CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

208042Orig1s000

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

CLINICAL PHARMACOLOGY REVIEW

NDA: 208-042	Submission Date(s): November 30, 2015; March 14, 2016
Proposed Brand Name	Buprenorphine hydrochloride and naloxone hydrochloride sublingual film
Generic Name	Buprenorphine and naloxone sublingual film
Reviewer	Wei Qiu, Ph.D.
Team Leader	Yun Xu, Ph.D.
OCP Division	DCPII
OND division	DAAAP
Sponsor	Teva Pharmaceuticals, USA
Relevant IND(s)	IND 118,625
Submission Type	Resubmission; 505(b)(2)
Formulation; Strength(s)	Sublingual film (buprenorphine/naloxone): 16 mg/4 mg (buprenorphine/naloxone)
Proposed Indication	For the maintenance treatment of opioid dependence

Table of Contents

1 Executive Summary

1.1 Recommendation

The Office of Clinical Pharmacology/Division of Clinical Pharmacology 2 (OCP/DCP-2) has reviewed the NDA resubmissions dated November 30, 2015 and March 14, 2016, and finds them acceptable from clinical pharmacology perspective. DNDBE/OSIS recommended accepting data for the pivotal bioavailability study 3007599 without an on-site inspection because the inspectional outcome for the requested sites as classified as No Action Indicated.

1.2 Phase IV Commitments

None.

1.3 Summary of Clinical Pharmacology Findings

Key clinical pharmacology findings:

1. Teva buprenorphine/naloxone sublingual film 1 x 16/4 mg exhibited equivalent systemic exposure (Cmax, AUClast, and AUCinf) to buprenorphine and naloxone in comparison to the listed drug, Suboxone sublingual film 2 x 8/2 mg.
2. Effect of Pretreatment with Cold Water: the systemic exposures (Cmax, AUClast, and AUCinf) of buprenorphine and naloxone following pretreatment with cold water was similar to that following pretreatment with a room temperature water.
3. Effect of Pretreatment with Hot Water: the systemic exposures of buprenorphine and naloxone following pretreatment with hot water was similar to that following pretreatment with a room temperature water except buprenorphine Cmax was increased by 15%.
4. Effect of Pretreatment with Low pH Beverage (Sprite): buprenorphine Cmax and AUC values were decreased by 14-15% and naloxone Cmax and AUC values were decreased by 30-36% following drinking Sprite.
5. Effect of Pretreatment with High pH Beverage (solution of ½ teaspoon of sodium bicarbonate): buprenorphine Cmax and AUC values were decreased by 14-16%.

Naloxone Cmax and AUClast were increased by 142% and 89-92%, respectively following drinking solution of ½ teaspoon of sodium bicarbonate. The Sponsor proposes to instruct patients to avoid high pH beverages prior to dosing.

The clinical and clinical pharmacology database for Teva buprenorphine/naloxone sublingual film consists of a pivotal comparative bioavailability study (Study 3007599), effect of temperature study (Study 4001650), and effect of pH study (Study 4001651). The final to-be-marketed formulation was used in all these PK Studies.

Relative Bioavailability of Teva Buprenorphine/Naloxone Sublingual film 1 x 16/4 mg in Comparison to Listed Drug Suboxone Sublingual Film 2 x 8/2 mg

Teva buprenorphine/naloxone sublingual film 1 x 16/4 mg exhibited equivalent systemic exposure (Cmax, AUClast, and AUCinf) to buprenorphine and naloxone in comparison to the listed drug, Suboxone sublingual film 2 x 8/2 mg, because the 90% CI of geometric mean ratios for Cmax, AUClast, and AUCinf values of buprenorphine and naloxone for Teva buprenorphine/naloxone sublingual film to Suboxone sublingual film fell within the bioequivalent limits of 80 to 125%.

The point estimate (90% CI) of the geometric mean ratio (Teva buprenorphine/naloxone sublingual film to Suboxone sublingual film) for buprenorphine Cmax, AUClast, and AUCinf values are 89.58% (83.98 – 95.56%), 89.22% (84.37 – 94.35%), and 89.36% (84.56 – 94.43%), respectively. Medium buprenorphine Tmax values were same (1.25 h)

The point estimate (90% CI) of the geometric mean ratio (Teva buprenorphine/naloxone sublingual film to Suboxone sublingual film) for naloxone Cmax, AUClast, and AUCinf values are 103.02% (95.80 – 110.78%), 100.91% (95.28 – 106.87%), and 101.55% (96.11 – 107.31%), respectively. Medium naloxone Tmax values were same (0.75 h).

Effect of Pretreatment with Water at Different Temperatures

Pretreatment of cold water had no effect on buprenorphine or naloxone Cmax and AUC values. The point estimate (90% CI) of the geometric mean ratio (cold water/room temperature water) for buprenorphine Cmax, AUClast, and AUCinf values are 102.77% (87.52 – 120.69%), 95.68% (81.50 – 112.33%), and 97.84% (84.02 – 113.94%) respectively. The point estimate (90% CI) of the geometric mean ratio (cold water/room

temperature water) for naloxone Cmax, AUClast, and AUCinf values are 97.51% (79.91 – 118.98%), 98.70% (82.00 – 118.81%), and 98.64% (81.95 – 118.74%) respectively.

Pretreatment with hot water increased buprenorphine Cmax by 15% and had no effect on buprenorphine AUC values or naloxone Cmax or AUC values. The point estimate (90% CI) of the geometric mean ratio (hot water/room temperature water) for buprenorphine Cmax, AUClast, and AUCinf values are 114.86% (97.65 – 135.10%), 98.98% (84.17 – 116.39%), and 100.09% (85.81 – 116.74%), respectively. The point estimate (90% CI) of the geometric mean ratio (hot water/room temperature water) for naloxone Cmax, AUClast, and AUCinf values are 105.26% (86.09 – 128.71%), 97.31% (80.69 – 117.35%), and 96.88% (80.33 – 116.83%), respectively.

Effect of Pretreatment with Beverages with Different pH Values

Pretreatment of low pH beverage (Sprite) decreased bupprenorpine Cmax and AUC values by 14-15% and decreased naloxone Cmax and AUC values by 30-36%, respectively. The point estimate (90% CI) of the geometric mean ratio (low pH beverage/water) for buprenorphine Cmax, AUClast, and AUCinf values are 86.30% (74.45 – 100.05%), 84.77% (75.78 – 94.83%), and 84.52% (75.63 – 94.46%), respectively. The point estimate (90% CI) of the geometric mean ratio (low pH beverage/water) for naloxone Cmax, AUClast, and AUCinf values are 69.56% (54.74 – 88.39%), 63.99% (52.29 – 78.32%), and 65.00% (53.35 – 79.20%), respectively.

Pretreatment with high pH beverage (solution of ½ teaspoon of sodium bicarbonate) decreased buprenorphine Cmax and AUC values by 14-16%. Naloxone Cmax and AUClast values were increased by 142% and 89-92%, respectively. The point estimate (90% CI) of the geometric mean ratio (high pH beverage/water) for buprenorphine Cmax, AUClast, and AUCinf values are 84.01% (72.58 – 97.25%), 85.73% (76.73 – 95.79%), and 85.61% (76.69 – 95.57%), respectively. The point estimate (90% CI) of the geometric mean ratio (high pH beverage/water) for naloxone Cmax, AUClast, and AUCinf values are 241.71% (190.69 – 306.39%), 191.62% (156.89 – 234.04%), and 188.81% (155.28– 229.58%), respectively.

2 Question Based Review

2.1 General Attributes of the Drug

1. What pertinent regulatory background or history contributes to the current assessment of the clinical pharmacology of this drug product?

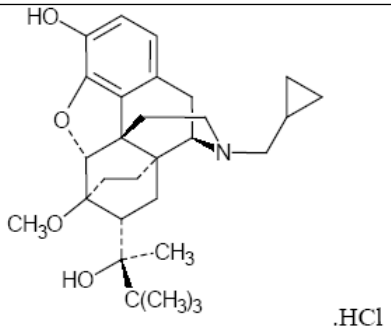
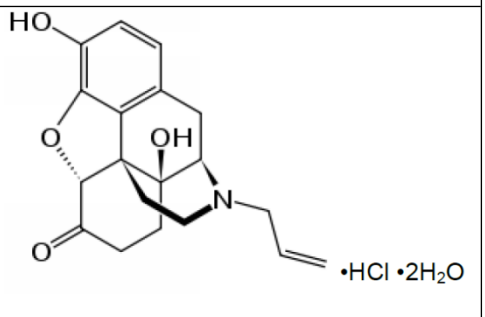
Buprenorphine is a synthetic opioid that is a mu-opioid receptor partial agonist. Naloxone is a potent antagonist at mu-opioid receptors and produces opioid withdrawal when administered parenterally in individuals physically dependent on full opioid agonists. When Teva buprenorphine/naloxone sublingual film is taken as intended, naloxone will have no effect or insignificant effect due to its low plasma levels.

Teva submitted the original NDA 208-042 for Teva buprenorphine/naloxone sublingual film with the strength of 16/4 mg buprenorphine/naloxone via 505(b)(2) route on October 29, 2014. It was refused to file because of incomplete application. On November 30, 2015, Teva resubmitted the NDA. Teva buprenorphine/naloxone sublingual film is proposed for the maintenance treatment of opioid dependence. At present, several NDA products including Subutex ® (buprenorphine) sublingual tablets, Suboxone® (buprenorphine and naloxone) sublingual films, and Zubsolv (buprenorphine and naloxone) sublingual tablets have been approved for the treatment of opioid dependence. Suboxone® (buprenorphine and naloxone) sublingual tablet and Bunavail (buprenorphine and naloxone) buccal film have been approved for the maintenance treatment of opioid dependence.

Teva proposed to use Suboxone sublingual film (NDA 22-410) as the listed drug to support this 505(b)(2) NDA. Teva buprenorphine and naloxone sublingual film is presented in a 4:1 ratio of free bases which is the same as the ratios in the approved sublingual tablet and sublingual film formulations under the trade name of Suboxone or Zubsolv® sublingual tablet.

2. ***What are the highlights of the chemistry and physico-chemical properties of the drug substances, and the formulation of the drug product?***

Table 1 Physical-Chemical Properties of Buprenorphine Hydrochloride and Naloxone Hydrochloride

Drug Name	Buprenorphine Hydrochloride	Naloxone Hydrochloride
Chemical Name	(2S)-2-[17-Cyclopropylmethyl-4,5a-epoxy-3-hydroxy-6-methoxy-6a,14-ethano-14a-morphinan-7a-yl]-3,3-dimethylbutan-2-ol hydrochloride	17-Allyl-4,5a-epoxy-3,14-dihydroxymorphinan-6 hydrochloride
Structure	 .HCl $C_{29}H_{41}NO_4$•HCl	 $C_{19}H_{21}NO_4$•HCl•$2H_2O$
Molecular Weight	504.10	399.87
Appearance	white to off-white crystalline powder	White to off-white powder
Solubility	Sparingly soluble in water, freely soluble in methanol, soluble in alcohol, and practically insoluble in cyclohexane	Freely soluble in water, dilute acids and strong alkali; slightly soluble in alcohol; practically insoluble in ether and chloroform

The components and compositions are listed in **Table 2**. The drug product is available in one strength: 16/4 mg buprenorphine/naloxone (both measured as free base) per unit.

Table 2 Components and Composition of Teva Buprenorphine/Naloxone Sublingual Film

#	Ingredient	Function	16 mg/4 mg	
			mg/Film	% w/w
(b) (4)	Buprenorphine Hydrochloride, USP	Active	17.25	(b) (4)
	Naloxone Hydrochloride Dihydrate, USP	Active	4.886	
	Polyethylene Oxide, NF (b) (4)		(b) (4)	
	Maltitol, NF (b) (4)			
	Lemon-Lime Flavor (b) (4)			
	Anhydrous Citric Acid, USP (b) (4)			
	Povidone, USP (b) (4) (b) (4			
	Acesulfame Potassium Salt, NF (b) (4)			
	Sodium Phosphate, Dibasic, Anhydrous, USP			
	FD&C Yellow #6 (b) (4)			
	Butylated Hydroxyanisole, NF (b) (4)			
(b) (4)	(b) (4)			(b) (4)
	(b) (4)			
	(b) (4)			
	(b) (4) Shellac, USP			
	Propylene Glycol, USP			
	FD&C Blue No.1 (b) (4)			
	(b) (4)			
	Total Weight:		**92.13**	**100**

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

Teva buprenorphine/naloxone sublingual films contain buprenorphine and naloxone. Buprenorphine is a partial agonist at the mu-opioid receptor and an antagonist at the kappa-opioid receptor. Naloxone is a potent antagonist at mu-opioid receptors and produces opioid withdrawal signs and symptoms in individuals physically dependent on full opioid agonists when administered parenterally.

Teva buprenorphine/naloxone sublingual film is proposed for the maintenance treatment of opioid dependence.

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

For maintenance treatment, the target dosage of buprenorphine hydrochloride and naloxone hydrochloride sublingual film is usually 16 mg/4 mg as a single daily dose. Prior to placement of the sublingual film strip, it is recommended to rinse the mouth with a small volume of room-temperature water. Place one buprenorphine hydrochloride and naloxone hydrochloride sublingual film under the tongue, close to the base on the left or right side and allow to completely dissolve. Film must be administered whole. Do not cut, chew, or swallow.

2.2 General Clinical Pharmacology

1. What is known about the PK characteristics of buprenorphine and naloxone for the listed drug, Suboxone sublingual tablet?

Plasma levels of buprenorphine increased with sublingual doses (in the range of 4 to 16 mg) but not in a directly dose-proportional manner. Naloxone did not affect the pharmacokinetics of buprenorphine. There was a trend toward an increase in naloxone concentrations with increase in dose. At the three naloxone doses of 1, 2, and 4 mg, levels above the limit of quantitation (0.05 ng/mL) were not detected beyond 2 hours in seven of eight subjects.

Buprenorphine is approximately 96% protein bound, primarily to alpha and beta globulin. Naloxone is approximately 45% protein bound, primarily to albumin.

Buprenorphine undergoes both N-dealkylation to norbuprenorphine and glucuronidation. The N-dealkylation pathway is mediated primarily by CYP3A4. Norbuprenorphine, the major metabolite, can further undergo glucuronidation. Norbuprenorphine has been found to bind opioid receptors in vitro; however, it has not been studied clinically for opioid-like activity. Naloxone undergoes direct glucuronidation to naloxone-3-glucuronide as well as N-dealkylation, and reduction of the 6-oxo group.

A mass balance study of buprenorphine showed complete recovery of radiolabel in urine (30%) and feces (69%) collected up to 11 days after dosing. Elimination half-life of buprenorphine ranges from 24 to 42 hours and naloxone has a mean elimination half-life ranging from 2 to 12 hours.

2. ***What moieties in the plasma appropriately identified and measured to assess the pharmacokinetics?***

Buprenorphine and its major metabolite norbuprenorphine and naloxone (unconjugated naloxone and total naloxone (unconjugated and conjugated naloxone)) are measured in all PK studies.

2.3 Intrinsic Factors

1. ***What is the pediatric plan?***

Teva does not plan to label or develop the product with any of the following: new indication, new dosing regimen, new active ingredient, new dosage form, or new route of administration. The agency agreed previously that pediatric studies will not be required under PREA for the proposed product (Written Response for PIND 118625 dated May 30, 2014).

2.4 General Biopharmaceutics

1. ***What are the relative bioavailabilities of buprenorphine and naloxone following the administration of Teva Buprenorphine/Naloxone Sublingual Film in comparison to the listed drug, Suboxone sublingual films?***

Teva buprenorphine/naloxone sublingual film 1 x 16/4 mg exhibited equivalent systemic exposure (Cmax, AUClast, and AUCinf) to buprenorphine and naloxone in comparison to the listed drug Suboxone sublingual film 2 x 8/2 mg. Note there is no 16/4 mg strength for Suboxone sublingual film.

The relative bioavailabilities of buprenorphine and naloxone following the administration of Teva buprenorphine/naloxone sublingual film administered as 1 x 16/4 mg dose in comparison to the listed drug, Suboxone sublingual film administered as 2 x 8/2 mg dose were evaluated in a single-dose, open-label, randomized, fasting, 4-period, 2-treatment, 2-sequence replicate cross-over study (Study 3007599) in 80 healthy subjects under naltrexone block. Naltrexone acts as a competitive antagonist at opioid receptor sites. Naltrexone 50 mg was administered at approximately 12 hours and at 0.5 hours prior to each dose of study medication, and at approximately 12 and 24 hours following each dose of study medication. The washout period between doses was at least 14 days. Subjects were given 60 mL of room temperature water to swish and swallow in order to moisten the mouth.

The buprenorphine plasma concentration-time profiles for Teva buprenorphine/naloxone sublingual film and Suboxone sublingual films are shown in **Figure 1**. The naloxone plasma concentration-time profiles for Teva buprenorphine/naloxone sublingual film and Suboxone sublingual films are shown in **Figure 2**. The summary of the PK parameters of buprenorphine, norbuprenorphine, naloxone, and total naloxone is presented in **Table 3**, **Table 4**, **Table 5**, **and Table 6**, respectively. Median (min, max) buprenorphine Tmax values for Teva buprenorphine/naloxone sublingual film and Suboxone sublingual film are 1.25 (0.33, 3.00) hr. Median (min, max) naloxone Tmax values for Teva buprenorphine/naloxone sublingual film is 0.75 (0.33, 2.00) hr, which is the same as that for Suboxone sublingual film 0.75 (0.33, 2.50) h.

Figure 1 Mean Buprenorphine Plasma Concentration (ng/mL) Time Profiles after Administration of 1 x 16/4 mg Teva Buprenorpine/Nalxone Sublingual Film (Treatment A) and 2 x 8/2 mg Suboxone Sublingual Film (Treatment B) (Study 3007599)

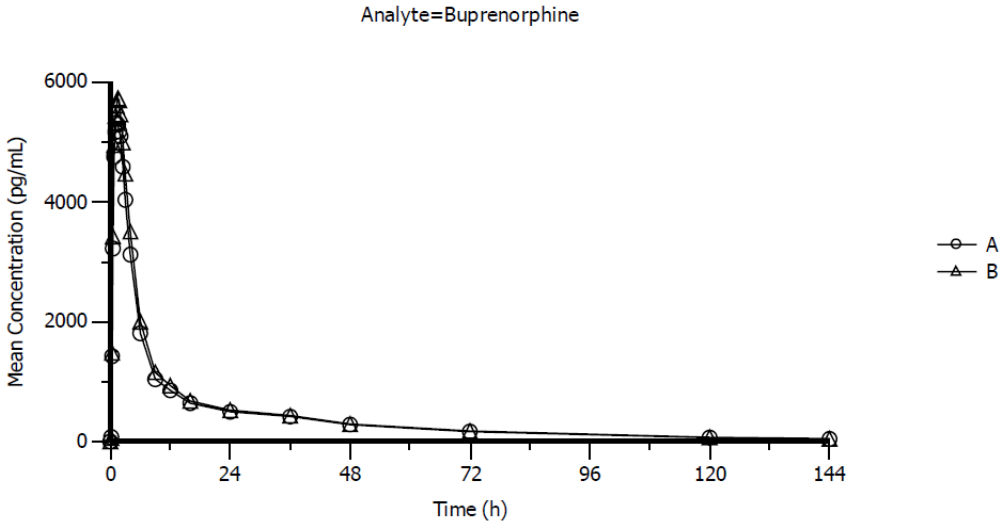


Figure 2 Mean Naloxone Plasma Concentration (pg/mL) Time Profiles after Administration of 1 x 16/4 Teva Buprenorphine/Naloxone Sublingual Film (Treatment A) and 2 x 8/2 mg Suboxone Sublingual Film (Treatment B) (Study 3007599)

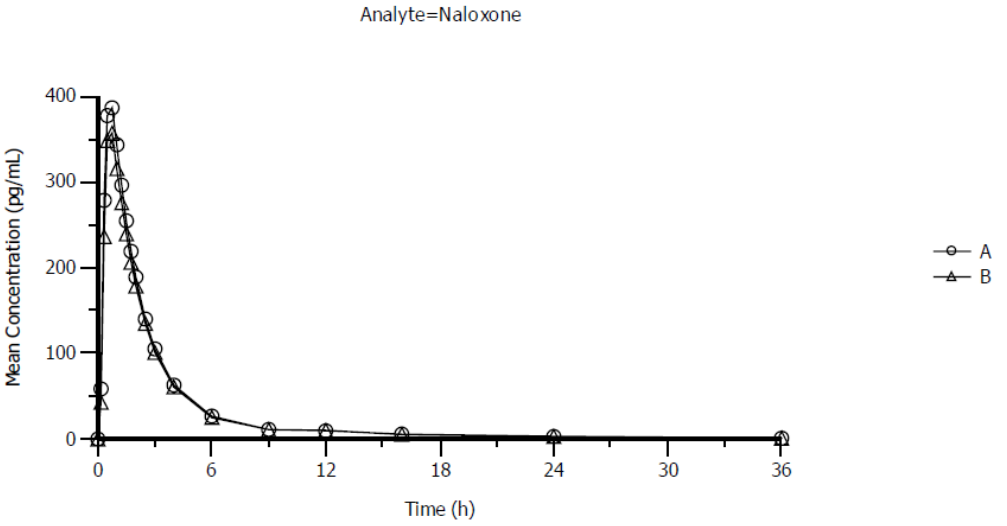


Table 3 Summary of the PK parameters of Buprenorphine following Administration of 1 x 16/4 mg Teva Buprenorphine/Naloxone Sublingual Film (Treatment A) and 2 x 8/2 mg Suboxone Sublingual Film (Treatment B) (Study 3007599)

	Treatment A (Teva Product)			Treatment B (Suboxone Film)		
	n	mean	SD	n	mean	SD
Cmax (pg/mL)	138	6223	3026	133	6752	3004
Tmax (h)	138	1.25	0.33, 3.00	133	1.25	0.33, 3.00
AUClast (h.pg/mL)	138	57392	22572	133	62350	22410
AUCinf (h.pg/mL)	138	60052	23463	133	65314	23398
T1/2 (h)	138	34.61	9.75	133	36.62	11.46

Note: Tmax shown as median (min, max).

Table 4 Summary of the PK parameters of Norbuprenorphine following Administration of 1 x 16/4 mg Teva Buprenorphine/Naloxone Sublingual Film (Treatment A) and 2 x 8/2 mg Suboxone Sublingual Film (Treatment B) (Study 3007599)

	Treatment A (Teva Product)			Treatment B (Suboxone Film)		
	n	mean	SD	n	mean	SD
Cmax (pg/mL)	137	2983	1673	133	3156	1602
Tmax (h)	137	1.00	0.33,48.00	133	1.00	0.49, 48.00
AUClast (h.pg/mL)	137	94096	39148	133	96584	38942
AUCinf (h.pg/mL)	136	104070	44896	132	107934	48882
T1/2 (h)	136	35.09	16.32	132	37.24	20.72

Note: Tmax shown as median (min, max).

Table 5 Summary of the PK parameters of Naloxone following Administration of 1 x 16/4 mg Teva Buprenorphine/Naloxone Sublingual Film (Treatment A) and 2 x 8/2 mg Suboxone Sublingual Film (Treatment B) (Study 3007599)

	Treatment A (Teva Product)			Treatment B (Suboxone Film)		
	n	mean	SD	n	mean	SD
Cmax (pg/mL)	138	439	245	133	413	237
Tmax (h)	138	0.75	0.33, 2.00	133	0.75	0.33, 2.50
AUClast (h.pg/mL)	138	1015	521	133	957	449
AUCinf (h.pg/mL)	138	1046	523	133	985	451
T1/2 (h)	138	6.56	6.16	133	5.85	4.39

Note: Tmax shown as median (min, max).

Table 6 Summary of the PK parameters of Total Naloxone following Administration of 1 x 16/4 mg Teva Buprenorphine/Naloxone Sublingual Film (Treatment A) and 2 x 8/2 mg Suboxone Sublingual Film (Treatment B) (Study 3007599)

	Treatment A (Teva Product)			Treatment B (Suboxone Film)		
	n	mean	SD	n	mean	SD
Cmax (ng/mL)	138	55.6	24.0	133	54.3	23.0
Tmax (h)	138	0.75	0.33, 6.03	133	0.75	0.33, 16.00
AUClast (h.ng/mL)	138	108.2	37.3	133	107.4	38.5
AUCinf (h.ng/mL)	138	111.9	37.7	132	111.0	38.8
T1/2 (h)	138	7.90	3.82	132	8.06	4.33

Note: Tmax shown as median (min, max).

The statistical analysis results for the assessment of relative bioavailability are presented in the **Tables 7** and **8**. Teva buprenorphine/naloxone sublingual film 1 x 16/4 mg exhibited equivalent Cmax, AUClast, and AUCinf to Suboxone film 2 x 8/2 mg as the 90% CIs of Teva buprenorphine/naloxone sublingual film to Suboxone sublingual film geometric mean ratios for buprenorphine and naloxone Cmax, AUClast, and AUCinf fell within the bioequivalence limits of 80 to 125%.

Table 7 Summary of the Statistical Analysis of PK Parameters of Buprenorphine Comparing 1 x 16/4 mg Teva Buprenorphine/Naloxone Sublingual Film (Test) to 2 x 8/2 mg Suboxone Sublingual Film (Reference) (Study 3007599)

Variable	Geometric Mean		Ratio (%) (A/B)	90% CI	
	Treatment A (Teva Product) (N = 138)	Treatment B (Suboxone Film) (N = 133)		Lower	Upper
Cmax (pg/mL)	5424	6055	89.58	83.98	95.56
AUClast (h.pg/mL)	51945	58222	89.22	84.37	94.35
AUCinf (h.pg/mL)	54435	60918	89.36	84.56	94.43

Table 8 Summary of the Statistical Analysis of PK Parameters of Naloxone Comparing 1 x 16/4 mg Teva Buprenorphine/Naloxone Sublingual Film (Test) to 2 x 8/2 mg Suboxone Sublingual Film (Reference) (Study 3007599)

Variable	Geometric Mean		Ratio (%) (A/B)	90% CI	
	Treatment A (Teva Product) (N = 138)	Treatment B (Suboxone Film) (N = 133)		Lower	Upper
Cmax (pg/mL)	364.2	353.5	103.02	95.80	110.78
AUClast (h.pg/mL)	877.7	869.8	100.91	95.28	106.87
AUCinf (h.pg/mL)	912.6	898.6	101.55	96.11	107.31

Reviewer's Comment: Sponsor initially conducted BE analysis using Reference-Scaled BE procedure for naloxone Cmax because of its high intra-subject variability following the administrations of the reference product, Suboxone sublingual film. Upon request, sponsor repeated the analysis using average BE approach and demonstrated BE because the 90% CI for the geometric mean ratios of naloxone Cmax, AUClast, and AUCinf fell within the 80-125% range.

2. ***How do the pretreatments with water at different temperatures affect the bioavailability of Teva Buprenorphine/Naloxone Sublingual Film?***

Pretreatment of cold water had no effect on buprenorphine or naloxone Cmax and AUC values. Pretreatment with hot water increased buprenorphine Cmax by 15% and had no effect on buprenorphine AUC values or naloxone Cmax or AUC values.

The effects of pretreatments with water at different temperatures on buprenorphine and naloxone absorption from Teva buprenorphine/naloxone sublingual film (16/4 mg buprenorphine/naloxone) was evaluated in Study 4001650. This was an open-label, single-dose, 3-period, 3-treatment, 3-way crossover study in 24 healthy subjects with naltrexone block. Naltrexone acts as a competitive antagonist at opioid receptor sites. Naltrexone 50 mg was administered at approximately 12 hours prior and at 0.5 hours prior to each dose of study medication, and at approximately 12 and 24 hours following

each dose of study medication. Each dose was administered after a 10-hour overnight fast. Before each dose, subjects were pretreated with cold water (mean temperature of 2.2°C (range 0.2-4.7°C), hot water (mean temperature of 50.8°C (range 48.5-53.7°C), or room temperature water (mean temperature of 21.5°C (range 19.1-24.9°C). Subjects were instructed to swish the 60 mL water in his or her mouth and to swallow the water approximately 30 seconds before dosing. Each drug administration was separated by a washout of 14 days.

Buprenorphine concentration-time profiles are shown in **Figure 3** and buprenorphine PK parameters are summarized in **Table 9**. Naloxone concentration-time profiles are shown in **Figure 4** and naloxone PK parameters are summarized in **Table 10**.

Figure 3 Mean Buprenorphine Concentration-Time Profiles after Administration of Teva Buprenorphine/Naloxone Sublingual Film 1 x 16/4 mg with Cold Water (Treatment A), Hot Water (Treatment B), or Room Temperature Water (Treatment C) (Study 4001650)

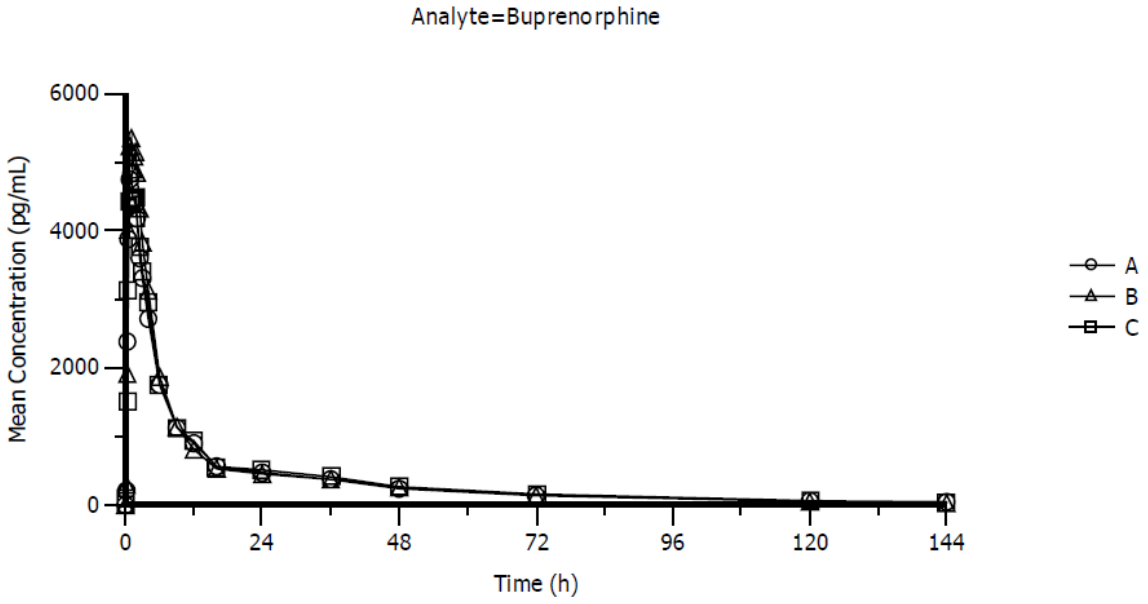


Table 9 Pharmacokinetic Parameters of Buprenorphine after Administration of Teva Buprenorphine/Naloxone Sublingual Film 1 x 16/4 mg with Cold Water (Treatment A), Hot Water (Treatment B), or Room Temperature Water (Treatment C) (Study 4001650)

Variable	Treatment A (N=20)	Treatment B (N=20)	Treatment C (N=20)
T_{max} (h)[a]	1.12 (0.33, 2.00)	1.00 (0.50, 3.00)	1.00 (0.33, 2.00)
C_{max} (pg/mL)	5940 (2720)	6670 (4250)	5410 (2560)
AUC_{last} (h*pg/mL)	52780 (19450)	54200 (24880)	55020 (20960)
AUC_{inf} (h*pg/mL)	56820 (22690)	56720 (26210)	57670 (22300)
AUC_{Extrap} (%)	5.97 (5.59)	4.87 (3.86)	4.46 (2.23)
λ_z (1/h)	0.0180 (0.0057)	0.0209 (0.0043)	0.0197 (0.0028)
$T_{1/2}$ (h)	42.94 (16.13)	34.74 (7.79)	35.83 (5.20)
T_{last} (h)	139.20 (9.85)	128.40 (26.15)	138.08 (10.52)
C_{last} (pg/mL)	54.0 (51.5)	45.8 (27.7)	48.2 (29.9)

SOURCE: Summary 14.2.5, Listing 16.2.6.1.
[a]Median (range) is presented for T_{max}.

Figure 4 Mean Naloxone Concentration-Time Profiles after Administration of Teva Buprenorphine/Naloxone Sublingual Film 1 x 16/4 mg with Cold Water (Treatment A), Hot Water (Treatment B), or Room Temperature Water (Treatment C) (Study 4001650)

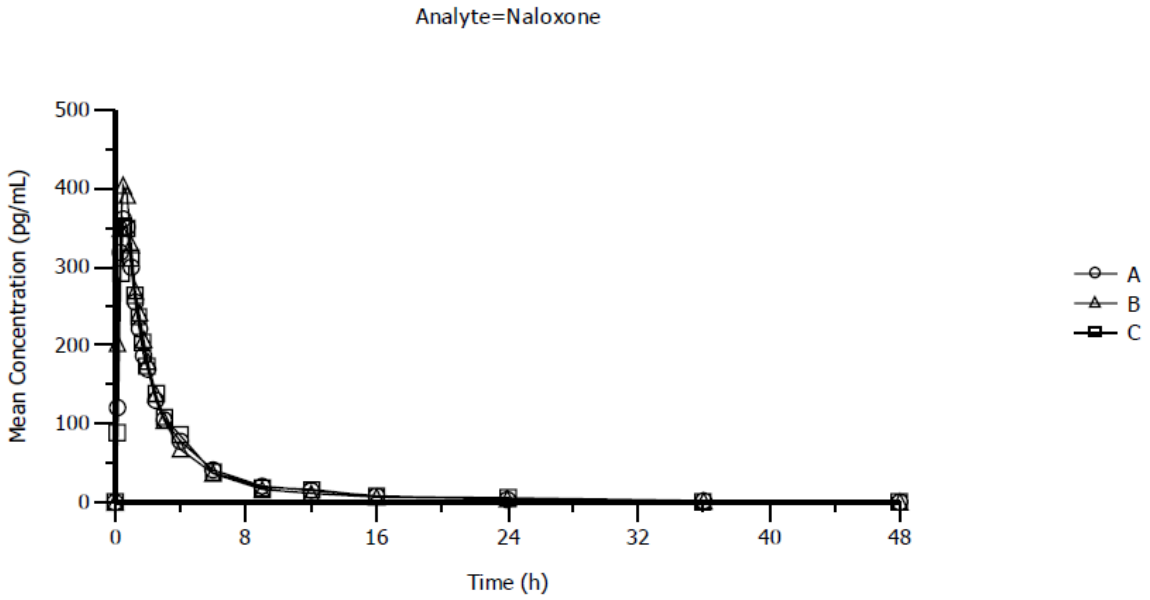


Table 10 Pharmacokinetic Parameters of Naloxone after Administration of Teva Buprenorphine/Naloxone Sublingual Film 1 x 16/4 mg with Cold Water (Treatment A), Hot Water (Treatment B), or Room Temperature Water (Treatment C) (Study 4001650)

Variable	Treatment A (N=20)	Treatment B (N=20)	Treatment C (N=20)
T_{max} (h)[a]	0.50 (0.33, 1.00)	0.50 (0.16, 1.25)	0.50 (0.33, 1.00)
C_{max} (pg/mL)	407 (205)	471 (334)	384 (149)
AUC_{last} (h*pg/mL)	1108 (546.1)	1132 (645.9)	1136 (720.0)
AUC_{inf} (h*pg/mL)	1139 (552.6)	1163 (664.0)	1169 (718.3)
AUC_{Extrap} (%)	2.92 (2.48)	3.00 (2.68)	3.55 (3.26)
λ_z (1/h)	0.1832 (0.0791)	0.1802 (0.0969)	0.1547 (0.0820)
$T_{1/2}$ (h)	4.89 (3.04)	5.16 (2.94)	6.47 (5.25)
T_{last} (h)	26.20 (9.75)	25.40 (11.18)	27.20 (10.90)
C_{last} (pg/mL)	4.49 (4.00)	3.72 (1.73)	3.68 (2.15)

SOURCE: Summary 14.2.7, Listing 16.2.6.3.
[a]Median (range) is presented for T_{max}.

Statistical analysis of the log-transformed PK parameters of buprenorphine and naloxone comparing pretreatment with cold water to room temperature water and hot water to room temperature water are shown in **Tables 11**, **12**, **13**, and **14**.

Table 11 Statistical Analysis of the Log-Transformed PK Parameters of Buprenorphine Comparing Teva Buprenorphine/Naloxone Sublingual Film 1 x 16/4 mg Administered with Pretreatment of Cold Water (Treatment A: Test) vs. Administered with Pretreatment of Room Temperature Water (Treatment C: Reference) (Study 4001650)

	Geometric Mean[a]			90% CI[c]	
Variable	Treatment A (N=20)	Treatment C (N=20)	Ratio (%)[b] (A/C)	Lower	Upper
C_{max}	5155.3489	5016.2013	102.77	87.52	120.69
AUC_{last}	47929.5799	50093.2727	95.68	81.50	112.33
AUC_{inf}	51227.6464	52357.3682	97.84	84.02	113.94

Table 12 Statistical Analysis of the Log-Transformed PK Parameters of Naloxone Comparing Teva Buprenorphine/Naloxone Sublingual Film 1 x 16/4 mg Administered with Pretreatment of Cold Water (Treatment A: Test) vs. Administered with Pretreatment of Room Temperature Water (Treatment C: Reference) (Study 4001650)

	Geometric Mean[a]			90% CI[c]	
Variable	Treatment A (N=20)	Treatment C (N=20)	Ratio (%)[b] (A/C)	Lower	Upper
C_{max}	358.7820	367.9538	97.51	79.91	118.98
AUC_{last}	959.4326	972.0428	98.70	82.00	118.81
AUC_{inf}	991.6208	1005.2567	98.64	81.95	118.74

Table 13 Statistical Analysis of the Log-Transformed PK Parameters of Buprenorphine Comparing Teva Buprenorphine/Naloxone Sublingual Film 1 x 16/4 mg Administered with Pretreatment of Hot Water (Treatment B: Test) vs. Administered with Pretreatment of Room Temperature Water (Treatment C: Reference) (Study 4001650)

	Geometric Mean[a]			90% CI[c]	
Variable	Treatment B (N=20)	Treatment C (N=20)	Ratio (%)[b] (B/C)	Lower	Upper
C_{max}	5761.6590	5016.2013	114.86	97.65	135.10
AUC_{last}	49581.3799	50093.2727	98.98	84.17	116.39
AUC_{inf}	52403.8842	52357.3682	100.09	85.81	116.74

Table 14 Statistical Analysis of the Log-Transformed PK Parameters of Naloxone Comparing Teva Buprenorphine/Naloxone Sublingual Film 1 x 16/4 mg Administered with Pretreatment of Hot Water (Treatment B: Test) vs. Administered with Pretreatment of Room Temperature Water (Treatment C: Reference) (Study 4001650)

	Geometric Mean[a]			90% CI[c]	
Variable	Treatment B (N=20)	Treatment C (N=20)	Ratio (%)[b] (B/C)	Lower	Upper
C_{max}	387.3220	367.9538	105.26	86.09	128.71
AUC_{last}	945.8740	972.0428	97.31	80.69	117.35
AUC_{inf}	973.8503	1005.2567	96.88	80.33	116.83

Pretreatment of cold water had no effect on buprenorphine or naloxone Cmax and AUC values. The point estimate (90% CI) of the geometric mean ratio (cold water/room temperature water) for buprenorphine Cmax, AUClast, and AUCinf values are 102.77% (87.52 – 120.69%), 95.68% (81.50 – 112.33%), and 97.84% (84.02 – 113.94%), respectively. The point estimate (90% CI) of the geometric mean ratio (cold water/room

temperature water) for naloxone Cmax, AUClast, and AUCinf values are 97.51% (79.91 – 118.98%), 98.70% (82.00 – 118.81%), and 98.64% (81.95 – 118.74%), respectively.

Pretreatment with hot water increased buprenorphine Cmax by 15% and had no effect on buprenorphine AUC values or naloxone Cmax or AUC values. The point estimate (90% CI) of the geometric mean ratio (hot water/room temperature water) for buprenorphine Cmax, AUClast, and AUCinf values are 114.86% (97.65 – 135.10%), 98.98% (84.17 – 116.39%), and 100.09% (85.81 – 116.74%), respectively. The point estimate (90% CI) of the geometric mean ratio (hot water/room temperature water) for naloxone Cmax, AUClast, and AUCinf values are 105.26% (86.09 – 128.71%), 97.31% (80.69 – 117.35%), and 96.88% (80.33 – 116.83%), respectively.

3. How do the pretreatment with beverages of different pH values affect the bioavailability of Teva Buprenorphine/Naloxone Sublingual Film?

Pretreatment of low pH beverage (Sprite) decreased bupprenorpine Cmax and AUC values by 14-15% and decreased naloxone Cmax and AUC values by 30-36%, respectively. Pretreatment with high pH beverage (solution of ½ teaspoon of sodium bicarbonate) decreased buprenorphine Cmax and AUC values by 14-16%. Naloxone Cmax and AUC values were increased by 142% and 89-92%, respectively.

The effects of pretreatments with beverages with different pH values on buprenorphine and naloxone absorption from Teva buprenorphine/naloxone sublingual film (16/4 mg buprenorphine/naloxone) was evaluated in Study 4001651. This was an open-label, single-dose, 3-period, 3-treatment, 3-way crossover study in 24 healthy subjects with naltrexone block. Naltrexone acts as a competitive antagonist at opioid receptor sites. Naltrexone 50 mg was administered at approximately 12 hours prior and at 0.5 hours prior to each dose of study medication, and at approximately 12 and 24 hours following each dose of study medication. Each dose was administered after a 10-hour overnight fast. Before each dose, subjects were pretreated with a low pH beverage (Sprite (mean pH of 3.34 (range 3.33-3.36)) at room temperature, a high pH beverage (solution of ½ teaspoon of sodium bicarbonate (mean pH 7.99 (range 7.94-8.02)) at room temperature, or room temperature water (mean pH value of 7.51 (range 7.47-7.60)). Subjects were

instructed to swish the 60 mL beverage in his or her mouth and to swallow the beverage approximately 30 seconds before dosing. Each drug administration was separated by a washout of 14 days.

Buprenorphine concentration-time profiles are shown in **Figure 5** and buprenorphine PK parameters are summarized in **Table 15**. Naloxone concentration-time profiles are shown in **Figure 6** and naloxone PK parameters are summarized in **Table 16**.

Figure 5 Mean Buprenorphine Concentration-Time Profiles after Administration of Teva Buprenorphine/Naloxone Sublingual Film 1 x 16/4 mg with a Room Temperature Low pH Beverage (Treatment A), Room Temperature High pH Beverage (Treatment B), or Room Temperature Water (Treatment C) (Study 4001651)

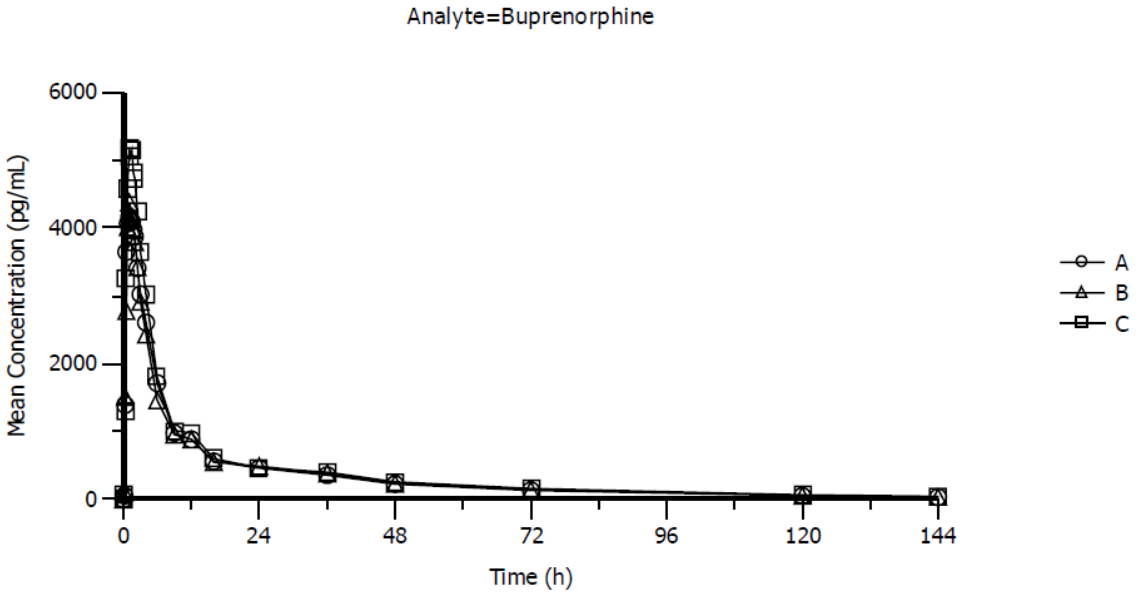


Table 15 Pharmacokinetic Parameters of Buprenorphine after Administration of Teva Buprenorphine/Naloxone Sublingual Film 1 x 16/4 mg with a Room Temperature Low pH Beverage (Treatment A), Room Temperature High pH Beverage (Treatment B), or Room Temperature Water (Treatment C) (Study 4001651)

Variable	A (N=21)	B (N=23)	C (N=21)
T_{max} (h)[a]	1.00 (0.50, 2.00)	1.00 (0.33, 2.50)	1.25 (0.50, 2.50)
C_{max} (pg/mL)	5180 (2070)	5070 (2010)	5990 (3650)
AUC_{last} (h*pg/mL)	48600 (16250)	48460 (13070)	54970 (20680)
AUC_{inf} (h*pg/mL)	50890 (16760)	50910 (13550)	58010 (21830)
AUC_{Extrap} (%)	4.69 (2.13)	4.92 (2.59)	5.18 (1.97)
λ_z (1/h)	0.0226 (0.0089)	0.0202 (0.0045)	0.0200 (0.0059)
$T_{1/2}$ (h)	34.12 (10.13)	36.09 (8.38)	37.36 (10.25)
T_{last} (h)	128.45 (28.77)	134.61 (21.39)	132.58 (25.87)
C_{last} (pg/mL)	46.5 (20.1)	47.1 (25.1)	56.9 (28.5)

SOURCE: Summary 14.2.5, Listing 16.2.6.1.
[a]Median (range) is presented for T_{max}.

Figure 6 Mean Naloxone Concentration-Time Profiles after Administration of Teva Buprenorphine/Naloxone Sublingual Film 1 x 16/4 mg with a Room Temperature Low pH Beverage (Treatment A), Room Temperature High pH Beverage (Treatment B), or Room Temperature Water (Treatment C) (Study 4001651)

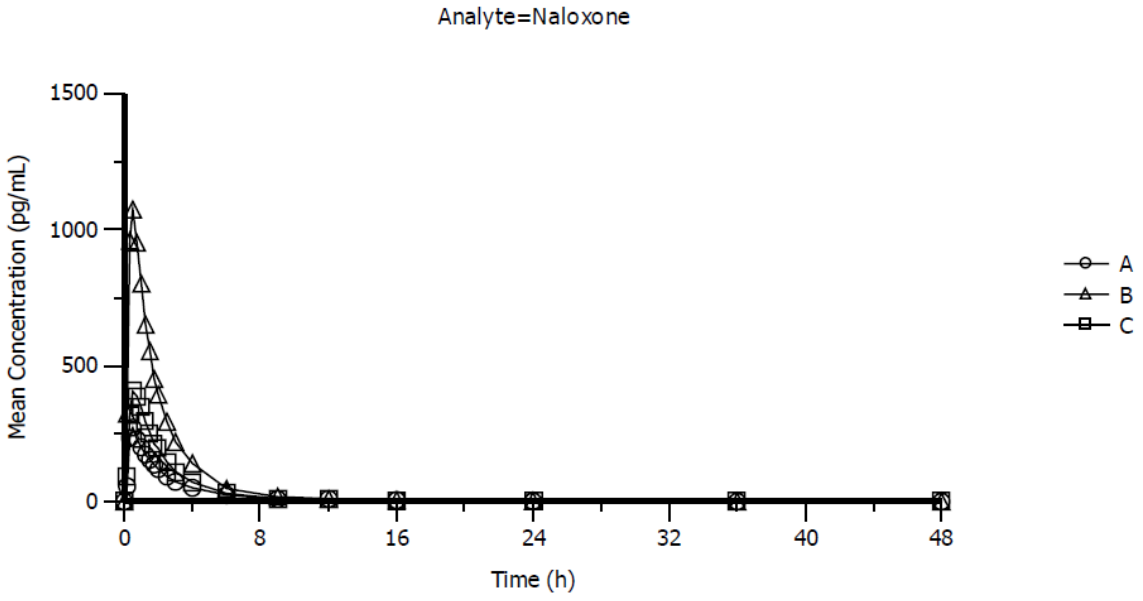


Table 16 Pharmacokinetic Parameters of Naloxone after Administration of Teva Buprenorphine/Naloxone Sublingual Film 1 x 16/4 mg with a Room Temperature Low pH Beverage (Treatment A), Room Temperature High pH Beverage (Treatment B), or Room Temperature Water (Treatment C) (Study 4001651)

Variable	A (N=21)	B (N=23)	C (N=21)
T_{max} (h)[a]	0.50 (0.33, 1.25)	0.50 (0.33, 1.00)	0.74 (0.33, 1.50)
C_{max} (pg/mL)	301 (162)	1200 (1120)	440 (431)
AUC_{last} (h*pg/mL)	701.8 (334.7)	2206 (1409)	1044 (729.5)
AUC_{inf} (h*pg/mL)	723.6 (336.0)	2222 (1408)	1068 (728.7)
AUC_{Extrap} (%)	4.12 (3.45)	1.02 (0.70)	2.79 (2.21)
λ_z (1/h)	0.2020 (0.0870)	0.2282 (0.1018)	0.1809 (0.0984)
$T_{1/2}$ (h)	4.21 (2.07)	3.90 (2.18)	5.56 (4.28)
T_{last} (h)	18.57 (6.17)	22.26 (5.76)	22.50 (5.87)
C_{last} (pg/mL)	3.83 (1.48)	3.09 (0.916)	3.00 (0.967)

SOURCE: Summary 14.2.7, Listing 16.2.6.3.
[a]Median (range) is presented for T_{max}.

Statistical analysis of the log-transformed PK parameters of buprenorphine and naloxone comparing pretreatment with low pH beverage to water and high pH beverage to water are shown in **Tables 17**, **18**, **19** and **20**.

Table 17 Statistical Analysis of the Log-Transformed PK Parameters of Buprenorphine Comparing Teva Buprenorphine/Naloxone Sublingual Film 1 x 16/4 mg Administered with Pretreatment of a Low pH Beverage (Treatment A: Test) vs. Administered with Pretreatment of Water (Treatment C: Reference) (Study 4001651)

	Geometric Mean[a]			90% CI[c]	
Variable	A (N=21)	C (N=21)	Ratio (%)[b] (A/C)	Lower	Upper
C_{max}	4589.0190	5317.2454	86.30	74.45	100.05
AUC_{last}	44168.2754	52104.1117	84.77	75.78	94.83
AUC_{inf}	46412.6134	54911.1838	84.52	75.63	94.46

Table 18 Statistical Analysis of the Log-Transformed PK Parameters of Naloxone Comparing Teva Buprenorphine/Naloxone Sublingual Film 1 x 16/4 mg Administered with Pretreatment of a Low pH Beverage (Treatment A: Test) vs. Administered with Pretreatment of Water (Treatment C: Reference) (Study 4001651)

	Geometric Mean[a]			90% CI[c]	
Variable	A (N=21)	C (N=21)	Ratio (%)[b] (A/C)	Lower	Upper
C_{max}	238.3285	342.6151	69.56	54.74	88.39
AUC_{last}	575.1872	898.8082	63.99	52.29	78.32
AUC_{inf}	600.9381	924.4982	65.00	53.35	79.20

Table 19 Statistical Analysis of the Log-Transformed PK Parameters of Buprenorphine Comparing Teva Buprenorphine/Naloxone Sublingual Film 1 x 16/4 mg Administered with Pretreatment of a High pH Beverage (Treatment B: Test) vs. Administered with Pretreatment of Water (Treatment C: Reference) (Study 4001651)

	Geometric Mean[a]			90% CI[c]	
Variable	B (N=23)	C (N=21)	Ratio (%)[b] (B/C)	Lower	Upper
C_{max}	4467.1495	5317.2454	84.01	72.58	97.25
AUC_{last}	44668.9238	52104.1117	85.73	76.73	95.79
AUC_{inf}	47011.2707	54911.1838	85.61	76.69	95.57

Table 20 Statistical Analysis of the Log-Transformed PK Parameters of Naloxone Comparing Teva Buprenorphine/Naloxone Sublingual Film 1 x 16/4 mg Administered with Pretreatment of a High pH Beverage (Treatment B: Test) vs. Administered with Pretreatment of Water (Treatment C: Reference) (Study 4001651)

	Geometric Mean[a]			90% CI[c]	
Variable	B (N=23)	C (N=21)	Ratio (%)[b] (B/C)	Lower	Upper
C_{max}	828.1384	342.6151	241.71	190.69	306.39
AUC_{last}	1722.3238	898.8082	191.62	156.89	234.04
AUC_{inf}	1745.5301	924.4982	188.81	155.28	229.58

Pretreatment of low pH beverage (Sprite) decreased bupprenorpine Cmax and AUC values by 14-15% and decreased naloxone Cmax and AUC values by 30-36%, respectively. The point estimate (90% CI) of the geometric mean ratio (low pH beverage/water) for buprenorphine Cmax, AUClast, and AUCinf values are 86.30%

(74.45 – 100.05%), 84.77% (75.78 – 94.83%), and 84.52% (75.63 – 94.46%), respectively. The point estimate (90% CI) of the geometric mean ratio (low pH beverage/water) for naloxone Cmax, AUClast, and AUCinf values are 69.56% (54.74 – 88.39%), 63.99% (52.29 – 78.32%), and 65.00% (53.35 – 79.20%), respectively.

Pretreatment with high pH beverage (solution of ½ teaspoon of sodium bicarbonate) decreased buprenorphine Cmax and AUC values by 14-16%. Naloxone Cmax and AUC values were increased by 142% and 89- 92%, respectively. The point estimate (90% CI) of the geometric mean ratio (high pH beverage/water) for buprenorphine Cmax, AUClast, and AUCinf values are 84.01% (72.58 – 97.25%), 85.73% (76.73 – 95.79%), and 85.61% (76.69 – 95.57%), respectively. The point estimate (90% CI) of the geometric mean ratio (high pH beverage/water) for naloxone Cmax, AUClast, and AUCinf values are 241.71% (190.69 – 306.39%), 191.62% (156.89 – 234.04%), and 188.81% (155.28 – 229.58%), respectively. Sponsor proposed to instruct patients to avoid high pH beverages prior to dosing.

2.5 Analytical Section

1. Do the bioanalytical methods adequately validated for determining plasma concentrations of buprenorphine, norbuprenorphine, naloxone, and total naloxone?

Validated LC-MS/MS methods were used for the determination of buprenorphine, unconjugated naloxone, norbuprenorphine, naloxone (unconjugated naloxone), and total naloxone (unconjugated and conjugated naloxone) in human plasma. The bioanalytical methods are summarized in the following **Table 21**.

Table 21 Summary of Bioanalytical Methods

Study	Analyte	Calibration Range	QC	QC Precision (%CV)	QC Accuracy (% Bias)
3007599	Buprenorphine	20.0 to 10000 pg/mL	50.0, 120, 450, 1600, and 7500 pg/mL	4.27 to 5.42%	-3.21 to 0.999%
	Norbuprenorphine	20.0 to 10000 pg/mL	50.0, 120, 450, 1600, and 7500 pg/mL	4.59 to 6.01%	-7.86 to -4.66%
	Naloxone	2.00 to 1000 pg/mL	5.00, 12.0, 45.0, 160, and 750 pg/mL	4.00 to 5.30%	-2.16 to -0.93%
	Total Naloxone	0.100 to 100 ng/mL	0.300, 0.750, 3.00, 12.0, and 75.0 ng/mL	5.02 to 6.15%	1.53 to 6.12%
4001650	Buprenorphine	20.0 to 10000 pg/mL	50.0, 120, 450, 1600, and 7500 pg/mL	2.32 to 5.40%	0.305 to 4.52%
	Norbuprenorphine	20.0 to 10000 pg/mL	50.0, 120, 450, 1600, and 7500 pg/mL	3.26 to 4.67%	1.34 to 2.79%
	Naloxone	2.00 to 1000 pg/mL	5.00, 12.0, 45.0, 160, and 750 pg/mL	2.97 to 7.52%	3.45 to 7.66%
	Total Naloxone	0.100 to 100 ng/mL	0.300, 0.750, 3.00, 12.0, and 75.0 ng/mL	3.75 to 7.41%	3.30 to 5.95%
4001651	Buprenorphine	20.0 to 10000 pg/mL	50.0, 120, 450, 1600, and 7500 pg/mL	2.82 to 4.07%	0.953 to 3.55%

	Norbuprenorphine	20.0 to 10000 pg/mL	50.0, 120, 450, 1600, and 7500 pg/mL	2.99 to 4.61%	0.547 to 3.70%
	Naloxone	2.00 to 1000 pg/mL	5.00, 12.0, 45.0, 160, and 750 pg/mL	2.85 to 6.17%	3.48 to 6.69%
	Total Naloxone	0.100 to 100 ng/mL	0.300, 0.750, 3.00, 12.0, and 75.0 ng/mL	4.56 to 6.71%	4.13 to 4.93%

3 Labeling Recommendations

As of today (6/2/2016) labeling negotiation with sponsor is still ongoing.

4 Appendix

4.1 Clinical Pharmacology Filing Memo

Office of Clinical Pharmacology

New Drug Application Filing and Review Form

General Information About the Submission

	Information		Information
NDA/BLA Number	208-042 resubmission	Proposed Brand Name	
OCP Division (I, II, III, IV, V)	II	Generic Name	buprenorphine and naloxone sublingual film
Medical Division	DAAAP	Drug Class	opioid
OCP Reviewer	Wei Qiu, Ph.D.	Indication(s)	For the maintenance treatment of opioid dependence
OCP Team Leader	Yun Xu, Ph.D.	Dosage Form, Strength	Sublingual film: 16 mg/4 mg
Pharmacometrics Reviewer	N/A	Dosing Regimen	
Date of Submission	November 30, 2015	Route of Administration	Sublingual
Primary Review Goal Date (GRMP)	August 19, 2016	Sponsor	Teva Pharmaceuticals USA
		Priority Classification	Standard
PDUFA Due Date	September 30, 2016	Relevant INDs	IND 118625

Clin. Pharm. and Biopharm. Information

	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	x			
Tabular Listing of All Human Studies	x			
HPK Summary	x			
Labeling	x			
Reference Bioanalytical and Analytical Methods	x			
I. Clinical Pharmacology				
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:	x	3		Studies 3007599, 4001650, and 4001651
multiple dose:				
Patients-				
single dose:				
multiple dose:				
Dose proportionality -				
fasting / non-fasting single dose:				
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				
In-vivo effects on primary drug:				
In-vivo effects of primary drug:				
In-vitro:				
Subpopulation studies -				
ethnicity:				
gender:				
pediatrics:				
geriatrics:				
renal impairment:				
hepatic impairment:				
PD -				
Phase 1:				
Phase 2:				
Phase 3:				
PK/PD -				
Phase 1 and/or 2, proof of concept:				

Phase 3 clinical trial:				
Population Analyses -				
Data rich:				
Data sparse:				
II. Biopharmaceutics				
Absolute bioavailability				
Relative bioavailability -				
solution as reference:				
alternate formulation as reference:				
Bioequivalence studies -				
traditional design; single / multi dose:				
replicate design; single / multi dose:	x	1		Study 3007599
Food-drug interaction studies	x	2		Study 4001650 (effect of temperature) Study 4001651 (effect of pH)
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		3		

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?			√	To be marketed formulation was used in all PK studies
2	Has the applicant provided metabolism and drug-drug interaction information?		√		No new findings in the proposed label.
3	Has the sponsor submitted bioavailability data satisfying the CFR requirements?	√			Relative BA study was conducted with the list drug, Suboxone (buprenorphine and naloxone) sublingual film (NDA 22410)
4	Did the sponsor submit data to allow the evaluation of the validity of the analytical assay?	√			
5	Has a rationale for dose selection been submitted?			√	Match the exposure of the list drug
6	Is the clinical pharmacology and biopharmaceutics section of the NDA organized, indexed and paginated in a manner to allow substantive review to begin?	√			
7	Is the clinical pharmacology and biopharmaceutics section of the NDA legible so that a substantive review can begin?	√			
8	Is the electronic submission searchable,	√			

	does it have appropriate hyperlinks and do the hyperlinks work?				
Criteria for Assessing Quality of an NDA (Preliminary Assessment of Quality)					
	Data				
9	Are the data sets, as requested during pre-submission discussions, submitted in the appropriate format (e.g., CDISC)?	√			
10	If applicable, are the pharmacogenomic data sets submitted in the appropriate format?			√	
	Studies and Analyses				
11	Is the appropriate pharmacokinetic information submitted?	√			
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)?			√	
13	Are the appropriate exposure-response (for desired and undesired effects) analyses conducted and submitted as described in the Exposure-Response guidance?			√	
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?			√	
15	Are the pediatric exclusivity studies adequately designed to demonstrate effectiveness, if the drug is indeed effective?			√	Request waiver and deferral
16	Did the applicant submit all the pediatric exclusivity data, as described in the WR?			√	
17	Is there adequate information on the pharmacokinetics and exposure-response in the clinical pharmacology section of the label?	√			
	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?	√			
19	Was the translation (of study reports or other study information) from another language needed and provided in this submission?			√	

IS THE CLINICAL PHARMACOLOGY SECTION OF THE APPLICATION FILEABLE?
___YES_____

The final to-be-marketed formulation was used in all PK studies which was confirmed by sponsor on November 25, 2014. PK datasets and bioanalytical reports were included. The original NDA was fileable from clinical pharmacology perspective. Review comment on the use of Reference Scaled Average Bioequivalence (RSAB) method for the analysis of naloxone exposure was conveyed to the sponsor. In this resubmission, Teva responded and stated that they believes the RSAB methodology was applied appropriately and they acknowledge that acceptability will be determined during the Agency's review.

The NDA resubmission is fileable from clinical pharmacology perspective.

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.

Provide bioequivalence analysis on naloxone pharmacokinetic data using average bioequivalence approach.

Reviewing Clinical Pharmacologist Date

Team Leader/Supervisor Date

Background:

On 29 October 2014, Teva Pharmaceuticals USA submitted a 505(b)(2) NDA 208042 for buprenorphine and naloxone sublingual film 16 mg/4 mg for the maintenance treatment of opioid dependence. This NDA relied on the Agency's previous findings of safety and effectiveness for Suboxone sublingual film (NDA 22-410) and literature. The to-be-marketed formulation was used in pivotal comparative bioavailability study (Study 3007599), effect of temperature (Study 4001650), and effect of pH (Study 4001651). The overall clinical and clinical pharmacology program consisted the 3 single-dose Phase 1 (Studies 3007599, 4001650, and 4001651). OSI inspection was requested for the pivotal relative BA Study 3007599.

Sponsor's summary on relative bioavailability of their proposed product in comparison to the list drug, Suboxone sublingual film, effect of temperature, and effect of pH:

- Teva buprenorphine/naloxone sublingual film 1 x 16/4 mg exhibited equivalent Cmax and AUC values of buprenorphine and naloxone in comparison to Suboxone sublingual film 2 x 8/2 mg
- Effect of temperature: with the exception of total naloxone following pretreatment with a hot beverage, the relative biovailability of buprenorphine, norbuprenorphine, OSI inspection needs to be requested for the pivotal comparative bioavailability Study

3007599. unconjugated naloxone, and total naloxone (cold beverage only) following pretreatment with cold and hot beverages was similar to that following pretreatment with a room temperature beverage, with geometric mean ratios ranging from 92.35% (hot beverage, norbuprenorphine AUClast) to 114.86% (hot beverage, buprenorphine Cmax). The geometric mean ratios for total naloxone after a hot beverage compared to a room temperature beverage were lower, ranging from 73.22% to 78.69%.

- Effect of pH: the relative bioavailability of buprenorphine, norbuprenorphine, and total naloxone following pretreatment with low pH and high pH beverages compared to that following pretreatment with room temperature water was similar, with geometric mean ratios ranging from 84.01% (high pH, buprenorphine Cmax) to 108.86% (low pH, norbuprenophine Cmax). The pretreatment conditions influenced the relative bioavailability of unconjugated naloxone; the geometric mean ratios for low pH versus water were 74.87% to 75.98% and the geometric mean ratios for high pH versus water were 187.98% to 241.17%.

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NDA 208-042
Buprenorphine and Naloxone Sublingual Film 16 mg/4 mg

Sponsor: Teva Pharmaceuticals

Filing Meeting

January 11, 2015

1

U.S. Food and Drug Administration

Clin Pharm Comment Conveyed to Sponsor

- Comment to Sponsor: Your evaluation of the bioequivalence for unconjugated naloxone between your product and the reference product in Study 3007599 employed the Reference Scaled Average Bioequivalence method. Note that that acceptability of this method will be determined during the course of the review.
- Sponsor's Response: Teva believes the Reference Scaled Average Bioequivalence methodology was applied appropriately and we acknowledge that acceptability will be determined during the Agency's review.
- Will ask sponsor to provide bioequivalence analysis on naloxone PK data using average bioequivalence approach (to be included in Day 74 letter).

2

Drug Product

- Proposed strength: 16 mg buprenorphine/4 mg naloxone SL film
- Proposed indication: for the maintenance treatment of opioid dependence.
- 505(b)(2) NDA
- Listed Drug: Suboxone sublingual film 2/0.5 mg, 4/1 mg, 8/2 mg, and 12/3 mg (NDA 22-410)

3

Clin Pharm Program

- Comparative BA Study 3007599
  - One Teva Bup/Nal SL film 16/4 mg
  - Two Suboxone SL film 8/2 mg
- Effect of temperature Study 4001650
  - Pretreatment with cold and hot vs room temperature beverage
- Effect of pH Study 4001651
  - Pretreatment with low and high pH vs water
- Each PK study was conducted in healthy adult subjects on a background of naltrexone blockage, consisting of naltrexone HCl tablets 50 mg administered orally at 12 h and at 30 min before study drug administration and at 12 h and 24 h after study drug administration (for a total of 4 naltrexone 50-mg doses

4

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Comparative BA Study (3007599)

- SD, R, 4-period, 2-treatment, 4-way full replicate design comparative BA study, healthy subjects (n = 80)
  - A: 1 x Teva Bup/Nal SL film 16 mg/4 mg (test)
  - B: 2 x Suboxone® SL film 8 mg/2 mg (reference)

5

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Study 3007599 Result – Equivalent BUP Exposure

Figure 11.4.3.1 Mean Buprenorphine Concentration-Time Profiles after Administration of the Test Formulation (Treatment A) and the Reference Product (Treatment B)

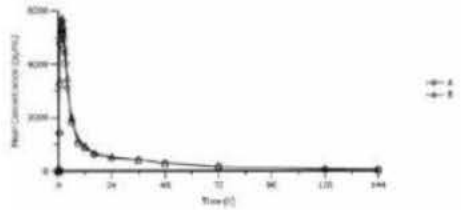

Table 11.4.3.10 Statistical Analysis of the Log-Transformed Systemic Exposure Parameters of Buprenorphine

Dependent Variable	Geometric Mean¹		Ratio (%)²	90% CI³		Power	ANOVA CV%	
	Test	Ref	(Test/Ref)	Lower	Upper		Test	Ref
$ln(C_{max})$	5425.3075	6017.8341	90.15	84.21	95.88	1.0000	38.20	28.99
$ln(AUC_{0-t})$	51961.2590	58054.7538	89.52	84.63	94.68	1.0000	35.08	23.99
$ln(AUC_{0-\infty})$	54458.1383	60749.3026	89.65	84.81	94.75	1.0000	34.51	19.87

6

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Study 3007599 Result – Equivalent NX Exposure

Figure 11.4.3.3 Mean Unconjugated Naloxone Concentration-Time Profiles after Administration of the Test Formulation (Treatment A) and the Reference Product (Treatment B)

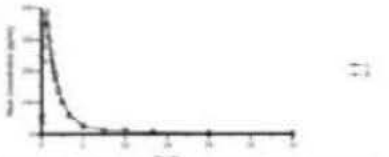

Table 11.4.3.12 Statistical Analysis of the Natural Log Transformed Systemic Exposure Parameters of Unconjugated Naloxone Using Reference Scaled Average Bioequivalence Analysis

Dependent Variable	n_{eff}	Ratio (%)[2] (Test/Ref)	95% Upper Bound[2]
$ln(C_{max})$	0.7044	107.93	45.06
$ln(AUC_{0-t})$	0.2435	-	-
$ln(AUC_{0-\infty})$	0.2276	-	-

Table 11.4.3.13 Statistical Analysis of the Log-Transformed Systemic Exposure Parameters of Unconjugated Naloxone

Dependent Variable	Geometric Mean[1] Test	Ref	Ratio (%)[2] (Test/Ref)	90% CI Lower	Upper	Power	ANOVA CV% Test	Ref
$ln(AUC_{0-t})$	870.4212	807.2803	110.28	93.62	107.26	1.0000	32.44	23.22
$ln(AUC_{0-\infty})$	913.3231	804.0158	110.53	94.15	107.71	1.0000	31.84	22.72

7

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Impact of Pretreatment with Beverages at Different Temperatures (Study 4001650)

- SD, 3-P, 3-Trt, 3-Way CO study, fasting, healthy subjects (n = 24), effect of pretreatment with beverages at different temperatures on BA of one Teva Bup/Nal SL film 16 mg/4 mg
  - A: 60 mL of cold water between 0°C and 4°C 1 min before dosing (test)
  - B: 60 mL of hot water between 48°C and 52°C 1 min before dosing (test)
  - C: 60 mL of room temperature water 1 min before dosing (reference)

8

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Study 4001650 Results – Buprenorphine
No effect with Cold, 15%↑ in Cmax with Hot

Table 11.4.3.9 Statistical Analysis of the Log-Transformed Systemic Exposure Parameters of Buprenorphine Comparing Buprenorphine HCl and Naloxone HCl Dihydrate Sublingual Film Administered with Cold Beverage (Treatment A) vs. Administered with Room Temperature Beverage (Treatment C)

Dependent Variable	Geometric Mean[a]		Ratio (%)[b]	90% CI[c]	
	Test	Ref	(Test/Ref)	Lower	Upper
$\ln(C_{max})$	5155.3489	5016.2013	102.77	87.52	120.69
$\ln(AUC_{last})$	47033.5847	50097.2270	95.68	81.49	112.34
$\ln(AUC_{inf})$	51231.2298	52361.3446	97.84	84.01	113.95

Table 11.4.3.10 Statistical Analysis of the Log-Transformed Systemic Exposure Parameters of Buprenorphine Comparing Buprenorphine HCl and Naloxone HCl Dihydrate Sublingual Film Administered with Hot Beverage (Treatment B) vs. Administered with Room Temperature Beverage (Treatment C)

Dependent Variable	Geometric Mean[a]		Ratio (%)[b]	90% CI[c]	
	Test	Ref	(Test/Ref)	Lower	Upper
$\ln(C_{max})$	5761.6500	5016.2013	114.86	97.65	135.10
$\ln(AUC_{last})$	49581.1384	50097.2270	98.97	84.16	116.39
$\ln(AUC_{inf})$	52484.0645	52361.3446	100.08	85.80	116.74

9

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Study 4001650 – Similar Naloxone Exposure

Table 11.4.3.13 Statistical Analysis of the Log-Transformed Systemic Exposure Parameters of Unconjugated Naloxone Comparing Buprenorphine HCl and Naloxone HCl Dihydrate Sublingual Film Administered with Cold Beverage (Treatment A) vs. Administered with Room Temperature Beverage (Treatment C)

Dependent Variable	Geometric Mean[a]		Ratio (%)[b]	90% CI[c]	
	Test	Ref	(Test/Ref)	Lower	Upper
$\ln(C_{max})$	358.7820	367.9538	97.51	79.91	118.98
$\ln(AUC_{last})$	959.8182	972.4399	98.70	81.99	118.82
$\ln(AUC_{inf})$	992.0028	1005.6687	98.64	81.94	118.74

Table 11.4.3.14 Statistical Analysis of the Log-Transformed Systemic Exposure Parameters of Unconjugated Naloxone Comparing Buprenorphine HCl and Naloxone HCl Dihydrate Sublingual Film Administered with Hot Beverage (Treatment B) vs. Administered with Room Temperature Beverage (Treatment C)

Dependent Variable	Geometric Mean[a]		Ratio (%)[b]	90% CI[c]	
	Test	Ref	(Test/Ref)	Lower	Upper
$\ln(C_{max})$	387.3220	367.9538	105.26	86.09	128.71
$\ln(AUC_{last})$	946.0954	972.4399	97.29	80.67	117.34
$\ln(AUC_{inf})$	974.0802	1005.6687	96.86	80.31	116.82

10

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Impact of Pretreatment with Beverages at Different pH Values (Study 4001651)

- SD, 3-P, 3-Trt, 3-Way CO study, fasting, healthy subjects (n = 24), effect of pretreatment with beverages at different pH on BA of one Teva Bup/Nal SL film 16 mg/4 mg (all beverages administered at room temperature)
  - A: 60 mL of low pH beverage (Sprite) 1 min before dosing
  - B: 60 mL of high pH beverage (solution of ½ teaspoon of sodium bicarbonate) 1 min before dosing
  - C: 60 mL of room temperature water 1 min before dosing

11

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Study 4001651 – Buprenorphine ~15%↓ in Cmax and AUC with low or high pH

Table 11.4.3.9 Statistical Analysis of the Log-Transformed Systemic Exposure Parameters of Buprenorphine Comparing Buprenorphine HCl and Naloxone HCl Dihydrate Sublingual Film Administered with a Low pH Beverage (Treatment A) vs. Administered with Room Temperature Water (Treatment C)

Dependent Variable	Geometric Mean[a]		Ratio (%)[b]	90% CI	
	Test	Ref	(Test/Ref)	Lower	Upper
$\ln(C_{max})$	4589.0190	5317.2454	86.30	74.45	100.05
$\ln(AUC_{last})$	44172.5538	52106.5156	84.77	75.78	94.83
$\ln(AUC_{inf})$	46416.1007	54913.4226	84.53	75.63	94.47

Table 11.4.3.10 Statistical Analysis of the Log-Transformed Systemic Exposure Parameters of Buprenorphine Comparing Buprenorphine HCl and Naloxone HCl Dihydrate Sublingual Film Administered with a High pH Beverage (Treatment B) vs. Administered with Room Temperature Water (Treatment C)

Dependent Variable	Geometric Mean[a]		Ratio (%)[b]	90% CI	
	Test	Ref	(Test/Ref)	Lower	Upper
$\ln(C_{max})$	4467.1495	5317.2454	84.01	72.58	97.25
$\ln(AUC_{last})$	44070.1946	52106.5156	85.73	76.72	95.79
$\ln(AUC_{inf})$	47012.0707	54913.4226	85.61	76.69	95.57

12

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Study 4001651 Results – Naloxone
25%↓ in Cmax and AUC with low pH
141%↑ in Cmax and 91%↑ in AUCt with high pH

Table 11.4.3.13 Statistical Analysis of the Log-Transformed Systemic Exposure Parameters of Unconjugated Naloxone Comparing Buprenorphine HCl and Naloxone HCl Dihydrate Sublingual Film Administered with a Low pH (Treatment A) vs. Administered with Room Temperature Water (Treatment C)

Dependent Variable	Geometric Mean[a]		Ratio (%)[b]	90% CI[c]	
	Test	Ref	(Test/Ref)	Lower	Upper
$\ln(C_{max})$	257.1528	342.2235	75.14	56.58	99.80
$\ln(AUC_{last})$	671.6138	897.0038	74.87	51.18	109.54
$\ln(AUC_{inf})$	701.0312	922.6482	75.98	52.15	110.71

Table 11.4.3.14 Statistical Analysis of the Log-Transformed Systemic Exposure Parameters of Unconjugated Naloxone Comparing Buprenorphine HCl and Naloxone HCl Dihydrate Sublingual Film Administered with a High pH Beverage (Treatment B) vs. Administered with Room Temperature Water (Treatment C)

Dependent Variable	Geometric Mean[a]		Ratio (%)[b]	90% CI[c]	
	Test	Ref	(Test/Ref)	Lower	Upper
$\ln(C_{max})$	825.1246	342.2235	241.17	181.67	320.14
$\ln(AUC_{last})$	1711.2039	897.0038	190.78	130.49	278.91
$\ln(AUC_{inf})$	1734.5805	922.6482	187.98	129.10	273.71

13

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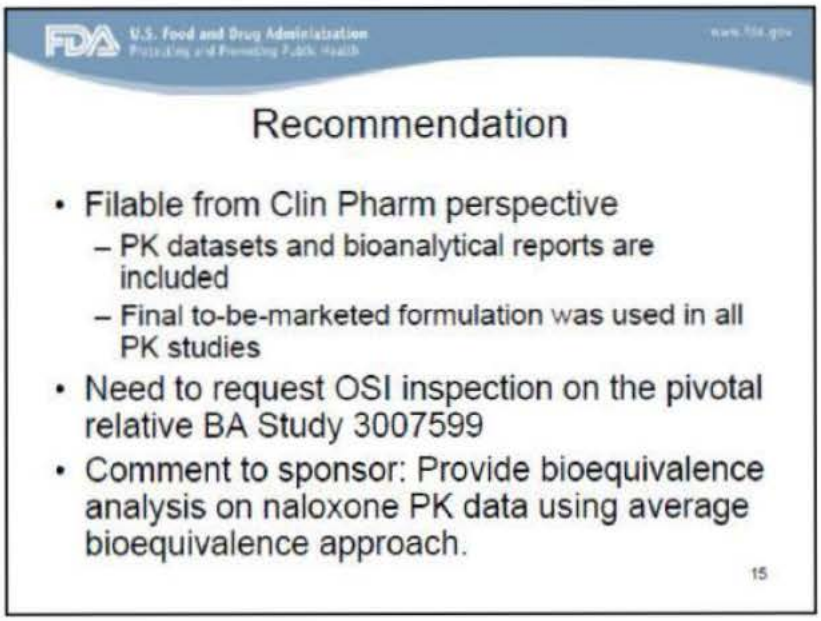
Summary

- BA of Teva BUP/NAL SL film 1 x 16 mg/4 mg vs. Suboxone SL film 2 x 8 mg/2 mg
  - BUP and NAL: equivalent exposure
- Effects of pretreatment with beverages at different temperatures
  - Low temperature: No effect
  - High temperature: BUP Cmax ↑15%
- Effects of pretreatment with low and high pH beverages
  - Low pH: 14-15%↓ in BUP exposure; 25%↓ in NAL exposure
  - High pH: 14-16%↓ in BUP exposure; 141%↑ in NAL Cmax and 91%↑ in NAL AUCt
- Proposed labeling: "Prior to placement of the sublingual film strip, it is recommended to rinse the mouth with a small volume of room-temperature water. High pH beverages should be avoided prior to dosing."

14



4.2 Individual Study Summary

4.2.1 Study 3007599 Synopsis

2. SYNOPSIS

Name of Sponsor/Company: Teva Pharmaceuticals USA	**Individual study table referring to part of dossier in which the individual study or study table is presented** **Volume:** **Reference:**	(For National Authority Use Only)
Name of Finished Product: Buprenorphine HCl and naloxone HCl dihydrate sublingual film, 16 mg/4 mg		
Name of Active Ingredients: Buprenorphine HCl and naloxone HCl		

Title of Study: A Single-Dose, Four-Period, Two-Treatment, Four-Way Full Replicate Bioequivalence Study of Buprenorphine Hydrochloride/Naloxone Hydrochloride Dihydrate 16 mg/4 mg Sublingual Film Strip under Fasted Conditions

Rationale for Amendment: A full clinical study report (CSR) for this study was submitted as part of the buprenorphine/naloxone 16 mg/4 mg sublingual film New Drug Application (NDA) in 2014. This CSR amendment supersedes the one in the original NDA submission to address the completion of a full study database, Medical Dictionary of Regulatory Activities (MedDRA) coding of all adverse events, addition of narratives for the subjects who discontinued from the study due to adverse events, and generation of a complete set of summary tables and listings for the study. Other minor text changes were incorporated for clarification and to ensure consistency across the document. These changes did not impact the pharmacokinetic results or conclusions or the overall study conclusions of the original study report.

Investigators and Study Centers:

Investigators: (b) (4) (b) (4)

Study Center: Worldwide Clinical Trials Early Phase Services, LLC (WCT), 2455 NE Loop 410, Suite 150, San Antonio, Texas 78217

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

Study Period: 13 January 2014 (first subject dosed) to 04 March 2014 (last subject completed)

Phase of Development: 1

Primary Objective: The objective of this single-dose, open-label, randomized, four-period, two-treatment full replicate design study was to compare the rate of absorption and oral bioavailability of a test formulation of buprenorphine and naloxone, 16 mg/4 mg (sublingual film) manufactured by LTS (Lohmann Therapy Systems Corp.) for Teva Pharmaceuticals USA to an equivalent oral dose of the commercially available reference product, Suboxone®, (2 x 8 mg/2 mg) manufactured by Monosol Rx LLC for Reckitt Benckiser Pharmaceuticals, Inc. The current NDA holder is Indivior Inc. The study was conducted under fasted conditions.

Number of Subjects (Planned and Analyzed): For this study, 80 subjects were planned to be enrolled; data from 80 subjects were analyzed for safety and data from a total of 74 subjects were analyzed for pharmacokinetics.

Diagnosis and Main Criteria for Inclusion: Subjects were included in the study if all of the following main criteria were met (not all inclusive): Healthy, non-smoking males or healthy, non-smoking females who were neither pregnant nor breastfeeding, between 18 and 50 years of age (inclusive), with body mass index (BMI) between 18 and 32 kg/m^2 (inclusive), and a minimum weight of 59 kg (130 lbs).

Main Criteria for Exclusion: Subjects were excluded from participating in this study if 1 or more of the following main criteria were met (not all inclusive): History or presence of clinically significant cardiovascular, pulmonary, hepatic, renal, hematologic, gastrointestinal, endocrine, immunologic, dermatologic, neurologic, oncologic, or psychiatric disease or any other condition that, in the opinion of the Investigator, jeopardized the safety of the subject or the validity of the study results; had used over-the-counter medication within 7 days, or prescription medication within 14 days prior to the first dose of study treatment; had significant dental issues noted at screening or presence of blisters, ulcers, sores, or lesions in the mouth at time of check-in to any study period.

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

Investigational Product:

Buprenorphine and Naloxone Sublingual Film, 16 mg/4 mg

Dose = 1 x 16 mg/4 mg sublingual film, sublingually administered

Lot: 9902493

Reference Product

Suboxone® (buprenorphine HCl and naloxone HCl) sublingual film, 8 mg/2 mg

Dose = 2 x 8 mg/2 mg sublingual film, sublingually administered

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

Duration of Treatment: Four single-dose treatments were administered with a 14-day washout period between doses.

General Design and Methodology: This was a single-dose, open-label, randomized, four-period, two-treatment full replicate study in which 80 healthy adult subjects were to receive two separate single-dose administrations of buprenorphine and naloxone sublingual film (16 mg/4 mg) and two separate single-dose administrations of Suboxone sublingual film (2 x 8 mg/2 mg) after a 10-hour overnight fast.

Safety Variables: The Investigator evaluated safety using the following assessments: clinical laboratory evaluations, electrocardiograms (ECGs), physical examinations (including oral cavity examinations), vital sign measurements (including pulse oximetry monitoring), and reported or observed adverse events (AEs). Subjects were monitored for any AEs from the beginning of confinement through the end-of-study visit.

Pharmacokinetic Variables: For each treatment of the buprenorphine HCl and naloxone HCl dihydrate sublingual film, the following pharmacokinetic parameters for buprenorphine, norbuprenorphine, unconjugated naloxone, and total naloxone were calculated, if appropriate:

- C_{max} by inspection (without interpolation)
- T_{max}
- C_{last}
- T_{last}
- λ_z
- $T_{1/2}$
- AUC_{last}
- AUC_{inf}
- AUC_{extrap} percentage extrapolation calculated as $(AUC_{inf}-AUC_{last})/(AUC_{inf})\times 100$

Statistical Considerations:

Comparison of the natural log-transformed pharmacokinetic parameters C_{max}, AUC_{last}, and AUC_{inf}, for buprenorphine, norbuprenorphine, unconjugated naloxone, and total naloxone with respect to the test and reference formulations were done using either the two one-sided tests procedure or the reference-scaled procedure depending on the within-subject standard deviation of the reference product (s_{WR}).

a) If $s_{WR} < 0.294$, the two one-sided tests procedure for a fully replicated design (Proc Mixed) was used to determine bioequivalence for the individual pharmacokinetic parameters. Confidence intervals (90%) were constructed for the treatment ratios (test-to-reference) of C_{max}, AUC_{last}, and AUC_{inf}. The point estimates and confidence limits were exponentiated back to the original scales. Bioequivalence was concluded if the confidence intervals for the three parameters are contained within the limits of 0.8 and 1.25. All evaluable subjects completing at least two study periods, receiving at least one test formulation and one reference product, were included in the statistical analysis.

b) If $s_{WR} \geq 0.294$, the reference-scaled procedure for a fully replicated design (Proc Mixed) was used to determine bioequivalence for the individual pharmacokinetic parameters. Bioequivalence was concluded if both of the following conditions are satisfied for C_{max}, AUC_{last}, and AUC_{inf}.

   1. The 95% upper confidence bound for $(Y_T - Y_R)^2 - \theta s^2_{WR}$ must be ≤ 0, AND
   2. The point estimate of the Test/Reference geometric mean ratio must fall within the limits of 0.8 and 1.25. Subjects completing at least both reference periods were used to calculate s_{WR}.

   Subjects completing at least both reference periods will be used to calculate s_{WR}. However, only subjects completing all four periods were included in the reference-scaled statistical analysis.

Summary of Results

Subject Disposition and Demography: Of the 80 subjects randomly assigned to a treatment sequence, all 80 received at least 1 dose of study drug and were evaluated for safety in the study. A total of 21 (26.3%) subjects discontinued from the study.

The reported reasons for discontinuation were: 13 (16.3%) due to adverse event; 5 (6.3%) due to protocol deviation (violation); 1 (1.3%) withdrawal by subject; 1 (1.3%) lost to follow up; and 1 (1.3%) physician decision.

The mean age of subjects was 34.3 years (range 18 to 50 years); 70.0% of subjects were men and 30.0% were women. The majority of subjects were white (67.5%) and evenly divided among Hispanic or Latino (50.0%) and not Hispanic or Latino (50.0%). Mean weight was 77.1 kg (range 59 to 106 kg) and mean BMI was 26.6 kg/m^2 (range 21 to 30 kg/m^2) (Table 8). Subjects randomly assigned to each of the two treatment sequences were similar with regard to demographic characteristics.

Dissolution Time of Sublingual Film: The mean dissolution time (seconds) for Treatment A (occurrence 1) was 454.86 (range 104.00 – 1230.00), for Treatment A (occurrence 2) was 369.04 (range 46.00 – 1259.00), for Treatment B (occurrence 1) 1 585.81 (range 140.00 – 3300.00), and for Treatment B (occurrence 2) 530.43 (range 108.00 – 2211.0). (Table 14.3.5.10; Listing 16.2.5.1).

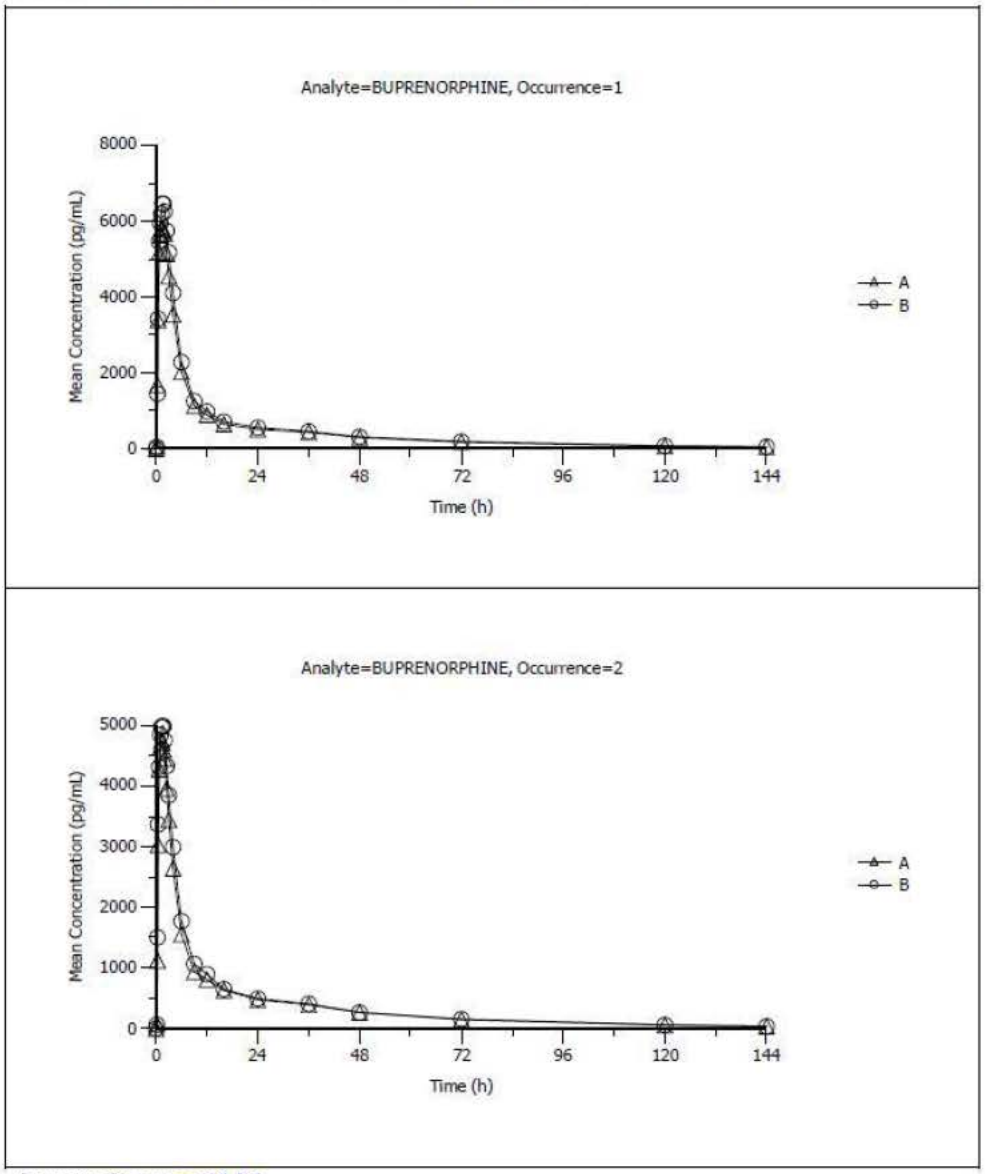
Pharmacokinetic Results: The pharmacokinetic analysis set includes those subjects in the safety analysis set who had sufficient data to calculate the pharmacokinetic parameters C_{max}, AUC_{last}, and AUC_{inf} for buprenorphine, norbuprenorphine, unconjugated naloxone, and total naloxone for at least two administration periods, receiving at least one test formulation and one reference product, and who have sufficient concentration-time data for pharmacokinetic analysis.

Several quantifiable predose buprenorphine and norbuprenorphine concentrations were observed throughout the study. The majority of quantifiable predose concentrations were less than 5% of the C_{max}; therefore, the concentration data were included in the pharmacokinetic and statistical analyses without adjustment. Subject (b) (6) had a quantifiable norbuprenorphine predose concentration (Treatment A/Period 4) that was above 5% of the respective C_{max}. The norbuprenorphine data for Subject (b) (6) in Treatment A/Period 4 were excluded from pharmacokinetic and statistical analyses.

Data from 74 subjects that completed at least 2 study periods (one test formulation and one reference product) were included in the pharmacokinetic analyses and two one-sided tests procedure. Data from 55 subjects for buprenorphine, unconjugated naloxone, and total naloxone that completed all 4 study periods were included in the reference-scaled procedure. Data from 54 subjects for norbuprenorphine were included in the reference scaled procedure.

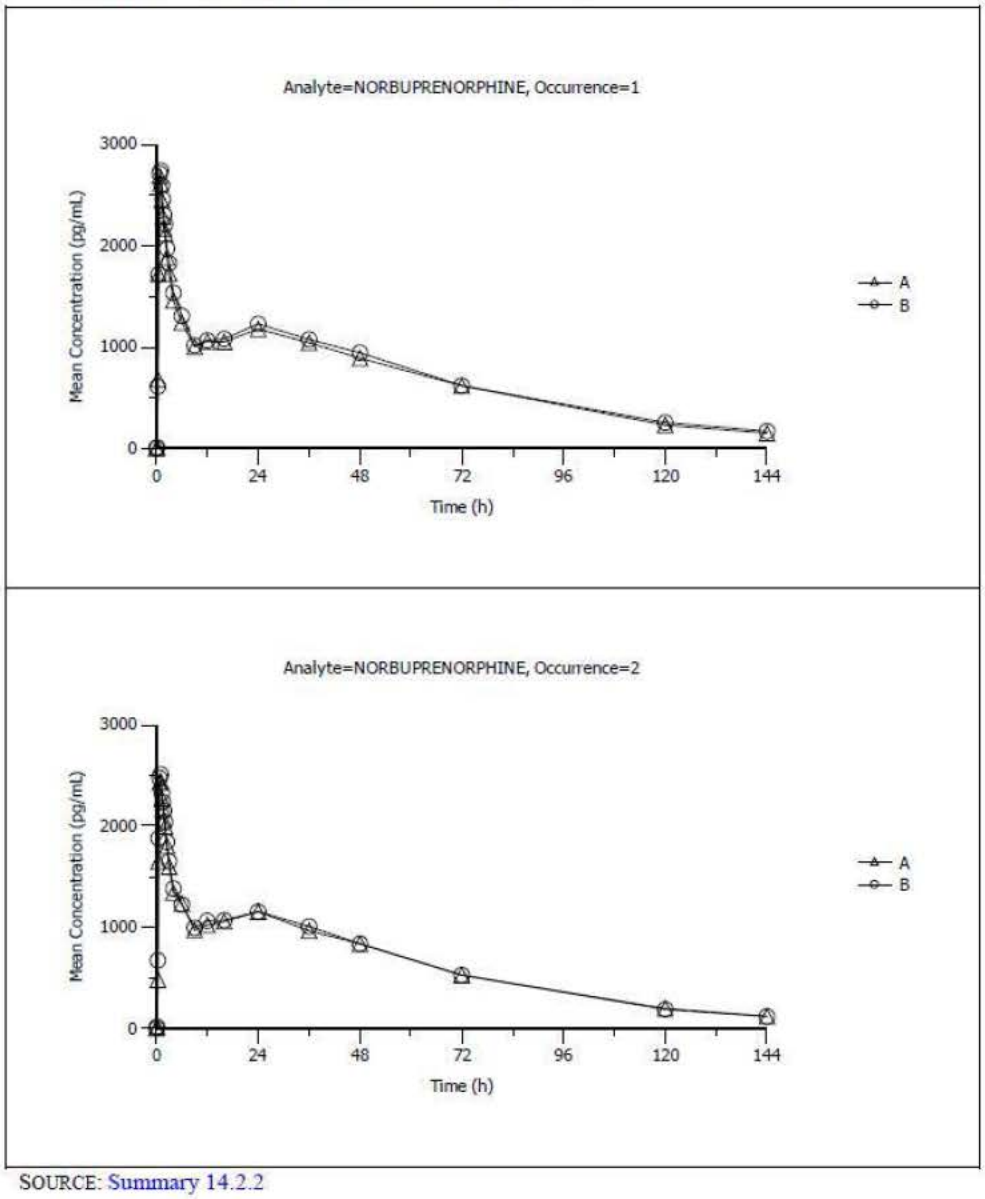
Mean concentration-time data by occurrence are shown in Synopsis Figures 1 through 4. Results of the pharmacokinetic (by occurrence) and statistical analyses are shown below in Synopsis Tables 1 through 10.

Synopsis Figure 1: Mean Plasma Concentration by Time Profiles for Buprenorphine in Healthy Subjects Administered Buprenorphine HCl and Naloxone HCl Dihydrate Sublingual Film (Treatment A) and Suboxone (Treatment B) (Pharmacokinetic Analysis Set)



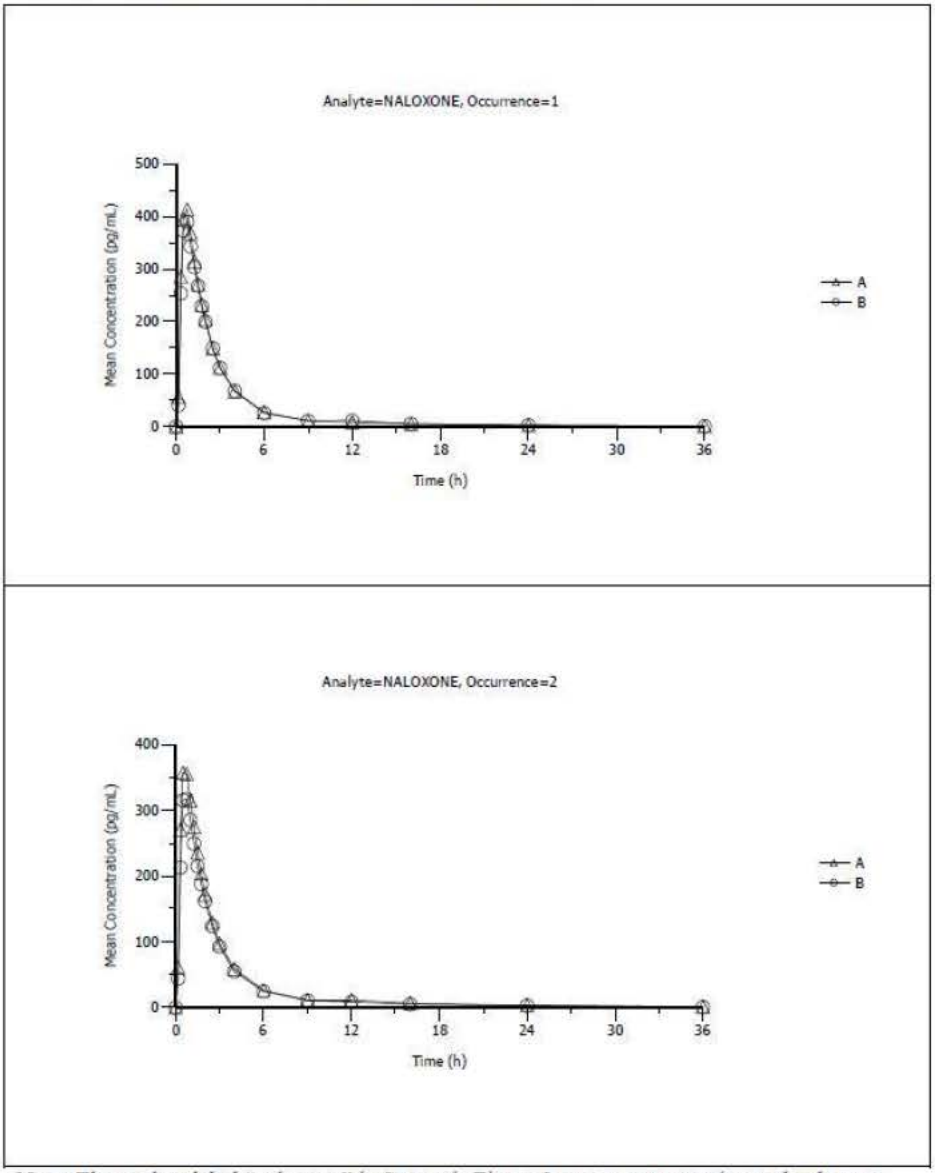
SOURCE: Summary 14.2.1

Synopsis Figure 2: Mean Plasma Concentration by Time Profiles for Norbuprenorphine in Healthy Subjects Administered Buprenorphine HCl and Naloxone HCl Dihydrate Sublingual Film (Treatment A) and Suboxone (Treatment B) (Pharmacokinetic Analysis Set)



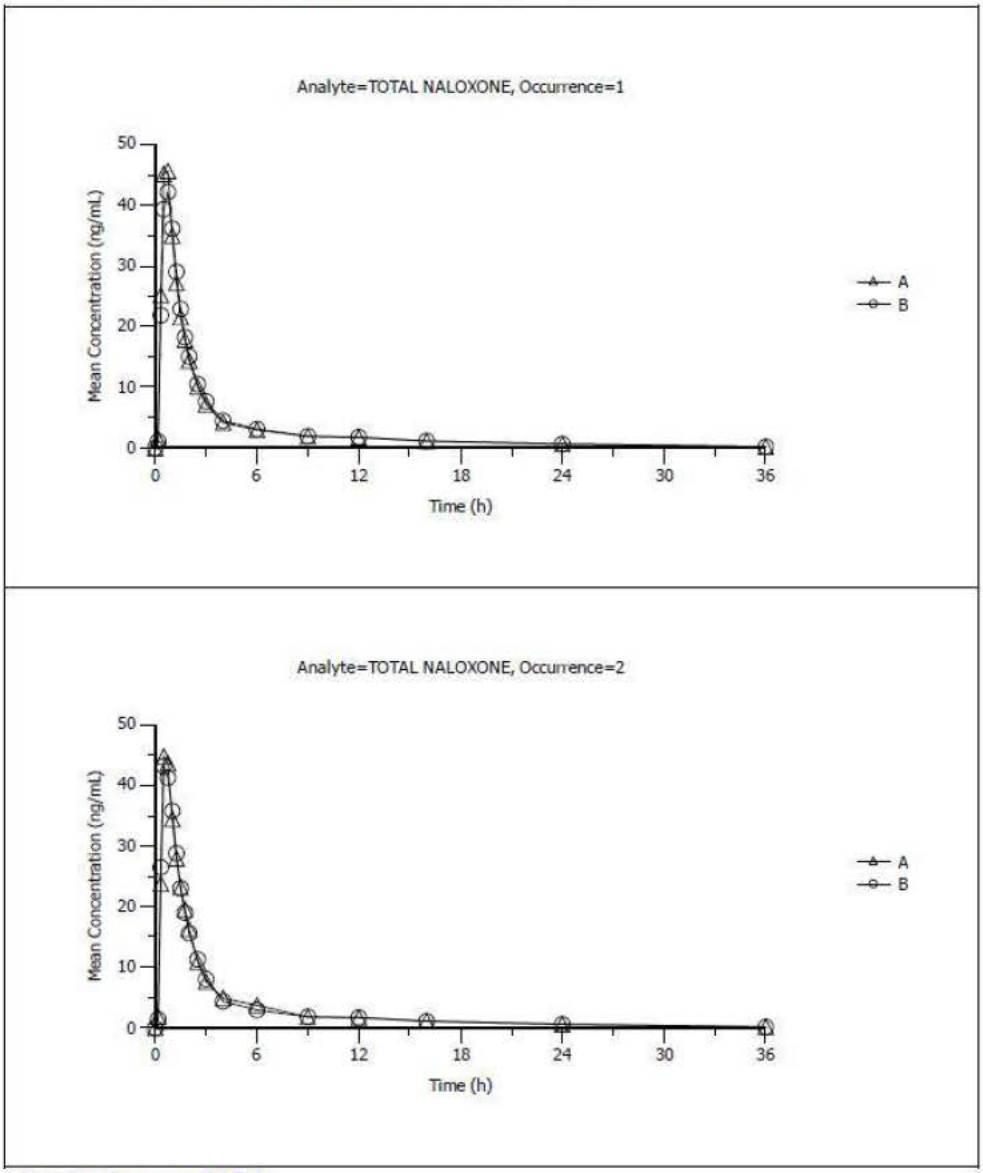
SOURCE: Summary 14.2.2

Synopsis Figure 3: Mean Plasma Concentration by Time Profiles for Unconjugated Naloxone in Healthy Subjects Administered Buprenorphine HCl and Naloxone HCl Dihydrate Sublingual Film (Treatment A) and Suboxone (Treatment B) (Pharmacokinetic Analysis Set)



Note: The analyte label "naloxone" in Synopsis Figure 3 represents unconjugated naloxone.
SOURCE: Summary 14.2.3

Synopsis Figure 4: Mean Plasma Concentration by Time Profiles for Total Naloxone in Healthy Subjects Administered Buprenorphine HCl and Naloxone HCl Dihydrate Sublingual Film (Treatment A) and Suboxone (Treatment B) (Pharmacokinetic Analysis Set)



SOURCE: Summary 14.2.4

Synopsis Table 1: Mean (Standard Deviation) Pharmacokinetic Parameters for Buprenorphine After Administration of Buprenorphine HCl and Naloxone HCl Dihydrate Sublingual Film (Treatment A) and Suboxone (Treatment B) (Pharmacokinetic Analysis Set)

Variable	A Occurrence 1 (N=74)	A Occurrence 2 (N=64)	B Occurrence 1 (N=71)	B Occurrence 2 (N=62)
T_{max} (h)[a]	1.25 (0.33, 3.00)	1.37 (0.50, 3.00)	1.50 (0.33, 3.00)	1.25 (0.50, 3.00)
C_{max} (pg/mL)	6870 (3110)	5470 (2760)	7460 (2950)	5940 (2880)
AUC_{last} (h*pg/mL)	61700 (22130)	52420 (22220)	67880 (22610)	56020 (20580)
AUC_{inf} (h*pg/mL)	64410 (22940)	55010 (23220)	71110 (23610)	58680 (21470)
AUC_{Extrap} (%)	4.27 (2.41)	4.90 (3.08)	4.43 (3.58)	4.53 (3.35)
λ_z (1/h)	0.0216 (0.0064)	0.0224 (0.0105)	0.0207 (0.0055)	0.0201 (0.0051)
$T_{1/2}$ (h)	34.44 (8.80)	34.81 (10.82)	36.58 (12.59)	36.66 (10.11)
T_{last} (h)	137.55 (18.77)	131.74 (25.72)	140.29 (8.75)	138.20 (14.83)
C_{last} (pg/mL)	51.1 (25.3)	46.8 (26.0)	53.4 (31.9)	46.2 (23.4)

SOURCE: Summary 14.2.5, Listing 16.2.6.1.
[a]Median (range) is presented for T_{max}.
C_{max}=maximum observed plasma drug concentration; AUC_{inf}=area under the plasma drug concentration-time curve (AUC) from time zero to infinity; AUC_{last}=AUC from time zero to the time of the last measurable drug concentration; T_{max}=time to maximum observed plasma drug concentration; $T_{1/2}$=elimination half-life; AUC_{Extrap}=100x(AUC_{inf}-AUC_{last})/AUC_{inf}; λ_z=apparent plasma terminal elimination rate constant; T_{last}=time to last measurable drug concentration; C_{last}=last measurable drug concentration.
A=Test Formulation, B=Reference Product.

Synopsis Table 2: Mean (Standard Deviation) Pharmacokinetic Parameters for Norbuprenorphine After Administration of Buprenorphine HCl and Naloxone HCl Dihydrate Sublingual Film (Treatment A) and Suboxone (Treatment B) (Pharmacokinetic Analysis Set)

Variable	A Occurrence 1 (N=74)	A Occurrence 2 (N=63)	B Occurrence 1 (N=71)	B Occurrence 2 (N=62)
T_{max} (h)[c]	1.00 (0.33, 48.00)	1.00 (0.50, 36.00)	1.00 (0.49, 36.00)	1.00 (0.50, 48.00)
C_{max} (pg/mL)	3090 (1780)	2850 (1540)	3290 (1680)	3000 (1500)
AUC_{last} (h*pg/mL)	97410 (40340)	90200 (37650)	101900 (38780)	90550 (38550)
AUC_{inf} (h*pg/mL)	107600 (47040)	99890 (42190)[a]	115800 (53950)	98820 (40800)[b]
AUC_{Extrap} (%)	8.47 (7.75)	8.48 (12.71)[a]	9.38 (9.54)	6.76 (5.84)[b]
λ_z (1/h)	0.0220 (0.0074)	0.0235 (0.0077)[a]	0.0210 (0.0080)	0.0232 (0.0077)[b]
$T_{1/2}$ (h)	35.54 (13.64)	34.55 (19.14)[a]	40.55 (25.58)	33.38 (12.08)[b]
T_{last} (h)	141.12 (14.31)	138.11 (21.84)	142.99 (4.86)	142.07 (6.59)
C_{last} (pg/mL)	162 (129)	126 (99.5)	173 (140)	122 (88.9)

SOURCE: Summary 14.2.6, Listing 16.2.6.2.
[a]N=62; [b]N=61
[c]Median (range) is presented for T_{max}.
C_{max}=maximum observed plasma drug concentration; AUC_{inf}=area under the plasma drug concentration-time curve (AUC) from time zero to infinity; AUC_{last}=AUC from time zero to the time of the last measurable drug concentration; T_{max}=time to maximum observed plasma drug concentration; $T_{1/2}$=elimination half-life; AUC_{Extrap}=100x(AUC_{inf}-AUC_{last})/AUC_{inf}; λ_z=apparent plasma terminal elimination rate constant; T_{last}=time to last measurable drug concentration; C_{last}=last measurable drug concentration.
A=Test Formulation, B=Reference Product.

Synopsis Table 3: Mean (Standard Deviation) Pharmacokinetic Parameters for Unconjugated Naloxone After Administration of Buprenorphine HCl and Naloxone HCl Dihydrate Sublingual Film (Treatment A) and Suboxone (Treatment B) (Pharmacokinetic Analysis Set)

Variable	A Occurrence 1 (N=74)	A Occurrence 2 (N=64)	B Occurrence 1 (N=71)	B Occurrence 2 (N=62)
T_{max} (h)[a]	0.75 (0.33, 1.75)	0.50 (0.33, 2.00)	0.75 (0.33, 1.50)	0.75 (0.33, 2.50)
C_{max} (pg/mL)	469 (248)	403 (239)	456 (261)	364 (197)
AUC_{last} (h*pg/mL)	1057 (506.8)	966.0 (535.8)	1038 (490.9)	865.1 (379.5)
AUC_{inf} (h*pg/mL)	1087 (511.8)	998.7 (536.5)	1064 (494.3)	894.9 (380.6)
AUC_{Extrap} (%)	3.26 (3.79)	4.08 (4.78)	2.65 (1.97)	3.69 (3.49)
λ_z (1/h)	0.1907 (0.1177)	0.1980 (0.1796)	0.1848 (0.1169)	0.1789 (0.1264)
$T_{1/2}$ (h)	6.30 (6.51)	6.87 (5.77)	5.43 (3.31)	6.33 (5.36)
T_{last} (h)	23.57 (8.07)	23.86 (8.97)	23.80 (7.97)	23.66 (7.63)
C_{last} (pg/mL)	3.63 (2.19)	3.46 (1.36)	3.36 (1.55)	3.31 (1.35)

SOURCE: Summary 14.2.7, Listing 16.2.6.3.
[a]Median (range) is presented for T_{max}.
C_{max}=maximum observed plasma drug concentration; AUC_{inf}=area under the plasma drug concentration-time curve (AUC) from time zero to infinity; AUC_{last}=AUC from time zero to the time of the last measurable drug concentration; T_{max}=time to maximum observed plasma drug concentration; $T_{1/2}$=elimination half-life; AUC_{Extrap}=100x(AUC_{inf}-AUC_{last})/AUC_{inf}; λ_z=apparent plasma terminal elimination rate constant; T_{last}=time to last measurable drug concentration; C_{last}=last measurable drug concentration.
A=Test Formulation, B=Reference Product.

Synopsis Table 4: Mean (Standard Deviation) Pharmacokinetic Parameters for Total Naloxone After Administration of Buprenorphine HCl and Naloxone HCl Dihydrate Sublingual Film (Treatment A) and Suboxone (Treatment B) (Pharmacokinetic Analysis Set)

Variable	A Occurrence 1 (N=74)	A Occurrence 2 (N=64)	B Occurrence 1 (N=71)	B Occurrence 2 (N=62)
T_{max} (h)[b]	0.53 (0.33, 6.00)	0.75 (0.33, 6.03)	0.75 (0.33, 2.99)	0.52 (0.33, 16.00)
C_{max} (ng/mL)	56.1 (23.0)	55.0 (25.3)	54.4 (21.8)	54.3 (24.4)
AUC_{last} (h*ng/mL)	106.6 (33.45)	110.1 (41.49)	107.4 (36.60)	107.4 (40.79)
AUC_{inf} (h*ng/mL)	110.5 (33.85)	113.5 (41.94)	110.8 (36.56)	111.3 (41.54)[a]
AUC_{Extrap} (%)	3.79 (3.73)	3.81 (4.30)	3.40 (2.80)	3.48 (3.20)[a]
λ_z (1/h)	0.0929 (0.0282)	0.1304 (0.1417)	0.0929 (0.0308)	0.1103 (0.0485)[a]
$T_{1/2}$ (h)	8.46 (4.02)	7.26 (3.49)	8.62 (4.69)	7.40 (3.79)[a]
T_{last} (h)	33.46 (5.15)	31.62 (8.45)	34.31 (4.20)	31.52 (7.10)
C_{last} (ng/mL)	0.307 (0.198)	0.303 (0.170)	0.263 (0.133)	0.289 (0.173)

SOURCE: Summary 14.2.8, Listing 16.2.6.4.
[a]N=61
[b]Median (range) is presented for T_{max}.
C_{max}=maximum observed plasma drug concentration; AUC_{inf}=area under the plasma drug concentration-time curve (AUC) from time zero to infinity; AUC_{last}=AUC from time zero to the time of the last measurable drug concentration; T_{max}=time to maximum observed plasma drug concentration; $T_{1/2}$=elimination half-life; AUC_{Extrap}=100x(AUC_{inf}-AUC_{last})/AUC_{inf}; λ_z=apparent plasma terminal elimination rate constant; T_{last}=time to last measurable drug concentration; C_{last}=last measurable drug concentration.
A=Test Formulation, B=Reference Product.

Synopsis Table 5: Statistical Analysis of the Log-Transformed Systemic Exposure Parameters of Buprenorphine (Pharmacokinetic Analysis Set) Using Reference Scaled Average Bioequivalence Analysis

Variable	s_{WR}[a]	Ratio (%)[b] (A/B)	95% Upper Bound[c]
C_{max}	0.2693	-	-
AUC_{last}	0.2066	-	-
AUC_{inf}	0.2039	-	-

SOURCE: Listings 16.1.9.1 and 16.1.9.2.
[a]The within-subject standard deviation of the reference product, which needs to be equal or greater than 0.294 for the reference scaled average bioequivalence approach to be used.
[b]Ratio (%) = Antilogarithm of Least Squares Means of (A-B)
[c]The 95% upper confidence bound for $(Y_T - Y_R)^2 - \theta s^2_{WR}$, which must be equal or less than 0 for bioequivalence to be declared using the reference scaled average bioequivalence approach.
C_{max}=maximum observed plasma drug concentration; AUC_{inf}=area under the plasma drug concentration-time curve (AUC) from time zero to infinity; AUC_{last}=AUC from time zero to the time of the last measurable drug concentration

Synopsis Table 6: Statistical Analysis of the Log-Transformed Systemic Exposure Parameters of Buprenorphine (Pharmacokinetic Analysis Set)

	Geometric Mean[a]			90% CI[c]	
Variable	A (N=138)	B (N=133)	Ratio (%)[b] (A/B)	Lower	Upper
C_{max}	5423.7562	6054.6468	89.58	83.98	95.56
AUC_{last}	51945.0314	58221.8758	89.22	84.37	94.35
AUC_{inf}	54434.9564	60917.6270	89.36	84.56	94.43

SOURCE: Listings 16.1.9.3 and 16.1.9.4.
[a] Geometric Mean for the Test Formulation (A) and the Reference Product (B) based on Least Squares Mean of log-transformed parameter values
[b] Ratio(%) = Geometric Mean (A)/Geometric Mean (B)
[c] 90% Confidence Interval
C_{max}=maximum observed plasma drug concentration; AUC_{inf}=area under the plasma drug concentration-time curve (AUC) from time zero to infinity; AUC_{last}=AUC from time zero to the time of the last measurable drug concentration

Synopsis Table 7: Statistical Analysis of the Log-Transformed Systemic Exposure Parameters of Norbuprenorphine (Pharmacokinetic Analysis Set) Using Reference Scaled Average Bioequivalence Analysis)

Variable	s_{WR}[a]	Ratio (%)[b] (A/B)	95% Upper Bound[c]
C_{max}	0.4176	93.01	-0.09
AUC_{last}	0.3047	94.02	-0.04
AUC_{inf}	0.2974	97.19	-0.05

SOURCE: Listings 16.1.9.5 and 16.1.9.6.
[a]The within-subject standard deviation of the reference product, which needs to be equal or greater than 0.294 for the reference scaled average bioequivalence approach to be used.
[b]Ratio (%) = Antilogarithm of Least Squares Means of (A-B)
[c]The 95% upper confidence bound for $(Y_T - Y_R)^2 - \theta s^2_{WR}$, which must be equal or less than 0 for bioequivalence to be declared using the reference scaled average bioequivalence approach.
C_{max}=maximum observed plasma drug concentration; AUC_{inf}=area under the plasma drug concentration-time curve (AUC) from time zero to infinity; AUC_{last}=AUC from time zero to the time of the last measurable drug concentration

Synopsis Table 8: Statistical Analysis of the Log-Transformed Systemic Exposure Parameters of Unconjugated Naloxone (Pharmacokinetic Analysis Set) Using Reference Scaled Average Bioequivalence Analysis)

Variable	s_{WR}[a]	Ratio (%)[b] (A/B)	95% Upper Bound[c]
C_{max}	0.3169	103.22	-0.06
AUC_{last}	0.2484	-	-
AUC_{inf}	0.2433	-	-

SOURCE: Listings 16.1.9.7 and 16.1.9.8.
[a]The within-subject standard deviation of the reference product, which needs to be equal or greater than 0.294 for the reference scaled average bioequivalence approach to be used.
[b]Ratio (%) = Antilogarithm of Least Squares Means of (A-B)
[c]The 95% upper confidence bound for $(Y_T - Y_R)^2 - \theta s^2_{WR}$, which must be equal or less than 0 for bioequivalence to be declared using the reference scaled average bioequivalence approach.
C_{max}=maximum observed plasma drug concentration; AUC_{inf}=area under the plasma drug concentration-time curve (AUC) from time zero to infinity; AUC_{last}=AUC from time zero to the time of the last measurable drug concentration

Synopsis Table 9: Statistical Analysis of the Log-Transformed Systemic Exposure Parameters of Unconjugated Naloxone (Pharmacokinetic Analysis Set)

	Geometric Mean[a]			90% CI[c]	
Variable	A (N=138)	B (N=133)	Ratio (%)[b] (A/B)	Lower	Upper
AUC_{last}	877.6949	869.7849	100.91	95.28	106.87
AUC_{inf}	912.5805	898.6168	101.55	96.11	107.31

SOURCE: Listings 16.1.9.9 and 16.1.9.10.
[a] Geometric Mean for the Test Formulation (A) and the Reference Product (B) based on Least Squares Mean of log-transformed parameter values
[b] Ratio(%) = Geometric Mean (A)/Geometric Mean (B)
[c] 90% Confidence Interval
C_{max}=maximum observed plasma drug concentration; AUC_{inf}=area under the plasma drug concentration-time curve (AUC) from time zero to infinity; AUC_{last}=AUC from time zero to the time of the last measurable drug concentration

Synopsis Table 10: Statistical Analysis of the Log-Transformed Systemic Exposure Parameters of Total Naloxone (Pharmacokinetic Analysis Set) Using Reference Scaled Average Bioequivalence Analysis

Variable	s_{WR}[a]	Ratio (%)[b] (A/B)	95% Upper Bound[c]
C_{max}	0.5832	100.40	-0.21
AUC_{last}	0.4124	97.63	-0.10
AUC_{inf}	0.4105	97.24	-0.10

SOURCE: Listings 16.1.9.11 and 16.1.9.12.
[a]The within-subject standard deviation of the reference product, which needs to be equal or greater than 0.294 for the reference scaled average bioequivalence approach to be used.
[b]Ratio (%) = Antilogarithm of Least Squares Means of (A-B)
[c]The 95% upper confidence bound for $(Y_T - Y_R)^2 - \theta s^2_{WR}$, which must be equal or less than 0 for bioequivalence to be declared using the reference scaled average bioequivalence approach.
C_{max}=maximum observed plasma drug concentration; AUC_{inf}=area under the plasma drug concentration-time curve (AUC) from time zero to infinity; AUC_{last}=AUC from time zero to the time of the last measurable drug concentration

Bioequivalence criteria were met for all analytes.

- The within-subject standard deviation of the reference product for buprenorphine (s_{WR}) was < 0.294 for C_{max}, AUC_{last}, and AUC_{inf}; therefore, the two one-sided tests procedure was used to evaluate $\ln(C_{max})$, $\ln(AUC_{last})$, and $\ln(AUC_{inf})$. The 90% confidence intervals for comparing peak and total systemic exposure, based on back-transformed C_{max}, AUC_{last}, and AUC_{inf}, are within the accepted 80% to 125% limits for buprenorphine.
- The within-subject standard deviation of the reference product for norbuprenorphine (s_{WR}) was ≥ 0.294 for C_{max}, AUC_{last}, and AUC_{inf}; therefore, the reference-scaled procedure was used to evaluate $\ln(C_{max})$, $\ln(AUC_{last})$, and $\ln(AUC_{inf})$. The point estimates of the Test/Reference geometric mean ratios (%) for C_{max}, AUC_{last}, and AUC_{inf} fell within the limits of 80% to 125%. The 95% upper bound for $(Y_T - Y_R)^2 - \theta s^2_{WR}$ of $\ln(C_{max})$, $\ln(AUC_{last})$, and $\ln(AUC_{inf})$ was less than zero for all three parameters.
- The within-subject standard deviation of the reference product for unconjugated naloxone (s_{WR}) was ≥ 0.294 for C_{max}; therefore, the reference-scaled procedure was used to evaluate $\ln(C_{max})$. The point estimate of the Test/Reference geometric mean ratio (%) for C_{max} fell within the limits of 80% to 125%. The 95% upper bound for $(Y_T - Y_R)^2 - \theta s^2_{WR}$ of $\ln(C_{max})$ was less than zero.
- The within-subject standard deviation of the reference product for unconjugated naloxone (s_{WR}) was < 0.294 for AUC_{last} and AUC_{inf}; therefore, the two one-sided tests procedure was used to evaluate $\ln(AUC_{last})$ and $\ln(AUC_{inf})$. The 90% confidence intervals for comparing peak and total systemic exposure, based on back-transformed AUC_{last} and AUC_{inf}, are within the accepted 80% to 125% limits for unconjugated naloxone.
- The within-subject standard deviation of the reference product for total naloxone (s_{WR}) was ≥ 0.294 for C_{max}, AUC_{last}, and AUC_{inf}; therefore, the reference-scaled procedure was used to evaluate $\ln(C_{max})$, $\ln(AUC_{last})$, and $\ln(AUC_{inf})$. The point estimates of the Test/Reference geometric mean ratios (%) for C_{max}, AUC_{last}, and AUC_{inf} fell within the limits of 80% to 125%. The 95% upper bound for $(Y_T - Y_R)^2 - \theta s^2_{WR}$ of $\ln(C_{max})$, $\ln(AUC_{last})$, and $\ln(AUC_{inf})$ was less than zero for all three parameters.

Safety Results: There were no deaths or other serious adverse events reported in the study. There were no adverse events assessed as severe. Three (3.8%) subjects discontinued from the study for adverse events following Treatment A, and 7 (8.9%) subjects discontinued from the study for adverse events following Treatment B.

There was no difference in the overall percentage of subjects with at least 1 adverse event (58% in both treatment groups). In general, the incidence of common adverse events (> 5%) was similar between the 2 treatment groups. The adverse events reported in this study were comparable with the adverse event profile of Suboxone.

There were no clinically meaningful differences in laboratory parameters as assessed between baseline and endpoint, and no subject had a laboratory parameter assessed as an adverse event, or that led to study discontinuation.

Following study drug administration, in general, the mean changes were comparable between the two treatment groups at each assessment time point with respect to vital signs. There were no clinically meaningful changes in mean vital signs between baseline and endpoint. There were no adverse events referable to vital signs and no vital sign finding led to study discontinuation.

There were no clinically meaningful differences in ECG parameters as assessed between baseline and endpoint. No subject had an ECG assessed as clinically significant. No subject met criteria for an ECG outlier. No ECG parameter or ECG finding was assessed as an adverse event or led to study discontinuation.

There were no relevant physical examination, oral cavity examination, or oral mucosal tolerability findings.

Conclusions: The test formulation of buprenorphine and naloxone, 16 mg/4 mg manufactured by LTS (Lohmann Therapy Systems Corp.) for Teva Pharmaceuticals USA is bioequivalent to the commercially available reference product, Suboxone, (2 x 8 mg/2 mg) manufactured by Monosol Rx LLC for Reckitt Benckiser Pharmaceuticals, Inc. The current NDA holder is Indivior Inc.

Overall, no new safety findings were identified in this study. The safety profile for the test drug was consistent with the known safety profile of the reference product.

2. SYNOPSIS

Name of Sponsor/Company: Teva Pharmaceuticals USA	**Individual study table referring to part of dossier in which the individual study or study table is presented**	(For National Authority Use Only)
Name of Finished Product: Buprenorphine HCl and naloxone HCl dihydrate sublingual film, 16 mg/4 mg	**Volume:**	
Name of Active Ingredients: Buprenorphine HCl and naloxone HCl	**Reference:**	

Title of Study: A Single-Dose, Three-Period, Three-Treatment, Three-Way Crossover Study Comparing the Effect of Temperature on the Relative Bioavailability of Buprenorphine Hydrochloride/Naloxone Hydrochloride Dihydrate Sublingual Film, 16 mg/4 mg when Administered with Beverages of Different Temperature

Rationale for Amendment: A full clinical study report (CSR) for this study was submitted as part of the buprenorphine/naloxone 16 mg/4 mg sublingual film New Drug Application (NDA) in 2014. This CSR amendment supersedes the one in the original NDA submission to address the completion of a full study database, Medical Dictionary of Regulatory Activities (MedDRA) coding of all adverse events, addition of narratives for the subjects who discontinued from the study due to adverse events, and generation of a complete set of summary tables and listings for the study. Other minor text changes were incorporated for clarification and to ensure consistency across the document. These changes did not impact the pharmacokinetic results or conclusions or the overall study conclusions of the original study report.

Investigators and Study Centers:

Investigators: (b) (4)

(b) (4)

Study Center: Worldwide Clinical Trials Early Phase Services, LLC (WCT), 2455 NE Loop 410, Suite 150, San Antonio, Texas 78217

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

Study Period: 02 August 2014 (first subject dosed) to 05 September 2014 (last subject completed)

Phase of Development: 1

Primary Objective: The objective of this single-dose, open-label, randomized, 3-period, 3-treatment crossover study was to assess the impact of beverage temperature on the relative bioavailability of buprenorphine HCl/naloxone HCl dihydrate sublingual film, 16 mg/4 mg.

Number of Subjects (Planned and Analyzed): For this study, 24 subjects were planned to be enrolled; data from 24 subjects were analyzed for safety and data from a total of 22 subjects (20 subjects per treatment) were analyzed for pharmacokinetics.

Diagnosis and Main Criteria for Inclusion: Subjects were included in the study if all of the following main criteria were met (not all inclusive): Healthy, non-smoking males or healthy, non-smoking females who were neither pregnant nor breastfeeding, between 18 and 50 years of age (inclusive), with body mass index (BMI) between 18 and 32 kg/m^2 (inclusive), and a minimum weight of 59 kg (130 lbs).

Main Criteria for Exclusion: Subjects were excluded from participating in this study if 1 or more of the following main criteria were met (not all inclusive): History or presence of clinically significant cardiovascular, pulmonary, hepatic, renal, hematologic, gastrointestinal, endocrine, immunologic, dermatologic, neurologic, oncologic, or psychiatric disease or any other condition that, in the opinion of the Investigator, jeopardized the safety of the subject or the validity of the study results; had used over-the-counter medication within 7 days, or prescription medication within 14 days prior to the first dose of study treatment; had significant dental issues noted at screening or presence of blisters, ulcers, sores, or lesions in the mouth at time of check-in to any study period.

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

Investigational Product:

Buprenorphine and Naloxone Sublingual Film, 16 mg/4 mg, (C3)

Dose = 1 x 16 mg/4 mg sublingual film, sublingually administered

Lot: 9902493

Treatment A (Test 1): Subjects consumed 60 mL (2 fl oz) of cold beverage starting 1 minute before dosing.

Treatment B (Test 2): Subjects consumed 60 mL (2 fl oz) of hot beverage starting 1 minute before dosing.

Treatment C (Reference): Subjects consumed 60 mL (2 fl oz) of room temperature water starting 1 minute before dosing.

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

Duration of Treatment: Three single-dose treatments were administered with a 14-day washout period between doses.

General Design and Methodology: This was a single-dose, open-label, randomized, 3-period, 3-treatment crossover study in which 24 healthy adult subjects were to receive three separate single-dose applications of buprenorphine HCl/naloxone HCl dihydrate sublingual film, 16 mg/4 mg. Each dose was administered after a 10-hour overnight fast. Before each dose, subjects were pretreated with a cold beverage, a hot beverage, or a reference room temperature beverage.

Safety Variables: The Investigator evaluated safety using the following assessments: clinical laboratory evaluations, electrocardiograms (ECGs), physical examinations (including oral cavity examinations), vital sign measurements (including continuous pulse oximetry monitoring), and reported or observed adverse events (AEs). Subjects were monitored for any AEs from the beginning of confinement through the end-of-study visit.

Pharmacokinetic Variables: For each treatment of the buprenorphine HCl and naloxone HCl dihydrate sublingual film, the following pharmacokinetic parameters for buprenorphine, norbuprenorphine, unconjugated naloxone, and total naloxone were calculated, if appropriate:

- C_{max} by inspection (without interpolation)
- AUC_{inf}
- AUC_{last}
- T_{max}
- AUC_{extrap} percentage extrapolation calculated as $(AUC_{inf}-AUC_{last})/(AUC_{inf})\times 100$
- λ_z and associated $T_{1/2}$
- C_{last}
- T_{last}

Statistical Considerations:

Concentration-time data were analyzed using noncompartmental methods in Phoenix™ WinNonlin® (Version 6.3, Pharsight Corporation). Concentration-time data that were below the limit of quantification (BLQ) were treated as zero in the data summarization and descriptive statistics. In the pharmacokinetic analysis, BLQ concentrations were treated as zero from time-zero up to the time at which the first quantifiable concentration was observed; embedded and/or terminal BLQ concentrations were treated as "missing". Actual sample times were used for all pharmacokinetic and statistical analyses.

Analysis of variance (ANOVA) and the Schuirmann's two one-sided t-test procedures at the 5% significance level were applied to the log-transformed pharmacokinetic exposure parameters, C_{max}, AUC_{last}, and AUC_{inf}. The 90% confidence interval for the ratio of the geometric means (Test/Reference) was calculated. Bioequivalence was declared if the lower and upper confidence intervals of the log-transformed parameters were within 80% to 125%.

Summary of Results

Subject Disposition and Demography: Of the 24 subjects randomly assigned to a treatment sequence, all 24 received at least 1 dose of study drug and were evaluated for safety in the study. A total of 4 (16.7%) subjects discontinued from the study.

The reported reasons for discontinuation were: 2 (8.3%) due to adverse event, 1 (4.2%) withdrawal by subject, and 1 (4.2%) physician decision.

The mean age of subjects was 31.8 years (range 18 to 47 years); 58.3% of subjects were men and 41.7% were women. The majority of subjects were white (79.2%) and Hispanic or Latino (62.5%). Mean weight was 76.7 kg (range 62 to 87 kg) and mean BMI was 27.2 kg/m^2 (range 22 to 32 kg/m^2) (Table 10). Subjects randomly assigned to each of the 6 treatment sequences were similar with regard to demographic characteristics.

Dissolution Time of Sublingual Film: The mean dissolution time (seconds) for Treatment A (cold beverage) was 241.32 (range 72.00 – 932.00), for Treatment B (hot beverage) 261.35 (range 84.00-670.00), and for Treatment C (room temperature water) 222.36 (range 72.00-557.00) (Table 14.3.5.10; Listing 16.2.5.1).

Beverage Temperature: Each subject was required to consume approximately 60 mL of hot water, cold water, or room temperature water 1 minute before study treatment administration. Exactly 1 minute prior to study drug administration, each subject was given 30 mL of water (cold, hot or room temperature), per the assigned randomization sequence. The subject swished for 15 seconds, swallowed, and then started consuming an additional 30 mL rinse (second aliquot) of the assigned pre-treatment. The second rinse started 15 seconds after the minute and was consumed 30 seconds prior to dose. The temperatures of both rinses were recorded immediately prior to administration of each aliquot. The mean temperatures of aliquot 1 and 2 of cold water were 2.43° C (range 0.30-4.40) and 1.97 ° C (range 0.20–4.70), respectively. The mean temperatures of aliquot 1 and 2 of hot water were 50.74 ° C (range 48.60–53.50) and 50.80 ° C (range 48.50–53.70), respectively. The mean temperatures of aliquot 1 and 2 of room temperature water were 21.58 ° C (range 19.90–24.90) and 21.40 ° C (range 19.10–24.30), respectively (Table 14.3.5.10; Listing 16.2.5.3).

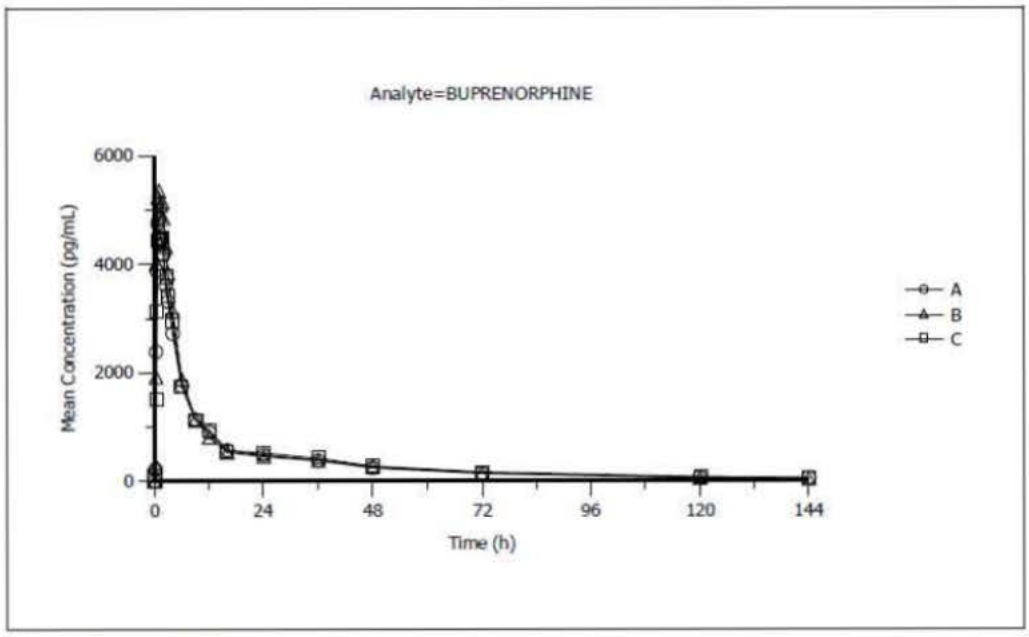
Pharmacokinetic Results: The pharmacokinetic analysis set includes those subjects in the safety analysis set who had sufficient data to calculate the pharmacokinetic parameters C_{max}, AUC_{last}, and AUC_{inf} for buprenorphine, norbuprenorphine, unconjugated naloxone, and total naloxone for at least one administration period.

Data from a total of 22 subjects (20 subjects per treatment) were included in the pharmacokinetic and statistical analyses.

Quantifiable buprenorphine and norbuprenorphine predose concentrations were observed for some subjects. Most quantifiable predose concentrations were less than 5% of the respective C_{max} values and were therefore included in the pharmacokinetic and statistical analyses without adjustment. Subject (b) (6) had a quantifiable predose norbuprenorphine concentration that was above 5% of the respective C_{max} during Period 3 (Treatment B); norbuprenorphine concentration data for Subject (b) (6) were excluded from pharmacokinetic and statistical analyses for Period 3 (n=19 for Treatment B).

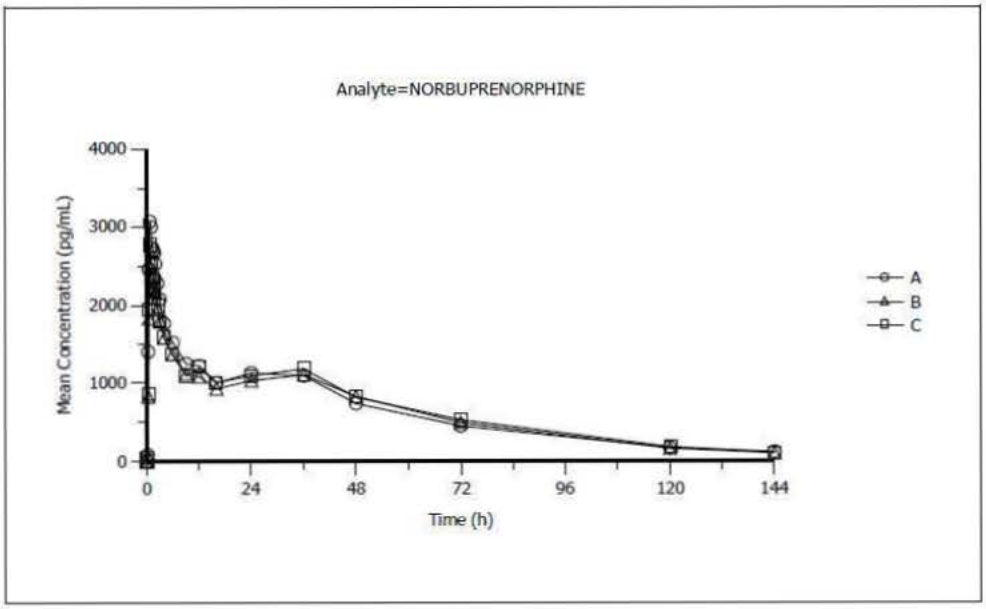
Mean concentration-time data are shown in Synopsis Figures 1 through 4. Results of the pharmacokinetic and statistical analyses are shown below in Synopsis Tables 1 through 8.

Synopsis Figure 1: Mean Plasma Concentration by Time Profiles for Buprenorphine in Healthy Subjects Administered Buprenorphine HCl and Naloxone HCl Dihydrate Sublingual Film with Cold Beverage (Treatment A), Hot Beverage (Treatment B), or Beverage at Room Temperature (Treatment C) (Pharmacokinetic Analysis Set)



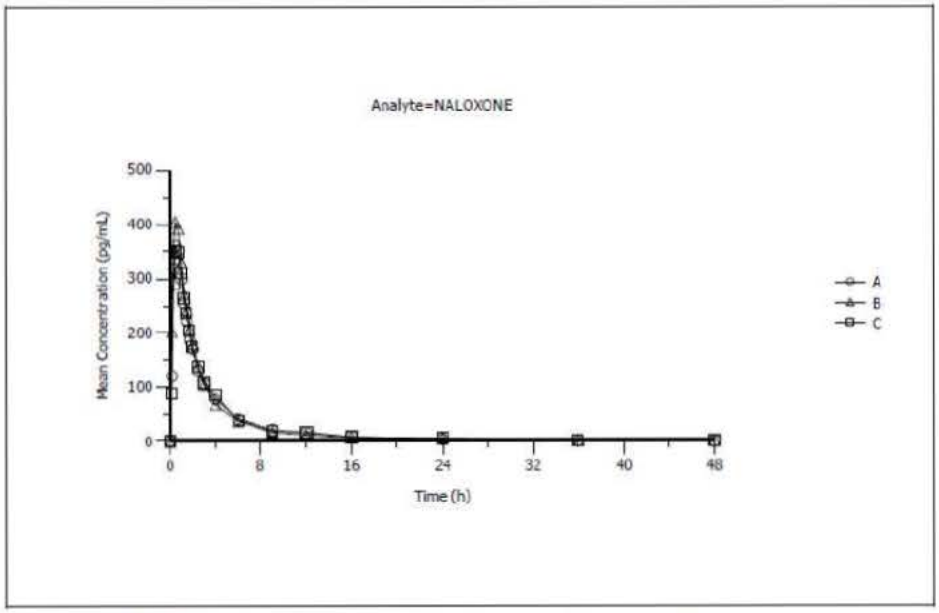
SOURCE: Summary 14.2.1

Synopsis Figure 2: Mean Plasma Concentration by Time Profiles for Norbuprenorphine in Healthy Subjects Administered Buprenorphine HCl and Naloxone HCl Dihydrate Sublingual Film with Cold Beverage (Treatment A), Hot Beverage (Treatment B), or Beverage at Room Temperature (Treatment C) (Pharmacokinetic Analysis Set)



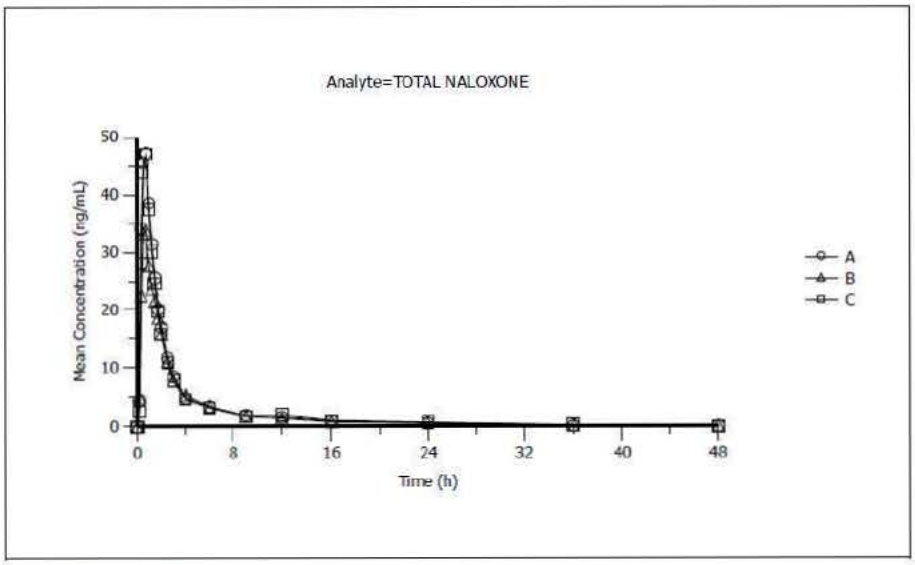
SOURCE: Summary 14.2.2

Synopsis Figure 3: Mean Plasma Concentration by Time Profiles for Unconjugated Naloxone in Healthy Subjects Administered Buprenorphine HCl and Naloxone HCl Dihydrate Sublingual Film with Cold Beverage (Treatment A), Hot Beverage (Treatment B), or Beverage at Room Temperature (Treatment C) (Pharmacokinetic Analysis Set)



Note: The analyte label "naloxone" in Synopsis Figure 3 represents unconjugated naloxone.
SOURCE: Summary 14.2.3

Synopsis Figure 4: Mean Plasma Concentration by Time Profiles for Total Naloxone in Healthy Subjects Administered Buprenorphine HCl and Naloxone HCl Dihydrate Sublingual Film with Cold Beverage (Treatment A), Hot Beverage (Treatment B), or Beverage at Room Temperature (Treatment C) (Pharmacokinetic Analysis Set)



SOURCE: Summary 14.2.4

Synopsis Table 1: Mean (Standard Deviation) Pharmacokinetic Parameters for Buprenorphine After Administration of Buprenorphine HCl and Naloxone HCl Dihydrate Sublingual Film with Cold Beverage (Treatment A), Hot Beverage (Treatment B), or Beverage at Room Temperature (Treatment C) (Pharmacokinetic Analysis Set)

Variable	A (N=20)	B (N=20)	C (N=20)
T_{max} (h)[a]	1.12 (0.33, 2.00)	1.00 (0.50, 3.00)	1.00 (0.33, 2.00)
C_{max} (pg/mL)	5940 (2720)	6670 (4250)	5410 (2560)
AUC_{last} (h*pg/mL)	52780 (19450)	54200 (24880)	55020 (20960)
AUC_{inf} (h*pg/mL)	56820 (22690)	56720 (26210)	57670 (22300)
AUC_{Extrap} (%)	5.97 (5.59)	4.87 (3.86)	4.46 (2.23)
λ_z (1/h)	0.0180 (0.0057)	0.0209 (0.0043)	0.0197 (0.0028)
$T_{1/2}$ (h)	42.94 (16.13)	34.74 (7.79)	35.83 (5.20)
T_{last} (h)	139.20 (9.85)	128.40 (26.15)	138.08 (10.52)
C_{last} (pg/mL)	54.0 (51.5)	45.8 (27.7)	48.2 (29.9)

SOURCE: Summary 14.2.5, Listing 16.2.6.1
[a]Median (range) is presented for T_{max}.
C_{max}=maximum observed plasma drug concentration; AUC_{inf}=area under the plasma drug concentration-time curve (AUC) from time zero to infinity; AUC_{last}=AUC from time zero to the time of the last measurable drug concentration; T_{max}=time to maximum observed plasma drug concentration; $T_{1/2}$=elimination half-life; AUC_{Extrap}=100x(AUC_{inf}-AUC_{last})/AUC_{inf}; λ_z=apparent plasma terminal elimination rate constant; T_{last}=time to last measurable drug concentration; C_{last}=last measurable drug concentration.
A=Cold Beverage, B=Hot Beverage, C=Room Temperature.

Synopsis Table 2: Mean (Standard Deviation) Pharmacokinetic Parameters for Norbuprenorphine After Administration of Buprenorphine HCl and Naloxone HCl Dihydrate Sublingual Film with Cold Beverage (Treatment A), Hot Beverage (Treatment B), or Beverage at Room Temperature (Treatment C) (Pharmacokinetic Analysis Set)

Variable	A (N=20)	B (N=19)	C (N=20)
T_{max} (h)[a]	0.75 (0.33, 4.00)	0.75 (0.50, 6.03)	1.00 (0.50, 36.00)
C_{max} (pg/mL)	3780 (2580)	3200 (1960)	3150 (1900)
AUC_{last} (h*pg/mL)	90360 (40690)	88580 (48870)	93220 (49010)
AUC_{inf} (h*pg/mL)	99280 (47910)	94060 (53880)	98740 (52160)
AUC_{Extrap} (%)	7.09 (7.78)	5.59 (4.13)	5.30 (3.30)
λ_z (1/h)	0.0228 (0.0083)	0.0252 (0.0061)	0.0240 (0.0061)
$T_{1/2}$ (h)	36.03 (18.04)	28.91 (6.81)	30.69 (7.67)
T_{last} (h)	140.41 (8.80)	135.16 (22.92)	141.60 (7.39)
C_{last} (pg/mL)	124 (111)	115 (103)	112 (77.7)

SOURCE: Summary 14.2.6, Listing 16.2.6.2
[a]Median (range) is presented for T_{max}.
C_{max}=maximum observed plasma drug concentration; AUC_{inf}=area under the plasma drug concentration-time curve (AUC) from time zero to infinity; AUC_{last}=AUC from time zero to the time of the last measurable drug concentration; T_{max}=time to maximum observed plasma drug concentration; $T_{1/2}$=elimination half-life; AUC_{Extrap}=100x(AUC_{inf}-AUC_{last})/AUC_{inf}; λ_z=apparent plasma terminal elimination rate constant; T_{last}=time to last measurable drug concentration; C_{last}=last measurable drug concentration.
A=Cold Beverage, B=Hot Beverage, C=Room Temperature.

Synopsis Table 3: Mean (Standard Deviation) Pharmacokinetic Parameters for Unconjugated Naloxone After Administration of Buprenorphine HCl and Naloxone HCl Dihydrate Sublingual Film with Cold Beverage (Treatment A), Hot Beverage (Treatment B), or Beverage at Room Temperature (Treatment C) (Pharmacokinetic Analysis Set)

Variable	A (N=20)	B (N=20)	C (N=20)
T_{max} (h)[a]	0.50 (0.33, 1.00)	0.50 (0.16, 1.25)	0.50 (0.33, 1.00)
C_{max} (pg/mL)	407 (205)	471 (334)	384 (149)
AUC_{last} (h*pg/mL)	1108 (546.1)	1132 (645.9)	1136 (720.0)
AUC_{inf} (h*pg/mL)	1139 (552.6)	1163 (664.0)	1169 (718.3)
AUC_{Extrap} (%)	2.92 (2.48)	3.00 (2.68)	3.55 (3.26)
λ_z (1/h)	0.1832 (0.0791)	0.1802 (0.0969)	0.1547 (0.0820)
$T_{1/2}$ (h)	4.89 (3.04)	5.16 (2.94)	6.47 (5.25)
T_{last} (h)	26.20 (9.75)	25.40 (11.18)	27.20 (10.90)
C_{last} (pg/mL)	4.49 (4.00)	3.72 (1.73)	3.68 (2.15)

SOURCE: Summary 14.2.7, Listing 16.2.6.3
[a]Median (range) is presented for T_{max}.
C_{max}=maximum observed plasma drug concentration; AUC_{inf}=area under the plasma drug concentration-time curve (AUC) from time zero to infinity; AUC_{last}=AUC from time zero to the time of the last measurable drug concentration; T_{max}=time to maximum observed plasma drug concentration; $T_{1/2}$=elimination half-life; AUC_{Extrap}=100x(AUC_{inf}-AUC_{last})/AUC_{inf}; λ_z=apparent plasma terminal elimination rate constant; T_{last}=time to last measurable drug concentration; C_{last}=last measurable drug concentration.
A=Cold Beverage, B=Hot Beverage, C=Room Temperature.

Synopsis Table 4: Mean (Standard Deviation) Pharmacokinetic Parameters for Total Naloxone After Administration of Buprenorphine HCl and Naloxone HCl Dihydrate Sublingual Film with Cold Beverage (Treatment A), Hot Beverage (Treatment B), or Beverage at Room Temperature (Treatment C) (Pharmacokinetic Analysis Set)

Variable	A (N=20)	B (N=20)	C (N=20)
T_{max} (h)[a]	0.50 (0.33, 3.00)	0.75 (0.40, 2.00)	0.62 (0.33, 6.00)
C_{max} (ng/mL)	61.9 (19.6)	47.7 (21.4)	57.5 (18.9)
AUC_{last} (h*ng/mL)	116.7 (27.82)	101.0 (40.40)	114.8 (30.82)
AUC_{inf} (h*ng/mL)	120.0 (27.34)	104.5 (41.42)	118.0 (31.91)
AUC_{Extrap} (%)	2.98 (2.93)	3.94 (3.19)	2.61 (1.68)
λ_z (1/h)	0.0869 (0.0390)	0.0939 (0.0572)	0.0884 (0.0225)
$T_{1/2}$ (h)	9.85 (5.38)	9.20 (3.64)	8.53 (3.11)
T_{last} (h)	37.20 (8.62)	37.05 (12.59)	37.80 (7.05)
C_{last} (ng/mL)	0.220 (0.102)	0.262 (0.225)	0.236 (0.109)

SOURCE: Summary 14.2.8, Listing 16.2.6.4
[a]Median (range) is presented for T_{max}.
C_{max}=maximum observed plasma drug concentration; AUC_{inf}=area under the plasma drug concentration-time curve (AUC) from time zero to infinity; AUC_{last}=AUC from time zero to the time of the last measurable drug concentration; T_{max}=time to maximum observed plasma drug concentration; $T_{1/2}$=elimination half-life; AUC_{Extrap}=100x(AUC_{inf}-AUC_{last})/AUC_{inf}; λ_z=apparent plasma terminal elimination rate constant; T_{last}=time to last measurable drug concentration; C_{last}=last measurable drug concentration.
A=Cold Beverage, B=Hot Beverage, C=Room Temperature.

Synopsis Table 5: Statistical Analysis of the Log-Transformed Systemic Exposure Parameters of Buprenorphine (Pharmacokinetic Analysis Set)

	Geometric Mean[a]			90% CI[c]	
Variable	A (N=20)	C (N=20)	Ratio (%)[b] (A/C)	Lower	Upper
C_{max}	5155.3489	5016.2013	102.77	87.52	120.69
AUC_{last}	47929.5799	50093.2727	95.68	81.50	112.33
AUC_{inf}	51227.6464	52357.3682	97.84	84.02	113.94

	Geometric Mean[a]			90% CI[c]	
Variable	B (N=20)	C (N=20)	Ratio (%)[b] (B/C)	Lower	Upper
C_{max}	5761.6590	5016.2013	114.86	97.65	135.10
AUC_{last}	49581.3799	50093.2727	98.98	84.17	116.39
AUC_{inf}	52403.8842	52357.3682	100.09	85.81	116.74

SOURCE: Listings 16.1.9.1 through 16.1.9.3

[a] Geometric Mean for Cold Beverage (A), Hot Beverage (B), and Room Temperature (C) based on Least Squares Mean of log-transformed parameter values

[b] Ratio(%) = Geometric Mean (A or B)/Geometric Mean (C)

[c] 90% Confidence Interval

C_{max}=maximum observed plasma drug concentration; AUC_{inf}=area under the plasma drug concentration-time curve (AUC) from time zero to infinity; AUC_{last}=AUC from time zero to the time of the last measurable drug concentration

Synopsis Table 6: Statistical Analysis of the Log-Transformed Systemic Exposure Parameters of Norbuprenorphine (Pharmacokinetic Analysis Set)

	Geometric Mean[a]			90% CI[c]	
Variable	A (N=20)	C (N=20)	Ratio (%)[b] (A/C)	Lower	Upper
C_{max}	3035.5999	2790.5475	108.78	83.42	141.86
AUC_{last}	83123.3405	83389.3958	99.68	77.92	127.52
AUC_{inf}	90165.6353	87748.0864	102.76	81.26	129.94

	Geometric Mean[a]			90% CI[c]	
Variable	B (N=19)	C (N=20)	Ratio (%)[b] (B/C)	Lower	Upper
C_{max}	2612.4013	2790.5475	93.62	71.26	122.99
AUC_{last}	77008.5130	83389.3958	92.35	71.69	118.95
AUC_{inf}	82629.7973	87748.0864	94.17	73.98	119.86

SOURCE: Listings 16.1.9.4 through 16.1.9.6

[a] Geometric Mean for Cold Beverage (A), Hot Beverage (B), and Room Temperature (C) based on Least Squares Mean of log-transformed parameter values

[b] Ratio(%) = Geometric Mean (A or B)/Geometric Mean (C)

[c] 90% Confidence Interval

C_{max}=maximum observed plasma drug concentration; AUC_{inf}=area under the plasma drug concentration-time curve (AUC) from time zero to infinity; AUC_{last}=AUC from time zero to the time of the last measurable drug concentration

Synopsis Table 7: Statistical Analysis of the Log-Transformed Systemic Exposure Parameters of Unconjugated Naloxone (Pharmacokinetic Analysis Set)

	Geometric Mean[a]			90% CI[c]	
Variable	A (N=20)	C (N=20)	Ratio (%)[b] (A/C)	Lower	Upper
C_{max}	358.7820	367.9538	97.51	79.91	118.98
AUC_{last}	959.4326	972.0428	98.70	82.00	118.81
AUC_{inf}	991.6208	1005.2567	98.64	81.95	118.74

	Geometric Mean[a]			90% CI[c]	
Variable	B (N=20)	C (N=20)	Ratio (%)[b] (B/C)	Lower	Upper
C_{max}	387.3220	367.9538	105.26	86.09	128.71
AUC_{last}	945.8740	972.0428	97.31	80.69	117.35
AUC_{inf}	973.8503	1005.2567	96.88	80.33	116.83

SOURCE: Listings 16.1.9.7 through 16.1.9.9

[a] Geometric Mean for Cold Beverage (A), Hot Beverage (B), and Room Temperature (C) based on Least Squares Mean of log-transformed parameter values

[b] Ratio(%) = Geometric Mean (A or B)/Geometric Mean (C)

[c] 90% Confidence Interval

C_{max}=maximum observed plasma drug concentration; AUC_{inf}=area under the plasma drug concentration-time curve (AUC) from time zero to infinity; AUC_{last}=AUC from time zero to the time of the last measurable drug concentration

Synopsis Table 8: Statistical Analysis of the Log-Transformed Systemic Exposure Parameters of Total Naloxone (Pharmacokinetic Analysis Set)

	Geometric Mean[a]			90% CI[c]	
Variable	A (N=20)	C (N=20)	Ratio (%)[b] (A/C)	Lower	Upper
C_{max}	55.9827	53.5065	104.63	75.89	144.25
AUC_{last}	111.4456	110.8245	100.56	74.30	136.09
AUC_{inf}	114.8419	114.1084	100.64	74.83	135.37

	Geometric Mean[a]			90% CI[c]	
Variable	B (N=20)	C (N=20)	Ratio (%)[b] (B/C)	Lower	Upper
C_{max}	39.1781	53.5065	73.22	52.94	101.28
AUC_{last}	86.4980	110.8245	78.05	57.49	105.95
AUC_{inf}	89.8469	114.1084	78.74	58.36	106.22

SOURCE: Listings 16.1.9.10 through 16.1.9.12

[a] Geometric Mean for Cold Beverage (A), Hot Beverage (B), and Room Temperature (C) based on Least Squares Mean of log-transformed parameter values

[b] Ratio(%) = Geometric Mean (A or B)/Geometric Mean (C)

[c] 90% Confidence Interval

C_{max}=maximum observed plasma drug concentration; AUC_{inf}=area under the plasma drug concentration-time curve (AUC) from time zero to infinity; AUC_{last}=AUC from time zero to the time of the last measurable drug concentration

The average bioavailability of buprenorphine, norbuprenorphine, unconjugated naloxone, and total naloxone after pretreatment with cold and hot beverages was generally within 20% of that after pretreatment with

AUC_{last}) to 114.86% (hot beverage, buprenorphine C_{max}), except for the geometric mean ratios for total naloxone after a hot beverage compared with room-temperature water which ranged from 73.22% (C_{max}) to 78.74% (AUC_{inf}). The most significant PK finding was an approximately 15% increase in buprenorphine C_{max} when buprenorphine/naloxone 16 mg/4 mg sublingual film was administered following pre-treatment with hot water, compared with room-temperature water.

Safety Results: There were no deaths or other serious adverse events reported in the study. There were no adverse events assessed as severe. Two subjects (1 subject each during Treatment A and Treatment C) discontinued from the study because of adverse events of vomiting. All adverse events resolved.

The percentage of subjects who had at least 1 adverse event after study drug administration was similar when buprenorphine HCl/naloxone HCl dihydrate sublingual film was administered after pretreatment with a cold beverage (Treatment A), hot beverage (Treatment B), or a room temperature beverage (Treatment C); 10 (44%), 11 (48%), and 9 (41%) subjects, respectively. A similar percentage of subjects reported at least 1 adverse event in the system organ classes with the highest percentage of adverse events; Gastrointestinal Disorder (39%, 44%, and 36% with Treatments A, B, and C, respectively) and Nervous System Disorders (22%, 30%, 23%, with Treatments A, B, and C, respectively). The most frequent adverse events (those occurring in 5% or more of subjects after any treatment) were consistent with the known safety profile of Suboxone® and included nausea, vomiting, abdominal pain, paresthesia oral, dizziness, and headache. The incidence of these common adverse events was generally similar following the 3 treatments, given the small sample size in this study.

There were no clinically meaningful differences in laboratory parameters as assessed between baseline and endpoint, and no subject had a laboratory parameter assessed as an adverse event or that led to study discontinuation.

Following study drug administration, in general, the mean changes from baseline were comparable among the 3 treatment groups at each assessment time point with respect to vital signs. There were no clinically meaningful changes in mean vital sign values between baseline and endpoint. Subjects meeting the criteria for a potentially clinically significant vital sign finding, had resolution of the finding without treatment. None of the potentially clinically significant vital sign findings were associated with any clinically significant sequelae. There were no adverse events referable to vital signs.

No subject had an ECG assessed as clinically significant. No subject met criteria for an ECG outlier with respect to PR interval, QRS interval, QTcB interval or QTcF interval. No ECG parameter or ECG finding was assessed as an adverse event.

There were no relevant physical examination findings reported in this study. Given the method of administration of the buprenorphine / naloxone sublingual film strip, adverse events that were reported and referable to the oral mucosa and surrounding structures following study drug administration were assessed. In this study, none of the oral mucosa adverse events or adverse events that were referable to surrounding structures was assessed as serious, or as moderate or severe in intensity. None of these adverse events required treatment, or led to study discontinuation. All of these adverse events resolved. In this study, 1 subject (1/23, 4.3%), had at least 1 adverse event following Treatment A, 2 subjects (2/22, 8.7%) had at least 1 adverse event following Treatment B, and 0 subjects (0/22, 0%), had at least 1 adverse event following Treatment C, that were referable to the oral mucosa and / or surrounding structures. All of the oral mucosal adverse events and / or adverse events referable to the surrounding structures were reported as 'paraesthesia oral'.

In this study of 24 healthy subjects, pre-treatment of the oral cavity prior to study drug administration with either hot water, cold water, or room temperature water, had no effect on the safety profile of the buprenorphine / naloxone sublingual film. Overall, no new safety findings were identified in this study.

Conclusions: The most significant PK result from this study was an approximately 15% increase in buprenorphine C_{max} when buprenorphine/naloxone 16 mg/4 mg sublingual film was administered following pre-treatment with hot water, compared with room-temperature water as the pre-treatment beverage. Otherwise, pre-treatment of the oral cavity with either a cold, hot, or room temperature beverage does not have an appreciable impact on buprenorphine, norbuprenorphine, and unconjugated naloxone exposure.

Pre-treatment of the oral cavity prior to study drug administration with either hot water, cold water, or room temperature water had no impact on the safety profile of the buprenorphine / naloxone sublingual film. Overall, no new or relevant safety findings were identified in this study.

2. SYNOPSIS

Name of Sponsor/Company: Teva Pharmaceuticals USA	**Individual study table referring to part of dossier in which the individual study or study table is presented** **Volume:** **Reference:**	(For National Authority Use Only)
Name of Finished Product: Buprenorphine HCl and naloxone HCl dihydrate sublingual film, 16 mg/4 mg		
Name of Active Ingredient: Buprenorphine HCl and naloxone HCl		

Title of Study: A Single-Dose, Three-Period, Three-Treatment, Three-Way Crossover Study Comparing the Effect of Beverage pH on the Relative Bioavailability of Buprenorphine Hydrochloride/Naloxone Hydrochloride Dihydrate Sublingual Film, 16 mg/4 mg

Rationale for Amendment: A full clinical study report (CSR) for this study was submitted as part of the buprenorphine/naloxone 16 mg/4 mg sublingual film New Drug Application (NDA) in 2014. This CSR amendment supersedes the one in the original NDA submission to address the completion of a full study database, Medical Dictionary of Regulatory Activities (MedDRA) coding of all adverse events, addition of narratives for the subjects who discontinued from the study due to adverse events, and generation of a complete set of summary tables and listings for the study. Other minor text changes were incorporated for clarification and to ensure consistency across the document. These changes did not impact the pharmacokinetic results or conclusions or the overall study conclusions of the original study report.

Investigators and Study Centers:

Investigators: (b) (4)

(b) (4)

Study Center: Worldwide Clinical Trials Early Phase Services, LLC (WCT), 2455 NE Loop 410, Suite 150, San Antonio, Texas 78217

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

Study Period: 10 August 2014 to 13 September 2014 Phase of Development: 1

Primary Objective: The objective of this single-dose, open-label, randomized, three-period, three-treatment crossover study was to assess the impact of beverage pH on the relative bioavailability of buprenorphine HCl/naloxone HCl dihydrate 16 mg/4 mg sublingual film.

Number of Patients (Planned and Analyzed): For this study, 24 subjects were planned to be enrolled; data from 24 subjects were analyzed for safety and data from a total of 24 subjects were analyzed for pharmacokinetics.

Diagnosis and Main Criteria for Inclusion: Subjects were included in the study if all of the following main criteria were met (not all inclusive): Healthy, non-smoking males or healthy, non-smoking females who were neither

pregnant nor breastfeeding, between 18 and 50 years of age (inclusive), with body mass index (BMI) between 18 and 32 kg/m^2 (inclusive), and a minimum weight of 59 kg (130 lbs).

Main Criteria for Exclusion: Subjects were excluded from participating in this study if 1 or more of the following main criteria were met (not all inclusive): History or presence of clinically significant cardiovascular, pulmonary, hepatic, renal, hematologic, gastrointestinal, endocrine, immunologic, dermatologic, neurologic, oncologic, or psychiatric disease or any other condition that, in the opinion of the Investigator, jeopardized the safety of the subject or the validity of the study results; had used over-the-counter medication within 7 days, or prescription medication within 14 days prior to the first dose of study treatment; had significant dental issues noted at screening or presence of blisters, ulcers, sores, or lesions in the mouth at time of check-in to any study period.

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

Investigational Product:

Buprenorphine and Naloxone Sublingual Film, 16 mg/4 mg, (C3)

Dose = 1 x 16 mg/4 mg sublingual film, sublingually administered

Lot: 9902493

Treatment A (Test 1): Subjects consumed 60 mL (2 fl oz) of low pH beverage (Sprite) starting 1 minute before dosing (administered at room temperature)

Treatment B (Test 2): Subjects consumed 60 mL (2 fl oz) of high pH beverage (solution of ½ teaspoon of sodium bicarbonate dissolved in room temperature water) starting 1 minute before dosing (administered at room temperature)

Treatment C (Reference): Subjects consumed 60 mL (2 fl oz) of room temperature water starting 1 minute before dosing

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

Duration of Treatment: Three single-dose treatments were administered with a 14-day washout period between doses.

General Design and Methodology: This was a single-dose, open-label, randomized, 3-period, 3-treatment crossover study in which 24 healthy adult subjects were to receive up to three separate single-dose applications of buprenorphine HCl/naloxone HCl dihydrate sublingual film, 16 mg/4 mg. Each dose was administered after a 10-hour overnight fast. Before each dose, subjects were pretreated with a low pH beverage, a high pH beverage, or a reference beverage (all administered at room temperature).

Safety Variables: The Investigator evaluated safety using the following assessments: clinical laboratory evaluations, electrocardiograms (ECGs), physical examinations (including oral cavity examinations), vital sign measurements (including continuous pulse oximetry monitoring), and reported or observed adverse events (AEs). Subjects were monitored for any AEs from the beginning of confinement through the end-of-study visit.

Pharmacokinetic Variables: For each treatment of the buprenorphine HCl and naloxone HCl dihydrate sublingual film, the following pharmacokinetic parameters for buprenorphine, norbuprenorphine, unconjugated naloxone, and total naloxone were calculated, if appropriate:

- C_{max} by inspection (without interpolation)
- AUC_{inf}
- AUC_{last}
- T_{max}
- AUC_{extrap} percentage extrapolation calculated as $(AUC_{inf}-AUC_{last})/(AUC_{inf})\times 100$
- λ_z and associated $T_{1/2}$
- C_{last}
- T_{last}

Statistical Considerations: Concentration-time data were received from (b) (4) and were subsequently analyzed using noncompartmental methods in Phoenix™ WinNonlin® (Version 6.3, Pharsight Corporation). Concentration-time data that were below the limit of quantification (BLQ) were treated as zero in the data summarization and descriptive statistics. In the pharmacokinetic analysis, BLQ concentrations were treated as zero from time-zero up to the time at which the first quantifiable concentration was observed; embedded and/or terminal BLQ concentrations were treated as "missing". Actual sample times were used for all pharmacokinetic and statistical analyses.

Analysis of variance (ANOVA) and the Schuirmann's two one-sided t-test procedures at the 5% significance level were applied to the log-transformed pharmacokinetic exposure parameters, C_{max}, AUC_{last}, and AUC_{inf}. The 90% confidence interval for the ratio of the geometric means (Test/Reference) was calculated. No treatment effect (bioequivalence) was declared if the lower and upper confidence intervals were within 80% to 125%.

Summary of Results

Subject Disposition and Demography: Of the 24 subjects randomly assigned to a treatment sequence, all 24 received at least 1 dose of study drug and were evaluated for safety in the study. A total of 4 (16.7%) subjects discontinued from the study.

The reasons for discontinuation were: 2 (8.3%) due to adverse event and 2 (8.3%) due to protocol deviation (assessed as protocol violations).

The mean age of subjects was 32.0 years (range 19 to 49 years); 66.7% of subjects were men and 33.3% were women. The majority of subjects were white (75.0%). Slightly less than half (41.7%) of subjects were Hispanic or Latino, while the remaining subjects (58.3%) were not Hispanic or Latino. Mean weight was 78.5 kg (range 61 to 106 kg) and mean BMI was 26.9 kg/m^2 (range 21 to 32 kg/m^2). Subjects randomly assigned to each of the 6 treatment sequences were, in general, similar with regard to demographic characteristics, given the small sample size.

Dissolution of Sublingual Film: Subjects were dosed with study drug in accordance with the protocol and were monitored for the dissolution of the sublingual film. The time to complete dissolution of the sublingual film was recorded following each administration to ensure completion of dosing. The mean dissolution time (seconds) for Treatment A (low pH beverage) was 303.09 (range 62.00–1149.0), for Treatment B (high pH beverage) 287.25

(range 65.00-1259.00), and for Treatment C (room temperature water) 327.74 (range 56.00-1312.00). (Table 14.3.5.10; Listing 16.2.5.1).

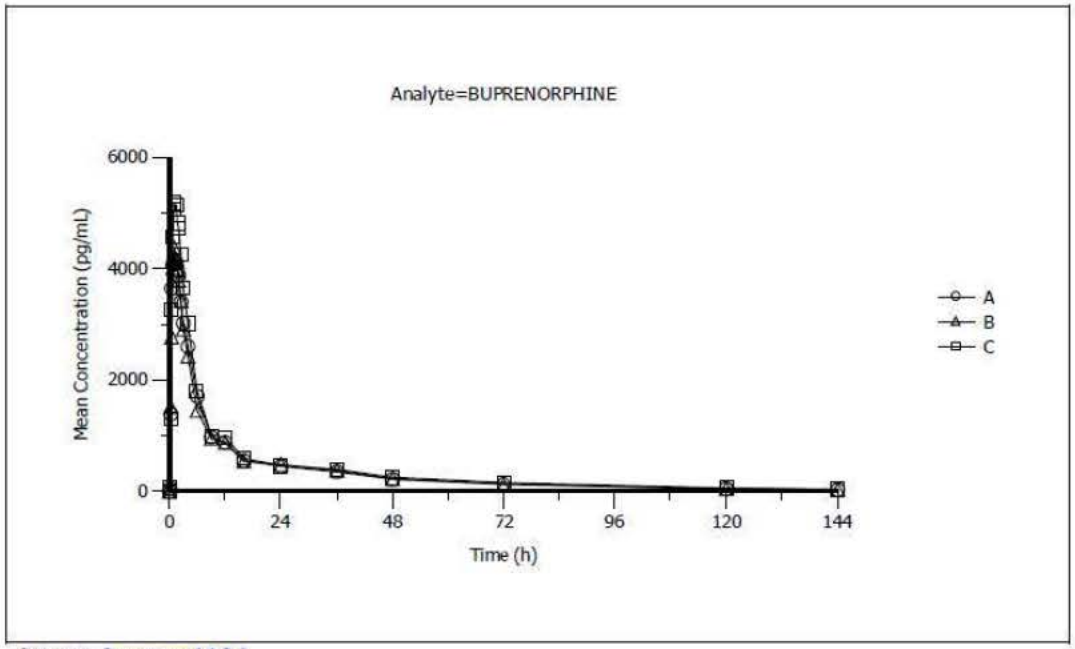
Beverage pH: Each subject was required to consume approximately 60 mL of a low pH beverage, a high pH beverage, or room temperature water 1 minute before study treatment administration. The mean pH of Treatment A (low pH beverage) was 3.34 (range 3.33-3.36). The mean pH of Treatment B (high pH beverage) was 7.99 (range 7.94–8.02). The mean pH of Treatment C (room temperature water) was 7.51 (range 7.47–7.60).

Pharmacokinetics Results: The pharmacokinetic analysis set includes those subjects in the safety analysis set who had sufficient data to calculate the pharmacokinetic parameters C_{max}, AUC_{last}, and AUC_{inf} for buprenorphine, norbuprenorphine, unconjugated naloxone, and total naloxone for at least one administration period.

Data from a total of 24 subjects were included in the pharmacokinetic and statistical analyses.

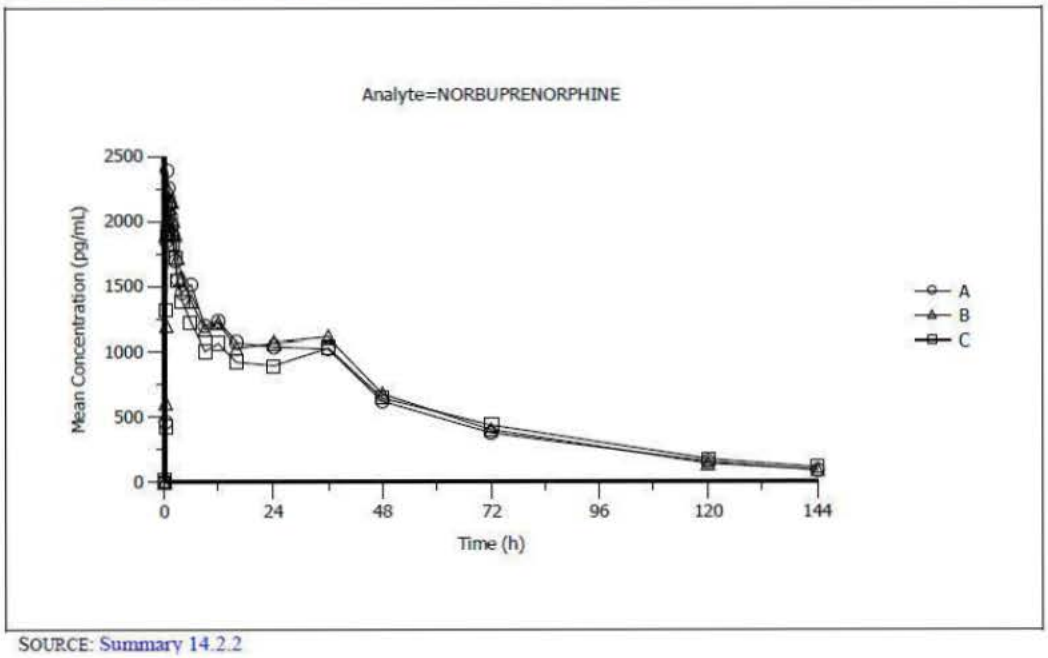
Mean concentration-time data are shown in Synopsis Figures 1 through 4. Results of the pharmacokinetic and statistical analyses are shown below in Synopsis Tables 1 through 8.

Synopsis Figure 1: Mean Plasma Concentration by Time Profiles for Buprenorphine in Healthy Subjects Administered Buprenorphine HCl and Naloxone HCl Dihydrate Sublingual Film with a Low pH Beverage (Treatment A), High pH Beverage (Treatment B), or Room Temperature Water (Treatment C) (Pharmacokinetic Analysis Set)



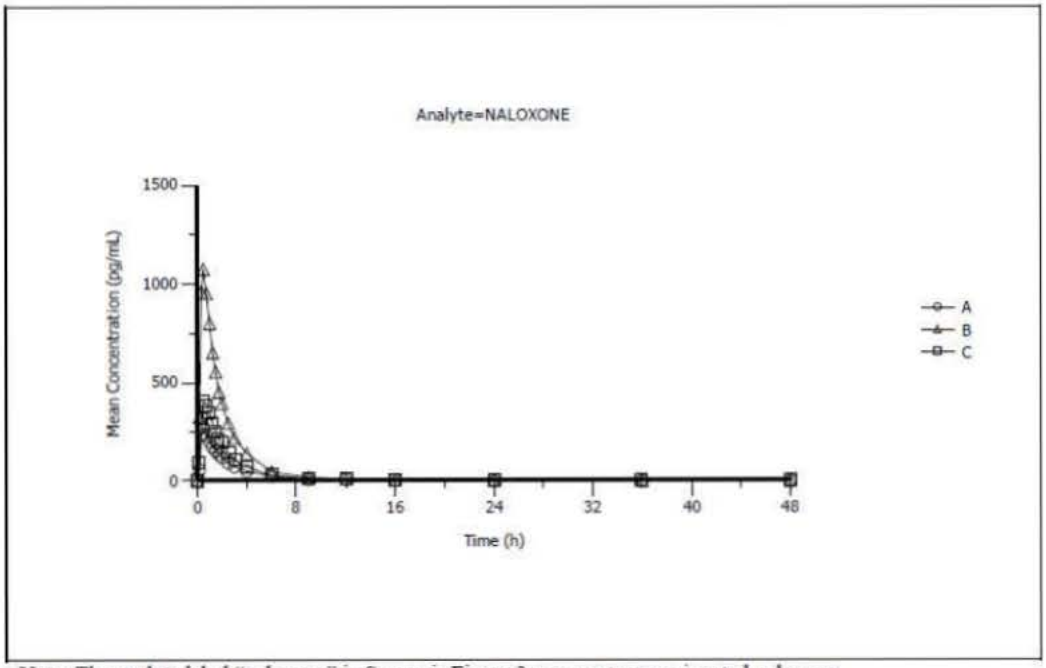
SOURCE: Summary 14.2.1

Synopsis Figure 2: Mean Plasma Concentration by Time Profiles for Norbuprenorphine in Healthy Subjects Administered Buprenorphine HCl and Naloxone HCl Dihydrate Sublingual Film with a Low pH Beverage (Treatment A), High pH Beverage (Treatment B), or Room Temperature Water (Treatment C) (Pharmacokinetic Analysis Set)



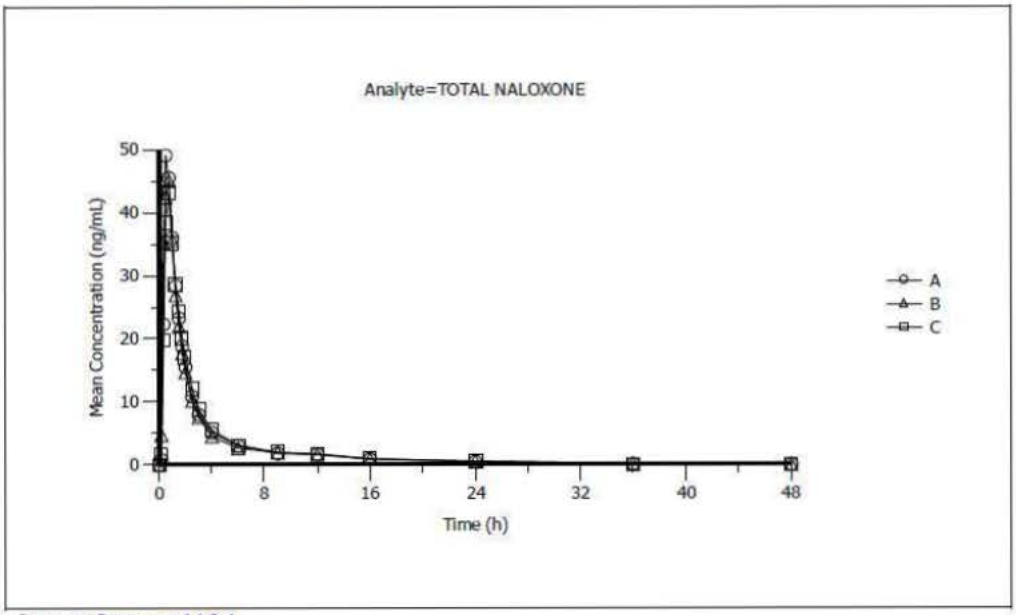
SOURCE: Summary 14.2.2

Synopsis Figure 3: Mean Plasma Concentration by Time Profiles for Unconjugated Naloxone in Healthy Subjects Administered Buprenorphine HCl and Naloxone HCl Dihydrate Sublingual Film with a Low pH Beverage (Treatment A), High pH Beverage (Treatment B), or Room Temperature Water (Treatment C) (Pharmacokinetic Analysis Set)



Note: The analyte label "naloxone" in Synopsis Figure 3 represents unconjugated naloxone.
SOURCE: Summary 14.2.3

Synopsis Figure 4: Mean Plasma Concentration by Time Profiles for Total Naloxone in Healthy Subjects Administered Buprenorphine HCl and Naloxone HCl Dihydrate Sublingual Film with a Low pH Beverage (Treatment A), High pH Beverage (Treatment B), or Room Temperature Water (Treatment C) (Pharmacokinetic Analysis Set)



SOURCE: Summary 14.2.4

Synopsis Table 1: Mean (Standard Deviation) Pharmacokinetic Parameters for Buprenorphine After Administration of Buprenorphine HCl and Naloxone HCl Dihydrate Sublingual Film with a Low pH Beverage (Treatment A), High pH Beverage (Treatment B), or Room Temperature Water (Treatment C) (Pharmacokinetic Analysis Set)

Variable	A (N=21)	B (N=23)	C (N=21)
T_{max} (h)[a]	1.00 (0.50, 2.00)	1.00 (0.33, 2.50)	1.25 (0.50, 2.50)
C_{max} (pg/mL)	5180 (2070)	5070 (2010)	5990 (3650)
AUC_{last} (h*pg/mL)	48600 (16250)	48460 (13070)	54970 (20680)
AUC_{inf} (h*pg/mL)	50890 (16760)	50910 (13550)	58010 (21830)
AUC_{Extrap} (%)	4.69 (2.13)	4.92 (2.59)	5.18 (1.97)
λ_z (1/h)	0.0226 (0.0089)	0.0202 (0.0045)	0.0200 (0.0059)
$T_{1/2}$ (h)	34.12 (10.13)	36.09 (8.38)	37.36 (10.25)
T_{last} (h)	128.45 (28.77)	134.61 (21.39)	132.58 (25.87)
C_{last} (pg/mL)	46.5 (20.1)	47.1 (25.1)	56.9 (28.5)

SOURCE: Summary 14.2.5, Listing 16.2.6.1.

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

C_{max}=maximum observed plasma drug concentration; AUC_{inf}=area under the plasma drug concentration-time curve (AUC) from time zero to infinity; AUC_{last}=AUC from time zero to the time of the last measurable drug concentration; T_{max}=time to maximum observed plasma drug concentration; $T_{1/2}$=elimination half-life; AUC_{Extrap}=100x(AUC_{inf}-AUC_{last})/AUC_{inf}; λ_z=apparent plasma terminal elimination rate constant; T_{last}=time to last measurable drug concentration; C_{last}=last measurable drug concentration.

A=Low pH Beverage, B=High pH Beverage, C=Room Temperature Water

Synopsis Table 2: Mean (Standard Deviation) Pharmacokinetic Parameters for Norbuprenorphine After Administration of Buprenorphine HCl and Naloxone HCl Dihydrate Sublingual Film with a Low pH Beverage (Treatment A), High pH Beverage (Treatment B), or Room Temperature Water (Treatment C) (Pharmacokinetic Analysis Set)

Variable	A (N=21)	B (N=23)	C (N=21)
T_{max} (h)[a]	0.75 (0.50, 12.00)	1.00 (0.50, 12.00)	1.00 (0.50, 2.50)
C_{max} (pg/mL)	2770 (1230)	2720 (1070)	2470 (968)
AUC_{last} (h*pg/mL)	80550 (33860)	83120 (22400)	79590 (26750)
AUC_{inf} (h*pg/mL)	85800 (36470)	88620 (24160)	86430 (32140)
AUC_{Extrap} (%)	5.78 (4.75)	5.89 (5.05)	6.69 (5.29)
λ_z (1/h)	0.0216 (0.0059)	0.0222 (0.0069)	0.0221 (0.0059)
$T_{1/2}$ (h)	34.85 (11.39)	34.49 (11.68)	33.77 (10.23)
T_{last} (h)	143.34 (4.11)	144.01 (0.04)	140.58 (8.61)
C_{last} (pg/mL)	90.2 (64.5)	95.9 (59.7)	119 (95.8)

SOURCE: Summary 14.2.6, Listing 16.2.6.2.
[a]Median (range) is presented for T_{max}.
C_{max}=maximum observed plasma drug concentration; AUC_{inf}=area under the plasma drug concentration-time curve (AUC) from time zero to infinity; AUC_{last}=AUC from time zero to the time of the last measurable drug concentration; T_{max}=time to maximum observed plasma drug concentration; $T_{1/2}$=elimination half-life; AUC_{Extrap}=100x(AUC_{inf}-AUC_{last})/AUC_{inf}; λ_z=apparent plasma terminal elimination rate constant; T_{last}=time to last measurable drug concentration; C_{last}=last measurable drug concentration.
A=Low pH Beverage, B=High pH Beverage, C=Room Temperature Water

Synopsis Table 3: Mean (Standard Deviation) Pharmacokinetic Parameters for Unconjugated Naloxone After Administration of Buprenorphine HCl and Naloxone HCl Dihydrate Sublingual Film with a Low pH Beverage (Treatment A), High pH Beverage (Treatment B), or Room Temperature Water (Treatment C) (Pharmacokinetic Analysis Set)

Variable	A (N=21)	B (N=23)	C (N=21)
T_{max} (h)[a]	0.50 (0.33, 1.25)	0.50 (0.33, 1.00)	0.74 (0.33, 1.50)
C_{max} (pg/mL)	301 (162)	1200 (1120)	440 (431)
AUC_{last} (h*pg/mL)	701.8 (334.7)	2206 (1409)	1044 (729.5)
AUC_{inf} (h*pg/mL)	723.6 (336.0)	2222 (1408)	1068 (728.7)
AUC_{Extrap} (%)	4.12 (3.45)	1.02 (0.70)	2.79 (2.21)
λ_z (1/h)	0.2020 (0.0870)	0.2282 (0.1018)	0.1809 (0.0984)
$T_{1/2}$ (h)	4.21 (2.07)	3.90 (2.18)	5.56 (4.28)
T_{last} (h)	18.57 (6.17)	22.26 (5.76)	22.50 (5.87)
C_{last} (pg/mL)	3.83 (1.48)	3.09 (0.916)	3.00 (0.967)

SOURCE: Summary 14.2.7, Listing 16.2.6.3.
[a]Median (range) is presented for T_{max}.
C_{max}=maximum observed plasma drug concentration; AUC_{inf}=area under the plasma drug concentration-time curve (AUC) from time zero to infinity; AUC_{last}=AUC from time zero to the time of the last measurable drug concentration; T_{max}=time to maximum observed plasma drug concentration; $T_{1/2}$=elimination half-life; AUC_{Extrap}=100x(AUC_{inf}-AUC_{last})/AUC_{inf}; λ_z=apparent plasma terminal elimination rate constant; T_{last}=time to last measurable drug concentration; C_{last}=last measurable drug concentration.
A=Low pH Beverage, B=High pH Beverage, C=Room Temperature Water

Synopsis Table 4: Mean (Standard Deviation) Pharmacokinetic Parameters for Total Naloxone After Administration of Buprenorphine HCl and Naloxone HCl Dihydrate Sublingual Film with a Low pH Beverage (Treatment A), High pH Beverage (Treatment B), or Room Temperature Water (Treatment C) (Pharmacokinetic Analysis Set)

Variable	A (N=21)	B (N=23)	C (N=21)
T_{max} (h)[a]	0.75 (0.50, 1.50)	0.50 (0.33, 1.00)	0.75 (0.50, 2.00)
C_{max} (ng/mL)	54.5 (21.8)	59.7 (16.6)	50.7 (14.1)
AUC_{last} (h*ng/mL)	106.2 (29.28)	105.8 (21.41)	108.6 (24.79)
AUC_{inf} (h*ng/mL)	108.8 (29.72)	108.1 (20.72)	111.0 (24.60)
AUC_{Extrap} (%)	2.55 (2.23)	2.37 (2.07)	2.27 (1.06)
λ_z (1/h)	0.1133 (0.0445)	0.0996 (0.0376)	0.1109 (0.0436)
$T_{1/2}$ (h)	7.11 (2.83)	8.25 (3.95)	7.27 (2.99)
T_{last} (h)	32.57 (9.41)	35.48 (7.66)	33.73 (8.13)
C_{last} (ng/mL)	0.267 (0.193)	0.196 (0.0759)	0.248 (0.111)

SOURCE: Summary 14.2.8, Listing 16.2.6.4.
[a]Median (range) is presented for T_{max}.
C_{max}=maximum observed plasma drug concentration; AUC_{inf}=area under the plasma drug concentration-time curve (AUC) from time zero to infinity; AUC_{last}=AUC from time zero to the time of the last measurable drug concentration; T_{max}=time to maximum observed plasma drug concentration; $T_{1/2}$=elimination half-life; AUC_{Extrap}=100x(AUC_{inf}-AUC_{last})/AUC_{inf}; λ_z=apparent plasma terminal elimination rate constant; T_{last}=time to last measurable drug concentration; C_{last}=last measurable drug concentration.
A=Low pH Beverage, B=High pH Beverage, C=Room Temperature Water

Synopsis Table 5: Statistical Analysis of the Log-Transformed Systemic Exposure Parameters of Buprenorphine (Pharmacokinetic Analysis Set)

	Geometric Mean[a]			90% CI[c]	
Variable	A (N=21)	C (N=21)	Ratio (%)[b] (A/C)	Lower	Upper
C_{max}	4589.0190	5317.2454	86.30	74.45	100.05
AUC_{last}	44168.2754	52104.1117	84.77	75.78	94.83
AUC_{inf}	46412.6134	54911.1838	84.52	75.63	94.46

	Geometric Mean[a]			90% CI[c]	
Variable	B (N=23)	C (N=21)	Ratio (%)[b] (B/C)	Lower	Upper
C_{max}	4467.1495	5317.2454	84.01	72.58	97.25
AUC_{last}	44668.9238	52104.1117	85.73	76.73	95.79
AUC_{inf}	47011.2707	54911.1838	85.61	76.69	95.57

SOURCE: Listings 16.1.9.1 through 16.1.9.3.
[a] Geometric Mean for Low pH Beverage (A), High pH Beverage (B), and Room Temperature Water (C) based on Least Squares Mean of log-transformed parameter values
[b] Ratio(%) = Geometric Mean (A or B)/Geometric Mean (C)
[c] 90% Confidence Interval
C_{max}=maximum observed plasma drug concentration; AUC_{inf}=area under the plasma drug concentration-time curve (AUC) from time zero to infinity; AUC_{last}=AUC from time zero to the time of the last measurable drug concentration

Synopsis Table 6: Statistical Analysis of the Log-Transformed Systemic Exposure Parameters of Norbuprenorphine (Pharmacokinetic Analysis Set)

	Geometric Mean[a]			90% CI[c]	
Variable	A (N=21)	C (N=21)	Ratio (%)[b] (A/C)	Lower	Upper
C_{max}	2484.7311	2282.5202	108.86	92.03	128.76
AUC_{last}	74517.3104	75999.1397	98.05	87.48	109.89
AUC_{inf}	79251.1027	81497.4652	97.24	86.57	109.23
	Geometric Mean[a]			90% CI[c]	
Variable	B (N=23)	C (N=21)	Ratio (%)[b] (B/C)	Lower	Upper
C_{max}	2459.9497	2282.5202	107.77	91.27	127.26
AUC_{last}	76800.1731	75999.1397	101.05	90.27	113.13
AUC_{inf}	81687.1015	81497.4652	100.23	89.34	112.45

SOURCE: Listings 16.1.9.4 through 16.1.9.6.
[a] Geometric Mean for Low pH Beverage (A), High pH Beverage (B), and Room Temperature Water (C) based on Least Squares Mean of log-transformed parameter values
[b] Ratio(%) = Geometric Mean (A or B)/Geometric Mean (C)
[c] 90% Confidence Interval
C_{max}=maximum observed plasma drug concentration; AUC_{inf}=area under the plasma drug concentration-time curve (AUC) from time zero to infinity; AUC_{last}=AUC from time zero to the time of the last measurable drug concentration

Table 7: Statistical Analysis of the Log-Transformed Systemic Exposure Parameters of Unconjugated Naloxone (Pharmacokinetic Analysis Set)

	Geometric Mean[a]			90% CI[c]	
Variable	A (N=21)	C (N=21)	Ratio (%)[b] (A/C)	Lower	Upper
C_{max}	238.3285	342.6151	69.56	54.74	88.39
AUC_{last}	575.1872	898.8082	63.99	52.29	78.32
AUC_{inf}	600.9381	924.4982	65.00	53.35	79.20
	Geometric Mean[a]			90% CI[c]	
Variable	B (N=23)	C (N=21)	Ratio (%)[b] (B/C)	Lower	Upper
C_{max}	828.1384	342.6151	241.71	190.69	306.39
AUC_{last}	1722.3238	898.8082	191.62	156.89	234.04
AUC_{inf}	1745.5301	924.4982	188.81	155.28	229.58

SOURCE: Listings 16.1.9.7 through 16.1.9.9.
[a] Geometric Mean for Low pH Beverage (A), High pH Beverage (B), and Room Temperature Water (C) based on Least Squares Mean of log-transformed parameter values
[b] Ratio(%) = Geometric Mean (A or B)/Geometric Mean (C)
[c] 90% Confidence Interval
C_{max}=maximum observed plasma drug concentration; AUC_{inf}=area under the plasma drug concentration-time curve (AUC) from time zero to infinity; AUC_{last}=AUC from time zero to the time of the last measurable drug concentration

Synopsis Table 8: Statistical Analysis of the Log-Transformed Systemic Exposure Parameters of Total Naloxone (Pharmacokinetic Analysis Set)

	Geometric Mean[a]			90% CI[c]	
Variable	A (N=21)	C (N=21)	Ratio (%)[b] (A/C)	Lower	Upper
C_{max}	50.9769	50.9841	99.99	84.73	117.99
AUC_{last}	103.3928	109.5787	94.35	86.12	103.38
AUC_{inf}	105.9130	111.8378	94.70	86.48	103.70
	Geometric Mean[a]			**90% CI[c]**	
Variable	B (N=23)	C (N=21)	Ratio (%)[b] (B/C)	Lower	Upper
C_{max}	55.3961	50.9841	108.65	92.23	128.00
AUC_{last}	101.1209	109.5787	92.28	84.31	101.01
AUC_{inf}	103.7127	111.8378	92.73	84.77	101.45

SOURCE: Listings 16.1.9.10 through 16.1.9.12.

[a] Geometric Mean for Low pH Beverage (A), High pH Beverage (B), and Room Temperature Water (C) based on Least Squares Mean of log-transformed parameter values

[b] Ratio(%) = Geometric Mean (A or B)/Geometric Mean (C)

[c] 90% Confidence Interval

C_{max}=maximum observed plasma drug concentration; AUC_{inf}=area under the plasma drug concentration-time curve (AUC) from time zero to infinity; AUC_{last}=AUC from time zero to the time of the last measurable drug concentration

The relative bioavailability of buprenorphine, norbuprenorphine, and total naloxone following pretreatment with low pH and high pH beverages compared to that following pretreatment with room temperature water was similar, with geometric mean ratios ranging from 84.01% (high pH, buprenorphine C_{max}) to 108.86% (low pH, norbuprenorphine C_{max}). The pretreatment conditions influenced the relative bioavailability of unconjugated naloxone; the geometric mean ratios for low pH versus water ranged from 63.99% to 69.56% and the geometric mean ratios for high pH versus water ranged from 188.81% to 241.71%.

Safety Results:

- There were no deaths or other serious adverse events reported in the study. There were no adverse events assessed as severe. All adverse events resolved.
- Two subjects (1 subject each during Treatment A and Treatment C) discontinued from the study because of adverse events of vomiting and resolved.
- The percentage of subjects who had at least 1 adverse event after study drug administration was highest with Treatment A, 57%, (pretreatment with a low pH beverage, compared with Treatment B, 46%, (pretreatment with a high pH beverage) and Treatment C, 30%, (pretreatment with room temperature water).
- A similar percentage of subjects reported at least 1 adverse event in the system organ classes with the highest percentage of adverse events; Gastrointestinal Disorder (30%, 33%, and 22% with Treatments A, B, and C, respectively) and Nervous System Disorders (22%, 25%, 22%, with Treatments A, B, and C, respectively).
- The most frequent adverse events (those occurring in 5% or more of subjects after any study treatment) was similar following each of the 3 study treatments.

- There were no clinically meaningful differences in laboratory parameters as assessed between baseline and endpoint, and no subject had a laboratory parameter assessed as an adverse event, or that led to study discontinuation.
- Following study drug administration, in general, the mean changes were comparable among the 3 treatment groups at each assessment time point with respect to vital signs. There were no clinically meaningful differences in vital signs as assessed between baseline and endpoint. There were no adverse events referable to vital signs and no vital sign finding led to study discontinuation.
- There were no clinically meaningful differences in ECG parameters as assessed between baseline and endpoint. No subject had an ECG assessed as clinically significant. No subject met criteria for an ECG outlier. No ECG parameter or ECG finding was assessed as an adverse event or led to study discontinuation.
- There were no relevant physical examination findings or new safety findings regarding the oral mucosa.
- Given the small sample size, pre-treatment of the oral cavity prior to study drug administration with either, a low pH beverage, a high pH beverage or room temperature water, had little effect on the safety profile of the buprenorphine / naloxone sublingual film. The safety profile of buprenorphine / naloxone sublingual film in this study was also consistent with the Suboxone label No new safety findings were identified in this study.

Conclusions: Given the small sample size, pre-treatment of the oral cavity prior to study drug administration with either, a low pH beverage, a high pH beverage or room temperature water, had little effect on the safety profile of the buprenorphine / naloxone sublingual film. The safety profile of buprenorphine / naloxone sublingual film in this study was also consistent with the Suboxone label. No new safety findings were identified in this study.

Overall, the most significant PK findings were an approximately 14% to 16% reduction in buprenorphine exposure levels (C_{max} and/or AUC) when buprenorphine/naloxone, 16 mg/4 mg sublingual film was administered following pretreatment with either a low or high pH beverage and an approximately 1.9- to 2.4-fold increase in naloxone AUC and C_{max}, respectively, following administration after pretreatment with a high pH beverage, compared with room-temperature water as the pretreatment beverage.

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