CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

210136Orig1s000

OTHER REVIEW(S)

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy

PATIENT LABELING REVIEW

Date:	April 21, 2023
To:	Rita Joshi, PharmD Regulatory Project Manager **Division of Anesthesiology, Addiction Medicine, and Pain Medicine (DAAP)**
Through:	LaShawn Griffiths, MSHS-PH, BSN, RN Associate Director for Patient Labeling **Division of Medical Policy Programs (DMPP)** Ruth Mayrosh, PharmD Senior Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)**
From:	Sharon R. Mills, BSN, RN, CCRP Senior Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)** Phillip Williams, PharmD, RAC Regulatory Review Officer **Office of Prescription Drug Promotion (OPDP)**
Subject:	Review of Patient Labeling: Medication Guide
Drug Name (established name):	BRIXADI (buprenorphine)
Dosage Form and Route:	extended-release injection for subcutaneous use, CIII
Application Type/Number:	NDA 210136
Applicant:	Braeburn Inc.

1 INTRODUCTION

On November 23, 2022, Braeburn Inc. resubmitted for the Agency's review their original New Drug Application (NDA) 210136 for BRIXADI (buprenorphine) extended-release injection, CIII. With this resubmission, the Applicant provides responses to the deficiencies outlined in the Agency's Complete Response (CR) Letter dated December 15, 2021.

This collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to a request by the Division of Anesthesiology, Addiction, Medicine, and Pain Medicine (DAAP) on December 6, 2022, for DMPP and OPDP to review the Applicant's proposed Medication Guide (MG) for BRIXADI (buprenorphine) extended-release injection, C-III.

2 MATERIAL REVIEWED

- Draft BRIXADI (buprenorphine) extended-release injection MG received by DMPP on April 13, 2023.
- Draft BRIXADI (buprenorphine) Prescribing Information (PI) received on November 23, 2022, revised by the Review Division throughout the review cycle, and received by DMPP on April 10, 2023
- Approved Subutex (buprenorphine hydrochloride) sublingual tablets, NDA 020732, Reference Listed Drug labeling dated June 17, 2022.
- Approved Suboxone (buprenorphine hydrochloride, naloxone, sublingual tablets, NDA 020733, Reference Listed Drug labeling dated June 17, 2022.

3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6th to 8th grade reading level, and have a reading ease score of at least 60%. A reading ease score of 60% corresponds to an 8th grade reading level.

Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APHont to make medical information more accessible for patients with vision loss.

In our collaborative review of the MG we:

- simplified wording and clarified concepts where possible
- ensured that the MG is consistent with the Prescribing Information (PI)

- removed unnecessary or redundant information
- ensured that the MG is free of promotional language or suggested revisions to ensure that it is free of promotional language
- ensured that the MG meets the Regulations as specified in 21 CFR 208.20
- ensured that the MG meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)

4 CONCLUSIONS

The MG is acceptable with our recommended changes.

5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DMPP and OPDP on the correspondence.
- Our collaborative review of the MG is appended to this memorandum. Consult DMPP and OPDP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the MG.

Please let us know if you have any questions.

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FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion

****Pre-decisional Agency Information****

Memorandum

Date: 04/20/2023

To: Rita Joshi, PharmD, Regulatory Project Manager
Division of Regulatory Operations, Neuroscience (DRO-N)

From: Phillip Williams, PharmD, RAC, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: Sam Skariah, PharmD, RAC, Team Leader, OPDP

Subject: OPDP Labeling Comments for BRIXADI™ (buprenorphine) extended-release injection, for subcutaneous use, CIII

NDA: 210136

Background:

In response to DAAP's consult request dated December 6, 2022, OPDP has reviewed the proposed prescribing information (PI) and Medication Guide for the original NDA submission for BRIXADI™ (buprenorphine) extended-release injection, for subcutaneous use, CIII.

PI/Medication Guide:

OPDP's review of the proposed PI is based on the draft labeling emailed to OPDP on April 10, 2023, and we do not have any comments at this time.

A combined OPDP and Division of Medical Policy Programs (DMPP) review will be completed for the proposed Medication Guide, and comments will be sent under separate cover.

Thank you for your consult. If you have any questions, please contact Phillip Williams at (240) 402-3974 or Phillip.Williams@fda.hhs.gov.

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PHILLIP A WILLIAMS
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LABEL AND LABELING REVIEW
Division of Medication Error Prevention and Analysis 1 (DMEPA 1)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

*** This document contains proprietary information that cannot be released to the public***

Date of This Review:	March 6, 2023
Requesting Office or Division:	Division of Anesthesiology, Addiction Medicine, and Pain Medicine (DAAP)
Application Type and Number:	NDA 210136
Product Name and Strength:	Brixadi (buprenorphine) extended-release injection Weekly: 8 mg/0.16 mL, 16 mg/0.32 mL, 24 mg/0.48 mL, 32 mg/0.64 mL Monthly: 64 mg/0.18 mL, 96 mg/0.27 mL, 128 mg/0.36 mL
Product Type:	Combination Product (Drug-Device)
Rx or OTC:	Prescription (Rx)
Applicant/Sponsor Name:	Braeburn Pharmaceuticals, Inc. (Braeburn)
FDA Received Date:	November 23, 2022; December 13, 2022
TTT ID #:	2022-3004
DMEPA 1 Safety Evaluator:	Damon Birkemeier, PharmD, FISMP, NREMT
DMEPA 1 Team Leader:	Valerie Vaughan, PharmD

1 REASON FOR REVIEW

As part of their Class 2 Resubmission, Braeburn submitted a revised Prescribing Information (PI) and Instructions for Use (IFU). On December 13, 2022, Braeburn also confirmed that there were no changes to their previously submitted container labels and carton labeling received on June 1, 2020, and September 1, 2020, for Brixadi. The Division of Anesthesiology, Addiction Medicine, and Pain Medicine (DAAP) requested that we review the proposed Brixadi instructions for use (IFU) and prescribing information (PI) as well as the previously submitted container labels and carton labeling for Brixadi for areas of vulnerability that may lead to medication errors.

1.1 REGULATORY HISTORY

On October 18, 2017, and December 18, 2017, we reviewed the labels, labeling, and human factors (HF) validation study results for Brixadi submitted to IND 114082 and NDA 210136. While we noted the HF validation study results identified areas of vulnerability that could lead to medication errors, we determined that the issues could be mitigated through labeling revisions and did not require additional validation. Therefore, we found the results of the HF study acceptable from a medication error perspective.[a,b]

On January 19, 2018, NDA 210136 was issued a Complete Response (CR) letter due to clinical, statistical, nonclinical, product quality, device, microbiology and drug product deficiencies.[c] On May 23, 2018, Braeburn submitted a response to address the deficiencies outlined in FDA's January 19, 2018, CR letter.

On June 22, 2018, the resubmission of NDA 210136 was deemed incomplete and an Acknowledge Incomplete Response Letter[d] was issued to Braeburn. On June 26, 2018, Braeburn submitted a Class 2 Resubmission to NDA 210136 to address the deficiencies identified in the June 22, 2018, Acknowledge Incomplete Response letter.

On October 10, 2018, we reviewed the labels and labeling provided in the resubmission and provided additional recommendations to Braeburn.[e] Braeburn implemented all of our

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[a]Wilson V. Label, Labeling, and Human Factors Results Review for buprenorphine injection (IND 114082 and NDA 210136). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2017 OCT 18. RCM No. 2017-1834 and 2017-1448.

[b] Wilson V. Label and Labeling Review Memorandum for buprenorphine injection (NDA 210136). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2017 DEC 18. RCM No.: 2017-1448-1.

[c] Sullivan M. Complete Response for Brixadi. Silver Spring (MD): FDA, CDER, OND, DAAAP (US); 2018 JAN 19. NDA 210136.

[d] Ayoola T. Acknowledge Incomplete Response for Brixadi. Silver Spring (MD): FDA, CDER, OND, DAAAP (US); 2018 JUN 22. NDA 210136.

[e] Wilson V. Label and Labeling Review for Brixadi (NDA 210136). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2018 OCT 10. RCM No.: 2017-1448-2.

recommendations and we had no additional concerns from a medication error perspective at that time.

On December 21, 2018, NDA 210136 received Tentative Approval under 21 CFR 314.105 with final approval being subject to expiration of a period of patent protection and/or exclusivity.

On June 1, 2020, Braeburn submitted a Request for Final Approval for NDA 210136. We reviewed the labels and labeling and provided recommendations for the PI.[f] However, on December 1, 2020, NDA 210136 received a CR[g] due to a facility inspection deficiency. In the CR letter, our recommendation for the PI was conveyed to Braeburn.

On June 25, 2021, Braeburn submitted a Class 2 Resubmission to NDA 210136 to address the facility inspection deficiency identified in the CR letter dated December 1, 2020. In the resubmission, Braeburn submitted a revised PI which incorporated recommendations that the Agency conveyed in the previous CR letter. We reviewed the labels and labeling, and Braeburn implemented all of our recommendations and we had no additional concerns from a medication error perspective at that time.[h] However, on December 15, 2021, NDA 210136 received another CR[i] due to a facility inspections deficiency.

On November 23, 2022, Braeburn submitted a Class 2 Resubmission to NDA 210136 to address the facility inspection deficiency identified in the CR letter dated December 15, 2021. In the resubmission, Braeburn submitted a revised PI, which is the subject of this review.

2 MATERIALS REVIEWED

Table 1. Materials Considered for this Label and Labeling Review

Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B
ISMP Newsletters*	C – N/A
FDA Adverse Event Reporting System (FAERS)*	D – N/A
Information Requests Issued During the Review	E
Labels and Labeling	F

[f] Johnson C. Label and Labeling Review for Brixadi (NDA 210136). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2020 SEP 17. RCM No.: 2017-1448-3.

[g] Sullivan M. Complete Response for Brixadi. Silver Spring (MD): FDA, CDER, OND, DAAAP (US); 2020 DEC 1. NDA 210136.

[h] Clark C. Label and Labeling Review for Brixadi (NDA 210136). Silver Spring (MD): FDA, CDER, OSE, DMEPA 1 (US); 2021 SEP 20. RCM No.: 2017-1448-4.

[i] Joshi R. Complete Response for Brixadi. Silver Spring (MD): FDA, CDER, OND, DAAP (US); 2021 DEC 15. NDA 210136.

Table 1. Materials Considered for this Label and Labeling Review	
Material Reviewed	Appendix Section (for Methods and Results)
N/A=not applicable for this review *We do not typically search FAERS or ISMP Newsletters for our label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance	

3 CONCLUSION

The proposed IFU, PI, container labels, and carton labeling are acceptable from a medication error perspective. We have no recommendations at this time.

APPENDICES: METHODS & RESULTS FOR EACH MATERIAL REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Brixadi that Braeburn Pharmaceuticals, Inc. submitted on November 23, 2022, and the listed drug (LD).

Table 4. Relevant Product Information for Listed Drug and Brixadi		
Product Name	Subutex (listed drug)	Brixadi
Initial Approval Date	October 8, 2022	N/A
Active Ingredient	Buprenorphine	
Indication	Treatment of opioid dependence and is preferred for induction. Subutex should be used as part of a complete treatment plan to include counseling and psychosocial support.	Treatment of moderate to severe opioid use disorder in patients who have initiated treatment with a single dose of a transmucosal buprenorphine product or who are already being treated with buprenorphine. Brixadi should be used as part of a complete treatment plan that includes counseling and psychosocial support.
Route of Administration	Oral	Subcutaneous
Dosage Form	Sublingual tablet	Injection
Strength	2 mg 8 mg	Weekly: 8 mg/0.16 mL, 16 mg/0.32 mL, 24 mg/0.48 mL, 32 mg/0.64 mL Monthly: 64 mg/0.18 mL, 96 mg/0.27 mL, 128 mg/0.36 mL
Dose and Frequency	Range of 4 mg to 24 mg buprenorphine per day. The recommended target dosage is 16 mg as a single daily dose.	Once weekly or once monthly
How Supplied	Supplied in desiccated high density polyethylene bottles of 30 tablets per bottle	Single-dose prefilled safety syringe per carton
Storage	Store at 25°C (77°F), excursions permitted to 15°C to 30°C (59°F to 86°F) [see USP Controlled Room Temperature]	Store at room temperature at 20°C to 25°C (68°F to 77°F); excursions permitted at 15°C to 30°C (59°F to 86°F) [see USP Controlled Room Temperature]

APPENDIX B. PREVIOUS DMEPA REVIEWS

On January 19, 2023, we searched for previous DMEPA reviews relevant to this current review using the terms NDA 210136. Our search identified five previous reviews[a,b,e,f,h] and we confirmed that our previous recommendations were implemented.

APPENDIX E. INFORMATION REQUESTS ISSUED DURING THE REVIEW

- On December 13, 2022, we issued an information request (IR) asking Braeburn to submit updated container labels/carton labeling to their submission. On December 13, 2022, Braeburn indicated via email that there were no changes to the container labels and carton labeling since their previous submission on June 1, 2020.

[EXTERNAL] RE_
[External Email]-NDA

APPENDIX F. LABELS AND LABELING

F.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,[j] along with postmarket medication error data, we reviewed the following Brixadi labels and labeling submitted by Braeburn Pharmaceuticals, Inc.

- Container Labels received on June 1, 2020
- Carton Labeling received on June 1, 2020
- Instructions for Use (IFU) (Image not shown) (available in the PI)
- Prescribing Information (Image not shown) available from \\CDSESUB1\EVSPROD\nda210136\0143\m1\us\draft-label-text-redline.pdf

[j] Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

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Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy

PATIENT LABELING REVIEW

Date:	November 22, 2021
To:	Rita Joshi Regulatory Project Manager **Division of Anesthesiology, Addiction Medicine, and Pain Medicine (DAAP)**
Through:	LaShawn Griffiths, MSHS-PH, BSN, RN Associate Director for Patient Labeling **Division of Medical Policy Programs (DMPP)** Barbara Fuller, RN, MSN, CWOCN Team Leader, Patient Labeling **Division of Medical Policy Programs (DMPP)**
From:	Sharon R. Mills, BSN, RN, CCRP Senior Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)** Phillip Williams, PharmD Regulatory Review Officer **Office of Prescription Drug Promotion (OPDP)**
Subject:	Review of Patient Labeling: (Medication Guide (MG)
Drug Name (established name):	BRIXADI (buprenorphine)
Dosage Form and Route:	extended-release injection for subcutaneous use, CIII
Application Type/Number, Supplement Number:	NDA 210136
Applicant:	Braeburn Inc.

1 INTRODUCTION

On June 15, 2021, Braeburn Inc. submitted for the Agency's review a resubmission to their New Drug Application (NDA) 210136 for BRIXADI (buprenorphine) extended-release injection. This resubmission provides responses to the Complete Response (CR) letter issued by the Agency and received by the Applicant on December 1, 2020 and revised labeling. The proposed indication is for the the treatment of moderate to severe opioid use disorder in patients who have initiated treatment with a single dose of a transmucosal buprenorphine product or who are already being treated with buprenorphine. BRIXADI should be used as part of a complete treatment plan to include counseling and psychosocial support.

This collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to a request by the Division of Anesthesiology, Addiction Medicine, and Pain Medicine (DAAP) on July 2, 2021, for DMPP and OPDP to review the Applicant's proposed Medication Guide (MG) for BRIXADI (buprenorphine) extended-release injection.

2 MATERIAL REVIEWED

- Draft BRIXADI (buprenorphine) extended-release injection MG received on June 15, 2021, and received by DMPP and OPDP on November 8, 2021.
- Draft BRIXADI (buprenorphine) extended-release injection Prescribing Information (PI) received on June 15, 2021, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on November 8, 2021.

3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6th to 8th grade reading level, and have a reading ease score of at least 60%. A reading ease score of 60% corresponds to an 8th grade reading level.

Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APHont to make medical information more accessible for patients with vision loss.

In our collaborative review of the MG we:

- simplified wording and clarified concepts where possible
- ensured that the MG is consistent with the Prescribing Information (PI)

- removed unnecessary or redundant information
- ensured that the MG is free of promotional language or suggested revisions to ensure that it is free of promotional language
- ensured that the MG meets the Regulations as specified in 21 CFR 208.20
- ensured that the MG meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)

4 CONCLUSIONS

The MG is acceptable with our recommended changes.

5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DMPP and OPDP on the correspondence.
- Our collaborative review of the MG is appended to this memorandum. Consult DMPP and OPDP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the MG.

Please let us know if you have any questions.

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FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion

****Pre-decisional Agency Information****

Memorandum

Date: 11/22/2021

To: Rita Joshi, PharmD, Regulatory Project Manager
Division of Regulatory Operations, Neuroscience (DRO-N)

From: Phillip Williams, PharmD, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: Sam Skariah, PharmD, RAC, Team Leader, OPDP

Subject: OPDP Labeling Comments for BRIXADI™ (buprenorphine) extended-release injection for subcutaneous use CIII

NDA: 210136

In response to DAAP's consult request dated July 2, 2021, OPDP has reviewed the proposed prescribing information (PI) and Medication Guide (MG) for BRIXADI™ (buprenorphine) extended-release injection for subcutaneous use CIII**.**

PI: OPDP's comments on the proposed labeling are based on the draft labeling received by electronic mail from DAAP on November 8, 2021, and are provided below.

MG: A combined OPDP and Division of Medical Policy Programs (DMPP) review will be completed, and comments on the proposed Medication Guide will be sent under separate cover.

Thank you for your consult. If you have any questions, please contact Phillip Williams at (240) 402-3974 or Phillip.Williams@fda.hhs.gov.

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PHILLIP A WILLIAMS
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MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING

Division of Medication Error Prevention and Analysis 1 (DMEPA 1)

Office of Medication Error Prevention and Risk Management (OMEPRM)

Office of Surveillance and Epidemiology (OSE)

Center for Drug Evaluation and Research (CDER)

Date of This Memorandum:	September 20, 2021
Requesting Office or Division:	Division of Anesthesiology, Addiction Medicine, and Pain Medicine (DAAP)
Application Type and Number:	NDA 210136
Product Name and Strength:	Brixadi (buprenorphine) extended-release injection , 8 mg/0.16 mL, 16 mg/0.32 mL, 24 mg/0.48 mL, 32 mg/ 0.64 mL, 64 mg/0.18 mL, 96 mg/0.27 mL, 128 mg/0.36 mL
Applicant/Sponsor Name:	Braeburn Pharmaceuticals, Inc.
OSE RCM #:	2017-1448-4
DMEPA 1 Safety Evaluator:	Cameron Clark, PharmD
DMEPA 1 Team Leader:	Valerie Vaughan, PharmD

1 PURPOSE OF MEMORANDUM

As part of their Class 2 Resubmission, Braeburn submitted a revised Prescribing Information (PI) and Instructions for Use (IFU). On August 25, 2021, Braeburn also confirmed that there were no changes to their previously submitted container labels and carton labeling received on June 1, 2020 and September 1, 2020 for Brixadi. The Division of Anesthesiology, Addiction Medicine, and Pain Medicine (DAAP) requested that we review the revised PI and IFU as well as the previously submitted container labels and carton labeling for Brixadi (Appendix A) to determine if they are acceptable from a medication error perspective.

2 REGULATORY HISTORY

On October 18, 2017 and December 18, 2017, we reviewed the labels, labeling, and human factors (HF) validation study results for Brixadi submitted to IND 114082 and NDA 210136. While we noted the HF validation study results identified areas of vulnerability that could lead to medication errors, we determined that the issues could be mitigated through labeling

revisions and did not require additional validation. Therefore, we found the results of the HF study acceptable from a medication error perspective.[ab]

On January 19, 2018, NDA 210136 was issued a Complete Response (CR) letter due to clinical, statistical, nonclinical, product quality, device, microbiology and drug product deficiencies.[c] On May 23, 2018, Braeburn submitted a response to address the deficiencies outlined in FDA's January 19, 2018 CR letter.

On June 22, 2018, the resubmission of NDA 210136 was deemed incomplete and an Acknowledge Incomplete Response Letter[d] was issued to Braeburn. On June 26, 2018, Braeburn submitted a Class 2 Resubmission to NDA 210136 to address the deficiencies identified in the June 22, 2018 Acknowledge Incomplete Response letter.

On October 10, 2018 we reviewed the labels and labeling provided in the resubmission and provided additional recommendations to Braeburn. Braeburn implemented all of our recommendations and we had no additional concerns from a medication error perspective, at that time.

On December 21, 2018, NDA 210136 received Tentative Approval under 21 CFR 314.105 with final approval being subject to expiration of a period of patent protection and/or exclusivity.

On June 1, 2020, Braeburn submitted a Request for Final Approval for NDA 210136. We reviewed the labels and labeling and provided recommendations for the PI.[e] However, on December 1, 2020, NDA 210136 received a CR[f] due to a facility inspection deficiency. In the CR letter, our recommendation for the PI was conveyed to Braeburn.

On June 25, 2021, Braeburn submitted a Class 2 Resubmission to NDA 210136 to address the facility inspection deficiency identified in the CR letter. In the resubmission, Braeburn submitted a revised PI which incorporated recommendations that the Agency conveyed in the previous CR letter.

3 CONCLUSION

The container labels, carton labeling, IFU and PI are acceptable from a medication error perspective. We have no recommendations at this time.

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[a]Wilson, V. Label, Labeling, and Human Factors Results Review for buprenorphine injection (IND 114082 and NDA 210136). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2017 OCT 18. RCM No. 2017-1834 and 2017-1448.

[b] Wilson, V. Label and Labeling Review Memorandum for buprenorphine injection (NDA 210136). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2017 DEC 15. RCM No.: 2017-1448-1.

[c] Sullivan, M. Complete Response for Brixadi. Silver Spring (MD): FDA, CDER, OND, DAAAP (US); 2018 JAN 19. NDA 210136.

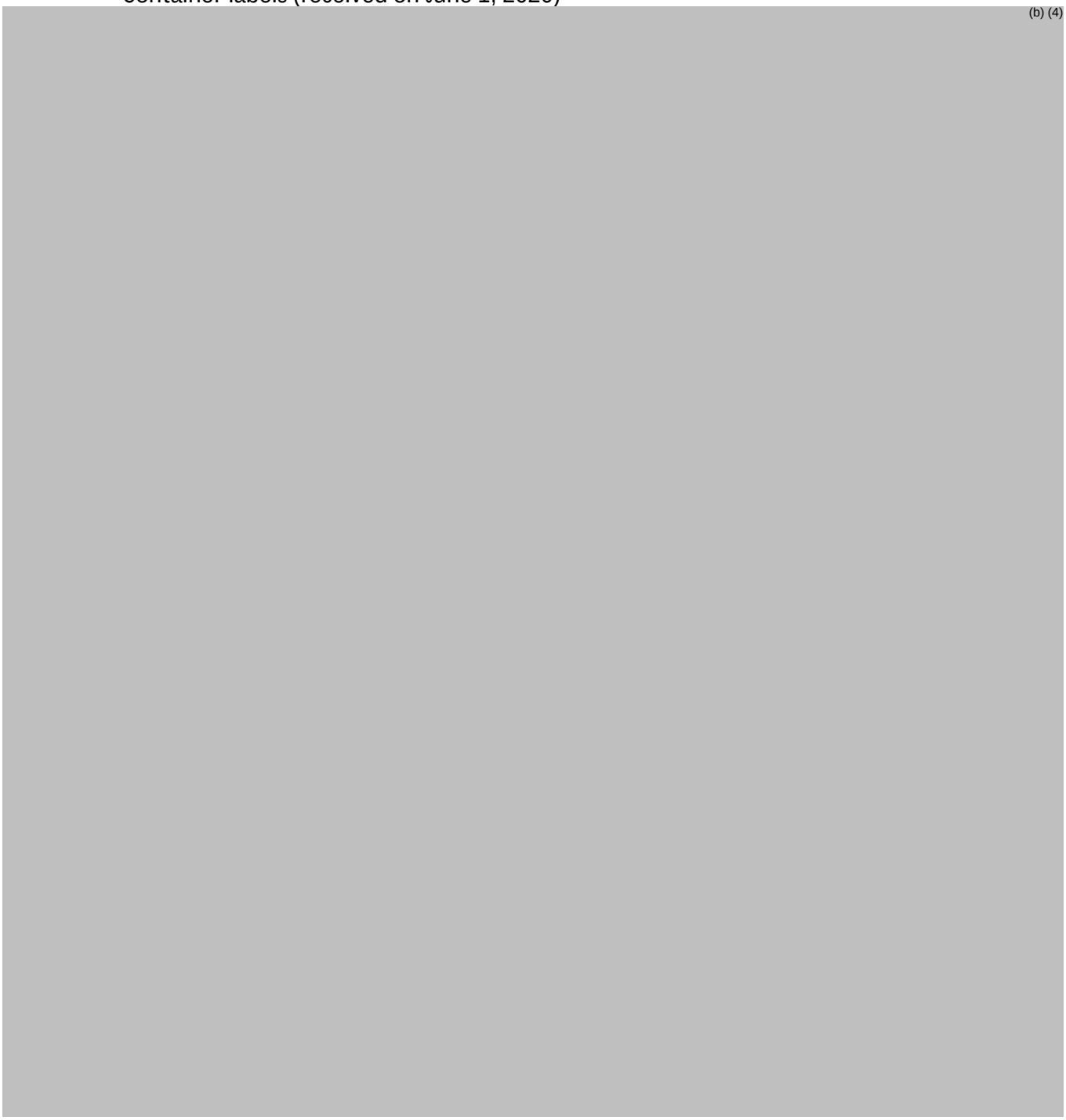
[d] Ayoola, T. Acknowledge Incomplete Response for Brixadi. Silver Spring (MD): FDA, CDER, OND, DAAAP (US); 2018 JUN 22. NDA 210136.

[e] Johnson, C. Label and Labeling Review for Brixadi (NDA 210136). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2020 SEP 17. RCM No.: 2017-1448-3.

[f] Sullivan, M. Complete Response for Brixadi. Silver Spring (MD): FDA, CDER, OND, DAAAP (US); 2020 DEC 01. NDA 210136.

APPENDIX A. IMAGES OF LABELS AND LABELIN

- Container labels (received on June 1, 2020)



- Carton labeling , received on June 1, 2021 can be accessed in EDR via the following link:
  - \\cdsesub1\evsprod\nda210136\0113\m1\us\carton-labels.pdf

- Representative container label and carton labeling for sample received on September 1, 2021, can be accessed in EDR via the following link:
    - \\CDSESUB1\evsprod\nda210136\0119\m1\us\bridge-pap-carton-r-g.pdf
- Instructions for Use (Image not shown) received on June 15, 2021, can be accessed in EDR via the following link:
    - \\CDSESUB1\evsprod\nda210136\0128\m1\us\ifu-red.pdf
- Prescribing Information (Image not shown) received on June 15, 2021 can be accessed in EDR vial the following link:
    - \\CDSESUB1\evsprod\nda210136\0128\m1\us\draft-label-text-redline-word.docx

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/s/

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VALERIE S VAUGHAN
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Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy

PATIENT LABELING REVIEW

Date:	November 27, 2020
To:	Matthew Sullivan, CPMS Regulatory Project Manager **Division of Anesthesiology, Addiction, Medicine, and Pain Medicine (DAAP)**
Through:	LaShawn Griffiths, MSHS-PH, BSN, RN Associate Director for Patient Labeling **Division of Medical Policy Programs (DMPP)**
From:	Morgan Walker, PharmD, MBA, CPH Senior Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)** Nima Ossareh, PharmD Regulatory Review Officer **Office of Prescription Drug Promotion (OPDP)**
Subject:	Review of Patient Labeling: Medication Guide (MG)
Drug Name (established name), Dosage Form and Route:	BRIXADI (buprenorphine) extended-release injection for subcutaneous use, CIII
Application Type/Number:	NDA 210136
Applicant:	Braeburn Pharmaceuticals

1 INTRODUCTION

On June 1, 2020, Braeburn Pharmaceuticals submitted for the Agency's review a New Drug Application (NDA) 210136 for BRIXADI (buprenorphine) extended-release injection. The Applicant received a Tentative Approval letter for this product on December 21, 2018 and is seeking Final Approval. The proposed indication is for the treatment of moderate to severe opioid use disorder in patients who have initiated treatment with a single dose of a transmucosal buprenorphine product or who are already being treated with buprenorphine.

This collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to a request by the Division of Anesthesiology, Addiction, Medicine, and Pain Medicine (DAAP) on November 19, 2020, for DMPP and OPDP to review the Applicant's proposed Medication Guide (MG) for BRIXADI (buprenorphine) extended-release injection.

2 MATERIAL REVIEWED

- Draft BRIXADI (buprenorphine) extended-release injection MG received on June 1, 2020, and received by DMPP and OPDP on November 20, 2020.
- Draft BRIXADI (buprenorphine) extended-release injection Prescribing Information (PI) received on June 1, 2020, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on November 20, 2020.

3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6th to 8th grade reading level, and have a reading ease score of at least 60%. A reading ease score of 60% corresponds to an 8th grade reading level.

Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APHont to make medical information more accessible for patients with vision loss.

In our collaborative review of the MG we:

- simplified wording and clarified concepts where possible
- ensured that the MG is consistent with the Prescribing Information (PI)
- removed unnecessary or redundant information
- ensured that the MG is free of promotional language or suggested revisions to ensure that it is free of promotional language
- ensured that the MG meets the Regulations as specified in 21 CFR 208.20

- ensured that the MG meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)

4 CONCLUSIONS

The MG is acceptable with our recommended changes.

5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DMPP and OPDP on the correspondence.
- Our collaborative review of the MG is appended to this memorandum. Consult DMPP and OPDP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the MG.

Please let us know if you have any questions.

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11/27/2020 10:56:40 AM
Signing for Nima Ossareh

LASHAWN M GRIFFITHS
11/27/2020 10:57:27 AM

FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion

****Pre-decisional Agency Information****

Memorandum

Date: 11/25/20

To: Matthew Sullivan
Regulatory Project Manager
Division of Anesthesia, Analgesia, and Addiction Products (DAAAP)

From: Nima Ossareh, PharmD, RAC
Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: Sam Skariah, Team Leader, OPDP

Subject: OPDP Labeling Comments for BRIXADI™ (buprenorphine) extended-release injection, for subcutaneous use CIII

NDA: 210136

In response to DAAAP's consult request dated November 19, 2020, OPDP has reviewed the proposed product labeling (PI) and medication guide (MG) for the original NDA submission for BRIXADI™ (buprenorphine) extended-release injection, for subcutaneous use CIII.

PI: OPDP's comments on the proposed labeling are based on the draft PI received by electronic mail from DAAAP on November 19, 2020 and are provided below.

MG: A combined OPDP and Division of Medical Policy Programs (DMPP) review of the MG will be completed under a separate cover.

Thank you for your consult. If you have any questions, please contact Nima Ossareh at (240) 402-2769 or nima.ossareh@fda.hhs.gov.

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NIMA OSSAREH
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M E M O R A N D U M

Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research

Date: October 9, 2020

To: Rigoberto Roca, MD, Director (Acting)
Division of Anesthesiology, Addiction Medicine and Pain Medicine

Through: Dominic Chiapperino, PhD, Director
Joshua Lloyd, MD, Medical Officer Team Leader
Controlled Substance Staff

From: Shalini Bansil, MD, Medical Officer
Controlled Substance Staff

Subject: **Product name:** Buprenorphine extended-release subcutaneous injection
Trade Name: Brixadi
Dosages:
Weekly: 8 mg, 16 mg, 24 mg, and 32mg;
Monthly: 64 mg, 96 mg, and 128 mg
NDA number: 210136
Indication: Treatment of opioid use disorder
Sponsor: Braeburn, Inc
PDUFA Goal Date: December 1, 2020

Materials Reviewed: NDA Resubmission; Supporting Document #: 113; June 1, 2020

I. SUMMARY

1. Background

This memorandum responds to a consult request by the Division of Anesthesiology, Addiction Medicine and Pain Medicine (DAAP), dated August 3, 2020, to the Controlled Substance Staff (CSS) for Buprenorphine extended-release subcutaneous injection, Trade Name Brixadi, submitted by Braeburn, Inc. (Applicant) under NDA 210136. Buprenorphine extended-release subcutaneous injection is indicated for the treatment of opioid use disorder.

DAAP issued a Tentative Approval (TA) letter to the Applicant on December 21, 2018. At that time, only exclusivity issues precluded the NDA from approval. This resubmission requesting final approval is a class 2 resubmission. No new clinical data were included in this resubmission. However, DAAP is requesting that CSS review the labeling changes made to the Draft prescribing information (PI), particularly in Section 9: Drug Abuse and Dependence. Changes made by the Applicant are in accordance with the new draft guidance issued by the Agency in July 2019, regarding Section 9 Drug Abuse and Dependence[1].

In addition to revised labeling, the Applicant submitted postmarketing data for the foreign-approved product relevant to drug abuse and dependence. Brixadi is marketed outside of the US under the tradename Buvidal by Camurus AB, an independent and separate business partner of Braeburn. Camurus prepares an annual Periodic Benefit-Risk Evaluation Report (PBRER) that includes an analysis of postmarketing (PM) safety data received up to July 30th of each year. This PM report noted the occurrence of a withdrawal syndrome in twenty cases. A patient was hospitalized due to antisocial behavior and hallucinations approximately 3.5 months after starting Buvidal treatment. The patient was concurrently abusing benzodiazepines and amphetamines, therefore, the psychotic symptoms were possibly related to the combination of the other drugs and Buvidal. No cases of intravenous administration were reported for Buvidal.

Buprenorphine is a Schedule III substance under the Controlled Substances Act.

2. Conclusions

- The postmarketing data do not require additional changes to the labeling, as the warnings and related safety information about dependence and withdrawal in the current labeling adequately describe these risks.

1. Drug abuse and Dependence Section of Labeling for Human Prescription Drug and Biological Products- Content and Format. Draft Guidance for Industry; July 2019

- Changes made by the Applicant to the tentatively approved labeling are acceptable and are in accordance with the new draft guidance issued by the Agency in July 2019, regarding Section 9 Drug Abuse and Dependence[1].

3. Recommendations:

The tentatively approved label is copied below. Changes made to the tentatively approved label by the Applicant are indicated in **bold underlined text.** CSS is in agreement with these changes.

9 DRUG ABUSE AND DEPENDENCE

9.1 Controlled Substance

BRIXADI contains buprenorphine, a Schedule III substance under the Controlled Substances Act.

Under the Drug Addiction Treatment Act (DATA) codified at 21 U.S.C. 823(g), prescription use of this product in the treatment of opioid dependence is limited to healthcare providers who meet certain qualifying requirements, and who have notified the Secretary of Health and Human Services (HHS) of their intent to prescribe this product for the treatment of opioid dependence and have been assigned a unique identification number that must be included on every prescription.

9.2 Abuse

Abuse is the intentional, non-therapeutic use of a drug, even once, for its desirable psychological or physiological effects. Misuse is the intentional use, for therapeutic purposes, of a drug by an individual in a way other than prescribed by a healthcare provider or for whom it was not prescribed.

BRIXADI contains buprenorphine, a Schedule III controlled substance that can be abused similar to other opioids. Patients who continue to misuse, abuse, or divert buprenorphine products or other opioids should be provided with or referred for more intensive and structured treatment. Abuse of buprenorphine poses a risk of overdose and death. This risk is increased with the abuse of buprenorphine and alcohol and other substances, especially benzodiazepines ***[see Warnings and Precautions (5.5)].***

BRIXADI is distributed through a restricted distribution program, which is intended to prevent the direct distribution to a patient. BRIXADI should only be dispensed directly to a healthcare provider for administration by a healthcare provider. It is supplied in prefilled syringes and is intended for administration only by subcutaneous injection by a healthcare provider. The entire contents of the prefilled syringe should be administered.

Upon injection, BRIXADI spontaneously transforms from a low viscous solution to a liquid crystalline gel that encapsulates buprenorphine and releases it at a steady rate as the depot biodegrades ***[see Warnings and Precautions (5.1)].***

Clinical monitoring for evidence at the injection site of tampering or attempting to remove the

depot should be ongoing throughout treatment. No attempts to remove BRIXADI have been reported in clinical trials.

9.3 Dependence

Physical dependence is a state that develops as a result of physiological adaptation in response to repeated drug use, manifested by withdrawal signs and symptoms after abrupt discontinuation or a significant dose reduction of a drug.

Buprenorphine is a partial agonist at the mu-opioid receptor and chronic administration produces physical dependence of the opioid type, characterized by moderate withdrawal signs and symptoms upon abrupt discontinuation or rapid taper. The withdrawal syndrome is typically milder than seen with full agonists and may be delayed in onset. **Monitor patients during discontinuation of BRIXADI for symptoms of withdrawal *[see Warnings and Precautions (5.8)].***

Due to the long-acting nature of BRIXADI, withdrawal signs and symptoms may not be evident immediately following the discontinuation of treatment.

Neonatal opioid withdrawal syndrome (NOWS) is an expected and treatable outcome of prolonged use of opioids during pregnancy *[see Warnings and Precautions (5.6)]*.

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10/13/2020 08:34:04 AM

LABEL AND LABELING REVIEW
Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

*** This document contains proprietary information that cannot be released to the public***

Date of This Review:	September 17, 2020
Requesting Office or Division:	Division of Anesthesiology, Addiction Medicine, and Pain Medicine (DAAP)
Application Type and Number:	NDA 210236
Product Name and Strength:	Brixadi (buprenorphine) extended-release injection, 8 mg/0.16 mL, 16 mg/0.32 mL, 24 mg/0.48 mL, 32 mg/ 0.64 mL, 64 mg/0.18 mL, 96 mg/0.27 mL, 128 mg/0.36 mL
Product Type:	Combination Product (Drug-Device)
Rx or OTC:	Prescription (Rx)
Applicant/Sponsor Name:	Braeburn Pharmaceuticals, Inc.
FDA Received Date:	June 1, 2020 and September 1, 2020
OSE RCM #:	2017-1448-3
DMEPA Safety Evaluator:	Cameron Johnson, PharmD
DMEPA Team Leader:	Otto L. Townsend, PharmD

1 REASON FOR REVIEW

As part of the final approval process for Brixadi (buprenorphine) extended-release injection, the Division of Anesthesiology, Addiction Medicine, and Pain Medicine (DAAP) requested that we review the revised Brixadi prescribing information (PI), container labels, and carton labeling for areas of vulnerability that may lead to medication errors.

2 REGULATORY HISTORY

On October 18, 2017 and December 18, 2017, we reviewed the labels, labeling, and human factors (HF) validation study results for Brixadi submitted to IND 114082 and NDA 210136. While we noted the HF validation study results identified areas of vulnerability that could lead to medication errors, we determined that the issues could be mitigated through labeling revisions and did not require additional validation. Therefore, we found the results of the HF study acceptable from a medication error perspective.[ab]

On January 19, 2018, NDA 210136 was issued a Complete Response (CR) letter due to clinical, statistical, nonclinical, product quality, device, microbiology and drug product deficiencies.[c] On May 23, 2018, Braeburn submitted a response to address the deficiencies outlined in FDA's January 19, 2018 CR letter.

On June 22, 2018, the resubmission of NDA 210136 was deemed incomplete and an Acknowledge Incomplete Response Letter[d] was issued to Braeburn. On June 26, 2018, Braeburn submitted a Class II Resubmission to NDA 210136 to address the deficiencies identified in the June 22, 2018 Acknowledge Incomplete Response letter.

On October 10, 2018 we reviewed the labels and labeling provided in the resubmission and provided additional recommendations to Braeburn. Braeburn implemented all of our recommendations and we had no additional concerns from a medication error perspective.

On December 21, 2018, NDA 210136 received Tentative Approval under 21 CFR 314.105 with final approval being subject to expiration of a period of patent protection and/or exclusivity.

On June 1, 2020, Braeburn submitted a Request for Final Approval for NDA 210136.

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[a]Wilson, V. Label, Labeling, and Human Factors Results Review for buprenorphine injection (IND 114082 and NDA 210136). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2017 OCT 18. RCM No. 2017-1834 and 2017-1448.

[b] Wilson, V. Label and Labeling Review Memorandum for buprenorphine injection (NDA 210136). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2017 DEC 15. RCM No.: 2017-1448-1.

[c] Hertz, S. Complete Response for Brixadi. Silver Spring (MD): FDA, CDER, OND, DAAAP (US); 2018 JAN 19. NDA 210136.

[d] Hertz, S. Acknowledge Incomplete Response for Brixadi. Silver Spring (MD): FDA, CDER, OND, DAAAP (US); 2018 JUN 22. NDA 210136.

3 MATERIALS REVIEWED

Table 1. Materials Considered for this Label and Labeling Review	
Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B
ISMP Newsletters*	C – N/A
FDA Adverse Event Reporting System (FAERS)*	D – N/A
Other	E – N/A
Labels and Labeling	F

N/A=not applicable for this review
*We do not typically search FAERS or ISMP Newsletters for our label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

4 FINDINGS AND RECOMMENDATIONS

On September 1, 2020, Braeburn submitted draft carton labeling for their Brixadi Bridge Program/Patient Assistance Program, a program that provides Brixadi to patients experiencing insurance delays. In the submission, Braeburn noted that the carton labeling differs from the commercial product in that it includes a "Not For Sale" statement as well as a distinct National Drug Code (NDC) for each strength presentation. Braeburn provided the proposed NDC's that will be included on each carton labeling and noted that they "will include these additional NDCs in the draft Prescribing Information at the time of the first labeling edits/prior to PDUFA." Furthermore, we note that although all of the product strengths will be available under the assistance program, Braeburn only included the 8 mg carton labeling as the representative carton labeling for all the strengths. The only differences between the assistance program product and the commercial product will be the additional "Not For Sale" statement and the distinct NDCs. Therefore, we do not object to Braeburns proposed labeling strategy for Brixadi that will be provided to patients under their assistance program provided the final labeling is designed as described in their "Bridge/Patient Assistance Program Carton Reviewer's Guide.[e]

[e] Bridge-Patient Assistance Program Carton Reviewer's Guide (Brixadi IND 210136). Plymouth Meeting (PA): Braeburn Pharmaceuticals. 2020 SEP 01. Available from: \\CDSESUB1\evsprod\nda210136\0119\m1\us\bridge-pap-carton-r-g.pdf

Table 2 below includes the identified medication error issue with the submitted prescribing information (PI), our rationale for concern, and the proposed recommendation to minimize the risk for medication error.

Table 2. Identified Issues and Recommendations for Division of Anesthesiology, Addiction Medicine, and Pain Medicine (DAAP)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
Highlights of Prescribing Information			
1.	The strength is presented (b) (4) in the Dosage Forms and Strengths section of the Highlights but as total quantity per total volume (e.g., 8 mg/0.16 mL) in the Full Prescribing Information, Container labels and Carton labeling.	Inconsistent presentation of strength may lead to confusion. Per the United States Pharmacopeia (USP) Chapter <7> Labeling, the strength on container labels should be expressed as the quantity per total volume .	Revise the presentation of strength in the Highlights so that it is presented as total quantity per total volume. For example revise the strength to: •BRIXADI (weekly) is available in 8 mg/0.16 mL, 16 mg/0.32 mL, 24 mg/0.48 mL, and 32 mg/0.64 mL; •BRIXADI (monthly) is available in 64 mg/0.18 mL, 96 mg/0.27 mL, and 128 mg/0.36 mL

5 CONCLUSION

Our evaluation of the proposed Brixadi prescribing information (PI) identified an area of vulnerability that may lead to medication errors. Above, we have provided a recommendation in Table 2 for the Division.

APPENDICES: METHODS & RESULTS FOR EACH MATERIAL REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 3 presents relevant product information for Brixadi that Braeburn Pharmaceuticals, Inc. submitted on June 1, 2020.

Table 3. Relevant Product Information for Brixadi	
Initial Approval Date	N/A
Active Ingredient	buprenorphine
Indication	• treatment of moderate to severe opioid use disorder in patients who have initiated treatment with a single-dose of a transmucosal buprenorphine product or who are already being treated with buprenorphine • BRIXADI should be used as part of a complete treatment program that includes counseling and psychosocial support
Route of Administration	Subcutaneous
Dosage Form	Extended-release injection
Strength	Weekly: 8 mg/0.16 mL, 16 mg/0.32 mL, 24 mg/0.48 mL, 32 mg/0.64 mL Monthly: 64 mg/0.18 mL, 96 mg/0.27 mL, 128 mg/0.36 mL
Dose and Frequency	Inject subcutaneously once weekly or once monthly
How Supplied	Weekly and monthly BRIXADI is available as a sterile, yellowish to yellow clear liquid solution in a single dose, prefilled safety syringe
Storage	USP Controlled Room Temperature
Container Closure	Prefilled syringe

APPENDIX B. PREVIOUS DMEPA REVIEWS

On July 16, 2020, we searched for previous DMEPA reviews relevant to this current review using the terms, Brixadi and 210136. Our search identified three previous reviews[f,g,h], and we confirmed that our previous recommendations were implemented.

[f]Wilson, V. Label and Labeling Review Memorandum for buprenorphine injection (NDA 210136). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2017 DEC 15. RCM No.: 2017-1448-1.

[g]Wilson, V. Label, Labeling, and Human Factors Results Review for buprenorphine injection (IND 114082 and NDA 210136). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2017 OCT 18. RCM No. 2017-1834 and 2017-1448.

[h]Wilson, V. Label and Labeling Review for Brixadi (NDA 210136). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2018 OCT 10. RCM No.: 2017-1448-2.

APPENDIX C. – N/A

APPENDIX D. – N/A

APPENDIX E. – N/A

APPENDIX F. LABELS AND LABELING

F.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,[i] along with postmarket medication error data, we reviewed the following Brixadi labels and labeling submitted by Braeburn Pharmaceuticals, Inc. received on June 1, 2020.

- Container label(s)
- Carton labeling can be accessed in EDR via the following link:
  - \\cdsesub1\evsprod\nda210136\0113\m1\us\carton-labels.pdf
- Representative container label and carton labeling for sample:
  - \\CDSESUB1\evsprod\nda210136\0119\m1\us\bridge-pap-carton-r-g.pdf
- Instructions for Use (Image not shown) can be accessed in EDR via the following link:
  - \\cdsesub1\evsprod\nda210136\0113\m1\us\ifu.pdf
- Prescribing Information (Image not shown) can be accessed in EDR vial the following link:
  - \\cdsesub1\evsprod\nda210136\0113\m1\us\draft-label-text-redline-word.docx

F.2 Label and Labeling Images

Container label(s)

[i] Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

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M E M O R A N D U M

Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research

Date: November 29, 2018

To: Sharon Hertz, M.D., Director
Division of Anesthesia, Analgesia, and Addiction Products

Through: Dominic Chiapperino, Ph.D., Director
Martin Rusinowitz, M.D., Senior Medical Officer
Controlled Substance Staff

From: Alan Trachtenberg, M.D., M.P.H., Medical Officer
Controlled Substance Staff

Subject: Brixadi (CAM2038), Buprenorphine injectable Subcutaneous (SC) depot,
NDA 210136 (IND 114082**)**
Doses, formulations, routes: Buprenorphine base in a pre-filled syringe for once weekly or once monthly administration. Once weekly provided in 8 mg, 16 mg, 24 mg, 32 mg, and 64 mg doses. Monthly strengths provided in 96 mg, 128 mg, (b) (4) doses.
Indication: Opioid Agonist Treatment (OAT) of Opioid Use Disorder (OUD (b) (4)
Sponsor: Braeburn Pharmaceuticals
PDUFA Goal Date: Originally January 19, 2018 (priority review), at which time the NDA received a CR. The PDUFA date for the resubmitted NDA is December 26, 2018, although DAAAP anticipates an early action by December 21, 2018

Materials Reviewed: NDA210136\0079 (5.23.18 resubmission)
NDA210136\0081 (6.26.18 resubmission)

I. SUMMARY

1. Background

This memorandum responds to a consult request from the Division of Anesthesia, Analgesia, and Addiction Products (DAAAP) to evaluate the abuse liability assessment and opioid blockade study submitted under 505(b)(2) by Braeburn Pharmaceuticals in NDA 210136 and IND 114082, for CAM2038/Brixadi (injectable subcutaneous (SC) depot buprenorphine).

The Sponsor resubmitted NDA 210136 on May 23, 2018, and the review team determined that the resubmission was an incomplete response to the deficiencies listed in the Complete Response letter dated January 19, 2018.The Sponsor's subsequent submission on June 26th was deemed by DAAAP to be complete. The 6-month review clock was started and the DAAAP plan is to take an early action by December 21, 2018. CSS was originally consulted primarily to evaluate the data from a blockade study of the weekly formulation. The data from this study were deemed to be acceptable during the initial review. The reasons for DAAAP's Complete Response concerned clinical data issues from the efficacy and safety studies and not from the blockade study. DAAAP did not require any further review of the NDA from CSS, and the NDA resubmission did not include any new information particular to CSS concerns. Consequently, CSS involvement with the resubmission will be primarily any comment we can contribute to the abuse-related sections of the label or any REMS issues related to the DATA 2000 waivers that might arise.

Buprenorphine is a partial mu-agonist opioid and is the only C-III opioid (with or without naloxone in combination) approved for the treatment of OUD. Therefore, it is the only opioid medication covered by the Drug Addiction Treatment Act of 2000 (DATA-2000). DATA-2000 established a legal pathway for Office-Based Opioid Treatment (OBOT) to be offered by physicians outside of the special clinics designated and licensed by DEA as "Narcotic Treatment Programs" (NTPs, or "Methadone clinics"). (Buprenorphine can also be used in these specially designated clinics.) It was first approved as a new molecular entity (NME), indicated for pain treatment, in 1981 and marketed as Buprenex injectable under NDA 018401. It was approved as a sublingual tablet for the treatment of OUD in 2002 under NDA 020732 for Subutex (BUP hydrochloride) sublingual tablet, and under NDA 020733 for Suboxone, another sublingual tablet formulated as combination with naloxone.

Opioid agonists or partial agonists such as BUP have several properties that may contribute to their effectiveness in the treatment of opioid addiction. They alleviate the acute symptoms of opioid withdrawal and drug craving. They also attenuate or block the acute effects of exogenous opioids when the patient may have a "lapse" to drug use and help prevent immediate repetition of the lapse and extension into a full relapse of uncontrolled self-administration of drugs. Opioid agonists such as BUP can also be diverted and abused by patients and others. While not posing as high a mortality risk of overdose as from full agonists such as methadone, BUP is itself a drug of abuse such that safeguards against abuse and diversion are required.

The first BUP product to provide long term treatment without need for dispensing or self-administration was this Sponsor's subcutaneously implanted BUP rod, marketed as Probuphine,

approved under NDA 204442 on May 26, 2016. Five of these rods can be surgically implanted to provide 6 months of continuous BUP. A minor surgical procedure is required for administration and another for removal at the end of their use. Approval was for only one additional implantation after the first. Such parenteral administration by health professionals offered advantages over the self-administration of sublingual BUP by potentially increasing treatment compliance and minimizing abuse and diversion of BUP. CAM2038 is intended to offer similar benefits, but without a need for surgery. Although CAM2038 will require weekly or monthly visits, rather than every 6 months, the decreased procedural risk, and increased access that could be offered by the growing pool of DATA-waived health professionals are two potential advantages of this formulation. Another monthly LA injectable SC depot product has recently been approved with 300 mg BUP under NDA 209819 as Sublocade from Indivior, the originator of the RLD, Subutex. This product is indicated for maintenance in OUD, only after initiation and stabilization with a SL BUP product for MAT. This leaves CAM2038 potentially more versatile, since it does not require such stabilization with SL BUP prior to first administration of the LA injection.

Buprenorphine is a controlled substance, listed in Schedule III of the Controlled Substance Act (CSA). The Sponsor does not propose any change in schedule for their product.

2. Conclusions

1. CAM2038 is a SC long-acting depot formulation of BUP for Buprenorphine Injection Medication Assisted Treatment (BI-MAT) in the treatment of OUD. If approved, this will be the 2nd BI-MAT product, following the recently approved Sublocade monthly injection from Indivior, NDA 209819. CAM2038 may offer a clinical or logistic advantage over the other product, in that the ability to induct patients directly onto CAM2038, without requiring an intermediate phase of SL-MAT, would provide OUD patients and providers with greater flexibility in the initiation of MAT. For instance, it may become feasible to start the medical aspects of addiction treatment directly in the Emergency Department (ED), immediately on presentation.

2. This NDA is a 505(b)(2) submission using Subutex (NDA 20732) as the Listed Drug. Buprenorphine is a well characterized partial mu-opioid receptor agonist and kappa-opioid receptor antagonist and is in currently marketed products for the treatment of OUD and pain.

3. Buprenorphine is a Schedule III opioid (“Narcotic”). The Sponsor is not requesting any change in this classification of their product.

4. As an opioid approved by FDA for the treatment of OUD, CAM2038’s medical use will be regulated under the Drug Addiction Treatment Act of 2000 (DATA-2000). Prescribers must document their adequate training to the Substance Abuse and Mental Health Services Administration (SAMHSA) and receive a DATA waiver from the DEA.

5. The large amount of BUP [redacted] (b) (4) in each device is formulated to congeal after injection. The easily injectable nature of the drug/device product creates a significant risk for intravascular self-injection by persons with OUD, potentially leading to severe life-threatening complications. Therefore, administrative and regulatory controls will be required to keep the product completely under the control of health professionals, until administration of the drug by such professionals, with any remainder of the drug being properly disposed.

6. This new type of product would provide a BUP treatment option that requires weekly or monthly, rather than daily (or once every 2-3 days), administration. This and other new long acting and injectable BUP products may lead to a variety of new possibilities for creating greater access to MAT for more patients with OUD, while decreasing any collateral diversion and abuse that might otherwise complicate this greater access.

7. Previously objectional statements included in the initial label, to which CSS raised objections, have been removed. [redacted] (b) (4)

8. Still pending is a determination as to whether the Sponsor's REMS as currently proposed meets the requirements of the CSA, DATA-2000, and the standards of training and practice promulgated by SAMHSA, so that it can be determined whether the benefits of this product, when utilized under the provisions of the REMS, will outweigh the potential risks of misuse, abuse, diversion and overdose.

3. Recommendations

1. From a CSS perspective, this product may be approved. The Sponsor's proposal for maintaining this buprenorphine product in Schedule III under the CSA is acceptable.

2. Sponsor should provide detailed narratives on misuse, abuse, addiction, diversion and overdose in their submission of post approval periodic safety reports. In particular, they should identify any new methods of obtaining, diverting, or tampering of this formulation, or otherwise having the product escape the administration safeguards put into place under DATA-2000 and the product's REMS.

3. The Sponsor should be encouraged to perform clinical trials to establish whether there is a role for this product in the final phase (discharge planning) of OD management in the ED setting, to prevent immediate relapse and a 2nd overdose after resuscitating patients with OUD who present with OD.

CSS will continue participating in any labelling or REMS meetings to which we are asked to contribute.

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/s/

ALAN I TRACHTENBERG
11/29/2018

MARTIN S RUSINOWITZ
12/06/2018

DOMINIC CHIAPPERINO
12/06/2018

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy

PATIENT LABELING REVIEW

Date:	December 4, 2018
To:	Sharon Hertz, MD Director **Division of Anesthesia, Analgesia, and Addiction Products (DAAAP)**
Through:	LaShawn Griffiths, MSHS-PH, BSN, RN Associate Director for Patient Labeling **Division of Medical Policy Programs (DMPP)**
From:	Morgan Walker, PharmD, MBA, CPH Senior Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)** Nima Ossareh, PharmD Regulatory Review Officer **Office of Prescription Drug Promotion (OPDP)**
Subject:	Review of Patient Labeling: Medication Guide (MG)
Drug Name (established name):	BRIXADI (buprenorphine)
Dosage Form and Route:	extended-release injection, for subcutaneous use, CIII
Application Type/Number:	NDA 210136
Applicant:	Braeburn Pharmaceuticals, Inc.

1 INTRODUCTION

On June 26, 2018, Braeburn Pharmaceuticals, Inc. submitted for the Agency's review a resubmission of their New Drug Application (NDA) 210136 for BRIXADI (buprenorphine extended-release) injection. The Applicant submitted this resubmission in response to Agency's Complete Response (CR) letter issued on June 22, 2018. The proposed indication is for weekly and monthly dosing and indicated for the treatment of moderate to severe opioid use disorder.

This collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to a request by the Division of Anesthesia, Analgesia, and Addiction Products (DAAAP) on August 2, 2018 for DMPP and OPDP to review the Applicant's proposed Medication Guide (MG) for BRIXADI (buprenorphine extended-release) injection.

The Risk Evaluation and Mitigation Strategy (REMS) is being reviewed by the Division of Risk Management (DRISK) and will be provided to DAAAP under separate cover.

2 MATERIAL REVIEWED

- Draft BRIXADI (buprenorphine extended-release) injection MG received on June 26, 2018, and received by DMPP and OPDP on November 21, 2018.
- Draft BRIXADI (buprenorphine extended-release) injection Prescribing Information (PI) received on June 26, 2018, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on November 21, 2018.

3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6th to 8th grade reading level, and have a reading ease score of at least 60%. A reading ease score of 60% corresponds to an 8th grade reading level.

Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APHont to make medical information more accessible for patients with vision loss.

In our collaborative review of the MG we:

- simplified wording and clarified concepts where possible
- ensured that the MG is consistent with the Prescribing Information (PI)
- removed unnecessary or redundant information
- ensured that the MG is free of promotional language or suggested revisions to ensure that it is free of promotional language

- ensured that the MG meets the Regulations as specified in 21 CFR 208.20
- ensured that the MG meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)

4 CONCLUSIONS

The MG is acceptable with our recommended changes.

5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DMPP and OPDP on the correspondence.
- Our collaborative review of the MG is appended to this memorandum. Consult DMPP and OPDP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the MG.

Please let us know if you have any questions.

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/s/

MORGAN A WALKER
12/04/2018

NIMA OSSAREH
12/04/2018

LASHAWN M GRIFFITHS
12/04/2018

FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion

****Pre-decisional Agency Information****

Memorandum

Date: 12/4/18

To: Taiye Ayoola
Regulatory Project Manager
Division of Anesthesia, Analgesia, and Addiction Products (DAAAP)

From: Nima Ossareh, PharmD, RAC
Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: Sam Skariah, Team Leader, OPDP

Subject: OPDP Labeling Comments for BRIXADI™ (buprenorphine) extended-release injection, for subcutaneous use CIII

NDA: 210136

In response to DAAAP's consult request dated October 10, 2017, OPDP has reviewed the proposed product labeling (PI) and medication guide (MG) and carton and container labeling for the original NDA submission for BRIXADI™ (buprenorphine) extended-release injection, for subcutaneous use CIII.

PI: OPDP's comments on the proposed labeling are based on the draft PI received by electronic mail from DAAAP on November 21, 2018 and are provided below.

MG: A combined OPDP and Division of Medical Policy Programs (DMPP) review of the PPI will be completed under a separate cover.

Carton and Container Labeling: OPDP has reviewed the attached proposed carton and container labeling submitted by the Sponsor to the electronic document room on November 8, 2018, and we do not have any comments.

Thank you for your consult. If you have any questions, please contact Nima Ossareh at (240) 402-2769 or nima.ossareh@fda.hhs.gov.

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/s/

NIMA OSSAREH
12/04/2018

Office of Prescription Drug Promotion

Internal Consults

****Pre-decisional Agency Information****

Please Note: The following review is for DRISK only and should not be used to provide comments to the sponsor.

To: Joan Blair, Health Communications Analyst,
Division of Risk Management (DRISK),
Office of Surveillance and Epidemiology (OSE)

From: Nima Ossareh, PharmD, RAC, Regulatory Review Officer, OPDP

CC: Sam Skariah, Team Leader, OPDP
Mathew Davis, Safety Regulatory Project Manager, OSE
Selena Ready, Team Leader, DRISK
Joan Blair, Risk Management Analyst, DRISK
Doris Auth, Associate Director, DRISK
Carole Broadnax, OPDP
Michael Wade, OPDP
CDER-OPDP-RPM

Date: 11/20/18

Re: NDA 210136
BRIXADI™ (buprenorphine) extended-release) injection, for subcutaneous use CIII
Comments on draft Risk Evaluation and Mitigation Strategies (REMS) Materials (Submission date: November 8, 2018)

Materials Reviewed

OPDP has reviewed the following proposed REMS materials for Brixadi REMS:

- Healthcare Provider (HCP) REMS Materials:
  - Dear Healthcare Provider Letter
  - Fact Sheet
  - Healthcare Setting (b) (4) Form
- Websites
  - Brixadi REMS Website (www.brixadirems.com) Screenshots

The version of the draft REMS materials used in this review were sent from DRISK (Joan Blair) via email on November 13, 2018. The draft REMS materials are attached to the end of this review memorandum.

OPDP offers the following comments on these draft REMS materials for Brixadi.

General Comment

Please remind the sponsor that REMS materials are not appropriate for use in a promotional manner.

OPDP notes the link www.brixadirems.com and toll-free numbers such as 1-866-492-9624. OPDP recommends that these items represent a direct link to only REMS related information and not be promotional in tone. Furthermore, we remind the sponsor that the REMS specific website should not be the sole source of approved REMS materials.

REMS Materials

OPDP does not object to including the following materials in the REMS program (please see Specific Comment[s] below):

- Healthcare Provider (HCP) REMS Materials:
  - Dear Healthcare Provider Letter
  - Fact Sheet
  - Healthcare Setting (b) (4) Form
- Websites
  - Brixadi REMS Website (www.brixadirems.com) Screenshots

Specific Comment[s]

OPDP considers the following statement[s] promotional in tone and recommends revising or deleting them from the REMS piece:

- Rems Website
  - Indications/Use
    - [redacted]

      The statement [redacted] OPDP recommends deleting this statement.

      In addition, the statement [redacted]

      OPDP recommends revising the statement to include this material information, and presenting the indication statement in a manner consistent with the draft PI.

We have no additional comments on these proposed REMS materials at this time.

Thank you for your consult.

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/s/

NIMA OSSAREH
11/20/2018

LABEL AND LABELING REVIEW

Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

***** This document contains proprietary information that cannot be released to the public*****

Date of This Review:	October 10, 2018
Requesting Office or Division:	Division of Anesthesia, Analgesia, and Addiction Products (DAAAP)
Application Type and Number:	NDA 210136
Product Name and Strength:	Brixadi (buprenorphine) Injection; Weekly: 8 mg/0.16 mL, 16 mg/0.32 mL, 24 mg/0.48 mL, 32 mg/ 0.64 mL Monthly: 64 mg/0.18 mL, 96 mg/0.27 mL, 128 mg/0.36 mL
Total Product Strength:	50 mg/mL and 356 mg/mL
Product Type:	Single Ingredient, Combination Product
Rx or OTC:	Rx
Applicant/Sponsor Name:	Braeburn Pharmaceuticals, Inc.
FDA Received Date:	May 23, 2018 and August 3, 2018
OSE RCM #:	2017-1448-2
DMEPA Safety Evaluator:	Valerie S. Wilson, PharmD
DMEPA Team Leader:	Otto L. Townsend, PharmD

1 REASON FOR REVIEW

As part of the approval process for Brixadi (buprenorphine) Injection, the Division of Anesthesia, Analgesia, and Addiction Products (DAAAP) requested that we review the proposed prescribing information, medication guide, container labels, and carton labeling for areas that may lead to medication errors.

2 REGULATORY HISTORY

On October 18, 2017 and December 15, 2017, we reviewed the label, labeling, and human factors study results for Brixadi submitted to IND 114082 and NDA 210136.[ab]

On January 19, 2018, NDA 210136 received a Complete Response for multiple deficiencies identified across several disciplines.[c] On May 23, 2018, Braeburn submitted a response to address the deficiencies outlined in FDA's January 19, 2018 Complete Response Letter.

On June 22, 2018, the resubmission of NDA 210136 was deemed incomplete and an Acknowledge Incomplete Response Letter[d] was issued to the Applicant. On June 26, 2018, the Applicant submitted a Class II Resubmission to NDA 210136 to address the deficiencies identified in the June 22, 2018 Acknowledge Incomplete Response letter.

3 MATERIALS REVIEWED

Table 1. Materials Considered for this Label and Labeling Review

Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B
ISMP Newsletters	C (N/A)
FDA Adverse Event Reporting System (FAERS)*	D (N/A)
Other	E (N/A)
Labels and Labeling	F

N/A=not applicable for this review
*We do not typically search FAERS for our label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

[a] Wilson, V. Label and Labeling Review Memorandum for buprenorphine injection (NDA 210136). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2017 DEC 15. RCM No.: 2017-1448-1.

[b] Wilson, V. Label, Labeling, and Human Factors Results Review for buprenorphine injection (IND 114082 and NDA 210136). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2017 OCT 18. RCM No. 2017-1834 and 2017-1448.

[c] Hertz, S. Complete Response for Brixadi. Silver Spring (MD): FDA, CDER, OND, DAAAP (US); 2018 JAN 19. NDA 210136.

[d] Hertz, S. Acknowledge Incomplete Response for Brixadi. Silver Spring (MD): FDA, CDER, OND, DAAAP (US); 2018 JUN 22. NDA 210136.

4 FINDINGS AND RECOMMENDATIONS

Tables 2 and 3 below include the identified medication error issues with the submitted prescribing information and carton labeling, DMEPA's rationale for concern, and the proposed recommendation to minimize the risk for medication error.

Table 2: Identified Issues and Recommendations for Division of Anesthesia, Analgesia, and Addiction Products

Prescribing Information			
	IDENTIFIED ISSUE	**RATIONALE FOR CONCERN**	**RECOMMENDATION**
Full Prescribing Information			
1.	The DOSAGE FORMS AND STRENGTHS section does not specify that Brixadi is available as "single-dose" pre-filled syringes.	Inclusion of the package type term, "single-dose" helps to minimize the risk of wrong administration technique errors.	To mitigate wrong administration technique errors, include "single-dose" in the description of Brixadi in the DOSAGE FORMS AND STRENGTHS section. For example, revise to state: *"Brixadi is a weekly and monthly injection in a single-dose, pre-filled syringe available in the following dosage strengths."*

Table 3: Identified Issues and Recommendations for Braeburn Pharmaceutical, Inc. (entire table to be conveyed to Applicant)

Container Label, Carton Labeling, and Packaging			
	IDENTIFIED ISSUE	**RATIONALE FOR CONCERN**	**RECOMMENDATION**
Carton Labeling			
1.	A statement indicating that Brixadi is for healthcare professional (HCP) administration only is not included on the carton labeling.	Due to the risks associated with Brixadi, it is restricted to use by healthcare professionals.	To further mitigate the risk of dispensing Brixadi directly to patients, consider including a statement on the principal display panel of the carton labeling that is indicative of a dispensing restriction. For example, include the statement, "For Healthcare Professional Administration

			Only, Do Not Dispense to Patient," or similar statement.
2.	The statement, (b) (4) (b) (4) is written in passive voice and directed only to pharmacists.	Brixadi is intended to be administered by HCP only and may not be dispensed directly to patients by the pharmacist; therefore, pharmacists may not be able to ensure each patient receives the medication guide. Additionally, HCP administering Brixadi could misinterpret the message to believe that a pharmacist has already provided the patient with a medication guide.	To mitigate the risk of patients not receiving the required medication guide for Brixadi, we recommend you revise the statement, using active voice, to read, for example: *"Attention: Dispense the enclosed Medication Guide to each patient."*
3.	We note the statement (b) (4)	This statement implies (b) (4) (b) (4)	Revise the statement on each monthly injection carton to read, "Once-monthly subcutaneous injection for treatment of opioid use disorder."

5 CONCLUSION

Our evaluation of the proposed prescribing information and carton labeling identified areas of vulnerability that may lead to medication errors. Above, we have provided recommendations in Table 2 for the Division and Table 3 for the Applicant. We ask that the Division convey Table 3 in its entirety to the Applicant so that recommendations are implemented prior to approval of this NDA.

APPENDICES: METHODS & RESULTS FOR EACH MATERIAL REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 4 presents relevant product information for Brixadi that Braeburn Pharmaceuticals submitted on May 23, 2018.

Table 4. Relevant Product Information for Brixadi	
Initial Approval Date	N/A
Active Ingredient	buprenorphine
Indication	Treatment of moderate to severe opioid use disorder
Route of Administration	Subcutaneous
Dosage Form	Injection
Strength	Weekly: 8 mg/0.16 mL, 16 mg/0.32 mL, 24 mg/0.48 mL, 32 mg/0.64 mL Monthly: 64 mg/0.18 mL, 96 mg/0.27 mL, 128 mg/0.36 mL
Dose and Frequency	Once weekly or Once monthly
How Supplied	Cartons containing a pre-filled, single-dose safety syringe
Storage	Store BRIXADI at room temperature at 20°C to 25°C (68°F to 77° F); with excursions permitted at 15°C to 30° C (59°F to 86°F) [see USP Controlled Room Temperature].
Container Closure System	Prefilled syringe

APPENDIX B. PREVIOUS DMEPA REVIEWS

B.1 Methods

On August 20, 2018, we searched the L:drive and AIMS using the terms, NDA 210136 to identify reviews previously performed by DMEPA.

B.2 Results

Our search identified two previous reviews,[ef] and we confirmed that our previous recommendations were implemented or considered.

[e] Wilson, V. Label and Labeling Review Memorandum for buprenorphine injection (NDA 210136). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2017 DEC 15. RCM No.: 2017-1448-1.

[f] Wilson, V. Label, Labeling, and Human Factors Results Review for buprenorphine injection (IND 114082 and NDA 210136). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2017 OCT 18. RCM No. 2017-1834 and 2017-1448.

APPENDIX F. LABELS AND LABELING

F.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,[g] along with postmarket medication error data, we reviewed the following Brixadi labels and labeling submitted by Braeburn Pharmaceuticals on May 23, 2018 and August 3, 2018.

- Container (Syringe) labels
- Carton labeling
- Professional Sample Carton Labeling
- Instructions for Use
- Medication Guide (Image not shown)
- Prescribing Information (Image not shown)

F.2 Label and Labeling Images

F.2.1. Container (Syringe) Labels

(b) (4)

[g] Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

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/s/

VALERIE S WILSON
10/10/2018

OTTO L TOWNSEND
10/10/2018

Deputy Director for Safety Memorandum to File

Division of Anesthesia, Analgesia, and Addiction Products
Office of Drug Evaluation 2, Office of New Drugs
Center for Drug Evaluation and Research
Food and Drug Administration

NDAs	*20732, 20733, 22410, 204242, 204442, 205637, 209819, 210136*
Drug names	*Subutex, Suboxone (tablet), Suboxone (film), Zubsolv, Probuphine, Bunavail, Sublocade, Brixadi (buprenorphine formulations indicated for the treatment of opioid dependence)*
TSI #	*880*
Safety Issue Names	*QT prolongation*
Author name	*Judith A. Racoosin, MD, MPH*
Date	*See DARRTS signature block*

BACKGROUND

NDA 22410 was approved in August 2010 for SUBOXONE (buprenorphine/naloxone) sublingual film. Prior to approval, DAAAP became aware of the results of a thorough QT (tQT) study conducted by Purdue Pharma with their transdermal buprenorphine product (BuTrans, NDA 21306). In this study, transdermal application of buprenorphine, 10 mcg/hr and 40 mcg/hr, were compared to a moxifloxacin control. This study identified a signal for QT prolongation that was considered to meet the threshold for regulatory concern, but that was not of clear clinical significance. The dose studied was substantially lower than the labeled dose used for sublingual buprenorphine products for treating opioid addiction.

In view of this new finding, and the knowledge gap that existed with respect to buprenorphine's potential to affect the cardiac conduction system at the doses that are used in addiction treatment, the Applicant was required to conduct a tQT study. The text of the postmarketing requirement (PMR) follows below:

> 1674-1: A clinical trial to assess the risk of QT prolongation with sublingual buprenorphine, i.e., a thorough QT (tQT) trial. A comparison to methadone at typical treatment doses should be included. It is likely that this trial will need to be conducted in opioid-tolerant volunteers or new entrants to opioid-dependence treatment.

A tQT PMR identical to the one above was issued for both Suboxone and Subutex SL tablets on December 12, 2011 under S-006/S-007 (PMR 1855-1) for Subutex and

S-007/S-008 (PMR 1856-1) for Suboxone SL tablets. The Division indicated that one study would be acceptable to fulfill all three PMRs.

After several years of discussions with the Applicant about various protocol designs, the protocol submitted on October 5, 2015 for the QT study was found acceptable on November 20, 2015. Subsequently, on June 20, 2016, Indivior informed the Division via email correspondence that they could not proceed with the study because of logistical and ethical concerns with the study design. On November 23, 2016, Indivior submitted a meeting request to discuss the PMR for the tQT study. The briefing package was received on March 24, 2017. In the preliminary comments dated April 21, 2017, the Division noted "assuming that the appropriate data were collected from your RBP-6000 development program (i.e., IND 107607 for a buprenorphine depot injection) and appropriately analyzed, it is possible that the PMR could be released based on the findings from that program, but that will be a matter for review."

Indivior submitted a meeting request on March 31, 2018, as a "written responses only" meeting to seek the Agency's input on whether the postmarketing requirement to conduct a QT trial for SUBOXONE sublingual film as per Approval Letter dated August 30, 2010, has been adequately addressed through the QTc-related analysis and the information provided for SUBLOCADE, under NDA 209819.

The briefing package was submitted along with the meeting request on March 31, 2018. A meeting request was accepted with an agreement to provide the responses by June 12, 2018.

During the years that QT study discussions were going on, other buprenorphine products for medication-assisted therapy were approved, and each got a similar PMR to assess the risk of QT prolongation with the drug product:

Zubsolv (Orexo), approved July 3, 2013, got the following PMR:

2059-1 A clinical trial to assess the risk of QT prolongation with Zubsolv sublingual tablet, i.e., a thorough QT (tQT) trial.

Current status of the study: In a letter dated January 11, 2018, Orexo posed the following question: "We note that there was a larger study performed on buprenorphine concentration – effect modelling on the QT as per RBP-6000 Briefing Document: 31 October, 2017 –FDA Advisory Committee Meeting. This study appears to cover the concentration range that our original study design proposed and may therefore make the post approval commitment redundant. If the agency is aware of any prolongation of QT signal, we would of course willingly accept appropriate language to be added to the Zubsolv Prescribing Information." Hence, they are awaiting Agency feedback on this point.

Bunavail (BDSI), approved June 6, 2014 got the following PMR:

2164-1 A clinical trial to assess the risk of QT prolongation with Bunavail (buprenorphine and naloxone) buccal film.

Current status of the study: QT/IRT has reviewed QT study protocols for both the Bunavail and Belbuca products, as well as a rationale submitted in January 2018 by BDSI to support why the study should be able to address both products PMR for a QT study. QT/IRT provided a review dated March 14, 2018 with comments for the Applicant responsive to the request to conduct just one study. Those comments have not yet been shared with BDSI.

Probuphine (Braeburn; now Titan), approved May 26, 2016, got the following PMR:

3078-2 Clinical trial to assess the risk of QT prolongation with subdermal PROBUPHINE (buprenorphine hydrochloride).

Current status of the study: QT/IRT completed an initial review of the protocol 11/27/2017, providing comments to the Applicant; they recently reviewed the Applicant's response in a review dated March 15, 2018, and provided some additional comments. Those comments have not yet been shared with Braeburn (Titan).

Sublocade development program- QT assessment

As part of the development program for RBP-6000 (buprenorphine ATRIGEL depot, branded as Sublocade) for treatment of opioid dependence under IND 107607, Indivior provided a brief overview of its approach to QT evaluation. As noted above, on April 21, 2017, in minutes from a meeting to discuss the QT study PMR, the Division stated "assuming that the appropriate data were collected from your RBP-6000 development program (i.e., IND 107607) and appropriately analyzed, it is possible that the PMR could be released based on the findings from that program, but that will be a matter for review."

Because of the difficulties experienced with trying to conduct a tQT study for Suboxone film, for the Sublocade NDA, Indivior provided ECG data collected in their clinical trial program for Sublocade. The QT/IRT consultant (Dr. Gottipati) concluded that the ECG data collected in the pivotal efficacy study (RB-US-13-0001) was able to support excluding large mean increases in the QTc interval, when comparing the QTc measurements at the maximum observed buprenorphine exposure compared to baseline. Additionally, few QTc categorical outliers were observed in the Phase 3 study (RB-US-13-0001) and its open- label extension, and there was an absence of clinically significant ventricular tachyarrhythmias based on evaluation of 24-h Holter recordings at each dosing visit.

To explore the changes in QTc as it related to exposure, the QT-IRT reviewer did not rely on Indivior's concentration-QT analysis (for reasons stated in the review), but rather evaluated the data collected in the Phase 3 trial (RB-US-13-0001), because it was a blinded study with two dose groups and placebo. There were no QTc values exceeding 480 ms and no ΔQTc values exceeding 60 ms at the Cmax for the 5th and 6th injection. These data suggested an absence of a large difference in the QTc effect in the exposure range studied. Finally, in the overall development program, there were no adverse events suggestive of malignant arrhythmia (e.g., syncope, seizures, ventricular arrhythmias, ventricular fibrillation, flutter, torsade de pointes, or sudden death). In her Cross-discipline Team Leader review, Dr. Winchell concluded, "Overall, the data are reassuring

in excluding large increases in QT interval, despite the high plasma exposures in the Sublocade studies."

RBP-6000 was approved under NDA 209819 as SUBLOCADE (buprenorphine extended-release) injection, for subcutaneous use, in November 2017, with the following information about use in patients at risk for arrhythmia:

5.15 Use in Patients at Risk for Arrhythmia

Buprenorphine has been observed to prolong the QTc interval in some patients participating in clinical trials. Consider these observations in clinical decisions when prescribing buprenorphine to patients with hypokalemia, hypomagnesemia, or clinically unstable cardiac disease, including unstable atrial fibrillation, symptomatic bradycardia, unstable congestive heart failure, or active myocardial ischemia. Periodic electrocardiographic (ECG) monitoring is recommended in these patients. Avoid the use of buprenorphine in patients with a history of Long QT Syndrome or an immediate family member with this condition or those taking Class IA antiarrhythmic medications (e.g., quinidine, procainamide, disopyramide) or Class III antiarrhythmic medications (e.g., sotalol, amiodarone, dofetilide), or other medications that prolong the QT interval *[see Clinical Pharmacology (12.2)]*.

Information was also included in the pharmacodynamics section (12.2) about the results of the assessment of the effect of SUBLOCADE on cardiac repolarization.

Cardiac Electrophysiology

Serial ECGs were collected following a single dose and at steady-state to evaluate the effect of SUBLOCADE on the QT interval in five clinical studies including the Phase 3 study. In a Phase 3 study, seven patients had an increase from baseline QTc greater than 60 msec at any time [2/203 patients (1.0%) in the 300 mg/100 mg group and 5/201 patients (2.0%) in the 300 mg/300 mg group] and one patient in the 300 mg/300 mg group was found to have a QTc greater than 500 msec. These QTc findings were all sporadic and transient and none led to aberrant ventricular rhythm. Review of ECG and adverse event data provided no evidence for syncope, seizure, or ventricular tachycardia or fibrillation.

No postmarketing requirement was issued for a QT study.

CAM2038 development program- QT assessment

During the development program for CAM2038 (buprenorphine extended-release injection, branded as Brixadi) for treatment of opioid dependence under IND 114082, Braeburn was also informed that they would need to provide data on the effects of CAM2038 on cardiac repolarization as demonstrated by changes in the QT interval of the ECG.

Rather than performing a specific QT study, Braeburn provided data collected in their clinical trial program for CAM2038. These included studies of volunteers under naltrexone blockade, which may not be informative[1], and ECGs collected during efficacy studies that did not include PK assessments. Braeburn also submitted in vitro studies of cardiac channel effects -- a comprehensive preclinical assessment that included

[1] A study of naltrexone-treated patients in another QT study demonstrated that naltrexone has its own effects on the QT interval (QT shortening); therefore, ECGs measured in naltrexone-blocked patients taking buprenorphine are uninterpretable for assessing the effect of the buprenorphine on the QT interval.

assessment of the major cardiac ionic currents (hERG, peak sodium, late sodium, L-type calcium, and KVLQT1/minK). The QT/IRT reviewer (Dr. Gottipati) noted that "…at concentrations in the micromolar range that buprenorphine and norbuprenorphine inhibits all the currents studied. However, these concentrations are well above the clinically relevant concentrations (subnanomolar range), and it therefore seems unlikely that buprenorphine or norbuprenorphine would cause QT prolongation via interaction with any of the cardiac ionic currents studied." Dr. Gottipati further summarized, "Overall, the data reviewed in this submission shows an absence of large mean increases in the QTc interval compared to a baseline where patients have been taking buprenorphine. In addition, the data shows that buprenorphine and its metabolite norbuprenorphine are unlikely to interact with any of the major cardiac ionic currents (Ikr, Iks, INa,Peak, INa,Late and ICa). However, as the data do not permit excluding changes in the QTc interval from a drug-free baseline, we suggest that the sponsor includes similar language in the label as is included for other buprenorphine products."

CONCLUSIONS

DAAAP has long been trying to understand whether the modest QT prolongation observed in the BuTrans tQT study occurs to a more substantial degree with the higher plasma levels of buprenorphine obtained with use of higher doses used to treat opioid dependence. Years of protocol development beginning with issuance of the first PMR for a tQT study for Suboxone sublingual film in August 2010 has not resulted in a completed study due to logistical and ethical concerns. With the development of the depot formulations of buprenorphine by Indivior and Braeburn, DAAAP noted an opportunity to collect other kinds of relevant data to help better understand whether we need to be concerned about life-threatening cardiac arrhythmias associated with the use of buprenorphine products. Following the evaluation of the effects of buprenorphine on the QT interval as assessed in the Sublocade and Brixadi development programs, DAAAP sought to have CDER's Division of Applied Regulatory Science (DARS) complete a comprehensive preclinical assessment of buprenorphine, norbuprenorphine (major metabolite), methadone, naltrexone, and naloxone using an approach like that employed by Braeburn.

Although there is literature documenting buprenorphine's effects on cardiac hERG (Katchman et al., 2002) and peak NaV1.5 currents (Leffler et al., 2012), no information is available regarding the drug's effect on late NaV1.5 and CaV1.2 currents (based on PubMed searches performed on 1/19/2018). Data regarding the latter two currents are necessary for analysis of drug effect on ventricular action potential and proarrhythmia propensity. Although individual sponsors such as Braeburn have also evaluated buprenorphine's effects using patch clamp electrophysiology methods, it is important to note that no contract research organization has performed experiments up to the data quality standards and at physiological temperature (temperature is a factor of drug-channel affinity) as established by DARS' electrophysiology unit. For regulatory acceptance of in vitro ion channel pharmacology data, DARS is in a unique position to generate the required data set that will inform the cardiac safety of buprenorphine-containing products.

The DARS experiments are currently under way. Because of this, the following response was provided to Indivior regarding their question about whether the Sublocade QT interval evaluation was adequate to release the tQT PMR for the other Indivior products (Suboxone sublingual film, Suboxone sublingual tablets, Subutex):

> Regarding quantification of the effect of SUBOXONE on cardiac repolarization, it is appropriate to use the SUBLOCADE ECG data to characterize this effect for SUBOXONE. However, we have some internal evaluations under way, and we will provide a final decision about the status of the QT study PMR, and any potential related labeling, once we have completed these evaluations.

Additionally, while we are waiting for the DARS experiments to be completed, it seems reasonable from a resource perspective to advise Orexo, BDSI, and Braeburn (Titan) to pause their activities on assessing the effects of their products on the QT interval. We plan to send the following text in an email to the three companies:

We acknowledge that you have a pending PMR (insert number) for a QT study to characterize the effect of buprenorphine on cardiac repolarization. FDA is in the process of conducting an internal review of the available data to determine if such data is adequate to fulfill the goals of the PMR.

We recommend that for now you do not move forward with your study, but rather wait for the Agency to give you further guidance on how and when to move forward.

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/s/

MARK A LIBERATORE
07/12/2018

JUDITH A RACOOSIN
07/12/2018

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy Initiatives
Division of Medical Policy Programs

REVIEW DEFERRAL MEMORANDUM

Date:	January 18, 2018
To:	Sharon Hertz, MD Director **Division of Anesthesia, Analgesia, and Addiction Products (DAAAP)**
Through:	LaShawn Griffiths, MSHS-PH, BSN, RN Associate Director for Patient Labeling **Division of Medical Policy Programs (DMPP)** Barbara Fuller, RN, MSN, CWOCN Team Leader, Patient Labeling **Division of Medical Policy Programs (DMPP)**
From:	Morgan Walker, PharmD, MBA, CPH Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)**
Subject:	Review Deferred: Medication Guide (MG)
Drug Name (established name):	TRADENAME (buprenorphine)
Dosage Form and Route:	injection for subcutaneous administration, CIII
Application Type/Number:	NDA 210136
Applicant:	Braeburn Pharmaceuticals, Inc.

1 INTRODUCTION

On July 19, 2017, Braeburn Pharmaceuticals, Inc. submitted for the Agency's review an original New Drug Application (NDA) 210136 for TRADENAME (buprenorphine) injection. On October 10, 2017, the Division of Anesthesia, Analgesia, and Addiction Products (DAAAP) requested that the Division of Medical Policy Programs (DMPP) review the Applicant's proposed Medication Guide (MG) for TRADENAME (buprenorphine) injection.

This memorandum documents the DMPP review deferral of the Applicant's proposed MG for TRADENAME (buprenorphine) injection.

2 CONCLUSIONS

Due to outstanding deficiencies, DAAAP plans to issue a Complete Response (CR) letter. Therefore, DMPP defers comment on the Applicant's patient labeling at this time. A final review will be performed after the Applicant submits a complete response to the CR letter. Please send us a new consult request at such time.

Please notify us if you have any questions.

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/s/

MORGAN A WALKER
01/18/2018

BARBARA A FULLER
01/18/2018

Clinical Inspection Summary

Date	January 12, 2018
From	Damon Green, M.D., M.S., Reviewer Good Clinical Practice Assessment Branch Division of Clinical Compliance Evaluation Office of Scientific Investigations (OSI)
To	Taiye Ayoola, PharmD, Regulatory Project Manager Gioia Guerrieri, D.O., Clinical Reviewer Celia Winchell, M.D., Clinical Team Leader Division of Anesthesia, Analgesia, and Addiction Products (DAAAP)
NDA #	210136
Applicant	Braeburn Pharmaceuticals Inc.
Drug	(b) (4) (Buprenorphine)
NME	No
Therapeutic Classification	Opioid analgesic—partial agonist/antagonist
Proposed Indication	Treatment of opioid use disorder
Consultation Request Date	October 2, 2017
Summary Goal Date	January 12, 2018
Action Goal Date	January 19, 2018
PDUFA Date	January 19, 2018

I. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

The clinical sites of Drs. Kelsh, Bernard, Dueno, and Anderson were inspected in support of this NDA. The sponsor, Braeburn Pharmaceuticals Inc., was also inspected. Based on the results of these inspections, the studies appear to have been conducted adequately, and the data generated by these sites and submitted by the sponsor appear acceptable in support of the respective indication.

The final classification of the inspections of the sponsor and Dr. Bernard was No Action Indicated (NAI). The final classification of the inspections of Drs. Dueno and Kelsh was Voluntary Action Indicated (VAI). The preliminary classification of the inspection of Dr. Anderson was VAI.

Of note, after completion of the sponsor inspection on November 30, 2017, OSI learned of the review division's (DAAAP's) concerns regarding the quality of the datasets submitted in support of the marketing application. The review division discussed these quality issues with the sponsor on December 14, 2017, and the sponsor agreed to conduct a database QC. The sponsor stated that they understood the timelines and the criticality of this activity and were committed to delivering corrected datasets by the following week with a clear and concise QC strategy which

would allow DAAAP to fully understand the QC approach, what corrections were made, and how. The sponsor did in fact submit the updated datasets, but the application will not be approved this cycle due to major CMC issues. OSI evaluation of this application will continue during the next review cycle.

II. BACKGROUND

The Applicant submitted this NDA to support the use of (b) (4) [buprenorphine (BPN)] subcutaneously injected depot for the treatment of opioid use disorder. Inspections were requested of the following protocols in support of this application:

Protocol HS-11-421, "A Phase III, Randomized, Double-Blind, Active-Controlled, Parallel Group, Multi-center Trial Assessing the Efficacy and Safety of a Once-Weekly and Once-Monthly, Long-Acting Subcutaneous Injection Depot of Buprenorphine (CAM2038) in Treatment of Adult Outpatients with Opioid Use Disorder."

This study took place at 36 sites within the United States only, beginning (b) (6) and ending on (b) (6) A total of 428 subjects were randomized.

The primary objective of the study was to demonstrate non-inferiority of the CAM2038 BPN treatment arm as compared to the sublingual (SL) BPN/naloxone (NX) arm in treating adult outpatients with opioid use disorder as measured by the primary efficacy measure of response rate. The definition of response was based on absence of positive urine toxicology results and self-reported illicit opioid use at particular time points.

Protocol HS-13-478, "A Multiple Dose Opioid Challenge Study to Assess Blockade of Subjective Opioid Effects of CAM2038 q1w (Buprenorphine FluidCrystal® Subcutaneous Injection Depots) in Adults with Opioid Use Disorder."

This study took place at 3 sites within the United States only, beginning (b) (6) and ending on (b) (6) A total of 47 subjects were randomized.

The primary objective of the study was to evaluate the degree and duration of opioid blocking effects of CAM2038 q1w following administration of intramuscular (IM) hydromorphone (6 mg and 18 mg) compared to administration of 0 mg hydromorphone (placebo) on subjective opioid effects in patients with opioid use disorder, as measured by the primary efficacy measure, Drug Liking visual analog scale (VAS).

Rationale for Site Selection

- Dr. Otto Dueno: high enrollment and number of serious adverse events
- Dr. John V. Bernard: a number of indeterminate lab results noted (i.e., urine drug screens), which could affect the primary efficacy measure.
- Dr. Jason Anderson: discrepancies noted in documentation concerning dates of subject visits for lab draws.

- Dr. Debra Kelsh: enrolled the vast majority of the subjects for Protocol HS-13-478

III. RESULTS (by site):

Site #/ Name of CI/ Address	**Protocol #/ # of Subjects Enrolled**	**Inspection Dates**	**Classification**
Sponsor **Braeburn Pharmaceuticals Inc.** 47 Hulfish Street, Suite 441 Princeton, New Jersey 08542	HS-11-421 HS-13-478	17-27 Nov 2017	NAI
Site #101 **Dr. Debra Kelsh** Vince & Associates Clinical Research, Inc. 10103 Metcalf Avenue Overland Park, KS 66212	HS-13-478 Subjects: 42	13-21 Nov 2017	VAI
Site #107 **Dr. John V. Bernard** Wellness and Research Center 526 Water Street Belvidere, NJ 07823	HS-11-421 Subjects: 12	12-16 Oct 2017	NAI
Site #138 **Dr. Otto Dueno** Midwest Clinical Research Center 1 Elizabeth Place South Building, Suite G-3 Dayton, OH 45417	HS-11-421 Subjects: 33	01-15 Nov 2017	VAI
Site #124 **Dr. Jason Anderson** Aspen Clinical Research, LLC 1215 South 1680 West Orem, UT 84058	HS-11-421 Subjects: 12	13-17 Nov 2017	VAI*

Key to Compliance Classifications
NAI = No deviation from regulations.
VAI = Deviation(s) from regulations.
OAI = Significant deviations from regulations; Data unreliable.

*Preliminary classification based on information in 483 or preliminary communication with the field; EIR has not been received from the field, and complete review of EIR is pending. Final classification occurs when the post-inspectional letter has been sent to the inspected entity.

1. Braeburn Pharmaceuticals Inc. (Sponsor)

For Protocol HS-11-42 and HS-14-478, some of the regulatory obligations were transferred to the CROs, (b) (4) respectively. In particular, these CROs selected the clinical investigators, created the monitoring plans, conducted monitoring site visits, and reported safety information to Braeburn.

This sponsor inspection included review of the following records: vendor/CRO contract agreements, monitoring plans, monitoring visit reports, standard operation procedures (SOPs), resumes, training records, test article accountability logs, shipment records, FDA Form 1572s, and financial disclosure forms.

It was found that the sponsor generally upheld the applicable regulations. There was no evidence of underreporting of adverse events.

A Form FDA 483 was not issued at the conclusion of the inspection. However, discussion items included the following:

- Training record retention was not adequate.
- There was inadequate vendor oversight. In particular, there was no SOP documenting how the sponsor selected vendors, and the sponsor did not perform any vendor oversight during the studies to ensure that the vendors were following the protocols and complying with applicable GCP regulations.

2. Dr. Debra Kelsh

At this site for Protocol HS-14-478, 427 subjects were screened, 116 subjects were enrolled, 42 subjects were randomized, with 41 completing the study.

Records reviewed included informed consents, IRB approvals, correspondence, subject records, primary efficacy endpoints, adverse events, monitoring activities, drug accountability, and staff training.

One hundred percent of the primary endpoint data (VAS scores for drug liking) for all 42 subjects dosed with study drug were reviewed. There were approximately 15 instances for 11 subjects where the VAS scores for drug liking were either incorrectly scored or entered incorrectly into the EDC. For example:

- For subject 306 on Day 6 at 45 minutes post-dose and 60 minutes post-dose, it appeared that the subject rated the same exact score for each, but one was measured at 58 and the other at 68
- For subject 247 on Day -2 at 300 minutes post-dose, the score was incorrectly measured at 98 when it should have been 88.
- For subject 147 at Day 5 300 minute post-dose, subject 332 Day 3 30 minutes post-dose, and subject 400 at Day -2 5 minutes post-dose, all were scored by the subjects as 50 but was entered into the EDC as 0

- For subject 275 at Day 4 180 minutes post-dose, the handwritten score was 64 but was entered into the EDC as 61.

During the inspection, the Senior Clinical Project Manager stated that there was no specific training given by the sponsor for VAS scoring but that the site had previous experience with a paper VAS. However, the site does have a SOP titled "Clinical Questionnaires" that addresses VAS scoring and became effective on January 1, 2016, halfway through the study.

Since issues were found with only a very small percentage of the VAS scores for drug liking, this should have minimum effect on the outcome of the study. Otherwise, there was no evidence of underreporting of adverse events. Informed consent was obtained properly for each of the subjects.

Although a Form FDA 483 was not issued at the conclusion of the inspection, the final classification for this inspection is VAI.

3. Dr. John V. Bernard

At this site for Protocol HS-11-421, 19 subjects were screened and 11 subjects were enrolled, with 10 completing the study.

Records reviewed included informed consents, IRB approvals, enrollment logs, subject records, primary endpoints, monitoring activities, drug accountability, and training. The primary efficacy endpoint data were verifiable. Informed consent was obtained properly for each of the subjects.

A Form FDA 483 was not issued at the conclusion of the inspection.

4. Dr. Otto Dueno

At this site for Protocol HS-11-421, 48 subjects were screened and 33 subjects were enrolled, with 22 completing the study.

Records reviewed included informed consents, laboratory reports, electrocardiograms, drug accountability records, IRB correspondence and approvals, correspondence with the sponsor, monitoring records, and site training documentation. The primary efficacy endpoint data were verifiable. Except for a single case of sinusitis, there was no evidence of underreporting of adverse events. Informed consent was obtained properly for each subject.

A Form FDA 483, Inspectional Observations, was issued at the conclusion of the inspection for:

- Inadequate investigational drug disposition records for a number of subjects.
- A failure to prepare or maintain accurate case histories with respect to observations and data pertinent to the investigation.
    - Specifically, the source data did not match the eCRF for Illicit Drug Use Self Report for 5 subjects. However, these discrepancies were generally minor, and none were related to opioid use.

5. Dr. Jason Anderson

For Protocol HS-11-421, 21 subjects were screened and 12 subjects were enrolled, with 4 completing the study.

The primary efficacy endpoint data were verifiable. There was no evidence of underreporting of adverse events. Informed consent was obtained properly for each of the subjects.

A Form FDA 483, Inspectional Observations, was issued at the conclusion of the inspection, which included the observation for an "investigation not conducted in accordance with the investigational plan." Specifically, protocol required random urine toxicological screening (UTS) was conducted on scheduled visit days (that is, random UTS was conducted on the same days as scheduled UTS) for two subjects on three occasions.

In his December 4, 2017 response to the inspectional observations, Dr. Anderson stated that, based on his interpretation of the protocol, it was permissible to collect a random UTS on scheduled visit days. He says that he only did so when he could not contact a subject to come in for a random UTS. Furthermore, he stopped this practice following the July 22, 2016 clarification memo from the sponsor regarding the collection of UTS.

{See appended electronic signature page}

Damon Green, M.D., M.S.
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

CONCURRENCE: *{See appended electronic signature page}*

Phillip Kronstein, M.D.
Team Leader,
Good Clinical Practice Assessment Branch
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Kassa Ayalew, M.D., M.P.H
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cc:

Central Doc. Rm.
DAAAP /Division Director/Hertz
DAAAP/Medical Team Leader/Winchell
DAAAP /Project Manager/ Ayoola
DAAAP/Medical Officer/Guerrieri
OSI/Office Director/Burrow
OSI/DCCE/ Division Director/Khin
OSI/DCCE/Branch Chief/Ayalew
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OSI/DCCE/GCPAB Reviewer/Green
OSI/ GCP Program Analysts/Patague
OSI/Database PM/Dana Walters

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/s/

DAMON C GREEN
01/12/2018

PHILLIP D KRONSTEIN
01/12/2018

NI A KHIN
01/12/2018
Covering for Kassa Ayalew

M E M O R A N D U M

Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research

Date: December 26, 2017

To: Sharon Hertz, M.D., Director
Division of Anesthesia, Analgesia, and Addiction Products

Through: Dominic Chiapperino, Ph.D., Acting Director
Silvia Calderon, Ph.D., Senior Pharmacologist
Martin Rusinowitz, M.D., Senior Medical Officer
Controlled Substance Staff

From: Alan Trachtenberg, M.D., M.P.H., Medical Officer
Controlled Substance Staff

Subject: CAM2038, Buprenorphine injectable Subcutaneous (SC) depot, **NDA 210136 (**IND 114082**)**
Doses, formulations, routes: Buprenorphine base in a pre-filled syringe for once weekly or once monthly administration. Once weekly provided in 8 mg, 16 mg, 24 mg, 32 mg, and 64 mg doses. Monthly strengths provided in 96 mg, 128 mg, (b) (4) doses.
Indication: Opioid Agonist Treatment (OAT) of Opioid Use Disorder (OUD) (b) (4)
Sponsor: Braeburn Pharmaceuticals
PDUFA Goal Date: January 19, 2018 (priority review)

Materials Reviewed:
Materials for Study HS-13-478 and abuse related data in NDA 210136, Received July 19, 2017;
Materials from Sponsor submitted for Advisory Committee (AC) hearing of November1, 2017;
Biostatistics consult, Dated July 19, 2017, by Wei Liu, Ph.D., Mathematical Statistician, Division of Biometrics VI.

Table of Contents

I. SUMMARY

1. Background

This memorandum responds to a consult request from the Division of Anesthesia, Analgesia, and Addiction Products (DAAAP) to evaluate the abuse liability assessment and opioid blockade study submitted under 505(b)(2) by Braeburn Pharmaceuticals in NDA 210136 and IND 114082, for CAM2038 (injectable subcutaneous (SC) depot buprenorphine). DAAAP asked CSS and the statistical team CSS consults, Division of Biometrics VI, to determine whether study HS-13-478 provides evidence that CAM2038 produces blockade of the effects of exogenous opioids throughout two weeks of weekly injection of 2 different doses of the weekly formulation. DAAAP has consistently emphasized to the Sponsor that FDA believes full opioid blockade, and not merely an attenuation of opioid effect, is the most important product attribute when patients who receive CAM2038 are exposed to opioid doses typically used by persons with an active opioid use disorder (OUD). This product is offered in prefilled syringes for once weekly or once

monthly administration. The weekly formulation is provided in 8 mg, 16 mg, 24 mg, 32 mg, and 64 mg doses. Monthly formulations are provided in 96 mg, 128 mg, (b) (4) doses of buprenorphine (BUP), carried in the proprietary BUP Fluid Crystal SC injection depot formulation based on Camurus' "Proprietary lipid-based and ambient responsive FluidCrystal® (FC)" injection depot technology delivery system, intended to provide a long-acting SC depot of BUP for systemic release of a stable level over the following week or month, respectively. The drug product is indicated for either weekly or monthly administration in the treatment of moderate to severe OUD and can be used as the initial medication in patients initiating medication assisted therapy (MAT), as well in patients who have already been inducted with transmucosal BUP containing products. The Sponsor is recommending that CAM2038 be used as part of a complete treatment plan to include counselling and psychosocial support. As with all previous BUP products for MAT, directions indicate that the initial dose should be administered only after objective signs of mild to moderate withdrawal have appeared (unless the patient is being transferred directly from another form of BUP).

If the patient's initiation to BUP is planned with this product, the starting dose is recommended to be 24 mg of weekly CAM2038. An additional 8 mg may be recommended after a minimum of 24 hours following the first injection, depending on patient status, including inadequate control of withdrawal symptoms or other clinical factors. The recommended dose for subsequent weekly injections is then based on the dose established during that first week. Subsequent dose adjustments can be made with each weekly injection, based on continuing craving or use of illicit opioids. Patients may be changed from weekly to monthly formulations whenever the clinician determines that the patient no longer needs to be seen over shorter intervals between visits.

Buprenorphine is a partial mu-agonist opioid and is the only C-III opioid (with or without naloxone in combination) approved for the treatment of OUD. Therefore, it is the only opioid medication covered by the Drug Addiction Treatment Act of 2000 (DATA-2000). DATA-2000 established a legal pathway for Office-Based Opioid Treatment (OBOT) to be offered by physicians outside of the special clinics designated and licensed by DEA as "Narcotic Treatment Programs" (NTPs, or "Methadone clinics"). (Buprenorphine can also be used in these specially designated clinics.) It was first approved as a new molecular entity (NME), indicated for pain treatment, in 1981 and marketed as Buprenex injectable under NDA 018401. It was approved as a sublingual tablet for the treatment of OUD in 2002 under NDA 020732 for Subutex (BUP hydrochloride) sublingual tablet, and under NDA 020733 for Suboxone, another sublingual tablet formulated as combination with naloxone.

Opioid agonists or partial agonists such as BUP have several properties that may contribute to their effectiveness in the treatment of opioid addiction. They alleviate the acute symptoms of opioid withdrawal and drug craving. They also attenuate or block the acute effects of exogenous opioids when the patient may have a "lapse" to drug use and help prevent immediate repetition of the lapse and extension into a full relapse of uncontrolled self-administration of drugs. Opioid agonists such as BUP can also be diverted and abused by patients and others. While not posing as high a mortality risk of overdose as from full agonists such as methadone, BUP is itself a drug of abuse such that safeguards against abuse and diversion are required.

The first BUP product to provide long term treatment without need for dispensing or self-administration was this Sponsor's subcutaneously implanted BUP rod, marketed as Probuphine,

approved under NDA 204442 on May 26, 2016. Five of these rods can be surgically implanted to provide 6 months of continuous BUP. A minor surgical procedure is required for administration and another for removal at the end of their use. Approval was for only one additional implantation after the first. Such parenteral administration by health professionals offered advantages over the self-administration of sublingual BUP by potentially increasing treatment compliance and minimizing abuse and diversion of BUP. CAM2038 is intended to offer similar benefits, but without a need for surgery. Although CAM2038 will require weekly or monthly visits, rather than every 6 months, the decreased procedural risk, and increased access that could be offered by the growing pool of DATA-waived health professionals are two potential advantages of this formulation. Another monthly LA injectable SC depot product has recently been approved with 300 mg BUP under NDA 209819 as Sublocade from Indivior, the originator of the RLD, Subutex. This product is indicated for maintenance in OUD, only after initiation and stabilization with a SL BUP product for MAT. This leaves CAM2038 potentially more versatile, since it does not require such stabilization with SL BUP prior to first administration of the LA injection.

Buprenorphine is a controlled substance, listed in Schedule III of the Controlled Substance Act (CSA). The Sponsor does not propose any change in schedule for their product.

2. Conclusions

1. CAM2038 is a SC long-acting depot formulation of BUP for Buprenorphine Injection Medication Assisted Treatment (BI-MAT) in the treatment of OUD. If approved, this will be the 2nd BI-MAT product, following the recently approved Sublocade monthly injection from Indivior, NDA 209819. CAM2038 may offer a clinical or logistic advantage over the other product, in that the ability to induct patients directly onto CAM2038, without requiring an intermediate phase of SL-MAT, would provide OUD patients and providers with greater flexibility in the initiation of MAT. For instance, it may become feasible to start the medical aspects of addiction treatment directly in the Emergency Department (ED), immediately on presentation.

2. This NDA is a 505(b)(2) submission using Subutex (NDA 20732) as the Reference Listed Product. Buprenorphine is a well characterized partial mu-opioid receptor agonist and kappa-opioid receptor antagonist, and is in currently marketed products for the treatment of OUD and pain.

3. Buprenorphine is a Schedule III opioid ("Narcotic"). The Sponsor is not requesting any change in this classification of their product.

4. As an opioid approved by FDA for the treatment of OUD, CAM2038's medical use will be regulated under the Drug Addiction Treatment Act of 2000 (DATA-2000). Prescribers must document their adequate training to the Substance Abuse and Mental Health Services Administration (SAMHSA) and receive a DATA waiver from the DEA.

5. The large amount of BUP [redacted] (b) (4) in each device is formulated to congeal after injection. The easily injectable nature of the drug/device product creates a significant risk for intravascular self-injection by persons with OUD, potentially leading to severe life threatening complications. Therefore, administrative and regulatory controls will be required to keep the product completely under the control of health professionals, until administration of the drug by such professionals, with any remainder of the drug being properly disposed.

6. This new type of product would provide a BUP treatment option that requires weekly or monthly, rather than daily (or once every 2-3 days), administration. This and other new long acting and injectable BUP products may lead to a variety of new possibilities for creating greater access to MAT for more patients with OUD, while decreasing any collateral diversion and abuse that might otherwise complicate this greater access.

7. SC injection with 24 or 32 mg of the weekly formulation of CAM2038 given weekly, twice over 2 weeks, provides significant attenuation of the reinforcing subjective effects of 6 to 18 mg of intramuscular (IM) hydromorphone (HM) over that time period. No blocking data were provided for the monthly formulation. Any assumptions about blockade effects of the monthly formulation will have to be extrapolated from the blockade effects observed after weekly injection, and based on PK data for BUP following weekly or monthly injection.

8. The Sponsor also makes a variety of other claims [redacted] (b) (4)

9. Overall, if the Sponsor's REMS meets the requirements of the CSA, DATA-2000, and the standards of training and practice promulgated by SAMHSA, the benefits of BI-MAT with this product should outweigh the potential risks of misuse, abuse, diversion and overdose.

3. Recommendations

1. From a CSS perspective, this product may be approved. The Sponsor's proposal for maintaining this buprenorphine product in Schedule III under the CSA is acceptable.

2. Sponsor should provide detailed narratives on misuse, abuse, addiction, diversion and overdose in their submission of post approval periodic safety reports. In particular, they should identify any new methods of obtaining, diverting, or tampering of this formulation, or otherwise having the product escape the administration safeguards put into place under DATA-2000 and the product's REMS.

3. Any claims about the blockade effectiveness of CAM2038 should be limited to the weekly formulation, since no blockade data were provided for the monthly formulation.

4. Any other such claims [redacted] (b) (4) will require careful pharmacokinetic review, and some may not be allowable.

5. The Sponsor should be encouraged to perform clinical trials to establish whether there is a role for this product in the final phase (discharge planning) of OD management in the ED setting, to prevent immediate relapse and a 2nd overdose after resuscitating patients with OUD who present with OD.

II. DISCUSSION

1. Chemistry

1.1 Substance Information

The active pharmaceutical ingredient (API) in CAM2038 is BUP base. Chemical name: (2S)-2-[17-(Cyclopropylmethyl)-4,5α-epoxy-3-hydroxy-6-methoxy-6α,14-ethano-14α-morphinan-7α-yl]-3,3-dimethylbutan-2-ol; or 21-Cyclopropyl-7α-[(S)-1-hydroxy-1,2,2-trimethylpropyl]-6,14-endoethano-6,7,8,14-tetrahydrooripavine; or 6,14-Ethenomorphinan-7-methanol,17-cyclopropylmethyl-α-(1,1-dimethylethyl)-4,5-epoxy-18,19-dihydro-3-hydroxy-6-methoxy-α-methyl-, [5α,7α (S)].

Buprenorphine base is a white to off-white crystalline powder, free from any visible particulate contamination. Buprenorphine is slightly soluble in water, freely soluble in acetone, soluble in methanol, slightly soluble in cyclohexane and highly soluble in Nmethyl-2-pyrrolidone (NMP)[1]. It dissolves in dilute solutions of acids. CAS registry number: 52485-79-7. Empirical Formula: C29H41NO4

1.2 Product Information

The Sponsor states that the lipid-based Fluid Crystal (FC) technology uses relatively low viscosity liquids into which the drug substance is dissolved. The FC formulation absorbs aqueous body fluid when injected into the SC tissue, and transforms to a higher viscosity, gel-like liquid crystal. This gel formation is the result of a lipid self-assembly that takes place at the surface boundary with aqueous interstitial fluid and propagates inward, toward the center of the depot, as the aqueous fluid penetrates. This process starts immediately upon injection. The surface gel formation essentially encapsulates the rest of the drug in the depot matrix. The Sponsor claims this results in a controlled release of the drug from the depot. Buprenorphine free base is used in CAM2038 weekly formulation for its solubility in the FC lipid matrix, which is greater than that of BUP HCl. After injection, the BUP inside the depot is released by biodegradation of the

1 Solubility Definitions; "very soluble" indicates that less than 1 mL of solvent is needed to dissolve 1 g of solute; "soluble" indicates that approximately 10- 30 mL of solvent are needed to dissolve 1 g of solute; "slightly soluble" indicates that 100 mL to 1,000 mL (1 l) are needed to dissolve 1 g of solute; and "very slightly soluble" indicates that volumes as high of 1- 10 liters of solvent are required to dissolve 1 g of solute. Sokoloski, T.D. (1995). Solutions and Phase Equilibria. Remington: The Science and Practice of Pharmacy A. G. Gennaro. Easton, Pennsylvania, Mack Publishing Company. **Volume I:** 195.

lipid matrix over time, and diffusion from there. The Sponsor's schematic of the SC injection and depot is shown below, in Figure 1. This Shows the phase transition proceeding from the initial gel boundary on the outside towards the center of the injected FC matrix by absorption of minute quantities of water. Thus, the Sponsor explains, an injection of the CAM2038 weekly formulation into SC tissue results in an immediate and spontaneous formation of controlled BUP release matrix, providing long-acting release in vivo with a minimum initial burst release. The sponsor "expects" the monthly formulation to result in "no differences" in BUP levels or exposure after similarly placed injections, since monthly CAM2038 is an"similar FC injection depot product."

Figure 1. Sponsor's Schematic Representation of CAM2038 Injection Depot Technology:

Figure 1 is the Sponsor's Schematic of CAM2038 Injection Depot Technology.

This product is packaged with a prefilled syringe with less than 1 mL of volume of drug, and includes a fine gauge needle (23G) with safety features. Neither mixing nor temperature adjustment is required prior to administration. This long-acting BUP depot will be marketed in weekly and monthly formulations as:

1) Weekly dosages of 8 mg [0.16 mL], 16 mg [0.32 mL], 24 mg [0.48 mL], 32 mg [0.64 mL]; and

2) Monthly dosage forms of 64 mg [0.18 mL], 96 mg [0.27 mL], 128 mg [0.36 mL]. (b) (4) (b) (4)

The CAM2038 weekly drug formulation contains 50 mg BUP /mL, 10% w/w absolute ethanol and soybean phosphatidyl choline (SPC)/ glycerol dioleate (GDO) in the weight ratio 50/50 to final volume.

The CAM2038 monthly drug product contains 356 mg/mL BUP /mL, 30% w/w N-methyl-2-pyrrolidone, and SPC/GDO in the weight ratio 40/60 to final volume.

2. Nonclinical Pharmacology

The Sponsor did not perform any new animal studies to examine abuse-related characteristics or other basic pharmacologic parameters of BUP. The Sponsor's new non-clinical studies were all conducted in support of the specific formulation and assessment of the CAM2038 product.

Buprenorphine has high affinity for mu and kappa opioid receptors with lower affinity for delta receptors. In vitro studies have shown low mu agonist activity, very low delta activity and undetectable kappa agonist activity. It is generally classified as a mu-opioid partial agonist with mixed agonist and antagonist effects. This leads to a lower abuse and physical dependence profile than typical full agonists such as morphine and lower respiratory depressant effects when compared to mu-opioid full agonists.

The in vivo opioid effects of BUP are consistent with its biochemical and in vitro activity. It acts as a mu-opioid partial agonist in antinociceptive assays and as a kappa antagonist. Compared to other opioids, BUP has a very high receptor affinity. It produces a gradual inhibition of guinea pig ileum contraction which is resistant to reversal by naloxone. Buprenorphine's offset time from opioid receptors, once bound in isolated tissue, is too long to measure, and in receptor binding assays can be 15 times slower than that for naloxone. This is consistent with a continued pharmacodynamic (PD) activity that continues somewhat longer than might be expected based only on pharmacokinetic (PK) measures and the observation that BUP's agonist effects can be prevented by prior presence of opioid antagonists, but not reversed by antagonist administered afterwards (Cowan 1977, Kajiwara 1986). Buprenorphine binds very tightly to the opioid receptor and this very strong association for the receptor leads to the long duration of clinical effect.

3. Clinical Pharmacology

Elimination of BUP occurs primarily through hepatic metabolism, principally to norbuprenorphine (norBUP), by cytochrome P450; CYP 3A4 and CYP2C8. Norbuprenorphine is subject to glucuronidation and does have some lesser pharmacologic opioid activity, but it has only limited penetration of the blood-brain barrier.

Dogs exposed chronically to either formulation of CAM2038 in a 9-month toxicity study showed no evidence of systemic toxicity observed with a steady-state systemic exposures (Cmax and AUC) at least 2-fold the human exposure for 32 mg weekly of the weekly formulation of

CAM2038 and 128 mg of the monthly formulation of CAM2038 in Study HS-15-549 (Sponsor Module 2.4/ Table 2.4.4-1). The Sponsor refers to studies they submitted under NDA 204442 for Probuphine, in which chronic exposure, carcinogenicity and reproductive toxicity data from the Subutex and Suboxone Labels was based on PK bridging using exposure data in rat, mouse and rabbits (Module 2.4/ Section 2.4.2.3.4 and Section 2.4.2.3.5). In study HS-15-549, margins to human exposure of 32 mg weekly CAM2038 or 128 mg of monthly CAM2038 were between 10 and 20-fold, based on the bridging PK data, (Module 2.4/ Table 2.4.4.2).

Five clinical studies, including studies that enrolled patients with OUD, were conducted to support the proposed dosing of CAM2038 in the Sponsor's clinical trials and to support the bridging of clinical PK data from SL Subutex to CAM2038 (Sponsor's Module 2.7.2). The PK of BUP and norBUP, after administration of SC CAM2038 weekly and monthly formulations, were compared with data following administration of SL Subutex and following a single IV injection of BUP (Temgesic) in healthy volunteers under naltrexone (NTX) blockade. BUP release following a SC injection of CAM2038 had a gradual onset with no lag-time, with a median Tmax of about 24 hours for weekly CAM2038 (HS-11-426, HS-13-487, HS-13-478 and HS-15-549) and from 4 to10 hours following a dose of monthly CAM2038 (HS-13-487 and HS-15-549). The median Tmax was 10 hours after repeated monthly administrations of 128 mg of monthly CAM2038 and 24 hours after repeated injections of 160 mg of the monthly formulation (HS-15-549).

After the peak, plasma concentrations of BUP slowly declined and demonstrated a terminal t½ of 3 to 5 days for weekly CAM2038, to support a one week dosing interval and 19 to 25 days for the monthly formulation. The Sponsor states that complete absolute bioavailability (BA) of BUP was seen following both formulations, with 6 to 9 times higher BA for the CAM2038 formulations than for comparable levels of Subutex. SC injections of weekly CAM2038 in the buttock, abdomen, thigh, and upper arm all provide comparable BUP exposure although SC injection into the thigh may yield a somewhat lower BUP peak concentration, as compared to SC injections into the buttock, abdomen and upper arm (HS-15-549). The sponsor "expects" the monthly formulation to result in "no differences" in BUP exposure after similarly placed injections, since monthly CAM2038 is a "similar FC injection depot product" to the weekly formulation. Steady-state conditions are reported after the 4th weekly dose and after the 4th monthly dose of the respective formulations.

The Sponsor claims to have demonstrated a dose equivalency between the weekly and monthly formulations, in that 4 weekly 16 mg doses of the weekly CAM2038 formulation provides the equivalent systemic BUP exposure (AUC) to that of a single 64 mg (16 mg x 4) dose of the monthly CAM2038 formulation (HS-13-487).

3.1 Drug/Product Interactions

When administered to a patient who has a physical dependence on opioid agonists (not already in withdrawal), BUP, as a partial agonist with high affinity for the mu receptor, will displace full agonists from the mu receptor and may precipitate an opioid withdrawal, much the same as administration of a full antagonist. When administered to a patient already in withdrawal, the

BUP will occupy available receptors and thereby alleviate withdrawal. For this reason, induction with BUP for MAT of OUD requires an assessment of current physical dependence and withdrawal prior to the first dose of BUP.

Benzodiazepines, other sedatives, and other CNS depressants such as alcohol may enhance or add to the potential depressant effects of BUP. As a partial agonist with a ceiling effect, BUP is unlikely on its own to cause loss of consciousness or life-threatening hypoventilation, it can contribute to these when combined with other CNS depressants, potentially leading to apnea and death.

4. Clinical Studies

4.1 Opioid Blockade Study in Human Subjects with Opioid Use Disorder

4.1.1 Design and Endpoints

Study HS-13-478 was a Phase 2, multiple-dose, within-patient comparison study of an opioid challenge, to assess the blockade of subjective opioid effects by weekly SC injections of CAM2038 in non-treatment-seeking subjects with moderate to severe opioid use disorder (OUD) [by criteria of the American Psychiatric Association's (APA) current Diagnostic and Statistical Manual (DSM-V)].

The primary objective of this study was to evaluate the efficacy of weekly SC injections of CAM2038 in blocking the subjective opioid effects from administration of IM HM (6 mg and 18 mg) compared to placebo in subjects with OUD. The primary endpoint and outcome measure was "Drug Liking" as measured by a bipolar visual analog scale (VAS). This study design is very similar to that of a human abuse potential (HAP) study and should be understood as a multi-dose HAP study for IM HM (a C-II narcotic full μ-opioid agonist), with the independent variable being the efficacy of CAM2038 to block the subjective effects of HM, which are already well known and not in question. Secondary objectives included the evaluation of opioid-blocking effects of weekly CAM2038 as a function of plasma BUP concentration at measured time points following injection and challenged with IM HM in the doses noted above. Secondary endpoints also included other VAS assessments, including "High," "Good Effects," "Bad Effects," "Any Effects," "Alertness/Drowsiness," and "Desire to Use." Suppression of withdrawal was measured with the Clinical Opiate Withdrawal Scale (COWS) and subjective Opiate Withdrawal Scale (SOWS), and PK/PD relationships were assessed. VAS scores utilized a 100mm bipolar (50=neutral response) or unipolar (0=no effect) scales: "Drug Liking" and "Alertness/Drowsiness" VAS scores were assessed as bipolar. "Any Drug Effects," "Good Effects," "High," "Bad Effects," and "Desire to Use Opioids" were unipolar. The safety and tolerability (in subjects with active moderate to severe OUD) of CAM2038 being co-administered with HM was also assessed.

Subjects were enrolled while physically dependent and self-reported a minimum of 21 days of IV or insufflated/intranasal opioid-use in the previous 30 days prior to screening, and with positive urine drug screens for opioids at the time of screening or check-in.

There were 4 phases to the study: Screening, Qualification, Treatment, and Follow-Up, as noted in Figure 2. Subjects were admitted to a clinical research unit (CRU) and stabilized with a short-acting oral opioid (30 mg immediate-release [IR] morphine) 4 times daily for 3-7 days. After stabilization, all subjects were qualified in the 3-dayqualification/baseline period by challenge with 3 IM treatments, 0, 6 and 18 mg hydromorphone (HM), administered once daily on Days -3, -2 and -1 in a double-blind, randomized crossover pattern.

Following qualification, eligible subjects were randomized in a 1:1 ratio to receive SC injections of either 24 or 32 mg of CAM2038, on Days 0 and 7. Subjects were housed in the CRU for up to 25 days. Four HM challenge periods, consisting of 3 consecutive days each, were conducted on Days 1-3, 4-6, 8-10 and 11-13 during the Treatment phase.

Figure 2: Study HS-13-478 Schematic

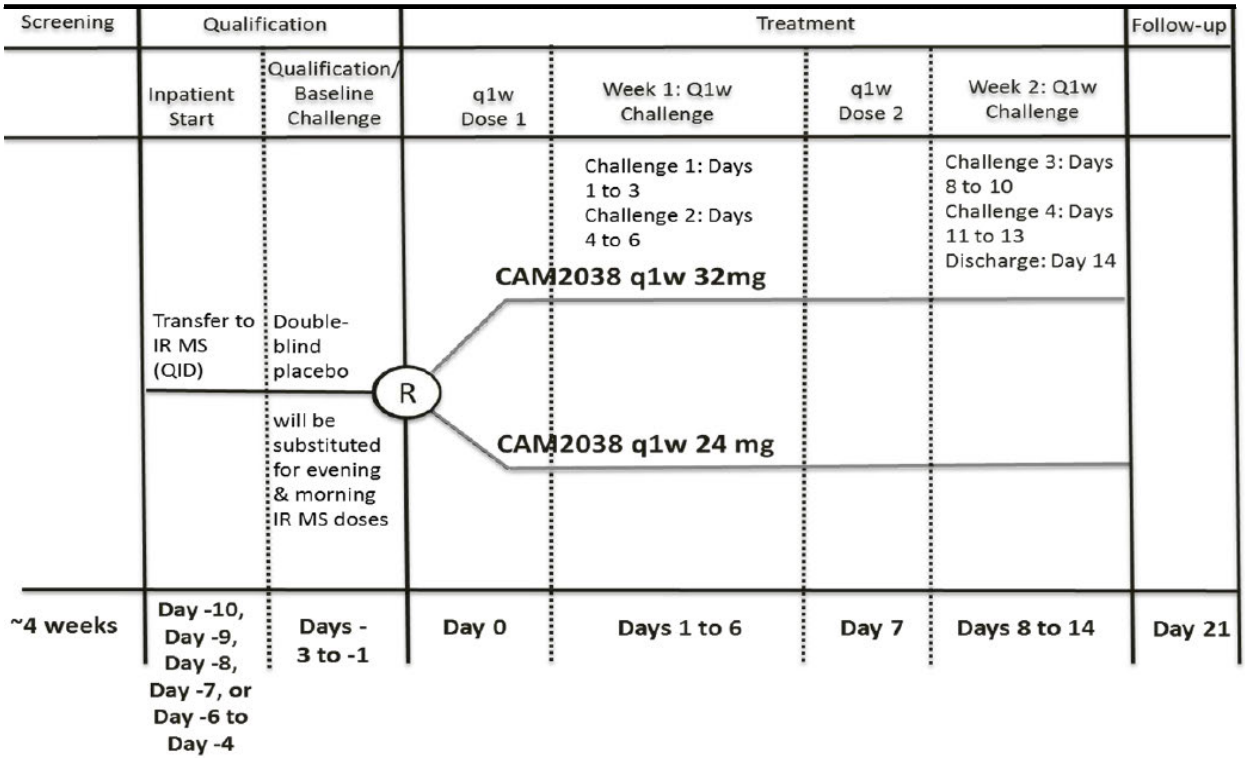


Figure 2, Sponsor Schematic for Study HS-13-478: IR MS = morphine sulfate immediate-release 30 mg PO; QID = four times daily; q1w = once weekly dosing; R = randomization

The weekly formulation, but not the monthly, was evaluated in this multi-site, randomized, double-blind, repeat-dose Phase 2 study evaluating CAM2038's blocking effect against IM HM in doses of 6 mg and 18 mg. CAM2038 doses of either 24 or 32 mg SC were administered once per week for 2 weeks, to 2 randomized cohorts of adult male and female subjects with moderate or severe OUD, who were not seeking treatment. Two doses of weekly formulation were injected 7 days apart from each other, consistent with directions in the product label. There were 2 groups, one receiving a weekly CAM2038 dose of 24 mg and the other receiving 32 mg.

Forty-seven subjects initially qualified for the study, by differentiating between IM HM doses of 6 mg and 18 mg and zero mg (placebo) in responses on a bipolar VAS measuring their drug-liking of the injections in a 3-day challenge set. Subjects were then randomized for the treatment phase of the study, with 22 subjects allocated to receive 24 mg SC CAM2038 each week for 2 weeks; and 25 allocated to receive 32 mg SC CAM2038 24 each week for 2 weeks. 22 subjects completed the 24mg arm and 23 completed the 32mg arm. One subject in the 32mg arm dropped out due to an adverse event (AE) (premature ventricular contractions). Notably, BUP induction from oral morphine was accomplished directly by the first SC dose of CAM2038, with no intermediate induction or stabilization with SL BUP.

The study was primarily designed to demonstrate, following 24 or 32 mg SC of CAM2038, that "Drug Liking" scores measured after challenge with 6 mg or 18 mg IM of HM were non-inferior to (not liked significantly better than) those measured after challenge with an IM placebo injection. Under a full blockade of subjective opioid effects by BUP treatment, there should be no significant subjective differences between placebo injections and HM injections. Each HM challenge was a 3-day set of IM injections, one each morning, of 18 mg, 6 mg, or 0 mg (placebo). In each 3-day set, the order of the doses was randomized. Subject's response to opioid challenges under blockade was measured this way, with 2 three-day challenge sets each week for 2 consecutive weeks, each week following the repeating injection of either 24 or 32 mg of CAM2038. "Drug Liking" was measured by subject report using a bipolar 100 mm VAS marked by the subject, with the scale anchored by "Like extremely" at 100 mm and disliked to the other extreme at 0 mm, with 50 mm set at neutral, for no effect either way. In addition to drug liking, alertness/drowsiness was also measured on a bipolar VAS, while any drug effects, good effects, high, bad effects, and desire to use opioids were measured on unipolar VAS. These were administered at 30 minutes before drug administration and for 5 hours thereafter at 5, 10, 15, 30, 45, 60, 75, 90, 120, 150, 180, 210, 240, 270, and 300 minutes after each day's HM injection.

BUP and norBUP levels were sampled with venous blood collected before each CAM2038 injection and 1, 4, 6, and 8 hours after; and 1 hour before each HM (or placebo) administration (days 1-6 and days 8-13), and day 14, and were measured by liquid chromatography/mass spectrometry. The safety of CAM2038 was also evaluated, as a depot injection of 24 or 32 mg, in these subjects with active OUD. Safety outcomes included AE reports, physical examinations, vital signs, pulse-oximetry, clinical laboratory assessments, and 12-lead electrocardiograms. Injection sites were examined before and after each CAM2038 injection. Electrocardiograms were conducted before each CAM2038 injection. Depression was assessed during screening, before CAM2038 administration, and upon discharge.

Twice weekly sets of 3 days in a row of HM challenge injections (0mg, 6mg or 18 mg of IM HM) with the assigned dose sequences changed randomly for both challenge sets each week (for 2 weeks for each of the 2 CAM2038 dose groups) were administered. The primary outcome, opioid blockade by CAM2038, would be established by failure to discriminate blinded doses of 6 or 18 mg HM from placebo, through the first 2 weeks following the first injection of CAM2038.

4.1.2 Population

Healthy adult volunteers, both males and females aged 18-55 years, meeting criteria of the American Psychiatric Association's (APA) current Diagnostic and Statistical Manual (DSM-V) for moderate to severe OUD, with current physical dependence on opioids and abusing short acting opioids for 21 or more of the 30 days prior to presentation and were not seeking treatment for OUD, were further evaluated for admission to the study. Subjects were recruited through local advertisements or investigator lists and were paid for participation. Exclusion criteria included physical dependence to drugs other than opioids indicating need for additional treatment, pregnancy, breastfeeding, obesity, medical use of opioids for chronic pain, AIDS, suicidal ideation, use of cytochrome P450-3A4 inhibitors/inducers or use of monoamine oxidase inhibitors or investigational drugs in the 30 days prior to enrollment. Additionally, any other clinically significant medical issues or co-morbidities, found on the investigator's evaluation of the subject's history or physical examination, including: liver enzyme levels elevated more than 3 times the upper limit of normal, and total bilirubin or creatinine levels greater than 1.5 times the upper limit of normal. Demographics of the full safety population are listed in Table 1.

Within 4 weeks of initial screening, eligible subjects were admitted to a CRU for the Qualification Phase. Subjects were transitioned to IR oral morphine 30 mg QID for 3 to 7 days, with up to 1 additional dose, each day as needed, for the first 3 days of admission. After stabilization on oral morphine, subjects passed a 3-day set of qualifying baseline HM injections as described previously:

To qualify for the treatment phase of the study, each subject's drug liking maximum effect (Emax) response to placebo injection (based on Drug Liking bipolar VAS) scored from 40 to 60 mm; 6 mg IM HM score exceeded that of placebo by at least 15 mm, and a difference of at least 20 mm between placebo and HM 18 mg). The subjects had to tolerate HM 6 mg and 18 mg, and demonstrate an ability to complete most efficacy assessments administered within 5 hours following each daily dose.

Table 1. Demographic Information (Safety Population), Study HS-13-478:

Demographic variables	24 mg CAM2038 weekly (N=22)	32 mg CAM2038 weekly (N=25)	All CAM2038(N=47)
Age, years			
Mean (SD)	**36.1 (9.3)**	**35.6 (9.1)**	**35.8 (9.1)**
Range (Min, Max)	**21, 53**	**18, 54**	**18, 54**
Sex, n (%)			
Male	**16 (72.7%)**	**19 (76.0%)**	**35 (74.5%)**
Female	**6 (27.3%)**	**6 (24.0%)**	**12 (25.5%)**
Race, n (%)			
Black or African American	**9 (40.9%)**	**15 (60.0%)**	**24 (51.1%)**
European American	**12 (54.5%)**	**10 (40.0%)**	**22 (46.8%)**
Other	**1 (4.5%)**	**0**	**1 (2.1%)**
Ethnicity, n (%)			
Non-Hispanic	**22 (100.0%)**	**24 (96.0%)**	**46 (97.9%)**
Hispanic or Latino	**0**	**1 (4.0%)**	**1 (2.1%)**
BMI, kg/m^2			
Mean (SD)	**25.2 (4.28)**	**24.4 (4.25)**	**24.8 (4.24)**
Range	**20, 34**	**17, 34**	**17, 34**

Table 1: Demographic Information (Safety Population), Study HS-13-478.
Source: Sponsor's Table 14.1.2, Listing 16.2.4.1. BMI = body mass index; SD = standard deviation.

4.1.3 Statistical Methodologies of the Blockade Study

This opioid blockade study was submitted by the Sponsor to be supportive of the primary efficacy study (described in Section 5.2, below). Study HS-13-478 of NDA 210136 was a Phase 2, multi-sited, double-blinded, randomized, repeat-dose within subject comparison study, to evaluate the degree and duration of action of multiple doses of the weekly formulation of CAM2038 in blocking the effects of HM, a Schedule II mu opioid agonist, in patients with moderate or severe OUD. The study involved 4 phases: Screening, Stabilization/Qualification, Treatment, and Follow-up (shown in Figure 2).

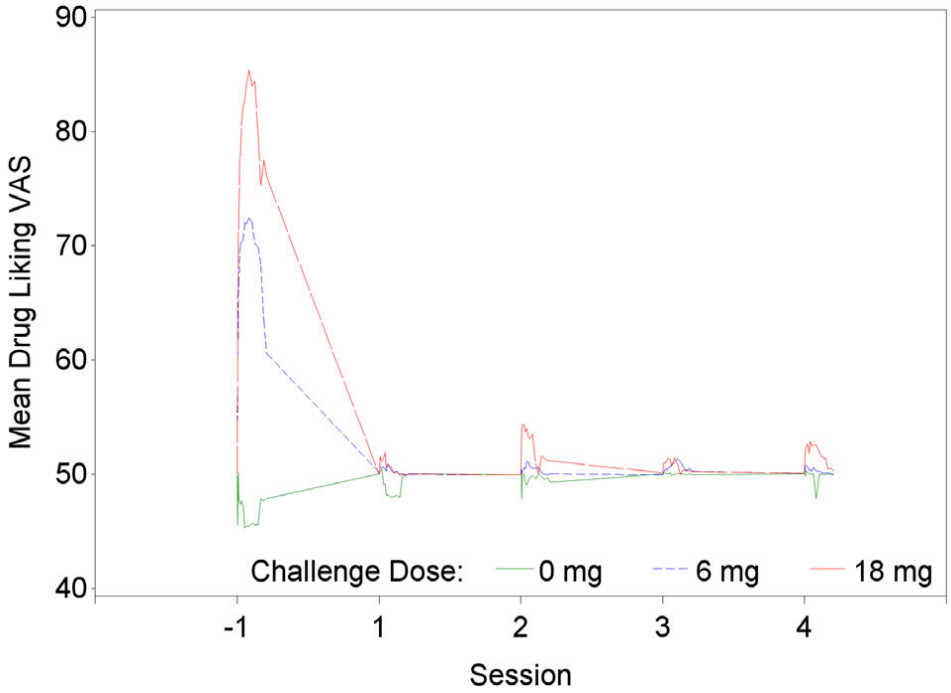
The primary endpoint was the Emax of "Drug liking" VAS. Secondary endpoints included Emax of VAS of "High," "Good drug effect," "Bag drug effect," "Any drug effect," and "Desire to use;" and Emin of VAS of effect on "Alertness/Drowsiness." The primary analysis used data from the completer population.

There were a total of 47 subjects who passed the Qualification Phase and were randomized into the Treatment Phase with 22 subjects (less than the originally-planned 24) in the group administered 24 mg CAM2038 and 25 subjects in the group administered 32 mg CAM2038. There were 22 completers in the 24 mg CAM2038 group and 24 completers in the 32 mg CAM2038 group (1 subject discontinued due to an AE).

The descriptive analyses of the primary and secondary endpoints were verified by FDA's Office of Biostatistics. The FDA statistical reviewer confirmed the Sponsor's results regarding the opioid blocking effects of weekly CAM2038 following administration of IM HM (6 mg and 18 mg) compared to placebo, as measured by the primary endpoint, peak "Drug Liking" VAS, based on the non-inferiority margin of 11 points that was pre-determined by the Sponsor. The FDA statistics reviewer noted a boundary efficacy for the HM challenge dose of 18 mg during Days 4-6 after the 2nd weekly administration of 24 mg CAM2038, with the upper limit of the 95% confidence interval greater than 10 points. The efficacy results on secondary endpoints support the findings of the primary analysis, including the statistically ambiguous blockade in Session 2 of the 24mg CAM2038 group.

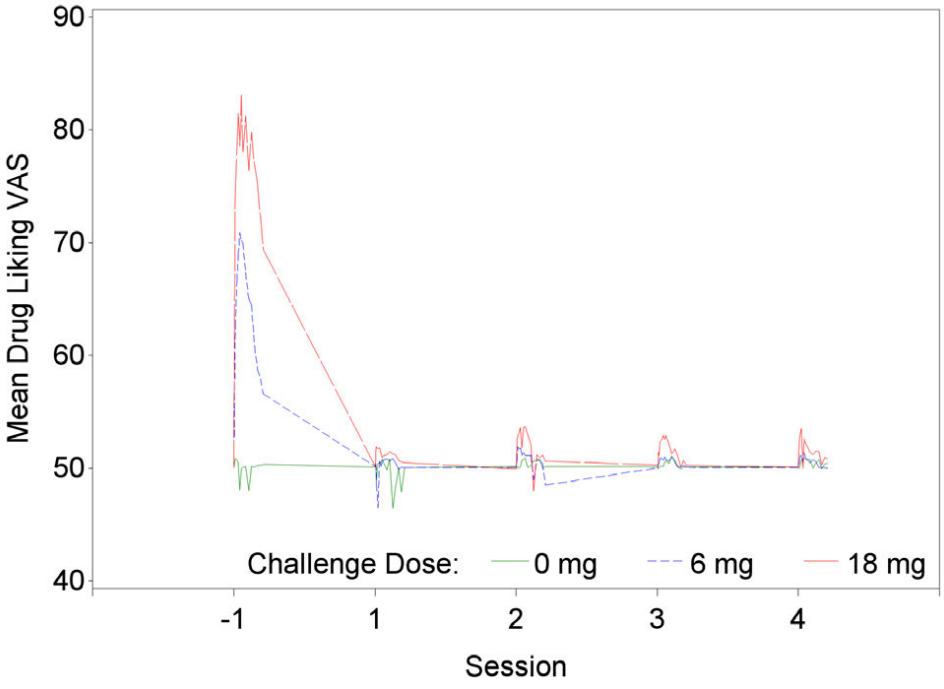
The results of the Sponsor's primary analysis are shown in Figures 3 and 4 . Some key secondary analyses are summarized in Table 2, both from the dataset of completers. Also, a significant and stable suppression of opioid withdrawal was observed following all CAM2038 injections, as measured by the COWS: Weekly 24 mg CAM2038 x 2 doses: effect size 0.617 ($P < .001$), and Weekly 32 mg CAM2038 x 2 doses: effect size 0.751 ($P < .001$). This is shown below in Sponsor's Figure 5.

Figure 3: Mean Drug Liking VAS Scores over Time for the weekly formulation of CAM2038 *24 mg* by Hydromorphone Challenge Session, Completer Population (N=22)



For both Figures 3 and 4 , the Drug Liking visual analog scale (VAS) item was presented to the subjects as: "At this moment, my liking of this drug is," where values can range from 0 ("Strong disliking") to 100 ("Strong liking") and 50 is the neutral point.
Source: Figure 3 in sponsor's HS-13-478-report-body-1.pdf.

Figure 4: Mean Drug Liking VAS Scores over Time for the weekly formulation of CAM2038 *32 mg* by Hydromorphone Challenge Session, Completer Population (N=24)



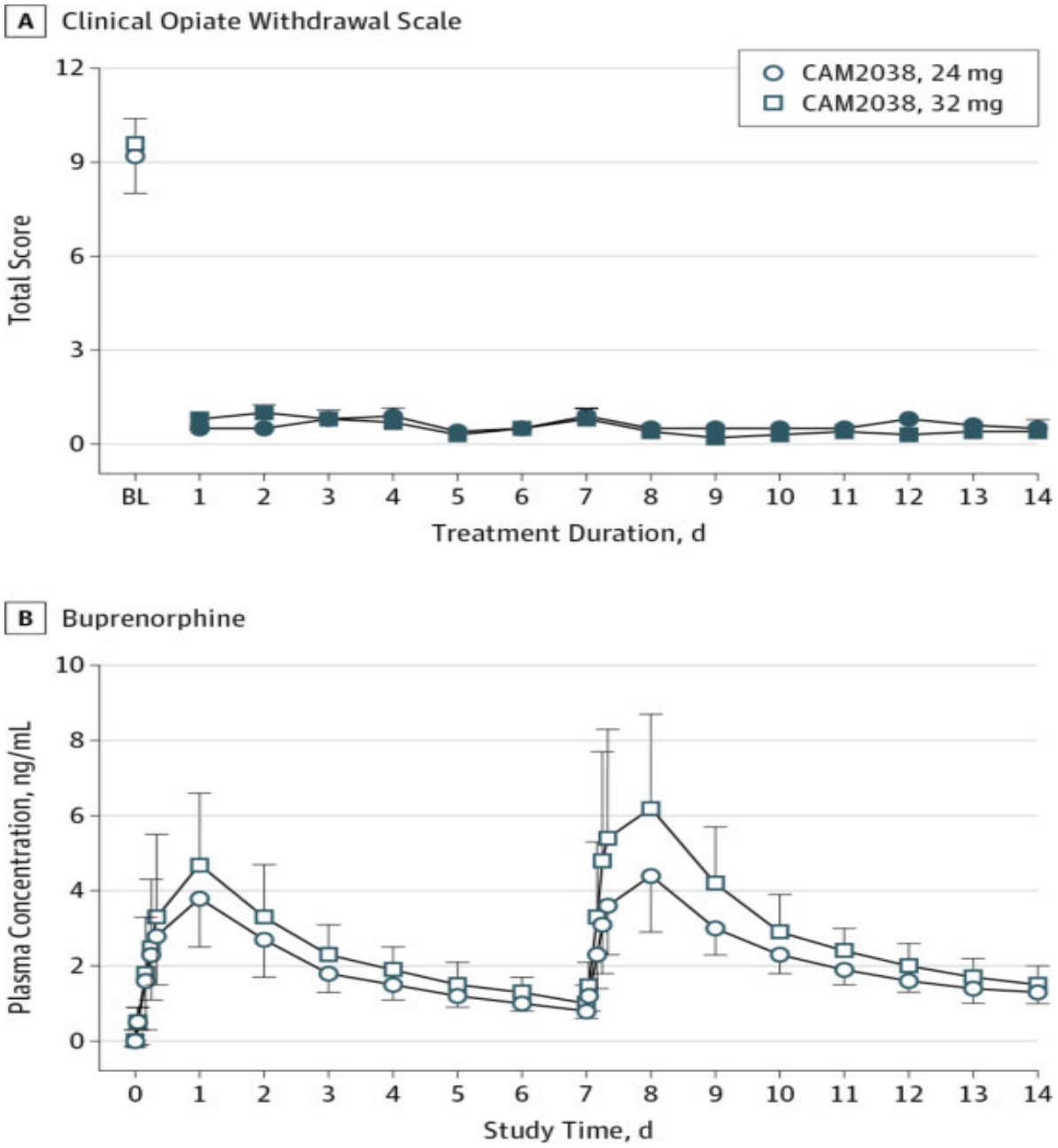
For both Figures 2.2 and 2.3, the Drug Liking visual analog scale (VAS) item was presented to the subjects as: "At this moment, my liking of this drug is," where values can range from 0 ("Strong disliking") to 100 ("Strong liking") and 50 is the neutral point. Source: Figure 4 in Sponsor's HS-13-478-report-body-1.pdf.

Table 2: Analysis Results for Bipolar Drug Liking VAS Emax (Completer Population)

	24 mg CAM2038 q1w N=22			32 mg CAM2038 q1w N=24		
	LS Mean Difference (SE)	**95% CI**	**Upper CI ≤11 Y/N**	**LS Mean Difference (SE)**	**95% CI**	**Upper CI ≤11 Y/N**
Qualification/Baseline Challenge Session						
HMO 6 mg – HMO 0 mg	32.7 (1.90)	28.8 – 36.5	-	26.7 (2.40)	21.8 - 31.5	-
HMO 18 mg – HMO 0 mg	42.1 (1.90)	38.3 – 45.9	-	40.3 (2.40)	35.5 - 45.2	-
HMO 18 mg – HMO 6 mg	9.5 (1.90)	5.6 - 13.3	-	13.7 (2.40)	8.8 - 18.5	-
Challenge Session 1 (Days 1-3)						
HMO 6 mg – HMO 0 mg	0.9 (1.12)	-1.3 – 3.1	Y	0.9 (1.05)	-1.2 – 3.0	Y
HMO 18 mg – HMO 0 mg	1.8 (1.12)	-0.4 – 4.0	Y	2.4 (1.05)	0.3 – 4.5	Y
HMO 18 mg – HMO 6 mg	0.9 (1.12)	-1.3 – 3.2	Y	1.5 (1.05)	-0.6 – 3.6	Y
Challenge Session 2 (Days 4-6)						
HMO 6 mg – HMO 0 mg	1.3 (1.12)	-0.9 – 3.5	Y	1.5 (1.05)	-0.6 – 3.6	Y
HMO 18 mg – HMO 0 mg	7.4 (1.12)	5.2 – 9.6	Y	4.5 (1.05)	2.4 – 6.5	Y
HMO 18 mg – HMO 6 mg	6.2 (1.12)	4.0 – 8.4	Y	3.0 (1.05)	0.9 – 5.1	Y
Challenge Session 3 (Days 8-10)						
HMO 6 mg – HMO 0 mg	1.5 (1.12)	-0.7 – 3.7	Y	0.5 (1.05)	-1.5 – 2.6	Y
HMO 18 mg – HMO 0 mg	1.8 (1.12)	-0.4 – 4.0	Y	2.5 (1.05)	0.4 – 4.6	Y
HMO 18 mg – HMO 6 mg	0.3 (1.12)	-1.9 – 2.5	Y	2.0 (1.05)	-0.1 – 4.1	Y
Challenge Session 4 (Days 11-13)						
HMO 6 mg – HMO 0 mg	0.9 (1.12)	-1.3 – 3.1	Y	1.0 (1.05)	-1.1 – 3.0	Y
HMO 18 mg – HMO 0 mg	3.6 (1.12)	1.4 – 5.8	Y	3.6 (1.05)	1.5 – 5.7	Y
HMO 18 mg – HMO 6 mg	2.7 (1.12)	0.5 – 4.9	Y	2.6 (1.05)	0.6 – 4.7	Y

LS Mean (SE), and 95% CI were based on the mixed model including hydromorphone challenge sequence, challenge dose (0 mg [placebo], 6 mg, or 18 mg), period (1, 2, or 3 to indicate first, second, or third day of each Challenge Session), session (Challenge Session 1, 2, 3, or 4), dosing-by-session interaction as fixed effects, and patient as random effects. CI = confidence interval; Emax = maximum score; HMO = hydromorphone; LS = least squares; N = no; q1w = onceweekly; SE = standard error; VAS = visual analog scale; Y = yes. Source: Table 12 in Sponsor's HS-13-478-report-body-1.pdf.

Figure 5: Clinical Opiate Withdrawal Scale (COWS) and Buprenorphine Concentrations



A. Mean (±1 SEM) Peak Ratings for the Clinical Opiate Withdrawal Scale for CAM2038, 24 mg and 32 mg are shown at baseline (i.e., before CAM2038 injection) and each study day thereafter. CAM2038 injections were administered on day 0 and day 7. The repeated-measures model revealed a significant main effect of day (all $P < .001$) for the Clinical Opiate Withdrawal Scale ($F_{14,294} = 39$ for 24 mg and $F_{14,322} = 78.4$ for 32 mg).
B. Graph shows the arithmetic mean (±1 SD) buprenorphine plasma concentrations for the cohorts over the course of the study. CAM2038, 24 mg: n = 22; 32 mg: n = 24.

4.1.4 Sponsor's Results and Conclusions of the Opioid Blockade Study

During the Qualification Phase, 4 patients were recorded as appearing sedated or intoxicated following oral IR morphine administration. The Sponsor's analysis reports, from this study, that administration of the weekly formulation of CAM2038 at the recommended doses of 24 mg and 32 mg demonstrated significant blockade of HM subjective effects, including reports of drug liking, high, good drug effects, and desire to use opioids. Differences between active HM doses and placebo failed to exceed the pre-identified non-inferiority margin of 11 mm on the primary endpoint of Drug Liking VAS Emax, thus meeting the pre-established criteria for full opioid blockade by both 24mg and 32 mg of the weekly formulation of CAM2038. This blockade is an important clinical determinant of the overall effectiveness of BUP treatment. In general, only minimal bad drug effects were reported both at baseline and following administration of the weekly formulation of CAM2038. Subjective and objective signs of opioid withdrawal were demonstrated throughout the treatment period.

4.1.5 FDA Reanalysis and Conclusions of the Opioid Blockade Study

The FDA statistical reviewer noted that the sample sizes in both treatment groups (CAM2038 24 mg arm with n=22 and CAM2038 32 mg arm with n=24) were not large enough to meet the assumptions required (by the central limit theorem to use the normal approximations required) for the parametric analysis used by the Sponsor. (See the CSS-Biostatistics review for details.) Since those parametric results may not be reliable, a non-parametric analysis (the sign test) was performed and met the NI margin (of 11) for both CAM2038 doses, except for the challenge of HM 18 mg at session #2 after the first CAM2038 24 mg dose group, as seen in Table 3 . This suggests that the initial administration of the lower dose of CAM2038 (24 mg) may not have completely blocked the effect of HM 18 mg during the second half of that first week. A similarly attenuated blockade by the lower CAM2038 dose was not observed after the second CAM2038 24 mg of CAM2038, suggesting that this dose may not be sufficient as an initial loading dose for this population.

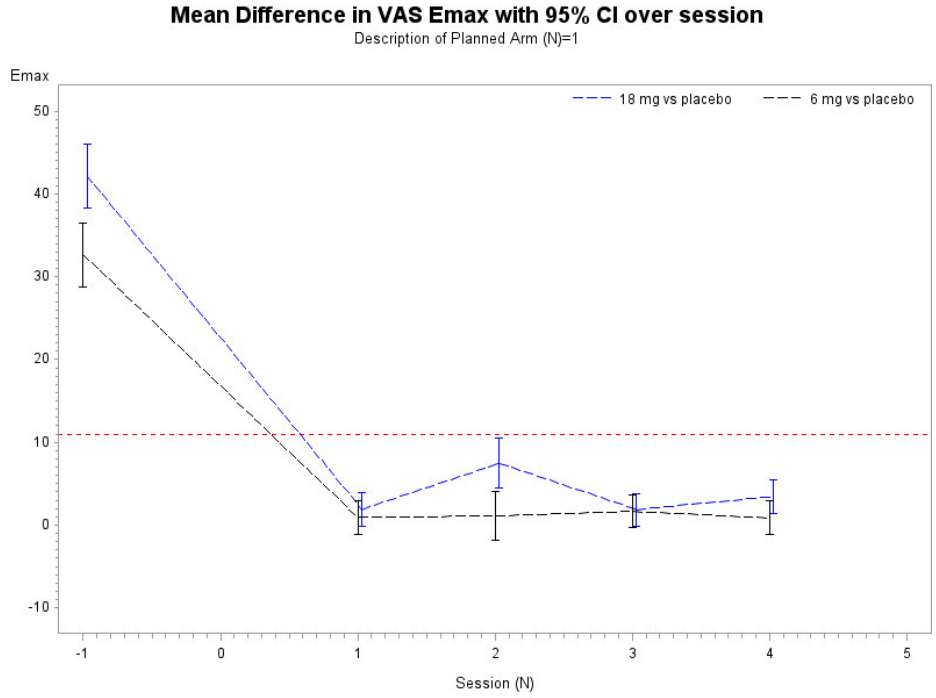
Table 3: Results of Primary Endpoint Emax "Drug liking" using Wilcoxon sign-rank test with a non-inferiority margin of 11 (Completers populations)

arm	sn	diff	N	mean	SE	Q1	Med	Q3	p-Sign test
1	-1	HMO 6 mg–0 mg	22	32.59	2.55	22	34.5	38	1
1	1	HMO 6 mg–0 mg	22	0.95	0.60	-1	0	1	0.0000
1	2	HMO 6 mg–0 mg	22	1.36	0.68	0	1	2	0.0000
1	3	HMO 6 mg–0 mg	22	1.59	0.97	0	0	1	0.0000
1	4	HMO 6 mg–0 mg	22	1.00	0.61	0	0	1	0.0000
1	-1	HMO 18 mg–0 mg	22	41.50	1.79	38	44	49	1
1	1	HMO 18 mg–0 mg	22	1.77	1.36	0	0	2	0.0000
1	2	HMO 18 mg–0 mg	22	7.41	1.92	0	3	17	0.0946
1	3	HMO 18 mg–0 mg	22	1.77	0.78	0	0	1	0.0000
1	4	HMO 18 mg–0 mg	22	3.59	1.27	0	0.5	7	0.0004
2	-1	HMO 6 mg–0 mg	24	26.75	2.90	19	25	35.5	1
2	1	HMO 6 mg–0 mg	24	0.88	0.64	0	0	1	0.0000
2	2	HMO 6 mg–0 mg	24	1.46	0.84	0	0	1	0.0000
2	3	HMO 6 mg–0 mg	24	0.50	0.34	0	0	1	0.0000
2	4	HMO 6 mg–0 mg	24	0.92	0.49	0	0	1.5	0.0000
2	-1	HMO 18 mg–0 mg	24	40.38	1.96	36	43.5	48.5	1
2	1	HMO 18 mg–0 mg	24	2.38	0.93	0	0.5	2.5	0.0000
2	2	HMO 18 mg–0 mg	24	4.46	1.21	0	1.5	7.5	0.0002
2	3	HMO 18 mg–0 mg	24	2.50	1.36	00	0	2	0.0000
2	4	HMO 18 mg–0 mg	24	3.58	1.49	0	0.5	3.5	0.0002

Arm: 1= CAM2038 24 mg; 2= CAM2038 32 mg
Sn: Session number, -1 (qualification phase), 1 (day 1-3), 2(day 4-6), 3 (day 8-10), and 4 (day 11-13)
HMO: hydromorphone; Lower and Upper are the lower and upper bounds of the 95% confidence interval, respectively. P-Sign test: p-value of Sign test with the Null hypothesis: median T – median-placebo ≥11.
p-normal: p-value of the normality test with the null hypothesis of normal distribution is true.

Figure 6 shows the time course of mean differences (adjusted) in "Drug Liking" between HM (6 mg and 18 mg) and placebo in the CAM2038 24 mg q1w arm, showing that rebound drug liking occurred at HM 18 mg of the second HM challenge. This pattern was also observed in the secondary endpoints (high, good drug effect, and bad drug effect) and are consistent with the sign test results, above.

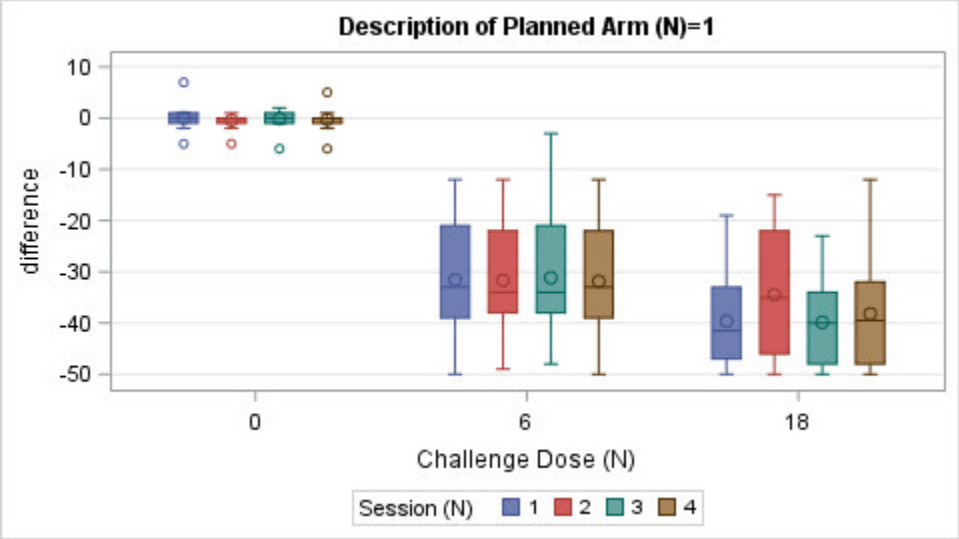
Figure 6. Time Course of Mean Difference between Hydromorphone Challenge and Placebo in Drug Liking VAS Peak Scores (ITT population). CAM2038 24 mg q1w, n=22



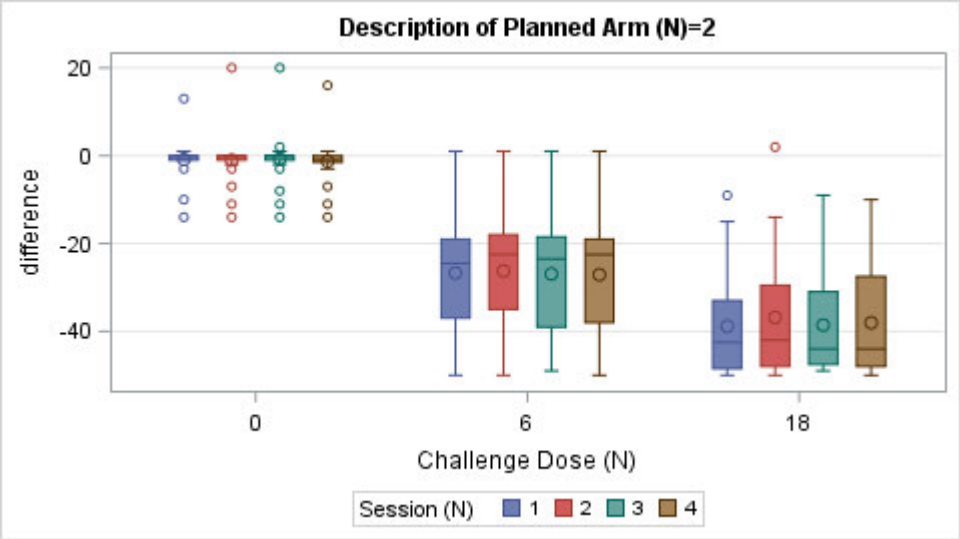
Further analysis showed significant decreases of Drug liking VAS Emax between pre- (Session -1) and post-CAM2038 exposure (Sessions 1 to 4) for both arms in all HM doses as shown in Figure 7.

Figure 7. Change in drug liking VAS Emax to the same hydromorphone dose (6 mg and 18 mg) before and after the weekly formulation of CAM2038 injection (Completers population)

A. CAM2038 Weekly 24 mg



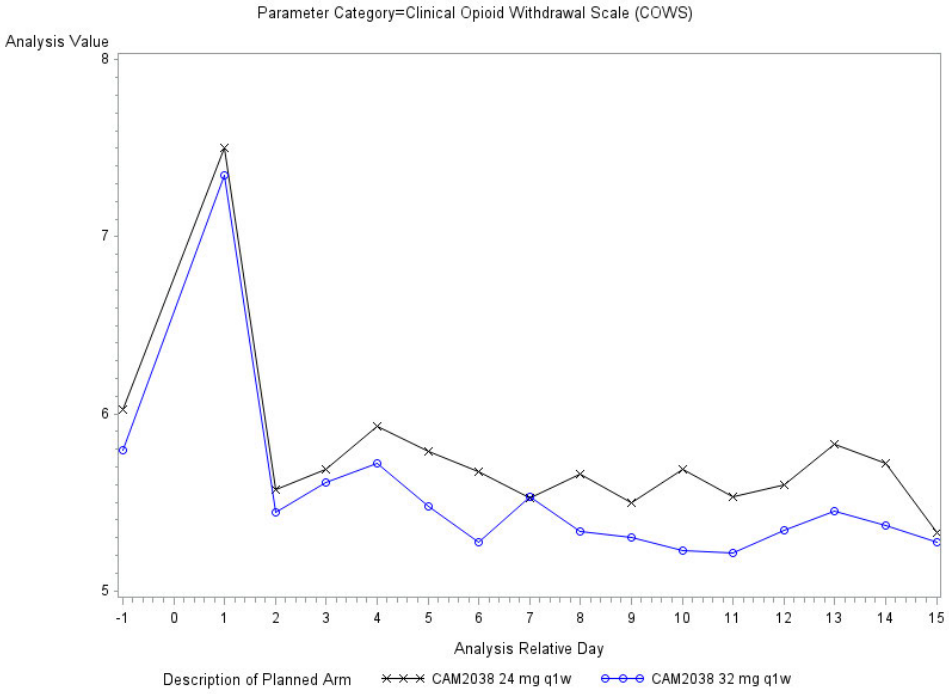
B. CAM2038 Weekly 32 mg



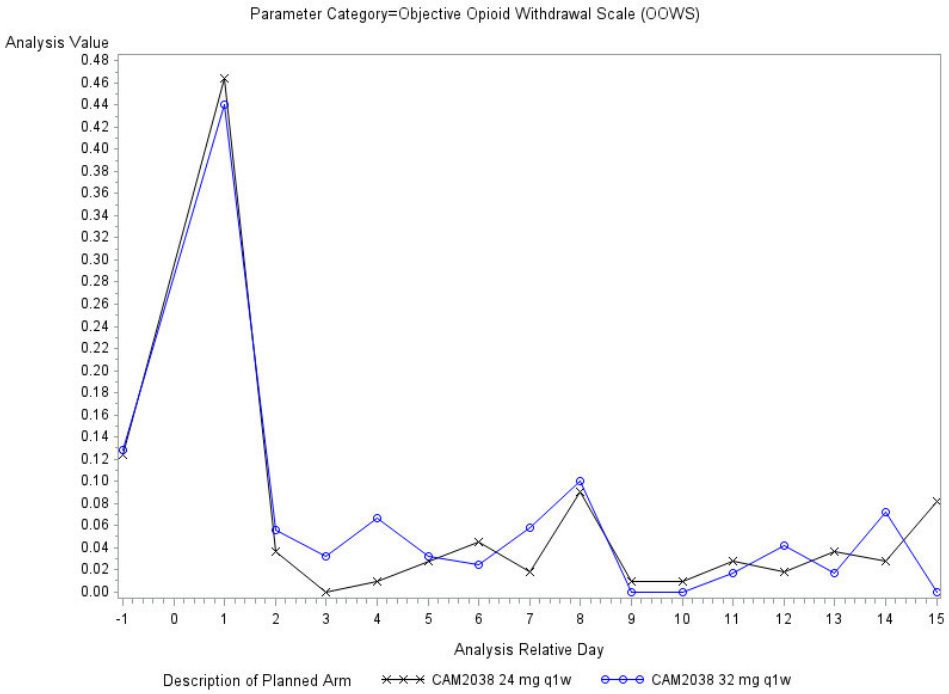
The FDA biostatistics reviewer also checked for withdrawal effects following CAM2038 at 24 mg and 32 mg on the Clinical Opioid Withdraw Scale (COWS) and Objective Opioid Withdraw Scale (OOWS) as seen in Figures 8A and 8B, respectively. These data do not indicate any obvious withdrawal effect following either initial or 2nd weekly injection of CAM2038, despite switching from full agonist (30 mg Morphine PO QID) directly to CAM2038, without any intermediate induction with SL BUP.

Figure 8. Plot of Clinical Opioid Withdraw Scale over Time by Arm

A.



B.



4.2 Other Clinical Studies in the CAM2038 Development Program

The clinical development program for CAM2038 consisted of the following studies. All studies enrolled subjects with a diagnosis of opioid dependence (Diagnostic and Statistical Manual of Mental Disorders, 4th Edition, Text Revision [DSM-V-TR]), or moderate or severe OUD (DSM-V). The Phase 3 studies included manual-guided individual drug counselling (IDC) as part of the treatment program.

Study HS-11-426 - A Phase 1, randomized, open-label study assessing PK, BA, safety and tolerability of single SC doses of 8, 16 and 32 mg of the weekly formulation of CAM2038 vs intravenous (IV) BUP (Temgesic) and SL BU (Subutex) in healthy volunteers under naltrexone blockade.

The primary objective was to characterize the PK profiles, including dose proportionality and linearity of BUP after SC single-dose injections of 8, 16 and 32 mg of the weekly formulation of CAM2038, in healthy volunteers under naltrexone blockade. The secondary objectives were to assess the absolute and relative BA of BUP, to assess the safety and tolerability of BUP and to assess and compare PK profiles of norBUP after SC single-dose injections of the weekly formulation of CAM2038 vs IV BUP and SL BUP.

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Study HS-13-487 - A Phase 1, randomized, open-label study assessing PK, BA, safety and tolerability of single SC doses of 64, 96, 128 and 192 mg of the monthly formulation of CAM2038 and of repeated weekly SC doses of 16 mg of the weekly formulation of CAM2038 vs IV Temgesic and SL Subutex in healthy volunteers under naltrexone blockade. The primary objective was to characterize the PK profiles of BUP after SC single-dose injections of 64, 96, 128 and 192 mg of the monthly formulation of CAM2038, and after 4 repeated SC doses of 16 mg of the weekly formulation of CAM2038.

HS-07-307 - A Phase 1/2, single-center, single-blind, single-dose, dose-escalation, first-time-in-man, study investigating tolerability, PK and PD of 4 different doses of the weekly formulation of CAM2038 in patients with opioid dependence. Primary objectives were to evaluate the systemic and local tolerability and to assess the PK profile of BUP of 4 different single doses of the weekly formulation of CAM2038 when delivered via SC buttock injection. Secondary objectives were to assess the PK profile of norBUP and the PD profile of BUP.

HS-15-549 - A Phase 2, open-label, partly randomized, repeated-dose study assessing PK after administration of the weekly formulation of CAM2038 and of the monthly formulation of CAM2038 at different injection sites in patients with opioid dependence and a history of chronic non-cancer pain. The primary objectives were to evaluate the steady-state PK of BUP and norBUP following repeated SC administration of the weekly formulation of CAM2038 at different injection sites (buttock, abdomen, thigh and back of upper arm) and to evaluate steady-state PK of BUP and norBUP following repeated SC administration of the monthly formulation of CAM2038 with the buttock as the injection site.

HS-11-421- A randomized, double-blind, double-dummy, active-controlled, parallel group multicenter study, designed to evaluate the non-inferiority of CAM2038 compared to an existing standard of care (sublingual BUP /naltrexone [SL BUP /NX]) in initiation and maintenance treatment with BUP . Men and women aged 18-65 years (inclusive) with a primary diagnosis of moderate to severe OUD (DSM-V) were eligible for study participation.

Study HS-14-499 - An open-label multi-center, long-term (12-month, 48-week) safety study of the weekly formulation of CAM2038 and of the monthly formulation of CAM2038 in adult outpatients with OUD. Patients were 18-65 years of age (inclusive), and had a current diagnosis of moderate to severe OUD (DSM-V) or past medical history of OUD currently being treated with SL BUP/NX. Patients were voluntarily seeking treatment for OUD (not currently on BUP treatment for at least last 60 days but seeking such treatment) or were currently on SL BUP /NX treatment.

4.3 Safety Profile and Adverse Events

The Sponsor reports, to date, that 7 clinical studies have been conducted. Two studies were Phase 1 healthy volunteer studies under naltrexone blockade (HS-11-426 and HS-13-487). Five studies were in patients with OUD, in which 3 studies were Phase 2 (HS-07-307, HS-13-478, and HS-15-549) and 2 studies were Phase 3 studies (HS-11-421 and HS-14-499). The Sponsor claims a safety profile for CAM2038 weekly and monthly formulations as being comparable to reference SL BPN, with acceptable local tolerability at injection sites. Injection site reactions were limited to only a few cases of transient, mild, local inflammation, pruritus and/or injection site pain. Several of the potential AEs may be associated with the administration of LA depots. The most severe side-effects reported by the Sponsor for the CAM2038 were those related to the principal ingredient, BUP. Most of the injection site reactions are mild to moderate, including: pain, edema, and pruritus at the site of injection after subcutaneous administration. No surgical removals or other invasive treatments were required at any injection sites, neither for local reactions such as abscess, nor systemic reactions, such as hepatitis, which have been associated with other depot or BUP therapeutics.

The Sponsor reports that all abuse-related AEs outlined in Section 5C of the CSS FDA Guidance were reviewed, and included in the abuse related AE analysis provided in their Abuse Liability Assessment, and that the TEAE profile across all studies was consistent with the known safety profile for BUP.

The overall incidence of abuse-related AEs across the phase 3 studies (HS-11-421 and HS-14-499) was 17.7% in the CAM2038 group and 16.3% in the SL BUP /NX group. These were observed in 440 subjects on CAM2038, and 215 subjects on SL BPN/NX; and included:
insomnia (3.9% on CAM2038, 2.8% for SL BPN/NX),
anxiety (3.0% on CAM2038, 3.3% on SL BPN/NX),
depression (2.7% on CAM2038, 0.9% on SL BPN/NX),
nausea (7.0% on CAM2038, 7.9% on SL BPN/NX),
sedation (0.5% on CAM2038, 0.5% on SL BPN/NX),
somnolence (0.5% on CAM2038, 0.9% on SLBPN/NX), and
substance induced psychotic disorder (0.2% on CAM2038, 0% on SL BPN/NX).

These are consistent with AEs reported in the Suboxone and Subutex labels.

The Sponsor has noted that an overdose of BUP could occur if too large a fraction of the drug load were released too soon after injection, but assessed the probability of this as being low. They report that no evidence of such dose dumping was observed, when looked for in any of their studies. They do note that 5 cases of non-fatal overdoses were reported during the phase 3 double-blind, double-dummy study (HS-11-421) with 4 reported as SAEs. All overdose cases (4 accidental, 1 intentional) came from the SL BUP /NX group. Of the 4 accidental overdoses, 3 were reported with heroin and one with clonazepam. The intentional overdose was with doxepin, prazosin, and venlafaxine. Full narratives for those were included with the HS-11-421 Clinical Study Report.

Injection sites were examined in all subjects at all study visits, including the end of study visit. No CAM2038 depots were surgically removed in any subject. There were no reports of attempted depot removal by subjects themselves.

4.4 Evidence of Abuse, Misuse and Diversion

All the unit doses contained in the products' prefilled syringes are less than 1 mL in volume and the Sponsor reports that they do not create a significantly palpable nodule. The potential effects on release rate of drug from external pressure or trauma were evaluated in nonclinical studies in rat, with no reported effects on plasma concentration or PK parameters. However, these were not further evaluated in any of the clinical trials. The Sponsor reports that Small Angle X-ray Diffraction was used to visualize the product's gel structure as a function of temperature and that the gel structure does not change significantly within the temperature interval 25-42°C. They claim this demonstrates a robust in vivo functional release matrix up to 5°C above normal body temperature. Since the depot matrix structure controls the release of BUP, and this remains unaffected by elevated temperature, they claim that "heating pads or hot baths are not expected to generate any marked excess BUP release."

5. Regulatory Issues and Assessment

The epidemic of OUD and overdose deaths continues to challenge the public health and demands both better utilization of existing treatments and development of new treatments more effective, or as effective and more accessible, than those existing. For many individuals with OUD, the most effective treatments are MAT, often assisted by opioid medications with at least partial agonist effect at the mu receptor. However, as these OAT medications become more prevalent, they themselves may increase the risk of abuse and addiction. While diverted BUP carries a lower risk of overdose death than full agonists such as methadone, concern remains for BUP's diversion potential to create its own increased risk of contributing to new OUD, as a potential "gateway" opioid.

Another depot injection (monthly formulation only, under NDA 209819) has recently been approved. However, the weekly formulation of CAM 2038 to begin with, and followed by a monthly formulation only when weekly visits are no longer required for the patient's level of clinical progress, may be better suited to the typical intervals by which patients are monitored as treatment with SL BUP progresses.

Since intentional intravascular injection always remains a concern in the treatment of OUD patients, many of whom have considerable experience with the self-administration of IV drugs, it is important that this product stay out of the hands of patients with OUD. The product's REMS must include measures to minimize this hazard by preventing any possible opportunity for patients to possess the product in any fashion other than by the intended "internal possession" of the SC depot after safe injection by a health professional.

Absent such controls, this product may be associated with a risk of improper self-administration by drug-injectors who might experiment with an intravascular route. This could potentially form a thrombus capable of limb-threatening occlusion of the vein (or artery) or an embolus, potentially travelling to the heart and lungs. The Sponsor's REMS should include elements to assure safe use (ETASU) equivalent to those being approved for Sublocade, with additional healthcare setting certification to 1) mitigate the risks of accidental overdose, misuse and abuse, 2) inform prescribers, pharmacists, and patients of the serious risks of the product, and 3) inform prescribers, pharmacists and patients about the long acting nature of CAM2038. The ETASU to be approved for all the new injectable buprenorphine MAT products should be ultimately enforceable by FDA, and therefore by the Sponsor and all subsequent legitimate purchasers, through legally enforceable contracts and scope of practice or other relevant regulations (as determined by State Health Professions Practice Acts), as well as DATA-2000 and the CSA. This will provide for as much enforceable legal control as possible, through the point of administration to the ultimate end-user/patient.

The Sponsor requested approval (b) (4)

No data were presented to support the request and the Sponsor's proposed (b) (4) was not further considered. While the Sponsor did not initially propose a REMS, one is now proposed, and under review with appropriate FDA staff.

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/s/

ALAN I TRACHTENBERG
12/26/2017

MARTIN S RUSINOWITZ
12/26/2017

DOMINIC CHIAPPERINO
12/26/2017

DEPARTMENT OF HEALTH & HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Devices and Radiological Health
Office of Compliance (OC)

Date:	December 22, 2017
To:	ICCR Lead-Center Contact, Office, Location, E-mail:
CC:	Office of Combination Product at: combination@fda.gov Regulatory Business Program Manager (RBPM)/Regulatory Program Manager (RPM): Steven Kinsley, Office of Pharmaceutical Quality/CDER Steven.Kinsley@fda.hhs.gov CDER/OPQ/OPF: Juandria.Williams@fda.hhs.gov
Through:	Nazia Rahman, Lead CSO, POND/DMQ/OC, CDRH, Nazia.rahman@fda.hhs.gov
From:	LCDR Elijah M. Weisberg, FEB/DICO/OC, CDRH, WO 66, Rm 3661, E-mail: Elijah.weisberg@fda.hhs.gov
Applicant/Licensure:	Braeburn Pharmaceuticals Inc. 47 HULFISH ST STE 441 PRINCETON, NEW JERSEY 08542 FEI#: 3012349378
Submission (Type & Number):	NDA-210136
Combination Product Name:	CAM2038
Combination Product Intended Use:	Blockade of opioid effects and suppression of withdrawal symptoms in adults with opioid use disorder
Device Constituent (Type):	Syringe
CTS ICCR Number:	ICC1700598
Sharepoint ICCR Number:	ICCR2017-01335 (Follow up)
ICCR Instruction (ICCR Form):	21 CFR 820 Requirements Review
Documentation Review (Status):	**Information - Inadequate**
CDRH/OC Recommendation:	**Withhold**

The Office of Compliance at CDRH received a consult from CDER requesting the identification of the device manufacturing sites for NDA-210136 which will require a device inspection. The previous CDRH recommendation included deficiencies that were transferred to the firm. The firm responded to deficiencies and this review captures the response to previous deficiencies.

Sites Requiring Inspections

Please see the previous memo for site inspection recommendations.

Documentation Review Recommendation

The adequacy of the firm responses to the previously identified deficiencies is outlined below in line with each deficiency.

(b) (4)

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(b) (4)

CDRH Office of Compliance Recommendation

The approvability of application CAM2038- NDA 210136 should be delayed for the following reasons:

Deficiencies were identified during the documentation review. Additional information from the firm is needed to complete the documentation review.

_____

Nazia Rahman

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/s/

STEVEN A KINSLEY
12/22/2017

MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING

Division of Medication Error Prevention and Analysis (DMEPA)

Office of Medication Error Prevention and Risk Management (OMEPRM)

Office of Surveillance and Epidemiology (OSE)

Center for Drug Evaluation and Research (CDER)

Date of This Memorandum:	December 15, 2017
Requesting Office or Division:	Division of Anesthesia, Analgesia, and Addiction Products (DAAAP)
Application Type and Number:	NDA 210136
Product Name and Strength:	Buprenorphine Injection, 50 mg/mL and 356 mg/mL
Total Product Strength:	8 mg/0.16 mL, 16 mg/0.32 mL, 24 mg/0.48 mL, 32 mg/0.64 mL, 64 mg/0.18 mL, 96 mg/0.27 mL, 128 mg/0.36 mL, (b) (4) (b) (4)
Applicant/Sponsor Name:	Braeburn Pharmaceuticals
Submission Date:	November 30, 2017 and December 11, 2017
OSE RCM #:	2017-1448-1
DMEPA Safety Evaluator:	Valerie S. Wilson, PharmD
DMEPA Team Leader:	Otto L. Townsend, PharmD

1 PURPOSE OF MEMO

The Division of Anesthesia, Analgesia, and Addiction Products (DAAAP) requested that we review the revised syringe labels, carton labeling, and Instruction for Use for buprenorphine weekly and monthly injections (Appendix A) to determine if they are acceptable from a medication error perspective. Some of the revisions are in response to recommendations that we made during a previous label and labeling review.[a] Additional revisions to the syringe label and carton labeling (i.e. color coding of each strength) were implemented by the Applicant voluntarily.

[a] Wilson, V. Label and Labeling Review for buprenorphine injection (NDA 210136). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2017 OCT 18. RCM No.: 2017-1448.

2 CONCLUSION/RECOMMENDATIONS

The revised syringe labels, carton labeling, and Instructions for Use for buprenorphine weekly and monthly injections are unacceptable from a medication error perspective. We identified the following issues outlined in Table 1 below that can be improved to provide clarity and mitigate wrong administration technique errors. We ask that the Division convey Table 1 to the Applicant so that recommendations are implemented prior to approval of this NDA.

Table 1. Identified Issues and Recommendations for the Applicant

	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATIONS FOR BRAEBURN PHARMACEUTICALS
Syringe Label and Carton Labeling			
1.	We note the inclusion of the statement, (b) (4) located on the carton; however, an area for the expiration date, as well as the lot number, is not designated on the revised syringe label as shown in Figure 1. **Figure 1.** Snapshot comparison of previous syringe label draft to the revised syringe label (b) (4)	The lot number statement and expiration date is required on the immediate container and carton per 21 CFR 201.10(i)(1) and 21 CFR 201.17, respectively.	Ensure the lot number and expiration date is included on the final syringe labels and cartons for each buprenorphine weekly and monthly injection per 21 CFR 201.10(i)(1) and 21 CFR 201.17. Additionally, we note the inclusion of an additional (b) (4) statement (b) (4) which should be removed.

2.	We note the unit of measurement (i.e. °C and °F) does not follow each numerical value of the temperature range within the storage statement on each carton.	The acceptable storage temperature could be misinterpreted and pose risk of improper storage leading to decrease product quality.	To provide clarity, we recommend revising the temperature statement on each carton to read: *Store at 20°C to 25°C (68°F to 77°F); with excursions permitted to 15°C to 30°C (59°F and 86°F) [see USP Controlled Room Temperature].*
3.	We acknowledge the revision to the product code of each NDC; however, we note the NDC package code (b) (4)	Each carton contains one unit of use, as such, the NDC package code typically aligns with the package size.	To provide clarity, we recommend you consider revising the NDC number on each syringe label and carton so the package code reflects "01" as the package size (e.g. revise to 58284-016-01, 58284-064-01, etc.). Additionally, ensure the NDCs are updated in the prescribing information accordingly.
Instructions for Use			
4.	You state in the SELECTING AN INJECTION SITE section that *[Trade name]* (b) (4) *should not be administered to the same site of injection for at least 8 weeks.* (b) (4) (b) (4)	It is unclear (b) (4) We note comprehension testing of the statement was not conducted during the HF validation study. We are concerned the statement may be misinterpreted resulting in wrong administration techniques errors.	To mitigate wrong administration technique errors, we recommend you clarify if there is a specific amount of time that should elapse (e.g. X weeks) before administering the monthly injection (b) (4) Additionally, clarify the intended meaning (b) (4)
5.	The highlighted area of the abdomen in Figure 5 under SELECTING AN INJECTION SITE appears (b) (4)	We previously communicated during review of the HF validation study protocol that this highlighted area could be misinterpreted (b) (4)	To mitigate wrong administration technique errors, we recommend you ensure the highlighted area (b) (4) of figure 5 in the final IFU.

	Figure 5 (b) (4)  We note Figure 5 was revised in the IFU used during the HF validation study, however, Figure 5 remained unchanged in the IFU included in the November 30, 2017 draft submission of the proposed intend-to-market IFU.		

APPENDIX A. LABEL AND LABELING SUBMITTED ON NOVEMBER 30, 2017 AND DECEMBER 11, 2017

Syringe labels

Application 210136 - Sequence 0065 - 1.14.1.1 Draft Carton and Container Labels

Carton labeling

Application 210136 - Sequence 0065 - 1.14.1.1 Draft Carton and Container Labels

Instructions for Use

Application 210136 - Sequence 0056 - 1.14.1.3 Draft Labeling Text

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/s/

VALERIE S WILSON
12/15/2017

OTTO L TOWNSEND
12/18/2017

Interdisciplinary Review Team for QT Studies Consultation: QT Study Review

IND or NDA	NDA 210136
Brand Name	(b) (4)
Generic Name	Buprenorphine injectable
Sponsor	Braeburn Pharmaceuticals Inc.
Indication	(b) (4)
Dosage Form	Subcutaneously (SC) injection
Drug Class	Partial mu-receptor agonist
Therapeutic Dosing Regimen	Once-weekly as 8 to 32 mg Once-monthly as 64 to (b) (4)
Duration of Therapeutic Use	Chronic
Maximum Tolerated Dose	Maximum dose studied is 32 mg once weekly and 192 mg once monthly.
Submission Number and Date	002, 07/19/2017
Review Division	DAAAP

Note: Any text in the review with a light background should be inferred as copied from the sponsor's document.

1 SUMMARY

1.1 Overall Summary of Findings

The provided information in this application supports an absence of large mean (i.e., 20 ms) increases in the QTc interval for buprenorphine (b) (4) at the time of expected maximum buprenorphine exposure for (b) (4) compared to a baseline where patients had been taking buprenorphine (with low systemic exposure).

To assess the effects of buprenorphine on the QT/QTc interval in NDA 210136, the sponsor collected time-matched ECG and PK samples in two healthy volunteer studies under naltrexone blockade and in a phase 2 study in patients as well as carried out a comprehensive preclinical assessment of buprenorphine, norbuprenorphine and naltrexone. The comprehensive preclinical assessment included assessment of the major cardiac ionic currents (hERG, peak sodium, late sodium, L-type calcium and KVLQT1/minK).

The comprehensive preclinical assessment indicated that at concentrations in the micromolar range that buprenorphine and norbuprenorphine inhibits all the currents studied. However, these concentrations are well above the clinically relevant

concentrations (subnanomolar range), and it therefore seems unlikely that buprenorphine or norbuprenorphine would cause QT prolongation via interaction with any of the cardiac ionic currents studied. In addition, the results also suggested that naltrexone does not block any of the cardiac ionic currents studied.

The clinical evaluation of buprenorphine under naltrexone blockade did not reveal a concentration-dependent relationship, which contradicts our experience from other healthy volunteer studies that did not include naltrexone. It is not clear why there is a difference as the preclinical results reviewed in this submission suggest that buprenorphine, norbuprenorphine and naltrexone do not interact with any of the major cardiac ionic currents. The sponsor also conducted clinical evaluation of the effects of buprenorphine on the ECG in a phase 2 study in patients. Few QTc outliers were observed in this study and no apparent concentration-dependent QTc prolongation between 2 and 14 ng/mL was observed.

Overall, the data reviewed in this submission shows an absence of large mean increases in the QTc interval compared to a baseline where patients have been taking buprenorphine. In addition, the data shows that buprenorphine and its metabolite norbuprenorphine are unlikely to interact with any of the major cardiac ionic currents (I_{kr}, I_{ks}, $I_{Na,Peak}$, $I_{Na,Late}$ and I_{Ca}). However, as the data do not permit excluding changes in the QTc interval from a drug-free baseline, we suggest that the sponsor includes similar language in the label as is included for other buprenorphine products.

2 PROPOSED LABEL

The sponsor did not propose any QT language in the label.

QT-IRT's following proposed labeling language is a suggestion only. We defer final labeling decisions to the Division.

5.x QTc prolongation

TRADENAME has been observed to prolong the QTc interval in some subjects participating in clinical trials. Consider these observations in clinical decisions when prescribing TRADENAME to patients with hypokalemia, hypomagnesemia, or clinically unstable cardiac disease, including unstable atrial fibrillation, symptomatic bradycardia, unstable congestive heart failure, or active myocardial ischemia. Periodic electrocardiographic (ECG) monitoring is recommended in these patients. Avoid the use of TRADENAME in patients with a history of Long QT Syndrome or an immediate family member with this condition or those taking Class IA antiarrhythmic medications (e.g., quinidine, procainamide, disopyramide) or Class III antiarrhythmic medications (e.g., sotalol, amiodarone, dofetilide), or other medications that prolong the QT interval. *[See Clinical Pharmacology (12.2)]*

12.2 Pharmacodynamics

Cardiac Electrophysiology

No thorough QT study for TRADENAME was conducted. Evaluation of the effects of TRADENAME on the QTc interval was evaluated in a phase 2 study in patients (n=65), which included three dose groups: 32 mg q1w, 128 q4w and 160 q4w. In this study ECGs were collected after doses 4 through 7 in the first group and after dose 4 in the two other

groups. In this study, no QTc measurements >500 ms were observed, and only one >480 ms in the 32 q1w dose group.

3 BACKGROUND

3.1 PRODUCT INFORMATION

Buprenorphine is a partial mu-opioid receptor agonist. It is currently indicated for the treatment of opioid use disorder or opioid dependence and for management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate.

QTc prolongation has been observed in healthy volunteer studies for other approved buprenorphine products.

3.2 MARKET APPROVAL STATUS

The list of buprenorphine products that are currently approved and still being marketed for the treatment of opioid use disorder or opioid dependence are shown in Table 1 below:

Table 1: Currently available treatments for opioid use disorder or opioid dependence. *[Source: Adapted based on the FDA AC Background Package for NDA 210136, Table 2]*

Daily Products			
Generic/Chemical Name	**Trade Name**	**Applicant**	**Dosage form(s)**
Buprenorphine/ naloxone	Suboxone tablet (generics only)	Indivior	Sublingual tablet
	Suboxone film (also generics)	Indivior	Sublingual film
	Bunavail (also generics)	Biodelivery Sci Intl	Buccal film
	Zubsolv (also generics)	Orexo AB	Sublingual tablet
Buprenorphine	Subutex (generics only)	Indivior	Sublingual tablet
Methadone HCl	Methadose (also generics)	Mallinckrodt	Oral solution Bulk powder Tablet Dispersible tab
Methadone HCl	Dolophine (also generics)	Roxane	Tablet Oral concentrat e

			Oral solution
Naltrexone HCl	ReVia (also generics)	Duramed	Tablet
Sustained release Products			
Naltrexone HCl	Vivitrol	Alkermes	Injectable suspension
Buprenorphine	Probuphine	Braeburn (Previously Titan)	Implant

3.3 PRECLINICAL INFORMATION

To understand the safety of buprenorphine, the FDA requested the sponsor to conduct in vitro pharmacology studies of buprenorphine, its major metabolite norbuprenorphine, and naltrexone on five cardiac ionic currents that underlie the ventricular action potentials. To fulfill this request, the sponsor submitted two preclinical study reports (TO-17-589 and TO-17-594). The five ionic currents are hERG and KVLQT1/minK currents that repolarize the action potential, peak Na+ current that generates action potential upstroke, and late Na+ and L-type Ca2+ currents that mediate action potential plateau or duration.

The sponsor's electrophysiology data are of reasonable quality, allowing for detailed evaluation. Independent review of the data showed that although buprenorphine inhibited all five ionic currents, it blocked inward (L-type Ca2+ and late Na+ current) and outward (hERG current) currents with similar potencies. Of note, the IC_{50} values needed to block cardiac ion channels directly were in the micromolar ranges, far above the subnanomolar free C_{max} for buprenorphine associated with QTc prolongation in vivo. These findings suggest that QTc prolongation with buprenorphine is not mediated via inhibition of the cardiac ionic currents studied.

Ventricular myocytes do not express μ-opioid receptors (Peng et al., 2012; The Human Protein Atlas). However, these receptors are found on the cardiac parasympathetic, sympathetic, and sensory neurons (Mousa et al., 2010). Buprenorphine mediated QTc prolongation may thus reflect this drug's effect on the neuromodulatory tone onto the heart that indirectly alters cardiac ion channel activity or binding to auxiliary ion channel proteins or signaling cascades that are not expressed by cell lines.

For a complete assessment of the preclinical data, please see the review from DARS.

3.4 PREVIOUS CLINICAL EXPERIENCE

QT prolongation has been observed in healthy volunteer studies for other approved buprenorphine products.

3.5 CLINICAL PHARMACOLOGY

Appendix 6.1 summarizes the key features of buprenorphine's clinical pharmacology.

4 SPONSOR'S SUBMISSION

4.1 OVERVIEW

ECGs were collected in multiple studies, but as discussed in a previous QT-IRT review dated 03/02/2017 the majority of the ECG collection were inadequate to capture the maximum effect of the product (trough samples), except for study HS-15-549. To help with interpretation of the data, the sponsor was encouraged to collect more extensive preclinical data (see section 3.3). The review by the IRT is therefore focused on analysis of the data collected in HS-15-549.

4.2 QT STUDY

4.2.1 Title

A Phase II, Open-label, Partially Randomized, Three Treatment Groups, Multi-Site Study Assessing Pharmacokinetics after Administration of the Once-Weekly and Once-Monthly, Long-Acting Subcutaneous Injectable Depot of Buprenorphine (CAM2038) at Different Injection Sites in Opioid-Dependent Subjects with Chronic Pain

4.2.2 Protocol Number

HS-15-549

4.2.3 Study Dates

- Study initiation date (first subject enrolled): (b) (6)
- Early Study Termination Date: (b) (6)

4.2.4 Objectives

Primary Objective:

- Evaluate the steady-state PK of BPN and norBPN following repeated SC administration of CAM2038 q1w (50 mg/mL) at 4 different injection sites in adult opioid-dependent subjects with chronic pain.
- Evaluate steady-state PK of BPN and norBPN following repeated SC administration of CAM2038 q4w (356 mg/mL) with the buttock as the injection site in adult opioid dependent subjects with chronic pain.

Secondary Objective:

- Evaluate the safety and tolerability of CAM2038 q1w and CAM2038 q4w in adult opioid-dependent subjects with chronic pain.
- Assess relative bioavailability of BPN at steady state following repeated SC administration of 160 mg CAM2038 q4w compared with repeated SL administration of 24 mg BPN/NX in adult opioid-dependent subjects with chronic pain.

Exploratory Objective:

- Evaluate maintenance of treatment efficacy when transferring adult opioid-dependent subjects from SL BPN to CAM2038 q1w and q4w, as determined by urine toxicology.
- Evaluate subject-rated worst daily pain and average daily pain, using an 11-point numerical rating scale (NRS), following repeated SC administration of CAM2038 q1w and CAM2038 q4w in adult opioid-dependent subjects.

4.2.5 Study Description

4.2.5.1 Design

This was a Phase 2, open-label, partially randomized, 3-treatment group study that evaluated the steady-state PK of BPN and norBPN in opioid-dependent subjects with a history of chronic noncancer pain following multiple weekly SC administrations of CAM2038 at different injection sites or multiple monthly SC administrations of CAM2038 in the buttock.

4.2.5.2 Controls

No positive or negative controls were included.

4.2.5.3 Blinding

Open label study.

4.2.6 Treatment Regimen

4.2.6.1 Treatment Arms

- Group 1: 3 single weekly SC injections of 32 mg CAM2038 q1w administered in the buttock, rotating between right and left buttock and injection site, followed by 4 single weekly SC injections of 32 mg CAM2038 q1w administered in the buttock (reference), abdomen, thigh, and back of upper arm with injection site sequence allocated using a randomized crossover design. On Day 50 (EOT visit for Group 1), subjects could continue in the Open-Label Safety Extension Phase and receive up to 6 injections of 32 mg CAM2038 q1w rotated in the abdomen, arm, buttocks, and thigh. The Investigator kept a record of the specific injection site location at each treatment visit. Injections were rotated such that no injections were administered into the same site.
- Group 2: 4 monthly SC injections of 128 mg CAM2038 q4w (0.36 mL) administered in the buttock, rotating between the right and left buttock such that no injections were administered into the same site. On Day 113 (EOT visit for Group 2), subjects could continue in the Open-Label Safety Extension Phase and receive up to 6 injections of 32 mg CAM2038 q1w rotated between the right and left buttock. The Investigator kept a record of the specific injection site location at each treatment visit. Injections were rotated such that no injections were administered into the same site.

- Group 3: Seven consecutive daily doses of 24 mg of SL BPN/NX, which after agreement was administered as 8 mg three times per day to a total of 24 mg, according to the patients' standard treatment in 17 subjects. One subject received 12 mg SL BPN/NX twice per day. The SL BPN/NX dosing was followed by 4 monthly SC injections of 160 mg CAM2038 q4w (0.45 mL) administered in the buttock, rotating between the right and left buttock such that no injections were administered into the same site.

4.2.6.2 Sponsor's Justification for Doses

The study involved 3 dose regimens for CAM2038: 32 mg CAM2038 q1w SC injection, 128 mg CAM2038 q4w SC injection, and 160 mg CAM2038 q4w SC injection. For CAM2038 q1w, the study was expected to provide data on the plasma BPN and norBPN levels across 4 injections sites (buttock, abdomen, thigh, and back of upper arm). The 32 mg dose was the highest single dose strength available for CAM2038 q1w, and steady-state plasma concentrations of BPN were expected to be within known therapeutic plasma levels based on previous studies (HS-11-426 and HS-13-487). During the Open-Label Safety Extension Phase for Groups 1 and 2, all subjects received 32 mg CAM2038 q1w.

Reviewer's Comment: Acceptable, the doses included are not adequate to waive the requirement for inclusion of a positive control per ICH E14 Q&A R3, but adequate to evaluate the cardiac safety of the highest clinical dose.

4.2.6.3 Instructions with Regards to Meals

Not applicable.

4.2.6.4 ECG and PK Assessments

ECG collection: ECGs were taken at the Screening and EOT visits, and pre-dose and 23 (±2) hours after the first CAM2038 q1w administration. ECGs were taken at 1, 4, 6, 10, 24, 48, 72, 96, and 168 hours post-dose for Doses 4 through 7.

PK collection: PK samples were collected at pre-dose and at 0.5, 1, 2, 4, 6, 10, 24, 30, 48, 72, 96, 120 and 168 hours post-CAM2038 q1w for Doses 4, 5, 6, and 7. When a pre-dose and 168 hours post-dose time point coincided, only 1 PK sample was collected.

Reviewer's Comment: Acceptable, the ECG/PK samples collected are expected to cover T_{max}.

4.2.6.5 Baseline

Baseline was defined as the last observed measurement prior to or on the day of randomization.

Reviewer's Comment: During the screening period subjects were on sublingual buprenorphine. As a result, no drug-free baseline ECG was available and the changes in ECG parameters from baseline should therefore be interpreted with caution.

4.2.7 ECG Collection

12-Lead ECGs will be performed after the subject has been resting in a recumbent/supine position for at least 3 minutes at the times specified in Group 1, Group 2, and Group 3. The QT intervals were automatically reported by the ECG recorder, and the same ECG recorder was used for all patients within each of the two sites for the study (IND 114082, Seq 0077, link).

Reviewer's Comment: Acceptable.

4.2.8 Sponsor's Results

4.2.8.1 Study Subjects

Overall, 81 subjects were screened and 66 subjects were enrolled and were randomized or entered into the study (28, Group 1; 20, Group 2; 18, Group 3). Sixty-five subjects received CAM2038 and were included in the safety population (28, Group 1; 20, Group 2; 17, Group 3). Fifty (82.0%) subjects in the safety population completed the PK portion of the study. Fifteen (23.1%) subjects discontinued the study, primarily due to withdrawal by subject (7 subjects; 10.8%), lost to follow-up (3 subjects; 4.6%), study terminated by sponsor (2 subjects; 3.1%), and other (3 subjects; 4.6%).

4.2.8.2 Statistical Analyses

4.2.8.2.1 By Timepoint Analysis

Mean and median values for the ECG parameters were similar across all groups at Baseline, and changes from Baseline in each parameter were minimal throughout the study. No clinically meaningful trends were observed.

Reviewer's Comments: As no baseline was available (see section 4.2.6.5), the assessment of the change from baseline in ECG parameters should be interpreted with appropriate caution.

4.2.8.2.2 Assay Sensitivity

No positive control was used in the study. Assay sensitivity is not assessed.

4.2.8.2.3 Categorical Analysis

The number of subjects who had a QTcF duration <450 ms at any post-baseline evaluation was 20 (74.1%) in Group 1, 14 (70.0%) in Group 2, and 16 (94.1%) in Group 3. Six (22.2%) subjects in Group 1, 6 (30.0%) subjects in Group 2, and 1 (5.9%) subjects in Group 3 had a QT duration ≥450 to <480 ms at any post-baseline evaluation. One (3.7%) subject in Group 1, no subjects in Group 2, and no subjects in Group 3 had a QTcF duration ≥480 to <500 ms. No subjects in any group had a QTcF duration of ≥500 ms at any post-baseline evaluation.

The number of subjects who had an increase from baseline in QTcF duration value <30 ms at any post-baseline evaluation was 17 (63.0%) subjects in Group 1, 15 (75.0%) subjects in Group 2, and 13 (76.5%) subjects in Group 3. Nine (33.3%) subjects in Group 1, 5 (25.0%) subjects in Group 2, and 3 (17.6%) subjects in Group 3 had a change from

Baseline in QTcF duration value ≥30 and <60 ms at any post-baseline evaluation. One (3.7%) subject in Group 1 (b) (6) no subjects in Group 2, and 1 (5.9%) subject in Group 3 (b) (6) had a change from baseline in QTcF duration value ≥60 ms at any post-baseline evaluation.

Table 2: Summary of QT Duration and QTcF Duration (Safety Population) *[Source: Sponsor's clinical study report Table 14.3.28]*

Parameter/Timepoint/Category	Group 1 N=28 n (%)	Group 2 N=20 n (%)	Group 3 N=17 n (%)
QT Duration			
Baseline			
<450 msec	28 (100.0)	20 (100.0)	17 (100.0)
≥450 to <480 msec	0 (0.0)	0 (0.0)	0 (0.0)
≥480 to <500 msec	0 (0.0)	0 (0.0)	0 (0.0)
≥500 msec	0 (0.0)	0 (0.0)	0 (0.0)
Any Post-Baseline Visit			
<450 msec	21 (77.8)	16 (80.0)	16 (94.1)
≥450 to <480 msec	5 (18.5)	2 (10.0)	1 (5.9)
≥480 to <500 msec	1 (3.7)	2 (10.0)	0 (0.0)
≥500 msec	0 (0.0)	0 (0.0)	0 (0.0)
Change (i.e., increase) from Baseline at any Post-Baseline Visit			
<30 msec	11 (40.7)	10 (50.0)	12 (70.6)
≥30 to <60 msec	14 (51.9)	10 (50.0)	3 (17.6)
≥60 msec	2 (7.4)	0 (0.0)	2 (11.8)
QTcF Duration			
Baseline			
<450 msec	26 (92.9)	20 (100.0)	17 (100.0)
≥450 to <480 msec	2 (7.1)	0 (0.0)	0 (0.0)
≥480 to <500 msec	0 (0.0)	0 (0.0)	0 (0.0)
≥500 msec	0 (0.0)	0 (0.0)	0 (0.0)
Any Post-Baseline Visit			
<450 msec	20 (74.1)	14 (70.0)	16 (94.1)
≥450 to <480 msec	6 (22.2)	6 (30.0)	1 (5.9)
≥480 to <500 msec	1 (3.7)	0 (0.0)	0 (0.0)
≥500 msec	0 (0.0)	0 (0.0)	0 (0.0)
Change (i.e., increase) from Baseline at any Post-Baseline Visit			
<30 msec	17 (63.0)	15 (75.0)	13 (76.5)
≥30 to <60 msec	9 (33.3)	5 (25.0)	3 (17.6)
≥60 msec	1 (3.7)	0 (0.0)	1 (5.9)

Overall, the most common CAM2038-related TEAEs were injection site swelling (3 subjects, Group 1; 0 subjects, Group 2; 0 subjects, Group 3) and injection site erythema (2 subjects, Group1; 1 subject, Group 2; 0 subjects, Group 3). Other drug-related TEAEs were single events of constipation (Group 1, mild), fatigue (Group 2, moderate), headache (Group 2, moderate), pruritus (Group 3, mild), and elevated AST (Group 3, mild). No TEAEs were reported during treatment with SL BPN/NX in Group 3.

There were no deaths during this study.

4.2.8.3 Clinical Pharmacology

4.2.8.3.1 Pharmacokinetic Analysis

The pharmacokinetic results of the different SC dosing regimens are shown below for buprenorphine and norbuprenorphine respectively.

Figure 1: Mean buprenorphine concentration-time profiles after SC administration of fourth to seventh dose of 32 mg. *[Source: Sponsor's clinical study report figure 2]*

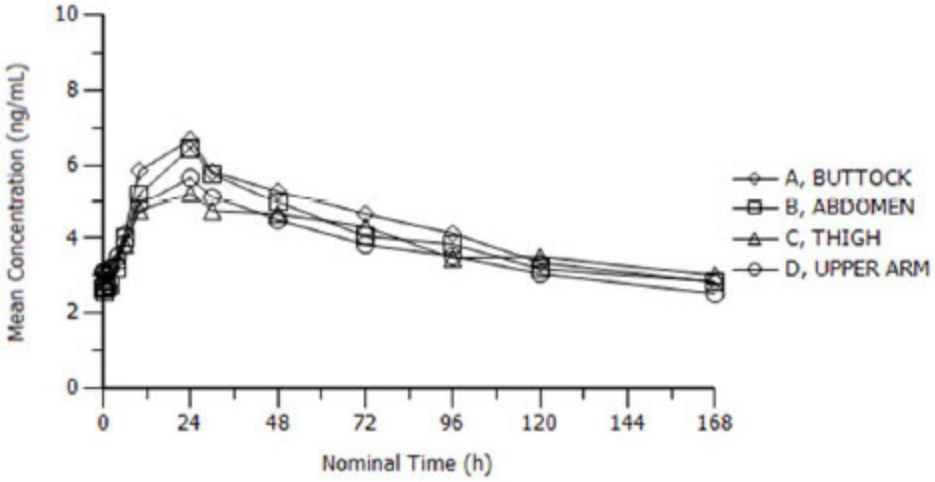


Figure 2: Mean norbuprenorphine concentration-time profiles after SC administration of fourth to seventh dose of 32 mg. *[Sponsor's clinical study report figure 3]*

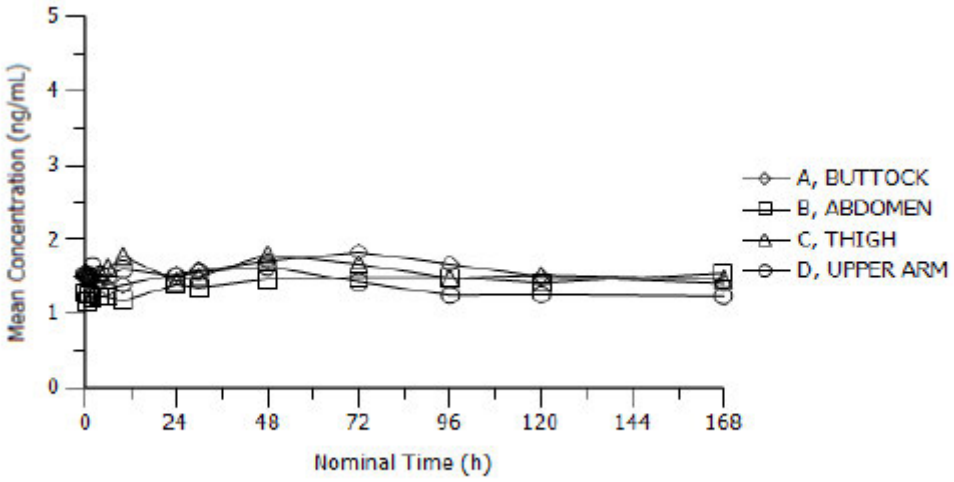


Figure 3: Mean buprenorphine concentration-time profiles after SC administration of fourth dose of 128 mg. *[Sponsor's clinical study report figure 4]*

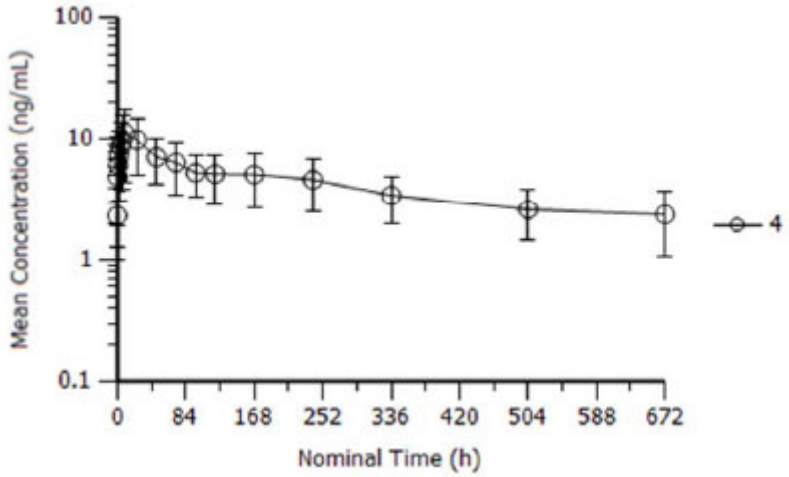


Figure 4: Mean norbuprenorphine concentration-time profiles after SC administration of fourth to seventh dose of 128 mg. [*Sponsor's clinical study report figure 5*]

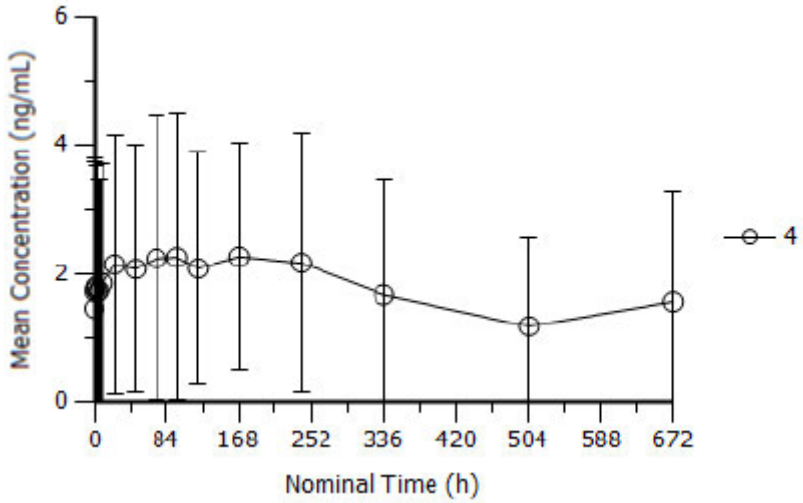


Figure 5: Mean buprenorphine concentration-time profiles after SC administration of fourth dose of 160 mg. [*Sponsor's clinical study report figure 7*]

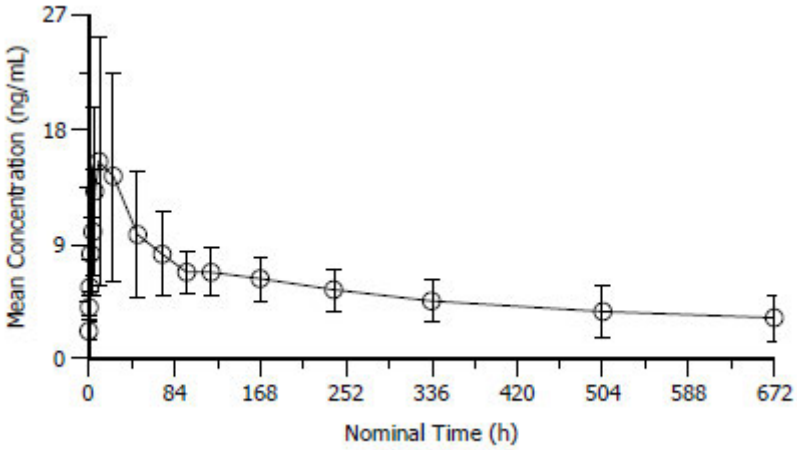
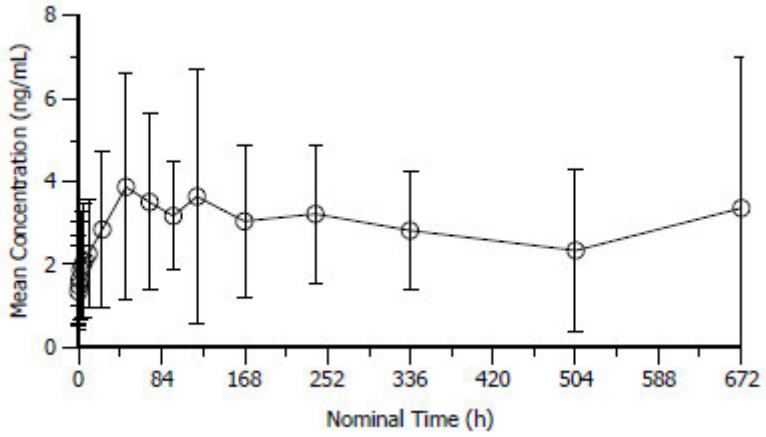


Figure 6: Mean norbuprenorphine concentration-time profiles after SC administration of fourth dose of 160 mg. [*Sponsor's clinical study report figure 9*]



4.2.8.3.2 Exposure-Response Analysis

The relationship between absolute QTcF and change in QTcF from baseline vs the BPN plasma concentration were assessed at or around Cmax. A scatter plot of the absolute QTcF values is shown in Figure 10, while the change in QTcF from baseline is shown in Figure 11. No absolute QTcF values above 500 msec were recorded. Furthermore, there were no trends of BPN plasma concentration changes in either absolute QTcF or QTcF change from baseline values.

Reviewer's Analysis: As noted previously, the study did not include collection of a drug-free baseline or sufficiently high concentrations to support waiving the requirement of a positive control and the lack of a concentration-dependent change in ΔQTc, without a valid baseline measurement. Therefore, it does not support an absence of large (i.e., 20 ms) mean QTc changes from a drug-free baseline.

5 REVIEWERS' ASSESSMENT

5.1 EVALUATION OF THE QT/RR CORRECTION METHOD

The sponsor used QTcF for the primary analysis.

5.2 STATISTICAL ASSESSMENTS

5.2.1 QTc Analysis

5.2.1.1 The By Timepoint Analysis for the Study Drug

The statistical reviewer performed descriptive summary analysis of ΔQTcF effect. The analysis results are listed in the following table given consideration of the small sample size. No large changes in the mean change from baseline QTc interval were detected. However, as noted previously the baseline ECG used was not a drug-free baseline.

Table 3: Descriptive Summary of ΔQTcF

Treatment	Study Day	Timepoint (H post-dose)	N	Mean	Lower 90% CI Limit	Upper 90% CI Limit
Group 1: CAM2038 q1w	2	23	27	1.3	-3.5	6.1
	22	1	23	-1.2	-7.9	5.6
	22	10	23	3.7	-2.7	10.0
	22	4	23	2.6	-2.9	8.1
	22	6	23	7.3	1.5	13.2
	23	24	23	-1.1	-6.5	4.4
	24	48	22	3.7	-1.9	9.3
	25	72	23	6.3	-0.7	13.4
	26	96	22	8.7	0.5	16.9
	29	1	22	1.8	-4.4	8.1
	29	10	23	1.6	-3.6	6.7
	29	168	22	-0.6	-6.7	5.4
	29	4	23	3.0	-3.3	9.2
	29	6	23	1.9	-4.5	8.3
	30	24	23	1.8	-3.5	7.2
	31	48	23	1.4	-3.8	6.7
	32	72	22	3.8	-3.8	11.4
	33	96	23	2.1	-3.2	7.4
	36	1	22	-3.2	-9.6	3.1
	36	10	21	5.0	-1.6	11.6
	36	168	20	1.6	-3.7	6.9
	36	4	22	5.6	-0.8	12.0
	36	6	22	0.6	-4.9	6.2
	37	24	22	3.1	-3.8	10.1
	38	48	20	2.5	-3.3	8.2
	39	72	22	-0.5	-5.0	3.9
	40	96	22	-1.9	-7.1	3.4
	43	1	22	-4.0	-14.1	6.2
	43	10	19	2.0	-5.7	9.7
	43	168	20	-0.1	-5.1	5.0
	43	4	22	0.6	-6.1	7.4
	43	6	22	2.1	-3.1	7.3
	44	10	4	-5.3	-21.6	11.1
	44	24	22	3.8	-0.9	8.4
	45	48	21	-0.8	-6.6	5.0
	46	72	22	-3.4	-10.3	3.6
	47	96	21	-3.1	-11.4	5.1

	50	168	20	-1.3	-6.8	4.2
Group 2: CAM2038 q4w	1	6	19	2.7	-3.1	8.4
	2	24	13	0.5	-6.5	7.6
	8	168	6	4.0	-7.0	15.0
	15	336	13	1.2	-6.0	8.4
	22	504	6	-4.0	-12.6	4.6
	29	6	16	-0.5	-5.5	4.5
	36	168	15	1.9	-5.3	9.2
	57	6	16	-5.8	-12.1	0.4
	59	48	9	1.4	-8.6	11.5
	64	168	11	5.4	-1.6	12.3
	71	336	14	-2.9	-11.4	5.7
	78	504	15	-2.9	-10.1	4.4
	85	1	15	-2.7	-7.8	2.3
	85	10	15	-1.7	-8.6	5.2
	85	4	15	4.7	-1.5	10.9
	85	6	15	-5.1	-11.2	0.9
	86	24	15	-5.7	-11.8	0.5
	88	72	15	-5.4	-13.2	2.4
	90	120	14	-3.7	-14.1	6.7
	92	168	15	-6.8	-20.2	6.6
	99	336	15	-1.7	-7.0	3.5
	113	672	15	-7.6	-17.3	2.1
Group 3: CAM2038 q4w	1	6	17	-1.8	-7.2	3.6
	29	6	16	1.6	-7.1	10.3
	57	6	13	3.0	-3.3	9.3
	84	1	3	-19.0	-33.6	-4.4
	84	10	3	-14.3	-32.2	3.5
	84	4	3	-11.7	-17.6	-5.7
	84	6	3	-17.3	-26.6	-8.0
	85	1	9	3.2	-7.4	13.9
	85	10	9	1.7	-8.6	11.9
	85	24	3	-20.0	-52.8	12.8
	85	4	9	3.0	-4.5	10.5
	85	6	9	3.6	-8.5	15.6
	86	24	9	1.7	-11.4	14.7
	88	72	9	-2.1	-9.5	5.2
	90	120	8	0.4	-8.4	9.2
	92	168	8	-2.0	-17.4	13.4
	99	336	9	7.6	-4.8	20.0
	113	672	9	-3.6	-13.9	6.8

5.2.1.2 Categorical Analysis

Table 4 lists the number of subjects as well as the number of observations whose QTcF values are ≤ 450 ms, between 450 ms and 480 ms, between 480 ms and 500 ms. No subject's QTcF was above 500 ms.

Table 4: Categorical Analysis for QTcF

	Total N		Value<=450 ms		450 ms<Value<=480 ms		480 ms<Value<=500 ms	
Treatment Group	**# Subj.**	**# Obs.**	**# Subj.**	**# Obs.**	**# Subj.**	**# Obs.**	**# Subj.**	**# Obs.**
Group 1: CAM2038 q1w	27	863	20 (74.1%)	805 (93.3%)	6 (22.2%)	57 (6.6%)	1 (3.7%)	1 (0.1%)
Group 2: CAM2038 q4w	20	332	13 (65.0%)	321 (96.7%)	7 (35.0%)	11 (3.3%)	0 (0.0%)	0 (0.0%)
Group 3: CAM2038 q4w	17	167	16 (94.1%)	166 (99.4%)	1 (5.9%)	1 (0.6%)	0 (0.0%)	0 (0.0%)

Table 5 lists the categorical analysis results for ΔQTcF. There are 2 subjects with change from baseline above 60 ms (1, Group 1; 1, Group 3).

Table 5: Categorical Analysis of ΔQTcF

	Total N		Value<=30 ms		30 ms<Value<=60 ms		Value>60 ms	
Treatment Group	**# Subj.**	**# Obs.**	**# Subj.**	**# Obs.**	**# Subj.**	**# Obs.**	**# Subj.**	**# Obs.**
Group 1: CAM2038 q1w	27	863	19 (70.4%)	834 (96.6%)	7 (25.9%)	28 (3.2%)	1 (3.7%)	1 (0.1%)
Group 2: CAM2038 q4w	20	332	15 (75.0%)	327 (98.5%)	5 (25.0%)	5 (1.5%)	0 (0.0%)	0 (0.0%)
Group 3: CAM2038 q4w	17	167	14 (82.4%)	157 (94.0%)	2 (11.8%)	9 (5.4%)	1 (5.9%)	1 (0.6%)

5.2.2 PR Analysis

The outlier analysis results for PR are presented in Table 6. There are 6 subjects who experienced PR interval greater than 200 ms (3, Group 1; 3, Group 2).

Table 6: Categorical Analysis for PR

	Total N		Value<=200 ms		Value>200 ms	
Treatment Group	**# Subj.**	**# Obs.**	**# Subj.**	**# Obs.**	**# Subj.**	**# Obs.**
Group 1: CAM2038 q1w	27	855	24 (88.9%)	817 (95.6%)	3 (11.1%)	38 (4.4%)
Group 2: CAM2038 q4w	20	324	17 (85.0%)	305 (94.1%)	3 (15.0%)	19 (5.9%)

	Total N		Value<=200 ms		Value>200 ms	
Treatment Group	**# Subj.**	**# Obs.**	**# Subj.**	**# Obs.**	**# Subj.**	**# Obs.**
Group 3: CAM2038 q4w	17	166	17 (100%)	166 (100%)	0 (0.0%)	0 (0.0%)

5.2.3 QRS Analysis

The outlier analysis results for QRS are presented in Table 7. There are 13 subjects who experienced QRS interval greater than 110 ms (4, Group 1; 6, Group 2; 3 Group 3).

Table 7: Categorical Analysis for QRS

	Total N		Value<=100 ms		100 ms<Value<=110 ms		Value>110 ms	
Treatment Group	**# Subj.**	**# Obs.**	**# Subj.**	**# Obs.**	**# Subj.**	**# Obs.**	**# Subj.**	**# Obs.**
Group 1: CAM2038 q1w	27	863	15 (55.6%)	714 (82.7%)	8 (29.6%)	130 (15.1%)	4 (14.8%)	19 (2.2%)
Group 2: CAM2038 q4w	20	332	5 (25.0%)	212 (63.9%)	9 (45.0%)	85 (25.6%)	6 (30.0%)	35 (10.5%)
Group 3: CAM2038 q4w	17	167	11 (64.7%)	135 (80.8%)	3 (17.6%)	27 (16.2%)	3 (17.6%)	5 (3.0%)

5.3 CLINICAL PHARMACOLOGY ASSESSMENTS

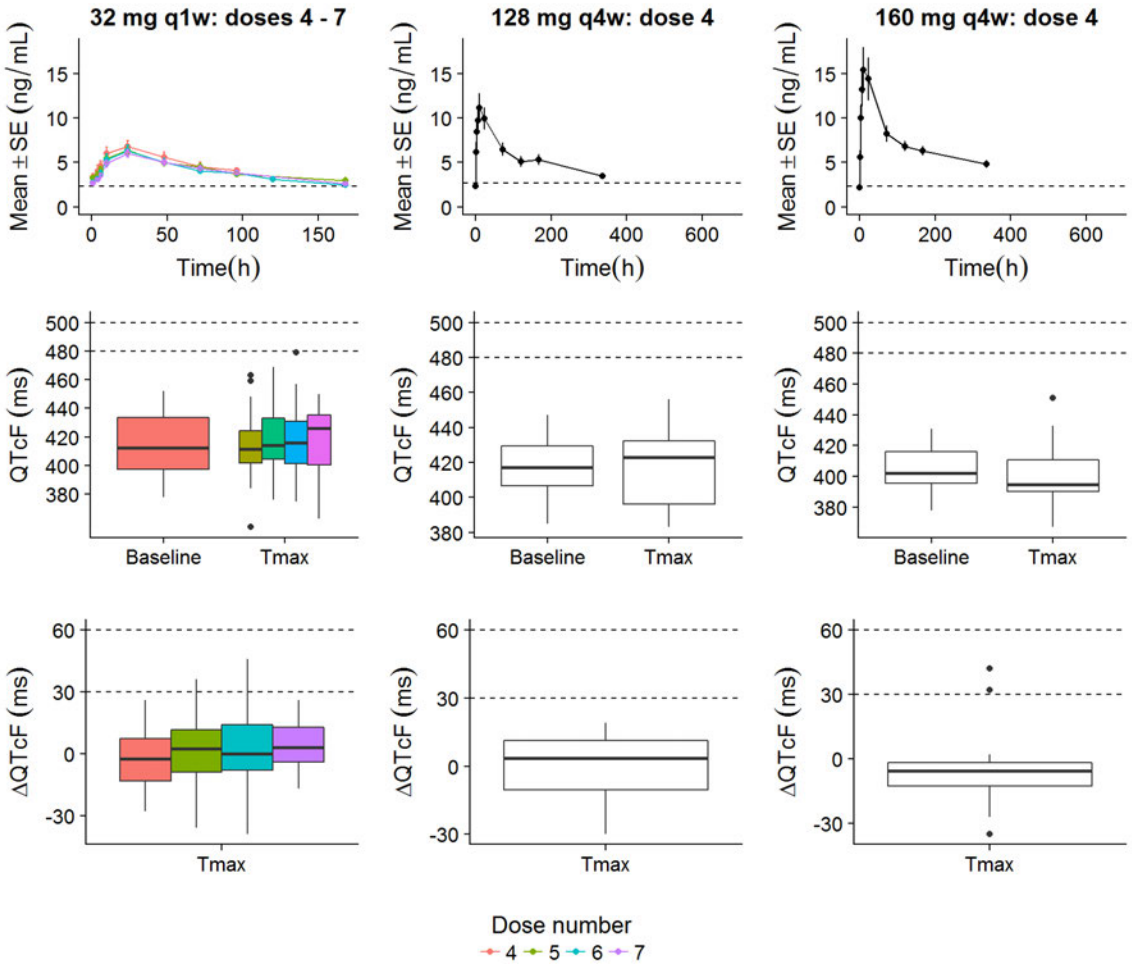
As noted in section 4.2.6.5, the baseline collected was not a true baseline as the patients were on buprenorphine prior to study initiation and as such traditional change from baseline analysis is not appropriate. The reviewer therefore compared the buprenorphine concentrations and QTc values at "baseline" with the median group T_{max} (24 h post-dose for groups 1 and 3 and 10 h for group 2). The results of this analysis shown below in Figure 7. From the figure the following observations can be made:

- At the baseline visit the mean buprenorphine levels were ~2 ng/mL for the 32 mg q1w and 128 q4w dose groups and ~4.3 ng/mL for the 160 mg q4w group. The concentrations at T_{max} were ~2.7 to ~4-fold as high (up to ~14 ng/mL).

- No QTc values greater than 480 or 500 ms were observed at the T_{max} time-point in any dose group and there were no ΔQTcF values >30 ms. Additionally, no trend towards an increase in the median QTcF values were observed. These observations, are consistent with the analysis presented in section 5.2.1.

These observations do not suggest the presence of a concentration-dependent increase in QTc (between 2 and 14 ng/mL). However, this does not support concluding an absence of QTc prolongation, as no drug-free baseline was available.

Figure 7: Assessment of the changes in pharmacokinetics (top row), absolute QTcF (middle row) and ΔQTc (bottom row) for 32 mg q1w dosing (left column), 128 q4w (middle column) and 160 q4w (right column). The dashed lines in the top row represent the buprenorphine levels corresponding to when the baseline ECG was collected. The dashed lines in the middle and bottom row represents cutoffs typically used for QTc outlier analysis.



5.4 CLINICAL ASSESSMENTS

5.4.1 Safety assessments

None of the events identified to be of clinical importance per the ICH E 14 guidelines i.e. syncope, seizure, significant ventricular arrhythmias or sudden cardiac death occurred in this study.

5.4.2 ECG assessments

Paper ECGs were submitted. All ECG intervals were machine read.

5.4.3 PR and QRS Interval

One subject in Group 1 and 1 subject in Group 2 had baseline and post-baseline PR values above 200 ms. One subject in Group 1 and 1 subject in Group 3 had baseline and post-baseline QRS values above 110 ms.

6 APPENDIX

6.1 HIGHLIGHTS OF CLINICAL PHARMACOLOGY

Therapeutic dose and exposure	**Single dose: CAM2038 50 ng/mL q1w** 8 mg: C_{max} = 1.71 ng/mL (36%), AUC_{inf} = 166 ng*h/mL (20%) 16 mg: C_{max} = 3.08 ng/mL (49%), AUC_{inf} = 335 ng*h/mL (13%) 32 mg: C_{max} = 5.27 ng/mL (45%), AUC_{inf} = 638 ng*h/mL (12%) Steady state (32 mg): C_{max} = 6.17 ng/mL (47%), AUC_{ss} = 632 ng*h/mL (36%) based on preliminary data (Trial HS-15-549) Steady state (16 mg): C_{max} = 4.30 ng/mL (44%), AUC_{ss} = 350 ng*h/mL (24%) **Single Dose CAM2038 356 mg/mL q4w** 64 mg: C_{max} = 3.81 ng/mL (60%), AUC_{inf} = 1360 ng*h/mL (33%) 96 mg: C_{max} = 5.47 ng/mL (56%), AUC_{inf} = 1830 ng*h/mL (26%) 128 mg: C_{max} = 6.59 ng/mL (68%), AUC_{inf} = 2550 ng*h/mL (26%) 192 mg: C_{max} = 7.54 ng/mL (58%), AUC_{inf} = 3260 ng*h/mL (31%) Steady state (128 mg): Evaluation ongoing. Values represent the geometric mean. Parenthesis the coefficient of variance	
Maximum tolerated dose	**CAM2038 q1w** Not applicable. Highest tested tolerated dose 32 mg. **CAM 2038 q4w** Not applicable. Highest tested tolerated dose 192 mg.	
Principal adverse events	The most commonly reported adverse drug reactions (ADRs; i.e. adverse events assessed as related to the IMP) reported until 19-Feb-2016 have been drug withdrawal syndrome, headache, injection site pain, nausea and vomiting. All of these events have been reported by less than 5% of the patients.	
Maximum dose tested	Single Dose	**CAM2038 q1w** 32 mg **CAM2038 q4w** 192 mg
	Multiple Dose	**CAM2038 q1w** 32 mg once weekly for more than 6 months in ongoing studies **CAM2038 q4w** 160 mg once monthly for more than 6 months in ongoing studies
Exposures Achieved at Maximum Tested Dose	Single Dose	**CAM2038 q1w** Single dose: C_{max} = 5.27 ng/mL (45%), AUC_{inf} = 638 ng*h/mL (12%) **CAM2038 q4w** Single dose: C_{max} = 7.54 ng/mL (58%), AUC_{inf} = 3260 ng*h/mL (31%)
	Multiple Dose	**CAM2038 q1w** Steady state (32 mg): C_{max} = 6.17 ng/mL (47%), AUC_{ss} = 632 ng*h/mL (36%) based on preliminary data (Trial HS-15-549) **CAM2038 q4w** Steady state (128 mg): Evaluation ongoing.
Range of linear PK	**CAM2038 q1w** Dose-independent PK between 8 and 32 mg. Time-independent PK for once weekly sc administration of 16 mg. **CAM2038 q4w** Dose-proportional AUC_{inf}. Slightly less than dose proportionally for C_{max} between 64 and 192 mg.	

<table>
<tr><td></td><td colspan="2">Time dependency to be addressed in the NDA submission.</td></tr>
<tr><td>Accumulation at steady state</td><td colspan="2">CAM2038 q1w Rac = 1.44 (25%) for once weekly sc administration of 16 mg

CAM2038 q4w To be addressed in the NDA submission.</td></tr>
<tr><td>Metabolites</td><td colspan="2">CAM2038 q1w and CAM2038 q4w treatment results in much lower maximum exposures of the major active metabolite norbuprenorphine versus the exposure after treatment with SL BPN products
<table>
<tr><th rowspan="2">Products</th><th rowspan="2">Dose (mg)</th><th colspan="3">Buprenorphine</th><th colspan="3">Norbuprenorphine</th></tr>
<tr><th>$C_{sd,max}$ (ng/mL)</th><th>$C_{ss,max}$ (ng/mL)</th><th>$C_{ss,av}$ (ng/mL)</th><th>$C_{sd,max}$ (ng/mL)</th><th>$C_{ss,max}$ (ng/mL)</th><th>$C_{ss,av}$ (ng/mL)</th></tr>
<tr><td>CAM2038 q1w[a]</td><td>16</td><td>3.05</td><td>4.30</td><td>2.09</td><td>0.763</td><td>0.921</td><td>0.643</td></tr>
<tr><td>CAM2038 q1w[b]</td><td>32</td><td>5.27</td><td>6.9[c]</td><td>3.8[d]</td><td>0.938</td><td>ND</td><td>ND</td></tr>
<tr><td>CAM2038 q4w[a]</td><td>128</td><td>6.59</td><td>7.0[c]</td><td>3.8[d]</td><td>1.36</td><td>ND</td><td>ND</td></tr>
<tr><td>CAM2038 q4w[a]</td><td>192</td><td>7.54</td><td>ND</td><td>ND</td><td>1.62</td><td>ND</td><td>ND</td></tr>
<tr><td>SL Buprenorphine[a]</td><td>24</td><td>8.23</td><td>8.45</td><td>2.66</td><td>4.96</td><td>9.29</td><td>5.81</td></tr>
</table>
[a] Trial HS-13-487; [b] Trial HS-11-426; [c] $C_{ss,peak}$ as predicted by simulation from a nonlinear mixed effects PK model describing observed PK data; [c] Predicted and calculated from AUC_{inf} after single dosing and assuming time-independent pharmacokinetics
ND = not determined</td></tr>
<tr><td rowspan="2">Absorption</td><td>Absolute/Relative Bioavailability</td><td>CAM2038 q1w
Absolute bioavailability
8 mg: 165% (16%)
16 mg: 171% (16%)
32 mg: 163% (15%)
Relative bioavailability versus Subutex (at 8, 16 and 24 mg)
8 mg: 611% (32%)
16 mg: 872% (42%)
32 mg: 840% (28%)

CAM2038 q4w
Absolute bioavailability
64 mg: 165% (25%)
96 mg: 151% (28%)
128 mg: 154% (22%)
192 mg: 129% (31%)
Relative bioavailability versus Subutex (at 8 and 24 mg)
64 mg: 570% (39%)
128 mg: 747% (21%)</td></tr>
<tr><td>Tmax</td><td>CAM2038 q1w
• 23 (4 – 72) hours for buprenorphine
• 72 (36 – 120) hours for norbuprenorphine

CAM2038 q4w
• 10 (0.5 – 120) hours for buprenorphine
• 74 (47 – 1009) hours for norbuprenorphine</td></tr>
<tr><td rowspan="2">Distribution</td><td>Vd/F or Vd</td><td>V_d = 1900 L (40%)</td></tr>
<tr><td>% bound</td><td>96% bound (reference to US Subutex label)</td></tr>
<tr><td>Elimination</td><td>Route</td><td>• subcutaneous; 30% in urine and 69% in</td></tr>
</table>

		faeces (reference to US Subutex label)
	Terminal t½	**CAM2038 q1w** • Buprenorphine: 8 mg: 70.7 hours (28%) 16 mg: 96.4 hours (44%) 32 mg: 112 hours (45%) • Norbuprenorphine: 8 mg: 83.6 hours (34%) 16 mg: 85.2 hours (41%) 32 mg: 97.1 hours (33%) **CAM2038 q4w** • Buprenorphine: 64 mg: 447 hours (52%) 96 mg: 555 hours (34%) 128 mg: 502 hours (52%) 192 mg: 611 hours (28%) • Norbuprenorphine: 64 mg: 346 hours (56%) 96 mg: 394 hours (54%) 128 mg: 386 hours (47%) 192 mg: 432 hours (34%)
	CL/F or CL	CL = 68 L/h (23%)
Intrinsic Factors	Age	To be addressed in the NDA submission.
	Sex	To be addressed in the NDA submission.
	Race	To be addressed in the NDA submission.
	Hepatic & Renal Impairment	Reference to US Subutex label. To be addressed in the NDA submission.
Extrinsic Factors	Drug interactions	Reference to US Subutex label. To be addressed in the NDA submission.
	Food Effects	Not applicable.
Expected High Clinical Exposure Scenario	To be addressed in the NDA submission.	
Preclinical Cardiac Safety	Cardiovascular effects of CAM2038 q1w and CAM2038 q4w were examined in repeat dose toxicity studies at weekly and monthly doses up to 32 mg and 192 mg. In the 9-month dog toxicity study, the drug products were associated with mild quantitative ECG changes post the Day 1 dose, with a decrease in heart rate and limited prolongation of the QT and QTc intervals. No ECG changes were observed after completion of the 9 months of exposure to CAM2038 q1w and CAM2038 q4w. The limited effects observed only post dose on Day 1 in the 9-months study were not observed in other repeat dose toxicity studies in dogs, including for CAM2038 q1w at a higher 60 mg/week dose in an 8 weeks study.	
Clinical Cardiac Safety	**HS-07-307 N=42** ***(Study completed and CSR submitted; Number randomized and enrolled)*** - Single doses of CAM2038 q1w 7.5 mg: 13 subjects 15 mg: 10 subjects 22.5 mg: 9 subjects	

	30 mg: 10 subjects - QTc: No subjects with ≥ 500 ms - No cardiac adverse events of interest per ICH E14 guidance **HS-11-426 N=60** ***(Study completed and CSR submitted; Number randomized and enrolled)*** - Single doses CAM2038 q1w 8 mg: 19 subjects 16 mg: 18 subjects 32 mg:19 subjects - QTc: No subjects with ≥ 500 ms - No cardiac adverse events of interest per ICH E14 guidance **HS-13-487 N=87** ***(Study completed and CSR submitted; Number randomized and enrolled)*** - Doses of CAM2038 q1w; and CAM2038 q4w 16 mg CAM2038 q1w: 17 subjects 64 mg CAM2038 q4w: 17 subjects 96 mg CAM2038 q4w: 14 subjects 128 mg CAM2038 q4w: 16 subjects 192 mg CAM2038 q4w: 15 subjects - QTc: No subjects with ≥ 500 ms - No cardiac adverse events of interest per ICH E14 guidance **HS-13-478 N=47** - 24 mg CAM2038 q1w: 22 subjects 32 mg CAM2038 q1w: 25 subjects - QTc: No subjects with ≥ 500 ms - AEs –8 total, all mild in severity; o possibly/probably related: tachycardia/palpitations (n=5) o unrelated: ventricular extrasystoles (n=2), bradycardia (n=1) o see attached spreadsheet for details **HS-11-421** (ongoing study); N=428 - Double blind double dummy active-controlled study: Ongoing - Investigational Product (CAM2038) Doses: o 8, 16, 24 and 32 mg CAM2038 q1w o 64, 96, 128 or 160 mg CAM2034 q4w - Active Control: o Buprenorphine/naloxone Tabs: 8 mg/2 mg to 32 mg/8 mg per day - - QTcB or QTcF ≥ 500 ms (6 single episodes in 6 subjects; no recurrence with continued treatment) -see attached summary - AEs- 7 events; 6 mild, 1 moderate; all unrelated see attached summary **HS-14-499** (ongoing study); N=228 - Investigational Product (CAM2038) Doses: o 8, 16, 24 and 32 mg CAM2038 q1w o 64, 96, 128 or 160 mg CAM2034 q4w - QTcB ≥ 500ms: 1 episode at 16 mg CAM2038; No recurrence at higher doses. All QTcF < 500ms - AEs: see attached summary o Seizures (2 pts, 1 episode each; unrelated)

	o Atrial fibrillation (1 episode; mild, unrelated) o No other cardiac events of interest per ICH E14 guidance **HS-15-549** (ongoing study) N=48 - 32 mg CAM2038 q1w: 28 subjects 128 mg CAM2038 q4w: 20 subjects - QTc: No subjects with ≥ 500 ms - No clinically significant EKG findings - AEs o Atrial Fibrillation (1 episode, moderate, unrelated; resolved same day) o No other cardiac events of interest per ICH E14 guidance

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/s/

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Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology

Drug Utilization Review

Date:	September 25, 2017
Reviewer:	Shekhar Mehta, PharmD, MS Drug Utilization Data Analyst Division of Epidemiology II
Team Leader:	Rajdeep Gill, Pharm.D. Drug Utilization Data Analysis Team Leader Division of Epidemiology II
Deputy Director:	LCDR Grace P. Chai, Pharm.D. Deputy Director for Drug Utilization Division of Epidemiology II
Associate Director:	Judy Staffa, Ph.D., R.Ph. Associate Director for Public Health Initiatives Office of Surveillance and Epidemiology
Subject:	Utilization trends of buprenorphine products labeled for the treatment of opioid dependence
Drug Name(s):	multiple
Application Type/Number:	NDA 210136
Applicant/sponsor:	Braeburn Inc.
OSE RCM #:	2017-1515

TABLE OF CONTENTS

EXECUTIVE SUMMARY

On November 1, 2017, a joint meeting of the Anesthetic and Analgesic Drug Products Advisory Committee (AADPAC) and the Drug Safety and Risk Management Advisory Committee Advisory Committee (DSaRM) will be held to discuss new drug application for Cam2038 (NDA 210136; buprenorphine subcutaneous injection), submitted by Braeburn for the proposed indication to treat opioid dependence.

To provide informational context and background information, this review summarizes U.S. outpatient retail pharmacy utilization trends of buprenorphine products (buprenorphine single-ingredient and combination buprenorphine/naloxone) currently marketed with labeling to treat opioid dependence from 2012 through 2016. Overall, the U.S. outpatient retail pharmacy utilization of buprenorphine products appears to have increased during the examined time period. The nationally estimated number of prescriptions dispensed for buprenorphine products increased (b) (4)% from (b) (4) million in 2012 to (b) (4) million prescriptions in 2016. Approximately (b) (4)% of the total buprenorphine prescriptions dispensed were written by primary care physicians in 2016. According to office-based physician survey data, the most common diagnoses reported in association with buprenorphine products were for opioid dependence and/or opioid abuse. The nationally estimated number of patients who received a dispensed prescription for buprenorphine products from U.S. outpatient retail pharmacies increased (b) (4)% from approximately (b) (4)million in 2012 to (b) (4) million patients in 2016.

1 INTRODUCTION

On October 31, 2017, a joint meeting of the Anesthetic and Analgesic Drug Products Advisory Committee (AADPAC) and the Drug Safety and Risk Management Advisory Committee Advisory Committee (DSaRM) will be held to discuss new drug application for Cam2038 (NDA 210136; buprenorphine subcutaneous injection), submitted by Braeburn for the proposed indication to treat opioid dependence. To provide informational context and background information, this review summarizes outpatient retail utilization analyses of buprenorphine products (buprenorphine single-ingredient and combination buprenorphine/naloxone) indicated to treat opioid dependence from 2012 through 2016 in U.S. pharmacies.

1.1 BACKGROUND

NDA 210136 was submitted by Braeburn. for an extended-release depot injection of single-ingredient buprenorphine with the proposed indication to treat opioid dependence. During the study period examined, there are two single-ingredient buprenorphine products and four buprenorphine/naloxone combination products with FDA-approved labeling indicated for the treatment of opioid dependence.[1]

[1] U.S. Food and Drug Administration: Drugs@FDA. Buprenorphine and buprenorphine/naloxone Prescribing Information. Accessed August 2017. Available at: https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=BasicSearch.process

1.2 PRODUCT INFORMATION[2]

Table 1 provides the list of buprenorphine and buprenorphine/naloxone products indicated for treatment of opioid dependence included in this review. All buprenorphine products approved for management of pain are not included in this review.

Buprenorphine Single Ingredient Products				
Active Ingredient	**Brand Name**	**Initial U.S Approval**	**Sponsor**	**Formulation**
Buprenorphine	Buprenorphine generic	Multiple	Multiple	Sublingual Tablet
	Probuphine†	May 26, 2016	Braeburn Pharms	Implant
	Subutex	October 8, 2002	Indivior Inc	Sublingual Tablet
Buprenorphine/Naloxone Combination Products				
Active Ingredient	**Brand Name**	**Initial U.S Approval**	**Sponsor**	**Formulation**
Buprenorphine/Naloxone combination	Bunavail	June 30, 2010	BioDelivery Sciences International	Buccal Film
	Suboxone	August 30, 2010*(October 8, 2002 original sublingual tablet)	Indivior Inc.	Sublingual Film
	Zubsolv	July 3, 2013	Orexo	Sublingual Tablet
	Buprenorphine HCl / Naloxone HCl generics	Multiple	Multiple	Multiple

†Probuphine is available only under a restricted distribution program called the Probuphine REMs program therefor Probuphine is not included in our analyses.[3]

2 METHODS AND MATERIALS

Proprietary drug utilization databases available to the Agency were used to conduct these analyses. See **Appendix 2** for detailed descriptions and limitations of the databases used to conduct these analyses. In this review, the term buprenorphine refers to both single-ingredient and combination buprenorphine/naloxone products indicated for the treatment of opioid dependence.

[2] U.S. Food and Drug Administration: Drugs@FDA. Accessed August 8, 2017. Website: http://www.accessdata.fda.gov/scripts/cder/drugsatfda/

[3] U.S. Food and Drug Administration: Probuphine Prescribing Information and REMs Program Accessed September 25, 2017. Websites: https://www.accessdata.fda.gov/drugsatfda_docs/rems/Probuphine_2017-04-19_Full.pdf; https://www.accessdata.fda.gov/drugsatfda_docs/label/2016/204442Orig1s000lbl.pdf

2.1 DATA SOURCES

The QuintilesIMS, National Sales Perspectives™ (NSP) database was used to obtain the nationally estimated number of eaches (bottles/packages) sold for buprenorphine products from manufacturers to all U.S. channels of distribution to determine settings of care for 2016. The sales distribution data do not reflect what is being sold to or administered to patients directly; but these data do provide a national estimate of units sold from the manufacturer into the various channels of distribution.

The QuintilesIMS, National Prescription Audit™ (NPA) database was used to obtain the nationally estimated number of prescriptions dispensed for buprenorphine products from 2012 through 2016, annually. In addition, the top prescriber specialties for buprenorphine products from U.S. outpatient retail pharmacies in 2016 were also obtained from this database.

The QuintilesIMS, Total Patient Tracker™ (TPT) database was used to obtain the nationally estimated number of patients, stratified by patient age (0-16 years, and 17 years and older) who received a dispensed prescription for buprenorphine products from U.S. outpatient retail pharmacies, from 2012 through 2016, annually.

inVentiv Health Research & Insights LLC., TreatmentAnswers™ with Pain Panel, a U.S. office-based physician survey database, was used to obtain top groups of diagnoses associated with the use of buprenorphine products in 2016. Diagnoses data by number of drug use mentions[4] were captured based on International Classification of Diseases (ICD-10-CM) codes and 95% confidence were applied to the estimates.

3 RESULTS

3.1 SETTINGS OF CARE

The QuintilesIMS, National Sales Perspectives™ (NSP) database was used to determine the various settings of care where buprenorphine products were distributed by the manufacturers. Sales data in 2016 showed that approximately (b)(4)% of buprenorphine products (bottles/packages) were sold to U.S. outpatient retail settings, (b)(4)% to non-retail pharmacies, and less than (b)(4)% to mail-order/specialty pharmacies.[5] As a result, only outpatient retail pharmacy utilization patterns were examined for buprenorphine products. Mail-order/specialty pharmacy and non-retail pharmacy settings data were not included in this analysis.

3.2 PRESCRIPTION DATA

Figure 1 below and Table 6.2.1 in Appendix 1 provide the nationally estimated number of prescriptions dispensed for total buprenorphine products (single-ingredient buprenorphine and combination buprenorphine/naloxone) from U.S. outpatient retail pharmacies, from 2012 through 2016, annually. The total number of prescription dispensed for buprenorphine products increased (b)(4)% from (b)(4) million prescriptions in 2012 to (b)(4) million prescriptions in 2016.

[4] A "drug use mention" refers to mentions of a drug in association with a diagnosis during a patient visit to an office-based physician. This term may be duplicated by the number of diagnoses for which the drug is mentioned. It is important to note that a "drug use" does not necessarily result in a prescription being generated. Rather, the term indicates that a given drug was mentioned during an office visit.

[5] Source: QuintilesIMS, National Sales Perspective (NSP) January 2016 – December 2016. Source file: NSP channel 2017-1468 Buprenorphine AC 9-25-2017.xlsx

Figure 1

Nationally Estimated Number of Dispensed Prescriptions for Buprenorphine Products* from U.S. Outpatient Retail Pharmacies, 2012-2016

Source: QuintilesIMS, National Prescription Audit (NPA). January 2012 - December 2016. Data extracted August 2017. File NPA mole CY 2017 bup AC 9-25-2017.xlsx
*Buprenorphine products refer to single-ingredient buprenorphine and combination buprenorphine/naloxone products indicated to treat opioid dependence.

3.3 PRESCRIBER SPECIALTY DATA

Table 6.2.2 in Appendix 1 provides the nationally estimated number of prescriptions dispensed for buprenorphine products from U.S. outpatient retail pharmacies by the top prescribing specialties in 2016. Family practice/internal medicine/general practice was the top specialty and prescribed approximately (b) (4)% of total buprenorphine prescriptions dispensed; followed by psychiatry ((b) (4)%), and osteopathic medicine ((b) (4)%) in 2016.

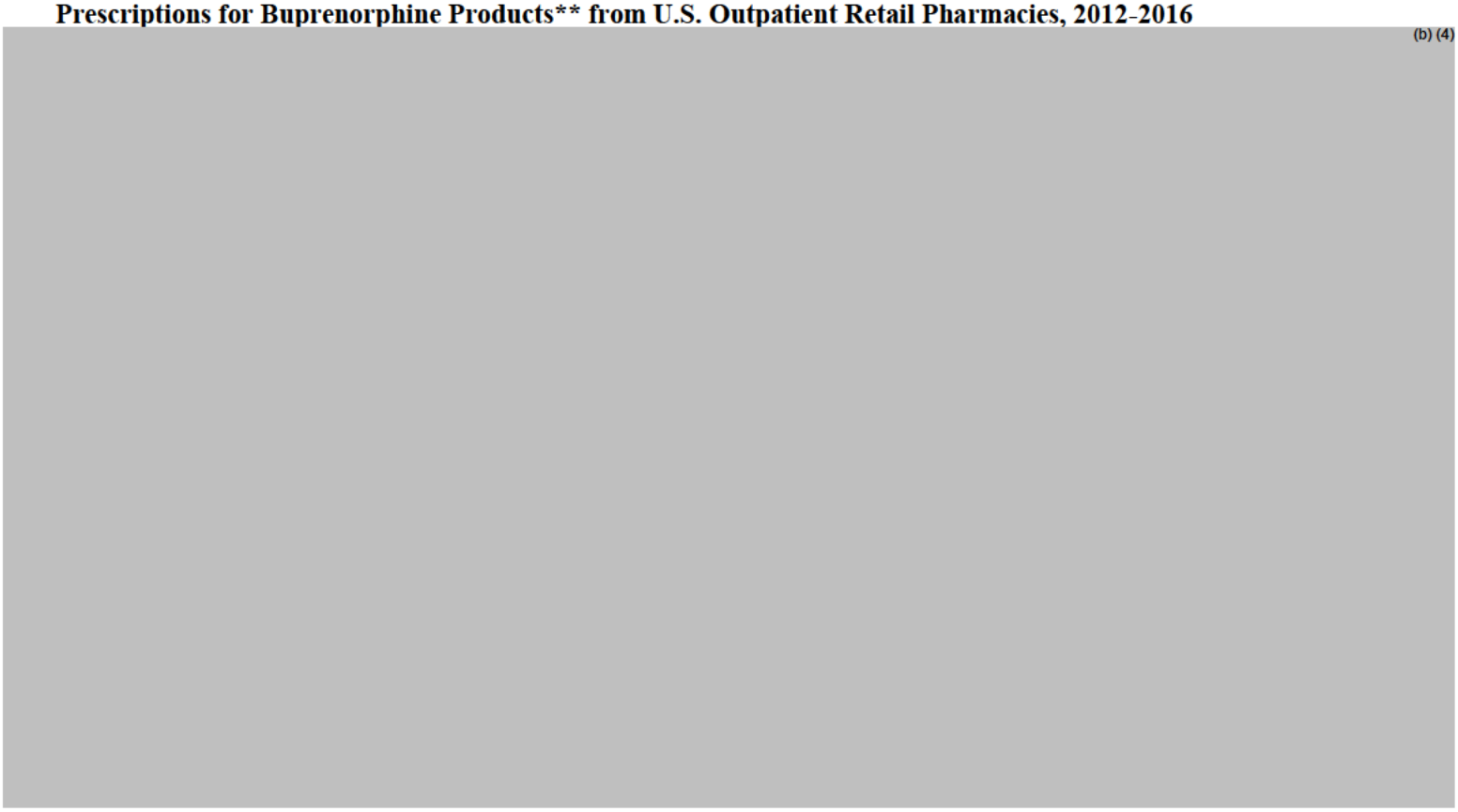
3.4 PATIENT DATA

Figure 2 below and Table 6.2.3 in Appendix 1 provide the nationally estimated number of patients who received a dispensed prescription for buprenorphine products, from U.S. outpatient retail pharmacies, 2012 through 2016, annually. Total number of patients who received dispensed prescription for buprenorphine products increased (b) (4)% increase from approximately (b) (4) million patients in 2012 to (b) (4) million patients in 2016. Pediatric patients 0-16 years of age accounted for (b) (4)% of the total patients annually with approximately (b) (4) pediatric patients in 2016.

Figure 2

Nationally Estimated Number of Patients* (0-16 years and 17 years and above) who Received a Dispensed Prescriptions for Buprenorphine Products from U.S. Outpatient Retail Pharmacies, 2012-2016**

(b) (4)



Source: QuintilesIMS, Total Patient Tracker (TPT). January 2012 - December 2016. Data Extracted August 2017. File: TPT L 2017-1468 bup AC 9-6-2017.xlsx
*Unique patient counts may not be added across time periods or across products due to the possibility of double counting those patients who are receiving treatment over multiple periods in the study.
** Total buprenorphine products refer to single-ingredient buprenorphine and combination buprenorphine/naloxone products indicated to treat opioid dependence.

3.5 DIAGNOSIS DATA

Table 6.2.4 in Appendix 1 provides the diagnosis codes (ICD-10) in terms of drug use mentions associated with the utilization of buprenorphine products as reported by a U.S. office-based physician survey database. In 2016, diagnoses associated with mental and behavioral disorders comprised 93.5% of total drug use mentions, followed by diseases of the musculoskeletal system and connective tissue at 4% of total drug use mentions. Mental health and behavioral disorders include diagnoses for ***opioid dependence and abuse disorders (ICD 10, Dx code F11)*** and ***other psychoactive substance related disorders (ICD 10, Dx code F19)***

4 DISCUSSION

This review provides drug utilization data for buprenorphine products with labeled indication to treat opioid dependence. The data provided will serve as informational context and background information to generate discussions at the advisory committee for new drug applications for long-acting buprenorphine injections.

Our analyses showed that the outpatient utilization of buprenorphine products increased from 2012 to 2016. There was an estimated (b) (4)% increase in the number of patients prescribed buprenorphine products to treat opioid dependence over the examined 5 year period. The steady increase in the overall utilization of

buprenorphine products may be attributed to multiple factors such as the increased prevalence of individuals addicted to opioids, increasing admission into drug treatment programs, and regulatory actions from the federal, state, and local levels in response to the continuing opioid epidemic in the nation. However, our study did not assess the reasons behind the trends in utilization.

The prescription data analysis of buprenorphine products showed that primary care physicians were the top prescribers in 2016. According to the office-based physician survey data in 2016, reported drug use mentions of buprenorphine products were primarily associated with opioid dependence or abuse, although treatment of pain was also mentioned infrequently for these products. In general, survey data are best used to identify the typical uses for the products from an office-based physician setting and thus does not represent other settings where buprenorphine may be prescribed such as treatment clinics, pain clinics, and hospitals.

Findings from this review should be interpreted in the context of the known limitations of the databases used. We estimated that buprenorphine products are distributed primarily to the outpatient retail pharmacy setting based on the IMS Health, IMS National Sales Perspectives™ in 2016. Probuphine is available only under a restricted distribution program called the Probuphine REMs program, therefor Probuphine was not included in this review as utilization is vastly underestimated in the proprietary drug utilization data sources used in these analyses. As a result, we focused our analysis on only the outpatient retail pharmacy settings; thus these estimates may not apply to other settings of care in which these products are used (i.e., mail-order pharmacies, clinics, non-federal hospitals, etc.)

5 CONCLUSIONS

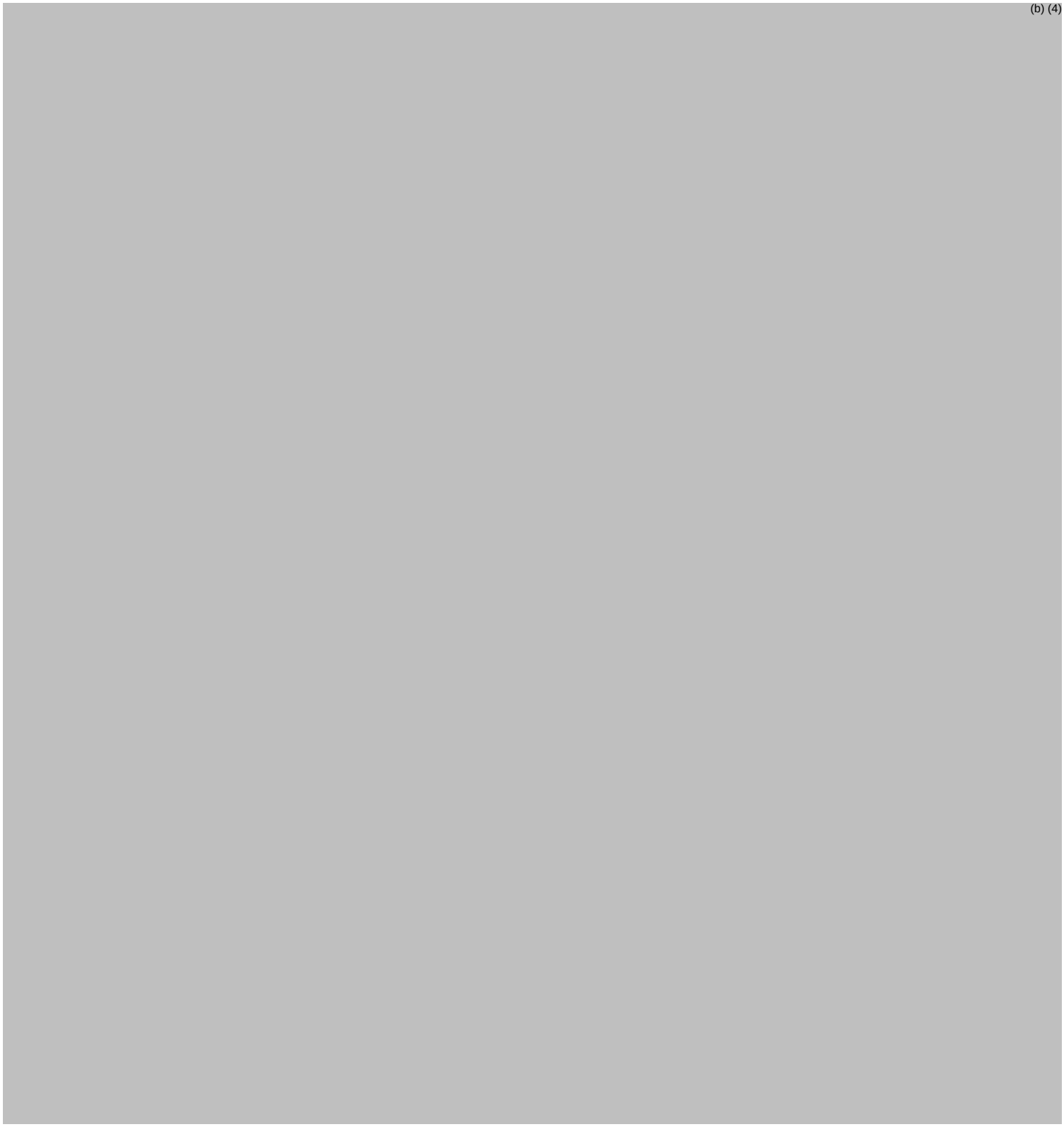
In preparation for the upcoming advisory committee on October 31, 2017 to discuss the new drug application for subcutaneous injection of buprenorphine, this review provides the drug utilization patterns of buprenorphine products currently marketed in the U.S. with labeled indications to treat opioid dependence.

The outpatient retail pharmacy utilization of buprenorphine products appears to have increased from 2012 through 2016. There were approximately (b) (4) million buprenorphine prescriptions dispensed and (b) (4) million patients who received a dispensed prescription for buprenorphine products in 2016.

6 APPENDICES

6.1 APPENDIX 1: TABLES AND FIGURES

(b) (4)



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6.2 APPENDIX 2: DRUG USE DATABASE DESCRIPTIONS

QuintilesIMS, National Sales Perspectives™: Retail and Non-Retail

The QuintilesIMS National Sales Perspectives™ measures the volume of drug products, both prescription and over-the-counter, and selected diagnostic products moving from manufacturers into various outlets within the retail and non-retail markets. Volume is expressed in terms of sales dollars, eaches, extended units, and share of market. These data are based on national projections. Outlets within the retail market include the following pharmacy settings: chain drug stores, independent drug stores, mass merchandisers, food stores, and mail service. Outlets within the non-retail market include clinics, non-federal hospitals, federal facilities, HMOs, long-term care facilities, home health care, and other miscellaneous settings.

QuintilesIMS National Prescription Audit™

The National Prescription Audit (NPA™) measures the "retail outflow" of prescriptions, or the rate at which drugs move out of retail pharmacies, mail service houses, or long-term care facilities into the hands of consumers via formal prescriptions in the U.S. The NPA audit measures what is dispensed by the pharmacist. Data for the NPA audit is a national level estimate of the drug activity from retail pharmacies. NPA receives over 3.5 billion prescription claims per year, captured from a sample of the universe of approximately 59,400 pharmacies throughout the U.S. The pharmacies in the database account for most retail pharmacies and represent nearly 88% of retail prescriptions dispensed nationwide. The type of pharmacies in the sample are a mix of independent, retail, chain, mass merchandisers, and food stores with pharmacies, and include prescriptions from cash, Medicaid, commercial third-party and Medicare Part-D prescriptions. Data is also collected from approximately 45 – 75% (varies by class and geography) of mail service pharmacies and approximately 70 – 85% of long-term care pharmacies. Data are available on-line for 72-rolling months with a lag of 1 month.

QuintilesIMS, Total Patient Tracker™ (TPT)

Total Patient Tracker (TPT) is a national-level projected audit designed to estimate the total number of unique patients across all drugs and therapeutic classes in the retail outpatient setting over time. TPT derives its data from the Vector One® database which integrates prescription activity from a sample received from payers, switches, and other software systems that may arbitrage prescriptions at various points in the sales cycle. Vector One® receives over 2.1 billion prescription claims per year.

Unique patient counts may not be added across time periods due to the possibility of double counting those patients who are receiving treatment over multiple periods in the study. Furthermore, patient age subtotals may not sum exactly due to patients aging during the study period, and may be counted more than once in the individual age categories. For this reason, summing across time periods or patient age bands is not advisable and will result in overestimates of patient counts.

inVentiv Health Research & Insights LLC., TreatmentAnswers™

inVentiv Health Research & Insights, LLC., TreatmentAnswers™ and TreatmentAnswers™ with Pain Panel is a monthly survey designed to provide descriptive information on the patterns and treatment of diseases encountered in office-based physician practices in the U.S. The survey consists of data collected from over 3,200 office-based physicians representing 30 specialties across the United States that report on all patient activity during one typical workday per month. These data may include profiles and trends of diagnoses, patients, drug products mentioned during the office visit and treatment patterns. The Pain Panel supplement surveys over 115 pain specialists physicians each month. With the inclusion of visits to pain specialists, this will allow additional insight into the pain market. The data are then projected nationally by physician specialty and region to reflect national prescribing patterns.

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/s/

SHEKHAR H MEHTA
11/17/2017

RAJDEEP K GILL
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Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology Review (OSE)
Office of Pharmacovigilance and Epidemiology (OPE)

Epidemiology: Pediatric Buprenorphine Exposures and Outcomes

Date:	October 26, 2017
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Drug Name:	Buprenorphine
Subject	Pediatric buprenorphine exposures and outcomes
Application Type/Number:	NDA 210136
Applicant/sponsor:	Braeburn Inc.
OSE RCM #:	2017-1467

****NEISS-CADES adverse drug event reports are obtained by FDA through an interagency agreement with the Centers for Disease Control and Prevention (CDC). The data/information cannot be released to the public/non-FDA personnel without CDC approval, obtained through the FDA/CDER Office of Surveillance and Epidemiology****

****This document contains proprietary data from the American Association of Poison Control Centers obtained by FDA under contract. The poison control center data/information cannot be released to the public/non-FDA personnel without contractor approval obtained through the FDA/CDER Office of Surveillance and Epidemiology.****

TABLE OF ABBREVIATIONS

AAPCC	American Association of Poison Control Centers
ADE	Adverse drug event
CI	Confidence interval
DAAAP	Division of Anesthesia, Analgesia, and Addiction Products
DEPI	Division of Epidemiology
DMAT	Data Management and Analysis Team
ED	Emergency department
FDA	Food and Drug Administration
MedDRA	Medical Dictionary for Regulatory Activities
NDA	New drug application
NDF-RT	National Drug File Reference Terminology
NEISS-CADES	National Electronic Injury Surveillance System–Cooperative Adverse Drug Event Surveillance
NPDS	National Poison Data Systems
NVSS-M	National Vital Statistics System – Mortality
ODEII	Office of Drug Evaluation II
OPE	Office of Pharmacovigilance and Epidemiology
OSE	Office of Surveillance and Epidemiology
PCCs	Poison Control Centers
QA	Quality Assurance
QC	Quality Control
RADARS	Researched Abuse, Diversion, and Addiction-Related Surveillance System
U.S.	United States

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EXECUTIVE SUMMARY

Braeburn Pharmaceuticals, Inc. submitted a new drug application (NDA), (NDA 210136) for buprenorphine formulated for subcutaneous (b) (4) injections (a substitute for oral formulations of buprenorphine [including formulations with naloxone]). In part, this new formulation has the potential to mitigate accidental pediatric exposures. The Division of Anesthesia, Analgesia, and Addiction Products (DAAAP) scheduled an Advisory Committee (AC) for 1 November 2017 meeting to discuss the benefits and risks of this new drug application.

DAAAP consulted the Division of Epidemiology II (DEPI-II) to characterize the magnitude of pediatric accidental exposure to buprenorphine products and describe any change that might have occurred over the last few years to provide some background and context for the AC meeting.

This review includes an updated analysis for pediatric (≤10 years old) accidental exposure to buprenorphine products using data from the American Association of Poison Control Centers-National Poison Data System (AAPCC-NPDS) and the National Electronic Injury Surveillance System–Cooperative Adverse Drug Event Surveillance (NEISS-CADES) project. The review also includes drug-involved mortality data from National Vital Statistics System – Mortality (NVSS-M) files linked with death certificate literal text.

Data from these three data sources below summarize the public health burden of accidental pediatric buprenorphine exposures from 2010 through 2015. Despite some decreases observed in the earlier years in the case counts and rates of poison control center (PCC) calls and projected numbers and rates of emergency department (ED) visits from NEISS-CADES, the public health burden of accidental pediatric buprenorphine exposures appears to have persisted in recent years. The data also revealed that children <6 years of age were most affected, and involvement of drugs other than buprenorphine or buprenorphine-naloxone in these exposures was not common. Hospitalization and moderate or major effects were common events among the affected children, while death was not a common outcome. DAAAP should be aware of the public health burden of accidental pediatric buprenorphine exposures in recent years.

Summary table: Total exposure calls to poison control centers, emergency department visits, and deaths involving buprenorphine or buprenorphine-naloxone, children ≤10 years of age, 2010-2015

Measure	2010	2011	2012	2013	2014	2015	Total
Calls for unintentional general exposure to buprenorphine (AAPCC-NPDS)							
Count	1,540	1,177	1,094	891	985	1,040	6,727
Age-specific call rate per 1 million census population	34.45	26.39	24.59	20.02	22.13	23.36	25.16
ED visits for unsupervised buprenorphine ingestions (NEISS-CADES)							
Projected estimate [95% CI]	3,095 [1,887-4,304]		2,142 [1,115-3,170]		2,136 [958-3,314]		7,374 [4,492-10,256]
Age-specific ED visit rate per 1 million census population	34.7 [21.1-48.2]		24.1 [12.5-35.6]		24.0 [10.8-37.2]		27.6 [16.8-38.4]
Deaths involving buprenorphine (NVSS-M linked with death certificate literal text)*							
Count	3	4	5	2	2	Not assessed	16

Age specific rates: 0-10 year olds from US 2010 Census population

* All deaths were of children <6 years old.

1 INTRODUCTION

In August 2017, the Division of Anesthesia, Analgesia, and Addiction Products (DAAAP) requested assistance from the Division of Epidemiology I and II (DEPI-I and DEPI-II) to examine updated information on the number of accidental pediatric exposures to buprenorphine, alone or in combination with naloxone. This information will be used to provide context for the DAAAP reviews and preparation for Advisory Committee (AC) meeting (November 1, 2017) was scheduled to discuss the benefits and risks of the new drug application (NDA) for buprenorphine.

Braeburn Pharmaceuticals, Inc. (the Sponsor) developed a new buprenorphine formulation for subcutaneous (b) (4) injections as a substitute for oral buprenorphine (including formulations that contain naloxone) (NDA 210136). The Sponsor developed this product, in part, to respond to concerns about accidental pediatric exposures to transmucosal buprenorphine products. This argument was made for Probuphine®, a buprenorphine product subdermally administered in rod implants.[1]

Published analyses have examined accidental pediatric buprenorphine exposures and outcomes using the following United States (U.S.) data sources: the Researched Abuse, Diversion, and Addiction-Related Surveillance System (RADARS), the Poison Control Center (PCC) Program, and the National Electronic Injury Surveillance System–Cooperative Adverse Drug Event Surveillance (NEISS-CADES) project. Lavonas and colleagues conducted a cross-sectional study that characterized calls to PCCs participating in the RADARS Poison Center Program from October 2009 through March 2012.[2] Children from 28 days to less than 6 years old were included in analyses, and formulations included products with buprenorphine only and products with buprenorphine in conjunction with naloxone. Cases were excluded if they were classified as "not followed, judged as nontoxic exposure (clinical effects not expected)" and "not followed, minimal clinical effects possible", and cases classified as "unable to follow, judged as a potentially toxic exposure" were included if the case was admitted to the hospital. There were 2,380 total calls for unintentional buprenorphine exposures in young children, of which 2,271 (95.4%) calls were for exposures involving only buprenorphine products.

Budnitz and colleagues used NEISS-CADES data to conduct a cross-sectional analysis of estimated number of emergency department (ED) visits for unsupervised buprenorphine/naloxone ingestions by children <6 years of age during 2008–2015.[3] During this study period, there were 8,136 ED visits (95% CI [4,892-11,380]) for buprenorphine/naloxone ingestions by young children. There were fewer ED visits per year during 2013-2015 (799 ED visits per year, 95% CI [324-1,274]) than during 2008-2010 (1,246 ED visits per year, 95% CI [662-1,830]). Most visits required hospitalization (61.6%, 95% CI [46.7%-76.5%]).

DAAAP specifically requested that DEPI characterize the magnitude of pediatric accidental exposure to buprenorphine products and describe any change that might have occurred over the last few years. To fulfill the request, DEPI provided updated data analyses from the two data sources above.

DEPI-I extended the study period for AAPCC-NPDS to 2015 to provide more updated information. For NEISS-CADES, the analysis was limited to years 2010-2015 rather than 2008-2015 because there was a change to unit-dose packaging[3] for most buprenorphine products beginning in 2010 which might have affected the interpretation of the published results.

DEPI-II expanded the analysis of NEISS-CADES to include single-ingredient buprenorphine, rather than just buprenorphine-naloxone products. DEPI-II also reviewed drug-involved mortality data to further describe the magnitude of the issue with accidental pediatric exposure to buprenorphine and buprenorphine containing products.

In addition, the age range was increased up to 10 years old, because there were no published data confirming that less than 6 years old is the age group of most concern. The 10 year old upper limit seemed appropriate as the NEISS-CADES definition of unsupervised ingestions includes children up to 10 years old. These data will provide background and context for the AC meeting.

2 METHODS AND MATERIALS

The methods used to describe exposure calls and adverse outcomes involving buprenorphine are described below by data source. This review describes:

- unintentional general exposure calls to U.S. PCCs of the AAPCC-NPDS and involving buprenorphine among children ≤10 years of age from 2010 through 2015;
- national estimates of ED visits for unsupervised buprenorphine ingestions by children ≤10 years of age from 2010 through 2015, using NEISS-CADES data; and
- deaths involving buprenorphine among children ≤10 years of age from 2010 through 2014, according to the NVSS-M files linked with death certificate literal text.

2.1 POISON CONTROL CENTER EXPOSURE CALLS – DATA SOURCE AND METHODS

Data source

The NPDS, maintained by the AAPCC, captures data on calls to U.S. PCCs on a near real-time basis. Currently, AAPCC's 55 PCCs serves the entire U.S. population, individuals across the 50 states as well as U.S. territories including, American Samoa, District of Columbia, Federated States of Micronesia, Guam, Puerto Rico, and the U.S. Virgin Islands. Over time the number of PCCs has varied; there were 60 participating centers in 2010 and 55 in 2015.[4] PCCs receive calls for exposures to a variety of substances through the Poison Help Line 24 hours per day, offer medical advice, and document reported events in the database. Quality control (QC) measures are used to ensure the accuracy and completeness of the data collected. This report is a retrospective analysis of data obtained from the NPDS.

Case records in the database reflect information provided when the public or healthcare professionals call about an actual or potential exposure to a substance or request information or educational materials. Each year the database is locked to prevent inadvertent changes and ensure consistent, reproducible reports. The 2015 database was locked in July 2016. Exposures do not necessarily represent a poisoning or overdose, as the AAPCC does not completely verify the accuracy of every report made to member centers.

AAPCC-NPDS information on poisoning events throughout the U.S. are captured in near real-time,[4] and is one of the few data sources that captures data on reasons for exposure.

Methods

Generic codes and product codes for pharmaceutical preparations with buprenorphine (N=1 generic code and N=246 product codes) were identified using Micromedex® Solutions.[5] Information on all human "unintentional" buprenorphine exposure calls involving children ≤10 years of age during the period of January 1, 2010 through December 31, 2015 were extracted on August 18, 2017. NPDS describes unintentional exposures as exposures resulting from the wrong dose, incorrect route of administration, administration to the wrong person, or administration of the wrong substance.[6] Unintentional exposure calls are further categorized by NPDS into unintentional general, environmental, occupational therapeutic error, and unknown. Definitions for these unintentional exposure reason categories can be found in **Appendix A.** The current review primarily focuses on calls for unintentional general buprenorphine exposures among children 0-10 years of age. Unintentional general exposures, according to NPDS, are the most common unintentional exposures in children and include scenarios where a toddler may get into and swallow medicine.[6]

Trends and patterns in buprenorphine exposure calls were analyzed separately for single-substance exposures (calls involving only one product), multiple-substance exposure (calls involving more than one product) and for total exposures (calls involving a single product or multiple products) by year. Trends and patterns in buprenorphine calls were further analyzed by select age groups (<6 years and 6-10 years). Age-specific annual unintentional general buprenorphine exposure call rates per million population were calculated using age-specific population estimates prepared by the Census Bureau in collaboration with the National Center for Health Statistics.[7]

This review describes the medical outcomes associated with unintentional general buprenorphine exposures, excluding clinical effects coded as "confirmed non-exposures" or "unrelated effect, the exposure was probably not responsible for the effect(s)". The following medical outcome categories[6] were examined: (1) no effect, (2) minor effect, (3) moderate effect, (4) major effect, (5) death/death indirect report, and (6) other[1]. Medical outcome tables generated in this report display counts classified as minor effects, moderate effects, major effects, or death/death indirect for exposures with a documented related clinical effect. Definitions for medical outcome categories can be found in **Appendix B.**

Analyses of AAPCC-NPDS data in this review included independent quality assurance (QA) / QC that was performed using the same criteria by a separate analyst. Results from the two independent analyses agreed.

2.2 EMERGENCY DEPARTMENT VISITS – DATA SOURCE AND METHODS

Data source

NEISS-CADES is a national stratified probability sample of approximately sixty hospitals with a minimum of six beds and a 24-hour ED in the United States and its territories. The NEISS-CADES project, which has been described in detail elsewhere,[8-10] is a joint effort of the Centers for Disease Control and Prevention, the U.S. Consumer Product Safety Commission, and the U.S. Food and Drug Administration. In brief, trained coders located at each participating hospital review clinical records of every ED visit to identify clinician-diagnosed adverse drug events (ADE), to report up to two medications implicated in each adverse event, and to record narrative descriptions of the incident. NEISS-CADES codes the clinical description and circumstances surrounding the ADE (including medication errors) using the Medical Dictionary for Regulatory Activities (MedDRA) version 9.1. Medications were categorized into standardized generic drug names based on the Veterans Health Administration National Drug File Reference Terminology (NDF-RT).

The NEISS-CADES data has a high positive predictive value (PPV = 92%)[9] for case identification, includes a nationally representative sample of EDs, has 93-100% completeness of patient demographics, and continuous operation since 2004.

Methods

Analyses projected national estimates ED visits for unsupervised ingestions (defined using MedDRA code 10064368, accidental drug intake by child) of buprenorphine or buprenorphine/naloxone by children ≤10 years old. Statistically stable estimates were attained for the whole study period and for two-year periods (2010-2011, 2012-2013, and 2014-2015). According to CDC, national estimates based on <20 cases in any given year, or a total estimate <1,200, or with a coefficient of variation greater than 30% are statistically unstable, and estimates for years 2011, 2012, 2013, and 2015 alone were considered statistically unstable based on these criteria. Trends in ED visits were described by age group (<6 years and 6-10 years) and by the number of medications involved in the ADE. The proportion of ED visits resulting in hospitalization (i.e., disposition of admitted, transferred, or observed) was also estimated for each two-year period and for the whole study period. Age-specific rates of ED visits per million population were calculated using age-specific population estimates prepared by the Census Bureau in collaboration with the National Center for Health Statistics.[7]

National estimates of ED visits from 2010 to 2015 and the corresponding 95% confidence intervals (CIs) were calculated using SAS, version 9.4 (SAS Institute), and accounted for the sample weights and complex sampling design.

[1] The other medical outcome category includes the following sub-categories: not followed, judged as nontoxic exposure (clinical effects not expected); not followed, minimal clinical effects possible (no more than minor effect possible); unable to follow, judged as a potentially toxic exposure; and missing.

2.3 DRUG-INVOLVED MORTALITY – DATA SOURCE AND METHODS

Data source

National data on drug-involved mortality were made available to the Agency by the National Center for Health Statistics. Drug-involved mortality data combine the cause-of-death, demographic, and geographic information from the NVSS-M, with information extracted from the death certificate literal text. These data allow for a more granular analysis of specific drugs involved in deaths.[11] The analytical dataset was constructed for analysis on October 6, 2016. The method used to extract information on drug-involved mortality has been described previously[11] and is briefly described here. The literal text information had been processed to allow for the identification of cases of drug-involved mortality, i.e., mortality cases having at least one literal text mention of a drug, drug class, or exposure not otherwise specified, excluding mentions where information in the literal text suggests that the drug was not involved in the death. For example, the drug "METHICILLIN" in the phrase "METHICILLIN RESISTANT STAPHYLOCOCCUS AUREUS INFECTION" does not suggest drug involvement in mortality, but rather a type of bacterial infection. Similarly, the phrase "NOT DRUG RELATED" clearly indicates that a death did not involve drugs.

The main strength of the drug-involved mortality data is the high accuracy in identifying the drugs mentioned and involved in mortality, according to death certificate literal text.[11]

Methods

Analyses quantified the number of deaths from any cause and with buprenorphine involvement among children ≤10 years old who were U.S. residents, from 2010 through 2014. Mentions of buprenorphine were identified using previously defined search terms.[11] Analyses examined whether deaths involved only buprenorphine (with or without naloxone involvement) or involved other drugs[2] as well. Trends and patterns in deaths were further analyzed by select age groups (<6 years and 6-10 years). Reasons for buprenorphine exposure were examined indirectly by quantifying the number of deaths which were definitely not due to accidental pediatric exposures, i.e., deaths that were suicides (underlying cause-of-death codes X60-X84, Y87.0, or U03) or homicides (underlying cause-of-death codes X85-Y09, Y87.1, U01-U02).

3 RESULTS

3.1 POISON CONTROL CENTER EXPOSURE CALLS - RESULTS

There were 6,819 unintentional buprenorphine exposures calls to AAPCC from 2010-2015 among children ≤10 years **(Table 1).** Of those unintentional buprenorphine exposures calls, 6,727 **(** 98.7%) were classified as unintentional general exposures. The majority of unintentional buprenorphine exposures calls, 6,513 (95.5%), were single-substance exposures.

[2] In determining involvement of drugs other than buprenorphine and naloxone, the following terms for drugs were not included: CHEMICAL, CNS DEPRESSANT, DRUG, MEDICINE, NARCOTIC, OPIATE, OPIOID, PHARMACEUTICAL, POLYPHARMACY, PSYCHOTROPIC, SEDATIVE, and SUBSTANCE. These terms were not included because they could have referred to buprenorphine. Drugs may have also included alcohol(s), such as ethanol and isopropyl alcohol.

Table 1: Proportion of Buprenorphine unintentional exposure calls by reason for exposure among children ≤ 10 years old, AAPCC 2010-2015

	Total Exposures		Single-Substance Exposures		Multi-Substance Exposures	
Unintentional Reason for Exposure	**N**	**%**	**N**	**%**	**N**	**%**
Unintentional General	6727	98.7%	6426	98.7%	301	98.4%
Unintentional Misuse	21	0.3%	21	0.3%	0	0.0%
Unintentional Therapeutic Error	61	0.9%	57	0.9%	4	1.3%
Unintentional Environmental	5	0.1%	5	0.1%	0	0.0%
Unintentional Unknown	5	0.1%	4	0.1%	1	0.3%
Total	6819		6513		306	

Multi-substance: Multiple-substance exposure calls in which the caller reported more than one product being involved.

Of the 6,819 unintentional buprenorphine exposure calls for children ≤10 years (**Table 1**), 6,660 (97.7%) calls were for children <6 years (**Table 2**). Of those calls in < 6 year-olds, 6,607 (> 99%) were classified as unintentional general exposures, and 6,308 (94.7%) were single-substance unintentional general exposures.

Of the 6,727 unintentional general buprenorphine exposure calls for children ≤10 years (**Table 1**), 6,607 (98.2%) calls were for children <6 years (**Table 2**). Only 120 (1.8%) of those calls were in children 6-10 years (**Table 2B of Appendix C**).

Table 2: Proportion of Buprenorphine unintentional exposure calls by reason for exposure among children < 6 years old, AAPCC 2010-2015

	Total Exposures		Single-Substance Exposures		Multi-Substance Exposures	
Unintentional Reason for Exposure	**N**	**%**	**N**	**%**	**N**	**%**
Unintentional General	6607	99.2%	6308	99.2%	299	98.7%
Unintentional Misuse	7	0.1%	7	0.1%	0	0.0%
Unintentional Therapeutic Error	39	0.6%	36	0.6%	3	1.0%
Unintentional Environmental	5	0.1%	5	0.1%	0	0.0%
Unintentional Unknown	2	0.0%	1	0.0%	1	0.3%
Total	6660		6357		303	

Multi-substance: Multiple-substance exposure calls in which the caller reported more than one product being involved.

The population-specific annual call rates for single-substance, multiple-substance, and total (single- and multiple-substance) unintentional general buprenorphine exposure calls involving children ≤10 years from 2010 through 2015 are displayed in **Figure 1**. For single-substance unintentional general buprenorphine exposures in children ≤10 years, the call rate decreased steadily from 32.8 calls per million population in 2010 to 19.9 calls per million population in 2013. From 2013-2015, a subsequent uptick in the call rate was observed for single-substance unintentional general buprenorphine exposures. Among multiple-substance unintentional general buprenorphine exposures, steady call rates were observed for children ≤10 years from 2010-2015.

Similar trends and patterns were observed for the population-specific annual call rates for single-substance, multiple-substance and total unintentional general buprenorphine exposures involving children <6 years from 2010-2015, as displayed in **Figure 1A of Appendix C**.

Some variability in the patterns of buprenorphine unintentional general calls for children 6-10, from 2010-2015 was observed, but the annual call rates were fairly small (**Figure 1B** of Appendix C).

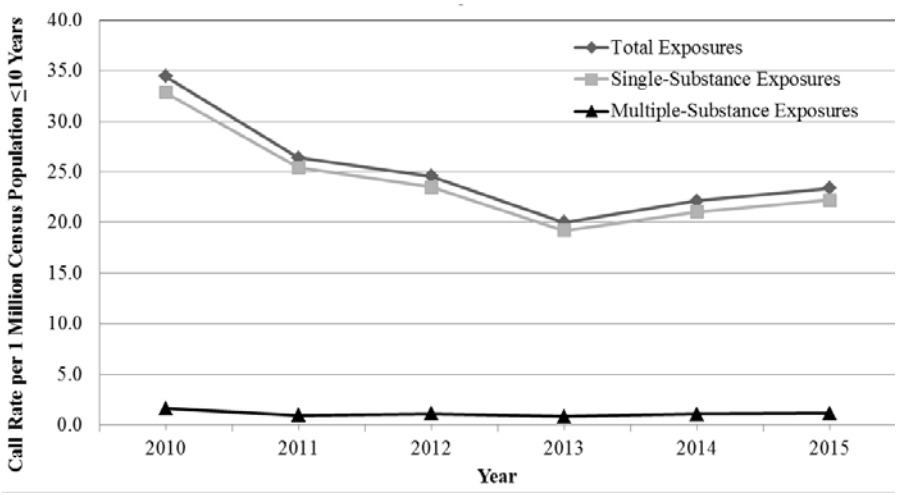

Figure 1: Age-specific annual call rates involving buprenorphine unintentional general exposures among children ≤ 10 years old, AAPCC 2010-2015

Medical outcomes for 6,289 buprenorphine unintentional general exposure calls among children ≤10 years from 2010-2015 are listed in **Table 3A of Appendix C**. The most common medical outcome associated with single-substance exposure calls and total unintentional general buprenorphine exposure calls was "minor effects", followed by "no effects", "moderate effects", and "major effects". Only two deaths were reported for unintentional general exposure to buprenorphine.

A similar pattern for medical outcome categories was observed for single-substance and total unintentional general buprenorphine exposure calls among children <6 years (**Table 3B in Appendix C)** and among children 6-10 years (**Table 3C in Appendix C)**. Only 2 (0.03%) calls for unintentional general buprenorphine exposure resulted in death and both were children <6 years old. No major effects or deaths were observed for unintentional general buprenorphine exposures in children 6-10 years.

3.2 EMERGENCY DEPARTMENT VISITS (NEISS-CADES) - RESULTS

The DEPI-II analysis of NEISS-CADES data mainly differs from the previously published analysis by Budnitz et al., 2016 in that this analysis also includes single-ingredient buprenorphine and not just buprenorphine-naloxone products. However, the results did not change substantially between the two analyses.

Table 3 summarizes the projected national estimates of ED visits for unsupervised ingestions of buprenorphine (alone or in combination with naloxone) by children ≤10 years old from 2010 through 2015. During the study period, there were 156 unprojected ED visits for these unsupervised ingestions, for a national estimate of 7,374 ED visits, 95% confidence interval (CI) [4,492-10,256]. The projected number of ED visits decreased from roughly 3,100 visits during the 2010-2011 period to roughly 2,100 visits during both the 2012-2013 and 2014-2015 periods. Nearly all ED visits were for children less than 6 years old, and the majority of ED visits were for unsupervised ingestions of buprenorphine or buprenorphine-naloxone only. Approximately 61% of ED visits resulted in hospitalization during every two-year period.

Table 3: National estimates of unsupervised ingestions of buprenorphine by children ≤10 years old, NEISS-CADES, 2010-2015

Time period	2010- 2011	2012-2013	2014-2015	Total
Projected estimate (95% CI) of ED Visits	3,095 [1,887-4,304]	2,142 [1,115-3,170]	2,136 [958-3,314]	7,374 [4,492-10,256]
Children < 6 years old	2,998 [1,818-4,177]	2,142 [1,115-3,170]	2,128 [949-3,307]	7,268 [4,456-10,080]
Projected percentage (95% CI) of ED visits of unsupervised ingestions of buprenorphine resulting in hospitalization	61.4% [41.7%-81.0%]	60.6% [37.6%-83.6%]	60.8% [39.1%-82.4%]	61.0% [45.4%-76.5%]
Children < 6 years old	63.1% [44.9%-81.3%]	60.6% [37.6%-83.6%]	60.6% [38.9%-82.3%]	61.6% [46.9%-76.3%]
Projected percentage (95% CI) of ED visits of unsupervised ingestions involving buprenorphine or buprenorphine/naloxone only	93.1% [82.1%-100%]	100% [100%-100%]	95.3% [87.5%-100%]	95.7% [88.9%-100%]

National estimates were not projected for some planned analyses because there were less than 20 cases of ED visits, and any resulting national projections would be statistically unstable. There were only seven ED visits that met the selection criteria and involved a drug other than buprenorphine or buprenorphine-naloxone, and there were only three ED visits for children 6-10 years old (all involved 6 year olds).

From 2010 through 2015, the rate of ED visits for unsupervised ingestions of buprenorphine by children ≤10 years old was 27.6 ED visits per 1 million children, 95% CI [16.8, 38.4]. This rate decreased from 35 ED visits per 1 million children in 2010-2011 to 24 ED visits per 1 million children in 2012-2013, but then remained steady at 24 ED visits per 1 million children in 2014-2015, as displayed in **Figure 2**. There was much overlap among the confidence intervals of every two-year estimate.

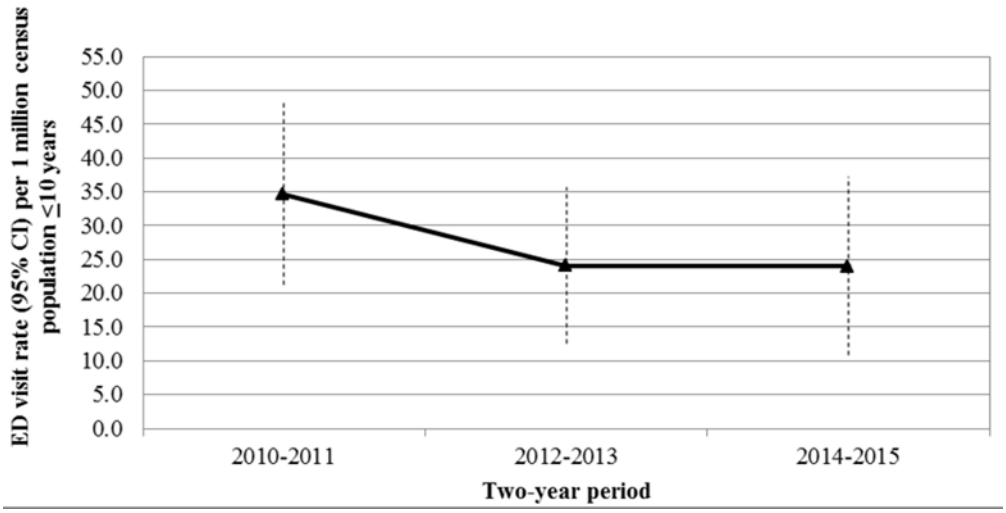

Figure 2: Two-year rates of emergency department visits for unsupervised ingestions of buprenorphine by children ≤10 years old, NEISS-CADES, 2010-2015

3.3 DRUG-INVOLVED MORTALITY - RESULTS

From 2010 through 2014, all 16 deaths involving buprenorphine were among children < 6 years old (**Table 4**); no deaths involving buprenorphine were identified for children 6 to 10 years old. Eleven (68.8%) deaths only involved buprenorphine or buprenorphine/naloxone. Only three (18.8%) of the 16 deaths were not due to pediatric accidental exposures to buprenorphine because they were homicides; no suicides involving buprenorphine were identified. The annual number of deaths did not vary much during the study period, despite improvements in the reporting of specific drugs on death certificates[12] and an overarching increase in total deaths[13] during the study period.

Table 4: Deaths involving buprenorphine among children <6, NVSS-M linked with death certificate literal text, 2010-2014

	2010	2011	2012	2013	2014	Total
Total deaths	3	4	5	2	2	16
Involvement of other drug(s)	1	0	3	1	0	5

4 DISCUSSION OF THE MAIN FINDINGS

Data from three data sources – AAPCC-NPDS, NEISS-CADES, and drug-involved mortality data (NVSS-M) – demonstrate the continuing public health burden of accidental pediatric buprenorphine exposures from 2010 through 2015.

Magnitude of pediatric accidental exposure to buprenorphine

Generally, the characteristics of the analyzed populations were consistent across the three data sources. Among children ≤10 years of age, the majority (98.2%) of unintentional buprenorphine exposure PCC calls are for unintentional general exposures to buprenorphine. Population rates of exposure calls to PCC for unintentional exposure to buprenorphine also indicate that children <6 years of age are disproportionately affected compared to children 6-10 years of age. However, NPDS PCC call data and referenced AAPCC data should not be construed to represent the complete incidence of national exposures to any substance. These data only capture events if the exposure resulted in a call to a PCC. There is the potential for recall bias or error; as information from calls are highly dependent on patient recall of events. PCC data are also known to underrepresent deaths that occur due to exposures.

The national estimates of ED visits from NEISS-CADES for unsupervised ingestions of buprenorphine (96.9%), and deaths from NVSS-M with buprenorphine involvement (100%) involved children <6 years of age. But, NEISS-CADES does not capture visits to ambulatory clinics, urgent care centers or private physician offices and also does not capture information on deaths. So, there could be an underestimation of the exposures in which medical care was sought in these settings or exposures leading to death.

The AAPCC-NPDS and the NEISS-CADES data suggest a high degree of morbidity among affected children. A high proportion (61.0%) of ED visits for unsupervised buprenorphine ingestions among children ≤10 years of age resulted in hospitalization. Furthermore, moderate (i.e., outcomes typically requiring some form of medical treatment) or major (i.e., outcomes that were life threatening or resulted in long-term disability) effects were recorded for nearly a quarter (1,420 among 6,289 calls) of exposure calls for unintentional general exposures to buprenorphine among this same age group.

Trends for of pediatric accidental exposure to buprenorphine

Although the number and population rate of exposure calls for unintentional general exposure to buprenorphine among children ≤10 years of age decreased from years 2010 through 2013, the increases in these PCC calls in years 2014 and 2015 reveal persistence in unintentional buprenorphine exposures. Furthermore, these increases occurred despite the number of AAPCC human exposure calls to PCCs

decreasing over the last decade.[4] So, call rates might be influenced by general changes in use of PCCs over time. AAPCC reported a decline in calls involving less serious exposures and an increase in calls involving more serious exposures since 2000.

Also, the estimated number and population rate of ED visits for unsupervised ingestions of buprenorphine in children of the same age persisted after a drop from the 2010-2011 period to the 2012-2013 period. But, the sensitivity for some drugs is low (33% overall based on chart reviews) in NEISS-CADES.[9] So, there could be an underestimation of the ED visits for this exposure.

The number of deaths involving buprenorphine among children <6 years of age was steady, but low between 2010 through 2014. This review likely describes the minimum number of buprenorphine-involved deaths as there is a possibility of non-reporting of drugs on death certificates among deaths that involved buprenorphine, and prior analyses have found that some drug-involved deaths lack information on the specific drugs involved in the death.[11]

5 CONCLUSION

Data from three data sources – AAPCC-NPDS, NEISS-CADES, and drug-involved mortality data – demonstrate the public health burden of accidental pediatric buprenorphine exposures from 2010 through 2015. Despite some decreases observed in the data from AAPCC-NPDS and NEISS-CADES, the public health burden of accidental pediatric buprenorphine exposures appears to have persisted in recent years. The data also revealed that children <6 years of age were most affected, and involvement of drugs other than buprenorphine or buprenorphine in combination with naloxone was not common. Hospitalization and moderate or major effects were common events among affected children, while death was not a common outcome.

DAAAP should be aware of the continuing public health burden of accidental pediatric buprenorphine exposures in recent years.

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7 APPENDIX A: NATIONAL POISON DATA SYSTEM DEFINITION OF EXPOSURE REASONS FOR UNINTENTIONAL EXPOSURES

Unintentional Exposure Categories	**National Poison Data System Definition[6]**
Unintentional Exposures	Exposure that results from an unforeseen or unplanned event.
Unintentional General[a]	All unintended exposures that are not specifically defined below. Most unintentional exposures in children should be coded here. May include scenario where a toddler got into (and swallowed) a grandparent's prescription medicine.
Unintentional - Environmental	Any passive, non-occupational exposure that results from contamination of air, water or soil.
Unintentional - Occupational[b]	Any exposure that occurs as a direct result of the person being on the job or in the workplace.
Unintentional - Therapeutic Error	An unintentional deviation from a proper therapeutic regimen that results in the wrong dose, incorrect route of administration, administration to the wrong person, or administration of the wrong substance.
Unintentional - Misuse	Unintentional improper or incorrect use of a non-pharmaceutical substance.
Unintentional - Bite/Stings[b]	All animal bites and stings, with or without envenomation.
Unintentional - Food Poisoning[b]	All suspected or confirmed food poisoning regardless of clinical manifestation.
Unintentional - Unknown	An exposure determined to be unintentional but the exact reason is unknown.

[a] The primary focus of this review involved unintentional general buprenorphine exposures in children ≤10 years
[b] Unintentional exposure categories not observed for analysis of unintentional buprenorphine exposures in children ≤10 years

8 APPENDIX B: NATIONAL POISON DATA SYSTEM DEFINITION OF MEDICAL OUTCOMES

Medical Outcomes	National Poison Data System Definition[6]
No effect	No symptoms (clinical effects) as a result of the exposure.
Minor effect[a]	Some symptoms as a result of the exposure... minimally bothersome…symptoms usually resolve rapidly.
Moderate effect[a]	Symptoms as a result of the exposure which are more pronounced, more prolonged or more of a systemic…usually requiring treatment.
Major effect[a]	Symptoms as a result of the exposure which were life-threatening or resulted in significant residual disability or disfigurement.
Death/Death, indirect report[a]	The patient died as a result of the exposure or as a direct complication of the exposure.
"Other" [b]	Patient was not followed, per clinical judgment the exposure was likely to be nontoxic; the patient was not followed because per clinical judgment the exposure was likely to results in only minimal toxicity of a trivial nature; the patient was lost to follow-up (or the poison center neglected to provide follow-up) and per clinical judgment the exposure was significant and may have results in toxic manifestations.
Unrelated effect[c]	Based on all available information, the exposure was probably not responsible for the effect(s).
Confirmed nonexposure[c]	Reliable and objective evidence that the exposure never occurred and that any symptoms exhibited by the patients were not related to the reported exposure.

[a] Analysis of medical outcomes included for exposures with a documented related clinical effect
[b] "Other" category for analysis of medical outcomes includes: Not followed, judged as nontoxic exposure; Not followed, minimal clinical effects possible; Unable to follow, judged as a potentially toxic exposure
[c] Categories excluded from analysis of medical outcomes

9 APPENDIX C: SUPPLEMENTAL TABLES AND FIGURES

Table 2B: Proportion of buprenorphine unintentional general exposure calls by year among children 6-10 years of age, AAPCC 2010-2015

	Total Exposures		Single-Substance		Multi-Substance	
Unintentional General Exposure Year	**N**	**%**	**N**	**%**	**N**	**%**
2010	22	18.3%	22	18.6%	0	0.0%
2011	19	15.8%	19	16.1%	0	0.0%
2012	32	26.7%	31	26.3%	1	50.0%
2013	23	19.2%	22	18.6%	1	50.0%
2014	13	10.8%	13	11.0%	0	0.0%
2015	11	9.2%	11	9.3%	0	0.0%
Total	120		118		2	

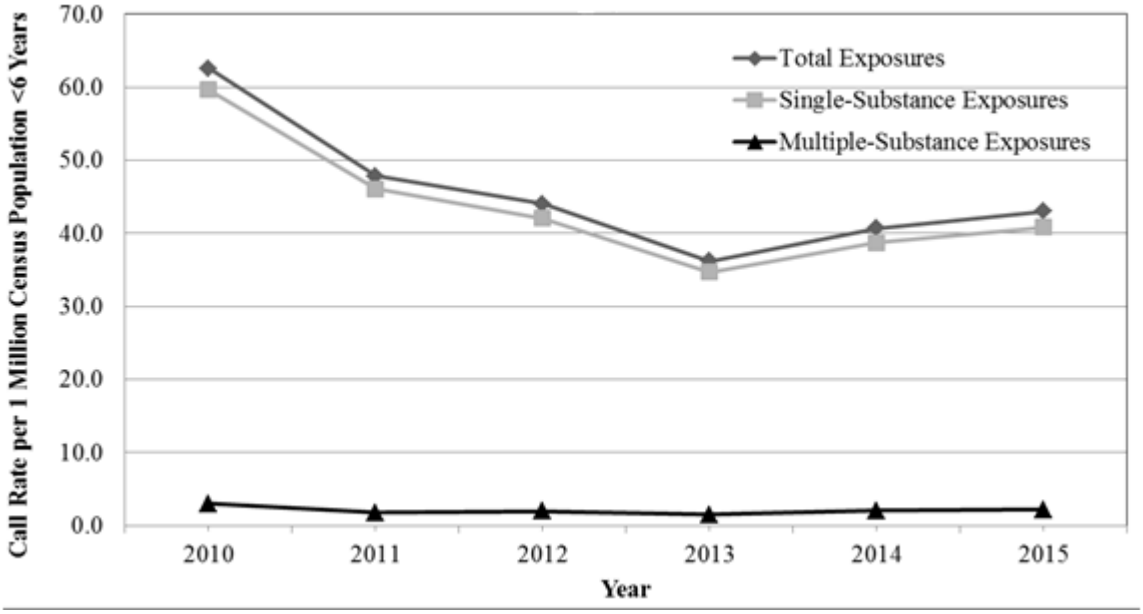

Figure 1A: Age-specific annual call rates involving buprenorphine unintentional general exposures among children <6 years old, AAPCC 2010-2015

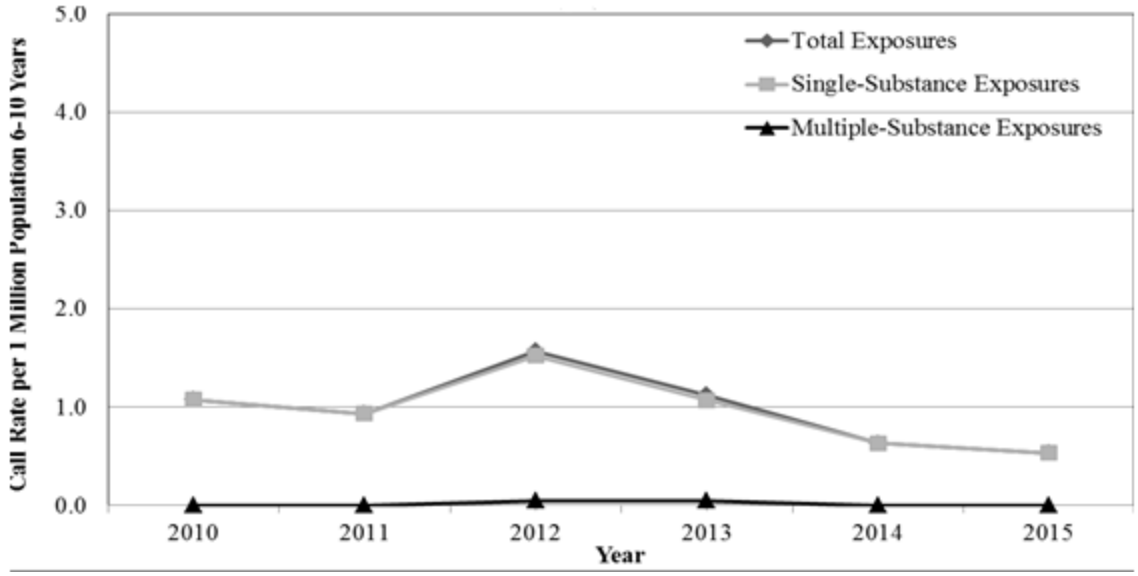

Figure 1A: Age-specific annual call rates involving buprenorphine unintentional general exposures among children 6-10 years old, AAPCC 2010-2015

Table 3A: Related medical outcomes involving buprenorphine unintentional general exposure calls by year among children ≤ 10 years old. AAPCC 2010-2015

Year	Total Exposures (N=6289)						Single-Substance Exposures (N=6011)						Multiple-Substance Exposures (N=278)					
	No Effect	Minor Effect	Moderate Effect	Major Effect	Death/Death, indirect Report	Other*	No Effect	Minor Effect	Moderate Effect	Major Effect	Death/Death, indirect Report	Other*	No Effect	Minor Effect	Moderate Effect	Major Effect	Death/Death, indirect Report	Other*
2010	331	516	280	25	0	286	315	490	261	23	0	284	16	26	19	2	0	2
2011	262	400	206	23	1	206	255	381	195	22	1	204	7	19	11	1	0	2
2012	268	326	221	20	0	194	259	315	203	19	0	187	9	11	18	1	0	7
2013	213	279	168	17	1	151	207	266	155	16	1	148	6	13	13	1	0	3
2014	209	332	218	14	0	148	202	315	200	13	0	147	7	17	18	1	0	1
2015	234	358	206	22	0	154	225	341	191	19	0	151	9	17	15	3	0	3
Total	1517	2211	1299	121	2	1139	1463	2108	1205	112	2	1121	54	103	94	9	0	18

* Other includes: Not followed, judged as nontoxic exposure (clinical effects not expected); Not followed, minimal clinical effects possible (no more than minor effect possible); Unable to follow, judged as a potentially toxic exposure.
Table Excludes: Confirmed nonexposure (N=124) and Unrelated effect, the exposure was probably not responsible for the effect(s) (N=89); missing or unreleated exposures (N=225)

Table 3B: Related medical outcomes involving buprenorphine unintentional general exposure calls by year among children < 6 years old. AAPCC 2010-2015

Year	Total Exposures (N=6174)						Single-Substance Exposures (N=5898)						Multiple-Substance Exposures (N=276)					
	No Effect	Minor Effect	Moderate Effect	Major Effect	Death/Death, indirect Report	Other*	No Effect	Minor Effect	Moderate Effect	Major Effect	Death/Death, indirect Report	Other*	No Effect	Minor Effect	Moderate Effect	Major Effect	Death/Death, indirect Report	Other*
2010	328	506	279	25	0	278	312	480	260	23	0	276	16	26	19	2	0	2
2011	258	394	204	23	1	201	251	375	193	22	1	199	7	19	11	1	0	2
2012	255	323	216	20	0	183	247	312	198	19	0	176	8	11	18	1	0	7
2013	210	273	163	17	1	143	204	261	150	16	1	140	6	12	13	1	0	3
2014	205	329	216	14	0	145	198	312	198	13	0	144	7	17	18	1	0	1
2015	232	356	205	22	0	149	223	339	190	19	0	146	9	17	15	3	0	3
Total	1488	2181	1283	121	2	1099	1435	2079	1189	112	2	1081	53	102	94	9	0	18

* Other includes: Not followed, judged as nontoxic exposure (clinical effects not expected); Not followed, minimal clinical effects possible (no more than minor effect possible); Unable to follow, judged as a potentially toxic exposure.
Table Excludes: Confirmed nonexposure (N=122) and Unrelated effect, the exposure was probably not responsible for the effect(s) (N=86); missing or unreleated exposures (N=225)

Table 3C: Related medical outcomes involving buprenorphine unintentional general exposure calls by year among children 6-10 years old, AAPCC 2010-2015

	Total Exposures (N=115)						Single-Substance Exposures (N=113)						Multiple-Substance Exposures (N=2)					
Year	No Effect	Minor Effect	Moderate Effect	Major Effect	Death/Death, indirect Report	Other*	No Effect	Minor Effect	Moderate Effect	Major Effect	Death/Death, indirect Report	Other*	No Effect	Minor Effect	Moderate Effect	Major Effect	Death/Death, indirect Report	Other*
2010	3	10	1	0	0	8	3	10	1	0	0	8	0	0	0	0	0	0
2011	4	6	2	0	0	5	4	6	2	0	0	5	0	0	0	0	0	0
2012	13	3	5	0	0	11	12	3	5	0	0	11	1	0	0	0	0	0
2013	3	6	5	0	0	8	3	5	5	0	0	8	0	1	0	0	0	0
2014	4	3	2	0	0	3	4	3	2	0	0	3	0	0	0	0	0	0
2015	2	2	1	0	0	5	2	2	1	0	0	5	0	0	0	0	0	0
Total	29	30	16	0	0	40	28	29	16	0	0	40	1	1	0	0	0	0

* Other includes: Not followed, judged as nontoxic exposure (clinical effects not expected); Not followed, minimal clinical effects possible (no more than minor effect possible); Unable to follow, judged as a potentially toxic exposure.

Table Excludes: Confirmed nonexposure (N=2) and Unrelated effect, the exposure was probably not responsible for the effect(s) (N=3)

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/s/

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LABEL, LABELING, AND HUMAN FACTORS RESULTS REVIEW

Division of Medication Error Prevention and Analysis (DMEPA)

Office of Medication Error Prevention and Risk Management (OMEPRM)

Office of Surveillance and Epidemiology (OSE)

Center for Drug Evaluation and Research (CDER)

***** This document contains proprietary information that cannot be released to the public*****

Date of This Review:	October 18, 2017
Requesting Office or Division:	Division of Anesthesia, Analgesia, and Addiction Products (DAAAP)
Application Type and Number:	IND 114082 & NDA 210136
Product Name and Strength:	CAM2038 (buprenorphine) Injection, 50 mg/mL and 356 mg/mL
Total Product Strength:	8 mg/0.16 mL, 16 mg/0.32 mL, 24 mg/0.48 mL, 32 mg/0.64 mL, 64 mg/0.18 mL, 96 mg/0.27 mL, 128 mg/0.36 mL (b) (4) (b) (4)
Product Type:	Single-Ingredient, Combination Product
Rx or OTC:	Rx
Applicant/Sponsor Name:	Braeburn Pharmaceuticals
Submission Date:	IND 114082: July 6, 2017, July 25, 2017, and August 25, 2017 NDA 210136: July 19, 2017 and September 15, 2017
OSE RCM #:	2017-1834 and 2017-1448
DMEPA Safety Evaluator:	Valerie S. Wilson, PharmD
DMEPA Team Leader:	Otto L. Townsend, PharmD
Associate Director of Human Factors:	Quynh Nhu Nguyen, MS

1 REASON FOR REVIEW

This review responds to two requests from the Division of Anesthesia, Analgesia, and Addiction Products to:

1) review the updated human factors (HF) risk analysis and protocol for the CAM2038 Safety Syringe submitted to IND 114082 on July 6, 2017 and
2) review the labels and labeling submitted to NDA 210136 to identify areas of vulnerability that may lead to medication errors.

We note the updated HF submission contains HF validation study results, as such; this review provides our evaluation of the study results to determine if the results support the safe and effective use of the safety syringe.

Braeburn developed pre-filled buprenorphine safety syringes, referred to as CAM2038, for use to deliver a single subcutaneous weekly or monthly dose of buprenorphine. The syringe is designed with a safety mechanism that activates to cover the exposed needle upon release of the plunger at the completion of an injection. This safety mechanism is intended to prevent needle stick injuries. Prior to use, a syringe plunger that is co-packaged with the prefilled syringe must be attached to the syringe body.

As part II of II of a rolling submission for NDA 210136, on July 19, 2017, Braeburn submitted proposed prescribing information, medication guide, Instructions for Use, container labels, and carton labeling for their buprenorphine injections.

1.1 REGULATORY HISTORY

January 31, 2017

We previously reviewed[a] the human factors risk analysis and validation study protocol submitted to IND 114082 on October 14, 2016. Our review identified several deficiencies and we provided recommendations to Braeburn to address the deficiencies, which were sent to Braeburn on January 31, 2017[b].

July 19, 2017

Upon initial review of the HF validation study report, we noted two deficiencies: 1) missing intend-to-market labels and labeling used in the validation study and 2) the report was missing the list of changes made to the user interface based on the results of the formative studies. An information request (IR) was sent to Braeburn on July 19, 2017. On July 25, 2017, Braeburn responded to our IR (Appendix F) supplying the requested information.

[a] Wilson, V. Human Factors Protocol Review for CAM2038 IND 114082. Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2017 JAN 17. RCM No.: 2016-2406.

[b] Hertz, S. Advice/Information Request for CAM 2038 (buprenorphine) Injection. Silver Spring (MD): FDA, CDER, OND, DAAAP (US); 2017 JAN 31. IND 114082.

2 MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide the methods and results for each material reviewed.

Table 1. Materials Considered for this Human Factors, Label, and Labeling Review

Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B
Human Factors Study	C
ISMP Newsletters	D (N/A)
FDA Adverse Event Reporting System (FAERS)*	E (N/A)
Information Request /Responses	F
Labels and Labeling	G

N/A=not applicable for this review

*We do not typically search FAERS for our label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

3 HUMAN FACTORS

3.1 STUDY DESIGN

Braeburn engaged the National Center for Human Factors in Healthcare (HF Center) to conduct human factors validation for the CAM2038 safety syringe. The simulated-use study included 15 nurses with prior experience administering injections ranging from once a year administration during the flu season to every shift throughout the year to represent the intended user population and use environment. Participants did not receive training on the CAM2038 safety syringe and no participant was recruited who could have had previous interactions with the CAM2038 safety syringe during formative studies. Participants completed 8 scenarios administering one subcutaneous injection with each prefilled dosage of CAM2038 per scenario (i.e. administered 8 mg for scenario 1, administered 16 mg for scenario 2, etc.). The study moderator assessed critical task performance through direct observation. Root cause and risk analysis for any use errors, close calls, or use difficulties was determined based on subjective feedback and moderator observation. Additionally, knowledge based questions were asked to assess participants' understanding and interpretation of the user interface. The full report of study objectives, methods, and data collection can be found in the HF validation study report (see Appendix C).

3.2 RESULTS AND ANALYSIS

Performance Task Assessment Results

Overall, we agree with the Applicant's assessment that no additional risk mitigations are needed. Table 2 describes the critical task failures observed, summarizes the Applicant's root cause analysis, and provides DMEPA's analysis of the failures. Our overall evaluation of performance failures did not identify unacceptable residual risks; however, we identified one discrepancy, which is discussed in #4 of Table 2 and provide recommendation to address.

Table 2. Critical Task Failures, Applicant Root Cause Analysis, and DMEPA's Analysis and Recommendation

Critical Task Description	Number of Failures/Close Calls/Use Difficulties	Description of Use Errors/Close Calls/Use Difficulties		Applicant's Root Cause Analysis	Additional Analysis and General Recommendations from DMEPA
1. Attach plunger to syringe* *The Sponsor classified this task as non-critical; however, we disagree because the administration of the drug and activation of the safety device cannot be achieved if the plunger is not attached.	Use difficulty: n = 1	Use difficulty: • P14 pulled plunger all the way out, then tried to put it back in but was unsuccessful. Decided they could not use that syringe and got another one	P14 exhibited use difficulty in scenario 1 only	P14 stated he was waiting for an audible cue (click) to indicate the plunger was attached. Patient stated some but not all of the rubber plungers connected to the plastic part of the plunger to make a tight seal (plunger keep turning and turning), so he assumed there may be a threading issue leading him to pull the plunger out in an attempt to reconnect it properly. No additional risk mitigations needed.	Buprenorphine is not an agent for emergency use. Although the plunger may not create a tight seal with the rubber stopper, this does not alter or prevent use of the device. Therefore, we find no additional risk mitigation is needed.
2. Pinch skin at the injection	Failures: n = 5	Failure: • Participant omitted step	P15 failed this task in scenarios 1-5	P15 stated they assumed the entire simulated tissue was fat.	We find this failure type is the result of test artifact; therefore,

site between thumb and finger				P15 did not reference the IFU during scenarios 1-5 but started using the IFU for scenario 6 and thereafter, at which time P15 started performing the task correctly. During the debriefing, P15 explained that it was clear from Figure 8 in the IFU that the skin needed to be pinched. No additional risk mitigations needed.	no additional risk mitigation is needed.
3. Slowly depress the plunger until plunger head latches between the syringe guard wings and all solution is injected	Failure: n = 1 Close call: n = 1	Failure: • P1 failed to push the plunger all the way down until it latched Close call: • P11 did not push the plunger all the way down before removing the needle from the skin. Recognizing the error, P11 then reinjected the needle to administer the rest of the dose, pushing the plunger all the way down the second time	P1 failed this task in scenario 8 only P11 had this close call in scenario 2 only	P1 stated he didn't notice that he had not pushed the plunger all the way down but explained he did notice it was a little harder to push the plunger down on the 160 mg injection and thought that maybe it was due to the 160 mg dose possibly being a more viscous solution or a defective device; however, the Sponsor did not identify an issue with the product user interface during their root cause analysis. P11 stated they are unsure why they made this error. No additional risk mitigations needed. Reinsertion of a used needle is a violation of safe medical practice that a healthcare provider would be expected to know through standard education and training.	Our evaluation of the subjective feedback indicated that the errors were not attributed to confusion with the information in the IFU or design of the syringe. We note both participants completed this task correctly in 7 of the 8 scenarios; therefore, we find no additional risk mitigation is needed.
4. Keep plunger fully depressed	Failures: n = 56	Failures: • Task omitted (n=35) • Task performed with an insufficient wait (n=21)	P1, P2, P3, P12 failed this task in all 8 scenarios	P1 suggested visually highlighting this step to emphasize holding the syringe in place for 2 seconds.	To fully evaluate these errors, we issued an information request to obtain additional information from the Applicant. In response

down and hold in place for 2 seconds			P4 & P5 failed this task in scenarios 3-8 P11 failed this task in scenarios 1-4, 6-8 P10 failed this task in scenarios 2, 5-8	Three participants indicated that they would not hold a syringe in place for 2 seconds in standard practice. P5 stated they did not hold the syringe in place for the additional 2 seconds because they were not dealing with an actual patient. P7 explained they did not recall reading the two second time but that they remembered reading to hold the plunger down all the way until the medication was delivered. This error is likely due to previous experience administering injections using standards that vary in different places of work and not necessarily a result of the product or its associated materials. Various standards in place are likely to influence performance of this task in the real world. While it may be best practice to leave the needle in the skin for an additional 2 seconds, omitting or shortening this task did not present critical safety result because no medication was observed leaking out of the syringes after removal from the tissue simulator. No additional mitigations needed.	to the August 22, 2017 information request (Appendix F), the Applicant clarified that the instruction for the user to keep the plunger in the final pressed position momentarily (2 seconds) is provided to serve as a reinforcement of the preceding step (latching of the plunger head onto the safety wings) and that it has no bearing, or effect, on the amount of medication injected. We find there is no risk of underdose error provided the proceeding step (latching the plunger head onto the safety wings) is performed correctly. Although, there is no underdose risk associated with not holding the plunger down for an additional 2 seconds, we note a discrepancy where the Applicant stated in their FMEA that this task would be emphasized in the IFU; however, it is not. Also, due to some participant feedback, which suggests highlighting or emphasizing this step would be helpful, we recommend the Applicant increase the prominence of the 2nd bullet point in step 8 to emphasize this task.

Knowledge Task Assessment Results

Table 3 describes the knowledge task assessment results, the Applicant's analysis, and DMEPA's analysis. We did not identify a need for additional risk mitigations based on participants' responses to the knowledge questions.

Table 3. DMEPA Analysis of Knowledge Task Assessment Results

Knowledge question	Responses	Applicant Analysis	DMEPA Analysis and Recommendation
1. What steps should you take prior to handling the syringe and medication to prevent contamination risks? Expected response: Wash hands thoroughly with soap and water	12/15 provided the expected response Partially correct responses: • Listed several correct things, missed hand wash • Don't use if it's broken, don't uncap until you're ready to use, protect the syringe from light • Gloving	Although the IFU was only referenced during 40% of the knowledge questions, participants who used it were more likely to give a complete correct response.	We acknowledge the study moderator but did not require participants to use the IFU when responding to the knowledge questions. All responses to the knowledge task assessment questions were either correct or partially correct based on participants' professional experience. We find that no additional risk mitigation is needed.
2. What should you inspect the safety syringe for prior to use? Expected response: Expiration date, liquid color, and visible particles	6/15 provided the expected response Partially correct responses: • Clarity, dosage • Syringe is intact and filled • Expiration, medicine presence, tamper signs • Medication is present • Medication in syringe, cover on the needle • No tampering or use signs • Correct amount of medication, no breakage • Bubbles, damage, healthy skin site • Actual dose, damage, tamper, expiration date		
3. What should you do for the patient following administering injection if there is blood at the injection site?	9/15 provided the expected response Partially correct responses: • Gauze, pressure at site		

Expected response: Cover injection site with small adhesive bandage	• No problem, keep administering, gauze, no rubbing • Pressure and wipe • Gauze • Apply pressure, wipe		
4. Where on a patient would you administer the injection? Expected response: Arms, legs, or abdomen	11/15 provided the expected response Partially correct responses: • Back of arm, stomach • Arms and abdomen • Either abdomen or outer/upper arm, fatty areas • Buttocks or abdomen or arm		
5. In what instance should a patient not receive buprenorphine? Expected response: If they have been shown to be hypersensitive to buprenorphine, as serious adverse reactions, including anaphylactic shock, have been reported	7/15 provided the expected response Partially correct responses: • Timing, counseling, hypersensitive • If there are any questions or concerns, wrong dose, any contraindications • Allergy, patient not confident in nurse, same site as last time, compromised packaging, breach of sterility, sensitive to latex • Allergic, sensitive reaction • Irritated skin, allergy, contraindication • Too early since last dose • Fever, or anything that you might question about the condition of the patient • Depends on last dose, mental status assessment		

4 LABELING AND PACKAGING

DMEPA's evaluation of the proposed prescribing information (PI), medication guide, Instructions for Use (IFU), syringe labels and carton labeling identified several areas of concern, which are explained in Tables 4 and 5. Tables 4 and 5 also include DMEPA's recommendations to minimize the risk for medication errors.

Table 4. Identified Issues and Recommendations for the Division

	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATIONS FOR THE DIVISION
Prescribing Information			
1.	Mild, moderate, and severe hepatic impairment is not defined (b) (4)	Dosing errors might occur if a prescriber misinterprets what is defined as mild, moderate, or severe hepatic impairment.	Define the severity levels of hepatic impairment (e.g. severe hepatic impairment (Child-Pugh *X*)) in section 2.7.
2.	We note Section 2.3 (b) (4) includes the statement, (b) (4) but does not specify how providers are to transition between the Monthly and Weekly injections.	Dosing or administration errors can occur if it is not clear how to transition between the Once Monthly and Once Weekly injections.	Clarify transition in section 2.3 (e.g. If transitioning from [Brand name] Once Monthly to [Brand name] Once Weekly begin next dose XX weeks after the last monthly injection. Do not exceed 32 mg per week or 160 mg per month).
3.	Section (b) (4) does not specify what steps need to be taken to discontinue use of [Brand name] buprenorphine injection.	It is unclear if discontinuation can occur abruptly or if there is a need to titrate a patient off buprenorphine injection slowly over a specific amount of time.	Clarify in section (b) (4) if discontinuation can occur abruptly or if the patient will require titration off buprenorphine over a specific amount of time.

4.	Section 3 and 16 does not specify that the [Brand name] Once Weekly and Once Monthly is a single-dose syringe.	According to 21 CFR 201.57(c)(4) and 21 CFR 201.57(c)(17), Section 3 and Section 16, respectively, must contain information on the available dosage forms. Inclusion of the package type term, "single-dose" helps to minimize the risk of wrong administration technique errors.	Include "single-dose" in the description of the syringe in sections 3 and 16.
Instructions for Use			
5.	The Applicant states in the Use FMEA that the task, "*Slowly depress the plunger head until plunger head latches between the syringe guard wings and all solution is injected"* would be emphasized in the IFU as a risk mitigation strategy to reduce the risk of failure to deliver a complete dose. However, we note this important information is not emphasized in step 8 of the IFU.	Two participants failed to fully depress the plunger head until it latched between the syringe guard wings during the HF validation study, which could result in underdose errors in real-world scenarios.	We recommend step 8 of the IFU be revised to increase the prominence of the statement, "Slowly press down the plunger head until it latches in the safety device 'wings' (see Figure 10)."
6.	The Applicant states in the SELECTING AN INJECTION SITE section that *CAM2038* (b) (4) *should not be administered to the same site of injection for at least 8 weeks.* (b) (4)	It is unclear (b) (4) We note user comprehension of these	Clarify if there is a specific amount of time that should elapse (e.g. X weeks) before administering the monthly injection (b) (4) (b) (4) Additionally, clarification is needed on the intended meaning (b) (4)

		statements was not tested during the HF validation study.	
7.	The highlighted area of the abdomen in Figure 5 under SELECTING AN INJECTION SITE appears (b) (4) *Figure 5* (b) (4)  We note Figure 5 was revised in the IFU used during the HF validation study, however, Figure 5 remained unchanged in the IFU included in the intend-to-market samples sent to the Agency and proposed IFU submitted to NDA 210136 on July 19, 2017.	We previously communicated during review of the HF validation study protocol that this highlighted area could be misinterpreted (b) (4)	Ensure the highlighted area (b) (4) of figure 5 in the final IFU, similar to figure 5 of the IFU used during the HF validation study, as shown below. *Figure 5* (b) (4) 

Table 5. Identified Issues and Recommendations for the Applicant

	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATIONS FOR BRAEBURN PHARMACEUTICALS
Syringe Label			
1.	The strength is presented as (b) (4) (b) (4) as shown in the snapshot below. (b) (4)	Given that (b) (4) can cause confusion or misinterpretation leading to wrong dose errors. Additionally, the United States Pharmacopeia (USP) recommends the strength per fraction of a milliliter be the only strength expression (e.g. 8 mg/0.16 mL)[c] for containers holding less than 1 mL.	In accordance with the United States Pharmacopeia (USP) General Chapter <7>, revise the strength to appear as XX mg/XX mL (e.g. 8 mg/0.16 mL) on each syringe label and remove the statements, (b) (4) (b) (4) from the syringe labels.
2.	The text is crowded on the small syringe label.	Due to the small size label, the text is crowded making it difficult to read, which can lead to medication errors. Additionally, at least one participant commented during the HF validation study that the writing on the side of the syringe is too small.	To improve legibility, we recommend removing 50 mg/mL in accordance with USP General Chapter <7>, decreasing the font size of the proprietary name, and utilizing the space to increase the font size of the strength. Additionally, we recommend revising the statement (b) (4) to appear in bolded title case as "**For Subcutaneous Use Only**." The route

[c] United States Pharmacopoeia (USP) General Chapter <7> Labeling

			of administration should be relocated to appear beneath the strength. Decrease the size and de-bold the "Rx Only" statement so it is not competing in size and prominence with important information on the syringe label.
3.	The NDC is located in the middle of the syringe label.	Although we note the NDC is not required to appear on the syringe label per 21 CFR 201.10(i). The NDC is often used as a secondary check to confirm correct product selection. The current position of the NDC makes it likely to be missed.	Although we note the NDC is not required on the label per 21 CFR 201.10(i), we recommend retaining the NDC because it is often used as a secondary check to confirm correct product selection. Additionally, we recommend repositioning the NDC to appear at the top of the syringe label away from the product strength.
4.	A linear bar code is missing from the syringe label.	The drug barcode is often used as an additional verification before drug administration in the inpatient setting; therefore, it is an important safety feature that should be part of the label whenever possible.	We recommend you add the product barcode to each individual syringe label as required per 21CFR 201.25(c)(2).
Carton Labeling			
5.	The established name listed on the carton is in a font size that is not at least half the size of the proprietary name.	The established name is not at least half the size of the proprietary name in accordance with 21 CFR 201.10(g)(2).	To be in accordance with 21 CFR 201.10(g)(2), we recommend you revise the font size of the established name.
6.	We note the route of administration is missing from the principal display panel	Overlooking the route of administration could lead to medication error. The top	Include the route of administration on the PDP in accordance with 21

	(PDP) and does not appear prominently on the top closure flap.	closure flap contains the most prominent product information compared to the remainder of the carton. As such, it is likely end-users will primarily review the top closure flap to obtain certain product information.	CFR 201.100(b)(3). Additionally, increase the prominence of the route of administration statement on the top closure flap of the carton.
7.	The product code (middle digits) of the NDC number for each of the weekly strengths (8 mg, 16 mg, 24 mg, and 32 mg) is (b) (4) Additionally, the product code of the NDC number for each of the monthly strengths (64 mg, 96 mg, 128 mg (b) (4)) is (b) (4) (b) (4)	This can lead to wrong strength errors because (b) (4) Thus, each of these injectable products should have a unique product code assigned.[d]	Ensure the product code in each NDC number is different between the strengths. Additionally, ensure the HOW SUPPLIED section in the full prescribing information is updated accordingly.
8.	We note the statement, (b) (4) *included* under the list of kit	Users may misinterpret this statement (b) (4)	Revise to state for example, "*One (1) prefilled syringe with needle shield*."

[d] Draft Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors. Food and Drug Administration. 2013. Available at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM349009.pdf.

	contents on the top closure flap of each carton and that it is inconsistent with the HOW SUPPLIED AND HANDLING section of the prescribing information.		
9.	We note the following statement included on the back panel of the carton, (b) (4)	We note (b) (4)	Reference is made to the *Response to FDA Request for Information* submitted to NDA 210136 on September 15, 2017 wherein clarification was provided on the use of the word "training" on the carton. We agree with the proposed revised language "For the Healthcare Provider: All Healthcare providers who administer [Brand name] should review the instructions for use prior to administering [Brand name]."
10.	The correct package type term "single-dose" is used on the carton; (b) (4)	Per Draft Guidance *Selection of the Appropriate Package Terms and Recommendations for Labeling Injectable Medical Products Packaged in Multi-Dose, Single-Dose, and Single-Patient-Use Containers for Human Use Guidance for Industry,* use of the term (b) (4) "single-dose."	To prevent confusion, we recommend changing the statement to read, "For Subcutaneous Administration Only."

5 CONCLUSION

DMEPA's evaluation of the human factors validation study results, labels, and labeling identified areas of vulnerability that may lead to medication errors. Table 4 includes recommendations for the Division's consideration. We ask that the Division conveys the following recommendation:

- Regarding the task to keep the plunger fully depressed down and held in place for 2 seconds, we note several participants either omitted or performed the task with an insufficient wait time. In response to the Agency's August 22, 2017 information request, you clarified that the instruction for the user to keep the plunger in the final pressed position momentarily (2 seconds) is provided to serve as a reinforcement of the preceding step (latching of the plunger head onto the safety wings) and that it has no bearing or effect on the amount of medication injected. We note some participant feedback suggests that this step needs to be highlighted or emphasized. Additionally, we note you state in your FMEA that this task would be emphasized in the IFU; however, it is not. We agree that holding the syringe in place for an additional 2 seconds helps to reinforce the proceeding step; therefore, we recommend you increase the prominence of the 2nd bullet point in step 8. This change would not require additional validation as it does not introduce new risk to the user interface.

Additionally, we ask that the Division convey the entirety of Table 5 to the Applicant so that recommendations are implemented prior to approval of this NDA.

6 APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for buprenorphine injection that Braeburn Pharmaceuticals submitted on July 19, 2017.

Table 2. Relevant Product Information for buprenorphine injection	
Initial Approval Date	N/A
Active Ingredient	buprenorphine
Indication	(b) (4)
Route of Administration	Subcutaneous
Dosage Form	Injection
Strength	Weekly: 8 mg/0.16 mL, 16 mg/0.32 mL, 24 mg/0.48 mL, 32 mg/0.64 mL Monthly: 64 mg/0.18 mL, 96 mg/0.27 mL, 128 mg/0.36 mL (b) (4)
Dose and Frequency	Once weekly or Once Monthly
How Supplied	Pre-filled, single-dose syringes
Storage	Store BRAND NAME at 20 to 25°C (68 to 77°); excursions permitted at 15 to 30° C (59 to 86° F) [see USP Controlled Room Temperature].

APPENDIX B. PREVIOUS DMEPA REVIEWS

B.1 Methods

On August 31, 2017, we searched the L: drive and AIMS using the terms, buprenorphine to identify reviews previously performed by DMEPA.

B.2 Results

Our search identified one previous review[e], and we confirmed that our previous recommendations were implemented.

[e] Wilson, V. Human Factors Protocol Review for CAM2038 (buprenorphine) injection. Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2017 JAN 17. RCM No.: 2016-2406.

APPENDIX C. HUMAN FACTORS STUDY

Human Factors Validation Study Report

- Human Factors Validation Study for the CAM2038 Safety Syringe submitted July 6, 2017 to IND 114082, available at: \\cdsesub1\evsprod\ind114082\0095\m1\us\cam2038-validation-report.pdf

Container Labels and Carton Labeling

- Container Labels and Carton Labeling used in the HF validation study submitted July 25, 2017 to IND 114082, available at: Application 114082 - Sequence 0097 - 1.14.1.1 Draft Carton and Container Labels -

APPENDIX F. INFORMATION REQUEST

- July 25, 2017 Response to July 19, 2017 Information Request IND 114082
  Available at: \\cdsesub1\evsprod\ind114082\0097\m1\us\cover-letter.pdf

- August 25, 2017 Response to August 22, 2017 Information Request IND 114082
  Available at: \\cdsesub1\evsprod\ind114082\0098\m1\us\cover-letter.pdf

- September 15, 2017 Response to September 13, 2017 Information Request NDA 210136
  Available at: \\cdsesub1\evsprod\nda210136\0015\m1\us\cover-letter.pdf

APPENDIX G. LABELS AND LABELING

G.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,[f] along with postmarket medication error data, we reviewed the following buprenorphine injection labels and labeling submitted by Braeburn Pharmaceuticals on July 19, 2017.

- Syringe Labels (No image)
- Container Labeling (No image)
- Instructions for Use (No image)
- Prescribing Information (No Image)

G.3 Label and Labeling (No Images)

- Syringe labels and carton labeling submitted to NDA 210136 on July 19, 2017. Available at: Application 210136 - Sequence 0002 - 1.14.1.1 Draft Carton and Container Labels -

- Instructions for Use submitted to NDA 210136 on July 19, 2017. Available at: Application 210136 - Sequence 0002 - Instructions for Use - (b) (4) I

[f] Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

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/s/

VALERIE S WILSON
10/18/2017

OTTO L TOWNSEND
10/18/2017