CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

210136Orig1s000

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

Office of Clinical Pharmacology Review

NDA: 210136	Submission Date: 07/04/2018
Link to EDR	\\cdsesub1\evsprod\NDA210136\0082
Relevant IND(s):	114082
Submission Type; Code:	505 (b) (2)
Drug	BRIXADI (CAM2038)
Generic Name:	Buprenorphine (BPN)
Reference Drugs:	Subutex Tablets (N 20732, held by Indivior Inc.)
Formulation; Strength(s):	Subcutaneous Injection Depot • q1w, 50 mg/mL BPN o 8 mg, 16 mg, 24 mg, and 32 mg • q4w, (b) (4) mg/mL BPN o 64 mg, 96 mg, 128 mg
Clinical Pharmacology Reviewer:	Suresh B Naraharisetti, Ph.D.
Clinical Pharmacology Team Leader:	Yun Xu, Ph.D.
Pharmacometrics Reviewer:	Michael Bewernitz, Ph.D.
Pharmacometrics Team Leader:	Kevin Krudys, Ph.D.
OCP Division:	Division of Clinical Pharmacology II
OND Division:	Division of Anesthesia and Analgesia Products
Sponsor:	Braeburn Pharmaceuticals, Inc.
Proposed Indication:	Treatments of opioid use disorder

1.0 Executive Summary

1.1 Recommendation

The Office of Clinical Pharmacology/Division of Clinical Pharmacology II (OCP/DCP-II) has reviewed the information submitted on 07/04/18 by the applicant (Response to FDA Request for Information: Clinical and Nonclinical) in the Sequence 0082 for NDA 210136. For this NDA, Agency issued a Complete Response (CR) Letter on 01/19/2018 indicating deficiencies from several disciplines. In the original NDA submission, there is no clinical pharmacology related deficiencies.

In this response to CR, the Applicant included clinical pharmacology related data to address deficiency # 8 (nonclinical), regarding the exposure margins for buprenorphine. From a clinical pharmacology perspective, the calculated mean ± SD of buprenorphine AUCss,24h for 32 mg q1w (149 ± 56 ng*h/mL) and 128 mg q4w (242 ±113 ng*h/mL) are acceptable. The nonclinical team will need to reassess the Applicant's proposed revisions to safety margins of this product. This review also discusses on the part of deficiency # 27 (Prescribing Information) regarding the

upper arm as injection site. On further evaluation and discussion with clinical team, the team has decided to allow upper arm as an injection site.

It is to note that out of the BRIXADI weekly and monthly formulations, only BRIXADI weekly formulation is being approved in this cycle.

Regulatory Background:
Braburn's NDA 210136, BRIXADI (buprenorphine extended-release subcutaneous injection depot, CAM2038) was given Complete Response (CR) on 01/19/2018. The clinical pharmacology review for the NDA is in DAARTS dated 12/21/2017.

Drug product:
CAM2038 is a modified-release formulation of buprenorphine (BPN) in a novel Fluid Crystal (FC) technology designed for administration by subcutaneous (not intramuscular) injection to be provided ready-for-use in a prefilled syringe for the treatment of moderate to severe opioid use disorder (OUD) in adults.
The proposed product is for Weekly and Monthly administration; the Weekly formulation is for initiating treatment in patients who have tolerated a test dose of a transmucosal buprenorphine-containing product; the Monthly formulation is for patients already in established treatment with another buprenorphine-containing product (including the Weekly formulation). The Weekly formulation doses are 8mg, 16 mg, 24 mg, and 32 mg, while the Monthly Weekly formulation doses are 64, 96, and 128 mg.
It is to note that out of the BRIXADI weekly and monthly formulations, only BRIXADI weekly formulation is being approved in this cycle.

In the CR letter, applicant was given deficiencies relating to several disciplines (for details, see CR letter dated 1/19/2018). This review specifically addresses deficiency # 8 (Nonclinical), regarding the exposure margins for buprenorphine. The review also comments on part of deficiency # 27 (Prescribing Information) regarding the upper arm as injection site.

Deficiency # 8, exposure margins for buprenorphine ($AUC_{ss,24h}$):
In the CR letter, to calculate the exposure margins for buprenorphine, the applicant was asked to provide the highest buprenorphine exposure in humans over any given 24-hour period at steady state ($AUC_{ss,24h}$) in humans. The following was the deficiency # 8 (Nonclinical) and the information needed to resolve deficiency.

- *You have not provided adequate pharmacokinetic data to appropriately calculate exposure margins for buprenorphine in your labeling. Although you have provided AUC0-24h data in animals, you have only provided human AUCss data. The exposure margins based on AUC in the labeling are to be based on the worst-case exposures in humans over the treatment period at steady state.*

Information needed to resolve deficiency

Provide mean partial AUC (24-hour interval) data in humans at steady state that represents the highest exposures over any given 24-hour period to inform labeling.

Applicant's response to Deficiency # 8:

For calculating the highest buprenorphine exposure in humans over any given 24-hour period at steady state ($AUC_{ss,24h}$), the applicant utilized Study HS-15-549. In this study, the steady state PK of highest CAM2038 q1w and q4w doses, 32 mg and, 128 mg, respectively after buttock injection was evaluated[1]. The details of the study are as follows:

The Study HS-15-549 was an open-label, partially randomized PK, efficacy and safety study in patients with OUD and a history of moderate to severe chronic non- cancer pain.

- Group 1 / q1w 32 mg: 7 weeks, 3 weekly doses in the buttock followed by 4 weekly doses in the buttock, abdomen, thigh and back of upper arm. The steady-state $AUC_{ss,24h}$ (partial AUC) after 4th weekly buttock injection was calculated.
- Group 2 / q4w 128 mg: 16 weeks - 4 monthly doses, buttock injection. The steady-state partial $AUC_{ss,24h}$ (partial AUC) after 4th monthly buttock injection was calculated.

The steady state $AUC_{ss,24h}$ (partial AUC) was calculated as AUC over a period of 12 hours before and after Tmax, or between 0 and 24 hours post administration if the Tmax was less than 12 hours.

- For subjects with Tmax <12h, the partial AUC_{0-24h} was calculated
- For subjects with Tmax >12h, the partial AUC 12h before and 12h after Tmax was calculated
  - 32 mg q1w: Out of n=21, 5 subjects had Tmax <12h; 16 subjects had Tmax >12h
  - 128 mg q4w: Out of n=16, 12 subjects had Tmax <12h; 4 subjects had Tmax >12 h

The mean ±SD of buprenorphine $AUC_{ss,24h}$ are:

- 149 ± 56 ng*h/mL (n=21) for CAM2038 q1w 32 mg
- 242 ±113 ng*h/mL (n=16) for CAM2038 q4w 128 mg

The individual $AUC_{ss,24h}$ values of q1w 32mg and q4w 128mg are presented in the Tables 1 and 2, respectively below (source: Applicant's submission):

[1] Note: We reanalyzed the Applicant's calculations on buprenorphine $AUC_{ss,24h}$ for the peak exposure of q1w 32 mg and q4w 128 mg. Our results match Applicant's calculations.

Table 1: Steady state individual PK data of 32mg q1w (source: Applicant's submission):

Group	Location	PT	Cmax (ng/mL)	Tmax (h)	AUC+-12h (ng*h/mL)	AUC0-24h (ng*h/mL)	AUC0-168h (ng*h/mL)	AUClast (ng*h/mL)	Cavg (ng/mL)
1	BUTTOCK	101-009	8.3	30	158	129	568	568	3.38
		101-011	6.75	24	155	130	814	814	4.85
		101-012	6.68	30	144	91.8	621	621	3.7
		101-013	4.98	24	111	95.8	504	504	3
		101-015	5.58	30	115	89.9	662	681	3.94
		101-019	7.05	24	164	147	791	790	4.71
		101-023	6.77	24	132	112	724	724	4.31
		101-024	5.1	24	103	85.7	479	479	2.85
		101-025	5.83	10	114	114	560	561	3.33
		101-026	14	24	257	199	1080	1080	6.44
		101-029	6.36	24	117	103	759	751	4.52
		101-035	10.1	10	216	216	925	921	5.51
		101-036	7.4	24	156	145	796	796	4.74
		101-039	5.19	30	115	81	591	600	3.52
		101-040	8.33	0	134	134	862	863	5.13
		101-042	7.01	72	153	99.1	732	735	4.36
		101-043	4.38	10	90	90	517	518	3.08
		102-002	5.04	30	112	88.1	600	603	3.57
		102-004	8.19	72	173	134	837	837	4.98
		102-005	3.95	24	91.6	84.5	497	497	2.96
		102-008	17.5	10	320	320	1300	1290	7.74
		N	**21**	**21**	**21**	**21**	**21**	**21**	**21**
		Mean	**7.36**	**26**	**149**	**128**	**725**	**725**	**4.31**
		SD	**3.21**	**17**	**56.2**	**57**	**207**	**205**	**1.23**
		Min	**3.95**	**0**	**90**	**81**	**479**	**479**	**2.85**
		Median	**6.75**	**24**	**134**	**112**	**724**	**724**	**4.31**
		Max	**17.5**	**72**	**320**	**320**	**1300**	**1290**	**7.74**
		CV%	**43.6**	**66.4**	**37.7**	**44.5**	**28.5**	**28.2**	**28.5**
		Geometric Mean	**6.87**		**141**	**120**	**700**	**701**	**4.17**
		CV% Geometric Mean	**37.2**		**33.1**	**36.6**	**27.1**	**26.9**	**27.1**

Table 2: Steady state individual PK data of 128mg q4w (source: Applicant's submission):

Group	PT	EXLOC	Cmax (ng/mL)	Tmax (h)	AUC+-12h (ng*h/mL)	AUC0-24h (ng*h/mL)	AUC0-672h (ng*h/mL)	AUClast (ng*h/mL)	Cavg (ng/mL)	Fluctuation%
2	101-001	LEFT BUTTOCK S	12.8	6	251	251	3600	3600	5.36	171
	101-007	LEFT BUTTOCK S	26.2	10	465	465	3580	3580	5.33	453
	101-008	LEFT BUTTOCK S	23.5	10	429	429	4380	4380	6.51	321
	101-010	LEFT BUTTOCK S	12.4	1	212	212	3640	3640	5.41	164
	101-014	LEFT BUTTOCK S	19.2	2	315	315	4740	4740	7.05	213
	101-021	LEFT BUTTOCK S	4.78	24	105	96.4	1250	1250	1.86	195
	101-022	LEFT BUTTOCK S	7.89	24	173	135	2220	2220	3.31	201
	101-030	LEFT BUTTOCK S	21.2	10	441	441	4660	4660	6.93	258
	101-031	LEFT BUTTOCK S	10.1	10	210	210	2520	2530	3.76	223
	101-033	LEFT BUTTOCK S	4.98	48	116	106	2140	2150	3.19	77.4
	101-034	LEFT BUTTOCK S	12.6	24	245	180	2330	2340	3.47	331
	101-037	LEFT BUTTOCK S	8.25	10	164	164	2420	2420	3.59	172
	102-003	LEFT BUTTOCK V	7.99	6	184	184	1550	1550	2.31	309
	102-007	RIGHT BUTTOCK Y	9.3	10	175	175	1840	1840	2.74	276
	102-012	RIGHT BUTTOCK Z	10.1	10	220	220	1960	1970	2.92	301
	102-017	RIGHT BUTTOCK Y	8.51	10	161	161	2220	2220	3.3	207
		N	**16**	**16**	**16**	**16**	**16**	**16**	**16**	**16**
		Mean	**12.5**	**13.4**	**242**	**234**	**2820**	**2820**	**4.19**	**242**
		SD	**6.55**	**11.6**	**113**	**117**	**1120**	**1120**	**1.66**	**88.4**
		Min	**4.78**	**1**	**105**	**96.4**	**1250**	**1250**	**1.86**	**77.4**
		Median	**10.1**	**10**	**211**	**197**	**2370**	**2380**	**3.53**	**218**
		Max	**26.2**	**48**	**465**	**465**	**4740**	**4740**	**7.05**	**453**
		CV%	**52.4**	**86.4**	**46.8**	**50.1**	**39.7**	**39.7**	**39.7**	**36.5**
		Geometric Mean	**11.1**	**9.55**	**220**	**210**	**2610**	**2620**	**3.89**	**226**
		V% Geometric Mea	**54.1**	**118.4**	**46.4**	**50.2**	**41.7**	**41.6**	**41.7**	**42**

Reviewer comments on Applicant's response to Deficiency # 8:

- *For calculating the exposure margins for buprenorphine, the calculated mean ± SD of buprenorphine $AUC_{ss,24h}$ for 32 mg q1w (149 ± 56 ng*h/mL) and 128 mg q4w (242 ±113 ng*h/mL) are acceptable.*
- *Applicant mentioned that, "the safety margins have been revised to reflect the revised clinical AUCss,24h values for the 32 mg CAM2038 q1w and 128 mg CAM2038 q4w products, these margins are presented in Table 2.6.6.9.1.1-2 and Table 2.6.6.9.1.1-3, Module 2.6.6 Toxicology Written Summary". The nonclinical team may need to reassess the Applicant's proposed revisions to safety margins of this product.*

Part of Deficiency # 27 (Prescribing Information), regarding the 'upper arm as injection site':

In the CR letter, as a part of deficiency # 27 (Prescribing Information), the following comment was communicated.

- *The recommended injection sites should be limited to the abdomen, buttock, and thigh because the arm site did not yield BE results.*

Applicant's Response to upper arm as injection site in the Resubmission:

> *"Please note that for the injection sites, Braeburn has put forward a justification based on efficacy and safety data to retain the arm as an injection site. The justification is included in Module 2.5, 2.7.3, and 2.7.4 and the overall conclusions are provided below for ease of review.*
>
> *Administration of 32 mg CAM2038 q1w into 4 different potential injection sites, including buttock, abdomen, upper arm, or thigh was evaluated through review of PK (Module 2.7.2), efficacy (Module 2.7.3) and safety data (Module 2.7.4) obtained during the clinical development of CAM2038. Most of the PK parameters measured for each injection site demonstrated similar values, except for AUC values, where the arm location was associated with lower exposures compared to the other 3 injection sites (HS-15-549). However, post hoc analyses were also conducted to evaluate efficacy and safety after administration in different injection sites in the pivotal Phase 3 study HS-11-421, which utilized the 4 injection locations, and demonstrated comparable results for injections into different SC administration sites. The efficacy analysis included reviewing urine toxicology data corresponding to each of the 4 locations of injection, showing that injections of CAM2038 q1w and CAM2038 q4w into the upper arm was associated with similar mean urine toxicology and self-reported illicit opioid use results as injections into the other SC injection sites (Module 2.7.3, Section 2.4.4.5). The same conclusion was drawn when comparing safety data after injections into the different SC locations (Module 2.7.4, Table 26).*
>
> *Additionally, to support the proposed injection site rotation recommendations the following rationale is provided:*
> *Support for local tolerability and rotation of sites every 4 (q4w) to 8 weeks (q1w) was provided by nonclinical data (Module 2.4), demonstrating that sites of injection for CAM2038 q1w should be rotated and repeated injection into the same site should be avoided for at least 8 weeks, while for CAM2038 q4w, the nonclinical data suggest that rotation is not needed and the same injection site can be used for each monthly dose".*

In NDA, in Study HS-15-549, the applicant evaluated effect of injection site on the PK of buprenorphine, in which systemic exposure for CAM2038 injection from thigh, abdomen or upper arm was compared to the buttock site (reference). Based on the study results, the upper

arm site showed lower buprenorphine trough levels compared to the other site and buttock (reference). The trough levels of upper arm site failed the bioequivalence criteria for the lower end compared to buttock site. As noted in clinical pharmacology review, "although Cmax and AUC between different injection sites are important for CAM2038, the trough levels are considered more important for the efficacy of this product". Hence, we recommended not to use upper arm as an injection site.

The PK parameters, bioequivalence assessment tables and PK profiles figure from clinical pharmacology review are shown below:

Table 1.3.6a: Injection site effect: PK parameters of buprenorphine after repeated weekly SC 32 mg CAM2038 q1w, in the buttock, abdomen, thigh and upper arm in study HS-15-549.

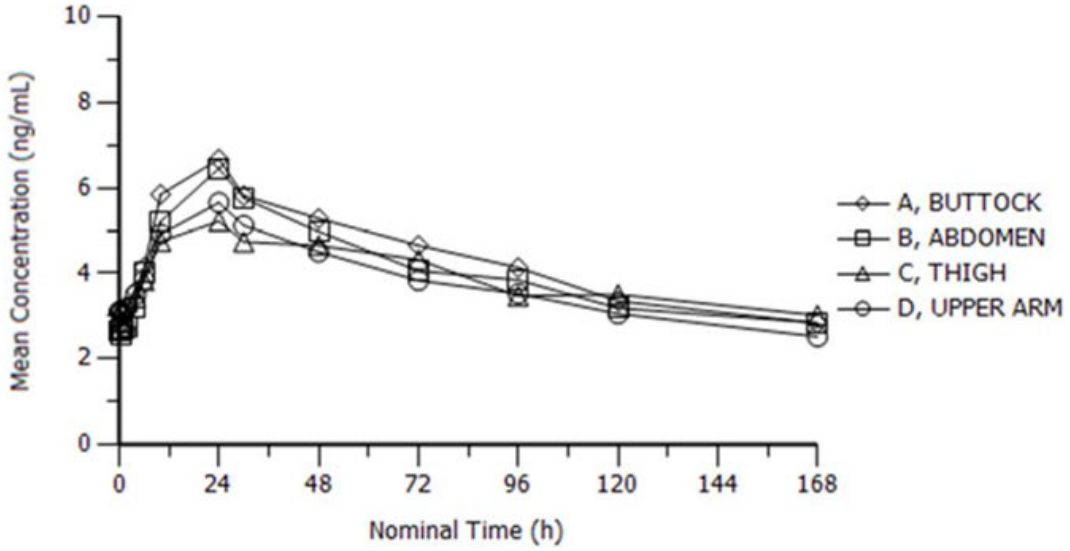
Product Dose	Dose No.	Injection site	Parameter [geometric mean (CV%)]				
			Css,max (ng/mL)	Tss,max[a] (h)	Css,trough[b] (ng/mL)	AUCss [c] (ng*h/mL)	Css,av (ng/mL)
CAM2038 q1w 32 mg	4-7[d] (n=21)	Buttock	6.87 (37)	24.0 (0-72)	2.63 (39)	700 (27)	4.17 (27)
	4-7[d] (n=21)	Abdomen	6.56 (30)	24.0 (0-168)	2.68 (36)	657 (27)	3.91 (27)
	4-7[d] (n=21)	Thigh	5.37 (44)	24.0 (10-120)	2.70 (48)	613 (37)	3.65 (37)
	4-7[d] (n=21)	Upper arm	5.69 (43)	24.0 (4-48)	2.37 (37)	591 (34)	3.52 (34)

Median (min-max); [b]C168h; [c]AUC between 0 and 168 hours for CAM2038 q1w; AUCss: AUC over the dosing interval at steady-state; Css,av: average concentration during the dosing interval at steady-state; Css,max: maximum observed plasma concentration at steady-state; Css,trough: observed concentration before the next actual or intended dose at steady- state; CV%: coefficient of variation percentage; Tss,max: time corresponding to occurrence of Css,max

Table 1.3.6b: The bioequivalence assessment between different injection sites using buttocks as a reference.

Site	Geometric mean ratio and 90% CI (lower, upper)			
	Css,max	AUCss	AUClast	Ctrough
Abdomen Vs. Buttock	96 (82, 112)	94 (84, 104)	94 (84, 104)	102 (88, 117)
Thigh Vs. Buttock	79 (68, 92)	88 (79, 97)	87 (79, 97)	103 (89, 118)
Upper Arm Vs. Buttock	83 (71, 97)	85 (77, 95)	85 (76, 95)	90 (78, 104)

Figure 2.4.2b: Plasma concentration-time profiles of buprenorphine after SC injection of 4th to 7th dose of 32 mg CAM2038 q1w in the buttock, abdomen, thigh and upper arm in study HS-15-549



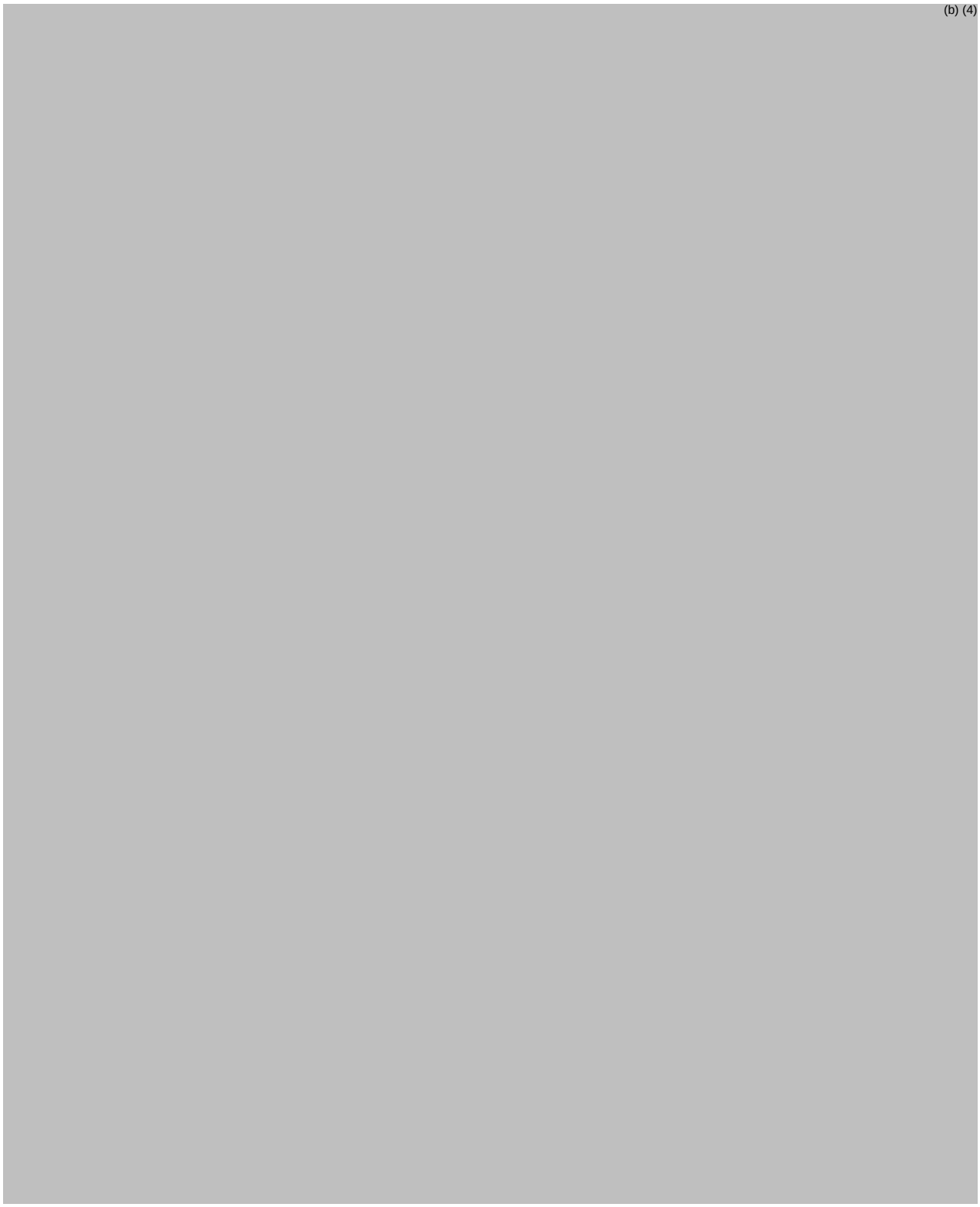
Reviewer comments on Applicant's response to Part of Deficiency # 27 (Prescribing Information):

- *For the applicant's proposal to accept upper arm as injection site, no new PK data was provided in this resubmission (other than PK results of injection-site effect study HS-15-549 conducted in the NDA). To utilize the upper arm as injection site for their product, the applicant conducted post hoc analyses on efficacy and safety data from Phase 3 Study 11-421. However, the post hoc analyses may not be adequate, because in Study 11-421, all injections sites were rotated and the data from one injection site may be confounded by injection from other sites.*
- *On further evaluation and discussion with clinical team, it was decided that although the steady trough levels from upper arm site (2.37 ng/mL) failed marginally (for 90% CI of bioequivalence limits at lower-end) compared to the buttock site (2. 63 ng/mL), these levels are higher when compared to the steady state trough levels of currently indicated SL buprenorphine 24 mg dose (1.24 to 1.61 ng/mL) by cross-study comparison. Based on this, clinical pharmacology team finds it acceptable to allow upper arm as an injection site, unless clinical or statistical review has identified issues with the upper site based on the Phase 3 trails. The clinical team agreed to allow upper arm as an injection site.*

Labeling:

The labeling changes pertaining to DDI, hepatic and renal impairment and pharmacokinetics were included in the first cycle clinical pharmacology review dated 12/21/2017. Since out of BRIXADI weekly and monthly formulations, only BRIXADI weekly is being approved in this

cycle, the modified labeling reflecting only BRIXADI weekly pharmacokinetics (section 12.3) was included the labeling and is shown below.



Overall Comments to the Review Team:

- *For calculating the exposure margins for buprenorphine, the calculated mean ± SD of buprenorphine $AUC_{ss,24h}$ for 32 mg q1w (149 ± 56 ng*h/mL) and 128 mg q4w (242 ±113 ng*h/mL) are acceptable**.** The nonclinical team may need to reassess the Applicant's proposed revisions to safety margins of this product.*
- *For the applicant's proposal to accept upper arm as injection site, no new PK data was provided in this resubmission (other than PK results of injection-site effect study HS-15-549 conducted in the NDA). To utilize the upper arm as injection site for their product, the applicant conducted post hoc analyses on efficacy and safety data from Phase 3 Study 11-421. This post hoc analyses may not be adequate, because in Study 11-421, all injections sites were rotated and the data from one injection site may be confounded by injection from other sites. On further evaluation and discussion with clinical team, it was decided that although the steady trough levels from upper arm site (2.37 ng/mL) failed marginally (for 90% CI of bioequivalence limits at lower-end) compared to the buttock site (2. 63 ng/mL), these levels are higher when compared to the steady state trough levels of currently indicated SL buprenorphine 24 mg dose (1.24 to 1.61 ng/mL) by cross-study comparison. Based on this, clinical pharmacology team finds it acceptable to allow upper arm as an injection site, unless clinical or statistical review has identified issues with the upper site based on the Phase 3 trails. The clinical team agreed to allow upper arm as an injection site.*

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/s/

SURESH B NARAHARISETTI
11/27/2018

YUN XU
11/27/2018

Office of Clinical Pharmacology Review

NDA: 210136	Submission Date: 05/08/2017
Link to EDR	\\cdsesub1\evsprod\nda210136
Relevant IND(s):	114082
Submission Type; Code:	505 (b) (2)
Drug	CAM2038
Generic Name:	Buprenorphine (BPN)
Reference Drugs:	Subutex Tablets (N 20732, held by Indivior Inc.)
Formulation; Strength(s):	Subcutaneous Injection Depot • q1w, 50 mg/mL BPN o 8 mg, 16 mg, 24 mg, and 32 mg • q4w, (b) (4) mg/mL BPN o 64 mg, 96 mg, 128 mg
Clinical Pharmacology Reviewer:	Suresh B Naraharisetti, Ph.D.
Clinical Pharmacology Team Leader:	Yun Xu, Ph.D.
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OND Division:	Division of Anesthesia and Analgesia Products
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1.0 Executive Summary

1.1 Recommendation

The Office of Clinical Pharmacology/Division of Clinical Pharmacology II (OCP/DCP-II) has reviewed the information submitted in the current application, NDA 210136, for CAM2038, weekly and monthly subcutaneous depot formulations of buprenorphine, submitted on 05/08/17. From a clinical pharmacology perspective, the information submitted in the NDA is acceptable. No further communication is necessary with the Applicant at this point. As of December 21, 2017, labeling negotiation is still ongoing with the Applicant.

1.2 Phase 4 Commitments

None

1.3 Summary of Clinical Pharmacology Findings

Braeburn Pharmaceuticals, Inc. submitted NDA 210136 for buprenorphine (BPN) subcutaneous injection depot, CAM2038, under section 505 (b) (2) of the Federal Food Drug and Cosmetic Act. The proposed indication is the treatment of opioid use disorder (OUD). The referenced drug for CAM2038 for relying on the Agency's previous findings of safety and efficacy is sublingual (SL) BPN tablets, Subutex (N 20732), held by Indivior Inc.

CAM2038 is a modified-release formulation of buprenorphine (BPN) in a novel Fluid Crystal (FC) technology designed for administration by subcutaneous (not intramuscular) injection to be provided ready-for-use in a prefilled syringe for the treatment of moderate to severe opioid use disorder (OUD) in adults. Per Applicant, this delivery technology results in a liquid-to-gel phase transition that occurs when the lipid-based FC system is exposed to the subcutaneous (SC) tissue. The phase transition from liquid to gel proceeds from the periphery of the FC injectable towards the center of the product by absorption of minute quantities of water. The injection of CAM2038 into SC tissue results in an immediate and spontaneous formation of a matrix providing release over the designated period in vivo. This product is available in weekly (CAM2038 q1w) and monthly (CAM2038 q4w) formulations, each of which contains different doses and excipients (Table 1.3a). The Applicant is also seeking approval for CAM2038 (b) (4) (b) (4)

Table 1.3a: Dosing and volume of injection of CAM2038

BPN Fluid Crystal SC injection depot			
CAM2038 Weekly (50 mg/mL)		CAM2038 Monthly ((b) (4) mg/mL)	
Dose (mg)	Volume of injection (mL)	Dose (mg)	Volume of injection (mL)
8	0.16	64	0.18
16	0.32	96	0.27
24	0.48	128	0.36
32	0.64	(b) (4)	
Weekly injection product contents		**Monthly injection product contents**	
BPN, soybean phosphatidylcholine, glycerol dioleate, ethanol		BPN, soybean phosphatidylcholine, glycerol dioleate, N-methyl-2-pyrrolidone	

Dosing Regimen:

The applicant proposed the following transitions (Table 1.3b) for patients who are on daily doses of SL BPN to initial weekly doses of CAM2038 q1w or monthly doses of CAM2038 q4w.

Table 1.3b: Proposed transfer from daily doses of SL BPN to initial weekly or monthly doses of CAM2038 q1w or CAM2038 q4w

Dose of daily SL BPN	**Dose of weekly CAM2038 q1w**
2-6 mg	8 mg
8-10 mg	16 mg
12-16 mg	24 mg
18-24 mg	32 mg
Dose of daily SL BPN	**Dose of monthly CAM2038 q4w**
8-10 mg	64 mg
12-16 mg	96 mg
18-24 mg	128 mg
(b) (4)	

The Applicant is also seeking approval for CAM2038 (b) (4) (b) (4)

[*Reviewer comment: The maximum dose level to be approved for the CAM2038 monthly formulation is 128 mg.*]

Conducted Clinical Pharmacology and Clinical Studies:

Clinical Pharmacology Studies:

The BPN PK following SC injection of CAM2038 has been investigated in 5 clinical studies, whereof 2 studies were conducted in healthy volunteers under naltrexone (NTX) blockage and 3 studies were conducted in patients with opioid dependence as described in Table 1.3c.

Table 1.3c: Overview clinical pharmacology studies of CAM2038 q1w and CAM2038 q4w

Study	**Study Description**	**Population (No. of subjects)**	**q1w (SC)**	**q4w (SC)**
HS-11-426	Open-label, RDZ, PK, BA, and safety study assessing 3 different SC doses of q1w versus IV and SL	Healthy, N=56	- 8 mg (single dose) - 16 mg (single dose) - 32 mg (single dose)	NA
HS-13-487	RDZ, open-label, single- and repeated-dose PK, BA, and safety study with q1w and q4w versus IV and SL BPN	Healthy, N=79	- 16 mg (4 repeated doses)	- 64 mg (single dose) - 96 mg (single dose) - 128 mg (single dose) - 192 mg (single dose)
HS-07-307[$]	Single-dose, dose-escalation PK, PD and safety study investigating 4 different doses of q1w	Patients with OUD, N=41	- 7.5 mg (single dose) - 15 mg (single dose) - 22.5 mg (single dose) - 30 mg (single dose)	NA
HS-15-549	Open-label, partially RDZ PK, efficacy and safety study	Patients with OUD and a history of moderate to severe chronic non- cancer pain, N=65	- 32 mg (7 repeated doses) whereof 3 weekly doses in the buttock followed by 4 weekly doses in the buttock, abdomen, thigh, and back of upper arm. Also, open-label safety extension including 6 additional weekly SC injections of 32 mg q1w in the buttock.	- 128 mg (4 repeated doses in the buttock) - 160 mg (4 repeated doses in the buttock)
HS-13-478*	RDZ, double-blind, repeated-dose, PK, efficacy and safety study	Patients with OUD, N=47	- 24 mg (2 repeated doses) - 32 mg (2 repeated doses)	NA

[$] In study HS-07-307, the dose used for CAM2038 q1w (7.5 mg, 15 mg, 22.5 mg and 30 mg) were not intended clinical dose of CAM2038 q1w. Hence this study was not reviewed.
* The reader is referred to the Control Substance Staff (CSS) review by Dr. Alan Trachtenberg and the Control Substance Staff (CSS) review by Dr. Wei Lui for additional details regarding the blockade study HS-13-478.

Clinical Studies:
The efficacy of CAM2038 versus active control was evaluated in one pivotal Phase 3 trial HS-11-421 and safety was evaluated in one long-term safety trial HS-14-499. The details are as follows:

- HS-11-421: Phase 3, double-blind, double-dummy, active-controlled, parallel-group multicenter study, designed to evaluate CAM2038 compared to an existing standard of care (SL BPN/NX) in initiation and maintenance treatment of patients with OUD.
- HS-14-499: Open-label multicenter, 12-month (48-week) safety study of CAM2038 once weekly (q1w) and once-monthly (q4w) in adult patients with OUD

1.3.1 Comparative bioavailability:

Sponsor has utilized population PK for deriving the PK parameters of CAM2038 q1w, CAM2038 q4w, and SL Subutex. Since observed PK data are available from clinical pharmacology studies for most of the doses of these products (especially for highest doses), observed data were used for comparison of PK parameters between CAM2038 and SL Subutex.

1.3.2 Steady-state exposure comparison for CAM2038 q1w, CAM2038 q4w, and SL Subutex

Since CAM2038 is a multiple dose product, the comparative bioavailability of CAM2038 q1w and CAM2038 q4w versus Subutex was evaluated using steady-state (ss) PK parameters, AUCss and Cmax-ss across studies (HS-11-426, HS-13-487, and HS-15-549) (Table 1.3.2a). In these studies, CAM2038 q1w was administered for 4 or 4 to 7 weekly doses, CAM2038 q4w was administered for 4 monthly doses, and Subutex was administered for 7 daily doses. Since these products have different dosing intervals, the AUCss was represented by the derived parameter from AUCss, the average concentrations (Cav, ss = AUCss,τ /dosing interval,τ). The following comparisons are made:

- Compared to the clinical dose of Subutex 24 mg, the highest dose CAM2038 q1w, 32 mg showed 12-19% lower steady- state Cmax (range based on two studies) and 57-78% higher steady-state Cav.
- Compared to the clinical dose of Subutex 24 mg, the highest dose of CAM2038 q4w, 160 mg showed 82-98% higher steady-state Cmax and 98-125% higher steady-state Cav.

Overall, the highest (b) (4) doses of CAM2038, 32 mg q1w or 160 mg q4w showed higher exposure (AUCss, represented by Cav) and CAM2038 128 and 160 mg q4w showed higher Cmaxss, compared to the clinical dose of Subutex at 24 mg.

Table 1.3.2a: Summary of steady-state PK parameters of buprenorphine after SC buttock injections of CAM2038 q1w and CAM2038 q4w and SL administration of Subutex (studies HS-11-426, HS-13-487, and HS-15-549)

Product	Dose (mg) (Study)	Dose No.	Population	Cmax,ss (ng/mL)	Tmax[a] (h)	Ctrough[b] (ng/mL)	AUCτ (ng*h/mL)	Cav,ss (ng/mL)
q1w	16 (HS-13-487)	4	HV (n=15)	4.30 (44)	23.2	0.842 (22)	350 (24)	2.09 (24)
	32 (HS-15-549)	4-7	Patient (n=21)	6.87 (37)	24.0	2.63 (39)	700 (27)	4.17 (27)
q4w	128 (HS-15-549)	4	Patient (n=16)	11.1 (54)	10.0	2.09 (55)	2610 (42)	3.89 (42)
	160 (HS-15-549)	4	Patient (n=12)	15.4 (52)	24.0	2.66 (61)	3540 (26)	5.27 (26)
SL BPN	24 (HS-11-426)	7	HV (n=16)	7.78 (37)	1.01	1.24 (44)	56.3 (29)	2.34 (29)
	24 (HS-13-487)	7	HV (n=16)	8.45 (54)	1.04	1.61 (40)	63.9 (34)	2.66 (34)

Values are geometric mean (geometric CV%); [a] Median; [b] C168h for CAM2038 q1w, C28d for CAM2038 q4w and C24h for Subutex; AUCinf: AUC extrapolated to infinity; AUCτ: AUC over the dosing interval; Cav: average concentration during the dosing interval; Cmax: maximum observed plasma concentration; Ctrough: observed concentration before the next actual or intended dose; CV%: coefficient of variation percentage; HV: healthy volunteer; t½: half-life; T_{max}: time corresponding to occurrence of C_{max}

1.3.3 Comparison of steady-state Cav, Cmax, and Ctrough for CAM2038 q1w, CAM2038 q4w, and Subutex during the proposed transition

The proposed transitions from daily doses of SL buprenorphine to initial weekly doses of CAM2038 q1w or monthly doses of CAM2038 q4w are shown in 1.3b above. As per that table, the cross-study comparison of steady-state C_{av}, $C_{max,}$ and C_{trough} between CAM2038 q1w, CAM2038 q4w and Subutex using observed data from studies HS-11-426, HS-13-487 and HS-15-549 were shown in 1.3.3a, 1.3.3b, and 1.3.3c, respectively. For doses that were not evaluated in the conducted PK studies (24 mg CAM2038 q1w and 64 and 96 mg CAM2038 q4w), the steady-state C_{av}, $C_{max,}$ and C_{trough} simulated by Applicant were utilized (source, Table 10, SDN 8, EOP2 meeting package).

Table 1.3.3a: Comparison of steady-state Cav between CAM2038 q1w, CAM2038 q4w and SL Subutex (studies HS-11-426, HS-13-487 and HS-15-549)

SL BPN QD dose	q1w weekly dose	q4w monthly dose	Cav (ng/mL)			q1w / SL ratio	q4w / SL ratio	q4w / q1w ratio
			SL BPN	q1w	q4w			
8 mg	16 mg	64 mg	1.13 (HS-11-426) 1.24 (HS-13-487)	2.1 (HS-13-487)	2.0 [a]	1.69 to 1.85	1.61 to 1.77	0.95
16 mg	24 mg	96 mg	1.60 (HS-11-426) 1.90 (HS-13-487)	2.9 [a]	2.9 [a]	1.53 to 1.81	1.53 to 1.81	1.0
24 mg	32 mg	128 mg	2.34 (HS-11-426) 2.66 (HS-13-487)	4.2 (HS-15-549)	3.9 (HS-15-549)	1.57 to 1.78	1.46 to 1.66	0.93
32 mg	NA	160 mg	Not studied	NA	5.3 (HS-15-549)	NA	NC	NC

Values are geometric mean; [a] Simulated; Cav: average concentration during the dosing interval; NA: not applicable; NC: not calculated; BPN: buprenorphine

Table 1.3.3b: Comparison of steady-state Cmax between CAM2038 q1w, CAM2038 q4w and SL Subutex (studies HS-11-426, HS-13-487 and HS-15-549)

SL BPN QD dose	q1w weekly dose	q4w monthly dose	Steady-state Cmax (ng/mL)			q1w/ SL ratio	q4w/ SL ratio	q4w/ q1w ratio
			SL BPN	q1w	q4w			
8 mg	16 mg	64 mg	4.7 (HS-11-426) 4.7 (HS-13-487)	4.3 (HS-13-487)	4.0 [a]	0.91	0.85	0.93
16 mg	24 mg	96 mg	6.3 (HS-11-426) 6.7 (HS-13-487)	5.5 [a]	6.0 [a]	0.82 to 0.87	0.9 to 0.95	1.09
24 mg	32 mg	128 mg	7.8 (HS-11-426) 8.5 (HS-13-487)	6.9 (HS-15-549)	11.1 (HS-15-549)	0.81 to 0.88	1.31 to 1.42	1.61
32 mg	NA	160 mg	Not studied	NA	15.4 (HS-15-549)	NA	NC	NC

Values are geometric mean; [a] Simulated; Cmax: maximum observed plasma concentration; NA: not applicable; NC: not calculated; BPN: buprenorphine

Table 1.3.3c: Comparison of steady-state Ctrough between CAM2038 q1w, CAM2038 q4w and SL Subutex (studies HS-11-426, HS-13-487 and HS-15-549)

SL BPN QD dose	q1w weekly dose	q4w monthly dose	Steady-state Ctrough [b] (ng/mL)			q1w/ SL ratio	q4w/ SL ratio	q4w/ q1w ratio
			SL BPN	q1w	q4w			
8 mg	16 mg	64 mg	0.61 (HS-11-426) 0.68 (HS-13-487)	0.84 (HS-13-487)	1.3 [a]	1.24 to 1.38	1.91 to 2.13	1.55
16 mg	24 mg	96 mg	0.79 (HS-11-426) 1.10 (HS-13-487)	1.40 [a]	2.0 [a]	1.27 to 1.77	1.82 to 2.53	1.43
24 mg	32 mg	128 mg	1.24 (HS-11-426) 1.61 (HS-13-487)	2.63 (HS-15-549)	2.1 (HS-15-549)	1.63 to 2.12	1.30 to 1.69	0.80
32 mg	NA	160 mg	Not studied	NA	2.7 (HS-15-549)	NA	NC	NC

Values are geometric mean; [a] Simulated; [b] C_{168h} for CAM2038 q1w, C_{28d} for CAM2038 q4w and C_{24h} for Subutex; NA: not applicable; NC: not calculated; BPN: buprenorphine

1.3.4 Accumulation after repeated doses

Within-study comparison:

The comparative bioavailability of single versus four repeat doses of CAM2038 was evaluated for q1w 16 mg in healthy volunteers in study HS-13-487. The same subjects were administered single dose versus four repeat doses; hence the study compares 'within-study' PK. After four repeated doses of 16 mg CAM2038 q1w, ~40% higher exposure was observed compared to the first dose, as noted by AUC0-7d, Cmax, and Ctrough (Study HS-13-487, Table 1.3.4a). Steady-state was achieved at the 4th dose based on a comparison of Ctrough concentrations after each dose. The PK profiles are shown in section 2.4.3.

Table 1.3.4a: Summary of PK parameters of buprenorphine after single versus four repeat doses of 16 mg CAM2038 q1w (study HS-13-487)

Product	Dose (mg) (Study)	Dose No.	Population	Cmax (ng/mL)	Tmax [a] (h)	Ctrough [b] (ng/mL)	AUCτ (0-7d) (ng*h/mL)	Rac (AUCτ)
q1w	16 (HS-13-487)	1	HV (n=15)	3.05 (46)	23.6	0.580 (25)	243 (30)	NA
	16 (HS-13-487)	4 [c]	HV (n=15)	4.30 (44)	23.2	0.842 (22)	350 (24)	1.44 (25)

Values are geometric mean (geometric CV %); [a] Median; [b] C168h for CAM2038 q1w; AUCτ: AUC over the dosing interval; Cmax: maximum observed plasma concentration; Ctrough: observed concentration before the next actual or intended dose; CV%: coefficient of variation percentage; HV: healthy volunteer; Tmax: time corresponding to occurrence of Cmax; NA: Not applicable

Cross-study comparison:
Using cross-study comparison, compared to a single-dose of 128 mg CAM2038 q4w, four repeated monthly doses of 128 mg CAM2038 q4w showed ~65% higher AUCτ (0-28d) and 68% higher Cmax (Table 1.3.4b).

Table 1.3.4b: Summary of PK parameters of buprenorphine after single versus four repeat doses of 128 mg CAM2038 q4w

Product	Dose (mg) (Study)	Dose No.	Population	Cmax (ng/mL)	Tmax[a] (h)	Ctrough[b] (ng/mL)	AUCτ (ng*h/mL)	Rac (AUC τ)
q4w	128 (HS-13-487)	1	HV (n=16)	6.59 (68)	6.1	0.934 (33)	1580 (44)	NA
	128 (HS-15-549)	4 [c]	Patient (n=16)	11.1 (54).	10.0	2.09 (55)	2610 (42)	1.65

Values are geometric mean (geometric CV %); [a] Median; [b] C28d for CAM2038 q4w; AUCτ: AUC over the dosing interval; Cmax: maximum observed plasma concentration; Ctrough: observed concentration before the next actual or intended dose; CV%: coefficient of variation percentage; HV: healthy volunteer; Tmax: time corresponding to occurrence of Cmax; NA: Not applicable

1.3.5 Dose proportionality:

The dose proportionality CAM2038 q1w and CAM2038 q4w were evaluated using single dose PK studies. The pharmacokinetics of single doses of 8, 16 and 32 mg CAM2038 q1w and single doses of 64, 96, 128 and 192 mg CAM2038 q4w was evaluated in studies HS-11-426 and HS-13-487, respectively. The PK parameters for single dose CAM2038 q1w and CAM2038 q4w are shown in Table 1.3.5. The PK profiles and dose proportionality assessment is shown in section 2.2.3.2.

The buprenorphine AUCinf increases dose-proportionally for CAM2038 q1w (8 to 32 mg) and CAM2038 q4w (64 to 192 mg). The Cmax increases dose-proportionally for CAM2038 q1w (8 to 32 mg) and less than dose-proportionally for CAM2038 q4w (64 to 192 mg). However, for CAM2038 q4w, the Cmax for the dose range of 64 to 128 mg is also dose-proportional.

Table 1.3.5: PK parameters of buprenorphine after single SC injections of CAM2038 q1w and CAM2038 q4w in studies HS-11-426 and HS-13-487

Product	Dose (mg)	Dose No.	Parameter [geometric mean (geometric CV%)]					
			Cmax (ng/mL)	Tmax[a] (h)	Ctrough[b] (ng/mL)	AUCτ[c] (ng*h/mL)	AUC_{inf} (ng*h/mL)	t½ (h)
CAM2038 q1w (HS-11-426)	8 (n=18)	1	1.71 (36)	23 (10-47)	0.304 (26)	131 (24)	166 (20)	71 (28)
	16 (n=15)	1	3.08 (49)	23 (10-47)	0.611 (25)	241 (28)	335 (13)	96 (44)
	32 (n=16)	1	5.27 (45)	23 (4-72)	1.13 (24)	431 (25)	638 (12)	112 (45)
CAM2038 q4w (HS-13-487)	64 (n=17)	1	3.81(60)	10 (1 -48)	0.449 (57)	955 (33)	1360 (33)	447 (52)
	96 (n=14)	1	5.47 (56)	10 (0.5-98)	0.538 (28)	1170 (29)	1830 (26)	555 (34)
	128 (n=16)	1	6.59 (68)	6 (0.5-95)	0.934 (33)	1580 (44)	2550 (26)	502 (52)
	192 (n=13)	1	7.54 (58)	4 (0.5-121)	1.26 (36)	1790 (34)	3260 (31)	611 (28)

[a] Median (minimum-maximum); [b] C168h for CAM2038 q1w, C28d for CAM2038 q4w; [c] AUC between 0 and 168 hours for CAM2038 q1w, AUC between 0 and 28 days for CAM2038 q4w; AUCτ: AUC over the dosing interval; AUCinf: AUC extrapolated to infinity; Cmax: maximum observed plasma concentration; Ctrough: observed concentration before the next actual or intended dose; CV%: coefficient of variation percentage; t½: half-life; Tmax: time corresponding to the occurrence of Cmax

1.3.6 Pharmacokinetics of CAM2038 q1w by injection site:

Study HS-15-549 evaluated the effect of different injection sites on the PK of buprenorphine after CAM2038 q1w injection. In this study, PK of buprenorphine after 32 mg CAM2038 q1w at three different injection sites, abdomen, thigh, and back of upper arm was compared using buttock as the reference, after steady-state was reached.

It is noteworthy that these four injection sites were also used in Phase 3 clinical safety and efficacy trials. For injection of CAM2038, Applicant proposed a total of 26 injection places around the sites of buttock (n=8), abdomen (n=6), thighs (n=8) and upper arm (n=4) (Figure 2.4.2, QBR below).

Similar PK profiles of buprenorphine were observed after SC injections of 32 mg CAM2038 q1w in the buttock, abdomen, thigh and upper arm (Figure in Section 2.4.2). The PK parameters are shown in Table 1.3.6a. The bioequivalence assessment (geometric mean ratios and 90% CI) between different injection sites was done using buttocks as a reference, shown in Table 1.3.6b. Although Cmax and AUC between different injection sites are important for CAM2038, the trough levels are considered more important for the efficacy of this product because trough concentration is associated with the lowest percentage of mu-receptor occupancy during the entire dosing interval. Out of three sites, compared to the buttock, the trough levels from upper arm site (1.3.6a) is lower and it also failed to meet the bioequivalence criteria for 80 to 125% (1.3.6b). Hence, upper arm site is not recommended for injection of this product. The product can be administered in the rest of the 22 injection places around the sites of buttock, abdomen, and thighs.

Table 1.3.6a: Injection site effect: PK parameters of buprenorphine after repeated weekly SC 32 mg CAM2038 q1w, in the buttock, abdomen, thigh and upper arm in study HS-15-549.

Product Dose	**Dose No.**	**Injection site**	**Parameter [geometric mean (CV%)]**				
			Css,max (ng/mL)	**Tss,max[a] (h)**	**Css,trough[b] (ng/mL)**	**AUCss [c] (ng*h/mL)**	**Css,av (ng/mL)**
CAM2038 q1w 32 mg	4-7[d] (n=21)	Buttock	6.87 (37)	24.0 (0-72)	2.63 (39)	700 (27)	4.17 (27)
	4-7[d] (n=21)	Abdomen	6.56 (30)	24.0 (0-168)	2.68 (36)	657 (27)	3.91 (27)
	4-7[d] (n=21)	Thigh	5.37 (44)	24.0 (10-120)	2.70 (48)	613 (37)	3.65 (37)
	4-7[d] (n=21)	Upper arm	5.69 (43)	24.0 (4-48)	2.37 (37)	591 (34)	3.52 (34)

Median (min-max); [b]C168h; [c]AUC between 0 and 168 hours for CAM2038 q1w; AUCss: AUC over the dosing interval at steady-state; Css,av: average concentration during the dosing interval at steady-state; Css,max: maximum observed plasma concentration at steady-state; Css,trough: observed concentration before the next actual or intended dose at steady- state; CV%: coefficient of variation percentage; Tss,max: time corresponding to occurrence of Css,max

Table 1.3.6b: The bioequivalence assessment between different injection sites using buttocks as a reference.

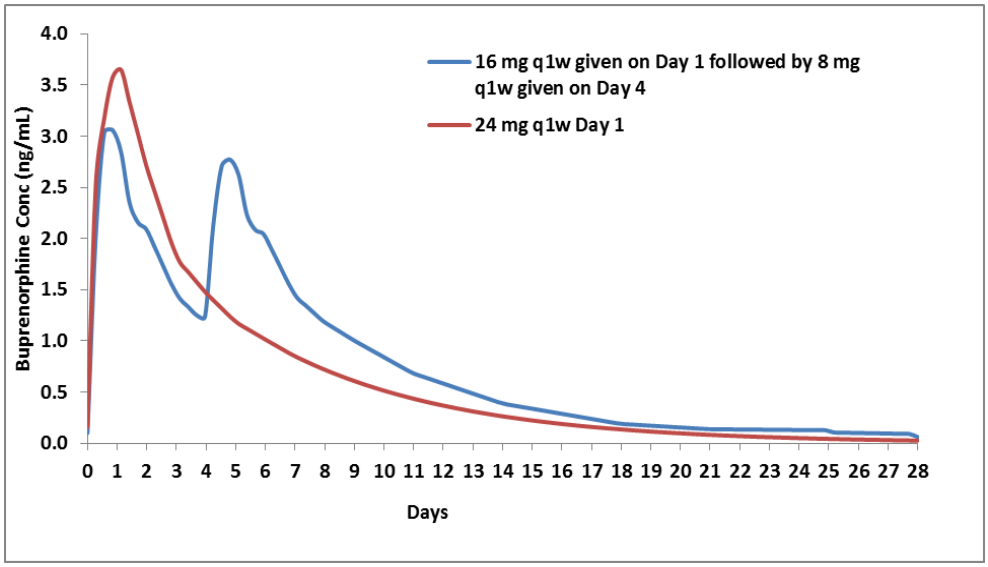
Site	**Geometric mean ratio and 90% CI (lower, upper)**			
	Css,max	AUCss	AUClast	Ctrough
Abdomen Vs. Buttock	96 (82, 112)	94 (84, 104)	94 (84, 104)	102 (88, 117)
Thigh Vs. Buttock	79 (68, 92)	88 (79, 97)	87 (79, 97)	103 (89, 118)
Upper Arm Vs. Buttock	83 (71, 97)	85 (77, 95)	85 (76, 95)	90 (78, 104)

1.3.7 Estimation of PK concentration profiles for 24 mg dose given as 24 mg q1w as a starting dose on Day-1 'versus' the same 24 mg dose split as 16 mg q1w given on Day-1 and followed by 8 mg q1w given on Day-4:

Per label, the recommended weekly dose in new patients (entrants) to buprenorphine treatment is 24 mg of weekly CAM2038 after tolerance to a transmucosal-containing product has been established. In the first week of treatment, this dosage is achieved by titrating to effect: beginning with 16 mg CAM2038 weekly dose followed by an 8 mg weekly dose within 3 days.

Since the PK profiles in the above-mentioned dosing scenario are not evaluated in the conducted PK studies, the concentration-time profiles were estimated using WinNonlin's NonParametric Superposition methodology. The CAM2038 single dose PK concentration profiles of q1w 16 mg, q1w 8 mg, and q1w 24 mg were used in the estimation. The estimated PK profiles are shown in the Figure 1.3.7. Although the exposures are not quantified, as can be noted, the exposure (AUC) and duration of exposure of the split doses (16 mg q1w given on Day 1 followed by 8 mg q1w given on Day 4; total 24 mg) seems higher compared to the single 24 mg q1w dose.

Figure 1.3.7: The estimated PK profiles of 'split 16 mg q1w on given Day 1 followed by 8 mg q1w given on Day 4; total 24 mg' versus single 24 mg q1w dose



1.3.8 Norbuprenorphine levels:

CAM2038 is designed for SC depot administration, which avoids the first-pass effect compared to buprenorphine formulations for oral or SL administration. For SL buprenorphine formulations (e.g. Subutex), the fraction absorbed sublingually also avoids the first-pass effect, whereas the swallowed fraction still undergoes the first-pass effect and is metabolized to norbuprenorphine, which will result in a higher exposure ratio of norbuprenorphine to buprenorphine. The norbuprenorphine concentrations were measured for both SC CAM2038 and SL Subutex. The norbuprenorphine to buprenorphine ratio was much higher for SL Subutex compared to SC CAM2038. The norbuprenorphine to buprenorphine AUCss ratio approximately ranges from 0.35 to 0.53 for SC CAM2038, but much higher for SL Subutex with the range of 1.6 to 2.5. This

observation confirms that buprenorphine after SC administration of CAM2038 results in lesser metabolism to norbuprenorphine compared to an SL buprenorphine product due to lack of the first-pass effect.

1.3.9 Drug interaction potential of CAM2038

Buprenorphine is mainly metabolized via CYP3A4, so co-administration of other drugs which are inhibitors or inducers of CYP3A4 activity can affect the pharmacokinetics of CAM2038. No dedicated pharmacokinetic studies were conducted between CAM2038 and 3A4 inhibitors or inducers. Due to lack of the first-pass effect for CAM2038, the magnitude of drug interaction with a 3A4 inhibitor or inducer is expected to be less for CAM2038 in comparison to SL buprenorphine products.

1.3.10 Hepatic and Renal Impairment:

No dedicated CAM2038 pharmacokinetic studies were conducted in hepatically-impaired or renally-impaired patients.

With respect to hepatic impairment, the effect on buprenorphine PK has been previously evaluated with Suboxone sublingual tablets (2 mg/0.5 mg buprenorphine/naloxone) in subjects with varied degrees of hepatic impairment as indicated by Child-Pugh criteria (see Subutex Tablet Prescribing Information 2017): The labeling states that "The disposition of buprenorphine in patients with hepatic impairment was compared to disposition in subjects with normal hepatic function. In subjects with mild hepatic impairment, the changes in mean Cmax, AUC0-last, and half-life values of buprenorphine were not clinically significant. (b) (4) (b) (4) For subjects with moderate and severe hepatic impairment, mean Cmax, AUC0-last, and half-life values of buprenorphine were increased." Due to lack of the first-pass effect, the effect on hepatic impairment on the pharmacokinetics of CAM2038 is expected to be less than the effect on SL buprenorphine drug products.

With respect to renal impairment, the information provided with Subutex Tablet was referenced, indicating that buprenorphine undergoes hepatic extraction and metabolism and that buprenorphine systemic clearance is not significantly related to renal function.

1.3.11 Blockade of drug-liking (study HS-13478):

The blockade of subjective opioid effects after multiple-dose opioid challenge, of 24 and 32 mg CAM2038 q1w in patients with moderate or severe opioid use disorder was assessed in study HS-13-478. PKPD analyses of this study is provided in further detail in Appendix 4.2.1.

The primary study objective was to evaluate the degree and duration of 24 and 32 mg CAM2038 q1w to block the subjective opioid effects of IM hydromorphone (6 mg and 18 mg) compared to administration of 0 mg hydromorphone (placebo) using the Drug Liking (DL) measure assessed on the visual analog scale (VAS). A non-inferiority margin of 11 mm was used to assess the blockade of placebo-corrected Emax VASDL of hydromorphone. The drug-liking was blocked at all sessions for both the 24 mg and 32 mg CAM2038 once weekly doses. There is an overall trend of decreasing drug-liking with increasing buprenorphine. Higher buprenorphine exposures are required to reduce the drug-liking following an 18 mg hydromorphone challenge compared to a 6 mg hydromorphone challenge. For additional details, please refer to sections 2.2.5 and 4.2.1.

1.3.12 Time-to-approach or drop below limit of quantification after final CAM2038 dose:

The time duration for which the drug remains in the plasma after the final CAM2038 injection is necessary to inform label statements regarding the discontinuation of CAM2038. The review team was interested to know how long after discontinuing CAM2038 patients can be expected to test positive on a buprenorphine drug test as well as expect reduced effectiveness in case opioids are administered as part of anesthesia (e.g. for surgery). As such, OCP investigated the buprenorphine PK profile after the last injection of CAM2038 at steady-state. Simulations were conducted to generate a PK profile following the final dose of CAM2038 at steady-state for the maximum proposed dose level for the CAM2038 WEEKLY formulation (32 mg once weekly) as well as the CAM2038 MONTHLY formulation (128 mg once monthly). The PK simulations indicate that the buprenorphine plasma concentrations remain above the LLOQ (0.025 ng/mL) for up to 6 weeks for 32 mg once weekly and for up to 6 months following 128 mg once monthly (see Appendix 4.1.2). However, the correlation between plasma concentrations of buprenorphine and those detectable in urine is not known.

2.0 Question-Based Review

2.1 General Attributes of the Drug

2.1.1 What are the highlights of the chemistry and physical-chemical properties of the drug substance, and the formulation of the drug product?

CAM2038 is a modified-release formulation of buprenorphine (BPN) in a novel Fluid Crystal (FC) technology designed for administration by subcutaneous (not intramuscular) injection to be provided ready-for-use in a prefilled syringe for the treatment of moderate to severe opioid use disorder (OUD) in adults. This delivery technology results in a liquid-to-gel phase transition that occurs when the lipid-based FC system is exposed to the subcutaneous (SC) tissue. The Phase transition from liquid to gel proceeds from the periphery of the FC injectable towards the center of the product by absorption of minute quantities of water. Per Applicant, the injection of CAM2038 into SC tissue results in an immediate and spontaneous formation of a matrix providing release over the designated period in vivo. This product is available in weekly (CAM2038 q1w) and monthly (CAM2038 q4w) formulations, each of which contains different doses and excipients (Table 2.1.1)

CAM2038 q1w Drug Product: The CAM2038 50 mg/mL buprenorphine q1w FC subcutaneous injection depot drug product is a sterile (b) (4) yellowish to yellow clear liquid (b) (4) (b) (4) 1 mL long clear glass syringes with grey plungers. It is a lipid-based parenteral (subcutaneous injection) extended-release product (once weekly dosing) based on the proprietary FluidCrystal® (hereinafter denoted FC) injection depot technology.

CAM2038 q4w Drug Product: The CAM2038 356 mg/mL buprenorphine q4w FC subcutaneous injection depot drug product is a sterile (b) (4) yellowish to yellow clear liquid (b) (4) (b) (4) 1 mL long clear glass syringes with grey plungers. It is a lipid-based parenteral (subcutaneous injection) extended-release product (once monthly dosing) based on the proprietary FluidCrystal® (hereinafter denoted FC) injection depot technology.

Drug product

The qualitative and quantitative composition of the proposed CAM2038 q1w and CAM2038 q4w drug product is described in Table 2.1.1.

Table 2.1.1: Description and composition of the proposed CAM2038 q1w and CAM2038 q4w

Component	Standard	Function	CAM2038 q1w Drug Product				CAM2038 q4w Drug Product		
			Composition (mg) per dose				Composition (mg) per dose		
			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
Buprenorphine Base	Ph. Eur.	Active ingredient	8	16	24	32	64	96	128
Ethanol Anhydrous	USP		(b) (4)						
N-Methyl-2-Pyrrolidone	USP								
Soybean Phosphatidyl choline	In-house								
Glycerol Dioleate	In-house								
Total weight (mg) for all components per dose	Not Applicable								

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

CAM2038 contains buprenorphine and is indicated for the treatment of moderate to severe OUD in patients. Buprenorphine is a partial agonist at the μ-opioid receptor and an antagonist at the kappa-opioid receptor in the central nervous system. Activation of mu-opioid receptors produce physiological effects of opioids such as pain relief, but also produce the reinforcing and physical dependence of opioids. Buprenorphine, as a partial agonist, produces a sub-maximal effect compared to that of a full opioid agonist; this may produce lesser degrees of respiratory depression in terms of safety, and, reinforcing and physical dependence of opioid, which, in turn, may provide an effective treatment of OUD.

2.1.3 What are the proposed dosage and route of administration?

CAM2038 is designed for administration by subcutaneous (not intramuscular) and is proposed in weekly and monthly formulations with the following doses and volume of injection. The proposed dosing and volume of injection of CAM2038 for CAM2038 q1w and CAM2038 q4w is shown in the Table 2.1.3a.

Table 2.1.3a: Dosing and volume of injection of CAM2038

BPN Fluid Crystal SC injection depot			
CAM2038 Weekly (50 mg/mL)		CAM2038 Monthly ((b) (4) mg/mL)	
Dose (mg)	Volume of Injection (mL)	Dose (mg)	Volume of Injection (mL)
8	0.16	64	0.18
16	0.32	96	0.27
24	0.48	128	0.36
32	0.64	(b) (4)	

The applicant proposed the following transitions (Table 2.1.3b) for patients who are on daily doses of SL BPN to initial weekly doses of CAM2038 q1w or monthly doses of CAM2038 q4w.

Table 2.1.3b: Proposed transfer from daily doses of SL BPN to initial weekly or monthly doses of CAM2038 q1w or CAM2038 q4w

Dose of daily SL BPN	**Dose of weekly CAM2038 q1w**
2-6 mg	8 mg
8-10 mg	16 mg
12-16 mg	24 mg
18-24 mg	32 mg
Dose of daily SL BPN	**Dose of monthly CAM2038 q4w**
8-10 mg	64 mg
12-16 mg	96 mg
18-24 mg	128 mg

(b) (4)

(b) (4)

The Applicant is also seeking approval for CAM2038

(b) (4)

2.1.4 What are the core studies submitted in this NDA?

The BPN PK following SC injection of CAM2038 has been investigated in 5 clinical studies, whereof 2 studies were conducted in healthy volunteers under naltrexone (NTX) blockage and 3 studies were conducted in patients with opioid dependence as described in Table 2.1.4.

Table 2.14: Overview clinical pharmacology studies of CAM2038 q1w and CAM2038 q4w

Study	**Study Description**	**Population (No. of subjects)**	**q1w (SC)**	**q4w (SC)**
HS-11-426	Open-label, RDZ, PK, BA, and safety study assessing 3 different SC doses of q1w versus IV and SL BPN	Healthy, N=56	- 8 mg (single dose) - 16 mg (single dose) - 32 mg (single dose)	NA
HS-13-487	RDZ, open-label, single- and repeated-dose PK, BA, and safety study with q1w and q4w versus IV and SL BPN	Healthy, N=79	- 16 mg (4 repeated doses)	- 64 mg (single dose) - 96 mg (single dose) - 128 mg (single dose) - 192 mg (single dose)
HS-07-307 $	Single-dose, dose-escalation PK, PD and safety study investigating 4 different doses of q1w	Patients with OUD, N=41	- 7.5 mg (single dose) - 15 mg (single dose) - 22.5 mg (single dose) - 30 mg (single dose)	NA
HS-15-549	Open-label, partially RDZ PK, efficacy and safety study	Patients with OUD and a history of moderate to severe chronic non- cancer pain, N=65	- 32 mg (7 repeated doses) whereof 3 weekly doses in the buttock followed by 4 weekly doses in the buttock, abdomen, thigh, and back of upper arm. Also, open-label safety extension including 6 additional weekly SC injections of 32 mg q1w in the buttock.	- 128 mg (4 repeated doses in the buttock) - 160 mg (4 repeated doses in the buttock)
HS-13-478	RDZ, double-blind, repeated-dose, PK, efficacy and safety study	Patients with OUD, N=47	- 24 mg (2 repeated doses) - 32 mg (2 repeated doses)	NA

[$] In study HS-07-307, the dose used for CAM2038 q1w (7.5 mg, 15 mg, 22.5 mg and 30 mg) were not intended clinical dose of CAM2038 q1w. Hence this study was not reviewed.

Clinical Studies:
The efficacy of CAM2038 versus active control is evaluated in one pivotal Phase 3 trial, HS-11-421 and safety was evaluated in one long-term safety trial, HS-14-499. The details are as follows:

- HS-11-421: Phase 3, double-blind, double-dummy, active-controlled, parallel-group multicenter study, designed to evaluate CAM2038 compared to an existing standard of care (SL BPN/NX) in initiation and maintenance treatment of patients with OUD.
- HS-14-499: Open-label multicenter, 12-month (48-week) safety study of CAM2038 once weekly (q1w) and once-monthly (q4w) in adult patients with OUD.

2.2 General Clinical Pharmacology

2.2.1 Are the active moieties in the plasma (or other biological fluid) appropriately identified and measured to assess pharmacokinetic parameters and exposure-response relationships?

CAM2038 activity is primarily due to the active pharmaceutical ingredient buprenorphine. In clinical pharmacology studies HS-11-426, HS-13-487 and HS-15-549, buprenorphine and its metabolite, norbuprenorphine were measured. Norbuprenorphine data was reviewed, but not reported in this review.

2.2.2 What are the general PK characteristics of the drug?

For the general PK characteristics with respect to buprenorphine, BPN, the information from Subutex/Suboxone Labels may be referred (Subutex (N020732; 9/7/17)].

2.2.3 What are the single dose and multiple dose PK parameters?

See below in section 2.4.2

2.2.4 What are the characteristics of drug absorption? Are BPN SC injection PK parameters dose proportional?

The CAM2038 is a modified-release subcutaneous formulation of BPN, designed for weekly (CAM2038 q1w) and monthly (CAM2038 q4w) release. This delivery technology of CAM2038 results in a liquid-to-gel phase transition that occurs when the lipid-based Fluid Crystal (FC) system is exposed to the subcutaneous tissue. The phase transition from liquid to gel proceeds from the periphery of the FC injectable towards the center of the product by absorption of minute quantities of water. Thus, the injection of CAM2038 into SC tissue results in an immediate and spontaneous formation of a matrix providing release over the designated period in vivo.

The dose proportionality PK of single dose CAM2038 q1w 8, 16 and 32 mg and CAM2038 q4w 64, 96, 128 and 192 mg was evaluated using PK studies, HS-11-426 and HS-13-487, respectively.

The buprenorphine plasma concentration-time profiles for 8, 16 and 32 mg CAM2038 q1w and 64, 96, 128 and 192 mg CAM2038 q4w are shown in Figure 2.2.4a and Figure 2.2.4b.

Figure 2.2.4a: Plasma concentration-time profiles of buprenorphine after single SC injection of 8, 16 and 32 mg CAM2038 q1w in study HS-11-426

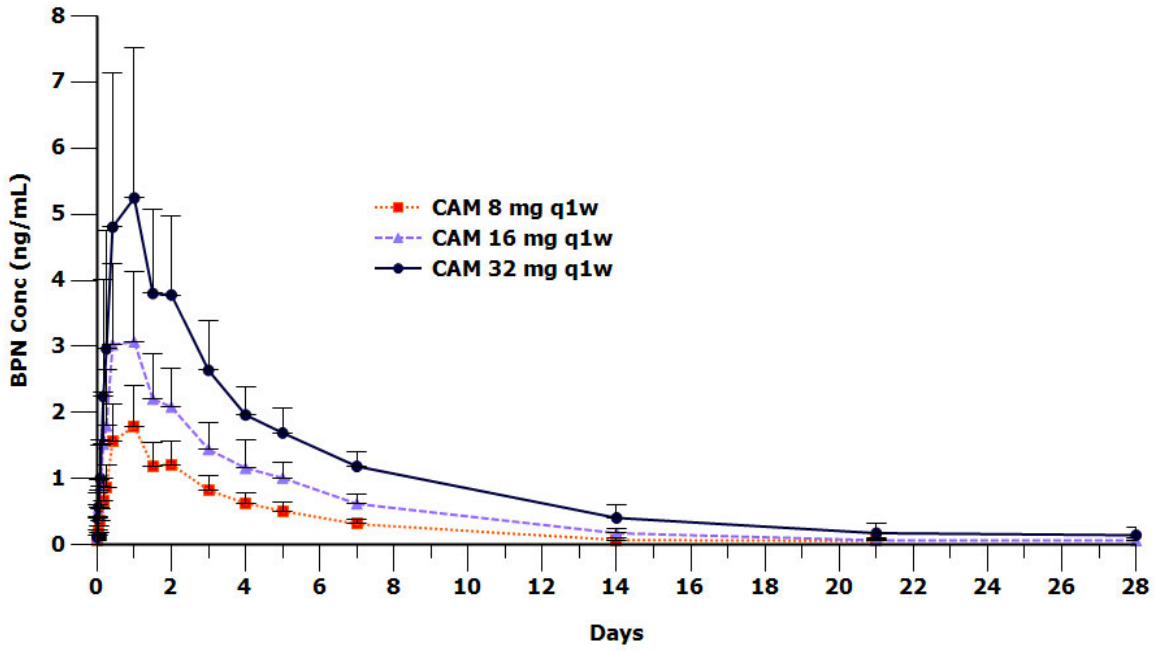
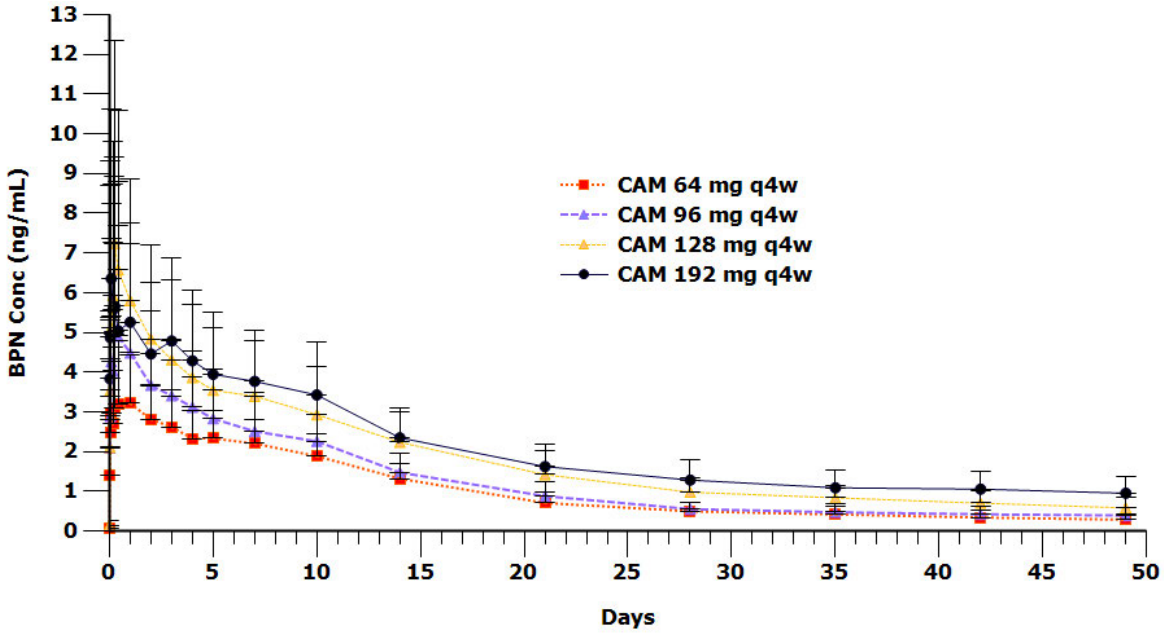


Figure 2.2.4b: Plasma concentration-time profiles of buprenorphine after single SC injection of 64, 96, 128 and 192 mg CAM2038 q4w in study HS-13-487



The PK parameters for 8, 16 and 32 mg CAM2038 q1w and 64, 96, 128 and 192 mg CAM2038 q4w are shown are shown in Table 2.2.4.

- For single doses of 8, 16 and 32 mg of CAM2038 q1w, the BPN Cmax and AUCinf increased in a dose-proportional manner. The slope estimate was 0.813 (95% CI: 0.610 to 1.016) for

log-transformed Cmax vs log-transformed dose and 0.973 (95% CI: 0.893 to 1.052) for log-transformed AUCinf vs log-transformed dose (Figure 2.2.4c). The median Tmax was approximately 23 hours across dose levels of q1w. The geometric mean terminal half-lives were 71, 96 and 112 hours for the 8, 16 and 32 mg, respectively.

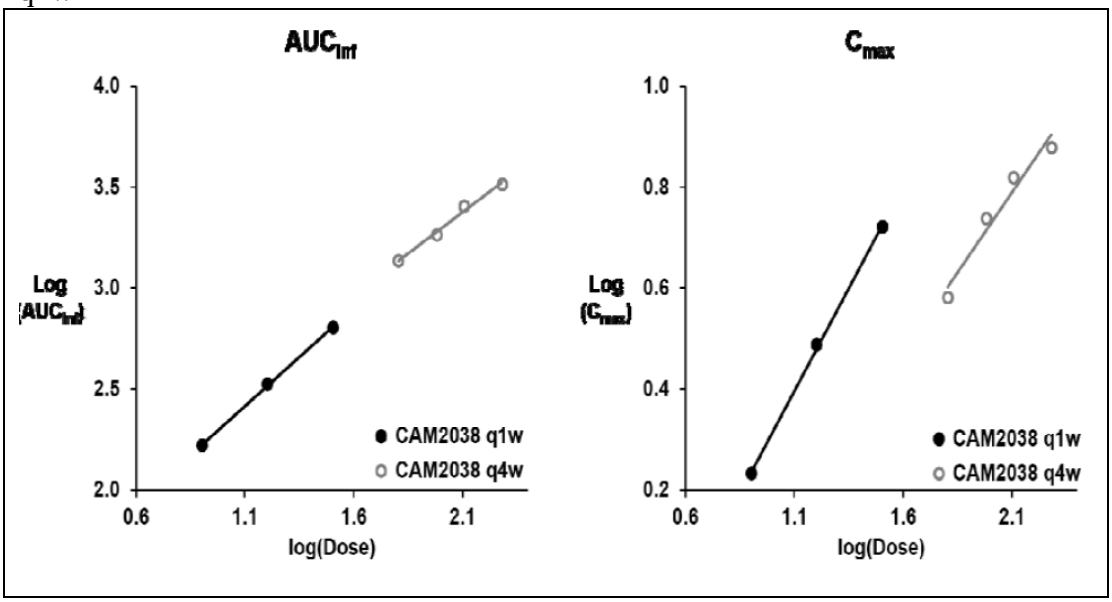
- For single doses of 64, 96, 128 and 192 mg CAM2038 q4w, the BPN AUCinf increased in a dose-proportionally, while Cmax increased less than dose proportionally. The slope estimate with 95% CI was 0.637 (0.279 to 0.994) for log-transformed Cmax vs log-transformed dose and 0.824 (0.641 to 1.007) for log-transformed AUCinf vs log-transformed dose (Figure 2.2.3.2b). However, Cmax for CAM2038 q4w is dose-proportional between (64 to 128 mg) based on the regression analysis. Median Tmax of CAM2038 q4w is about 4 to 10 hours.

Table 2.2.4 PK parameters of buprenorphine after single SC injections of CAM2038 q1w and CAM2038 q4w in studies HS-11-426 and HS-13-487

Product	**Dose (mg)**	**Dose No.**	**Parameter [geometric mean (geometric CV%)]**					
			Cmax (ng/mL)	**Tmax[a] (h)**	**Ctrough[b] (ng/mL)**	**AUCτ[c] (ng*h/mL)**	**AUC_{inf} (ng*h/mL)**	**t½ (h)**
CAM2038 q1w (HS-11-426)	8 (n=18)	1	1.71 (36)	23 (10-47)	0.304 (26)	131 (24)	166 (20)	71 (28)
	16 (n=15)	1	3.08 (49)	23 (10-47)	0.611 (25)	241 (28)	335 (13)	96 (44)
	32 (n=16)	1	5.27 (45)	23 (4-72)	1.13 (24)	431 (25)	638 (12)	112 (45)
CAM2038 q4w (HS-13-487)	64 (n=17)	1	3.81(60)	10 (1 -48)	0.449 (57)	955 (33)	1360 (33)	447 (52)
	96 (n=14)	1	5.47 (56)	10 (0.5-98)	0.538 (28)	1170 (29)	1830 (26)	555 (34)
	128 (n=16)	1	6.59 (68)	6 (0.5-95)	0.934 (33)	1580 (44)	2550 (26)	502 (52)
	192 (n=13)	1	7.54 (58)	4 (0.5-121)	1.26 (36)	1790 (34)	3260 (31)	611 (28)

[a] Median (minimum-maximum); [b] C168h for CAM2038 q1w, C28d for CAM2038 q4w; [c] AUC between 0 and 168 hours for CAM2038 q1w, AUC between 0 and 28 days for CAM2038 q4w; AUCτ: AUC over the dosing interval; AUCinf: AUC extrapolated to infinity; Cmax: maximum observed plasma concentration; Ctrough: observed concentration before the next actual or intended dose; CV%: coefficient of variation percentage; t½: half-life; Tmax: time corresponding to the occurrence of Cmax

Figure 2.3.4c.: The dose linearity of BPN Cmax and AUCinf for CAM2038 q1w and CAM2038 q4w



Overall, the buprenorphine AUCinf increases dose-proportionally for CAM2038 q1w and CAM2038 q4w. The Cmax increases dose-proportionally for CAM2038 q1w and less than dose-proportionally for CAM2038 q4w.

2.2.5 To what extent does the available clinical pharmacology information provide pivotal or supportive evidence of effectiveness?

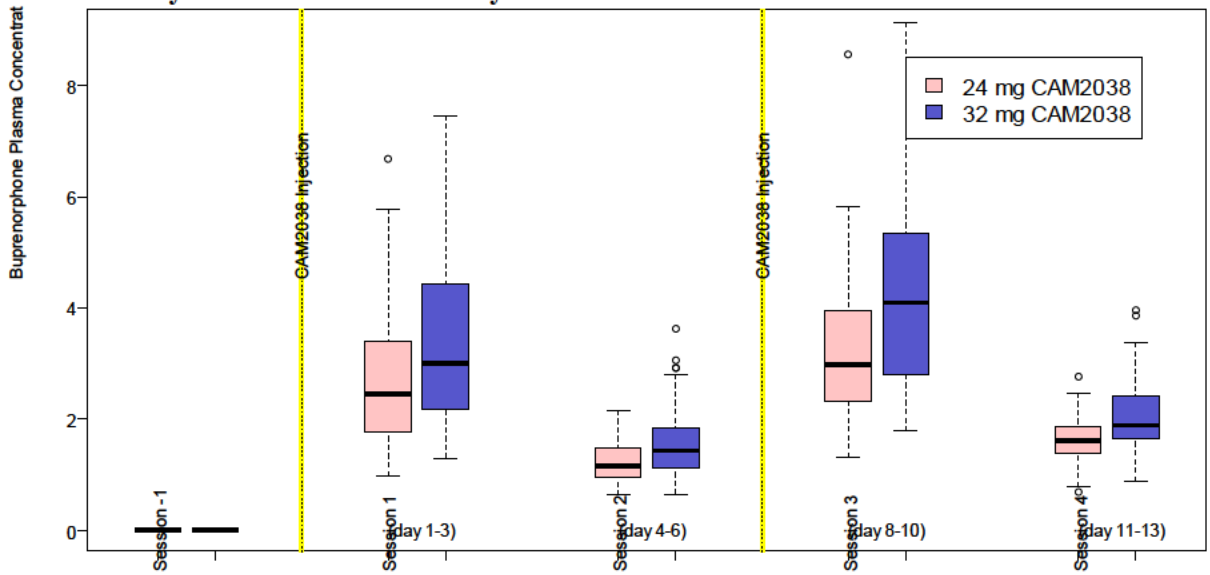
Concerns have been raised by the Clinical and Statistical disciplines regarding the efficacy data from the pivotal efficacy trial HS-11-421. Their reviews are still ongoing when this review is documented in DARRTS. Please refer to reviews from the Clinical discipline and Statistical discipline for details.

Reviewer analyses of blockade data from study HS-13-478: The blockade study HS-13-478 provided evidence of effectiveness of CAM2038. OCP conducted PKPD analyses to further assess the potential for HS-13-478 study data to provide evidence of effectiveness.

PK and PD data were available from n=47 subjects in the blockade study. The blockade study assessed the effect of buprenorphine on a measure of how much a subject "likes" hydromorphone. A hydromorphone testing session consists of a 3-day period where a single dose of hydromorphone (0, 6, or 18 mg) was administered once per day for 3 consecutive days in a blinded randomized manner. Five hydromorphone test sessions were conducted during study HS-13-478; one hydromorphone testing session during baseline/qualification (where patients are not exposed to buprenorphine) and four hydromorphone testing sessions after administration of Weekly CAM2038 (two test sessions after each weekly CAM2038 injection). Subjects were randomized to receive two CAM2038 injections spaced one week apart at the 24 mg or 32 mg level.

PK data consisted of buprenorphine plasma concentrations measured immediately before each hydromorphone challenge. The figure below shows the distribution of buprenorphine plasma concentrations measured prior to each hydromorphone testing session in study HS-13-478.

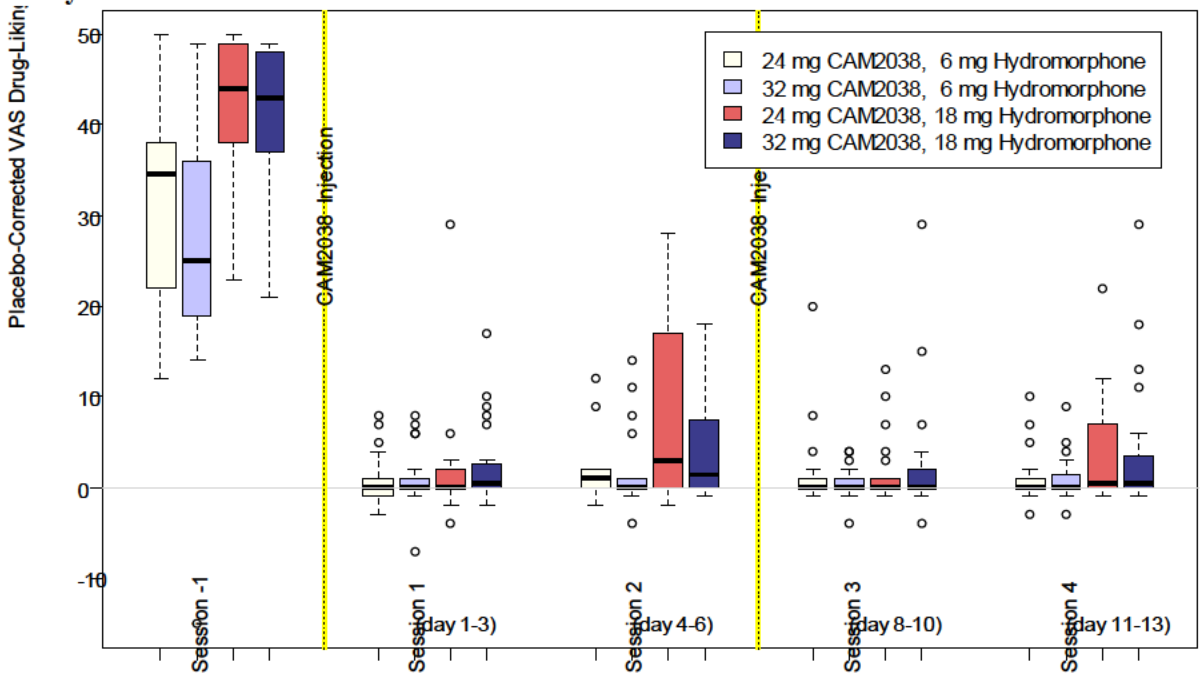
Figure 2.2.5a: Distribution of Buprenorphine Concentration Measured Immediately Prior to Hydromorphone Session by Hydromorphone Session Number for both 24 mg and 32 mg Once Weekly SC CAM2038 in Study HS-13-478



**Vertical yellow lines indicate the timing of SC injections of CAM2038.*

The PD measurement of interest was the Emax drug-liking assessment observed during each 3-day hydromorphone test session. The drug-liking is assessed using the bipolar Visual Analog Scale (VAS) in which subjects point to the spot on a 10 cm line segment on a piece of paper to quantify their current amount of "like" for the drug. A score of 0 mm is strongest dislike, 50 mm is neutral, and 100 mm is strongest like. The Applicant's analyses subtracted the drug-liking score for placebo (0 mg hydromorphone) from the drug-liking score for both the 6 mg and 18 mg hydromorphone doses administered within each weekly 3-day testing session. The plot below shows the distribution of placebo-corrected Emax drug-liking scores.

Figure 2.2.5b: Distribution of Placebo-Corrected Drug-Liking Scores by Hydromorphone Dose Level, by CAM2038 Dose Level, and By Hydromorphone Test Session Number in Study HS-13-478



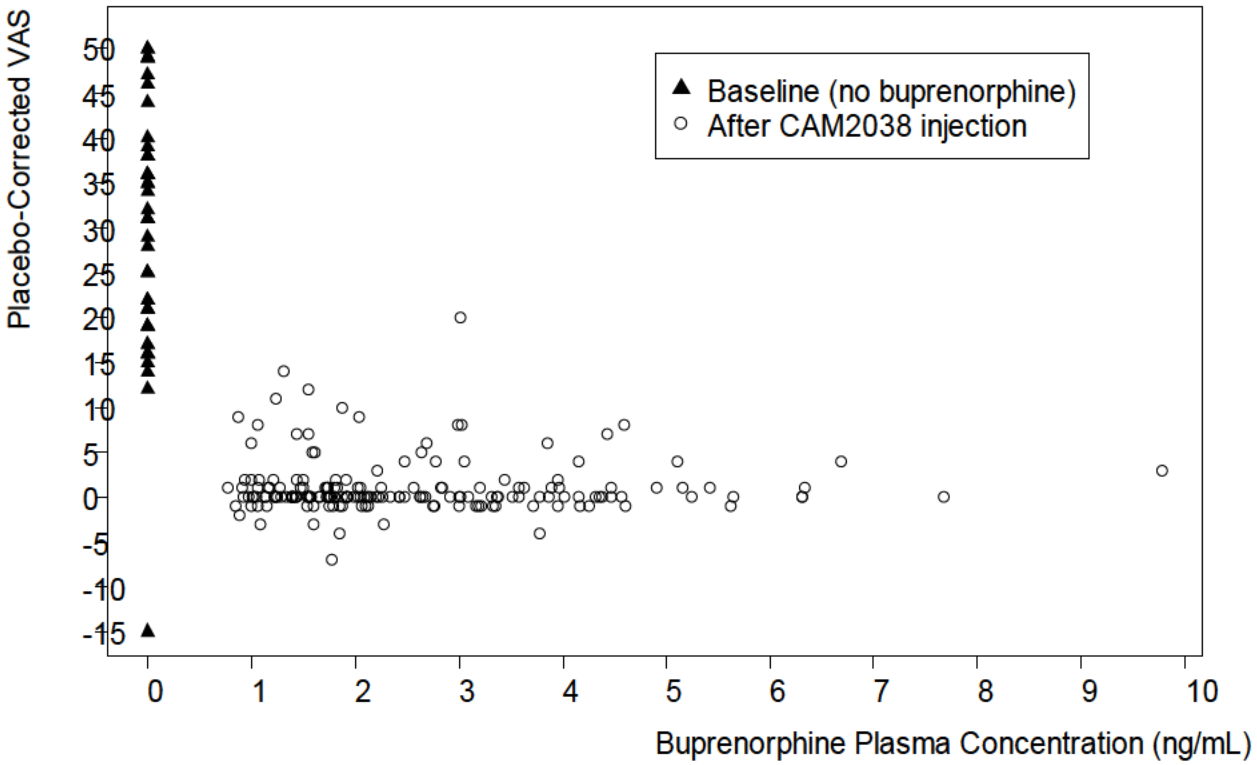
** Vertical yellow lines indicate the timing of SC injections of CAM2038. The boxplots represent the placebo-corrected Emax drug-liking score distribution observed during the hydromorphone challenge for 6 and 18 mg while on 24 mg or 32 mg CAM2038. The 2 hydromorphone sessions are presented in order of increasing hydromorphone dose value for ease of viewing but in the trial the hydromorphone dose sequence was randomized for each patient for each visit.*

Looking at the figure above, the following observations are apparent:

- Drug liking is highest during the Session -1, the baseline/qualification session, where the hydromorphone challenge was conducted in the absence of buprenorphine
- Drug-liking is reduced after CAM2038 administration (at and after Session 1) compared to baseline
- CAM2038 appears to be more effective at reducing the "like" for the 6 mg hydromorphone dose than the 18 mg hydromorphone dose
- The drug-liking scores tend to be higher at the end of the dosing interval compared to the beginning (e.g. Session 2 vs 1, or Session 4 vs 3). The increase in drug-liking over the course of a dosing interval may be related to decreasing buprenorphine exposure throughout the course of the dosing interval.
- "Drug like" scores at the end of the dosing interval were generally higher for 24 mg CAM2038 than for 32 mg CAM2038.

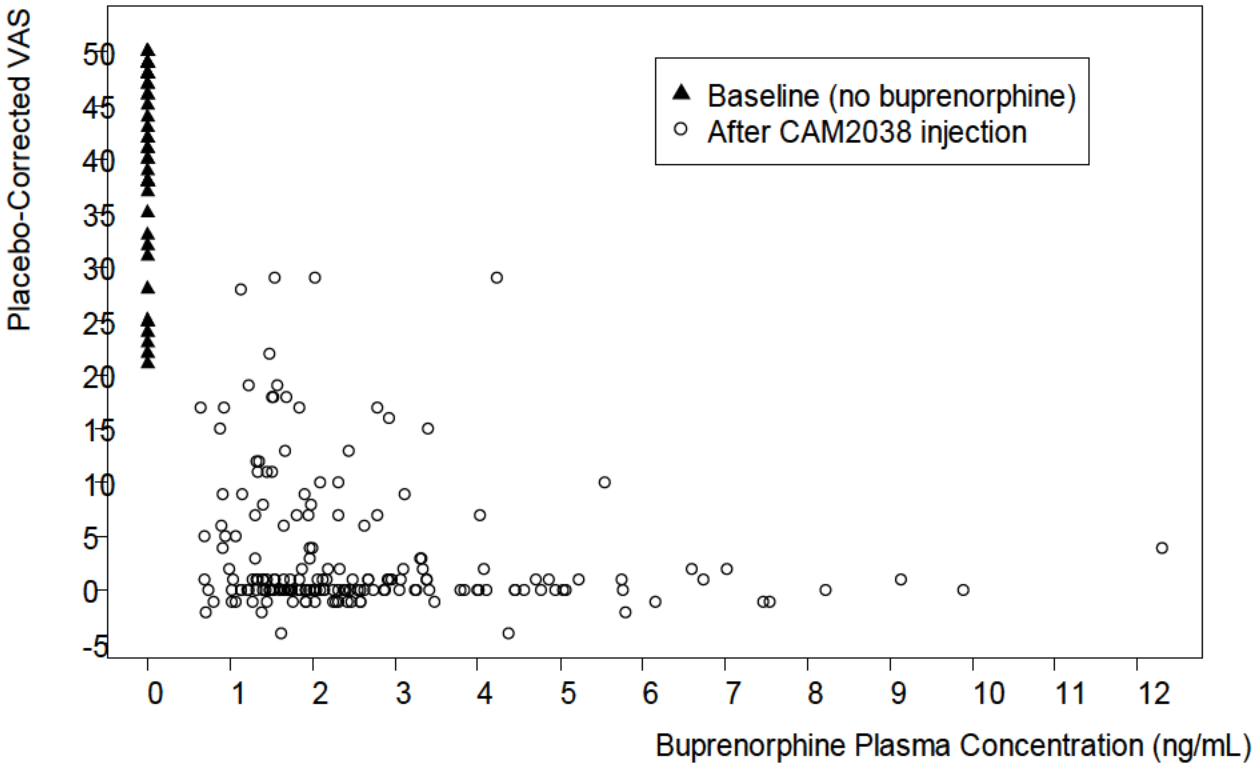
A graphical analysis was conducted to explore the relationship between PK and PD. Scatter plots were generated with PK data and the corresponding PD measurement for both the 6 mg hydromorphone dose (see Figure 2.2.5c) and the 18 mg hydromorphone dose (see Figure 2.2.5d).

Figure 2.2.5c: Scatter Plot of Placebo-Corrected Drug-Liking Scores With Corresponding Buprenorphine Concentration for the 6 mg Hydromorphone Dose at Baseline and Throughout 2 Week Study Period for Pooled 24 mg and 32 mg CAM2038 Arms



The solid triangle points represent the drug-liking scores observed during Session -1 (baseline/qualification period) in the absence of buprenorphine and the circles represent observations acquired after initiating SC CAM2038.

Figure 2.2.5d: Scatter Plot of Placebo-Corrected Drug-Liking Scores With Corresponding Buprenorphine Concentration for the 18 mg Hydromorphone Dose at Baseline and Throughout 2 Week Study Period for Pooled 24 mg and 32 mg CAM2038 Arms

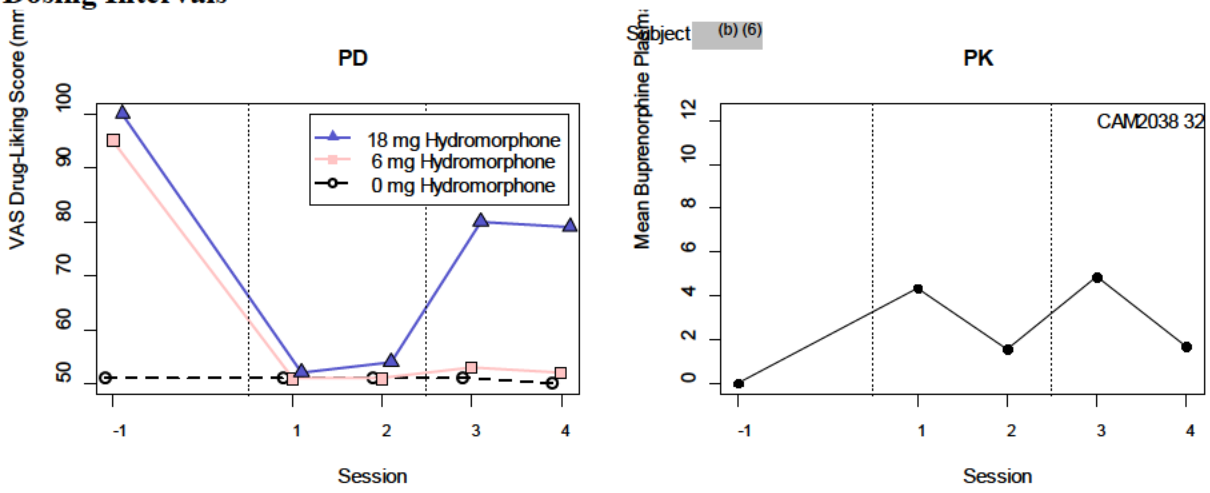


The solid triangle points represent the drug-liking scores observed during Session -1 (baseline/qualification period) in the absence of buprenorphine and the circles represent observations acquired after initiating SC CAM2038.

Overall, the data show an apparent central tendency of increasing effectiveness (reduced "liking" of hydromorphone) with increasing exposure. However, the scatter plots above also demonstrate that the dispersion in drug-liking scores is wider at the lower buprenorphine exposures compared to higher buprenorphine exposures. The dispersion in the drug-liking scores was further investigated to explore and potentially uncover a reason for the wide range of drug-liking scores observed at lower buprenorphine exposures.

When looking at the individual time course of buprenorphine concentration alongside the time course of drug-liking scores, several individuals were found to display vast differences in the drug-liking scores from one dosing interval to the next despite having comparable exposures. The following plot shows the time-course of PK and PD data for one representative individual (subject (b) (6)). Approximately one quarter of the subjects enrolled exhibited this phenomenon.

Figure 2.2.5e: Representative Individual With Abrupt Changes in Drug-Liking Between Dosing Intervals



The left panel shows the drug liking scores which remain comparable during Session 1 and 2, then increase abruptly at session 3 and are maintained into session 4 without correlation with the PK profile. The reason for these abrupt changes in drug liking observed in Subject (b) (6) as well as other subjects is currently unknown.

Overall, the available PK and PD data provide supportive evidence of opioid blockade. There is an overall trend of increasing response (that is, reduced drug-liking) with increasing buprenorphine exposure. As expected, higher buprenorphine exposures are required to reduce the drug-liking following an 18 mg hydromorphone challenge compared to a 6 mg hydromorphone challenge.

However, the data demonstrate that there are some subjects in whom the drug-liking scores undergo seemingly abrupt changes of large magnitude which do not correlate with the buprenorphine. These observations, such as the PK and PD profiles for Subject (b) (6) shown in the plot above (and observed in ~1/4 of subjects in study HS-13-478), suggest that, in addition to buprenorphine concentration, that other factors, factors which are currently unknown, are likely influencing the drug liking scores.

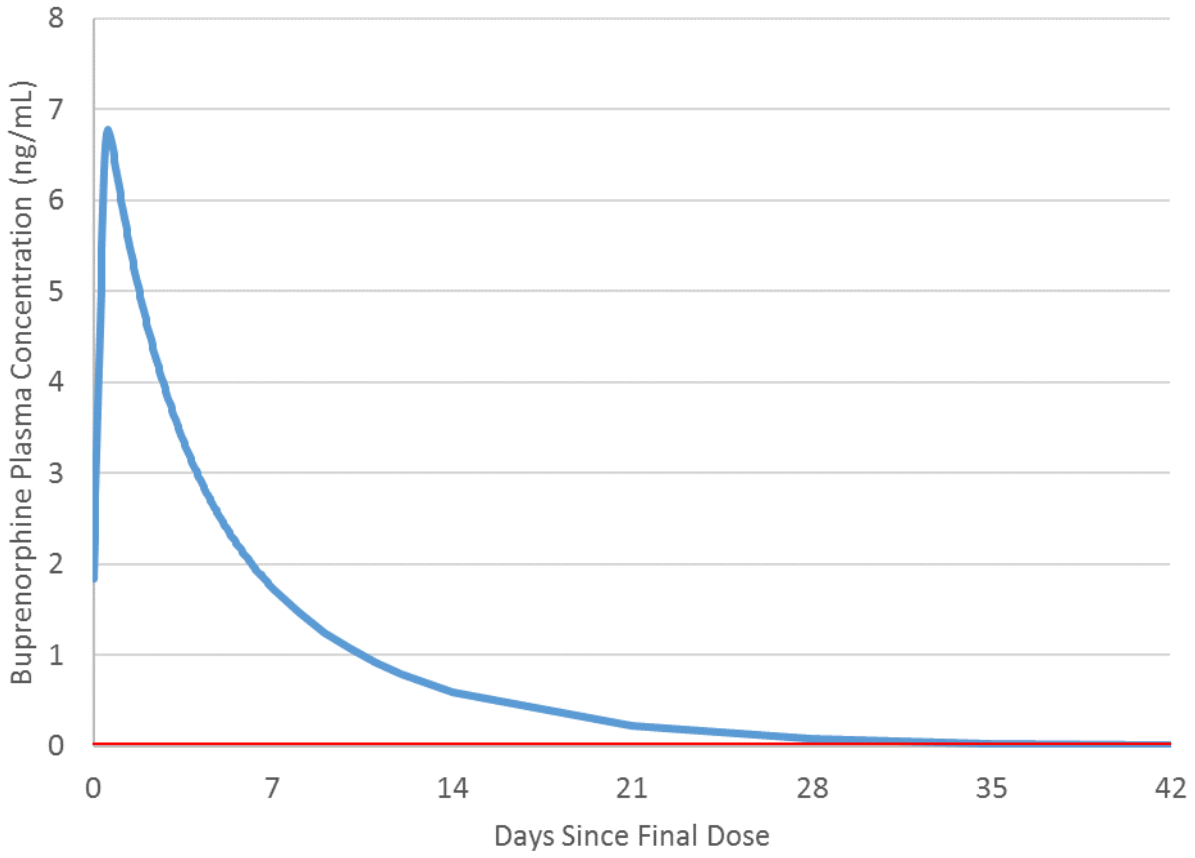
For additional details regarding these analyses, please refer to section 4.2.1 in the appendix.

2.2.6 How long does the drug remain in the plasma after the final injection?

The time duration for which the drug remains detectable in plasma after the final CAM2038 injection is necessary to inform a label statement regarding discontinuation of CAM2038. The review team was interested to know how long after discontinuing CAM2038 can patients be expected to test positive on a buprenorphine drug test as well as expect reduced effectiveness in case opioids are administered as part of anesthesia (e.g. for surgery). As such, OCP assessed the PK profile after the last injection of CAM2038 at steady-state.

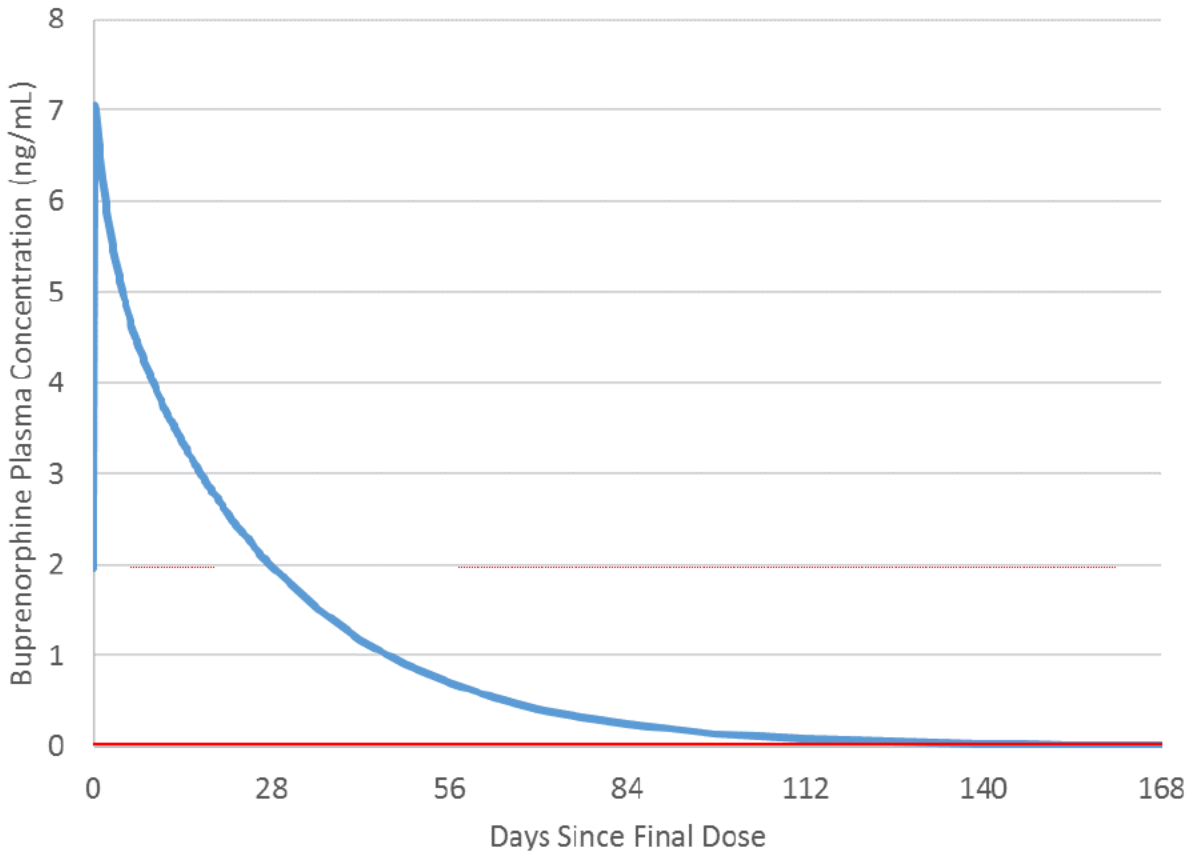
The reviewer conducted PK simulations to generate a PK profile following the final dose of CAM2038 at steady-state for each formulation (32 mg once weekly and 128 mg once monthly). The reviewer utilized the Applicant's population PK model to generate the PK simulations (please refer to section 4.3.1 in the appendix for details regarding the population PK model which OCP finds acceptable). A virtual patient was created to present the central tendency of the population PK profile. The virtual patient was male, was assigned the median weight of 72.4 kg and the median age of 35 years. The maximum dose levels proposed for labeling for each formulation were simulated to steady-state; 5 injections of 32 mg CAM2038 WEEKLY and 5 injections of 128 mg CAM2038 MONTHLY. After the 5th injection of each formulation (a time when steady-state is reasonably approximated) dosing was ceased and the PK profile was simulated until after the buprenorphine plasma concentration dropped below the LLOQ (0.025 ng/mL) for both formulations (see figures below).

Figure 2.2.6a: Simulated PK Profile Following a Final Injection at Steady-State from a 32 mg Once-Weekly SC CAM2038 Regimen



Time zero represents the final SC injection at steady-state from a 32 mg CAM2038 once weekly regimen. The red horizontal line is the LLOQ (0.025 ng/mL).

Figure 2.2.6b: Simulated PK Profile Following a Final Injection at Steady-State from a 128 mg Once-Monthly SC CAM2038 Regimen



Time zero represents the final SC injection at steady-state from a 128 mg CAM2038 once monthly regimen. The red horizontal line is the LLOQ (0.025 ng/mL). The monthly CAM2038 formulation is administered every 28 days.

Overall, based on PK simulations, when a patient ceases SC CAM2038 treatment while at steady-state, plasma buprenorphine concentration is expected to remain detectable (assuming LLOQ = 0.025 ng/mL) for up to 6 weeks after the final injection of the weekly formulation and for 6 months after the final injection of the monthly formulation.

In section 2.5 of the proposed label a statement was inserted to indicate that patients discontinuing CAM2038 may have detectable levels for up to (b) (4) months for CAM2038 MONTHLY and up to (b) (4) weeks for CAM2038 WEEKLY. In section 2.5, another statement was included indicating that the correlation between plasma concentrations of buprenorphine and those detectable in urine is not known. Finally, section 5.12 "Risks Associated with Treatment of Emergent Acute Pain" was edited to indicate (b) (4)

2.3 Extrinsic Factors

2.4 General Biopharmaceutics

2.4.1 What is the relative bioavailability of BPN SC injection compared to the reference drug SL Subutex?

Since CAM2038 is a multiple dose product, the comparative bioavailability of CAM2038 q1w and CAM2038 q4w versus Subutex was evaluated using steady-state (ss) PK parameters, AUCss and Cmax-ss across studies (HS-11-426, HS-13-487, and HS-15-549) (Table 2.4.1). Since these products have different dosing intervals, the AUCss was represented by the derived parameter from AUCss, the average concentrations (Cav, ss = AUCss,τ /dosing interval,τ). In these studies, CAM2038 q1w was administered 4 or 4 to 7 weekly doses, CAM2038 q4w was administered 4 monthly doses, and Subutex was administered 7 daily doses. The following comparisons are made:

- Compared to the clinical dose of Subutex 24 mg, the highest dose CAM2038 q1w, 32 mg showed 12-19% lower steady- state Cmax (range based on two studies) and 57-78% higher steady-state Cav.
- Compared to the clinical dose of Subutex 24 mg, the highest dose of CAM2038 q4w, 160 mg showed 82-98% higher steady-state Cmax and 98-125% higher steady-state Cav.

Overall, the highest (b) (4) doses of CAM2038, 32 mg q1w or 160 mg q4w showed higher exposure (AUCss, represented by Cav) and CAM2038 128 and 160 mg q4w showed higher Cmaxss, compared to the clinical dose of Subutex at 24 mg.

Table 2.4.1: Summary of steady-state PK parameters of buprenorphine after SC buttock injections of CAM2038 q1w and CAM2038 q4w and SL administration of Subutex (studies HS-11-426, HS-13-487, and HS-15-549)

Product	Dose (mg) (Study)	Dose No.	Population	Cmax,ss (ng/mL)	Tmax[a] (h)	Ctrough[b] (ng/mL)	AUCτ (ng*h/mL)	Cav,ss (ng/mL)
q1w	16 (HS-13-487)	4	HV (n=15)	4.30 (44)	23.2	0.842 (22)	350 (24)	2.09 (24)
	32 (HS-15-549)	4-7	Patient (n=21)	6.87 (37)	24.0	2.63 (39)	700 (27)	4.17 (27)
q4w	128 (HS-15-549)	4	Patient (n=16)	11.1 (54)	10.0	2.09 (55)	2610 (42)	3.89 (42)
	160 (HS-15-549)	4	Patient (n=12)	15.4 (52)	24.0	2.66 (61)	3540 (26)	5.27 (26)
SL BPN	24 (HS-11-426)	7	HV (n=16)	7.78 (37)	1.01	1.24 (44)	56.3 (29)	2.34 (29)
	24 (HS-13-487)	7	HV (n=16)	8.45 (54)	1.04	1.61 (40)	63.9 (34)	2.66 (34)

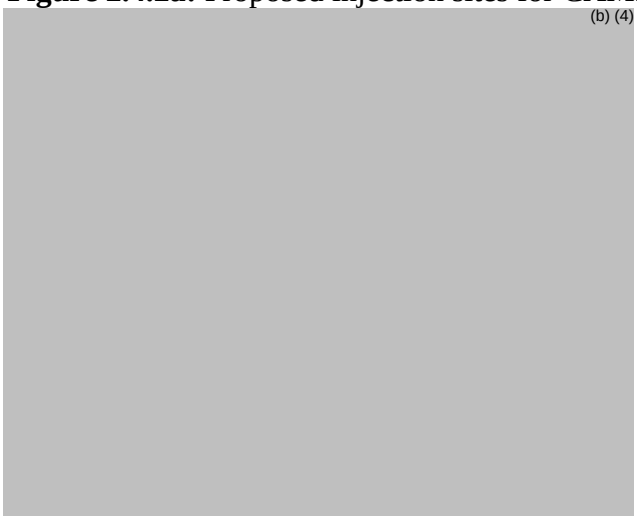
Values are geometric mean (geometric CV%); [a] Median; [b] C168h for CAM2038 q1w, C28d for CAM2038 q4w and C24h for Subutex; AUCinf: AUC extrapolated to infinity; AUCτ: AUC over the dosing interval; Cav: average concentration during the dosing interval; Cmax: maximum observed plasma concentration; Ctrough: observed concentration before the next actual or intended dose; CV%: coefficient of variation percentage; HV: healthy volunteer; t½: half-life; Tmax: time corresponding to occurrence of Cmax

2.4.2 What is the effect of injection-site differences on the PK of this product?

The Study HS-15-549 evaluated the effect of different injection sites on the PK of buprenorphine after CAM2038 q1w injection. In this study, PK of buprenorphine after 32 mg CAM2038 q1w at three different injection sites, abdomen, thigh, and back of upper arm was compared using buttock as the reference, after steady-state was reached.

It is to note that these four injection sites were also used in Phase 3 clinical safety and efficacy trials. For injection of CAM2038, Applicant proposed (b) (4) injection places around the sites of buttock (b) (4) abdomen (b) (4) thighs (b) (4) and upper arm (b) (4) as shown in the Figure 2.4.2a.

Figure 2.4.2a: Proposed injection sites for CAM2038



Similar PK profiles of buprenorphine were observed after SC injections of 32 mg CAM2038 q1w in the buttock, abdomen, thigh and upper arm (Figure 2.4.2b) The PK parameters are shown in Table 2.4.2a. The bioequivalence assessment (geometric mean ratios and 90% CI) between different injection sites was done using buttocks as a reference, shown in Table 2.4.2b.

Although Cmax and AUC between different injection sites are important for CAM2038, the trough levels are more important for the efficacy of this product. Out of three sites, compared to the buttock, the trough levels from upper arm site (Table 2.4.2a) is lower and it also failed to meet the bioequivalence criteria for 80 to 125% (Table 2.4.2b). Hence, upper arm site is not recommended for injection of this product. The product can be administered in the rest of the 22 injection places around the sites of buttock, abdomen, and thighs.

Figure 2.4.2b: Plasma concentration-time profiles of buprenorphine after SC injection of 4th to 7th dose of 32 mg CAM2038 q1w in the buttock, abdomen, thigh and upper arm in study HS-15-549

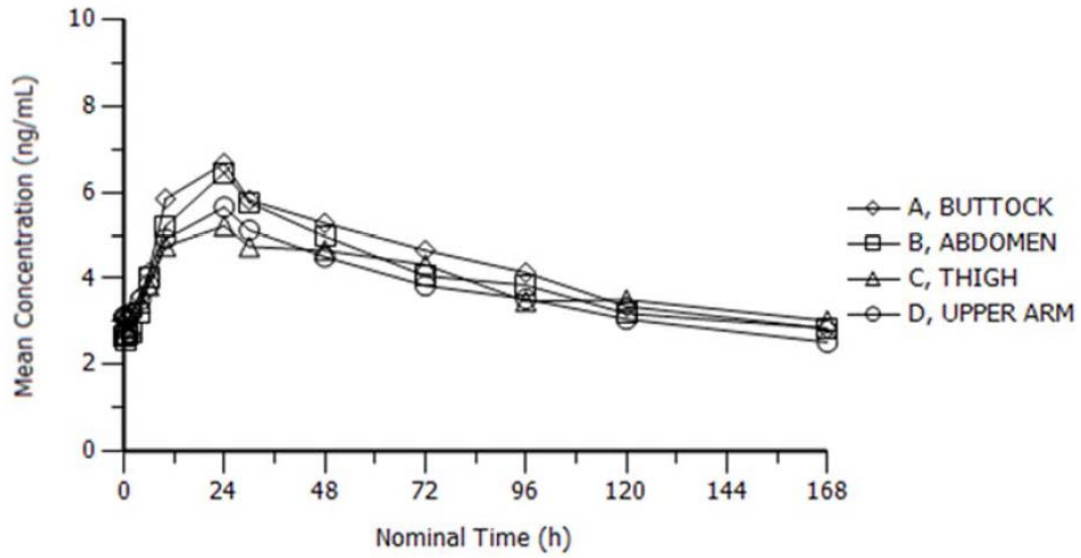


Table 2.4.2a: Injection site effect: PK parameters of buprenorphine after repeated weekly SC 32 mg CAM2038 q1w, in the buttock, abdomen, thigh and upper arm in study HS-15-549.

Product Dose	**Dose No.**	**Injection site**	**Parameter [geometric mean (CV%)]**				
			Css,max (ng/mL)	**Tss,max[a] (h)**	**Css,trough[b] (ng/mL)**	**AUCss [c] (ng*h/mL)**	**Css,av (ng/mL)**
CAM2038 q1w 32 mg	4-7[d] (n=21)	Buttock	6.87 (37)	24.0 (0-72)	2.63 (39)	700 (27)	4.17 (27)
	4-7[d] (n=21)	Abdomen	6.56 (30)	24.0 (0-168)	2.68 (36)	657 (27)	3.91 (27)
	4-7[d] (n=21)	Thigh	5.37 (44)	24.0 (10-120)	2.70 (48)	613 (37)	3.65 (37)
	4-7[d] (n=21)	Upper arm	5.69 (43)	24.0 (4-48)	2.37 (37)	591 (34)	3.52 (34)

Median (min-max); [b]C168h; [c]AUC between 0 and 168 hours for CAM2038 q1w; AUCss: AUC over the dosing interval at steady-state; Css,av: average concentration during the dosing interval at steady-state; Css,max: maximum observed plasma concentration at steady-state; Css,trough: observed concentration before the next actual or intended dose at steady- state; CV%: coefficient of variation percentage; Tss,max: time corresponding to occurrence of Css,max

Table 2.4.2b: The bioequivalence assessment between different injection sites using buttocks as a reference.

Site	**Geometric mean ratio and 90% CI (lower, upper)**			
	Css,max	AUCss	AUClast	Ctrough
Abdomen Vs. Buttock	96 (82, 112)	94 (84, 104)	94 (84, 104)	102 (88, 117)
Thigh Vs. Buttock	79 (68, 92)	88 (79, 97)	87 (79, 97)	103 (89, 118)
Upper Arm Vs. Buttock	83 (71, 97)	85 (77, 95)	85 (76, 95)	90 (78, 104)

Reviewers Comments:

Based on the lower trough levels from the upper arm site, it is recommended not to use this site for injection of this product.

2.4.3 What is the multiple dose pharmacokinetic parameters of SC injection of CAM2038 and SL-Subutex

CAM2038:

A) Within study: Single vs repeat dose CAM2038 q1w 16 mg

The comparative bioavailability of single versus four repeat doses of CAM2038 was evaluated for q1w 16 mg in healthy volunteers in study HS-13-487. The same subjects were administered single dose versus four repeat doses; hence the study compares 'within-study' PK. The plasma concentration-time profiles of buprenorphine comparing SC injection after 1st and 4th repeated dose of 16 mg CAM2038 q1w is shown in the Figure 2.4.3.

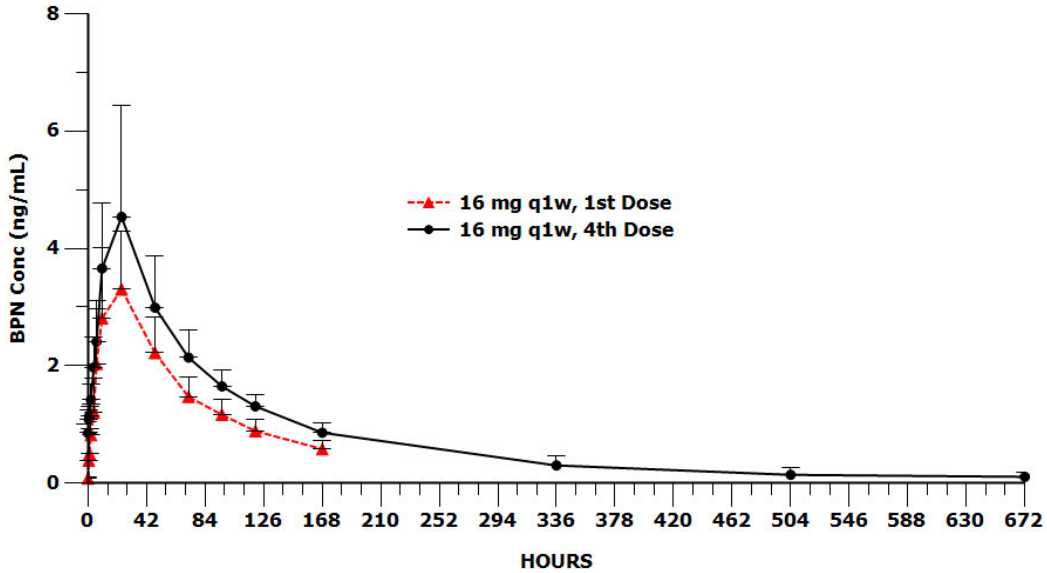
After four repeated doses of 16 mg CAM2038 q1w, ~40% higher exposure was observed compared to the first dose, as noted by AUC0-7d, Cmax, and Ctrough (Table 2.4.3.a). The steady state was achieved at the 4th dose, based on geometric mean Ctrough values of 0.580, 0.810, and 0.876 ng/mL and 0.842 ng/mL measured at 168 hours after 1st, 2nd, 3rd doses and 4th dose, respectively.

Table 2.4.3a: Summary of PK parameters of buprenorphine after single versus four repeat doses of 16 mg CAM2038 q1w (study HS-13-487)

Product	Dose (mg) (Study)	Dose No.	Population	Cmax (ng/mL)	Tmax[a] (h)	Ctrough[b] (ng/mL)	AUCτ (0-7d) (ng*h/mL)	Rac (AUCτ)
q1w	16 (HS-13-487)	1	HV (n=15)	3.05 (46)	23.6	0.580 (25)	243 (30)	NA
	16 (HS-13-487)	4[c]	HV (n=15)	4.30 (44)	23.2	0.842 (22)	350 (24)	1.44 (25)

Values are geometric mean (geometric CV %); [a] Median; [b] C168h for CAM2038 q1w; AUCτ: AUC over the dosing interval; Cmax: maximum observed plasma concentration; Ctrough: observed concentration before the next actual or intended dose; CV%: coefficient of variation percentage; HV: healthy volunteer; Tmax: time corresponding to occurrence of Cmax; NA: Not applicable

Figure 2.4.3a: Plasma concentration-time profiles of buprenorphine comparing SC injection after 1st and 4th repeated dose of 16 mg CAM2038 q1w in study HS-13-487.



B) Cross-study comparison: Single vs repeat dose CAM2038 q1w 32 mg and CAM2038 q4w 128 mg

- 32 mg CAM2038 q1w: Based on the cross-study comparison, single versus four to seven repeat weekly doses of 32 mg CAM2038 q1w show ~86% higher AUCτ (0-7d), 56% higher Cmaxss and 164% higher Ctrough levels(Table 2.4.3b)
- 128 mg CAM2038 q4w: Based on the cross-study comparison, single versus four repeat monthly doses of 128 mg CAM2038 q4w show ~68% higher AUCτ (0-28d), 65% higher Cmaxss and 124% higher Ctrough levels (Table 2.4.3b).

Table 2.4.3b: Summary of steady-state PK parameters of BPN after single versus four repeat doses of q1w 32 mg and q4w 128 mg

Product	Dose (mg) (Study)	Dose No.	Population	Cmax (ng/mL)	Tmax[a] (h)	Ctrough[b] (ng/mL)	AUCτ (ng*h/mL)	Rac (AUCτ)
q1w	32 (HS-13-478)	1	Patient (n=24)	4.39 (43)	24.0	0.993 (32)	376 (31)	
	32 (HS-15-549)	4-7 [c]	Patient (n=21)	6.87 (37)	24.0	2.63 (39)	700 (27)	1.86
q4w	128 (HS-13-487)	1	HV (n=16)	6.59 (68)	6.1	0.934 (33)	1580 (44)	
	128 (HS-15-549)	4 [c]	Patient (n=16)	11.1 (54).	10.0	0 209 (55)	2610 (42)	1.65

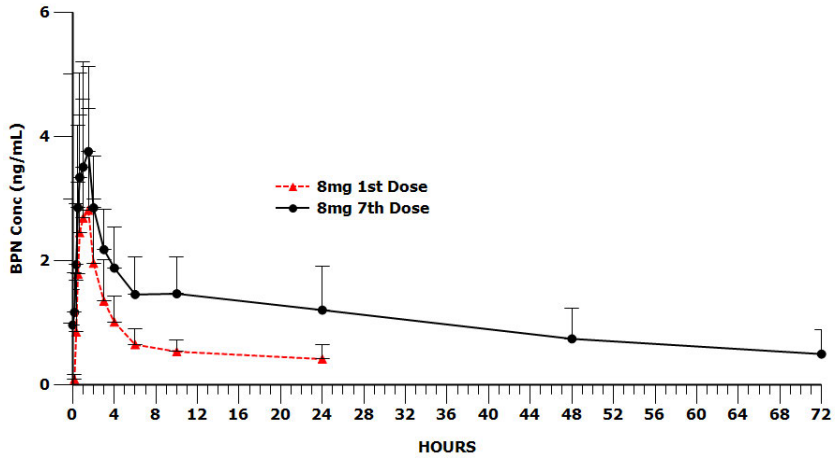
Values are geometric mean (geometric CV%); [a] Median; [b] C_{168h} for CAM2038 q1w, C_{28d} for CAM2038 q4w; AUCτ: AUC over the dosing interval; Cmax: maximum observed plasma concentration; Ctrough: observed concentration before the next actual or intended dose; CV%: coefficient of variation percentage; HV: healthy volunteer; Tmax: time corresponding to occurrence of Cmax

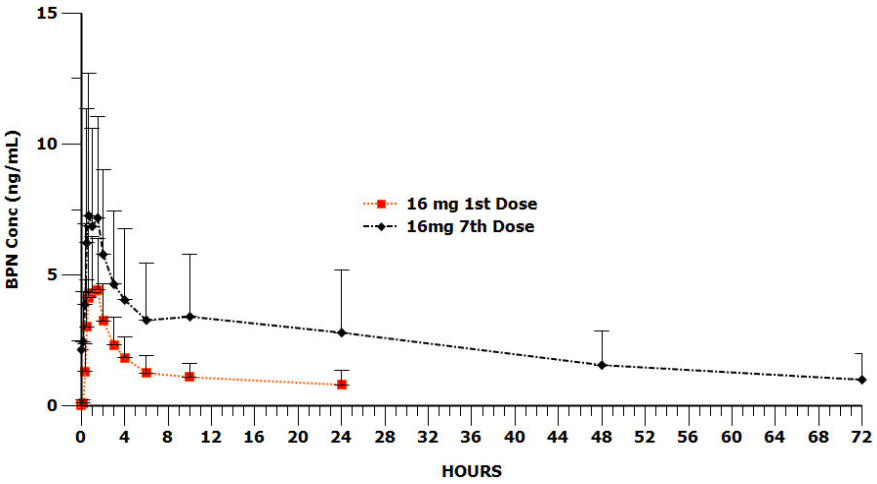
SL –Subutex:

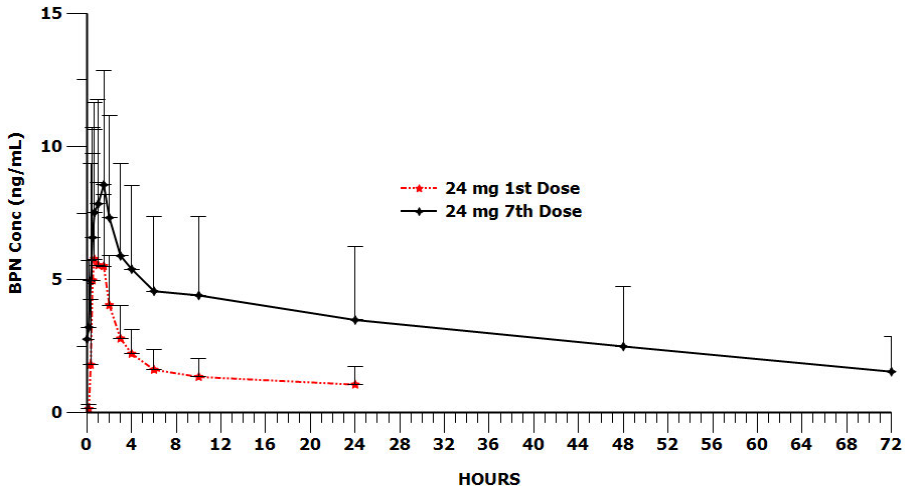
The comparative bioavailability of single versus seven repeat doses of SL Subutex was evaluated for 8, 16 and 24 mg doses in healthy volunteers in studies HS-11-426 and HS-13-487. The same subjects were administered single dose versus seven repeat doses; hence the study compares 'within-study' PK for both studies.

The plasma concentration-time profiles of buprenorphine comparing 1st and 7th repeated dose of SL-Subutex 8, 16 and 24 mg from study HS-13-487 is shown in the figure 2.4.3b.

Figure2.4.3b: Plasma concentration-time profiles of buprenorphine comparing 1st and 7th repeated dose of SL-Subutex 8, 16 and 24 mg in study HS-13-487.







After seven repeated doses of SL-Subutex 8, 16 and 24 mg shows ~ 55 to 61%, 52 to 73% and 70 to 84%, respectively higher exposure compared to the first dose, as noted by AUC0-7d (Table 2.4.3.c). Based on the study HS-11-426, the steady-state BPN Cmax and AUCss for SL BPN increased sub-proportionally in the dose range 8 to 24 mg. Corresponding slope estimates were 0.445 (95% CI: 0.218 to 0.672) for Cmax and 0.642 (95% CI: 0.442 to 0.843) for AUCss.

Table 2.4.3c Summary of steady-state PK parameters of BPN after single versus seven repeat doses for 8, 16 and 24 mg doses in healthy volunteers in studies HS-11-426 and HS-13-487

Product	Dose (mg) (Study)	Dose No.	Population	Cmax (ng/mL)	Tmax[a] (h)	Ctrough[b] (ng/mL)	AUCτ (ng*h/mL)	t½ (h)	Rac (AUCτ)
Subutex	8 (HS-11-426)	1	HV (n=18)	4.32 (32)	1.49	0.249 (38)	17.5 (29)	NC	
		7[c]	HV (n=18)	4.74 (29)	1.25	0.606 (46)	27.2 (34)	35.8 (35)	1.55
	8 (HS-13-487)	1	HV (n=17)	4.35 (41)	1.03	0.259 (35)	18.5 (30)	NC	
		7[c]	HV (n=17)	4.74 (36)	1.48	0.677 (52)	29.8 (33)	42.5 (34)	1.61
	16 (HS-11-426)	1	HV (n=15)	6.71 (62)	1.03	0.381 (36)	25.4 (45)	NC	
		7[c]	HV (n=15)	6.25 (49)	1.48	0.794 (58)	38.5 (37)	38.7 (28)	1.52
	16 (HS-13-487)	1	HV (n=15)	5.88 (31)	1.00	0.374 (44)	26.5 (34)	NC	
		7[c]	HV (n=15)	6.72 (47)	1.02	1.05 (46)	45.7 (33)	42.8 (16)	1.73
	24 (HS-11-426)	1	HV (n=16)	7.08 (19)	1.03	0.490 (39)	33.1 (25)	NC	
		7[c]	HV (n=16)	7.78 (37)	1.01	1.24 (44)	56.3 (29)	39.0 (23)	1.70
	24 (HS-13-487)	1	HV (n=16)	8.23 (60)	0.83	0.544 (44)	34.8 (34)	NC	
		7[c]	HV (n=16)	8.45 (54)	1.04	1.61 (40)	63.9 (34)	38.3 (33)	1.84

Values are geometric mean (geometric CV%); [a] Median; [b] C_{24h} for Subutex; [c] Steady-state PK parameter; AUC_τ: AUC over the dosing interval; Cmax: maximum observed plasma concentration; Ctrough: observed concentration before the next actual or intended dose; CV%: coefficient of variation percentage; HV: healthy volunteer; Tmax: time corresponding to the occurrence of Cmax; NC- Not calculated.

2.5 Intrinsic Factors

2.5.1 Pediatrics

Applicant requested a waiver for the development of CAM2038 in pediatric subjects with opioid dependence from birth -17 years of age.

2.6 Analytical Section

2.6.1 Are the active moieties identified and measured in the plasma in the clinical pharmacology and biopharmaceutics studies? What is the QC sample plan? What are the accuracy, precision, and selectivity of the method?

Studies HS-11-426, HS-13-487, and HS-13-478:
Clinical and Bio-analytical Facility: (b) (4)

- Plasma concentrations of buprenorphine and nor-buprenorphine were analyzed using validated HPLC-MS/MS assays. The range of calibrators and QCs used for studies were:
  - Buprenorphine Calibrators: 0.025, 0.05, 0.2, 0.5, 2.0, 5.0, 9.0 and 10.0 ng/mL
  - Buprenorphine Quality controls: 0.075 , 0.75, and 7.5 ng/mL
  - Norbuprenorphine Calibrators: 0.02, 0.04, 0.16, 0.4, 4.0 , 7.2 and 8 ng/mL
  - Norbuprenorphine Quality controls: 0.06, 0.6, and 6.0 ng/mL
- Accuracy and Precision of the range:
  - Accuracy (expressed as % bias) : < ± 15%
  - Precision (expressed as % CV) : < 15%
- Internal standards: buprenorphine-D4 and Norbuprenorphine-D3

- Stability (HS-11-426): The established long-term stability of 438 days at -20 °C for buprenorphine and norbuprenorphine in human K2-EDTA plasma covers the period of study sample storage.

Date of First Sample Collection	Date of Last Sample Analysis (including ISR)	Duration of Sample Storage
07 January 2014	09 June 2014	153 days

- Stability (HS-13-487): The established long-term stability of 1178 days at -20 °C for buprenorphine and norbuprenorphine in human K2-EDTA plasma covers the period of study sample storage.

Date of First Sample Collection	Date of Last Sample Analysis (including ISR)	Duration of Sample Storage
28 May 2014	30 April 2015	337 days

- Stability (HS-13-478): The established long-term stability of 218 days at -20 °C for buprenorphine and norbuprenorphine in human K2-EDTA plasma covers the period of study sample storage.

Date of First Sample Collection	Date of Last Sample Analysis (including ISR)	Duration of Sample Storage*
29 October 2015	05 May 2016	109 days

Study HS-15-549:

Clinical and Bio-analytical Facility: (b) (4) (b) (4)

- Plasma concentrations of buprenorphine and nor-buprenorphine were analyzed using validated HPLC-MS/MS assays. The range of calibrators and QCs used for studies were:
  - Buprenorphine Calibrators: 0.025, 0.05, 0.2, 0.5, 2.0, 5.0, 9.0 and 10.0 ng/mL
  - Buprenorphine Quality controls: 0.075 , 0.75, and 7.5 ng/mL
  - Norbuprenorphine Calibrators: 0.02, 0.04, 0.16, 0.4, 4.0 , 7.2 and 8 ng/mL
  - Norbuprenorphine Quality controls: 0.06, 0.6, and 6.0 ng/mL
- Stability (HS-15-549): The established long-term stability of 535days at -20 °C for buprenorphine and norbuprenorphine in human K2-EDTA plasma covers the period of study sample storage.

Date of First Sample Collection	Date of Last Sample Analysis (including ISR)	Duration of Sample Storage*
16 February 2016	10 May 2017	337 days

3 Labeling Comments:

The following text refers to the current label sections which OCP has edited or are otherwise relevant to OCP.

(b) (4)

11 Pages of Draft Labeling have been Withheld in Full as B4 (CCI/ TS) immediately following this page

4 Appendices

4.1 Population PK Analyses

4.1.1 Reviewer of REP-2-CAM-2038-PMX-1 – PPK of Studies 426, 487, 478, 549

Report rep-2-cam2038-pmx-1 is titled "Population Pharmacokinetic Analysis of Buprenorphine after CAM2038 Administration in Studies HS-11-426, HS-13-487, HS-13-478, and HS-15-549".

The Applicant conducted population pharmacokinetic analyses for buprenorphine following repeat sub-cutaneous injections of CAM2038 in healthy volunteers (studies 426 and 487) and patients with opioid dependence (studies 478 and 549). Additional buprenorphine products with PK data included in the analyses are IV Temgesic® and SL Subutex®. The purpose of these analyses was to develop a population PK model to describe the buprenorphine concentration-time profile, evaluate PK covariates, and simulate single-dose PK and steady-state PK for SL and SC buprenorphine.

Data from the following clinical studies were included in the analyses:

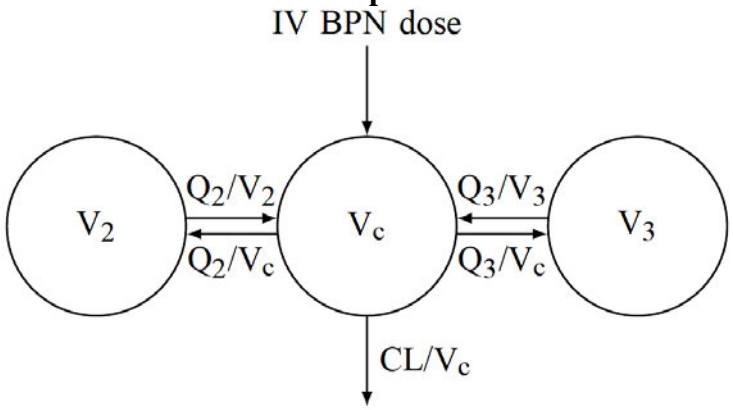
- **HS-11-426 (Phase 1)**: A randomized, open-label study to assess buprenorphine PK following single doses of 8, 16, and 32 mg CAM2038, 0.6 mg IV buprenorphine, and 8, 16, and 24 mg SL buprenorphine in n=60 healthy volunteers under naltrexone blockade.
    - Rich PK - IV buprenorphine: pre-dose, 5, 10, 15, 20, 30 and 40 minutes post-dose, and 1, 1.5, 2, 4, 6, 10 and 24 hours post dosing
    - Rich PK – SL buprenorphine: pre-dose, 10, 20, 30 and 40 minutes post-dose, and 1, 1.5, 2, 3, 4, 6, 10 and 24 hours post dosing for the 1st dose and 7th dose. Also at 48 and 72 hours post dosing for the 7th dose
    - Rich PK – SC CAM2038: pre-dose, 30 minutes post-dose, 1, 2, 4, 6, 10, 24, 36 and 48 hours post dose, and 3, 4, 5, 7, 14, 21 and 28 days post-dose.
- **HS-13-487 (Phase 1)**: A randomized, open-label study to assess buprenorphine PK following repeat CAM2038 injections at 64, 96, 128, and 192 mg as well as compare bioavailability with single IV and SL administrations in n=79 healthy volunteers under naltrexone blockade.
    - Rich PK - IV buprenorphine: In relation to the IV injection: pre-dose (within 45 minutes) and 5, 10, 15, 20, 30, and 40 minutes, and 1, 1.5, 2, 4, 6, 10 and 24 hours post-dose. For Treatment groups D and E, additional samples were taken at 32 and 48 hours post-dose.
    - Rich PK – SL buprenorphine: Day 8 (1st dose) and Day 14 (7th dose): Pre-dose (within 45 minutes) and 10, 20, 30 and 40 minutes, and 1, 1.5, 2, 3, 4, 6, 10 and 24 hours post-dose. For the 7th dose, additional samples were taken at 48 and 72 hours post-dose.
    - Rich PK – SC CAM2038 Once Weekly: pre-dose (within 45 minutes) on Days 21, 28, 35, and 42, as well as:
        - Day 21 (1st dose) 30 minutes and 1, 2, 4, 6, 10, 24 and 48 hours post-dose.

        - Day 28 (2nd dose) 24 hours post-dose (morning of Day 29).
        - Day 35 (3rd dose) 24 hours post-dose (morning of Day 36).
        - Day 42 (4th dose) 30 minutes and 1, 2, 4, 6, 10, 24 and 48 hours post-dose.
        - At ambulatory visits to the Clinical Unit on Days 24, 25, 26, 45, 46, 47, 49, 56, 63, 70 and 77.
    - Rich PK – SC CAM2038 Once Monthly:
        - treatment groups A and B: pre-dose (within 45 minutes) on Day 21 and 30 minutes and 1, 2, 4, 6, 10, 24 hours (Day 22), and 48 hours (Day 23) post-dose, and on Days 24, 25, 26, 28, 31, 35, 42, 49, 56, 63, 70 and 77.
        - Treatment groups D and E: pre-dose (within 45 minutes) on Day 8 and 30 minutes and 1, 2, 4, 6, 10, 24 hours (Day 9), and 48 hours (Day 10) post-dose, and on Days 11, 12, 13, 15, 18, 22, 29, 36, 43, 50, 57 and 64.
- **HS-13-478 (Phase 2)**: A randomized, double-blind, multicenter study to assess ability of 24 mg and 32 mg SC CAM2038 once per week for 2 weeks to provide blockade of drug-liking effects resulting from once daily administration of 0, 6, and 18 mg IM hydromorphone in n=46 adults with moderate-to-severe opioid use disorder.
    - PK Samples – SC CAM2038:
    - Days 0 and 7: Pre-dose and at 1, 4, 6, and 8 hours after drug administration.
    - Days 1-6 and 8-13: approximately 1 h before hydromorphone challenge.
    - Day 14: approximately 168 h after the last dose.
- **HS-15-549 (Phase 2)**: Partially randomized, open-label, multicenter study to assess steady-state PK of SC CAM2038 injected at 4 different body sites (buttock, abdomen, thigh, back of upper arm) administered as 32 mg every 1 week for 4 weeks, 128 mg every 4 weeks for 4 months, or 160 mg every 4 weeks for 4 months.
    - Rich PK – SC CAM2038:
    - Group 1:
        - Pre-dose before CAM2038 q1w doses 1, 2, and 3.
        - Pre-dose and at 0.5, 1, 2, 4, 6, 10, 24, 30, 48, 72, 96, 120 and 168 h post CAM2038 q1w doses 4, 5, 6, and 7.
    - Group 2:
        - Pre-dose, 168 h (7 days), 336 h (14 days) and 504 h (21 days) after CAM2038 q4w dose 1.
        - Pre-dose, one sample any time between 4 and 8 h post-dose, approximately 48 h, 168 h (7 days), 336 h (14 days) and 504 h (21 days) after CAM2038 q4w doses 2 and 3.
        - Pre-dose, 0.5, 1, 2, 4, 6, 10, 24, 48, 72, 96, 120, 168 (7 days), 240 (10 days), 336 (14 days), 504 (21 days) and 672 (28 days) h after CAM2038 q4w dose 4.

Population PK Model (run336)
The population PK model incorporated parameters that were specific to IV, SL, SC once weekly, and SC once monthly, as well as components that were common among all formulations. The IV buprenorphine formulation (Temgesic®) was modelled as being infused directly into the central compartment. The SL buprenorphine formulation (Subutex®), SC CAM2038 once weekly formulation, and SC CAM2038 once monthly were all modelled with formulation-specific dual absorption pathways. One of the two absorption pathways used to model the SL formulation absorption included a as lag time parameter as well as an absorption time duration parameter. One of the two absorption pathways used to model the absorption of the SC CAM2038 once weekly formulation included an absorption time duration parameter (see figures below for details).

Structural Model: The IV, SL, once weekly SC, and once monthly SC formulations feed into a central compartment, V_c from which buprenorphine is undergoes first-order elimination (CL). Two peripheral compartments (V_2, V_3) were also included. The model schematic figures are presented below. The clearance and volume terms are presented separately from the formulation-specific absorption models.

Figure 4.1.1a: Population PK Model with Disposition Terms and IV Administration Term



Vc is the central volume of distribution, CL is the clearance, Q2 is the inter-compartmental clearance to second compartment, V2 is the volume of second compartment, Q3 is the inter-compartmental clearance to third compartment, and V3 is the volume of third compartment.

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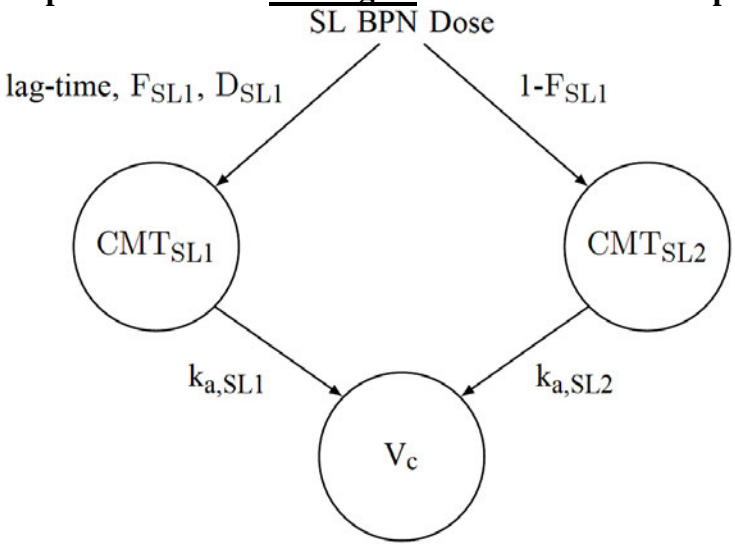
Figure 4.1.1b: Absorption Model for <u>Sublingual</u> Administration in Population PK Model



Vc is the central volume of distribution, FSL1 is the fraction of bioavailable dose going into compartment SL1, DSL1 is the duration of drug input to compartment SL1, ka,SL1 is the first-order rate constant from compartment SL1, and ka,SL2 is the first-order rate constant from compartment SL2.

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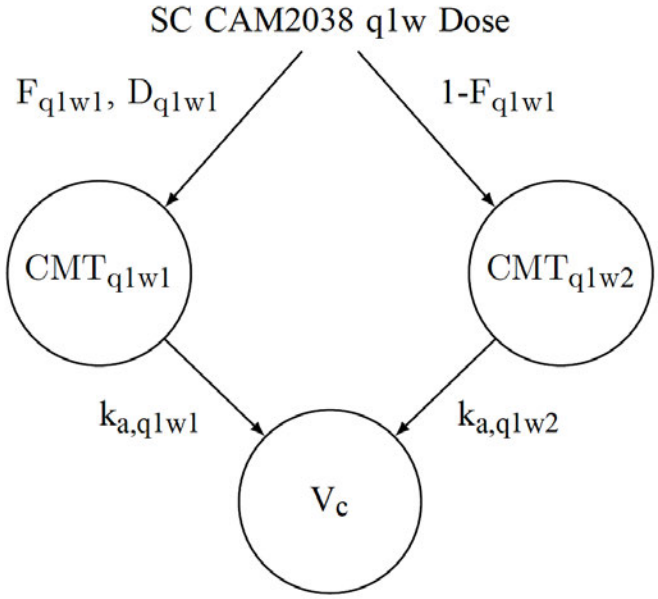
Figure 4.1.1c: Absorption Model for CAM2038 <u>Once Weekly</u> Administration in Population PK Model



Vc is the central volume of distribution, Fq1w1 is the fraction of dose going into compartment q1w1, DQ1W1 is the duration of drug input to compartment q1w1, ka,q1w1 is the first-order rate constant from compartment q1w1, and ka,q1w2 is the first-order rate constant from compartment q1w2.

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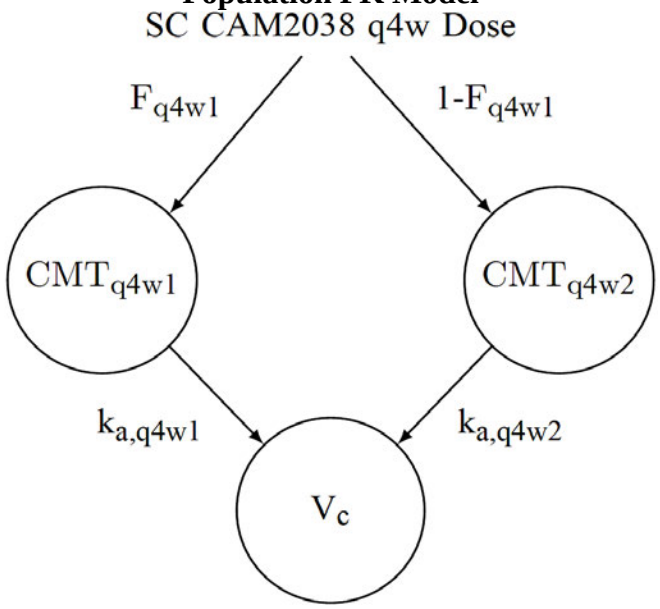
Figure 4.1.1d: Absorption Model for CAM2038 Once Monthly Administration in Population PK Model



Vc is the central volume of distribution, Fq4w1 is the fraction of dose going into compartment q4w1, ka,q4w1 is the first-order rate constant from compartment q4w1, and ka,q4w2 is the first-order rate constant from compartment q4w2.

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Allometric Scaling: Clearance was scaled using body weight normalized to median body weight (72.4 kg) as well as age normalized to median age (35 years) using a power model where both exponents were estimated.
Inter-Individual Variability: The variance-covariance matrix included variance estimates of the interindividual variability for Cl, Vc, Q3, V3, FSL, KSL2, IF4, Kq1w2, Kq4w2, IF5, and IF6. No off-diagonal (covariance) elements were estimated.
Residual Variability: Proportional residual error model.
Covariates: Covariates in the final model were age and weight on CL (via a power model; see "Allometric Scaling" heading above), sex on Fq1w1, and patient versus healthy volunteer ("population effect") on Fq1w1 and Vc.
The parameter estimates for the final model are shown in the table below. All the PK parameters included in the final model were estimated (none of the PK parameters listed below were held constant).

Table 4.1.1a: Estimates of the Final Population Pharmacokinetic Model (run336) for SC CAM2038 Once Weekly, SC CAM2038 Once Monthly, SL Buprenorphine (Subutex®), and IV Buprenorphine (Temgesic®)

	Final model for BPN (run336)			
OFV		−12630.4		
Condition number		160.4		

	Final model for BPN (run336)			
	Unit	Value	RSE (%)	SHR (%)
CL	L/h	52.1	1.80	
V_c	L	64.3	10.3	
Q_2	L/h	186	2.51	
V_2	L	130	1.86	
Q_3	L/h	60.3	4.13	
V_3	L	1580	3.88	
F_{SL}		0.140	3.54	
$t_{lag,SL1}$	h	0.171	1.85	
$k_{a,SL1}$	h^{-1}	1.72	4.33	
$k_{a,SL2}$	h^{-1}	0.0875	15.7	
F_{SL1}		0.759	2.65	
D_{SL1}	h	0.419	4.40	
F_{SL}-Dose		-0.371	18.4	
$k_{a,q1w1}$	h^{-1}	0.0401	4.67	
$k_{a,q1w2}$	h^{-1}	0.00565	6.77	
F_{q1w1}		0.455	8.07	
D_{Q1W1}	h	10.1	4.68	
$k_{a,q4w1}$	h^{-1}	0.0397	3.46	
$k_{a,q4w2}$	h^{-1}	0.00155	7.92	
F_{q4w1}		0.0900	11.7	
Age covariate on CL		-0.233	23.4	
WT covariate on CL		0.413	20.9	
Population covariate on F_{q1w1} [a]		-0.671	30.3	
Sex covariate on F_{q1w1} [b]		0.576	36.1	
Population covariate on V_c [a]		2.69	20.7	
IIV CL	(CV)	0.209	5.83	7.06
IIV V_c	(CV)	0.786	8.21	11.9
IIV Q_3	(CV)	0.380	9.14	21.7
IIV V_3	(CV)	0.298	6.74	30.1
IIV F_{SL}	(CV)	0.311	9.70	5.10
IIV $k_{a,SL2}$	(CV)	0.863	9.82	17.1
IIV F_{SL1}	(CV)	0.762	13.5	17.9
IIV $k_{a,q1w2}$	(CV)	0.570	7.49	12.1
IIV F_{q1w1}	(CV)	0.901	8.12	15.8
IIV $k_{a,q4w2}$	(CV)	0.400	9.83	7.60
IIV F_{q4w1}	(CV)	0.891	9.08	5.11
Prop. RUV		0.277	0.303	6.26

a = Patients versus healthy volunteers. b = Females versus males. Parameter estimates are rounded to 3 significant digits. CL: clearance; CV: coefficient of variation; DSL1: duration of drug input to compartment SL1; DQ1W1: duration of drug input to compartment q1w1; FSL1: fraction of bioavailable dose going into compartment SL1; Fq1w1: fraction of dose going into compartment q1w1; Fq4w1: fraction of dose going into compartment q4w1; FSL: bioavailability after SL BPN dosing; IIV: inter-individual variability; ka,SL1: first-order rate constant from compartment SL1; ka,SL2: first-order rate constant from compartment SL2; ka,q1w1: first-order rate constant from compartment q1w1; ka,q1w2: first-order rate constant from compartment q1w2; ka,q4w1: first-order rate constant from compartment q4w1; ka,q4w2: first-order rate constant from compartment q4w2; OFV: objective function value; Q2: inter-compartmental clearance to second compartment; Q3: inter-compartmental clearance to third compartment; RSE: relative standard error; RUV: residual unexplained variability; SD: standard deviation; SHR: shrinkage; tlag,SL1: lag-time to compartment SL1;V2: volume of second compartment; V3: volume of third compartment; Vc: central volume of distribution.

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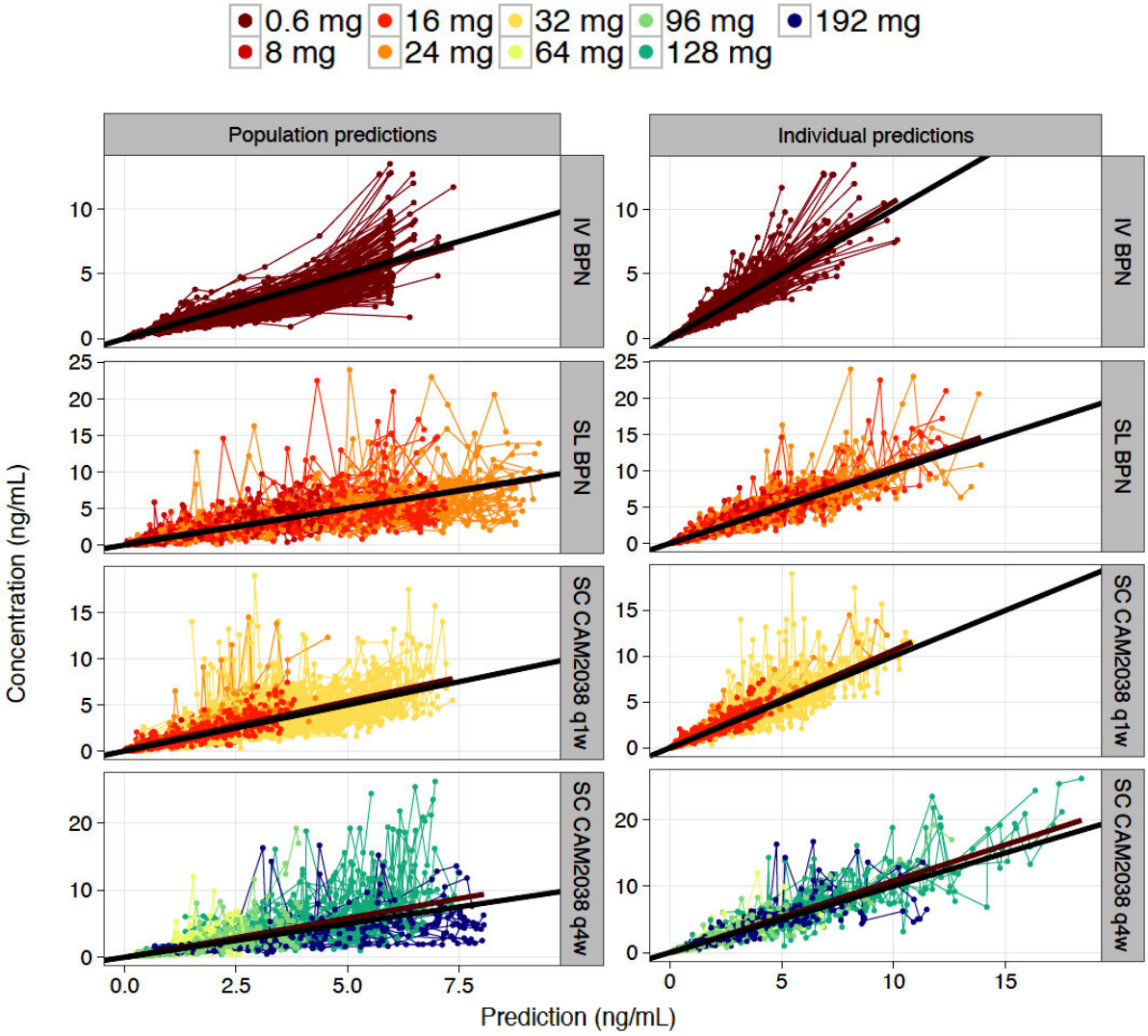
The diagnostic plots for the final population PK model (run336) are shown in the figures below.

Figure 4.1.1e: Diagnostic Plots for Applicant's Final Population PK Model (run336)



Individual data points are indicated by dots and the points for each individual and visit are connected with a line. The points and lines are colored according to the dose. The diagonal black line is the line of identity and the red line is a smooth.

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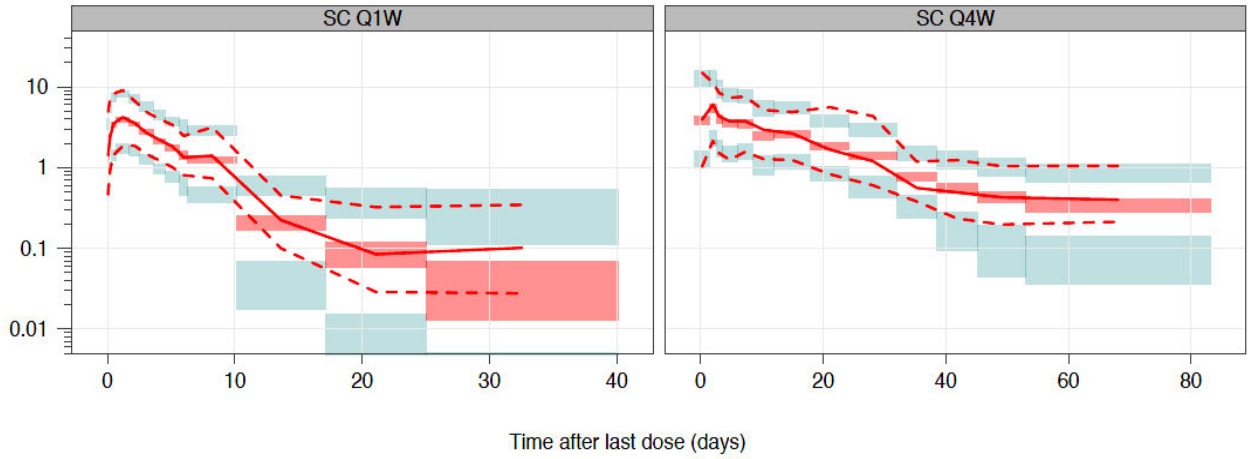
The following plot presents results from the Applicant's visual predictive check of the final population PK model (run336).

Figure 4.1.1f: Visual Predictive Check for Applicant's Final Population PK Model (run336)



Prediction corrected visual predictive check of BPN concentrations, for the final BPN population PK model. BPN concentrations are displayed versus time after last dose in days, on a semi-logarithmic scale, and stratified by formulation. The solid and dashed red lines represent the median, 2.5th and 97.5th percentiles of the observations; the shaded red and blue areas represent the 95% confidence interval of the median, 2.5th and 97.5th percentiles predicted by the model. The left panel represents the weekly formulation and the right panel represents the monthly formulation

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[*Reviewer comment: Though there are some outliers with 3-4 fold underprediction (e.g. for SC CAM2038 q4w concentration versus prediction plot), the diagnostic plots do not demonstrate any systematic bias across the available range of PK samples.*

The VPC indicates that the Applicant's population PK model appears to overpredict starting at approximately 30 days following an injection when simulating the weekly formulation. The over-prediction is especially apparent for the lower end of the concentrations. However, the overprediction appears to occur in the vicinity of the assay's LLOQ.

A similar trend is seen for simulations of for the monthly formulation. However, the overpredicting for the monthly formulation is less severe presumably due to the buprenorphine plasma concentration being higher (and thus a greater proportion of the PK samples are above the LLOQ).

If the model truly overpredicts, then the estimates of the time until BLQ based on population PK simulation may be conservative (that is, the actual time to BLQ may be less than the predicted time until BLQ). ***Overall, the population PK model is acceptable.***]

4.1.2 Reviewer's PK Analyses – Determining PK Profile After Last Injection At Steady-State

OCP investigated the PK profile after the last injection of CAM2038 at steady-state for both CAM2038 weekly and CAM2038 monthly formulations. This information was sought to inform labeling statements regarding the duration for which subjects have detectable buprenorphine exposure after discontinuation.

The reviewer conducted PK simulations to determine the concentration-time profile after the last CAM2038 injection for both the maximum recommended CAM2038 weekly dose (32 mg once weekly) as well as the maximum recommended CAM2038 monthly dose (128 mg once monthly). The Applicant's population PK model was used to conduct the PK simulations (please refer to section 4.3.1 for details regarding the model). A virtual patient was created to present the central tendency of the population PK profile. The virtual patient was male, was assigned the median weight of 72.4 kg and the median age of 35 years.

The virtual patient received 5 injections of 32 mg once weekly CAM2038 and in a separate scenario 5 injections of 128 mg once monthly CAM2038 in order to represent steady-state PK for both CAM2038 formulations. The mean PK profiles for these two scenarios are shown in the figures below.

Figure 4.1.2a: Simulated PK Profile for Five Injections of 32 mg Once Weekly SC CAM2038

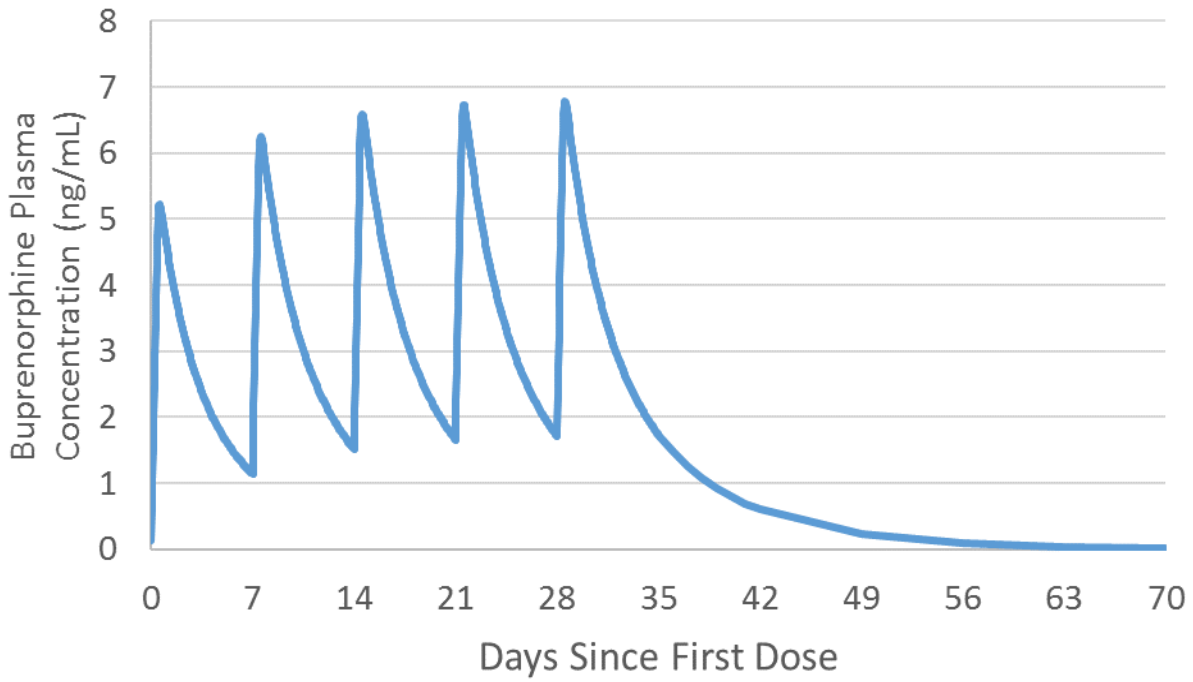
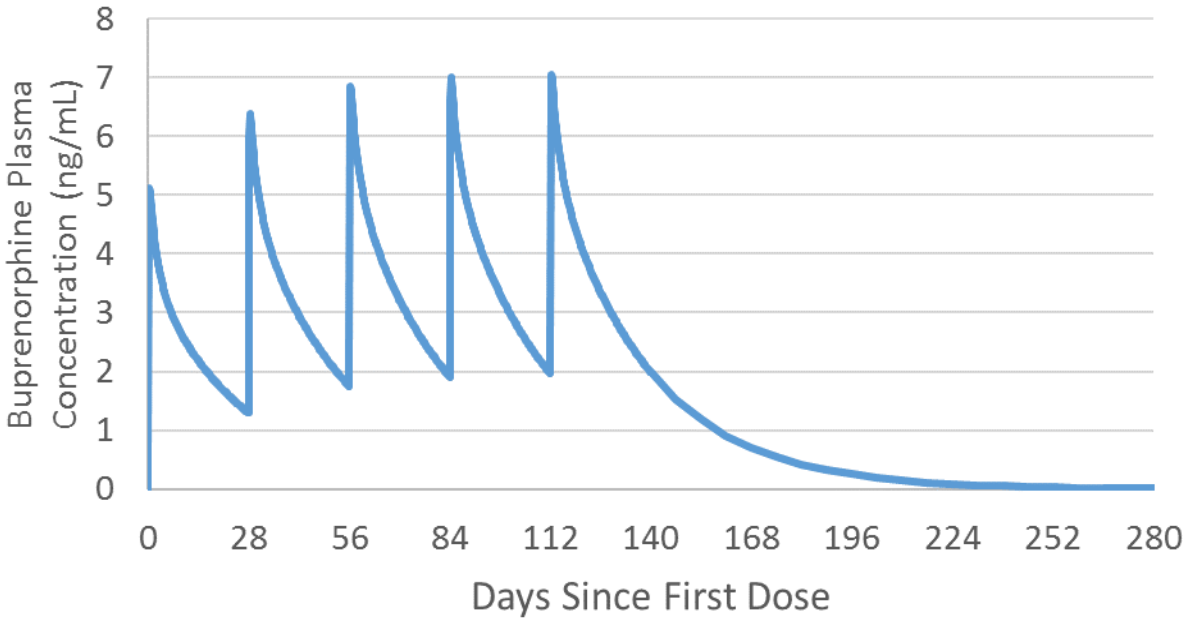


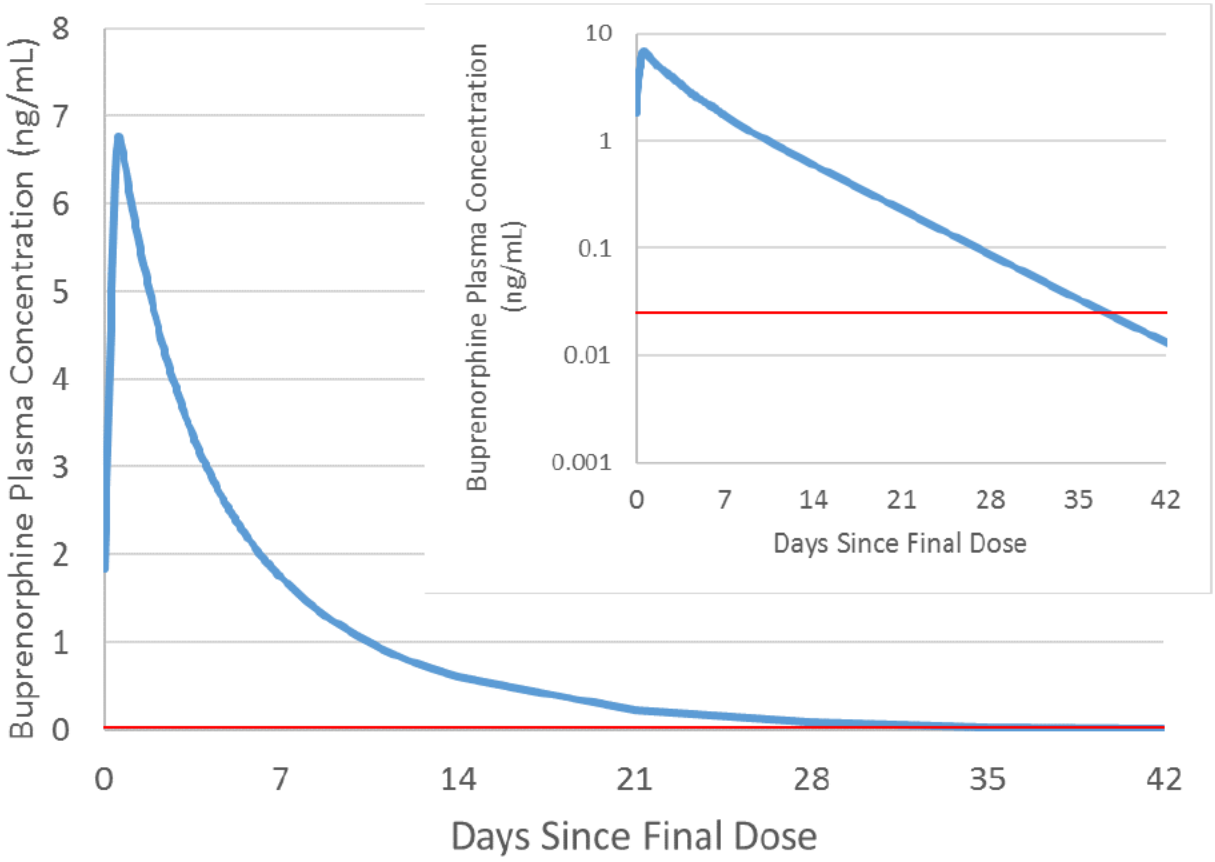
Figure 4.1.2b: Simulated PK Profile for Five Injections of 128 mg Once Monthly SC CAM2038



*****A month was considered to be 28 days for the purposes of this simulation.

The following figures show the above PK profiles starting from the last injection where time zero is the time of the last injection.

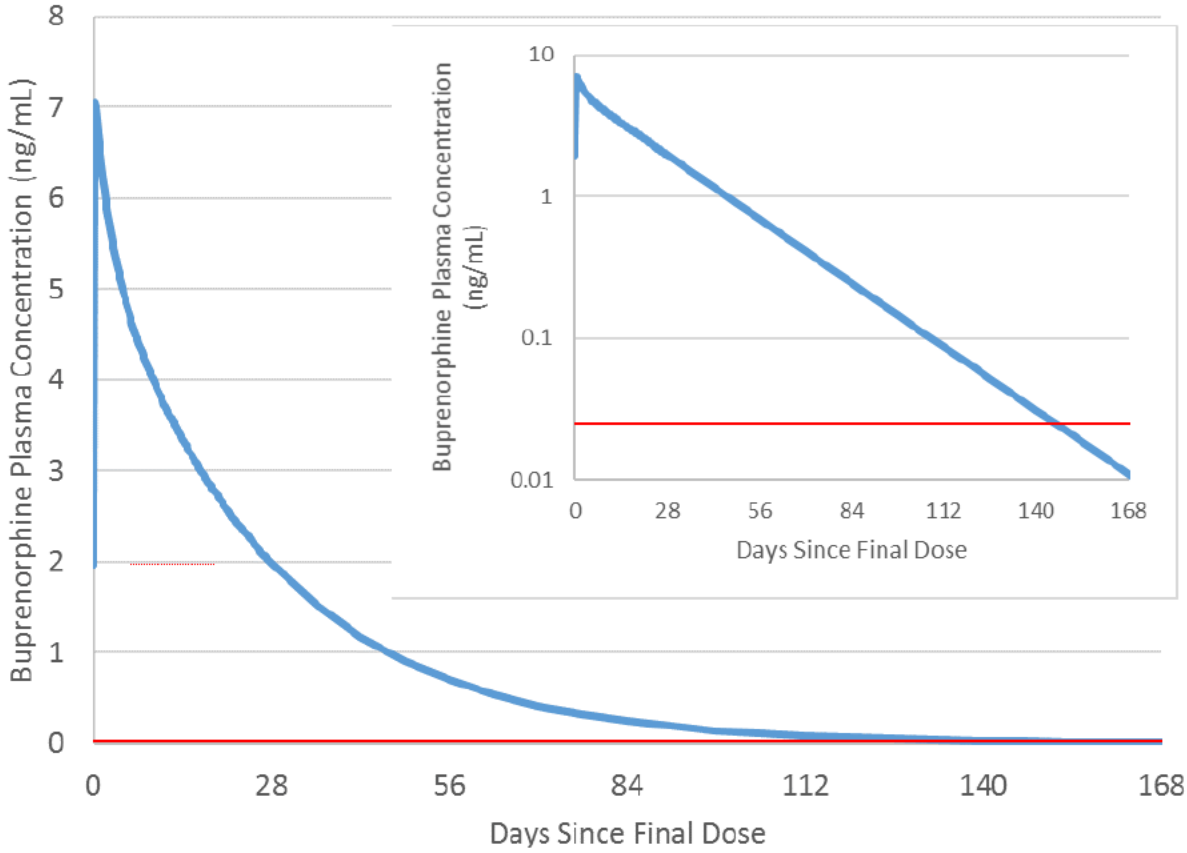
Figure 4.1.2c: Simulated PK Profile Following a Final Injection at Steady-State from a 32 mg Once-Weekly SC CAM2038 Regimen



Main figure shows the PK profile with the y-axis (buprenorphine concentration) on a linear scale. The inset figure shows the same data with the y-axis on a $\log_{10}$ scale to provide a clearer view of when the buprenorphine plasma concentration profile is expected to drop below the LLOQ (0.025 ng/mL; the red horizontal line).

A patient receiving 32 mg once weekly SC CAM2038 and at steady-state can be expected to have plasma exposures that are detectable for up to 6 weeks following the final injection.

Figure 4.1.2d: Simulated PK Profile Following a Final Injection at Steady-State from a 128 mg Once-Monthly SC CAM2038 Regimen



Main figure shows the PK profile with the y-axis (buprenorphine concentration) on a linear scale. The inset figure shows the same data with the y-axis on a $\log_{10}$ scale to provide a clearer view of when the buprenorphine plasma concentration profile is expected to drop below the LLOQ (0.025 ng/mL; the red horizontal line).

A patient receiving 128 mg once monthly SC CAM2038 and at steady-state can be expected to have plasma exposures that remain detectable for 6 months following the final CAM2038 injection.

Overall, based on PK simulations, when a patient ceases SC CAM2038 treatment while at steady-state, plasma buprenorphine concentration is expected to, on average, remain detectable up to 6 weeks after the final injection of the weekly formulation and for up to 6 months after the final injection of the monthly formulation.

4.2 Exposure-Response and PKPD Analyses

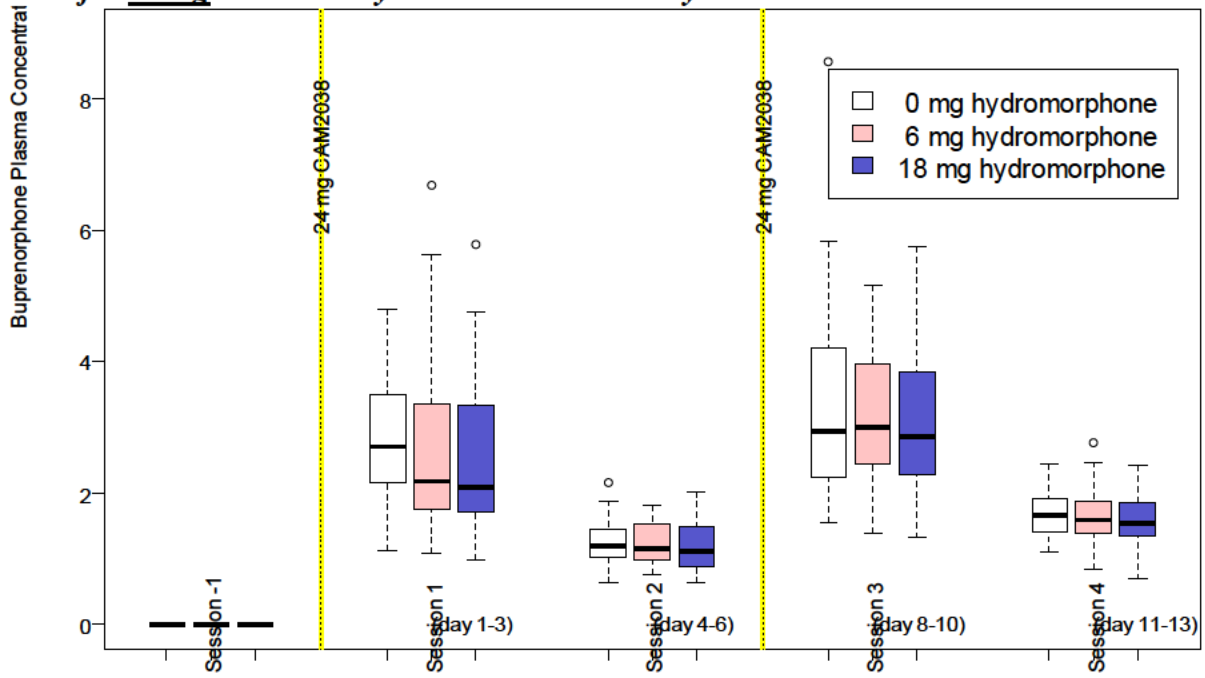
4.2.1 Reviewer's PKPD Analyses of Drug-Liking Data from Blockade Study HS-13-478

The blockade study HS-13-478 provided evidence of effectiveness of CAM2038. OCP conducted analyses to assess the relationship between the maximum (Emax) drug liking score and buprenorphine exposure following CAM2038 administration. These analyses were performed to further assess the potential for HS-13-478 study data to provide evidence of effectiveness.

PK and PD data were available from n=47 subjects in study HS-13-478, the blockade study. The blockade study assessed the effect of buprenorphine on the measure of how much a subject "likes" hydromorphone. Hydromorphone testing sessions were conducted throughout the study. A hydromorphone testing session consists of a 3-day period where a single dose of hydromorphone (0, 6, or 18 mg) was administered once per day for 3 consecutive days in a blinded randomized manner. Five hydromorphone test sessions were conducted during study HS-13-478; one hydromorphone testing session during baseline/qualification (where patients are not exposed to buprenorphine) and four hydromorphone testing sessions after administration of Weekly CAM2038. The 4 hydromorphone testing sessions were split such that two occurred during the week following the CAM2038 weekly injection for both CAM2038 weekly injections. Patients were randomized to receive two CAM2038 injections spaced one week apart at the 24 mg or 32 mg level. The Applicant's analyses subtracted the drug-liking score from placebo (0 mg hydromorphone" from the drug-liking score for 6 mg and 18 mg hydromorphone doses administered in each 3-day testing session each week.

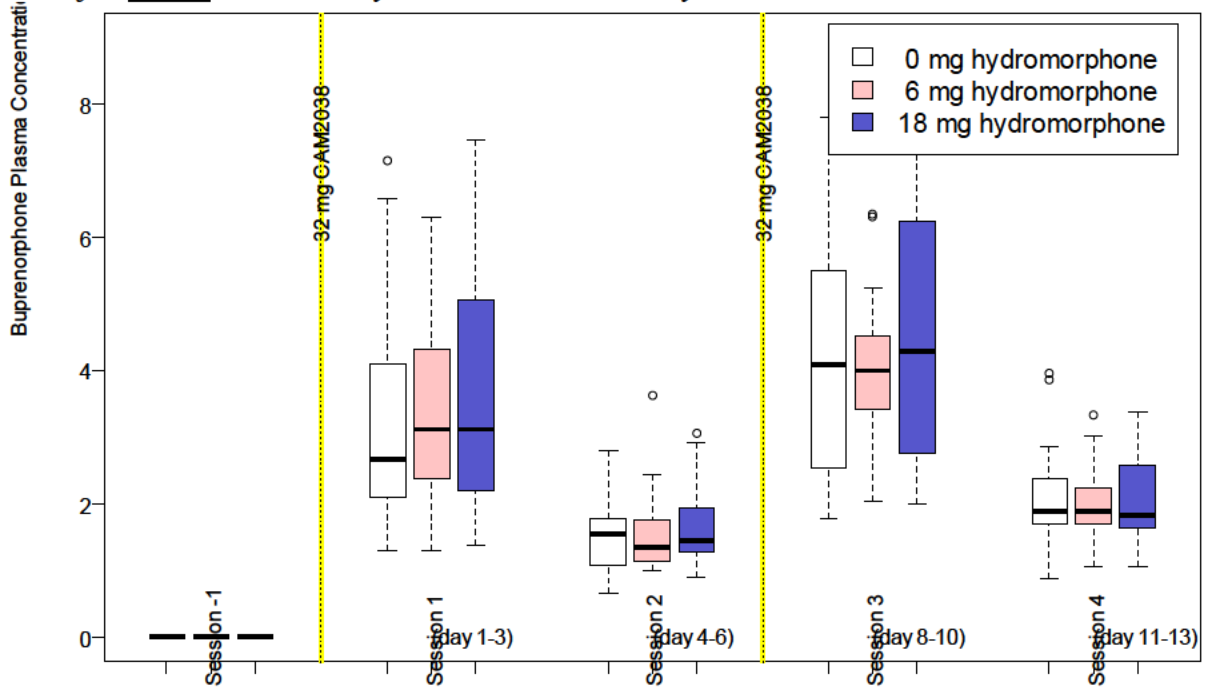
PK data were buprenorphine plasma concentrations measured immediately before each hydromorphone challenge. The figure below shows the distribution of buprenorphine plasma concentrations measured prior to each hydromorphone testing session in study HS-13-478.

Figure 4.2.1a: Distribution of Buprenorphine Concentration Measured Immediately Prior to Hydromorphone Session by Hydromorphone Session Number and By Hydromorphone Dose Level for <u>24 mg</u> Once Weekly SC CAM2038 in Study HS-13-478



*Vertical yellow lines indicate the timing of SC injections of CAM2038. The white, pink, and blue boxplots represent the buprenorphine concentration distribution immediately prior to the hydromorphone challenge for 0, 6, and 18 mg, respectively. The 3 hydromorphone sessions are presented in order of increasing hydromorphone dose level for ease of viewing but in the trial the hydromorphone dose sequence was randomized for each patient for each visit.

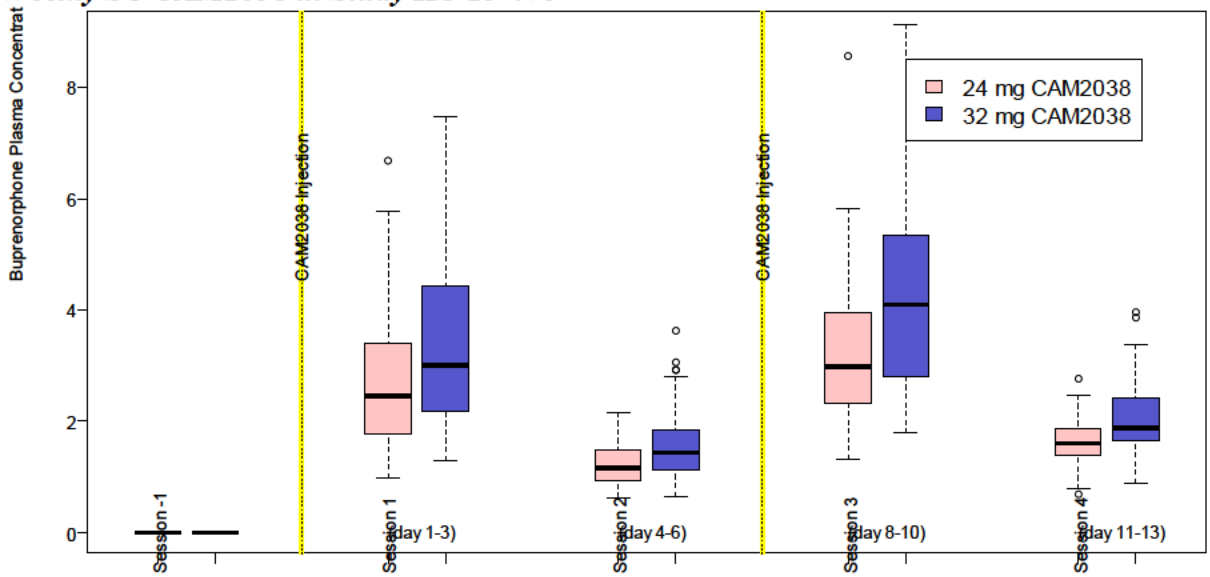
Figure 4.2.1b: Distribution of Buprenorphine Concentration Measured Immediately Prior to Hydromorphone Session by Hydromorphone Session Number and By Hydromorphone Dose Level for <u>32 mg</u> Once Weekly SC CAM2038 in Study HS-13-478



*Vertical yellow lines indicate the timing of SC injections of CAM2038. The white, pink, and blue boxplots represent the buprenorphine concentration distribution immediately prior to the hydromorphone challenge for 0, 6, and 18 mg, respectively. The 3 hydromorphone sessions are presented in order of increasing hydromorphone dose level for ease of viewing but in the trial the hydromorphone dose sequence was randomized for each patient for each visit.

The previous two figures demonstrate that hydromorphone administration does not affect buprenorphine exposure, as expected. As such, the data in the figure above were pooled to include all buprenorphine exposures measured prior to all 3 hydromorphone test sessions per in each test session.

Figure 4.2.1c: Distribution of Buprenorphine Concentration Measured Immediately Prior to Hydromorphone Session by Hydromorphone Session Number for both 24 mg and 32 mg Once Weekly SC CAM2038 in Study HS-13-478

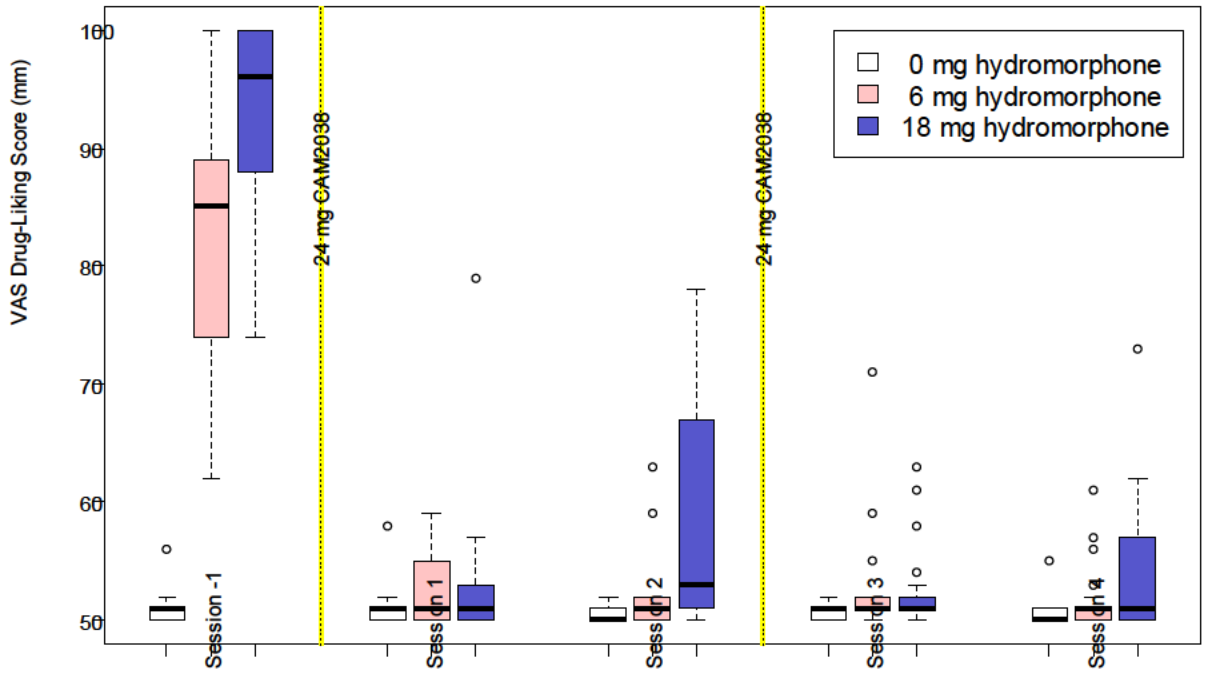


*Vertical yellow lines indicate the timing of SC injections of CAM2038.

The figure above shows that the buprenorphine exposure decreases over the interval such there is modest accumulation following the second weekly injection compared to the first injection for both 24 mg and 32 mg SC CAM2038. The accumulation is most apparent in the early portion of the dosing interval (e.g. comparing Session 3 to Session 1).

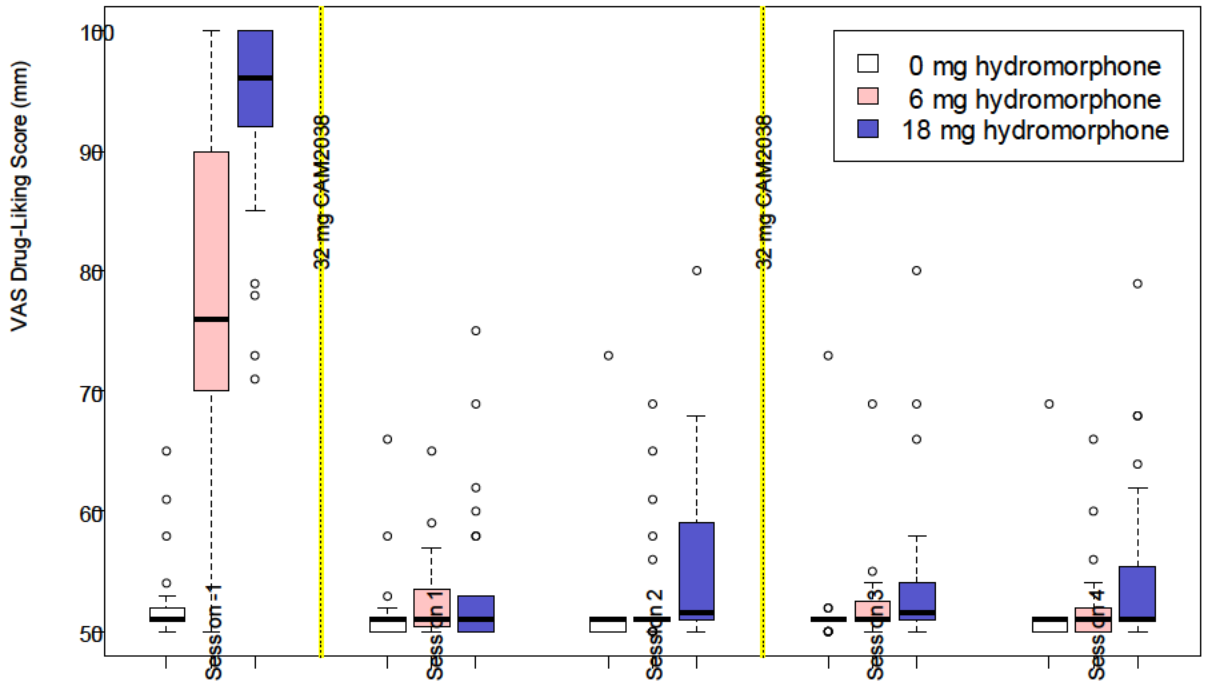
The PD measurement was the maximum drug-liking assessment (E_{max}) during each 3-day hydromorphone test session. The drug-liking is assessed using the bipolar Visual Analog Scale (VAS) where a 10 cm line segment on a piece of paper is presented to a subject and their "drug liking" is measured by pointing to the location on the line segment that corresponds to their current "like" for hydromorphone. A score of 0 mm is strongest dislike, 50 mm is neutral, and 100 mm is strongest like. The plots below show the distribution of E_{max} drug liking scores for the 24 mg and 32 mg SC CAM2038 once weekly dose levels.

Figure 4.2.1d: Distribution of Drug-Liking Scores by Hydromorphone Dose Level and by Hydromorphone Test Session Number for <u>24 mg</u> Once Weekly SC CAM2038 in Study HS-13-478



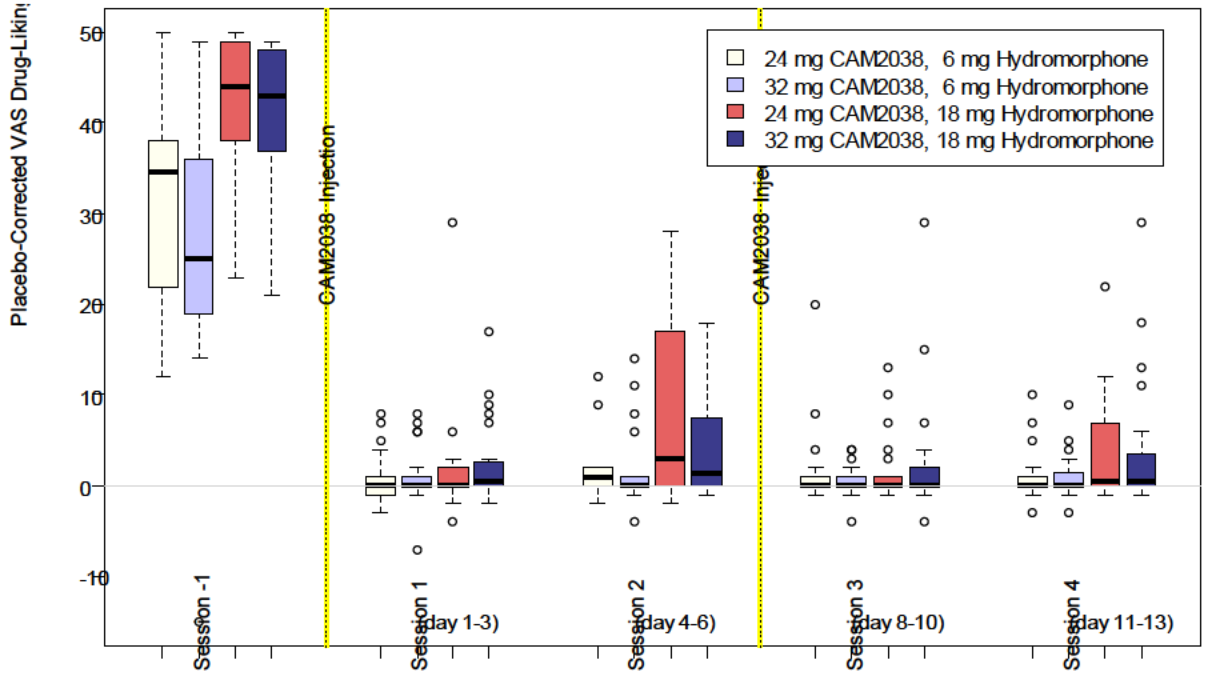
*Vertical yellow lines indicate the timing of SC injections of SC CAM2038. The white, pink, and blue boxplots represent the Emax drug-liking score distribution observed during the hydromorphone challenge for 0, 6, and 18 mg, respectively. The 3 hydromorphone sessions are presented in order of increasing hydromorphone dose for ease of viewing but in the trial the hydromorphone dose sequence was randomized for each patient for each visit.

Figure 4.2.1e: Distribution of Drug-Liking Scores by Hydromorphone Dose Level and by Hydromorphone Test Session Number for <u>32 mg</u> Once Weekly SC CAM2038 in Study HS-13-478



The previous two figures demonstrate that the "placebo-response" (drug-liking for the 0 mg hydromorphone session) was comparable across all hydromorphone test sessions and for both CAM2038 dose levels. As the placebo-response is consistent across all arms, and since the Applicant utilized placebo-corrected E_{max} values for 6 mg and 18 mg hydromorphone for data analysis, the distribution of placebo-corrected E_{max} scores was also plotted (see figure below).

Figure 4.2.1f: Distribution of Placebo-Corrected Drug-Liking Scores by Hydromorphone Dose Level, by CAM2038 Dose Level, and By Hydromorphone Test Session Number in Study HS-13-478



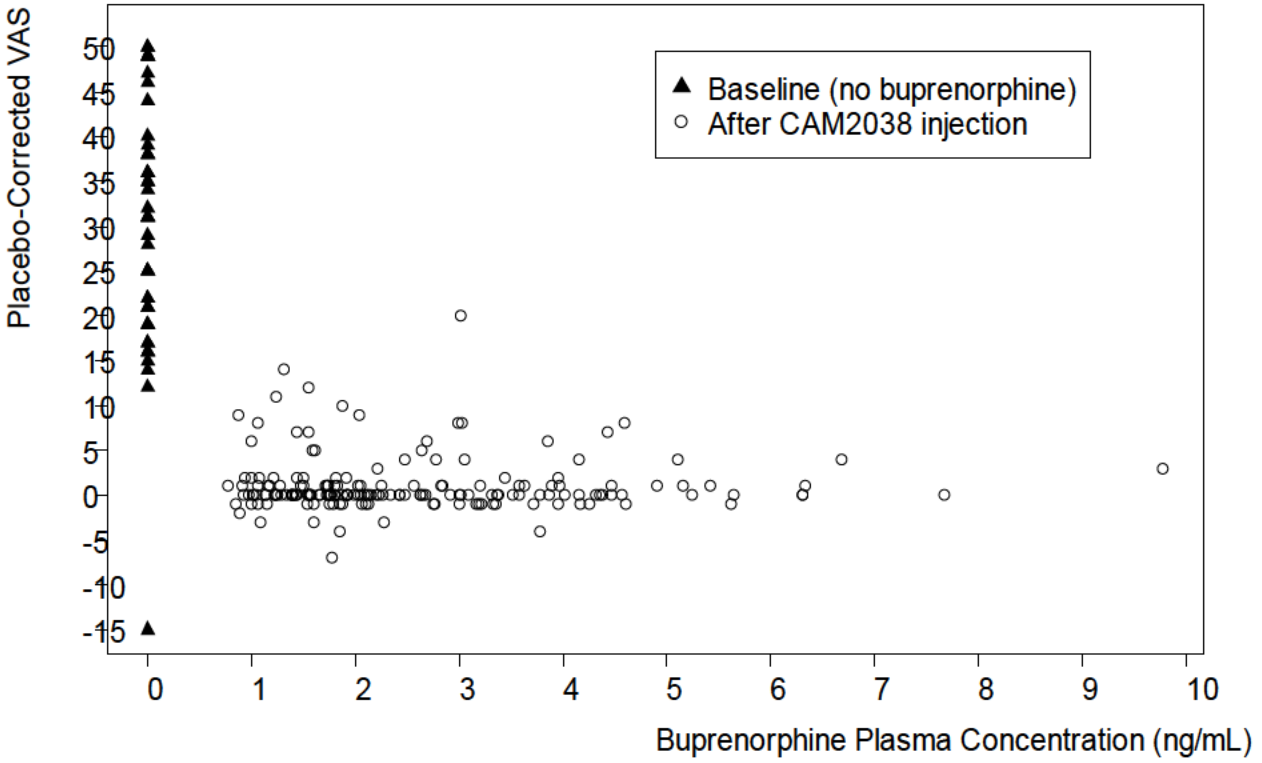
*Vertical yellow lines indicate the timing of SC injections of CAM2038. The boxplots represent the placebo-corrected Emax drug-liking score distribution observed during the hydromorphone challenge for 6 and 18 mg while on 24 mg or 32 mg CAM2038. The 2 hydromorphone sessions are presented in order of increasing hydromorphone dose value for ease of viewing but in the trial the hydromorphone dose sequence was randomized for each patient for each visit.

Looking at the figure above, the following observations are apparent:

- *Drug liking is highest during the Session -1, the baseline/qualification session, where the hydromorphone challenge was conducted in the absence of buprenorphine*
- *Drug-liking is reduced after CAM2038 administration (at and after Session 1) compared to drug-liking assessed during baseline*
- *CAM2038 appears to be more effective at reducing the "like" for the 6 mg hydromorphone dose than the 18 mg hydromorphone dose*
- *The drug-liking scores tend to be higher at the end of the dosing interval compared to the beginning (e.g. Session 2 vs 1, or Session 4 vs 3). The increase in drug-liking over the course of a dosing interval may be related to decreasing buprenorphine exposure throughout the course of the dosing interval.*
- *"Drug like" scores at the end of the dosing interval were generally higher for 24 mg CAM2038 than for 32 mg CAM2038.*

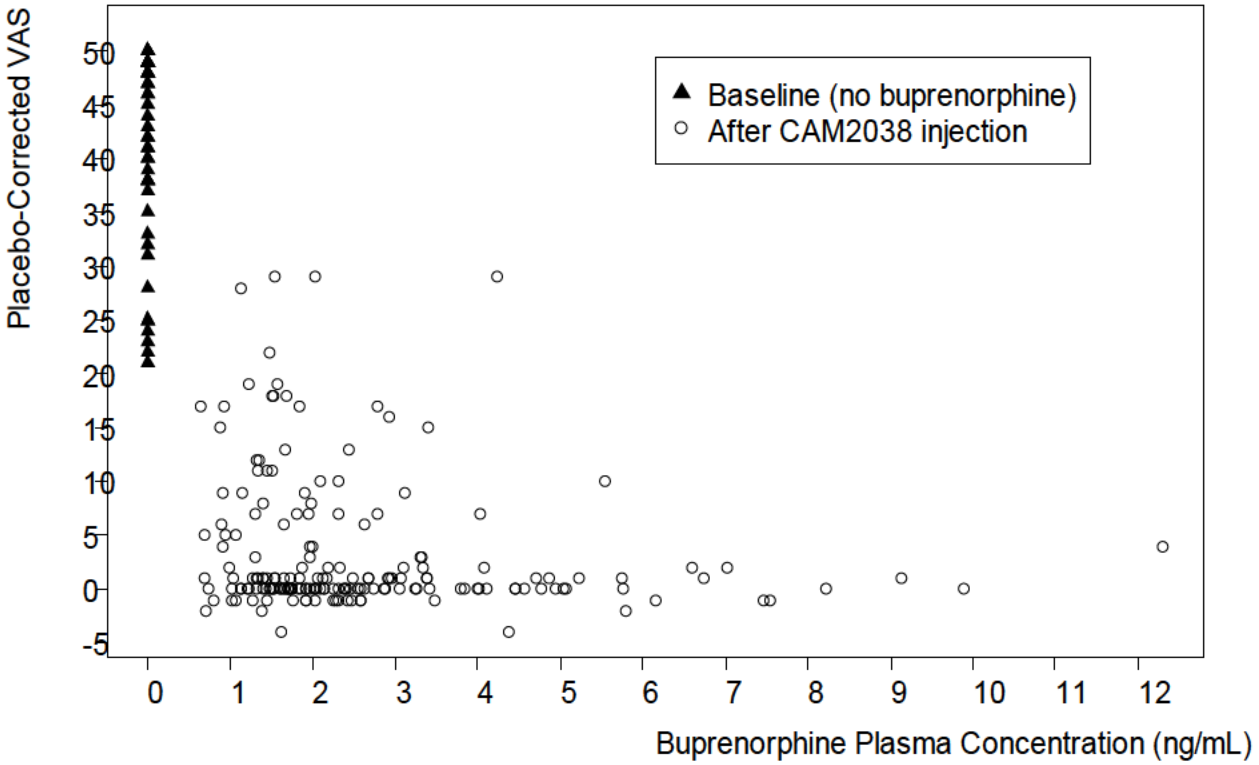
The plots of buprenorphine concentration versus time and placebo-corrected Emax versus time show the exposure and "response" independent to one another. A graphical analysis was conducted to explore the relationship between PK and PD. Scatter plots as well as decile plots were generated to assess the relationship between PK and PD (see figures below).

Figure 4.2.1g: Scatter Plot of Placebo-Corrected Drug-Liking Scores With Corresponding Buprenorphine Concentration for the 6 mg Hydromorphone Dose at Baseline and Throughout 2 Week Study Period for Pooled 24 mg and 32 mg CAM2038 Arms in Study HS-13-478



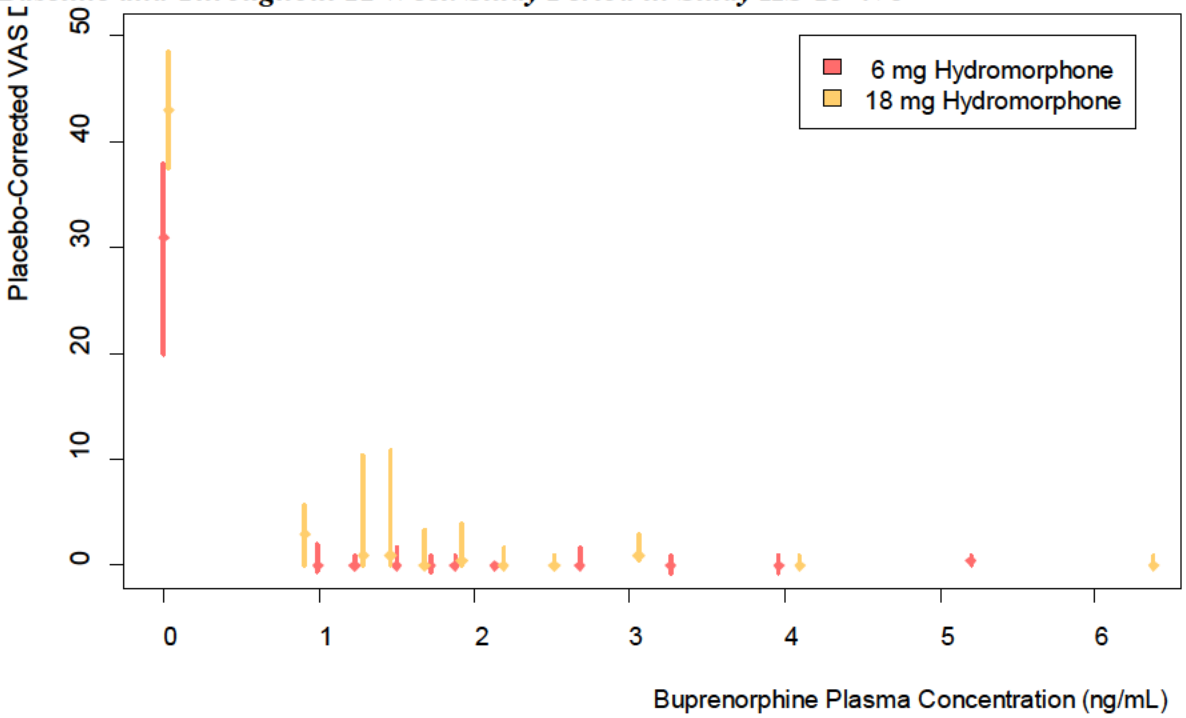
The solid triangle points represent the drug-liking scores observed during Session -1 (baseline/qualification period) in the absence of buprenorphine and the circles represent observations acquired after initiating SC CAM2038.

Figure 4.2.1h: Scatter Plot of Placebo-Corrected Drug-Liking Scores With Corresponding Buprenorphine Concentration for the <u>18 mg</u> Hydromorphone Dose at Baseline and Throughout 2 Week Study Period for Pooled 24 mg and 32 mg CAM2038 Arms in Study HS-13-478



The solid triangle points represent the drug-liking scores observed during Session -1 (baseline/qualification period) in the absence of buprenorphine and the circles represent observations acquired after initiating SC CAM2038.

Figure 4.2.1i: Quantiles of Placebo-Corrected Drug-Liking Scores With Corresponding Buprenorphine Concentration Deciles for 6 mg and 18 mg Hydromorphone Dose Levels at Baseline and Throughout 12 Week Study Period in Study HS-13-478

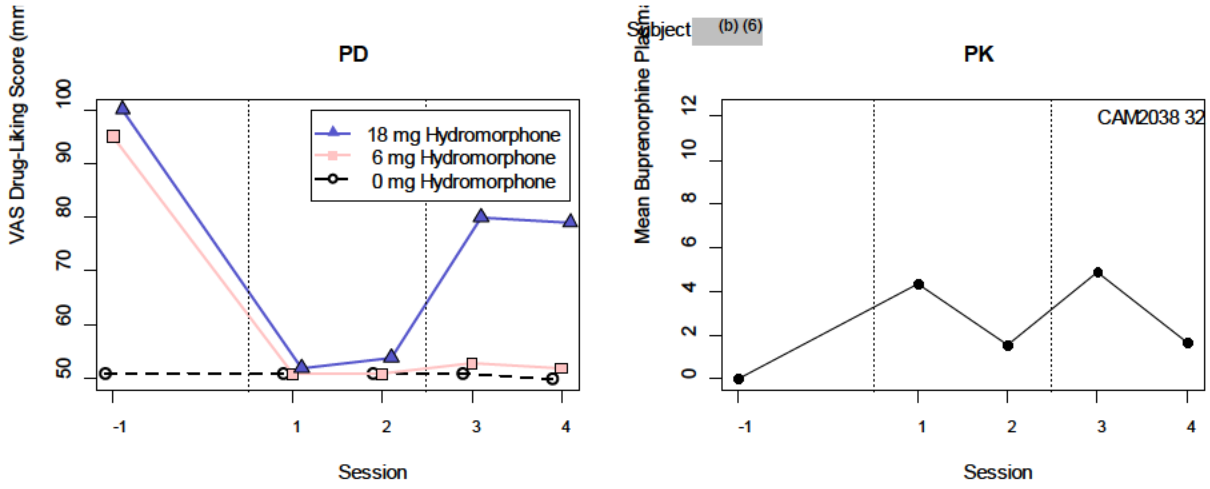


The red and orange bars represent the 25th, 50th, and 75th percentiles of placebo-corrected Emax drug liking scores for 6 mg and 18 mg hydromorphone challenge sessions, respectively. Each pair of red and orange bars represents the distribution of placebo-corrected Emax drug liking scores at baseline (in absence of buprenorphine) and within the bins of each of 10 buprenorphine concentration deciles.

The three previous plots demonstrate an apparent central tendency of increasing effectiveness with increasing exposure. However, these plots also demonstrate that the dispersion in drug-liking scores is wider at the lower buprenorphine exposures compared to higher buprenorphine exposures. The dispersion in the drug-liking scores was further investigated to explore and potentially uncover a reason for the wide range of drug-liking scores observed at lower buprenorphine exposures.

When looking at the individual time course of buprenorphine concentration alongside the time course of drug-liking scores, several individuals were discovered to display vast differences in the drug-liking scores from one dosing interval to the next despite having comparable exposures. The following plot shows the time-course of PK and PD data for one representative individual (subject (b) (6)). Approximately one quarter of the subjects enrolled exhibited this phenomenon.

Figure 4.2.1j: Representative Individual With Abrupt Changes in Drug-Liking Between Dosing Intervals



The left panel shows the drug liking scores which remain comparable during Session 1 and 2, then increase abruptly at session 3 and are maintained into session 4 without correlation with the PK profile. The reason for these abrupt changes in drug liking observed in Subject (b) (6) *as well as others is currently unknown.*

Overall, the available PK and PD data provide supportive evidence of opioid blockade*. There is an overall trend of increasing response (that is, reduced drug-liking) with increasing buprenorphine exposure. As expected, higher buprenorphine exposures are required to reduce the drug-liking following an 18 mg hydromorphone challenge compared to a 6 mg hydromorphone challenge.*

However, ***there are some subjects in whom the drug-liking scores undergo seemingly abrupt changes of large magnitude which do not correlate with the buprenorphine*** *(as was the case in approximately one quarter of the subjects, and was illustrated in the figure above when comparing drug-liking before and after the 2nd CAM2038 injection).* ***These observations suggest that factors other than buprenorphine concentration, factors that are currently unidentified, likely contribute to the drug-liking scores****.*

4.3 Study Designs with links to Studies:

Clinical Pharmacology Studies:

HS-07-307: A Phase I/II, Single-Blind, Single-Dose, Dose-Escalation, Parallel-Group, First-Time-In-Man Trial to Investigate the Tolerability, Pharmacokinetics, and Pharmacodynamics of CAM2038-G in Patients with Opioid Dependence

\\cdsesub1\evsprod\nda210136\0002\m5\53-clin-stud-rep\533-rep-human-pk-stud\5332-patient-pk-init-tol-stud-rep\hs-07-307

Study: HS-11-426: A Phase I, Randomized, Open-label, Active-Controlled, Three-way Treatment Trial Assessing Pharmacokinetics, Bioavailability and Safety of Three Doses of CAM2038 q1w (Once weekly) (Buprenorphine FluidCrystal® Injection Depot), Versus Active Comparators, Intravenous and Sublingual Buprenorphine, in Healthy Volunteers under Naltrexone Blockage

\\cdsesub1\evsprod\nda210136\0002\m5\53-clin-stud-rep\533-rep-human-pk-stud\5331-healthy-subj-pk-init-tol-stud-rep\hs-11-426

Study HS-13-487*: A Phase I, Randomized, Open-label, Active-Controlled, Three-way Treatment Trial Assessing Pharmacokinetics, Bioavailability and Safety of Four Single Doses of CAM2038 (Buprenorphine FluidCrystal® Injection Depot) q4w (Once Monthly) and Four Repeat Doses of CAM2038 q1w (Once-Weekly) Versus Active Comparators, Intravenous and Sublingual Buprenorphine in Healthy Volunteers under Naltrexone Blockage*

\\cdsesub1\evsprod\nda210136\0002\m5\53-clin-stud-rep\533-rep-human-pk-stud\5331-healthy-subj-pk-init-tol-stud-rep\hs-13-487

Study 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

\\cdsesub1\evsprod\nda210136\0002\m5\53-clin-stud-rep\534-rep-human-pd-stud\5342-patient-pd-stud-rep\hs-13-478

Study HS-15-549: 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

\\cdsesub1\evsprod\nda210136\0002\m5\53-clin-stud-rep\533-rep-human-pk-stud\5332-patient-pk-init-tol-stud-rep\hs-15-549

Population PK report: Population Pharmacokinetic Analysis of Buprenorphine after CAM2038 Administration in Studies HS-11-426, HS-13-487, HS-13-478, and HS-15-549

\\cdsesub1\evsprod\nda210136\0002\m5\53-clin-stud-rep\533-rep-human-pk-stud\5335-popul-pk-stud-rep\cam2038-pmx-1

Clinical Studies:

Study 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 Injectable Depot of Buprenorphine (CAM2038) in Treatment of Adult Outpatients with Opioid Use Disorder

\\cdsesub1\evsprod\nda210136\0002\m5\53-clin-stud-rep\535-rep-effic-safety-stud\opioid-use-disorder\5351-stud-rep-contr\hs-11-421

Study HS-14-499: An Open-Label Multicenter Study Assessing the Long-Term Safety of a Once-Weekly and Once-Monthly, Long-Acting Subcutaneous Injection Depot of Buprenorphine (CAM2038) in Adult Outpatients with Opioid Use Disorder

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4.4 Filing Form

CLINICAL PHARMACOLOGY FILING FORM

Application Information			
NDA/BLA Number	210136; 505(b)(2)	**SDN**	002
Applicant	Braeburn Pharmaceuticals, Inc.	**Submission Date**	5/08/17 Rolling NDA
Generic Name	CAM2038 (buprenorphine-depot); q1w- one week depot SC inj. q4w- one month depot SC inj.	**Brand Name**	(b) (4)
Drug Class	Addiction		
Current Indication	Treatments of opioid use disorder.		
Dosage Regimen and Doses	• q1w, 50 mg/mL BPN ○ 8 mg (0.16 mL volume), 16 mg, 24 mg, and 32 mg (0.64 mL) (b) (4) • q4w, (b) (4) mg/mL BPN ○ 64 mg (0.18 mL), 96 mg, 128 mg (b) (4) (b) (4)		
Dosage Strength	q1w, 50 mg/mL BPN q4w, (b) (4) mg/mL BPN		
Dosage Form	Solution	**Route of Administration**	Subcutaneous injection
OCP Division	DCP 2	**OND Division**	DAAAP

OCP Review Team	Primary Reviewer(s)	Secondary Reviewer/ Team Leader
Division	Suresh B Naraharisetti	Yun Xu
Pharmacometrics	Michael Bewernitz	Kevin Krudys
Genomics		

Review Classification	☐ Standard ☑ Priority ☐ Expedited		
Filing Date	8/30/17	**60-Day Letter Date**	
Review Due Date		**PDUFA Goal Date**	
Advisory Committee Date	11/01/17 scheduled		

Application Fileability

Is the Clinical Pharmacology section of the application fileable?

☑Yes

☐No

If no list reason(s):

Are there any potential review issues/ comments to be forwarded to the Applicant in the 74-day letter?

☐Yes
☑ No
If yes list comment(s):

Is there a need for clinical trial(s) inspection?
☐Yes
☑ No
If yes explain:

Clinical Pharmacology Package

Tabular Listing of All Human Studies	☑ Yes ☐ No	Clinical Pharmacology Summary	☑ Yes ☐ No
Bioanalytical and Analytical Methods	☑ Yes ☐ No	Labeling	☑ Yes ☐ No

Clinical Pharmacology Studies

Study Type		Count	Comment(s)
In Vitro Studies			
☐ Metabolism Characterization			
☐ Transporter Characterization			
☐ Distribution			
☑ Drug-Drug Interaction			Drug interaction assessed with PB-PK modeling
In Vivo Studies			
Biopharmaceutics			
☑ Absolute Bioavailability			Buprenorphine exposure compared to IV dosage form • Studies - HS-11-426 and HS-13-487
☑ **Relative Bioavailability**			Buprenorphine exposure compared to sublingual dosage form • Studies - HS-11-426 and HS-13-487
☐ Bioequivalence			
☐ Food Effect			
☐ Other			
Human Pharmacokinetics			
Healthy Subjects	☑Single Dose		Healthy; Phase1: HS-11-426 and HS-13-487
	☑Multiple Dose		Healthy; Phase1: HS-11-426 and HS-13-487
Patients	☑ Single Dose	3	Opioid-dependent subjects; Phase 1: Study No. HS-07-307
	☑ Multiple Dose	4	Opioid Challenge Study; Phase1: HS-13-478 Opioid-dependent subjects; Phase 1: Study No. HS-07-307 Treatment seeking opioid-dependent subjects; Phase 3: HS-11-421, HS-14-499 Pop PK analyses (Report- Cam2038-pmx-1)
☐ Mass Balance Study			
☑ Other (e.g. dose			Linearity assessed in single dose and multiple dose PK

proportionality)		studies
Intrinsic Factors		
☐ Race		
☐ Sex		
☐ Geriatrics		
☐ Pediatrics		
☐ Hepatic Impairment		
☐ Renal Impairment		
☐ Genetics		
Extrinsic Factors		
☐ Effects on Primary Drug		
☐ Effects of Primary Drug		
Pharmacodynamics		
☐ Healthy Subjects		
☐ Patients		
Pharmacokinetics/Pharmacodynamics		
☐ Healthy Subjects		
☐ Patients		
☑ QT	1	• Serial measurements of BPN plasma concentration (including Cmax) and ECG were assessed after administration of IV BPN (Temgesic), SL BPN (Subutex), SC q1w and SC q4w in healthy volunteers under NTX blockage (HS-11-426 and HS-13-487) and after administration of q1w and q4w in patients with opioid dependence and a history of chronic non-cancer pain (HS-15-549) • PK/PD relationships between BPN and ECG and measured QT intervals corrected for heart rate using the Fridericia's correction (QTcF) were evaluated for CAM2038 q1w, CAM2038 q4w, Subutex and Temgesic
Pharmacometrics		
☑ Population Pharmacokinetics	6	Report- Cam2038-pmx-1 • Population PK analysis of BPN was performed including data for IV BPN (Temgesic), SL BPN (Subutex) and SC q1w and q4w from studies HS-11-426, HS-13-487, HS-13-478 and HS-15-549 • Population PK model of BPN was used for evaluation of the influence of covariates on the PK of BPN and for simulations of different treatment schedules with q1w, q4w and SL BPN (Subutex) (b) (4) predicted PBPK modeling
☑ Exposure-Efficacy		
☐ Exposure-Safety		

Total Number of Studies	**In Vitro**		**In Vivo**	11
Total Number of Studies to be Reviewed				11

Criteria for Refusal to File (RTF)		
RTF Parameter	**Assessment**	**Comments**
1. Did the applicant submit bioequivalence data comparing to-be-marketed product(s) and those used in the pivotal clinical trials?	☐Yes ☐No ☑N/A	
2. Did the applicant provide metabolism and drug-drug interaction information? (Note: RTF only if there is complete lack of information)	☑Yes ☐No ☐N/A	(b) (4) predicted PBPK modeling
3. Did the applicant submit pharmacokinetic studies to characterize the drug product, or submit a waiver request?	☑Yes ☐No ☐N/A	
4. Did the applicant submit comparative bioavailability data between proposed drug product and reference product for a 505(b)(2) application?	☑Yes ☐No ☐N/A	Relying for approval, in part, on Subutex SL tablet (N 20732) and literature for safety/toxicity (Pharmacology/Toxicology team)
5. Did the applicant submit data to allow the evaluation of the validity of the analytical assay for the moieties of interest?	☑Yes ☐No ☐N/A	
6. Did the applicant submit study reports/rationale to support dose/dosing interval and dose adjustment?	☑Yes ☐No ☐N/A	
7. Does the submission contain PK and PD analysis datasets and PK and PD parameter datasets for each primary study that supports items 1 to 6 above (in .xpt format if data are submitted electronically)?	☐Yes☑No ☐N/A	Information requests for datasets were communicated to Sponsor on 07/25/2017
8. Did the applicant submit the module 2 summaries (e.g. summary-clin-pharm, summary-biopharm, pharmkin-written-summary)?	☑Yes ☐No ☐N/A	
9. Is the clinical pharmacology and biopharmaceutics section of the submission legible, organized, indexed and paginated in a manner to allow substantive review to begin? If provided as an electronic submission, is the electronic submission searchable, does it have appropriate hyperlinks and do the hyperlinks work leading to appropriate sections, reports, and appendices?	☑Yes ☐No ☐N/A	
Complete Application **10.** Did the applicant submit studies including study reports, analysis datasets, source code, input files and key analysis output, or justification for not conducting studies, as agreed to at the pre-NDA or pre-BLA meeting? If the answer is 'No', has the sponsor submitted a justification that was previously agreed to before the NDA submission?	☐Yes ☑No ☐N/A	This is a rolling NDA. Information requests for datasets were communicated to Sponsor on 07/25/2017. Rolling submission sequences 0001 and 0002 did not contain NONMEM code or datasets. An IR was sent to the Sponsor requesting these items. Sequence 0004 contained NONMEM control streams, output logs, and input data files. Sequence 0007 contained dataset for the PK studies.
Criteria for Assessing Quality of an NDA (Preliminary Assessment of Quality) Checklist		
Data		
1. Are the data sets, as requested during pre-	☐Yes☑No ☐N/A	This is a rolling NDA. Information

submission discussions, submitted in the appropriate format (e.g., CDISC)?		requests for datasets were communicated to Sponsor on 07/25/2017
2. If applicable, are the pharmacogenomic data sets submitted in the appropriate format?	☐Yes ☐No ☑N/A	
Studies and Analysis		
3. Is the appropriate pharmacokinetic information submitted?	☑Yes ☐No ☐N/A	
4. Has the applicant made an appropriate attempt to determine reasonable dose individualization strategies for this product (i.e., appropriately designed and analyzed dose-ranging or pivotal studies)?	☑Yes ☐No ☐N/A	
5. Are the appropriate exposure-response (for desired and undesired effects) analyses conducted and submitted as described in the Exposure-Response guidance?	☑Yes ☐No ☐N/A	
6. Is there an adequate attempt by the applicant to use exposure-response relationships in order to assess the need for dose adjustments for intrinsic/extrinsic factors that might affect the pharmacokinetic or pharmacodynamics?	☑Yes ☐No ☐N/A	
7. Are the pediatric exclusivity studies adequately designed to demonstrate effectiveness, if the drug is indeed effective?	☐Yes ☐No ☑N/A	Same as other sublingual buprenorphine product such as Subutex, this product is unlikely to be used in pediatrics due to its indication.
General		
8. Are the clinical pharmacology and biopharmaceutics studies of appropriate design and breadth of investigation to meet basic requirements for approvability of this product?	☑Yes ☐No ☐N/A	
9. Was the translation (of study reports or other study information) from another language needed and provided in this submission?	☐Yes ☐No ☑N/A	

Filing Memo

The Applicant has submitted a New Drug Application (NDA) for [redacted] (CAM2038), buprenorphine- depot solution for injection under 505(b)(2) with Subutex® (sublingual [SL] BPN) as the reference product. The CAM2038 drug products are subcutaneous (SC) BPN depot injections of 1 week (CAM2038 50 mg/mL q1w) or 1 month (CAM2038 [redacted] mg/mL q4w), are indicated for the treatment of opioid dependence within a framework of medical, social and psychological treatment in adults and adolescents aged 16 years or older.

The Applicant describes that CAM2038 is based on the FC technology and are relatively low viscosity liquids. [redacted] When injected, the FC formulation immediately starts to transform into a liquid crystalline gel depot in contact with interstitial aqueous fluids and solvent release *in situ*. The gel formation results in effective encapsulation of the drug substance (BPN), which then is slowly released from the depot matrix over target of one week or one month treatment period. Release durations are controlled [redacted] The dual nature of the FC system with a liquid drug product *in vitro* before injection and stable gel *in vivo* after injection, enables manufacturing of ready-to-use products in pre-filled syringes. In addition, the CAM2038 injection volumes are low (0.16 to 0.64 mL) and the products are administered using a fine gauge (G) needle (23G).

The Applicant submitted the current NDA through the 505(b)(2) pathway and is relying for approval, in part, on the Agency's findings of safety and efficacy of Subutex sublingual table, N 20732.

Sponsor proposed the following transitions (Table 1) from daily doses of SL BPN to initial weekly doses of CAM2038 q1w or monthly doses of CAM2038 q4w.

Table 1: Proposed transfer from daily doses of SL BPN to initial weekly or monthly doses of CAM2038 q1w or CAM2038 q4w

Dose of daily SL BPN	**Dose of weekly CAM2038 q1w**
2-6 mg	8 mg
8-10 mg	16 mg
12-16 mg	24 mg
18-24 mg	32 mg
Dose of daily SL BPN	**Dose of monthly CAM2038 q4w**
8-10 mg	64 mg
12-16 mg	96 mg
18-24 mg	128 mg
[redacted]	

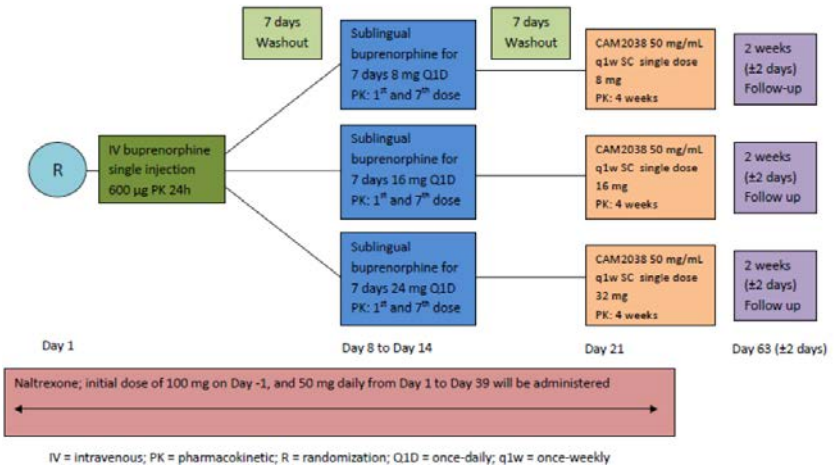
The CAM2038 development program consisted of seven (7) clinical studies under IND 114082. The following studies are submitted.

Pharmacokinetic Studies

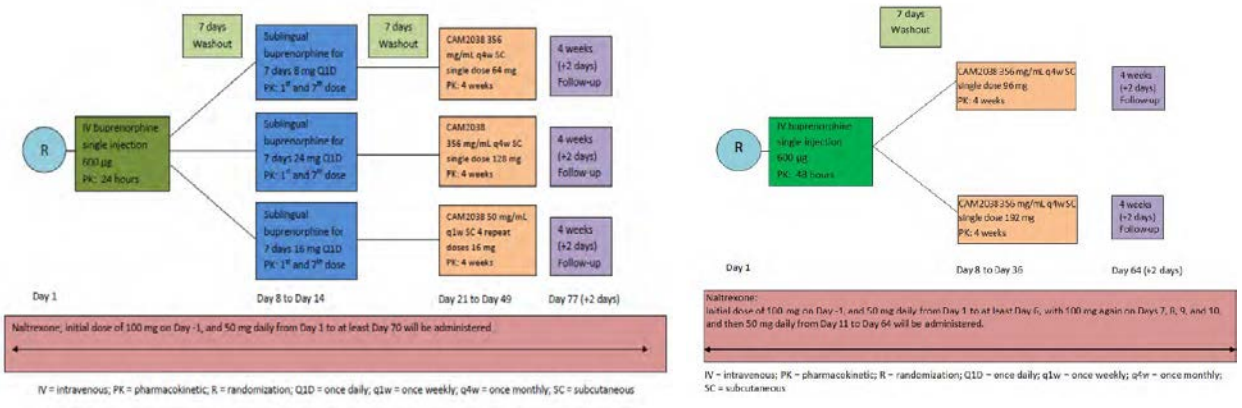
- **HS-07-307:** A Phase I/II, single-blind, single-dose, dose-escalation, parallel-group, first-time-in-man trial to investigate the tolerability, pharmacokinetics, and pharmacodynamics of CAM2038-G in patients with opioid dependence
  - q1w SAD study in opioid dependent patients; Site of Injection- Buttock
  - CAM2038-G- 50 mg/mL (batch # 2433961)

- Dose- 7.5, 15, 22.5 and 30mg (volume was adjusted as per dose, not final TBM doses)
- N=6 subjects in each dose-group

- **HS-11-426:** A Phase I, randomized, open-label, active controlled, three-way treatment trial assessing pharmacokinetics, bioavailability and safety of three doses of cam2038 q1w (once weekly) (buprenorphine fluidcrystal® injection depot), versus active comparators, intravenous and sublingual buprenorphine, in healthy volunteers under naltrexone blockage
  - Healthy, under naltrexone blockade; cross over study; Site of Injection- Buttock
  - IV Single dose: Group A, B, and C received 0.6 mg
  - SL BPN QDx7 days Steady state PK: Group A, B, and C received 8, 16, and 24 mg, respectively
  - q1w, Single dose Single dose PK: Group A, B, and C received 8, 16 and 32 mg, respectively



- **HS-13-487:** A Phase I, randomized, open-label, active controlled, three-way treatment trial assessing pharmacokinetics, bioavailability and safety of four single doses of cam2038 (buprenorphine fluidcrystal® injection depot) q4w (once monthly) and four repeat doses of cam2038 q1w (once weekly) versus active comparators, intravenous and sublingual buprenorphine in healthy volunteers under naltrexone blockage
  - Healthy, under naltrexone blockade cross over study; Site of Injection- Buttock
  - IV single dose: 0.6 mg
  - SL Subutex QD X 7 days: 8, 16, 24 mg; Steady state PK
  - q1w 4 repeat doses: 16 mg - Steady state PK
  - q4w Single dose: 64, 96, 128 or 192 mg – Single dose PK



- **HS-15-549:** 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
    - Group 1/ q1w 32 mg: 7 weeks, 3 wkly doses of 32 mg q1w in the buttock followed by 4 weekly doses in the buttock, abdomen, thigh and back of upper arm (injection site effect and steady state)
    - Group 2/ q4 w 128 mg: 16 weeks - 4 monthly doses - Steady state PK
    - Group 3/ q4w 160 mg daily doses of 24 mg SL Suboxone film for 7 days followed by 4 monthly q4w SC doses of in the buttock (steady state PK)

Opioid challenge study

- **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
    - q1w (8 mg, 24 mg, and 32 mg) weekly for 2 weeks

Clinical Studies

- **HS-11-421**: (Efficacy and Safety- 24wks): 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 injectable depot of buprenorphine (CAM2038) in treatment of adult outpatients with opioid use disorder
    - Phase I: 8 mg during first wk, thereafter 16, 24 or 32 mg q1w wkly for 11 weeks;
    - Phase II: 64, 96, 128 or 160 mg q4w monthly for 12 wks
    - Injections in the buttock, abdomen, thigh and back of upper arm
    - No PK sampling
- **HS-14-499**: An open-label multicenter study assessing the long-term safety of a once-weekly and once-monthly, long-acting subcutaneous injection depot of buprenorphine (CAM2038) in adult outpatients with opioid use disorder
    - Long-term safety and efficacy of 8, 16, 24 or 32 mg q1w and 64, 96, 128 or 160 mg CAM2038 q4w in patients with opioid use disorder (12 months)

Since CAM2038 is a multiple dose product, relative BA comparison will be done using AUCss and Cmax-ss of highest clinical dose of CAM2038, 160 mg to highest dose of SL-Subutex, 24

mg. The current review will also focus on injection site effect on PK, the steady state trough levels, Cmax and Cavg, when the subjects were switched from SL –Subutex to CAM2038.

Population PK analyses information from studies HS-11-426, HS-13-487, HS-13-478 and HS-15-549 will be assessed (by Pharmacometrics team) to address the influence of covariates on the PK of BPN and for simulations of different treatment schedules with q1w, q4w and SL BPN (Subutex) (b) (4) predicted PBPK modeling will be assessed (by Pharmacometrics team). Additionally, PK/PD relationships between BPN and ECG and measured QT intervals corrected for heart rate using the Fridericia's correction (QTcF) were evaluated for CAM2038 q1w, CAM2038 q4w will be assessed by QT-IRT team.

The following information requests with regards to the datasets were communicated to Sponsor

Information Request-1 (Provide information by August 4, 2017)

We cannot locate the data set/codes of the population PK analysis for evaluation of the influence of covariates on the PK of buprenorphine and for simulations of different treatment schedules with CAM2038, and the PBPK modeling of buprenorphine for CAM2038 with inhibitors and inducers of CYP3A4. Submit this information by 8/04/2017. If such information has already been submitted, indicate their location in the submission. Note the data set/codes submitted should allow the Division to reproduce your analysis and perform new analysis if necessary.

- *For the population PK analyses all datasets used for model development and validation should be submitted as SAS transport files (*.xpt). A description of each data item should be provided in a define.pdf file. Any concentration and or/subjects that have been excluded from the analysis should be flagged and maintained in the datasets. Model codes or control streams and output listings should be provided for all major building steps, e.g., base structural model, covariate modes, and final model. These files should be submitted as ASCII text files with *.txt extension (e.g., myfile_ctl.txt, myfile_out.txt).*
- *For the PBPK analyses please see the recent guidance (https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM531207.pdf)*

Information Request-2 (Provide information by August 18, 2017)

We cannot locate the datasets for PK studies (HS-11-426, HS-13-487, HS-07-307 and HS-15-549) in the submission. If you have already provided, indicate the location of datasets in the submission.

- *When submitting, please note that the datasets of concentrations and non-compartmental analyses- PK parameters in SAS transport files (.xpt) must include (but not limited to) the information of treatment, dose, subject number, nominal time, actual time, sequence, period, etc. The dataset should allow the Agency to conduct non-compartmental analysis using WinNonlin directly without any transformation of the dataset. An example for concentration dataset is shown in the Table below. Include any additional information with regards to study as applicable (time deviation, protocol deviation, etc.). A definition file, "define.pdf" file should list all the datasets identifying the variable used.*

Study ID	*Subject ID*	*Nominal Time (h)*	*Actual Time (h)*	*Concentration (ng/mL)*	*Treatment*	*Period*	*Sequence*	*Race*	*Sex*	*Gender*
X	*001*	*0*	*X*	*X*	*X*	*1*	*2*	*X*	*X*	*X*
x	*001*	*0.5*	*0.52*	*X*	*X*	*1*	*2*	*X*	*X*	*X*
x	*001*	*1*	*1.01*	*X*	*X*	*1*	*2*	*X*	*X*	*X*
x	*001*	*2*	*2*	*X*	*X*	*1*	*2*	*X*	*X*	*X*
x	*001*	*3*	*3*	*X*	*X*	*1*	*2*	*X*	*X*	*X*

x	*002*	*0*	*X*	*X*	*X*	*1*	*2*	*X*	*X*	*X*	*X*	*X*
x	*002*	*0.5*	*0.5*	*X*	*X*	*1*	*2*	*X*	*X*	*X*	*X*	*X*
x	*002*	*1*	*1*	*X*	*X*	*1*	*2*	*X*	*X*	*X*	*X*	*X*
x	*002*	*2*	*2.02*	*X*	*X*	*1*	*2*	*X*	*X*	*X*	*X*	*X*
x	*002*	*3*	*3*	*X*	*X*	*1*	*2*	*X*	*X*	*X*	*X*	*X*
x	*003*	*0*	*X*	*X*	*Y*	*2*	*1*	*X*	*X*	*X*	*X*	*X*
x	*003*	*0.5*	*0.5*	*X*	*Y*	*2*	*1*	*X*	*X*	*X*	*X*	*X*
x	*003*	*1*	*1*	*X*	*Y*	*2*	*1*	*X*	*X*	*X*	*X*	*X*
x	*003*	*2*	*2*	*X*	*Y*	*2*	*1*	*X*	*X*	*X*	*X*	*X*
x	*003*	*3*	*3.03*	*X*	*Y*	*2*	*1*	*X*	*X*	*X*	*X*	*X*

The Sponsor responded to the IRs above. Sequence 0004 contained NONMEM control streams, output logs, and input data files. Sequence 0007 contained dataset for the PK studies.

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

/s/

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