CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

210136Orig1s000

STATISTICAL REVIEW(S)

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

Statistical Review and Evaluation

CLINICAL STUDIES

NDA #:	210-136
Drug Name:	Brixadi [Development name: CAM2038] (buprenorphine extended-release) injection for subcutaneous use
Indication(s):	Treatment of moderate to severe opioid use disorder
Applicant:	Braeburn Pharmaceuticals
Date(s):	Received: June 26, 2018 PDUFA: December 26, 2018
Review Priority:	Class II Resubmission
Biometrics Division:	Division of Biometrics II
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Keywords: NDA review, active control/non-inferiority, clinical trial

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1 EXECUTIVE SUMMARY

On June 26, 2018 Braeburn submitted a complete response to the complete response letter issued by the Agency on January 19, 2018. The purpose of this review is to access whether the applicant's responses are sufficient to address the following issue that was communicated to the applicant in the complete response letter and to address whether the submitted data are sufficient to support approval.

- The submitted clinical datasets were found to include a number of discrepancies and errors, which you have determined were likely caused by limited QC/edit function checks between the IVR database and the clinical database.

In response, the applicant conducted a thorough audit and root cause analysis to identify and correct any issues with the data. The audit report states that the primary root cause of data issues were unreconciled differences between two study-data handling systems, the applicant's primary Electronic Data Capture (EDC) system and the Interactive Web Response/Interactive Voice Response systems (IWRS). The report states that the "1) discrepant data resided primarily in data fields that these two systems having in common, and 2) the data management group confirmed that there was limited cross checking between these two (2) systems."

The report also stated there were no data corrections that were expected to have a direct and material impact on the prior analyses performed and submitted to FDA. While this is true for the primary analysis, several of my supportive analyses designed to understand the conduct of the study were impacted by the data corrections. However, the conclusions did not change.

It is my conclusion that the applicant has met the pre-specified and pre-agreed criteria for demonstrating the non-inferiority of the utilized regimen of CAM2038 to the utilized regimen of sublingual buprenorphine and that CAM2038 should be approved for the proposed indication of treatment of moderate to severe opioid use disorder.

2 INTRODUCTION

2.1 Overview

The applicant conducted a single double-blind, double-dummy, active-controlled efficacy and safety study in new entrants to treatment with moderate to severe opioid use disorder. Key details of this study are summarized in Table 1. I previously reviewed this study in my review dated December 22, 2017. In this review I discussed several data quality issues that cast doubt on the accuracy and reliability of the submitted data. In response the applicant conducted an additional audit to identify the root cause and correct these issues. The focus of this review will be to examine the impact that these corrections had on the analyses that I previously conducted.

Table 1: List of all studies included in analysis

Study	Phase and Design	Treatment Period	Follow-up Period	# of Patients per Arm	Study Population
HS-11-421 NCT# 02651584	Phase 3, Double-blind, double-dummy, active control	24 Weeks	1 month	CAM2038: 213 SL BPN/NX: 215	New Entrants to treatment with Moderate to Severe Opioid Use Disorder

Source: Reviewer

2.2 Data Sources

The data were provided electronically by the Applicant as SAS transport files in the CDISC and ADaM data format. The original submission can be found at the following location in the CDER electronic document room (EDR):
\\CDSESUB1\evsprod\NDA210136\0002\m5\datasets

The data were re-audited to identify and correct a number of issues identified during the previous review cycle. The corrected data were resubmitted with the complete response and are available at the following location:
\\CDSESUB1\evsprod\NDA210136\0079\m5\datasets

3 STATISTICAL EVALUATION

3.1 Data and Analysis Quality

In this Section I will give an overview of the data issues that were identified by either the Agency or the applicant during the initial review cycle and were corrected in the current submission.

Issues that were identified in the previous review cycle are shown in Table 2. Errors noted included duplicated records of administered doses and site visits and incorrect dosing records.

Table 2: Summary of Data Quality Issues

Issue	Explanation Provided by the Applicant	Number of Patients	Treatment Arm Affected
Patients received a starting dose of 8 mg instead of the protocol specified 16 mg	This was confirmed by the applicant to be a data entry error	5	Both
Multiple injections reported at on the same day	Several of the duplicated entries were uncorrected data entry errors. Others were actual duplicated doses.	11	Both
Patient listed as having received a 32 mg CAM2038 dose on day 3 of study	The patient did not visit the site on this day and the applicant confirmed with the site that no injection was given.	1	SL/BPN
Multiple entries referencing the same sublingual tablet kit ID were reported	The applicant attributes these to data entry errors by the site that were missed during the cleaning process.	22	Both
A patient was reported as having received 32 mg CAM2038 with a dose frequency of every 4 weeks.	The applicant reported that this was a mistake by the site and that a 128 mg injection was administered	1	CAM2038
Multiple scheduled visits occurred on the same day	The applicant reported that these were data entry errors	2	Both
Dose units for injections were listed as mL instead of mg	This was not confirmed with the applicant	4	CAM2038

Source: FDA Statistical Review, December 22, 2017

Based on the complete response letter received, the applicant performed a thorough audit of the data from study HS-11-421. In this audit they attempted to identify the root causes of these data errors and correct all detected errors. The following summary was provided in the Applicant's audit report:

> Initial QC findings from the first three domains (EX, DA, SY) revealed discrepant data that were realized to be data points that were captured in two (2) different, but parallel study-data handling systems. These 2 systems are the study's primary Electronic Data Capture (EDC) system and the IWR/IYR which is an electronic study support system (hereinafter referred to as IWRS). The discrepant data between these two (2) systems revealed a root cause that will be further analyzed under a formal Corrective Action Preventative Action (CAPA) and associated Root Cause Analysis by Braeburn. The likelihood of this being the primary root cause is based on two key factors: 1) discrepant data resided primarily in data fields that these two (2) systems have in common, and 2) the data management group confirmed that there was limited cross checking between these two (2) systems.

In addition to QC of the data, the monitoring processes and database validation activities were evaluated to understand to what extent, if any, they may have contributed to the problem. It was found that there was a gap in the data cleaning process and specifically pertaining to the QC and reconciliation of the data fields that the IWRS and the EDC had in common. Further evaluation is warranted and will be performed by Braeburn.

Of importance, several queries were generated, and errant data was [sic] addressed; however, there were no data corrections that are expected to have a direct and material impact on the prior analyses performed and submitted to FDA.

Table 3 shows the applicant's summary of the SDTM domains where issues were found and corrected. Of these domains, only the lab results domain (LB) is utilized in the analysis of the primary endpoint. The data clarification requests for the LB domain are shown in the APPENDICES in Table 18. There were no modifications in this listing which would affect the analysis of the primary endpoints.

Table 3: Overview of Data Clarifications by Domain

Domain	Method of Issue Identification	No. of Data Clarification Requests	No. Resolved	No. Resolved through Explanation	No. Resolved through Dataset Correction
DA	Edit check/Visual QC	163	163	50	113
SV	Edit check/Visual QC	182	182	70	112
LB	Edit check/Visual QC	23	23	20	3
TBL	Edit check/Visual QC	1	1	1	0
EX	Edit check/Visual QC	151	151	71	80
FA	Visual QC	11	11	11	0
AE	Visual QC	440	440	440	0
DM	Visual QC	1	1	1	0
	TOTALS	**972**	**972**	**664**	**308**

Source: Table 9, HS-11-421 Data Quality Control (QC) Report, March 7, 2018

Table 4 shows the applicant's review of the possible route causes for the data quality issues. Monitoring, data entry, and communication were all identified as possible contributing factors, with the lack of cross-checking specifically noted under both monitoring and communication issue.

Table 4: Review of Root Causes

Factor	Possible contributing factor?	QC Personnel Comment
Monitoring	Yes	Review of the monitoring plan and verbal discussion with Braeburn confirmed that the monitors were not responsible for cross-check between the IWRS and the EDC. The monitors are responsible to review IP assignments from the IWRS (printed and kept on site) to the EDC; however, it is recommended that quality of monitoring be considered during the formal root cause investigation.
Data Entry	Yes	Data entry was not considered a direct root cause; however, entry of information into the EDC resulted in some discrepant data. For this reason, data should be considered during the formal root cause assessment.
Database Validation	No	Validation of the database is likely not a contributing factor; however, it is recommended that the documentation surrounding expectation of the data management group be closely evaluated as there was limited planned or executed QC cross check of 2 parallel and critical data management systems, the IWRS and the EDC.
Communication	Yes	Based upon discussions with Braeburn, communication may have played a role. It was Braeburn's understanding that a cross check of the IWRS and the EDC would be undertaken prior to database lock, and discussed during Data Management calls; however, the documentation provided by the data management group does not include this cross check. In addition, the data management group verbally reported that this was not requested and therefore not performed.

Source: Table 7, HS-11-421 Data Quality Control (QC) Report, March 7, 2018

3.2 Evaluation of Efficacy

The applicant evaluated the efficacy of CAM2038 in a single randomized, double-blind, double-dummy, active controlled study which compared CAM2038 to sublingual buprenorphine/naloxone (SL BPN/NX) in patients with opioid use disorder who were new entrants to treatment. In my review dated December 22, 2017 I noted that there were numerous data quality issues that cast doubt on the accuracy of the submitted data. As described in Section 3.1 of this review, the applicant conducted a thorough audit and root cause analysis to identify and correct all detectable data quality issues. This review will focus on the analyses that were impacted by these changes.

3.2.1 Study Design and Endpoints

Consult my previous review dated December 22, 2017 for a detailed summary of the study design. While not defined or identified in my previous review, the estimand used in this study was the difference in response status at 6 months comparing patients with moderate-to-severe opioid use disorder assigned to CAM2038 versus those assigned SL BPN/NX where a responder

is defined below. Although discontinuation was not explicitly considered in the definition of response, urinalyses after a subject discontinued were considered positive. Use of supplemental buprenorphine was allowed and not considered as part of the responder definition. The four attributes of the estimand in the format used in ICH E9(R1) are listed below:

A. Population: Patients with moderate to severe opioid use disorder, who have not received medication-assisted treatment for within the past 60 days, who investigators believed were good candidates for buprenorphine treatment.
B. Endpoint: Patients clinical response status, defined as:
    a. No evidence of illicit opioid use during week 12 (evaluated during Week 13 visit).
    b. No more than one positive urinalysis in the six illicit opioid use assessments performed in weeks 10 to 12.
    c. No evidence of illicit opioid use during the week 25 visit (end of month 6).
    d. No more than one positive urinalysis in the six illicit opioid use assessments performed during phase 2.
C. Intercurrent events: Missed visits were classified as positive urinalysis results. Discontinuation and supplemental medications were not considered when evaluating response status; however, missed urinalyses after discontinuation were classified as positive.
D. Population-level summary: The proportion of patients who met the clinical response criteria.

3.2.2 Statistical Methodologies

Consult my previous review dated December 22, 2017 for a summary of the statistical methodology.

3.2.3 Patient Disposition, Demographic and Baseline Characteristics

Consult my previous review dated December 22, 2017 for a summary of the patient disposition, demographics and baseline characteristics.

3.2.4 Results and Conclusions

The updated primary efficacy analysis is shown in Table 5. The results were unaffected by the changes made to the corrected data. Since the lower bound of the confidence interval (-3.9%) exceeds the 10% margin that was agreed upon with the Agency, it is my conclusion that CAM2038 was non-inferior to sublingual buprenorphine/naloxone. It should be noted that my results do not agree with the applicant's results as there were two patients (HS-11-421-(b) (6) and HS-11-421-(b) (6)) incorrectly defined as responders by the applicant. These patients failed to meet the responder definition due to positive urinalyses at their final visit and were classified as non-responders in my analyses.

Table 5: FDA Reviewer's Analysis: Responder Rate

Category	CAM2038 N=213	SL BPN/NX N=215	Proportion Difference (95% CI)	Non-Inferiority P-value 2-sided
Responder, n (%)	36 (16.9%)	30 (13.9%)	2.9%	< 0.001

			(−3.9%, 9.8%)
Non-Responder, n (%)	177 (83.1%)	185 (86.0%)	

Source: Reviewer
Abbreviations: CI, Confidence interval; ITT, intent to treat; SL BPN/NX, sublingual buprenorphine/naloxone

The number and percentage of patients with missing visits and the average number of missed visits is shown in Table 6.

Table 6: Summary of Missing Visits

Treatment Arm	Number (%) of Patients with Missing Visits	Average Number of Missed Visits
CAM2038	113/213 (53.1%)	4.78
SL BPN/NX	112/215 (52.1%)	4.47

Source: Reviewer

The applicant classified a urinalysis as indeterminant if at least one of the individual panels was classified as "unanalyzable" and considered these samples as negative in their analyses. In my analysis, I considered these indeterminant samples as positive. Results are shown in Table 7. Even though the number of responders in each treatment arm decreases slightly, the estimated treatment effect remains similar and the conclusion of non-inferiority does not change as the lower bound of the 95% confidence exceeds the pre-specified margin of 10%.

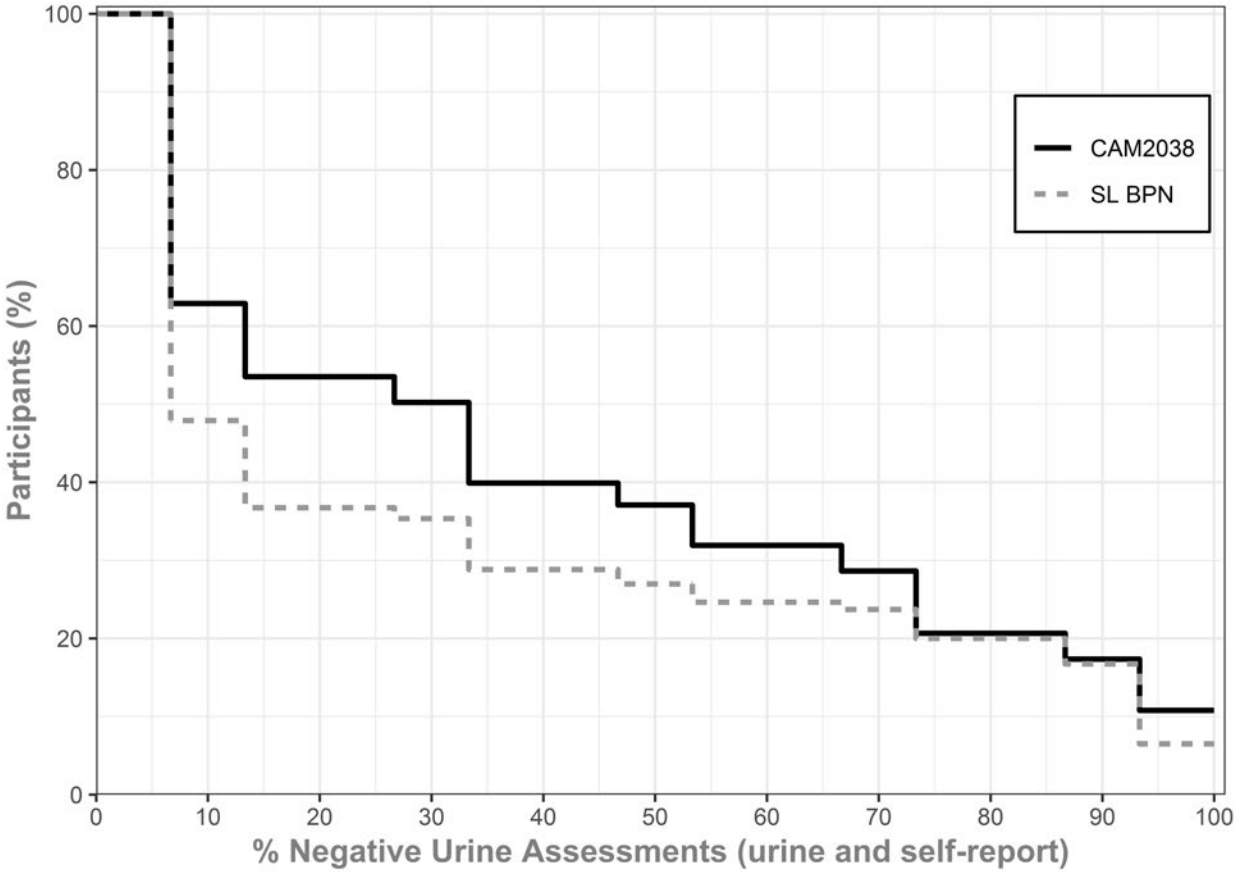
Table 7: Sensitivity Analysis: Responder Rate with Indeterminate Results Classified as Positive (ITT Population)

Category	CAM2038 N=213	SL BPN/NX N=215	Proportion Difference (95% CI)
Responder, n (%)	33 (15.5%)	27 (12.6%)	2.9% (−3.6%, 9.5%)
Non-Responder, n (%)	180 (84.5%)	188 (87.4%)	

Source: Reviewer
Abbreviations: CI, Confidence interval; ITT, intent to treat; SL BPN/NX, sublingual buprenorphine/naloxone

In addition to the responder analyses presented above, the applicant presented analyses of the cumulative distribution function of the percentage of negative opioid use assessments over weeks 5-25. These are shown are shown in Figure 1, with corresponding numbers in Table 8. Numerically, a greater proportion of patients provided greater percentages of negative urine samples for patients receiving CAM2038 compared to sublingual buprenorphine. This is confirmed by the statistical hypothesis test shown in Table 9. These results are unchanged from the applicant's original analyses.

Figure 1: Cumulative Distribution Function (CDF) of Percentage of Negative Opioid Use Assessments over Weeks 5-25



Source: Reviewer

Table 8: Cumulative Distribution Function (CDF) of Percentage of Urine Samples Negative for Illicit Opioids Supported by Self-Reported Illicit Opioid Use over Weeks 5-25

% Self-Reports Negative for Illicit Opioid Use	Number (%) of Patients	
	CAM2038 N=213	SL BPN/NX N=215
≥ 0%	213 (100.0)	215 (100.0)
≥ 10%	121 (56.8)	87 (40.5)
≥ 20%	114 (53.5)	79 (36.7)
≥ 30%	95 (44.6)	67 (31.2)
≥ 40%	85 (39.9)	62 (28.8)
≥ 50%	74 (34.7)	56 (26.0)
≥ 60%	68 (31.9)	53 (24.7)
≥ 70%	51 (23.9)	49 (22.8)
≥ 80%	44 (20.7)	43 (20.0)
≥ 90%	28 (13.1)	27 (12.6)
≥ 100%	23 (10.8)	14 (6.5)

Source: Reviewer

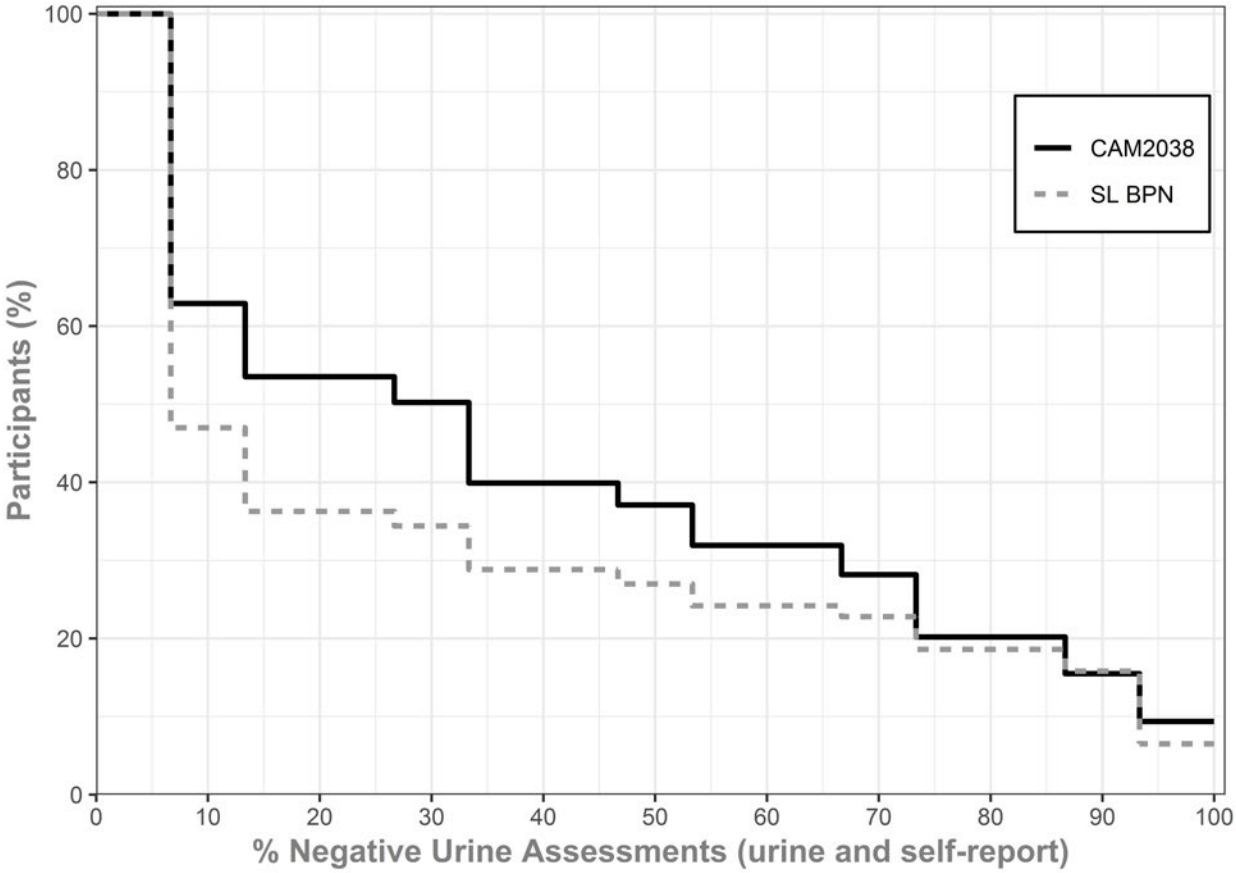
Table 9: Analysis Results for CDF of Percentage of Urine Samples Negative for Illicit Opioids Supported by Self-Reported Illicit Opioid Use over Weeks 5-25

Statistic	CAM2038 N=213	SL BPN/NX N=215
Mean (SD)	35.1 (37.17)	26.7 (37.15)
Median	26.7	0
Min, Max	0.0 – 100.0	0.0 – 100.0
Wilcoxon Rank Sum Test P-value	0.004	

Source: Table 14, Applicant's Study Report
Abbreviations: CDF, cumulative distribution function; SD, standard deviation; SL BPN/NX, sublingual buprenorphine/naloxone.

The corresponding analyses of the CDF of the percentage of negative urine samples for the sensitivity analysis where indeterminate results were classified as positive is shown in Figure 2, Table 10 and Table 11. The conclusions are the consistent with the previous analysis using the applicant's methodology.

Figure 2: Cumulative Distribution Function (CDF) of Percentage of Negative Opioid Use Assessments over Weeks 5-25 with Indeterminate Results Classified as Positive



Source: Reviewer

Table 10: Cumulative Distribution Function (CDF) of Percentage of Urine Samples Negative for Illicit Opioids Supported by Self-Reported Illicit Opioid Use over Weeks 5-25 with Indeterminate Results Classified as Positive

% Self-Reports Negative for Illicit Opioid Use	Number (%) of Patients	
	CAM2038 N=213	SL BPN/NX N=215
≥ 0%	213 (100.0)	215 (100.0)
≥ 10%	121 (56.8)	86 (40.0)
≥ 20%	114 (53.5)	78 (36.3)
≥ 30%	95 (44.6)	67 (31.2)
≥ 40%	85 (39.9)	62 (28.8)
≥ 50%	74 (34.7)	55 (25.6)
≥ 60%	68 (31.9)	52 (24.2)
≥ 70%	50 (23.5)	46 (21.4)
≥ 80%	43 (20.2)	40 (18.6)
≥ 90%	24 (11.3)	25 (11.6)
≥ 100%	20 (9.4)	14 (6.5)

Source: Reviewer

Table 11: Analysis Results for CDF of Percentage of Urine Samples Negative for Illicit Opioids Supported by Self-Reported Illicit Opioid Use over Weeks 5-25 with Indeterminate Results Classified as Positive

Statistic	CAM2038 N=213	SL BPN/NX N=215
Mean (SD)	34.6 (36.57)	26.1 (36.67)
Median	26.7	0
Min, Max	0.0 – 100.0	0.0 – 100.0
Wilcoxon Rank Sum Test P-value	0.003	

Source: Table 14, Applicant's Study Report
Abbreviations: CDF, cumulative distribution function; SD, standard deviation; SL BPN/NX, sublingual buprenorphine/naloxone.

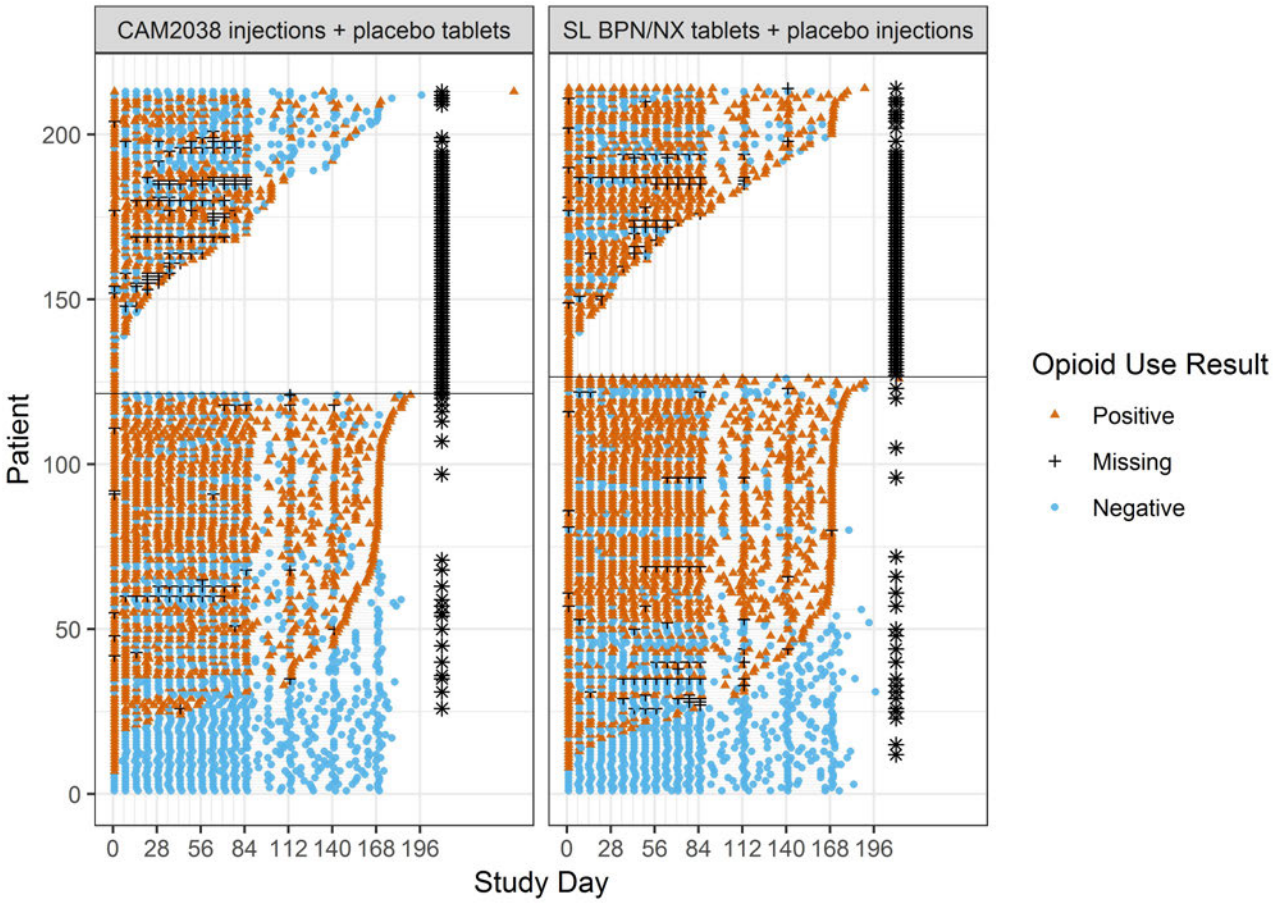
Utilizing the corrected datasets, updated plots of the opioid use assessment results are displayed in Figure 3 –Figure 5. For Figure 3 partially inconclusive results are classified according to the status of the remaining results, that is if there were any positive results then the result was positive, otherwise the assessment was classified as negative. If all panels are inclusive, then test was classified as missing and treated as positive.

In these patient-level presentations, each test result for each individual patient is represented along the y-axis. On the x-axis are the time points during which opioid use assessments were completed. In this study, opioid use assessments were completed weekly for the first twelve weeks, followed by monthly scheduled tests with three randomly scheduled assessments during the final twelve weeks. Light blue circular dots are used to represent opioid- negative

assessments, while orange triangular dots are used to represent opioid-positive assessments. Ideally, a patient achieving treatment success would have many more blue data points than red data points, particularly along the right-hand side of the x-axis which represents later periods of the study. The data points that appear as black '+' symbols denote missing samples. Black stars indicate patients who did not complete all three randomly scheduled assessments during the final three months.

Patients who did not complete the full study are shown at the top of each display, ordered by the total time in the study. Opioid use assessments after discontinuation were assumed to be positive. Completers are shown in the bottom of each display, arranged by time to last positive opioid use assessment. In both treatment arms, there were several patients who did not complete the required follow-up after completion of the double-blind portion of the study but were considered responders

Figure 3: Plot of the Opioid Use Assessment Results

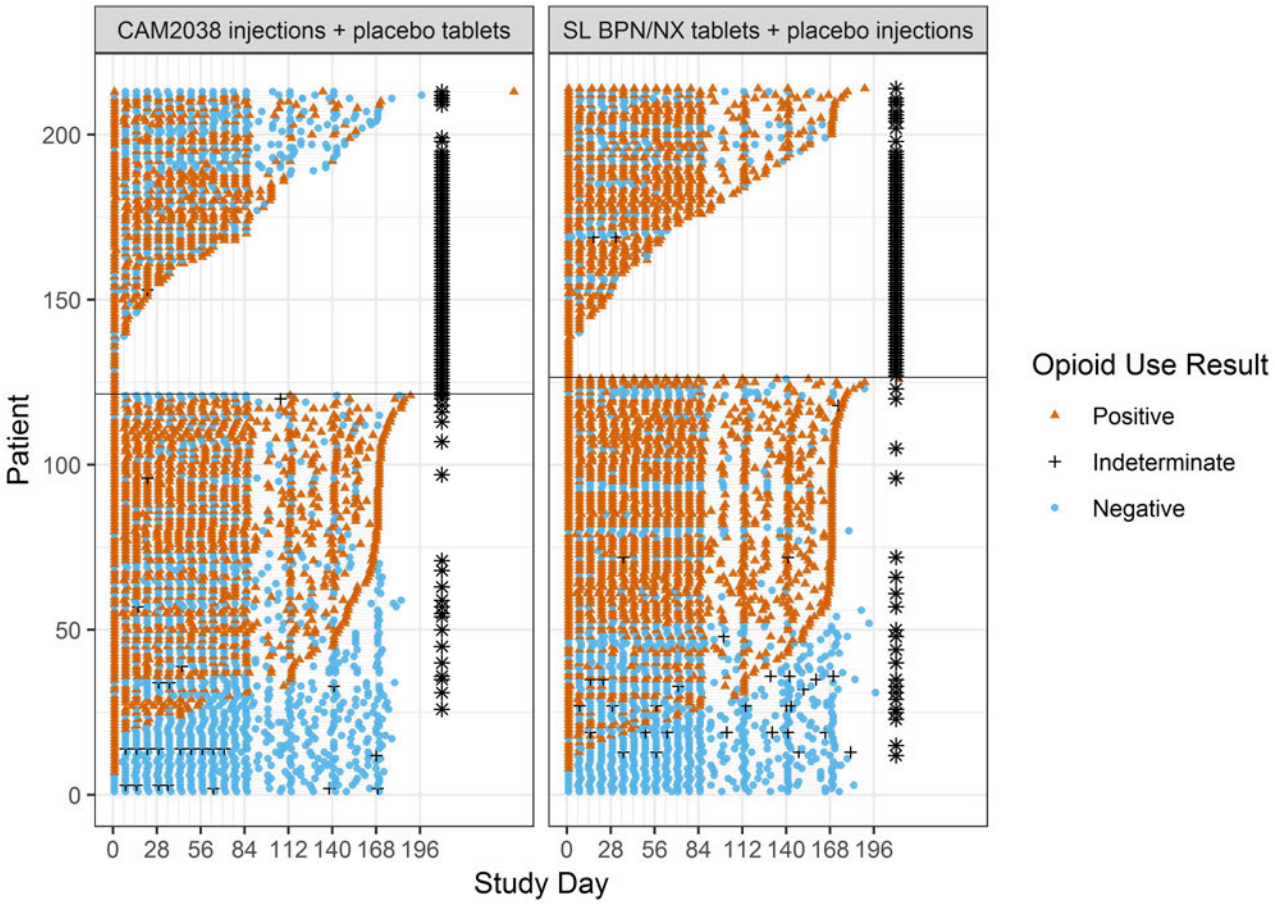


Source: Reviewer
Note: Patients with missed random tests are indicated by a star on the right-hand side of the plot. Patients above the horizontal line were classified as

In

Figure 4 missing results are now classified as positive and any partially indeterminate results are indicated as such.

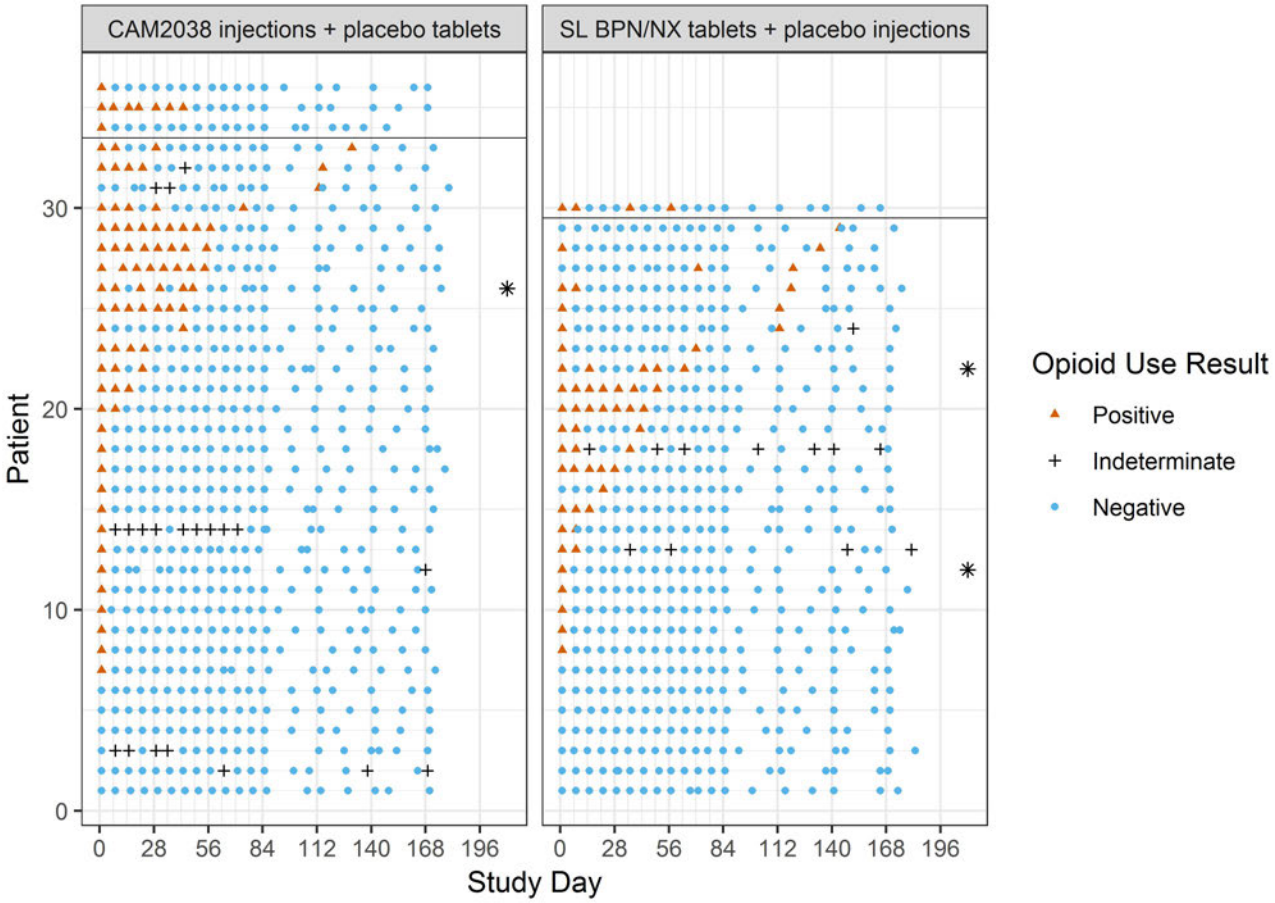
Figure 4: Plot of the Urinalysis Results with Missing Counted as Positive and Indeterminate Results Indicated



Source: Reviewer
Note: Patients with missed random tests are indicated by a star on the right-hand side of the plot.

Finally, Figure 5 shows the urinalysis results for patients classified as responders.

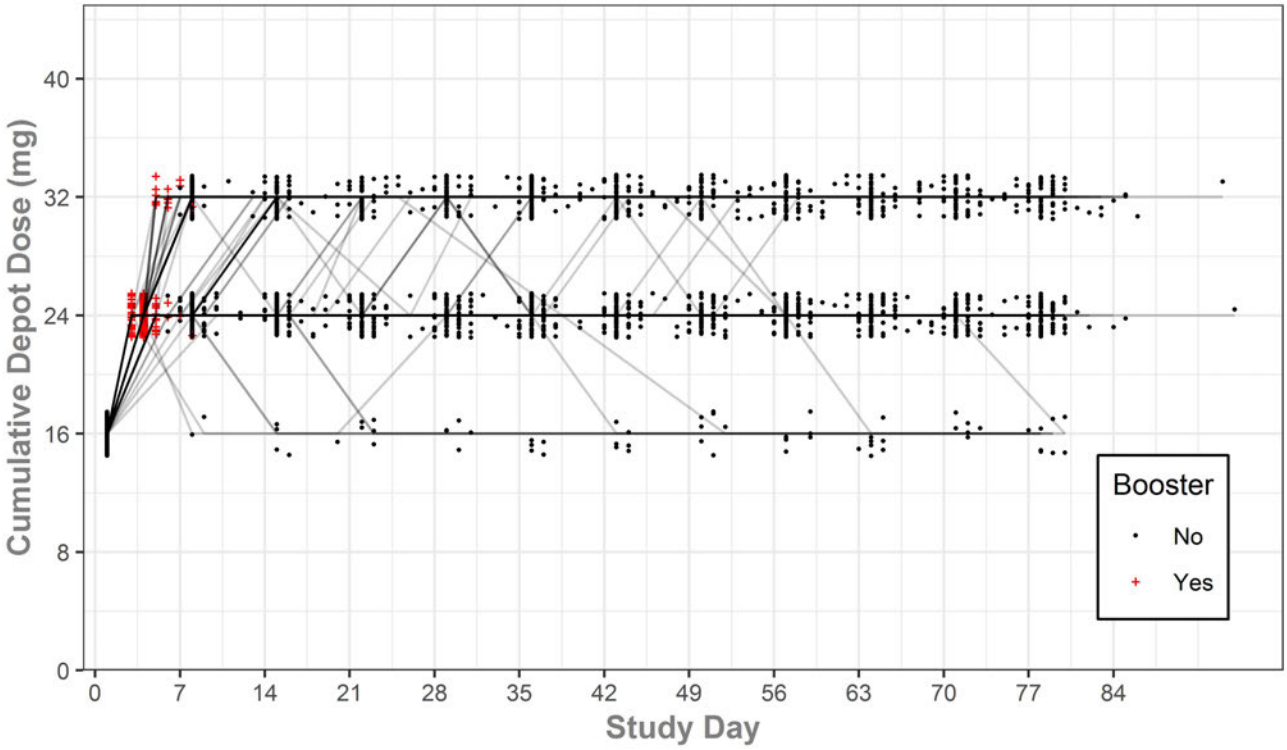
Figure 5: Plot of the Urinalysis results for Responders



Source: Reviewer
Note: Patients with missed random tests are indicated by a star on the right-hand side of the plot.

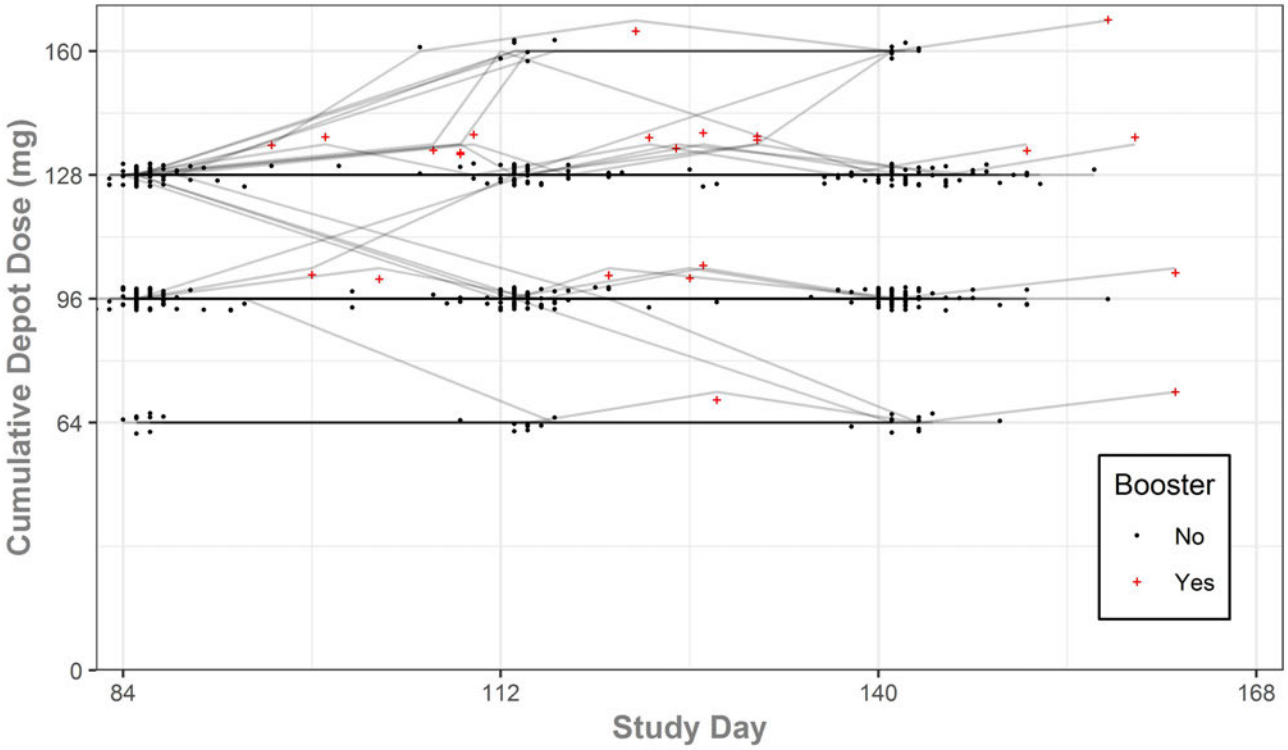
To understand how CAM2038 was used we plotted the administered dose of CAM2038 over time for each patient. These are shown in Figure 6 for phase 1 which used the weekly doses and in Figure 7 for phase 2 which used the monthly doses. The 8 mg dose of the weekly formulation was mostly used in the first week as a booster dose for patients who needed it. It was also allowed as a booster dose for patients who required additional supplemental doses later in the study. In both cases it is added to the previously received dose and is indicated by a red + symbol in both plots. Dose adjustments were permitted throughout the entire study.

Figure 6: CAM2038 Dose for Phase 1 (Months 1-3)



Source: Reviewer

Figure 7: CAM2038 Dose for Phase 2 (Months 4-6)



Source: Reviewer

Updated summaries of the range of doses received are shown in Table 12-Table 15.

Table 12: Number of Patients Exposed to Each Dose and Formulation of CAM2038 and Placebo Injection

		Number of Patients Exposed	
Dose (mg)	Formulation	CAM2038	SL BPN/NX
8	Weekly	200	198
16	Weekly	213	215
24	Weekly	142	153
32	Weekly	85	90
64	Monthly	11	4
96	Monthly	88	85
128	Monthly	68	73
160	Monthly	9	9

Source: Reviewer

Table 13: Total number of Injections for Each Dose and Formulation of CAM2038

		Total Number of Injections	
Dose (mg)	Formulation	CAM2038	SL BPN/NX
8	Weekly	238	239
16	Weekly	277	257
24	Weekly	1045	1163
32	Weekly	729	714
64	Monthly	28	11
96	Monthly	224	233
128	Monthly	166	182
160	Monthly	15	15

Source: Reviewer

Table 14: Number of Booster Injections Provided for each Treatment Arm

Treatment Arm	Number of Booster Injections
CAM2038	23
SL BPN/NX	28

Source: Reviewer

Table 15: Number of Patients Receiving Booster Injections by Treatment Arm

Treatment Arm	Number (%) of Patients Who Used Booster Injections	N (%) of these Patients who were Responders
CAM2038	14 (6.6%)	4 (30.8%)
SL BPN/NX	17 (7.9%)	4 (23.5%)

Source: Reviewer

3.3 Evaluation of Safety

The clinical reviewer, Dr. Gioia Guerrieri, conducted a comprehensive evaluation of the safety of this product. Her review of the safety included studies HS-11-421 and HS-14-499, a long-term open-label safety study. Even though, based on area under the curve at steady state (AUC_{ss}), the highest proposed doses of CAM2038 (32 mg Weekly and 128 mg Monthly) showed higher exposure than the highest monthly recommended sublingual dose of subutex (buprenorphine and naloxone sublingual film), Dr. Guerrieri concluded that the pattern of severe adverse events (SAEs) did not identify any novel systemic findings that were inconsistent with the known safety profile of buprenorphine.

There were two specific safety issues identified in the clinical review, injection site reactions and hepatic effects. Dr. Guerrieri concluded that the rate of injection site reactions in terms of the type of reaction (pain, erythema, swelling, and pruritus) and the percent of injection site reactions reported were similar between CAM2028 and active comparator, [n=40 (18.8%) and

n=48 (22.3%) in the CAM2038 and active comparator groups, respectively]. In her opinion, this suggests that buprenorphine, itself, is not responsible for tissue reactions over and above those of the vehicle. She also concluded that the CAM2038 safety database revealed no new hepatic safety concerns beyond those previously identified.

I have no additional statistical concerns concerning the evaluation of safety of CAM2038.

4 FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

4.1 Gender, Race, Age, and Geographic Region

Analyses by demographic subgroup (sex, race, and age) are shown in Table 16. Since the study enrolled only two patients aged 65 and older and meaningful analysis of efficacy by under 65, and 65 or over was not possible. Instead, the applicant used the median age of 36 years to subdivide patients. The outcomes are unchanged from my previous review, though two race categories which were missed in my previous review (Native Hawaiian or Other Pacific Islander and Other) are included. There do not appear to be any notable differences in the efficacy between any of these subgroups.

Table 16: Primary Analysis by Demographic Subgroup

Category	CAM2038 N=213	SL BPN/NX N=215	Proportion Difference (95% CI)
Sex			
Male	17/121 (14.0%)	18/142 (12.7%)	1.4% (-6.9%, 9.6%)
Female	19/92 (20.7%)	12/73 (16.4%)	4.2% (-7.6%, 16.1%)
Race			
White	31/159 (19.5%)	27/164 (16.5%)	3.0% (-5.3%, 11.4%)
Black or African American	3/47 (6.4%)	2/48 (4.2%)	2.2% (-6.8%, 11.2%)
American Indian or Alaska native	1/2 (50.0%)	1/1 (100.0%)	-50.0% (-119.3%, 19.3%)
Asian	1/1 (100.0%)	0/0	-
Native Hawaiian or Other Pacific Islander	0/1 (0.0%)	0/0	-
Other	0/3 (0.0%)	0/2 (0.0%)	0.0% (0.0%, 0.0%)
Age			
< 36 years old	19/99 (19.2%)	11/100 (11.0%)	8.2% (-1.7%, 18.1%)
≥ 36 years old	17/114 (14.9%)	19/115 (16.5%)	-1.6% (-11.0%, 7.8%)

Source: Reviewer.

4.2 Other Special/Subgroup Populations

Analyses for two special subgroups (primary opioid of use at initiation and route of illicit opioid) were requested by the clinical team and are shown in Table 17. Patients reported primarily as heroin users who received SL BPN/NX had a lower response rate (4.6%) than seen overall (13.9%) while those who received CAM2038 had a similar response rate (14.5%) to the overall CAM2038 response rate (16.9%). Patients who primarily used prescription opioid pain relievers had a higher response rate in both treatment groups compared to the overall rate. The same effect is seen for injection vs non-injection users in both treatment groups. This trend is reversed for patients who reported primarily prescription opioid pain reliever use at baseline with patients receiving SL BPN responding at a higher rate (35.9%) than patients who received CAM2038 (23.0%).

While these results appear to be consistent with the expectation that patients with more severe opioid use disorder would be more likely to benefit from the enforced compliance of depot

formulations, this analysis is post-hoc [redacted] (b) (4)

[redacted] (b) (4)

Table 17: Primary Analysis by Opioid Use History

Category	CAM2038 N=213	SL BPN/NX N=215	Proportion Difference (95% CI)
Primary opioid of use at initiation			
Heroin	22/152 (14.5%)	7/151 (4.6%)	9.8% (3.3%, 16.4%)
Prescription opioid pain reliever	14/61 (23.0%)	23/64 (35.9%)	-13.0% (-28.8%, 2.8%)
Route of illicit opioid			
Injection	17/113 (15.0%)	8/111 (7.2%)	7.8% (-0.3%, 16.0%)
Non-injection	19/100 (19.0%)	22/104 (21.2%)	-2.2% (-13.1%, 8.8%)

Source: Reviewer

5 SUMMARY AND CONCLUSIONS

5.1 Statistical Issues

In my previous review, I noted that there were numerous cases of uncorrected data errors that should have been detected and corrected in the applicant's original audit of the data which brought into question the overall quality and integrity of the submitted datasets. In response to these concerns the applicant conducted an additional audit which confirmed and corrected the noted data errors. It is my conclusion that the statistical issues noted in the original cycle have been adequately addressed.

5.2 Conclusions and Recommendations

It is my conclusion that the submitted study met the pre-defined and pre-agreed non-inferiority and thus that the efficacy of the studied CAM2038 regimen is non-inferior to the studied sublingual buprenorphine regimen. I recommend that CAM2038 be approved for an indication that corresponds to the studied population.

5.3 Labeling Recommendations

I recommend that the format for Section 14 should be modified to match the structure and format used for the other approved buprenorphine extended release injection product. I also recommend including a description of the dosing flexibility employed in the clinical study.

6 APPENDICES

Table 18: Items Queried in the Audit of the SDTM Lab Domain

Patient Id	Related to	Descriptions	Evaluation/Action Planned	Data requires modification
(b) (6)	Phase 1 Week 12	Urinalysis shows “not reported” for oxymorphone and oxymorphone corrected for creatinine.	Per Braeburn, portions of the tests simply could not be completed, or results could not be determined. These are not data errors	No
	Phase 2 Week 17	Urinalysis shows “not reported” for oxymorphone and oxymorphone corrected for creatinine.	Per Braeburn, portions of the tests simply could not be completed, or results could not be determined. These are not data errors	No
	Phase 2 Week 21	Urinalysis shows "NONE DETECTED" for all opioids, however, shows INDETERMINATE for the related "corrected for Creatinine" test.	Per Braeburn, portions of the tests simply could not be completed, or results could not be determined. These are not data errors	No
	Phase 1 Week 6	Urinalysis shows "NONE DETECTED" for most tests. However, it states opioids, but also states Not Reported for Norfentanyl corrected for Creatinine and Norfentanyl. So was the analysis reported and these just missed?	Per Braeburn, portions of the tests simply could not be completed, or results could not be determined. These are not data errors	No
	Screening	To be included in study the subject must be moderate or severe opioid use disorder. However screening urinalysis shows no opioid use.	Per Braeburn, correct. Some patients didn't have a positive UT at screening. The DSMv substance dependence criteria and OUD checklist was used to characterize the patients	No
	Phase 1 Week 5	URINALYSIS shows "NONE DETECTED" for most tests. However, it states opioids, but also states Not Reported for Norfentanyl corrected for	Per Braeburn, portions of the tests simply could not be completed or results could not be determined. These are not data errors	No

(b) (6)		Creatinine and Norfentanyl. So was the analysis reported and these just missed?		
	Screening	To be included in study the subject must be moderate or severe opioid use disorder. However, screening urinalysis shows no opioid use.	Per Braeburn, correct. Some patients didn't have a positive UT at screening. The DSMv substance dependence criteria and OUD checklist was used to characterize the patients	No
	Phase 1 Week 12	Visit was reported as both Phase 1 WEEK 12 and UNSCHEDULED VISIT 2.	Sponsor handled review and resolution directly with Data Management and Biostatistician Groups.	No
	General	I only see 1 of 3 required (per protocol) random Urine Toxicology performed (performed Phase 2 Week 16). To confirm this is not missing data, were the other analysis 2 not done?	Per Braeburn: Confirmed, only M4 Random Urine done	No
	Phase 2 Week 16	Visit is reported as Phase 2 Week 16 and as Unscheduled visit 1. Which is the correct visit label?	Per Braeburn, if site did both planned/scheduled and unplanned/unscheduled labs at the same visit then the unplanned have an "unscheduled" designation	No
	Phase 2 Week 17	Visit is reported as Phase 2 Week 17 and as UNSCHEDULED visit.	Per Braeburn, if site did both planned/scheduled and unplanned/unscheduled labs at the same visit then the unplanned have an "unscheduled" designation	No
	Phase 2 Week 17 & Phase 2 Week 15	Visit is reported as Phase 2 Week 15 and Phase 2 WEEK 17. Which is the correct visit label?	Per Braeburn: Yes, problematic patients, reviewed and documented. Details submitted to FDA	No
	Phase 2 Week 21	Visit is reported as Phase 2 Week 20 and Phase 2 Week 21. Which is the correct	Per Braeburn: Yes, problematic patients, reviewed and documented. Details	No

(b) (6)	& Phase 2 Week 20	visit label?	submitted to FDA	
	General	No data for Phase 1 Week 2 Labs. Visit data shows visit on DATE and IVR shows drug administration on a visit on DATE and DATE. Is this missing data or was a Phase 1 Week 2 urinalysis not done?	Per Braeburn, Subject did not have W2 visit (was missed). DATE was Phase 1 D4. So, no UA for W2 done, as visit was missed	No

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This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

JAMES E TRAVIS
11/29/2018

DAVID M PETULLO
11/29/2018
I concur.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA #:	NDA210-136
Related IND #:	114,082
Drug Name:	CAM2038 (Buprenophine) Injection for subcutaneous administration
Indication(s):	Treatment of opioid use disorder
Applicant:	Braeburn Pharmaceuticals, Inc.
Date(s):	Received: July 20, 2017
	PDUFA: January 19, 2017
Review Priority:	Priority
Biometrics Division:	Division of Biometrics II
Statistical Reviewer:	James Travis, Ph.D.
Concurring Reviewers:	David Petullo, M.S.
Medical Division:	Division of Anesthesia, Analgesia, and Addictions Products (DAAAP)
Clinical Team:	Medical Officer: Gioia Guerrieri, D.O.
	Medical Team Leader: Celia Winchell, M.D.
Project Manager:	Taiye Ayoola

Keywords: NDA review, active control/non-inferiority, clinical trial

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1 EXECUTIVE SUMMARY

On July 20, 2017 Braeburn submitted a New Drug Application for CAM2038 (name used during development), which consists of two new subcutaneous depot injection formulation of the opioid buprenorphine. The two formulations have different intended dosing intervals (weekly and monthly), (b) (4) Buprenorphine is commonly used to treat opioid use disorder and is available in sublingual tablet, sublingual film and subdermal implant formulations. Prescription of buprenorphine for opioid disorder is restricted to prescribers who have undergone certification under the Drug Abuse and Treatment Act 2000 (DATA 2000).

The applicant conducted a single adequate and well-controlled efficacy study for CAM2038 in patients who met the diagnostic criteria for moderate to severe opioid use disorder as described in the Diagnostic and Statistical Manual of Mental Disorders – Fifth Edition (DSM-V) who had not been receiving any other medication assisted treatment for opioid use disorder within 60 days prior to randomization. Patients who had a current DSM-V diagnosis of moderate to severe substance use disorder for any other psychoactive substances other than opioids, caffeine, or nicotine which might in the investigator's judgment interfere with the study assessments.

The study was conducted as a pragmatic study which meant it was designed to mirror the expected clinical practice. Patients were randomized to receive either sublingual buprenorphine and a placebo injection or placebo sublingual tablets and a buprenorphine injection. Once randomized patients in both arms were titrated to an individualized dose and continued to receive dose adjustments throughout the study. This meant that it was not possible to establish whether there was any difference in the response for the different dose levels, since patients were not randomized between these doses.

Even though there does appear to be evidence of efficacy it is my conclusion that CAM2038 is not currently approvable based on concerns with the overall quality and integrity of the datasets submitted by the applicant. We have found numerous uncorrected data entry errors in the datasets that were confirmed by the applicant. The presence of these errors brings into doubt the accuracy of the submitted data. These data entry errors include delivery of dosing kits of study medication on days when the patient didn't have a site visit, duplicated injection entries, duplicated sublingual tablet dispensing records with the same kit number, mismatches between the recorded dose and the actual doses, multiple scheduled site visits listed on the same day, and dose units for injections were mislabeled. Many of these errors either contradict the prespecified conduct of protocol or fall outside the range of plausible outcomes. To me these errors were obvious and should have been easily caught in the applicant's audit of the data. This information was conveyed to the applicant in a telephone call on December 14, 2017. In response, the applicant is conducting a thorough audit of all data submitted to the Agency. In a communication received on December 19, 2017 the applicant stated that they had identified inconsistences between the interactive voice response database and the submitted clinical database that were caused by limited quality control checks between the two systems. The Applicant anticipated re-sending corrected datasets by close of business on December 22, 2017.

2 INTRODUCTION

2.1 Overview

Buprenorphine is a partial opioid agonist and was first approved in 1981. Buprenorphine was first approved for the treatment of opioid dependence in 2002 under the trade names Subutex® and Suboxone®. CAM2038 consists of two different formulations of buprenorphine that are intended for use as a subcutaneous depot injection that were developed for the treatment of moderate to severe opioid use disorder, which is described in the Diagnostic and Statistical Manual of Mental Disorders (DSM-5). The two formulations are designed to have different treatment intervals, with one formulation intended for weekly injection, and one for monthly injection. Each formulation was developed in four different doses with which the applicant intends to cover the entire range of doses commonly used for sublingual treatment.

The applicant conducted a single clinical efficacy study which is summarized in Table 1. See Section 3.2 for a thorough discussion of this study.

Table 1: List of all studies included in analysis

	Phase and Design	Treatment Period	Follow-up Period	# of Patients per Arm	Study Population
HS-11-421 NCT# 02651584	Phase 3, Double-blind, double-dummy, active control	24 Weeks	1 month	CAM2038: 213 SL BPN/NX: 215	New Entrants to treatment with Moderate to Severe Opioid Use Disorder

The development program was conducted under Investigation New Drug (IND) application number 114,082 which was originally submitted by Braeburn on April 20, 2015. This was preceded by a Pre-IND that was submitted on December 5, 2001 by Camurus. I will now summarize any interactions between the applicant and the Agency where the design and analysis of the clinical efficacy study was discussed.

The first interaction between the Agency and the applicant was a Pre-IND meeting that was held on March 13, 2012. At this meeting the design of the development program was discussed. This included discussion of the intended patient population for the study, the requirement for blinding of the study, the length of the study, and the intended endpoint for the study.

The next meeting was the End of Phase 2 meeting which was held on February 24, 2015. During this meeting the applicant provided more details on their intended efficacy study. There was further discussion on the design and how the applicant expects CAM2038 to be utilized clinically. The proposed endpoint for the study was the proportion of negative urine opioid tests at month 3 and month 6. This was later modified to be an analysis of the proportion of responders in the study.

On June 11, 2015, the development program was placed on clinical hold due to safety concerns including the sufficiency of the support for the proposed dose and duration of the clinical

efficacy study. On July 9, 2015, further comments were provided to the applicant regarding the design of the clinical efficacy study, including discussion on the selection of the clinical endpoint and the justification for the non-inferiority margin. The clinical hold was lifted on October 2, 2015.

On October 22, 2015, the Agency provided further feedback on the design of the clinical efficacy study. Issues discussed included the applicant's proposal for the responder definition and the non-inferiority margin. Now a responder was defined as a patient who had no evidence of illicit opioid use in at least 50% of the urines collected in the study after an initial grace period. The Agency stated that the applicant must provide a justification for this endpoint, or propose an alternative endpoint.

The study was initiated on December 29, 2015. The applicant provided an amended version of the protocol in February 2016. The applicant further modified the responder definition to be as follows: No opioids detected in at least 33% of the twelve urine toxicology results in the first twelve weeks of the study and at least 67% of urine toxicology results collected during the final twelve weeks. The applicant also narrowed the non-inferiority margin from (b) (4)% to (b) (4)%. Further feedback was provided by the Agency on September 1, 2016. The Agency stated that there was insufficient historical evidence for the (b) (4)% non-inferiority margin and a more conservative approach with a 5% non-inferiority margin was proposed.

On October 14, 2016, the applicant requested clarification on the selection of the non-inferiority margin prior to planned database lock on November 4th. As previously discussed, the agency had proposed a non-inferiority margin of 5% compared to the applicant's previously proposed (b) (4)% margin. On November 4, 2016, the Agency provided a response to the applicant that a 10% margin would be acceptable.

The Pre-NDA meeting for this application was held on March 16, 2017.

2.2 Data Sources

The data was provided electronically by the Applicant as SAS transport files in the CDISC and ADaM data format. The initial data submission and can be found at the following location in the CDER electronic document room (EDR):

\\CDSESUB1\evsprod\NDA210136\0002\m5\datasets

In the initial data submission, the applicant didn't provide information regarding the sublingual tablet kits that were used in the study. This information was provided in the following data submission:

\\CDSESUB1\evsprod\NDA210136\0016\m5\datasets

3 STATISTICAL EVALUATION

In this section I will evaluate Study HS-11-421, the single efficacy study conducted by the applicant.

3.1 Data and Analysis Quality

Though I could reproduce the results from applicant's primary efficacy analysis using the provided data, there were numerous issues with the quality of the data submitted that raise concerns over the integrity and quality of the submitted data. A summary of the issues that we have identified is provided in Table 2. I do not believe this list is all-inclusive.

Table 2: Summary of Data Quality Issues

Issue	Explanation Provided by the Applicant	Number of Patients Affected	Treatment Arm Affected
Patients received a starting dose of 8 mg instead of the protocol specified 16 mg	This was confirmed by the applicant to be a data entry error	5	Both
Multiple injections reported at on the same day	Several of the duplicated entries were uncorrected data entry errors. Others were actual duplicated doses.	11	Both
Patient listed as having received a 32 mg CAM2038 dose on day 3 of study	The patient did not visit the site on this day and the applicant confirmed with the site that no injection was given.	1	SL/BPN
Multiple entries referencing the same sublingual tablet kit ID were reported	The applicant attributes these to data entry errors by the site that were missed during the cleaning process.	22	Both
A patient was reported as having received 32 mg CAM2038 with a dose frequency of every 4 weeks.	The applicant reported that this was a mistake by the site and that a 128 mg injection was administered	1	CAM2038
Multiple scheduled visits occurred on the same day	The applicant reported that these were data entry errors	2	Both
Dose units for injections were listed as mL instead of mg	This was not confirmed with the applicant	4	CAM2038

Source: Reviewer

3.2 Evaluation of Efficacy

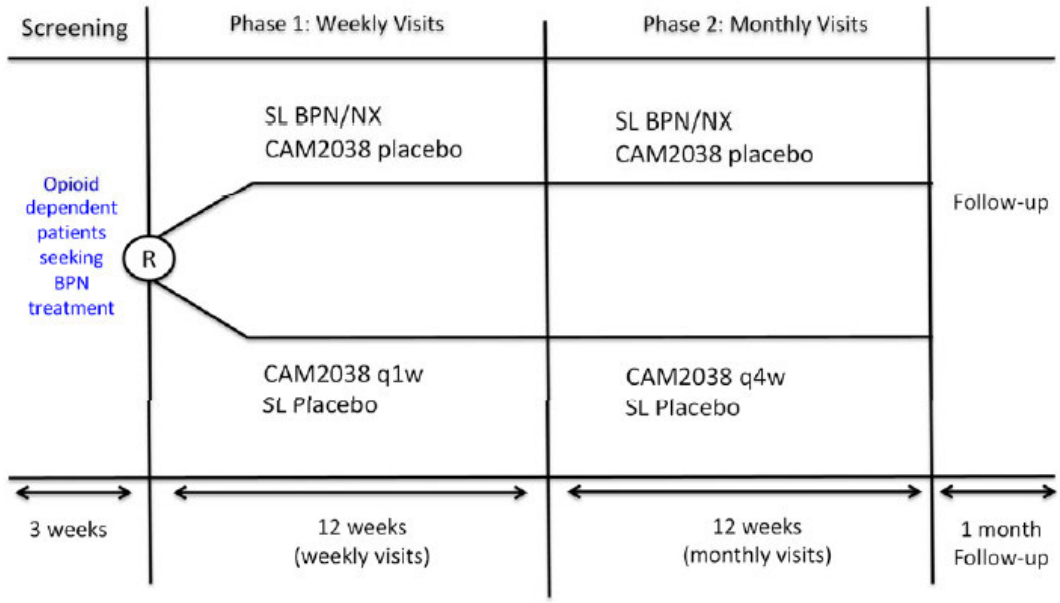
3.2.1 Study Design and Endpoints

Study HS-11-421 was a randomized, double-blind, double-dummy, active-controlled study designed to evaluate the efficacy and safety of CAM2038 compared to sublingual buprenorphine/naloxone (SL BPN/NX) in patients with opioid use disorder who are new entrants to treatment. Patients were eligible for inclusion in the study if they met the following requirements:

- Male or female, 18-65 years of age, inclusive.
- Diagnosis of moderate or severe opioid use disorder as described in the Diagnostic and Statistical Manual of Mental Disorders – Fifth Edition (DSM-V).
- Voluntarily sought treatment for opioid use disorder.
- Had not received medication-assisted treatment for opioid use disorder within 60 days prior to randomization.
- Considered by the investigator to be a good candidate for buprenorphine treatment, based on medical and psychosocial history.
- Must not have a current diagnosis of chronic pain requiring opioids for treatment.
- Must not have a current DSM-V diagnosis of moderate to severe substance use disorder on any other psychoactive substance other than opioids, caffeine, or nicotine.

Eligible patients were randomized in a 1:1 ratio to receive either CAM2038 injections with placebo sublingual tablets, or placebo injections with sublingual SL BPN/NX tablets. The schedule of the study is illustrated below in Figure 1. Of note, there were three scheduled visits during the first week of the study, followed by weekly visits through the rest of the first phase of the study.

Figure 1: Study Schema for HS-11-421



Abbreviations: BPN/NX, buprenorphine/naloxone; q1w, once weekly; q4w, once monthly; R = randomization; SL = sublingual
Source: Figure 1, Applicant's Study Report

The dosing scheme used in this study was designed to mimic the usual clinical practice and allowed dose adjustments throughout the trial. I will now describe the dosing scheme in detail. On the first day of treatment patients received an open-label 4 mg test dose of sublingual buprenorphine. Patients who tolerated the test dose were randomized and given a 16 mg injection of CAM2038 or matched placebo. During the next six days patients were allowed up to two further 8 mg injections as needed. Patients received an injection of 16, 24, or 32 mg on Day 8

matched to the dose they received in the previous seven days. Patients received injections weekly for twelve weeks total and then transitioned to an equivalent dose of the monthly formulation for the remaining twelve weeks. Dose adjustments and supplemental 8 mg injections were permitted for the duration of the study. Supplemental 8 mg doses of CAM2038 weekly were allowed during the study in both treatment arms. The sublingual buprenorphine dose was managed similarly. Patients were initiated on a dose of 8 mg per day, which could be adjusted in increments of 8 mg up to a total of 24 mg per day.

The primary endpoint for this study was the percentage of patients who are responders in phase 1 and phase 2. The responder definition for phase 1 was as follows:

- No evidence of illicit opioid use during week 12 (evaluated during Week 13 visit).
- No more than one positive urinalysis in the six illicit opioid use assessments performed in weeks 10 to 12.

The responder definition for phase 2 was as follows:

- No evidence of illicit opioid use during the week 25 visit (end of month 6).
- No more than one positive urinalysis in the six illicit opioid use assessments performed during phase 2.

Illicit opioid use was defined as either a positive urine toxicology results or a self-reported illicit opioid use. Missing results were imputed as positive. As discussed in Section 2.1, the study used a 10% non-inferiority margin for the study was agreed with the Agency prior to initiation of the study.

The Agency requested a secondary analysis of the cumulative distribution function (CDF) of the percentage of urine samples negative for illicit opioids between week 5 and 25. The purpose of analyzing efficacy starting from Week 5 instead of Week 1 was to allow patients to stabilize in treatment. Percentage abstinence was computed for each patient as the number of weeks of abstinence divided by 15. For example, if a patient had 10 weeks of negative urine samples and self-report negative for opioids, the percentage abstinence of this patient was 67%.

3.2.2 Statistical Methodologies

As discussed in Section 3.2.1, the primary endpoint for this study was the percentage of patients who met the response criteria for both phases of the study. The primary efficacy analysis was conducted on the ITT population, which was defined as all randomized patients. Analyses based on this population will group patients per the treatment that they were randomized to receive, regardless of actual treatment received.

Non-inferiority (NI) of CAM2038 would be concluded if the lower bound of 95% confidence interval of the difference in the response rates between CAM2038 and SL BPN/NX is greater than the pre-specified non-inferiority margin of 10%. The confidence interval of the difference in response rates was calculated using the normal approximation to the binomial distribution and is given by the following formula

$$(P_T - P_C) \pm 1.96 * \sqrt{\frac{P_T(1-P_T)}{N_T} + \frac{P_C(1-P_C)}{N_c}}$$

Where, P_T and P_C are the observed percentages of responders in the treatment and control arms respectively, and N_T and N_C are the number of patients enrolled in the treatment and control arms respectively.

The CDF endpoint was analyzed using the Wilcoxon rank-sum test. The CAM2038 arm was tested against sublingual buprenorphine for superiority at the 0.05 level. NI was not considered.

3.2.3 Patient Disposition, Demographic and Baseline Characteristics

Demographics of randomized patients are shown in Table 3. There do not appear to be any major differences between the two treatment arms.

Table 3: Demographics of randomization patients in HS-11-421

Category	CAM2038 N=213	SL BPN/NX N=215	Total N=428
Age (years)			
Mean (SD)	38.7 (11.17)	38.0 (10.89)	38.4 (11.02)
Min, Max	19.0 - 65.0	18.0 - 65.0	18.0 - 65.0
Sex, n (%)			
Male	121 (56.8)	142 (66.0)	263 (61.4)
Female	92 (43.2)	73 (34.0)	165 (38.6)
Race, n (%)			
White	159 (74.6)	164 (76.3)	323 (75.5)
Black or African American	47 (22.1)	48 (22.3)	95 (22.2)
American Indian Or Alaska Native	2 (0.9)	1 (0.5)	3 (0.7)
Asian	1 (0.5)	0 (0.0)	1 (0.2)
Native Hawaiian or Other Pacific Islander	1 (0.5)	0 (0.0)	1 (0.2)
Other	3 (1.4)	2 (0.9)	5 (1.2)
Ethnicity, n (%)			
Hispanic Or Latino	25 (11.7)	24 (11.2)	49 (11.4)
Not Hispanic Or Latino	188 (88.3)	191 (88.8)	379 (88.6)
BMI (kg/m^2)			
Mean (SD)	25.6 (5.03)	26.2 (5.55)	25.9 (5.30)
Min, Max	14.9 - 42.8	15.8 - 53.2	14.9 - 53.2

Source: Table 6, Applicant's Study Report

The disposition for the randomized patients is shown in Table 4. The completion rates are similar for the two treatment arms (56.8% vs 58.6%) and there do not appear to be any substantial differences between the two arms in the reasons for study discontinuation.

Table 4: Patient Disposition in HS-11-421

	CAM2038 N=213 n (%)	SL BPN/NX N=215 n (%)	Total N=428 n (%)
Completed	121 (56.8%)	126 (58.6%)	247 (57.7%)
Discontinued	92 (43.2%)	89 (41.4%)	181 (42.3%)
Primary Reason for Early Discontinuation			
Adverse Event	6 (0.5%)	1 (0.5%)	7 (1.6%)
Death	1 (0.5%)	0 (0.0%)	1 (0.2%)
Lost to Follow	27 (12.7%)	29 (13.5%)	56 (13.1%)
Physician Decision	8 (3.8%)	4 (1.9%)	12 (2.8%)
Pregnancy	0 (0.0%)	1 (0.5%)	1 (0.2%)
Withdrawal by Patient	44 (20.7%)	46 (21.4%)	90 (21.0%)
Other	6 (2.8%)	8 (3.7%)	14 (3.3%)

Source: Table 6, Applicant's Study Report

The history of prior opioid use is summarized in Table 5. There do not appear to be any major differences between the two treatment groups.

Table 5: Substance Use History in randomized population of HS-11-421

Category	CAM2038 N=213 n (%)	SL BPN/NX N=215 n (%)	Total N=428 n (%)
Primary opioid of use at initiation			
Heroin	152 (71.4)	151 (70.2)	303 (70.8)
Prescription Pain Reliever	61 (28.6)	64 (29.8)	125 (29.2)
Route of illicit opioid			
Injection	114 (53.5)	110 (51.2)	224 (52.3)
Non-injection	99 (46.5)	105 (48.8)	204 (47.7)
Positive Screening result for:			
Amphetamines	38 (18.0)	32 (14.9)	
Barbiturates	3 (1.4)	1 (0.5)	
Benzodiazepine	30 (14.2)	35 (16.3)	
Cocaine	53 (25.1)	53 (24.7)	
Marijuana	57 (27.0)	64 (29.8)	
Phencyclidine	2 (0.9)	0	

Source: Table 7, Applicant's Study Report
Abbreviations: SL BPN/NX, sublingual buprenorphine/naloxone.

3.2.4 Results and Conclusions

Note: The results presented in this section reflect the issues and corrections to the source data that have been identified and discussed in Section 3.1. I do not believe that this list is comprehensive.

The results of my replication of the applicant's primary analysis are shown in Table 6. In all analyses, the applicant combined all the patients in each arm and did not distinguish between patients receiving different dose levels of CAM2038 or SL BPN/NX. There were three patients (two CAM2038, one SL BPN/NX) which were classified as responders in the applicant's primary analysis which did not appear to meet the applicant's responder definition. These patients were classified as non-responders in my analyses.

The applicant concluded CAM2038 was NI to SL BPN/NX since the lower bound of the 95% confidence interval of the difference in the percentage of responders was greater than the pre-specified −10% NI margin. However, as the 95% confidence interval of the difference contained zero, CAM2038 was not demonstrated to be superior to the SL BPN/NX.

Table 6: Applicant's Primary Analysis: Responder Rate (ITT Population)

Category	CAM2038 N=213	SL BPN/NX N=215	Proportion Difference (95% CI)	Non-Inferiority P-value 2-sided
Responder, n (%)	36 (16.9%)	30 (13.9%)	2.9% (−3.9%, 9.8%)	< 0.001
Non-Responder, n (%)	177 (83.1%)	185 (86.0%)		

Source: Reviewer
Abbreviations: CI, Confidence interval; ITT, intent to treat; SL BPN/NX, sublingual buprenorphine/naloxone

To further explore efficacy, the applicant performed an analysis of the percentage of negative tests. Results of which are shown in Table 7. The applicant explored different grace periods in this analysis but it made little difference to the findings and so these results are omitted.

Table 7: Percentage of Urine Samples Negative for Illicit Opioids (Without Patients' Self-Reported Opioid Use)

Statistic	CAM2038 N=213	SL BPN/NX N=215	Difference (%) (95% CI)	P-Value
Mean (SD)	35.1 (36.00)	28.4 (36.46)		
Median	22.2	5.6		
Min, Max	0.0 – 100.0	0.0 – 100.0		
LS Mean (SE)	35.1 (2.48)	28.4 (2.47)	6.7	< 0.001
95% CI	30.3 – 40.0	23.5 – 33.3	−0.1 – 13.6	

Source: Table 12, Applicant's Study Report

Even though there was a significant difference in the overall percent of negative tests, this analysis does not differentiate between, for example, a patient who is abstinent for half the study and then relapses to daily illicit drug use, a patient who continues to use illicit drugs daily for half the study and then stops completely, and a patient who uses intermittently, half the days throughout the study. These patients might have 50% of their tests negative. To allow an appreciation of the temporal sequence of patients' test results, the graphic depictions below in Figure 2 show the results of each test for each patient. The plot also distinguishes between tests that were imputed as positive because they were missing, and actual positive tests or

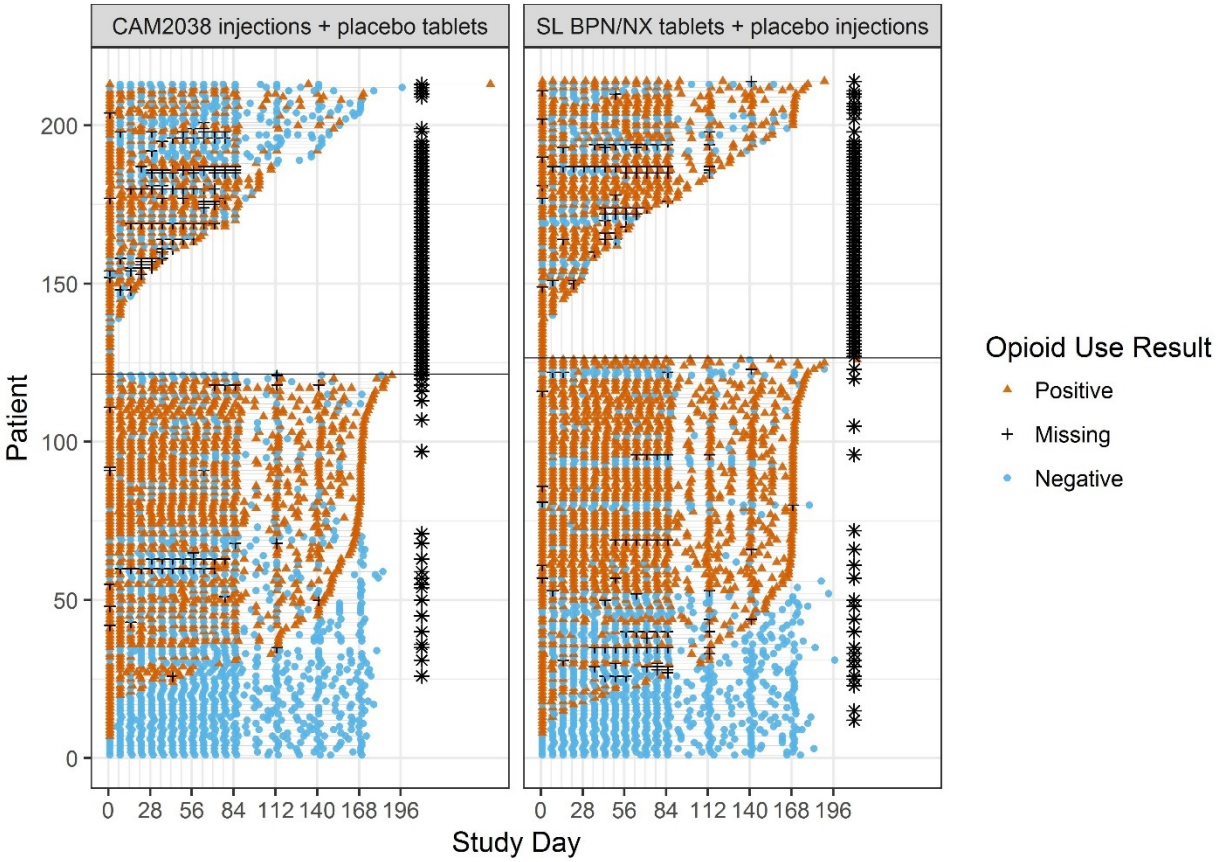
self-reported use. Patients with missed random tests are indicated by a star on the right side of the figure.

In these patient-level presentations, each individual patient is represented along the y-axis. On the x-axis are the time points during which opioid use assessments were completed. In this study, opioid use assessments were completed weekly for the first twelve weeks, followed by monthly scheduled tests with three randomly scheduled assessments during the final twelve weeks. Light blue circular dots are used to represent opioid- negative assessments, while orange triangular dots are used to represent opioid-positive assessments. Ideally, a patient achieving treatment success would have many more blue data points than red data points, particularly along the right-hand side of the x-axis which represents later periods of the study. The data points that appear as black '+' symbols denote missing samples. Black stars indicate patients who did not complete all three randomly scheduled assessments during the final three months.

Patients who did not complete the full study are shown at the top of each display, ordered by the total time in the study. Opioid use assessments after discontinuation were assumed to be positive. Completers are shown in the bottom of each display, arranged by time to last positive opioid use assessment. In both treatment arms, there were several patients who did not complete the required follow-up after completion of the double-blind portion of the study but were considered responders

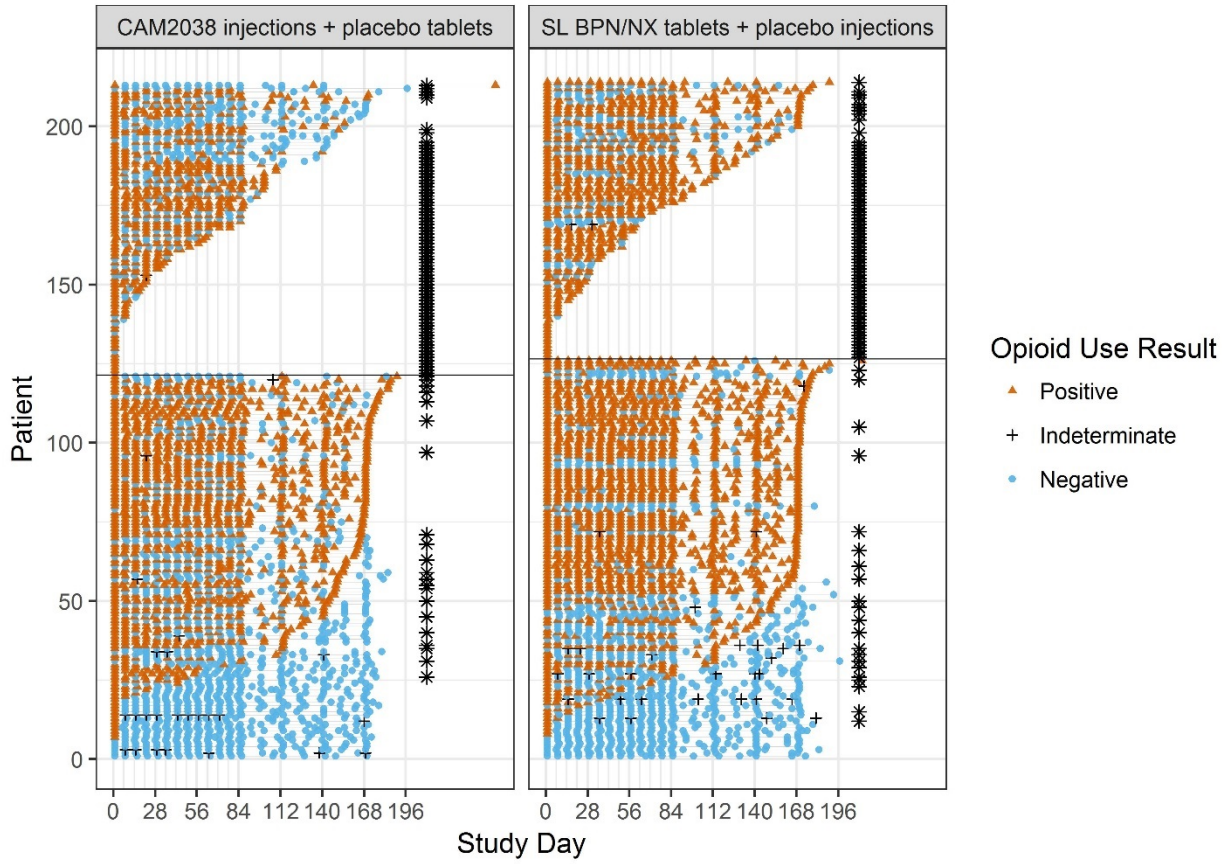
There were also several opioid use assessments where the results for some of the panels within the opioid urine test were reported as indeterminate by the applicant. If no illicit opioids were detected, then these samples were considered to be negative in the applicant's primary analysis. These are shown in Figure 3 and denoted by black plus symbols. Figure 4 is a reproduction of Figure 3 with the patients considered to be responders in the applicant's primary analysis.

Figure 2: Plot of the Opioid Use Assessment Results



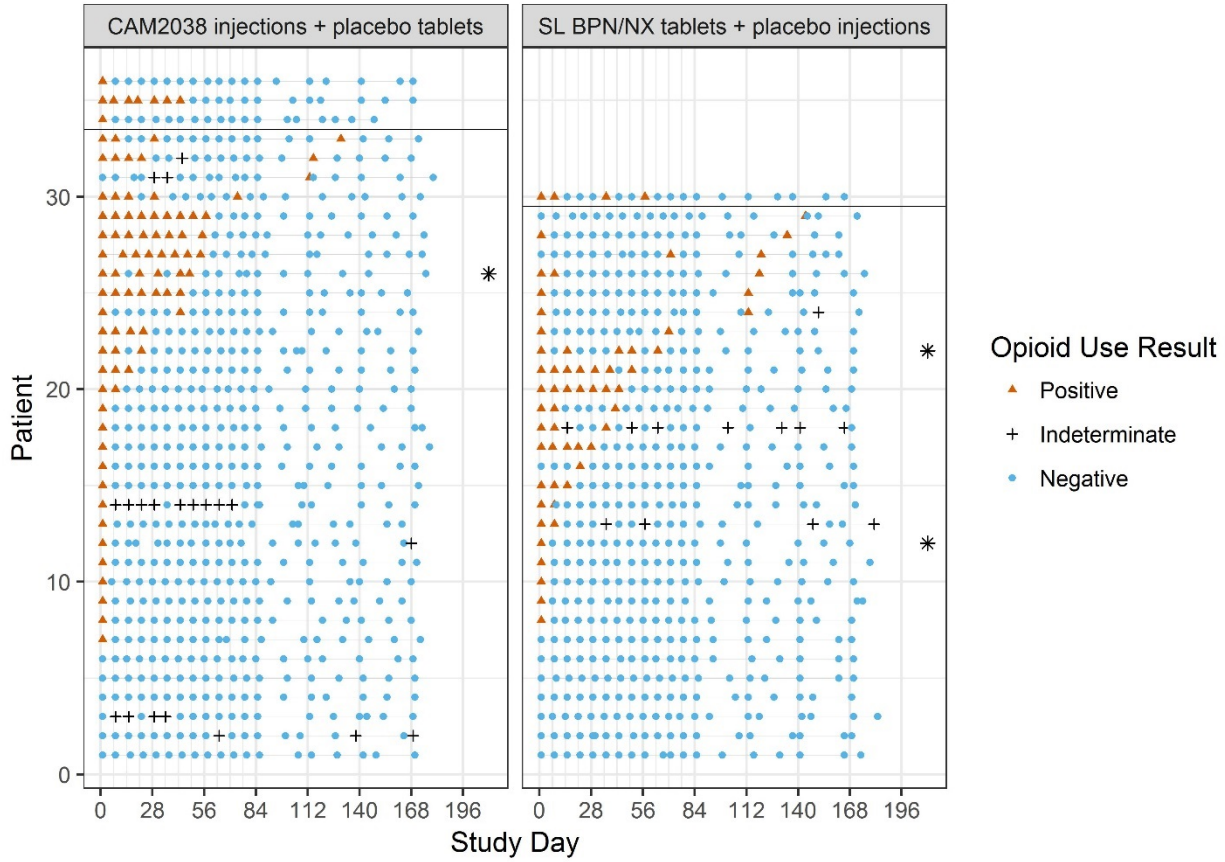
Source: Reviewer
Note: Patients with missed random tests are indicated by a star on the right-hand side of the plot.

Figure 3: Plot of the Urinalysis Results with Missing Counted as Positive and Indeterminate Results Indicated



Source: Reviewer
Note: Patients with missed random tests are indicated by a star on the right-hand side of the plot.

Figure 4: Plot of the Urinalysis results for Responders



Source: Reviewer
Note: Patients with missed random tests are indicated by a star on the right-hand side of the plot.

To explore the effects of the indeterminate opioid use assessments on the study conclusion we asked the applicant to perform a sensitivity analysis, where indeterminate opioid use assessments were imputed as positive. My reproduction of the results of this analysis are shown in Table 8. As expected, the responder rates in both treatment arms are slightly lower than seen in the primary analysis (Table 6); however, the lower bound of the 95% confidence interval for the difference is less than 10%, thus NI would still be concluded.

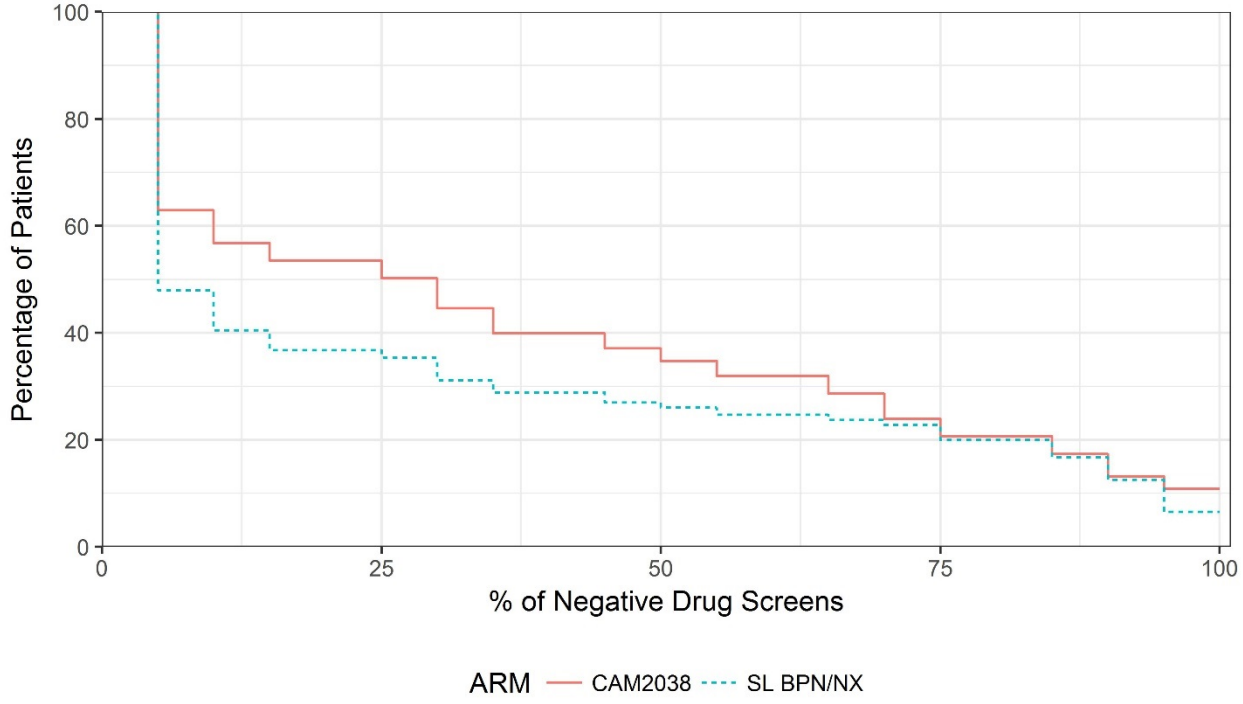
Table 8: Applicant's Sensitivity Analysis: Responder Rate (ITT Population)

Category	CAM2038 N=213	SL BPN/NX N=215	Proportion Difference (95% CI)
Responder, n (%)	33 (15.5%)	27 (12.6%)	2.9% (−3.6%, 9.5%)
Non-Responder, n (%)	180 (84.5%)	188 (87.4%)	

Source: Reviewer
Abbreviations: CI, Confidence interval; ITT, intent to treat; SL BPN/NX, sublingual buprenorphine/naloxone

The results of the applicant's analysis of the CDF are illustrated in Figure 5. The corresponding values plotted in the figure are shown in Table 9 and the applicant's statistical analysis of this endpoint is shown in Table 10. As you will see in Figure 5, a greater percentage of patients who received CAM2038 provided more negative urine samples and self-reported less use in Weeks 5 through 25 than patients who received sublingual buprenorphine plus naloxone. The applicant's analysis found that this difference is statistically significant in a Wilcoxon rank sum test (Table 10, $p = 0.004$). However, the statistical significance is driven by the disparity in the number of patients with less than 70% negative opioid use assessments. There is very little difference in the right-hand side of the curves where most or all the urine assessments were negative. The clinical significance of these differences is not known.

Figure 5: Cumulative Distribution Function (CDF) of Percentage of Negative Opioid Use Assessments over Weeks 5-25



Source: Reviewer

Table 9: Cumulative Distribution Function (CDF) of Percentage of Urine Samples Negative for Illicit Opioids Supported by Self-Reported Illicit Opioid Use over Weeks 5-25

% Self-Reports Negative for Illicit Opioid Use	Number (%) of Patients	
	CAM2038 N=213	SL BPN/NX N=215
≥ 0%	213 (100)	215 (100)
≥ 10%	121 (56.8)	87 (40.5)
≥ 20%	114 (53.5)	79 (36.7)
≥ 30%	95 (44.6)	67 (31.2)
≥ 40%	85 (39.9)	62 (28.8)
≥ 50%	74 (34.7)	56 (26)
≥ 60%	68 (31.9)	53 (24.7)
≥ 70%	51 (23.9)	49 (22.8)
≥ 80%	44 (20.7)	43 (20)
≥ 90%	28 (13.1)	27 (12.6)
≥ 100%	23 (10.8)	14 (6.5)

Source: Reviewer

Table 10: Analysis Results for CDF of Percentage of Urine Samples Negative for Illicit Opioids Supported by Self-Reported Illicit Opioid Use over Weeks 5-25

Statistic	CAM2038 N=213	SL BPN/NX N=215
Mean (SD)	35.1 (37.17)	26.7 (37.15)
Median	26.7	0
Min, Max	0.0 – 100.0	0.0 – 100.0
Wilcoxon Rank Sum Test P-value	0.004	

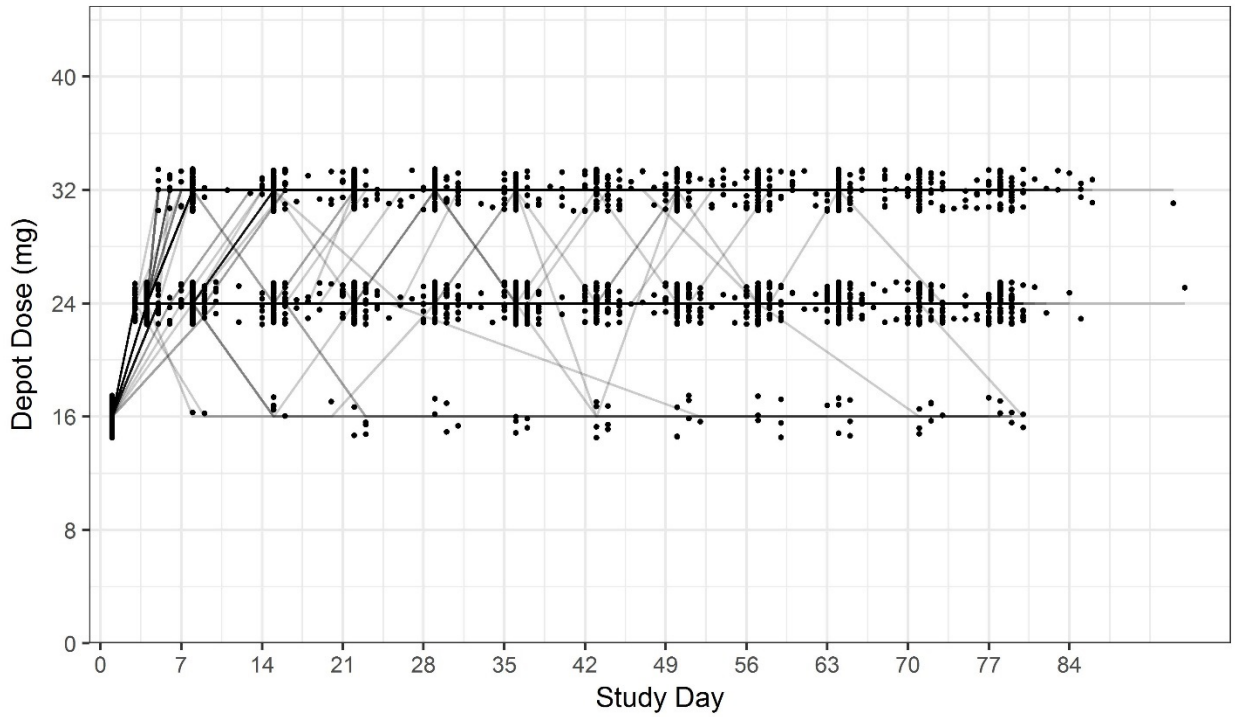
Source: Table 14, Applicant's Study Report
Abbreviations: CDF, cumulative distribution function; SD, standard deviation; SL BPN/NX, sublingual buprenorphine/naloxone.

The final discussion for this section will focus on the dose regimen used in the study. As described in Section 3.2.1, the study was designed pragmatically and attempted to mimic the expected clinical practice in this patient population. This meant that providers could adjust a patient's dose up or down depending on their needs, as is currently done in clinical practice with sublingual buprenorphine. Since patients were titrated to individualized doses and not randomized between doses, establishing a dose response effect is not possible. I will however provide graphical summaries of how CAM2038 was dosed in this study.

The dose of CAM2038 given to each patient during the study is shown in Figure 6 for Phase 1 (Months 1-3) and in Figure 7 for Phase 2 (Months 4-6). On the first day of the study, prior to randomization, patients were given a test dose of buprenorphine to make sure that they could tolerate it. If they had no issues, then they were randomized into treatment. According to the protocol, patients were then given a 16 mg injection of the weekly formulation. Patients were to return to the study site several times during the first week of the study. If the 16 mg dose was

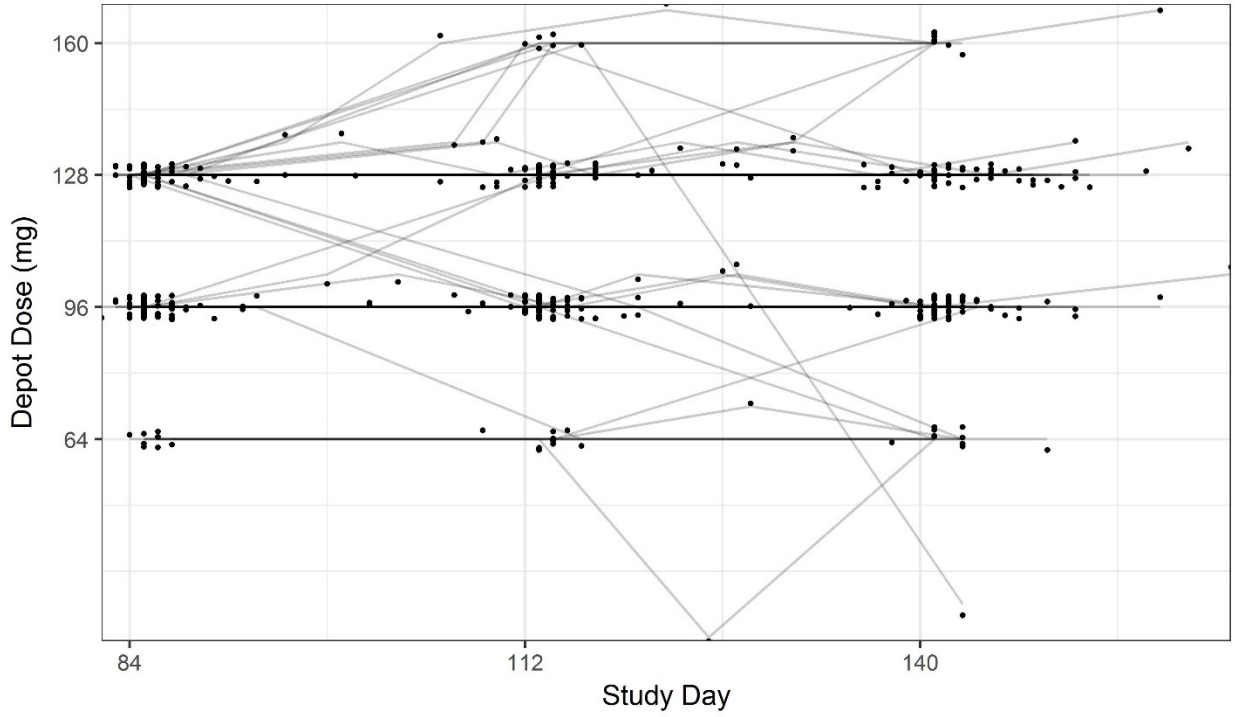
judged to be insufficient by the provider and the patient, then up to two 8 mg "booster" doses could be administered to the patient. These 8 mg doses were added to the patient's previous dose. On the first day of Week 2 patients received an individualized dose of either 16, 24, or 32 mg of the weekly formulation. This continued until the start of Phase 2 (Week 13) when patients were transitioned to the monthly formulation. The lowest three doses of the monthly formulation, 64, 96, and 128 mg, were designed to match the exposures of the three highest weekly formulation doses, 16, 24, and 32 mg, respectively. The 160 mg monthly dose was designed to provide higher exposure for patients for whom the other doses were determined to be insufficient. Some patients received additional 8 mg doses of the weekly formulation after the initial titration. Again, these were added to the patients' previous dose. The titration for the oral dose was managed in a similar fashion, but is not shown here.

Figure 6: CAM2038 Dose for Phase 1 (Months 1-3)



Source: Reviewer

Figure 7: CAM2038 Dose for Phase 2 (Months 4-6)



Source: Reviewer

The total number of patients exposed to each dose and formulation of study medication is shown in Table 11 and the total number of injections of each dose and formulation is shown in Table 12. As can be seen in Figure 6 and Figure 7, there was minimal long-term exposure to lowest doses, 8 and 16 mg weekly and 64 mg monthly, and to the 160 mg monthly dose. The 24 and 32 mg weekly doses, and the 96 and 128 mg monthly doses were the most commonly used doses in the study.

Table 11: Number of Patients Exposed to Each Dose and Formulation of CAM2038 and Placebo Injection

		Number of Patients Exposed	
Dose (mg)	Formulation	CAM2038	SL BPN/NX
8	Weekly	200	196
16	Weekly	213	215
24	Weekly	146	156
32	Weekly	84	89
64	Monthly	11	5
96	Monthly	89	84
128	Monthly	68	74
160	Monthly	9	9

Source: Reviewer

Table 12: Total number of Injections for Each Dose and Formulation of CAM2038

		Total Number of Injections	
Dose (mg)	Formulation	CAM2038	SL BPN/NX
8	Weekly	237	238
16	Weekly	279	265
24	Weekly	1050	1160
32	Weekly	720	708
64	Monthly	27	13
96	Monthly	223	227
128	Monthly	159	182
160	Monthly	14	15

Source: Reviewer

As discussed in Section 3.2.1 and seen above in Figure 6 and Figure 7 the applicant allowed as needed dose adjustments for patients in the study. Investigators also had the option of providing open-label "booster" injections which were 8 mg of the weekly formulation of CAM2038 for patients in the study who felt that their current dose was insufficient. Table 13 shows the total number of booster injections given starting with the Week 9 visits. Week 9 was chosen since it is the beginning of the period that the applicant used for determining their responder definition for the primary analysis.

Table 13 shows that fewer injections were provided for patients in the CAM2038 arm compared to the SL BPN/NX arm. Table 14 shows that fewer patients required injections in the CAM2038 arm.

Table 13: Number of Booster Injections Provided for each Treatment Arm

Treatment Arm	Number of Booster Injections
CAM2038	21
SL BPN/NX	29

Source: Reviewer

Table 14: Number of Patients Receiving Booster Injections by Treatment Arm

Treatment Arm	Number of Patients Who Used Booster Injections	N (%) of these Patients who were Responders
CAM2038	13	4 (30.8%)
SL BPN/NX	17	4 (23.5%)

Source: Reviewer

3.3 Evaluation of Safety

See the clinical review by Dr. Gioia Guerrieri for an evaluation of the safety of this product.

4 FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

4.1 Gender, Race, Age, and Geographic Region

The results of the applicant's analyses by demographic subgroup (sex, race, and age) are shown in Table 15. The study enrolled only two patients aged 65 and older and so analysis of efficacy by under 65, and 65 or over was not possible. Instead, the applicant used 36 years of age or younger and older than 36.

Table 15: Primary Analysis by Demographic Subgroup

Category	CAM2038 N=213	SL BPN/NX N=215	Proportion Difference (95% CI)
Sex			
Male	17/121 (14.0%)	18/142 (12.7%)	1.4% (-6.9%, 9.6%)
Female	19/92 (20.7%)	12/73 (16.4%)	4.2% (-7.6%, 16.1%)
Race			
White	31/159 (18.4%)	27/164 (16.5%)	3.0% (-5.3%, 11.4%)
Black or African American	3/47 (6.4%)	2/48 (4.2%)	2.2% (-6.8%, 11.2%)
American Indian or Alaska native	1/2 (50%)	1/1 (100%)	-50% (-119%, 19%)
Asian	1/1 (100%)	0/0 (NA)	NA
Other	1/3 (33.3%)	0/0 (NA)	NA
Age			
< 36 years old	19/99 (19.2%)	11/100 (11%)	8.2% (-1.7%, 18.1%)
≥ 36 years old	17/114 (14.9%)	19/115 (16.5%)	-1.6% (-11.0%, 7.8%)

Source: Applicant's Submission number 13.

For the analysis by sex, overall, females responded at a higher rate than males in the study in both treatment groups. For the analysis by race, patients who identified as black or African American responded at a much lower rate than patients who identified as white. One possible cause of this is a difference is the primary opioid of use at initiation. Ninety-five percent (95%) of patients who identified as black or African American reported heroin as their primary opioid at initiation compared to 64% for patients who identified as white.

4.2 Other Special/Subgroup Populations

In this section I will discuss the efficacy results based on history of opioid use. Results are shown in Table 16. Opioid use history was categorized by two different variables, primary

opioid of use at initiation, and route of illicit use. Primary opioid of use at initiation was used to divide the patients into two categories: primarily heroin user, and primarily prescription opioid pain reliever user. Route of administration was used to divide the patient population into two groups: those who had recently injected either intravenously or intramuscularly, and those who had not.

Table 16: Primary Analysis by Opioid Use History

Category	CAM2038 N=213	SL BPN/NX N=215	Proportion Difference (95% CI)
Primary opioid of use at initiation			
Heroin	22/152 (14.5%)	7/151 (4.6%)	9.8% (3.3%, 16.4%)
Prescription opioid pain reliever	14/61 (23.0%)	23/64 (35.9%)	-13.0% (-28.8%, 2.8%)
Route of illicit opioid			
Injection	17/113 (15.0%)	8/11 (7.2%)	7.8% (-0.3%, 16.0%)
Non-injection	19/100 (19.0%)	22/104 (21.2%)	-2.2% (-13.1%, 8.8%)

Source: Reviewer

Patients reported as primary heroin users who received SL BPN/NX had a lower response rate (4.6%) than seen overall (14.4%) while primary heroin users who received CAM2038 had a similar response rate (15.8%) to the overall CAM2038 response rate (17.8%). Patients who primarily used prescription opioid pain relievers had a higher response rate in both treatment groups compared to the overall rate. The same effect is seen for injection vs non-injection users in both treatment groups. While these results appear to be consistent with the expectation that patients with more severe opioid use disorder would be more likely to benefit from the enforced compliance of depot formulations, this analysis is post-hoc (b) (4) (b) (4)

5 SUMMARY AND CONCLUSIONS

5.1 Statistical Issues

As discussed in Section 3.1, there were multiple cases of uncorrected data entry errors that should have been detected and corrected in the applicant's audit of the data. These errors bring into question the overall quality and integrity of the datasets submitted in this application. Even though I do think there is evidence of efficacy, until the applicant has conducted a thorough audit of all data and identified and corrected all data errors, I cannot conclude that there is substantial evidence.

I was also concerned about the inability of this study design to reach any conclusions about the dose-response for efficacy. The efficacy study was designed to be pragmatic, and individually titrated the patients' doses in the study. While pragmatic designs are useful for providing easily

interpretable results and recommendations for clinical practice, this design did not allow for any reliable interpretation of the efficacy of the individual doses. Additionally, since only 9 patients received 14 injections of the 160 mg dose, which was designed to give higher than currently approved oral exposure, there is not sufficient safety information for this dose and because of the design of the study, additional benefit cannot be concluded and so I believe this dose should not be approved.

The 10% non-inferiority margin was discussed and agreed upon with the agency prior to initiation of the study. Retrospectively this margin does not appear to be justified, since the response rate for the sublingual buprenorphine treatment arm is only 14% and so the study would only rule out a response rate of less than 4%. If we assume a low response rate for placebo (0-5%) then the observed confidence interval would rule out a margin that corresponds to 50-66% of the assumed effect, and so I don't believe that this issue would affect the approvability of this product. We would however need to re-examine this once the we can verify that there are no outstanding data errors.

5.2 Conclusions and Recommendations

It is my conclusion that this application is not approvable at the current time. As discussed in Sections 3.1 and 5.1 there are many data quality issues that cast doubt on the accuracy of the submitted data. I recommend that the applicant conduct a thorough audit to ensure that the submitted data accurately portrays the actual conduct and outcomes of the study.

5.3 Labeling Recommendations

My labeling recommendations will be provided once I have verified that there are no data errors that will affect the conclusion of the study.

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

/s/

JAMES E TRAVIS
12/22/2017

DAVID M PETULLO
12/22/2017
I concur.