

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

205637Orig1s000

**CLINICAL PHARMACOLOGY AND
BIOPHARMACEUTICS REVIEW(S)**

BIOPHARMACEUTICS REVIEW
Office of New Drug Quality Assessment

Application No.:	NDA 205-637	Reviewer: Kareen Riviere, Ph.D.	
Submission Date:	8/7/2013; 12/18/13; 1/30/14; 2/24/14; 2/26/14; 3/17/14		
Division:	DAAAP	Secondary Signature: Tapash Ghosh, Ph.D.	
Applicant:	BioDelivery Sciences International, Inc.	Supervisor: Richard Lostritto, Ph.D.	
Trade Name:	Bunavail	Date Assigned:	8/16/13
Generic Name:	buprenorphine/naloxone buccal film	Date of Review:	5/6/14
Indication:	maintenance treatment of opioid dependence	Type of Submission: 505(b)(2) NDA	
Formulation/strengths:	Buccal Film; (b) (4), 2.1/0.348 mg, 4.2/0.696 mg, 6.3/1.044 mg buprenorphine/ naloxone		
Route of Administration:	Oral		

SUMMARY:

This submission is a 505(b)(2) New Drug Application for (b) (4) mg, 2.1/0.348 mg, 4.2/0.696 mg, and 6.3/1.044 mg of Bunavail (buprenorphine/naloxone) buccal films. The proposed indication is for the maintenance treatment of opioid dependence. The reference drug product is Suboxone sublingual tablet (NDA 20733) held by Reckitt Benckiser Healthcare.

The Biopharmaceutics review for this NDA will be focused on the evaluation and acceptability of the proposed dissolution methodology and acceptance criteria as well as biowaiver for the (b) (4) mg and 2.1/0.348 mg strengths of the proposed product based on dissolution profile comparisons.

A. Dissolution Method

The proposed dissolution method is shown below.

USP Apparatus	Rotation Speed	Media Volume	Temp	Medium
I	100 rpm	500 mL	37°C	sodium phosphate buffer pH 4.5

The proposed dissolution method is deemed acceptable.

B. Acceptance Criteria

The proposed dissolution acceptance criteria are shown below.

Buprenorphine Acceptance Criterion

$$Q = \frac{(b)}{(4)}\% \text{ at 50 min}$$

Naloxone Acceptance Criterion

$$Q = \frac{(b)}{(4)}\% \text{ at 40 min}$$

The proposed dissolution acceptance criteria are acceptable.

C. Biowaiver to Support Approval of (b) (4) 2.1/0.348 mg Strengths

The Applicant provided multi-point dissolution profile comparisons with *f2* testing results for the lower two strengths versus the 4.2/0.696 mg strength using multi-media pHs. These data support a biowaiver for the 2.1/0.348 mg strength (b) (4). Therefore, a biowaiver is granted for the 2.1/0.348 mg strength only.

RECOMMENDATION:

1. A biowaiver is granted for the 2.1/0.348 mg strength based on the following information:
 - The 2.1/0.348 strength and 4.2/0.696 mg strength products have the same dosage form;
 - The 2.1/0.348 strength is proportionally similar in its active and inactive ingredients to the 4.2/0.696 mg strength; and
 - The 2.1/0.348 strength and the 4.2/0.696 mg strength products have similar dissolution profiles in three different dissolution media (pH 1.2, 2.5, 4.5).
2. Bunavail (buprenorphine/naloxone) 2.1/0.348 mg, 4.2/0.696 mg and 6.3/1.044 mg strength buccal films are recommended for approval from a Biopharmaceutics standpoint with the following dissolution method and acceptance criteria for each strength.
 - i. Dissolution Method: Apparatus I, 100 rpm agitation rate, 500 mL media volume, 37 °C, sodium phosphate buffer pH 4.5.
 - ii. Buprenorphine Dissolution acceptance criterion: $Q = \frac{(b)}{(4)}\%$ at 50 minutes.
 - iii. Naloxone Dissolution acceptance criterion: $Q = \frac{(b)}{(4)}\%$ at 40 minutes.
3. (b) (4)

Kareen Riviere, Ph.D.
Biopharmaceutics Reviewer
Office of New Drug Quality Assessment

Tapash Ghosh, Ph.D.
Biopharmaceutics Team Leader
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cc: Dr. Richard Lostritto

ASSESSMENT OF BIOPHARMACEUTICS INFORMATION

1. Background

Drug Substance

Figure 1 displays the structure of buprenorphine hydrochloride and naloxone hydrochloride dihydrate.

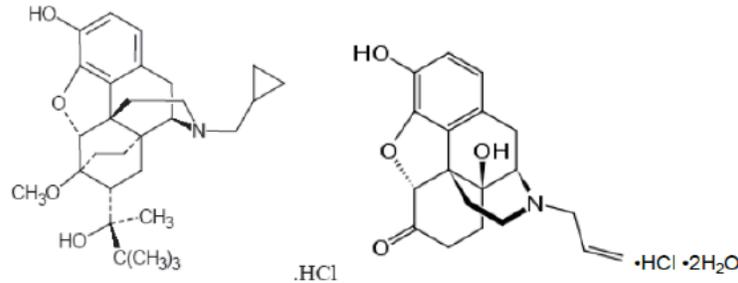
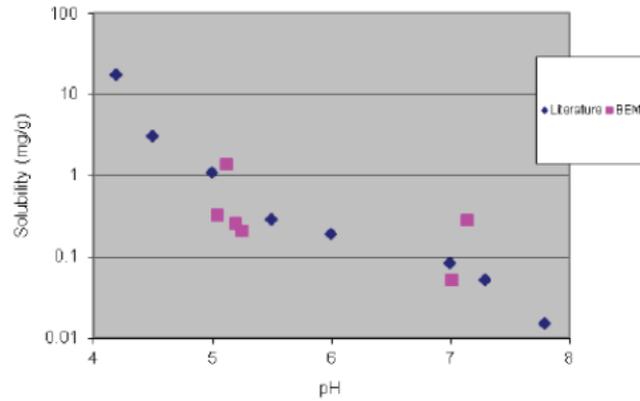


Figure 1. Chemical Structure of Buprenorphine Hydrochloride (left) and Naloxone Hydrochloride Dihydrate (right)

The solubility profile of buprenorphine hydrochloride is shown in Figure 2. The Applicant did not provide solubility data for naloxone hydrochloride dihydrate but stated that naloxone is highly soluble.

Figure 2. Buprenorphine Solubility as a Function of pH (phosphate buffer, 25°C)



Drug Product

The proposed product is a two layer film - the layers are uniform in thickness. The strength of the product is defined by the size or surface area of the product. The proposed product is manufactured (b) (4)

The Applicant stated that they designed the proposed product to enable buccal absorption of buprenorphine, with minimal systemic absorption of naloxone when used as directed, and co-extraction of naloxone with buprenorphine in situations of attempted abuse. The proposed product uses BDSI's BioErodible MucoAdhesive (BEMA®) delivery technology comprised of flexible, water soluble polymeric films which adhere to the moist buccal mucosa and erode, so that there is no residual film to remove from the mucosa.

Figure 3a. Schematic of the Buprenorphine/Naloxone Bilayer Film – Side View

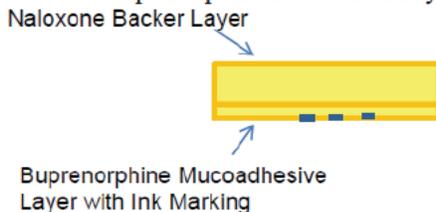


Figure 3b. Photograph of the BEMA® Buprenorphine/Naloxone Bilayer Films

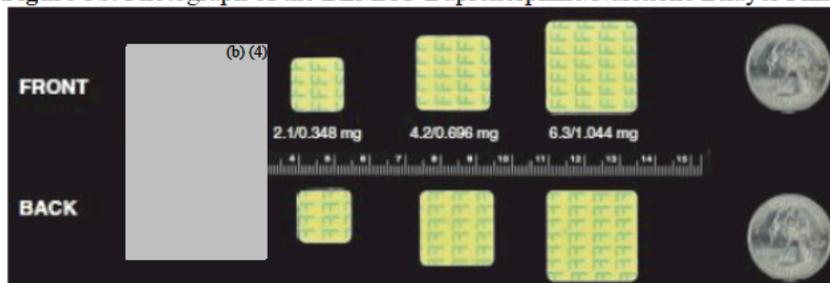


Table 1. Approximate Dimensions of BEMA® Buprenorphine NX Films

Strength (mg)	Area (cm ²)	Length (mm)	Width (mm)
2.1/0.348	2.179	14.876	14.876
4.2/0.696	4.357	20.956	20.956
6.3/1.044	6.536	25.632	25.632

The commercial composition of each strength of the proposed product is shown in Table 2.

Table 2. Composition of the Proposed Buprenorphine/Naloxone Buccal Films

Component	% w/w	Strength (mg Buprenorphine/naloxone free base)			
		(b) (4)	2.1/0.348	4.2/0.696	6.3/1.044
Purified Water ¹	-	-	-	-	
Buprenorphine Hydrochloride	3.456	(b) (4)	2.264	4.527	6.791
Propylene Glycol		(b) (4)			
Sodium Benzoate		(b) (4)			
Methylparaben		(b) (4)			
Propylparaben		(b) (4)			
Ferric Oxide, Yellow		(b) (4)			
Citric Acid	(b) (4)	(b) (4)			
Vitamin E Acetate		(b) (4)			
Monobasic Sodium Phosphate,	(b) (4)	(b) (4)			
Polycarbophil		(b) (4)			
Hydroxypropyl Cellulose		(b) (4)			
Hydroxyethyl Cellulose		(b) (4)			
Carboxymethylcellulose Sodium		(b) (4)			
Sodium Hydroxide		(b) (4)			
Dibasic Sodium Phosphate,	(b) (4)	(b) (4)			
Saccharin Sodium		(b) (4)			
Citrus Blend Flavor		(b) (4)			
Naloxone Hydrochloride	0.650	(b) (4)	0.425	0.850	1.275
(b) (4) Blue Ink		(b) (4)			
Total Weight (mg)	100.00	(b) (4)	65.492	130.985	196.477

Reviewer's Assessment:

All strengths are proportionally similar in composition.

2. Dissolution Method

The proposed dissolution method is:

USP Apparatus	Rotation Speed	Media Volume	Temp	Medium
I	100 rpm	500 mL	37°C	sodium phosphate buffer pH 4.5

Note that according to the FDA's external Dissolution Methods database, the recommend dissolution method for Buprenorphine HCl/Naloxone HCl sibilngual tablets and sublingual films are:

Drug Name	Dosage Form	USP Apparatus	Speed (RPMs)	Medium	Volume (mL)	Recommended Sampling Times (minutes)	Date Updated
Buprenorphine HCl/Naloxone HCl	Tablet (Sublingual)	I (Basket)	100	Water	500	1, 3, 5, 7.5, 10, 15 and 20	07/01/2010
Buprenorphine HCl/Naloxone HCl	Film (Sublingual)	V (Paddle over Disk) with 56 mm, 40 mesh stainless steel disk.	100	Acetate Buffer, pH 4.0 (12.5mM Sodium acetate trihydrate and 60mM glacial acetic acid. Adjust the pH with glacial acetic acid or ammonium hydroxide).	900	1, 2, 3, 5, 7 and 10	10/31/2013

The Applicant's data and justification to support the proposed dissolution method are discussed below.

Apparatus Selection

Apparatus I (Baskets) is generally used for capsules and for dosage forms that tend to float or disintegrate slowly. They selected Apparatus I because they considered it to be the best choice amongst the available apparati based upon previous use with other buccal films.

Medium Selection

The Applicant performed dissolution testing at various pH's to understand the effects of media pH. They evaluated the films using USP Apparatus I, 100 rpm, at 37°C and with a dissolution volume of 500 mL. Figure 4 shows the buprenorphine release and Figure 5 shows the naloxone release at different pH conditions.

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/s/

KAREEN RIVIERE
05/06/2014

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Addendum

DATE April 30, 2014
NDA 205-637
PRODUCT Bunavail (buprenorphine and naloxone) Buccal Film
SUBJECT OSI Inspection Results for Pivotal Bioavailability Study BNX-110
CLIN PHARM Wei Qiu, Ph.D., Clinical Pharmacology Reviewer
REVIEWER
CLIN PHARM Yun Xu, Ph.D., Clinical Pharmacology Team Leader
TEAM LEADER

The OSI inspection results for the pivotal bioavailability study BNX-110 became available after the clinical pharmacology review was put in DARRTS (April 28, 2014).

It was concluded that OSI recommend that data for the clinical and analytical portions of study BNX-110 are acceptable following the inspection. For details, please find Dr. Arindam Dasgupta's review dated April 29, 2014 in DARRTS.

Therefore, this NDA is acceptable from clinical pharmacology perspective.

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/s/

WEI QIU
04/30/2014

YUN XU
05/05/2014

CLINICAL PHARMACOLOGY REVIEW

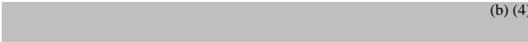
NDA: 205-637	Submission Date(s): August 6, 2013, September 23, 2013, and March 24, 2014
Proposed Brand Name	Bunavail Buccal Film
Generic Name	Buprenorphine and naloxone
Reviewer	Wei Qiu, Ph.D.
Team Leader	Yun Xu, Ph.D.
OCP Division	DCPII
OND division	DAAAP
Sponsor	BioDelivery Sciences International Inc. (BDSI)
Relevant IND(s)	IND 110,267
Submission Type	Original Submission; 505(b)(2)
Formulation; Strength(s)	Buccal film (buprenorphine/naloxone):  (b) (4) 2.10/0.348 mg (buprenorphine/naloxone) 4.20/0.696 mg (buprenorphine/naloxone) 6.3/1.044 mg (buprenorphine/naloxone)
Indication	For the maintenance treatment of opioid dependence

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1 Executive Summary

1.1 Recommendation

The Office of Clinical Pharmacology/Division of Clinical Pharmacology 2 (OCP/DCP-2) has reviewed the NDA submissions dated August 6, 2013, September 23, 2013, and March 24, 2014 and finds them acceptable from clinical pharmacology perspective, pending on the OSI inspection results for the pivotal bioavailability study BNX-110.

Comments to the medical officer: The Sponsor did not conduct any PK study with Bunavail buccal film (b) (4) mg; and the biowaiver request for this strength is not granted (b) (4)

(b) (4)

(b) (4)

(b) (4)

(b) (4)

(b) (4)

1.2 Phase IV Commitments

None.

1.3 Summary of Clinical Pharmacology Findings

Key clinical pharmacology findings:

1. Bunavail buccal film 1 x 4.2/0.7 mg exhibited equivalent systemic exposure (C_{max}, AUC_{last}, and AUC_{inf}) to buprenorphine in comparison to the listed drug, Suboxone sublingual tablet 1 x 8/2 mg.
2. Bunavail buccal film 1 x 4.2/0.7 mg had 27% lower naloxone C_{max}, 33% lower naloxone AUC_{last}, and 34% lower naloxone AUC_{inf} values in comparison to Suboxone sublingual tablet 1 x 8/2 mg.

3. Dose-proportionality was not demonstrated for buprenorphine C_{max} and AUC values over the range of 0.875 mg to 5.25 mg following the administration of Bunavail buccal films of 1 x 0.875/0.15 mg, 1 x 3.5/0.6 mg, and 1 x 5.25/0.9 mg. The increases in systemic exposure were slightly less than dose proportional as dose increased from 0.875 to 5.25 mg. There was a dose proportional increase in buprenorphine C_{max} and AUC values as dose increased from 4.2 to 6.3 mg following the administration of Bunavail buccal films of 1 x 4.2/0.7 mg and 1 x 6.3/1.04 mg.
4. Dose-proportionality was not demonstrated for naloxone C_{max} and AUC values over the range of 0.15 mg and 0.9 mg following the administration of Bunavail buccal films of 1 x 0.875/0.15 mg, 1 x 3.5/0.6 mg, and 1 x 5.25/0.9 mg. The increases in systemic exposure were slightly less than dose proportional as dose increased from 0.15 to 0.9 mg. There was a dose proportional increase in naloxone C_{max} and AUC values as dose increased from 0.7 to 1.04 mg following the administration of Bunavail buccal films of 1 x 4.2/0.7 mg and 1 x 6.3/1.04 mg.
5. Co-administration of low or high pH liquids lowered the C_{max} and AUC values of both buprenorphine and naloxone. The low pH fluid intake had the greater effect, with C_{max}, AUC_{last}, and AUC_{inf} values for buprenorphine being reduced by 59%, 52%, and 49%, respectively, compared to when no liquids were co-administered. The C_{max}, AUC_{last}, and AUC_{inf} values for naloxone were reduced by 76%, 74%, and 72%, respectively. The high pH fluid intake also reduced the systemic exposures of buprenorphine and naloxone. Buprenorphine C_{max}, AUC_{last}, and AUC_{inf} were reduced by 26%, 24%, and 24%, respectively, and naloxone C_{max}, AUC_{last}, and AUC_{inf} were reduced by 41%, 42%, and 40%, respectively. Caution language will be added to the label stating not to take the product with drink or food.
6. Biowaiver for Bunavail buccal film 2.1/0.348 mg has been granted based on dissolution data. However, the biowaiver request for Bunavail buccal film (b) (4) mg is not granted (b) (4) (see ONDQA/Biopharm review for details).

7. (b) (4)

8. As of today (April 28, 2014), OSI inspection for the pivotal bioavailability study BNX-110 is still pending. When the OSI inspection results are available, an addendum will be written up and put in DARRTS.

Bunavail buccal film uses BDSI's BioErodible MucoAdhesive (BEMA) delivery technology comprised of flexible, water soluble polymeric films that adhere to the moist buccal mucosa and erode, so that there is no residual film to remove from the mucosa. During the development of this product, the name of BEMA Buprenorphine NX film was used in many studies and it is interchangeable with Bunavail buccal film in this review.

The clinical and clinical pharmacology database for Bunavail buccal film consists of six Phase 1 PK studies (BNX-101, BNX-102, BNX-103, BNX-106, BNX-107, and BNX-110) and one safety study BNX-201. Earlier formulations BBN011-2 and BBN011-6 were used in pilot Studies BNX-101 and BNX-102, respectively, to determine the final formulation and strengths. The final to-be-marketed formulation BBN012-1 was used in PK Studies BNX-103, BNX-106, BNX-107, and BNX-110 and the 12-week safety study BNX-201.

Study BNX-103 evaluated relative bioavailability of Bunavail buccal film 1 x 3.5/0.6 mg with Suboxone sublingual tablet 8/2 mg, PK results suggested that a 20% increase (3.5/0.6 mg to 4.2/0.7 mg) in the Bunavail buccal film dose would result in equivalent buprenorphine exposure in comparison to the 8/2 mg Suboxone sublingual tablet. In the pivotal relative bioavailability study BNX-110, Bunavail buccal film 1 x 4.2/0.696 mg was compared with the listed drug Suboxone sublingual tablet 1 x 8/2 mg (Suboxone sublingual film 1 x 8/2 mg was also included in this study). In dose proportionality and dosage form study BNX-106, Bunavail buccal film 1 x 0.875/0.145 mg, 1 x 3.5/0.58 mg, 1 x 5.25/0.87 mg, 1 x 3.5/0.58 mg, and 4 x 0.875/0.145 mg were used. Although not the final proposed strengths, all these strengths have the same formulation and the doses

are determined only by the sizes of the films. In the pH effect and relative bioavailability Study BNX-107, Bunavail buccal film 1 x 4.2/0.696 mg given with no liquid, with low pH or high pH liquids, and 1 x 6.3/1.044 mg with no liquid were studied to assess the effect of co-administration with liquids with different pH values and the relative bioavailability between the highest Bunavail buccal film 6.3/1.04 mg with the strength of 4.2/0.696 mg which was studied in the pivotal BA Study BNX-110. BDSI is planning to market the strengths of (b) (4) mg, 2.10/0.348 mg, 4.20/0.696 mg and 6.30/1.044 mg. This review will focus on dose proportionality study (BNX-106), effect of co-administration of liquids with different pH values and relative bioavailability study (BNX-107), and relative bioavailability study (BNX-110).

As agreed in Pre-IND and Pre-NDA meetings, sponsor needs to demonstrate that Bunavail buccal film 4.20/ (b) (4) mg will have equivalent buprenorphine exposure to Suboxone sublingual tablet 8/2 mg. It was also agreed that lower naloxone exposure in Bunavail buccal film as compared to Suboxone sublingual tablet 8/2 mg is acceptable because naloxone is not expected to play a role only when the product is used as intended.

Relative Bioavailability of Bunavail buccal film 1 x 4.20/0.696 mg in Comparison to Listed Drug Suboxone Sublingual Tablet 1 x 8/2 mg

Bunavail buccal film 1 x 4.20/0.696 mg exhibited equivalent systemic exposure (C_{max}, AUC_{last}, and AUC_{inf}) to buprenorphine in comparison to the listed drug, Suboxone sublingual tablet 1 x 8/2 mg, because the 90% CI of Bunavail buccal film:Suboxone sublingual tablet geometric mean ratios for buprenorphine C_{max}, AUC_{last}, and AUC_{inf} fell within the bioequivalent limits of 80 to 125%. The point estimate (90% CI) of the geometric mean ratio (Bunavail buccal film:Suboxone sublingual tablet) for buprenorphine C_{max}, AUC_{last}, and AUC_{inf} values are 109% (100 – 118%), 95% (89 – 102%), and 95% (88 – 101%) respectively. Medium buprenorphine T_{max} values were 2.25 hours and 1.50 hours for Bunavail buccal film and Suboxone sublingual tablet, respectively.

Bunavail buccal film 1 x 4.2/0.696 mg exhibited lower C_{max}, AUC_{last} and AUC_{inf} values in comparison to Suboxone sublingual tablet 1 x 8/2 mg. The point estimates (90% CI) of the geometric mean ratios (Bunavail buccal film:Suboxone sublingual tablet) for

naloxone C_{max}, AUC_{last} and AUC_{inf} values are 73% (66 – 80%), 67% (62 – 73%), and 66% (61 – 72%), respectively. Lower naloxone systemic exposure in comparison to Suboxone, when they are used as intended, is acceptable because naloxone is not expected to play a role only when the product is used as intended.

Dose Proportionality:

Dose proportionality of buprenorphine and naloxone PK parameters following the administration of Bunavail buccal films (1 x 0.875/0.15 mg, 1 x 3.5/0.6 mg, and 1 x 5.25/0.9 mg) was not demonstrated over the buprenorphine dose range of 0.875 mg to 3.5 mg and naloxone dose range of 0.15 to 0.9 mg because the estimates of beta 1, the slopes of the power model, were significantly different from unity (1.0000). Buprenorphine and naloxone PK parameters (e.g., C_{max}, AUC₀₋₂₄, AUC_{last}, and AUC_{inf}) increased slightly less than proportional with dose over the buprenorphine dose range of 0.875 mg to 3.5 mg and naloxone dose range of 0.15 mg to 0.9 mg, respectively. Statistical analysis of the dose normalized log transformed C_{max}, AUC_{last} and AUC_{inf} between the 6.3/1.04 mg (1 x 6.3/1.04 mg) and 4.2/0.7 mg (1 x 4.2/0.7 mg) doses of Bunavail buccal films found that the 90% CI for all PK parameters for both buprenorphine and naloxone were within the 80-125% range implies that the increase in buprenorphine and naloxone exposure is proportional to dose between the 4.2/0.7 mg and 6.3/1.04 mg Bunavail buccal film dose strengths.

Effect of Co-administration of Low or High pH Liquids

Co-administration of low or high pH liquids lowered the C_{max} and AUC values of both buprenorphine and naloxone. The low pH fluid intake had the greater effect, with C_{max}, AUC_{last}, and AUC_{inf} values for buprenorphine being reduced by 59%, 52%, and 49%, respectively, compared to when no liquids were co-administered. The C_{max}, AUC_{last}, and AUC_{inf} values for naloxone were reduced by 76%, 74%, and 72%, respectively. The high pH fluid intake also reduced the systemic exposures of buprenorphine and naloxone. Buprenorphine C_{max}, AUC_{last}, and AUC_{inf} were reduced by 26%, 24%, and 24%, respectively, and naloxone C_{max}, AUC_{last}, and AUC_{inf} were reduced by 41%, 42%, and 40%, 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 Bunavail buccal film is taken as intended, naloxone will have no effect or insignificant effect due to its low plasma levels.

BDSI submitted a 505(b)(2) NDA 205-637 for Bunavail buccal film, which is also known as BEMA Buprenorphine NX film, with the strengths of (b) (4)

2.1/0.348 mg (2.179 cm² film), 4.2/0.696 mg (4.357 cm² film), and 6.3/1.044 mg (6.536 cm² film) buprenorphine/naloxone. The difference among these proposed strengths are the sizes of the films. Bunavail buccal film is proposed for the maintenance treatment of opioid dependence. At present, two sublingual tablet products (Subutex ® (buprenorphine alone), Suboxone® (buprenorphine and naloxone)) have been approved for the treatment of opioid dependence. Suboxone® sublingual film (buprenorphine and naloxone) and Zubsolv® sublingual tablet (buprenorphine and naloxone) have been approved for the maintenance treatment of opioid dependence.

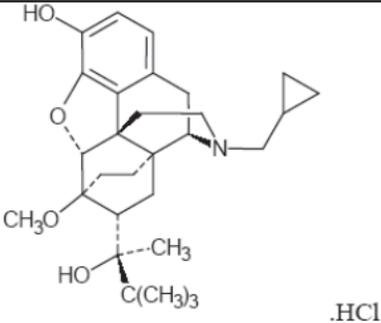
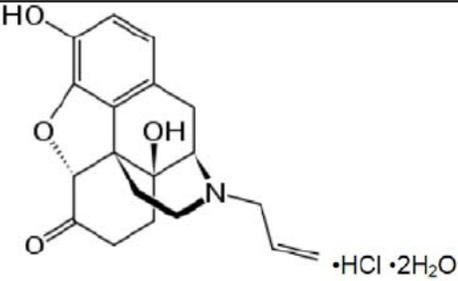
BDSI proposed to use Suboxone sublingual tablet (NDA 20-733) as the listed drug to support this 505(b)(2) NDA. Bunavail (buprenorphine and naloxone) buccal film is presented in a 6:1 ratio of free bases which is different from the ratio of 4:1 which has been used in the approved sublingual tablet and sublingual film formulations under the trade name of Suboxone or Zubsolv® sublingual tablet. BDSI conducted Study LCR-04-101-01 to show that the amount of naloxone in Bunavail buccal film is sufficient to cause withdrawal when co-administered with buprenorphine by injection to patients with physical dependence to full mu agonist opioids (see Medical Officer’s review).

As agreed in Pre-IND and Pre-NDA meetings, sponsor needs to demonstrate that Bunavail buccal film 4.20/ (b) (4) mg will have equivalent buprenorphine exposure to Suboxone sublingual tablet 8/2 mg. It was also agreed that lower naloxone exposure in Bunavail buccal film as compared to Suboxone sublingual tablet 8/2 mg is acceptable. The completed PK studies evaluated the relative bioavailability in comparison with listed drug (Study BNX-110), dose proportionality (Studies BNX-106 and BNX-107), dosage form equivalence (Study BNX-106), and effect of co-administration of liquids with different pH values (Study BNX-107).

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-	17-Allyl-4,5a-epoxy-3,14-

	4,5a-epoxy-3-hydroxy-6-methoxy-6a,14-ethano-14a-morphinan-7a-yl]-3,3-dimethylbutan-2-ol hydrochloride	dihydroxymorphinan-6 hydrochloride
Structure	 <p style="text-align: center;">$C_{29}H_{41}NO_4 \cdot HCl$</p>	 <p style="text-align: center;">$C_{19}H_{21}NO_4 \cdot HCl \cdot 2H_2O$</p>
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 of all strengths are listed in **Table 2**. Bunavail (buprenorphine and naloxone) buccal film is an oral transmucosal form of buprenorphine hydrochloride and naloxone hydrochloride dehydrate (6:1 ratio of free bases) intended for application to the buccal mucosa. Bunavail uses the BioErodible MucoAdhesive (BEMA) delivery technology. The concentration of buprenorphine within the muscoadhesive layer and the concentration of naloxone in the backing layer are the same for all product strengths. Bunavail buccal film dose strength is determined by the film size and defined by the surface area. The drug product is available in four strengths: (b) (4) 2.1/0.348 mg, 4.2/0.696 mg, and 6.3/1.044 mg buprenorphine/naloxone (both measured as free base) per unit. The relative dimensions of all strengths are shown in **Table 3**.

Table 2 Components and Composition of Bunavail Buccal Film

Component	% w/w	Strength (mg Buprenorphine/naloxone free base)		
		(b) (4)	2.1/0.348	4.2/0.696
Purified Water ^a	-	-	-	-
Buprenorphine Hydrochloride	3.456	(b) (4)	2.264	4.527
Propylene Glycol				(b) (4)
Sodium Benzoate				
Methylparaben				
Propylparaben				
Ferric Oxide, Yellow				
Citric Acid	(b) (4)			
Vitamin E Acetate				
Monobasic Sodium Phosphate,	(b) (4)			
Polycarbophil				
Hydroxypropyl Cellulose				
Hydroxyethyl Cellulose				
Carboxymethylcellulose Sodium				
Sodium Hydroxide				
Dibasic Sodium Phosphate,	(b) (4)			
Saccharin Sodium				
Citrus Blend Flavor				
Naloxone Hydrochloride Dihydrate	0.650	(b) (4)	0.425	0.850
(b) (4) Blue Ink				(b) (4)
Total Weight (mg)	100.00	(b) (4)	65.492	130.985
				196.477
				(b) (4)

Table 3 Approximate Dimensions of Bunavail Buccal Films

Strength (mg)	Area (cm ²)	Length (mm)	Width (mm)
			(b) (4)
2.1/0.348	2.179	14.876	14.876
4.2/0.696	4.357	20.956	20.956
6.3/1.044	6.536	25.632	25.632

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

Bunavail buccal 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.

Bunavail buccal film is indicated for the maintenance treatment of opioid dependence.

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

Administer Bunavail buccal film buccally as a single daily dose. The recommended daily dose for maintenance is $\frac{(b)}{(4)}$ mg buprenorphine.

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) are measured in all PK studies.

3. Do the exposures of buprenorphine and naloxone following the administration of Bunavail buccal films increase in a dose proportional manner?

Based on the power model, definitive dose proportionality of buprenorphine and naloxone PK parameters following the administration of BEMA Buprenorphine NX films (1 x 0.875/0.15 mg, 1 x 3.5/0.6 mg, and 1 x 5.25/0.9 mg) was not demonstrated over the buprenorphine dose range of 0.875 mg to 3.5 mg and naloxone dose range of 0.15 to 0.9 mg because the estimates of beta 1, the slopes of the power model, were significantly different from unity (1.0000). Buprenorphine and naloxone PK parameters (e.g., C_{max}, AUC₀₋₂₄, AUC_{last}, and AUC_{inf}) increased slightly less than proportional with dose over the buprenorphine dose range of 0.875 mg to 3.5 mg and naloxone dose range of 0.15 mg to 0.9 mg, respectively. Statistical analysis of the dose normalized log transformed C_{max}, AUC_{last} and AUC_{inf} between the 6.3/1.04 mg (1 x 6.3/1.04 mg) and 4.2/0.7 mg (1 x 4.2/0.7 mg) doses of BEMA Buprenorphine NX films found that the 90% CI for all PK parameters for both buprenorphine and naloxone were within the 80-125% range implies that the increase in buprenorphine and naloxone exposure is proportional to dose between the 4.2/0.7 mg and 6.3/1.04 mg BEMA Buprenorphine NX dose strengths.

Dose Range of 0.875/0.15 mg, 3.5/0.6 mg, and 5.25/0.9 mg:

The dose proportionality of buprenorphine and naloxone pharmacokinetics following single dose administration of BEMA Buprenorphine NX Film 1 x 0.875/0.15 mg, 1 x 3.5/0.6 mg, and 1 x 5.25/0.9 mg was assessed in 20 healthy subjects under naltrexone block in Study BNX-106. Study BNX-106 was a single-dose, randomized, four-period crossover study in healthy subjects under fasting state. Each dose was separated by at least 7 days.

Dose proportionality was primarily examined using the power model, i.e., $PK = \text{Beta0} \times \text{Dose}^{\text{Beta1}}$. Log-transformation was used to transform the power model to the following equation:

$$\ln(PK) = \ln(\text{Beta0}) + \text{Beta1} \cdot \ln(\text{Dose}) + \text{Epsilon}$$

where $\ln(PK)$ represents the natural log-transformed PK parameter such as C_{max} , AUC_{last} , and AUC_{inf} , $\ln(\text{Beta0})$ is the y-intercept, Beta1 is the slope, $\ln(\text{Dose})$ is the natural log-transformed dose, and Epsilon is the error term. The power model was fit to individual subject data using the linear mixed effects analysis with subject as a random effect. A significant difference from unity (1.0000) and lack of proportionality was defined a priori as $p < 0.05$.

Mean plasma concentration-time profiles of buprenorphine are shown in **Figure 1**. Buprenorphine PK parameters are summarized in **Table 4**. The median times to peak concentrations were similar and varied between 2.5 hour and 2.75 hour. Mean terminal half-life values were about 10 hours for all dose levels.

Figure 1 Mean Buprenorphine Concentration-Time Profiles after Administration of BEMA Buprenorphine NX 1 x 0.875/0.15 mg (Treatment A), 1 x 3.5/0.6 mg (Treatment B), 1 x 5.25/0.9 mg (Treatment C), and 4 x 0.875/0.15 mg (Treatment D) (Study BNX-106)

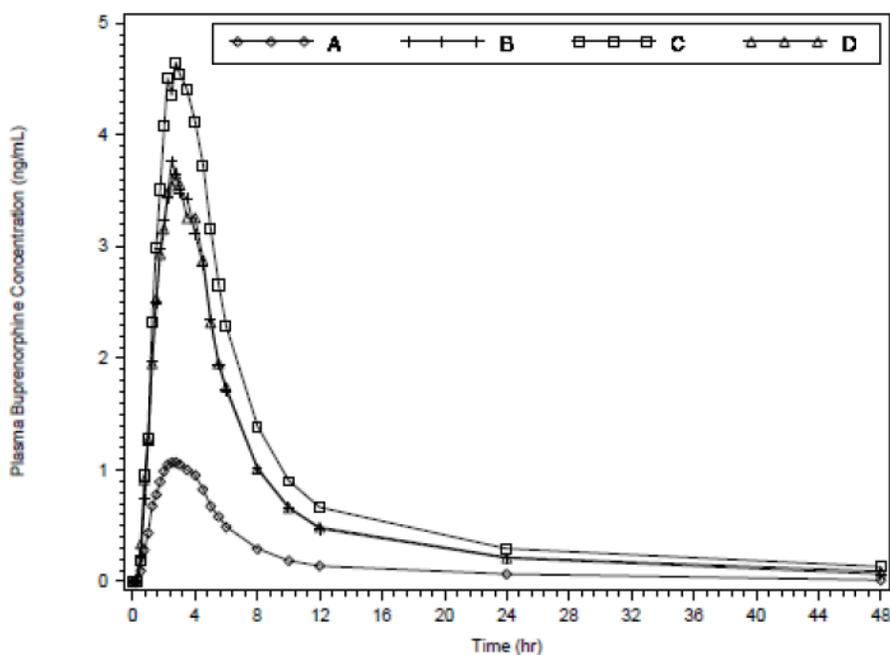


Table 4 Mean (SD) PK parameter of Buprenorphine (Study BNX-106)

Pharmacokinetic Parameter	Treatment A: 0.875/0.15 mg BEMA Buprenorphine NX film N= 18	Treatment B: 3.5/0.6 mg BEMA Buprenorphine NX film N= 20	Treatment C: 5.25/0.9 mg BEMA Buprenorphine NX film N= 19	Treatment D: 4 x 0.875/0.15 mg BEMA Buprenorphine NX film N=18
	Mean (SD)			
C_{max} (ng/mL)	1.15 (0.331)	4.03 (1.79)	5.13 (1.96)	3.89 (1.39)
T_{max} (h) ^a	2.75 (1.50, 4.00)	2.50 (1.75, 4.00))	2.75 (1.50, 4.52)	2.75 (1.50, 4.00))
$AUC_{(0-24)}$ (ng*h/mL)	7.210 (1.520)	24.13 (6.265)	31.94 (9.820)	24.35 (6.974)
$AUC_{(last)}$ (ng*h/mL)	7.372 (1.604)	24.77 (6.416)	33.28 (9.333)	25.33 (7.064)
$AUC_{(inf)}$ (ng*h/mL)	8.395 (2.052)	27.47 (6.709)	36.59 (10.38)	28.19 (8.226)
$T_{1/2}$ (h)	10.44 (4.22)	10.17 (2.90)	10.01 (2.69)	10.95 (4.18)

^a Median (min, max)

Mean plasma concentration-time profiles of naloxone are shown in **Figure 2**. Naloxone PK parameters are summarized in **Table 5**. The median T_{max} values were similar and ranged from 1.25 hours to 1.50 hours. Mean terminal half-life values were similar and ranged from 1.58 to 2.65 hours.

Figure 2 Mean Naloxone Concentration-Time Profiles after Administration of BEMA Buprenorphine NX 1 x 0.875/0.15 mg (Treatment A), 1 x 3.5/0.6 mg (Treatment B), 1 x 5.25/0.9 mg (Treatment C), and 4 x 0.875/0.15 mg (Treatment D) (Study BNX-106)

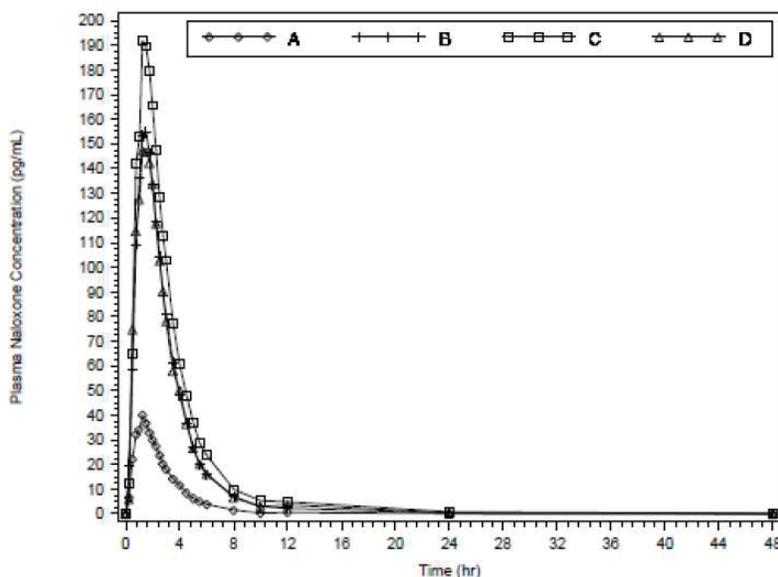


Table 5 Mean (SD) PK Parameter of Naloxone (Study BNX-106)

Pharmacokinetic Parameter	Treatment A: (0.875/0.15 mg BEMA Buprenorphine NX film) N=18	Treatment B: 3.5/0.6 mg BEMA Buprenorphine NX film N=20	Treatment C: 5.25/0.9 mg BEMA Buprenorphine NX film N=19	Treatment D: 4 x 0.875/0.15 mg BEMA Buprenorphine NX film N=18
	Mean (SD)			
C_{max} (pg/mL)	44.3 (25.4)	179 (114)	218 (133)	182 (123)
T_{max} (h) ^a	1.25 (0.75, 2.25)	1.38 (0.75, 2.75)	1.50 (0.75, 2.50)	1.38 (0.50, 2.25)
$AUC_{(0-24)}$ (pg*h/mL)	118.7 (56.80)	488.5 (242.9)	639.3 (334.9)	499.7 (288.9)
$AUC_{(last)}$ (pg*h/mL)	116.6 (56.12)	480.1 (243.8)	628.6 (333.7)	489.2 (288.3)
$AUC_{(inf)}$ (pg*h/mL)	115.0 (53.70)	491.7 (255.7)	604.0 (336.0)	506.5 (304.7)
$T_{1/2}$ (h)	1.58 (0.62)	1.93 (0.51)	2.65 (2.04)	2.24 (0.85)

^a Median (min, max)

Based on the power model, definitive dose proportionality of buprenorphine and naloxone PK parameters was not demonstrated over the buprenorphine dose range of 0.875 to 5.25 mg and naloxone dose range of 0.15 to 0.9 mg because the slopes were significantly different from unity (**Table 6**). Buprenorphine and naloxone C_{max} , AUC_{last} , and AUC_{inf} values increased slightly less than proportional.

Table 6 Power Model Proportionality Analysis of PK Parameters of Buprenorphine and Naloxone (Study BNX-106)

	Slope	90% CI for Slope ^a	p value ^b	Rho ^c
Buprenorphine				
C_{max}	0.8416	(0.7854, 0.8977)	<0.0001	3.8220
AUC_{0-24}	0.8381	(0.7896, 0.8865)	<0.0001	3.9254
AUC_{last}	0.8486	(0.8008, 0.8965)	<0.0001	4.2369
AUC_{inf}	0.8353	(0.7859, 0.8846)	<0.0001	3.8327
Naloxone				
C_{max}	0.9054	(0.8302, 0.9806)	<0.0001	5.4411
AUC_{0-24}	0.9576	(0.8890, 1.0263)	<0.0001	13.3657
AUC_{last}	0.9565	(0.8865, 1.0264)	<0.0001	12.6034
AUC_{inf}	0.9532	(0.8798, 1.0265)	<0.0001	10.9549

Power Model: $\ln(P) = \ln(\beta_0) + \beta_1 \cdot \ln(\text{Dose}) + \varepsilon$ where P is the pharmacokinetic parameter tested, $\ln(\beta_0)$ is the y-intercept, β_1 is the slope, and ε is an error term (Subject was used as the random effects term in the analysis)

a. 90% confidence intervals (CI) (lower, upper)

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

c. High/low dose ratio in which dose proportionality can be demonstrated definitely, relative to the lowest dose in the analysis dataset

1. Smith BP et al., Confidence Interval Criteria for Assessment of Dose Proportionality. *Pharmaceutical Research* 17:1278-83 (2000)

Dose Range of 4.2/0.7 mg and 6.3/1.04 mg:

The relative bioavailabilities of buprenorphine and naloxone between the 6.2/1.04 mg and 4.2/0.7 mg BEMA Buprenorphine NX films were evaluated in Study BNX-107. Study BNX-107 is an open-label, single-dose, 4-period, crossover study in 24 healthy subjects under naltrexone block. Each treatment was separated by at least 7 days. The plasma concentration-time profiles for buprenorphine and naloxone are shown in **Figures 3** and **4**. Buprenorphine and naloxone PK parameters are summarized in **Tables 7** and **8**. The analysis of the dose-normalized log transformed systemic exposure of buprenorphine and naloxone is summarized in **Table 9**. Statistical analysis of the dose normalized log transformed C_{max}, AUC_{last}, and AUC_{inf} between the 6.3/1.04 mg and 4.2/0.7 mg doses found that the 90% confidence intervals for all PK parameters for both drugs were within the 80-125% range. Thus, the increase in buprenorphine and naloxone exposure is proportional to dose between the 4.2/0.7 mg and 6.3/1.04 mg BEMA Buprenorphine NX dose strengths.

Figure 3 Mean Buprenorphine Concentration-Time Profiles after Administration of 1 x 4.2/0.7 mg BEMA Buprenorphine NX Film without Co-administered Liquid (Treatment A), 1 x 4.2/0.7 mg BEMA Buprenorphine NX Film with Low pH Liquid (Treatment B), 1 x 4.2/0.7 mg BEMA Buprenorphine NX Film with High pH Liquid (Treatment C), and 1 x 6.3/1.04 mg BEMA Buprenorphine NX Film without Co-administered Liquid (Treatment D)

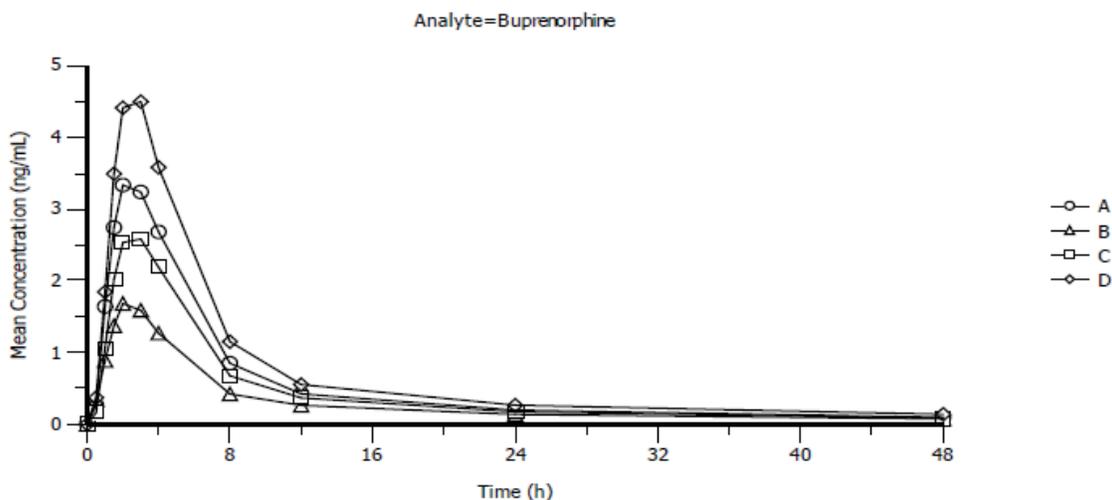


Figure 4 Mean Naloxone Concentration-Time Profiles after Administration of 1 x 4.2/0.7 mg BEMA Buprenorphine NX Film without Co-administered Liquid (Treatment A), 1 x 4.2/0.7 mg BEMA Buprenorphine NX Film with Low pH Liquid (Treatment B), 1 x 4.2/0.7 mg BEMA Buprenorphine NX Film with High pH Liquid (Treatment C), and 1 x 6.3/1.04 mg BEMA Buprenorphine NX Film without Co-administered Liquid (Treatment D)

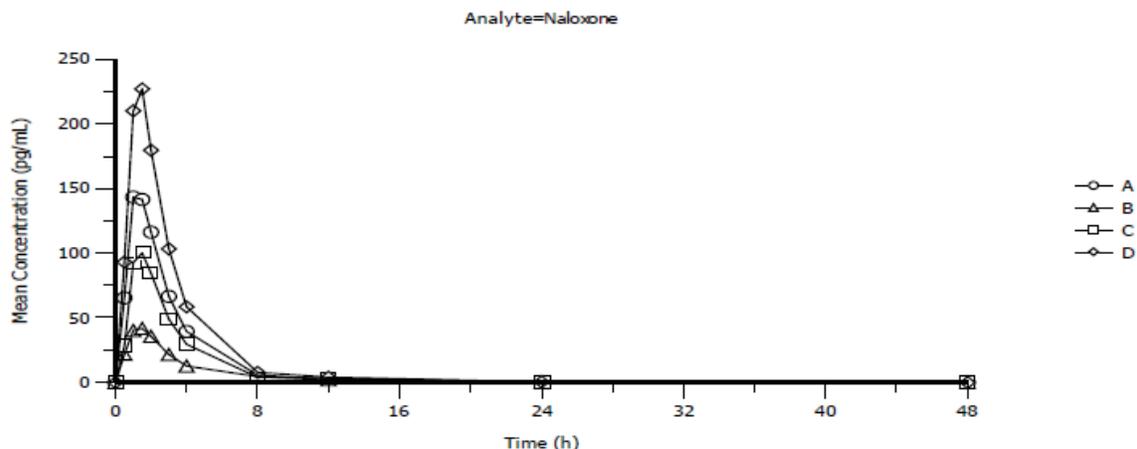


Table 7 Summary of Buprenorphine PK Parameters (Study BNX-107)

Parameter	Treatment A: 4.2/0.7 mg BEMA Buprenorphine NX Film			Treatment B: 4.2/0.7 mg BEMA Buprenorphine NX Film with Low pH Liquid Co-administered		
	n	Mean	SD	n	Mean	SD
T_{max} (h) ^a	22	2.50 (1.50, 4.00)		21	2.00 (0.50, 3.00)	
C_{max} (ng/mL)	22	3.62	1.15	21	1.84	1.32
AUC_{last} (h*ng/mL)	22	26.13	6.971	21	14.51	7.811
AUC_{inf} (h*ng/mL)	22	28.61	7.666	21	16.73	8.830
$T_{1/2}$ (h)	22	16.98	3.74	21	19.55	4.62
Parameter	Treatment C: 4.2/0.7 mg BEMA Buprenorphine NX Film with High pH Liquid Co-administered			Treatment D: 6.3/1.04 mg BEMA Buprenorphine NX Film		
	n	Mean	SD	n	Mean	SD
T_{max} (h) ^a	22	2.50 (1.50, 4.00)		22	2.50 (1.50, 4.00)	
C_{max} (ng/mL)	22	2.86	1.34	22	4.90	1.73
AUC_{last} (h*ng/mL)	22	21.30	9.362	22	35.06	10.27
AUC_{inf} (h*ng/mL)	22	23.57	10.39	22	38.47	11.43
$T_{1/2}$ (h)	22	16.56	4.97	22	16.45	3.86

^aMedian (min, max)

Table 8 Summary of Naloxone PK Parameters (Study BNX-107)

Parameter	Treatment A: 4.2/0.7 mg BEMA Buprenorphine NX Film			Treatment B: 4.2/0.7 mg BEMA Buprenorphine NX Film with Low pH Liquid Co-administered		
	n	Mean	SD	n	Mean	SD
T_{max} (h) ^a	22	1.50 (0.50, 2.00)		21	1.00 (0.50, 2.00)	
C_{max} (pg/mL)	22	161	74.5	21	48.5	31.7
AUC_{last} (h*pg/mL)	22	468.1	213.7	21	163.8	140.6
AUC_{inf} (h*pg/mL)	22	473.5	214.8	21	173.4	150.4
$T_{1/2}$ (h)	22	1.88	1.25	21	2.90	1.77
Parameter	Treatment C: 4.2/0.7 mg BEMA Buprenorphine NX Film with High pH Liquid Co-Administered			Treatment D: 6.3/1.04 mg BEMA Buprenorphine NX Film		
	n	Mean	SD	n	Mean	SD
T_{max} (h) ^a	22	1.50 (1.00, 3.00)		22	1.50 (0.50, 2.00)	
C_{max} (pg/mL)	22	113	79.2	22	260	131
AUC_{last} (h*pg/mL)	22	334.4	221.7	22	706.8	325.9
AUC_{inf} (h*pg/mL)	22	342.5	229.0	22	713.5	328.7
$T_{1/2}$ (h)	22	1.92	1.19	22	2.17	1.28

^aMedian (min, max)**Table 9** Statistical Analysis of the Dose-Normalized Log-Transformed Systemic Exposure Parameters of Buprenorphine and Naloxone Comparing 1 x 6.3/1.04 mg BEMA Buprenorphine NX Film (Test) to 1 x 4.2/0.7 mg BEMA Buprenorphine NX Film (Reference)

Dependent Variable	Geometric Mean ^a		Ratio (%) ^b	90% CI ^c		Power	ANOVA
	Test	Reference	(Test/Ref)	Lower	Upper		CV%
Buprenorphine							
$\ln(C_{max}/Dose)$	0.7670	0.8166	93.93	87.89	100.38	0.9996	12.38
$\ln(AUC_{last}/Dose)$	5.5388	6.0919	90.92	85.32	96.89	0.9998	11.84
$\ln(AUC_{inf}/Dose)$	6.0587	6.6565	91.02	85.77	96.60	0.9999	11.07
Naloxone							
$\ln(C_{max}/Dose)$	235.0728	208.3265	112.84	102.21	124.57	0.9784	18.52
$\ln(AUC_{last}/Dose)$	647.0212	612.8846	105.57	96.22	115.83	0.9872	17.35
$\ln(AUC_{inf}/Dose)$	653.1989	620.7849	105.22	95.90	115.45	0.9872	17.35

^a Geometric Mean for BEMA Buprenorphine NX 6.3/1.04 mg Film without co-administered liquid (Test) and BEMA Buprenorphine NX 4.2/0.7 mg Film without co-administered liquid (Ref) based on Least Squares Mean of log-transformed parameter values^b Ratio(%) = Geometric Mean (Test)/Geometric Mean (Ref)^c 90% Confidence Interval

Parameters were dose normalized by dividing parameter values by the buprenorphine administered dose.

2.3 Intrinsic Factors

1. *What is the pediatric plan?*

The full PREA waiver for all pediatric groups was granted because studies would be highly impracticable based on the most recent prevalence estimates and previous feasibility assessments.

2.4 General Biopharmaceutics

1. *What are the relative bioavailabilities of buprenorphine and naloxone following the administration of BEMA Buprenorphine NX Films in comparison to the listed drug, Suboxone sublingual tablet?*

BEMA Buprenorphine NX film 4.2/0.7 mg exhibited equivalent systemic exposure to buprenorphine but lower exposure to naloxone in comparison to the listed drug Suboxone sublingual tablet 8/2 mg.

The relative bioavailabilities of buprenorphine and naloxone following the administration of BEMA Buprenorphine NX Film administered as 1 x 4.2/0.7 mg dose in comparison to the listed drug, Suboxone sublingual tablet administered as 1 x 8/2 mg dose, and Suboxone sublingual film administered as 1 x 8/2 mg dose were evaluated in a single-dose, open-label, randomized, fasting, 3-period cross-over study (Study BNX-110) in seventy healthy subjects under naltrexone block. The washout period between doses was at least 14 days.

The buprenorphine plasma concentration-time profiles for BEMA Buprenorphine NX Film and Suboxone sublingual tablets and films are shown in **Figure 5**. The naloxone plasma concentration-time profiles for BEMA Buprenorphine NX Film and Suboxone sublingual tablets and films are shown in **Figure 6**. The summary of the PK parameters of buprenorphine and naloxone is presented in **Table 10**. Median buprenorphine t_{max} was slightly longer for BEMA Buprenorphine NX Film (2.25 h) in comparison to Suboxone sublingual tablet (1.50 h). Median naloxone t_{max} values were similar for BEMA Buprenorphine NX Film (1 h) to Suboxone sublingual tablet (0.75 h).

Figure 5 Mean Buprenorphine Plasma Concentration (ng/mL) Time Profiles after Administration of 1 x 8/2 mg Suboxone Sublingual Tablet (Treatment A), 1 x 8/2 mg Suboxone Sublingual Film (Treatment B), and 1 x 4.2/0.7 mg BEMA Buprenorphine NX Film (Treatment C) (BNX-110)

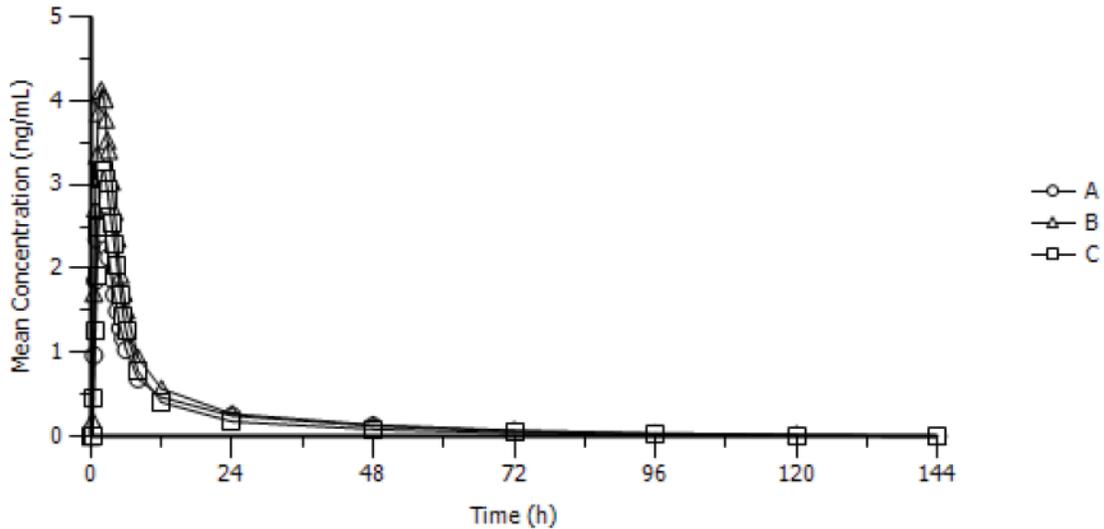


Figure 6 Mean Naloxone Plasma Concentration (pg/mL) Time Profiles after Administration of 1 x 8/2 mg Suboxone Sublingual Tablet (Treatment A), 1 x 8/2 mg Suboxone Sublingual Film (Treatment B), and 1 x 4.2/0.7 mg BEMA Buprenorphine NX Film (Treatment C) (Study BNX-110)

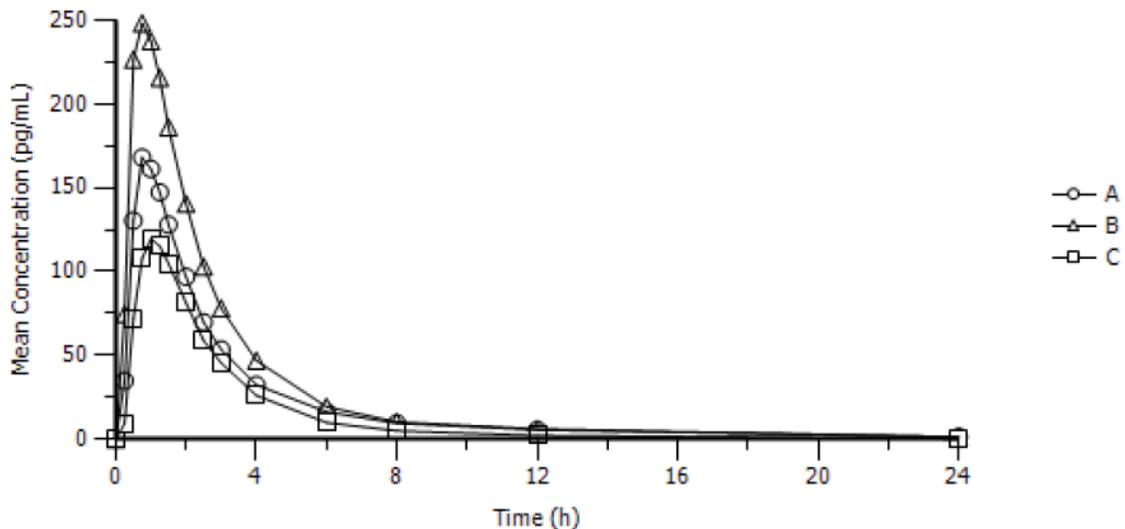


Table 10 Summary of the PK parameters of Buprenorphine, Norbuprenorphine, and Naloxone following Administration of 1 x 8/2 mg Suboxone Sublingual Tablet (Treatment A), 1 x 8/2 mg Suboxone Sublingual Film (Treatment B), and 1 x 4.2/0.7 mg BEMA Buprenorphine NX Film (Treatment C) (Study BNX-110)

Treatment	A: 8/2 mg Suboxone sublingual tablet	B: 8/2 mg Suboxone sublingual film	C: 4.2/0.70 mg BEMA Buprenorphine NX buccal film (BBN012-1)
Pharmacokinetic Parameters			
Buprenorphine (Mean (SD))			
N	68	70	65
C_{max}, ng/mL	3.06 (1.28)	4.68 (2.07)	3.41 (1.26)
T_{max}, hr^b	1.50 (0.50 – 2.75)	1.75 (0.50 – 3.05)	2.25 (0.75 – 4.00)
AUC_{last}, ng·hr/mL	26.98 (10.50)	36.72 (14.79)	25.75 (8.612)
AUC_{inf}, ng·hr/mL	28.67 (10.78)	38.38 (15.23)	27.17 (8.784)
T_{1/2}, hr	28.67 (12.82)	31.71 (14.51)	27.53 (11.99)
Norbuprenorphine (Mean (SD))			
N	68	70	65
C_{max}, ng/mL	1.27 (0.590)	1.32 (0.794)	0.529 (0.283)
T_{max}, hr^b	1.25 (0.50 – 24.00)	1.25 (0.50 – 24.00)	2.25 (0.50 – 24.00)
AUC_{last}, ng·hr/mL	36.79 (16.19)	37.99 (17.37)	18.02 (8.608)
AUC_{inf}, ng·hr/mL	39.88 (18.05)	41.64 (20.92)	20.54 (8.658) ^a
T_{1/2}, hr	32.64 (12.16)	34.77 (16.77)	34.17 (13.38) ^a
Naloxone (Unconjugated) (Mean (SD))			
N	67	69	65
C_{max}, pg/mL	182 (89.1)	277 (129)	134 (69.7)
T_{max}, hr^b	0.75 (0.50 – 2.00)	0.75 (0.25 – 1.50)	1.00 (0.50 – 2.00)
AUC_{last}, pg·hr/mL	488.3 (235.8)	693.6 (336.8)	333.5 (155.7)
AUC_{inf}, pg·hr/mL	505.8 (247.0)	709.1 (341.7)	340.5 (159.1)
T_{1/2}, hr	4.93 (3.10)	4.83 (2.92)	2.37 (1.59)

^a N=64;

^b Median (min, max)

The statistical analysis results for the assessment of relative bioavailability are presented in the **Table 11**. BEMA Buprenorphine NX Film 4.2/0.7 mg exhibited equivalent C_{max}, AUC_{last}, and AUC_{inf} to Suboxone tablet 8/2 mg as the 90% CIs of BEMA Buprenorphine NX film:Suboxone sublingual tablet geometric mean ratios for buprenorphine C_{max}, AUC_{last}, and AUC_{inf} fell within the bioequivalence limits of 80 to

125%. BEMA Buprenorphine NX Film 4.2/0.7 mg exhibited 27% lower C_{max}, 33% lower AUC_{last}, and 34% lower AUC_{inf} values than those for Suboxone sublingual tablet 8/2 mg.

Table 11 Summary of the Statistical Analysis of PK Parameters of Buprenorphine and Naloxone Comparing 1 x 4.2/0.7 mg BEMA Buprenorphine NX Film (Test) to 1 x 8/2 mg Suboxone Sublingual Tablet (Reference) (Study BNX-110)

	Geometric Mean ^a		Geometric Mean Ratio ^b	90% CI ^c of the Geometric Mean Ratio	
	4.2/0.7 mg BEMA Buprenorphine NX film (Test)	8/2 mg Suboxone sublingual tablet (Reference)		Lower	Upper
Buprenorphine					
ln(C _{max})	3.1472	2.8854	109.07	100.49	118.39
ln(AUC _{last})	24.2135	25.3950	95.35	88.92	102.24
ln(AUC _{inf})	25.5736	27.0274	94.62	88.48	101.19
Naloxone (Unconjugated)					
ln(C _{max})	117.5700	161.3667	72.86	65.94	80.51
ln(AUC _{last})	298.1396	442.2842	67.41	61.98	73.31
ln(AUC _{inf})	304.3873	458.9519	66.32	61.14	71.94

^a Geometric Mean for 4.2/0.7 mg BEMA Buprenorphine NX Film (Test) and 8/2 mg tablet Suboxone (Ref) based on Least Squares Mean of log transformed parameter values

^b Ratio(%) = Geometric Mean (Test)/Geometric Mean (Ref)

^c CI= confidence interval

OSI inspected the clinical and analytical sites of this pivotal study BNX-110 and results are pending. An addendum will be written up and put in DARRTS when the OSI inspection results are available.

2. *What are the systemic exposure of buprenorphine and naloxone for the lowest to-be-marketed strength ((b) (4) mg)?*

The lowest to-be-marketed strength, (b) (4) mg film, was neither studied in PK study, nor granted biowaiver (b) (4) (please find ONDQA/Biopharm reviewer Dr. Kareen Riviere's review for details). (b) (4)

3. *Is the dosage form equivalence demonstrated for BEMA Buprenorphine NX Film?*

The exposure delivered from a single 3.5 mg BEMA Buprenorphine NX Film containing 0.6 mg naloxone was shown to be bioequivalent to the buprenorphine exposure from four 0.875 mg buprenorphine films with 0.15 mg naloxone (**Table 13**) in Study BNX-106. This was an open-label, single dose, 4-period crossover study in 20 healthy subjects. These films have the same formulations as the to-be-marketed strengths and differ only in sizes. The buprenorphine and naloxone concentration time profiles are shown in **Figures 1** and **2**. Buprenorphine and naloxone PK parameters are presented in **Tables 4** and **5**.

Table 13 Summary of the Statistical Analysis of the PK Parameters of Buprenorphine and Naloxone Comparing 4 x 0.875 mg BEMA Buprenorphine NX (Test) to 1 x 3.5/0.6 mg BEMA Buprenorphine NX (Reference) in Healthy Subjects (Study BNX-106)

Pharmacokinetic Parameter	Geometric Mean ^a		Geometric Mean Ratio (%) ^b	90% CI ^c of the Geometric Least Squares Mean Ratio	
	Test	Reference	Test/Reference	Lower	Upper
Buprenorphine					
ln(C _{max})	3.6199	3.8119	94.96	84.28	107.00
ln(AUC ₀₋₂₄)	23.2198	23.7312	97.84	88.35	108.36
ln(AUC _{last})	24.0736	24.4860	98.32	88.70	108.97
ln(AUC _{inf})	26.7441	27.2627	98.10	88.27	109.02
Naloxone					
ln(C _{max})	146.4191	150.8675	97.05	80.28	117.33
ln(AUC ₀₋₂₄)	418.4396	439.6260	95.18	79.62	113.78
ln(AUC _{last})	407.4022	430.3851	94.66	79.09	113.30
ln(AUC _{inf})	413.0374	456.9935	90.38	70.53	115.82

^a Geometric Mean for 4 x 0.875/0.15 mg BEMA Buprenorphine NX (Test) and 1 x 3.5/0.6 mg BEMA Buprenorphine NX (Ref) based on Least Squares Mean of log-transformed parameter values

^b Ratio(%) = Geometric Mean (Test)/Geometric Mean (Ref)

^c CI = confidence interval

4. *How do the co-administered liquids with different pH values affect the bioavailability of BEMA Buprenorphine NX Film?*

Co-administration of both low and high pH liquids lowered the C_{max} and AUC_{inf} of both buprenorphine and naloxone. The low pH fluid intake had the greater effect, with C_{max} and AUC_{inf} values for buprenorphine being reduced by 59% and 49%, respectively,

compared to when no liquids were co-administered. The high pH liquid reduced buprenorphine C_{max} and AUC_{inf} by 26% and 24%, respectively. Sponsor proposed to refrain from drinking until after the BEMA Buprenorphine NX Film has dissolved.

The effect of co-administration of liquids with different pH values on buprenorphine and naloxone absorption from BEMA Buprenorphine NX Film (4.2//0.7 mg buprenorphine/naloxone) was evaluated in Study BNX-107. This was an open-label, single-dose, 4-period, crossover study in 24 healthy subjects. The low pH liquid was decaffeinated Coke (pH < 4) and the high pH liquid was Essentia water (pH > 8). Subjects assigned to treatment with co-administered liquid began sipping the liquid 5 minutes after administration of BEMA Buprenorphine NX and finished the liquid within 15 minutes. Buprenorphine concentration-time profiles are shown in **Figure 3** and buprenorphine PK parameters are summarized in **Table 7**. Naloxone concentration-time profiles are shown in **Figure 4** and naloxone PK parameters are summarized in **Table 8**.

Statistical analysis of the log-transformed PK parameters of buprenorphine and naloxone comparing low pH liquid to no liquid intake and high pH liquid to no liquid intake are shown in **Tables 14** and **15**. Co-administration of both low and high pH liquids lowered the C_{max}, AUCl_{ast}, and AUC_{inf} values of both buprenorphine and naloxone. The low pH fluid intake had the greater effect, with C_{max} and AUC_{inf} values for buprenorphine being reduced by 59%, 52%, and 49%, respectively, compared to when no liquids were co-administered. The high pH liquid reduced buprenorphine C_{max}, AUCl_{ast}, and AUC_{inf} by 26%, 24%, and 24%, respectively. Low pH fluid intake reduced naloxone C_{max}, AUCl_{ast}, and AUC_{inf} by 76%, 74%, and 72%, respectively. High pH fluid intake reduced naloxone C_{max}, AUCl_{ast}, and AUC_{inf} by 41%, 42%, and 40%, respectively. Caution language will be added to the label stating not to take the product with drink or food.

Table 14 Statistical Analysis of the Log-Transformed PK Parameters of Buprenorphine and Naloxone Comparing 1 x 4.2/0.7 mg BEMA Buprenorphine NX Film Co-administered with Low pH Liquid (Test) to 1 x 4.2/0.7 mg BEMA Buprenorphine NX without any Liquid Intake (Reference) (Study BNX-107)

Pharmacokinetic Parameter	Geometric Mean ^a		Geometric Mean Ratio (%) ^b	90% CI ^c of the Geometric Least Squares Mean Ratio	
	Test	Reference		Lower	Upper
Buprenorphine					
ln(C _{max})	1.4087	3.4473	40.86	33.32	50.11
ln(AUC _{last})	12.2896	25.6435	47.92	40.06	57.34
ln(AUC _{inf})	14.4627	28.0983	51.47	43.45	60.98
Naloxone					
ln(C _{max})	35.5202	148.2604	23.96	19.08	30.09
ln(AUC _{last})	115.4217	434.3830	26.57	21.05	33.55
ln(AUC _{inf})	125.7583	440.2150	28.57	22.84	35.74

^a Geometric Mean for 4.2/0.7 mg BEMA Buprenorphine NX Film with high pH liquid (Test) and 4.2/0.7 mg BEMA Buprenorphine NX Film without co-administered liquid (Ref) based on Least Squares Mean of log-transformed parameter values

^b Ratio(%) = Geometric Mean (Test)/Geometric Mean (Ref)

^c CI = confidence interval

Table 15 Statistical Analysis of the Log-Transformed PK Parameters of Buprenorphine and Naloxone Comparing 1 x 4.2/0.7 mg BEMA Buprenorphine NX Film Co-administered with High pH Liquid (Test) to 1 x 4.2/0.7 mg BEMA Buprenorphine NX without any Liquid Intake (Reference) (Study BNX-107)

Pharmacokinetic Parameter ^a	Geometric Mean ^a		Geometric Mean Ratio (%) ^b	90% CI ^c of the Geometric Least Squares Mean Ratio	
	Test	Reference		Lower	Upper
Buprenorphine					
ln(C _{max})	2.5570	3.4379	74.38	64.44	85.85
ln(AUC _{last})	19.3104	25.5409	75.61	65.69	87.02
ln(AUC _{inf})	21.3170	27.9548	76.26	66.74	87.13
Naloxone					
ln(C _{max})	87.0494	147.2819	59.10	47.34	73.80
ln(AUC _{last})	251.1613	432.7933	58.03	45.41	74.16
ln(AUC _{inf})	262.4522	439.0725	59.77	47.54	75.16

^a Geometric Mean for 4.2/0.7 mg BEMA Buprenorphine NX Film with high pH liquid (Test) and 4.2/0.7 mg BEMA Buprenorphine NX Film without co-administered liquid (Ref) based on Least Squares Mean of log-transformed parameter values

^b Ratio(%) = Geometric Mean (Test)/Geometric Mean (Ref)

^c 90% Confidence Interval

2.5 Analytical Section

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

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

Table 16 Summary of BEMA Buprenorphine NX Bioanalytical Methods

Study	Method	Validation	Calibration Range	Weighting	QC Precision (% CV)		QC Accuracy (% Bias)	
					Intra-	Inter-	Intra-	Inter-
BNX-101	ATM-1344r3	1002974, 1002413, 1003346	Bup: 0.0250-5.00 ng/mL Norbup: 0.020-4.00 ng/mL	Bup: 1/x ² Norbup: 1/x	1.6 to 4.5 ¹ 1.5 to 6.3 ¹	2.5 to 5.9 ² 2.8 to 5.3 ²	-5.7 to 6.5 ¹ -2.7 to 10.3 ¹	-5.7 to -3.3 ² 0.3 to 6.3 ²
	ATM-1154r3	1001428, 1004300	Total naloxone: 0.050-50.0 ng/mL	1/x ²	0.9 to 9.6 ³	2.4 to 8.6 ³	-4.7 to 13.3 ³	6.0 to 9.0 ³
BNX-102	ATM-1344r3	1002974, 1002413, 1003346	Bup: 0.0250-5.00 ng/mL Norbup: 0.020-4.00 ng/mL	Bup: 1/x ² Norbup: 1/x	1.6 to 4.5 ¹ 1.5 to 6.3 ¹	2.5 to 5.9 ² 2.8 to 5.3 ²	-5.7 to 6.5 ¹ -2.7 to 10.3 ¹	-5.7 to -3.3 ² 0.3 to 6.3 ²
	ATM-1268r4	1001815, 1000063, 11-B04-V2	Naloxone: 1.00-250 pg/mL	1/x ²	0.9 to 12.9 ⁴	2.5 to 9.1 ⁴	-3.3 to 5.4 ⁴	-1.3 to 3.0 ⁴
	ATM-1154r3	1001428, 1004300	Total naloxone: 0.050-50.0 ng/mL	1/x ²	0.9 to 9.6 ³	2.4 to 8.6 ³	-4.7 to 13.3 ³	6.0 to 9.0 ³
BNX-106	ATM-1864	1002974, 1002413, 1003346	Bup: 0.0250-5.00 ng/mL Norbup: 0.020-4.00 ng/mL	Bup: 1/x ² Norbup: 1/x	1.6 to 4.5 ¹ 1.5 to 3.1 ⁵	2.5 to 5.9 ² 2.8 to 5.3 ²	-5.7 to 6.5 ¹ -6.0 to 4.8 ⁵	-5.7 to -3.3 ² 0.3 to 6.3 ²
	ATM-1268r5	1001815, 1000063, 11-B04-V2	Naloxone: 1.00-250 pg/mL	1/x ²	0.9 to 12.9 ⁴	2.5 to 9.1 ⁴	-3.3 to 5.4 ⁴	-1.3 to 3.0 ⁴
BNX-103	ATM-1864	1002974, 1002413, 1003346	Bup: 0.0250-5.00 ng/mL Norbup: 0.020-4.00 ng/mL	Bup: 1/x ² Norbup: 1/x	1.6 to 4.5 ¹ 1.5 to 3.1 ⁵	2.5 to 5.9 ² 2.8 to 5.3 ²	-5.7 to 6.5 ¹ -6.0 to 4.8 ⁵	-5.7 to -3.3 ² 0.3 to 6.3 ²
	ATM-1268r5	1001815, 1000063, 11-B04-V2	Naloxone: 1.00-250 pg/mL	1/x ²	0.9 to 12.9 ⁴	2.5 to 9.1 ⁴	-3.3 to 5.4 ⁴	-1.3 to 3.0 ⁴
BNX-110	ATM-1864	1002974, 1002413, 1003346	Bup: 0.0250-5.00 ng/mL Norbup: 0.020-4.00 ng/mL	Bup: 1/x ² Norbup: 1/x	1.6 to 4.5 ¹ 1.5 to 3.1 ⁵	2.5 to 5.9 ² 2.8 to 5.3 ²	-5.7 to 6.5 ¹ -6.0 to 4.8 ⁵	-5.7 to -3.3 ² 0.3 to 6.3 ²
	ATM-1268r5	1001815, 1000063, 11-B04-V2	Naloxone: 1.00-250 pg/mL	1/x ²	0.9 to 12.9 ⁴	2.5 to 9.1 ⁴	-3.3 to 5.4 ⁴	-1.3 to 3.0 ⁴
BNX-107	ATM-1864	1002974, 1002413, 1003346	Bup: 0.0250-5.00 ng/mL Norbup: 0.020-4.00 ng/mL	Bup: 1/x ² Norbup: 1/x	1.1 to 2.8 ⁶ 1.5 to 3.1 ⁵	2.5 to 5.9 ² 2.8 to 5.3 ²	-5.1 to 0.0 ⁶ -6.0 to 4.8 ⁵	-5.7 to -3.3 ² 0.3 to 6.3 ²
	ATM-1268r6	1001815, 1000063, 11-B04-V2	Naloxone: 1.00-250 pg/mL	1/x ²	0.9 to 12.9 ⁴	2.5 to 9.1 ⁴	-3.3 to 5.4 ⁴	-1.3 to 3.0 ⁴

¹Results taken from 1002974 dated JUN2008. ²Results taken from 1002413 dated JAN2008. ³Results taken from 1001428 dated JUN2007. ⁴Results taken from 1001815 dated JUN2007. ⁵Results taken from 1002974_am7 dated MAY2012. ⁶Results taken from 102974_am9 dated DEC2012.

3 Labeling Recommendations

As of today (4/28/2014) labeling negotiation with sponsor is still ongoing.

4 Appendix

4.1 Clinical Pharmacology Filing Memo

CLINICAL PHARMACOLOGY FILING FORM/CHECKLIST

Office of Clinical Pharmacology				
<i>New Drug Application Filing and Review Form</i>				
<i>General Information About the Submission</i>				
	Information		Information	
NDA/BLA Number	205-637	Proposed Brand Name	Bunavail	
OCP Division (I, II, III, IV, V)	II	Generic Name	buprenorphine and naloxone buccal 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	Buccal film: (b) (4) 2.10/0.348 mg, 4.20/0.696 mg, and 6.30/1.044 mg	
Pharmacometrics Reviewer	N/A	Dosing Regimen		
Date of Submission	July 31, 2013	Route of Administration	Buccal	
Primary Review Goal Date (GRMP)	May 3, 2014	Sponsor	BioDelivery Sciences International	
		Priority Classification	Standard	
PDUFA Due Date	June 7, 2014	Relevant INDs	IND 110267	
<i>Clin. Pharm. and Biopharm. Information</i>				
	"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	6		Studies BNX-101, 102, 103, 106, 107, and 110 (101, 102, and 103 are pilot studies)
multiple dose:				
Patients-				
single dose:				
multiple dose:				
Dose proportionality -				
fasting / non-fasting single dose:	x	1		Study BNX-106
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 -				

CLINICAL PHARMACOLOGY FILING FORM/CHECKLIST

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:	x	4	Studies BNX-101, 102, 103, and 110
Bioequivalence studies -			
traditional design; single / multi dose:	x	1	Study BNX-110
replicate design; single / multi dose:			
Food-drug interaction studies	x	1	Study BNX-107: 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		6	

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 PK studies 106, 107 and 110.
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 tablet (NDA 20-733)
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,	√			

CLINICAL PHARMACOLOGY FILING FORM/CHECKLIST

	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?			√	

CLINICAL PHARMACOLOGY FILING FORM/CHECKLIST

IS THE CLINICAL PHARMACOLOGY SECTION OF THE APPLICATION FILEABLE?

YES

In the initial submission, it was noted that sponsor did not submit the PK raw data (concentrations at each time point for calculation of PK parameters) and dataset with PK parameters for all PK studies. The following comments were conveyed to the sponsor:

1. We are not able to find datasets of PK raw data and PK parameters for your PK studies. For Studies BNX-106, -107 and -110, provide the datasets with all PK raw data for your calculation of PK parameters and the final dataset of PK parameters that you used for your statistical analysis.

2. All the datasets should be ready for analysis using WinNonlin.

Sponsor submitted the requested datasets on September 23, 2013.

This NDA 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.

There are no comments for sponsor at this time.

Reviewing Clinical Pharmacologist

Date

Team Leader/Supervisor

Date

Background:

On 31 July 2013, BioDelivery Sciences International submitted a 505(b)(2) NDA 205637 for Bunavail (buprenorphine and naloxone) buccal films for the maintenance treatment of opioid dependence.

This NDA relies on the Agency's previous findings of safety and effectiveness for Suboxone sublingual tablet (NDA 20-733) and literature. The to-be-marketed formulation was used in pivotal relative bioavailability study (Study BNX-110), dose proportionality study (Study BNX-106), and effect of pH (Study BNX-107).

The overall clinical and clinical pharmacology program consisted the 6 single dose Phase 1 (Studies BNX-101, 102, 103, 106, 107, and 110). Earlier formulations were used in Studies BNX-101 and -102 to select the final commercial formulation. The final formulation was used in pivotal relative bioavailability study (Study BNX-110), dose proportionality study (Study BNX-106), and effect of pH (Study BNX-107). The final formulation but different strength was

CLINICAL PHARMACOLOGY FILING FORM/CHECKLIST

also used in another pilot study (Study BNX-103). This review will focus on Studies BNX-110, -106, and -107. OSI inspection was requested for the pivotal relative BA/BE Study BNX-110.

Sponsor's summary on relative bioavailability of Bunavail in comparison to the list drug, Suboxone tablet, dose proportionality, and effect of pH:

- Bunavail 1 x 4.2/0.696 mg film exhibited equivalent C_{max} and AUC values of buprenorphine in comparison to Suboxone tablet 8/2 mg
- Bunavail 1 x 4.2/0.696 mg film exhibited 30% lower exposure (C_{max} and AUCs) to naloxone in comparison to Suboxone tablet 8/2 mg
- Less than dose proportional increase in buprenorphine exposure with dose over the range of 0.875 mg to 5.25 mg
- Equivalent buprenorphine exposure for 4 x 0.875/0.15 mg and 1 x 3.5/0.6 mg films
- Equivalent normalized buprenorphine and naloxone exposure for 1 x 6.3/1.04 mg and 1 x 4.2/0.696 mg films
- Low pH decreased buprenorphine exposure by 50-60% and decreased naloxone exposure by 72-76%
- High pH decreased buprenorphine exposure by 25% and decreased naloxone exposure by 40%

4.2 Individual Study Summary

Study BNX-101

Clinical Study Report BNX-101

BEMA[®] Buprenorphine NX

2. SYNOPSIS

Name of Sponsor/Company: BioDelivery Sciences International, Inc.	Individual Study Table Referring to Part of the Dossier	<i>(For National Authority Use Only)</i>
Name of Finished Product: BEMA [®] Buprenorphine NX	Volume: Page:	
Name of Active Ingredients: Buprenorphine hydrochloride and naloxone hydrochloride dihydrate		
Title of Study: BEMA [®] Buprenorphine NX Study BNX-101: An Evaluation of Pharmacokinetics, Tolerability, and Safety Following Single Dose Administration of BEMA [®] Buprenorphine NX and Suboxone in Healthy Subjects Receiving Concurrent Naltrexone		
Principal Investigator: Mark Leibowitz, MD		
Study center: The study was conducted at Worldwide Clinical Trials Drug Development Solutions located in the United States (US).		
Publications (reference): None		
Studied period (years): Date first subject enrolled: 20 Jun 2011 Date last subject completed: 08 Aug 2011	Phase of development: 1	
Objectives: Primary: Estimate the relative bioavailability of buprenorphine and naloxone following single doses of BEMA Buprenorphine NX films and Suboxone sublingual tablets Secondary: Assess the safety and tolerability of BEMA Buprenorphine NX films in healthy subjects receiving concurrent naltrexone by adverse event (AE), vital sign, and pulse oximetry monitoring, electrocardiogram (ECG), and clinical laboratory assessments		
Methodology: BEMA Buprenorphine NX was studied in a single dose, 2-period, crossover design with 24 subjects randomized to one of two groups (12 subjects in each). Each group received 2 doses of study drug in random sequence (A/B, B/A, or C/D, D/C); 1 dose administered in each of the 2 study periods. Group 1 Treatment A: single 0.75/0.19 mg (buprenorphine/naloxone) BEMA Buprenorphine NX buccal soluble film (actual 0.19 mg dosage is 0.1875 mg, but will be referred to as 0.19 mg from here on forward) Treatment B: single 2/0.5 mg (buprenorphine/naloxone) Suboxone sublingual tablet Group 2 Treatment C: single 3/0.75 mg (buprenorphine/naloxone) BEMA Buprenorphine NX buccal soluble film Treatment D: single 8/2 mg (buprenorphine/naloxone) Suboxone sublingual tablet		

<p>Serial blood samples were collected for determination of buprenorphine, norbuprenorphine, and total naloxone (unconjugated and conjugated) plasma concentrations predose and at multiple time points postdose. Adverse events, vital signs, and pulse oximetry were assessed at intervals throughout the study. Clinical laboratory assessments and 12 lead ECGs were also performed.</p>
<p>Number of subjects (planned and analyzed): It was planned that 24 subjects would be enrolled into this study; a total of 24 subjects were enrolled, 12 per treatment group.</p>
<p>Diagnosis and main criteria for inclusion: Healthy males or healthy non-pregnant non-nursing females aged 18 to 55 years, inclusive, with a body mass index ≥ 18 and ≤ 30 kg/m² and a minimum weight of 59 kg were eligible to participate in this study.</p>
<p>Test product, dose and mode of administration, batch number: The following study drug was provided: 3/0.75 mg BEMA Buprenorphine NX film (Batch number 830-181-1A); 0.75/0.19 mg BEMA Buprenorphine NX film (Batch number 830-182-1).</p>
<p>Duration of treatment: The total duration of participation for each subject was 4 weeks and included a Screening visit, 2 inpatient study periods of approximately 36 hours (2 overnights) each separated by at least 5 days, and a Follow-up visit approximately 7 to 11 days after administration of the last study drug dose.</p>
<p>Reference therapy, dose and mode of administration Suboxone sublingual tablets, each containing 2/0.5 (Lot number 106202) or 8/2 mg (Lot number 106202) buprenorphine/naloxone, administered sublingually</p>
<p>Criteria for evaluation:</p> <p>Pharmacokinetics: Plasma buprenorphine and norbuprenorphine were determined from blood samples (10 mL). Pharmacokinetic parameters analyzed in this study included C_{max}, T_{max}, AUC₀₋₄₈, AUC_{0-last}, AUC_{0-inf}, K_{el} (λ_z), and t_{1/2}. No urine pharmacokinetic (PK) samples were collected. Study drug bitterness was assessed at multiple time points using a 5-point bitterness intensity scale.</p> <p>Safety: Adverse events, vital signs and pulse oximetry were assessed at intervals throughout the study. Clinical laboratory assessments and a 12-lead ECG were also performed at intervals throughout the study.</p>
<p>Statistical methods: This was an open label study in healthy subjects. A total of 24 subjects were enrolled. The primary aim of the statistical analysis was to estimate the relative bioavailability of buprenorphine and total naloxone following single doses of BEMA Buprenorphine NX films to Suboxone sublingual tablets. The bioavailability of buprenorphine and total naloxone was compared between the two study drug treatments within each study group by constructing 90% confidence intervals (CIs) for the ratio of geometric means (A/B in Group 1, and C/D in Group 2). For each parameter, point estimates for the geometric mean and associated 90% CIs were computed for the ratio of geometric means. The statistical model used log of the PK parameter as the dependent variable and, sequence, study drug treatment, period and subject within sequence as the independent variables. The differences and the 90% CIs between the treatments (A/B in Group 1, and C/D in Group 2) from above model yielded geometric mean ratios and 90% CIs for A/B and C/D.</p> <p>The overall bitterness intensity value for each subject was calculated as the average of all of the bitterness scores for an individual.</p>

SUMMARY AND CONCLUSIONS

Pharmacokinetic data were available from 24 subjects. Their mean age was 31.2 years; 16 (67%) were men and 8 (33%) were women.

Mean Plasma Pharmacokinetic Parameters Summary:**Analysis of Pharmacokinetic Parameters (Pharmacokinetic Population)**

^a	Geom. LSMean		Geom. LSMean Ratio (90% CI)
	A ^b	B ^c	A/B
Group 1^d			
Buprenorphine			
C _{max} (ng/mL)	0.53	1.22	0.44 (0.35, 0.55)
AUC ₍₀₋₄₈₎ (ng*h/mL)	3.53	8.90	0.40 (0.33, 0.47)
AUC _(0-t) (ng*h/mL)	3.22	8.82	0.37 (0.30, 0.44)
AUC _(0-inf) (ng*h/mL)	3.69	10.44	0.35 (0.29, 0.43)
Total Naloxone			
C _{max} (ng/mL)	2.08	5.60	0.37 (0.31, 0.45)
AUC ₍₀₋₄₈₎ (ng*h/mL)	4.18	12.47	0.33 (0.31, 0.36)
AUC _(0-t) (ng*h/mL)	3.89	11.95	0.33 (0.30, 0.35)
AUC _(0-inf) (ng*h/mL)	4.47	12.83	0.35 (0.33, 0.37)
Group 2^e			
Buprenorphine			
C _{max} (ng/mL)	1.98	2.35	0.84 (0.71, 1.01)
AUC ₍₀₋₄₈₎ (ng*h/mL)	13.98	21.31	0.66 (0.55, 0.78)
AUC _(0-t) (ng*h/mL)	13.83	21.31	0.65 (0.54, 0.78)
AUC _(0-inf) (ng*h/mL)	16.11	25.00	0.64 (0.54, 0.77)
Total Naloxone			
C _{max} (ng/mL)	8.98	24.73	0.36 (0.30, 0.44)
AUC ₍₀₋₄₈₎ (ng*h/mL)	21.73	59.51	0.37 (0.34, 0.40)
AUC _(0-t) (ng*h/mL)	20.93	57.23	0.37 (0.34, 0.40)
AUC _(0-inf) (ng*h/mL)	22.08	59.46	0.37 (0.34, 0.40)

CI=confidence interval; LSM=least squares mean

a. Source Data: Table 14.2.1.1, Table 14.2.2.1

b. BEMA Buprenorphine NX film

c. Suboxone sublingual tablet

d. Group 1= single 2/0.5 mg Suboxone sublingual tablet and single 0.75/0.19 mg BEMA Buprenorphine NX film

e. Group 2= single 8/2 mg Suboxone sublingual tablet and single 3/0.75 mg BEMA Buprenorphine NX film

PHARMACOKINETICS CONCLUSIONS:

- Buprenorphine exposure from the BEMA Buprenorphine NX film was approximately dose linear.
- The BEMA Buprenorphine NX formulation and dosages evaluated in this study are not bioequivalent to the corresponding Suboxone sublingual tablets. Formulation changes are necessary to increase the buprenorphine exposure.
- Unconjugated naloxone should be measured and compared between BEMA Buprenorphine NX and corresponding Suboxone sublingual tablets in future PK studies.

SAFETY CONCLUSIONS:

Buprenorphine NX and Suboxone in Study BNX-101. All 24 subjects took both doses of study drug and were included in the Safety Population. All subjects completed the study.

No deaths or other SAEs occurred during the study. No subjects were withdrawn from the study.

At least 1 TEAE occurred in 12 (50%) of 24 subjects. Eleven of the subjects with a TEAE had at least 1 drug-related event. All of the AEs were mild or moderate in severity and all the AEs recovered/resolved during the study. Nausea, vomiting, and dizziness were the most frequently reported AEs. Comparison of the AEs across doses of BEMA Buprenorphine NX and Suboxone revealed a dose-related increase in AEs. More nausea was seen with the BEMA Buprenorphine NX doses than with comparable Suboxone doses. The incidence of other AEs was similar across study treatments.

Similar changes in mean vital signs were observed both between groups and within groups. There was one outlier, who had increased systolic blood pressure values throughout the study. There were no clinically significant changes in electrocardiogram data or clinical laboratory test results.

OVERALL CONCLUSIONS:

BEMA Buprenorphine NX administered along with Suboxone sublingual tablets was generally well tolerated in this healthy population.

The PK results indicate the C_{max} and AUC values for buprenorphine, norbuprenorphine, and total naloxone from the BEMA Buprenorphine NX films were less than the values observed from the corresponding Suboxone sublingual tablets, and buprenorphine bioequivalence was not established with this BEMA Buprenorphine NX formulation (Formulation BBN011-2) and dosages.

Date of the report: 14 Jan 2013

Study BNX-102

2. SYNOPSIS

Name of Sponsor/Company: BioDelivery Sciences International, Inc.	Individual Study Table Referring to Part of the Dossier	<i>(For National Authority Use Only)</i>
Name of Finished Product: BEMA [®] Buprenorphine NX	Volume: Page:	
Name of Active Ingredients: Buprenorphine hydrochloride and naloxone hydrochloride dihydrate		
Title of Study: BEMA [®] Buprenorphine NX Study BNX-102: An Evaluation of Pharmacokinetics, Tolerability, and Safety Following Single Dose Administration of BEMA [®] Buprenorphine NX and Suboxone in Healthy Subjects Receiving Concurrent Naltrexone		
Principal Investigator: Cynthia Zamora, MD		
Study center: The study was conducted at Worldwide Clinical Trials Drug Development Solutions located in the United States (US).		
Publications (reference): None		
Studied period (years): Date first subject enrolled: 02 Nov 2011 Date last subject completed: 02 Dec 2011	Phase of development: 1	
Objectives: Primary: <ul style="list-style-type: none"> Estimate the relative bioavailability of buprenorphine and naloxone following single doses of BEMA Buprenorphine NX films and Suboxone sublingual tablets Secondary: <ul style="list-style-type: none"> Assess the safety and tolerability of BEMA Buprenorphine NX films in healthy subjects receiving concurrent naltrexone by adverse event (AE), vital sign, and pulse oximetry monitoring; electrocardiogram (ECG); and clinical laboratory assessments 		
Methodology: BEMA Buprenorphine NX was studied in a single dose, 2-period, crossover design with 22 subjects randomized to one of two groups (11 subjects in each). Each group received 2 doses of study drug in random sequence (A/B, B/A, or C/D, D/C); 1 dose administered in each of the 2 study periods. Naltrexone was co-administered approximately 12 hours and 30 minutes prior to and approximately 12 and 24 hours after the single study drug doses.		
Group 1 Treatment A: single 0.75/0.19 mg (buprenorphine/naloxone) BEMA Buprenorphine NX buccal soluble film (actual 0.19 mg dosage is 0.188 mg, but will be referred to as 0.19 mg from here forward) Treatment B: single 2/0.5 mg (buprenorphine/naloxone) Suboxone sublingual tablet		
Group 2 Treatment C: single 3/0.75 mg (buprenorphine/naloxone) BEMA Buprenorphine NX buccal soluble film Treatment D: single 8/2 mg (buprenorphine/naloxone) Suboxone sublingual tablet		

<p>Serial blood samples were collected for determination of buprenorphine and naloxone (parent and total (parent + glucuronide metabolites)) plasma concentrations predose and at multiple time points postdose. Adverse events, vital signs, and pulse oximetry were assessed at intervals throughout the study. Clinical laboratory assessments and 12 lead ECGs were also performed.</p>
<p>Number of subjects (planned and analyzed): It was planned that 24 subjects would be enrolled into this study; a total of 22 subjects were enrolled, 11 in Group 1 and 11 in Group 2. One subject withdrew from the study due to an AE which was considered to be unrelated to study drug.</p>
<p>Diagnosis and main criteria for inclusion: Healthy males or healthy non-pregnant non-nursing females aged 18 to 55 years, inclusive, with a body mass index ≥ 18 and ≤ 30 kg/m² and a minimum weight of 59 kg were eligible to participate in this study.</p>
<p>Test product, dose and mode of administration, batch number: The following study drug was provided and administered buccally: 3/0.75 mg BEMA Buprenorphine NX film (Batch number 847-058-1); 0.75/0.19 mg BEMA Buprenorphine NX film (Batch number 847-059-1)</p>
<p>Duration of treatment: The total duration of participation for each subject was 4 weeks and included a Screening visit, 2 inpatient study periods of approximately 36 hours (2 overnights) each separated by at least 5 days, and a Follow-up visit approximately 7 to 11 days after administration of the last study drug dose.</p>
<p>Reference therapy, dose and mode of administration: Suboxone sublingual tablets, each containing 2/0.5 mg (Lot Number 119303) or 8/2 mg (Lot Number 119303) buprenorphine/naloxone, administered sublingually</p>
<p>Criteria for evaluation: Pharmacokinetics: Pharmacokinetic parameters analyzed in this study included C_{max}, T_{max}, AUC_{0-t}, AUC_{last}, AUC_{inf}, K_{el} (λ_z), and $t_{1/2}$. No urine PK samples were collected. Safety: Adverse events, vital signs and pulse oximetry were assessed at intervals throughout the study. Clinical laboratory assessments and a 12-lead ECG were also performed at intervals throughout the study.</p>
<p>Statistical methods: This was an open label, crossover study. The primary aim of the statistical analysis was to determine the PK profiles and estimate the relative bioavailability of buprenorphine and naloxone (unconjugated and total) following single doses of BEMA Buprenorphine NX films and Suboxone sublingual tablets. The bioavailability of buprenorphine and naloxone was compared between the two study drug treatments within each study group by constructing 90% confidence intervals (CIs) for the ratio of geometric means (A/B in Group 1, and C/D in Group 2). For each parameter, point estimates for the geometric mean and associated 90% CIs were computed for the ratio of geometric means. The statistical model used log of the PK parameter as the dependent variable and, sequence, study drug treatment, period and subject within sequence as the independent variables. The differences and the 90% CIs between the treatments (A/B in Group 1, and C/D in Group 2) from above model yielded geometric mean ratios and 90% CIs for A/B and C/B.</p>

SUMMARY AND CONCLUSIONS

Pharmacokinetic data were available from 22 subjects. Their mean age was 30.2 years; 15 (68%) were men and 7 (32%) were women.

Mean Plasma Pharmacokinetic Parameters Summary**Analysis of Pharmacokinetic Parameters (Pharmacokinetic Population)**

^a	Geom. LSMean A^b	Geom. LSMean B^c	Geom. LSMean Ratio (90% CI) A/B
Buprenorphine			
ln (C _{max})	1.0883	0.9385	115.96 (98.51, 136.49)
ln (AUC _{last})	5.2523	6.7573	77.73 (69.46, 86.98)
ln (AUC _{0-t})	5.6979	6.8249	83.49 (75.09, 92.82)
ln (AUC _{inf})	5.7769	7.7110	74.92 (67.11, 83.63)
Parent Naloxone			
ln (C _{max})	50.8615	44.8975	113.28 (75.76, 169.38)
ln (AUC _{last})	124.6165	123.1244	101.21 (71.73, 142.81)
ln (AUC _{0-t})	131.3790	129.5917	101.38 (72.10, 142.56)
ln (AUC _{inf})	129.9803	129.2029	100.60 (71.81, 140.94)
Total Naloxone			
ln (C _{max})	1.6505	5.4787	30.13 (24.84, 36.54)
ln (AUC _{last})	3.8354	11.7359	32.68 (29.57, 36.12)
ln (AUC _{0-t})	4.2767	12.8748	33.22 (30.72, 35.92)
ln (AUC _{inf})	4.4428	13.2804	33.45 (29.85, 37.49)
	C^d	D^e	C/D
Buprenorphine			
ln (C _{max})	3.1601	3.0321	104.22 (90.55, 119.95)
ln (AUC _{last})	18.1097	21.3493	84.83 (75.43, 95.39)
ln (AUC _{0-t})	18.1097	21.3493	84.83 (75.43, 95.39)
ln (AUC _{inf})	20.0467	27.3580	73.28 (62.64, 85.71)
Parent Naloxone			
ln (C _{max})	207.0207	144.5994	143.17 (118.92, 172.36)
ln (AUC _{last})	520.6722	435.8512	119.46 (98.53, 144.84)
ln (AUC _{0-t})	526.5117	439.6113	119.77 (99.35, 144.39)
ln (AUC _{inf})	528.1156	453.8999	116.35 (95.77, 141.35)
Total Naloxone			
ln (C _{max})	5.3457	17.9637	29.76 (26.01, 34.05)
ln (AUC _{last})	14.7203	42.8173	34.38 (31.22, 37.86)
ln (AUC _{0-t})	16.0593	45.0129	35.68 (32.24, 39.48)
ln (AUC _{inf})	15.9882	45.2525	35.33 (32.40, 38.52)

CI = confidence interval; LSM = least squares mean

a. Source Data: Pharmacokinetic Report Table 13, Table 14, Table 17, Table 18, Table 19, Table 20

b. A = Single 0.75/0.19 mg (buprenorphine/naloxone) BEMA Buprenorphine NX film

c. B = Single 2/0.5 mg (buprenorphine/naloxone) Suboxone sublingual tablet

d. C = Single 3/0.75 mg (buprenorphine/naloxone) BEMA Buprenorphine NX film

e. D = Single 8/2 mg (buprenorphine/naloxone) Suboxone sublingual tablet

PHARMACOKINETICS CONCLUSIONS:

- Buprenorphine exposure from the BEMA Buprenorphine NX films was approximately dose linear.
- The BEMA Buprenorphine NX formulation and dosages evaluated in this study are not biosimilar to the corresponding Suboxone sublingual tablets, with respect to buprenorphine and naloxone exposure. A dose adjustment is necessary to increase the buprenorphine exposure and a formulation change is necessary to decrease naloxone exposure.

SAFETY RESULTS CONCLUSIONS:

A total of 22 subjects were enrolled in study BNX-102; 11 in Group 1 and 11 in Group 2. Each of the 22 subjects received study drug.

All of the AEs were mild or moderate in severity and all the AEs were resolved. There were no deaths or other SAEs. One subject was withdrawn from the study due to an AE which was considered to be unrelated to study drug.

Overall, there were no safety differences between the treatment groups.

OVERALL CONCLUSIONS:

BEMA Buprenorphine NX administered along with Suboxone sublingual tablets as generally well tolerated in this healthy population.

The PK results indicate that BEMA Buprenorphine NX (Formulation BBN011-6) is able to deliver buprenorphine plasma concentrations in the range of those from Suboxone tablets, but a dose adjustment is required to increase exposure to buprenorphine. A formulation change is required to reduce the systemic exposure of naloxone to an exposure range similar or below that of Suboxone.

Date of the report: 13 Feb 2013

Study BNX-103

2. SYNOPSIS

Name of Sponsor/Company: BioDelivery Sciences International, Inc.	Individual Study Table Referring to Part of the Dossier	<i>(For National Authority Use Only)</i>
Name of Finished Product: BEMA [®] Buprenorphine NX	Volume:	
Name of Active Ingredients: Buprenorphine hydrochloride and naloxone hydrochloride dihydrate	Page:	
Title of Study: BEMA [®] Buprenorphine NX Study BNX-103: A Comparison of the Rate and Extent of Buprenorphine Absorption from BEMA [®] Buprenorphine NX and Suboxone in Healthy Subjects Receiving Concurrent Naltrexone		
Principal Investigator: Cynthia Zamora, MD		
Study center: The study was conducted at Worldwide Clinical Trials Drug Development Solutions located in the United States (US).		
Publications (reference): None		
Studied period (years): Date first subject enrolled: 26 Jun 2012 Date last subject completed: 17 Sep 2012	Phase of development: 1	
<p>Objectives:</p> <p>Primary: Demonstrate the absence of a significant difference in the rate and extent of buprenorphine absorption following single doses of BEMA Buprenorphine NX films and Suboxone sublingual tablets</p> <p>Secondary: Demonstrate that the extent of unconjugated naloxone absorption from BEMA Buprenorphine NX films was less than that from a dose of Suboxone tablets providing equivalent buprenorphine exposure.</p> <p>Assess the safety and tolerability of BEMA Buprenorphine NX films in healthy subjects receiving concurrent naltrexone by adverse event (AE), vital sign and pulse oximetry monitoring, electrocardiogram (ECG), and clinical laboratory assessments</p>		
<p>Methodology: This was an open label, single dose, 2-period, crossover study in healthy subjects. Subjects received a single 8/2 mg (buprenorphine/naloxone) Suboxone sublingual tablet and a single 3.5/0.6 mg (buprenorphine/naloxone) BEMA Buprenorphine NX film in a random sequence. Each dose was separated by at least 14 days. The rate and extent of buprenorphine exposure was evaluated after each dose and the products compared.</p> <p>Oral naltrexone was co-administered to reduce the incidence of nausea and vomiting as well as the risk of respiratory depression.</p>		
Number of subjects (planned and analyzed): It was planned that 80 subjects would be enrolled into this study; a total of 78 subjects were enrolled.		

<p>Diagnosis and main criteria for inclusion: Healthy males or females aged 18 to 55 years, inclusive, with a body mass index ≥ 18 and ≤ 30 kg/m² and a minimum weight of 59 kg were eligible to participate in this study.</p>
<p>Test product, dose and mode of administration, lot number: The following study drug was provided: 3.5/0.6 mg (buprenorphine/naloxone) BEMA Buprenorphine NX film (Lot number 857-004-1); Suboxone sublingual tablets, each containing 8/2 mg buprenorphine/naloxone (Lot number 206704-2), administered sublingually</p>
<p>Duration of treatment: The total duration of participation for each subject was 9 weeks and included a Screening visit, 2 inpatient study periods of approximately 36 hours (2 overnights) each separated by at least 14 days, 5 outpatient clinic visits following each inpatient study period, and a Follow up visit approximately 7 to 11 days after administration of the last study drug dose (may have been combined with the last outpatient clinic visit).</p>
<p>Reference therapy, dose and mode of administration None</p>
<p>Criteria for evaluation:</p> <p>Pharmacokinetics: Buprenorphine, norbuprenorphine, and naloxone (unconjugated) plasma concentrations were determined from blood samples (10 mL). Pharmacokinetic parameters analyzed in this study included C_{max}, T_{max}, AUC_t, AUC_{0-last}, AUC_{0-inf}, K_{el} (λ_z), and $t_{1/2}$. No urine pharmacokinetic (PK) samples were collected.</p> <p>Safety: Adverse events, physical examination, vital signs, pulse oximetry, ECGs, and clinical laboratory assessments (including hematology, chemistry, and urinalysis).</p>
<p>Statistical methods: This was an open label, single dose, 2-period, crossover study in healthy subjects. A total of 78 subjects were enrolled. The primary aim of the statistical analysis was to demonstrate the absence of a significant difference in the rate and extent of buprenorphine absorption following single doses of BEMA Buprenorphine NX films and Suboxone sublingual tablets. Comparison of the log-transformed PK parameters C_{max}, AUC_{last}, and AUC_{inf} for buprenorphine and unconjugated naloxone across treatments was performed using an analysis of variance (ANOVA) model and the two one-sided t-tests procedure. The ANOVA model included factors for sequence, subject within sequence, treatment, and period. The ratios of the geometric means (Test to Reference) and 90% CIs were reported. Bioequivalence was concluded if the 90% CIs for C_{max}, AUC_{last}, and AUC_{inf} were contained within the limits of 80.00 and 125.00% for buprenorphine and unconjugated naloxone.</p>

SUMMARY – CONCLUSIONS**Mean Plasma Pharmacokinetic Parameters Summary:**

Mean (SD) Buprenorphine Pharmacokinetic Parameters		
Parameter	Single 3.5/0.6 mg BEMA Buprenorphine NX film (BBN012-1) N=65	Single 8/2 mg Suboxone sublingual tablet (BBN012-1) N=69
C _{max} (ng/mL)	2.99 (1.27)	3.15 (1.33)
T _{max} (h) ^b	2.25 (1.25-4.5)	1.75 (0.5-4.03)
AUC ₍₀₋₄₈₎ (ng*h/mL)	19.78 (6.714)	22.93 (6.769)
AUC ₍₀₋₇₂₎ (ng*h/mL)	21.07 (7.052)	25.29 (7.479)
AUC ₍₀₋₁₄₄₎ (ng*h/mL)	22.07 (7.673)	27.52 (8.661)
AUC _{last} (ng*h/mL)	21.62 (7.579)	27.15 (8.839)
AUC _{inf} (ng*h/mL)	23.19 (7.734) ^c	28.96 (8.995)
T _½ (h)	30.59 (17.39)	31.85 (14.10)
C _{last} (ng/mL)	0.0348 (0.0113)	0.0390 (0.0276)
T _{last} (h)	83.45 (26.87)	104.14 (28.58)
Mean (SD) Norbuprenorphine Pharmacokinetic Parameters		
Parameter	Single 3.5/0.6 mg BEMA Buprenorphine NX film (BBN012-1) N=65	Single 8/2 mg Suboxone sublingual tablet (BBN012-1) N=69
C _{max} (ng/mL)	0.424 (0.247)	1.34 (0.836)
T _{max} (h) ^b	2.50 (0.75-48.00)	1.25 (0.75-72.00)
AUC ₍₀₋₁₄₄₎ (ng*h/mL)	16.80 (7.507)	40.97 (19.29)
AUC _{last} (ng*h/mL)	16.61 (7.634)	40.83 (19.38)
AUC _{inf} (ng*h/mL)	18.53 (8.388) ^c	44.23 (22.85)
T _½ (h)	38.12 (16.01) ^c	34.28 (13.91)
C _{last} (ng/mL)	0.0369 (0.0189)	0.0576 (0.0446)
T _{last} (h)	120.38 (27.96)	134.96 (20.62)
Mean (SD) Unconjugated Naloxone Pharmacokinetic Parameters		
Parameter	Single 3.5/0.6 mg BEMA Buprenorphine NX film (BBN012-1) N=65	Single 8/2 mg Suboxone sublingual tablet (BBN012-1) N=69
C _{max} (pg/mL)	102 (65.0)	135 (75.1)
T _{max} (h) ^b	1.25 (0.50-2.00)	1.00 (0.25-2.50)
AUC ₍₀₋₂₄₎ (pg*h/mL)	260.0 (128.7)	363.2 (132.8)
AUC _{last} (pg*h/mL)	252.0 (128.1)	356.5 (134.5)
AUC _{inf} (pg*h/mL)	257.7 (127.2)	371.7 (138.5)
T _½ (h)	1.86 (1.12)	5.46 (3.73)
C _{last} (pg/mL)	2.16 (1.15)	2.13 (1.03)
T _{last} (h)	10.62 (3.64)	18.78 (5.99)

BBN012-1=Formulation BBN012-1

a. Source data: Pharmacokinetic Report Table 4, Table 5, and Table 6; Pharmacokinetic Analysis Section of the Pharmacokinetic Report

b. Median (range)

c. N=64

PHARMACOKINETICS CONCLUSIONS:

The 90% confidence intervals for buprenorphine were within the 80% to 125% range for establishing bioequivalence for the C_{max} , AUC_{0-24} , and AUC_{0-48} values but not for AUC_{last} or AUC_{inf} . The extent of naloxone absorption from BEMA Buprenorphine NX films was between 25%-33% less than that from a clinically used dose of Suboxone tablets.

SAFETY CONCLUSIONS:

A total of 78 subjects enrolled in Study BNX-103. All 78 subjects took at least 1 dose of study drug and were included in the Safety Population.

All of the AEs reported during the study were mild or moderate in severity. There were no deaths or other SAEs and 4 subjects were withdrawn from the study due to AEs.

OVERALL CONCLUSIONS:

Buprenorphine bioavailability from the BEMA Buprenorphine NX films was comparable, but not bioequivalent to that from Suboxone sublingual tablets. Norbuprenorphine and unconjugated naloxone exposure was less with the BEMA Buprenorphine NX films than from Suboxone Sublingual Tablets. Both study treatments were reasonably well tolerated in this population of healthy, opioid naïve subjects.

Date of the report: 18 MAR 2013

Study BNX-106

2. SYNOPSIS

Name of Sponsor/Company: BDSI	Individual Study Table Referring to Part of the Dossier Volume: Page:	<i>(For National Authority Use Only)</i>
Name of Finished Product: BEMA [®] Buprenorphine NX		
Name of Active Ingredients: Buprenorphine hydrochloride, Naloxone hydrochloride dihydrate		
Title of Study: BEMA [®] Buprenorphine NX Study BNX-106: An Evaluation of the Dose Linearity of BEMA [®] Buprenorphine NX in Healthy Subjects Receiving Concurrent Naltrexone		
Principal Investigator: Cynthia Zamora, MD		
Study center: The study was conducted at Worldwide Clinical Trials Drug Development Solutions located in the United States (US).		
Publications (reference): None		
Studied period (years): Date first subject enrolled: 03 Apr 2012 Date last subject completed: 16 May 2012	Phase of development: 1	
Objectives: Primary: <ul style="list-style-type: none"> Determine the relationship between buprenorphine dose and plasma concentration following single doses of BEMA Buprenorphine NX Secondary: <ul style="list-style-type: none"> Compare the buprenorphine plasma concentration profile following multiple BEMA Buprenorphine NX films with an equivalent dose administered as a single film. Assess the exposure to naloxone following single doses of BEMA Buprenorphine NX Assess the safety and tolerability of BEMA Buprenorphine NX films in healthy subjects receiving concurrent naltrexone by adverse event (AE), vital sign, and pulse oximetry monitoring, electrocardiogram (ECG), and clinical laboratory assessments 		

Methodology: BEMA Buprenorphine NX was studied in a single dose, 4-period, crossover design with 20 subjects. Each subject received 4 doses of BEMA Buprenorphine NX in a random sequence; each dose separated by at least 7 days. The doses to be administered are 0.875/0.15 mg (actual 0.15 mg dosage is 0.145 mg but will be referred to as 0.15 mg from here on forward), 3.5/0.6 mg (actual 0.6 dosage is 0.058 mg but will be referred to as 0.6 mg from here on forward), 5.25/0.9 mg (actual 0.9 mg dosage is 0.87 mg but will be referred to as 0.9 mg from here on forward), and 4 x 0.875/0.15 mg (buprenorphine/naloxone) BEMA Buprenorphine NX films. Naltrexone was co-administered approximately 12 hours and 30 minutes prior to and approximately 12 and 24 hours after the single study drug doses.

Serial blood samples were collected for determination of buprenorphine and naloxone plasma concentrations predose and at multiple time points postdose. Adverse events, vital signs, and pulse oximetry were assessed at intervals throughout the study. Clinical laboratory assessments and 12 lead ECGs were also performed.

Number of subjects (planned and analyzed): It was planned that 20 subjects would be enrolled into this study; a total of 20 subjects were enrolled.

Diagnosis and main criteria for inclusion: Healthy males or females aged 18 to 55 years, inclusive, with a body mass index ≥ 18 and ≤ 30 kg/m² and a minimum weight of 59 kg were eligible to participate in this study.

Test product, dose and mode of administration, batch number: The following study drug was provided and administered buccally: 0.875/0.15 mg BEMA Buprenorphine NX film (Batch number 426865); 3.5/0.6 mg BEMA Buprenorphine NX film (Batch number 426864); 5.25/0.9 mg BEMA Buprenorphine NX (Batch number 427843); and 4 x 0.875/0.15 mg BEMA Buprenorphine NX (Batch number 426865).

Duration of treatment: The total duration of participation for each subject was approximately 6 weeks and included a Screening visit, 4 inpatient study periods of approximately 36 hours (2 overnights) each separated by at least 7 days, and a Follow-up visit approximately 7 to 11 days after administration of the last study drug dose.

Reference therapy, dose and mode of administration: None

Criteria for evaluation:

Pharmacokinetics: Plasma buprenorphine and naloxone were determined from blood samples (6 mL). Pharmacokinetic parameters analyzed in this study included C_{max} , T_{max} , AUC_{0-24} , AUC_{0-last} , AUC_{0-inf} , K_{el} (λ_z), and $t_{1/2}$. No urine PK samples were collected.

Safety: Adverse events, vital signs and pulse oximetry were assessed at intervals throughout the study. Clinical laboratory assessments and a 12-lead ECG were also performed at intervals throughout the study.

Statistical methods: This was an open label study in healthy subjects. A total of 20 subjects were enrolled. The primary aim of the statistical analysis was to estimate dose linearity and proportionality of buprenorphine and naloxone following single doses of BEMA Buprenorphine NX films. Statistical analyses used a power model with mixed effects (Smith, 2000) of the following general form:

$$\ln(PK) = \ln(\beta_0) + \beta_1 \cdot \ln(\text{Dose}) + \varepsilon$$

where PK is the pharmacokinetic parameter tested (e.g. C_{max} or AUC); $\ln(\beta_0)$ is the y-intercept; β_1 is the slope (a value of $\beta_1 \approx 1$ indicates linearity); and ε is an error term (Subject will be used as the random effects term).

The estimate of β_1 was reported along with the associated p-value and the dose range for proportionality. A significant difference from unity (1.0000) and lack of proportionality was defined a priori as $p < 0.05$. The range in which dose proportionality was demonstrated was determined by multiplying the ratio Rho (high/low dose ratio) by the lowest dose administered. Rho was calculated in the power analysis and was the maximum dose range over which proportionality could be concluded, starting with the lowest dose. In addition, dose-normalized parameter values were plotted versus the administered dose and analyzed using linear regression.

SUMMARY – CONCLUSIONS

PHARMACOKINETIC RESULTS:

Mean Plasma Pharmacokinetic Parameters

Parameter	0.875/0.15 mg BEMA Buprenorphine NX (BBN012-1; buprenorphine/ naloxone)	3.5/0.6 mg BEMA Buprenorphine NX (BBN012-1; buprenorphine/ naloxone)	5.25/0.9 mg BEMA Buprenorphine NX (BBN012-1; buprenorphine/ naloxone)	4 x 0.875/0.15 mg BEMA Buprenorphine NX (BBN012-1; buprenorphine/ naloxone)
Mean (SD) Buprenorphine Pharmacokinetic Parameters				
C_{max} (ng/mL)	n=18 1.15 (0.331)	n=20 4.03 (1.79)	n=19 5.13 (1.96)	n=18 3.89 (1.39)
T_{max} (h)	n=18 2.84 (0.79)	n=20 2.78 (0.69)	n=19 2.71 (0.72)	n=18 2.75 (0.69)
AUC₀₋₂₄ (ng*h/mL)	n=18 7.210 (1.520)	n=20 24.13 (6.265)	n=19 31.94 (9.820)	n=18 24.35 (6.974)
AUC_{last} (ng*h/mL)	n=18 7.372 (1.604)	n=20 24.77 (6.416)	n=19 33.28 (9.333)	n=18 25.33 (7.064)
AUC_{inf} (ng*h/mL)	n=17 8.395 (2.052)	n=20 27.47 (6.709)	n=18 36.59 (10.38)	n=18 28.19 (8.226)
T_{1/2} (h)	n=17 10.44 (4.22)	n=20 10.17 (2.90)	n=18 10.01 (2.69)	n=18 10.95 (4.18)
Mean (SD) Naloxone (parent) Pharmacokinetic Parameters				
C_{max} (pg/mL)	n=18 44.3 (25.4)	n=20 179 (114)	n=19 218 (133)	n=18 182 (123)
T_{max} (h)	n=18 1.34 (0.37)	n=20 1.48 (0.52)	n=19 1.44 (0.46)	n=18 1.38 (0.54)
AUC₀₋₂₄ (pg*h/mL)	n=18 118.7 (56.80)	n=20 488.5 (242.9)	n=19 639.3 (334.9)	n=18 499.7 (288.9)
AUC_{last} (pg*h/mL)	n=18 116.6 (56.12)	n=20 480.1 (243.8)	n=19 628.6 (333.7)	n=18 489.2 (288.3)
AUC_{inf} (pg*h/mL)	n=17 115.0 (53.70)	n=18 491.7 (255.7)	n=17 604.0 (336.0)	n=14 506.5 (304.7)
T_{1/2} (h)	n=17 1.58 (0.62)	n=18 1.93 (0.51)	n=17 2.65 (2.04)	n=14 2.24 (0.85)

BBN012-1 = Formulation BBN012-1

SAFETY RESULTS:

A total of 20 subjects enrolled in Study BNX-106 took at least 1 dose of study drug and were included in the Safety Population.

Seventeen (17) subjects experienced AEs, all of which were mild or moderate in severity and resolved prior to end of study participation. The most common AEs were nausea, dizziness, headache, and somnolence. There were no deaths or other SAEs. One (1) subject was lost to follow-up and 1 subject was discontinued due to vomiting.

CONCLUSION:

The results of this single dose, 4-period, crossover study demonstrate linearity in buprenorphine and naloxone exposure across BEMA Buprenorphine NX doses of 0.875/0.15, 3.5/0.6, and 5.25/0.9 mg for C_{max} and AUC. Across the 6-fold dose range, the increase in C_{max} and AUC values for buprenorphine was less than dose proportional. However, dose proportionality was demonstrated by the power model analysis over a 3.8-fold dose range. This apparent dose proportionality is supported by results that demonstrated bioequivalent buprenorphine exposure from a single 3.5/0.6 mg BEMA Buprenorphine NX film and from 4 x 0.875/0.15 mg BEMA Buprenorphine NX films. Thus, dose proportionality from the BEMA Buprenorphine NX films exists over a 4-fold dose range.

BEMA Buprenorphine NX administration was generally well tolerated in this healthy population.

Study BNX-107

2. SYNOPSIS

Name of Sponsor/Company: BioDelivery Sciences International, Inc.	Individual Study Table Referring to Part of the Dossier Volume: Page:	<i>(For National Authority Use Only)</i>
Name of Finished Product: BEMA [®] Buprenorphine NX		
Name of Active Ingredients: Buprenorphine hydrochloride and naloxone hydrochloride dihydrate		
Title of Study: An evaluation of the effects of co-administered liquids on the absorption of buprenorphine from BEMA [®] Buprenorphine NX and relative bioavailability in healthy subjects (BNX-107)		
Principal Investigator: Cynthia Zamora, MD		
Study center: The study was conducted at Worldwide Clinical Trials Drug Development Solutions located in the United States (US).		
Publications (reference): None		
Studied period (years): Date first subject enrolled: 14 Feb 2013 Date last subject completed: 30 Mar 2013	Phase of development: 1	
Objectives: Primary: <ul style="list-style-type: none"> Evaluate the effects of co-administered liquids on the absorption of buprenorphine and naloxone from BEMA Buprenorphine NX Secondary: <ul style="list-style-type: none"> Determine the relative bioavailability of buprenorphine and naloxone following single doses of BEMA Buprenorphine NX when administered under different conditions Determine the relationship between BEMA Buprenorphine NX dose and plasma buprenorphine and naloxone concentrations Assess the safety and tolerability of BEMA Buprenorphine NX films in healthy subjects receiving concurrent naltrexone by adverse event (AE), vital sign and pulse oximetry monitoring, electrocardiogram (ECG), and clinical laboratory assessments 		

<p>Methodology: This was an open label study in healthy subjects.</p> <p>BEMA Buprenorphine NX was studied in a single dose, 4-period, crossover design with approximately 24 subjects. Each subject received the following single dose treatments in random sequence, each separated by at least 7 days:</p> <ul style="list-style-type: none"> • 4.2/0.7 mg (buprenorphine/naloxone) BEMA Buprenorphine NX film without co-administered liquid • 4.2/0.7 mg (buprenorphine/naloxone) BEMA Buprenorphine NX film with low pH liquid • 4.2/0.7 mg (buprenorphine/naloxone) BEMA Buprenorphine NX film with high pH liquid • 6.3/1.04 mg (buprenorphine/naloxone) BEMA Buprenorphine NX film without co-administered liquid <p>Naltrexone was co-administered approximately 12 hours and 30 minutes prior to and approximately 12 and 24 hours after the single study drug doses.</p> <p>Serial blood samples were collected for determination of buprenorphine and naloxone plasma concentrations predose and at multiple time points postdose. Adverse events, vital signs, and pulse oximetry were assessed at intervals throughout the study. Clinical laboratory assessments and 12 lead ECGs were also performed.</p>
<p>Number of subjects (planned and analyzed): No formal sample size and power calculation were performed for this study. Enrollment of 24 subjects was anticipated to provide 18 completers, a sample size considered sufficient to estimate the PK profiles and parameters; a total of 24 subjects were enrolled.</p>
<p>Diagnosis and main criteria for inclusion: Healthy males or females aged 18 to 55 years, inclusive, with a body mass index ≥ 18 and ≤ 30 kg/m² and weight ≥ 59 kg and ≤ 100 kg were eligible to participate in this study.</p>
<p>Test product, dose and mode of administration, lot number: The following study drug was provided and administered buccally: BEMA Buprenorphine NX film, containing 4.2/0.7 mg (Batch number 3684242) and 6.3/1.04 mg buprenorphine/naloxone (Batch number 3684245).</p>
<p>Duration of treatment: The total duration of participation for each subject was approximately 8 weeks and included a Screening visit, 4 inpatient study periods of approximately 36 hours (2 overnights) each separated by at least 7 days, an outpatient clinic visit following each inpatient study period, and a Follow-up visit 7 to 11 days after the final dose of study drug.</p>
<p>Reference therapy, dose and mode of administration: None</p>
<p>Criteria for evaluation:</p> <p>Pharmacokinetics: Serial blood samples for analysis of buprenorphine, norbuprenorphine, and unconjugated naloxone plasma concentrations were determined from blood samples. The following PK parameters were calculated: C_{max}, T_{max}, AUC_{last}, AUC_{inf}, K_{el} (λ_z), and $t_{1/2}$. No urine PK samples were collected.</p> <p>Safety: Adverse events, vital signs and pulse oximetry were assessed at intervals throughout the study. Clinical laboratory assessments and a 12-lead ECG were also performed at intervals throughout the study.</p>

Statistical methods: This was an open label study in healthy subjects. A total of 24 subjects were enrolled. Pharmacokinetic parameters were estimated from the buprenorphine, norbuprenorphine, and naloxone (unconjugated) plasma concentration profiles using noncompartmental PK definitions from appropriate software. Each profile started at the time of dose administration (time zero) with the concentration at t=0 assumed to be zero. All PK parameters were calculated using the elapsed time in hours from the actual dosing time to the actual sampling time. In addition, the relative bioavailability for D vs. A was calculated as below:

$$F = [\text{Dose (A)} * \text{AUC (D)}] / [\text{Dose (D)} * \text{AUC (A)}]$$

The relative bioavailability, F, was summarized using N, mean, standard deviation, minimum, maximum, and CV%. Note: The reference (Treatment A) for the bioavailability assessment was modified from the clinical study protocol and from the analysis stated in the Statistical Analysis Plan, where the comparison of A vs D was stated.

Study BNX-110

2. SYNOPSIS

Name of Sponsor/Company: BDSI	Individual Study Table Referring to Part of the Dossier Volume: Page:	<i>(For National Authority Use Only)</i>
Name of Finished Product: BEMA [®] Buprenorphine NX		
Name of Active Ingredients: Buprenorphine hydrochloride, Naloxone hydrochloride dihydrate		
Title of Study: BEMA [®] Buprenorphine NX Study BNX-110: A comparison of the rate and extent of buprenorphine absorption from BEMA [®] Buprenorphine NX films and Suboxone tablets and films		
Principal Investigator: Cynthia Zamora, MD		
Study center: The study was conducted at Worldwide Clinical Trials Drug Development Solutions located in the United States (US).		
Publications (reference): None		
Studied period (years): Date first subject enrolled: 22 Oct 2012 Date last subject completed: 17 Dec 2012	Phase of development: 1	
<p>Objectives:</p> <p>Primary:</p> <ul style="list-style-type: none"> Compare the rate and extent of buprenorphine and naloxone absorption following single doses of BEMA Buprenorphine NX films and Suboxone sublingual tablets <p>Secondary:</p> <ul style="list-style-type: none"> Compare the rate and extent of buprenorphine and naloxone absorption following single doses of BEMA Buprenorphine NX films and Suboxone sublingual films Assess the safety and tolerability of BEMA Buprenorphine NX films in healthy subjects receiving concurrent naltrexone by adverse event (AE), vital sign, and pulse oximetry monitoring, electrocardiogram (ECG), and clinical laboratory assessments 		
<p>Methodology: This was an open label, single dose, 3-period, crossover design with up to 81 healthy subjects. Each subject received a single 8/2 mg (buprenorphine/naloxone) Suboxone sublingual tablet, a single 8/2 mg (buprenorphine/naloxone) Suboxone sublingual film, and a single 4.2/0.7 mg (buprenorphine/naloxone) BEMA Buprenorphine NX film in random sequence, each separated by at least 14 days.</p> <p>Naltrexone was co-administered approximately 12 hours and 30 minutes prior to and approximately 12 and 24 hours after the single study drug doses.</p> <p>Serial blood samples were collected for determination of buprenorphine and naloxone plasma concentrations predose and at multiple time points postdose. Adverse events, vital signs, and pulse oximetry were assessed at intervals throughout the study. Clinical laboratory assessments and 12-lead ECGs were also performed.</p>		

<p>Number of subjects (planned and analyzed): It was planned that up to 81 subjects to provide 60 evaluable subjects (suggested sample size of $n = 52$) would be enrolled into this study; a total of 80 subjects were enrolled.</p>
<p>Diagnosis and main criteria for inclusion: Healthy males or females aged 18 to 55 years, inclusive, with a body mass index ≥ 18 and ≤ 30 kg/m² and weight ≥ 59 kg and ≤ 100 kg were eligible to participate in this study.</p>
<p>Test product, dose and mode of administration, lot number: The following study drug was provided: Suboxone sublingual tablet, containing 8/2 mg buprenorphine/naloxone (Lot number 206704-2); Suboxone sublingual film, containing 8/2 mg buprenorphine/naloxone (Lot number C12GW104), and BEMA Buprenorphine NX film, containing 4.2/0.7 mg (buprenorphine/naloxone) (Lot number 855-70-1).</p>
<p>Duration of treatment: The total duration of participation for each subject was approximately 10 weeks and included a Screening visit, 3 inpatient study periods of approximately 36 hours (2 overnights) each separated by at least 14 days, 5 outpatient clinic visits following each inpatient study period, and a Follow-up visit 7 to 11 days after the final dose of study drug (may be combined with the last outpatient clinic visit).</p>
<p>Reference therapy, dose and mode of administration: None</p>
<p>Criteria for evaluation:</p> <p>Pharmacokinetics: Plasma buprenorphine and naloxone were determined from blood samples (6 mL). Pharmacokinetic parameters analyzed in this study included C_{max}, T_{max}, AUC_{last}, AUC_{inf}, K_{el} (λ_z), and $t_{1/2}$. No urine PK samples were collected.</p> <p>Safety: Adverse events, vital signs and pulse oximetry were assessed at intervals throughout the study. Clinical laboratory assessments and a 12-lead ECG were also performed at intervals throughout the study.</p>
<p>Statistical methods: This was an open label study in healthy subjects. A total of 80 subjects were enrolled. Comparison of the log-transformed PK parameters C_{max}, AUC_{last}, and AUC_{inf} for buprenorphine and naloxone across treatments was performed using an analysis of variance (ANOVA) model and the two one-sided t-tests procedure. The ANOVA model included factors for sequence, subject within sequence, treatment, and period. The ratios of the geometric means (Test to Reference) and 90% CIs was reported. The following comparisons were made:</p> <ul style="list-style-type: none"> • BEMA Buprenorphine NX vs. Suboxone tablet (primary analysis) • BEMA Buprenorphine NX vs. Suboxone film (secondary analysis) <p>Bioequivalence was concluded if the 90% CIs for C_{max}, AUC_{last}, and AUC_{inf} were contained within the limits of 80.00 and 125.00% for buprenorphine and naloxone.</p> <p>For norbuprenorphine individual and mean concentrations, individual and mean PK parameters, and geometric means and ratios of means for C_{max}, AUC_{last}, and AUC_{inf} were provided as supportive evidence of comparable therapeutic outcome.</p>

SUMMARY – CONCLUSIONS			
PHARMACOKINETICS RESULTS:			
Mean Plasma Pharmacokinetic Parameters			
Parameter	BEMA Buprenorphine NX film, containing 4.2/0.7 mg buprenorphine/naloxone	Suboxone sublingual tablet, containing 8/2 mg buprenorphine/naloxone	Suboxone sublingual film, containing 8/2 mg buprenorphine/naloxone
Mean (SD) Buprenorphine Pharmacokinetic Parameters			
	N = 65	N = 68	N = 70
T_{max} (h)	2.25 (0.75-4.00) ^a	1.50 (0.50-2.75) ^a	1.75 (0.50-3.05) ^a
C_{max} (ng/mL)	3.41 (1.26)	3.06 (1.28)	4.68 (2.07)
AUC_{last} (ng*h/mL)	25.75 (8.612)	26.98 (10.50)	36.72 (14.79)
AUC_{inf} (ng*h/mL)	27.17 (8.784)	28.67 (10.78)	38.38 (15.23)
AUC_{extrap} (%)	5.58 (3.12)	6.26 (3.98)	4.54 (2.56)
T_{1/2} (h)	27.53 (11.99)	28.67 (12.82)	31.71 (14.51)
T_{last} (h)	86.76 (30.52)	96.68 (31.82)	109.03 (29.94)
C_{last} (h)	0.0437 (0.0403)	0.0502 (0.0707)	0.0367 (0.0149)
Mean (SD) Norbuprenorphine Pharmacokinetic Parameters			
	N = 65	N = 68	N = 70
T_{max} (h)	2.25 (0.50-24.00) ^a	1.25 (0.50-24.00) ^a	1.25 (0.50-24.00) ^a
C_{max} (ng/mL)	0.529 (0.283)	1.27 (0.590)	1.32 (0.794)
AUC_{last} (ng*h/mL)	18.02 (8.608)	36.79 (16.19)	37.99 (17.37)
AUC_{inf} (ng*h/mL)	20.54 (8.658) ^b	39.88 (18.05)	41.64 (20.92)
AUC_{extrap} (%)	12.75 (13.33) ^b	7.20 (7.97)	8.01 (8.24)
T_{1/2} (h)	34.17 (13.38) ^b	32.64 (12.16)	34.77 (16.77)
T_{last} (h)	110.74 (35.94)	127.82 (28.69)	129.96 (24.70)
C_{last} (h)	0.0485 (0.0568)	0.0629 (0.127)	0.0572 (0.0480)
Mean (SD) Naloxone Pharmacokinetic Parameters			
	N = 65	N = 67	N = 69
T_{max} (h)	1.00 (0.50-2.00) ^a	0.75 (0.50-2.00) ^a	0.75 (0.25-1.50) ^a
C_{max} (ng/mL)	134 (69.7)	182 (89.1)	277 (129)
AUC_{last} (ng*h/mL)	333.5 (155.7)	488.3 (235.8)	693.6 (336.8)
AUC_{inf} (ng*h/mL)	340.5 (159.1)	505.8 (247.0)	709.1 (341.7)
AUC_{extrap} (%)	2.05 (1.03)	3.58 (3.01)	2.38 (2.27)
T_{1/2} (h)	2.37 (1.59)	4.93 (3.10)	4.83 (2.92)
T_{last} (h)	12.56 (4.29)	19.28 (5.99)	20.23 (5.78)
C_{last} (h)	2.03 (0.878)	2.53 (2.00)	2.39 (1.65)

a. Median (range) is reported for T_{max}

b. N = 64

Primary analysis: BEMA Buprenorphine NX vs. Suboxone Sublingual Tablet											
Statistical Analysis of the Natural Log-Transformed Systemic Exposure Parameters of Buprenorphine Comparing BEMA Buprenorphine NX Film 4.2/0.7 mg (Treatment C) to Suboxone Sublingual Tablet 8/2 mg (Treatment A)											
Dependent Variable	LS Mean ^a	LS Mean ^a	Geo Mean ^b	Geo Mean ^b	Diff ^c	Ratio(%) ^d (Test/Ref)	90% CI ^e		p value ^f	Power	ANOVA CV%
	Test	Ref	Test	Ref			Lower	Upper			
ln(C _{max})	1.1465	1.0597	3.1472	2.8854	0.0868	109.07	100.49	118.39	0.0817	0.9972	27.23
ln(AUC _{last})	3.1869	3.2346	24.2135	25.3950	-0.0476	95.35	88.92	102.24	0.2582	0.9997	23.07
ln(AUC _{inf})	3.2416	3.2968	25.5736	27.0274	-0.0553	94.62	88.48	101.19	0.1737	0.9999	22.17

a. Least Squares Mean for BEMA Buprenorphine NX Film (Test) and Suboxone Tablet (Ref)
 b. Geometric Mean based on Least Squares Mean
 c. Difference = LS Mean (Test) - LS Mean (Ref)
 d. Ratio(%) = Geometric Mean (Test)/Geometric Mean (Ref)
 e. 90% Confidence Interval
 f. p-value for the difference in the treatment estimates, Significant difference defined *a priori* as $p < 0.05$

The 90% CI for the rate and extent of buprenorphine exposure from BEMA Buprenorphine NX compared to Suboxone tablet, as assessed by ln (C_{max}), ln (AUC_{last}), and ln (AUC_{inf}), ranged from 88 to 118%, all within the accepted 80% to 125% limits. Therefore, buprenorphine exposure from BEMA Buprenorphine NX film is bioequivalent to the reference drug, Suboxone sublingual tablet.

The 90% CI for comparing the rate and extent of naloxone (parent) exposure from BEMA Buprenorphine NX compared to Suboxone tablet, as assessed by ln (C_{max}), ln (AUC_{last}), and ln (AUC_{inf}) ranged from 61 to 81%, and were not within the accepted 80% to 125% limits. Therefore, naloxone (parent) exposure from BEMA Buprenorphine NX film is not bioequivalent to the reference drug, Suboxone sublingual tablet.

Secondary analysis: BEMA Buprenorphine NX vs. Suboxone Sublingual Film

The exposure of both buprenorphine and naloxone (parent) following administration of both the BEMA Buprenorphine NX film and Suboxone sublingual tablet were lower than that following administration of the Suboxone sublingual film.

SAFETY RESULTS:

All of the AEs were mild or moderate in severity and resolved prior to the end of study participation. The most common AEs were nausea, dizziness, headache, and vomiting. Adverse events and changes to vital signs were typical of opioid administration to a healthy volunteer population receiving concurrent naltrexone. There were no deaths or other SAEs. Eight (8) subjects were discontinued from the study due to AEs and 1 subject was lost to follow-up. The naltrexone dose used in this study appears adequate to prevent SAEs associated with the doses of buprenorphine used in this study.

CONCLUSIONS:

The rate and extent of buprenorphine absorption following single doses of BEMA Buprenorphine NX films is bioequivalent to Suboxone sublingual tablets, while naloxone exposure is lower with the BEMA Buprenorphine NX product and not bioequivalent to the Suboxone tablet.

Single dose BEMA Buprenorphine NX administration was generally well tolerated in this healthy population.

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CLINICAL PHARMACOLOGY FILING FORM/CHECKLIST

Office of Clinical Pharmacology				
<i>New Drug Application Filing and Review Form</i>				
<i>General Information About the Submission</i>				
	Information		Information	
NDA/BLA Number	205-637	Proposed Brand Name	Bunavail	
OCP Division (I, II, III, IV, V)	II	Generic Name	buprenorphine and naloxone buccal 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	Buccal film: (b) (4) 2.10/0.348 mg, 4.20/0.696 mg, and 6.30/1.044 mg	
Pharmacometrics Reviewer	N/A	Dosing Regimen		
Date of Submission	July 31, 2013	Route of Administration	Buccal	
Primary Review Goal Date (GRMP)	May 3, 2014	Sponsor	BioDelivery Sciences International	
		Priority Classification	Standard	
PDUFA Due Date	June 7, 2014	Relevant INDs	IND 110267	
<i>Clin. Pharm. and Biopharm. Information</i>				
	"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	6		Studies BNX-101, 102, 103, 106, 107, and 110 (101, 102, and 103 are pilot studies)
multiple dose:				
Patients-				
single dose:				
multiple dose:				
Dose proportionality -				
fasting / non-fasting single dose:	x	1		Study BNX-106
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 -				

CLINICAL PHARMACOLOGY FILING FORM/CHECKLIST

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:	x	4		Studies BNX-101, 102, 103, and 110
Bioequivalence studies -				
traditional design; single / multi dose:	x	1		Study BNX-110
replicate design; single / multi dose:				
Food-drug interaction studies	x	1		Study BNX-107: 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		6		

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 PK studies 106, 107 and 110.
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 tablet (NDA 20-733)
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,	√			

CLINICAL PHARMACOLOGY FILING FORM/CHECKLIST

	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?			√	

CLINICAL PHARMACOLOGY FILING FORM/CHECKLIST

IS THE CLINICAL PHARMACOLOGY SECTION OF THE APPLICATION FILEABLE?

YES

In the initial submission, it was noted that sponsor did not submit the PK raw data (concentrations at each time point for calculation of PK parameters) and dataset with PK parameters for all PK studies. The following comments were conveyed to the sponsor:

1. We are not able to find datasets of PK raw data and PK parameters for your PK studies. For Studies BNX-106, -107 and -110, provide the datasets with all PK raw data for your calculation of PK parameters and the final dataset of PK parameters that you used for your statistical analysis.

2. All the datasets should be ready for analysis using WinNonlin.

Sponsor submitted the requested datasets on September 23, 2013.

This NDA 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.

There are no comments for sponsor at this time.

Reviewing Clinical Pharmacologist

Date

Team Leader/Supervisor

Date

Background:

On 31 July 2013, BioDelivery Sciences International submitted a 505(b)(2) NDA 205637 for Bunavail (buprenorphine and naloxone) buccal films for the maintenance treatment of opioid dependence.

This NDA relies on the Agency's previous findings of safety and effectiveness for Suboxone sublingual tablet (NDA 20-733) and literature. The to-be-marketed formulation was used in pivotal relative bioavailability study (Study BNX-110), dose proportionality study (Study BNX-106), and effect of pH (Study BNX-107).

The overall clinical and clinical pharmacology program consisted the 6 single dose Phase 1 (Studies BNX-101, 102, 103, 106, 107, and 110). Earlier formulations were used in Studies BNX-101 and -102 to select the final commercial formulation. The final formulation was used in pivotal relative bioavailability study (Study BNX-110), dose proportionality study (Study BNX-106), and effect of pH (Study BNX-107). The final formulation but different strength was

CLINICAL PHARMACOLOGY FILING FORM/CHECKLIST

also used in another pilot study (Study BNX-103). This review will focus on Studies BNX-110, -106, and -107. OSI inspection was requested for the pivotal relative BA/BE Study BNX-110.

Sponsor's summary on relative bioavailability of Bunavail in comparison to the list drug, Suboxone tablet, dose proportionality, and effect of pH:

- Bunavail 1 x 4.2/0.696 mg film exhibited equivalent C_{max} and AUC values of buprenorphine in comparison to Suboxone tablet 8/2 mg
- Bunavail 1 x 4.2/0.696 mg film exhibited 30% lower exposure (C_{max} and AUCs) to naloxone in comparison to Suboxone tablet 8/2 mg
- Less than dose proportional increase in buprenorphine exposure with dose over the range of 0.875 mg to 5.25 mg
- Equivalent buprenorphine exposure for 4 x 0.875/0.15 mg and 1 x 3.5/0.6 mg films
- Equivalent normalized buprenorphine and naloxone exposure for 1 x 6.3/1.04 mg and 1 x 4.2/0.696 mg films
- Low pH decreased buprenorphine exposure by 50-60% and decreased naloxone exposure by 72-76%
- High pH decreased buprenorphine exposure by 25% and decreased naloxone exposure by 40%

Please find the filing slides for more details.



NDA 205-637 BUNAVAIL (BEMA Buprenorphine NX, buprenorphine and naloxone buccal film)

Sponsor: BDSI
Filing Meeting
September 18, 2013

1



Drug Product

- Buccal buprenorphine and naloxone (BUP/NX) combination film in a 6:1 ratio of free bases
 - Proposed indication: for the maintenance treatment of opioid dependence.
 - Proposed strengths: (single formulation containing the (b)(4) concentration of buprenorphine and naloxone; dose determined by the film size (surface area))
 - 2.10/0.348 mg
 - 4.20/0.696 mg
 - 6.30/1.044 mg
 - 505(b)(2) NDA
 - Listed Drug: Suboxone sublingual tablet 2/0.5 mg and 8/2 mg (NDA 20-733)

2

Previous Agreements

- Demonstrate equivalent exposure to buprenorphine in comparison to the listed drug, Suboxone tablets
- Lower NLX exposure is acceptable since its main purpose is for abuse deterrence
- Address dose proportionality and dosage form equivalence
- Agreed with sponsor's proposal to evaluate effect of ingested liquids on PK, no food effect study is needed

3

Clin Pharm/Clin Development Program

- Six (6) Single Dose Clin Pharm Studies
 - Two pilot studies using earlier formulations to determine the final formulation: Study BNX-101 and BNX-102
 - Four studies were conducted with the commercial formulation
 - 1 Pivotal relative BA/BE **Study BNX-110**: 4.2/0.696 mg BEMA buprenorphine NX film vs. 8/2 mg Suboxone SL tablet and film
 - Comment: There is no Suboxone tablet strength corresponding to the new 6.3/1.044 mg film. So the pivotal BE study was conducted using the new 4.2/0.696 mg film with the 8/2 mg suboxone tablet
 - 1 dose proportionality and dosage form **Study BNX-106**: Dose range of 0.875/0.145 mg, 3.5/0.58 mg, and 5.25/0.87 mg; 1 x 3.5/0.58 mg film vs. 4 x 0.875/0.145 mg films
 - Comment: Although similar, these are not exactly the final proposed strengths. However, all these strengths have the (b) (4) formulation, the dose is determined only by size of the film. In addition, the range of the strengths are comparable with the final proposed strengths, so this approach is acceptable. Similar justification (i.e. same formulation, different size) was used for approval of the Suboxone film supplement with extra film strengths
 - 1 pH effect and relative BA **Study BNX-107**: no liquid, low pH and high pH liquids on 4.2/0.696 mg; relative BA between 4.2/0.696 mg and 6.3/1.044 mg films
 - Relative BA Study BNX-103: 3.5/0.6 mg BEMA Buprenorphine NX film vs. 8/2 mg Suboxone (not BE)
 - 1 safety study BNX-201

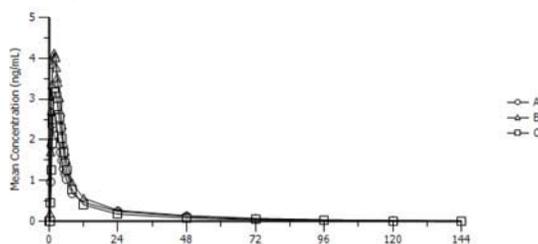
4

Comparative BA Study (BNX-110)

- OL, SD, R, 3-period CV comparative BA study, healthy (n=80), PK, tolerability, safety
 - Trt A: 8/2 mg Suboxone® sublingual tablet
 - Trt B: 8/2 mg Suboxone® sublingual film
 - Trt C: 4.2/0.696 mg BEMA Buprenorphine NX film

5

Study BNX-110 Result – BUP

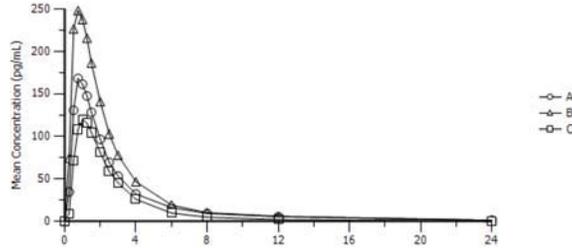


Category ^a	C ^b N=65 Mean (SD)	A ^c N=68 Mean (SD)	B ^d N=70 Mean (SD)
T _{max} (h) ^e	2.25 (0.75-4.00)	1.50 (0.50-2.75)	1.75 (0.50-3.05)
C _{max} (ng/mL)	3.41 (1.26)	3.06 (1.28)	4.68 (2.07)
AUC _{last} (ng ^h /mL)	25.75 (8.612)	26.98 (10.50)	36.72 (14.79)
AUC _{inf} (ng ^h /mL)	27.17 (8.784)	28.67 (10.78)	38.38 (15.23)
AUC _{ex300} (%)	5.58 (3.12)	6.26 (3.98)	4.54 (2.56)
T _{1/2} (h)	27.53 (11.99)	28.67 (12.82)	31.71 (14.51)
T _{1/2β} (h)	86.76 (30.52)	96.68 (31.82)	109.03 (29.94)
C _{1/2β} (h)	0.0437 (0.0403)	0.0502 (0.0707)	0.0367 (0.0149)

Treatment C=Single 4.2/0.7 mg (buprenorphine/naloxone) BEMA Buprenorphine NX film
 Treatment A=Single 8/2 mg (buprenorphine/naloxone) Suboxone sublingual tablet
 Treatment B=Single 8/2 mg (buprenorphine/naloxone) Suboxone sublingual film

6

Study BNX-110 Result – NX



Category ^a	C ^b	A ^c	B ^d
	N=65 Mean (SD)	N=67 Mean (SD)	N=69 Mean (SD)
T _{max} (h) ^e	1.00 (0.50-2.00)	0.75 (0.50-2.00)	0.75 (0.25-1.50)
C _{max} (ng/mL)	134 (69.7)	182 (89.1)	277 (129)
AUC _{last} (ng ^h /mL)	333.5 (155.7)	488.3 (235.8)	693.6 (336.8)
AUC _{inf} (ng ^h /mL)	340.5 (159.1)	505.8 (247.0)	709.1 (341.7)
AUC _{extrap} (%)	2.05 (1.03)	3.58 (3.01)	2.38 (2.27)
T _{1/2} (h)	2.37 (1.59)	4.93 (3.10)	4.83 (2.92)
T _{last} (h)	12.56 (4.29)	19.28 (5.99)	20.23 (5.78)
C _{last} (h)	2.03 (0.878)	2.53 (2.00)	2.39 (1.65)

Treatment C=Single 4.2/0.7 mg (buprenorphine/naloxone) BEMA Buprenorphine NX film
 Treatment A=Single 8/2 mg (buprenorphine/naloxone) Suboxone sublingual tablet
 Treatment B=Single 8/2 mg (buprenorphine/naloxone) Suboxone sublingual film

7

Equivalent Exposure to BUP and Lower NX for BEMA BUP/NX Film in Comparison to Suboxone Tablets

	Geometric Mean ^a		Geometric Mean Ratio ^b	90% CI ^c of the Geometric Mean Ratio	
	4.2/0.7 mg BEMA Buprenorphine NX film (Test)	8/2 mg Suboxone sublingual tablet (Reference)		Lower	Upper
Buprenorphine					
ln(C _{max})	3.1472	2.8854	109.07	100.49	118.39
ln(AUC _{last})	24.2135	25.3950	95.35	88.92	102.24
ln(AUC _{inf})	25.5736	27.0274	94.62	88.48	101.19
Naloxone (Unconjugated)					
ln(C _{max})	117.5700	161.3667	72.86	65.94	80.51
ln(AUC _{last})	298.1396	442.2842	67.41	61.98	73.31
ln(AUC _{inf})	304.3873	458.9519	66.32	61.14	71.94

8

Dose Proportionality Study BNX-106

- OL, SD, R, 4-period CO study, healthy (n=20), dose proportionality, dosage form equivalence, tolerability, safety
 - Trt A: BEMA BUP/NX 1 x 0.875/0.15 mg
 - Trt B: BEMA BUP/NX 1 x 3.5/0.6 mg
 - Trt C: BEMA BUP/NX 1 x 5.25/0.9 mg
 - Trt D: BEMA BUP/NX 4 x 0.875/0.15 mg

9

Study BNX-106 – BUP exposure increase with dose but less than dose proportional

Pharmacokinetic Parameter	Treatment A: 0.875/0.15 mg BEMA Buprenorphine NX film N= 18	Treatment B: 3.5/0.6 mg BEMA Buprenorphine NX film N= 20	Treatment C: 5.25/0.9 mg BEMA Buprenorphine NX film N= 19	Treatment D: 4 x 0.875/0.15 mg BEMA Buprenorphine NX film N=18
Mean (SD)				
C _{max} (ng/mL)	1.15 (0.331)	4.03 (1.79)	5.13 (1.96)	3.89 (1.39)
T _{max} (h) ^a	2.75 (1.50, 4.00)	2.50 (1.75, 4.00)	2.75 (1.50, 4.52)	2.75 (1.50, 4.00)
AUC ₍₀₋₂₄₎ (ng•h/mL)	7.210 (1.520)	24.13 (6.265)	31.94 (9.820)	24.35 (6.974)
AUC _(last) (ng•h/mL)	7.372 (1.604)	24.77 (6.416)	33.28 (9.333)	25.33 (7.064)
AUC _(inf) (ng•h/mL)	8.395 (2.052)	27.47 (6.709)	36.59 (10.38)	28.19 (8.226)
T _{1/2} (h)	10.44 (4.22)	10.17 (2.90)	10.01 (2.69)	10.95 (4.18)
	Slope	90% CI for Slope^a	p value^b	Rho^c
Buprenorphine				
C _{max}	0.8416	(0.7854, 0.8977)	<0.0001	3.8220
AUC ₀₋₂₄	0.8381	(0.7896, 0.8865)	<0.0001	3.9254
AUC _{last}	0.8486	(0.8008, 0.8965)	<0.0001	4.2369
AUC _{inf}	0.8353	(0.7859, 0.8846)	<0.0001	3.8327

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Study BNX-106 – BEMA BUP/NX 4 x 0.875/0.15 mg vs 1 x 3.5/0.6 mg

Pharmacokinetic Parameter	Geometric Mean ^a		Geometric Mean Ratio (%) ^b	90% CI ^c of the Geometric Least Squares Mean Ratio	
	Test	Reference		Lower	Upper
Buprenorphine					
ln(C _{max})	3.6199	3.8119	94.96	84.28	107.00
ln(AUC ₀₋₂₄)	23.2198	23.7312	97.84	88.35	108.36
ln(AUC _{last})	24.0736	24.4860	98.32	88.70	108.97
ln(AUC _{inf})	26.7441	27.2627	98.10	88.27	109.02
Naloxone					
ln(C _{max})	146.4191	150.8675	97.05	80.28	117.33
ln(AUC ₀₋₂₄)	418.4396	439.6260	95.18	79.62	113.78
ln(AUC _{last})	407.4022	430.3851	94.66	79.09	113.30
ln(AUC _{inf})	413.0374	456.9935	90.38	70.53	115.82

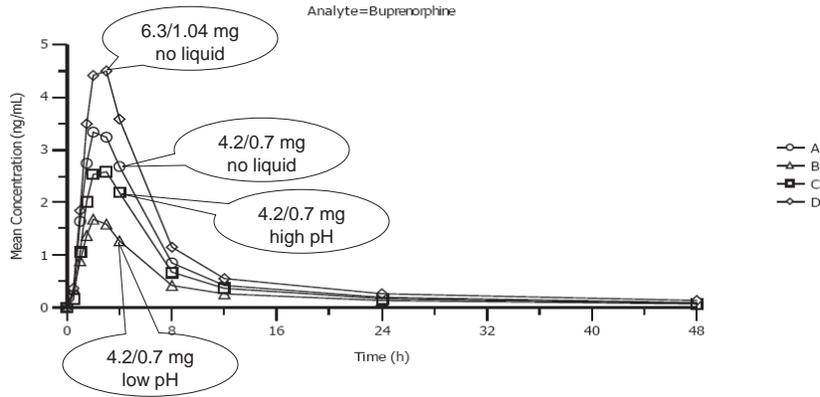
11

pH Effect and Relative BA Study BNX-107

- OL, SD, R, 4-period CO study, healthy (n=24), effect of pH, relative BA, tolerability, safety
 - Trt A: BEMA BUP/NX 1 x 4.2/0.7 mg film with no liquid
 - Trt B: BEMA BUP/NX 1 x 4.2/0.7 mg film with low pH liquid (decaffeinated Coke pH < 4)
 - Trt C: BEMA BUP/NX 1 x 4.2/0.7 mg film with high pH liquid (Essentia water pH > 8)
 - Trt D: BEMA BUP/NX 1 x 6.3/1.04 mg film with no liquid

12

Study BNX-107



13

Study BNX-107

Parameter	Treatment A: 4.2/0.7 mg BEMA Buprenorphine NX Film			Treatment B: 4.2/0.7 mg BEMA Buprenorphine NX Film with Low pH Liquid Co-administered		
	n	Mean	SD	n	Mean	SD
T _{max} (h) ^a	22	2.50 (1.50, 4.00)		21	2.00 (0.50, 3.00)	
C _{max} (ng/mL)	22	3.62	1.15	21	1.84	1.32
AUC _{last} (h*ng/mL)	22	26.13	6.971	21	14.51	7.811
AUC _{inf} (h*ng/mL)	22	28.61	7.666	21	16.73	8.830
T _{1/2} (h)	22	16.98	3.74	21	19.55	4.62
Parameter	Treatment C: 4.2/0.7 mg BEMA Buprenorphine NX Film with High pH Liquid Co-administered			Treatment D: 6.3/1.04 mg BEMA Buprenorphine NX Film		
	n	Mean	SD	n	Mean	SD
T _{max} (h) ^a	22	2.50 (1.50, 4.00)		22	2.50 (1.50, 4.00)	
C _{max} (ng/mL)	22	2.86	1.34	22	4.90	1.73
AUC _{last} (h*ng/mL)	22	21.30	9.362	22	35.06	10.27
AUC _{inf} (h*ng/mL)	22	23.57	10.39	22	38.47	11.43
T _{1/2} (h)	22	16.56	4.97	22	16.45	3.86

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Effects of Co-Administration with Low pH Liquid

Pharmacokinetic Parameter	Geometric Mean ^a		Geometric Mean Ratio (%) ^b	90% CI ^c of the Geometric Least Squares Mean Ratio	
	Test	Reference		Lower	Upper
Buprenorphine					
ln(C _{max})	1.4087	3.4473	40.86	33.32	50.11
ln(AUC _{last})	12.2896	25.6435	47.92	40.06	57.34
ln(AUC _{inf})	14.4627	28.0983	51.47	43.45	60.98
Naloxone					
ln(C _{max})	35.5202	148.2604	23.96	19.08	30.09
ln(AUC _{last})	115.4217	434.3830	26.57	21.05	33.55
ln(AUC _{inf})	125.7583	440.2150	28.57	22.84	35.74

15

Effects of Co-Administration with High pH Liquid

Pharmacokinetic Parameter ^a	Geometric Mean ^a		Geometric Mean Ratio (%) ^b	90% CI ^c of the Geometric Least Squares Mean Ratio	
	Test	Reference		Lower	Upper
Buprenorphine					
ln(C _{max})	2.5570	3.4379	74.38	64.44	85.85
ln(AUC _{last})	19.3104	25.5409	75.61	65.69	87.02
ln(AUC _{inf})	21.3170	27.9548	76.26	66.74	87.13
Naloxone					
ln(C _{max})	87.0494	147.2819	59.10	47.34	73.80
ln(AUC _{last})	251.1613	432.7933	58.03	45.41	74.16
ln(AUC _{inf})	262.4522	439.0725	59.77	47.54	75.16

16

Study BNX-107 – Dose normalized BUP and NX between 6.3/1.04 mg and 4.2/0.7 mg

Dependent Variable	Geometric Mean ^a		Ratio (%) ^b	90% CI ^c		Power	ANOVA
	Test	Reference	(Test/Ref)	Lower	Upper		CV%
Buprenorphine							
ln(C _{max} /Dose)	0.7670	0.8166	93.93	87.89	100.38	0.9996	12.38
ln(AUC _{last} /Dose)	5.5388	6.0919	90.92	85.32	96.89	0.9998	11.84
ln(AUC _{inf} /Dose)	6.0587	6.6565	91.02	85.77	96.60	0.9999	11.07
Naloxone							
ln(C _{max} /Dose)	235.0728	208.3265	112.84	102.21	124.57	0.9784	18.52
ln(AUC _{last} /Dose)	647.0212	612.8846	105.57	96.22	115.83	0.9872	17.35
ln(AUC _{inf} /Dose)	653.1989	620.7849	105.22	95.90	115.45	0.9872	17.35

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Summary

- BEMA BUP/NX film 1 x 4.2/0.7 mg vs. Suboxone tablet 1 x 8/2 mg
 - BUP: equivalent exposure
 - NX (unconjugated): ~ 30% lower C_{max} and AUCs
- Dose proportionality of BEMA BUP/NX film:
 - Slightly less than dose proportional increase in both C_{max} and AUCs values of BUP over the range of 0.875 mg – 5.25 mg
- BEMA BUP/NX 4 x 0.875/0.15 mg vs 1 x 3.5/0.6 mg:
 - BUP exposure BE
 - Equivalent C_{max} and 20-30% lower AUCs of NX in 4 x 0.875/0.15 mg
- BEMA BUP/NX 6.3/1.04 mg vs 4.2/0.7 mg
 - Dose normalized BUP and NX exposure equivalent
- Effects of low and high pH liquids
 - Low pH: 50-60 % ↓ in BUP exposure; 72-76% ↓ in NX exposure
 - High pH: ~ 25 % ↓ in BUP exposure; ~ 40% ↓ in NX exposure
 - Proposed labeling “...Avoid drinking or eating food until the film(s) dissolve”

18

Recommendation

- Filable from Clin Pharm perspective (pending sponsor submitted datasets on time)
- Request OSI inspection on the pivotal relative BA Study BNX-110 on September 11, 2013 and OSI Review requested by May 1, 2014.
- Comments sent to Sponsor:
 - 1. We are not able to find datasets of PK raw data and PK parameters for your studies. For Studies BNX-106, -107 and -110, provide the datasets with all PK raw data for your calculation of PK parameters and the final dataset of PK parameters that you used for your statistical analysis.
 - 2. All the datasets should be ready for analysis using WinNonlin.

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Backup Slides

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Approval of Suboxone film

- 2/0.5 mg and 8/2 mg film was approved based on these three BE studies
 - BE study at 2/0.5 mg between film and tablet (BE)
 - BE study at 8/2 mg between film and tablet (not BE)
 - BE study at 12/3 mg (8+2+2) between film and tablet (BE)

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

/s/

WEI QIU
09/26/2013

YUN XU
09/26/2013