ERRATA to FDA Briefing Document
Joint Meeting of Psychopharmacologic Drugs Advisory Committee
and Drug Safety and Risk Management Advisory Committee
November 1, 2017

1. The following table replaces Table 3 on Pages 18 and 19 in the background document:

Table 1: Studies included in the CAM2038 clinical development program

Study/location	Design	Duration	Population (N)
HS-07-307 PK/BA* Europe	Phase 1/2, single-center, single-blind, single dose-escalation, first in human. 4 doses of CAM2038 q1w. Uncontrolled.	7 weeks (including 1 week of exposure to CAM2038)	OUD patients: on SL BPN ≥6 months; 41 enrolled [one was treated in 2 groups (groups B and D)]
HS-11-421 **Pivotal** USA	Phase 3, RCT, DB, DD**, parallel group, multi-center study. Control: Daily SL BPN/NX tablets at 16 or 24mg/day (up to 32 mg during Phase 2) and placebo injections/tablets	24 weeks	Mod-severe OUD patients. 428 enrolled. 247 completed.
HS-11-426 PK/BA Europe	P1, RCT, OL (open label), single dose study of 3 CAM2038 weekly doses (8, 16, 32 mg). Control: IV Temgesic, SL Subutex (8,16,24mg)	1 week	Healthy volunteers on naltrexone blockade. 60 enrolled, 54 completed.
HS-13-478 PK USA	P2, RCT, DB, multicenter, repeat dose. Control: IM Hydromorphone, IR morphine sulfate Tablets	7 weeks (including 2 weeks of exposure to CAM2038)	Mod-severe OUD patients. 47 enrolled. 46 completed.
HS-13-487 PK/BA Europe	P1, RCT, OL, single and repeated monthly and weekly dose. Control: I.V. Temgesic, SL Subutex	4 weeks	Healthy volunteers on naltrexone blockade. 87enrolled, 75 completed.
HS-14-499 **Safety** USA, Europe	P3, OL, multicenter study (29 sites). Uncontrolled.	48 weeks	Mod-severe OUD patients 227 enrolled, 156 completed.
HS-15-549 PK USA	P2, OL, partially randomized, multicenter, CAM2038 weekly /monthly at different injection Sites. Three groups (Grp) Control: 24 mg SL BPN/NX.	Grp 1:7-13 weeks Grp 2:16-22 weeks Grp 3: 17 weeks	Mod-severe OUD patients. Enrolled (completed): Grp 1=28 (23); Grp 2-20(16); Grp 3= 18(12).

2. The following table replaces Table 10 on Page 25 in the background document:

Table 10: Summary of PK parameters of buprenorphine after single versus four repeat doses of 128 mg CAM2038 q4w

Product	Dose (mg)	Dose No.	Population	Cmax (ng/mL)	Tmax[a] (h)	Ctrough[b] (ng/mL)	AUCτ (ng*h/mL)	Rac (AUCτ)
q4w	128 (HS-13-487)	1	Healthy (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	0.209 (55)	2610 (42)	1.65

Values are geometric mean (geometric CV%); [a] Median; [b] C28d for CAM2038 q4w; [c]Steady-state PK parameters; 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; Tmax: time corresponding to occurrence of Cmax; NA: Not applicable

3. The following table replaces Table 20 on Page 48 in the background document:

Table 20: Applicant's Primary Analysis: Responder Rate (ITT Population)

Category	CAM2038 N=213	SL BPN/NX N=215	Proportion Difference (95% CI)	Non-Inferiority P-value 2-sided
Responder, n (%)	38 (17.8)	31 (14.4)	3.4 (-3.5, 10.4)	< 0.001
Non-Responder, n (%)	175 (82.2)	184 (85.6)		

Source: Table 11, Applicant's Study Report

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

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4. The following table represents text changes with corresponding page numbers in the background document:

Page number	Original text	Revised text
12	Across all studies in the clinical development program, 729 patients with OUD were exposed to at least one dose of CAM2038.	Across all studies in the clinical development program, 729 subjects were exposed to at least one dose of CAM2038.
16	The clinical development program of CAM2038 for the treatment of opioid dependence was comprised of seven studies that encompassed Phase 2 and Phase 3 clinical trials in healthy volunteers and in patients with opioid use disorder (OUD).	The clinical development program of CAM2038 for the treatment of opioid dependence was comprised of seven studies that encompassed Phases 1, 2, and 3 clinical trials in healthy volunteers and in patients with opioid use disorder (OUD).
30	• After multiple dose injections, the highest proposed doses of CAM2038, 32 mg CAM2038 q1w and 160 mg CAM2038 q4w showed higher steady state exposure (steady-state average concentrations, Cav, ss) by 57-78% and 82-98% , respectively compared to the clinical dose of Subutex at 24 mg.	• After multiple dose injections, the highest proposed doses of CAM2038, 32 mg CAM2038 q1w and 160 mg CAM2038 q4w showed higher steady state exposure (steady-state average concentrations, Cav, ss) by 57-78% and 98-125% , respectively compared to the clinical dose of Subutex at 24 mg.
44	• No more than one positive urinalysis in the six illicit opioid use assessments performed in weeks 10 to 12.	• No more than one positive urinalysis in the three illicit opioid use assessments performed in sample weeks 10 to 12.
46	Source: Table 6	Source: Figure 2 of the applicant report

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1. Page 84: The count of deaths involving buprenorphine in the Summary table should be changed from 3 deaths in 2012 to 5 deaths, and from 14 total deaths in 2010-2015 to 16 total deaths. The Summary table should have a footnote indicating that all deaths were for children <6 years old. The corrected table is as follows:

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

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

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

* All deaths were of children <6 years old.

2. Page 92: The first paragraph should be changed from:

"**Table 4** summarizes the number of deaths involving buprenorphine among children ≤10 years old from 2010 through 2014. There were 14 deaths identified, of which 13 (92.9%) were among children <6 years old. Eleven (78.6%) deaths only involved buprenorphine or buprenorphine/naloxone. Only three (21.4%) of the 14 deaths were not due to pediatric accidental exposures to buprenorphine because they were homicides; no suicides involving buprenorphine were identified. The annual number of deaths did not vary much during the study period, despite improvements in the reporting of specific drugs on death certificates[12] and an overarching increase in total deaths[13] during the study period."

to: "From 2010 through 2014, all 16 deaths involving buprenorphine were among children < 6 years old (**Table 4**); no deaths involving buprenorphine were identified for children 6 to 10 years old. Eleven (68.8%) deaths only involved buprenorphine or buprenorphine/naloxone. Only three (18.8%) of the 16 deaths were not due to pediatric accidental exposures to buprenorphine because they were

homicides; no suicides involving buprenorphine were identified. The annual number of deaths did not vary much during the study period, despite improvements in the reporting of specific drugs on death certificates[12] and an overarching increase in total deaths[13] during the study period."

3. Page 92: Table 4 should be changed from:

Table 4: Deaths involving buprenorphine among children ≤10, NVSS-M linked with death certificate literal text, 2010-2014

	2010	2011	2012	2013	2014	Total
Total deaths	3	4	3	2	2	14
Children <6 years old	3	4	2	2	2	13
Children 6-10 years old	0	0	1	0	0	1
Involvement of other drug(s)	1	0	1	1	0	3
Children < 6 years old	1	0	0	1	0	2
Children 6-10 years old	0	0	1	0	0	1

to:

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

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

4. Page 92: The first sentence in the second to last paragraph should be changed from: "…and deaths from NVSS-M with buprenorphine involvement (92.9%) involved children <6 years of age" to "…and deaths from NVSS-M with buprenorphine involvement (100%) involved children <6 years of age."

5. Page 93. The first sentence of the third paragraph should be changed from "The number of deaths involving buprenorphine among children ≤10 years of age was steady…" to "The number of deaths involving buprenorphine among children <6 years of age was steady…"