CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

022410Orig1s000

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

Addendum to the Primary Clinical Pharmacology Review Dated June 23, 2009

NDA	22-410	*Submission Date(s)*	Oct 21, 2008
Brand Name		Suboxone (b) (4)	
Generic Name		Buprenorphine (bup) and Naloxone (nal)	
Reviewer		Sheetal Agarwal, Ph.D.	
Team Leader		Suresh Doddapaneni, Ph.D.	
OCP Division		Division of Clinical Pharmacology-2	
OND Division		Division of Anesthesia, Analgesia, and Rheumatology	
Sponsor		Reckitt Benckiser Pharmaceuticals Inc.	
Submission Type; Code		505 (b) (1)	S
Formulation; Strength(s)		Sublingual film strips; 2 mg bup/0.5 nal and 8 mg bup/2 mg nal	
Indication		Maintenance treatment of opioid dependence	
Proposed Dosing Regimen		Recommended target dose for maintenance is 16 mg bup/4 mg nal per day	

This addendum addresses the two following specific issues that were not captured in the primary Clinical Pharmacology review authored by this reviewer dated June 23, 2009; (1) Division of Scientific Investigations (DSI) inspection results of pivotal BA/BE Study 20-273-SA and (2) Implications on the bioavailability of the sublingual film strips if the strips were to be placed on the floor of the mouth (b) (4) These two issues are discussed below:

(1) <u>DSI Inspection report of study 20-273-SA:</u>
At the time of signing off the primary review for NDA 22-410, report of the DSI inspection of Study 20-273-SA was pending. Subsequently, DSI finalized their report on June 29, 2009 (see review by Dr. Sean Kassim, Ph.D. dated 6/29/2009 for details).

The conclusions from DSI report were:

1. Accuracy of the reported naloxone concentrations for subjects 407 (period 2) and 443 (all periods) has not been assured due to unresolved chromatographic interference in at least half the reportable naloxone values in each period. The naloxone data for these periods should be omitted and bioequivalence should be re-evaluated.
2. The Clinical portion and the remaining analytical data from 20-273-SA are acceptable for review.

This reviewer reanalyzed the data as suggested by DSI omitting the naloxone concentrations for subjects 407 and 443. The reanalysis showed no significant differences between the original and reanalyzed data (see table below) and

consequently the conclusions made in the primary review dated June 23, 2009 regarding the outcome of this study stand.

BE analysis results for Study 20-273-SA (8/2 mg Suboxone strips vs. tablets)

Buprenorphine	90% CI lower limit (original)	90% CI upper limit (original)	90% CI lower limit (after reanalysis)	90% CI upper limit (after reanalysis)
Cmax	116.98	139.77	117.09	140.53
AUClast	111.34	129.61	111.96	130.59
AUCinf	111.18	128.34	111.7	129.14
Naloxone				
Cmax	127.32	155.75	127.84	156.93
AUClast	119.35	141.15	119.43	141.55
AUCinf	111.02	134.25	111.19	134.82

(2) (b) (4) [redacted] Although, not sought for approval, sponsor tested the buccal mode of administration as well in several of the PK studies. Although not reviewed in detail, a quick overview of the studies showed that the strips administered by buccal route were either bioequivalent (for example 2 mg, 4 mg, and 8 mg doses) or the bioavailability differences were minor (12 mg dose). Buccal and sublingual routes are considered to be two distinct routes of administration and the observation that these two routes of administration yielded similar bioavailability indicates lends further comfort that any bioavailability differences resulting from the potentially different ways in which the sublingual strips may have been used in the NDA database may not be clinically significant.

Linked Applications	Submission Type/Number	Sponsor Name	Drug Name / Subject
NDA 22410	ORIG 1	RECKITT BENCKISER PHARMACEUTICALS INC	BUPRENORPHINE/NALOXONE 2MG/8MG FILM STRP

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/s/

SHEETAL S AGARWAL
07/28/2009

SURESH DODDAPANENI
07/28/2009

CLINICAL PHARMACOLOGY REVIEW

NDA	22-410	*Submission Date(s)*	Oct 21, 2008
Brand Name		Suboxone (b) (4)	
Generic Name		Buprenorphine (bup) and Naloxone (nal)	
Reviewer		Sheetal Agarwal, Ph.D.	
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Sponsor		Reckitt Benckiser Pharmaceuticals Inc.	
Submission Type; Code		505 (b) (1)	S
Formulation; Strength(s)		Sublingual film strips; 2 mg bup/0.5 nal and 8 mg bup/2 mg nal	
Indication		Maintenance treatment of opioid dependence	
Proposed Dosing Regimen		Recommended target dose for maintenance is 16 mg bup/4 mg nal per day	

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1.0 Executive summary

This is a 505 (b) (1) NDA for Suboxone (b) (4) C-III (buprenorphine and naloxone soluble film) for sublingual administration. The indication sought for the strips is maintenance of opioid withdrawal and the product was developed as an alternative to Suboxone® sublingual tablets (NDA 20-733, approved October 8, 2002, marketed in the US since January 2003 and currently approved in 39 countries).

Per the sponsor, buprenorphine and naloxone soluble film is being developed as an alternative to Suboxone® tablets for the following reasons:
• Mitigation against unintentional pediatric exposure by providing child-resistant packaging in unit dose format.
• Improvement in patient convenience.
• Protection against diversion by providing a dosage form that is very difficult for the patient to remove from the SL mucosa once it is administered. This will provide assurance to the caregiver that the dose has actually been taken appropriately.
• Provision of a robust unit dose product form for hospital and institutional use.
(b) (4)

The sponsor proposes that the Suboxone® sublingual (SL) tablets be continued to be used for induction of therapy. The dosage strengths of Suboxone (b) (4) for which marketing approval is being sought are the same as those currently approved for Suboxone® sublingual tablets, i.e. buprenorphine 8 mg with naloxone 2 mg indicated as 8/2 mg strips and buprenorphine 2 mg with naloxone 0.5 mg indicated as 2/0.5 mg strips.

Buprenorphine, the primary active compound in Suboxone (b) (4) (as well as in Suboxone® sublingual tablets), is a partial opioid agonist with a high affinity for the mu-opioid receptor and lower intrinsic activity than full opioid agonists. Naloxone (an antagonist at the mu-opioid receptor) is included in the formulation to discourage diversion and abuse of Suboxone® Tablets (b) (4). The primary purpose of inclusion of naloxone in these products is to prevent the intravenous misuse of buprenorphine (concept originally used in currently marketed pentazocine product, Talwin® NX). This could be done because naloxone exhibits poor oral and sublingual bioavailability. Therefore, if Suboxone (b) (4) is misused or abused by injection, the naloxone component is expected to antagonize the opioid agonist effects of buprenorphine and potentially precipitate withdrawal in an individual dependent on full opioid agonists and therefore discourage the individual to abuse the product.

1.1 Recommendation

The Office of Clinical Pharmacology / Division of Clinical Pharmacology 2 (OCP/DCP-2) has reviewed NDA 22-410 for Suboxone (b) (4) C-III (buprenorphine and naloxone soluble film) for sublingual administration and finds it acceptable provided that (a) the DSI audit report for the BE study (Study 20-273 SA) finds the study acceptable and (b) the Agency and the sponsor agree on the labeling.

1.2 Phase 4 Commitments

None.

1.3 Summary of Important Clinical Pharmacology Findings

The Clinical Pharmacology package submitted for this NDA consisted of 19 Phase 1 PK studies conducted in healthy adult volunteers (including pilot, pivotal BE and dose and dosage form proportionality studies, studies with other strengths of Suboxone (b) (4) and 1 clinical study in a patient population to determine local oral tolerability with the soluble film dosage form. The primary support for the clinical safety and efficacy of the Suboxone (b) (4) 8mg/2mg and 2mg/0.5mg formulations comes from the established safety and efficacy data on Subutex® (NDA 20-732) and Suboxone® sublingual tablets (NDA 20-733). No special population or drug-drug interaction studies were conducted in this NDA. The Sponsor is relying on Agency's previous findings for Suboxone® sublingual tablets to construct their labeling for special populations (e.g., renal and hepatic impairment patients, elderly patients) and drug-drug interactions. Refer to Clinical Pharmacology review by Dr. Suresh Doddapaneni for NDA 20-733 for details.

Out of the 19 PK studies submitted, 7 were deemed relevant for this NDA and were reviewed. Out of the 7 studies reviewed, 4 were thoroughly reviewed because they form the basis of approval for the subject matter of this NDA and the other 3 are considered additional supportive studies. The other 10 PK studies submitted included testing of (b) (4) the buccal route of administration for (b) (4) the (b) (4) Suboxone (b) (4) Conclusions from the four relative BA studies employing the two film strips for which approval is sought are presented below:

Study 20-250-SA (Buprenorphine and Naloxone 1 x 2 mg/0.5 mg Soluble Film v/s Tablet)

The upper 90% CI limit for buprenorphine just misses the upper limit of 125% for Cmax (131.43) but the 90% CI limits are within 80-125% of the reference treatment for AUClast and AUCinf for SL strips indicating that the SL strips are not equivalent with respect to (w.r.t) the rate of absorption but are equivalent w.r.t the extent of absorption of buprenorphine to the reference product, SL tabs. In addition, the two treatments are equivalent w.r.t rate of absorption of naloxone. Since naloxone plasma concentrations were below the limit of quantification for a number of subjects, its AUC values are unreliable. Nonetheless, the 90% CI limits for naloxone are within 80-125% of the reference treatment for AUClast and AUCinf.

Study 20-273-SA (Buprenorphine and Naloxone 1 x 8 mg/2 mg Soluble Film v/s Tablet)

The upper 90% CI limits for buprenorphine and naloxone are slightly above 125% for all the three PK parameters measured Cmax, AUClast and AUCinf for SL strips indicating

that the SL strips are not bioequivalent based on both, the rate and extent of absorption, of buprenorphine or naloxone, to the reference product, SL tabs.

Study 20-272-SA (Buprenorphine and Naloxone two of 2 mg/0.5 mg Soluble Films v/s Tablets for a total dose of 4 mg buprenorphine/ 1 mg naloxone)

The 90% CI limits for buprenorphine and naloxone are all within 80-125% for all the three PK parameters measured Cmax, AUClast and AUCinf for the SL strips indicating that the SL strips are bioequivalent based on both, the rate and extent of absorption, of buprenorphine or naloxone to the reference product, SL tabs for a total dose of 4 mg buprenorphine and 1 mg naloxone when administered as a combination of two 2/0.5 mg strips together.

Study 1003395 (Buprenorphine and Naloxone one of 8 mg/2 mg and two of 2 mg/0.5 mg Soluble Films v/s Tablets for a total dose of 12 mg buprenorphine/ 3 mg naloxone)

The 90% CI limits for buprenorphine and naloxone are all within 80-125% for all the three PK parameters measured Cmax, AUClast and AUCinf for the SL strips indicating that the SL strips are bioequivalent based on both, the rate and extent of absorption, of buprenorphine or naloxone to the reference product, SL tabs for a total dose of 12 mg buprenorphine and 3 mg naloxone when administered as a combination of one 8/2 mg and two 2/0.5 mg strips together.

Therefore, overall the 2/0.5, 4/1 and 12/3 doses of the Suboxone (b) (4) are or are close to being bioequivalent to the tablets. The 8/2 mg dose of the Suboxone (b) (4) fails the BE test on both rate and extent of absorption for both the buprenorphine and opioid components; however the levels overall are only slightly higher than the tablets.

For the 2/0.5 and 8/2 doses, since the failure in BE for buprenorphine and naloxone is on the higher end, the therapeutic efficacy of the new product (strips) w.r.t buprenorphine and naloxone is not expected to be compromised. However, safety implications of the higher exposure with SL strips relative to the approved SL tablets (and the clinical trial formulation of aqueous ethanolic solution in the SL Tablets NDAs) has to be considered. It should be noted that the exposure of buprenorphine from Suboxone® SL film strips is much lower than that for the aqueous ethanolic solution of buprenorphine which was employed as the Clinical Trial formulation supporting the original NDAs 20-732 and 20-733. For the Suboxone® SL tablet NDA, the Division Director's Review of NDA and Basis for Action concluded that the relative bioavailability for the 8 mg/2 mg Suboxone® tablet relative to the solution was 0.66 (66%). Thus, relative to the approved Suboxone® tablet, the bioavailability of the solution was 1.52 (the reciprocal of 0.66 is 152%). Therefore, even though the bioavailability of buprenorphine from the buprenorphine and naloxone soluble film (Suboxone (b) (4) is somewhat higher than the tablets (overall, about 20% higher than the tablets), it is still less than that observed for the aqueous ethanolic solution. So applying the same basis of acceptance of safety of higher buprenophine levels from Suboxone® tablets when compared to the ethanolic solution as

employed in NDA # 20-733 (for Suboxone® tablets), the relative bioavailability for the 8 mg/2 mg Suboxone [redacted] relative to the solution can be considered as 0.84 (0.66 + 20% of 0.66) which is still lower than the solution and therefore the safety of the higher bioavailability of buprenorphine from Suboxone [redacted] is covered by the available data from NDAs 20-732 and 20-733.

Naloxone plasma levels though higher when Suboxone® film strips were administered when compared to Suboxone® tablets, are still below those that can precipitate withdrawal symptoms and compromise efficacy and therefore are deemed not to be of concern. In clinical study RB-US-07-0001, submitted in the current NDA, despite the sub-optimal design of the study, (refer to the review by Dr. Celia Winchell for additional details), it did not appear that there was significant concern about precipitation of withdrawal from the SL strips, lending additional support that the slightly higher naloxone exposure is not high enough to cause precipitation of withdrawal.

1.4 Overall conclusions

1.4.1 Although the 2/0.5 mg and the 8/2 mg Suboxone [redacted] exhibited enhanced bioavailability of buprenorphine in two out of the four studies employing these strips, the levels are lower than those established for a safe and effective sublingual solution of buprenorphine that was employed as a Clinical Trial formulation for approval of precursor Subutex® and Suboxone® tablets.

1.4.2 Higher naloxone levels seen for SL [redacted] relative to those seen with SL tablets are still considered low to cause precipitation of opioid withdrawal.

2.0 Question Based Review

2.1 General Attributes of the Drug

2.1.1 *What pertinent regulatory background or history contributes to the current assessment of the clinical pharmacology and biopharmaceutics of this drug?*

Buprenorphine is a thebaine-derived partial agonist of the opioid (morphine-type) μ-receptor and an antagonist of the opioid (dynorphin-type) κ-receptor initially approved by the FDA (1982) in an injectable formulation, Buprenex®, for the treatment of moderate to severe pain.

Since initial approval, addiction researchers have explored buprenorphine's utility in maintenance treatment for opiate addiction. Most of the research on buprenorphine in this clinical context was performed through NIH funding (National Institute on Drug Abuse) through individual research grants. Reckitt & Colman Pharmaceuticals Inc. and National Institute on Drug Abuse (NIDA) have been engaged in a Cooperative Research and Development Agreement (CRADA) to develop buprenorphine alone (Subutex®) and in combination with naloxone (Suboxone®) for the treatment of opiate dependence.

The development of buprenorphine in high doses as a treatment for opiate dependence began with a sublingual ethanolic solution. Indeed most of the clinical research that has been conducted with this drug substance used that formulation. (b) (4) Thus, the sponsor initiated a new development program using a sublingual tablet. Since alcohol increases the bioavailability of buprenorphine, it was soon discovered that the new sublingual tablet was not bioequivalent to the sublingual solution, milligram for milligram. The ensuing development program for the tablet formulation, therefore, focused on three factors (1) establishing a relationship between the tablet and the sublingual solution which, in the absence of bioequivalence, would allow for the treating physician to accurately approximate the dosing regimen shown to be effective and safe in clinical trials using the solution (2) absent the above relationship, adequate and well controlled studies demonstrating the efficacy of the sublingual buprenorphine tablet in the treatment of opiate addiction and (3) the development of a combination product with naloxone and buprenorphine which would have equivalent efficacy but would, by virtue of the small dose of naloxone present, and the poor sublingual bioavailability, be a deterrent to intravenous abuse, therefore improving its safety profile. Pursuant to this, Subutex® and Suboxone® tablets were approved under NDA 20-732 and 20-733 respectively. The safety and efficacy claims for buprenorphine and buprenorphine and naloxone for both Subutex® and Suboxone® sublingual tablets respectively, came from buprenorphine sublingual solution.

The NDA (20-732) for Subutex® was submitted in 1997 and an approvable action was taken in 1998 pending resolution of several deficiencies. Although the clinically tested sublingual 30% alcoholic solution and the to-be-marketed Subutex® sublingual tablet

(strengths of 2 and 8 mg) dosage forms were not found to be bioequivalent with respect to buprenorphine (the solution being more bioavailable as compared to the tablets), available data permitted adequate conversion of tablet doses achieved to corresponding efficacious solution doses; the main consideration being that since the tablets have a lower bioavailability relative to the solution and the highest tablet dose proposed is 24 mg, there is a considerable safety margin with the tablet in the proposed dosage regimen.

The NDA (20-733) for Suboxone® was submitted in 1999 and approved in 2002. In this NDA, proposed maintenance dosing range of 4 mg to 24 mg with Suboxone® tablets approximated the buprenorphine sublingual solution doses of 2.8 mg to 16.8 mg applying a constant relative bioavailability of 0.7 throughout the dose range. 16 mg dose of Suboxone® and Subutex® were found to result in similar Cmax and AUC values indicating that naloxone does not affect the pharmacokinetics of buprenorphine. This combined with the fact that the two formulations are compositionally similar led to the conclusion that Suboxone® and Subutex® will deliver similar buprenorphine concentrations. In part, the basis for accepting the buprenorphine SL solution efficacy data in support of the Suboxone® application was the premise that the naloxone in Suboxone® was inactive when used as directed. It was known that there were extremely low but detectable levels of naloxone associated with the 8:2 and16:4 doses of Suboxone®. The application had to therefore demonstrate that these low levels did not affect the overall efficacy of the product. The efficacy of both Suboxone® and Subutex® in Study 1008a was established with a placebo control and the success rate, albeit for one month of treatment, was comparable. In addition, the absence of precipitated withdrawal in patients treated with Suboxone® or in patients switching from Subutex to Suboxone® (following induction) was the most compelling evidence in support of this premise. Naloxone in buprenorphine/naloxone is not significantly absorbed sublingually, and therefore, most of the dose is available for GI absorption. There has not been a robust evaluation of the chronic oral toxicity of naloxone, which was initially developed as a single-use agent for intravenous administration. The development plan for buprenorphine/naloxone should, therefore, have included a up to a minimum of 6-months to a year of safety data for the combination product doses of naloxone of up to 6 mg/day (more typically 2 mg/day). In the open label extension, Study 1008(b) approximately 250 patients were exposed to naloxone for up to 6 months in doses for which this product will be labeled. No unexpected adverse events were noted in this experience. In addition, naloxone plasma concentrations were in general found to be very low, when Suboxone® was administered in the dose range of 4 to 16 mg.

The objective of the clinical development program for buprenorphine and naloxone soluble film, Suboxone (b) (4) (the subject of this NDA # 22-410) was to generate comparative pharmacokinetic (PK) data between the approved Suboxone® sublingual tablet and the soluble film dosage forms. This comparison was then to be used to connect the established safety and efficacy of Suboxone® SL tablets (NDA #20-733) to buprenorphine and naloxone soluble film dosage forms (NDA #22-410).

A type B pre-NDA meeting was held for this product under IND #s (b) (4) and 75,811 on June 24, 2008. This 505 (b) (1) NDA for Suboxone (b) (4) C-III (buprenorphine and

naloxone soluble film) for sublingual administration was submitted to FDA on October 21, 2008. A standard review status was granted for this NDA.

The indication sought for the strips is maintenance of opioid withdrawal and the product was developed as an alternative to Suboxone® sublingual tablets (NDA 20-733, approved October 8, 2002, marketed in the US since January 2003 and currently approved in 39 countries). FDA's Office of Orphan Product Development has determined that buprenorphine qualifies for orphan designation for the treatment of opiate addiction in opiate users based on the projected low commercial potential. Because of the orphan drug status, the sponsor is exempt from pediatric study requirements under PREA.

2.1.2 *What are the highlights of the properties of the drug or the formulation as they relate to clinical pharmacology review?*

Buprenorphine is a weak base with a pKa of 8.4. As such, pH of the saliva will play a role in the amount of buprenorphine absorbed from the oral mucosa. The solubility of buprenorphine is 1.1 mg/mL at pH 6 but only 0.11 at pH 7, a 10-fold decrease. It is highly lipid soluble (log partition coefficient of octanol/pH 6.6 is 3.37). Buprenorphine occurs as a white to off-white, crystalline powder, sparingly soluble in water, freely soluble in methanol, soluble in alcohol and practically insoluble in cyclohexane.

Naloxone is white, or almost white crystalline powder and is hygroscopic. It is freely soluble in water, soluble in alcohol; practically insoluble in toluene.

Suboxone (b) (4) (buprenorphine/ naloxone) soluble film is a pale orange film strip, imprinted with a logo identifying the product and strength in white ink. Suboxone (b) (4) is available in the following strengths/dimensions:

• Suboxone (b) (4) (8 mg buprenophine/2 mg naloxone), soluble film contains 8 mg buprenorphine (as 8.64 mg buprenorphine hydrochloride [HCl]) and 2 mg naloxone (as 2.44 mg naloxone HCl dihydrate); dimensions 0.875 inch x 0.5 inch

• Suboxone (b) (4) (2 mg buprenophine/0.5 mg naloxone), soluble film contains 2 mg buprenorphine (as 2.16 mg buprenorphine HCl) and 0.5 mg naloxone (as 0.61 mg naloxone HCl dihydrate); dimensions 0.875 inch x 0.5 inch

Each Suboxone (b) (4) strength utilizes a different formulation and these are designated 'high strength' and 'low strength' for the 8 mg/ 2 mg and 2 mg/ 0.5 mg products respectively.

Quantitative Formula for Suboxone (b) (4)

	High Strength Suboxone (b) (4) (8 mg buprenorphine / 2 mg naloxone) soluble film		Low Strength Suboxone (b) (4) (2 mg buprenorphine / 0.5 mg naloxone) soluble film	
Component	**Composition % (w/w)**	**Quantity/strip (mg)**	**Composition % (w/w)**	**Quantity/strip (mg)**
Buprenorphine HCl	17.28	8.64	5.40	2.16
Naloxone HCl Dihydrate	4.88	2.44	1.53	0.61
Acesulfame Potassium	(b) (4)			
Citric Acid, Anhydrous				
(b) (4)				
Polyethylene Oxide				
(b) (4)				
Polyethylene Oxide				
(b) (4)				
Polyethylene Oxide				
(b) (4)				
Sodium citrate				
(b) (4)				
(b) (4) Lime Flavor (b) (4)				
FD&C Yellow No. 6				
White Ink				
Total	100.0	50.0	100.0	40.0

(b) (4)

Although at this time, approval is sought only for the 2/0.5 and the 8/2 mg strips, the 12/3 and the 16/4 mg strips were employed in relative BA studies 20-B90-AU and 20-A90-AU respectively and also in Study 20-291-SA, a dose proportionality study, reviewed in this NDA. (b) (4)

The following two tables list the strip dimensions and the compositions.

Film strip strength (buprenorphine/naloxone mg)	Film formulation	Theoretical film strip size (width x length, inches)	Theoretical film strip weight (mg)
2/0.5	Low strength film	0.875 x 0.5	40
8/2	High strength film	0.875 x 0.5	50
(b) (4)			

Ingredients	Reference to Standards	Function	Product strength (buprenorphine/naloxone)							
			16/4		12/3		8/2		2/0.5	
			%w/w	mg/strip	%w/w	Mg/strip	%w/w	mg/strip	%w/w	mg/strip
Active ingredients										
Buprenorphine Hydrochloride	USP/RB	API	(b) (4)				17.28	(b) (4)	5.40	(b) (4)
Naloxone Hydrochloride Dihydrate	USP/RB	API					4.88		1.53	
Inactive ingredients										
Polyethylene Oxide (b) (4)	NF									(b) (4)
Polyethylene Oxide	NF									
Polyethylene Oxide	NF									
Hydroxypropyl methylcellulose (b) (4)	USP									
Hydroxypropyl methylcellulose	USP									
Maltitol (b) (4)	NF									
Acesulfame-k	USP									
Citric Acid (b) (4)	USP									
Sodium citrate (b) (4)	USP									
Lime flavor (b) (4)	In-house	Flavoring								(b) (4)
FD&C Yellow #6 (b) (4)	In-house	Colorant								
White Ink (b) (4)	In-house	White Ink								
Total						(b) (4)	100.00	50	100.00	40

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

Buprenorphine, the primary active compound in Suboxone (b) (4) (as well as in Suboxone® sublingual tablets), is a partial opioid agonist with a high affinity for the mu-opioid receptor and lower intrinsic activity than full opioid agonists.

Naloxone (USP monograph name naloxone hydrochloride) is used by the injection route to reverse opioid overdose or opioid side effects such as respiratory depression. As an antagonist, the naloxone binds to the receptor but does not give resultant pharmacological effects. When full agonists are occupying the receptors in the brain and exerting an effect, the naloxone displaces the agonist and binds to the receptor, thereby removing the effect of the agonist and allowing the body to recover. The net effect is a reversal of the opioid agonist effects. Naloxone is poorly bioavailable by the sublingual route but has increased bioavailability when injected. The inclusion of naloxone with buprenorphine in the Suboxone® product is designed to reduce the abuse potential compared to a buprenorphine only product.

The therapeutic indication is for maintenance treatment of opioid dependence.

2.1.4 *What are the proposed dosage and route of administration?*

The dosage strengths of Suboxone (b) (4) for which marketing approval is being sought are the same as those currently approved for Suboxone® sublingual tablets, i.e. buprenorphine 8 mg with naloxone 2 mg indicated as 8/2 mg strips and buprenorphine 2 mg with naloxone 0.5 mg indicated as 2/0.5 mg strips.

2.2 General Clinical Pharmacology

The Clinical Pharmacology package submitted for this NDA consisted of 19 Phase 1 PK studies conducted in healthy adult volunteers (including pilot, pivotal BE and dose and dosage form proportionality studies) and 1 clinical study in a patient population to determine local oral tolerability with the soluble film dosage form. The primary support for the clinical safety and efficacy of the Suboxone (b) (4) 8mg/2mg and 2mg/0.5mg formulations comes from the established safety and efficacy data on Suboxone® sublingual tablets (NDA 20-733). No special population or drug-drug interaction studies were conducted in this NDA. The Sponsor is relying on Agency's previous findings for Suboxone® sublingual tablets to construct their labeling for special populations (e.g., renal and hepatic impairment patients, elderly patients) and drug-drug interactions. Refer to Clinical Pharmacology review by Dr. Suresh Doddapaneni for NDA 20-733 for all General Clinical Pharmacology details (including information related to ADME, Intrisic and Extrinsic factors).

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

Nineteen PK studies were submitted in the Clinical Pharmacology package of this NDA. Out of the 19, 7 were deemed relevant and reviewed for this NDA. The design features of those 7 studies are presented below in a tabular format:

Study No.	Study Objective(s)	Study Design	No. Subjects Age Range (Mean)	Treatment, Dose [Lot or Product ID]
Buprenorphine and Naloxone Pivotal Bioequivalence Studies (All studies conducted in healthy volunteers under naltrexone block)				
20-250-SA	Compare the rate and extent of both SL and buccal absorption of an investigational formulation of buprenorphine and naloxone soluble film dosage 2 mg/0.5 mg to an equivalent SL dose of the commercially available reference product, Suboxone® tablets.	OL, R, single-dose, 3-period, 3-treatment (14-day washout), balanced crossover SL and buccal following an overnight fast of at least 10 hours	45 (31M/14F) Completed: 39 18-43 (30)	Suboxone® SL tablet 1 x 2 mg/0.5 mg [Lot #723403]
				Test 1 SL buprenorphine and naloxone soluble film C-III 1 x 2 mg/0.5 mg [Lot #H07DW101-288]
				Test 2 Buccal buprenorphine and naloxone soluble film C-III 1 x 2 mg/0.5 mg [Lot #H07DW101-288]
20-272-SA	Compare the rate and extent of both SL and buccal absorption of an investigational formulation of buprenorphine and naloxone soluble film dosage (4 mg/1 mg administered as two 2 mg/0.5 mg soluble films) to an equivalent SL dose of the commercially available reference product, Suboxone® tablets.	Single-dose, OL, R, 3-period, 3-treatment (14-day washout), 3-way balanced crossover study SL and buccal following an overnight fast of at least 10 hours	Enrolled: 48 (39M/9F) Completed: 37 19-45 (32)	Ref Suboxone® SL tablet 2 x 2 mg/0.5 mg tablet [Lot #730901]
				Test 1 SL buprenorphine and naloxone soluble film C-III 2 x 2 mg/0.5 mg [Lot #A08DW101-024]
				Test 2 Buccal buprenorphine and naloxone soluble film C-III2 x 2 mg/0.5 mg [Lot #A08DW101-024]

20-273-SA	Compare the rate and extent of both SL and buccal absorption of an investigational formulation of buprenorphine and naloxone 12 mg/3 mg soluble film, to an equivalent SL dose of the commercially available reference product, (one 8 mg/2 mg plus two 2 mg/0.5 mg tablets), Suboxone® tablets.	Single-dose, OL, R, 3-period, 3-treatment (14-day washout), 3-way balanced crossover SL and buccal following an overnight fast of at least 10 hours	Enrolled: 48 (26M/22F) Completed: 42 18-45 (30)	Ref Suboxone® SL tablet 1 x 12 mg/3 mg [1 x 8 mg/2 mg+2 x 2 mg/0.5 mg] [Lot #730902]
				Test 1 SL buprenorphine and naloxone soluble film C-III 12 mg/3 mg [Lot #A80EY101-028]
				Test 2 Buccal buprenorphine and naloxone soluble film C-III 12 mg/3 mg [Lot #A08EY101-028]
20-B20-AU	Compare the rate and extent of both SL and buccal absorption of an investigational formulation of buprenorphine and naloxone 12 mg/3 mg soluble film, to an equivalent SL dose of the commercially available reference product, (one 8 mg/2 mg plus two 2 mg/0.5 mg tablets), Suboxone® tablets.	Single-dose, OL, R, 3-period, 3-treatment (14-day washout), 3-way balanced crossover SL and buccal following an overnight fast of at least 10 hours	Enrolled: 48 (26M/22F) Completed: 42 18-45 (30)	Ref Suboxone® SL tablet 1 x 12 mg/3 mg [1 x 8 mg/2 mg+2 x 2 mg/0.5 mg] [Lot #730902]
				Test 1 SL buprenorphine and naloxone soluble film C-III 12 mg/3 mg [Lot #A80EY101-028]

				Test 2 Buccal buprenorphine and naloxone soluble film C-III 12 mg/3 mg [Lot #A08EY101-028]
20-A90-AU	Compare the rate and extent of both SL and buccal absorption of an investigational formulation of buprenorphine and naloxone 2 mg/0.5 mg soluble film to an equivalent SL dose of the commercially available reference product, Suboxone® tablets.	Single-dose, OL, R, 2-period; 3-treatment (14-day washout) balanced crossover SL and buccal following an overnight fast of at least 10 hours	Enrolled: 48 (29M/19F) Completed: 43 19-39 (29)	Ref Suboxone® SL tablet 2 x 8 mg/2 mg tablets [Lot #722103-1]
				SL buprenorphine and naloxone soluble film C-III 1 x 16 mg/4 mg [L07ET101-311]
				Buccal buprenorphine and naloxone soluble film C-III 1 x 16 mg/4 mg [L #07ET101-311]
1003395	Compare the rate and extent of both sublingual and buccal absorption of investigational formulations of buprenorphine/naloxone 8 mg/2 mg plus 2 x 2 mg/0.5 mg film strips, manufactured by (b) (4) for Reckitt Benckiser Pharmaceuticals Inc., to an equivalent sublingual dose of the commercially available reference product, Suboxone® (one 8 mg/2 mg plus 2 x 2 mg/0.5 mg tablets),	Single-dose, open-label, randomized, 3-period, 3-treatment, 3-way crossover study in which 48 healthy adult subjects (under naltrexone block) were scheduled to receive three separate single-dose administrations of buprenorphine/naloxone 8	Enrolled: 48 Completed: 46	Ref Suboxone® SL tablet 12 mg/3 mg (1 x 8 mg/2 mg plus 2 x 2 mg/0.5 mg) [Lot #815101-4
				SL buprenorphine and naloxone soluble film C-III 12 mg/3 mg (1 x 8 mg/2 mg plus 2 x 2 mg/0.5 mg) film strips [Lot A08EJ102-025]

	manufactured by Reckitt Benckiser Healthcare (UK) Ltd., following an overnight fast of at least 10 hours.	mg/2 mg plus 2 x 2 mg/0.5 mg film strips administered sublingually, buprenorphine/naloxone 8 mg/2 mg plus 2 x 2 mg/0.5 mg film strips administered buccally, or one Suboxone® 8 mg/2 mg plus 2 x 2 mg/0.5 mg tablets administered sublingually following an overnight fast of at least 10 hours.		Buccal buprenorphine and naloxone soluble film C-III 12 mg/3 mg (1 x 8 mg/2 mg plus 2 x 2 mg/0.5 mg) [A08DW104-028]
20-291-SA	Compare the rate and extent of absorption of five dosages (2/0.5 mg, 4/1 mg (2 x 2/0.5 mg), 8/2 mg, 12/3 mg, and 16/4 mg) of SL buprenorphine and naloxone soluble film investigational formulations.	Single-dose, 3-period, 5-treatment, 3-way, unbalanced crossover SL following an overnight fast of at least 10 hours	Enrolled: 60 (37M/23F) Completed: 50 18-42 (28)	Test 1 SL buprenorphine and naloxone soluble film C-III 1 x 2 mg/0.5 mg [Lot #A08DW101-024]
				Test 2 SL buprenorphine and naloxone soluble film C-III 4/1 mg (2 x 2/0.5 mg) [Lot #A08DW101-024]
				Test 3 SL buprenorphine and naloxone soluble film C-III 1 x 8 mg/2 mg [Lot #A08EJ103-025]
				Test 4 SL buprenorphine and naloxone soluble film C-III 1 x 12/3 mg [Lot # A08EY101-028]
				Test 5 SL buprenorphine and naloxone soluble film C-III 1 x 16/4 mg [Lot #A08ET101-035]

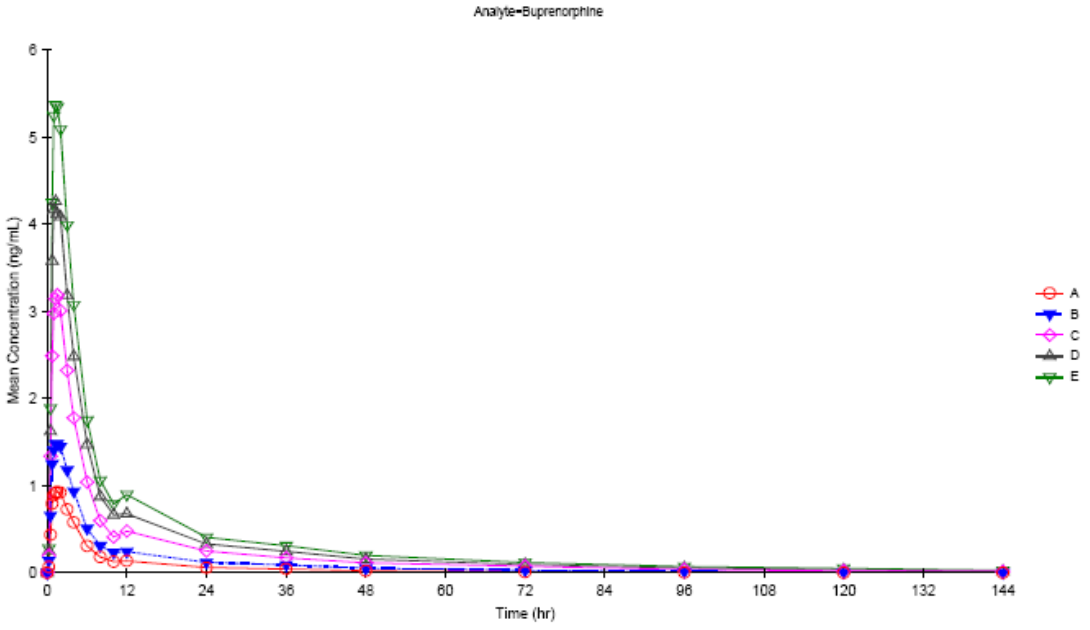
2.2.2 *Are the active moieties in the plasma (or other biological fluid) appropriately identified and measured to assess pharmacokinetic parameters and exposure response relationships?*

Buprenorphine and naloxone concentrations in the plasma were measured. In addition to buprenorphine, its CYP3A4 metabolite, norbuprenorphine, considered to be the major metabolite was measured in the plasma as well. Although found to possess some pharmacological activity in-vitro, its role in-vivo has not been evaluated in any clinical studies and for all practical purposes, is not known to possess any analgesic properties in humans. In evaluating the bioequivalence of the reference product to the test product, the plasma concentrations of norbuprenorphine were not taken into consideration.

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

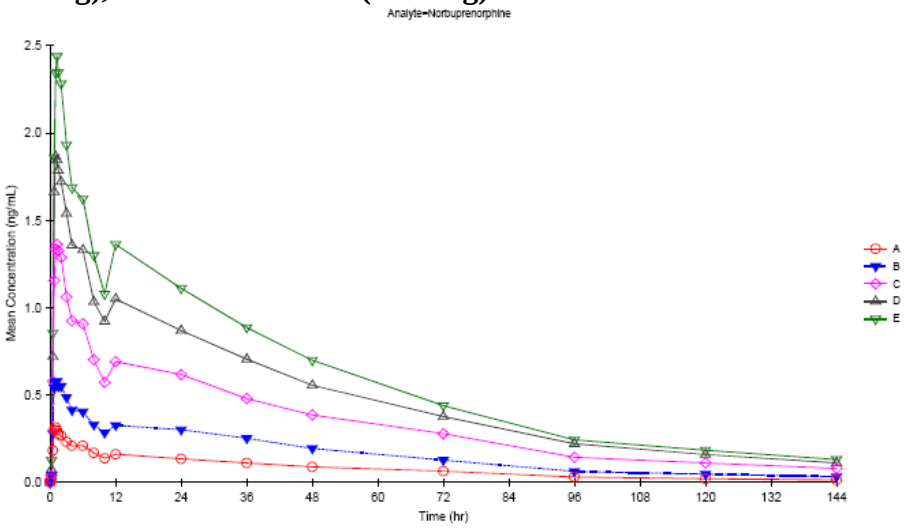
Exposure to buprenorphine increased with dose of buprenorphine/naloxone film strips. In general, peak exposure to buprenorphine was observed at approximately 1.5 hours and mean estimates of Cmax ranged from 1.07 ± 0.525 ng/mL after 2/0.5 mg to 6.05 ± 2.42 ng/mL after 16/4 mg. Likewise, overall systemic exposure, based on AUC values, increased with dose. Mean estimates of AUClast ranged from 7.178 ± 2.836 hr*ng/mL after 2/0.5 mg to 50.32 ± 16.38 after 16/4 mg. Mean estimates of AUCinf were similar to those of AUClast and followed the same rank order, ranging from 8.434 ± 3.207 hr*ng/mL after 2/0.5 mg to 53.40 ± 18.58 hr*ng/mL after 16/4 mg. Mean estimates of the t1/2 of buprenorphine ranged from 22.71 ± 13.01 hr to 40.37 ± 17.22 hr.

Mean Buprenorphine Concentration-Time Profile after Administration of Treatment A (2/0.5 mg), Treatment B (4/1 mg), Treatment C (8/2 mg), Treatment D (12/3 mg), and Treatment E (16/4 mg):

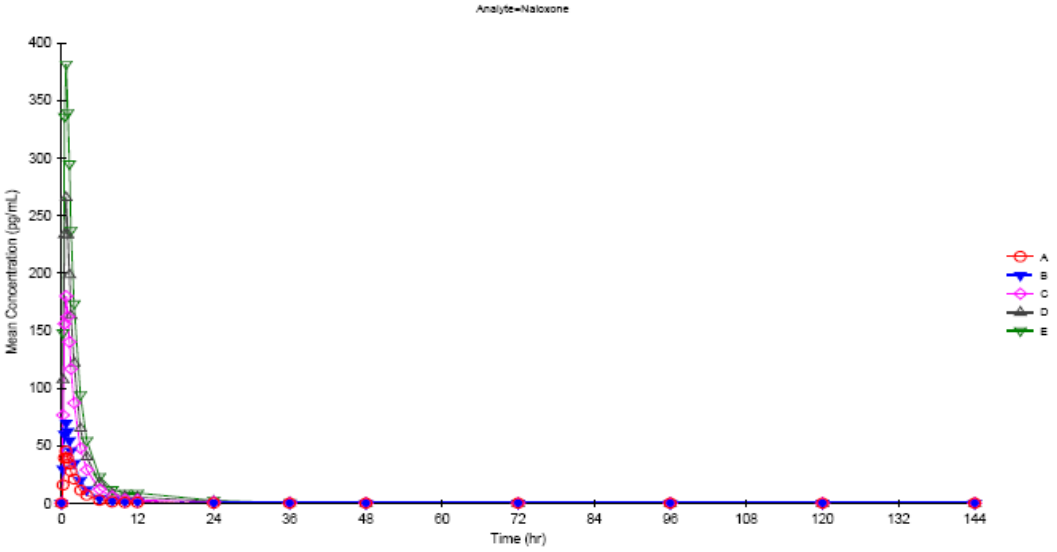


As observed for buprenorphine, exposure to norbuprenorphine and naloxone increased with dose of buprenorphine/naloxone film strips. In general, peak exposure to norbuprenorphine was observed on average from 1.32 to 1.87 hr, and mean estimates of Cmax ranged from 0.352 ± 0.163 ng/mL after 2/0.5 mg to 2.73 ± 1.64 ng/mL after 16/4 mg and peak exposure to naloxone was observed on average from 0.73 to 0.79 hr, and mean estimates of Cmax ranged from 48.5 ± 25.9 pg/mL after 2/0.5 mg to 401 ± 226 pg/mL after 16/4 mg.

Mean Norbuprenorphine Concentration-Time Profile after Administration of Treatment A (2/0.5 mg), Treatment B (4/1 mg), Treatment C (8/2 mg), Treatment D (12/3 mg), and Treatment E (16/4 mg):



Mean Naloxone Concentration-Time Profile after Administration of Treatment A (2/0.5 mg), Treatment B (4/1 mg), Treatment C (8/2 mg), Treatment D (12/3 mg), and Treatment E (16/4 mg):



In the linear regression plots of the dose-normalized values of Cmax, AUClast, and AUCinf, there was a negative slope in the regression line, suggesting a less than proportional increase in exposure to buprenorphine with increasing dose. The negative slope in the regression line appeared to be due to the first two dose levels, 2/0.5 and 16/4 mg.

For norbuprenorphine and naloxone, the slopes of the regression lines were small, almost parallel to the x-axis for AUClast and AUCinf, suggesting that overall systemic exposure to norbuprenorphine and naloxone were proportional to the administered dose in buprenorphine/naloxone film strips.

When all dose levels were included in the dose-proportionality assessment of buprenorphine using a mixed effects model based on a power function, the β1 estimates and associated 90% confidence intervals were 0.93 (0.86, 1.00) for Cmax, 1.04 (0.97, 1.11) for AUClast, and 0.98 (0.91, 1.06) for AUCinf. The β1 estimates were closer to 1.00 when the upper dose levels were considered in the power analysis. The power analysis results indicated that buprenorphine exposure was directly proportional to the administered dose of buprenorphine/naloxone film strips over the dose range considered in this study, 2/0.5 mg to 16/4 mg.

When all dose levels were included in the dose-proportionality assessment of naloxone, the β1estimates and associated 90% confidence intervals were 1.05 (0.98, 1.13) for Cmax, 1.13 (1.06, 1.12) for AUClast, and 1.11 (1.05, 1.18) for AUCinf. The power analysis results indicated that peak exposure to naloxone was directly proportional to the buprenorphine/naloxone dose for the dose range considered in the study, 2/0.5 mg to 16/4mg.

It should be noted that the buprenorphine 12 mg/naloxone 3 mg strength and buprenorphine 16 mg/nalaoxone 4 mg strength are not sought for approval at this time.

Assessment of Dose Proportionality using Mixed-Effects Statistical Model Based on a Power Function (Buprenorphine, Norburprenorphine, and Naloxone):

Dependent Variable	Model Variable	Estimate (β_1)	p-value[a]	Lower CI[b]	Upper CI[b]	Dose P[c]
Buprenorphine, Dose Range 2/0.5 to 16/4 mg						
$\ln(AUC_{inf})$	ln(Dose)	0.9846	<0.0001	0.9142	1.0550	28.5590
$\ln(AUC_{last})$	ln(Dose)	1.0389	<0.0001	0.9700	1.1078	14.4346
$\ln(C_{max})$	ln(Dose)	0.9327	<0.0001	0.8634	1.0021	8.2158
Norbuprenorphine, Dose Range 2/0.5 to 16/4 mg						
$\ln(AUC_{inf})$	ln(Dose)	1.0169	<0.0001	0.9419	1.0918	22.9415
$\ln(AUC_{last})$	ln(Dose)	1.0565	<0.0001	0.9722	1.1408	7.7188
$\ln(C_{max})$	ln(Dose)	1.0301	<0.0001	0.9536	1.1065	14.8814
Naloxone, Dose Range 2/0.5 to 16/4 mg						
$\ln(AUC_{inf})$	ln(Dose)	1.1112	<0.0001	1.0451	1.1773	5.0649
$\ln(AUC_{last})$	ln(Dose)	1.1282	<0.0001	1.0605	1.1958	4.3452
$\ln(C_{max})$	ln(Dose)	1.0544	<0.0001	0.9773	1.1314	8.9267

Power Model: $\ln(PK) = \ln(\beta_0) + \beta_1 \cdot \ln(Dose) + \varepsilon$

where PK is the pharmacokinetic parameter tested,

$\ln(\beta_0)$ is the y-intercept, β_1 is the slope,

and ε is an error term (Subject was used as the random effects term in the analysis)

a = Significant difference from unity (1.0000), defined *a priori* as $p < 0.05$

b = 90% confidence intervals (lower and upper)

c = High/low dose ratio in which dose proportionality can be demonstrated definitely, relative to the lowest dose in the analysis data set

2.3 General Biopharmaceutics

2.3.1 *What is the relative bioavailability of the two formulations (reference and test) based on the pivotal BE studies?*

The sponsor is seeking the approval of two strengths of Suboxone® sublingual strips at this time: 2/0.5 mg and 8/2 mg. However, the recommended dose for proposed indication is 16/4 mg per day which is to be administered employing the 2/0.5 and the 8/2 mg strips. Therefore in addition to studies 20-250-SA and 20-273-SA which are relative BA studies comparing Suboxone (b) (4) to tablets, we also reviewed studies 20-272-SA and 1003395, which were relative BA studies employing 4/1 mg dose (administered as two of 2/0.5 mg strips) and 12/3 mg dose (administered as one of 8/2 mg strip and two of 2/0.5 mg strips). The latter two studies provide the PK characteristics of a combination of these two different dosage forms when administered together to deliver a specific amount of buprenorphine and naloxone.

Relative BA of the Suboxone® SL strips 2/0.5 mg and 8/2 mg against the respective reference products Suboxone® SL tablets 2/0.5 mg and 8/2 mg were evaluated in studies 20-250-SA and 20-273-SA respectively.

Study 20-250-SA: A Single-Dose, 3-Period, 3-Treatment, 3-Way Crossover Study of a 2 mg/0.5 mg Buprenorphine/Naloxone Film Formulation versus Suboxone® under Fasting Conditions

PK Parameters of Buprenorphine and Naloxone after Sublingual Administration of Suboxone® Tablets and Suboxone (b) (4) (2/0.5 mg)

	Buprenorphine		Naloxone (concentrations in pg)	
	SL tab	SL strip	SL tab	SL strip
Tmax [h]	1.55 (0.53)	1.72 (0.60)	0.80 (0.26)	0.77 (0.26)
Cmax [ng/mL]	0.780 (0.323)	0.947 (0.374)	51.3 (21.1)	54.1 (23.0)
AUClast [h x ng/mL]	6.789 (2.536)	7.820 (2.706)	128.6 (48.76)	128.6 (43.20)
AUCinf [h x ng/mL]	7.651 (2.650)	8.654 (2.854)	124.2 (52.49)	137.3 (43.10)

Statistical Analysis of the Log-Transformed Systemic Exposure Parameters Comparing Sublingual Administration of Suboxone® Tablets and Suboxone (b) (4) (2/0.5 mg)

	Buprenorphine	Naloxone
	SL tab v/s SL strip	SL tab v/s SL strip
Cmax	121.66 (112.62-131.43)	104.01 (95.79-112.93)
AUC last	116.40 (108.70-124.63)	101.84 (94.84-109.36)
AUC inf	114.22 (106.65-122.32)	107.28 (96.98-118.69)

The upper 90% CI limits for buprenorphine are above 125% for Cmax (131.43) but within 80-125% for AUClast and AUCinf for SL strips indicating that the SL strips did not meet the BE criterion for buprenorphine.

The geometric mean and the upper and lower 90% CI limits for naloxone for Cmax are within 80-125% of the reference indicating that the SL strips meet the equivalency

criterion for naloxone for Cmax. Naloxone plasma concentrations were not quantifiable for several of the subjects therefore AUClast and AUCinf values for naloxone are not considered reliable for BE comparisons. Having said that, the geometric mean and the upper and lower 90% CI limits for both AUClast and AUCinf are within 80-125% of the reference for the 2 mg/0.5 mg buprenorphine/naloxone film formulation.

Study 20-273-SA: A Single-Dose, 3-Period, 3-Treatment, 3-Way Crossover Study of a 8 mg/2 mg Buprenorphine/Naloxone Film Formulation versus Suboxone® under Fasting Conditions

PK Parameters of Buprenorphine and Naloxone after Sublingual Administration of Suboxone® Tablets and Suboxone (b) (4) (8/2 mg)

	Buprenorphine		Naloxone (concentrations in pg)	
	SL tab	SL strip	SL tab	SL strip
Tmax [h]	1.48 (0.56)	1.53 (0.66)	0.80 (0.22)	0.81 (0.19)
Cmax [ng/mL]	2.58 (1.10)	3.37 (1.80)	135 (57.3)	193 (91.2)
AUClast [h x ng/mL]	23.65 (9.196)	28.74 (12.95)	347.4 (124.2)	458.7 (192.7)
AUCinf [h x ng/mL]	25.31 (9.500)	30.45 (13.03)	374.6 (132.8)	480.8 (201.0)

Statistical Analysis of the Log-Transformed Systemic Exposure Parameters Comparing Sublingual Administration of Suboxone® Tablets and Suboxone (b) (4) (8/2 mg)

	Buprenorphine	Naloxone
	SL tab v/s SL strip	SL tab v/s SL strip
Cmax	127.80 (116.11-140.66)	141.04 (126.87-156.80)
AUC last	120.15 (110.24-130.96)	130.04 (119.51-141.50)
AUC inf	119.51 (110.28-129.51)	121.19 (108.44-135.44)

The upper 90% CI limits for buprenorphine and naloxone are above 125% for all the three PK parameters measured Cmax, AUClast and AUCinf for SL strips indicating that

the SL strips **did not meet the bioequivalence criterion for either buprenorphine or naloxone.** After administration of the SL film, buprenorphine Cmax and AUCinf values are approximately 28% and 20% higher than those produced by Suboxone® tablets. Naloxone Cmax and AUCinf values are approximately 41% and 21% higher, respectively.

Study 20-272-SA: A Single-Dose, 3-Period, 3-Treatment, 3-Way Crossover Study of Two 2 mg/0.5 mg (4 mg/1 mg) Buprenorphine/Naloxone Film Formulations versus Suboxone® under Fasting Conditions

PK Parameters of Buprenorphine and Naloxone after Sublingual Administration of Suboxone® Tablets and Suboxone (b) (4) (two of 2/0.5 mg)

	Buprenorphine		Naloxone (concentrations in pg)	
	SL tab	SL strip	SL tab	SL strip
Tmax [h]	1.65 (0.74)	1.56 (0.65)	0.80 (0.25)	0.82 (0.23)
Cmax [ng/mL]	1.34 (0.565)	1.40 (0.687)	70.8 (34.7)	69.8 (37.8)
AUClast [h x ng/mL]	11.24 (4.637)	12.37 (5.912)	186.7 (97.96)	187.2 (96.67)
AUCinf [h x ng/mL]	12.46 (4.635)	13.71 (5.875)	204.6 (114.9)	204.3 (108.4)

Statistical Analysis of the Log-Transformed Systemic Exposure Parameters Comparing Sublingual Administration of Suboxone® Tablets and Suboxone (b) (4) (two of 2/0.5 mg)

	Buprenorphine	Naloxone
	SL tab v/s SL strip	SL tab v/s SL strip
Cmax	104.61 (94.58-115.69)	100.86 (90.95-111.84)
AUC last	108.64 (99.89-118.17)	99.93 (91.31-109.36)
AUC inf	104.55 (96.42-113.37)	106.48 (93.26-121.58)

The upper CI limits for buprenorphine are equivalent w.r.t rate and extent of absorption of buprenorphine and naloxone (based on Cmax, AUClast and AUCinf) to the reference product, SL tabs. Overall, this study indicates that when two 2 mg/0.5 mg buprenorphine/naloxone strips are administered together (as 4 mg/1 mg), they are bioequivalent to the reference product, however, when the 2/0.5 mg strip is administered as a 2 mg dose (a single strip of 2/0.5 mg in Study 20-250-SA), it is not bioequivalent to the reference product.

Study 1003395: A Single-Dose, 3-Period, 3-Treatment, 3-Way Crossover Study of Buprenorphine/Naloxone 8 mg/2 mg plus 2 x 2 mg/0.5 mg film strips versus Suboxone® under Fasting Conditions

PK Parameters of Buprenorphine and Naloxone after Sublingual Administration of Suboxone® Tablets and Suboxone (b) (4) (one of 8/2 mg and two of 2/0.5 mg)

	Buprenorphine		Naloxone (concentrations in pg)	
	SL tab	SL strip	SL tab	SL strip
Tmax [h]	1.26 (0.53)	1.36 (0.48)	0.78 (0.28)	0.75 (0.18)
Cmax [ng/mL]	3.44 (1.53)	4.05 (2.63)	170 (77.6)	207 (143)
AUClast [h x ng/mL]	35.14 (13.60)	38.51 (15.26)	502.3 (246.0)	561.2 (325.6)
AUCinf [h x ng/mL]	37.11 (14.14)	40.50 (15.93)	524.0 (253.6)	582.7 (324.9)

Statistical Analysis of the Log-Transformed Systemic Exposure Parameters Comparing Sublingual Administration of Suboxone® Tablets and Suboxone (b) (4) (one of 8/2 mg and two of 2/0.5 mg)

	Buprenorphine	Naloxone
	SL tab v/s SL strip	SL tab v/s SL strip
Cmax	115.05 (106.44-124.35)	117.24 (106.80-128.71)
AUC last	111.73 (106.11-117.64	110.46 (102.51-119.03)
AUC inf	111.21) (105.62-117.09)	110.47 (102.90-118.60)

The two treatments are equivalent w.r.t rate and extent of absorption of buprenorphine (based on Cmax, AUClast and AUCinf). The upper 90% CI limits for naloxone were above 125% for Cmax but within the 80-125% limits for AUClast and AUCinf for SL strips indicating that the SL strips are not equivalent w.r.t rate but equivalent w.r.t extent of absorption of naloxone to the reference product, SL tabs. Overall, this study indicates that when a single 8/2 mg strip is administered along with two 2 mg/0.5 mg strips to administer a total dose of 4 mg/1 mg buprenorphine/naloxone, the strips are almost equivalent to the reference product.

Overall summary from the four relative BA studies:

Overall the 2/0.5, 4/1 and 12/3 doses of the Suboxone (b) (4) are or are close to being bioequivalent to the tablets. The 8/2 mg dose of the Suboxone (b) (4) fails the BE test on both rate and extent of absorption for both the buprenorphine and opioid components; however the levels overall are only slightly higher than the tablets. In addition, the higher dose of 12/3 mg did demonstrate bioequivalence with respect to buprenorphine and narrowly missed the bioequivalence criteria for naloxone with respect to Cmax.

For the 2/0.5 and 8/2 doses, since the failure in BE for buprenorphine and naloxone is on the higher end, the therapeutic efficacy of the new product (strips) w.r.t buprenorphine and naloxone is not expected to be compromised. However, safety implications of the higher exposure with SL strips relative to the approved SL tablets (and the clinical trial formulation of aqueous ethanolic solution in the SL Tablets NDA) has to be considered.

It should be noted that the exposure of buprenorphine from Suboxone® sublingual film strips is much lower than that for the aqueous ethanolic solution of buprenorphine which was employed as the Clinical Trial formulation supporting the original NDAs 20-732 and 20-733. For the Suboxone® SL tablet NDA, the Division Director's Review of NDA and Basis for Action concluded that the relative bioavailability for the 8 mg/2 mg Suboxone® tablet relative to the solution was 0.66 (66%). Thus, relative to the approved Suboxone® tablet, the bioavailability of the solution was 1.52 (the reciprocal of 0.66 is 152%). Therefore, even though the bioavailability of buprenorphine from the buprenorphine and naloxone soluble film (Suboxone (b) (4) is somewhat higher than the tablets (overall, 20% higher than the tablets), it is still less than that observed for the aqueous ethanolic solution. So applying the same basis of acceptance of safety of higher buprenophine levels from Suboxone® tablets when compared to the ethanolic solution as employed in NDA # 20-733 (for Suboxone® tablets), the relative bioavailability for the 8 mg/2 mg Suboxone (b) (4) relative to the solution can be considered as 0.84 (0.66 + 20% of 0.66) which is still lower than the solution and therefore higher bioavailability of buprenorphine from Suboxone (b) (4) seems acceptable.

Naloxone plasma levels though higher when Suboxone® film strips were administered when compared to Suboxone® tablets, are still below those that can precipitate withdrawal symptoms and compromise efficacy and therefore are deemed not to be of concern.

2.3.2 *What is the significance of the observed higher naloxone levels from Suboxone (b) (4) relative to Suboxone® tablets with respect to precipitation of opioid withdrawal symptoms when the Suboxone (b) (4) are orally administered?*

After administration of the 8 mg / 2 mg Suboxone® SL film, naloxone Cmax and AUCinf values are approximately 41% and 21% higher respectively relative to 8 mg/ 2 mg Suboxone® SL tablets, potentially raising concerns of precipitation of opioid withdrawal symptoms when administered sublingually. However, based on the review of the clinical study RB-US-07-0001 submitted in this NDA, despite its sub-optimal design, (refer to the review by Dr. Celia Winchell for additional details), it did not appear that there was significant concern about precipitation of withdrawal when the strips were employed, lending additional support that the slightly higher naloxone exposure is not high enough to cause precipitation of withdrawal.

2.4 Analytical Section

2.4.1 *What bioanalytical methods are used to assess concentrations?*

Human EDTA plasma samples were analyzed by LC-MS/MS for buprenorphine, norbuprenorphine, and naloxone according to (b) (4) procedures ATM-994, Original and ATM-1189, Original. The method was validated for a range of 0.0125 to 5.00 ng/mL for buprenorphine and 0.0100 to 4.00 ng/mL for norbuprenorphine based on the analysis of 0.500 mL of plasma. Human plasma containing buprenorphine, norbuprenorphine, and the internal standards, (b) (4)

2.4.2 *Which metabolites have been selected for analysis and why?*

Plasma samples were analyzed for buprenorphine (active drug), norbuprenorphine (major metabolite of the active drug), and naloxone.

2.4.3 *For all moieties measured, is free, bound, or total measured? What is the basis for that decision, if any, and is it appropriate?*

Total plasma concentrations of buprenorphine, major metabolite norbuprenorphine and naloxone were measured.

2.4.4 *What are the lower and upper limits of quantification (LLOQ/ULOQ)?*

The methods used in this study utilized a range of 0.0125 to 2.50 ng/mL for buprenorphine and 0.0100 to 2.00 ng/mL for norbuprenorphine based on the analysis of 0.500 mL of plasma, and 0.500 to 250 pg/mL for naloxone based on the analysis of 1.00 mL of plasma.

2.4.5 *What are the accuracy, precision, and selectivity at these limits?*

Precision and accuracy were evaluated by treating the peak area of the calibration standards as unknowns and entering them into the derived equation for the least squares regression line to obtain "back-calculated" values. The CV and bias ranges are presented below:

Analyte	CV		Bias	
	From	To	From	To
Buprenorphine	1.4%	4.6%	-10.9%	6.4%
Norbuprenorphine	0.5%	5.9%	-3.4%	4.0%

Analyte	CV		Bias	
	From	To	From	To
Naloxone	0.8%	4.9%	-5.9%	4.0%

Precision and accuracy at the LLOQ were verified by analyzing six samples at the lowest standard concentration of 0.0125 ng/mL for buprenorphine and 0.0100 ng/mL for norbuprenorphine in each validation run. As shown below, intrarun CV was out of acceptance criteria at 20.3% for norbuprenorphine in Run 5. However, at least two-thirds of the overall LLOQ intrarun data and the overall LLOQ inter-run data met acceptance criteria.

Analyte	Intrarun				Inter-run	
	CV		Bias		CV	Bias
	From	To	From	To		
Buprenorphine	4.6%	13.2%	-15.2%	11.2%	14.3%	-1.6%
Norbuprenorphine	10.1%	20.3%	-13.0%	-0.1%	16.3%	-6.4%

Analyte	Intrarun				Inter-run	
	CV		Bias		CV	Bias
	From	To	From	To		
Naloxone	7.3%	18.3%	-10.2%	14.4%	15.4%	2.8%

Six samples from each QC pool (high, medium, and low) for buprenorphine and norbuprenorphine were processed in each validation run:

Analyte	Intrarun				Inter-run			
	CV		Bias		CV		Bias	
	From	To	From	To	From	To	From	To
Buprenorphine	1.2%	4.9%	-8.0%	8.5%	1.9%	5.9%	-7.2%	5.3%
Norbuprenorphine	1.5%	10.3%	-11.0%	4.4%	2.5%	7.9%	-7.3%	2.9%

Analyte	Intrarun				Inter-run			
	CV		Bias		CV		Bias	
	From	To	From	To	From	To	From	To
Naloxone	0.9%	12.9%	-3.3%	5.4%	2.5%	9.1%	-1.3%	3.0%

Six replicates of the very high dilution QC samples for buprenorphine and norbuprenorphine were diluted 10X prior to analysis:

Intrarun		
Analyte	CV	Bias
Buprenorphine	3.9%	-8.4%
Norbuprenorphine	1.9%	-2.0%

Intrarun		
Analyte	CV	Bias
Naloxone	1.1%	0.0%

2.4.6 *What was the QC sample plan?*

Qualifying QC samples from high, medium, and low pools were processed along with each study sample run. High, medium, and low QC samples were prepared at 3.75, 0.900, and 0.0375 ng/mL for buprenorphine, and 3.00, 0.720, and 0.0300 ng/mL for norbuprenorphine. High, medium, and low QC samples were prepared at 200, 50.0, and 1.50 pg/mL for naloxone. Dilution QCs were included in the sample runs in which samples requiring a similar dilution scheme were analyzed. Sample runs were valid when

at least two-thirds of the qualifying QC samples were within ±15% of their theoretical values and at least 50% of the QCs at each level met these criteria. The calculated values were recorded for monitoring of the precision and accuracy of the assay.

2.4.7 *What is the sample stability under the conditions used in the study (long-term, freeze-thaw, sample-handling, sample transport, autosampler)?*

Short-Term Stability Studies: Extract stability in human plasma was performed. A set of triplicate samples was extracted and injected; the extracts were then reinjected after approximately 145 hours at room temperature. All of the stability samples in each pool were within ±15% of their theoretical concentrations.

Long-Term Stability Studies: Human plasma pools were fortified with the analytes, divided into individual aliquots, and stored at approximately -20 ºC. Subsequent analysis of these samples against a freshly prepared calibration curve, provided insight into the extended stability of the analytes. All of the stability samples in each pool were within ±15% of their theoretical concentrations after 130 days of storage.

3.0 Labeling comments

Following are the highlights of the labeling comments at the time of the submission of this review. Additional changes may follow in the course of the labeling meetings. This section only highlights the new additions and changes proposed to the approved Suboxone® label (RLD) for this product.

(Reviewer suggested changes: ~~Strikeout text~~ should be removed from labeling and underlined text should be added to labeling)

2 DOSAGE AND ADMINISTRATION

(b) (4)

2.1 Maintenance

(b) (4)

7 DRUG INTERACTIONS

7.1 Cytochrome P-450 3A4 (CYP3A4) Inhibitors and Inducers

(b) (4)

12 CLINICAL PHARMACOLOGY

12.3 Pharmacokinetics

(b) (4)

Metabolism:

(b) (4)

Drug-drug interactions:

CYP-3A4 Inhibitors and Inducers:

4.0 Appendices

4.1 Individual Study Reviews

4.1.1 Study 20-250-SA: A Single-Dose, 3-Period, 3-Treatment, 3-Way Crossover Study of a 2 mg/0.5 mg Buprenorphine/Naloxone Film Formulation versus Suboxone® under Fasting Conditions

Study Design:	Single-dose, open-label, randomized, 3-period, 3-treatment, 3-way crossover study in which healthy adult subjects (under naltrexone block) received 3 separate single-dose administrations of buprenorphine/naloxone 2 mg/0.5 mg, following an overnight fast of at least 10 hours.
Objectives:	To compare the rate and extent of both sublingual and buccal absorption of an investigational formulation of buprenorphine/naloxone 2 mg/0.5 mg sublingual film, manufactured by (b) (4) for Reckitt Benckiser Pharmaceuticals Inc., to an equivalent sublingual dose of the commercially available reference product, Suboxone tablets, manufactured by Reckitt Benckiser Pharmaceuticals Inc., following an overnight fast of at least 10 hours.
Protocol Number:	20-250-SA
Study Center(s):	(b) (4)
Study Period (days):	34
Number of Subjects enrolled:	45 [7 (16%) Non-Hispanic/Latino Black or African American, 2 (4%) Hispanic/Latino Black or African American, 17 (38%) Non-Hispanic/Latino White, 17 (38%) Hispanic/Latino White, and 2 (4%) Hispanic/Latino American Indian or Alaska Native subjects]
Number of Subjects analyzed:	42
Diagnosis and Main Criteria for Inclusion:	Healthy adult male or non-pregnant, non-breastfeeding female volunteers, 18-45 years of age (inclusive), BMI between 18 and 30 kg/m2 (inclusive) and weighed a minimum of 50 kg (110 lbs).
Test Formulations:	Treatment A: Buprenorphine/naloxone (1 x 2 mg/0.5 mg sublingual film strip) Lot H07DW101-288 Mfg date: 10/17/2007 Treatment C: Buprenorphine/naloxone (1 x 2 mg/0.5 mg buccal film strip) Lot H07DW101-288 Mfg date: 10/17/2007

Reference Product:	Treatment B: Suboxone® (1 x 2 mg/0.5 mg sublingual tablet) Lot # 723403 Expiration Date: 01 Feb 09
Study Phase:	Phase I
Study Initiation Date:	13 November 2007
Study Completion Date:	17 December 2007
Principal Investigator:	(b) (4)

Bioanalytical validation:

Human EDTA plasma samples were analyzed for buprenorphine, norbuprenorphine, and naloxone according to (b) (4) procedures ATM-994, Original and ATM-1189, Original. The assay validations were finalized and reported under (b) (4) for buprenorphine and norbuprenorphine and 1001815 for naloxone. The methods used in this study utilized a range of 0.0125 to 2.50 ng/mL for buprenorphine and 0.0100 to 2.00 ng/mL for norbuprenorphine based on the analysis of 0.500 mL of plasma, and 0.500 to 250 pg/mL for naloxone based on the analysis of 1.00 mL of plasma.

Drug Concentration Measurements:

Blood (plasma) pharmacokinetic characteristics were assessed after each dose of study medication. Blood samples were drawn at 0 (pre-dose) and at 0.25, 0.5, 0.75, 1, 1.25, 1.5, 2, 3, 4, 6, 8, 10, 12, 24, 36, 48, 72, 96, 120, and 144 hours after dose administration.

Table 1: PK Parameters of Buprenorphine, Norbuprenorphine, and Naloxone after Sublingual Administration of Suboxone Tablets and Sublingual and Buccal Administration of Buprenorphine and Naloxone Soluble Film

	Buprenorphine			Norbuprenorphine			Naloxone Note: Conc. values in pg		
	SL tab	SL strip	BL strip	SL tab	SL strip	BL strip	SL tab	SL strip	BL strip
T_{max} [h]	1.55 (0.53)	1.72 (0.60)	1.68 (0.54)	1.97 (1.91)	2.26 (2.03)	1.92 (1.50)	0.80 (0.26)	0.77 (0.26)	0.81 (0.17)
C_{max} [ng/mL]	0.780 (0.323)	0.947 (0.374)	0.974 (0.364)	0.30 (0.13)	0.312 (0.140)	0.294 (0.145)	51.3 (21.1)	54.1 (23.0)	58.3 (26.9)
AUC_{last} [h x ng/mL]	6.789 (2.536)	7.820 (2.706)	7.975 (2.754)	11.82 (4.24)	11.83 (4.424)	12.07 (4.914)	128.6 (48.76)	128.6 (43.20)	145.2 (57.89)
AUC_{inf} [h x ng/mL]	7.651 (2.650)	8.654 (2.854)	8.682 (2.832)	13.59 (4.89)	14.52 (5.776)	14.01 (5.619)	124.2 (52.49)	137.3 (43.10)	153.4 (60.57)

Mean ± SD buprenorphine Cmax values are 0.780 ± 0.323 ng/mL (Suboxone), 0.947 ± 0.374 ng/mL (SL buprenorphine and naloxone soluble film), and 0.974 ± 0.364 ng/mL (buccal buprenorphine and naloxone soluble film) reached at 1.55 ± 0.53 h, 1.72 ± 0.60 h, and 1.68 ± 0.54 h, respectively. Concentrations declined with apparent t1/2 values of 30.75 ± 15.04 h, 33.41 ± 13.01 h, and 31.54 ± 11.26 h, respectively. Absorption of naloxone after administration of SL and buccal buprenorphine and naloxone soluble film are similar, with Cmax values of 54.1 ± 23.0 pg/mL and 58.3 ± 26.9 pg/mL reached at 0.77 ± 0.26 h and 0.81 ± 0.17 h, respectively. Concentrations declined with an apparent t1/2 value of 5.00 ± 5.52 h and 4.74 ± 3.96 h, respectively. The mean maximum plasma concentration of naloxone is lower after Suboxone administration, with the mean maximum concentration C_{max} value of 51.3 ± 21.1 pg/mL observed at 0.80 ± 0.26 h post-treatment. Concentrations of naloxone declined with an apparent t1/2 value of 5.15 ± 5.28 h.

Table 2: Statistical Analysis of the Log-Transformed Systemic Exposure Parameters Comparing Sublingual and Buccal Administration of Buprenorphine and Naloxone Soluble Film to Sublingual Administration of Suboxone Tablets

	Buprenorphine			Norbuprenorphine			Naloxone		
	SL tab v/s SL strip	SL tab v/s BL strip	SL strip v/s BL strip	SL tab v/s SL strip	SL tab v/s BL strip	SL strip v/s BL strip	SL tab v/s SL strip	SL tab v/s BL strip	SL strip v/s BL strip
Cmax	121.66 (112.62-131.43)	125.31 (113.87-137.90)	103.50 (95.56-112.11)	105.41 (99.33-111.85)	102.24 (92.72-112.74)	95.77 (87.44-104.89)	104.01 (95.79-112.93)	110.71 (99.77-122.85)	105.95 (96.68-116.10)
AUC last	116.40 (108.70-124.63)	119.38 (109.22-130.49)	101.73 (95.08-108.84)	99.67 (93.31-106.45)	103.94 (95.01-113.71)	102.38 (95.05-110.27)	101.84 (94.84-109.36)	113.11 (102.86-124.39)	109.81 (101.04-119.34)
AUC inf	114.22 (106.65-122.32)	114.85 (105.57-124.95)	100.69 (94.24-107.58)	105.96 (97.93-114.66)	104.69 (95.67-114.55)	98.19 (90.30-106.77)	107.28 (96.98-118.69)	116.49 (104.89-129.38)	104.79 (96.22-114.13)

PK summary:

1. SL tabs v/s SL strips: The upper CI limits for buprenorphine are above 125% for Cmax (131.43) but within 80-125% for AUClast and AUCinf for SL strips indicating that the SL strips are **not equivalent w.r.t the rate of absorption but are equivalent w.r.t extent of absorption of buprenorphine** to the reference product, SL tabs. Since the failure in BE is on the higher side (plasma level of buprenorphine is higher when the test product is administered as compared to when the reference product is administered), the therapeutic efficacy of the new product (strips) w.r.t buprenorphine is not expected to be compromised. The two treatments (SL tabs and SL strips) are **equivalent w.r.t rate and extent of absorption of naloxone and norbuprenorphine** (based on Cmax, AUClast and AUCinf).

2. SL tabs v/s BL strips: The upper CI limits for buprenorphine are above 125% for Cmax (137.90) and AUClast (130.49) for BL strips indicating that the BL strips are **not equivalent w.r.t rate and extent of absorption of buprenorphine** to the reference product, SL tabs. The upper CI limits for naloxone are within the 80-125% range for Cmax and AUClast and above 125% for AUCinf (129.38) for SL strips indicating that the SL strips are **equivalent w.r.t rate but not equivalent w.r.t extent of absorption of naloxone** to the reference product, SL tabs. The two treatments (SL tabs and BL strips) are **only equivalent w.r.t rate and extent of absorption norbuprenorphine** (based on Cmax, AUClast and AUCinf).

3. SL strips v/s BL strips: When SL route is compared with the BL route for buprenorphine plasma concentrations, the 90% CIs for Cmax, AUClast, and AUCinf are all within the limits of 80% to 125% indicating that the strips may be considered **equivalent w.r.t rate and extent of absorption of buprenorphine, naloxone and norbuprenorphine** when administered by either route.

4.1.2 Study 20-273-SA: A Single-Dose, 3-Period, 3-Treatment, 3-Way Crossover Study of a 8 mg/2 mg Buprenorphine/Naloxone Film Formulation versus Suboxone® under Fasting Conditions

Study Design:	Single-dose, open-label, randomized, 3-period, 3-treatment, 3-way crossover study in which healthy adult subjects (under naltrexone block) received 3 separate single-dose administrations of buprenorphine/naloxone 8 mg/2 mg, following an overnight fast of at least 10 hours.
Objectives:	To compare the rate and extent of both sublingual and buccal absorption of an investigational formulation of buprenorphine/naloxone 8 mg/2 mg sublingual film, manufactured by (b) (4) for Reckitt Benckiser Pharmaceuticals Inc., to an equivalent sublingual dose of the commercially available reference product, Suboxone tablets, manufactured by Reckitt Benckiser Pharmaceuticals Inc., following an overnight fast of at least 10 hours.
Protocol Number:	20-273-SA
Study Center(s):	(b) (4)
Study Period (days):	34
Number of Subjects enrolled:	47
Number of Subjects analyzed:	44 [9 (19.15%) Non-Hispanic/Latino Black or African American, 20 (42.55%) Non-Hispanic/Latino White, 16 (34.04%) Hispanic/Latino White, 1 (2.13%) Non-Hispanic/Latino Asian, and 1 (2.13%) Hispanic/Latino American Indian or Alaska Native subjects]
Diagnosis and Main Criteria for Inclusion:	Healthy adult male or non-pregnant, non-breastfeeding female volunteers, 18-45 years of age (inclusive), BMI between 18

	and 30 kg/m2 (inclusive) and weighed a minimum of 50 kg (110 lbs).
Test Formulations:	Treatment B: buprenorphine/naloxone (1 x 8 mg/2 mg film - sublingual) Lot # A08EJ103-025 Mfg Date: 01/28/08 Treatment C: buprenorphine/naloxone (1 x 8 mg/2 mg film - buccal) Lot # A08EJ103-025 Mfg Date: 01/28/08
Reference Product:	Treatment A: Suboxone® (1 x 8 mg/2 mg tablet - sublingual) Lot # 731901-4 Exp. Date: 05/01/09
Study Phase:	Phase I
Study Initiation Date:	11 February 2008
Study Completion Date:	16 March 2008
Principal Investigator:	(b) (4)

Bioanalytical validation:

EDTA plasma samples were analyzed for buprenorphine and norbuprenorphine according to (b) (4) procedure ATM-1269, Original. EDTA plasma samples were analyzed for naloxone according to (b) (4) procedure ATM-1268, Revision 1. The assay validation was finalized and reported under (b) (4) for buprenorphine and norbuprenorphine and 1001815 for naloxone. The methods used in this study were validated for a range of 0.025 to 5.00 ng/mL for buprenorphine, 0.020 to 4.00 ng/mL for norbuprenorphine, and 1.00 to 250 pg/mL for naloxone, based on the analysis of 0.500 mL of plasma for buprenorphine and norbuprenorphine and 1.00 mL of plasma for naloxone.

For precision and accuracy, please refer to Individual study review 1 for the 2 mg/ 0.5 mg SL strips.

Drug Concentration Measurements:

Blood (plasma) pharmacokinetic characteristics were assessed after each dose of study medication. Blood samples were drawn at 0 (pre-dose) and at 0.25, 0.5, 0.75, 1, 1.25, 1.5, 2, 3, 4, 6, 8, 10, 12, 24, 36, 48, 72, 96, 120, and 144 hours after dose administration.

Table 1: Pharmacokinetic Parameters of Buprenorphine, Norbuprenorphine, and Naloxone after Sublingual Administration of Suboxone® Tablets and Suboxone [redacted] (8/2 mg)

	Buprenorphine			Norbuprenorphine			Naloxone Note: Conc. values in pg		
	SL tab	SL strip	BL strip	SL tab	SL strip	BL strip	SL tab	SL strip	BL strip
T_{max} [h]	1.48 (0.56)	1.53 (0.66)	1.67 (0.64)	1.70 (1.93)	2.17 (2.63)	2.75 (5.14)	0.80 (0.22)	0.81 (0.19)	0.78 (0.24)
C_{max} [ng/mL]	2.58 (1.10)	3.37 (1.80)	3.44 (1.51)	1.35 (0.977)	1.40 (1.08)	1.20 (0.647)	135 (57.3)	193 (91.2)	214 (94.0)
AUC_{last} [h x ng/mL]	23.65 (9.196)	28.74 (12.95)	29.20 (10.66)	46.77 (26.64)	48.33 (32.81)	44.56 (24.31)	347.4 (124.2)	458.7 (192.7)	504.8 (202.8)
AUC_{inf} [h x ng/mL]	6.97 (3.40)	6.39 (4.21)	6.21 (2.80)	52.84 (31.15)	54.91 (36.01)	50.82 (28.46)	374.6 (132.8)	480.8 (201.0)	545.5 (208.7)

Mean ± SD buprenorphine Cmax values are 2.58 ± 1.10 ng/mL (Suboxone), 3.37 ± 1.80 ng/mL (SL buprenorphine and naloxone soluble film), and 3.44 ± 1.51 ng/mL (buccal buprenorphine and naloxone soluble film) reached at 1.48 ± 0.56 h, 1.53 ± 0.66 h, and 1.67 ± 0.64 h, respectively. Concentrations declined with apparent t1/2 values of 31.94 ± 15.27 h, 32.82 ± 9.81 h, and 34.28 ± 12.11 h, respectively. Absorption of naloxone after treatment with SL and buccal buprenorphine and naloxone soluble film is similar, with Cmax values of 193 ± 91.2 pg/mL and 214 ± 94.0 pg/mL reached at 0.81 ± 0.19 h and 0.78±0.24 h, respectively. Concentrations declined with apparent t1/2 values of 6.25 ± 3.14 h and 6.96 ± 8.41 h, respectively. The mean maximum plasma concentration of naloxone is lower after Suboxone, with the mean maximum concentration Cmax value of 135.0 ± 57.3 pg/mL observed at 0.80 ± 0.22 h post-treatment. Concentrations of naloxone declined with an apparent t1/2 value of 7.65 ± 3.99 h.

Table 2: Statistical Analysis of the Log-Transformed Systemic Exposure Parameters Comparing Sublingual Administration of Suboxone® Tablets and Suboxone [redacted] (8/2 mg)

	Buprenorphine			Norbuprenorphine			Naloxone		
	SL tab v/s SL strip	SL tab v/s BL strip	SL strip v/s BL strip	SL tab v/s SL strip	SL tab v/s BL strip	SL strip v/s BL strip	SL tab v/s SL strip	SL tab v/s BL strip	SL strip v/s BL strip
Cmax	127.80 (116.11-140.66)	133.57 (122.03-146.19)	104.34 (96.14-113.24)	101.78 (93.26-111.09)	93.29 (86.26-100.89)	91.58 (82.97-101.09)	141.04 (126.87-156.80)	154.35 (140.24-169.87)	109.62 (98.80-121.62)
AUC last	120.15 (110.24-130.96)	124.92 (116.36-134.10)	103.95 (96.77-111.67)	101.76 (94.61-109.46)	97.51 (90.76-104.76)	96.08 (87.84-105.11)	130.04 (119.51-141.50)	143.24 (132.87-154.42)	110.49 (100.48-121.49)
AUC inf	119.51 (110.28-129.51)	123.87 (115.67-132.65)	103.65 (96.96-110.80)	101.06 (93.87-108.79)	96.69 (89.01-105.04)	96.03 (87.60-105.28)	121.19 (108.44-135.44)	136.76 (124.99-149.64)	107.65 (96.72-119.82)

PK summary:

4. SL tabs v/s SL strips: The upper CI limits for buprenorphine and naloxone are above 125% for all the three PK parameters measured Cmax, AUClast and AUCinf for SL strips indicating that the SL strips are **not equivalent w.r.t the rate and extent of absorption of buprenorphine or naloxone** to the reference product, SL tabs. Since the failure in BE is on the upper side (plasma levels of buprenorphine and naloxone are higher when the test product is administered as compared to when the reference product is administered), the therapeutic efficacy of the new product (strips) w.r.t buprenorphine or naloxone is not expected to be compromised. The two treatments (SL tabs and SL strips) are **only equivalent w.r.t rate and extent of absorption of norbuprenorphine** (based on Cmax, AUClast and AUCinf). Overall, the SL film treatments exhibited enhanced absorption of buprenorphine and naloxone relative to Suboxone tablets and are **not bioequivalent to the reference product**. After administration of the SL film, buprenorphine Cmax and AUCinf values are approximately 28% and 20% higher than those produced by Suboxone tablets. Naloxone Cmax and AUCinf values are approximately 41% and 21% higher, respectively.

5. SL tabs v/s BL strips: The upper CI limits for buprenorphine and naloxone are above 125% for all the three PK parameters measured Cmax, AUClast and AUCinf for SL strips indicating that the SL strips are **not equivalent w.r.t the rate and extent of absorption of buprenorphine or naloxone** to the reference product, SL tabs. The two treatments (SL tabs and BL strips) are **only equivalent w.r.t rate and extent of absorption of norbuprenorphine** (based on Cmax, AUClast and AUCinf). Overall, the BL film treatments exhibited enhanced absorption of buprenorphine and naloxone relative to Suboxone tablets and are **not bioequivalent to the reference product**. After buccal administration, buprenorphine Cmax and AUCinf values are approximately 34% and 24% higher than those produced by Suboxone tablets and naloxone Cmax and AUCinf values are approximately 54% and 37% higher, respectively.

6. SL strips v/s BL strips: When SL route is compared with the BL route for buprenorphine, naloxone and norbuprenorphine plasma concentrations, the 90% CIs for Cmax, AUClast, and AUCinf are all within the limits of 80% to 125% indicating that the strips may be considered **bioequivalent w.r.t rate and formation of buprenorphine, naloxone** and **norbuprenorphine** when administered by either route.

4.1.3 Study 20-272-SA: A Single-Dose, 3-Period, 3-Treatment, 3-Way Crossover Study of Two 2 mg/0.5 mg (4 mg/1 mg) Buprenorphine/Naloxone Film Formulations versus Suboxone® under Fasting Conditions

Study Design:	Single-dose, open-label, randomized, 3-period, 3-treatment, 3-way crossover study in which healthy adult subjects (under naltrexone block) received 3 separate single-dose administrations of buprenorphine/naloxone 2*2 mg/0.5 mg, following an overnight fast of at least 10 hours.
Objectives:	To compare the rate and extent of both sublingual and buccal absorption of an investigational formulation of buprenorphine/naloxone film dosage: 4 mg/1 mg; administered as two, 2 mg/0.5 mg film strips, manufactured by (b) (4) for Reckitt Benckiser Pharmaceuticals Inc., to an equivalent sublingual dose of the commercially available reference product, Suboxone tablets, manufactured by Reckitt Benckiser Pharmaceuticals Inc., following an overnight fast of at least 10 hours.
Protocol Number:	20-272-SA
Study Center(s):	(b) (4)
Study Period (days):	34
Number of Subjects enrolled:	48 [9 (18.75%) Non-Hispanic/Latino Black or African American, 13 (27.08%) Non-Hispanic/Latino White, 20 (41.67%) Hispanic/Latino White, 2 (4.17%) Non-Hispanic/Latino Asian, 1 (2.08%) Non-Hispanic/Latino American Indian or Alaska Native, and 3 (6.25%) Hispanic/Latino American Indian or Alaska Native subjects]
Number of Subjects analyzed:	42
Diagnosis and Main Criteria for Inclusion:	Healthy adult male or non-pregnant, non-breastfeeding female volunteers, 18-45 years of age (inclusive), BMI between 18 and 30 kg/m2 (inclusive) and weighed a minimum of 50 kg (110 lbs).
Test Formulations:	Treatment A Buprenorphine/naloxone 2 x 2 mg/0.5 mg film (sublingual) Lot # A08DW101-024 Mfg Date: 01/24/08 – 01/25/08 Treatment C Buprenorphine/naloxone 2 x 2 mg/0.5 mg film (buccal) Lot # A08DW101-024 Mfg Date: 01/24/08 – 01/25/08
Reference Product:	Treatment B Suboxone® 2 x 2 mg/0.5 mg tablet (sublingual) Lot # 730901

	Expiration Date: 04/01/09
Study Phase:	Phase I
Study Initiation Date:	4 February 2008
Study Completion Date:	9 March 2008
Principal Investigator:	(b) (4)

Bioanalytical validation:

Human EDTA plasma samples were analyzed for buprenorphine and norbuprenorphine according to (b) (4) procedure ATM-1269, Original. The assay validation was finalized and reported under (b) (4). The method used in this study utilized a range of 0.0250 to 5.00 ng/mL for buprenorphine and 0.0200 to 4.00 ng/mL for norbuprenorphine, based on the analysis of 0.500 mL of human plasma. Human EDTA plasma samples were analyzed for naloxone according to (b) (4) procedure ATM-1268, Revision 1. The assay validation was finalized and reported under (b) (4). The method used in this study utilized a range of 1.00 to 250 pg/mL for naloxone, based on the analysis of 1.00 mL of human plasma.

For precision and accuracy, please refer to individual study review 1 for the 2 mg/ 0.5 mg SL strips.

Drug Concentration Measurements:

Blood (plasma) pharmacokinetic characteristics were assessed after each dose of study medication. Blood samples were drawn at 0 (pre-dose) and at 0.25, 0.5, 0.75, 1, 1.25, 1.5, 2, 3, 4, 6, 8, 10, 12, 24, 36, 48, 72, 96, 120, and 144 hours after dose administration.

Table 1: Pharmacokinetic Parameters of Buprenorphine, Norbuprenorphine, and Naloxone after Sublingual Administration of Suboxone® Tablets and Suboxone (b) (4) (2 of 2/0.5 mg)

	Buprenorphine			Norbuprenorphine			Naloxone Note: Conc. values in pg		
	SL tab	SL strip	BL strip	SL tab	SL strip	BL strip	SL tab	SL strip	BL strip
T_{max} [h]	1.65 (0.74)	1.56 (0.65)	1.76 (0.66)	2.23 (2.15)	3.30 (7.67)	1.65 (1.41)	0.80 (0.25)	0.82 (0.23)	0.86 (0.29)
C_{max} [ng/mL]	1.34 (0.565)	1.40 (0.687)	1.67 (0.580)	0.623 (0.334)	0.617 (0.311)	0.580 (0.214)	70.8 (34.7)	69.8 (37.8)	83.0 (37.7)
AUC_{last} [h x ng/mL]	11.24 (4.637)	12.37 (5.912)	13.95 (5.275)	18.91 (9.187)	20.94 (9.229)	18.93 (6.440)	186.7 (97.96)	187.2 (96.67)	224.9 (88.76)
AUC_{inf} [h x ng/mL]	12.46 (4.635)	13.71 (5.875)	15.15 (5.440)	22.53 (9.986)	23.73 (10.60)	21.13 (7.634)	204.6 (114.9)	204.3 (108.4)	249.6 (94.95)

Mean ± SD buprenorphine Cmax values were 1.34 ± 0.565 ng/mL (Suboxone), 1.40 ± 0.687 ng/mL (SL buprenorphine and naloxone soluble film), and 1.67 ± 0.580 ng/mL (buccal buprenorphine and naloxone soluble film) reached at 1.65 ± 0.74 h, 1.56 ± 0.65 h, and 1.76 ± 0.66 h, respectively. Concentrations declined with t1/2 values of 24.42 ± 12.50 h, 24.30 ± 11.03 h, and 23.69 ± 10.39 h, respectively. Absorption of naloxone after treatment was similar with SL buprenorphine and naloxone and only slightly higher with buccal buprenorphine and naloxone soluble film, with Cmax values of 69.8 ± 37.8 pg/mL and 83.0 ± 37.7 pg/mL reached at 0.82 ± 0.23 h and 0.86 ± 0.29 h, respectively, relative to Suboxone tablets. Concentrations declined with apparent t1/2 values of 3.91 ± 3.37 h and 3.22 ± 1.88 h, respectively. The mean maximum plasma concentration of naloxone was lower after Suboxone, with the mean maximum concentration Cmax value of 70.8 ± 34.7 pg/mL observed at 0.80 ± 0.25 h post-treatment. Concentrations of naloxone declined with an apparent t1/2 value of 3.18 ± 2.09 h.

Table 2: Statistical Analysis of the Log-Transformed Systemic Exposure Parameters Comparing Sublingual Administration of Suboxone® Tablets and Suboxone (b) (4) (2 of 2/0.5 mg)

	Buprenorphine			Norbuprenorphine			Naloxone		
	SL tab v/s SL strip	SL tab v/s BL strip	SL strip v/s BL strip	SL tab v/s SL strip	SL tab v/s BL strip	SL strip v/s BL strip	SL tab v/s SL strip	SL tab v/s BL strip	SL strip v/s BL strip
Cmax	104.61 (94.58-115.69)	122.53 (109.55-137.04)	104.34 (96.14-113.24)	104.48 (93.74-116.44)	99.92 (87.86-113.63)	91.58 (82.97-101.09)	100.86 (90.95-111.84)	120.13 (106.91-134.98)	109.62 (98.80-121.62)
AUC last	108.64 (99.89-118.17)	123.07 (111.59-135.74)	103.95 (96.77-111.67)	115.66 (103.76-128.93)	105.29 (94.23-117.64)	96.08 (87.84-105.11)	99.93 (91.31-109.36)	123.78 (113.30-135.22)	110.49 (100.48-121.49)
AUC inf	104.55 (96.42-113.37)	117.84 (108.10-128.46)	103.65 (96.96-110.80)	106.07 (95.84-117.38)	100.42 (91.16-11062)	96.03 (87.60-105.28)	106.48 (93.26-121.58)	118.62 (105.59-133.26)	107.65 (96.72-119.82)

PK summary:

7. SL tabs v/s SL strips: The upper CI limits for buprenorphine **are equivalent w.r.t rate and extent of absorption of buprenorphine, naloxone and norbuprenorphine** (based on Cmax, AUClast and AUCinf) to the reference product, SL tabs. Overall, this study indicates that when two 2 mg/0.5 mg buprenorphine/naloxone strips are administered together (as 4 mg/1 mg), they **are bioequivalent to the reference product**, however, when the 2/0.5 mg strip is administered as a 2 mg dose (a single strip of 2/0.5 mg in Study 20-250-SA), it is not bioequivalent to the reference product.

8. SL tabs v/s BL strips: The upper 90% CI limits for buprenorphine and naloxone are above 125% for all the three PK parameters measured Cmax, AUClast and AUCinf for BL strips indicating that the BL strips **are not equivalent w.r.t rate and extent of absorption of buprenorphine and naloxone** to the reference

product, SL tabs. Since the failure in BE is on the upper side (plasma levels are higher when the test product is administered as compared to when the reference product is administered), the therapeutic efficacy of the new product (strips) w.r.t buprenorphine or naloxone is not expected to be compromised. The two treatments (SL tabs and BL strips) **are only equivalent w.r.t rate and extent of absorption of norbuprenorphine** (based on Cmax, AUClast and AUCinf).

9. SL strips v/s BL strips: When sublingual route is compared with the buccal route for buprenorphine and naloxone plasma concentrations, the upper 90% CI limits for buprenorphine and naloxone are above 125% for all the three PK parameters measured Cmax, AUClast and AUCinf for BL strips indicating that the BL strips **are not equivalent w.r.t rate and extent of absorption of buprenorphine and naloxone** when compared to the SL route. When sublingual route is compared with the buccal route for norbuprenorphine plasma concentrations, the 90% confidence intervals for Cmax, AUClast, and AUCinf are all within the limits of 80% to 125% indicating that the strips may be considered **equivalent w.r.t rate and extent of absorption of norbuprenorphine** when administered by the SL or the BL route.

4.1.4 Study 20-B20-AU: A Single-Dose, 3-Period, 3-Treatment, 3-Way Crossover Study of 12 mg/3 mg Buprenorphine/Naloxone Film Formulations versus Suboxone® under Fasting Conditions

Study Design:	Single-dose, open-label, randomized, 3-period, 3-treatment, 3-way crossover study in which healthy adult subjects (under naltrexone block) received 3 separate single-dose administrations of buprenorphine/naloxone 12 mg/3 mg, following an overnight fast of at least 10 hours.
Objectives:	To compare the rate and extent of both sublingual and buccal absorption of an investigational formulation of buprenorphine/naloxone 12 mg/3 mg film strip, manufactured by (b) (4) for Reckitt Benckiser Pharmaceuticals Inc., to an equivalent sublingual dose of the commercially available reference product, Suboxone (one 8 mg/2 mg plus two 2 mg/0.5 mg tablets), manufactured by Reckitt Benckiser Pharmaceuticals Inc., following an overnight fast of at least 10 hours.
Protocol Number:	20-B20-AU
Study Center(s):	(b) (4)
Study Period (days):	35
Number of Subjects enrolled:	48 [12 (25.00%) Non-Hispanic/Latino Black or African American, 21 (43.75%) Non-Hispanic/Latino White, 9 (18.75%) Hispanic/Latino White, 2 (4.17%) Non-Hispanic/Latino Asian, 3 (6.25%) Hispanic/Latino American Indian or Alaska Native, 1 (2.08%) Hispanic/Latino Native

	Hawaiian or other Pacific Islander subjects]
Number of Subjects analyzed:	44
Diagnosis and Main Criteria for Inclusion:	Healthy adult male or non-pregnant, non-breastfeeding female volunteers, 18-45 years of age (inclusive), BMI between 18 and 30 kg/m2 (inclusive) and weighed a minimum of 50 kg (110 lbs).
Test Formulations:	Treatment B Buprenorphine/Naloxone (12 mg/3 mg film strip) administered sublingually Lot # A08EY101-028 Expiration April 12, 2008 Treatment C Buprenorphine/Naloxone (12 mg/3 mg film strip) administered buccally Lot # A08EY101-028 Expiration April 12, 2008
Reference Product:	Treatment A Suboxone (12 mg/3 mg [1 x 8 mg/2 mg + 2 x 2 mg/ 0.5 mg] tablets) administered sublingually Lot # 730902 Expiration April 01, 2009
Study Phase:	Phase I
Study Initiation Date:	17 February 2008
Study Completion Date:	22 March 2008
Principal Investigator:	(b) (4)

Bioanalytical validation:

Human EDTA plasma samples were analyzed for buprenorphine, norbuprenorphine, and naloxone according to (b) (4) procedures ATM-1267, Revision 1, and ATM-1268, Revision 1. The assay validations were finalized and reported under (b) (4) and 1001815, respectively. The methods used in this study were validated for a range of 0.0250 to 10.0 ng/mL for buprenorphine and 0.0200 to 8.00 ng/mL for norbuprenorphine, based on the analysis of 0.500 mL of plasma, and 1.0 to 250 pg/mL for naloxone, based on the analysis of 1.00 mL of plasma.

For precision and accuracy, please refer to individual study review 1 for the 2 mg/ 0.5 mg SL strips.

Drug Concentration Measurements:

Blood (plasma) pharmacokinetic characteristics were assessed after each dose of study medication. Blood samples were drawn at 0 (pre-dose) and at 0.25, 0.5, 0.75, 1, 1.25, 1.5, 2, 3, 4, 6, 8, 10, 12, 24, 36, 48, 72, 96, 120, and 144 hours after dose administration.

Table 1: Pharmacokinetic Parameters of Buprenorphine, Norbuprenorphine, and Naloxone after Sublingual Administration of Suboxone® Tablets (1 of 8/2 mg and 2 of 2/0.5 mg Tablets) and Suboxone (b) (4) (12/3 mg)

	Buprenorphine			Norbuprenorphine			Naloxone Note: Conc. values in pg		
	SL tab	SL strip	BL strip	SL tab	SL strip	BL strip	SL tab	SL strip	BL strip
T_{max} [h]	1.35 (0.48)	1.51 (0.56)	1.65 (0.57)	2.09 (3.71)	1.70 (1.65)	1.91 (2.13)	0.82 (0.26)	0.85 (0.24)	0.93 (0.27)
C_{max} [ng/mL]	3.12 (1.33)	4.55 (2.50)	4.73 (2.21)	2.44 (1.50)	2.37 (1.87)	2.15 (1.27)	152 (92.8)	238 (144)	289 (212)
AUC_{last} [h x ng/mL]	32.00 (12.06)	40.13 (14.34)	41.93 (13.74)	68.03 (28.16)	66.96 (28.29)	69.16 (30.70)	432.0 (201.5)	629.7 (303.1)	718.2 (373.0)
AUC_{inf} [h x ng/mL]	33.77 (12.52)	42.06 (14.64)	44.15 (14.36)	74.79 (29.09)	71.77 (29.38)	76.39 (34.31)	469.3 (209.3)	653.1 (308.5)	761.7 (368.5)

Mean ± SD buprenorphine Cmax values are 3.12 ± 1.33 ng/mL (Suboxone), 4.55 ± 2.50 ng/mL (SL buprenorphine and naloxone), and 4.73 ± 2.21 ng/mL (buccal buprenorphine and naloxone) reached at 1.35 ± 0.48 h, 1.51 ± 0.56 h, and 1.65 ± 0.57 h, respectively. Concentrations declined with apparent t1/2 values of 33.67 ± 8.58 h, 34.66 ± 9.16 h, and 38.36 ± 14.01 h, respectively. Absorption of naloxone after SL and buccal buprenorphine and naloxone are similar, with maximum plasma concentrations of 238 ± 144 pg/mL and 289 ± 212 pg/mL reached at 0.85 ± 0.24 h and 0.93 ± 0.27 h, respectively. Concentrations declined with apparent t1/2 values of 11.91 ± 13.80 h and 9.47 ± 4.30 h, respectively. The mean maximum plasma concentration of naloxone is lower after Suboxone; mean maximum naloxone plasma concentrations of 152 ± 92.8 pg/mL are observed at 0.82 ± 0.26 h post-treatment. Concentrations of naloxone declined with an apparent t1/2 value of 8.56 ± 5.97 h.

Table 2: Statistical Analysis of the Log-Transformed Systemic Exposure Parameters Comparing Sublingual Administration of Suboxone® Tablets (1 of 8/2 mg and 2 of 2/0.5 mg Tablets) and Suboxone [redacted] (12/3 mg)

	Buprenorphine			Norbuprenorphine			Naloxone		
	SL tab v/s SL strip	SL tab v/s BL strip	SL strip v/s BL strip	SL tab v/s SL strip	SL tab v/s BL strip	SL strip v/s BL strip	SL tab v/s SL strip	SL tab v/s BL strip	SL strip v/s BL strip
Cmax	143.49 (127.99-160.86)	151.73 (137.84-167.02)	104.85 (94.00-116.96)	99.85 (81.69-122.05)	91.51 (77.07-108.66)	96.08 (84.37-109.42)	162.94 (139.82-189.88)	180.98 (153.33-213.63)	109.13 (94.62-125.85)
AUC last	128.62 (115.95-142.67)	133.95 (121.67-147.48)	105.42 (96.21-115.52)	103.52 (90.02-119.04)	102.39 (88.73-118.15)	103.89 (93.49-115.46)	149.20 (131.62-169.14)	163.40 (143.41-186.16)	108.46 (96.14-122.37)
AUC inf	127.34 (115.36-140.57)	133.16 (121.40-146.06)	105.85 (96.85-115.69)	99.06 (88.01-111.49)	99.70 (89.08-111.59)	106.50 (95.33-118.97)	143.41 (126.79-162.20)	162.19 (138.22-190.32)	114.71 (100.85-130.47)

PK summary:

10. SL tabs v/s SL strips: The upper 90% CI limits for buprenorphine and naloxone were above 125% for all the three PK parameters measured Cmax, AUClast and AUCinf for SL strips indicating that the SL strips **are not equivalent w.r.t rate and extent of absorption of buprenorphine and naloxone** to the reference product, SL tabs. Since the failure in BE is on the upper side (plasma levels are higher when the test product is administered as compared to when the reference product is administered), the therapeutic efficacy of the new product (strips) w.r.t buprenorphine or naloxone is not expected to be compromised. The two treatments (SL tabs and BL strips) **are only equivalent w.r.t rate and extent of absorption of norbuprenorphine** (based on Cmax, AUClast and AUCinf). Overall, the 12 mg/3 mg SL Suboxone strips when administered via the SL route are **not bioequivalent** to the reference product.

11. SL tabs v/s BL strips: The upper 90% CI limits for buprenorphine and naloxone were above 125% for all the three PK parameters measured Cmax, AUClast and AUCinf for BL strips indicating that the BL strips **are not equivalent w.r.t rate and extent of absorption of buprenorphine and naloxone** to the reference product, SL tabs. The lower 90% CI limit was below 80% for norbuprenorphine for the Cmax; however AUClast and AUCinf met the bioequivalence criteria. Overall, the 12 mg/3 mg SL Suboxone strips when administered via the BL route **are not bioequivalent** to the reference product.

12. SL strips v/s BL strips: When SL route is compared with the BL route for buprenorphine and norbuprenorphine, the 90% confidence intervals for Cmax, AUClast, and AUCinf are all within the limits of 80% to 125% indicating that the strips **are equivalent w.r.t rate and extent of absorption of buprenorphine and norbuprenorphine** when administered by the SL or the BL routes. However,

when SL route is compared with the BL route for naloxone plasma concentrations, the upper 90% CI limits are over the 125% limit for Cmax and AUCinf indicating that the strips **are not equivalent w.r.t rate and extent of absorption of naloxone** when administered by the SL or the BL route.

4.1.5 Study 20-A90-AU: A Single-Dose, 2-Period, 3-Treatment, 2-Way Crossover Study of a 16 mg/4 mg Buprenorphine/Naloxone Film Formulation Versus Suboxone® Under Fasting Conditions

Study Design:	Single-dose, open-label, randomized, 2-period, 3-treatment, 2-way crossover study in which 48 healthy adult subjects (under naltrexone block) were scheduled to receive 2 separate single-dose administrations of buprenorphine/naloxone 16 mg/4 mg, following an overnight fast of at least 10 hours.
Objectives:	To compare the rate and extent of both sublingual and buccal absorption of' an investigational formulation of buprenorphine/naloxone 2 mg/0.5 mg sublingual film, manufactured by (b) (4) for Reckitt Benckiser Pharmaceuticals Inc., to an equivalent sublingual dose of the commercially available reference product, Suboxone tablets, manufactured by Reckitt Benckiser Pharmaceuticals Inc., following an overnight fast of at least 10 hours.
Protocol Number:	20-A90-AU
Study Center(s):	(b) (4)
Study Period (days):	20
Number of Subjects enrolled:	48 [14 (29.17%) Non-Hispanic/Latino Black or African American, 16 (33.33%) Non-Hispanic/Latino White, 17 (35.42%) Hispanic/Latino White, and 1 (2.08%) Hispanic/Latino American Indian or Alaska Native subjects]
Number of Subjects analyzed:	43 [completed at least two treatments]
Diagnosis and Main Criteria for Inclusion:	Healthy adult male or non-pregnant, non-breastfeeding female volunteers, 18-45 years of age (inclusive), BMI between 18 and 30 kg/m2 (inclusive) and weighed a minimum of 50 kg (110 lbs).
Test Formulations:	Treatment B Buprenorphine/naloxone (1 x 16 mg/4 mg film-sublingual) Lot Number L07ET101-311 Expiration date: 06 February 2008 Treatment C Buprenorphine/naloxone (1 x 16 mg/4 mg film-buccal) Lot Number L07ET101-311 Expiration date: 06 February 2008
Reference Product:	Treatment A

	Suboxone® (2 x 8 mg/2 mg tablets-sublingual) Lot Number 722103-1 Expiration date: 01 February 2009
Study Phase:	Phase I
Study Initiation Date:	26 November 2007
Study Completion Date:	16 December 2007
Principal Investigator:	(b) (4)

Bioanalytical validation:

Human EDTA plasma samples were analyzed for buprenorphine, norbuprenorphine, and naloxone according to (b) (4) procedure ATM-1267, Revision 1 and ATM-1268, Original. The assay validations were finalized and reported under (b) (4) and 1001815. The method used in this study was validated for a range of 0.0250 to 10.0 ng/mL for buprenorphine and 0.0200 to 8.00 ng/mL for norbuprenorphine based on the analysis of 0.500 mL of plasma, and 1.00 to 250 pg/mL for naloxone based on the analysis of 1.00 mL plasma.

For precision and accuracy, please refer to individual study review 1 for the 2 mg/ 0.5 mg SL strips.

Drug Concentration Measurements:

Blood (plasma) pharmacokinetic characteristics were assessed after each dose of study medication. Blood samples were drawn at 0 (pre-dose) and at 0.25, 0.5, 0.75, 1, 1.25, 1.5, 2, 3, 4, 6, 8, 10, 12, 24, 36, 48, 72, 96, 120, and 144 hours after dose administration.

Table 1: Pharmacokinetic Parameters of Buprenorphine, Norbuprenorphine, and Naloxone after Sublingual Administration of Suboxone® Tablets (2 of 8/2 mg Tablets) and Suboxone (b) (4) (a single 16/4 mg Strip)

	Buprenorphine			Norbuprenorphine			Naloxone Note: Conc. values in pg		
	SL tab	SL strip	BL strip	SL tab	SL strip	BL strip	SL tab	SL strip	BL strip
T_{max} [h]	1.25 (0.55)	1.33 (0.51)	1.46 (0.64)	1.39 (0.93)	1.83 (1.61)	1.52 (1.11)	0.73 (0.20)	0.79 (0.19)	0.81 (0.25)
C_{max} [ng/mL]	4.51 (1.51)	5.47 (1.99)	5.78 (2.40)	3.60 (1.37)	3.11 (1.28)	2.80 (1.35)	259 (200)	324 (161)	361 (231)
AUC_{last} [h x ng/mL]	44.99 (13.26)	55.30 (19.56)	57.53 (16.84)	97.95 (28.99)	99.39 (34.18)	96.31 (33.27)	649.6 (363.7)	873.6 (404.8)	876.9 (413.8)
AUC_{inf} [h x ng/mL]	47.31 (13.81)	58.53 (20.59)	59.79 (17.86)	108.4 (36.18)	112.0 (42.37)	108.2 (38.59)	677.7 (366.4)	930.4 (421.3)	934.9 (407.8)

Mean ± SD buprenorphine Cmax values are 4.51 ± 1.51 ng/mL (Suboxone), 5.47 ± 1.99 ng/mL (SL buprenorphine and naloxone soluble film), and 5.78 ± 2.40 ng/mL (buccal buprenorphine and naloxone soluble film) reached at 1.25 ± 0.55 h, 1.33 ± 0.51 h, and 1.46 ± 0.64 h, respectively. The t1/2 values are comparable across treatments (all evaluations combined). Concentrations declined with apparent t1/2 values of 35.94 ± 9.80 h, 42.02 ± 10.73 h, and 40.58 ± 8.10 h, respectively. Absorption of naloxone after treatment with SL buprenorphine and naloxone soluble film C-III and buccal soluble film are higher relative to Suboxone, with Cmax values of 324 ± 161 pg/mL and 361 ± 231 pg/mL reached at 0.79 ± 0.19 h and 0.81 ± 0.25 h, respectively. Concentrations declined with apparent t1/2 values of 11.33 ± 7.70 h and 9.22 ± 2.52 h, respectively. The mean maximum plasma concentration of naloxone is lower after Suboxone, with the mean maximum concentration Cmax value of 259 ± 200 pg/mL observed at 0.73 ± 0.20 h post-treatment. Concentrations of naloxone declined with an apparent t1/2 value of 9.25 ± 4.35 h.

Table 2: Statistical Analysis of the Log-Transformed Systemic Exposure Parameters Comparing Sublingual Administration of Suboxone® Tablets (2 of 8/2 mg Tablets) and Suboxone [redacted] (b) (4) (a single 16/4 mg Strip)

	Buprenorphine			Norbuprenorphine			Naloxone		
	SL tab v/s SL strip	SL tab v/s BL strip	SL strip v/s BL strip	SL tab v/s SL strip	SL tab v/s BL strip	SL strip v/s BL strip	SL tab v/s SL strip	SL tab v/s BL strip	SL strip v/s BL strip
Cmax	133.64 (117.52-151.98)	129.0 (112.91-147.83)	106.68 (90.05-126.38)	91.04 (79.46-104.31)	92.25 (80.00-106.38)	85.81 (69.42-106.08)	143.79 (116.86-176.92)	145.99 (115.35-184.76)	108.92 (81.97-144.74)
AUC last	132.42 (120.33-145.71)	115.64 (107.09-124.87)	99.47 (87.49-113.09)	101.17 (89.39-114.51)	95.45 (84.88-107.34)	84.58 (72.79-98.26)	148.82 (129.47-171.06)	135.79 (120.12-153.49)	102.60 (82.72-127.27)
AUC inf	132.50 (120.63-145.54)	113.41 (105.56-121.83)	97.80 (86.47-110.61)	100.80 (88.45-114.87)	94.36 (82.65-107.72)	82.36 (69.62-97.43)	137.71 (121.19-156.49)	134.81 (119.83-151.66)	104.63 (82.18-133.21)

PK summary:

13. SL tabs v/s SL strips: The upper 90% CI limits for buprenorphine and naloxone are above 125% for all the three PK parameters measured Cmax, AUClast and AUCinf for SL strips indicating that the SL strips **are not equivalent w.r.t rate and extent of absorption of buprenorphine and naloxone** to the reference product, SL tabs. Since the failure in BE is on the upper side (plasma levels are higher when the test product is administered as compared to when the reference product is administered), the therapeutic efficacy of the new product (strips) w.r.t buprenorphine or naloxone is not expected to be compromised. In addition, the two treatments (SL tabs and BL strips) **are not equivalent w.r.t rate and extent of absorption of norbuprenorphine** (lower 90% CI limit for Cmax is 79.46).

14. SL tabs v/s BL strips: The upper 90% CI limits for buprenorphine and naloxone are above 125% for all the three PK parameters measured Cmax, AUClast and AUCinf for BL strips indicating that the BL strips **are not equivalent w.r.t rate and extent of absorption of buprenorphine and naloxone** to the reference product, SL tabs. The two treatments (SL tabs and BL strips) **are only equivalent w.r.t rate and extent of absorption of norbuprenorphine** (based on Cmax, AUClast and AUCinf).

15. SL strips v/s BL strips: When SL route is compared with the BL route for buprenorphine the upper 90% CI for Cmax barely misses the 125% limit whereas the 90% CI for its AUClast, and AUCinf are all within the limits of 80% to 125% indicating that the strips **are not equivalent w.r.t rate but are equivalent w.r.t extent of absorption of buprenorphine** when administered by the SL or the BL route. In addition, the two routes **are not equivalent w.r.t rate and extent of absorption of norbuprenorphine** (lower 90% CI limit for Cmax is 69.42).

4.1.6 Study 1003395: A Single-Dose, 3-Period, 3-Treatment, 3-Way Crossover Study of Buprenorphine/Naloxone 8 mg/2 mg plus 2 x 2 mg/0.5 mg film strips versus Suboxone® under Fasting Conditions

Study Design:	Single-dose, open-label, randomized, 3-period, 3-treatment, 3-way crossover study in which 48 healthy adult subjects (under naltrexone block) were scheduled to receive three separate single-dose administrations of buprenorphine/naloxone 8 mg/2 mg plus 2 x 2 mg/0.5 mg film strips administered sublingually, buprenorphine/naloxone 8 mg/2 mg plus 2 x 2 mg/0.5 mg film strips administered buccally, or one Suboxone 8 mg/2 mg plus 2 x 2 mg/0.5 mg tablets administered sublingually following an overnight fast of at least 10 hours.
Objectives:	To compare the rate and extent of both sublingual and buccal absorption of investigational formulations of buprenorphine/naloxone 8 mg/2 mg plus 2 x 2 mg/0.5 mg film strips, manufactured by (b) (4) for Reckitt Benckiser Pharmaceuticals Inc., to an equivalent sublingual dose of the commercially available reference product, Suboxone (one 8 mg/2 mg plus 2 x 2 mg/0.5 mg tablets), manufactured by Reckitt Benckiser Healthcare (UK) Ltd., following an overnight fast of at least 10 hours.
Protocol Number:	1003395
Study Center(s):	(b) (4)
Study Period (days):	34
Number of Subjects enrolled:	48 [1 (2.08%) Non-Hispanic/Latino Black, American Indian or Alaskan Native; 9 (18.75%) Non-Hispanic/Latino Black or African American, 1 (2.08%) Hispanic/Latino Native

	Hawaiian or other Pacific Islander, 20 (41.67%) Non-Hispanic/Latino White, and 17 (35.42%) Hispanic/Latino White subjects]
Number of Subjects analyzed:	46 [completed at least two study periods (one test formulation period and the reference product period)]
Diagnosis and Main Criteria for Inclusion:	Healthy adult male or non-pregnant, non-breastfeeding female volunteers, 18-45 years of age (inclusive), BMI between 18 and 30 kg/m2 (inclusive) and weighed a minimum of 50 kg (110 lbs).
Test Formulations:	Treatment B Buprenorphine/naloxone 12 mg/3 mg (1 x 8 mg/2 mg plus 2 x 2 mg/0.5 mg) film strips administered sublingually 8 mg/2 mg Lot A08EJ102-025 Mfg. Date 01/27/2008 2 mg/0.5 mg Lot A08DW104-028 Mfg. Date 1/29-30/2008 Treatment C Buprenorphine/naloxone 12 mg/3 mg (1 x 8 mg/2 mg plus 2 x 2 mg/0.5 mg) film strips administered buccally 8 mg/2 mg Lot A08EJ102-025 Mfg. Date 01/27/2008 2 mg/0.5 mg Lot A08DW104-028 Mfg. Date 1/29-30/2008
Reference Product:	Treatment A Suboxone® 12 mg/3 mg (1 x 8 mg/2 mg plus 2 x 2 mg/0.5 mg) tablets administered sublingually 8 mg/2 mg Lot 815101-4 Exp. Date 11/01/2009 2 mg/0.5 mg Lot 815603 Exp. Date 11/01/2009
Study Phase:	Phase I
Study Initiation Date:	05 August 2008
Study Completion Date:	08 September 2008

Principal Investigator:	(b) (4)

Bioanalytical validation:

Human EDTA plasma samples were analyzed for buprenorphine and norbuprenorphine according to (b) (4) procedure ATM-1336, Revision 1. The assay validation was finalized and reported under (b) (4). The method used in this study was validated for a range 0.0250 to 10.0 ng/mL for buprenorphine and of 0.0200 to 8.00 ng/mL for norbuprenorphine, based on the analysis of 0.500 mL of plasma. Human EDTA plasma samples were analyzed for naloxone according to (b) (4) procedure ATM-1268, Revision 1. The assay validation was finalized and reported under (b) (4) The method used in this study was validated for a range of 1.00 to 250 pg/mL based on the analysis of 1.00 mL of plasma.
For precision and accuracy, please refer to individual study review 1 for the 2 mg/ 0.5 mg SL strips.

Drug Concentration Measurements:

Blood (plasma) pharmacokinetic characteristics were assessed after each dose of study medication. Blood samples were drawn at 0 (pre-dose) and at 0.25, 0.5, 0.75, 1, 1.25, 1.5, 2, 3, 4, 6, 8, 10, 12, 24, 36, 48, 72, 96, 120, and 144 hours after dose administration.

Table 1: Pharmacokinetic Parameters of Buprenorphine, Norbuprenorphine, and Naloxone after Sublingual Administration of Suboxone® Tablets and Suboxone (b) (4) (both administered as 1 of 8/2 mg and 2 of 2/0.5 mg)

	Buprenorphine			Norbuprenorphine			Naloxone Note: Conc. values in pg		
	SL tab	SL strip	BL strip	SL tab	SL strip	BL strip	SL tab	SL strip	BL strip
T_{max} [h]	1.26 (0.53)	1.36 (0.48)	1.49 (0.57)	1.76 (3.53)	1.29 (0.84)	2.24 (2.16)	0.78 (0.28)	0.75 (0.18)	0.78 (0.16)
C_{max} [ng/mL]	3.44 (1.53)	4.05 (2.63)	4.37 (1.99)	2.32 (1.34)	2.07 (1.14)	2.00 (1.06)	170 (77.6)	207 (143)	234 (126)
AUC_{last} [h x ng/mL]	35.14 (13.60)	38.51 (15.26)	43.04 (17.05)	67.70 (27.24)	66.93 (32.94)	65.06 (31.06)	502.3 (246.0)	561.2 (325.6)	642.8 (327.9)
AUC_{inf} [h x ng/mL]	37.11 (14.14)	40.50 (15.93)	45.16 (17.96)	74.40 (30.54)	73.40 (36.51)	72.84 (37.18)	524.0 (253.6)	582.7 (324.9)	661.5 (330.1)

Table 2: Statistical Analysis of the Log-Transformed Systemic Exposure Parameters Comparing Sublingual Administration of Suboxone® Tablets and Suboxone (b) (4) (both administered as 1 of 8/2 mg and 2 of 2/0.5 mg)

	Buprenorphine			Norbuprenorphine			Naloxone		
	SL tab v/s SL strip	SL tab v/s BL strip	SL strip v/s BL strip	SL tab v/s SL strip	SL tab v/s BL strip	SL strip v/s BL strip	SL tab v/s SL strip	SL tab v/s BL strip	SL strip v/s BL strip
Cmax	115.05 (106.44-124.35)	127.45 (117.26-138.52)	113.02 (100.92-126.58)	93.06 (85.97-100.73	86.68 (80.17-93.71)	95.33 (88.05-103.21)	117.24 (106.80-128.71)	137.82 (119.91-158.41)	119.16 (103.38-137.35)
AUC last	111.73 (106.11-117.64	123.20 (115.70-131.19)	111.44 (103.19-120.35)	97.14) (97.54-103.08	94.17 (89.36-99.24)	96.81 (89.56-104.65)	110.46 (102.51-119.03)	129.98 (117.26-144.08)	118.74 (106.69-132.15)
AUC inf	111.21) (105.62-117.09)	122.30 (115.13-129.93)	111.25 (103.23-119.89)	97.51) (91.66-103.73)	95.21 (89.78-100.98)	98.58 (90.60-107.25)	110.47 (102.90-118.60)	128.38 (116.38-141.61)	116.92 (105.87-129.12)

PK summary:

16. SL tabs v/s SL strips: The two treatments **are equivalent w.r.t rate and extent of absorption of buprenorphine and norbuprenorphine** (based on Cmax, AUClast and AUCinf). The upper 90% CI limits for naloxone were above 125% for Cmax but within the 80-125% limits for AUClast and AUCinf for SL strips indicating that the SL strips **are not equivalent w.r.t rate but equivalent w.r.t extent of absorption of naloxone** to the reference product, SL tabs.

17. SL tabs v/s BL strips: The upper 90% CI limits for buprenorphine and naloxone are above 125% for all the three PK parameters measured Cmax, AUClast and AUCinf for BL strips indicating that the BL strips **are not equivalent w.r.t rate and extent of absorption of buprenorphine and naloxone** to the reference product, SL tabs. The two treatments (SL tabs and BL strips) **are only equivalent w.r.t rate and extent of absorption of norbuprenorphine** (based on Cmax, AUClast and AUCinf).

18. SL strips v/s BL strips: When SL route is compared with the BL route for buprenorphine the upper 90% CI for Cmax barely misses the 125% limit whereas the 90% CI for its AUClast, and AUCinf are all within the limits of 80% to 125%, whereas for naloxone the upper 90% CI limits for naloxone are above 125% for all the three PK parameters measured Cmax, AUClast and AUCinf indicating that the two routes **are not equivalent w.r.t rate and extent of absorption of both buprenorphine and naloxone.** The two treatments (SL strips and BL strips) are **only equivalent w.r.t rate and extent of absorption of norbuprenorphine** (based on Cmax, AUClast and AUCinf).

4.1.7 Study 20-291-SA: A Single-Dose, 3-Period, 5-Treatment, 3-Way Crossover Dose Proportionality Study of Buprenorphine/Naloxone Film Strips Administered Sublingually under Fasting Conditions

Study Design:	Single-dose, open-label, randomized, 3-period, 5-treatment, 3-way crossover study in which 60 healthy adult subjects (under naltrexone block) were scheduled to receive three separate single-dose administrations of study drug after a 10-hour overnight fast.
Objectives:	To compare the rate and extent of absorption of five dosages (2/0.5 mg, 4/1 mg (2 x 2/0.5 mg), 8/2 mg, 12/3 mg, and 16/4 mg) of buprenorphine/naloxone film strip (sublingual) investigational formulations, manufactured by (b) (4) for Reckitt Benckiser Pharmaceuticals Inc., following an overnight fast of at least 10 hours.
Protocol Number:	20-291-SA
Study Center(s):	(b) (4)
Study Period (days):	34
Number of Subjects enrolled:	60 [14 (29.17%) Non-Hispanic/Latino Black or African American, 16 (33.33%) Non-Hispanic/Latino White, 17 (35.42%) Hispanic/Latino White, and 1 (2.08%) Hispanic/Latino American Indian or Alaska Native subjects]
Number of Subjects analyzed:	50 [completed at least two treatments]
Diagnosis and Main Criteria for Inclusion:	Healthy adult male or non-pregnant, non-breastfeeding female volunteers, 18-45 years of age (inclusive), BMI between 18 and 30 kg/m2 (inclusive) and weighed a minimum of 50 kg (110 lbs).
Test Formulations:	Test Formulation 1: Treatment A Buprenorphine/naloxone Dose = 1 x 2/0.5 mg film strip administered sublingually Lot A08DW101-024 Mfg Date 01/24/08 – 01/25/08 Test Formulation 2: Treatment B Buprenorphine/naloxone Dose = 4/1 mg (2 x 2/0.5 mg) film strips administered sublingually Lot A08DW101-024 Mfg Date 01/24/08 – 01/25/08 Test Formulation 3: Treatment C Buprenorphine/naloxone Dose = 1 x 8/2 mg film strip administered sublingually Lot A08EJ103-025

	Mfg Date 01/28/08 Test Formulation 4: Treatment D Buprenorphine/naloxone Dose = 1 x 12/3 mg film strips administered sublingually Lot A08EY101-028 Mfg Date 02/02/08 – 02/03/08 Test Formulation 5: Treatment E Buprenorphine/naloxone Dose = 1 x 16/4 mg film strips administered sublingually Lot A08ET101-035 Mfg Date 02/05/08 – 02/06/08
Study Phase:	Phase I
Study Initiation Date:	1 April 2008
Study Completion Date:	5 May 2008
Principal Investigator:	(b) (4)

Bioanalytical validation:

Human EDTA plasma samples were analyzed for buprenorphine and norbuprenorphine according to (b) (4) procedure ATM-1336, Revision 1. The assay validation was finalized and reported under (b) (4). The method used in this study was validated for a range of 0.0250 to 10.0 ng/mL for buprenorphine and 0.0200 to 8.00 ng/mL for norbuprenorphine based on the analysis of 0.500 mL of human EDTA plasma. Human EDTA plasma samples were analyzed for naloxone according to (b) (4) procedure ATM-1268, Revision 1. The assay validation was finalized and reported under (b) (4). The method used in this study utilized a range of 1.00 to 250 pg/mL for naloxone, based on the analysis of 1.00 mL of human plasma. Quantitation was performed using separate weighted (1/x2) linear least squares regression analysis generated from calibration standards.

For precision and accuracy, please refer to individual study review 1 for the 2 mg/ 0.5 mg SL strips.

Drug Concentration Measurements:

Blood (plasma) pharmacokinetic characteristics were assessed after each dose of study medication. Blood samples were drawn at 0 (pre-dose) and at 0.25, 0.5, 0.75, 1, 1.25, 1.5, 2, 3, 4, 6, 8, 10, 12, 24, 36, 48, 72, 96, 120, and 144 hours after dose administration.

Table 1: Pharmacokinetic Parameters of Buprenorphine after Sublingual Administration of Suboxone [redacted] (2 mg/0.5 mg through 16 mg/4 mg)

	2/0.5	4/1	8/2	12/3	16/4
T_{max} [h]	1.54 (0.68)	1.48 (0.57)	1.40 (0.45)	1.43 (0.53)	1.29 (0.37)
C_{max} [ng/mL]	1.07 (0.525)	1.66 (0.794)	3.55 (1.23)	4.80 (2.14)	6.05 (2.42)
AUC_{last} [h x ng/mL]	7.178 (2.836)	13.42 (6.133)	28.71 (8.826)	39.86 (14.71)	50.32 (16.38)
AUC_{inf} [h x ng/mL]	8.434 (3.207)	14.62 (6.446)	30.66 (9.241)	41.74 (15.08)	53.40 (18.58)
T1/2 (h)	22.71 (13.01)	25.67 (13.30)	36.55 (16.38)	36.07 (10.48)	40.37 (17.22)

Table 2: Pharmacokinetic Parameters of Naloxone after Sublingual Administration of Suboxone [redacted]

	2/0.5	4/1	8/2	12/3	16/4
T_{max} [h]	0.73 (0.19)	0.74 (0.18)	0.79 (0.23)	0.74 (0.21)	0.78 (0.19)
C_{max} [pg/mL]	48.5 (25.9)	72.8 (33.7)	193 (84.6)	286 (155)	401 (226)
AUC_{last} [h x pg/mL]	100.6 (41.30)	164.1 (68.02)	442.9 (134.4)	647.5 (227.4)	937.9 (368.8)
AUC_{inf} [h x pg/mL]	105.1 (14.08)	171.0 (69.53)	454.8 (135.0)	665.1 (230.8)	958.4 (372.6)
T1/2 (h)	2.01 (1.03)	2.18 (1.53)	5.15 (3.66)	6.81 (4.45)	7.00 (3.45)

Table 3: Pharmacokinetic Parameters of Norbuprenorphine after Sublingual Administration of Suboxone [redacted]

	2/0.5	4/1	8/2	12/3	16/4
T_{max} [h]	1.32 (1.01)	1.35 (0.80)	1.51 (1.05)	1.87 (1.74)	1.60 (1.29)
C_{max} [pg/mL]	0.352 (0.163)	0.679 (0.270)	1.55 (0.664)	2.19 (1.59)	2.73 (1.64)
AUC_{last} [h x pg/mL]	10.61 (4.391)	22.68 (10.54)	48.14 (16.85)	69.46 (38.20)	85.45 (38.41)
AUC_{inf} [h x pg/mL]	12.73 (5.217)	25.96 (12.46)	56.22 (22.52)	77.42 (41.72)	95.94 (43.88)
T1/2 (h)	44.23 (23.40)	42.46 (19.47)	55.71 (48.02)	45.74 (17.22)	44.77 (21.78)

In general, peak exposure to buprenorphine was observed at approximately 1.5 h and mean ± SD estimates of maximum concentration (Cmax) ranged from 1.07 ± 0.525 ng/mL (buprenorphine and naloxone 2/0.5 mg) to 6.05 ± 2.42 ng/mL (buprenorphine and naloxone 16/4 mg). Likewise, total systemic exposure of buprenorphine, based on AUClast, increased with dose. Concentrations of buprenorphine declined with an apparent t1/2 value of 22.71 to 40.37 h. As observed for buprenorphine, exposure to norbuprenorphine increased with the dose of buprenorphine in the soluble film. Mean ± SD peak exposure to norbuprenorphine was observed from 1.32 to 1.87 h, and mean ± SD estimates of Cmax ranged from 0.352 ± 0.163 ng/mL (buprenorphine and naloxone 2/0.5 mg) to 2.73 ± 1.64 ng/mL (buprenorphine and naloxone 16/4 mg). Exposure to naloxone increased with dose of naloxone in the soluble film. Mean ± SD peak exposure to naloxone was observed at approximately 0.75 h, and mean ± SD estimates of Cmax ranged from 48.5 ± 25.9 pg/mL (buprenorphine and naloxone 2/0.5 mg) to 401 ± 226 pg/mL (buprenorphine and naloxone 16/4 mg). Concentrations of naloxone declined with an apparent t1/2 of 2.01 to 7.00 h.

In the linear regression plots of the dose-normalized values of Cmax, AUClast, and AUCinf, there was a negative slope in the regression line, suggesting a less than proportional increase in exposure to buprenorphine with increasing dose. The negative slope in the regression line appeared to be due to the first two dose levels, 2/0.5 and 16/4 mg. For norbuprenorphine and naloxone, the slopes of the regression lines were small, almost parallel to the x-axis for AUClast and AUCinf, suggesting that overall systemic exposure to norbuprenorphine and naloxone were proportional to the administered dose in buprenorphine/naloxone film strips.

Overall, the increases in Cmax and AUC for buprenorphine, norbuprenorphine and naloxone with increases in dose, were dose linear but somewhat less than dose proportional.

Table 4: Assessment of Dose Proportionality of Buprenorphine and Naloxone Sublingual Soluble Film (Dose Range 2/0.5 mg to 16/4 mg) Using Mixed-effects Statistical Model based on a Power Function (Study 20-291-SA)

Dependent Variable	Model Variable	Estimate (β_1)	p-value[a]	90% CI		Dose P[b]
				Lower	Upper	
Buprenorphine						
ln (C_{max})	ln (dose)	0.9327	<0.0001	0.8634	1.0021	8.2158
ln (AUC_{last})	ln (dose)	1.0389	<0.0001	0.9700	1.1078	14.4346
ln (AUC_{inf})	ln (dose)	0.9846	<0.0001	0.9142	1.0550	28.5590
Norbuprenorphine						
ln (C_{max})	ln (dose)	1.0301	<0.0001	0.9536	1.1065	14.8814
ln (AUC_{last})	ln (dose)	1.0565	<0.0001	0.9722	1.1408	7.7188
ln (AUC_{inf})	ln (dose)	1.0169	<0.0001	0.9419	1.0918	22.9415
Naloxone						
ln (C_{max})	ln (dose)	1.0544	<0.0001	0.9773	1.1314	8.9267
ln (AUC_{last})	ln (dose)	1.1282	<0.0001	1.0605	1.1958	4.3452
ln (AUC_{inf})	ln (dose)	1.1112	<0.0001	1.0451	1.1773	5.0649

Power Model: $\ln(PK) = \ln(\beta_0) + \beta_1 \times \ln(dose) + \varepsilon$ (subject was used as the random effects in the analysis)

[a] Significant difference from unit (1.0000), defined *a priori* as $p < 0.05$.

[b] High/low dose ratio in which dose proportionality can be demonstrated definitely, relative to the lowest dose in the analysis data set.

When all dose levels were included in the dose-proportionality assessment of buprenorphine using a mixed effects model based on a power function, the slope (β1) estimates and associated 90% CIs are summarized in Table 4. The β1 estimates were closer to 1.0000 when the upper dose levels were considered in the power analysis. Exposure to buprenorphine, norbuprenorphine, and naloxone increased with increased dose of SL buprenorphine and naloxone soluble film. The power analysis results indicated that buprenorphine Cmax and AUCinf and naloxone Cmax were directly proportional to the SL administered dose of buprenorphine and naloxone soluble film over the dose range of 2/0.5 mg to 16/4 mg. Although the dose proportionality of naloxone AUCinf could not be confirmed over the entire 8-fold dose range, the power analysis indicated that this parameter was proportional over a 5.06-fold range.

4.2 Filing Checklist

Office of Clinical Pharmacology

New Drug Application Filing and Review Form

General Information About the Submission

	Information		Information
NDA/BLA Number	**22410**	**Brand Name**	**Suboxone® (b) (4)**
OCP Division (I, II, III, IV, V)	**2**	**Generic Name**	**Buprenorphine HCl/naloxone HCl**
Medical Division	**DAARP**	**Drug Class**	**Opioid agonist/ opioid antagonist**
OCP Reviewer	**Sheetal Agarwal**	**Indication(s)**	**Treatment of opioid dependence**
OCP Team Leader	**Suresh Doddapaneni**	**Dosage Form**	**Film strips (2/0.5mg and 8/2 mg)**
Pharmacometrics Reviewer	**-**	**Dosing Regimen**	
Date of Submission	**10/21/2008**	**Route of Administration**	**Sublingual**
Estimated Due Date of OCP Review	**06/21/2009**	**Sponsor**	**Reckitt Benckiser Pharmaceuticals Inc.**
Medical Division Due Date	**06/21/2009**	**Priority Classification**	**S3**
PDUFA Due Date	**08/21/2009**		

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:				
multiple dose:				
Patients-				
single dose:				
multiple dose:				
Dose proportionality -				

fasting / non-fasting single dose:	**X**	**4**	**1**	**DOSE PROP STUDIES FOR THE BL ROUTE EMPLOYING FILM STRIPS AND DOSE PROPORTIONALITY STUDIES EMPLOYING SUBUTEX FOR SL OR BL ROUTES WILL NOT BE REVIEWED**
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				
In-vivo effects on primary drug:	**X**			**KETOCO + BUPRE**
In-vivo effects of primary drug:				**NOT DONE; " TO BE CLOSELY MONITORED IF ADM WITH CYP3A4 INDUCERS"**
In-vitro:				
Subpopulation studies -				
ethnicity:				
gender:				
pediatrics:				
geriatrics:				
renal impairment:				
hepatic impairment:				
PD -				
Phase 2:				
Phase 3:				
PK/PD -				
Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial:				
Population Analyses -				
Data rich:	**X**			
Data sparse:				
II. Biopharmaceutics				
Absolute bioavailability				
Relative bioavailability -				
solution as reference:				
Alternate FORMULATION as reference:	**X**	**4**		**FORMULATION DEV STUDIES WILL NOT BE NOT REVIEWED**
Alternate ROUTE as reference:				(b) (4) [redacted]
Bioequivalence studies -				
traditional design; single / multi dose:	**X**	**11**	**6**	**BE STUDIES WITH** (b) (4) **WILL NOT BE REVIEWED**
replicate design; single / multi dose:				
Food-drug interaction studies				
Bio-waiver request based on BCS				
BCS class				
Dissolution study to evaluate alcohol induced dose-dumping				
III. Other CPB Studies				
Genotype/phenotype studies				
Chronopharmacokinetics				
Pediatric development plan				
Literature References				
Total Number of Studies		**19**	**7**	

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?	Y			
2	Has the applicant provided metabolism and drug-drug interaction information?	Y			
3	Has the sponsor submitted bioavailability data satisfying the CFR requirements?	Y			
4	Did the sponsor submit data to allow the evaluation of the validity of the analytical assay?	Y			
5	Has a rationale for dose selection been submitted?				
6	Is the clinical pharmacology and biopharmaceutics section of the NDA organized, indexed and paginated in a manner to allow substantive review to begin?	Y			
7	Is the clinical pharmacology and biopharmaceutics section of the NDA legible so that a substantive review can begin?	Y			
8	Is the electronic submission searchable, does it have appropriate hyperlinks and do the hyperlinks work?	Y			
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)?	Y			
10	If applicable, are the pharmacogenomic data sets submitted in the appropriate format?			NA	
	Studies and Analyses				
11	Is the appropriate pharmacokinetic information submitted?	Y			
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)?			NA	
13	Are the appropriate exposure-response (for desired and undesired effects) analyses conducted and submitted as described in the Exposure-Response guidance?			NA	
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?			NA	
15	Are the pediatric exclusivity studies adequately designed to demonstrate effectiveness, if the drug is indeed effective?			NA	
16	Did the applicant submit all the pediatric exclusivity data, as described in the WR?			NA	
17	Is there adequate information on the pharmacokinetics and exposure-response in the clinical pharmacology section of the label?	Y			
	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?	Y			
19	Was the translation (of study reports or other study information) from another language needed and provided in this submission?			NA	

IS THE CLINICAL PHARMACOLOGY SECTION OF THE APPLICATION FILEABLE?

Yes.

If the NDA/BLA is not fileable from the clinical pharmacology perspective, state the reasons and provide comments to be sent to the Applicant.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

SHEETAL AGARWAL

Reviewing Clinical Pharmacologist Date

Team Leader/Supervisor Date

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

/s/

Sheetal Agarwal
6/23/2009 01:09:13 PM
BIOPHARMACEUTICS

Suresh Doddapaneni
6/23/2009 01:35:08 PM
BIOPHARMACEUTICS