CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

205637Orig1s000

MEDICAL REVIEW(S)

CLINICAL REVIEW

Application Type	NDA
Application Number(s)	205637
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Submit Date(s)	August 7, 2013
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Division / Office	DAAAP/ ODEII
Reviewer Name(s)	Pamela Horn, M.D.
Review Completion Date	
Established Name	buprenorphine and naloxone
(Proposed) Trade Name	Bunavail
Therapeutic Class	opioid agonist and antagonist
Applicant	BDSI
Formulation(s)	Buccal film
Dosing Regimen	once a day
Indication(s)	maintenance treatment of opioid dependence
Intended Population(s)	patients with opioid dependence

Template Version: March 6, 2009

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1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

Based on the review of clinical data and consideration of clinical issues, I recommend approval of the application.

The Combination Rule states that each component of a combination of two or more drugs must make a contribution to the claimed effects of the drug. The claimed effect of naloxone in the referenced application is to produce an aversive reaction under conditions of intravenous misuse. The lowest strength of Bunavail contains less naloxone than the lowest strength of the referenced product and contains naloxone in a different ratio to buprenorphine than the referenced product. Therefore, the Applicant needed to provide evidence that the amount of naloxone that could be extracted from the lowest proposed strength and that the extracted naloxone in combination with a higher ratio of buprenorphine (6:1 in Bunavail compared to 4:1 in the referenced product) would be sufficient to produce an aversive reaction under conditions of intravenous misuse.

The Applicant submitted adequate evidence based on a clinical laboratory study to conclude that the naloxone contained in all proposed Bunavail strengths is high enough and in an adequate ratio to be expected to produce an aversive reaction under conditions of misuse in individuals dependent on full agonist opioids. Therefore, there is adequate support in the application to justify the combination of buprenorphine and naloxone at all proposed strengths.

The Applicant has submitted clinical pharmacokinetic data intended to demonstrate that the 4.2 mg/0.7 mg strength of Bunavail is bioequivalent to the 8 mg/ 2 mg strength of Suboxone tablet, allowing the application to rest on previous findings of efficacy for Suboxone tablet.

The safety data collected in the clinical studies reveals no safety concern unique to this new formulation of buprenorphine and naloxone.

At this writing, a lack of clinical pharmacology data and concerns about data supporting a biowaiver may preclude approval of the lowest proposed strength, intended to correspond with Suboxone tablet dose of 2 mg/0.5 mg. I recommend that the highest three strengths be approved even if the lowest strength is not approved, because the product can be dosed for the maintenance therapy indication being sought at the target dose of 8.4 mg buprenorphine and in the range of 2.1 mg to 12.6 mg recommended in

the product label with combinations of the highest three strengths of 2.1, 4.2, and 6.3 mg buprenorphine.

1.2 Risk Benefit Assessment

The Applicant is relying on a previous Agency finding that the risk/benefit profile for Suboxone tablets is favorable. The clinical safety data from the clinical studies do not alter the risk/benefit profile. The risk/benefit profile for including naloxone in the product at the proposed strengths remains favorable.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

A Risk Evaluation and Mitigation Strategy (REMS) is in place for the referenced product consisting of a Medication Guide, elements to assure safe use, an implementation system, and a timetable for submission of REMS assessments. The goal of the REMS is to mitigate the risks of accidental exposure, misuse, and abuse. The elements to assure safe use are designed to inform patients of the serious risks associated with buprenorphine/naloxone tablets and appropriate conditions of safe use and storage, and to ensure adequate clinical monitoring of patients by healthcare providers.

The review of the Applicant's proposed Risk Evaluation and Evaluation and Mitigation Strategy documents is in progress. See the Division of Risk Management review.

1.4 Recommendations for Postmarket Requirements and Commitments

The Agency is aware of data indicating that buprenorphine may cause QT interval prolongation at therapeutic concentrations. I recommend requiring that the Applicant conduct a study to further evaluate this safety concern as a Postmarketing Requirement.

2 Introduction and Regulatory Background

Buprenorphine is a partial agonist at the μ-opiate receptor. A parenteral formulation of buprenorphine was approved in 1981 for the treatment of pain, two sublingual tablet formulations were approved in 2002 for the treatment of opioid dependence, a sublingual film formulation for opioid dependence and an extended-release transdermal film formulation for pain were approved in 2010, and a sublingual tablet formulation for opioid dependence was approved in 2013.

Because it is a partial agonist, buprenorphine has the potential to precipitate withdrawal symptoms when used by an individual who is dependent on full opioid agonists such as heroin, methadone, or oxycodone.

Buprenorphine was developed as a treatment for opioid dependence because some of its pharmacological properties suggested it could serve as a safer alternative to methadone, a full agonist at the μ-receptor. Like methadone, buprenorphine's activity at the μ-receptor was expected to relieve patients' urge to use illicit opioids, but like methadone, the long duration of action would allow patients to achieve a steady state, without the alternating highs and lows associated with opioid abuse that impair daily functioning. Additionally, at sufficiently high doses, buprenorphine blocks full opioid full agonists from achieving their full effects, further deterring abuse of these substances for buprenorphine-maintained patients.

Due to its partial agonist properties, the euphorigenic effects of buprenorphine are understood to reach a "ceiling" at moderate doses, beyond which increasing doses of the drug do not produce the increased effect that would result from full opioid agonists. This was expected to limit its attractiveness as a drug of abuse relative to full agonists.

This product references the application for Suboxone, NDA 20733 (Reckitt Benckiser), a sublingual tablet formulation of buprenorphine that also contains naloxone. The naloxone is intended to be inactive when the product is used as intended, but to add an additional measure of abuse deterrence by precipitating more severe withdrawal if the product is crushed and injected by an individual dependent on full agonists.

The current Agency approach to evaluating the abuse deterrent properties of drug products was not in place in 2002, when Suboxone tablets were approved, and the evidence supporting the abuse-deterrent properties of Suboxone would not necessarily meet current standards for the approval of an abuse-deterrent drug product.

The recommended target dose for Suboxone tablets is 16/4 mg in a single daily dose. The maintenance dose can range from 4/1 mg to 24/6 mg per day and should be tailored to the individual patient. The recommended dose for treatment of pain is much lower, and for this reason, warnings against prescribing Suboxone for pain are part of the prescribing information.

2.1 Product Information

This product references the Agency's previous finding of efficacy and safety for Suboxone. The Applicant pursued the NDA pathway for approval rather than the ANDA pathway because the formulation is more bioavailable and contains less active ingredient than the reference product.

Four dosage strengths are proposed for marketing. These are

- (b) (4) (corresponds to 2 mg/ 0.5 mg Suboxone tablet)
- 2.1/0.35
- 4.2/0.7 (corresponds to 8 mg/ 2 mg Suboxone tablet)
- 6.3/1.04

The Applicant has submitted clinical pharmacokinetic data intended to demonstrate that the 8 mg/ 2 mg strength of Suboxone is bioequivalent to the 4.2 mg/0.7 mg strength. The Applicant requested biowaivers for the two lower strengths and the highest strength.

2.2 Tables of Currently Available Treatments for Proposed Indications

CURRENTLY AVAILABLE TREATMENTS FOR OPIOID DEPENDENCE			
Generic/Chemical Name	**Trade Name**	**Sponsor**	**Dosage form(s)**
Buprenorphine/naloxone	Suboxone, Zubsolv (also generics)	Reckitt Benckiser, Orexo	• Sublingual tablet • Sublingual film
Buprenorphine	Subutex (also generics)	Reckitt Benckiser	• Sublingual tablet
Methadone HCl	Methadose (also generic)	Mallinckrodt	• Oral solution • Bulk powder • Tablet • Dispersible tab
Methadone HCl	Dolophine (also generic)	Roxane	• Tablet • Oral concentrate • Oral solution
Naltrexone HCl	ReVia (also generics)	Duramed	• Tablet
Naltrexone HCl	Vivitrol	Alkermes	• Injectable suspension

2.3 Availability of Proposed Active Ingredient in the United States

Buprenorphine combined with naloxone is available as Suboxone tablets, Zubsolv tablets, and Suboxone film. There are also generic versions of the tablets available.

2.4 Important Safety Issues With Consideration to Related Drugs

Oral transmucosal buprenorphine-containing products indicated for opioid dependence currently have a REMS. The REMS goals address the most important safety issues associated with these products and are:

- to minimize the risk of
    - accidental overdose, including pediatric exposure

  - misuse and abuse
- inform patients of the serious risks associated with the products, which also include:
  - respiratory depression, especially in combination with CNS depressants
  - liver function abnormalities

2.5 Summary of Presubmission Regulatory Activity Related to Submission

The Division provided the following advice during the development program

- Pre-IND meeting, January 18, 2011
  - The Sponsor stated that the product would have a uniform color to hinder attempts to separate the buprenorphine and naloxone layer and the film would be opaque so that the ink marking would only be visible on one side of the product
  - The Division advised that:
    - the extraction study needs to measure the ratio of buprenorphine to naloxone and the total extracted doses
    - behavioral pharmacology studies may be necessary to show that the product will be aversive under conditions of misuse if any strengths of the product contain less naloxone than what is already known to be aversive
    - lower exposure to naloxone when the product is used as intended is acceptable
    - buprenorphine exposure must be bioequivalent to obviate the need for clinical efficacy or safety data
    - data from a thorough QT study is not required to be submitted with the NDA application
    - because the product the Sponsor plans to reference is not indicated for (b) (4) the Sponsor would need to provide additional data to support an indication for (b) (4)
    - exposure to at least 200 patients for at least 12 weeks is needed to assess the potential for local toxicity of the new formulation
- Type A meeting: February 7, 2012
  - The Division stated that on face, the precipitated withdrawal brief study report appears to be supportive of the naloxone dose in the lowest proposed strength of your product (b) (4))[1] and the proposed 6:1 ratio in the highest strength of your product
- Pre-NDA meeting, May 2, 2013
  - The Division gave the following advice:

[1] At the time of the meeting, the lowest proposed strength was (b) (4) mg. The lowest strength was subsequently lowered to (b) (4) mg.

- It is reasonable to include an adverse event table for Suboxone and other buprenorphine products like the Suboxone label, but you cannot use these tables to make promotional comparative claims
- It may be appropriate to include a conversion scheme in the label if it is supported by strong scientific evidence from Study 201 or pharmacokinetic data
- It is reasonable to mark only one side of the film to indicate the orientation of the film for application
- If you are not seeking any abuse-deterrent language, no extraction studies are required

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

There were no issues with the quality of the submission that affected my ability to complete my review.

3.2 Compliance with Good Clinical Practices

The Applicant reported that the four clinical studies submitted in support of their NDA application were conducted in accordance with Good Clinical Practices

3.3 Financial Disclosures

The Applicant included financial disclosure information for all four clinical studies. There were no reported financial interests.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

Product Design:

The product design differs from currently approved buprenorphine and naloxone combination products because the buprenorphine and naloxone are contained in two separate layers within the film. The product is intended to be placed against the buccal mucosa on the side that has the buprenorphine. The opposite side has the naloxone in it. The Applicant did not include an evaluation of how much buprenorphine and naloxone is delivered if the wrong side of the film is placed on the buccal mucosa. Therefore, as part of the review, the team obtained a placebo film to evaluate the design of the film and estimate how clear it would be to patients that they need to apply the film on the correct side only and how easy it is to determine the correct side for application. The sides can be distinguished by print that is legible from the correct side and appears fainter and backwards on the incorrect side for application. For further details, see the DMEPA review.

Additionally, because the film has two separate layers for buprenorphine and naloxone, it is physically different than the Suboxone tablet in a way that could affect the purpose of naloxone in the product. Suboxone tablet did not provide the comprehensive data described in the Guidance for abuse-deterrent products and the label does not make abuse-deterrent claims about the syringability of the product, for example. However, in the Suboxone tablet label in section 12.2, there is a description of the effect of naloxone stating that "naloxone may deter injection of buprenorphine/naloxone". The proposed label for Bunavail also contains this language. In order for Bunavail to use this same language, there cannot be obvious physical differences in the way the product is made that would allow a user to remove the naloxone from the product. For example, if one were able to simply scrape off the layer of naloxone because it is separate from buprenorphine in this product and that is not the case in the referenced product, then there is a problem with this product that could affect approvability. The Applicant designed the product so that the two layers are visually indistinguishable and it is not possible to scrape off one of the layers to allow for separation of the buprenorphine and naloxone. Because the Applicant is not seeking abuse-deterrence claims in the product labeling beyond what is included in the referenced product labeling, the product design is acceptable for the proposed labeling and a full battery of testing for abuse-deterrence is not required for approval.

Strengths:
The Applicant requested a biowaiver for the lowest two strengths: (b) (4) mg (b) (4), which corresponds to 2 mg/ 0.5 mg Suboxone tablet, and 2.1/0.35 mg. At the writing of this review, it appears likely that the biopharm team will not recommend granting biowaivers for these strengths and the only strengths recommended for approval will be 4.2/0.7, which corresponds to 8 mg/ 2 mg Suboxone tablet and 6.3/1.04. For the maintenance therapy indication being sought, the product label will recommend a target dose of 8.4 mg buprenorphine, which corresponds to the recommended target dose of 16 mg buprenorphine in Suboxone tablets, and the range of recommended therapeutic doses will be 4.2 mg to 12.6 mg buprenorphine, which corresponds to 8 mg to 24 mg of buprenorphine in Suboxone tablets. Because the

Sponsor is not seeking an indication for the [redacted] and the two highest strengths can deliver the recommended dose range for maintenance therapy, it is acceptable from a clinical perspective for the Applicant to market only the two highest strengths without making the two lower strengths available.

The Suboxone tablet label recommends titrating in 2 to 4 mg increments of buprenorphine, which would correspond to [redacted] to 2.1 mg increments of buprenorphine in Bunavail, but with only the two highest strengths available, a clinician would only be able to titrate by 2.1 mg increments (one 4.2 mg film to one 6.3 mg film, or one 6.3 mg film to two 4.2 mg films, for example). By using these two strengths, the clinician could titrate the entire recommended range in 2.1 mg intervals, but not in [redacted] mg intervals. At the maintenance phase, there is no safety or efficacy concern with titrating the daily dose by 2.1 mg rather than [redacted] mg. Clinicians may find it inconvenient not to have the option to prescribe the lower strengths, but it would not affect their ability to treat patients for opioid addiction at the maintenance stage of therapy and it is not grounds for recommending that the application not be approved. Therefore, to allow approval of the two highest strengths without the two lowest strengths, the prescribing information needs to reflect that patients can only be titrated in 2.1 mg increments of buprenorphine in Bunavail and the dosing instructions can otherwise be analogous to the referenced product.

4.2 Clinical Microbiology

N/A

4.3 Preclinical Pharmacology/Toxicology

The proposed drug product did not trigger the need for new preclinical pharmacology or toxicology data.

4.4 Clinical Pharmacology

The Applicant has submitted clinical pharmacokinetic data intended to demonstrate that the 8 mg/ 2 mg strength of Suboxone tablet is bioequivalent to the 4.2 mg/0.7 mg strength. Because 8/2 mg is the highest Suboxone tablet strength, the Applicant did not need to demonstrate bioequivalence for their highest proposed strength. The Clinical Pharmacology review team has made a preliminary finding that the Applicant has demonstrated bioequivalence for buprenorphine.

The Applicant requested a biowaiver for the lowest two strengths proposed for marketing. However, after receiving feedback from the biopharm review team that it does not appear that the data submitted will support a biowaiver for the lowest strength,

the Applicant contended that there is sufficient clinical pharmacology data to support the dose proportionality of the product over a range that would cover the lowest strength.

(b) (4)

[redacted]

For further information about the function of naloxone see section **Error! Reference source not found.**.

See the Clinical Pharmacology review for full results and conclusions.

5 Sources of Clinical Data

5.1 Tables of Studies/Clinical Trials

There were no studies included in the application to inform clinical efficacy.
Studies used to evaluate safety are located in **Error! Reference source not found.**

5.2 Review Strategy

There are two clinical issues addressed in this review.

The first issue is the role of naloxone in Bunavail. Naloxone is a potent opioid antagonist with high affinity for the mu opioid receptor. Injected buprenorphine and naloxone in a 4:1 ratio has been shown to cause opioid withdrawal symptoms in subjects dependent on the full mu opioid agonists, methadone and morphine. In the sublingual formulations, the naloxone is intended to be inactive when the product is used sublingually as intended due to poor sublingual absorption. The Sponsor expects this same principle of poor naloxone absorption to apply to buccal formulations like Bunavail. Naloxone is meant to add an additional measure of abuse deterrence by precipitating more severe withdrawal if the product is crushed and injected by an individual dependent on full agonists than would occur if the product only contained buprenorphine. This added abuse deterrence would not be expected to extend to all opioid-dependent persons. Those with a low level of full mu opioid physical dependence or those whose opioid physical dependence is predominantly to buprenorphine would be expected to be able to abuse buprenorphine/naloxone

combinations by the intravenous or intranasal route without the strong aversive experience noted in the studies. Epidemiologic and anecdotal evidence indeed indicates that some opioid users insufflate or inject buprenorphine/naloxone combination products without experiencing aversive reactions that deter further misuse.

Bunavail, differs from Suboxone tablets in two important ways. First, it contains buprenorphine and naloxone in 6:1 ratio rather than a 4:1 ratio.

Second, the amount of naloxone in Bunavail is less than the naloxone in the corresponding strength of Suboxone sublingual tablets. The lowest dose of Suboxone contains 0.5 mg of naloxone and the lowest dose of Bunavail contains (b) (4) mg naloxone.

Each active ingredient in a combination product must provide a therapeutic benefit. In the case of Suboxone, the review team found that naloxone had a benefit for the approved indication of maintenance treatment of opioid dependence, because it could decrease the likelihood that people dependent on full opioid agonists would use it by the intravenous route, which would be a misuse of the product. The Applicant cannot rely on the previous Agency finding that naloxone will contribute to discouraging misuse, because the dose available for extraction and injection from the Applicant's product is lower than from the reference product, is in a different ratio to buprenorphine than the reference product, and may not be large enough or in a suitable ratio to cause an aversive reaction even in those dependent on full agonists. Therefore, the Applicant needed to show that this smaller dose of naloxone would be expected to produce an aversive reaction when injected.

To determine whether the ratio of naloxone and dose of naloxone in Bunavail is acceptable, the Sponsor submitted Study LCR-04-01-101, a double-blind, placebo-controlled, four-treatment, four-period crossover study to determine the lowest dose of naloxone that will produce a withdrawal response when administered with buprenorphine in opioid-dependent subjects. I reviewed this study report under Section 5.3 Discussion of Individual Studies/Clinical Trials

The second issue is the safety of the drug product. The Applicant is relying on the previous finding of safety for the drug substance. Because the exposure to buprenorphine from the new formulation falls into the range demonstrated to have an acceptable risk-benefit profile in the referenced NDA and the exposure to naloxone is lower than in the referenced NDA, this is appropriate, and extensive evaluation of systemic safety was not required. This review will evaluate any evidence of local adverse reactions and medication administration errors for this new formulation and new buccal route of administration by focusing on the safety data from one open-label safety study, BNX-201. A summary of BNX-201follows the discussion of Study LCAR-04-01-101 in this section and the study results are discussed in section 7 of the document.

Deleted sections

I deleted sections 2.6, 4.4.1, 4.4.2, 4.4.3, 6.1.1-10, 7.2.2-6, 7.3.4, 7.4.5, 7.4.6, 7.5, 7.6.1, 7.6.3, 7.6.4, 8, 9.1, and 9.3 because they were not relevant to this application.

5.3 Discussion of Individual Studies/Clinical Trials

Study LCR-04-01-101
Title: A double-blind, placebo-controlled, four-treatment, four-period crossover study to determine the lowest dose of naloxone that will produce a withdrawal response when administered with buprenorphine in opioid-dependent subjects

Objectives:

- To determine the minimum effective dose of naloxone that will produce a withdrawal response when administered with a 0.75 mg dose of buprenorphine in opioid-dependent subjects
- To determine whether administration of a 0.75 mg dose of buprenorphine without naloxone will produce a withdrawal response in opioid-dependent subjects

Design: Subjects with chronic moderate-to-severe non-cancer pain requiring at least 100 mg per day of oral morphine for at least 3 months were to continue to receive opioid at the same dose on the same schedule and receive four test articles intended to induce withdrawal symptoms consecutively in random order. Withdrawal in response to the test articles was to be measured using the Clinical Opiate Withdrawal Scale, physiologic, and subject rated-measurements. The primary analysis comparing test articles was to be performed on the COWS scores.

There were to be three days between test articles to minimize any carryover effects.

Reviewer Comment: A dose of 100 mg of oral morphine per day is likely to be lower than the daily equivalent of illicit or prescription opioid most patients with an opioid use disorder will be taking. Therefore, the production of withdrawal symptoms in this population should be generalizable to the target population in terms of level of physical dependence.

Three days is likely to be sufficient to minimize carryover effects based on the PK profile of parenteral buprenorphine and naloxone.

Population:
To be eligible, potential subjects were to meet the following entry criteria:

1. Had chronic moderate to severe non-cancer pain that has been treated with opioid analgesics for at least 3 months (with stabilized pain control and stabilized dose, as judged by the Investigator, for 28 days prior to enrollment).
2. Received an opioid dose >100 mg morphine equivalents per day.
3. Displayed signs and symptoms of withdrawal [i.e., Clinical Opioid Withdrawal Scale (COWS) score ≥5] following naloxone administration during the Naloxone Challenge.
4. Was at least 21 years of age and a male or non-pregnant, non-lactating female.
5. If female, using adequate contraception

Potential subjects were to be excluded if they met any of the following criteria:

1. Clinically significant abnormal liver test results
2. Positive screen for alcohol or non-opioids
3. History of substance use disorder within the past five years
4. BMI over 45 kg/m^2

Reviewer Comment: It is appropriate to enrich the study population with subjects who are sensitive to parental administration of naloxone prior to administering the test articles because individual response to naloxone challenge varies. The naloxone challenge differs from the test articles, because naloxone is given alone in the naloxone challenge and is given with buprenorphine at the subsequent study visits.

Study Drug Administration

- Screening: Patients were to have received 0.05 mg IV naloxone every 5 minutes until they had a COWS score of at least 5 or had received 0.2 mg naloxone as part of the screening and eligibility evaluation
- Study Visits: Subjects were to have received a single IV bolus dose of each of the four following test articles in random order
    - Buprenorphine 0.75 mg
    - Buprenorphine 0.75 mg + naloxone 0.1 mg
    - Buprenorphine 0.75 mg + naloxone 0.2 mg
    - Placebo

Management of withdrawal: Moderate withdrawal symptoms (COWS score of >13) were to be medically managed as follows:

- Midazolam (Versed®), 1-2 mg IV every 2-3 minutes (no upper limit) for anxiety and restlessness.
- Hydromorphone, 1-2 mg IV every 5 minutes for opioid replacement

Pharmacodynamic assessments:

- COWS
- Drug Effect Questionnaire
- Opioid Agonist Scale

- Physiological Measures
    - Pupil diameter
    - Heart rate
    - Blood pressure
    - Respiratory rate
    - Oxygen saturation

Analysis

- No planned formal testing
- Summary statistics of all PD assessments

Planned sample size was 12 based on previous publications

Results
Fifteen subjects enrolled and completed the study.

Protocol Violations: One subject had been admitted to a substance abuse clinic 18 months prior to screening. This subject (ID 1013) received rescue hydromorphone for all test articles, including placebo and was taking 1050 mg of morphine equivalents per day prior to entering the study. Due to the pattern of rescue medication use after receiving placebo, this subject's patient reported outcome measures may be unreliable. If this subject was motivated to receive rescue medication for the positive subjective effects of the opioid and benzodiazepine rather than to relieve opioid withdrawal symptoms, I would expect the patient-reported outcome measures and items to be falsely elevated for all test articles for this subject, which would be expected to obscure differences in effect between test articles in the group means. The COWS has subjective items that contribute to the score. The highest COWS score recorded for this subject was 23 and occurred after receiving placebo. Of note, placebo was the only test article where the subject waited until the first planned assessment at 15 minutes after test article administration. After all other test articles, the subject required rescue prior to the first planned assessment based on COWS scores, indicating that the subject may well have been experiencing true withdrawal. This pattern is not evident simply by looking at maximum COWS scores. I conducted a sensitivity analysis of change in COWS scores with this subject's scores removed and found that the differences between groups were larger.

Baseline characteristics:
Subjects ranged in age from 24 to 63 years old with a mean age of 50 and were 40% female. The 2012 NSDUH survey results indicate that illicit substance abuse and dependence past year prevalence peaks around age 18[2]. In terms of age, the population studied is much more representative of a chronic pain population than an opioid addicted population. Based on what is known about the pharmacokinetics and pharmacodynamics of buprenorphine and naloxone, the age differences in the two

[2] Table 5.3A, 2012 NSDUH report, www.samhsa.gov/data

populations would not be expected to result in different responses to the test articles and the results should still be relevant. According to figure 7.6 of the NSDUH report, substance abuse and dependence is around twice as common in males than females. Therefore, having more males than females in the study population is not problematic.

Baseline opioid use is summarized in the table below.

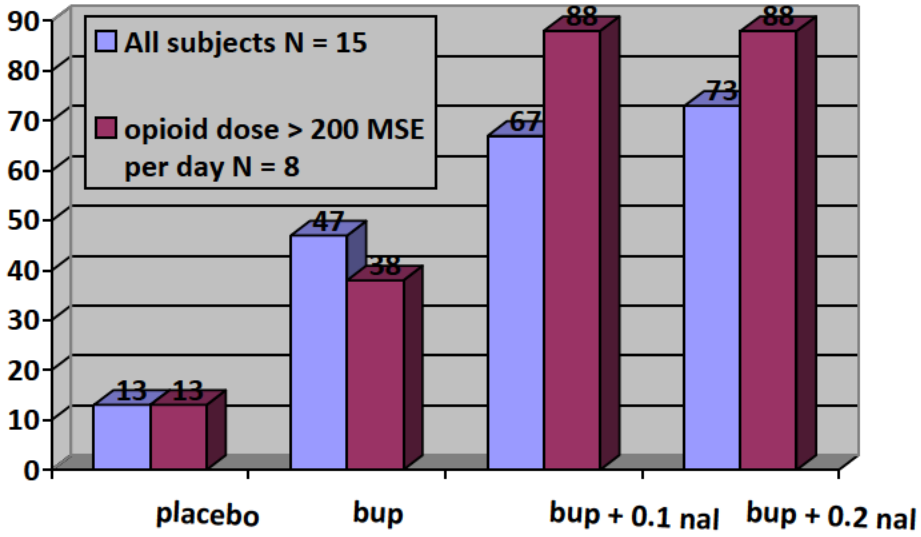
Subject ID	Opioid regimen	Total Daily Morphine Equivalent Dose (mg)
1002	Morphine and oxycodone	120
1003	Oxycodone	120
1005	Morphine and oxycodone	225
1006	Morphine and hydrocodone	90
1007	Fentanyl and oxycodone	587
1009	Morphine and oxycodone	100
1012	Oxycodone	300
1013	Methadone	1050
1015	Methadone	180
1016	Methadone	1260
1017	Morphine	420
1020	Morphine	520
1021	Morphine and hydrocodone	150
1023	Fentanyl and oxycodone	450
1024	Morphine	180

Source: CM dataset and CSR Table 6

Around half of the study subjects were taking morphine, half were taking oxycodone, one fifth were taking methadone, and around one in ten were taking fentanyl and hydrocodone. All are full agonist opioids and buprenorphine and naloxone would be expected to displace these opioids from the mu receptor and lead to withdrawal symptoms. The total daily dose ranged from 90 mg to 1260 mg in morphine equivalents and is a reasonable representation of the doses that people in the community that would be interested in injecting the product would be expected to be taking.

Rescue Medication Use: The percent of subjects requiring rescue varied widely between test articles. Rescue use was most frequent when subjects received 0.2 mg naloxone, followed by 0.1 mg naloxone, buprenorphine alone, and placebo in all subjects as well as in the subjects with the highest daily morphine equivalent dose. According to Table 14.3.4 of the study report, rescue by test article was as follows:

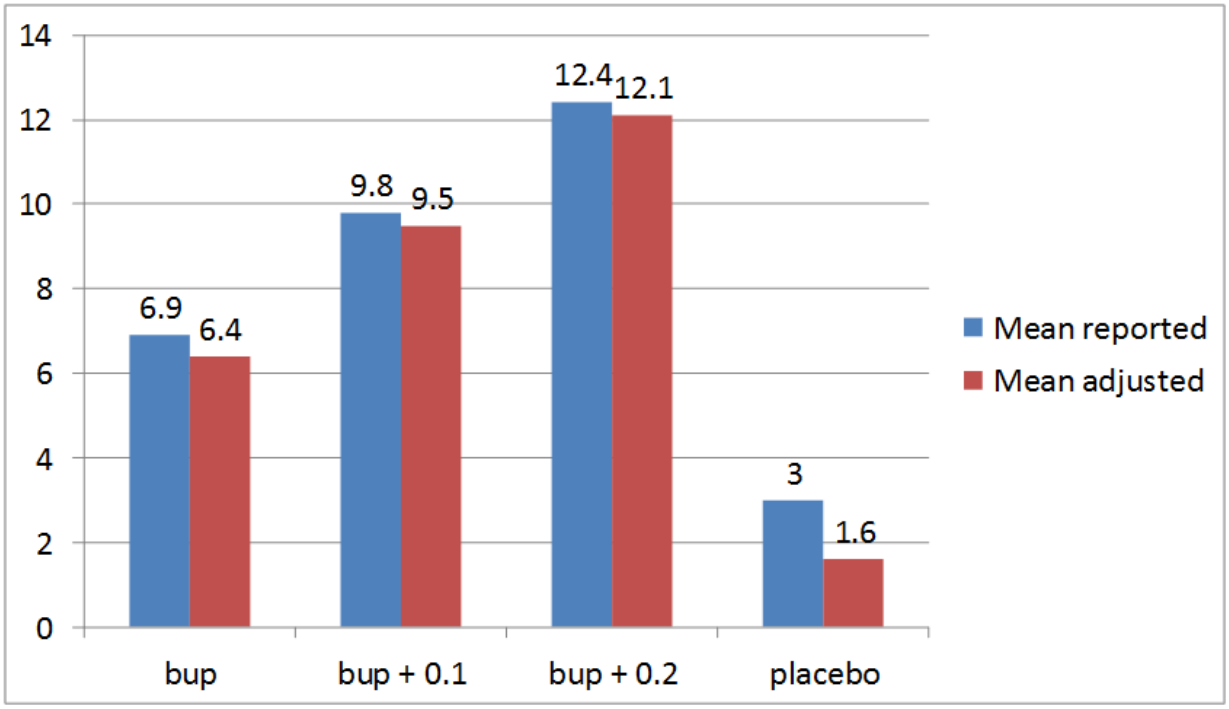
Figure 1 Percentage of Subjects Requiring Rescue with Hydromorphone



Based on need for rescue medication (COWS > 13), buprenorphine alone and with both doses of naloxone caused withdrawal in a meaningful number of subjects. There is also a clear increase in the proportion of subjects requiring rescue when as little as 0.1 mg naloxone was administered. Doubling the naloxone dose to 0.2 mg did not result in as large a change in the number of subjects requiring rescue as did adding on the 0.1 mg naloxone to buprenorphine alone. This supports the effectiveness of a 0.1 mg dose of naloxone in producing meaningful withdrawal symptoms.

The following chart summarizes the mean change from baseline to COWS prior to rescue or COWS 15 minutes after rescue if there was no rescue in the first 15 minutes after test article administration. A large proportion of the COWS scores collected occurred prior to the first scheduled COWS assessment. The mean reported includes all 15 subjects and the mean adjusted is without subject 1013, whose data is unreliable in my assessment.

Figure 2 COWS mean change from baseline to first COWS assessment by test article



Source: Reviewer-generated from Table 7 and Listing 16.2.8.2

There is a trend toward larger changes in COWS scores with increasing amounts of naloxone administered. This trend is consistent with the rescue medication use and indicates that both the 0.1 mg and 0.2 mg of naloxone are contributing to the withdrawal signs and symptoms that subjects experienced. There is around 3 points difference on the mean COWS change from baseline between buprenorphine alone and buprenorphine with naloxone 0.1 mg. It also appears that there is a dose-response relationship in change in COWS scores between the 0.1 mg naloxone dose and 0.2 mg naloxone dose.

The authors had no planned formal statistical analyses. They calculated 95% confidence intervals for mean differences between each of the groups and reported p-values. P-values were less than 0.001 for all comparisons between groups. The confidence intervals for mean differences between the 0.1 mg naloxone group and all other groups did not cross zero, indicating that the differences on the COWS between naloxone 0.1 mg and the other test articles are statistically significant. The analysis does not appear to be adjusted for multiple comparisons.

Table 1 Mean Difference in COWS Scores Between Groups

	Difference in Means	**95% CI**	**P-value**

Placebo vs. nal 0.1	-6.932	(-7.990, -5.875)	<0.001
Bup vs. nal 0.1	-2.999	(-4.057, -1.941)	<0.001
Nal 0.1 vs. nal 0.2	-3.735	(-4.849, -2.621)	<0.001

Source: Table 14.2.1.2.c

The study authors also reported change in pupil diameter, blood pressure, heart rate, and oxygen saturation, drug effect questionnaire, and opioid agonist scale between baseline and 15 minutes after test article administration. However, because these assessments were not done prior to rescue, differences from baseline and between test articles were likely obscured by rescue medication. Even with rescue medication, changes in pupil diameter, heart rate, and blood pressure were greatest in the naloxone conditions, as shown below.

Table 2 Mean change from baseline to 15 min assessment on physiologic measures by test article

	Placebo	Bup	0.1 mg nal	0.2 mg nal
Pupil diameter (mm)	0.1	0.6	0.9	1.3
SBP (mm Hg)	0.5	0.7	6.8	4.3
DBP (mm Hg)	2.6	0.8	7.6	8.6
HR (bpm)	2.9	1.8	3.4	10.9

Source: CSR Table 9

The drug effects questionnaire and opioid agonist scale were not done prior to rescue and the differences between test articles were also likely somewhat obscured. However, changes from baseline in bad effect and feeling sick on the drug effects questionnaire were still higher in all active test articles than placebo.

There were no deaths, SAEs, or severe AEs in the study. Adverse events that occurred in at least two subjects in a test article condition are summarized below.

Table 3 AEs that occurred in more than one subject in any test article condition by PT

SOC	PT	Placebo	Bup	0.1 mg nal	0.2 mg nal
General disorders	Drug withdrawal syndrome	20%	13%	47%	67%
	Fatigue	0%	13%	7%	7%
Nervous System Disorders	Somnolence	20%	20%	7%	13%
	Headache	20%	0%	20%	13%
	Dizziness	13%	20%	0%	13%
Psychiatric	Withdrawal	0%	27%	13%	20%

Disorders	syndrome				
Gastrointestinal Disorders	Nausea	0%	13%	0%	27%
Musculoskeletal and Connective Tissue Disorders	Back pain	0%	0%	7%	13%
	Myalgia	0%	0%	13%	0%

Source: CSR Table 14.3.1.2

Drug withdrawal syndrome preferred terms were reported most frequently in the naloxone test articles, which aligns with the results discussed above.

Reviewer Conclusions
The most reliable data comes from the COWS scores, because the COWS was administered prior to rescue, and the rescue medication use. According to the clinical experience with the COWS instrument and the available literature, scores of over 13 are likely to be meaningful to clinicians who use the instrument in a clinical setting and to correlate with moderate withdrawal severity. The results in change from baseline in COWS scores support the effectiveness of buprenorphine and buprenorphine with naloxone at the two doses studied in causing clinically significant withdrawal in a substantial proportion of subjects. Naloxone appeared to worsen withdrawal symptoms in a dose-dependent fashion above what was observed with buprenorphine alone. The results on the COWS were supported by the trends observed in the physiological measures, even though many of the physiological measures were taken after rescue medication administration.

The COWS results are well-supported by the pattern of rescue medication use, which was administered based on COWS scores above 13 and indicated that subjects were experiencing withdrawal in a pattern consistent with the overall COWS data.

The subjects were on clinically relevant opioid maintenance doses in this study and the results can be reasonably be generalized to those with a physical dependence to full opioid agonists who would attempt to inject this product. Buprenorphine and naloxone in a ratio of 7.5 to 1 at a naloxone dose of 0.1 mg resulted in more withdrawal than buprenorphine alone, indicating that this ratio of buprenorphine to naloxone and this amount of naloxone is sufficient to increase the aversive effects of the product when injected. The amount of naloxone in the lowest dose of the product is (b) (4), which is more than 0.1 mg and it is combined with (b) (4) mg buprenorphine in a 6:1 ratio, which is a lower ratio than the 7.5:1 ratio in the study.

Therefore, the study results support including naloxone at the dose and ratio contained in the product.

Study BNX-201

Objectives:

- To assess the safety and tolerability of BEMA Buprenorphine NX administered once daily for 12 weeks to opioid-dependent subjects stabilized on Suboxone tablets or films
- To determine the most appropriate conversion ratio for opioid-dependent subjects treated with Suboxone tablets or films to BEMA Buprenorphine NX

Design:

- Open-label study in subjects that had been maintained on 8-32 mg Suboxone tablets or film for at least 30 days
- Subjects were to be evaluated and excluded for abnormalities of the buccal mucosa that could affect drug absorption
- Subjects were to be screened, have a baseline visit on the day after discontinuing Suboxone and take the corresponding dose of BEMA buprenorphine for 12 weeks
- The following conversion table was to be used

Table 4 BNX-201 Conversion from Suboxone to Bunavail

Current Suboxone tablet or film dose (buprenorphine/naloxone)	Initial BEMA Buprenorphine NX dose (size) (buprenorphine/naloxone)
8/2 mg	(b) (4)
12/3 mg	
16/4 mg	
24/6 mg	
32/8 mg	

Source: CSR Table 5

- Subjects were to be returned to Suboxone treatment at the end of the 12-week period and have one follow-up visit
- Subjects were to be eligible for dose adjustments in accordance with the practice guidelines outlined in SAMHSA's TIP40.

Assessments

- Oral mucosa exam
  - Physician investigators were to be trained by dentist to perform exam and evaluated for proficiency in accordance with the Council of Interstate Testing Agencies for US dental licensure
- Vital signs
- AEs
- Suicidality scale
- Concomitant medications
- Clinical Opiate Withdrawal Scale (COWS)

- Pulse oximetry
- Clinical labs
- Urine toxicology
- Urine buprenorphine and norbuprenorphine
- Pregnancy testing
- ECG

Table 5 BNX-201 Schedule of Assessments

Study Period	Screening	Baseline	Open Label Treatment Period							Follow-up
Study Visits – Days	-40 to -1	0/1	7	14	28	42	56	70	84/ET	7 to 11 days after the Day 84 visit
Informed consent	X									
Eligibility criteria	X	X								
Medical and substance abuse history	X	X[a]								
Oral examination	X	X	X	X	X		X		X	
Physical examination[b]	X	X							X	
Vital signs[c]	X	X	X	X	X	X	X	X	X	X
Pulse oximetry[d]	X	X								
Electrocardiogram	X	X							X	
Urine toxicology screen	X	X	X	X	X	X	X	X	X	
Urine buprenorphine testing	X	X	X	X	X	X	X	X	X	
Urine pregnancy test[e]	X	X			X		X		X	
Virus serology	X									
Clinical laboratory tests	X[f]	X			X		X		X	
Clinical opiate withdrawal scale (COWS)		X[g]								
Suicidality assessment		X	X						X	
Global assessments		X							X[h]	
Opioid medication preference questionnaire										X
Study drug dispensing/return		X	X	X	X	X	X	X	X	
Adverse events		X	X	X	X	X	X	X	X	
Concomitant medications	X	X	X	X	X	X	X	X	X[i]	

a. Medical history only
b. Height and weight measured at Screening visit only; brief exam (general appearance, abdomen, lungs, and cardiovascular system) if ≤7 days from Screening
c. Vital signs included seated blood pressure, heart rate, respiratory rate, and oral temperature.
d. Pulse oximetry was measured predose and 3 hours postdose (all subjects) and measured continuously from predose to 4 hours postdose (at a single study site, in a subset of approximately 50 subjects.
e Females of child-bearing potential only
f. Prothrombin time assessed at Screening only
g. COWS: predose and at 3 hours postdose
h. Early Termination: Global assessments were not required
i. Subjects were dispensed an adequate supply (approximately 1-week) of their prior Suboxone medication.

Source: CSR Table 2

Study Drug Administration

- The initial dose of study drug was to be administered by study personnel
- The following instructions were to be given to subjects for subsequent study drug administration
    - Use your tongue to wet the inside of your cheek or rinse your mouth with water to moisten the area where you will place BEMA Buprenorphine NX.
    - Immediately prior to use, open the BEMA Buprenorphine NX package using scissors to cut along the printed dotted lines.
    - Hold the BEMA Buprenorphine NX film in place on a clean, dry finger with the ink marked side facing up.
    - Carefully place the BEMA Buprenorphine NX film inside your mouth with the ink marked side against the inside of your moistened cheek.

    - With your finger, press the BEMA Buprenorphine NX film against your cheek and hold it there for 5 seconds.
    - Take your finger away from the BEMA Buprenorphine NX film. It will stick to the inside of your cheek. Leave the film in place until it dissolves.
    - Avoid touching or moving the film while it dissolves.
    - Do not drink any liquids or eat any food until after the film dissolves.
    - Do not cut or tear the BEMA Buprenorphine NX film
    - Do not chew or swallow the BEMA Buprenorphine NX film.
- When 2 films were required, 1 film was to be applied to the inside of each cheek. For other multiple film doses, no more than 2 films were to be applied on a single side

Reviewer Comment
The planned population and design was appropriate to assess safety and tolerability of a new formulation. The planned conversion table, procedures for conversion and dose adjustment, and assessments for adverse events and withdrawal symptoms and signs are adequate to evaluate the chosen conversion ratio from Suboxone to Bunavail. The conversion table was based on an assumption about the doses of Bunavail that would correspond to various doses of Bunavail. Because these assumptions turned out to be incorrect, and the Bunavail doses studied were too low, the study results could not be used to inform conversion from Suboxone to Bunavail in labeling and the Applicant subsequently increased the dose strengths proposed for marketing. However, because the different strengths are (b) (4), the only difference between the studied doses and the to-be-marketed strengths is the size. Therefore, this study, as designed, could still provide relevant information about the local tolerability of the Bunavail film in various sizes.

6 Review of Efficacy

Efficacy Summary

The Applicant is relying on the previous finding of efficacy for Suboxone (NDA 20733) and has provided a bridge between Suboxone and Bunavail based on clinical pharmacology data.

6.1 Indication

The proposed indication is for the maintenance treatment of opioid dependence. The Applicant did not submit clinical studies that evaluated the efficacy and safety of the product (b) (4)

7 Review of Safety

Safety Summary

There were no adverse events identified in the development program that indicate a unique safety issue with the proposed formulation. Safety was evaluated in one 12-week open-label safety study that was designed to identify formulation-specific oral mucosal toxicity through serial oral examinations and safety data was also collected in four single-dose clinical pharmacology studies that tested the to-be-marketed formulation.

7.1 Methods

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

Study BNX-201 was an open label safety study. The study enrolled a population of subjects who were taking Suboxone tablets or film for at least 30 days prior to study entry for the treatment of opioid addiction.

7.1.2 Categorization of Adverse Events

Adverse events were categorized using MedDRA version 12.0.

7.1.3 Pooling of Data Across Studies/Clinical Trials to Estimate and Compare Incidence

Study BNX-201 was conducted to assess product safety.

There were also four clinical pharmacology studies (Studies BNX-103, BNX-106, BNX-107, and BNX-110) in the development program that used the to-be-marketed

(b) (4)

formulation and collected safety data. These were all single-dose studies with as many as 4 single doses given to an individual subject in a crossover design.

7.2 Adequacy of Safety Assessments

7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

There were 249 subjects exposed to Bunavail and evaluated for local tolerability.

Studying a population of subjects with opioid addiction taking buprenorphine/naloxone was appropriate for study BNX-201. The mean age of subjects was 39 with a range of 20 to 62. Males comprised 66% of the study population. These demographics are adequately representative of the general target population for the product.

The mean dose of Suboxone at study entry was 16 mg per day with a range of 8 to 32 mg per day. This is representative of the general target population.

Subjects were converted from Suboxone tablets and film to Bunavail using a buprenorphine dose conversion factor (b) (4)

The table below summarizes the dose adjustments made during the study.

Table 6 Study BNX-201 Dose Adjustments

Starting Dose	Final Dose						
	A n (%)	B n (%)	C n (%)	D n (%)	E n (%)	F n (%)	G n (%)
A (n=48)	**29 (60.4)**	8 (16.7)	9 (18.8)	2 (4.2)	0	0	
B (n=40)	0	**27 (67.5)**	10 (25.0)	3 (7.5)	0	0	
C (n=110)	0	0	**68 (61.8)**	32 (29.1)	3 (2.7)	5 (4.5)	2 (1.8)
D (n=43)	0	1 (2.3)	0	**26 (60.5)**	6 (14.0)	10 (23.3)	
E (n=8)	0	0	0	0	**8 (100.0)**	0	
F (n=0)	0	0	0	0	0	0	
Total subjects	29	36	87	63	17	15	2
# subjects with dose adjustments	0	9	19	37	9	15	2
Average starting dose=6.9/1.2 mg	Average final dose=8.0/1.4 mg						

The initial conversion dose is bolded.
a. Source Data: Table 14.3.5.4
A=BNX (b) (4)
B=BNX
C=BNX
D=BNX
E=BNX
F=BNX
G=BNX
Source: BNX-201 Table 18

Only one subject's dose went down in the study and roughly one third of subjects had a dose increase over the study. Roughly two thirds of all subjects completed the study at the same Bunavail dose that they started on and all subjects that entered the study on Suboxone 32/8 mg ended the study on the 14/2.3 mg dose of Bunavail.

(b) (4)

Based on the results of BNX-201 and the PK studies, the conversion scheme used in this study is not recommended.

The doses studied and administered are adequately representative of the general target population to assess local tolerability of the formulation.

7.3 Major Safety Results

7.3.1 Deaths

There were no deaths in the development program.

7.3.2 Nonfatal Serious Adverse Events

Two subjects had serious adverse events in Study BNX-201. One subject was diagnosed with right hallux osteomyelitis and one subject had suicidal ideation. The subject with osteomyelitis was hospitalized and discontinued the study. The subject with suicidal ideation also discontinued the study. Neither event is likely to be associated with the formulation. Both of these subjects were taking Suboxone tablet at study entry and a change in buprenorphine/naloxone formulation would not be expected to have any impact on the development of these adverse events.

There were no SAEs in the clinical pharmacology studies.

7.3.3 Dropouts and/or Discontinuations

The table below summarizes subject disposition from Study BNX-201:

Table 7 BNX-201 Subject Disposition

Subject Disposition
All Subjects

	Total (N=249)
Safety Population	249 (100.0%)
Completed Study	197 (79.1%)
Discontinued	52 (20.9%)
Reasons for Discontinuation	
Adverse event	6 (2.4%)
Subject experiencing withdrawal symptoms	5 (2.0%)
Withdrew consent	16 (6.4%)
Lost to Follow-up	7 (2.8%)
Study terminated by sponsor	0
Other	18 (7.2%)

Source: CSR Table 14.1.1

Adverse events that led to discontinuation were the two SAEs discussed above, headache, two positive urine toxicology screens and an oral ulcer in a subject whose urine was negative for buprenorphine. Of subjects who withdrew consent, 8 cited personal problems, transportation, or job issues, one said it was ineffective for tooth pain, one was having irritability and lack of concentration, one wanted to go back on Suboxone, one didn't want to be in the study anymore, two relapsed to opioid use, one didn't want to disclose information about losing a dose to staff and withdrew, and one had difficulty applying the film because of orthodontic appliances. Of subjects who were categorized as "other", ten were not complying with the medication or study visit schedule, one had uncontrolled diabetes, one had a pregnancy, one moved out of the area, two were on disallowed medications, and one had an elevated baseline creatinine.

This was an open-label study with no comparator group. The proportion of dropouts and reasons for dropout are consistent with observed treatment retention rates and barriers to retention in treatment for patients with opioid addiction in clinical practice and the results do not indicate a safety issue for this product.

In the clinical pharmacology studies, there were discontinuations for vomiting, blood pressure that was out of range, dizziness, and presyncope. These events are consistent with what would be expected in a healthy volunteer population receiving buprenorphine/naloxone and naltrexone block.

7.3.5 Submission Specific Primary Safety Concerns

Study BNX-201 included oral exams to assess local toxicity of the formulation. Three subjects had mild mucosal redness during the study, which resolved without discontinuing treatment. Two subjects were observed to have swelling or raised lesions, which also resolved without discontinuing treatment. There was one subject with a mild mouth ulceration at the Day 7 visit. However, no buprenorphine or norbuprenorphine was detected in the subject's urine on Day 7, indicating that the subject was not taking the product. Therefore, the study did not reveal any local toxicity concerns with the proposed formulation.

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

Study BNX-201 was an open-label study with no comparator. Adverse event findings are likely to be subject to subject and investigator bias. Subjects had at least a 30 day history of treatment with a different formulation of buprenorphine/naloxone immediately prior to study entry, making identification of treatment-emergent adverse events very challenging.

The following table summarizes adverse events that occurred in more than 2 subjects.

Table 8 TEAEs Occurring in more than 2 Subjects

Adverse Event Preferred Term[a]	All Subjects N=249 n (%)
All Adverse Events	192 (77.1)
Drug Withdrawal Syndrome	89 (35.7)
Lethargy	22 (8.8)
Headache	20 (8.0)
Nasopharyngitis	14 (5.6)
Drug abuse	12 (4.8)
Fatigue	8 (3.2)
Upper Respiratory Tract Infection	8 (3.2)
Chills	7 (2.8)
Constipation	7 (2.8)
Toothache	7 (2.8)
Urinary Tract Infection	7 (2.8)
Back Pain	6 (2.4)
Drug Dependence	6 (2.4)
Hyperhidrosis	6 (2.4)
Insomnia	6 (2.4)
Viral Infection	6 (2.4)
Nausea	5 (2.0)
Anxiety	4 (1.6)
Gastroenteritis Viral	4 (1.6)
Hypertension	4 (1.6)
Oropharyngeal Pain	4 (1.6)
Sinusitis	4 (1.6)
Somnolence	4 (1.6)
Vomiting	4 (1.6)
Abdominal Pain	3 (1.2)
Asthenia	3 (1.2)
Bronchitis	3 (1.2)
Cough	3 (1.2)
Dermatitis Contact	3 (1.2)
Flushing	3 (1.2)
Influenza	3 (1.2)
Influenza-like Illness	3 (1.2)
Migraine	3 (1.2)
Oral Mucosal Erythema	3 (1.2)
Pain	3 (1.2)
Rhinorrhea	3 (1.2)

a. Source Data: Table 14.3.1.1.a, Table 14.3.1.2.a
Source: Table 20 BNX-201 CSR

The most frequently occurring adverse event by far was drug withdrawal syndrome. This was reported in a third of subjects, which correlates closely with the proportion of subjects who underwent dose increases during the study. This fits with the clinical pharmacology study results that showed that the dose conversion paradigm used in this study placed patients on too low a dose of Bunavail. The other adverse events are not concerning based on what is known about the adverse event profile of other formulations of buprenorphine/naloxone and the study population.

There were no concerning adverse events reported in studies BNX-103, BNX-106, BNX-107, or BNX-110.

7.4.2 Laboratory Findings

Changes in laboratory findings, vital signs, and ECGs attributable to buprenorphine/naloxone would likely be difficult to detect due to the entry criterion of being on buprenorphine/naloxone at baseline and lack of control group.

There were no concerning trends in changes in laboratory findings identified in Studies BNX-103, BNX-106, BNX-107, BNX-110, or BNX-201.

7.4.3 Vital Signs

There were no concerning trends in changes in vital signs identified in Studies BNX-103, BNX-106, BNX-107, BNX-110, or BNX-201.

7.4.4 Electrocardiograms (ECGs)

There were no concerning trends in changes in ECG findings identified in Studies BNX-103, BNX-106, BNX-107, BNX-110, or BNX-201.

7.6 Additional Safety Evaluations

7.6.2 Human Reproduction and Pregnancy Data

One subject had a positive pregnancy test on Day 14 of the study and was discontinued in September 2012. The subject gave birth to a healthy, full-term baby in (b) (6).

7.7 Additional Submissions / Safety Issues

Study drug administration
In an efficacy information amendment dated 12/11/13, the Sponsor submitted a summary of patients who reported problems using the film. No patients reported difficulty in applying the correct side of the film to the buccal mucosa. The problems with handling and applying the film are reproduced below from pages 2 and 3 of the submission.

Table 1 Medication Errors Observed as a Result of Study Drug Non-compliance

Subject Number	Gender	Age (years)	Study Day	Description Provided by the Subject	Subject's Assessment of Ease of Use
01-0026	M	28	7	Subject had difficulty applying the films and used 2 extra films as replacements.	Difficult to use
			14	Subject tore 1 film while opening the packet; it was not used and not returned.	
01-0029	M	28	7	Subject used 3 extra films of study drug. Reasons were: 1 clumped, 1 tore, and 1 stuck to finger during application. These 3 films were discarded.	Easy to use
			14	Subject used 3 extra films of study drug. Reasons were that they fell off after application and so they were replaced.	
01-0033	F	34	ET	Subject reported using 1 extra dose of study drug due to poor adherence to the oral mucosa.	Difficult to use
02-2017	M	39	7	Subject misunderstood dosing and was taking study drug twice daily. Subject was re-educated regarding dosing.	Unavailable
02-2071	M	46	7	Subject reported using extra study drug as replacements for films that stuck to his dentures.	Very easy to use
02-2098	M	28	ET	Subject reported having difficulty using the films. Subject had no complaints of associated adverse events.	Unavailable
02-2152	F	41	14	Subject reported that extra films were used due to nonadhereance of films. Subject was re-instructed on application.	Very easy to use
03-3021	F	31	7	Subject cut a film in half and took a half of a film.	Very easy to use
03-3030	M	32	7	Subject reports that they forgot if they dosed so he took another dose.	Unavailable
05-5034	F	37	7	Subject stated 1 film was dropped and 1 film got wet before application, so both were discarded.	Very easy to use
07-7005	M	38	42	Subject used extra drug because they had a viral syndrome and worried that the films were not absorbing due to nausea and vomiting.	Difficult to use
07-7023	M	50	42	Subject reports using extra study drug because they get gummy and the subject was worried that they were not working. Also, reports that some films were swallowed.	Very easy to use
08-8042	M	41	42	Subject reported that 1 film did not stick.	Easy to use
10-1001	F	32	7	Subject reported that films sometimes "balled up in fingers" so she replaced these and didn't return the "used" study drug.	Unavailable
10-1007	M	24	7	Subject reported that films sometimes "balled up in fingers" so he replaced these and didn't return the "used" study drug.	Difficult to use
			14	Subject reports having problems with films not sticking to the mucosa and having to be replaced.	
10-1017	M	34	7	Subject having difficulty attaching films.	Very difficult to use
			14	The subject still reported having difficulty with application.	
			56	Subject reported poor adhesion.	

ET: early termination

The problems reported are similar to postmarketing reports that have been submitted for Suboxone sublingual film and are not unexpected.

The following table, reproduced from page 4 of the submission summarizes the proportion of subjects who reported problems with using the film by study visit.

Table 2 **Number of Subjects Reporting Medication Errors as a Result of Study Drug Non-compliance by Visit and Overall**

Study Visit N (%)								
Day 7 237 (100)	**Day 14 228 (100)**	**Day 28 218 (100)**	**Day 42 211 (100)**	**Day 56 204 (100)**	**Day 70 198 (100)**	**Day 84 197 (100)**	**ET 37 (100)**	**Overall 249 (100)**
10 (4.2)	5 (2.2)	0 (0)	3 (1.4)	1 (0.5)	0 (0)	0 (0)	2 (5.4)	16 (6.4)
ET: early termination								

Of 249 subjects enrolled, one subject with an orthodontic appliance discontinued the study because of difficulty applying the films. Issues relating to difficulty placing the films were reported by 5 subjects (2%), poor adhesion was reported by 6 (2%), and sticking to dentures by 1 (<1%). Overall, 79% of subjects completed the study. Therefore, it does not appear that problems with handling and administering the product caused patients to stop using the product in the open-label study.

There were no study drug administration or dosing errors reported in the three pharmacokinetic studies.

9 Appendices

9.2 Labeling Recommendations

Strengths and dose titration: If the lowest strength of Bunavail is not recommended for approval based on biowaiver or clinical pharmacology data, as appears to be the case at the time of this writing, the titration instructions for Bunavail need to be modified to reflect the available strengths of the product. The Suboxone tablet label recommends titrating in 2 to 4 mg increments of buprenorphine, which would correspond to (b) (4) to 2.1 mg increments of buprenorphine in Bunavail, but without the lowest strength available, a clinician would only be able to titrate by 2.1 mg increments. By using these three strengths, the clinician could titrate the entire recommended range in 2.1 mg intervals, but not in (b) (4) mg intervals. At the maintenance phase, there is no safety or efficacy concern with titrating the daily dose by 2.1 mg rather than (b) (4) mg. Clinicians may find it inconvenient not to have the option to prescribe the lowest strength, but it would not affect their ability to treat patients for opioid addiction at the maintenance stage of therapy and it is not grounds for recommending that the application not be approved. Therefore, to allow approval of the three highest strengths without the lowest strength, the prescribing information needs to reflect that patients can only be titrated in 2.1 mg increments of buprenorphine in Bunavail and the dosing instructions can otherwise be analogous to the referenced product.

Hepatic impairment: The results of a postmarketing pharmacokinetic study conducted with the referenced product, Suboxone sublingual tablets, indicate that there is a safety concern with administering the combination of buprenorphine and naloxone to patients with severe hepatic impairment and that it may not be appropriate to administer the combination to patients with moderate hepatic impairment for maintenance treatment. Dose adjustments are not possible in these populations because this is a fixed-dose combination drug product and the effect on naloxone exposure is greater than the effect on buprenorphine exposure. I recommend that Sections 2, 5, 8, and 12 be revised to inform prescribers of these findings and their clinical implications.

9.4 Clinical Investigator Financial Disclosure Review Template

Application Number: 205637

Submission Date(s): August 7, 2013

Applicant: BDSI

Product: Bunavail

Reviewer: Pamela Horn, MD

Date of Review: February 3, 2014

Covered Clinical Study (Name and/or Number): BNX-106, BNX-107, BNX-110, and BNX-201

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from applicant)
Total number of investigators identified: 8		
Number of investigators who are sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 0		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: _____ Significant payments of other sorts: _____ Proprietary interest in the product tested held by investigator: _____ Significant equity interest held by investigator in sponsor of covered study: _____		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☐	No ☐ (Request details from applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☐	No ☐ (Request information from applicant)

Number of investigators with certification of due diligence (Form FDA 3454, box 3) 0		
Is an attachment provided with the reason:	Yes ☐	No ☐ (Request explanation from applicant)

Discuss whether the applicant has adequately disclosed financial interests/arrangements with clinical investigators as recommended in the guidance for industry *Financial Disclosure by Clinical Investigators*.[4] Also discuss whether these interests/arrangements, investigators who are sponsor employees, or lack of disclosure despite due diligence raise questions about the integrity of the data:

- If not, why not (e.g., study design (randomized, blinded, objective endpoints), clinical investigator provided minimal contribution to study data)
- If yes, what steps were taken to address the financial interests/arrangements (e.g., statistical analysis excluding data from clinical investigators with such interests/arrangements)

Briefly summarize whether the disclosed financial interests/arrangements, the inclusion of investigators who are sponsor employees, or lack of disclosure despite due diligence affect the approvability of the application.

Not applicable

[4] See http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM341008.pdf.

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/s/

PAMELA J HORN
04/28/2014

CELIA J WINCHELL
05/01/2014

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

NDA/BLA Number: 205637 **Applicant: BDSI** **Stamp Date: August 7, 2013**

Drug Name: buprenorphine/naloxone buccal film **NDA/BLA Type: Standard**

On initial overview of the NDA/BLA application for filing:

	Content Parameter	Yes	No	NA	Comment
FORMAT/ORGANIZATION/LEGIBILITY					
1.	Identify the general format that has been used for this application, e.g. electronic CTD.	X			It is eCTD
2.	On its face, is the clinical section organized in a manner to allow substantive review to begin?	X			
3.	Is the clinical section indexed (using a table of contents) and paginated in a manner to allow substantive review to begin?	X			
4.	For an electronic submission, is it possible to navigate the application in order to allow a substantive review to begin (*e.g.*, are the bookmarks adequate)?	X			
5.	Are all documents submitted in English or are English translations provided when necessary?	X			
6.	Is the clinical section legible so that substantive review can begin?	X			
LABELING					
7.	Has the applicant submitted the design of the development package and draft labeling in electronic format consistent with current regulation, divisional, and Center policies?	X			
SUMMARIES					
8.	Has the applicant submitted all the required discipline summaries (*i.e.*, Module 2 summaries)?	X			
9.	Has the applicant submitted the integrated summary of safety (ISS)?			X	
10.	Has the applicant submitted the integrated summary of efficacy (ISE)?			X	
11.	Has the applicant submitted a benefit-risk analysis for the product?	X			
12.	Indicate if the Application is a 505(b)(1) or a 505(b)(2). If Application is a 505(b)(2) and if appropriate, what is the reference drug?	X			Suboxone tablets NDA 20733
DOSE					
13.	If needed, has the applicant made an appropriate attempt to determine the correct dosage and schedule for this product (*i.e.*, appropriately designed dose-ranging studies)? Study Number: Study Title: Sample Size: Arms: Location in submission:			X	
EFFICACY					
14.	Do there appear to be the requisite number of adequate and well-controlled studies in the application? Pivotal Study #1 Indication:			X	

File name: 5_Clinical Filing Checklist for NDA_BLA or Supplement 010908

Reference ID: 3382579

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
	Pivotal Study #2 Indication:				
15.	Do all pivotal efficacy studies appear to be adequate and well-controlled within current divisional policies (or to the extent agreed to previously with the applicant by the Division) for approvability of this product based on proposed draft labeling?			X	
16.	Do the endpoints in the pivotal studies conform to previous Agency commitments/agreements? Indicate if there were not previous Agency agreements regarding primary/secondary endpoints.			X	
17.	Has the application submitted a rationale for assuming the applicability of foreign data to U.S. population/practice of medicine in the submission?			X	
SAFETY					
18.	Has the applicant presented the safety data in a manner consistent with Center guidelines and/or in a manner previously requested by the Division?	X			
19.	Has the applicant submitted adequate information to assess the arrhythmogenic potential of the product (*e.g.*, QT interval studies, if needed)?			X	eval of arrhythmogenic potential will be a PMR if needed
20.	Has the applicant presented a safety assessment based on all current worldwide knowledge regarding this product?			X	
21.	For chronically administered drugs, have an adequate number of patients (based on ICH guidelines for exposure[1]) been exposed at the dose (or dose range) believed to be efficacious?			X	
22.	For drugs not chronically administered (intermittent or short course), have the requisite number of patients been exposed as requested by the Division?			X	
23.	Has the applicant submitted the coding dictionary[2] used for mapping investigator verbatim terms to preferred terms?	X			MedDRA 12.0
24.	Has the applicant adequately evaluated the safety issues that are known to occur with the drugs in the class to which the new drug belongs?			X	
25.	Have narrative summaries been submitted for all deaths and adverse dropouts (and serious adverse events if requested	X			

[1] For chronically administered drugs, the ICH guidelines recommend 1500 patients overall, 300-600 patients for six months, and 100 patients for one year. These exposures MUST occur at the dose or dose range believed to be efficacious.

[2] The "coding dictionary" consists of a list of all investigator verbatim terms and the preferred terms to which they were mapped. It is most helpful if this comes in as a SAS transport file so that it can be sorted as needed; however, if it is submitted as a PDF document, it should be submitted in both directions (verbatim -> preferred and preferred -> verbatim).

Reference ID: 3382579

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
	by the Division)?				
OTHER STUDIES					
26.	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?	X			Withdrawal study to support naloxone dose
27.	For Rx-to-OTC switch and direct-to-OTC applications, are the necessary consumer behavioral studies included (*e.g.*, label comprehension, self selection and/or actual use)?			X	
PEDIATRIC USE					
28.	Has the applicant submitted the pediatric assessment, or provided documentation for a waiver and/or deferral?	X			
ABUSE LIABILITY					
29.	If relevant, has the applicant submitted information to assess the abuse liability of the product?	X			Withdrawal study
FOREIGN STUDIES					
30.	Has the applicant submitted a rationale for assuming the applicability of foreign data in the submission to the U.S. population?			X	
DATASETS					
31.	Has the applicant submitted datasets in a format to allow reasonable review of the patient data?	X			
32.	Has the applicant submitted datasets in the format agreed to previously by the Division?	X			
33.	Are all datasets for pivotal efficacy studies available and complete for all indications requested?			X	
34.	Are all datasets to support the critical safety analyses available and complete?	X			
35.	For the major derived or composite endpoints, are all of the raw data needed to derive these endpoints included?			X	
CASE REPORT FORMS					
36.	Has the applicant submitted all required Case Report Forms in a legible format (deaths, serious adverse events, and adverse dropouts)?	X			
37.	Has the applicant submitted all additional Case Report Forms (beyond deaths, serious adverse events, and adverse drop-outs) as previously requested by the Division?			X	
FINANCIAL DISCLOSURE					
38.	Has the applicant submitted the required Financial Disclosure information?	X			
GOOD CLINICAL PRACTICE					
39.	Is there a statement of Good Clinical Practice; that all clinical studies were conducted under the supervision of an IRB and with adequate informed consent procedures?	X			

IS THE CLINICAL SECTION OF THE APPLICATION FILEABLE? ____Yes____

If the Application is not fileable from the clinical perspective, state the reasons and provide comments to be sent to the Applicant.

Reference ID: 3382579

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

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

1. More information is needed to support the waiver request for pediatric studies in the (b) (4) through (b) (4) age group, as outlined in the request below.
2. A recently approved buprenorphine/naloxone product for opioid addiction treatment received a waiver for ages 15 and 16 in addition to ages 12 through 14 because the waiver request included information that demonstrated that the necessary studies are impossible or highly impracticable due to the low prevalence of patients seeking agonist treatment for opioid dependence in the entire 12 through 16 age group. This Sponsor may also want to make a waiver request for the entire 12 through 16 age group.

The following requests and comments should be conveyed to the Sponsor:

The Pediatric Research Equity Act (PREA) (21 U.S.C. 355c) covers children age 0 through 16. We acknowledge that you are requesting a waiver for ages 0 through (b) (4).

1. We also acknowledge that you are requesting a waiver for ages (b) (4) through (b) (4) because the population in this age group requiring treatment for opioid dependence is too small, rendering the necessary studies impossible or impracticable to conduct. The following information is needed to support the waiver request for ages (b) (4) through (b) (4):
   - An assessment of the pediatric use of pharmacotherapy for opioid dependence for ages (b) (4) through (b) (4). This should include a report of pediatric use data for currently marketed buprenorphine/naloxone products, which could include prevalence data, literature review, expert interviews, and review of insurance databases. Additionally, include an assessment of the prevalence of opioid dependence in this age group, including all illicit and prescription opioids, and the proportion of these cases that are treatment-seeking.
2. It may be possible to receive a waiver for ages (b) (4) 16, as well, if you provide information that demonstrates that the necessary studies are impossible or highly impracticable due to the low prevalence of patients seeking agonist treatment for opioid dependence in this population. If you think that it would support a waiver for ages (b) (4) (b) (4) 16, you may submit an assessment, as outlined above, for ages 12 through 16 inclusive, rather than only for ages (b) (4) through (b) (4)

Reviewing Medical Officer Date

Clinical Team Leader Date

Reference ID: 3382579

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/s/

PAMELA J HORN
10/02/2013

CELIA J WINCHELL
10/02/2013