.
Secondary analyses also applied MMRM models with fixed terms for treatment, sequence, period and a random term for subject. The relative dose-adjusted systemic bioavailabilities (Frelt, and FreIINF) were calculated from the ratios of AUCt and, where possible AUCINF values for the comparisons outlined below:
· OXN PR tablet 2.5 mg/1.5 mg vs OXN PR tablet 40/20 mg
· OXN PR tablet 10 mg/5 mg vs OXN PR tablet 40/20 mg
· OXN PR tablet 15 mg/7.5 mg vs OXN PR tablet 40/20 mg
· OXN PR tablet 30 mg/15 mg vs OXN PR tablet 40/20 mg
· OXN PR tablet 60 mg/30 mg vs OXN PR tablet 40/20 mg
· OXN PR tablet 80 mg/40 mg vs OXN PR tablet 40/20 mg
Dose-adjusted Cmax ratios were calculated making the comparisons outlined above.
To perform the dose-adjustment, the recorded parameter values (AUCt, AUCINF and Cmax) for each treatment was divided by the dose (mg) for that treatment before inclusion in the model. Dose-adjustments, in terms of actual data transformations, were used with the secondary analyses or pair-wise equivalence tests only.For oxycodone and naloxone (or surrogate naloxone-3-glucuronide) AUCt, AUCINF, and Cmax, a mixed-model analysis of variance was used to compare logarithmic-transformed (base e) values with fixed effects for sequence, period, and treatment, and a random effect of subject within sequence. The 90% CI were estimated for the ratio of exponentiated least square (LS) means. Equivalence margins were set at 80% and 125%. The parameters tmax, LambdaZ (if available) and t.Z were analysed similarly but using untransformed data.
Pharmacokinetic results:
Oxycodone Results:
Each of the OXN PR test treatments provided an equivalent dose-adjusted availability of oxycodone to the reference treatment in terms of AUCt and AUCINF. Geometric mean

ratios for the comparisons ranged from 100.3% to 105.8% for AUCt. Associated 90% confidence interval (CI) values were all within the 80-125% limits of acceptability for bioequivalence. For AUCINF, geometric mean ratios for the comparisons ranged from 100.1% to 108.4%. Associated 90% CI values were also within the limits of acceptability for bioequivalence.

Dose-adjusted Cmax ratios were equivalent for all comparisons, with the exception of the 2.5/1.25 mg treatment where the geometric mean ratio was 127.6%, and the upper 90% CI fell above the 125% limit for bioequivalence at 133.4%. Geometric mean ratios from the other treatments ranged from 101.0% to 118.7%, with associated 90% CI were within the limits of acceptability for bioequivalence.

AUCt, AUCINF and Cmax were to be considered dose-proportional if the estimates of the coefficient of log(dose) were within the interval [0.936, 1.064]. Results from the power model demonstrated AUCt and AUCINF to be proportional to dose, with estimates for the coefficient for log(dose) of 0.985 and 0.978 respectively. The 90% CI values were within the 0.936-1.064 range for both parameters (0.976-0.994 for AUCt and 0.969-0.987 for AUCINF). Application of the power model to assess Cmax, yielded a coefficient for log(dose) estimate of 0.930, and the lower 90% CI fell below the lower limit, with a value of 0.919.

The mean half-life for oxycodone ranged from 3.90 to 5.30 hours and the median tmax ranged from 2.5 to 3.8 hours.

Figure 3 Mean Plasma Concentration Versus Time Plot on a Linear Scale for the Analyte Oxycodone

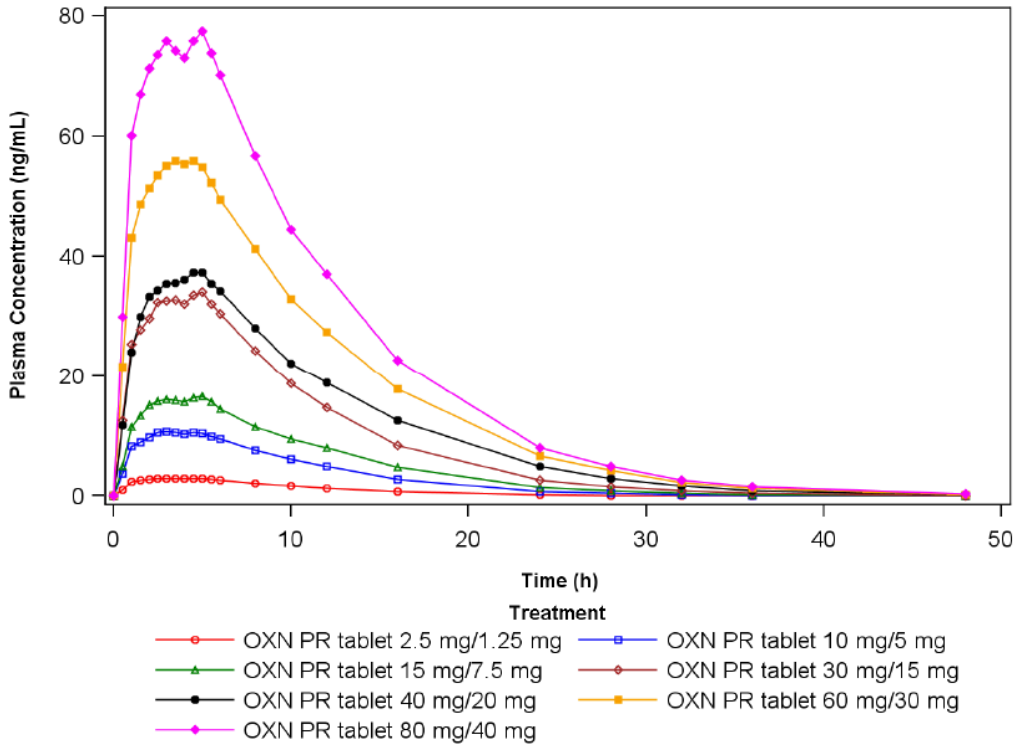


Table 14 Summary Statistics for the Pharmacokinetic Parameters for the Analyte Oxycodone: Pharmacokinetic Population

PK Parameter (unit)		OXN PR 2.5/1.25 mg (N=31)	OXN PR 10/5 mg (N=31)	OXN PR 15/7.5 mg (N=32)	OXN PR 30/15 mg (N=31)	OXN PR 40/20 mg (N=32)	OXN PR 60/30 mg (N=31)	OXN PR 80/40 mg (N=30)
AUCt (ng•h/mL)	n	31	31	32	31	32	31	30
	Geometric Mean	33.4	126.5	197.9	395.7	488.7	721.3	972.9
	log(SD/SE)	0.26/0.05	0.21/0.04	0.27/0.05	0.25/0.04	0.25/0.04	0.28/0.05	0.26/0.05
	Mean	34.45	129.08	205.06	407.87	504.01	749.32	1004.5
	(SD/SE)	(8.99/1.62)	(25.42/4.57)	(55.79/9.86)	(105.87/19.01)	(127.55/22.55)	(213.53/38.35)	(250.94/45.81)
	Median	32.6	130.4	202.3	386.5	501.5	693.1	950.4
	Min, Max	22, 57	79, 166	117, 338	275, 735	308, 825	446, 1259	618, 1426
AUCINF (ng•h/mL)	n	31	31	32	31	32	31	30
	Geometric Mean	34.4	127.4	199.1	397.2	491.0	723.5	977.0
	log(SD/SE)	0.25/0.04	0.21/0.04	0.27/0.05	0.25/0.04	0.25/0.04	0.28/0.05	0.26/0.05
	Mean	35.41	129.98	206.32	409.40	506.29	751.62	1008.5
	(SD/SE)	(8.93/1.60)	(25.58/4.59)	(56.31/9.95)	(106.11/19.06)	(127.54/22.55)	(214.10/38.45)	(251.32/45.89)
	Median	34.0	131.2	203.4	388.7	503.4	697.5	953.9
	Min, Max	23, 58	80, 167	117, 339	277, 737	309, 827	448, 1262	619, 1428
Cmax (ng/mL)	n	31	31	32	31	32	31	30
	Geometric Mean	3.23	11.79	17.74	36.28	39.80	58.32	82.03
	log(SD/SE)	0.222/0.040	0.208/0.037	0.266/0.047	0.228/0.041	0.233/0.041	0.213/0.038	0.221/0.040
	Mean	3.311	12.05	18.35	37.24	40.86	59.60	83.94
	(SD/SE)	(0.746/0.134)	(2.670/0.480)	(4.826/0.853)	(9.042/1.624)	(9.516/1.682)	(12.53/2.252)	(17.83/3.257)
	Median	3.300	11.80	17.75	36.40	40.45	60.60	89.30
	Min, Max	2.27, 5.030	8.34, 21.70	11.1, 28.80	25.6, 64.90	24.4, 60.80	36.4, 87.20	57.6, 113.0
tmax (h)	n	31	31	32	31	32	31	30
	Mean	2.74	2.74	3.03	3.21	3.25	3.34	3.35
	(SD/SE)	(1.33/0.24)	(1.36/0.24)	(1.29/0.23)	(1.38/0.25)	(1.33/0.23)	(1.32/0.24)	(1.61/0.29)
	Median	2.5	3.0	3.0	3.0	3.5	3.5	3.8
	Min, Max	1, 6	1, 6	1, 6	1, 6	1, 6	1, 5	1, 6

Table 15 Statistical results of Bioequivalence Assessments for the Pharmacokinetic Parameters for the Analyte Oxycodone: Pharmacokinetic Population

		AUCt			AUCINF			Cmax		
Treatment Group	Versus Reference Group	n	Test/ Reference (a)	90% Confidence Interval (b)	n	Test/ Reference (a)	90% Confidence Interval (b)	n	Test/ Reference (a)	90% Confidence Interval (b)
OXN PR 2.5/1.25 mg	OXN PR 40/20 mg	31	105.8	(101.9 , 109.8)	31	108.4	(104.4 , 112.4)	31	127.6	(122.0 , 133.4)
OXN PR 10/5 mg	OXN PR 40/20 mg	31	101.8	(98.0 , 105.7)	31	102.1	(98.3 , 106.0)	31	117.1	(111.9 , 122.6)
OXN PR 15/7.5 mg	OXN PR 40/20 mg	32	104.8	(100.9 , 108.9)	32	104.9	(101.1 , 109.0)	32	118.6	(113.3 , 124.2)
OXN PR 30/15 mg	OXN PR 40/20 mg	31	103.9	(100.0 , 108.0)	31	103.7	(99.9 , 107.7)	31	118.7	(113.4 , 124.3)
OXN PR 60/30 mg	OXN PR 40/20 mg	31	100.5	(96.8 , 104.4)	31	100.3	(96.6 , 104.1)	31	101.0	(96.5 , 105.7)
OXN PR 80/40 mg	OXN PR 40/20 mg	30	100.3	(96.5 , 104.2)	30	100.1	(96.4 , 104.0)	30	103.8	(99.1 , 108.7)

Cross reference: Table 14.2.4 and Listing 16.2.6.2.
a: Estimate from mixed-effects linear model. Natural log parameter estimates calculated by transforming the log-scale estimates back to the linear scale, that is estimates of ratios.
b: 90% CI obtained by transforming the CI on the log-scale to the ratio scale.
Data analysed using a fixed effects linear model with treatment, sequence and period as fixed effect factors and subject blocked within sequence as a random effect. Treatment comparisons not shown in the table were not estimated due to lack of valid results. Note: The analyses consider all subjects whether or not both sequences of the respective treatment comparison were completed.

Table 14.2.7.A
Statistical Results of Power Model for PK Parameters (excluded OXN PR tablet 2.5 mg/1.25 mg)

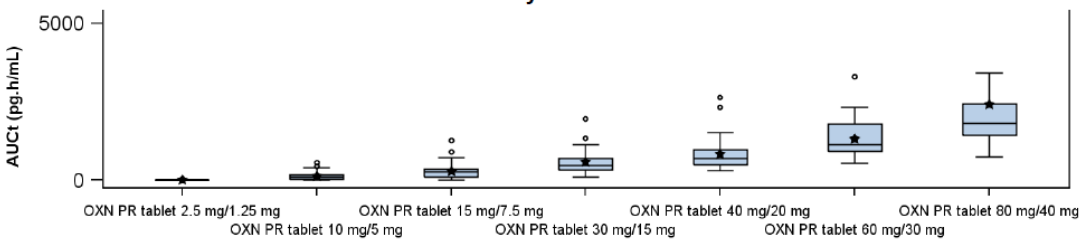
Full Analysis Population for Pharmacokinetic Parameters
Analyte: Oxycodone

Parameter	Contrast or Coefficient	Estimate	SE / degrees of freedom	90% Confidence Interval	p-value
AUCINF (ng.h/mL)	log(Dose)	0.981	0.01 / 135.2	0.9654, 0.9959	
	Intercept	2.657	0.10 / 53.6	2.4915, 2.8226	
	Sequence (F-Statistic)		41.3		0.4261
	Period (F-Statistic)		134.7		<.0001
	Between-Subject CV	0.240			
	Within-Subject CV	0.087			
AUCt (ng.h/mL)	log(Dose)	0.982	0.01 / 135.2	0.9670, 0.9977	
	Intercept	2.645	0.10 / 53.7	2.4790, 2.8107	
	Sequence (F-Statistic)		41.3		0.4261
	Period (F-Statistic)		134.7		<.0001
	Between-Subject CV	0.240			
	Within-Subject CV	0.088			
Cmax (ng/mL)	log(Dose)	0.913	0.01 / 136.3	0.8934, 0.9329	
	Intercept	0.382	0.09 / 69.7	0.2274, 0.5366	
	Sequence (F-Statistic)		41.5		0.3544
	Period (F-Statistic)		135.5		0.3784
	Between-Subject CV	0.204			
	Within-Subject CV	0.113			

Naloxone Results:

A number of profiles were below the limit of quantification (LLOQ) of the assay, mostly for oxymorphone and naloxone and generally at the two lowest dose levels. It was anticipated that low oral bioavailability could prevent complete pharmacokinetic assessment of naloxone, especially at the lower doses tested. This is reflected in the number of AUCINF values available for naloxone from the various treatments, ranging from 1 out of 31 for the 2.5/1.25 mg dose, to 27 out of 30 for the 80/40 mg dose. Conclusions for the naloxone component are therefore based on naloxone-3-glucuronide parameters.

Figure 14.4.6
Pharmacokinetic Parameters
Full Analysis Population for Pharmacokinetic Parameters
Analyte= Naloxone



Pharmacokinetic Parameters
Full Analysis Population for Pharmacokinetic Parameters
Analyte= Naloxone

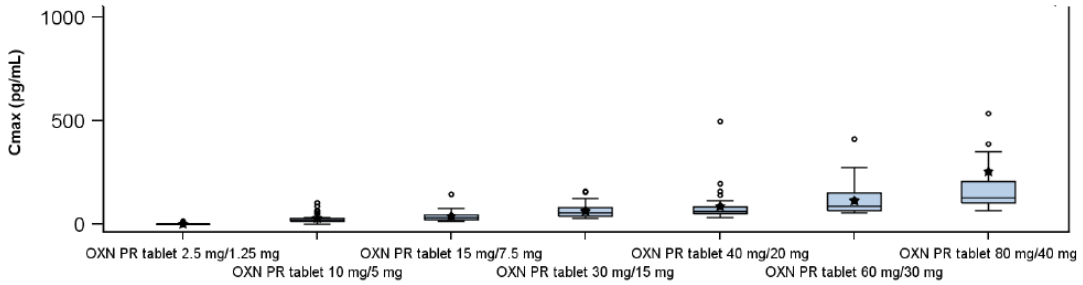


Table 14.2.7.A
Statistical Results of Power Model for PK Parameters (excluded OXN PR tablet 2.5 mg/1.25 mg)

Full Analysis Population for Pharmacokinetic Parameters
Analyte: Naloxone

Parameter	Contrast or Coefficient	Estimate	SE / degrees of freedom	90% Confidence Interval	p-value
AUCINF (pg.h/mL)	log(Dose)	1.095	0.07 / 64.9	0.9700, 1.2197	
	Intercept	2.946	0.36 / 89.2	2.3416, 3.5506	
	Sequence (F-Statistic)		36.5		0.8357
	Period (F-Statistic)		59.9		0.3766
	Between-Subject CV	0.384			
	Within-Subject CV	0.385			
AUCt (pg.h/mL)	log(Dose)	1.633	0.07 / 135.8	1.5185, 1.7470	
	Intercept	0.626	0.38 / 117.9	-0.0101, 1.2627	
	Sequence (F-Statistic)		41.6		0.5382
	Period (F-Statistic)		134.1		0.4752
	Between-Subject CV	0.648			
	Within-Subject CV	0.643			
Cmax (pg/mL)	log(Dose)	0.929	0.04 / 134.3	0.8568, 1.0010	
	Intercept	0.895	0.25 / 108.7	0.4794, 1.3104	
	Sequence (F-Statistic)		40.4		0.6901
	Period (F-Statistic)		132.7		0.4973
	Between-Subject CV	0.442			
	Within-Subject CV	0.405			

Naloxone-3-Glucuronide Results:

Each of the OXN PR test treatments provided an equivalent dose-adjusted availability of naloxone-3-glucuronide to the reference treatment in terms of AUCt and AUCINF. Geometric mean ratios for the comparisons ranged from 92.0% to101.9% for AUCt. Associated 90% CI were all within the 80-125% limits of acceptability for bioequivalence. For AUCINF, geometric mean ratios for the comparisons ranged from 93.0% to 106.8%. Associated 90% CI were also within the limits of acceptability for bioequivalence. Dose-adjusted Cmax ratios were equivalent for all comparisons, with geometric mean ratios ranging from 102.8% to 115.6% and associated 90% CI within the limits of acceptability for bioequivalence.

Results from the power model demonstrated AUCINF and AUCt to be proportional to dose, with estimates for the coefficient for log(dose) of 1.019 for both parameters. The 90% CI values were within the 0.936-1.064 range for both parameters (1.007-1.031 for AUCINF and 1.007-1.030 for AUCt). Application of the power model to assess Cmax, yielded an coefficient for log(dose) estimate of 0.975, with 90% CI values falling within the limits. The mean half-life of naloxone-3-glucuronide was similar across all treatments, ranging from 8.53 to 10.54 hours.

The median tmax was also similar across all treatments, ranging from 0.5 to 1 hour.

Table 17 Statistical results of Bioequivalence Assessments for the Pharmacokinetic Parameters for the Analyte Naloxone-3-Gluronide: Pharmacokinetic Population

		AUCt			AUCINF			Cmax		
Treatment Group	Versus Reference Group	n	Test/ Reference (a)	90% Confidence Interval (b)	n	Test/ Reference (a)	90% Confidence Interval (b)	n	Test/ Reference (a)	90% Confidence Interval (b)
OXN PR 2.5/1.25 mg	OXN PR 40/20 mg	31	97.4	(93.0 , 101.9)	17	96.7	(92.0 , 101.8)	31	115.6	(107.2 , 124.6)
OXN PR 10/5 mg	OXN PR 40/20 mg	31	92.0	(87.8 , 96.5)	26	93.0	(88.9 , 97.3)	31	104.1	(96.4 , 112.3)
OXN PR 15/7.5 mg	OXN PR 40/20 mg	32	97.3	(92.8 , 102.0)	29	94.1	(89.8 , 98.5)	32	103.8	(96.2 , 112.1)
OXN PR 30/15 mg	OXN PR 40/20 mg	31	97.3	(92.8 , 102.0)	18	96.9	(92.1 , 102.0)	31	114.5	(106.1 , 123.6)
OXN PR 60/30 mg	OXN PR 40/20 mg	31	101.6	(97.0 , 106.5)	27	99.1	(94.8 , 103.7)	31	102.8	(95.3 , 110.9)
OXN PR 80/40 mg	OXN PR 40/20 mg	30	101.9	(97.2 , 106.8)	28	99.8	(95.3 , 104.5)	30	105.4	(97.5 , 113.9)

Cross reference: Table 14.2.4 and Listing 16.2.6.2.
Data analysed using a fixed effects linear model with treatment, sequence and period as fixed effect factors and subject blocked within sequence as a random effect. Treatment comparisons not shown in the table were not estimated due to lack of valid results. Note: The analyses consider all subjects whether or not both sequences of the respective treatment comparison were completed.
a: Estimate from mixed-effects linear model. Natural log parameter estimates calculated by transforming the log-scale estimates back to the linear scale, that is estimates of ratios.
b: 90% CI obtained by transforming the CI on the log-scale to the ratio scale.

Table 14.2.7.A
Statistical Results of Power Model for PK Parameters (excluded OXN PR tablet 2.5 mg/1.25 mg)

Full Analysis Population for Pharmacokinetic Parameters
Analyte: Naloxone Glucuronide

Parameter	Contrast or Coefficient	Estimate	SE / degrees of freedom	90% Confidence Interval	p-value
AUCINF (ng.h/mL)	log(Dose)	1.036	0.01 / 102.2	1.0187, 1.0526	
	Intercept	2.745	0.13 / 50.9	2.5255, 2.9646	
	Sequence (F-Statistic)		41.4		0.5160
	Period (F-Statistic)		102.1		0.0157
	Between-Subject CV	0.324			
	Within-Subject CV	0.089			
AUCt (ng.h/mL)	log(Dose)	1.042	0.01 / 135.0	1.0234, 1.0615	
	Intercept	2.652	0.13 / 51.9	2.4324, 2.8711	
	Sequence (F-Statistic)		41.2		0.5732
	Period (F-Statistic)		134.6		0.1501
	Between-Subject CV	0.321			
	Within-Subject CV	0.109			
Cmax (ng/mL)	log(Dose)	0.995	0.02 / 135.9	0.9624, 1.0268	
	Intercept	0.882	0.14 / 77.9	0.6550, 1.1087	
	Sequence (F-Statistic)		40.6		0.7597
	Period (F-Statistic)		134.9		0.7233
	Between-Subject CV	0.285			
	Within-Subject CV	0.185			

4.2.11 Synopsis of Multiple dose PK study OXN1011 (Targniq 40/20 mg)

Title of the Study: An open-label, multiple-dose, 3-treatment, 3-period, randomised crossover study to determine the bioequivalence of oxycodone and naloxone glucuronide from oxycodone/naloxone prolonged-release (PR) tablet 40/20 mg (OXN 40/20) compared with oxycodone from oxycodone PR tablet 40 mg, and naloxone glucuronide from naloxone controlled-release (CR) tablets 2 x 10 mg.

Objectives: To determine the bioequivalence of oxycodone and naloxone glucuronide from OXN 40/20 mg tablet compared with oxycodone from oxycodone PR tablet 40 mg, and naloxone glucuronide from naloxone CR tablets 2 x 10 mg at steady state.

Methodology: Open-label, single-centre, multiple-dose, 3-treatment, 3-period, randomised, crossover design.

Number of Subjects: It was planned to randomise 34 subjects with the aim that 26 subjects completed the study and provided valid pharmacokinetic data. A total of 34 subjects were actually randomised and 28 subjects completed the study.

Indication and Criteria for Inclusion: Healthy males and females, 18 - 55 years of age, free of significant abnormal findings as determined by medical history, physical examination, vital signs, and electrocardiogram (ECG).

Test Treatment, Dose, and Mode of Administration:

Oxycodone/naloxone prolonged-release (PR) tablets 40/20 mg (OXN 40/20), a PR combination tablet containing 40 mg of oxycodone HCl and 20 mg of naloxone HCl, manufactured by Mundipharma ResearchGmbH & Co. KG, Germany.

• Treatment A: One OXN 40/20 tablet administered 12-hourly on Days 1-3 and the morning of Day 4 (7 doses in total).

Reference Treatment, Dose, and Mode of Administration:

Oxycodone hydrochloride prolonged-release tablet 40 mg (oxycodone PR tablet 40 mg) manufactured by [redacted] (b) (4).

Naloxone controlled-release (CR) tablet 10 mg manufactured by Mundipharma Research GmbH & Co. KG, Germany.

• Treatment B: One oxycodone PR tablet 40 mg administered 12-hourly on Days 1-3 and the morning of Day 4 (7 doses in total).

• Treatment C: Two naloxone CR tablets 10 mg administered 12-hourly on Days 1-3 and the morning of Day 4 (7 doses in total).

Naltrexone Administration: Naltrexone was administered with the study drug in this trial to reduce opioid-related side effects. For consistency naltrexone was included in the naloxone CR tablet 2 x 10 mg arm.

Naltrexone hydrochloride tablets 50 mg (Nalorex® tablets, Bristol-Myers Squibb Pharmaceuticals Limited, UK). *Changed to Nemexin® tablets, Bristol Myers Squibb Pharmaceuticals Limited, Germany by Administrative Change 1, dated 27 May 2005.*

One naltrexone tablet 50 mg, taken every 12 hours from the evening of Day -1 until the morning of Day 5 (10 doses).

Statistical Methods:

Pharmacokinetic Analysis: Logarithmic-transformed values for steady-state pharmacokinetic metrics AUCτ, Cmaxss and Cminss were compared between treatments (test versus reference). The 90% confidence intervals were estimated for the ratios (test/reference) of exponentiated Least Square Means. The primary comparisons were performed for oxycodone and naloxone-3-glucuronide, and the secondary comparisons

were performed for oxycodone metabolites and naloxone and its other metabolites.
Sample Size Rationale: The study was designed to have an overall power of more than 90% to demonstrate the bioequivalence of oxycodone from OXN 40/20 and oxycodone PR tablet 40 mg, and naloxone-3-glucuronide from OXN 40/20 versus naloxone CR tablets 2 x 10 mg. Assuming a true population ratio (test/reference) of 1 (100%) and an intra-subject deviation of 0.2 on the log-scale, this could be achieved with 26 completing subjects.

Results:

Pharmacokinetic:

Steady state conditions were confirmed by examining the trough concentrations for oxycodone and naloxone-3-glucuronide, and showing them to be no longer rising on Day 4, the pharmacokinetic sampling day.

Oxycodone results

The geometric mean AUCτ values for oxycodone from OXN 40/20 were consistent with observations from previous single dose studies (OXN1008 and OXN1016).

OXN 40/20 provided an equivalent availability of oxycodone to oxycodone PR tablet in terms of AUCτ, Cmaxss and Cminss, with the 90% confidence intervals for these comparisons falling within the 80-125% limits of acceptability for bioequivalence (see table below).

The mean half-life of oxycodone was similar for the oxycodone PR tablet (6.27 h) and for OXN 40/20 (5.33 h). Both values were consistent with previous data collected on the OXN combination product and on oxycodone given as a single prolonged-release entity.

Figure 3. Mean Plasma Oxycodone Concentration – Time Curves

Safety Population (N=32)
Cross-reference: Figure 14.2.3.1

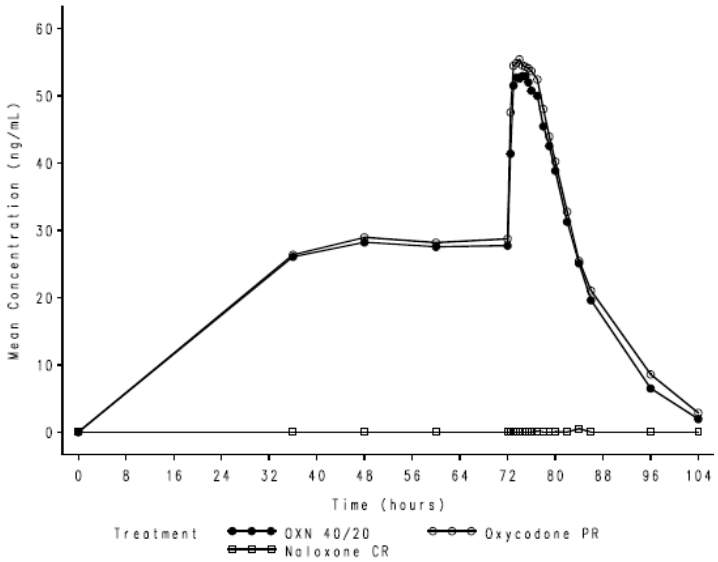


Table 11. Summary Statistics for Oxycodone Pharmacokinetic Parameters: Full Analysis Pharmacokinetic Population

PK Metrics	Statistics	OXN 40/20	Oxycodone PR	Naloxone CR
AUCτ (ng.h/ml)	n	29	30	1
	Mean (SD)	507 (100)	531 (105)	4.21 (NA)
	Median	468	511	4.21
	Min, Max	357, 772	395, 818	4.21, 4.21
	Geometric Mean	498	522	4.21
Cmaxss (ng/ml)	n	29	30	1
	Mean (SD)	57.0 (10.0)	60.9 (11.0)	3.87 (NA)
	Median	55.1	60.9	3.87
	Min, Max	43.1, 82.7	42.6, 86.7	3.87, 3.87
	Geometric Mean	56.2	59.9	3.87
Cminss (ng/ml)	n	29	30	1
	Mean (SD)	24.7 (5.68)	25.3 (7.04)	0 (NA)
	Median	22.3	23.8	0
	Min, Max	16.5, 38.3	14.8, 46.2	0, 0
	Geometric Mean	24.1	24.5	NA
tmaxss (h)	n	29	30	1
	Mean (SD)	2.00 (1.04)	2.07 (1.27)	5.00 (NA)
	Median	2.00	2.00	5.00
	Min, Max	0.500, 5.00	0.500, 5.00	5.00, 5.00
	Geometric Mean	NA	NA	NA
FI	n	29	30	0
	Mean (SD)	2.35 (0.300)	2.48 (0.393)	NA
	Median	2.31	2.44	NA
	Min, Max	1.91, 2.99	1.88, 3.51	NA
	Geometric Mean	NA	NA	NA
t1/2Z (h)	n	29	30	0
	Mean (SD)	5.29 (0.731)	6.25 (1.06)	NA
	Median	5.23	6.25	NA
	Min, Max	4.17, 6.96	4.07, 8.67	NA
	Geometric Mean	NA	NA	NA
LambdaZ (h^{-1})	n	29	30	0
	Mean (SD)	0.133 (0.0177)	0.114 (0.0204)	NA
	Median	0.133	0.111	NA
	Min, Max	0.0996, 0.166	0.0799, 0.171	NA
	Geometric Mean	NA	NA	NA

Cross-Reference: Table 14.2.2.1 and Appendix 16.2.12.1, 16.2.13.1

Summary of Ratios for Oxycodone Pharmacokinetic Parameters: Full Analysis Pharmacokinetic Population

PK Metrics	Treatment comparison	LS Means Ratio[a]	90% confidence interval	
			-Lower-	-Upper-
AUCτ (ng.h/ml)	OXN 40/20 vs. Oxycodone PR	96.2	93.09	99.33
Cmaxss (ng/ml)	OXN 40/20 vs. Oxycodone PR	94.6	90.71	98.57
Cminss (ng/ml)	OXN 40/20 vs. Oxycodone PR	99.3	95.22	103.47

[a] Transformed back to the linear scale, expressed as a percent.

Naloxone:

Figure 7. Mean Plasma Naloxone Concentration – Time Curves

Safety Population (N=32)
Cross-reference: Figure 14.2.3.5

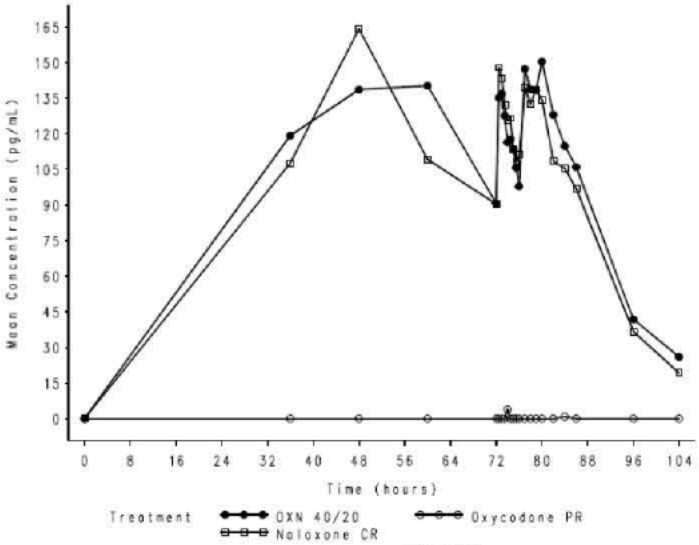


Table 14.2.2.5
OXN1011 Summary Statistics for Naloxone AUCτ, Cmaxss, Cminss, tmaxss, Fl, t1/2Z, and LambdaZ by Treatment
(Part 1 of 2)

Full Analysis Population for Plasma Pharmacokinetic Metrics

PK Metrics	Statistics	OXN 40/20	Oxycodone PR	Naloxone CR
AUCτ (pg.h/mL)	n	29	1	29
	Mean (SD)	1546 (1015)	57.0 (NA)	1488 (957)
	Median	1240	57.0	1305
	Min, Max	525, 4807	57.0, 57.0	542, 5152
	Geometric Mean	1319	57.0	1276
Cmaxss (pg/mL)	n	29	1	29
	Mean (SD)	217 (173)	114 (NA)	202 (134)
	Median	161	114	145
	Min, Max	72.5, 843	114, 114	52.5, 660
	Geometric Mean	176	114	170
Cminss (pg/mL)	n	29	1	29
	Mean (SD)	71.1 (41.0)	0 (NA)	66.7 (34.5)
	Median	59.8	0	57.6
	Min, Max	0, 226	0, 0	28.3, 188
	Geometric Mean	NA	NA	60.1
tmaxss (h)	n	29	1	29
	Mean (SD)	4.19 (3.54)	2.00 (NA)	4.33 (3.36)
	Median	5.00	2.00	5.00
	Min, Max	0.500, 12.0	2.00, 2.00	0.500, 12.0
	Geometric Mean	NA	NA	NA

Cross-Reference: Appendix 16.2.13.5

Table 14.2.2.5
OXN1011 Summary Statistics for Naloxone AUCτ, Cmaxss, Cminss, tmaxss, Fl, t1/2Z, and LambdaZ by Treatment
(Part 2 of 2)

Full Analysis Population for Plasma Pharmacokinetic Metrics

PK Metrics	Statistics	OXN 40/20	Oxycodone PR	Naloxone CR
Fl	n	28	0	29
	Mean (SD)	2.93 (1.52)	NA	2.99 (1.08)
	Median	2.51	NA	2.83
	Min, Max	1.65, 8.74	NA	1.50, 6.01
	Geometric Mean	NA	NA	NA
t1/2Z (h)	n	16	0	19
	Mean (SD)	10.6 (3.69)	NA	9.59 (3.94)
	Median	9.13	NA	9.27
	Min, Max	6.43, 17.9	NA	3.40, 19.2
	Geometric Mean	NA	NA	NA
LambdaZ (h^{-1})	n	16	0	19
	Mean (SD)	0.0721 (0.0216)	NA	0.0866 (0.0427)
	Median	0.0762	NA	0.0748
	Min, Max	0.0387, 0.108	NA	0.0361, 0.204
	Geometric Mean	NA	NA	NA

Cross-Reference: Appendix 16.2.13.5

4.2.12 Synopsis of Multiple-dose PK Study OXN1017 (Targiniq 10/5 mg)

Title of the Study: An open-label, multiple-dose, parallel group study to compare the steady-state pharmacokinetics of oxycodone and naloxone from an oxycodone/naloxone (OXN) prolonged release (PR) tablet 10/5 mg (OXN 10/5) in healthy elderly and younger subjects.

Objectives: The objectives of this study were to compare the steady-state pharmacokinetics of oxycodone, naloxone and their metabolites from OXN 10/5 in healthy elderly subjects and healthy younger subjects, and to identify any potentially medically important age-related differences. Additionally, the safety of OXN 10/5 when administered to healthy elderly and younger subjects was assessed.

Methodology: An open-label, multiple-dose, elderly group and younger group comparator study.

Number of Subjects: It was planned to enrol a total of 36 subjects, comprising 18 subjects aged 65 years and above in the elderly group, and 18 subjects aged 18 to 45 years inclusive in the younger group.

Attempts were made to include some subjects aged ≥75 years in the elderly group. A total of 18 elderly subjects (including two subjects aged ≥75 years) and 21 younger subjects were actually enrolled and 18 elderly and 18 younger subjects completed the study.

Test Treatment, Dose, and Mode of Administration: Oxycodone/naloxone PR tablet 10/5 mg (OXN 10/5), a PR combination tablet containing 10 mg of oxycodone HCl and 5 mg of naloxone HCl.

OXN 10/5 tablets were manufactured by Mundipharma Research GmbH & Co. KG, Germany.

One OXN 10/5 tablet was administered orally, 12-hourly on Days 1 to 3 and on the morning of Day 4 (7 doses in total). Batch number: PN2906.

Reference Treatment, Dose, and Mode of Administration: Not applicable.

Naltrexone Cover: The test treatment was taken under the cover of naltrexone to reduce opioid related side-effects.

One naltrexone HCl tablet 50 mg, taken orally every 12 hours from the evening of Day -1 until the morning of Day 5 (10 doses in total). Batch number: PN3045.

Duration of Treatment: Screening was within 21 days before dosing on Day 1. There was one study period. Subjects were administered the study treatment on Days 1 to 4. Pharmacokinetic blood sampling and safety monitoring continued for up to 32 hours after dosing on Day 4. Subjects had a post-study evaluation 7 to 10 days after their last OXN 10/5 dose.

Total duration of the study was up to 35 days.

Treatment Schedule: Each dose of OXN 10/5 was given with 140 ml water to subjects in a standing position. Each dose of naltrexone was given with 100 ml water to subjects in a standing position.

Bioanalytical Methods: The plasma samples were analysed for oxycodone, noroxycodone, oxymorphone and noroxymorphone, and for naloxone, 6β-naloxol, naloxone-3-glucuronide, and 6β-naloxol-3-glucuronide using validated bioanalytical assays.

Results:

Pharmacokinetic:

Oxycodone results

The geometric mean AUCτ, Cmaxss and Cminss values for multiple doses of OXN 10/5 in the healthy younger subjects were consistent with dose-adjusted observations from a previous study (OXN1011).
The availability of oxycodone from OXN 10/5 in the elderly subjects was around 18% higher than for the younger subjects, and the upper 90% CI was outside the bioequivalence limit. This difference between elderly and younger subjects was more apparent in female subjects (mean increase in AUCτ of 33%) than male subjects (mean increase in AUCτ of 3%). However, due to the small sample size this result should not be seen as definitive and should be interpreted with caution.
One component that appears to correlate with the increase in oxycodone availability in the elderly is creatinine clearance. Creatinine clearance is known to decrease with age and it is noticeable that there were differences in creatinine clearance between elderly and younger subjects that were of a similar magnitude to the oxycodone bioavailability differences between the elderly and younger subjects. It is worth noting that a separate study in renally-impaired subjects (OXN1007) has confirmed that subjects with impaired renal function exhibit higher systemic exposure of oxycodone.
Similar oxycodone bioavailability was seen in a previous **OxyContin®** study (Study OC93-0101 in elderly subjects) and in light of this it is suggested that in elderly subjects, the starting dose of **Targin®** should be a low one.
There was a corresponding increase in the Cmaxss (14%) and Cminss (28%) values; either the Cmaxss ratio nor the Cminss ratio met the criteria for bioequivalence.
The mean half-life of oxycodone was similar for the younger and the elderly subjects.

Figure 3. Mean Steady-State Plasma Oxycodone Concentration – Time Curves by Age Group (Normal Scale)

Safety Population (N=36 [elderly group: N=18; younger group: N=18])
Cross-reference: Figure 14.2.3.1

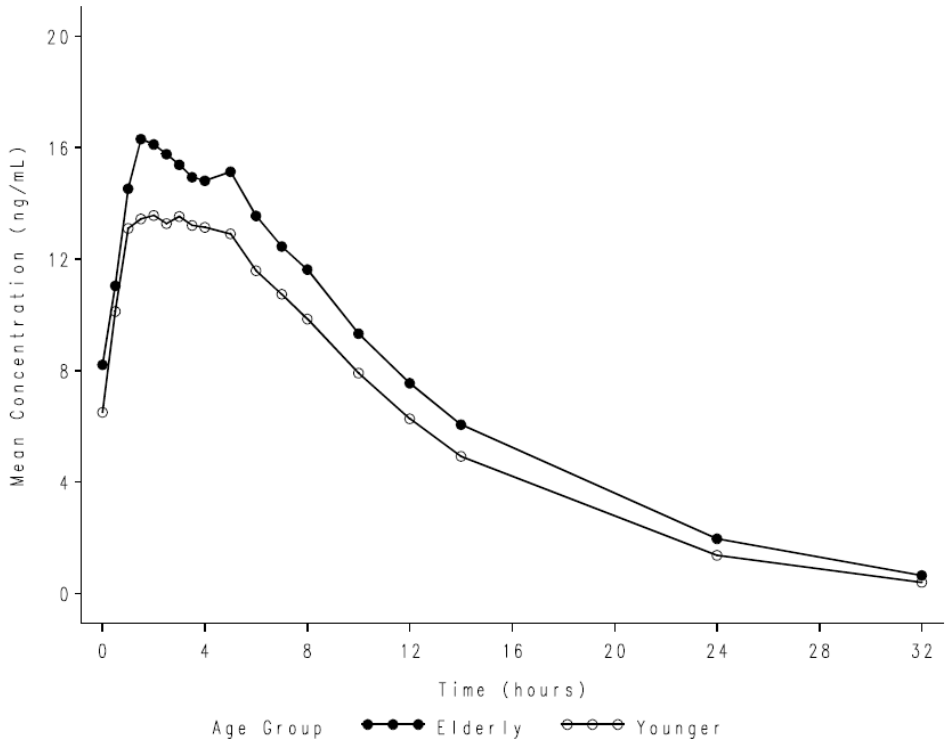


Table 10. Summary Statistics for Oxycodone Pharmacokinetic Parameters by Age Group: Full Analysis Pharmacokinetic Population

PK Parameter	Statistic	Elderly	Younger
AUCτ (ng.h/ml)	n	18	18
	Geometric Mean	147	125
	Geometric (SD/SE)	0.219/0.0517	0.259/0.0611
	Mean	150	129
	SD/SE	32.1/7.58	33.4/7.86
	Median	153	123
	Min, Max	106, 210	87.3, 191
Cmaxss (ng/ml)	n	18	18
	Geometric Mean	16.7	14.6
	Geometric (SD/SE)	0.184/0.0433	0.205/0.0484
	Mean	16.9	15.0
	SD/SE	3.07/0.723	3.25/0.767
	Median	16.9	14.5
	Min, Max	12.5, 22.4	11.4, 23.5
Cminss (ng/ml)	n	18	18
	Geometric Mean	6.91	5.42
	Geometric (SD/SE)	0.289/0.0681	0.325/0.0766
	Mean	7.18	5.69
	SD/SE	1.92/0.453	1.78/0.421
	Median	7.47	5.64
	Min, Max	3.68, 10.1	2.89, 9.37
tmaxss (h)	n	18	18
	Geometric Mean	NA	NA
	Geometric (SD/SE)	NA/NA	NA/NA
	Mean	2.00	2.06
	SD/SE	1.08/0.256	1.19/0.280
	Median	1.75	1.75
	Min, Max	1.00, 5.00	1.00, 5.00

Summary of Ratios for Oxycodone Pharmacokinetic Parameters: Full Analysis Pharmacokinetic Population

			90% Confidence Interval[a]	
PK Parameter	Comparison	LS Means Ratio[a]	-Lower-	-Upper-
AUCτ	Elderly vs. Younger	118	102.73	134.67
Cmaxss	Elderly vs. Younger	114	102.02	127.06
Cminss	Elderly vs. Younger	128	107.29	151.75

[a] Transformed back to the linear scale, expressed as a percent

Naloxone results

As expected from the data gathered in previous studies, the healthy younger subjects had plasma profiles that contained low and irregular naloxone concentrations. The naloxone data should therefore be interpreted with caution.

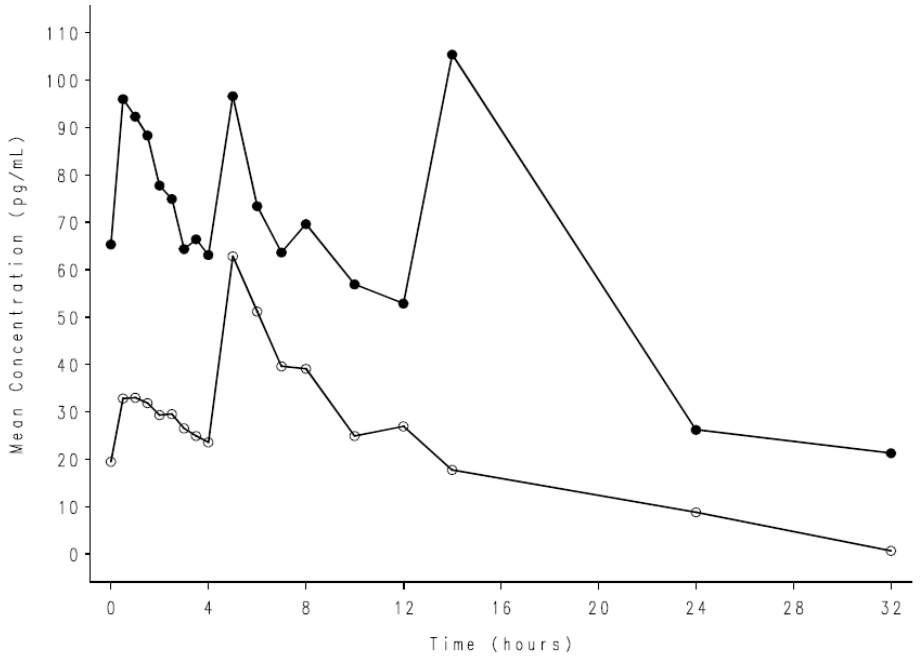
The plasma naloxone concentrations were higher in the elderly group, resulting in an increase in availability of naloxone of 82%. This difference between elderly and younger subjects was more apparent in female subjects (mean increase in AUCτ of 135%) than male subjects (mean increase in AUCτ of 36%).

However, in contrast to what was seen with oxycodone, the changes in naloxone exposure were much more variable and the CIs are too wide to allow a definitive conclusion to be drawn, emphasizing again that these naloxone results should be interpreted with caution. The differences seen in this study, and their clinical relevance, will be examined further in the course of the Phase 3 program.

Because the increase in oxycodone concentrations for this group was to a lesser extent, the resulting ratio of oxycodone:naloxone concentrations was lower in the elderly group than in the younger group.

Figure 11. Mean Steady-State Plasma Naloxone Concentration – Time Curves by Age Group (Normal Scale)

Safety Population (N=36 [elderly group: N=18; younger group: N=18])
Cross-reference: Figure 14.2.3.5



OXN1017 Summary Statistics for Naloxone AUCτ, Cmaxss, Cminss by Age Group Full Analysis Population for Plasma PK Metrics for Male and Female subjects

PK Metrics	Statistic	Elderly	Younger	Elderly	Younger
		Male		Female	
AUCτ (pg h/mL)	n	8	9	10	9
	Geometric Mean	533	391	698	296
	Geometric (SD/SE)	0 934/0 330	0 685/0 228	0 721/0 228	0 428/0 143
	Mean	840	506	912	326
	SD/SE	1048/371	488/163	826/261	174/57 9
	Median	494	393	579	252
	Min, Max	228, 3347	183, 1750	285, 2979	195, 726
Cmaxss (pg/mL)	n	8	9	10	9
	Geometric Mean	75 9	57 5	97 1	44 1
	Geometric (SD/SE)	1 07/0 378	0 863/0 288	0 860/0 272	0 665/0 222
	Mean	131	88 3	146	56 7
	SD/SE	162/57 2	115/38 3	178/56 4	53 8/17 9
	Median	62 8	45 5	78 4	33 7
	Min, Max	24 4, 499	24 0, 387	37 3, 633	25 2, 188
Cminss (pg/mL)	n	8	9	10	9
	Geometric Mean	27 4	NA	27 2	NA
	Geometric (SD/SE)	0 928/0 328	NA/NA	0 564/0 178	NA/NA
	Mean	45 7	17 1	31 6	13 7
	SD/SE	66 2/23 4	10 2/3 40	20 2/6 39	7 41/2 47
	Median	24 0	17 8	29 2	13 1
	Min, Max	10 6, 208	0, 38 3	10 5, 83 0	0, 28 4

Cross-Reference: Appendix 16.2.12.5
For Cminss, Geometric Mean and Geometric (SD/SE) could not be calculated due to values of 0.

Table 13. Summary of Ratios for Naloxone AUCτ by Gender: Full Analysis Pharmacokinetic Population

PK Parameter	Gender	Comparison	LS Means Ratio[a]	90% Confidence Interval[a]	
				-Lower-	-Upper-
AUCτ	Female	Elderly vs. Younger	235	135.79	408.25
	Male	Elderly vs. Younger	136	76.25	244.24

Naloxone-3-glucuronide results

The geometric mean AUCτ, Cmaxss and Cminss values for multiple doses of OXN 10/5 in healthy younger subjects were consistent with dose-adjusted observations from a previous study (OXN1011).

The availability of naloxone-3-glucuronide from OXN 10/5 in the elderly subjects was around 28% higher than for the younger subjects, and the upper 90% CI was outside the bioequivalence limit. There was a corresponding increase in the Cmaxss (27%) and Cminss (25%) values; neither the Cmaxss ratio nor the Cminss ratio met the criteria for bioequivalence.

The mean half-life of naloxone-3-glucuronide was 8.2 h for the elderly subjects and 7.1 h for the younger subjects.

Table 14. Summary Statistics for Naloxone-3-glucuronide Pharmacokinetic Parameters by Age Group: Full Analysis Pharmacokinetic Population

PK Parameter	Statistic	Elderly	Younger
AUCτ (ng.h/ml)	n	18	18
	Geometric Mean	192	150
	Geometric (SD/SE)	0.257/0.0606	0.208/0.0489
	Mean	198	153
	SD/SE	48.7/11.5	32.3/7.61
	Median	198	145
	Min, Max	106, 305	92.6, 224
Cmaxss (ng/ml)	n	18	18
	Geometric Mean	33.1	26.1
	Geometric (SD/SE)	0.231/0.0545	0.210/0.0495
	Mean	33.9	26.6
	SD/SE	7.53/1.77	5.54/1.31
	Median	33.2	26.7
	Min, Max	19.1, 49.6	17.9, 37.9
Cminss (ng/ml)	n	18	18
	Geometric Mean	8.05	6.46
	Geometric (SD/SE)	0.332/0.0783	0.261/0.0615
	Mean	8.43	6.67
	SD/SE	2.48/0.585	1.86/0.438
	Median	8.12	6.10
	Min, Max	3.08, 13.9	3.83, 11.3
tmaxss (h)	n	18	18
	Geometric Mean	NA	NA
	Geometric (SD/SE)	NA/NA	NA/NA
	Mean	0.917	0.944
	SD/SE	0.393/0.0926	0.616/0.145
	Median	1.00	0.500
	Min, Max	0.500, 1.50	0.500, 2.50

Summary of Ratios for Naloxone-3-glucuronide Pharmacokinetic Parameters: Full Analysis Pharmacokinetic Population

PK Parameter	Comparison	LS Means Ratio[a]	90% Confidence Interval[a]	
			-Lower-	-Upper-
AUCτ	Elderly vs. Younger	128	112.58	146.52
Cmaxss	Elderly vs. Younger	127	112.06	143.75
Cminss	Elderly vs. Younger	125	105.35	147.53

[a] Transformed back to the linear scale, expressed as a percent.

Conclusions:

• There was an increase in oxycodone and naloxone-3-glucuronide bioavailability when OXN 10/5 was administered 12-hourly to elderly subjects compared with younger subjects. The increase in oxycodone bioavailability was anticipated based on data gathered in a previous oxycodone study.

Because of the increase in oxycodone and naloxone, it would be appropriate to start an elderly patient on a low dose of OXN and carefully titrate the dose according to optimal pain control while carefully monitoring adverse reactions.

4.2.13 Synopsis of Hepatic Impairment Study OXN1006:

<table>
<tr><td>Name of Company:
Mundipharma Research GmbH & Co. KG</td><td>INDIVIDUAL STUDY TABLE</td><td>(For National Authority Use Only)</td></tr>
<tr><td>Name of Finished Product:
Not applicable</td><td rowspan="2">Referring to Part IV of the Dossier
Volume: Page:</td><td rowspan="2"></td></tr>
<tr><td>Name of Active Ingredient:
oxycodone hydrochloride (HCl) and naloxone HCl</td></tr>
<tr><td colspan="3">Title of the Study: An open-label, single-dose, parallel group study to compare the pharmacokinetics of oxycodone and naloxone from an oxycodone/naloxone (OXN) prolonged release (PR) tablet 10/5 mg in patients with varying degrees of hepatic impairment and healthy volunteers</td></tr>
<tr><td colspan="3">Investigator(s)/Center(s): Multi-center study carried out in the Czech Republic.
Investigator: Dr. Blanka Cieslarová</td></tr>
<tr><td colspan="3">Publication (Reference): None</td></tr>
<tr><td>Study Dates:
15-Aug-2005 to 09-Feb-2006</td><td>Study Status:
Completed</td><td>Phase of Development:
Phase 1</td></tr>
<tr><td colspan="3">Objectives: To compare the pharmacokinetics of oxycodone, naloxone and their metabolites from OXN 10/5 in patients with varying degrees of hepatic impairment and healthy volunteers and to identify an appropriate dose recommendation for patients with hepatic impairment.</td></tr>
<tr><td colspan="3">Methodology: An open-label, single-dose, hepatic impairment patient group and healthy volunteer comparator study.
• Subjects (hepatic impairment patients and healthy volunteers) attended a screening visit within 21 days of the dosing day.
• Subjects checked in to the study unit on the day before dosing (Day -1).
• Subjects were administered the study treatment the following morning (Day 1) and then remained in the study unit for 72 hours.
• Study treatment was administered after a minimum of 8 hours of overnight fasting.
• Pharmacokinetic (PK) blood samples (6 mL) were taken pre-dose and until 72 hours after administration of the study medication. An additional blood sample was taken pre-dose and at 3 hours after dosing for investigation of protein binding. Urine was collected until 72 hours after dosing.
• During the study period, vital signs were monitored pre-dose, and at 1, 2, 4, 6, 8, 12, 24, 36, 48, and 72 hours after dosing.
• Adverse events (AEs) were recorded throughout the study.
• Subjects had a post-study medical assessment 7-10 days after dosing with study medication.</td></tr>
<tr><td colspan="3">Number of Subjects: 6 healthy volunteers, and 18 patients with varying degrees of hepatic impairment. The aim was to include 6 hepatic impairment patients in each of three groups based on the Child Pugh Grading where mild = 5-6, moderate = 7-9 and severe = 10-15.
6 healthy , 6 Child Pugh A, 6 Child Pugh B, and 6 Child Pugh C subjects were planned, randomized and completed the study.</td></tr>
<tr><td colspan="3">Indication and Criteria for Inclusion: Males and females, healthy or with hepatic impairment, aged 18 - 70 years inclusive.</td></tr>
<tr><td colspan="3">Test Treatment, Dose, and Mode of Administration: Oxycodone/naloxone prolonged release tablet 10/5 mg (OXN 10/5), a PR combination tablet containing 10 mg of oxycodone HCl and 5 mg of naloxone HCl. The investigated medical product was manufactured by Mundipharma Research GmbH & Co. KG.
Treatment administered: 1 tablet OXN 10/5 taken orally.</td></tr>
<tr><td colspan="3">Reference Treatment, Dose, and Mode of Administration: Not applicable.</td></tr>
<tr><td colspan="3">Duration of Treatment: Screening within 21 days before dosing on Day 1 of Study Period 1. There was one study period. Subjects were administered the study treatment on Day 1.
Pharmacokinetic blood sampling and safety monitoring was continued for up to 72 hours after dosing. Subjects had a post-study evaluation 7-10 days after dosing.
Total duration of the study was 28 - 30 days.</td></tr>
<tr><td colspan="3">Treatment Schedule: A single dose of OXN 10/5 was given to the subjects. Each dose of study medication was given with 240 mL of water to subjects in a standing position.</td></tr>
</table>

Criteria for Evaluation:

Analysis Populations: The enrolled population was defined as the subject population that has provided their written informed consent to participate in the study.
The full analysis population for pharmacokinetic metrics was defined as those subjects who had at least one pharmacokinetic metric.
The safety population was defined as the set of subjects who received study medication and who had at least one post-dose safety assessment.

Safety: Safety was assessed using adverse events recordings, clinical laboratory results, vital signs, physical examinations, and electrocardiograms (ECGs).

Bioanalytical Methods: The plasma and urine samples were analyzed for oxycodone, noroxycodone, oxymorphone, and noroxymorphone, and for naloxone, 6ß-naloxol, naloxone-3-glucuronide, and 6ßnaloxol-3-glucuronide by validated bioanalytical assays (LC/ESI/MS/MS).
Protein binding for oxycodone, naloxone and metabolites was investigated using the additional blood samples collected pre-dose and 3 hours after dosing. Protein binding samples were analyzed by equilibrium dialysis followed by LC-MS/MS.

Statistical Methods: Pharmacokinetic Data:
Where data were available, for each analyte, natural log-transformed AUCt, AUCINF, and Cmax, and non-transformed t1/2Z, % dose recovered, and renal clearance were analyzed using an ANOVA model. Tmax was also analyzed using a Wilcoxon rank-sum test. Within the framework of the ANOVA, the ratios of group geometric means and 90% confidence intervals were estimated.
The following comparisons were explored:

- Mild impairment vs. Healthy volunteer group
- Moderate impairment vs. Healthy volunteer group
- Severe impairment vs. Healthy volunteer group

Relationships between selected pharmacokinetic metrics for oxycodone and naloxone-3-glucuronide and hepatic function abnormalities (serum albumin, bilirubin, prothrombin) were explored using separate regression models. A regression analysis across the Child Pugh categories was performed.
Extent (% bound) of protein binding was analyzed as for the pharmacokinetic data.
The calculation of the confidence intervals, as well as the statistical tests, was performed on an exploratory basis only.

Urinary Excretion (mean [SD]) of Oxycodone, Naloxone, and Their Metabolites in Subjects with Varying Degrees of Hepatic Impairment Following a Single Dose of OXN 10/5 mg in Study OXN1006 (PK Population)

Analyte	Percent (%) of Dose Recovered in Urine in 72 Hrs			
	Normal Function (n = 6)	Mild Impairment (n = 6)	Moderate Impairment (n = 6)	Severe Impairment (n = 6)
Oxycodone	3.52 (1.61)	4.98 (1.89)	13.7 (7.00)	12.7 (3.60)
Noroxycodone	9.88 (5.19)	15.9 (5.40)	17.3 (6.17)	26.8 (4.81)
Oxymorphone	0.162 (0.0866)	0.134 (0.0568)	0.296 (0.183)	0.322 (0.214)
Noroxymorphone	4.14 (0.83)	3.14 (0.83)	2.17 (1.09)	2.42 (1.53)
TOTAL	17.7	24.2	33.5	42.2
Naloxone	0.0246 (0.0170)	0.0687 (0.0483)	0.581 (0.543)	0.323 (0.0745)
6β-Naloxol	0.121 (0.0224)	0.255 (0.179)	0.576 (0.159)	0.916 (0.307)
Naloxone-3β-glucuronide	16.1 (6.84)	17.9 (7.18)	23.9 (6.34)	23.7 (6.93)
6β-naloxol-3β-glucuronide	12.1 (6.22)	12.5 (5.99)	8.65 (4.73)	7.49 (2.24)
TOTAL	28.3	30.7	33.7	32.4

Source: OXN1006 CSR Table 14.2.2.9, Table 14.2.2.10, Table 14.2.2.11, 14.2.2.12, Table 14.2.2.13, Table 14.2.2.14, Table 14.2.2.15, Table 14.2.2.16.

Pharmacokinetic Results:

Oxycodone:

For AUCINF of oxycodone, on average there was an increase to 143% (90% Confidence interval: 111, 184), 319% (90% Confidence interval: 248, 411) and 310% (90% Confidence interval: 241, 398) for mild, moderate and severe hepatically impaired subjects, respectively, compared with healthy volunteers.

For Cmax of oxycodone, on average there was an increase to 120% (90% Confidence interval: 99, 144), 201% (90% Confidence interval: 166, 242) and 191% (90% Confidence interval: 158, 231) for mild, moderate and severe hepatically impaired subjects, respectively, compared with healthy volunteers.

For t1/2Z of oxycodone, on average there was an increase to 108% (90% Confidence interval: 70, 146), 176% (90% Confidence interval: 138, 215) and 183% (90% Confidence interval: 145, 221) for mild, moderate and severe hepatically impaired subjects, respectively, compared with healthy volunteers.

Naloxone:

For AUCt of naloxone, on average there was an increase to 411% (90% Confidence interval: 152, 1112), 11518% (90% Confidence interval: 4259, 31149) and 10666% (90% Confidence interval: 3944, 28847) for mild, moderate and severe hepatically impaired subjects, respectively, compared with healthy volunteers.

For Cmax of naloxone, on average there was an increase to 193% (90% Confidence interval: 115, 324), 5292% (90% Confidence interval: 3148, 8896) and 5252% (90% Confidence interval: 3124, 8830) for mild, moderate and severe hepatically impaired subjects, respectively, compared with healthy volunteers.

Due to insufficient amount of data available t1/2Z and the corresponding AUCINF of naloxone were not calculated. The bioavailability comparisons for naloxone were therefore based on AUCt values.

Naloxone-3-glucuronide:

For AUCINF of naloxone-3-glucuronide, on average there was an increase to 157% (90% Confidence interval: 89, 279), 128% (90% Confidence interval: 72, 227) and 125% (90% Confidence interval: 71, 222) for mild, moderate and severe hepatically impaired subjects, respectively, compared with healthy volunteers.

For Cmax of naloxone-3-glucuronide, on average there was an increase to 141% (90% Confidence interval: 100, 197), 118% (90% Confidence interval: 84, 166) and a decrease to 98% (90% Confidence interval: 70, 137) for mild, moderate and severe hepatically impaired subjects, respectively, compared with healthy volunteers.

For t1/2Z of naloxone-3-glucuronide, on average there was an increase to 117% (90% Confidence interval: 72, 161), a decrease to 77% (90% Confidence interval: 32, 121) and a decrease to 94% (90% Confidence interval: 49, 139) for mild, moderate and severe hepatically impaired subjects, respectively, compared with healthy volunteers.

Safety: The incidence of adverse events was similar for healthy and hepatically impaired subjects. Two of 6 healthy subjects reported adverse events after receiving OXN 10/5, one of 6 in the mild hepatically impaired group and two of 6 in the moderate hepatically impaired group reported adverse events after receiving OXN 10/5. The adverse events reported were headache, gastrointestinal disorder and pruritus. All adverse events were rated as mild. No trends were observed for changes in physical examination, laboratory values, vital signs or ECG following administration of a single dose of OXN 10/5 for healthy subjects, or subjects with hepatic impairment.

Plasma Protein Binding (Mean [SD]) of Oxycodone, Naloxone, and Their Metabolites in Subjects with Varying Degrees of Hepatic Impairment Following a Single Dose of OXN 10/5 mg in Study OXN1006 (PK Population)

Analyte	Percent (%) Bound to Proteins in Plasma			
	Normal Function (n = 6)	Mild Impairment (n = 6)	Moderate Impairment (n = 6)	Severe Impairment (n = 6)
Oxycodone	22.2 (9.03)	22.8 (4.28)	15.5 (2.50)	14.4 (4.12)
Noroxycodone	21.8 (8.22)	20.6 (3.20)	20.7 (3.44)	15.5 (3.94)
Oxymorphone	14.5 (8.75)	17.8 (4.64)	11.8 (6.08)	13.1 (1.56)
Noroxymorphone	24.9 (2.86)	15.6 (4.61)	11.2 (5.06)	7.60 (4.29)
Naloxone	57.9 (16.5)	54.4 (4.20)	44.6 (4.86)	41.3 (2.35)
6β-Naloxol	17.7 (11.6)	25.0 (3.85)	24.3 (3.24)	19.8 (5.82)

Source: OXN1006 CSR Table 14.2.1.17, Table 14.2.1.18, Table 14.2.1.19, Table 14.2.1.20, 14.2.1.21, Table 14.2.1.22

Conclusions:

- Single dose oral administration of OXN 10/5 extended release formulation was well tolerated in healthy subjects and in subjects with varying degrees of hepatic impairment.
- Based on an evaluation of AEs, clinical laboratory tests, vital signs and ECGs, no differences in tolerability were observed between the healthy subjects and subjects with mild, moderate or severe hepatic impairment.
- There was a 3-fold increase in the bioavailability of the oxycodone component and a more than 100-fold increase in the bioavailability of the naloxone component of the 10/5 mg dose of OXN in the moderate and severe hepatically impaired group compared with the healthy subject group. The high naloxone ratios may, at least in part, be a consequence of the inability to quantify the naloxone plasma concentrations in the healthy subjects which is a consequence of the extremely low oral bioavailability of the drug. The clinical consequences of this will be investigated further in later studies.
- OXN 10/5 pharmacokinetics were markedly affected by hepatic impairment, suggesting that a careful titration should be considered when starting and maintaining therapy with the fixed combination of oxycodone and naloxone in patients with moderately or severely compromised hepatic function.

Date of the Report: 22-FEB-2007

4.2.14 Synopsis of Renal Impairment Study OXN1007

Name of Company: Mundipharma Research GmbH & Co. KG	INDIVIDUAL STUDY TABLE	(For National Authority Use Only)
Name of Finished Product: Not applicable	Referring to Part IV of the Dossier	
Name of Active Ingredient: oxycodone hydrochloride (HCl) and naloxone HCl	Volume: Page:	
Title of the Study: An Open-Label, Single-Dose, Parallel-group Study to Compare the Pharmacokinetics of Oxycodone and Naloxone from an Oxycodone/Naloxone (OXN) Prolonged Release (PR) Tablet 10/5 mg in Patients With Varying Degrees of Renal Impairment and Healthy Volunteers		
Investigator(s)/Center(s): Single-center study carried out in the Czech Republic. Investigator: Dr. Petr Šrámek		
Publication (Reference): None		
Study Dates: 03-Aug-2005 to 19-Dec-2005	**Study Status:** Completed	**Phase of Development:** Phase 1
Objectives: To compare the pharmacokinetics of oxycodone, naloxone and their metabolites from OXN 10/5 in patients with varying degrees of renal impairment and healthy volunteers, and to identify an appropriate dose recommendation for patients with renal impairment		
Methodology: An open-label, single-dose, renal impairment patient group and healthy volunteer comparator study. • Subjects (renal impairment patients and healthy volunteers) attended a screening visit within 21 days of the dosing day. • Subjects checked-in to the study unit on the day before dosing (Day -1). • Subjects were administered the study treatment the following morning (Day 1) and then remained in the study unit for 72 hours. • Study treatment was administered after a minimum of 8 hours of overnight fasting. • Pharmacokinetic (PK) blood samples (6 mL) were taken pre-dose and up to 72 hours after administration of the study medication. An additional blood sample was taken pre-dose and at 3 hours after dosing for investigation of protein binding. Urine was collected up to 72 hours after dosing. • During the study period, vital signs were monitored pre-dose, and at 1, 2, 4, 6, 8, 12, 24, 36, 48, and 72 hours after dosing. • Adverse events (AEs) were recorded throughout the study. • Subjects had a post-study medical assessment 7-10 days after dosing with study medication.		
Number of Subjects: 6 healthy volunteers, and 18 patients with varying degrees of renal impairment. The aim was to include 6 renal impairment patients in each of 3 groups based on creatinine clearance (Cr Cl) values obtained using two determinations of the Cr Cl derived from 24 hour urine collections. 6 healthy subjects, 6 mild, 6 moderate, and 6 severe renal impaired subjects were planned, randomized and completed the study.		
Indication and Criteria for Inclusion: Males and females, healthy or with renal impairment, aged 18 - 70 years inclusive.		
Test Treatment, Dose, and Mode of Administration: Oxycodone/naloxone prolonged release tablet 10/5 mg (OXN10/5), a PR combination tablet containing 10 mg of oxycodone HCl and 5 mg of naloxone HCl. The test treatment was manufactured by Mundipharma Research GmbH & Co. KG. Treatment A: 1 x OXN10/5 taken orally.		
Reference Treatment, Dose, and Mode of Administration: Not applicable.		
Duration of Treatment: Screening within 21 days before dosing on Day 1 of Study Period 1. There was one study period. Subjects were administered the study treatment on Day 1. Pharmacokinetic blood sampling and safety monitoring was continued for up to 72 hours after dosing. Subjects had a post-study evaluation 7-10 days after dosing. Total duration of the study was 28 - 30 days.		

Treatment Schedule: A single dose of OXN10/5 was given to the subjects. Each dose of study medication was given with 240 mL of water to subjects in a standing position.
Criteria for Evaluation: Analysis Populations: The enrolled population was defined as the subject population that has provided their written informed consent to participate in the study. The full analysis population for pharmacokinetic metrics was defined as those subjects who have at least one pharmacokinetic metric. The safety population was defined as the set of subjects who received study medication and who had at least one post-dose safety assessment.
Safety: Safety was assessed using adverse events, clinical laboratory results, vital signs, physical examinations and electrocardiograms (ECGs).
Bioanalytical Methods: The plasma and urine samples were analysed for oxycodone, noroxycodone, oxymorphone, and noroxymorphone, and for naloxone, 6ß-naloxol, naloxone-3-glucuronide, and 6ßnaloxol-3-glucuronide by validated bioanalytical assays (LC/ESI/MS/MS). Protein binding for oxycodone, naloxone and metabolites was investigated using the additional blood samples collected predose and 3 hours after dosing. Protein binding samples were analysed by equilibrium dialysis followed by LC-MS/MS.
Statistical Methods: Pharmacokinetic Data: Where data were available, for each analyte, natural log-transformed AUCt, AUCINF, and Cmax, and non-transformed t1/2Z, % dose recovered, and renal clearance were analysed using an ANOVA model. Tmax was also analysed using a Wilcoxon rank-sum test. Within the framework of the ANOVA, the ratios of group geometric means and 90% confidence intervals were estimated. The following comparisons were explored: • Mild impairment vs. Healthy volunteer group • Moderate impairment vs. Healthy volunteer group • Severe impairment vs. Healthy volunteer group Log transformed data for AUCt, AUCINF, and Cmax for oxycodone and naloxone-3-glucuronide, and renal clearance for oxycodone and naloxone were analysed using a regression model, with Cr Cl as a continuous predictor variable. Extent (% bound) of protein binding was analysed as for the pharmacokinetic data. The calculation of the confidence intervals, as well as the statistical tests, was performed on an exploratory basis only.

Urinary Excretion (mean [SD]) of Oxycodone, Naloxone, and Their Metabolites in Subjects with Varying Degrees of Renal Impairment Following a Single Dose of OXN 10/5 mg in Study OXN1007 (PK Population)

Analyte	Percent (%) of Dose Recovered in Urine in 72 Hrs			
	Normal Function (n = 6)	Mild Impairment (n = 6)	Moderate Impairment (n = 6)	Severe Impairment (n = 6)
Oxycodone	4.87 (1.70)	4.30 (1.43)	3.64 (2.18)	4.63 (2.29)
Noroxycodone	16.7 (4.70)	15.5 (6.50)	11.0 (5.77)	9.29 (3.28)
Oxymorphone	0.177 (0.051)	0.107 (0.0519)	0.0864 (0.0817)	0.101 (0.0855)
Noroxymorphone	3.32 (0.514)	2.11 (1.10)	1.41 (0.70)	1.36 (0.90)
TOTAL	25.1	22.0	16.1	15.3
Naloxone	0.0295 (0.00823)	0.137 (0.208)	0.0338 (0.0264)	0.0587 (0.0444)
6β-Naloxol	0.229 (0.134)	0.208 (0.123)	0.161 (0.0384)	0.224 (0.0827)
Naloxone-3β-glucuronide	17.1 (3.17)	21.3 (6.90)	15.2 (8.87)	15.0 (3.45)
6β-naloxol-3β-glucuronide	13.1 (3.26)	14.8 (6.27)	13.7 (6.79)	10.7 (3.98)
TOTAL	30.5	36.4	29.1	26.0

Source: OXN1007 CSR Table 14.2.2.9, Table 14.2.2.10, Table 14.2.2.11, Table 14.2.2.12, Table 14.2.2.13, Table 14.2.2.14, Table 14.2.2.15, Table 14.2.2.16.

Plasma Protein Binding (mean [SD]) of Oxycodone, Naloxone, and Their Metabolites in Subjects with Varying Degrees of Renal Impairment Following a Single Dose of OXN 10/5 mg in Study OXN1007 (PK Population)

Analyte	Percent (%) Bound to Proteins in Plasma			
	Normal Function (n = 6)	Mild Impairment (n = 6)	Moderate Impairment (n = 6)	Severe Impairment (n = 6)
Oxycodone	23.5 (3.34)	26.0 (5.41)	20.3 (4.53)	21.8 (2.58)
Noroxycodone	18.7 (5.15)	21.5 (5.41)	17.6 (4.22)	19.4 (3.04)
Oxymorphone	19.7 (7.32)	17.5 (8.50)	13.4 (6.27)	17.8 (5.25)
Noroxymorphone	10.8 (3.34)	18.2 (5.51)	11.5 (8.54)	11.2 (9.01)
Naloxone	41.3 (14.5)	54.4 (6.65)	52.1 (5.75)	45.8 (12.5)
6β-Naloxol	18.3 (3.69)	24.0 (10.6)	21.4 (6.91)	16.8 (6.05)

Source: OXN1007 CSR Table 14.2.1.17, Table 14.2.1.18, Table 14.2.1.19, Table 14.2.1.20, 14.2.1.21, Table 14.2.1.22

Table 23. PK Parameter Values of Oxycodone, Naloxone, and Naloxone-3β-glucuronide in Subjects with Varying Degrees of Renal Impairment Following a Single Dose of OXN 10/5 mg, and Statistical Results by Level of Renal Impairment in Study OXN1007 (PK population)

Analyte	Healthy, Normal Renal Function OXN 10/5 mg (n =6)			Mild Renal Impairment OXN 10/5 mg (n = 6)		
	C_{max} (ng/mL)	t_{max}[b] (hr)	AUC_{0-t} (hr*ng/mL)	C_{max} (ng/mL)	t_{max}[b] (hr)	AUC_{0-t} (hr*ng/mL)
Oxycodone	10.6 (12.1%)	2.3 (1.0-6.0)	110 (11.9%)	11.7 (8.00%)	5.0 (1.5-5.0)	169 (14.2%)
Naloxone	0.0345[c] (0.0522)	1.0 (0.5-8.0)	0.115[c] (0.162)	0.0435 (202%)	4.8 (0.5-10)	0.285 (378%)
Naloxone-3β-glucuronide	18.6 (42.2%)	0.50 (0.5-1.5)	147 (38.8%)	27.4 (17.9%)	1.3 (1.0-2.0)	303 (23.8%)
	Moderate Renal Impairment OXN 10/5 mg (n = 6)			Severe Renal Impairment OXN 10/5 mg (n = 6)		
	C_{max} (ng/mL)	t_{max}[b] (hr)	AUC_{0-t} (hr*ng/mL)	C_{max} (ng/mL)	t_{max}[b] (hr)	AUC_{0-t} (hr*ng/mL)
Oxycodone	14.4 (26.5%)	3.25 (3.0-4.0)	183 (19.2%)	17.8 (12.0%)	3.5 (3.0-5.0)	248 (21.4%)
Naloxone	0.0347 (99%)	9.0 (1.0-12)	0.391 (69.5%)	0.0678 (216%)	7.0 (5.0-12)	0.762 (113%)
Naloxone-3β-glucuronide	37.6 (37.3%)	1.8 (1.0-3.0)	509 (48.9%)	44.4 (12.4%)	3.0 (1.5-12)	726 (43.0%)

Statistical Results		
	C_{max} GLSM Ratio (90% CI) Mild Impairment/Healthy	AUC[a] GLSM Ratio (90% CI) Mild Impairment/Healthy
Oxycodone	110 (93.7-129)%	153 (130-182)%
Naloxone	1076 (154, 7502)%	2850 (369, 22042)%
Naloxone-3β-glucuronide	148 (110-197)%	220 (148-327)%
	C_{max} GLSM Ratio (90% CI) Moderate Impairment/Healthy	AUC[a] GLSM Ratio (90% CI) Moderate Impairment/Healthy
Oxycodone	135 (115-159)%	166 (140-196)%
Naloxone	858 (123, 5981)%	3910 (506, 30243)%
Naloxone-3β-glucuronide	202 (151-271)%	370 (249-550)%
	C_{max} GLSM Ratio (90% CI) Severe Impairment/Healthy	AUC[a] GLSM Ratio (90% CI) Severe Impairment/Healthy
Oxycodone	167 (142-196)%	224 (189-265)%
Naloxone	1675 (240, 11676)%	7612 (984, 58871)%
Naloxone-3β-glucuronide	239 (179-320)%	525 (354-781)%

[a] AUC for oxycodone and naloxone-3-glucuronide, AUC_{0-t} for naloxone.
[b] median (range); [c] Mean (SD)
Source: ISCP Table D-1, ISCP Table D-2, ISCP Table D-3; OXN1007 CSR Table 9, Table 10, Table 25, Table 26, Table 29, Table 30

Pharmacokinetic Results:

Oxycodone:

For AUCINF of oxycodone, on average there was an increase to 153% (90% CI: 130, 182), 166% (90% CI: 140, 196) and 224% (90% CI: 190, 266) for mild, moderate and severe renally impaired subjects, respectively, compared with healthy volunteers.

For Cmax of oxycodone, on average there was an increase to 110% (90% CI: 94, 129), 135% (90% CI: 115, 159) and 167% (90% CI: 142, 196) for mild, moderate and severe renally impaired subjects, respectively, compared with healthy volunteers.

For t1/2Z of oxycodone, on average there was an increase to 149%, 123% and 142% for mild, moderate and severe renally impaired subjects, respectively, compared with healthy volunteers.

Naloxone:

For AUCt of naloxone, on average there was an increase to 2850% (90% CI: 369, 22042), 3910% (90% CI: 506, 30243) and 7612% (90% CI: 984, 58871) for mild, moderate and severe renally impaired subjects, respectively, compared with healthy volunteers.

For Cmax of naloxone, on average there was an increase to 1076% (90% CI: 154, 7502), 858% (90% CI: 123, 5981) and 1675% (90% CI: 240, 11676) for mild, moderate and severe renally impaired subjects, respectively, compared with healthy volunteers.

Due to insufficient amount of data available t1/2Z and the corresponding AUCINF of naloxone were not calculated. The bioavailability comparisons for naloxone were therefore based on AUCt values.
The ratios may have been influenced by the inability to fully characterize the naloxone plasma profiles for the healthy subjects.

Naloxone-3-glucuronide:

For AUCINF of naloxone-3-glucuronide, on average there was an increase to 220% (90% CI: 148, 327), 370% (90% CI: 249, 550) and 525% (90% CI: 354, 781) for mild, moderate and severe renally impaired subjects, respectively, compared with healthy subjects.

For Cmax of naloxone-3-glucuronide, on average there was an increase to 148% (90% CI: 110, 197), 202% (90% CI: 151, 271) and 239% (90% CI: 179, 320) for mild, moderate and severe renally impaired subjects, respectively, compared with healthy subjects.

For t1/2Z of naloxone-3-glucuronide, on average there was no significant change between the renally impaired subjects and the healthy subjects.

Regression analyses:

The regression analyses between the pharmacokinetic metrics of oxycodone, naloxone and naloxone-3-glucuronide, and the renal function (Cr Cl) showed no correlation.

Safety: The incidence of adverse events slightly increased with renally impaired subjects compared to healthy subjects. One of 6 healthy subjects reported adverse events after receiving OXN10/5, 2 of 6 in the mild renally impaired group, 3 of 6 in the moderate renally impaired group and 2 of 6 in the severe renally impaired group reported adverse events after receiving OXN10/5. The adverse events reported were headache and dizziness, gastrointestinal disorders, hyperkalaemia, hypertension and phlebitis. All adverse events were rated as mild or moderate. The adverse events headache and hypertension in the mild renally impaired group, the adverse events headache and hyperkalaemia in the moderate renally impaired group and phlebitis in one severe renally impaired subject were evaluated as "not related" to study drug. The gastrointestinal disorders in the moderate renally impaired group were evaluated as "possibly related" to study drug. Gastrointestinal and nervous system disorders in the severe renally impaired group were evaluated as "possibly related" or "unlikely related" to study medication. No serious adverse events were reported in this study. No trends were observed for changes in vital signs or ECG following administration of a single dose of OXN10/5 for healthy subjects or subjects with renal impairment.

Conclusions:

- Single dose oral administration of OXN10/5 extended release formulation was well tolerated in healthy subjects and in subjects with varying degrees of renal impairment with a slight trend to higher incidence of adverse events proportional to the stage of renal impairment. From the data generated it is not possible to assess the clinical relevance of this observation. Based on an evaluation of AEs, clinical laboratory tests, vital signs and ECGs, no differences in tolerability were observed between the healthy subjects and subjects with mild, moderate or severe renal impairment.

- There was a 1.5-fold, 1.7-fold and 2-fold increase in the bioavailability of the oxycodone component, a 28.5-fold, 39-fold and 76-fold increase in the bioavailability of the naloxone component and a 2.2-fold, 3.7-fold and 5.3-fold increase in the bioavailability of the naloxone-3-glucoronide component of the 10/5 mg dose of OXN in the mild, moderate and severe renally impaired group respectively, compared with the healthy subject group. The high naloxone ratios may, at least in part, be a consequence of the inability to quantify the naloxone plasma concentrations in the healthy subjects which is a consequence of the extremely low oral bioavailability of the drug. The clinical consequences of this will be investigated further in later studies. As the naloxone values measured in the healthy volunteers were very near the limit of quantification, the naloxone-3-glucuronide values probably reflect the influence of renal impairment on the bioavailability of this drug more precisely.

- OXN10/5 pharmacokinetics were markedly affected by renal impairment, suggesting that a careful titration when starting and maintaining therapy with the fixed combination of oxycodone and naloxone should be considered for patients with moderately or severely compromised renal function.

Date of the Report: 29 June 2007

4.2.15 Synopsis of Dosage form Proportionality Study OXN1403.

Name of Company: Mundipharma Research GmbH & Co. KG	INDIVIDUAL STUDY TABLE	(For National Authority Use Only)
Name of Finished Product: n/a	Referring to Part IV of the Dossier	
Name of Active Ingredient: Oxycodone hydrochloride Naloxone hydrochloride	Volume: Page:	

Title of the Study: An open-label, single dose, 4-treatment, 4-period, randomized crossover study in healthy subjects to assess the pharmacokinetic and bioavailability characteristics of three different strengths of a fixed combination OXN and a combination of Oxygesic® plus Naloxone CR

Investigator/Center: Dago Mazur, MD, PhD, Scope International Life Sciences AG, Frohbösestrasse 14, D-22525 Hamburg

Publication (Reference): None

Study Dates:	**Study Status:**	**Phase of Development:**
22-Mar-2004 to 13-May-2004	Completed	Phase 1

Objectives:

- To evaluate pharmacokinetic and bioavailability parameters of controlled-release oxycodone and naloxone and their main metabolites when administered as a fixed combination tablet.
- To assess the interchangeability between the 3 different strengths of the fixed combination.
- To compare the fixed combination with marketed Oxygesic® given together with a naloxone CR tablet.
- To assess the safety and tolerability of the fixed combination as compared to the combination of Oxygesic® plus naloxone CR.

Methodology: Open-label, single dose, randomized, 4-treatment, 4-period crossover

Number of Subjects: Enrolled: 46; Safety population: 28; Pharmacokinetic population: 26; Completed: 23 subjects; Discontinued: 5 (2 due to adverse events, 2 subjects' choice, 1 non compliance)

Indication and Criteria for Inclusion: Healthy males and females of any ethnic group, 18 - 45 years of age, with no clinically significant medical history, who provided their written informed consent and whose general practitioners (if applicable) confirmed that they were suitable to take part in clinical studies.

Test Treatment, Dose, and Mode of Administration:

OXN 10/5, a controlled-release combination tablet containing 10 mg of oxycodone hydrochloride and 5 mg of naloxone hydrochloride in an extruder formulation
OXN 20/10, a controlled-release combination tablet containing 20 mg of oxycodone hydrochloride and 10 mg of naloxone hydrochloride in an extruder formulation
OXN 40/20, a controlled-release combination tablet containing 40 mg of oxycodone hydrochloride and 20 mg of naloxone hydrochloride in an extruder formulation
All formulations were manufactured by Mundipharma Research GmbH & Co. KG
The treatments were given orally in the fasted state as follows:

- Treatment A: 4 x tablets of OXN 10/5
- Treatment B: 2 x tablets of OXN 20/10
- Treatment C: 1 x tablets of OXN 40/20

Reference Treatment, Dose, and Mode of Administration:

Oxygesic® 20 mg manufactured by (b) (4).
Naloxone 10 mg CR (b) (4) tablet manufactured by Mundipharma Research GmbH & Co. KG.
The treatment were given orally in the fasted state as follows:

- Treatment D: 2 tablets of Oxygesic® 20 mg and 2 tablets of Naloxone CR 10 mg

Duration of Treatment: 21 days screening period; 4 study periods each with a single dose of study drug followed by a 7-day washout period. Poststudy medical 7-10 days after dosing of Study Period 4, or 7-10 days after discontinuation from the study. Total duration: 49-52 days.

Treatment Schedule: Single dose of study drug in each of 4 study periods; each dose of study drug separated by a 7-day washout period.

Criteria for Evaluation:

Pharmacokinetic Parameters: AUCt, t1/2Z, AUCINF, Cmax, LambdaZ and tmax for oxycodone, noroxycodone, oxymorphone, noroxymorphone, naloxone, 6β-naloxol and naloxone-3-glucuronide

Safety: Safety was assessed by analyzing spontaneously reported adverse events, clinical laboratory results, vital signs (including pulse oximetry and respiratory rate), physical examinations and electrocardiograms (ECGs).

Bioanalytical Methods: The plasma samples were analyzed for oxycodone, noroxycodone, oxymorphone, noroxymorphone, naloxone, 6β-naloxol and naloxone-3-glucuronide by validated bioanalytical assays.

Statistical Methods: The most important outcomes were Cmax and AUCINF of oxycodone in order to assess the equivalence of the 4 treatments. All other outcomes were of secondary interest. AUCt was calculated using the linear trapezoidal method. Where possible, LambdaZ was estimated using those points determined to be in the terminal log-linear phase. t½Z were determined from the ratio of ln 2 to LambdaZ. The areas under the plasma concentration-time curve between the last measured point and infinity were calculated from the ratio of the final observed plasma concentration (Clast) to LambdaZ. This was added to the AUCt to yield the area under the plasma concentration-time curve between the time of administration and infinity (AUCINF).
The dose adjusted relative systemic availabilities (FrelI, and FrelINF) and the Cmax ratio were obtained from the ratio of AUCt, AUCINF and Cmax values, respectively, for differences defined in the following comparisons of interest:

- fixed combination A vs. open combination D
- fixed combination B vs. open combination D
- fixed combination C vs. open combination D
- fixed combination A vs. fixed combination B
- fixed combination A vs. fixed combination C
- fixed combination B vs. fixed combination C

The full analysis population for pharmacokinetics were used for these analyses.
The metabolite: parent drug AUCt and AUCINF ratios were estimated for each treatment, where possible.
All safety data were evaluated by descriptive methods only.

Pharmacokinetic Results: Naloxone-3-glucuronide was the primary analyte for naloxone. For naloxone-3-glucuronide, the AUCt [mean and (SD)] for 4 x OXN 10/5, 2 x OXN 20/10, 1 x OXN 40/20 and 2 X Oxygesic® 20 + 2 x Naloxone 10 were 539.93 (142.241), 522.45 (128.569), 520.10 (133.175) and 523.37 (119.752) respectively. The Cmax was 62.01 (15.961), 63.62 (19.511), 61.95 (18.369) and 63.55 (16.748) respectively.

For oxycodone, the AUCt [mean and (SD)] for 4 x OXN 10/5, 2 x OXN 20/10, 1 x OXN 40/20 and 2 X Oxygesic® 20 + 2 x Naloxone 10 were 473.49 (72.160), 491.22 (82.181), 488.89 (91.040) and 502.28 (84.128) respectively. The Cmax was 34.91 (4.361), 35.73 (4.391), 34.46 (5.025) and 40.45 (4.706) respectively.

Safety: Overall, the incidence and nature of TEAEs was similar across all treatments. The most common TEAEs (nausea, headache, dizziness) are consistent with the expected adverse event profile of opioids. One SAE occurred posttreatment and was not considered to be related to study drug.

Conclusions:

- In terms of oxycodone and naloxone-3-glucuronide, each of the fixed combination tablet strengths are interchangeable.
- The fixed combination tablets were also shown to be bioequivalent to Oxygesic® + naloxone CR.
- There were no deaths. One SAE, which was unrelated to study drug, occurred posttreatment.
- Five subjects discontinued from the study; one due to an SAE, one due to an AE, one due to non compliance and 2 due to subject choice.
- Overall, the incidence of TEAEs was similar across all treatments.
- The most common TEAEs across all treatment groups were: nausea, headache, and dizziness.
- There was no difference in the incidence of TEAEs between oxycodone and naloxone administered as a fixed OXN combination, and oxycodone and naloxone administered as an open combination.
- No clinically relevant changes in laboratory tests, vital signs, or ECG were observed in this study.

Date of the Report: 01-MAR-2005

Table 4. PK Parameters [geometric mean (%CV)] of Oxycodone, Naloxone and Naloxone-3β-Glucuronide and Statistical Analysis Results for OXN Tablet Interchangeability (Study OXN1403)

Analyte	Treatment A 4 x OXN 10/5 mg tablets (n = 24)		Treatment B 2 x OXN 20/10 mg tablets (n = 23)	
	C_{max} (ng/mL)	AUC_{0-t} (hr*ng/mL)	C_{max} (ng/mL)	AUC_{0-t} (hr*ng/mL)
Oxycodone	34.7 (12.4)	468 (15.3)	35.4 (13.8)	485 (17.1)
Naloxone	0.0588 (68.1)	0.673 (72.4)	0.0626 (71.1)	0.701 (78.4)
Naloxone-3β-glucuronide	59.9 (28.2)	520 (29.6)	60.7 (32.6)	507 (26.3)
	Treatment C 1 x OXN 40/20 mg tablet (n = 23)			
Oxycodone	34.1 (14.3)	481 (18.4)		
Naloxone	0.0609 (74.0)	0.678 (80.8)		
Naloxone-3β-glucuronide	59.3 (31.5)	502 (28.4)		
Statistical Analysis Results				
	C_{max} GLSM Ratio (90% CI)		AUC[a] GLSM Ratio (90% CI)	
	Treatment A/Treatment B		Treatment A/Treatment B	
Oxycodone	97.5 (92.9-102)%		96.2 (92.6-99.9)%	
Naloxone	94.1 (80.8-110)%		94.7 (82.4-109)%	
Naloxone-3β-glucuronide	98.8 (91.7-107)%		104 (97.9-111)%	
	Treatment A/Treatment C		Treatment A/Treatment C	
Oxycodone	101 (95.8-105)%		96.5 (92.9-100)%	
Naloxone	98.4 (84.6-114)%		100 (87.3-115)%	
Naloxone-3β-glucuronide	100 (93.1-108)%		103 (97.3-109)%	
	Treatment B/Treatment C		Treatment B/Treatment C	
Oxycodone	103 (98.2-108)%		100 (96.5-104)%	
Naloxone	105 (89.7-122)%		106 (92.0-122)%	
Naloxone-3β-glucuronide	102 (94.1-109)%		99.2 (93.5-105)%	

Abbreviations: AUC_{0-t} = area under the plasma drug concentration-time curve from time zero to the last measurable concentration after dosing; C_{max} = Maximum concentration of drug in plasma; CI = confidence interval; CV = coefficient of variation GLSM = geometric least squares mean; hr = hour; mg = milligram; mL = milliliter; n = number of subjects; ng = nanogram.

[a] AUC for oxycodone and naloxone-3β-glucuronide; AUC_{0-t} for naloxone.

Source: post-text Table D-1, post-text Table D-2, post-text Table D-3; OXN1403CSR Table 11, Table 13, Table 15

4.2.16 Synopsis of Study OXN1005

Name of Company: Mundipharma Research GmbH & Co. KG	INDIVIDUAL STUDY TABLE	(For National Authority Use Only)
Name of Finished Product: Not applicable	Referring to Part IV of the Dossier	
Name of Active Ingredient: Oxycodone hydrochloride (HCl) and naloxone HCl	Volume: Page:	

Title of the Study: An open-label, single-dose, 5-part, randomised, placebo-controlled, crossover study to investigate the effects on intestinal motility of oxycodone, given alone as an oxycodone prolonged release (PR) tablet and in combination with naloxone given as an oxycodone/naloxone (OXN) PR tablet, using scintigraphic and pharmacokinetic analyses in healthy male subjects.

Investigators/Centre: Dr Karuppan Palaniappan (Principal Medical Investigator) (b) (4)

Publication (Reference): None

Study Dates:	**Study Status:**	**Phase of Development:**
21 June 2007 to 24 August 2007	Completed	Phase I

Objectives:

- To assess the effect of single doses of oxycodone (10 and 20 mg) on gastrointestinal (GI) transit time.
- To assess the degree to which a single dose of naloxone in combination with oxycodone reverses the oxycodone-induced effect on GI transit time, at two dose levels.
- To characterise the pharmacokinetic profiles of oxycodone, naloxone, and naloxone-3-glucuronide and to attempt to correlate these to the scintigraphic measurements.

Methodology: Open-label, single-dose, 5-period, randomised, placebo controlled, crossover. Evaluations of scintigraphic data were performed in an evaluator-blinded manner. The study involved five treatments and five study periods. Study medication was administered in a fasted state, at the same time as administration of a capsule containing ion-exchange resin radiolabelled with up to 1.0 MBq ^{111}In. Each formulation of oxycodone, OXN, and placebo was labelled with up to 4.0 MBq ^{99m}Tc using a (b) (4) technique. This method was verified with post-labelling dissolution testing against the specification on the Certificate of Analysis for each formulated product.

Number of Subjects: It was planned to enrol and randomise a total of 15 subjects, with the aim that 10 subjects completed Study Periods 1 to 5. Subjects that discontinued, due to reasons other than adverse events, may have been replaced at the discretion of the Sponsor and Investigator. A total of 15 subjects were actually enrolled and randomised, and 13 subjects completed the study.

Indication and Criteria for Inclusion: Healthy males, 18 to 65 years of age inclusive, free of significant abnormal findings as determined by medical history, physical examination, vital signs and electrocardiogram (ECG), and whose primary care physician had confirmed within the previous 12 months that they had no objections to the subject participating in clinical studies.

Test Treatment, Dose, and Mode of Administration: Oxycodone/naloxone PR tablet 10/5 mg (OXN 10/5), a PR combination tablet containing 10 mg of oxycodone HCl and 5 mg of naloxone HCl, and oxycodone/naloxone PR tablet 20/10 mg (OXN 20/10), a PR combination tablet containing 20 mg oxycodone HCl and 10 mg naloxone HCl. OXN 10/5 (batch number: PN3130) and OXN 20/10 (batch number: PN3131) tablets were manufactured by Mundipharma Research GmbH & Co. KG, Germany.

Treatment A: 1 x OXN 10/5 tablet taken orally

Treatment B: 1 x OXN 20/10 tablet taken orally

Each formulation of OXN was radiolabelled with up to 4.0 MBq ^{99m}Tc using a (b) (4) technique by (b) (4)

Reference Treatment, Dose, and Mode of Administration: Oxycodone PR tablet 10 mg (***OxyContin***®) and oxycodone PR tablet 20 mg (***OxyContin***®), and placebo tablet (to match the appearance of OXN 10/5). Oxycodone PR tablet 10 mg (batch number: PN2894) and oxycodone PR tablet 20 mg (batch number: PN2895) were manufactured by (b) (4) Placebo tablets (batch number: PN3240) were manufactured by (b) (4)

Treatment C: 1 x oxycodone PR tablet 10 mg taken orally

Treatment D: 1 x oxycodone PR tablet 20 mg taken orally

Treatment E: 1 x placebo tablet taken orally

Each formulation of oxycodone PR tablets and the placebo tablet was radiolabelled with up to 4.0 MBq ^{99m}Tc using a (b) (4)" technique by (b) (4).

Duration of Treatment: Screening was within 28 days before Day 1 of Study Period 1. There were five study periods, with at least a 7-day washout between each study period. Subjects were administered the study treatment according to a random allocation schedule (RAS). Pharmacokinetic blood sampling continued for up to 48 hours, and scintigraphic imaging and safety monitoring continued for up to 72 hours after dosing with each treatment. Subjects had a post-study medical evaluation 5 to 10 days after their last dose of study medication, in the case of completion or discontinuation from the study.

The planned study duration was up to 66 days.

Treatment Schedule: Each treatment was given to subjects according to the RAS. Each dose of study medication and radiolabelled capsule was given with 240 ml of water to subjects in a standing position.

Criteria for Evaluation:

Analysis Populations:

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

For the scintigraphic analysis, the full analysis population was defined as those subject-periods with a group of geometric centre data points which enabled characterisation of the profile.

The full analysis population for pharmacokinetic parameters was defined as those subject-periods with a valid pharmacokinetic parameter.

The safety population was defined as those subjects who received one dose of study medication and had at least one subsequent safety assessment.

Drug Concentration Measurements:

Treatments A, B, C & D (no blood sampling in placebo group, Treatment E):

Pre-dose on Day 1 of the respective study period, and at 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 5, 6, 8, 10, 12, 16, 24, 30, 36, and 48 hours post-dose (19 blood samples per dosing period).

Up to 494 ml blood (19 samples of 6.5 ml, which included a 0.5 ml discard for each blood draw, on four occasions) were taken from each subject for pharmacokinetic measurements.

Bioanalytical Methods:

The plasma samples were analysed for oxycodone, naloxone, and naloxone-3-glucuronide using validated bioanalytical assays.

Scintigraphic Measurements:

All scintigraphic data analyses were performed in an evaluator-blinded manner.

Colonic Geometric Centre Analysis of the capsule formulation was the primary endpoint.

- Scintigraphic images of the gastrointestinal region were taken at approximately 20 minute intervals until 12 hours post-dose, hourly from 12 to 16 hours post-dose, and at 24, 30, 36, 48, and 72 hours post-dose (or until no radioactivity remained in the gastrointestinal tract, whichever occurred sooner).
- The colonic geometric centre of the radioactive resin was derived (as a surrogate of the location of the geometric centre of food in the colon at that specific point in time) using the method described below at the following time points: 4, 8, 12, 16, 24, 30, 36, 48, and 72 hours post-dose.

- The movement of food through the colon after dosing was characterised for each treatment using the mean geometric centre time profile for the radiolabelled resin and comparing these profiles between treatments.
- Colonic geometric centre analysis involved dividing the colon into seven separate regions of interest (ROIs): caecum/ascending colon, hepatic flexure, transverse colon, splenic flexure, descending colon, sigmoid colon/rectum and excreted faeces. Data from each ROI was used to generate a single number that represented the centre of overall progression of the radionuclide through the colon at any given time. The geometric centre was calculated by dividing the geometric mean of counts in an ROI by the corrected counts at the start of the imaging and multiplied by the region number.

In addition to the primary endpoint, the following secondary endpoints were derived from the scintigraphic profiles for the radiolabelled resin:

- Rate of gastric emptying (T50% [or time to 50% emptying])
- Small intestinal transit (T50%)
- Rate of colon arrival (T50%)

For the ^{99m}Tc radiolabelled tablets, the following qualitative parameters were determined:

- Gastric emptying time
- Small intestinal transit time
- Colonic arrival time
- Transit histograms (transit of the tablet formulation through each region of the colon).

No parameters were determined following complete disintegration of the tablets.

Pharmacokinetic measures: Blood samples for pharmacokinetic analysis were taken pre-dose and at intervals up to 48 hours post-dose on Day 1 of each study period. Plasma concentrations of oxycodone, naloxone and naloxone-3-glucuronide were analysed to determine the following pharmacokinetic parameters: AUCt, AUCINF, Cmax, tmax, LambdaZ and t1/2Z.

The treatments compared were as follows, dose adjusted as necessary:

1. OXN 10/5 vs. oxycodone PR tablet 10 mg
2. OXN 20/10 vs. oxycodone PR tablet 20 mg
3. OXN 20/10 vs. OXN 10/5

Safety Assessments:

Safety was assessed by documentation of spontaneously reported adverse events, clinical laboratory results, vital signs, physical examinations, and ECGs.

Statistical Methods:

Scintigraphic Data:

Colonic geometric centre data were listed for subjects in the scintigraphic full analysis population. Colonic geometric centre data were summarised descriptively by time point and treatment for subjects in the scintigraphic full analysis population. Individual and mean colonic geometric centre data were also plotted over time for each treatment.

Little information is available about the shape of the colonic geometric centre time profiles. Based upon the appropriateness of the fit to the data, the profile was characterised using a mixed non-linear logistic regression model. The same general model (parameters) was used to characterise all treatments. The estimated fixed effect parameters were compared between treatments.

Scintigraphic data from subjects experiencing emesis, resulting in a greater than 25% loss of radiolabelled resin, were excluded from analysis.

To compare the rates of GI transit, the mean values of the following parameters were compared and summarised by treatment:

For the ^{111}In radiolabelled resin: Initial, T50% and complete values for gastric emptying and colon arrival and T50% values for small intestine transit.

For the ^{99m}Tc tablet: Gastric emptying, small intestinal transit and colon arrival.

Pharmacokinetic Analyses:

Plasma concentration data and pharmacokinetic parameters were listed for subjects in the safety population.

Plasma concentration data for each analyte were summarised descriptively by time point and treatment for subjects in the safety population. Individual and mean plasma concentrations for each analyte were also plotted over time for each treatment.

Pharmacokinetic parameters (AUCt, AUCINF, Cmax, tmax, LambdaZ and t1/2Z) for each analyte were summarised descriptively by treatment for subjects in the full analysis population for pharmacokinetic parameters.

Log transformed data for oxycodone AUCt, AUCINF and Cmax were analysed using a mixed effect linear model, with fixed terms for treatment and period and a random effect for subject. Treatment ratios/ differences and their associated 90% confidence intervals were calculated from the least square means.

Correlation between Scintigraphic Data and Pharmacokinetic Data:

Colonic geometric centre data and plasma concentration data for oxycodone, naloxone, and naloxone-3-glucuronide were summarised descriptively by time point and treatment. Attempts were made to assess the correlation between the colonic geometric centre profiles and the pharmacokinetic profiles.

Safety Analyses:

Adverse events: The subject incidence (%) and number of reports of adverse events were calculated and presented by Medical Dictionary for Regulatory Activities (MedDRA™) Preferred Term and System Organ Class. Individual subject listings of all adverse events were provided.

Vital signs data were listed. Abnormal vital sign and laboratory values were identified as those outside (above or below) a specified range.

ECG results were classified as Not Clinically Significant or Clinically Significant. Clinically significant findings were recorded on the case report form (CRF). The data recorded on the CRF were listed.

Laboratory data were listed.

Sample Size Rationale:

This was an exploratory study. The sample size of 10 completing subjects is usual for a study of this type and was not based on statistical power calculations.

Results:

Scintigraphic:

Upper Gastrointestinal Tract Transit

There appeared to be no difference between the treatments in gastric emptying times of the tablet.

Small intestinal transit and colon arrival times were similar for the OXY PR 10 mg tablet compared with the placebo tablet, and for OXN 10/5 compared with OXY PR 10 mg, indicating no effect of oxycodone 10 mg on gastrointestinal transit.

Small intestinal transit and colon arrival times were statistically significantly longer for the OXY PR 20 mg tablet compared with the placebo tablet (p=0.0205 and p=0.0159, respectively), indicating that oxycodone 20 mg increased GI transit time. Small intestinal transit and colon arrival times were shorter for the OXN 20/10 tablet (4.40 and 5.16 hours, respectively) compared with the OXY PR 20 mg tablet (6.17 and 7.19 hours, respectively), although the differences between OXN 20/10 and OXY PR 20 mg did not reach statistical significance. Therefore naloxone partly reversed the oxycodone-induced prolongation of transit time.

Summary of Treatment Comparisons for Gastrointestinal Transit Times (Hours) for ^{99m}Tc Tablet: Scintigraphic Full Analysis Population

Parameter	Treatment comparison	Estimate (SE)	Significance	95% confidence interval	
				-Lower-	-Upper-
Gastric emptying	OXY PR 20 mg vs. placebo	-0.06 (0.392)	0.8871	-0.84	0.73
	OXN 20/10 vs. OXY PR 20 mg	0.07 (0.394)	0.8546	-0.72	0.87
	OXY PR 10 mg vs. placebo	0.04 (0.376)	0.9162	-0.72	0.80
	OXN 10/5 vs. OXY PR 10 mg	-0.01 (0.376)	0.9770	-0.77	0.75
Small intestinal transit	OXY PR 20 mg vs. placebo	1.85 (0.771)	0.0205	0.30	3.41
	OXN 20/10 vs. OXY PR 20 mg	-1.23 (0.801)	0.1327	-2.84	0.39
	OXY PR 10 mg vs. placebo	0.53 (0.744)	0.4795	-0.97	2.03
	OXN 10/5 vs. OXY PR 10 mg	-0.49 (0.763)	0.5219	-2.03	1.04
Colon arrival	OXY PR 20 mg vs. placebo	1.82 (0.726)	0.0159	0.36	3.28
	OXN 20/10 vs. OXY PR 20 mg	-1.42 (0.754)	0.0653	-2.94	0.09
	OXY PR 10 mg vs. placebo	0.58 (0.701)	0.4164	-0.84	1.99
	OXN 10/5 vs. OXY PR 10 mg	-0.60 (0.718)	0.4112	-2.04	0.85

The T50% values for gastric emptying, small intestinal transit and colon arrival times of the resin co-administered with OXY PR 10 mg and OXN 10/5 were similar to those of the resin co-administered with placebo. The comparisons of OXY PR 10 mg versus placebo and OXN 10/5 versus OXY PR 10 mg were not statistically significant.

The mean T50% values for gastric emptying and colon arrival time were later, and the mean T50% value for small intestinal transit time was longer for the resin co-administered with OXY PR 20 mg (1.47, 6.14 and 7.61 hours) compared with the resin co-administered with placebo (0.93, 5.23 and 6.16 hours). The effect of oxycodone 20 mg was partly reversed by naloxone, with mean T50% values for gastric emptying, small intestinal transit and colon arrival times of 1.31, 5.61 and 6.92 hours, respectively, for the resin co-administered with OXN 20/10. However, the comparisons of OXY PR 20 mg versus placebo and OXN 20/10 versus OXY PR 20 mg were not statistically significant.

Summary of Treatment Comparisons for T50% Values (Hours) for Gastrointestinal Transit (^{111}In Ion-exchange Resin): Scintigraphic Full Analysis Population

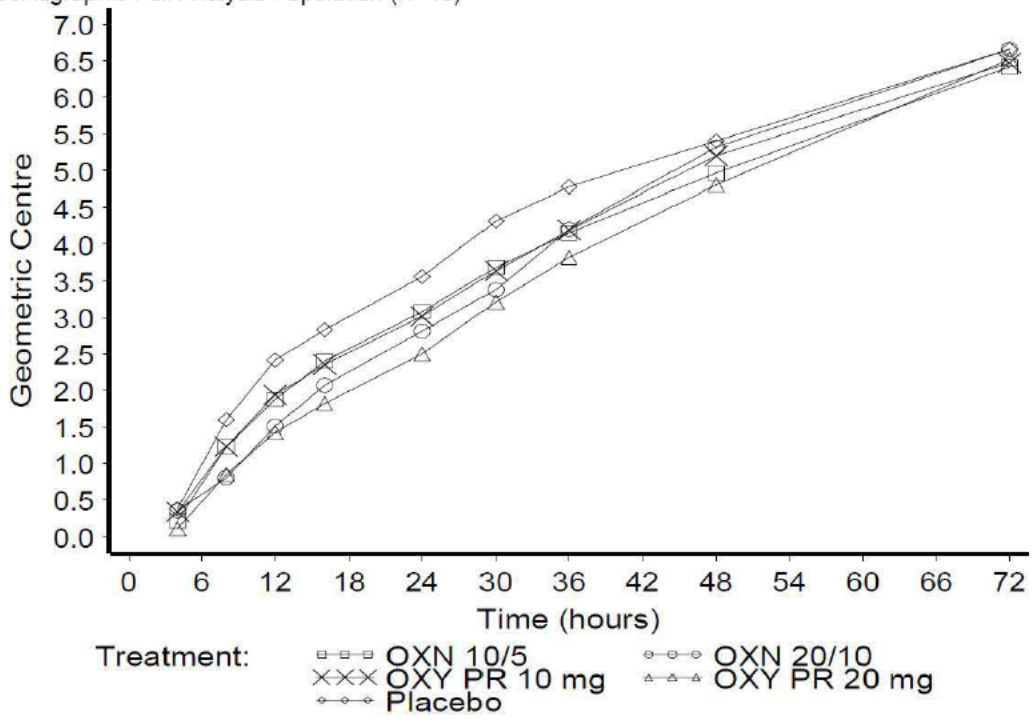
Parameter	Treatment comparison	Estimate (SE)	Significance	95% confidence interval	
				-Lower-	-Upper-
Gastric emptying	OXY PR 20 mg vs. placebo	0.51 (0.376)	0.1803	-0.25	1.27
	OXN 20/10 vs. OXY PR 20 mg	-0.10 (0.378)	0.8009	-0.86	0.67
	OXY PR 10 mg vs. placebo	0.04 (0.361)	0.9035	-0.68	0.77
	OXN 10/5 vs. OXY PR 10 mg	-0.17 (0.369)	0.6488	-0.91	0.57
Small intestinal transit	OXY PR 20 mg vs. placebo	0.74 (0.971)	0.4493	-1.21	2.70
	OXN 20/10 vs. OXY PR 20 mg	-0.31 (0.978)	0.7517	-2.28	1.66
	OXY PR 10 mg vs. placebo	-0.30 (0.938)	0.7534	-2.18	1.59
	OXN 10/5 vs. OXY PR 10 mg	-0.06 (0.959)	0.9515	-1.99	1.87
Colon arrival	OXY PR 20 mg vs. placebo	1.25 (0.993)	0.2158	-0.75	3.24
	OXN 20/10 vs. OXY PR 20 mg	-0.40 (0.999)	0.6914	-2.41	1.61
	OXY PR 10 mg vs. placebo	-0.24 (0.959)	0.8036	-2.17	1.69
	OXN 10/5 vs. OXY PR 10 mg	-0.25 (0.956)	0.7967	-2.17	1.68

Colonic transit

Quantitative assessment of colon transit of the resin co-administered with the five treatments indicated differences in the transit between treatments. The mean geometric centre data at 4, 8, 12, 16, 24, 30 and 36 hours post-dose were lower for all of the active treatments compared with placebo. These data indicate that a single dose of oxycodone resulted in a slowing of colonic transit compared with normal.

Mean Colonic Geometric Centre – Time Curves for ^{111}In Radiolabelled Ion-exchange Resin

Scintigraphic Full Analysis Population (N=15)



The results of the colonic geometric centre analysis showed that the oxycodone PR tablets (10 mg and 20 mg) slowed the colonic transit of the co-administered resin compared with the placebo tablets; these differences were statistically significant. The oxycodone PR 20 mg tablet had the greatest effect on colonic transit. There was no statistically significant difference between OXY PR 10 mg and OXN 10/5. However, colonic transit time was statistically significantly reduced with OXN 20/10 compared with OXY PR 20 mg for the unadjusted results but not the adjusted results.

The adjusted results indicate that OXY PR 20 mg and OXY PR 10 mg have a direct effect on geometric centre whilst the drug is in the colon, above and beyond any differences that may have occurred whilst the drug is in the small intestine.

The unadjusted results reflect the conglomeration of effects occurring whilst the drug is in either the small intestine or the colon. The unadjusted contrast between OXN 20/10 and OXY PR 20 mg implies that the presence of naloxone lessened the effect of 20 mg oxycodone on colonic transit; the non-significant contrast in the adjusted analysis suggests that this effect of naloxone occurred whilst the drug was in the small intestine.

There were no statistically significant treatment differences in scale implying that the effects of the treatments were to shift in parallel the geometric centre curves along the time axis, but not to stretch or compress the curves at all.

Summary of Treatment Comparisons of Geometric Centre Parameters (Hours): Scintigraphic Full Analysis Population

Parameter	Treatment comparison	Estimate	SE	Signif. level	95% confidence interval -Lower-	-Upper-
Adjusted for initial colon arrival time						
T50%	OXY PR 10 mg vs. placebo	4.58	0.848	0.0001	2.75	6.41
	OXY PR 10 mg vs. OXN 10/5	-0.30	0.890	0.7441	-2.22	1.63
	OXY PR 20 mg vs. placebo	7.16	0.933	<.0001	5.14	9.17
	OXY PR 20 mg vs. OXN 20/10	1.44	0.894	0.1324	-0.50	3.37
	Initial Colon Arrival Time	-0.27	0.170	0.1417	-0.63	0.10
Scale	OXY PR 10 mg vs. placebo	1.72	0.832	0.0586	-0.07	3.52
	OXY PR 10 mg vs. OXN 10/5	-0.58	0.890	0.5272	-2.50	1.35
	OXY PR 20 mg vs. placebo	1.02	0.850	0.2512	-0.82	2.86
	OXY PR 20 mg vs. OXN 20/10	0.22	0.839	0.8011	-1.60	2.03
Unadjusted for initial colon arrival time						
T50%	OXY PR 10 mg vs. placebo	5.33	0.849	<.0001	3.49	7.16
	OXY PR 10 mg vs. OXN 10/5	-0.38	0.907	0.6820	-2.34	1.58
	OXY PR 20 mg vs. placebo	8.83	0.873	<.0001	6.94	10.72
	OXY PR 20 mg vs. OXN 20/10	2.08	0.899	0.0376	0.14	4.02
Scale	OXY PR 10 mg vs. placebo	1.71	0.854	0.0671	-0.14	3.55
	OXY PR 10 mg vs. OXN 10/5	-0.55	0.908	0.5579	-2.51	1.42
	OXY PR 20 mg vs. placebo	0.93	0.867	0.3016	-0.94	2.81
	OXY PR 20 mg vs. OXN 20/10	0.21	0.847	0.8089	-1.62	2.04

Pharmacokinetic:

Oxycodone results

The geometric mean AUCt, AUCINF and Cmax values for OXN 10/5 and OXN 20/10 were consistent with observations from previous studies (OXN1403 and OXN1009) when taking dose into consideration.

Compared with the oxycodone PR tablet 10 mg, OXN10/5 had a mean oral availability of oxycodone of 99.7% and a mean Cmax ratio of 109.1%. The bioequivalence assessments for these comparisons all had 90% confidence intervals that met the criteria for bioequivalence.

Compared with the oxycodone PR tablet 20 mg, OXN 20/10 had a mean dose-adjusted oral bioavailability of oxycodone of 97.0% and a mean Cmax ratio of 106.1%. The bioequivalence assessments for these comparisons all had 90% confidence intervals that met the criteria for bioequivalence.

Compared with OXN 10/5, OXN 20/10 had a mean oral availability of oxycodone of 100.3% and a mean Cmax ratio of 101.5%. Again, the bioequivalence assessments for these comparisons all had 90% confidence intervals that met the criteria for bioequivalence.

The mean half-life values for oxycodone were similar across all treatments, ranging from 4.8 to 5.0 hours for OXN tablets, and 5.7 to 6.4 hours for oxycodone PR tablets. These values are within the ranges that have been recorded previously.

The OXN tablets and OXN PR tablets all had very similar median tmax values.

Summary of Treatment Comparisons for Oxycodone Pharmacokinetic Parameters: Full Analysis Pharmacokinetic Population

PK Parameter	Treatment comparison	Test/ Reference[a]	90% confidence interval[b]
AUCt	OXN 10/5 vs. OXY PR 10 mg	96.5	85.7, 108.7
	OXN 20/10 vs. OXN 10/5 [c]	99.7	88.3, 112.5
	OXN 20/10 vs. OXY PR 20 mg	104.2	92.1, 118.0
AUCINF	OXN 10/5 vs. OXY PR 10 mg	99.7	95.8, 103.7
	OXN 20/10 vs. OXN 10/5 [c]	100.3	96.3, 104.4
	OXN 20/10 vs. OXY PR 20 mg	97.0	93.2, 101.1
Cmax	OXN 10/5 vs. OXY PR 10 mg	109.1	103.8, 114.6
	OXN 20/10 vs. OXN 10/5 [c]	101.5	96.4, 106.7
	OXN 20/10 vs. OXY PR 20 mg	106.1	100.7, 111.8

[a] Ratio of parameter means for natural log transformed parameters (expressed as a percent). Natural log transformed ratios transformed back to linear scale.
[b] 90% confidence interval for ratio of parameter means of natural log transformed parameters (expressed as a percent). Natural log transformed confidence limits transformed back to linear scale.
[c] This contrast is dose adjusted: 0.5 times the ratio of OXN 20/10 to OXN 10/5.

Naloxone results

As expected from the data gathered in previous studies, the subjects had plasma profiles that contained low and irregular naloxone concentrations. Because of this, it was not possible to calculate AUCINF values for naloxone, and any bioavailability assessments were based on AUCt values. The naloxone data should be interpreted with caution.

Compared with OXN 10/5, OXN 20/10 had a mean oral bioavailability of naloxone of 281.7% and a Cmax ratio of 101.5%. The Cmax ratio had 90% confidence intervals that met the criteria for bioequivalence.

It was not possible to measure half-life values for naloxone, because the concentrations in the terminal elimination phase did not conform to a mono-exponential decline.

The OXN tablets had similar median tmax values for naloxone, with individual values ranging from 0.5 to 16 hours.

Summary of Treatment Comparisons for Naloxone Pharmacokinetic Parameters: Full Analysis Pharmacokinetic Population

PK Parameter	Treatment comparison	Test/ Reference[a]	90% confidence interval[b]
AUCt	OXN 20/10 vs. OXN 10/5 [c]	281.7	179.7, 441.6
Cmax	OXN 20/10 vs. OXN 10/5 [c]	101.5	87.5, 117.8

[a] Ratio of parameter means for natural log transformed parameters (expressed as a percent). Natural log transformed ratios transformed back to linear scale.
[b] 90% confidence interval for ratio of parameter means of natural log transformed parameters (expressed as a percent). Natural log transformed confidence limits transformed back to linear scale.
[c] This contrast is dose adjusted: 0.5 times the ratio of OXN 20/10 to OXN 10/5.

Naloxone-3-glucuronide results

The geometric mean AUCt, AUCINF and Cmax values for OXN 10/5 and OXN 20/10 were consistent with observations from previous studies (OXN1403 and OXN1009) when taking dose into consideration.

Compared with OXN 10/5, OXN 20/10 had a mean oral bioavailability of naloxone-3-glucuronide of 101.9% and a mean Cmax ratio of 100.9%. The bioequivalence assessments for these comparisons all had 90% confidence intervals that met the criteria for bioequivalence.

The mean half-life values for naloxone-3-glucuronide were similar across the treatments, ranging from 8.0 to 8.5 hours.

The OXN tablets had similar median tmax values for naloxone-3-glucuronide, with individual values ranging from 0.5 to 3 hours.

Summary of Treatment Comparisons for Naloxone-3-glucuronide Pharmacokinetic Parameters: Full Analysis Pharmacokinetic Population

PK Parameter	Treatment comparison	Test/ Reference[a]	90% confidence interval[b]
AUCt	OXN 20/10 vs. OXN 10/5 [c]	102.7	97.6, 108.1
AUCINF	OXN 20/10 vs. OXN 10/5 [c]	101.9	97.0, 106.9
Cmax	OXN 20/10 vs. OXN 10/5 [c]	100.9	92.6, 109.9

[a] Ratio of parameter means for natural log transformed parameters (expressed as a percent). Natural log transformed ratios transformed back to linear scale.

[b] 90% confidence interval for ratio of parameter means of natural log transformed parameters (expressed as a percent). Natural log transformed confidence limits transformed back to linear scale.

[c] This contrast is dose adjusted: 0.5 times the ratio of OXN 20/10 to OXN 10/5.

Correlation between Scintigraphic Data and Pharmacokinetic Data

A qualitative assessment was performed, examining the individual plasma oxycodone profile in conjunction with the times to gastric emptying and times to colon arrival, obtained from the scintigraphic analysis. It was concluded that the majority of oxycodone absorption occurs before the tablet reaches the colon.

Safety: There were no deaths or other serious adverse events. One subject permanently discontinued the study following dosing with OXY PR 20 mg due to nausea and vomiting, which were considered probably related to study medication by the investigator.

The number of subjects experiencing adverse events was highest after dosing with OXN 20/10 (six subjects [43%]), followed by OXY PR 10 mg (five subjects [33%]), OXN 10/5 (four subjects [29%]) and OXY PR 20 mg (two subjects [14%]). No subjects reported adverse events after dosing with placebo. The most frequently reported adverse events (reported by two or more subjects overall) were headache, dizziness, nausea, vessel puncture site haematoma and back pain. Headache, dizziness and nausea are consistent with the expected adverse event profile of opioid analgesics. The vessel puncture site haematoma and back pain adverse events were considered unrelated or unlikely to be related to study medication by the investigator. There were no clinically notable changes in laboratory tests, vital signs or ECGs.

Conclusions:

- Gastrointestinal transit times for the ^{99m}Tc tablet showed that a single dose of oxycodone 20 mg statistically significantly extended small intestinal transit and colon arrival times compared with placebo. There was a trend for the addition of naloxone to reverse this delay in GI transit times.
- Based on the mean T50% data for the ^{111}In ion-exchange resin, gastric emptying and colon arrival occurred later, and small intestinal transit was extended, following administration of oxycodone at the 20 mg dose compared with placebo; although these differences were not statistically significant. This effect was partly reversed by naloxone.
- The results of the colonic geometric centre analysis showed that the oxycodone PR tablets (10 mg and 20 mg) slowed the colonic transit of the co-administered resin compared with the placebo tablets; these differences were statistically significant. The oxycodone PR 20 mg tablet had the greatest effect on colonic transit. The presence of naloxone at the 10 mg oxycodone level had a limited effect on the transit of the resin compared with 10 mg oxycodone only. The effect of 20 mg oxycodone on colonic transit was significantly lessened by the presence of naloxone.
- Bioequivalence was demonstrated between the dose-adjusted parameters for the two OXN tablet strengths for oxycodone and naloxone-3-glucuronide. The OXN tablets were also shown to be bioequivalent in terms of oxycodone to corresponding strengths of oxycodone PR tablet.
- The OXN tablets were not bioequivalent to each other in terms of naloxone, however this result was not unexpected as, particularly for the lower strength tablet, the subjects had plasma profiles that contained low and irregular naloxone concentrations, which is in line with observed naloxone concentrations from other studies.

- Following qualitative assessment it was concluded that the majority of oxycodone absorption occurs before the tablet reaches the colon.
- There were no deaths or other serious adverse events. One subject discontinued the study following dosing with OXY PR 20 mg due to nausea and vomiting that were considered probably related to study medication by the investigator. The number of subjects experiencing adverse events was highest after dosing with OXN 20/10 (six subjects [43%]), followed by OXY PR 10 mg (five subjects [33%]), OXN 10/5 (four subjects [29%]) and OXY PR 20 mg (two subjects [14%]). No subjects reported adverse events after dosing with placebo. The most frequently reported adverse events (reported by two or more subjects overall) were headache, dizziness, nausea, vessel puncture site haematoma and back pain. Headache, dizziness and nausea are consistent with the expected adverse event profile of opioid analgesics. The vessel puncture site haematoma and back pain adverse events were considered unrelated or unlikely to be related to study medication by the investigator.
- There were no clinically notable changes in laboratory tests, vital signs or ECGs.
- Despite the clear effect of oxycodone on colonic transit, review of the clinical data suggests the effect of a single dose is sub-clinical. Only one subject had a reported adverse event of constipation, 6 days after receiving OXY PR 10 mg.

Date of the Report: 28 March 2008

4.2.17 Synopsis of Study OXN2401

Name of Company: Mundipharma GmbH	INDIVIDUAL STUDY TABLE	(For National Authority Use Only)
Name of Finished Product: n/a	Referring to Part IV of the Dossier	
Name of Active Ingredient: Oxycodone hydrochloride Naloxone hydrochloride	Volume: Page:	
Title of the Study: Optimization of Naloxone - Oxycodone ratio in pain patients		
Investigator(s)/Center(s): This study was conducted by qualified investigators under the Sponsorship of Mundipharma GmbH at 28 sites in Germany. The principal investigator (LKP - Leiter der Klinischen Prüfung, principal investigator in Germany) was Dr. med. Wolfgang Fleischer. The signature of the principal investigator (LKP) is contained in Appendix 16.1.5.		
Publication (Reference): None.		
Study Dates: 07-May-2002 to 12-Apr-2003	**Study Status:** Completed	**Phase of Development:** Phase 2
Objectives: The primary objective of this study was to investigate whether an oxycodone/naloxone combination will lead to a comparable analgesia with a decrease in constipation in patients with severe chronic pain of tumor- and non-tumor origin when compared with oxycodone alone, and to investigate the optimal dose ratio of oxycodone and naloxone. The secondary objective was to compare the incidence of other side effects between treatment groups.		
Methodology: This was a multicenter, prospective, controlled, randomized, double-blind (with placebo-dummy), 4 parallel group Phase 2 study with oral CR oxycodone, oral CR naloxone and corresponding naloxone placebo. The study had three core phases: a pre-randomization phase, a 4 week double-blind treatment period (maintenance phase) and a follow-up phase. The pre-randomization phase consisted of screening and titration/run-in. Following screening, patients entered either a titration or run-in period. Patients with insufficient pain control at screening entered a minimum 2 week titration period and were individually titrated and stabilized at an oxycodone dose between 40 and 80 mg per day. Patients on stable oxycodone pretreatment at screening (40-80 mg/day) and with concomitant constipation, entered a 1 week run-in period and were eligible for the maintenance phase without prior titration.. At the end of the titration/run-in period, patients who were receiving a stable maintenance dose of oxycodone (with no more than 5 rescue medication intakes per week) and had a medical need for the regular intake of laxatives were randomized to one of 3 naloxone treatment groups or a naloxone placebo treatment group and received their maintenance dose of oxycodone plus either 10 mg, 20 mg, 40 mg or naloxone placebo CR tablets daily. After the treatment period, patients maintained their maintenance dose of oxycodone only for a further two week follow-up phase.		
Number of Patients: In total 202 patients were randomized and 152 patients were to receive both naloxone and oxycodone; 50 patients were to receive oxycodone and naloxone placebo. The ITT population consisted of 196 (97.0%) patients. The PP population consisted of 99 (49.0%) patients.		
Indication and Criteria for Inclusion: Male or female patients, aged ≥18 years, who were suffering from severe chronic pain of tumor and non-tumor origin and who required opioid treatment were enrolled in the study. Patients with insufficient efficacy or tolerability to a WHO II or III analgesic and patients with stable oxycodone therapy (40-80 mg/day) were suitable for screening. Patients included in the double-blind treatment period were on stable oxycodone treatment and had a medical need for the regular intake of laxatives..		

Test Treatment, Dose, and Mode of Administration: Blinded naloxone CR tablets (5 mg and 10 mg) were supplied in bottles. The dosage regimen was constant for the entire double-blind treatment period and no dose adjustments were allowed. Patients received either 5, 10 or 20 mg of oral naloxone each morning and evening (see **Treatment Schedule**).

Medication	Batch/Lot number	Expiration Date
Naloxone 5 mg CR tablets	OXN5-087-01	12-Dec-2003
Naloxone 10 mg CR tablets	OXN10-088-01	12-Dec-2003

Open label oxycodone CR tablets (10 mg and 20 mg) were supplied in blister packs. Dose adjustments could be performed during the titration/run-in period and 10 mg CR oxycodone tablets were available as rescue medication throughout the entire study. The dosage regimen was constant for the entire double-blind treatment period. Patients received either 20, 30 or 40 mg of oral oxycodone each morning and evening (see **Treatment Schedule**).

Medication	Batch/Lot number	Expiration Date
Oxycodone 10 mg CR tablets	10012443	12-Dec-2003
Oxycodone 20 mg CR tablets	10012302	12-Dec-2003

Reference Treatment, Dose, and Mode of Administration: Blinded naloxone placebo tablets were optically identical to naloxone tablets 5 mg and 10 mg. Dose and mode of administration were as for naloxone CR tablets.

Medication	Batch/Lot number	Expiration Date
Naloxone placebo tablets	OXN-086-01	12-Dec-2003

Duration of Treatment: The total study duration was up to 10 weeks, including a screening period, a minimum 2 week titration period (maximum 3 weeks) (or a 1 week run-in period), a 4 week treatment period (oxycodone and naloxone/naloxone placebo) and a follow-up phase of 2 weeks.

Treatment Schedule: For the titration/run-in period oxycodone only was administered in starting doses of 20-80 mg per day. Only patients with stable pain control, either 2 x 20 mg, 2 x 30 mg or 2 x 40 mg daily (tablets taken in the morning and evening) were randomized to one of 3 naloxone treatment groups or a naloxone placebo treatment group:

	Group 1	Group 2	Group 3	Group 4
Naloxone daily dose (mg)	Placebo	5 + 5	10 + 10	20 + 20
Oxycodone daily dose (mg)	2x20, 2x30, 2x40	2x20, 2x30, 2x40	2x20, 2x30, 2x40	2x20, 2x30, 2x40
Oxycodone/ naloxone dose ratio	40/placebo, 60/placebo, 80/placebo	40/10, 60/10, 80/10 4/1, 6/1, 8/1	40/20, 60/20, 80/20 2/1, 3/1, 4/1	40/40, 60/40, 80/40 1/1, 1.5/1, 2/1

Note: Identical dose ratios were obtained for 40/10 and 80/20 (4/1) and for 40/20 and 80/40 (2/1)

For blinding purposes each patient received 2 tablets naloxone/placebo every morning and evening.

Following the treatment period, patients maintained their dose of oxycodone only (2 x 20 mg, 2 x 30 mg or 2 x 40 mg daily) for a further two week follow-up phase.

Criteria for Evaluation:

Efficacy: The primary efficacy outcomes of interest were: patient's assessment of pain intensity (mean pain) and patient's assessment of bowel function (based on ease of defecation, feeling of incomplete bowel evacuation and judgment of constipation). Secondary efficacy outcomes were: daily pain intensity, use of rescue medication, ease of defecation, feeling of incomplete bowel evacuation, judgment of constipation, stool frequency, stool consistency, laxative intake/mean laxative dose, sumscores of elicited opioid and naloxone typical side effects and a global assessment of efficacy/tolerability/preference. Patient and/or investigator rating scales were used to assess all endpoints except rescue medication, stool frequency, laxative intake/dose and sumscores for side effects.

Safety: Safety was assessed using AEs, clinical laboratory results and physical examinations.

Statistical Methods: Summary statistics were provided for all outcome measures, either for the intent-to-treat (ITT) population or the per protocol (PP) population. The primary population for statistical analysis was the ITT population, with additional focus on the PP population for the analysis of pain intensity. For the primary efficacy outcomes, mean pain and bowel function, it was investigated if the addition of naloxone to oxycodone lead to an improvement in bowel function (test of difference) without a clinically relevant increase in pain intensity (confidence intervals and non-inferiority test). Hence, the influence of the absolute dose of naloxone (10 mg naloxone, 20 mg naloxone, 40 mg naloxone) on bowel function and pain intensity was tested in an exploratory way using t-tests with each dose compared with placebo. In order to take imbalances in mean pain intensity at baseline into account, the t-tests were based on an ANOVA analysis, and also on a post-hoc analysis on the ANCOVA, with the baseline value as covariate. In addition, response surface analysis was performed within an additional analysis for pain intensity and bowel function as well as for SOWS, global assessment of tolerability, and rescue medication intake. The response surface analyses, based on the before mentioned parameters, aimed to investigate the effect of the oxycodone/naloxone ratio. For the analysis of the secondary endpoints rescue medication, ease of defecation, feeling of incomplete bowel evacuation, judgment of constipation, laxative intake and sumscores of elicited opioid and naloxone typical side effects the Wilcoxon test (modified to handle the Behrens-Fischer problem) was used to test for treatment differences for the absolute dose of naloxone. In addition, for stool frequency and percentage change in mean laxative dose t-tests for the absolute dose of naloxone were performed for treatment differences. All calculated p-values were of an exploratory nature.

Results:

Efficacy: Overall, the treatment groups were generally balanced regarding demographic and baseline characteristics, anamnesis and medical profile. A total of 36 (17.8%) patients discontinued during the treatment or follow-up phase with the primary reason for discontinuation being an AE (19 patients, 9.4%). During the maintenance phase no apparent differences in the intensity of pain were observed between any treatment groups or dose ratios, indicating that there was no clinically meaningful influence of naloxone on the analgesic effect of oxycodone. By absolute naloxone dose (10mg, 20mg and 40 mg), mean pain score differences from naloxone placebo and 90% confidence intervals, in both the ITT and Per Protocol populations, did not indicate any clinically relevant differences in analgesic efficacy between oxycodone/naloxone and oxycodone alone. In the ITT population, mean pain scores (+-SD), ranged from 38.3 (±18.49) to 38.8 (±16.59) compared to 36.9 (±15.74) for placebo during the last 7 days prior to Visit 4 and 37.2 (±17.24) to 38.7 (±17.05) compared to 37.8 (±18.22) for placebo during the last 7 days at the end of the maintenance phase. Analgesic efficacy did not change at V4 and V5 with oxycodone dose or oxycodone/naloxone ratio in a quadratic response surface model using oxycodone dose and the ratio as factors and baseline mean pain as covariate. In a quadratic response surface model with oxycodone and naloxone dose as factors, it was demonstrated that there was no relevant effect of naloxone dose on analgesic efficacy at V4 and V5.

A trend towards improved mean bowel function with increased dose of naloxone was seen. During the last 7 days at the end of the maintenance phase, mean bowel function scores (±SD) were lowest (low score values represent low bowel dysfunction) with the 1/1 (21.9±22.25), 1.5/1 (21.8±21.35) and 2/1 (26.7±23.98) dose ratios (ITT population). Bowel function appeared to worsen as the amount of naloxone decreased (45.4 (±22.28), 40.3 (±23.09), 31.3 (±25.82) and 26.1 (±25.08) for placebo, 10 mg, 20 mg and 40 mg respectively at the end of maintenance – Visit 5) with statistically significant differences to placebo in favor of 20 mg and 40 mg naloxone at the end of maintenance ($p<0.05$, t-test for difference). The statistical significant improvement in the 20mg and 40mg doses vs naloxone placebo was also demonstrated when the Visit 4 value was carried forward for subjects with missing Visit 5 data. The 2/1 and the 1.5/1 ratios demonstrated significant differences compared to the corresponding oxycodone dose plus naloxone placebo at V4 and V5, based on statistical significance testing of the mean bowel function data modeled using the quadratic model. At Visit 5, the size of the improvement in bowel function estimated for each dose ratio, versus the corresponding oxycodone dose plus naloxone placebo, was 11.0 ($p = 0.0089$) for the 4/1 ratio, 13.4 ($p = 0.0042$) for 3/1, 16.2 ($p = 0.0005$) for 2/1 and 16.5 ($p = 0.0014$) for 1.5/1. The improvement estimated at 2/1 was superior by 5.2 units on the bowel function scale over 4/1 ($p = 0.0180$). The analysis of the estimated response model confirmed that bowel function at V4 and V5 remains relatively constant within the dose ratio.

The oxycodone/naloxone combination provided improvements in ease of defecation, feeling of incomplete bowel evacuation and judgment of constipation. The greatest improvements were seen at dose ratios of 1/1, 1.5/1 and 2/1 or an absolute dose of 40 mg. Improvements in ease of defecation were seen during the last 7 days at the end of the maintenance phase ($p<0.05$ for all doses of naloxone versus placebo) and during the last 7 days prior to Visit 4 ($p<0.05$ for 20 mg and 40 mg naloxone versus placebo) as the dose of naloxone increased. Improvements in feeling of incomplete bowel evacuation were seen during the last 7 days at the end of the maintenance phase ($p<0.05$ for 20 mg and 40 mg naloxone versus placebo) and during the last 7 days prior to Visit 4 ($p<0.05$ for 40 mg naloxone versus placebo) as the dose of naloxone

4.2.18 Synopsis of Study ONU3701

Name of Sponsor/Company: Purdue Pharma L.P.	**Protocol No.** ONU3701	
Name of Active Ingredient: Oxycodone/naloxone	**Name of Finished Product:** Oxycodone/naloxone (OXN) controlled-release tablets	
IND No.: 70,851		
Title of the Study: A Randomized, Double-blind, Placebo-controlled, Multicenter Trial with an Enriched Study Design to Assess the Efficacy and Safety of Oxycodone/Naloxone Controlled-release Tablets (OXN) Compared to Placebo in Opioid-experienced Subjects with Moderate to Severe Pain due to Chronic Low Back Pain who Require Around-the-clock Opioid Therapy		
Investigators, Sites: Multicenter, 132 sites in USA		
Publication (Reference): None		
Study Dates: 25-May-2011 (first subject first visit) to 15-Oct-2012 (last subject last visit)	**Study Status:** Completed	**Phase of Development:** Phase 3
Objective: The primary objective of this study was to assess the efficacy and safety of OXN compared to placebo in opioid-experienced subjects with moderate to severe pain due to chronic low back pain who required around-the-clock opioid therapy.		
Study Design (Methodology): This was a double-blind, placebo-controlled, parallel group, randomized, enriched design study of OXN in subjects with moderate to severe pain due to chronic low back pain. The study consisted of 3 phases comprising 4 periods: the prerandomization phase included the screening period (up to 14 days) and an open-label titration period (up to 28 days; during which subjects were switched from their incoming opioids to OXN); the double-blind phase included the double-blind period (12 weeks); and the safety follow-up phase included the safety follow-up period (1 week). Each subject entering the 12 week double-blind period had to demonstrate analgesic benefit and acceptable tolerability with OXN treatment during the open-label titration period and was randomized to receive either OXN (on 1 of 4 regimens: OXN 10/5 mg, OXN 20/10 mg, OXN 30/15 mg, and OXN 40/20 mg, every 12 hours) or matching placebo, based on their OXN dose at the end of the open-label titration period. Supplemental pain medication (immediate-release oxycodone HCl capsules) for breakthrough low back pain was allowed except during the 30 hours preceding visits 5 through 8 in the double-blind period.		
Number of Subjects (Planned and Analyzed): Planned total number: 600 (300 subjects in each of the 2 treatment groups). Enrolled/screened: 1924; open-label titration period: 1109 (14 not dosed); randomized: 601 (placebo, 302; OXN, 298; 1 subject was randomized but never received double-blind treatment); completed: 399 (placebo 181; OXN, 218).		
Diagnosis and Main Criteria for Inclusion/Exclusion: Male and female subjects aged 18 years or older; with a clinical diagnosis of low back pain for at least 3 months related to nonmalignant and nonneuropathic conditions (Quebec Task Force Classification 1 or 2); whose pain was not adequately treated prior to the screening visit with their stable incoming opioid analgesic medication(s); whose average daily total opioid dose was equivalent to 20 to 160 mg/day (inclusive) of morphine, and whose "average pain over the last 24 hours" and "average pain over the last 14 days" scores were ≥ 5 on the 11 point numerical rating scale (NRS) were eligible for the study. Subjects not taking and tolerating opioid(s) at screening and those with evidence of impaired liver/kidney function were excluded.		
Test Product, Dose, and Mode of Administration, Batch Number: (Appendix 16.1.6) Open-label titration period: OXN 10/5 mg, OXN 20/10 mg, OXN 30/15 mg (dispensed as 1 OXN 20/10 mg tablet and 1 OXN 10/5 mg tablet), and OXN 40/20 mg tablets, every 12 hours taken orally. Double-blind period: OXN 10/5 mg, OXN 20/10 mg, OXN 30/15 mg (dispensed as 1 OXN 20/10 mg tablet and 1 OXN 10/5 mg tablet), and OXN 40/20 mg tablets or matching placebo, every 12 hours taken orally. Supplemental analgesic medication Immediate-release oxycodone HCl capsules were provided as supplemental pain (rescue) medication for low back pain during the open-label titration period and the double-blind period. During the open-label titration period, the allowed immediate-release oxycodone HCl dose was up to 40 mg/day, and, during the double-blind period, the maximum oxycodone rescue dose was 10 mg/day except during the 30 hours preceding visits 5 through 8, when no oxycodone rescue was allowed.		

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Treatment Schedule (Procedure):
Prerandomization Phase (≤ 42 days):

Visit 1 and screening period (up to 14 days): At visit 1, after written informed consent was obtained, the subject underwent evaluation for study eligibility. Subjects provided their medical history, underwent a physical examination (including vital signs and weight), had laboratory testing (including blood tests [including a serum pregnancy test for women of child-bearing potential], urinalysis, and urine drug and breath alcohol testing), and had electrocardiogram (ECG) testing. The subject's "average pain over the last 24 hours" and "average pain over the last 14 days" were assessed. Scores were obtained for the Clinical Opioid Withdrawal Scale (COWS) and the modified Subjective Opioid Withdrawal Scale (SOWS).

During the screening period, subjects were allowed to continue on their incoming medications. They had to continue to require an average daily dose of 20 to 160 mg (inclusive) of morphine or its equivalent. Subjects taking tramadol ≥ 100 mg daily were also considered to have met this requirement.

To continue in the study, a subject was required to meet all inclusion criteria, including the pain score requirement (eg, "average pain over the last 24 hours" score must have been ≥ 5 on an 11-point NRS in which 0=no pain and 10=pain as bad as you can imagine), and not meet any exclusion criteria.

During the screening period, the investigator/medically qualified designee (had to be MD or DO) reviewed the subject's laboratory results (eg, pregnancy tests, hematology, serum chemistry, urinalysis, and breath alcohol and urine drug test results) and ECG results upon receipt from the central provider.

If the laboratory assessments and ECG report from the central ECG provider showed that the subject continued to meet the eligibility criteria, the subject proceeded to the open-label titration period. A subject who did not qualify for continuing in the study was discontinued from the study as a screen failure.

Visit 2 and open-label titration period (up to 28 days):

At visit 2, subjects rated their "average pain over the last 24 hours" scores on an 11-point NRS; Medical Outcomes Study (MOS) sleep scale, Brief Pain Inventory-Short Form (BPI-SF), and Oswestry Disability Index (ODI) scores, COWS, and modified SOWS scores were obtained; and the subject's use of opioid medication during the screening period was reviewed.

To proceed to the open-label titration period, a subject was required to meet all of the following criteria:

- The subject's "average pain over the last 24 hours" score had to be ≥ 5 (on an 11-point NRS in which 0=no pain and 10=pain as bad as you can imagine).
- The subject's total average daily opioid dose over the screening period had to be equivalent to 20 to 160 mg morphine (inclusive). Subjects taking tramadol ≥ 100 mg daily during the screening period were also considered to have met this criterion.
- The subject had to continue to be an appropriate candidate for this study, in the opinion of the investigator.

Subjects who did not meet these criteria were considered screen failures and discontinued from the study. Subjects proceeding to the open-label titration period were converted from their current opioid therapy to OXN based on a provided conversion table and an individualized assessment by the investigator. Other nonopioid medication used for chronic pain, including acetaminophen, NSAIDs, COX-2 inhibitors, aspirin, gabapentin and other neuropathic pain medications, muscle relaxants, antiepileptics, and antidepressants, had to be discontinued before treatment with OXN was initiated. However, if the investigator determined that nonopioid medication for chronic pain required tapering (eg, antiepileptics or anticonvulsants), such medication could be continued into the open-label titration period but had to be discontinued completely 7 days before the start of the double-blind period. NSAIDs, aspirin, COX-2 inhibitors, and acetaminophen could be used intermittently for headache, fever, or acute pain other than low back pain; low dose aspirin for cardiovascular disease prophylaxis was allowed. Muscle relaxants could be used intermittently during the course of the study for treatment of acute muscle spasms. Medications such as antiepileptics and antidepressants could be continued

only if not used for chronic pain.

During the open-label titration period the subject was given a diary to record daily 1) OXN intake, 2) use of immediate-release oxycodone HCl capsules as supplemental pain medication for low back pain, 3) "pain right now" score before each use of supplemental pain medication for low back pain, 4) "average pain over the last 24 hours" score using an 11-point NRS, and 5) modified SOWS score.

Study center staff reviewed diary data daily and contacted the subjects at least twice a week to assess efficacy, safety, tolerability, and study drug compliance.

At the titration visit (visit 2), the investigator/designee instructed the subject to discontinue their incoming opioid therapy and dispensed OXN. If the subject had taken any long-acting opioids on the day of visit 2 (including application of a fentanyl or buprenorphine patch), the investigator instructed the subject regarding timing of the first dose of OXN. Subjects were required to contact the study center before any dose change (up or downtitration), and the study center staff instructed the subject on how to adjust dosing. The dose of OXN could be uptitrated by the investigator every 1 to 2 days as needed based on efficacy, safety, and tolerability considerations. Downtitrations could be made by the investigator at any time for safety and/or tolerability reasons. The OXN dose could not be greater than 40/20 mg, administered every 12 hours. Subjects may have needed to visit the study center for re-supply. Immediate-release oxycodone HCl capsules were available as supplemental pain medication for low back pain, and subjects were instructed to take 1 or 2 immediate-release oxycodone HCl 5-mg capsules every 4 hours, as needed, but not more than 8 capsules per day. If a subject required more than 2 rescue immediate-release oxycodone HCl 5-mg capsules daily, uptitration was to be considered.

To be considered as having achieved a stable and effective OXN dose, the subject had to meet the following criteria for a period of 7 consecutive days, after having discontinued any incoming nonopioid medications requiring tapering:

- Remained on the same dose of OXN during the 7 consecutive days, and
- Had an "average pain over the last 24 hours" score on an 11-point NRS of ≤ 4 and at least 2 points lower than their screening mean pain score (where screening mean pain was defined as the mean of the "average pain over the last 24 hours" score collected at visits 1 and 2) for the last 3 days out of these 7 days, and
- Not taken more than 2 immediate-release oxycodone HCl 5-mg capsules on any given day during these 7 days.

When the subject was within 2 days of qualifying for entry into the double-blind period, the subject was to be contacted by telephone to schedule visit 3. Subjects who did not meet the double-blind entry criteria within 28 days were considered titration failures.

If the investigator confirmed that the subject continued to be an appropriate candidate for this study and could be stabilized on 1 of the 4 OXN regimens (OXN 10/5 mg, OXN 20/10 mg, OXN 30/15 mg, OXN 40/20 mg, every 12 hours), then the subject proceeded to the randomization visit (visit 3), which was required to occur within 28 days after visit 2.

Double-blind Phase

Double-blind Period (12 Weeks):

Visit 3: Subjects who did not meet the double-blind period entry criteria underwent titration failure procedures; subjects who met the double-blind period entry criteria were stratified by their stabilized dose of OXN at the end of the open-label titration period and randomized to receive OXN or matching placebo tablets. Optional pharmacogenomic (PG) samples were obtained from subjects who had consented to this procedure.

All subjects underwent a blinded taper during the first 2 to 10 days of the double-blind period; during this time, subjects randomized to matching placebo received OXN taper tablets in addition to the placebo tablets, and subjects randomized to OXN received dummy taper tablets in addition to the active tablets. Subjects could take

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1 immediate-release oxycodone HCl 5-mg capsule up to 2 times per day as supplemental pain medication for low back pain. After the first 10 days of double-blind treatment, subjects were allowed to downtitrate their dose once to the next lower dose of OXN or matching placebo for tolerability reasons. If subjects who downtitrated their dose were tolerating but not adequately responding to the lower dose, they could backtitrate to their initial dose. No other titration was allowed. Subjects had to continue to forgo all non-study drugs for chronic pain during the double-blind period, except those permitted per protocol.

During the double-blind period, the subject recorded in the diary (1) OXN intake (2) daily "average pain over the last 24 hours", (3) use of immediate-release oxycodone HCl supplemental pain medication for low back pain (4) "pain right now" just prior to each use of supplemental immediate-release oxycodone HCl and (5) daily modified SOWS score (from visit 3 until visit 5 of the double-blind period).

Visits 4 through 8: Scheduled visits to the study center occurred at week 1 (visit 4), week 2 (visit 5), week 4 (visit 6), week 8 (visit 7) and week 12 (visit 8 or early study discontinuation [ESD]) after randomization, for a total of 5 scheduled visits during the double-blind period. At each visit the subject was evaluated by the investigator/ medically qualified designee (had to be MD or DO) for pain control and safety. The subject diary was reviewed at each visit at a minimum, and it could be reviewed to assess compliance at any time during the study.

Supplemental pain medication (immediate-release oxycodone HCl) for low back pain was not permitted during the 30 hours prior to visits 5 through 8. Other medications with analgesic effects (eg, acetaminophen, NSAIDS, COX-2 inhibitors, or aspirin) but taken for reasons other than chronic pain (eg, headache, fever, and acute pain other than low back pain) were to be avoided if possible during these 30-hour windows; aspirin prophylaxis for cardiovascular disease was allowed. At visits 5 through 8, subject's pain level as reported by the subject ("average pain over the last 24 hours" score) was recorded using an 11-point NRS; BPI was also obtained.

At visits 3, 4, 5, 6, 7, and 8, the COWS was performed, subject's modified SOWS scores and vital signs were also obtained. At visits 3, 5, 6, 7, and 8, subject's responses on the ODI were obtained. At visits 3, 6, 7, and 8, MOS-Sleep Scale scores were collected. At visits 3 and 6, clinical laboratory tests, urine drug and breath alcohol tests, pregnancy testing (for female subjects of childbearing potential), and ECG testing were performed. During visit 8 (the week 12 visit or at any earlier visit if the subject was discontinuing participation in the study), the subject provided a Patient Global Impression of Change (PGIC) and underwent a complete physical examination, ECG testing, clinical laboratory testing, urine drug and breath alcohol tests. Also at visits 3 and 8, a physical examination was performed.

Between visits, the study center was to monitor diaries daily to confirm compliance and contact subjects to remind them to fill out the diaries if necessary.

At any time during the double-blind period, the subject could discontinue study drug for any reason. Subjects who discontinued double-blind study drug early were expected to complete the remaining visits and procedures unless they discontinued from the study. A subject continuing in the study returned to the investigational site for an unscheduled visit (study drug discontinuation visit) as soon as possible (within 2 days after study drug discontinuation) and completed all study procedures for the unscheduled study drug discontinuation visit. The subject was provided with instructions for ongoing pain management as deemed medically appropriate and instructed to complete all remaining visits and procedures. If the subject discontinued from the study, they were to return to the investigational site as soon as possible (within 2 days after study drug discontinuation) and complete all "visit 8/ESD" procedures. Subjects who discontinued from the study were provided with instructions for ongoing pain management as deemed medically appropriate.

Blood samples for determining oxycodone HCl, naloxone HCl and naloxone-3-glucuronide plasma concentrations were obtained at visit 3 for all randomized subjects, at visit 6, and at the first visit after the last dose of double-blind study drug (visit 8/ESD or unscheduled study drug discontinuation visit).

At any visit during the double-blind period, blood samples for determining oxycodone HCl, naloxone HCl and naloxone-3-glucuronide plasma concentrations were to obtained from subjects if either of the following criteria was met:

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- The subject had a COWS score ≥ 13, or
- The subject had an adverse event (AE) of opioid withdrawal.

Optional PG samples were obtained from subjects who had consented to this procedure at visit 8/ESD or unscheduled study drug discontinuation visit during the double-blind period.

Safety Follow-Up Phase

Safety Follow-Up period: (1 week):

The follow-up period was designed to evaluate the proper conversion from OXN to the subject's individual pain regimen upon completion of or discontinuation from the study drug treatment and to evaluate the safety of the study drug treatment. All subjects returned to the study center 1 week after open-label titration failure, double-blind completion, or ESD for a safety follow-up visit. Assessments at this visit included COWS, modified SOWS, and AEs (including those potentially related to opioid withdrawal).

Duration of Treatment:

- Screening period – up to 14 days
- Open-label titration period – up to 28 days
- Double-blind period – 84 days
- Safety follow-up period – 7 days

Bioanalytical Methods: Plasma concentrations of oxycodone, naloxone, and naloxone-3-glucuronide were quantified by a validated liquid chromatography tandem mass spectrometric method.

Criteria for Evaluation

Efficacy: The primary efficacy variable was the "average pain over the last 24 hours" score obtained at visits 5 through 8, with the primary efficacy outcome being at week 12 of the double-blind period. The primary comparison between groups was based on estimates and contrasts at week 12 using the statistical model discussed below.

The secondary efficacy variables were the Sleep Disturbance Subscale of the MOS-Sleep Scale (assessed at visits 6, 7, and 8) and the PGIC (assessed at visit 8 or at the time of ESD). Other efficacy variables were pain responder analysis, use of supplemental pain medication for low back pain, the ODI, "pain right now" on an NRS immediately before using supplemental pain medication, the BPI severity and interference subscales, and the weekly average of the "average pain over the last 24 hours" score during the double-blind period (based on the daily diary data).

Safety: Safety was assessed using AEs, COWS, modified SOWS, clinical laboratory results, vital signs, and ECGs.

Other: Demography, medical history, prior and concomitant opioid and nonopioid medications, and exposure to treatment were summarized. Abuse/diversion of study drug was also assessed.

Drug Concentration Measurements: Blood samples for determining oxycodone, naloxone and naloxone-3-glucuronide plasma concentrations were obtained:

- At visit 3 for all randomized subjects
- At any visit during the double-blind period for the subjects if either of the following criteria was met:
  - The subject had a COWS score ≥ 13, or
  - The subject had an AE of opioid withdrawal.
- At visit 6 (week 4 of the double-blind period) for all subjects
- At the first visit after the last dose of double-blind study drug as follows:
  - At visit 8 for subjects who completed study on study drug, or
  - At ESD visit for subjects who discontinued the double-blind study drug early and discontinued from the study at the same time, or
  - At the unscheduled study drug discontinuation visit

The site recorded the date, time, and reason(s) for the sample.

Statistical Methods

Demographics and Baseline Characteristics: Demographic variables included age (years), gender, race, and weight (kg). Baseline variables included disease/condition causing pain, average pain during the 14 days

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prior to screening, prior medication(s) used for low back pain, and screening mean pain that qualified a subject for entry into the open-label titration period. Continuous variables were summarized using mean, standard deviation (SD), median, minimum, and maximum values, and categorical variables were summarized using the number and percent.

Dosing and Extent of Exposure: Numbers and percentages of subjects exposed to placebo or OXN by time interval overall and during the double-blind period, cumulative number of days of placebo or OXN exposure, and cumulative continuous days of placebo or OXN exposure were summarized descriptively.

Sample Size Determination: In order to estimate the power of the primary efficacy test, simulations were performed using various scenarios for the expected treatment difference, the rates of discontinuation of study drug due to AE, due to other reasons, and with evidence of opioid withdrawal, and assuming different rates of retrieved dropout. These simulations were run, assuming a 2-sided significance level of 0.05 and different combinations of sample size (250 or 300 per arm), percentages of retrieved dropout (0%, 10%, 20%, 40%), and treatment differences (ranging from none to the expected difference of 0.73, based on the observed difference between BTDS 5 and immediate release oxycodone HCl in study BUP3015). For n=300 subjects per treatment arm, the estimated power was between 86% and 94% for retrieved dropout rates ranging from 0% to 40%, assuming the expected treatment difference of 0.73.

Efficacy Analyses: The primary efficacy variable in this study was the "average pain over the last 24 hours" score. The "average pain over the last 24 hours" scores (on the 11-point NRS: 0=no pain, 10=pain as bad as you can imagine) was recorded at visits 5, 6, 7, and 8/early discontinuation in the double-blind period, and in the daily diary during the open-label titration period. For analysis, the screening mean pain score was defined as the mean of the "average pain over the last 24 hours" scores recorded at visits 1 and 2. The prerandomization mean pain score was defined as the "average pain over the last 24 hours" score averaged over the last 3 days of the open-label titration period. For the primary efficacy analysis, the "average pain over the last 24 hours" scores during the double-blind period were the ones collected at study visits 5 to 8 (weeks 2, 4, 8 and 12). The planned analysis of the primary efficacy variable expanded upon the traditional mixed-model repeated measures (MMRM) analysis, which is applicable to situations where data are missing at random (MAR) under Little and Rubin's classification. The analysis included an MMRM analysis of pain data using a pattern mixture model (PMM) framework, which is applicable in the case where data are not missing at random (NMAR). This analysis approach is an adaptation of a hybrid single imputation approach that falls within the PMM framework and accounts for sources of variability introduced by the missing data mechanism. The Sleep Disturbance Subscale of the MOS-Sleep Scale was analyzed using a mixed effects linear model with repeated measures. The PGIC was analyzed using an exact test. Hypothesis tests were 2 sided using α=0.05, and confidence intervals (CIs) have 95% coverage probability. A gate-keeping strategy and a Bonferroni-Holm method was used to control the family-wise (primary and secondary efficacy analysis) error rate at the 5% level.

Safety Analyses: Safety analyses were conducted on both the safety population (including subjects exposed to placebo or OXN whether during the open-label titration period or double-blind period) and the randomized safety population (including subjects exposed to placebo or OXN during the double-blind period). All AEs were coded using the Medical Dictionary for Regulatory Activities (MedDRA, version 14).

Treatment-emergent AEs (TEAEs) were summarized to examine overall incidence of TEAEs and the incidence of TEAEs by relationship to study drug and maximum severity. AEs leading to study drug discontinuation were also summarized. An independent blinded adjudication committee assessed all discontinuations from the double-blind period to confirm the investigators' assessments. Additionally, the adjudication committee reviewed all subject data for evidence of possible opioid withdrawal prior to the unblinding of the database.

Clinical Laboratory Tests: Laboratory data were summarized for the end of open-label titration and the end of double-blind treatment by providing mean values, and for changes between assessments by providing mean, SD, minimum, and maximum values. Laboratory test results were assigned an L/N/H classification according to whether the value was below (L), within (N), or above (H) the laboratory reference range. Clinical laboratory results for each subject were evaluated to determine whether they were markedly abnormal.

Vital Signs: Descriptive statistics for vital sign parameters (mean, SD, minimum, and maximum values) at each assessment time were summarized. Subjects with abnormal vital signs or clinically notable vital sign abnormalities were identified using predefined criteria.

ECG: Data were summarized by treatment group for values at each time point and change from the screening

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or prerandomization value. Subjects with predefined changes in QT, QTcB (QT corrected for heart rate (HR) using Bazett's correction), and QTcF (QT corrected for HR using Fridericia's correction) from screening or open-label titration, subjects with outlier ECG data during the double-blind period, and subjects with predefined specific ECG abnormalities were identified.

Other: COWS and modified SOWS were summarized as continuous variables and categorically as the number of subjects with a COWS score ≥ 5, with a COWS score ≥ 13, and with a SOWS score ≥ 10. The number of subjects meeting or exceeding these thresholds 0 times, 1 or more times, 2 or more times, etc, is displayed by treatment group separately for each threshold.

Drug Concentration Measurements: Plasma oxycodone, naloxone, and naloxone-3-glucuronide concentrations and sampling times were collected and listed by subject and summarized by sampling time points.

Interim Analyses: None.

Abuse/Diversion: Cases of abuse/diversion are listed and individual cases are presented.

Analysis Populations:
The enrolled population (N = 1924) consisted of all individuals who provided informed consent.
The safety population (N = 1095) consisted of all subjects who received at least 1 dose of open-label study drug.
The randomized safety population (N = 600) consisted of all subjects who were randomized and received at least one dose of double-blind study drug.
The full analysis population (FAP) (N = 600) consisted of subjects who were randomized and received at least one dose of double-blind study drug. The FAP and randomized safety populations were equivalent.
The per-protocol population (N = 540) was a subset of the FAP and consisted of all subjects in the FAP who did not have major protocol violations that could have affected efficacy evaluations, as determined before unblinding the study. The per-protocol population was not utilized.

Efficacy Results:

This study met its primary endpoint, demonstrating the superiority of OXN compared with placebo in an enriched population of opioid-experienced subjects who had moderate to severe low back pain requiring opioid therapy for a prolonged period of time:

- In the primary analysis, there was a clinically and statistically significant improvement in the "average pain over the last 24 hours" score obtained at Week 12 for subjects receiving OXN compared with subjects receiving placebo.
  - The least-square mean "average pain over the last 24 hours" scores at week 12 were 4.32 for subjects receiving placebo vs 3.86 for subjects receiving OXN.
  - The least-square mean difference between placebo and OXN for week 12 "average pain over the last 24 hours" scores was 0.45 (95% CI: 0.13 to 0.77; P = .0055).
- Results of the 5 sensitivity analyses were consistent with the primary analysis.
  - All were statistically significant (P <.05) favoring subjects receiving OXN, and the least-square mean differences from placebo were similar to the primary analysis (results ranged from 0.37 to 0.50 in the 5 sensitivity analyses).

This study demonstrated superiority of OXN compared with placebo with respect to the secondary endpoints. These endpoints were statistically significant and supported the primary results.

- The PGIC result indicated that the proportion of subjects choosing "very much improved" or "much improved" at week 12 was significantly greater for subjects receiving OXN compared with the proportion of subjects receiving placebo (55.6% for subjects receiving OXN vs 39.9% for subjects receiving placebo [P = .0002]).
- At week 12, the mean MOS Sleep Disturbance Subscale score least-square mean difference (placebo minus OXN) indicated a significant improvement in sleep disturbance with OXN as compared with placebo (5.3 [95% CI: 0.9 to 9.8; P = .0191]).

Results of the other efficacy endpoints supported the primary and secondary findings:

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In the responder analysis, the proportion of subjects with a response of 30% or greater was significantly greater for subjects receiving OXN (55.0% vs 41.1% among subjects receiving OXN vs placebo, respectively [P = .0006]).
Discontinuation rates due to lack of therapeutic effect were more than twice as high in the placebo group than the OXN treatment group (24.2% vs 10.4%).

OXN provided pain relief that was sustained over time for the duration of the 12-week double-blind period:

- During the double-blind period in the OXN treatment group, "average pain over the last 24 hours" scores were stable and consistently better than scores in the placebo group.
- Durability of effect was also observed with the MOS Sleep Disturbance Subscale, and scores were also consistently better for the OXN treatment group compared with the placebo group.

OXN provided pain relief at all doses tested (up to 80/40 mg/day):

- The "average pain over the last 24 hours" scores at week 12 were similar for subjects receiving OXN at all dose levels (range: 3.02– 4.33).
  - At all dose levels, the week 12 scores for subjects receiving OXN were lower (indicating less pain) than those for the corresponding subjects receiving placebo (range: 3.30 – 4.89).
- Consistency of effectiveness was observed across dose groups for the PGIC and responder analysis, but not for the MOS Sleep Disturbance Subscale:
  - For the PGIC analysis, the proportions of subjects responding "very much improved" or "much improved" at week 12 were similar for subjects at all dose levels of OXN (range: 48.2% – 60.8%).
    - At all dose levels, these proportions were greater than those for the corresponding subjects receiving placebo (range: 27.0% – 50.9%).
- For the responder analysis, the proportion responding was greater for subjects receiving OXN compared with placebo at all 4 dose levels, at any response level and at 30% and 50% response levels.
- While showing a main effect of benefit to OXN, the MOS Sleep Disturbance Subscale did not show consistency in effectiveness across dose groups.

Safety Results: In this study, OXN had a safety profile similar to that of other opioids.
Adverse Events

- In general, the TEAEs observed in this study were consistent with those associated with the use of opioid analgesics. The incidences of mild and moderate TEAEs were similar during the open-label period (89.9%) and the double-blind period (89.8%).
- Discontinuation rates due to AE were similar between the placebo and OXN treatment groups (7.6% vs 8.1%, respectively).
- The same types of events were observed in the open-label titration period and double-blind period, as well as between both treatment groups during the double-blind period.
  - During the open-label titration period, the most common individual TEAEs (incidence ≥ 2%) seen were nausea, headache, diarrhea, constipation, vomiting, drug screen positive, and abdominal pain upper.
  - During the double-blind period, the TEAEs that were observed more frequently (≥ 2 percentage points difference) in the OXN treatment group than in the placebo group were drug screen positive, nausea, vomiting, constipation, and anxiety.
- Only 2 subjects required dose reduction during the double-blind period, 1 in each treatment arm.

Deaths and Other Serious Adverse Events

- There was 1 death during the study (fatal gunshot wound) of a subject receiving placebo; the death was considered unrelated to study treatment.
- During the open-label titration period, 11 subjects (1.0% of the safety population) experienced a total of 16 SAEs. Of these, 8 subjects (0.7%) had 9 SAEs of either drug screen positive or drug abuse. (Note: Per protocol, cases of new onset of drug abuse were to be reported as SAEs.) Three subjects (0.3%) experienced a total of 6 non-abuse-related SAEs in the open-label titration period. All 6 of these cases

were considered not related to study drug by the investigator.

- During the double-blind period, a total of 30 subjects (5.0% subjects) experienced nonfatal SAEs: 11 (3.6%) subjects receiving placebo and 19 (6.4%) subjects receiving OXN. The most common SAEs during double-blind treatment were (for the total, placebo, and OXN groups, respectively):
  - drug screen positive (10 subjects [1.1%]; 1 [0.3%] vs 9 [3.0%] subjects)
  - acute myocardial infarction (2 subjects [0.3%]; 2 [0.7%] vs 0 subjects)
  - pneumonia (2 subjects [0.3%]; 1 [0.3%] vs 1 [0.3%] subjects), and
  - substance use (2 subjects [0.3%]; 2 [0.7%] vs 0 subjects).

Discontinuations Due to Adverse Events

- During the open-label titration period, 8.6% subjects discontinued the study treatment due to AEs, including nausea (2.1%), drug screen positive (0.9%), vomiting (0.8%), and abdominal pain upper, drug abuse, diarrhea, drug withdrawal syndrome, and headache (each 0.5%).
- During double-blind treatment, 20 subjects (6.6%) in the placebo group and 21 (7.0%) subjects in the OXN group discontinued study treatment due to AEs, including (for the placebo and OXN groups, respectively):
  - drug screen positive (1.3% vs 3.7%)
  - drug withdrawal syndrome (1.0% vs 0.3%)
  - drug abuse (0.7% vs 0.3%)
  - nausea (0.7% vs 0.3%), and
  - vomiting (0.3% vs 0.7%).
- During open-label titration, nausea led to dose interruption in 2 subjects. No other individual TEAE led to dose interruption for more than 1 subject. During double-blind treatment, no single TEAE led to dose interruption for more than 1 subject.

Abuse

- A total of 82 subjects were identified for abuse during this study.
  - Seventy-three of these cases were for abuse of illicit drugs, prohibited drugs, and alcohol.
  - Eleven of these cases were for abuse of study drug
    - 8 cases of abuse not otherwise specified (7 during the open-label titration period and 1 case in the OXN treatment group during the double-blind period)
    - 2 cases of abuse of Oxy IR (1 during the open-label titration period and 1 in the placebo group during the double-blind period), and
    - 1 case of abuse of both Oxy IR and OXN during the open-label titration period.

Diversion

- During the open-label period, 43 subjects (3.9%) diverted study drug: 7 subjects (0.6%) diverted OXN only, 21 (1.9%) diverted Oxy IR only, and 15 subjects (1.4%) diverted both treatments.
- During the double-blind period, 23 subjects (3.8%) diverted study drug: 2 subjects (0.3%) diverted blinded OXN only, 14 (2.3%) diverted Oxy IR only, and 7 subjects (1.2%) diverted both treatments.
- Overall, Oxy IR was diverted by more subjects than was OXN, during both the open-label period and the double-blind period.

Opioid Withdrawal

- Forty-three treatment-emergent cases of opioid withdrawal or possible opioid withdrawal were identified in 41 subjects. Of these cases, 95.3% were mild to moderate in severity.
  - In 26 subjects (2.4% of the safety population), opioid withdrawal was attributable to conversion to a lower dose of opioid based on morphine equivalents.
  - In 2 subjects (0.7% of the placebo treatment group), subjects were receiving a stable dose of blinded placebo therapy.
  - In 15 subjects (1.4% of the safety population), opioid withdrawal was observed and morphine equivalents remained the same or increased (5 of these 15 cases were receiving a stable OXN dose in the double-blind period).

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IND No.: 70,851	

- There was no clear relationship between plasma concentrations of naloxone (or oxycodone, or naloxone-3-glucouronide) and opioid withdrawal. However, the possibility of naloxone contributing to opioid withdrawal in approximately 1% of all subjects exposed to OXN in this study cannot be excluded.

Other Safety Assessments

- Comparisons of pretreatment and posttreatment clinical laboratory tests, vital sign assessments, and ECGs did not reveal any apparent safety concerns with OXN treatment.

Conclusions: This double-blind, placebo-controlled, parallel group, randomized, enriched design study demonstrated the analgesic efficacy of OXN compared with placebo in subjects with moderate to severe pain due to chronic low back pain. The primary efficacy analysis showed a statistically significant treatment difference in favor of OXN vs placebo. Results of the sensitivity analyses showed consistency of treatment effect, and the secondary and other (exploratory) analyses supported the primary efficacy analysis. OXN was generally well-tolerated. In general, the safety profile of OXN observed in this study was consistent with that of other opioid analgesics and that previously reported for OXN.

Date of the Report: 13-Jun-2013

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/s/

SRIKANTH C NALLANI
06/18/2014

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06/18/2014

BIOPHARMACEUTICS REVIEW Office of New Drug Quality Assessment			
Application No.:	NDA 205-777	**Reviewer:** Kareen Riviere, Ph.D.	
Submission Date:	9/23/13; 3/24/14		
Division:	DAAAP	**Secondary Signature:** Tapash Ghosh, Ph.D.	
Applicant:	Purdue Pharma L.P.	**Supervisor:** Richard Lostritto, Ph.D.	
Trade Name:	Targiniq ER	**Date Assigned:**	9/30/13
Generic Name:	oxycodone HCl/naloxone HCl controlled release tablets	**Date of Review:**	6/16/14
Indication:	The management of [redacted] (b) (4) pain [redacted] (b) (4), around-the-clock [redacted] (b) (4)	**Type of Submission:** 505(b)(2) NDA	
Formulation/strengths:	CR Tablet; 10 mg/5 mg, 20 mg/10 mg and 40 mg/20 mg Strength		
Route of Administration:	Oral		

SUMMARY:

This submission is a 505(b)(2) New Drug Application for 10 mg/5 mg, 20 mg/10 mg and 40 mg/20 mg of Targiniq (Oxycodone HCl/Naloxone HCl) ER Tablet. The proposed indication is for the management of [redacted] (b) (4) pain [redacted] (b) (4), around-the-clock [redacted] (b) (4).

The focus of this Biopharmaceutics review is on the evaluation and acceptability of the proposed dissolution method, the proposed dissolution acceptance criteria, information/data on alcohol dose dumping, data supporting the bioequivalence of the proposed product manufactured in US and Europe for each strength, and data supporting the *in vitro in vivo* relationship (IVIVR) for the oxycodone component of the proposed drug product.

A. Dissolution Method

USP Apparatus	Rotation Speed	Media Volume	Temp	Medium
2	50 rpm	900 mL	37 °C	SGF (pH 1.2) w/o enzyme

The dissolution method is acceptable.

B. Acceptance Criteria

The proposed acceptance criteria for both oxycodone HCl and naloxone HCl are:

10 mg/5 mg and 20mg/10 mg Strengths

Acceptance Criteria	
15 min:	[redacted] (b) (4) %
2 hr:	[redacted] %
10 hr:	NLT [redacted] (b) (4) %

40 mg/20 mg Strength

Acceptance Criteria	
15 min:	(b) (4)%
2 hr:	%
10 hr:	NLT (b) (4)%

The proposed dissolution acceptance criteria are acceptable.

C. In vitro Alcohol Interaction Studies

The Applicant provided *in vitro* data demonstrating no potential for alcohol dose-dumping.

D. Data Supporting the Bioequivalence of the Proposed Product Manufactured in US and Europe

The Applicant provided adequate data to demonstrate the bioequivalence of the proposed product manufactured in US and Europe. Thus, clinical and clinical pharmacology data generated with the European product can be used to support approval of the US product.

E. The *In Vitro/In Vivo* Relationship (IVIVR) for the Oxycodone Component

The Applicant attempted to establish a model with the relationship between in vitro tablet dissolution rates and in vivo absorption/bioavailability for the oxycodone component of the proposed product. However, the submitted report lacked detailed information on the assumptions and procedures taken to develop and validate this model. Therefore, it serves no regulatory purposes to implement any possible change that will affect oxycodone alone in this combination controlled release product.

RECOMMENDATION:

1. Targiniq ER (Oxycodone HCl/Naloxone HCl) 10 mg/5 mg, 20 mg/10 mg and 40 mg/20 mg strength controlled release tablets are recommended for approval from a Biopharmaceutics standpoint with the following dissolution method and acceptance criteria for each strength.
    i. Dissolution Method: Apparatus 2, 50 rpm agitation rate, 900 mL media volume, 37 °C, SGF (w/o enzyme) pH1.2 buffer.
    ii. Dissolution Acceptance Criteria for 10 mg/5 mg & 20 mg/10 mg strengths: (b) (4)% at 15 min, (b) (4)% at 2 hours, NLT (b) (4)% at 10 hours
    iii. Dissolution Acceptance Criteria for 40 mg/20 mg strength: (b) (4)% at 15 min, (b) (4)% at 2 hours, NLT (b) (4)% at 10 hours

Kareen Riviere, Ph.D.
Biopharmaceutics Reviewer
Office of New Drug Quality Assessment

Tapash Ghosh, Ph.D.
Biopharmaceutics Team Leader
Office of New Drug Quality Assessment

cc: Dr. Richard Lostritto

ASSESMENT OF BIOPHARMACEUTICS INFORMATION

1. Background

Drug Subtances

The chemical structures of the drug substances are shown in Figure 1.

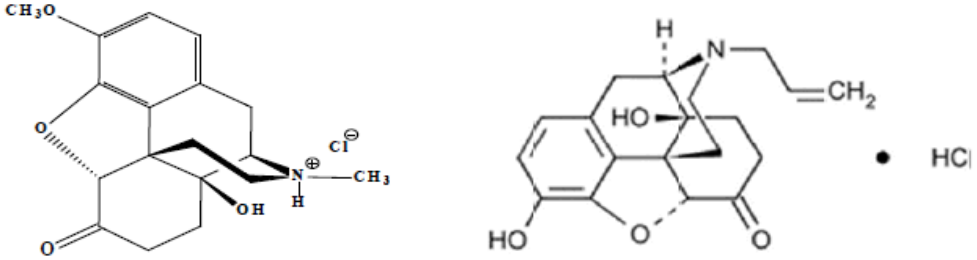


Figure 1. Chemical structure of oxycodone hydrochloride (left) aand naloxone hydrochloride (right).

The pH solubility profile of oxycodone hydrochloride and naloxone hydrochloride in aqueous media is shown in Table 2.

Table 2. Solubility of Oxycodone HCl and Naloxone HCl in Aqueous Media at Room Temperature

Medium	Oxycodone HCl (mg/mL)	Naloxone HCl (mg/mL)
Water	169.8	142.1
Simulated Gastric Fluid without enzyme	140.3	117.2
0.2M KCl, pH 1.2	135.1	108.2
0.2M $KHC_6H_4(COO)_2$, pH 3	170.5	114.5
0.02M $NaCH_3COOH$,pH 4.5	164.9	144.1
0.2M $KHC_6H_4(COO)_2$, pH 5	178.7	150.9
0.2M KH_2PO_4, pH 6.8	174.6	125.1
0.2M KH_2PO_4, pH 7	175.1	124.4
0.2M KH_2PO_4, pH 7.5	169.8	122.2
0.2M H_3BO_3+KCl, pH 9	38.5	125.0
0.05M Na_2HPO_4, pH 11	39.1	127.9
0.2M KCl, pH 13	2.1	95.2

Reviewer's Assessment:

Table 2 demonstrates that the solubility of oxycodone hydrochloride and naloxone hydrochloride is greater than 100mg/mL in the physiological pH range. To achieve sink conditions for the strengths of the proposed product, the solubility of oxycodone hydrochloride should be at least 0.133 mg/ml (which is 40 mg / 900 mL * 3) and the solubility of naloxone hydrochloride should be at least 0.067 mg/ml (which is 20 mg / 900 mL * 3) in 900 mL of the proposed medium. Thus, all the media in Table 2 would achieve sink conditions for the three strengths of the proposed product.

Drug Product

The proposed drug product was developed as a controlled-release oral combination product formulated as a tablet with a fixed 2:1 ratio of oxycodone hydrochloride to naloxone hydrochloride. Three tablet strengths (10/5, 20/10, and 40/20 mg) for twice-daily dosing are proposed to be marketed in the US.

Table 3. Composition of the Commercial Oxycodone HCl and Naloxone HCl Tablet Formulation

Component	Quantity (mg/tablet)		
	OXN 10/5	OXN 20/10	OXN 40/20
Oxycodone hydrochloride	10.00	20.00	40.00
Naloxone hydrochloride[1]	5.45	10.90	21.80
Povidone (b) (4)	(b) (4)		
Ethylcellulose			
Stearyl alcohol			
Lactose monohydrate			
Talc			
Magnesium stearate			
(b) (4)			
Talc			
Total film tablet	127.27	142.17	284.34

Reviewer's Assessment:
The 20/10 mg and 40/20 mg strength tablets (b) (4) ***. The 10/5 mg strength tablet*** (b) (4) ***. Note that all three proposed strengths were tested in phase 3 studies.***

2. Dissolution Method

The proposed dissolution method is:

USP Apparatus	Rotation Speed	Media Volume	Temp	Medium
2	50 rpm	900 mL	37 °C	SGF (pH 1.2) w/o enzyme

Selection of Media

The Applicant performed multimedia dissolution testing on 12 tablets each of the three strengths using pH 1.2, pH 4.5, pH 6.8 and pH 7.5 buffers (refer to Figures 4, 5 and 6).

Figure 4. Dissolution Rate Profiles of Oxycodone and Naloxone from OXN 10/5 mg Tablets in SGF, USP Buffers pH 4.5, 6.8 and 7.5

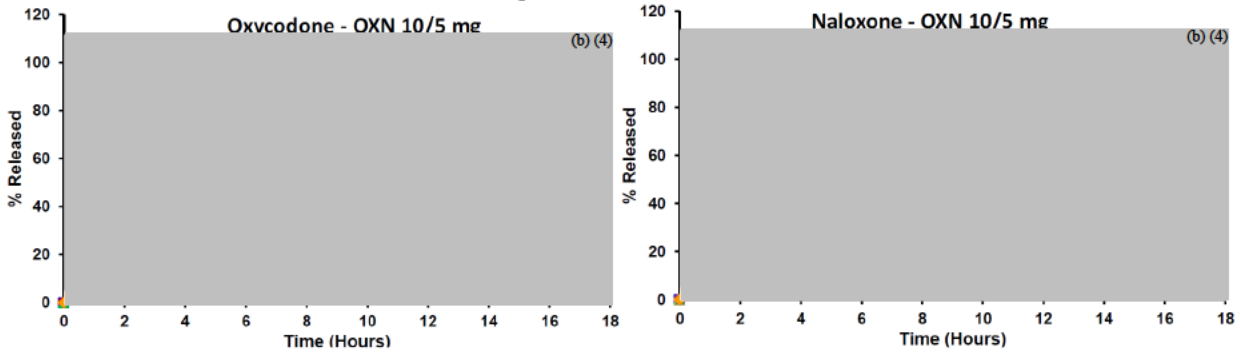


Figure 5. Dissolution Rate Profiles of Oxycodone and Naloxone from OXN 20/10 mg Tablets in SGF, USP Buffers pH 4.5, 6.8 and 7.5

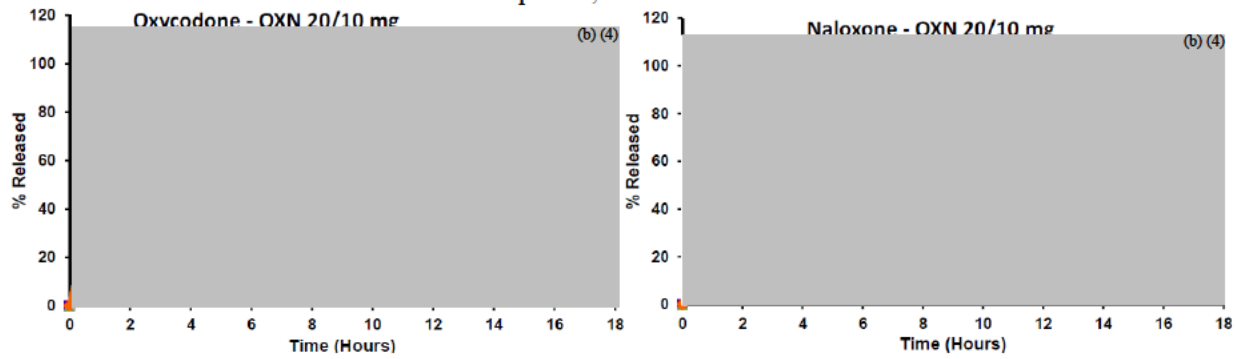
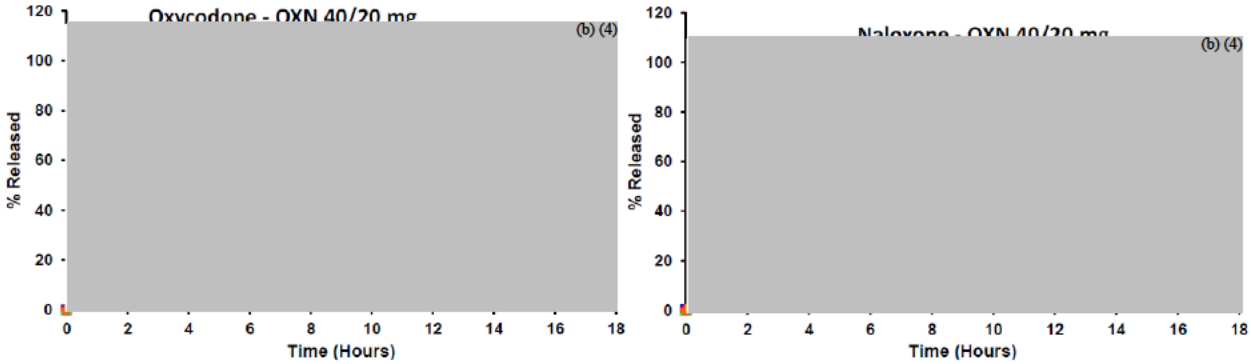


Figure 6. Dissolution Rate Profiles of Oxycodone and Naloxone from OXN 40/20 mg Tablets in SGF, USP Buffers pH 4.5, 6.8 and 7.5



The Applicant stated that they selected simulated gastric fluid (SGF) without enzyme at pH 1.2 as the dissolution medium since it used for dissolution testing of other oxycodone controlled release products.

Selection of Apparatus

The Applicant compared the dissolution profiles of the proposed product using pH1.2 media and either with the (b) (4) paddle (50 rpm agitation speed) apparatus. Tables 4 and 5 show a comparison of the average dissolution data for oxycodone and naloxone generated with these apparatuses as well as the f2 test results.

Table 4. Average Dissolution Rates for Oxycodone from OXN Tablets 10/5 mg, 20/10 mg and 40/20 mg

Time Point (h)	% Average Dissolution (b) (4)
0.25	
1	
2	
3	
4	
5	
6	
7	
8	
9	
10	

Table 5. Average Dissolution Rates for Naloxone from OXN Tablets 10/5 mg, 20/10 mg and 40/20 mg

Time Point (h)	% Average Dissolution (b) (4)
0.25	
1	
2	
3	
4	
5	
6	
7	
8	
9	
10	

The similarity factor (f2) test results obtained by the Applicant were greater than 50 for all comparisons. The Applicant stated that they selected USP apparatus 2 since it is regarded as the equipment of choice for routine in vitro dissolution testing of pharmaceutical products.

Selection of Paddle Speed

The Applicant evaluated the effect of paddle rotation speed on dissolution performance of OXN 20/10 mg strength tablets (refer to Tables 6 and 7).

Table 6: Average Dissolution Rates for Oxycodone and Naloxone from OXN Tablets, 20/10 mg Lot #CWFP50 ((b) (4) rpm Paddle Speeds)

Time Point	% Average Dissolution	
	Oxycodone	Naloxone
		(b) (4)

Table 7. Average Dissolution Rates for Oxycodone and Naloxone from OXN Tablets, 20/10 mg Lot #156A-04 (50 to (b) (4) rpm Paddle Speeds)

Time Point	% Average Dissolution	
	Oxycodone	Naloxone
		(b) (4)

The Applicant's results showed that changing the paddle speed had no significant impact on the dissolution rates of both oxycodone and naloxone. They selected to use a paddle speed of 50 rpm.

Comparison of Dissolution Rates for Different Tablet Strengths

The Applicant compared the drug release rates for the 20/10 mg strength to the corresponding rates for the 10/5 and 40/20 mg strengths in each dissolution medium investigated. The Applicant's calculated f2 values for oxycodone and naloxone are reported in Table 8.

Table 8: Summary of f2 Values for OXN 20/10 mg Compared to OXN 10/5 and 40/20 mg Tablets

Dissolution Medium	Comparison of Test vs. Reference			
	Oxycodone		Naloxone	
	20/10 vs 10/5	20/10 vs 40/20	20/10 vs 10/5	20/10 vs 40/20
[redacted]				

(b) (4)

According to the Applicant's f2 values, the drug release profiles of oxycodone and naloxone for the 20/10 mg strength were similar to those for the 10/5 mg and 40/20 mg strengths under all test conditions.

Reviewer's Assessment:
The Applicant provided ample data and information to justify the proposed dissolution testing parameters. Thus, the proposed dissolution method is acceptable.

3. Dissolution Acceptance Criteria

The proposed acceptance criteria for both oxycodone HCl and naloxone HCl are:

10 mg/5 mg Strength

Acceptance Criteria	
15 min:	[redacted] %
2 hr:	%
10 hr:	NLT (b) (4) %

20 mg/10 mg Strength

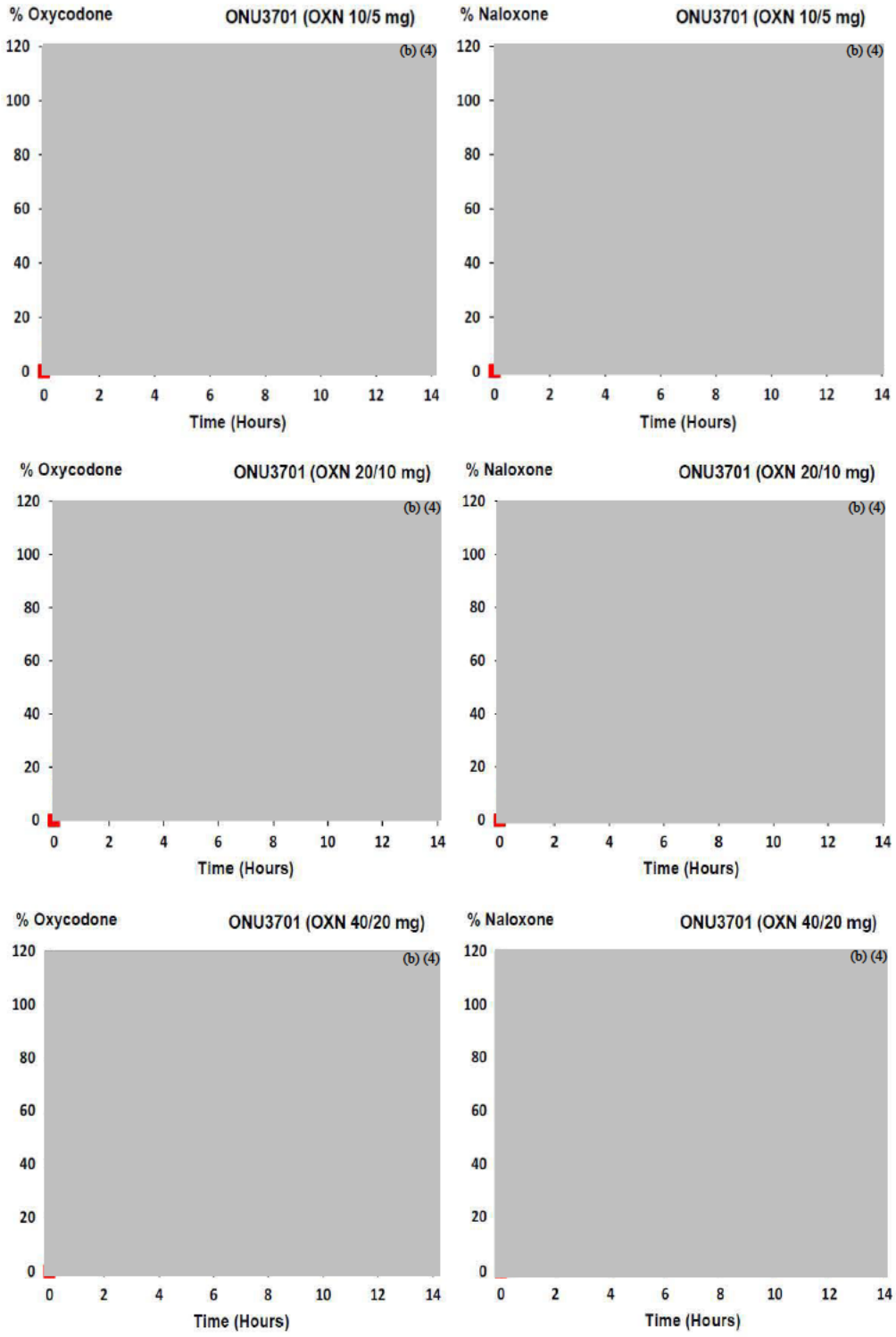
Acceptance Criteria	
15 min:	[redacted] %
2 hr:	%
10 hr:	NLT (b) (4) %

40 mg/20 mg Strength

Acceptance Criteria	
15 min:	[redacted] %
2 hr:	%
10 hr:	NLT (b) (4) %

The applicant provided dissolution data from the pivotal clinical batches (refer to Figure 7). The pivotal clinical study ONU3701 is a randomized, double-blind, placebo controlled, multicenter trial with an enriched study design to assess the efficacy and safety of OXN compared to placebo in opioid-experienced subjects with moderate to severe chronic low back pain who require around-the-clock opioid therapy. Two lots each of the three strengths of OXN tablets were used for the study.

Figure 7. Dissolution Rate Profiles of OXN 10/5 mg, 20/10 mg and 40/20 mg used in Pivotal Efficacy Study ONU3701



The Applicant also provided a summary of the dissolution data for each strength of the proposed product used in the US clinical studies (refer to Table 9). All data were obtained using USP apparatus 2 (paddle) at 50 rpm in 900 mL simulated gastric fluid without pepsin at 37°C.

Table 9. In Vitro Dissolution Data Summary for OXN Tablets used in US Clinical Studies

Clinical Study	Batch No.	Strength (mg)	No. Units	Mean % Dissolved (Range) – Oxycodone HCl							
				0.25hr	1hr	2hr	4hr	6hr	8hr	10hr	12hr
ONU1001*	152778**	10/5	12								(b) (4)
ONU1001* ONU1004 ONU3701*	CW9H20	10/5	12								
ONU3701*	CW9H10	10/5	12								
ONU3704 ONU3705*	CW9H00	10/5	12								
ONU3704* ONU3705*	CWFP20	10/5	12								
ONU3704* ONU3705*	CWKJ30	10/5	12								
ONU3704* ONU3705*	VWJJ40	10/5	12								
ONU3704* ONU3705*	VWJJ50	10/5	12								
ONU1004 ONU1008 ONU1009 ONU3701* ONU3704* ONU3705*	CW9H30	20/10	12								
ONU3701*	CWBD30	20/10	12								
ONU3704* ONU3705*	CWFP50	20/10	12								
ONU3704* ONU3705*	CWKJ40	20/10	12								
ONU3704* ONU3705*	CWJJ80	20/10	12								
ONU1002*	151518**	40/20	12								
ONU1002* ONU1003 ONU1004 ONU1007 ONU3704* ONU3705*	CW9H40	40/20	12								
ONU3701*	CW9H50	40/20	12								
ONU1008 ONU3701*	CW9H60	40/20	12								
ONU3705*	CWFP40	40/20	12								
ONU3704* ONU3705*	CWKJ50	40/20	12								
ONU3704* ONU3705*	VWJJ60	40/20	12								
ONU3704* ONU3705*	VWJJ70	40/20	12								

NT= Not Tested
*BE or pivotal clinical study

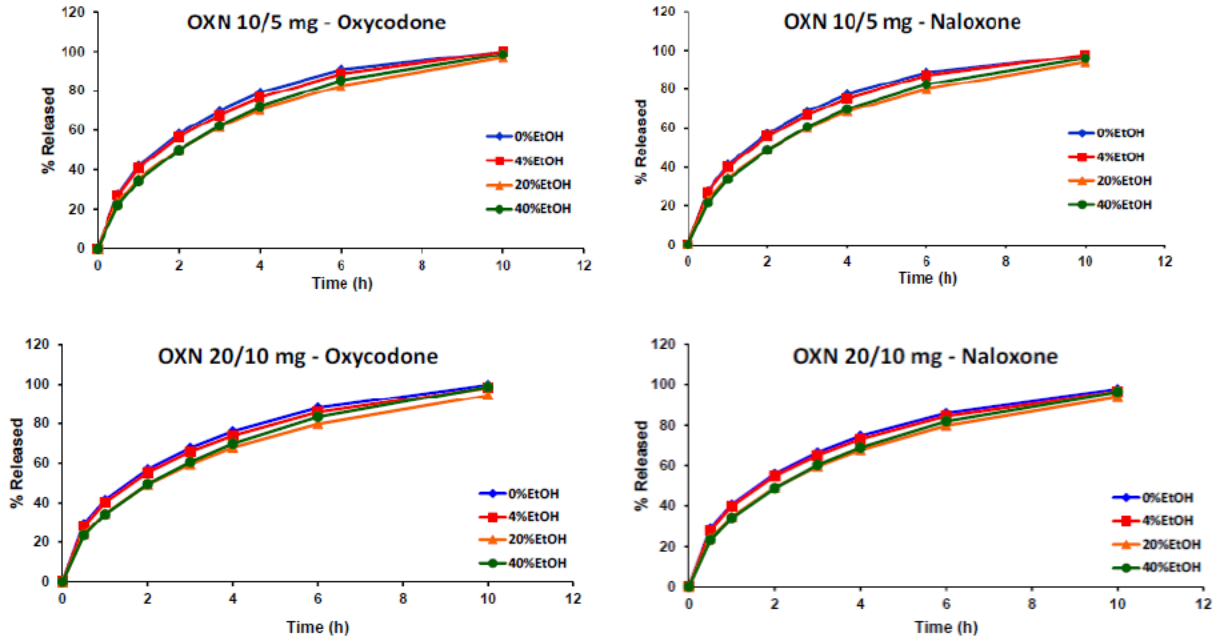
Reviewer's Assessment:

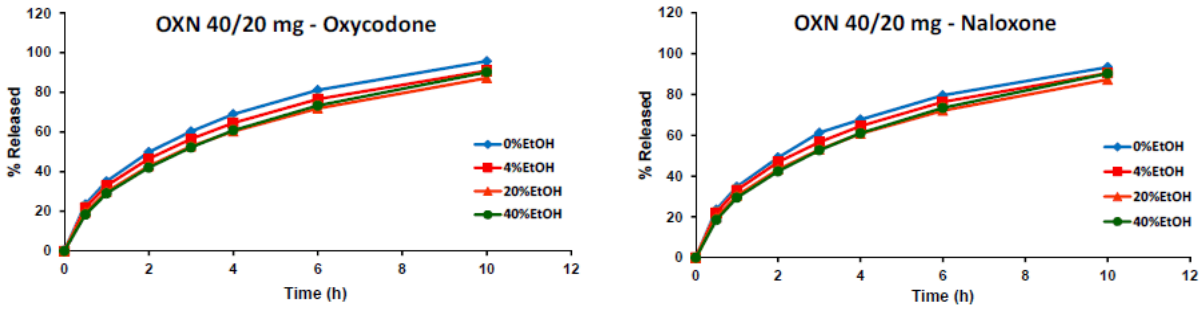
The proposed dissolution acceptance criteria are supported by the dissolution profile data for the clinical batches shown in Figure 6 and Table 9 and the stability batch in the submission. Thus, the proposed dissolution acceptance criteria are acceptable.

4. Information on *In Vitro* Alcohol Dose Dumping

The Applicant evaluated the effects of 4%, 20%, and 40% ethanol on the *in vitro* dissolution profiles for all strengths of the proposed product in the proposed dissolution method. The data are shown in Figure 8.

Figure 8. Dissolution Profile Data of Oxycodone HCl and Naloxone from 10/5 mg, 20/10 mg, and 40/20 mg Strength Tablets in the Proposed Dissolution Media with Different Concentration of Ethanol





The Applicant's f2 test results for the above data are shown in Tables 10 and 11.

Tables 10. Similarity Factor (f2) Compared to SGF for Oxycodone HCl

Strength	f_2		
	4% EtOH	20% EtOH	40% EtOH
OXN 10/5 mg	83	58	58
OXN 20/10 mg	83	57	60
OXN 40/20 mg	72	56	57

Table 11. Similarity Factor (f2) Compared to SGF for Naloxone HCl.

Strength	f_2		
	4% EtOH	20% EtOH	40% EtOH
OXN 10/5 mg	89	58	60
OXN 20/10 mg	89	61	62
OXN 40/20 mg	75	59	60

Reviewer's Assessment

The data in Tables 10-11 show that all f2 values were above 50, indicating that the dissolution profiles are similar. Thus, there is no in vitro alcohol dose dumping potential for all strengths of the proposed product.

5. Data Supporting the Bioequivalence of the Proposed Product Manufactured in US and Europe

The Applicant conducted two BE studies (one for lowest strength and one for highest strength).to determine whether oxycodone/naloxone tablets produced at the (b) (4) were bioequivalent to tablets manufactured at the (b) (4) facility. The purpose of these studies was to demonstrate that the clinical and clinical pharmacology data generated with the European product can be used to support approval of the US product.

Study ONU1001 was an open-label, single-dose, randomized, 2-treatment, 2-period crossover study in healthy subjects. A total of 50 healthy subjects (38 males and 12 females), 18-54 years old (mean: 33 years) were enrolled and randomized to receive study drugs [Treatment A: OXN 10/5 mg tablet manufactured at the (b) (4) facility (Test) and Treatment B: OXN 10/5 mg tablet manufactured at the (b) (4) facility (Reference)] with at least a 7-day washout period between treatments under fasted conditions.

The Applicant reported that one subject voluntarily discontinued the study after the first dose, and the other subject was lost to follow up after the first dose of study treatment. Thus, 48/50 subjects completed the study. PK analysis (refer to Tables 12 and 13) was performed on plasma concentration data of oxycodone and naloxone-3β-glucuronide obtained from 49 subjects completing Treatment A (Test) and Treatment B (Reference), respectively. One subject experienced emesis within 12 hours after the first dose (Treatment A), and this subject's PK data were not included in summary or statistical analysis as per the statistical analysis plan.

Table 12. Statistical Results of Oxycodone Pharmacokinetic Metrics: Fasting Bioequivalence of Oxycodone/Naloxone 10/5-mg tablets Manufactured at Two Different Sites (Study ONU1001)

Metric	Units	N	LS Means[a] (Test)	N	(Reference)	Test/ Reference[b]	90% Confidence Interval[c]	Intersubject Variability[d]	Intrasubject Variability[d]	Intrasubject CV (%)[d]
C_{max}	ng/mL	48	10.9	49	10.5	103	(97.28 , 109.97)	0.0238	0.0319	18
AUC_t	ng*h/mL	48	106	49	108	98.6	(94.36 , 103.04)	0.0425	0.0163	13
AUC_{inf}	ng*h/mL	48	108	49	109	98.6	(94.44 , 102.93)	0.0420	0.0156	13

Table 13. Statistical Results of Naloxone-3-Glucuronide Pharmacokinetic Metrics: Fasting Bioequivalence of Oxycodone/Naloxone 10/5-mg tablets Manufactured at Two Different Sites (Study ONU1001)

Metric	Units	N	LS Means[a] (Test)	N	(Reference)	Test/ Reference[b]	90% Confidence Interval[c]	Intersubject Variability[d]	Intrasubject Variability[d]	Intrasubject CV (%)[d]
C_{max}	ng/mL	48	24.6	49	21.8	112	(104.15 , 121.47)	0.0461	0.0501	23
AUC_t	ng*h/mL	48	139	49	140	98.9	(94.78 , 103.25)	0.0556	0.0154	12
AUC_{inf}	ng*h/mL	48	141	49	143	98.9	(94.78 , 103.19)	0.0544	0.0152	12

Study ONU1002 was an open-label, single-dose, randomized, 2-treatment, 2-period crossover study in healthy subjects. A total of 55 healthy subjects (29 males and 26 females), 18-55 years old (mean: 32 years) were enrolled and randomized to receive study drugs (Treatment A: OXN 40/20 mg tablet manufactured at the (b) (4) facility (Test); Treatment B: OXN 40/20 mg tablet manufactured at the (b) (4) facility (Reference) with at least a 7-day washout period between treatments under fasted conditions.

The Applicant reported that five subjects voluntarily discontinued the study after the first dose, 1 subject voluntarily discontinued after the second dose, and 1 subject (ID: 02033/1074) was discontinued due to an AE (pericarditis, (b) (6) days after study drug administration and not considered to be drug related) after the first dose of study treatment. Thus, 48/55 subjects completed the study. Four subjects experienced emesis within 12 hrs of dosing after the first dose of study treatment. Plasma concentration data of oxycodone and naloxone-3β-glucuronide were obtained from 50 subjects completing Treatment A (Test) and 54 subjects completing Treatment B (Reference). In 1 subject after both treatments, plasma oxycodone concentrations were all below the limit of quantitation and thus excluded from PK analysis; but plasma naloxone- 3β-glucuronide concentrations were measurable in this subject and thus included in PK analysis. The reason for this was unknown. PK data (refer to Tables 14 and 15) from the 4 subjects with emesis in the first dose period (1 receiving Treatment A, and 3 receiving Treatment B) were excluded from summary statistics or statistical analysis.

Table 14. Statistical Results of Oxycodone Pharmacokinetic Metrics: Fasting Bioequivalence of Oxycodone/Naloxone 10/5-mg tablets Manufactured at Two Different Sites (Study ONU1002)

Metric	Units	N	LS Means[a] (Test)	N	(Reference)	Test/ Reference[b]	90% Confidence Interval[c]	Intersubject Variability[d]	Intrasubject Variability[d]	Intrasubject CV (%)[d]
C_{max}	ng/mL	48	36.0	50	36.1	99.7	(96.32 , 103.29)	0.0374	0.00980	10
AUC_t	ng*h/mL	48	434	50	446	97.4	(94.47 , 100.51)	0.0477	0.00766	9
AUC_{inf}	ng*h/mL	47	439	49	447	98.2	(95.26 , 101.33)	0.0470	0.00728	9

Table 15. Statistical Results of Naloxone-3-Glucuronide Pharmacokinetic Metrics: Fasting Bioequivalence of Oxycodone/Naloxone 40/20 mg Tablets Manufactured at Two Different Sites (Study ONU1002)

Metric	Units	N	LS Means[a] (Test)	N	(Reference)	Test/ Reference[b]	90% Confidence Interval[c]	Intersubject Variability[d]	Intrasubject Variability[d]	Intrasubject CV (%)[d]
C_{max}	ng/mL	49	72.0	51	71.1	101	(91.51 , 112.23)	0.0613	0.0887	30
AUC_t	ng*h/mL	49	569	51	552	103	(92.80 , 114.20)	0.0712	0.0916	31
AUC_{inf}	ng*h/mL	47	568	43	619	91.8	(84.87 , 99.29)	0.0574	0.0436	21

Reviewer's Assessment:

The data in Tables 12-13 demonstrate that the 90% CI of the GLSM ratio of test to reference treatment for AUC and Cmax of both oxycodone and naloxone-3β-glucuronide fell within the range of 80-125%. Thus, the OXN 10/5 mg tablets manufactured at the (b) (4) facility are considered bioequivalent to those manufactured at the (b) (4) facility.

The data in Table 12 demonstrate that the 90% CI of the GLSM ratio, Test to Reference treatment, for AUC and Cmax of both oxycodone and naloxone-3β-glucuronide fell within the range of 80-125%. Thus, the OXN 40/20 mg tablets manufactured at the (b) (4) facility are considered bioequivalent to those manufactured at the (b) (4) facility.

Since the OXN 20/10 mg strength and OXN 40/20 mg strength tablets (b) (4) (refer to Table 3) and both strengths have f2 (b) (4) dissolution profiles (refer to f2 results in Table 8), the OXN 20/10 mg strength tablets manufactured at the (b) (4) facility are also deemed bioequivalent to those manufactured at the (b) (4) facility.

6. Data supporting the IVIVR model for the oxycodone component

(b) (4)

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

/s/

KAREEN RIVIERE
06/16/2014

TAPASH K GHOSH
06/16/2014

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

Office of Clinical Pharmacology

New Drug Application Filing and Review Form

General Information About the Submission

	Information		Information
NDA/BLA Number	**205777**	**Brand Name**	**Targiniq**
OCP Division (I, II, III, IV, V)	**DCP2**	**Generic Name**	**Oxycodone HCl + Naloxone HCl**
Medical Division	**Division of Anesthesia, Analgesia and Addiction Products**	**Drug Class**	**Opioid Analgesic**
OCP Reviewer	**Srikanth C. Nallani, Ph.D.**	**Indication(s)**	**(b) (4) Pain Management**
OCP Team Leader	**Yun Xu, Ph.D.**	**Dosage Form**	**Tablet**
Pharmacometrics Reviewer	**-**	**Dosing Regimen**	**BID**
Date of Submission	**9/23/2013**	**Route of Administration**	**Oral**
Estimated Due Date of OCP Review	**2/27/2013**	**Sponsor**	**Purdue Pharma LLC**
Medical Division Due Date	**3/23/2014**	**Priority Classification**	**Priority**
PDUFA Due Date	**3/23/2014**		

Clin. Pharm. and Biopharm. Information

	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	**X**			
Tabular Listing of All Human Studies	**X**			
HPK Summary	**X**			
Labeling	**X**			
Reference Bioanalytical and Analytical Methods	**X**			
I. Clinical Pharmacology				
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:	**X**	**4**		
multiple dose:	**X**	**2**		
Patients-				
single dose:	**X**	**2**		
multiple dose:	**X**			
Dose proportionality -				
fasting / non-fasting single dose:	**X**	1		
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				
In-vivo effects on primary drug:				
In-vivo effects of primary drug:				
In-vitro:				
Subpopulation studies -				

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ethnicity:				
gender:				
pediatrics:				
geriatrics:	**X**	**1**		
renal impairment:	**X**	**1**		
hepatic impairment:	**X**	**1**		
PD -				
Phase 2:	**X**	**1**		
Phase 3:	**X**	**1**		
PK/PD -				
Phase 1 and/or 2, proof of concept:	**X**	**1**		
Phase 3 clinical trial:				
Population Analyses -				
Data rich:				
Data sparse:				
II. Biopharmaceutics				
Absolute bioavailability	**X**	**1**		
Relative bioavailability -				
solution as reference:				
alternate formulation as reference:				
Bioequivalence studies -				
traditional design; single / multi dose:	**X**	**1**		
replicate design; single / multi dose:				
Food-drug interaction studies	**X**	**4**		
Bio-waiver request based on BCS				
BCS class				
Dissolution study to evaluate alcohol induced dose-dumping	**X**	**1**		**Biopharm team in ONDQA will review *in vitro alcohol* interaction study**
III. Other CPB Studies				
Genotype/phenotype studies				
Chronopharmacokinetics				
Pediatric development plan				
Literature References				
Total Number of Studies		**19**		

On **initial** review of the NDA/BLA application for filing:

	Content Parameter	Yes	No	N/A	Comment
Criteria for Refusal to File (RTF)					
1	Has the applicant submitted bioequivalence data comparing to-be-marketed product(s) and those used in the pivotal clinical trials?	X			
2	Has the applicant provided metabolism and drug-drug interaction information?			X	
3	Has the sponsor submitted bioavailability data satisfying the CFR requirements?	X			
4	Did the sponsor submit data to allow the evaluation of the validity of the analytical assay?	X			
5	Has a rationale for dose selection been submitted?	X			
6	Is the clinical pharmacology and biopharmaceutics section of the NDA organized, indexed and paginated in a manner to allow substantive review to begin?	X			
7	Is the clinical pharmacology and biopharmaceutics section of the NDA legible so that a substantive review can begin?	X			

File name: 5_Clinical Pharmacology and Biopharmaceutics Filing Form/Checklist for NDA_BLA or Supplement 090808

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

8	Is the electronic submission searchable, does it have appropriate hyperlinks and do the hyperlinks work?	X			
Criteria for Assessing Quality of an NDA (Preliminary Assessment of Quality)					
	Data				
9	Are the data sets, as requested during pre-submission discussions, submitted in the appropriate format (e.g., CDISC)?	X			
10	If applicable, are the pharmacogenomic data sets submitted in the appropriate format?			X	
	Studies and Analyses				
11	Is the appropriate pharmacokinetic information submitted?	X			
12	Has the applicant made an appropriate attempt to determine reasonable dose individualization strategies for this product (i.e., appropriately designed and analyzed dose-ranging or pivotal studies)?	X			
13	Are the appropriate exposure-response (for desired and undesired effects) analyses conducted and submitted as described in the Exposure-Response guidance?			X	
14	Is there an adequate attempt by the applicant to use exposure-response relationships in order to assess the need for dose adjustments for intrinsic/extrinsic factors that might affect the pharmacokinetic or pharmacodynamics?			X	
15	Are the pediatric exclusivity studies adequately designed to demonstrate effectiveness, if the drug is indeed effective?			X	
16	Did the applicant submit all the pediatric exclusivity data, as described in the WR?			X	
17	Is there adequate information on the pharmacokinetics and exposure-response in the clinical pharmacology section of the label?	X			
	General				
18	Are the clinical pharmacology and biopharmaceutics studies of appropriate design and breadth of investigation to meet basic requirements for approvability of this product?	X			
19	Was the translation (of study reports or other study information) from another language needed and provided in this submission?			X	

IS THE CLINICAL PHARMACOLOGY SECTION OF THE APPLICATION FILEABLE?
YES

General Comments/Background:
Purdue Pharma LLC., submitted NDA 205777 for the approval of oxycodone HCl and naloxone HCl combination to manage (b) (4) pain. For this 505(b)(2) NDA, Purdue has conducted the relative bioavailability study ONU1009, which established a pharmacokinetic (PK) bridge of each component of Targiniq (oxycodone and naloxone) to approved NDA products, OxyContin (oxycodone) and Narcan (Naloxone, NDA 016-636, via an ANDA generic designated as the Reference Listed Drug for Narcan). Purdue developed the combination where both oxycodone and naloxone will be released from the tablet in the GI tract. Naloxone is not significantly absorbed into the systemic circulation via the oral route; however, (b) (4)

During drug development Purdue was advised that a clinical trial will be needed if detectable levels of naloxone in systemic circulation was confirmed. Although highly variable, systemic levels of naloxone

were noted following normal use and under circumstances resembling opioid drug abuse by chewing, crushing, etc.
The sponsor altered the regulatory strategy by adding a plan to claim abuse deterrence properties for the oxycodone naloxone product under conditions of intranasal and intravenous abuse. Notably, the naloxone released following chewing is not adequate to block recreational abuse of oxycodone.

The studies planned for clinical pharmacology review are attached in the table below. Recently, Office of Clinical Pharmacology revised its memorandum of understanding where review of certain bioavailability and bioequivalence studies has been delegated to Biopharmaceutics team in ONDQA. The table of studies planned for review is based on discussion with Dr. Tapash Ghosh, Biopharmaceutics team leader in ONDQA.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

- No review issues have been identified for communication with the sponsor.

Srikanth C. Nallani, Ph.D.

Reviewing Clinical Pharmacologist Date

Yun Xu, Ph.D.

Team Leader/Supervisor Date

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

List of clinical pharmacology studies planned for review:

Study No.	Study Objective	Study Design	Treatment (Dose, Dosage Form, Route) [Product ID]	Subjects No. M/F Type Age: mean (range)
ONU1003	Evaluate the Abuse Potential, Pharmacokinetics, and Safety of Oxycodone/Naloxone (OXN) Tablets Administered via the Oral, Intranasal and Intravenous Routes	Single-center, double-blind, parallel-group, randomized crossover, single-dose	**Group 1**: OXN 40/20 mg, chewed oral (PPLP; lot number:CB-2010-35) Oxycodone 40 mg, oral solution((b) (4) ; lot numbers: 6CC, 19CC) OXN placebo tablets, oral((b) (4) lot number: CB-2009-24) **Group 2:** OXN 40/20 mg, crushed IN (PPLP; lot number:CB-2010-35) OXY API40 mg, IN((b) (4) lot number: 24-10XYK) Lactose powder, IN ((b) (4) lot number: 09050043; PPLP; lot number:10100037) **Group 3:** Oxycodone 0.07 mg/kg, IV((b) (4) lot numbers: 6CC, 19CC) Naloxone HCl 0.035 mg/kg, IV((b) (4) lot number: AR2903)	Healthy, adult recreational opioid users Group 1: 16 (14/2); 36.6 (19, 54) Group 2: 27 (20/7); 33.1 (20, 50) Group 3: 24 (21/3); 34.9 (20, 54)
ONU1004	Evaluate the Pharmacodynamics, Pharmacokinetics, and Safety of Oxycodone/Naloxone (OXN) in Opioid Dependent Subjects	single-center, double-blind, placebo-controlled, randomized, block-order crossover, single-dose	**Session 1**: Chewed 30/15 mg OXN + placebo solution: One 10/5 mg OXN tablet (PPLP; Lot number: CB-2010-33) + one 20/10 mg OXN tablet (PPLP; Lot number: CB-2010-34) + 240 mL placebo solution 30 mg OXY API in solution + chewed placebo: One 10/5 mg OXN placebo tablet (PPLP; Lot number: CB-2009-22) + one 20/10 mg OXN placebo tablet (PPLP; Lot number: CB-2009-23) + 30 mg OXY API (oxycodone hydrochloride USP powder; (b) (4) Lot number: 24-10XYK) in a 240 mL solution Placebo solution + chewed placebo: One 10/5 mg OXN placebo tablet (Purdue Pharma, L.P.; Lot number: CB-2009-22) + one 20/10 mg OXN placebo tablet (PPLP; Lot number: CB-2009-23) + 240 mL placebo solution **Session 2**: Chewed 60/30 mg OXN + placebo solution: One 20/10 mg OXN tablet (Purdue Pharma, L.P.; Lot number: CB-2010-34) + one 40/20 mg OXN tablet (PPLP; Lot number: CB-2010-	Methadone-maintained opioid-dependent subjects Session 1: 18 (9/9); 31.7 (22, 46) Session 2: 16 (9/7); 30.5 (22, 38)

Study No.	Study Objective	Study Design	Treatment (Dose, Dosage Form, Route) [Product ID]	Subjects No. M/F Type Age: mean (range)
			35) + 240 mL placebo solution 60 mg OXY API in solution + chewed placebo: One 20/10 mg OXN placebo tablet (PPLP; Lot number: CB-2009-23) + one 40/20 mg OXN placebo tablet (Purdue Pharma, L.P.; Lot number: CB-2009-24) + 60 mg OXY API (oxycodone hydrochloride USP powder; (b) (4) Lot number: 24-10XYK) in a 240 mL solution Placebo solution + chewed placebo: One 20/10 mg OXN placebo tablet (PPLP; Lot number: CB-2009-23)+ one 40/20 mg OXN placebo tablet (Purdue Pharma, L.P.; Lot number: CB-2009-24) + 240 mL placebo solution Subjects received their daily methadone dose at their prescribed dose level (between 20 mg/day to 40 mg/day) as methadone hydrochloride oral concentrate, USP, 10 mg/ml solution prepared in approximately 100 mL orange flavored Tang® (Metadol™; Paladin Labs, Inc.; Lot number: 449376).	
ONU1007	Evaluate the oral abuse potential, pharmacodynamics, pharmacokinetics, and safety of intact and chewed OXN tablets in non-dependent subjects	single-center, double-blind, randomized, crossover	**Treatment A:** OXN 40/20 mg tablet, intact + OXN PBO tablet, chewed + PBO oral solution **Treatment B:** OXN PBO tablet, intact + OXN 40/20 mg tablet, chewed + PBO oral solution **Treatment C:** OXN PBO tablet, intact + OXN PBO tablet, chewed + oxycodone 40 mg oral solution **Treatment D:** OXN PBO tablet, intact + OXN PBO tablet, chewed + PBO oral solution Oxycodone hydrochloride, USP powder; administered as a 40 mg, oral solution ((b) (4) lot number: 10-11XYK) OXN 40/20 mg, (PPLP; lot number: CB-2010-35) OXN PBO tablets (PPLP; lot number: CB-2010-43)	37 (32/5) Healthy, adult, non-physically dependent recreational opioid users with a history of oral chewing abuse/misuse 38.5 (24, 52)
ONU1008	Evaluate the Pharmacodynamics, Pharmacokinetics, and Safety of Intact and Chewed Oxycodone/Naloxone (OXN) Tablets in	single-center, double-blind, triple-dummy, PBO-controlled randomized 4-way crossover	Treatment A: OXN 60/30 mg, intact Treatment B: OXN 60/30 mg, chewed Treatment C: OXY API 60 mg, in oral solution Treatment D: PBO Treatment doses were comprised of the following, alone or in	33 (21/12) Methadone-maintained, opioid-dependent subjects 32.4 (23, 55)

Study No.	Study Objective	Study Design	Treatment (Dose, Dosage Form, Route) [Product ID]	Subjects No. M/F Type Age: mean (range)
	Opioid-Dependent Subjects		combination: OXN 20/10 mg tablets (PPLP; Lot number: CB-2010-34) OXN 40/20 mg tablets (PPLP; Lot number: CB-2010-37) PBO to match OXN 20/10 mg tablets (PPLP; Lot number: CB-2010-42) PBO to match OXN 40/20 mg tablets (PPLP; Lot number: CB-2010-43) Oxycodone hydrochloride, USP powder; administered as a 240 mL oral solution ((b) (4) Lot number: 55-11XYK)	
OXN1005	Investigate the effects on intestinal motility of oxycodone, given alone as an oxycodone CR tablet and in combination with naloxone given as an oxycodone/naloxone (OXN) tablet, using scintigraphic and pharmacokinetic analyses in healthy male subject	Open-label, single-dose, 5-treatment, 5-period, randomized, placebo controlled, crossover study using scintigraphic and pharmacokinetic analysis	**Treatment A**: 1 x OXN10/5 mg tablet ((b) (4) batch number: PN3130) taken orally **Treatment B**: 1 x OXN20/10 mg tablet ((b) (4) batch number: PN3131taken orally **Treatment C**: 1 x oxycodone tablet 10 mg ((b) (4) batch number: PN2894) taken orally **Treatment D**: 1 x oxycodone tablet 20 mg ((b) (4) batch number: PN2895) taken orally **Treatment E**: 1 x placebo tablet ((b) (4) batch number: PN3240) taken orally All treatments were radiolabelled	15 (15/0) Healthy male subjects 34.7 (21, 56)
OXN1006	Compare the pharmacokinetics of oxycodone and naloxone and their metabolites from OXN10/5 mg in patients with varying degrees of hepatic impairments and healthy subjects	Open-label, single-dose, hepatic impairment patient group and healthy volunteer comparator study.	1 x OXN10/5 mg tablet orally ((b) (4) Batch # PN2906)	Healthy subjects and subjects with mild, moderate and severe hepatic impairment: Healthy subjects: 6 (3/3); 55 (48, 58) Mild hepatic impairment: 6 (4/2); 52 (46, 61) Moderate hepatic impairment: 6 (3/3); 51 (46, 58) Severe hepatic impairment: 6 (3/3); 48 (38, 61)

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Study No.	Study Objective	Study Design	Treatment (Dose, Dosage Form, Route) [Product ID]	Subjects No. M/F Type Age: mean (range)
OXN1007	Compare the pharmacokinetics of oxycodone, naloxone and their metabolites from OXN 10/5 in patients with varying degrees of renal impairment and healthy volunteers, and to identify an appropriate dose recommendation for patients with renal impairment	Open-label, single-dose, renal impairment patient group and healthy volunteer comparator study.	Healthy subjects and subjects with mild, moderate and severe renal impairment received: 1 x OXN10/5 mg tablet orally [(b) (4) batch # PN2906	Healthy subjects: 6 (3/3); 46 (34, 53) Mild renal impairment: 6 (4/2); 50 (28, 63) Moderate renal impairment: 6 (3/3); 57 (48, 64) Severe renal impairment: 6 (2/4); 55 (47, 61)
OXN1011	Bioavailability of OXN40/20 mg PR compared with oxycodone CR tablet 40 mg and naloxone CR tablets 2 x 10 mg	Open-label, multiple-dose, randomized, 3-treatment, 3-period crossover	Treatment A: 1 x OXN40/20 mg tablet, q12h [(b) (4) batch # OXN40/20 182A-04] Treatment B: 1 x Oxy CR 40 mg tablet, q12h [(b) (4) (b) (4) batch # 10030163] Treatment C: 2 x Naloxone CR 10 mg tablets, q12h [(b) (4) batch # OXN10-188-05] Blockade: Naltrexone hydrochloride tablets 50 mg [(b) (4) (b) (4) batch # A033]	34 (28/6) Healthy subjects 36 (19, 52)
OXN1017	Compare the steady-state pharmacokinetics of oxycodone and naloxone and their metabolites from OXN10/5 mg in healthy elderly and healthy younger subjects	Open-label, multiple-dose, parallel-group	Treatment: 1 x OXN10/5 mg ([(b) (4) batch # PN2906) Naltrexone 50 mg blockade, q12h for 10 doses ([(b) (4) (b) (4) batch # PN3045	Elderly: 18 (8/10); 68 (65, 77) Younger: 21 (10/11); 35 (19, 44)

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

Study No.	Study Objective	Study Design	Treatment (Dose, Dosage Form, Route) [Product ID]	Subjects No. M/F Type Age: mean (range)
OXN2401	Investigate whether an oxycodone/naloxone combination has analgesic efficacy with a decrease in constipation in patients with severe chronic pain when compared with oxycodone alone	Multicenter, prospective, controlled, randomized, double-blind (with placebo dummy), 4 parallel group Phase 2 study	All doses were twice daily, Oral Group 1: 20 mg, 30 mg or 40 mg Oxy CR tab. + 2 Nal. Placebo tab. Group 2: 20 mg, 30 mg or 40 mg Oxy CR tab. + 5 mg Nal. CR tab. And Nal. Placebo tab. Group 3: 20 mg, 30 mg or 40 mg Oxy CR tab. + 10mg Nal. PR tab. And Nal. Placebo tab. Group 4: 20 mg, 30 mg or 40 mg Oxy CR tab. + 2 x 10mg Nal. PR tab. For manufacturer and lot/batch # see CSR table 9.5.2.	Total: 202 subjects patients with severe chronic pain of tumor- and non-tumor origin Naloxone placebo: 50 (19/31); 53.8 (29, 84) Naloxone 10 mg: 51 (18/33); 58.4 (28, 86) Naloxone 20 mg: 51 (17/34); 56.0 (33, 80) Naloxone 40 mg: 50 (21/29); 57.0 (27, 78)

Biopharmaceutics studies (Bioavailability, Food-effect, etc) planned for review.

Study No.	Study Objective	Study Design	Treatment (Dose, Dosage Form, Route) [Product ID]	Subjects No. (M/F) Type Age: mean (range)
ONU1009 (United States)	Relative BA of oral naloxone in OXN vs. SL naloxone in Suboxone and vs. IV naloxone Relative BA of oral oxycodone in OXN vs. reformulated OxyContin	Open, randomized, 4-way crossover, single dose	OXN20/10 mg tablet oral fast [CB-2010-34] Reformulated OxyContin 20 mg oral fast [WLH-41] Suboxone Buprenorphine/Naloxone 2/0.5mg SL Film fast [G12DW102] Naloxone 0.4mg/1 mL IV fast [20625LL]	30 (18/12) Healthy volunteer 34 (19, 55)
OXN1003 (Germany)	Food Effect on OXN 40/20 mg and OXN 10/5 mg	Open, randomized, 4-way crossover, single dose	A: OXN 40/20 mg tablet oral fed [Batch OXN 40/20-157A-04] B: OXN 10/5 mg tablet oral fed [Batch OXN 10/5-155A-04] C: OXN 40/20 mg tablet oral fast D: OXN 10/5 mg tablet oral fast	28 (18/10) Healthy volunteer 32.0 (22, 45)

Study No.	Study Objective	Study Design	Treatment (Dose, Dosage Form, Route) [Product ID]	Subjects No. (M/F) Type Age: mean (range)
OXN1005 (United	Relative bioavailability of OXN and original	Open, randomized, Placebo-controlled, 5-way crossover, single-	A: OXN 10/5 mg tablet oral fast [Batch PN3130] B: OXN 20/10 mg tablet oral fast [Batch PN3131]	15 (15/0) Healthy male
Kingdom)	formulations of Oxycodone CR	dose(s) (oxycodone CR 10 & 20 mg) on transit time using gamma scintography; effect of naloxone on (5 or 10 mg) in combination with oxycodone (10 or 20 mg); to determine relative bioavailability of oxycodone from OXN vs. original formulation of oxycodone CR tablet.	C: OXY CR 10 mg tablet oral fast [Batch PN2894] D: OXY CR 20 mg tablet oral fast [Batch PN2895] E: Placebo tablet oral fast [Batch PN3240] (each tablet in test treatments were radiolabelled with up to 4.0 MBq ^{99m}Tc.)	volunteers 34.7 (21, 56)
OXN1008 (Germany)	Food effect on OXN 40/20 mg; relative BA of OXN 40/20 mg tablet vs. oral solution oxycodone 20 mg and Naloxone 10 mg	Open, randomized, 3-way crossover, single-dose high fat meal and relative bioavailability tablets vs. solution	A: OXN 40/20 mg tablet oral fast [Batch 182A-04] B: OXN 40/20 mg tablet oral fed C: Oxycodone IR liquid 20 mg (20 mL of 5mg/5mL solution)[Batch PN2941] and naloxone injection 10 mg (10 mL of 1mg /mL) [Batch PN2964] injection given as an oral solution) Naltrexone hydrochloride 50 mg tablet oral [Batch A023]	29 (18/11) Healthy volunteers 38 (23, 53)
OXN1009 (United Kingdom)	Food effect, BA on OXN 10/5 mg. Relative BA of OXN10/5 mg tablet vs. oral solution oxycodone 10 mg + naloxone 5 mg	Open, randomized, 3-treatment, 3-period, crossover, single dose in fasted and fed state	A: OXN 10/5 tablet oral fast [Batch PN2906] B: OXN 10/5 tablet oral fed C: Oxycodone IR liquid (10 mL of 5 mg/5mL solution) [Batch PN2941] and naloxone injection 5 mg (5 mL of 1 mg/1mL injection given as oral solution) [Batch PN2978]	20 (9/11) Healthy volunteers 34 (21, 55)

Study No.	Study Objective	Study Design	Treatment (Dose, Dosage Form, Route) [Product ID]	Subjects No. (M/F) Type Age: mean (range)
OXN1011 (Germany)	Bioequivalence of oxycodone and naloxone from OXN 40/20 mg tablet vs. oxycodone from original OXY CR tablet 40 mg, and naloxone from naloxone CR tablets 20 mg.	Open, multiple-dose, 3-treatment, 3-period, randomized crossover study	A: OXN 40/20 mg tablet orally given q 12 h on Days 1-3 and the morning of Day 4 (7 doses in total), [Batch OXN40/20-182A-04] B: 1x OXY CR 40 mg tablet orally was given q 12 hr on Days 1-3 and the morning of Day 4 (7 doses in total). [Batch 10030163] C: 2 x naloxone CR 10 mg tablet orally given q 12 hr on Days 1-3 and the morning of Day 4 (7 doses in total). [Batch OXN10-188-05] Naltrexone HCl 50 mg tablet oral [Batch A 033]	34 (28/6) Healthy volunteers 36 (19, 52)

Study No.	Study Objective	Study Design	Treatment (Dose, Dosage Form, Route) [Product ID]	Subjects No. (M/F) Type Age: mean (range)
OXN1403 (Germany)	PK of all dose strengths of OXN; BA relative to that of oxycodone in the marketed form, Oxygesic®, given together with an experimental naloxone CR tablet	Open, single-dose, randomized, 4-treatment, 4-period crossover	A: 4 x OXN 10/5 mg tablet oral fast [Batch: OXN 10/5-151a-04] B: 2 x OXN 20/10 mg tablet oral fast [Batch: OXN 20/10-150a-04] C: 1 x OXN 40/20 mg tablet oral fast [Batch: OXN 40/20-152a-04] D: 2 x Oxygesic 20 mg tablet oral fast [Batch: 0010022892] and 2 x Naloxone CR 10 mg tablet oral fast [Batch: OXN10-153-04]	28 (22/6) Healthy volunteers 32.3 (24, 42)
OXN1505 (Northern Ireland)	PK and bioavailability of OXN 80/40 mg tablet in a fed and fasted state, and oxycodone hydrochloride liquid and naloxone hydrochloride liquid in fast state.	Open, single-dose, randomized, 3-treatment, 3-period crossover	OXN 80/40 mg tablet oral fed or fast [Batch PN3663] Oxycodone hydrochloride liquid (20 mg) [Batch PN3663] + naloxone hydrochloride liquid (10 mg) [Batch PN3664], fast Naltrexone 50 mg tablet oral [Batch PN3447]	28 (16/12) Healthy volunteers 28.96 (18, 51)
OXN1506 (Northern Ireland)	PK and dose-proportionality of 5 new (2.5/1.25 mg, 15/7.5mg, 30/15 mg, 60/30mg and 80/40 mg) and 2 existing strengths (10/5 mg and 40/20 mg) of OXN tablets.	Open, single-dose, 7-treatment, 5-period, randomized, incomplete crossover	OXN tablets at different strengths oral fast: OXN 2.5/1.25 mg [Batch PN3672] OXN 10/5 mg [Batch PN3659] OXN 15/7.5 mg [Batch PN3675] OXN 30/15 mg [Batch PN3656] OXN 40/20 mg [Batch PN3660] OXN 60/30 mg [Batch PN3657] OXN 80/40 mg [Batch PN3663] Naltrexone 50 mg tablet oral [Nalorex®]	48 (33/15) Healthy volunteers 30.98 (18, 54)

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/s/

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