Office of Clinical Pharmacology Review

NDA Number	21-306 S027
Link to EDR	\\CDSESUB1\evsprod\NDA021306\0167
Submission Date	December 15, 2016
Submission Type	Standard
Brand Name	Butrans®
Generic Name	Buprenorphine Transdermal System (BTDS)
Dosage Form and Strength	5, 7.5, 10, 15, 20 mcg/hr
Route of Administration	Transdermal application
Proposed Indication	Treatment of moderate-to-severe chronic pain requiring continuous, around-the-clock opioid treatment for an extended period of time in pediatric patients ages (inclusive) 7 through 16
Sponsor	Purdue Pharma
OCP Review Team	Gopichand Gottipati, Ph.D., Wei Qiu, Ph.D., Kevin Krudys, Ph.D., Yun Xu, Ph.D.

Table of Contents

1. EXECUTIVE SUMMARY

1.1 Recommendations

The submission is acceptable from a clinical pharmacology perspective and the PMR is considered fulfilled. However, we do not provide dosing recommendations due to the inadequacy of the safety database to support an indication in the age range (inclusive) 7 through 16 years as determined by the Division of Anesthesia, Analgesia and Addiction Products (DAAAP).

1.2 Post-Marketing Requirements and Commitments

None.

2. SUMMARY OF CLINICAL PHARMACOLOGY ASSESSMENT

2.1 Pharmacology and Clinical Pharmacokinetics

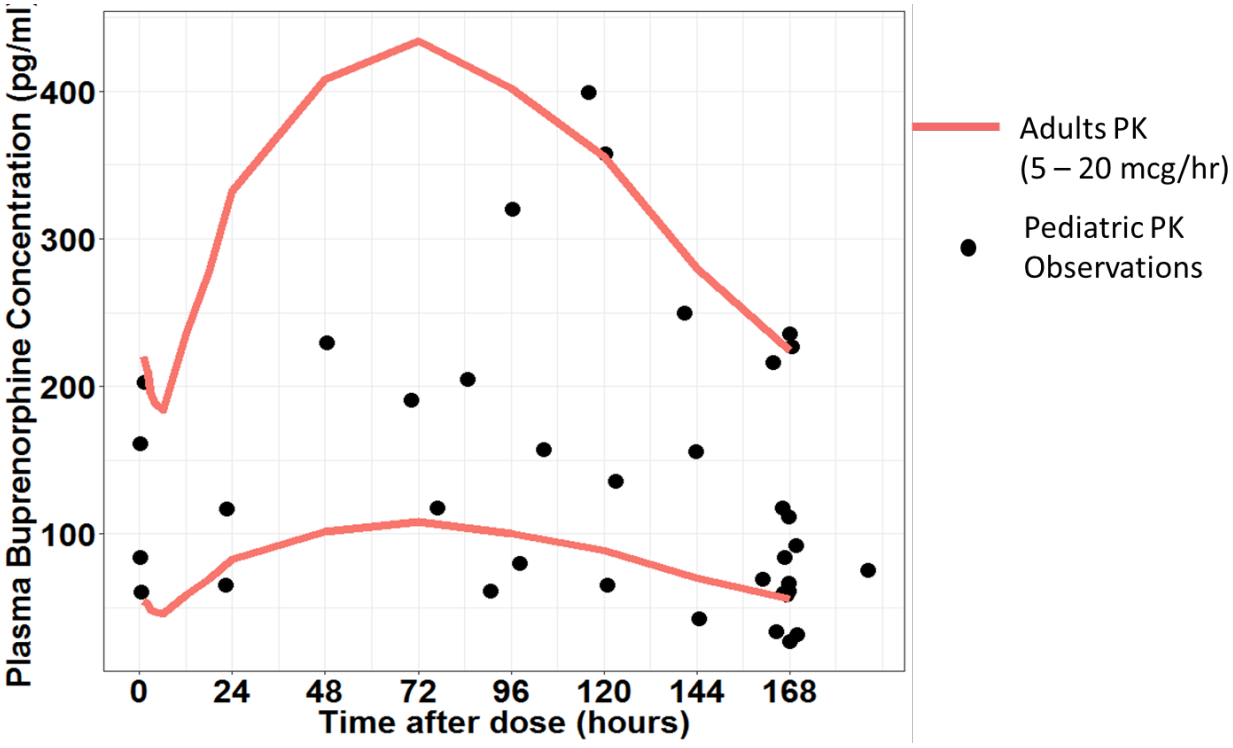
Purdue submitted an efficacy supplement comprising of a post marketing requirement (PMR) final clinical study report for study BUP3031, an open label, multicenter study to evaluate the safety, pharmacokinetics and efficacy of buprenorphine transdermal system (BTDS) for the treatment of moderate-to-severe chronic pain requiring continuous, around-the-clock opioid treatment for an extended period of time in pediatric patients ages (inclusive) 7 through 16. At the time of adult approval, the pediatric study was waived for ages birth through 6 years because the Agency agreed that such studies are infeasible, given the small number of patients in this age cohort that need treatment with an extended-release or long-acting opioid analgesic. A post marketing study requirement (PMR) under the Pediatric Research Equity Act (PREA) in the age range (inclusive) 7 through 16 years was deferred because the product was ready for approval in adults. Subsequently, the sponsor conducted the pediatric study BUP3031 and submitted the report in this efficacy supplement. Additionally, Purdue also submitted pediatric population pharmacokinetics modeling and simulation report "Pharmacokinetics and exposure of transdermal buprenorphine in pediatric patients 7 – 16 years of age".

Butrans®, buprenorphine transdermal system (BTDS) is a partial opioid agonist product and is approved for the indication of management of pain severe enough to require daily, around-the-clock, long term opioid treatment and for which alternative treatment options are inadequate.

Butrans® system is available in dosage strengths of 5, 7.5, 10, 15, and 20 mcg/hr (NDA 021306). The adult starting dose in opioid-naïve patients is 5 mcg/hr and the maximum dose is 20 mcg/hr. For the purpose of study BUP3031, a lower dose strength of BTDS - 2.5 mcg/hr was introduced to expand the dose range in pediatric subjects. In this study, all patients in the younger age cohort (age inclusive 7 through 11 years) were initiated treatment with BTDS 2.5 mcg/hr, while patients in the older age cohort (age inclusive 12 through 16 years) were initiated treatment with BTDS 5 mcg/hr. The dose of BTDS was adjusted upward or downward as needed (based on tolerability, adequate pain control, AEs) throughout the study and the maximum allowed dose in the study was BTDS 20 mcg/hr.

The observed pediatric buprenorphine plasma concentrations following the final titrated BTDS dosage in study BUP3031 are within the expected steady-state adult buprenorphine exposures after the recommended BTDS dosage range (5-20 mcg/hr) as shown in **Figure 1** below.

Figure 1: Buprenorphine PK: Observed Pediatric vs. Adult Exposures



The solid lines represent the buprenorphine pharmacokinetic profile in adults following the recommended dosage range of 5 (lower) and 20 mcg/hr (upper) of Butrans® system

2.2 Summary of Labeling Recommendations

OCP recommends not to include PK data in the label if Butrans does not receive an indication in the pediatric population.

3. APPENDICES

3.1 Summary of Bioanalytical Method Validation and Performance

Plasma concentrations of buprenorphine and the internal standards were determined by a validated analytical method using LC-MS/MS that was reviewed and considered acceptable. The quantitative linear calibration ranges for buprenorphine were from 25-2,500 pg/ml. For the QC samples of buprenorphine (75, 500, and 2000 pg/mL), the precision (%CV) was between 4.38 and 8.14% and the accuracy was between 98.6 and 100%, respectively.

3.2 Sponsor's Population PK Analyses

The sponsor conducted population PK (PopPK) analyses to characterize the pharmacokinetics of transdermal buprenorphine including estimating the fixed and random sources of variability in PK in pediatric subjects. The treatment period was up to 24 weeks and sparse PK blood samples were collected up to 5 times during the first 4 weeks of the study sampled at: (1) 18 – 24 hours after application of the first BTDS patch, (2) end of week 1, (3) 2 – 3 days after the end of week 1, (4) end of week 2, (5) end of week 4 or at discontinuation, if it happened prior to the last scheduled draw.

A total of 41 patients received treatments with 6 patients in the younger age cohort of 7-11 years and 35 patients in the older age cohort of 12 -16 years. The final buprenorphine pediatric PK analysis dataset included 38 subjects (n = 3 with plasma buprenorphine concentrations that were not quantifiable) and a total of 151 plasma concentrations. The structural PK model consisted of a two compartmental model with sequential zero- and first-order absorption. Additionally, ideal body weight (IBW) was included in the model using fixed, allometric relationships for CL/F, V_c/F, Q/F and V_p/F.

Owing to the sparsely sampled PK data, small sample size, and the complexity of the absorption process involved with the transdermal formulation, prior information from a previously developed adult population PK model was used for all of the parameters except for CL/F, which was estimated based on the pediatric PK data. The parameter estimates of the final PopPK model are shown in **Table 1** and **Table 2**.

Table 1 BTDS pediatric population PK model parameter estimates

PK Parameter (Unit)	NONMEM Parameter*	Estimate	95%CI**
CL/F_{70kg} (L/hr)	$\exp(\theta_1)$	293	(264,326)
Vc/F_{70kg} (L)	$\exp(\theta_2)$	2350	(1950,2820)
D1 (hr)	$\exp(\theta_3)$	28.2	(24.0,33.2)
$k_a (hr)^{-1}$	$\exp(\theta_4)$	0.00751	(0.00672,0.00840)
Vp/F_{70kg} (L)	$\exp(\theta_5)$	5520	(4670,6530)
Q/F_{70kg} (L/hr)	$\exp(\theta_6)$	299	(203,440)
IIVvar CL/F $(\omega^2_{CL/F})$	$\Omega_{1,1}$ (η_1)	0.0488 (%CV=22.4)	(0.00970,0.0880)
IIVcov $CL/F, Vc/F$ $(\omega_{CL/F}, \omega_{Vc/F})$	$\Omega_{2,1}$	0.0704	(-0.0366,0.178)
IIVvar Vc/F $(\omega^2_{Vc/F})$	$\Omega_{2,2}$ (η_2)	0.353 (%CV=65.0)	(0.0249,0.681)
IOVvar F (ω^2_F)	$\Omega_{3,3}$ (η_3)	0.0959 (%CV=31.7)	(0.0744,0.117)
IOVvar $D1$ (ω^2_{D1})	$\Omega_{7,7}$ (η_7)	0.505 (%CV=81.1)	(0.315,0.695)
IOVvar k_a $(\omega^2_{k_a})$	$\Omega_{11,11}$ (η_{11})	0.260 (%CV=54.4)	(0.200,0.319)
Res_{prop} (σ^2)	$\Sigma_{1,1,\text{prop}}$ (ε_1)	0.0475 (%CV=22.0)	(0.0213,0.0737)

F was fixed at 1. Fixed allometric exponents for all clearance (0.75) and volume (1) terms were included in the model

*Estimates of θ modeling in the log domain were exponentiated and are reported in the table.

**95%CI derived on the log domain from standard errors obtained from the NONMEM $COVARIANCE step and reported after back transformation.

Source: Pharmacokinetics and exposure of transdermal buprenorphine in pediatric patients 7 – 16 years of age study report (PRD0101F) – Table 3 on Page 26

Table 2 BTDS Pediatric population PK model – Shrinkage estimates of inter-individual and inter-occasion random effects

PK Parameter (Unit)	NONMEM Parameter*	Estimate	Shrinkage (%)
IIVvar CL/F ($\omega^2_{CL/F}$)	$\Omega_{1,1}$ (η_1)	0.0488	25.5
IIVvar Vc/F ($\omega^2_{Vc/F}$)	$\Omega_{2,2}$ (η_2)	0.353	61.8
IOVvar F (ω^2_F)	$\Omega_{3,3}$ (η_3)	0.0959	56.1
IOVvar $D1$ (ω^2_{D1})	$\Omega_{7,7}$ (η_7)	0.505	69.3
IOVvar k_a ($\omega^2_{k_a}$)	$\Omega_{11,11}$ (η_{11})	0.260	59.6

Inter-individual and inter-occasion random effects associated with CL/F (η_1), Vc/F (η_2), F (η_3), D1 (η_7), and K_a (η_{11}), ; η Shrinkage (%) $= 100 \cdot (1 - \frac{sd(\hat{\eta})}{\omega})$

Source code: ../script/NMruns_PK.R
Source table: ../deliv/table/PKShrinkEta.tex

where:

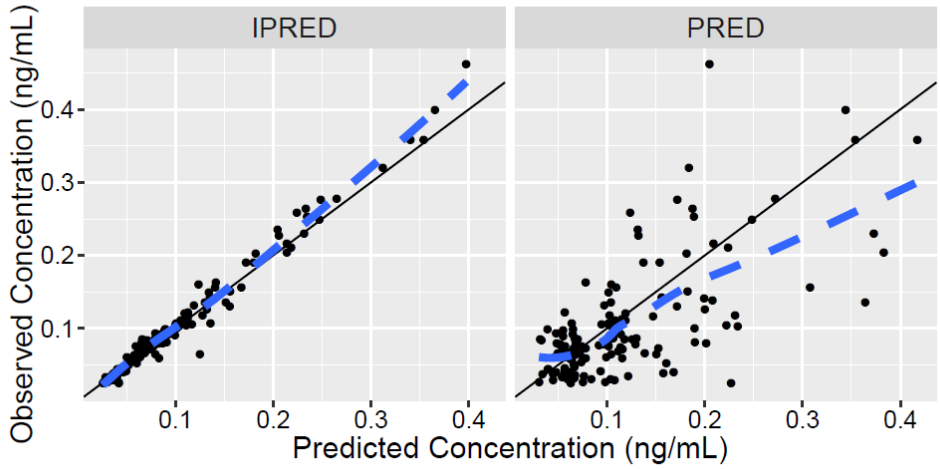
IIV = interindividual variability (variance, ω^2); IOV = interoccasion variability (variance, ω^2); CL/F = apparent clearance after patch dosing; V_c/F = apparent central volume of distribution after patch dosing; F = bioavailability; k_a = absorption rate constant; D1 = duration of zero-order input rate. All other parameters are as defined in the text.

Source: Pharmacokinetics and exposure of transdermal buprenorphine in pediatric patients 7 – 16 years of age study report (PRD0101F) – Table 4 on Page 27

The qualification of the final PopPK model was performed using goodness of fits plots, shown in **Figures 2 – 4**. Furthermore, the individual predictions from the simulation of 500 replicates with the same design using the population means and variability from the final PopPK model were summarized (median, 5th and 95th percentiles of data within a binned time interval) and overlaid with the observed data and visualized using Prediction Corrected Visual Predictive Checks (PCVPC) shown in **Figure 5**.

Figure 2 Observed vs. individual and population predictions based on final PopPK model

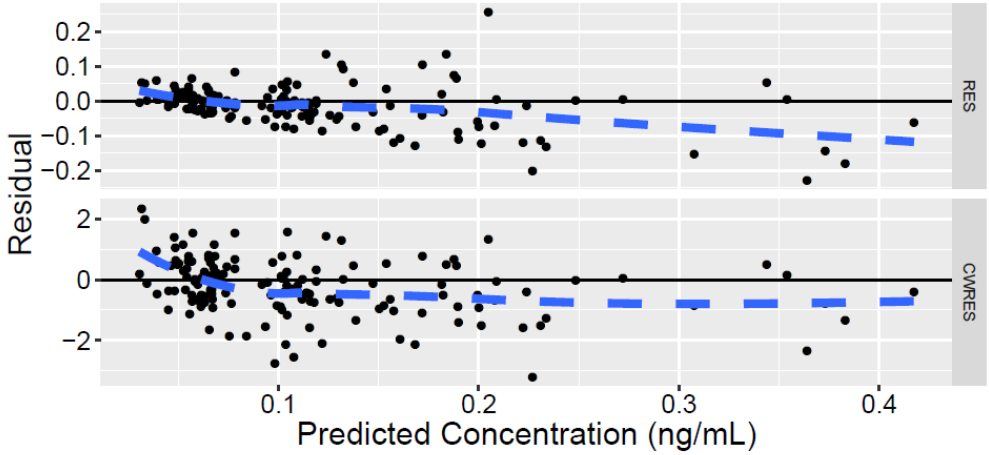
Observed Buprenorphine concentrations (ng/mL) are plotted vs. individual and population predictions. Values are indicated by black dots. The blue dashed line is a loess smooth. The line of identity (solid black) is included as reference.



Source: Pharmacokinetics and exposure of transdermal buprenorphine in pediatric patients 7 – 16 years of age study report (PRD0101F) – Figure 4 on Page 34

Figure 3 Residuals vs. population predictions based on final PopPK model

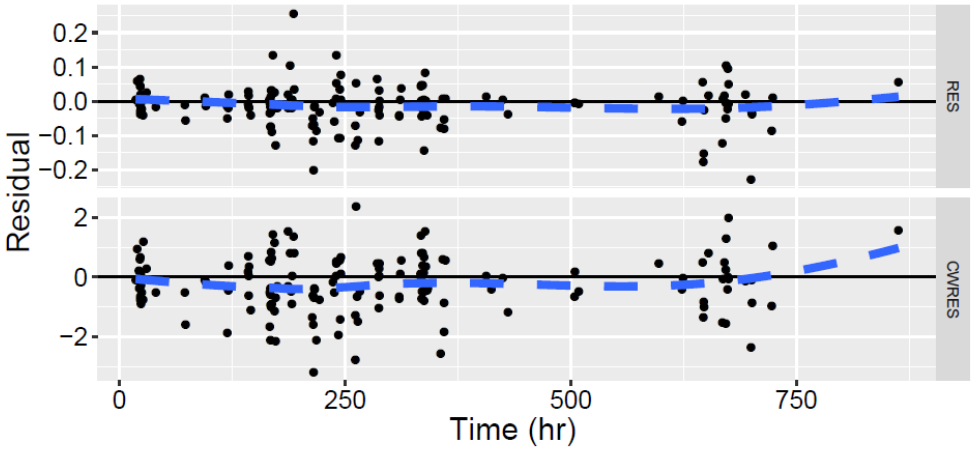
Residuals (standard and conditional weighted) are plotted vs. population predicted concentration (ng/mL). Values are indicated by black dots. The blue dashed line is a loess smooth. A solid black line at y=0 is included as reference.



Source: Pharmacokinetics and exposure of transdermal buprenorphine in pediatric patients 7 – 16 years of age study report (PRD0101F) – Figure 5 on Page 35

Figure 4 Residuals vs. time for the final PopPK model

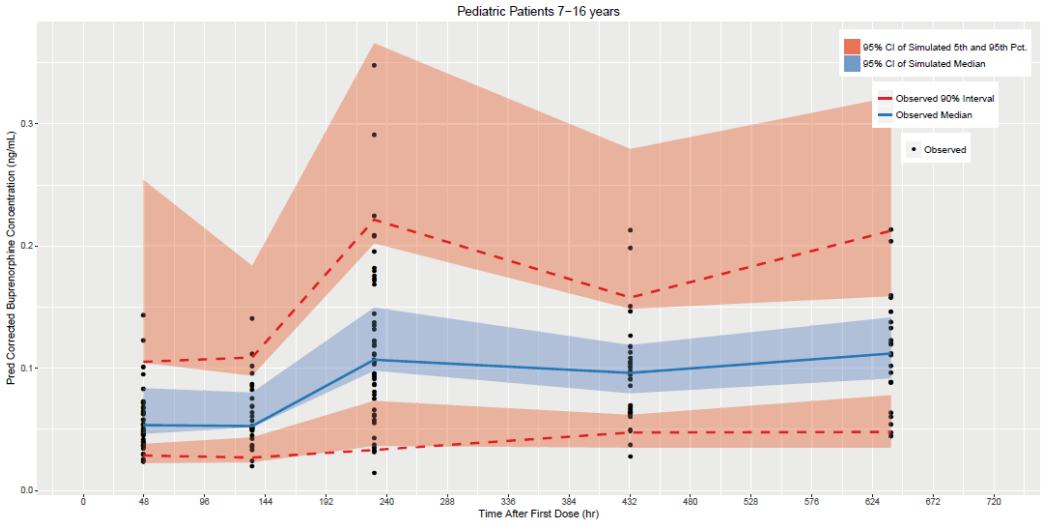
Residuals (standard and conditional weighted) are plotted vs. time. Values are indicated by black dots. The blue dashed line is a loess smooth. A solid black line at y=0 is included as reference.



Source: Pharmacokinetics and exposure of transdermal buprenorphine in pediatric patients 7 – 16 years of age study report (PRD0101F) – Figure 7 on Page 37

Figure 5 Prediction-Corrected Visual Predictive Check (PCVPC) final PopPK model

PCVPC for buprenorphine study BUP3031. The solid blue line represents the median of the observed, prediction-corrected plasma concentrations (black circles). The blue shaded area represents the 95% CI of the simulated median. The red dashed lines represent the 5th and 95th percentiles of observed, prediction-corrected plasma concentrations. Red shaded areas represent the 95% CI of the simulated, prediction-corrected 5th and 95th percentiles.



Source: Pharmacokinetics and exposure of transdermal buprenorphine in pediatric patients 7 – 16 years of age study report (PRD0101F) – Figure 14 on Page 54

The final population PK model was used to simulate the optimal doses across the 7-16 years age range to match the expected adult exposure following a BTDS dose of 10 mcg/hr which resulted in steady-state exposure (AUC_{ss}) of 34.1 ng*hr/ml and are shown in **Table 3**

Table 3 Predicted buprenorphine AUC_{ss} (ng*hr/ml) in pediatric patients to match adult BTDS 10 mcg/hr exposure (34.1 ng*hr/ml) or following BTDS 2.5, 5, 7.5, 10, 15, 20 mcg/hr

Age (year)	IBW (kg)	Optimal Dose* (mcg/hr)	AUCss 2.5 (ng*hr/mL)	AUCss 5 (ng*hr/mL)	AUCss 7.5 (ng*hr/mL)	AUCss 10 (ng*hr/mL)	AUCss 15 (ng*hr/mL)	AUCss 20 (ng*hr/mL)
7	24.2	4.56	18.7	37.4	56.1	74.7	112	149
		(2.90,7.20)	(11.8,29.4)	(23.7,58.7)	(35.5,88.1)	(47.3,117)	(71.0,176)	(94.7,235)
8	28.4	5.14	16.6	33.2	49.8	66.4	99.6	133
		(3.27,8.11)	(10.5,26.1)	(21.0,52.2)	(31.5,78.2)	(42.0,104)	(63.1,156)	(84.1,209)
9	34.2	5.90	14.4	28.9	43.3	57.8	86.6	116
		(3.76,9.32)	(9.14,22.7)	(18.3,45.4)	(27.4,68.1)	(36.6,90.7)	(54.9,136)	(73.1,181)
10	40.5	6.70	12.7	25.4	38.2	50.9	76.3	102
		(4.27,10.6)	(8.05,20.0)	(16.1,40.0)	(24.2,59.9)	(32.2,79.9)	(48.3,120)	(64.4,160)
11	45.6	7.32	11.6	23.3	34.9	46.6	69.9	93.2
		(4.66,11.6)	(7.38,18.3)	(14.8,36.6)	(22.1,54.9)	(29.5,73.2)	(44.3,110)	(59.0,146)
12	50.5	7.91	10.8	21.6	32.3	43.1	64.7	86.2
		(5.03,12.5)	(6.83,16.9)	(13.7,33.9)	(20.5,50.8)	(27.3,67.7)	(41.0,102)	(54.6,135)
13	56.7	8.63	9.88	19.8	29.6	39.5	59.3	79.1
		(5.49,13.6)	(6.26,15.5)	(12.5,31.1)	(18.8,46.6)	(25.0,62.1)	(37.5,93.2)	(50.1,124)
14	57.2	8.68	9.82	19.6	29.5	39.3	58.9	78.5
		(5.53,13.7)	(6.22,15.4)	(12.4,30.8)	(18.7,46.3)	(24.9,61.7)	(37.3,92.5)	(49.7,123)
15	60.6	9.07	9.40	18.8	28.2	37.6	56.4	75.2
		(5.77,14.3)	(5.95,14.8)	(11.9,29.5)	(17.9,44.3)	(23.8,59.1)	(35.7,88.6)	(47.6,118)
16	61.5	9.17	9.30	18.6	27.9	37.2	55.8	74.4
		(5.84,14.5)	(5.89,14.6)	(11.8,29.2)	(17.7,43.8)	(23.6,58.4)	(35.3,87.6)	(47.1,117)
7-11	34.4	5.94	14.4	28.7	43.1	57.4	86.2	115
		(3.78,9.37)	(9.09,22.6)	(18.2,45.1)	(27.3,67.7)	(36.4,90.2)	(54.6,135)	(72.8,180)
12-16	56.6	8.61	9.90	19.8	29.7	39.6	59.4	79.2
		(5.48,13.6)	(6.27,15.5)	(12.5,31.1)	(18.8,46.6)	(25.1,62.2)	(37.6,93.3)	(50.1,124)

Results are presented as Median (95% prediction interval)
AUCss= predicted AUCss (ng*hr/mL) for typical patient at indicated dose (2.5, 5, 7.5, 10, 15, or 20 mcg/hr), IBW=Median Ideal Body Weight
*Optimal Dose calculated as the BTDS dose which matches the exposure for an adult with IBW=70kg (34.1 ng*hr/mL)

Source: Pharmacokinetics and exposure of transdermal buprenorphine in pediatric patients 7 – 16 years of age study report (PRD0101F) – Table 5 on Page 28

Reviewer's Comments:

The sponsor modeled the PK of transdermal buprenorphine in pediatric subjects from study BUP3031. Overall, the approach followed by the sponsor, i.e., informing the pediatric population PK model by using informative priors based on a previously developed adult population PK model seems acceptable. The final PopPK model parameter estimates shown in ***Table 1*** *indicate relatively large inter-individual variability (IIV) for V_c/F (apparent central volume of distribution after BTDS dosing) and large inter-occasion variability (IOV) for D1 (duration of zero-order input rate) and k_a (absorption rate constant). Additionally, the shrinkage values for all the random variance parameters except CL/F (the only parameter estimated based on the pediatric data without using any prior information from adults) shown in* ***Table 2*** *also seem to be high. The plausible explanation for such high IIV and IOV could be due to complexity of the absorption process, sparse PK samples and small sample size. The diagnostic plots as well as the PCVPC of the final PopPK model seem to suggest that it was able to describe the pediatric PK adequately with the observed data in reasonable agreement with the simulations. Even with its limitations, the final PopPK model can be used for simulations to identify the "target" pediatric BTDS dose, which matches the steady-state exposures in adults following recommended starting dose of 5 mcg/hr. A summary of simulated buprenorphine exposures in the younger age cohort (7 to 11 years) at a BTDS dose of 2.5 mcg/hr and the older age cohort (12 – 16 years) at a BTDS dose of 5 mcg/hr is provided in* ***Table 4*** *based on the final PopPK model at the respective doses and age cohorts.*

Table 4 Exposures of Buprenorphine at Steady-state in Younger Age Cohort (7 -11 Years) Receiving at a 2.5 mcg/hr Dose And Older Age Cohort (12-16 Years) at a 5 mcg/hr Dose

Age Cohort	***Pediatric subjects 7 - 11 years (n=5) following BTDS 2.5 mcg/hr (Median (Range))***	***Pediatric subjects 12-16 years (n=33) following BTDS 5 mcg/hr (Median (Range))***
Buprenorphine Steady State Exposures [AUCss (ng.h/ml)]	*15.7 (12.3, 23.2)*	*18.9 (13.3, 30.3)*

It is important to note that the sponsor used age as a cutoff. However, body weight was found to be the most important factor influencing buprenorphine pharmacokinetics following BTDS administration in pediatric patients. Therefore, weight-based dosing recommendations can also be derived based on the final PopPK model that match the pediatric exposures to those in the adults.

In conclusion, from a clinical pharmacology perspective, the review team believes that dosing recommendations can be derived in a pediatric population (up to age of 7 years) based on body weight that match the exposure in adults based on the final PopPK model. However, we do not provide recommendations due to the inadequacy of the safety experience from study BUP3031 (n = 6 in the age range of 6-11 years and n = 35 in the age range of 7-12 years) to support a pediatric indication. Please refer to the clinical review by Dr. Robert Levin for further details.

3.3 Review of ECG Abnormalities

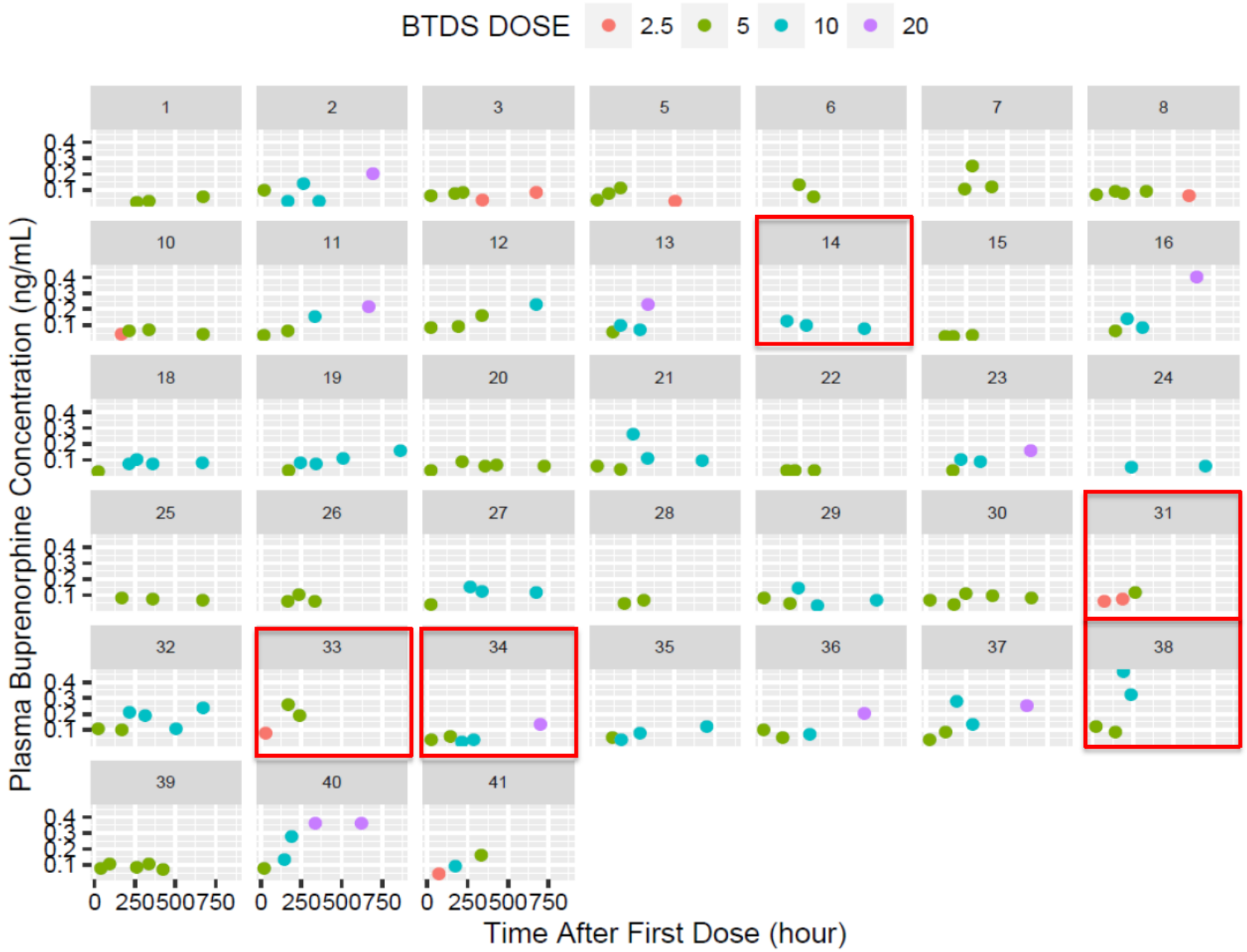
The medical officer identified a list of five individuals from study BUP3031 in whom ECG-related adverse events resulted in discontinuation of the drug product. OCP was asked to review if these events were exposure related. The pharmacometrics reviewer helped identify these individuals and the BTDS dosage they received and the respective plasma concentrations are shown below in **Table 5** and **Figure 6**

Table 5 Individuals in study BUP3031 with ECG abnormalities

ECG Abnormalities	Specific Individuals	Notes
QTc prolongation	0008003: ID **14**	Doses: 10* mcg/hr
	0010011: ID **38**	Doses: 5→ 10* mcg/hr; (Highest concentration in dataset)
QRS prolongation	0010006: ID **34**	Doses: 5 → 10 → 20* mcg/hr
Other ECG abnormalities	9009004: ID **31**	Doses: 2.5→ 5* mcg/hr
	0010005: ID **33**	Doses: 2.5→ 5* mcg/hr

**Represents the final titrated/tolerated dose*

Figure 6 Plasma buprenorphine concentrations of subjects in study BUP3031 (subjects with ECG abnormalities with red outline)



In both the individuals with QTc prolongation, the final titrated (/tolerated) BTDS dosage strength was 10 mcg/hr. Although the plasma buprenorphine concentration in one of them (subject ID: 38) was the highest in the entire PK database, this patient received a dose (10 mcg/hr) at which clinically relevant QT prolongation is not expected. For the one subject with QRS prolongation, the final titrated BTDS dosage was 20 mcg/hr, but the concentration observed in this patient at that dose was within the range of concentrations observed in the overall population. For the other two individuals with other ECG-related abnormalities, the final titrated BTDS was 5 mcg/hr and therefore, it is unlikely to be drug product-related event. Please refer to the clinical review by Dr. Robert Levine for detailed account on these individuals.

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

/s/

GOPICHAND GOTTIPATI
09/11/2017

WEI QIU
09/11/2017

YUN XU
09/11/2017

KEVIN M KRUDYS
09/11/2017