OFFICE OF CLINICAL PHARMACOLOGY (OCP) REVIEW	
NDA/SDN/Supplement	NDA210806/369/S-07 NDA210807/324/S-08
Submission Type	Pediatric efficacy supplement
Applicant Name	MERCK SHARP AND DOHME CORP A SUB OF MERCK AND CO INC
Submission Date	7/27/2021
Generic Name	NDA210806: Doravirine (DOR, MK-1439) NDA210807: Fixed dose combination of Doravirine (DOR), lamivudine (3TC) and tenofovir disoproxil fumarate (TDF) (MK-1439A)
Brand Name	NDA210806: PIFELTRO NDA210807: DELSTRIGO
Dosage Form (Strength)	NDA210806: tablets, for oral use (DOR, 100mg) NDA210807: tablets, for oral use (DOR/3TC/TDF, 100mg/300mg/300mg)
Indication	PIFELTRO: in combination with other antiretroviral agents for the treatment of HIV-1 infection in adults and pediatric patients weighing at least 35 kg DELSTRIGO: as a complete regimen for the treatment of HIV-1 infection in adults and pediatric patients weighing at least 35 kg
Review Team	Xiaoxia Yang, PhD, Eliford Kitabi, PhD, Justin Earp, PhD, and Kunyi Wu, PharmD

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1. Executive summary

Background

PIFELTRO (doravirine, DOR, tablet) has been approved by FDA in combination with other antiretroviral agents for the treatment of HIV-1 infection in adult patients. DELSTRIGO (a fixed dose combination (FDC) of doravirine (DOR), lamivudine (3TC), and tenofovir disoproxil fumarate (TDF) tablet) has been approved by FDA as a complete regimen for the treatment of HIV-1 infection in adult patients. The recommended dosage for PIFELTRO in adult patients is one tablet (100 mg DOR) once daily regardless of food. The recommended dosage for DELSTRIGO in adult patients is one table (100 mg of DOR, 300 mg of 3TC, and 300 mg of TDF) once daily with or without food.

The Applicant submitted a pediatric efficacy supplement to support the use of the same dosing regimen of PIFELTRO and DELSTRIGO in pediatric patients weighing at least 35 kg. This supplement includes one PK study (Study MK-1439-P027) in HIV-1 infected pediatric patients 12 years to less than 18 years of age and weighing at least 35 kg (study report P027V01MK1439) and a population pharmacokinetic (PopPK) analysis report of DOR in adolescents.

Study P027 consisted of 2 cohorts: Cohort 1, intensive PK (IPK) for a single dose of DOR (100 mg) in 9 pediatric patients (12 to16 years of age, 40.3 to 90.8 kg); Cohort 2, semi-IPK for DOR and IPK for 3TC/tenofovir (TFV) at week 1 following multiple daily dosing of FDC of DOR/3TC/TDF (100 mg/300 mg/300 mg) tablets in 10 subjects, along with sparse PK samples collected in all enrolled subjects (n=45, 12 to 17 years of age, 45.1 to 79.8 kg). The dose selection of DOR, 3TC, and TDF in pediatric patients weighing at least 35 kg is based on exposure matching (i.e., extrapolation of efficacy from adults to pediatrics when exposures are comparable).

Different simulation strategies for DOR were applied to pediatric patients in two weight brackets (≥45 kg, ≥35 and < 45 kg) because only one patient in Study P027 was in the weight bracket of ≥35 and <45 kg. Post-hoc estimates were applied to pediatric patients ≥ 45 kg and simulation based on virtual patients was conducted for pediatric patients weighing ≥35 and <45 kg. For pediatric patients weighing ≥ 45 kg, geometric mean ratios (GMRs) of DOR C_{max}, AUC_{0-24}, and C_{24} in pediatric patients (post-hoc estimates, study P027) vs. adults (post-hoc estimates, phase 3 trials P018 and P021) ranged from 0.96-1.07 (Response to IR submitted on 10/25/2021). All pediatric DOR PK parameter values fell within the range of adult values. For pediatric patients weighing ≥ 35 kg and < 45 kg, the model predicted population mean of C_{24} for the virtual population was comparable to adult post-hoc estimates. The predicted population means of AUC_{0-24} and C_{max} are expected to be higher than adult mean values. Only 1.9 % and 1.3% of simulated virtual pediatric subjects whose C_{max} and AUC_{0-24} levels exceeded the upper bounds of C_{max} and AUC_{0-24} for safety based on exposure-response analyses in the original NDA approval.

The doses of 3TC (300 mg) and TDF (300 mg) in the FDC of DOR/3TC/TDF tablets administered to adolescents in Study P027 were based on US prescribing information for TDF (VIREAD) and 3TC (EPIVIR). The adolescent PK data of 3TC and TFV from Study P027 were graphically compared as means and SD to the historical PK data in adults and determined to be comparable to historical adult exposures of 3TC and TFV, supporting the proposed dosing of 3TC and TDF in the FDC of DOR/3TC/TDF tablets for pediatric patients weighing ≥ 35 kg.

Recommendation

The Office of Clinical Pharmacology has reviewed the submission and concluded that the proposed dosing regimens for PIFELTRO and DELSTRIGO in pediatric patients weighing at least 35 kg are acceptable and recommend approval of this efficacy supplement. This submission also fulfills the following:

PMR 3415-1: *Conduct a study to evaluate the pharmacokinetics, safety and antiviral activity (efficacy) of DOR in HIV-1 infected pediatric subjects less than 18 years of age and weighing at least 35 kg* and

PMR 3416-1: *Conduct a study to evaluate the pharmacokinetics, safety, and antiviral activity (efficacy) of DOR/3TC/TDF fixed dose combination (FDC) product in HIV-1 infected pediatric subjects less than 18 years of age and weighing at least 35 kg.*

2. Labeling Comments/Recommendations

The labeling language is still under discussion at the time when this review was finalized.

3. Study MK-1439-P027 (Study Report P027V01MK1439)

Title
Phase I/II Study of the Pharmacokinetics, Safety and Tolerability of Doravirine (MK-1439) and Doravirine/Lamivudine/Tenofovir Disoproxil Fumarate (MK-1439A) in HIV-1-infected Children and Adolescents

Study Design
MK-1439-027 (also known as International Maternal Pediatric Adolescent AIDS Clinical Trials Network [IMPAACT] 2014 and as Division of AIDS [DAIDS] Study No. #34150) was a Phase 1/2, multi-site, open-label study to evaluate the PK, safety, and tolerability of doravirine (DOR) and doravirine/lamivudine/tenofovir disoproxil fumarate (DOR/3TC/TDF) in adolescents with HIV-1 infection, 12 years to <18 years of age, and who weigh at least 35 kg. This study consisted of two cohorts:

- Cohort 1: DOR tablet (100 mg), single oral dose (N=9, 12 to 16 years of age, 40.3 to 90.8 kg and only 1 participant weighed between 35 kg and ≤ 45 kg). Cohort 1 was completed.
- Cohort 2: DOR/3TC/TDF tablet (100/300/300 mg), once daily (QD) oral dose (N=45, 12 to 17 years of age, 45.1 to 79.8 kg). Cohort 2 is ongoing through week 96.

In Cohort 1, intensive PK of DOR was assessed for all the 9 participants on Day 1 and PK results from Cohort 1 confirmed the dose of DOR (100 mg QD) in Cohort 2. In Cohort 2, intensive (TFV and 3TC) and semi-intensive (DOR) PK were evaluated at week 1 (approximately 8 days) in 10 participants and sparse PK samples were collected for all the participants (N=45) through week 48.

PK Assessment
Cohort 1 (intensive PK for DOR): pre-dose, 1, 2, 4, 8, 12, 24, 48 and 72 hours post-dose
Cohort 2 (week1, semi-intensive PK for DOR): pre-dose, 2, 4, 12 and 24 hours post-dose
(week1, intensive PK for 3TC and TFV): pre-dose, 1, 2, 4, 8, 12 and 24 hours post-dose
Cohort 2 (sparse PK for DOR, 3TC, and TFV):

- Entry and Week 4: pre-dose
- Week 8 and 12: Random
- Week 24 and 48: Pre-dose and 0.5-2 hours post-dose (week 48 data not available in the current submission)

Demographics
All participants in Cohort 1 were virologically suppressed at baseline. Most participants in Cohort 2 were virologically suppressed with 2 treatment-naïve participants. Seven males and 2 females were enrolled for Cohort 1, whereas for Cohort 2, 19 males and 26 females.

Protocol Deviations

No protocol deviation was reported for Cohort 1. For Cohort 2, seven protocol deviations were reported, including missing of week 16 on-site visit due to COVID-19 pandemic (N=4) and PK sample processed outside the window period of 30 min (N=3, ID [redacted], ID [redacted], and ID [redacted]). None of the 3 subjects were included in the IPK and semi-IPK analysis for 3TC/TFV and DOR. Additionally, pre-dose sparse PK samples from these three subjects at week 4 and week 24 did not precede ingestion of the study drug and thus were not included for observed C_{24} analysis for DOR. Also, this observation has been conveyed to Dr. Eliford Kitabi, the Pharmacometrics reviewer. Per assessment by Dr. Eliford Kitabi, PK samples from these three subjects did not cause any bias in population PK analyses of DOR and their individual PK estimates are consistent with the rest of the subjects. Overall, in our assessment, the reported protocol deviations are not expected to affect PK analysis results.

Sample Analysis

Plasma concentrations of DOR and 3TC/TVF were measured using validated LC-MS/MS methods at [redacted]. (Study# 180223ATLB) and [redacted] (Study# 2018-4515), respectively. The analytical site for DOR, [redacted], and the analytical site for 3TC/TVF, [redacted] were inspected in [redacted] and [redacted], respectively. The final classification for both inspections was No Action Indicated (NAI) (OSIS Inspection Report, DARRTS 10/20/2021, NDA210806/210807). These analytical methods were found to be acceptable (Table 1 and Table 2).

Table 1. Assessment of LC-MS/MS method validation reports.

Method Validation Report	Analyte	Calibration range	Accuracy and precision values of calibration and QC samples within 15% (20% at LLOQ)	Major deviations	Interference from other analytes	Duration of stability
(b) (4) Study number 157103ANVL	DOR	1.00 to 1000.00 ng/mL	Yes (including dilution QC samples)	No	No	819 days at -20ºC
(b) (4) Study report 1453-13-01	3TC	5.00 to 3000 ng/mL	Yes (including dilution QC sample)	No	No	1148 days at -25 ± 10ºC; 1146 days at -25 ± 10ºC in the presence of TFV
(b) (4). Study report 1752-18-01	TFV	2.00 - 500 ng/mL	Yes	No	No	679 days at -25 ± 10ºC 878 days at -25 ± 10ºC in the presence of 3TC

Source: Reviewer prepared from bioanalytical report.

Table 2. Assessment of LC-MS/MS method performance.

Analyte	Calibration range	Accuracy and precision values of calibration and QC samples within 15%	Major deviations	Sample reassays	Samples measured within the duration of stability	Incurred sample reanalysis pass rate (at least 67% should be ± 20% of the mean)	Chromatograms
DOR	1.00 to 1000.00 ng/mL	Yes	No	66 out of 397 study samples; mostly due to concentrations above upper limit of quantitation	Yes (135 days at -20ºC)	100% (51/51)	No anomalies observed in the submitted representative chromatograms
3TC	5.00 to 3000 ng/mL	Yes	No	29 out of 329 study samples; mostly to confirm presence of peak in pre-dose samples	Yes (252 days at -25 ± 10ºC)	100% (37/37)	No anomalies observed in the submitted representative chromatograms
TFV	2.00 - 500 ng/mL	Yes	No	19 of 329 study samples; mostly to confirm presence of peak in pre-dose samples	Yes (253 days at -25 ± 10ºC)	100% (37/37). [a total of 38 samples were analyzed, but the repeat of one sample had no value].	No anomalies observed in the submitted representative chromatograms

Source: Reviewer prepared from bioanalytical report.

PK Results

DOR

Though it was attempted to enroll approximately 4 evaluable participants between 35 to ≤ 45 kg in Cohort 1, only one subject weighing ≤ 45 kg (BW = 40.3 kg) was enrolled among the 9 participants. Therefore, in Cohort 2, only subjects weighing greater than 45 kg were enrolled (n=45).

The applicant determined the dose of DOR (100 mg) for the multiple-dose administration in Cohort 2 for participants weighing ≥45 kg based on the $AUC_{0\text{-inf}}$ (geometric mean of 34.8 µM*hr, which met the target of <64.8 µM*hr as specified by the Applicant) and predicted $C_{24,ss}$ (geometric mean of 690 nM, which met the target of > 560 nM as specified by the Applicant) from Cohort 1.

In Cohort 2, the observed DOR plasma concentrations (geometric mean $C_{24,ss}$=282 nM) at Week 1 for the 10 participants were lower than expected (Table 3). This may be caused by the drug-drug interaction with efavirenz (EFV), a moderate CYP3A inducer, as 8 of the 10 participants had switched from efavirenz (EFV). Based on current PIFELTRO US label, the geometric mean ratios (90% CI) of DOR C_{24} with/without co-administration of 600 mg efavirenz QD at the first day and 14 days following the cessation of efavirenz therapy are 0.15 (0.10, 0.23) and 0.50 (0.39, 0.64), respectively. The geometric mean ratio of $C_{24,ss}$ observed at week 1 for the 10 participants vs. the adult value (C_{24} = 930 nM) was ~0.30. As such, we agree with the Applicant that the lower concentrations observed at week 1 were likely due to the residual CYP3A induction effect from EFV. Steady state conditions for DOR were not attained at Week 1 for participants who switched from EFV.

Table 3. DOR PK parameters following oral administration of DOR/3TC/TDF once daily for participants with semi-intensive sampling at Week 1, Cohort 2

Descriptive Statistics	Age (yr)	Weight (kg)	AUC0-24,ss (h.µM)	C0,ss (nM)	C24,ss (nM)	Cmax,ss (µM)	Tmax (h)	CL/F (L/h)
N	10	10	10	10	10	10	10	10
Geometric Mean	15.5	55.1	22.9	266	282	2.13	-	10.3
Geometric CV (%)	9.3	20.0	47.0	61.2	73.8	42.7	-	47.0
Minimum	14.0	45.2	8.03	91.4	76.0	0.80	1.92	6.14
Median	16.0	56.1	24.3	330	347	2.13	1.95	9.67
Maximum	17.0	79.8	38.3	486	596	3.56	3.95	29.3
Mean	15.6	56.1	24.7	301	331	2.27	-	11.4
SD	1.43	11.7	8.82	137	166	0.776	-	6.72
CV (%)	9.2	20.9	35.8	45.3	50.0	34.2	-	58.8

All doses were adult tablets.

Source: Submitted study report for P027.

Therefore, the PK parameter estimates of DOR in pediatrics in this submission were primarily supported by popPK analysis. The applicant's popPK analysis is determined to be acceptable for characterizing PK of DOR in pediatric subjects ≥ 35 Kg and for projection of exposures in pediatric subjects ≥ 35 Kg (Please refer to Pharmacometrics review section for details).

3TC and TDF

PK parameters of 3TC and TFV were based on intensive sampling at Week 1, Cohort 2 (Table 4 and Table 5).

Table 4. 3TC PK parameters following oral administration of DOR/3TC/TDF once daily for participants with intensive sampling at Week 1, Cohort 2

Descriptive Statistics	Age (yr)	Weight (kg)	AUC0-24,ss (h.ng/mL)	C0,ss (ng/mL)	C24,ss (ng/mL)	Cmax,ss (ng/mL)	Tmax (h)	CL/F (L/h)
N	10	10	10	10	10	10	10	10
Geometric Mean	15.5	55.1	11300	59.8	66.3	2100	-	26.5
Geometric CV (%)	9.3	20.0	27.9	68.4	54.7	23.6	-	27.9
Minimum	14.0	45.2	7820	24.8	35.8	1540	0.90	16.8
Median	16.0	56.1	11700	60.8	63.4	2110	1.94	25.7
Maximum	17.0	79.8	17800	212	189	2970	3.95	38.4
Mean	15.6	56.1	11700	72.4	75.6	2160	-	27.4
SD	1.43	11.7	3310	54.8	46.7	513	-	7.23
CV (%)	9.2	20.9	28.2	75.7	61.7	23.8	-	26.4

All doses were adult tablets.

Source: Submitted study report for P027.

Table 5. TFV PK parameters following oral administration of DOR/3TC/TDF once daily for participants with intensive sampling at Week 1, Cohort 2

Descriptive Statistics	Age (yr)	Weight (kg)	AUC0-24,ss (h.ng/mL)	C0,ss (ng/mL)	C24,ss (ng/mL)	Cmax,ss (ng/mL)	Tmax (h)	CL/F (L/h)
N	10	10	10	10	10	10	10	10
Geometric Mean	15.5	55.1	2550	48.4	50.2	293	-	53.3
Geometric CV (%)	9.3	20.0	14.3	22.2	9.4	36.6	-	14.3
Minimum	14.0	45.2	2000	36.6	45.5	175	0.90	44.0
Median	16.0	56.1	2510	49.6	49.7	278	0.95	54.3
Maximum	17.0	79.8	3090	68.8	60.1	500	3.95	68.1
Mean	15.6	56.1	2570	49.5	50.4	310	-	53.8
SD	1.43	11.7	362	10.8	4.91	114	-	7.69
CV (%)	9.2	20.9	14.1	21.8	9.7	36.6	-	14.3

All doses were adult tablets.

Source: Submitted study report for P027.

4. Comparison of DOR exposures in pediatrics vs. adults

4.1 Exposure-response analysis in the original NDA approval

Exposure-response analyses for efficacy and safety were conducted in the original NDA submission for adult approval (Table 6).

Table 6. Datasets for exposure-response analysis.

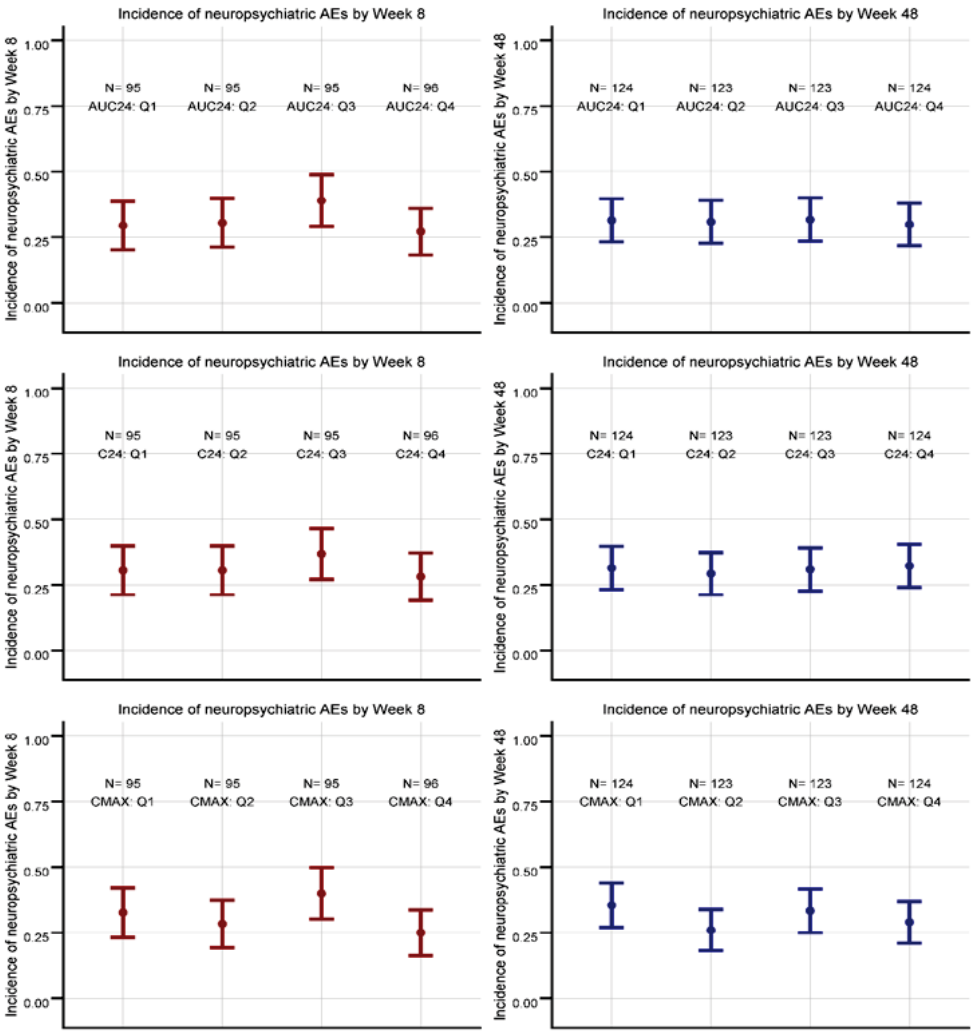
Dataset label	Included studies	DOR dose levels	Response variables
Ph2b efficacy	P007	25 mg QD, 50 mg QD, 100 mg QD, 200 mg QD	HIV-1 RNA responses and virologic failure
Ph3 efficacy	P018 + P021	100 mg QD	HIV-1 RNA responses and virologic failure
Neuropsychiatric AEs	P007 + P021	25 mg QD, 50 mg QD, 100 mg QD, 200 mg QD	Neuropsychiatric AEs
Lipids	P007 + P018 + P021	25 mg QD, 50 mg QD, 100 mg QD, 200 mg QD	Fasting LDL-C and fasting non-HDL-C

Source: Submitted DOR exposure-response analysis report in the original NDA application.

As stated in the clinical pharmacology review for original approval in adults (DARRTS, NDA210806, entered on 8/29/2018), exposure-safety analyses included DOR AUC0-24 and Cmax vs. neuropsychiatric adverse effects (AEs) at week 8 and week 48 (study P007 and P021) and lipid profiles change at week 48 (change in LDL-C and non-HDL-C from baseline, study P007, P018, and P021).

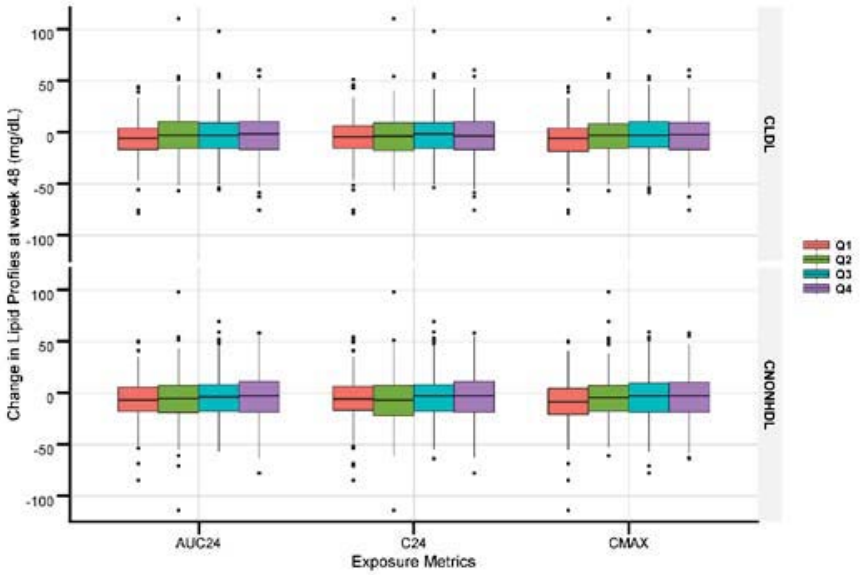
- Neuropsychiatric AEs: The observed incidence rates appear to be comparable across different exposure quartiles and exposure was not associated with the occurrence of neuropsychiatric AEs in logistic regression (Figure 1)
- Change in lipid profiles (Figure 2):
  - The change in lipid profiles from baseline appears similar across DOR exposure quartiles
  - A positive trend of exposure-response relationship was observed between DOR PK and change in LDL-C from baseline at week 48, but the relationship was not statistically significant
  - For non-HDL-C, a significant non-zero slope of DOR PK on change from baseline was detected; lower DOR exposure was associated with slightly larger decreases in lipids from baseline, which is considered not clinically meaningful
  - Change in lipid profiles is not described in labeling under Adverse Reactions
- Overall, our conclusion from the adult exposure-safety analysis results abovementioned is that safety was acceptable within the range of DOR exposures observed in adults. The upper bound of C_{max} is 5215 nM and the upper bound of AUC_{0-24} is 98.6 µM*hr (Table 7).

Figure 1. Observed incidence of neuropsychiatric AEs across exposure quartiles in trials P007 and P021.



Source: Multi-disciplinary review for the original NME submission.

Figure 2. Boxplots of observed change in lipid profiles from baseline in different exposure quartiles at Week 48 in trials P007, P018, and P021.



Source: Multi-disciplinary review for the original NME submission.

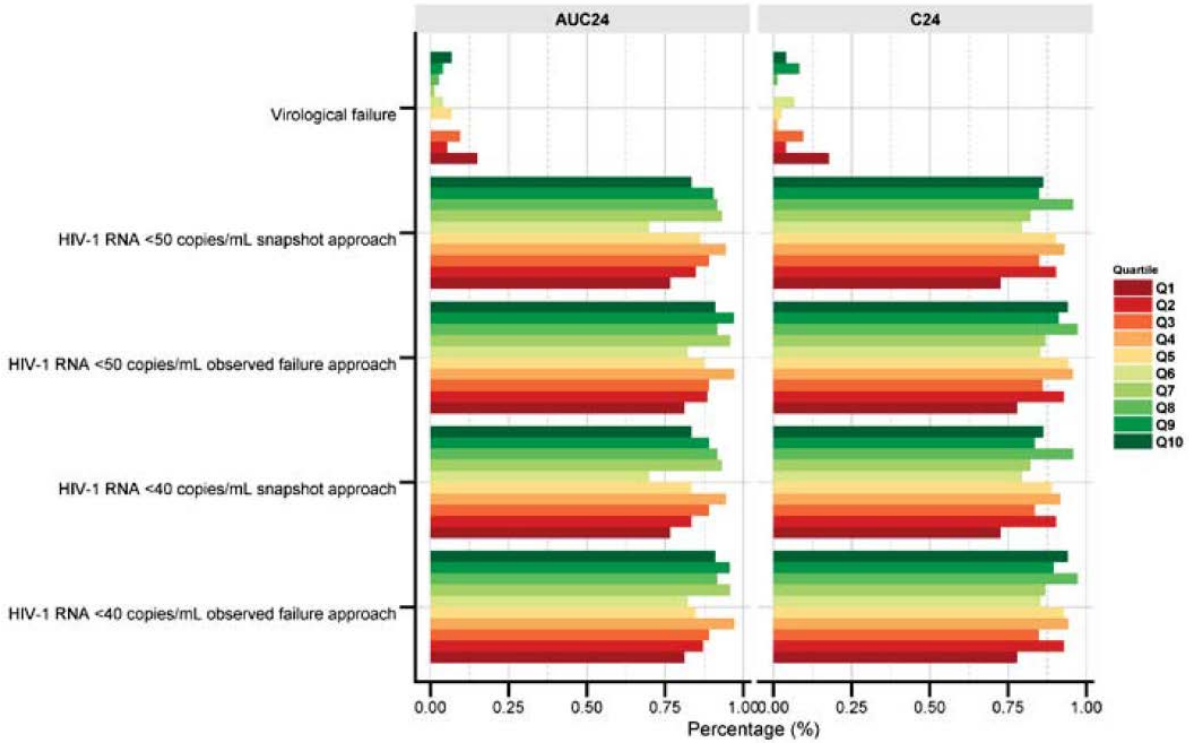
Table 7. Upper bounds of C_{max} and AUC_{0-24} values used for exposure-response analysis for safety from adult Phase 2 (P007) and Phase 3 (P018 and P021) trials.

Dataset label	Included studies	Week8		Week48	
		C_{max} (nM)	AUC_{0-24} (µM*hr)	C_{max} (nM)	AUC_{0-24} (µM*hr)
Neuropsychiatric AEs	P007 + P021	4955	90.5	5215	98.6
Lipids	P007 + P018+ P021	/	/	5215	99.7

Source: Reviewer's table based on E-R datasets for neuropsychiatric AEs and lipid profiles in the original adult submission.

- As in the clinical pharmacology review for original approval in adults (DARRTS, NDA210806, entered on 8/29/2018), exposure-efficacy analyses included the observed proportion of subjects achieving HIV-1 RNA levels at two cutoffs: <50 copies/mL and <40 copies/mL.
- Phase 2 trial: The proportion of responses or virologic failure appeared to be similar across the 4 exposure quartiles and exposure was not associated with efficacy variables in logistic regression.
- Phase 3 trials (P018 and P021):
  - Statistically significant exposure-response relationships were identified between DOR PK (AUC_{0-24} and C_{24}) and nearly all evaluated efficacy endpoints over the exposures achieved at the 100 mg QD dose
  - A trend of lower response and higher virologic failure rates were observed for DOR exposures below the 10^{th} percentile
- The review team selected lower bound of C_{24} of 560 nM and AUC_{0-24} of 27.6 µM*hr, corresponding to the 10^{th} percentile of adult values in the Phase 3 trials, for efficacy assessment in pediatric patients.

Figure 3. Observed efficacy endpoints across exposure percentiles in phase 3 trials P018 and P021.



Source: clinical pharmacology review of the original approval for adults (DARRTS, NDA210806, entered on 8/29/2018)

4.2 DOR exposure in pediatric subjects weighing ≥ 45 kg vs. adults

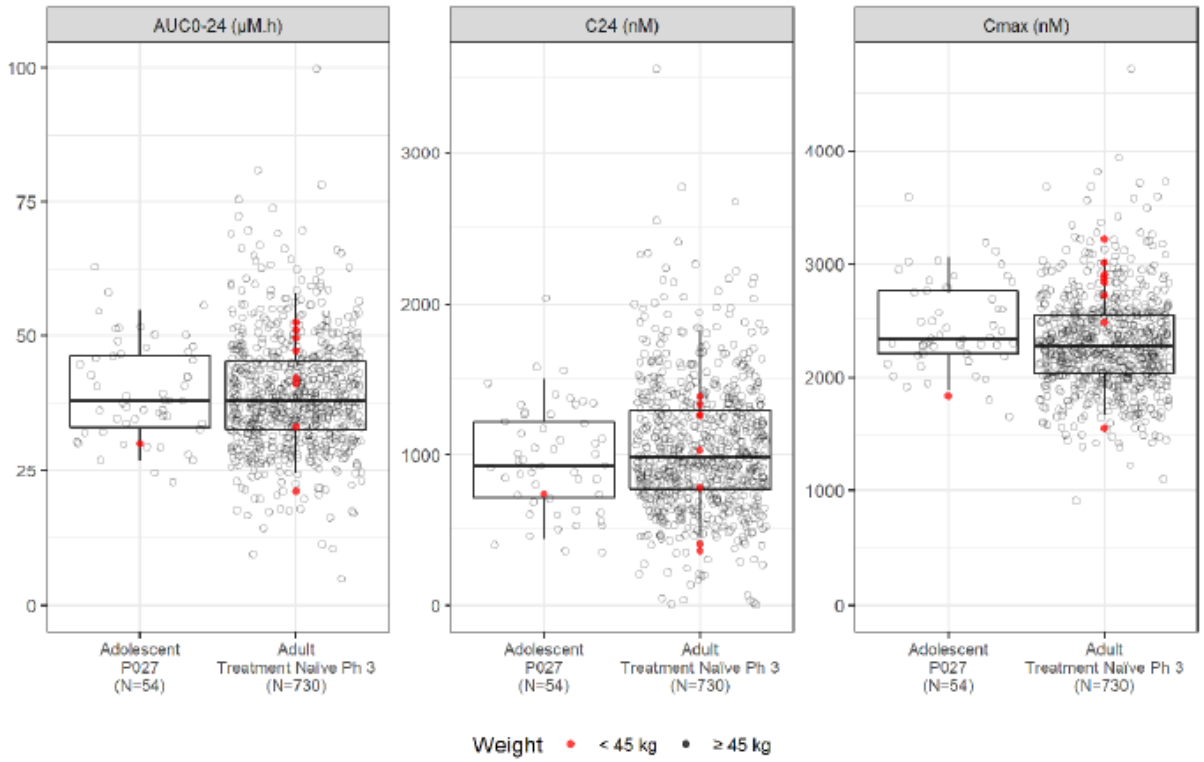
Post-hoc estimates of DOR PK parameters in pediatric subjects in trial P027 fell within the range (post-hoc estimates) as observed in Phase 3 adult subjects (Table 8 and Figure 4). However, 15% and 8% of the subjects have DOR C_{24} and $AUC_{0\text{-}24}$ values below the lower bounds for efficacy (C_{24} of 560 nM and $AUC_{0\text{-}24}$ of 27.6 µM*hr) (Response to IR submitted on 10/25/2021).

Table 8. Summary of pediatric/adult geometric mean ratios and 90% confidence intervals for pediatric subjects ≥ 45 kg in Study P027.

PK Parameter	Population	Number of Subjects	GM (95% CI)	GMR (90% CI) Pediatric / Adult
AUC0-24 (µM·h)	Adult	730	37.8 (37.0, 38.6)	
	Pediatric	53	38.8 (36.4, 41.3)	1.03 (0.97, 1.08)
Cmax (nM)	Adult	730	2260 (2230, 2300)	
	Pediatric	53	2430 (2320, 2530)	1.07 (1.03, 1.11)
C24 (nM)	Adult	730	930 (892, 970)	
	Pediatric	53	894 (800, 998)	0.96 (0.87, 1.06)

Source: Response to IR submitted on 10/25/2021.

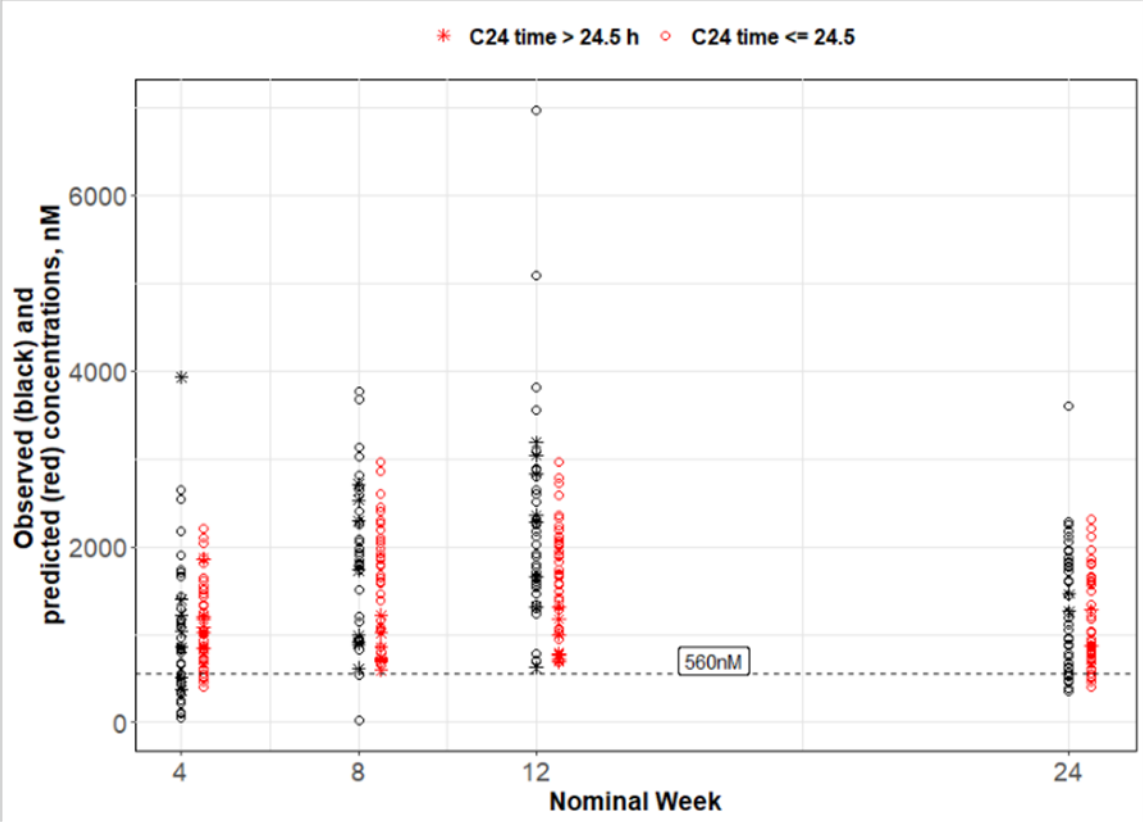
Figure 4. Adolescent (P027) and Phase 3 adult treatment naïve steady state DOR PK following administration of DOR 100 mg QD.



Source: Population Pharmacokinetics Analysis report submitted by the Applicant. Circles are post-hoc estimates using popPK analysis. Center lines are medians, boxes are 25th and 75th quartiles, and whiskers are 5th and 95th percentiles. Red circles represent subjects with body weight < 45 kg.

In addition, 44% (18 of 44) and 16% (7 of 43) of observed trough concentration (C_{24}) at week 4 and 24, respectively, were below 560nM (Figure 5). This discordance was carefully evaluated by taking all C_{24} collected in Study P027 into consideration. Per Pharmacometrics reviewer's independent analysis, although the cause for those observed low C24 concentrations is unknown, model predicted C_{24} values at steady state is reliable based on totality of the data including C24 concentrations collected at other time points in Study P027 and should be used for DOR exposure assessment (see Pharmacometrics review for details).

Figure 5. Observed versus predicted doravirine concentrations stratified by nominal weeks after start of treatment



Source: Reviewer's independent analysis
The horizontal line represents the lower bound of 560 nM for C_{24}.

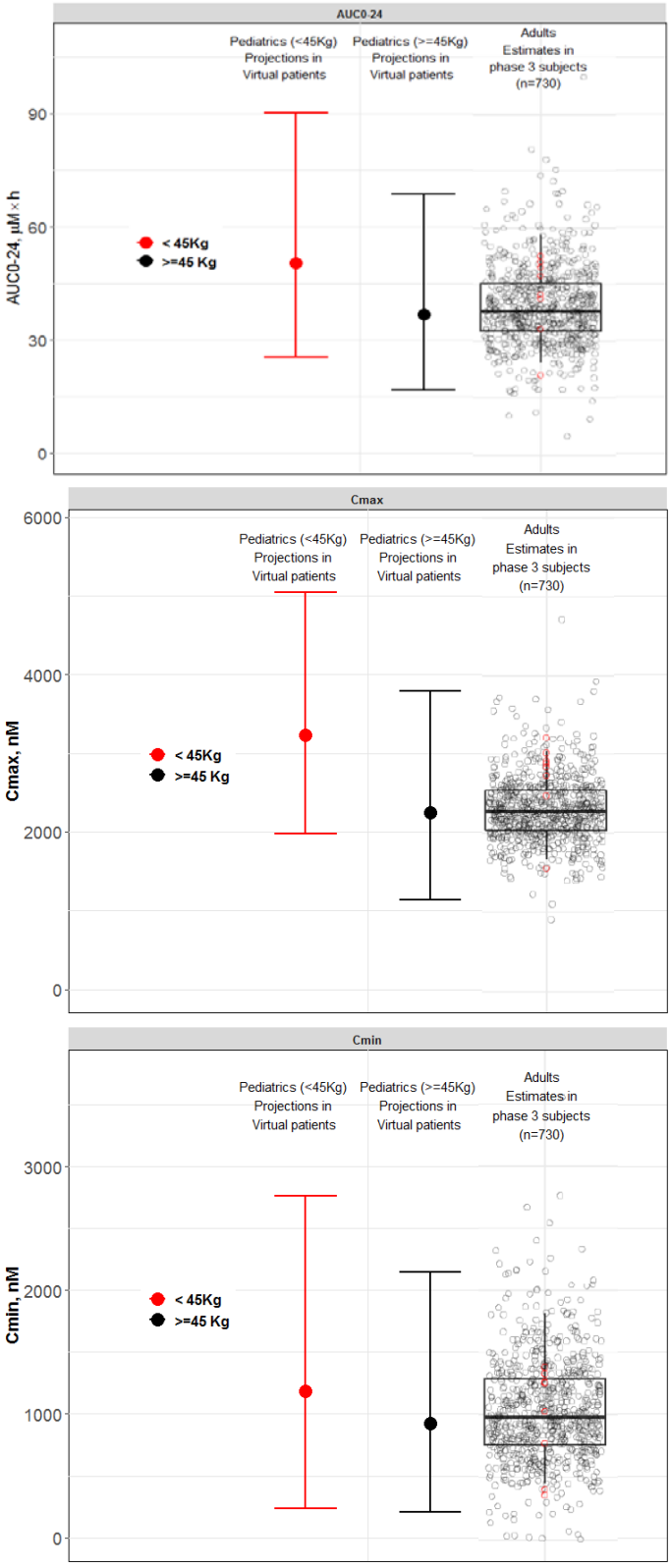
In summary, the GMRs of DOR C_{max}, AUC_{0-24} and C_{24} in pediatrics ≥ 45 kg vs. adults ranged from 0.96-1.07. All PK parameter values for individual subjects fell within the range of exposures in adult patients. In addition, most subjects (85% and 92%) have C_{24} levels greater than 560 nM and AUC_{0-24} levels greater than 27.6 µM*hr, respectively. As such, we conclude that DOR exposures are comparable between pediatrics ≥ 45 kg vs. adults.

4.3 DOR exposure in pediatric subjects weighing ≥ 35 kg and < 45 kg vs. adults

Given there was only one subject weighing < 45 kg in study P027, simulations based on virtual pediatric patients <45 kg regardless of age, were conducted. The predicted exposures are in Figure 6. The simulation results indicate the projected population means for AUC_{24} and C_{max} are higher in pediatric subjects weighting ≥ 35 kg and < 45 kg compared to adults (Table 9).

To assess the relatively higher exposure projected for pediatric subjects weighing < 45 kg, we referred to the upper bounds of exposure for safety (C_{max} of 5215 nM and AUC_{0-24} of 98.6 µM*hr) aforementioned. Only 1.9 % and 1.3% of simulated virtual pediatric subjects are expected to have steady state C_{max} > 5215 nM and AUC_{0-24} > 98.6 µM*h, respectively. We defer the safety assessment to the Clinical review team.

Figure 6. Comparisons of model predicted population mean and 95% prediction intervals (PI) of PK parameters in pediatric subjects compared to model estimated PK parameters in adult patients. Error-bar represent mean and 95% PI, while box plots represent mean and inter-quartile range.



Source: Generated by Dr. Eliford Kitabi.

Table 9. Model predicted mean C_{max} and AUC_{0-24} in virtual pediatric patients weighing ≥ 35 kg.

Weight Groups	Mean C_{max} (95% PI), nM	Mean AUC_{0-24} (95% PI), µM*hr
≥ 35 kg and < 45 kg	3225 (1973-5009)	50.3 (25.6-89.5)
≥ 45 kg	2243 (1134-3786)	36.7 (16.7-68.6)

Source: Generated by Dr. Eliford Kitabi. PI, prediction interval.

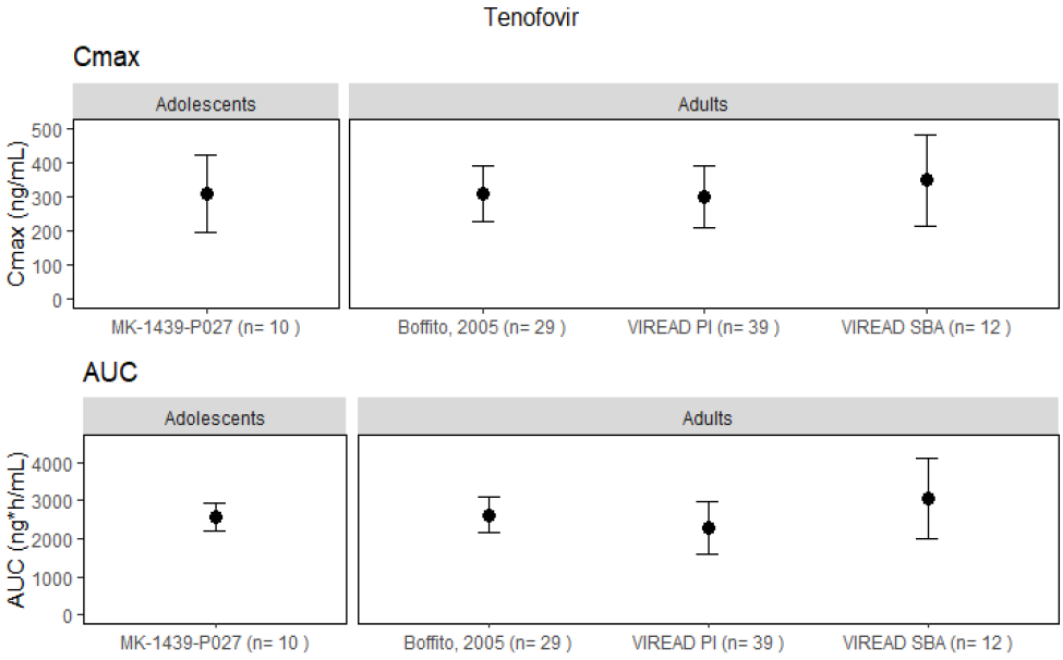
5. Comparison of 3TC and TFV exposures in pediatrics vs. adults

In Study P027 Cohort 2, adolescents 12 to < 18 years old and weighing ≥ 45 kg, were administered the adult tablet of DOR/3TC/TDF at doses of 100 mg/300mg/300mg, respectively. The 3TC/TDF doses of 300 mg/300mg were the recommended doses of EPIVIR® and VIREAD® in adults and children weighing ≥ 35 kg.

The relative bioavailability of 3TC and TDF in DELSTRIGO was previously assessed in adult subjects and determined to be comparable to their corresponding components in EPIVIR® and VIREAD® under fasting conditions, respectively. In addition, no clinically relevant differences were observed for 3TC and TDF exposures under fasted and fed conditions (Study P026, Refer to clinical pharmacology review for original approval in adults (DARRTS, NDA210806, entered on 8/29/2018). Single dose PK for 3TC and TFV are similar to multiple dose PK. In addition, the PK of 3TC and TFV is comparable between HIV-infected participants and healthy volunteer subjects (Clinical pharmacology review for VIREAD (TDF), NDA21356, entered into DARRTS on 10/26/2001 and US prescribing information for EPIVIR (3TC)). Therefore, it is reasonable to compare the exposures (AUC_{0-24} and C_{max}) of 3TC and TFV at steady state following administration of DOR/3TC/TDF to adolescent participants in P027 to historical values for 3TC and TDF administered as single agents or once daily in adults from USPI for EPIVIR® and VIREAD®, respectively, and from the literature, as the Applicant conducted.

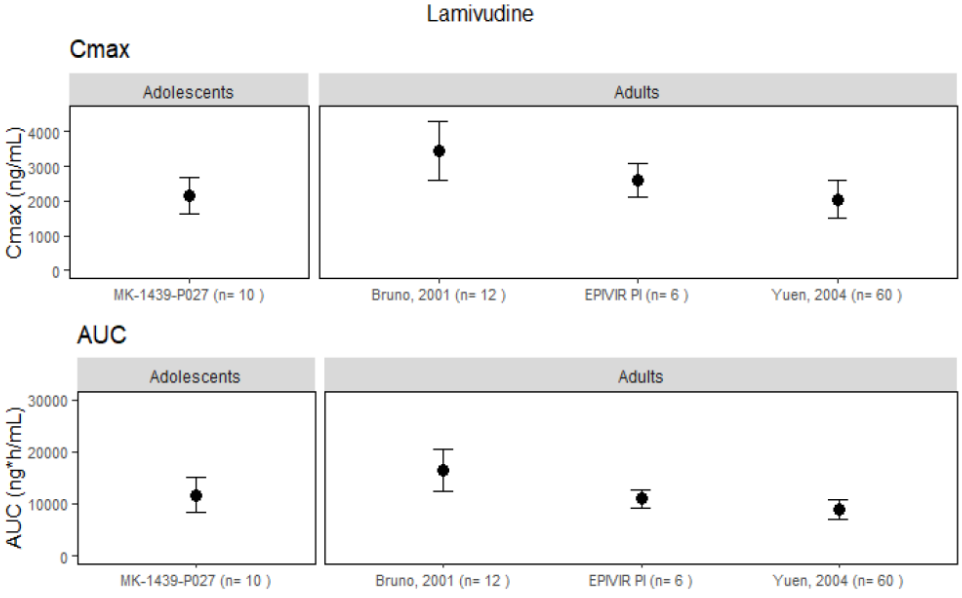
The adolescent PK data from P027 were graphically compared as means and SD to the historical PK data in adults and determined to be comparable to historical adult exposures of 3TC and TFV in adults (Figure 7 and Figure 8).

Figure 7. Comparison of arithmetic mean (SD) C_{max} and AUC_{0-24} for Tenofovir following oral administration of DOR/3TC/TDF 100 mg/300 mg/300 mg to adolescents and single or multiple dose Tenofovir Disoproxil Fumarate 300 mg to healthy and HIV-1 infected adults.



Source: Submitted comparison of 3TC and TDF in adolescents and adults.

Figure 8. Comparison of arithmetic mean (SD) C_{max} and AUC_{0-24} for lamivudine (3TC) following oral administration of DOR/3TC/TDF 100 mg/300 mg/300 mg to HIV-1 infected adolescents and single or multiple dose 3TC 300 mg in healthy and HIV-1 infected adults.



Source: Submitted comparison of 3TC and TDF in adolescents and adults.

6. Pharmacometrics Review

6.1 Population PK Analysis

6.1.1 Review Summary

The applicant's population PK analysis is acceptable for characterizing the population PK of doravirine in adolescents ≥ 45 Kg and for projection of exposures in pediatrics from <45 Kg down to 35 Kg. The final population PK model was an one compartment model parameterized by apparent clearance (CL/F), apparent volume of distribution (V/F), and absorption rate constant (Ka). Identified sources of variability for CL were age, body weight (WT), and efavirenz use. In general, CL/F increased allometrically with an allometric exponent for the effect of body weight of 0.75, but for subjects with same weight, CL/F is lower in older subjects by 0.54% per year older. Subjects switching from efavirenz had higher CL/F during the first week after switching to doravirine. Body weight was the only identified source of variability for V/F, with an allometric exponent of 1. The inter-individual variability (IIV) for CL/F (31.8%), and V (31.3%) were small. IIV for Ka was fixed to 0%. Eta shrinkage for CL/F (25.1%) was small but large for V (49%). Both goodness-of-fit plots and visual predictive checks indicate that the final population PK model is adequate in characterizing the PK profile of Doravirine in adolescent subjects infected with HIV weighting ≥ 35 Kg. Creatinine clearance was not a source of PK variability for doravirine consistent with the fact that renal excretion account for only 6% of elimination of unchanged doravirine. The estimated PK parameters, Ka, CL and V are consistent with those estimated for adult patients. The applicant's analyses were verified by the reviewer, with no significant discordance identified.

The developed model was used to support labelling of doravirine in the current submission as outlined in Table 10.

Table 10. Reviewer's Specific Comments on Applicant's Final Population PK model

Utility of the final model			**Reviewer's Comments**
Support applicant's proposed labeling statements about intrinsic and extrinsic factors	**Intrinsic factor**	Pediatric dosing is dependent on body weight. Body weight is a significant covariate on CL and V	Through monte-carlo simulations, the applicant shows that pediatric subjects weighting >35 Kg receiving 100 mg QD have comparable exposure to adolescents and adults
	Extrinsic factor	Extrinsic factors were not evaluated for effect on PK parameters	
Derive exposure metrics for exposure-matching/exposure-response analyses	The model predicted exposures in pediatrics ≥35 Kg were compared to those estimated in adolescents and treatment naive adults patients		Monte-carlo simulation for exposure matching is acceptable since the model predictive performance was reasonable as indicated by visual predictive checks (VPC)

Predict exposures at alternative dosing regimen	The model was not used to assess predicted exposures at other doses than 100mg QD	Doravirine is available alone (Pifeltro 100 mg tablets) or in fixed dose combination (Doravirine, 100 mg; Lamivudine, 300 mg; Tenofovir, 300 mg)

Source: Reviewer's independent analyses

6.1.2. Introduction

The primary objectives of this analysis were:

- To estimate population PK parameters of oral doravirine in adolescent HIV infected patients, 12 - 18 years, weighting $\geq 35\ Kg$.
- Determine covariates influencing doravirine PK in adolescents.
- Compare pediatric versus adult PK to support the appropriateness of 100 mg QD dose in pediatric patients weighting $\geq 35\ Kg$

6.1.3 Model development

6.1.3.1 Data

The analyses were based on PK data from a phase 1/2 study (Study P027) in adolescents to assess pharmacokinetics, safety and tolerability of doravirine in this patient population. The trial consisted of two staggered cohorts: cohort 1 subjects received a single 100 mg dose of doravirine followed by intensive PK sampling; after evaluation of PK in cohort 1, cohort 2 was recruited and they received 100 mg once daily for evaluation of long-term efficacy and safety. Brief descriptions of PK sampling are presented in Table 11.

The final NONMEM data file for analysis contained 341 PK observations from 54 subjects. Table 12 provides summary statistics of the baseline demographic covariates in the analysis dataset.

Table 11. Summary of Studies with PK Sampling Included in Population PK Analysis

Study.Number	Cohort	Patient.Population	Dose.Regimen	PK.Sample.Collection
MK-1439-027	1	Adolescents, >=12 Yrs, >= 35Kg (N = 9)	100 mg single dose on day 1	Intensive: Predose, and at 1, 2, 4, 8, 12, 24, 48, 72-hour post-dose
	2	Adolescents, >=12 Yrs, >= 45Kg (N = 10)	100 mg once daily	Semi-intensive: Week 1 (at SS): predose, and 2, 4, 12, 24 hr post-dose
		Adolescents, >=12 Yrs, >= 45Kg (N = 35)		Sparse: Study entry (predose); Week 4 (predose); Week 8 and 12 (random); Week 24 (predose, 0.5 – 2 hr post-dose); Week 48 (predose, 0.5 – 2 hr post-dose)

Source: Reviewer's independent analyses

Table 12. Summary of Baseline Demographic Covariates for Analysis

		Adolescents > = 35 Kg	
Characteristics	level	Cohort 1	Cohort 2
N		9	45
SEX (n (%))	Male	7 (77.8)	19 (42.2)
	Female	2 (22.2)	26 (57.8)
Race (n (%))	Asian	0 (0.0)	35 (77.8)
	Black/African American	7 (77.8)	10 (22.2)
	White	2 (22.2)	0 (0.0)
Ethinicity (n (%))	Hispanic or Latino	0 (0.0)	1 (2.2)
	Non-Hispanic	9 (100.0)	44 (97.8)
Switch from EFV (n (%))	Naive	9 (100.0)	23 (51.1)
	Yes	0 (0.0)	22 (48.9)
Age (Yrs), (Mean (Sd))		14.33 (1.58)	15.04 (1.61)
Weight (Kg), (Mean (Sd))		55.89 (15.84)	53.79 (7.95)
BMI (Kg/M^2), (Mean (Sd))		21.03 (5.98)	20.89 (2.64)
BSA (m^2), (Mean (Sd))		1.58 (0.22)	1.55 (0.13)
eGFR (mL/min/1.73 m^2), (Mean (Sd))		178.10 (61.19)	161.16 (60.35)
CRCL (mL/min), (Mean (Sd))		134.44 (29.12)	138.4232.65)

Source: Reviewer's independent analyses

6.1.3.2 Base Model

The base model was a population PK model developed using doravirine PK data pooled from phase 1, phase 2b and phase 3 trials in healthy and HIV infected adult patients. The base model was a one-compartment model described by first-order absorption (Ka), apparent volume of distribution (V/F), and apparent linear clearance (CL/F) from the central compartment. Since only one dose was tested in adolescents, the dose-dependency of bioavailability was not assessed in adolescents as it was done in adult patients. Inter-individual variability (IIV) on CL/F and V/F were included in the base model. The IIVs were modeled using exponential error models. The additive residual error model was employed for log-transformed data. Informative Bayesian prior was included for Ka since PK data before 1 hour after dose were not collected. Informative Bayesian priors were also included for IIV-CL and IIV-V due to the small sample size. Model evaluations and selection of the base model were based on standard statistical criteria of goodness-of-fit, e.g. diagnostic plots.

6.1.3.3 Covariate Analysis

Covariate analysis in adolescent PK relied on prior knowledge of covariates in adult population PK model. Covariates identified to influence PK variability in adult patients were selected and tested for influence on adolescent PK. The following covariates were included in the adolescent model.

- Age on CL/F: Age was included as a linear covariate of CL/F with reference age being 15 years ($CL_i = CL_T \times \left(1 + \beta \times (AGE - 15)\right)$, CL_i = individual CL/F, CL_T = Typical CL/F for a 15-year-old weighing 52 Kg, β= change in CL/F per 1 year age difference). The β parameter was estimated for adolescent data with an informative Bayesian prior from adult model of -0.54% per year. Informative prior was used in this case because of the narrow age range in adolescents and the expected small value of β

- Weight on CL/F: Allometric scaling was used to model the effect of weight on CL/F with fixed exponent of 0.75, instead of estimated exponent as it was done in adult pop PK model ($CL_i = CL_T \times \left(\frac{WT}{52}\right)^{0.75}$, CL_i = individual CL/F, CL_T = Typical CL/F for a 15-year-old weighing 52 Kg). The allometric exponent was fixed in this case because of the narrow weight range and this practice is supported by literature by both theory and experimental evidence.

- Prior efavirenz use on CL/F: The impact of efavirenz on doravirine CL/F, during the first week after switching from efavirenz, was estimated in subjects in cohort 2 who participated in the week 1 semi-intensive PK sampling. A fractional difference in CL/F between the first week and later weeks was estimated.

- Weight on V/F: Allometric scaling was used to model the effect of weight on V/F with fixed exponent of 1 ($V_i = V_T \times \left(\frac{WT}{52}\right)$, V_i = individual V/F, V_T = Typical V/F for a 15-year-old weighing 52 Kg).

6.1.3.4 Final Model

The parameter estimates for the final covariate model are listed in Table 13. The goodness-of-fit (GOF) plots for the final covariate model for all data are shown in Figure 9. The Visual Predictive Checks (VPC) plot for the final covariate model are given in Figure 10.

Table 13. Parameter Estimates and Objective Function Values of Applicant's Final Model

Parameter	Unit	Prior	Estimate	%RSE	%CV	CI95Low	CI95 High	%Shrinkage
CL/F	L/h	--	5.95	5.40	--	5.32	6.57	--
V/F	L	--	133	9.16	--	109	156	--
KA	1/h	1.42	1.39	0.851	--	1.37	1.42	--
Age on CL	%/yr	-0.540	-0.538	0.305	--	-0.541	-0.535	--
EFV on CL	%	--	73.1	20.7	--	43.4	103	--
IIV CL/F	--	0.104	0.101	1.59	32.6	0.0977	0.104	25.1
IIV V/F	--	0.098	0.0977	1.09	32.0	0.0956	0.0997	49.4
RV	--	--	0.520	10.6	55.7	0.412	0.628	8.54

CL/F = apparent clearance; V/F = apparent volume; KA = absorption rate;
IIV = inter-individual variability (log-normal variance);
RV = residual variability (log-normal standard deviation);
CL/F_i = apparent clearance for i^{th} individual adjusted for individual covariates = CL/F * $CLAGE_i$ * $CLEFV_i$ * $(WT_i / 52)^{0.75}$;
$CLAGE_i$ = 1 + AgeOnCL * (AGE_i - 15);
$CLEFV_i$ = 1 + EFVonCL * EFV_i (switch from EFV, Cohort 2, Week 1);
V/F_i = apparent volume adjusted for individual covariates = V/F * (WT_i / 52);
%RSE = % relative standard error = 100 * SE / Estimate;
%CV = % coefficient of variation = 100 * $\sqrt{(e^{Variance}-1)}$;
CI95% = 95% confidence interval = Estimate ± 1.96*SE;

Source: Applicant's report on population PK analysis of doravirine in adolescents with HIV-1 infection (Page 28 of 63)

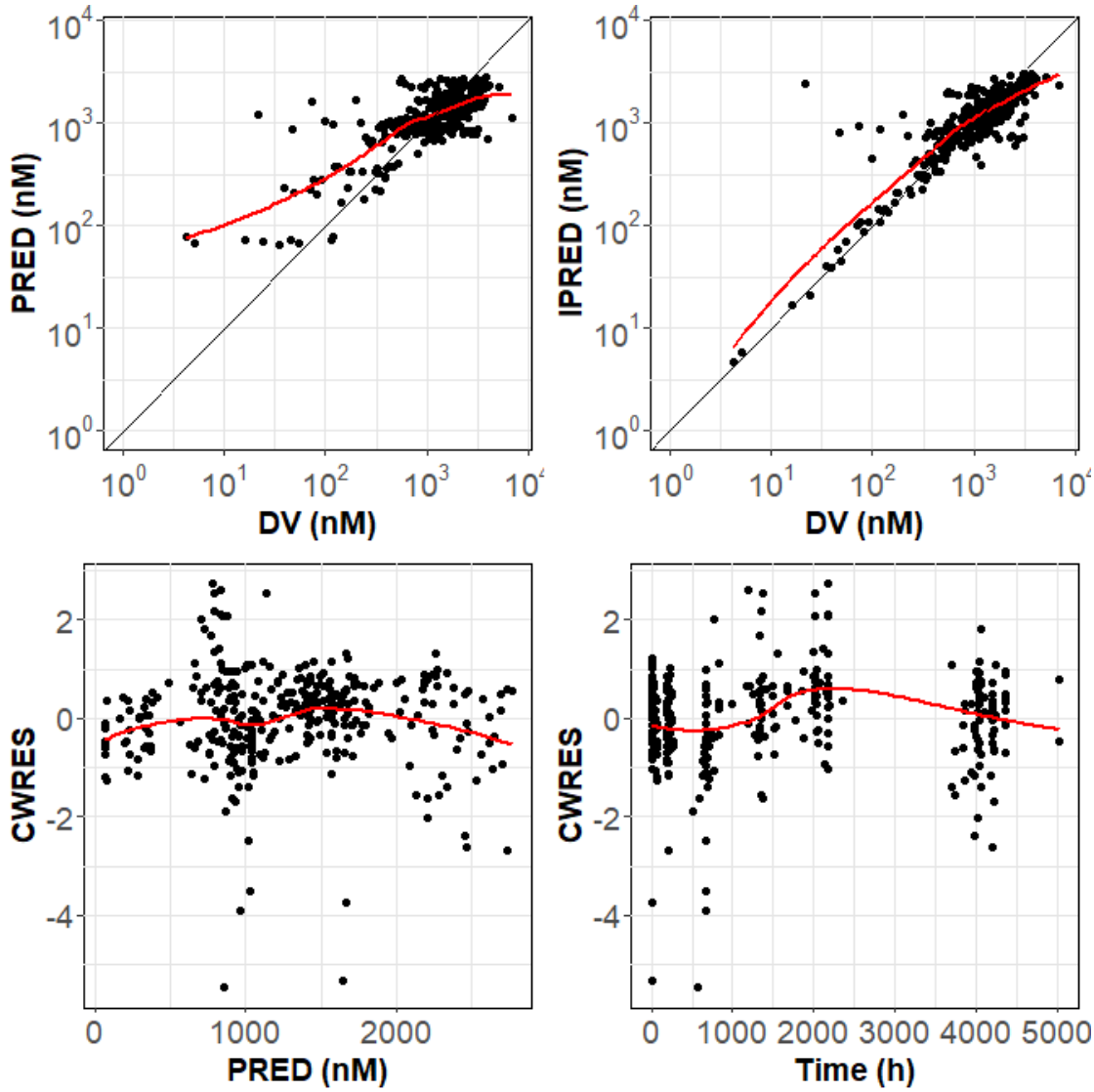


Figure 9. Goodness of fit plots for doravirine population PK model in adolescent patients (Applicant's Final model)

Source: Reviewer's independent analysis

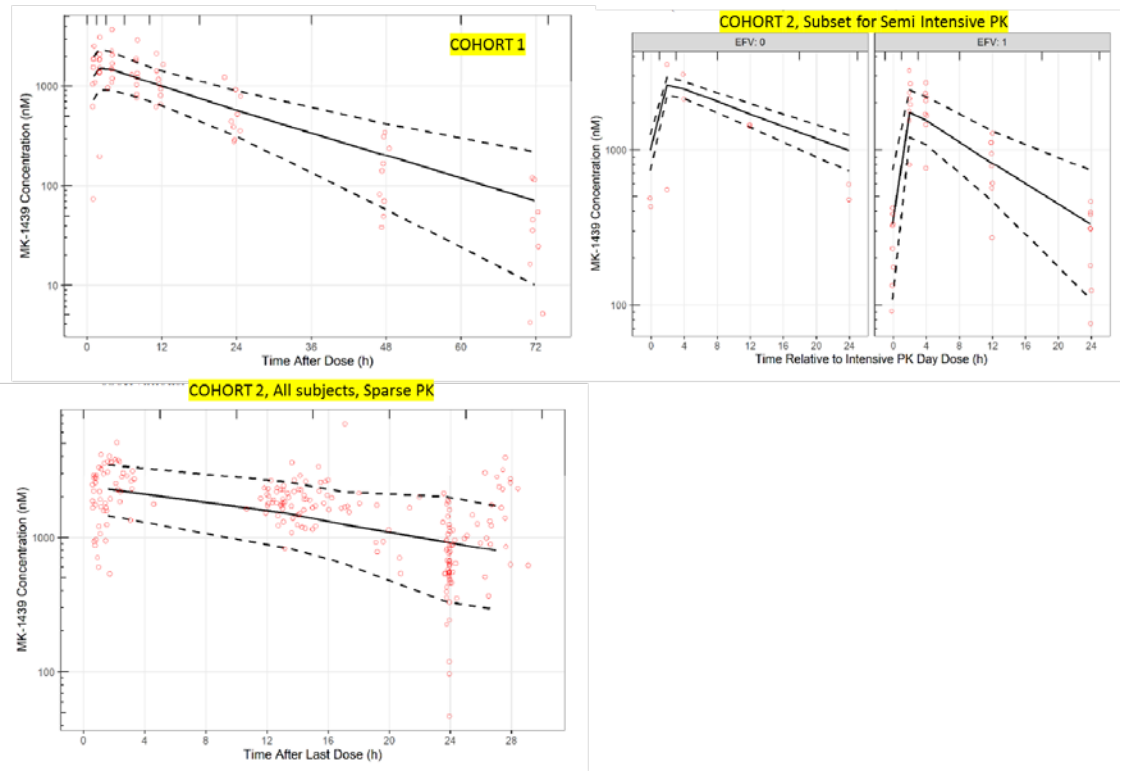


Figure 10. Visual predictive checks of the final model. Black lines are model predictions (median and 95% prediction interval) and red circles are observations

Source: Applicant's report on population PK analysis of doravirine in adolescents with HIV-1 infection (Page 51 -52 of 63)

6.1.3.5 Reviewer's comments

The reviewer finds the applicant's model development steps and identification of covariate effects to be acceptable for characterizing the population PK of doravirine in adolescents. For example, although the effect of body weight on CL and V was not estimated but fixed to the literature values of 0.75 and 1 respectively, the ETAs vs body weight plot (See Figure 11*) do not show significant trends and therefore indicate that these coefficients are adequate to characterize such effects. The choice of the weight exponents of 0.75 and 1 for CL and V respectively is an acceptable practice and is supported by both theory and experimental evidence. Therefore, the reviewer did not perform independent exploration of covariate effects. The reviewer repeated the applicant's analyses and found similar results as those reported by the applicant. For example,* Table 14 *summarizes central tendency and ranges of the selected PK parameters at steady state for all subjects in study P027. The geometric means and coefficient of variations are similar to those reported by the applicant in Pifeltro label, section 12.3. The reviewer used the applicant's final POPPK model to estimate steady state exposures reported in* Table 14*. In this analysis the population PK parameters were used to estimate individual PK parameters for each subject in P027. The derived PK parameters were subsequently used to simulate doravirine concentration-time profile after single dose and at steady state. The profiles were analyzed to obtain AUC, Cmin and Cmax after single dose and at steady state. Single dose and steady state AUCs were used to determine accumulation ratio and hence effective half-life of doravirine in adolescents. In contrast to adult PK reported in the Pifeltro label, the accumulation factor for doravirine in adolescents is about 1.6 and effective half-life is about 16 hours.*

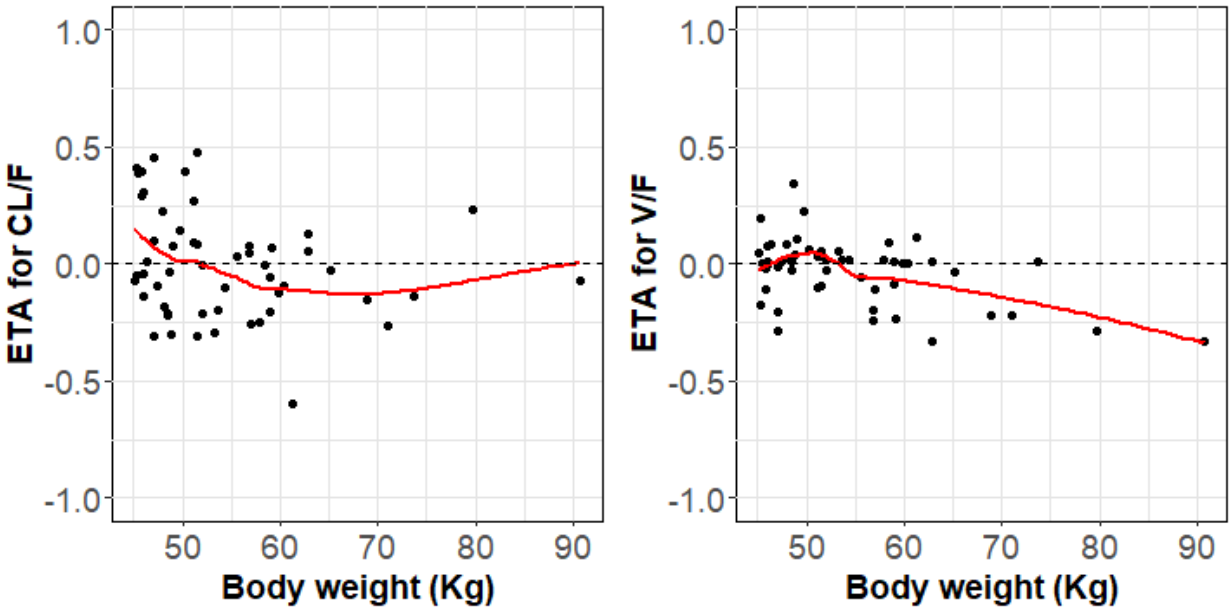


Figure 11. ETAs versus body weight for the applicant's final population PK model in adolescents.

Source: Reviewer's independent analysis

Table 14. Estimated steady state PK parameters for 54 adolescents in study P027

Parameters	Geometric Mean (CV%)	Mean (sd)	Median	Min - Max
CL/F (L/h)	6.09 (23.49)	6.25 (1.47)	6.18	3.73 - 10.37
VC/F (L)	133.49 (15.81)	135.11 (21.23)	134.39	89.89 - 189
KA (/h)	1.39 (0)	1.39 (0)	1.39	1.39 - 1.39
Beta half-Life (h)	15.2 (28.04)	15.77 (4.31)	15.82	7.83 - 32.34
Accumulation Factor	1.55 (15.15)	1.57 (0.24)	1.56	1.15 - 2.55
Effective half-life (h)	15.68 (28.02)	16.26 (4.44)	16.32	8.08 - 33.35
AUCss (mcg*h/mL)	16.43 (23.49)	16.87 (3.89)	16.19	9.64 - 26.79
CMIN (mcg/mL)	0.38 (41.48)	0.41 (0.15)	0.39	0.15 - 0.87
CMAX (mcg/mL)	1.03 (16.06)	1.04 (0.17)	0.99	0.71 - 1.53
TMAX (h)	2.23 (3.81)	2.23 (0.08)	2.20	2 - 2.4

Source: Reviewer's independent analysis

*Exploration of the raw data indicated that about 44% (18 of 44) and 16% (7 of 43) of observed trough concentration (C_{24}) at week 4 and 24 respectively were below 560nM (a chosen threshold for efficacy). In contrast, model predictions of C24, indicated that only about 11% were below the threshold at both week 4 and 24. This discordance caused some doubts on whether the predictions from the final model were acceptable for exploration of exposures in pediatrics. To resolve the uncertainty, a totality of evidence approach was used to support acceptability of the final model for comparisons of exposures between pediatric and adult patients. Firstly, the GOF plots and VPC indicate a good model fit to the data (*Figure 9 *and* Figure 10*). Secondly, except for week 4, the plots of observed versus predicted C_{24} at week 8, 12, and 24 indicate good agreement between observed and predicted data (*Figure 12*). Thirdly, the plot of conditional weighted residuals (CWRES) versus population predictions (PRED) indicate that some C_{24} are outliers at week 4 (*Figure 13*). Lastly, C_{24} samples were not strictly corrected at 24 hours post dose, an allowance was made to collect samples up to 26 hours post-dose thus a possibility for discordance if actual sample collection times were not recorded for some samples.*

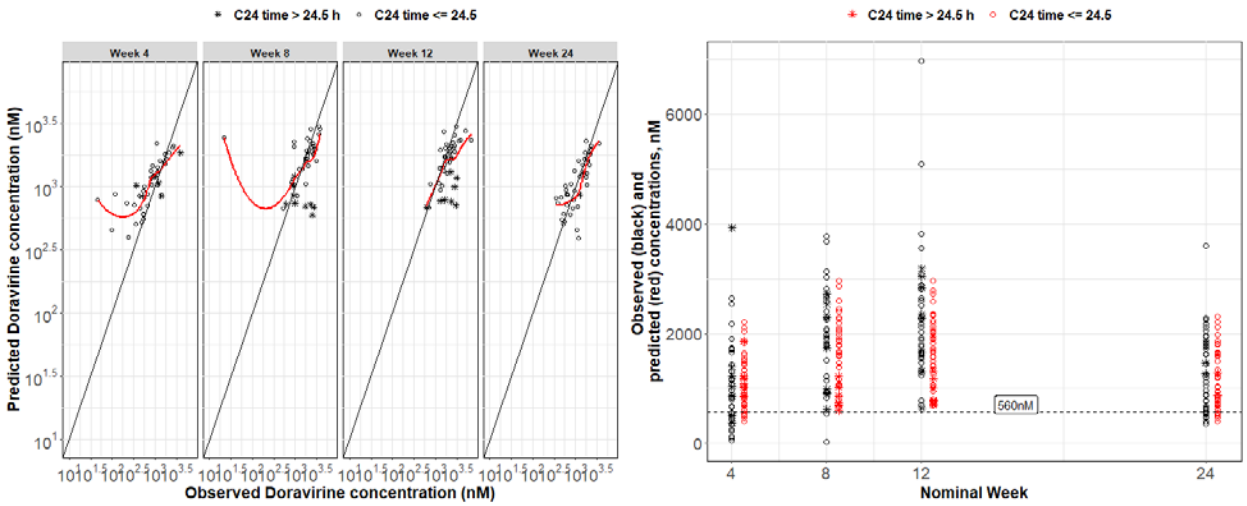


Figure 12. Observed versus predicted doravirine concentrations stratified by nominal weeks after start of treatment.

Source: Reviewer's independent analysis

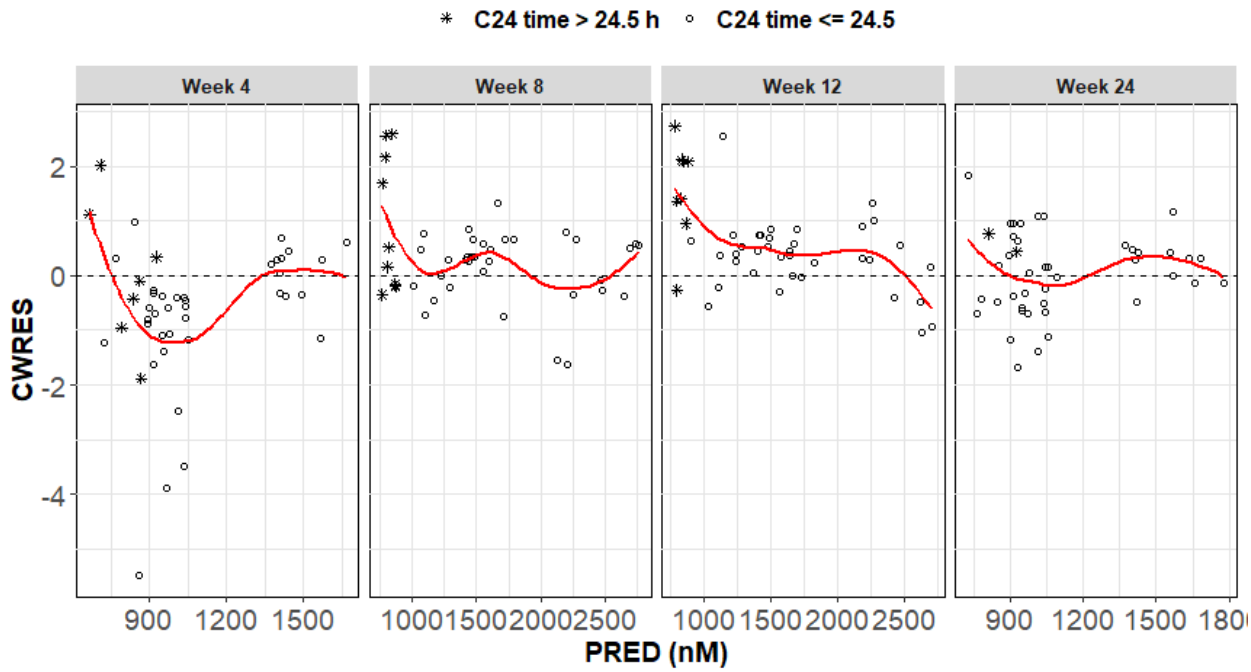


Figure 13. Conditional weighted residuals (CWRES) versus population prediction of doravirine concentrations stratified by nominal week after start of treatment. Open circles with CWRES < -2 in the week 4 panel indicate that these C24 are outlying from the rest of the residuals.

Source: Reviewer's independent analysis

6.1.4 Identification of weight cut-off for 100 mg QD DOR dosing in pediatric patients.

The applicant performed Monte Carlo simulations to identify a weight cut-off above which children and adolescents will receive the daily DOR dose of 100 mg. In these simulations, the applicant created a virtual pediatric population with weight $\geq 35\ Kg$ regardless of age. The virtual patients were assumed to have

normal renal function. The virtual pediatric population was created by sampling 1000 individuals from the NHANES database and thus maintained the pre-existing correlation between age and weight.

For each virtual patient, the final population PK model was used to generate individual PK parameters clearance (CL, V, and KA). The individual PK parameters were in turn used to calculate steady state exposures AUC0-24, Cmax, and Cmin using analytical equations for 1 compartment model. The descriptive statistics of the steady state exposures (AUC0-24, Cmax, and Cmin) in the virtual population were compared to estimated exposures in adolescents and treatment naive adult patients. Similarly, as a subset analysis, the descriptive statistics of the steady state exposures in virtual pediatric population weighting < 45 Kg were compared to those estimated in adolescents and to treatment naive adult patients weighting < 45 Kg or > 45 Kg.

Table 15 compares descriptive statics of exposures between the virtual pediatric population ≥ 35 Kg and the adolescent patients ≥ 35 Kg. The table shows that the projected steady state exposures in pediatric patients ≥ 35 Kg (regardless of age) is comparable to that estimated in adolescents (≥ 12 years) ≥ 35 Kg.

Table 15. Estimated and projected doravirine summary statistics of steady state exposures in adolescent patients >= 35 kg and virtual pediatric population >= 35 Kg respectively, after 100 mg QD dosing

Simulation	Parameter	Unit	Min	P05	P25	Median	P75	P95	Max	Mean	Std Dev	Geo Mean	Geo CV
P027 (N=54)	AUC0-24	µM.h	22.7	27.0	33.0	38.0	46.4	55.1	62.9	39.6	9.14	38.6	23.5
	C24	nM	346	433	706	925	1210	1500	2040	958	354	891	41.5
	Cmax	nM	1660	1890	2200	2330	2770	3060	3580	2440	395	2410	16.1
NHANES (N=1000)	AUC0-24	µM.h	10.3	20.3	29.5	37.8	48.7	69.6	109	40.1	15.1	37.4	38.9
	C24	nM	22.8	318	606	883	1240	1980	3750	980	525	844	63.4
	Cmax	nM	761	1350	1880	2380	2990	3980	5810	2490	826	2360	34.7

Source: Applicant's report on population PK analysis of doravirine in adolescents with HIV-1 infection (Page 37 of 63)

Figure 14 compares estimated steady state exposures between adolescents ≥ 35 Kg to those estimated in treatment naive adult patients. The figure shows that the estimated steady state exposures in adolescents ≥ 35 Kg is comparable to that estimated in treatment naive adults weighting ≤ 45 Kg and adults ≥ 45 Kg.

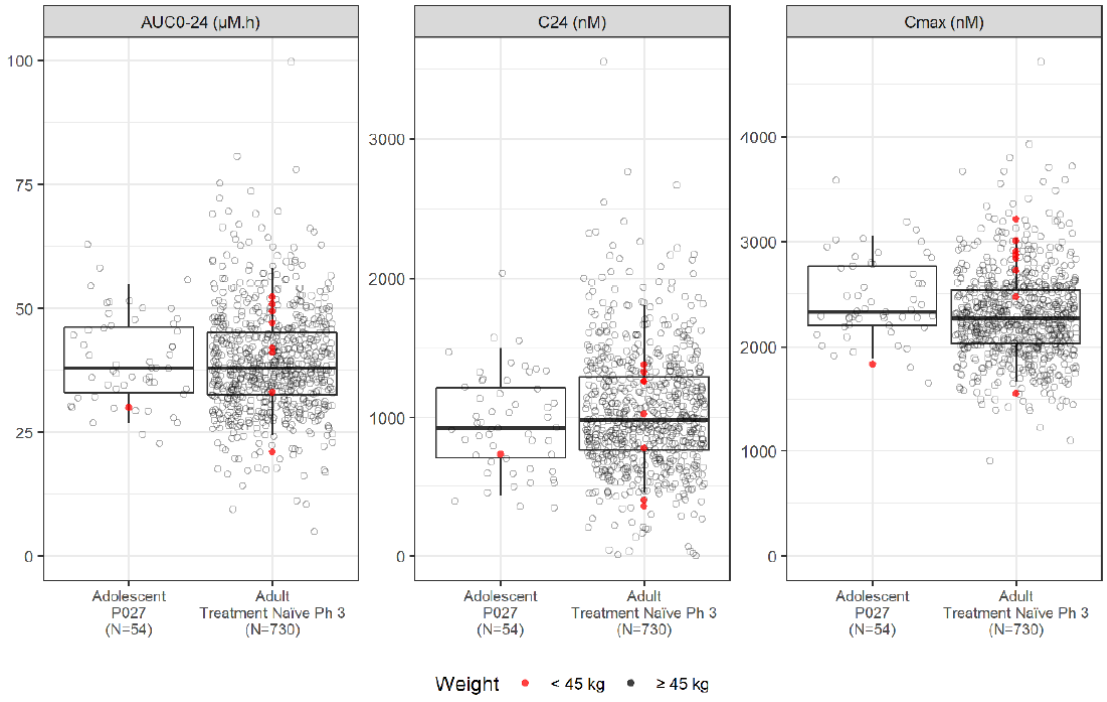


Figure 14. Estimated doravirine steady state exposures in adolescent patients ≥ 35 kg compared to the estimates in treatment naive adult patients after 100 mg QD dosing

Source: Applicant's report on population PK analysis of doravirine in adolescents with HIV-1 infection (Page 36 of 63)

Figure 15 compares projected steady state exposures in pediatric patients ≥ 35 Kg (regardless of age) to those estimated in treatment naive adult patients. The figure shows that the projected steady state exposures in the pediatric patients is comparable to that estimated in treatment naive adults. The figure also shows

that the projected exposure in pediatrics < 45 Kg is comparable to that estimated in adults < 45 Kg. Similarly, the projected exposures in pediatrics ≥ 45 Kg is comparable to that estimated in adults weighting ≥ 45 Kg.

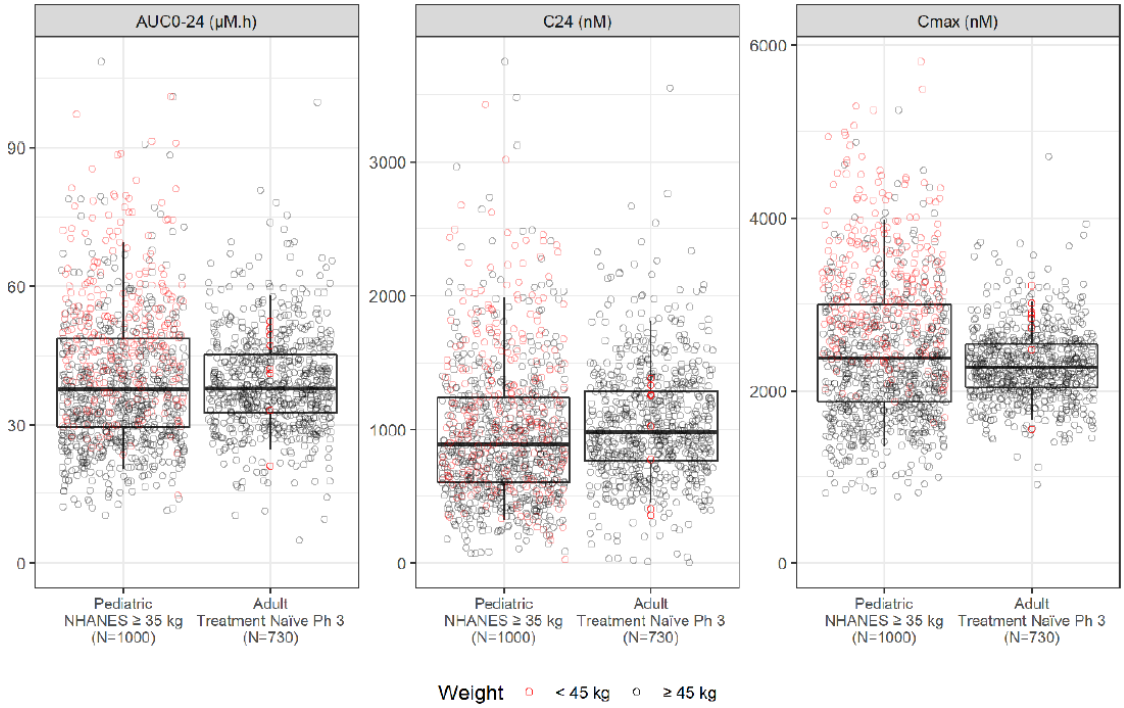


Figure 15. Projected doravirine steady state exposures in pediatric patients >= 35 kg stratified by weight compared to the estimates in treatment naive adult patients after 100 mg QD dosing

Source: Applicant's report on population PK analysis of doravirine in adolescents with HIV-1 infection (Page 39 of 63)

Figure 16 compares projected steady state exposures in pediatric patients ≥ 12 years or < 12 years to those estimated in treatment naive adult patients. The figure shows that the projected steady state exposures in the pediatric patients ≥ 12 years is comparable to those < 12 years.

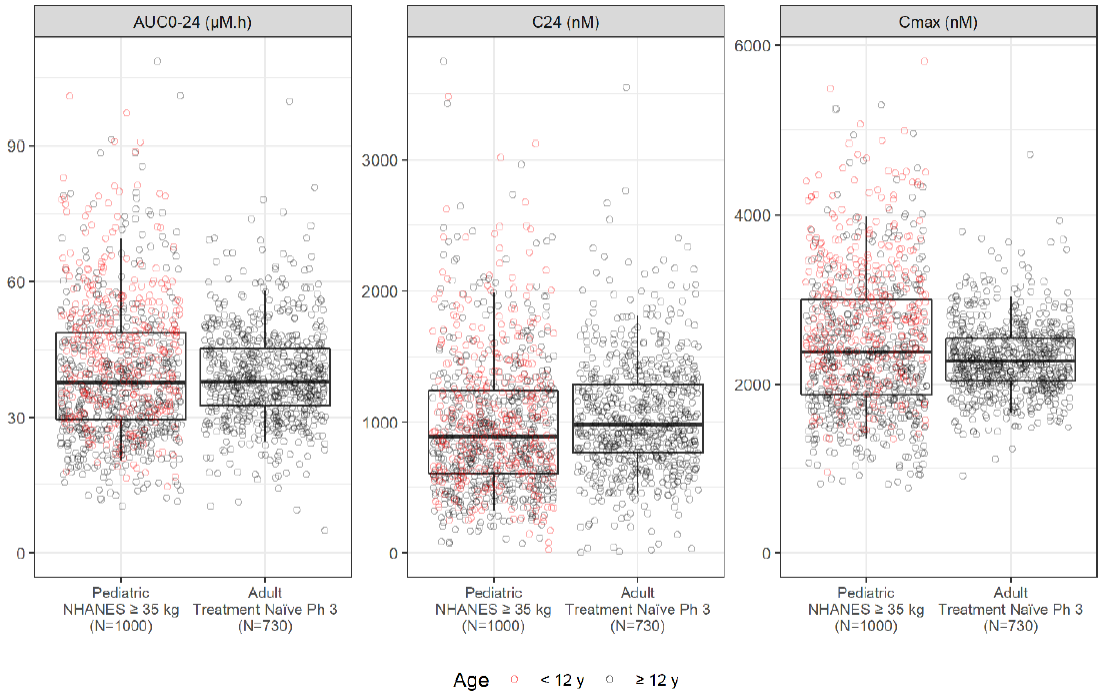


Figure 16. Projected doravirine steady state exposures in pediatric patients >= 35 kg stratified by age compared to the estimates in treatment naive adult patients after 100 mg QD dosing

Source: Applicant's report on population PK analysis of doravirine in adolescents with HIV-1 infection (Page 38 of 63)

6.1.5 Reviewer's comments

Comparing estimated exposures between adolescents and treatment naive adult patients is acceptable for evaluating whether 100 mg daily dose provides safe and effective exposures in adolescents. On the contrary, matching estimated exposures with exposures projected from one bootstrap pediatric sample and one stochastic sample of PK parameters may not be appropriate as the simulated sample may show a narrow and extreme distribution of exposures compared the expected population distribution. For this reason, matching a single projection of exposures in virtual pediatric population with estimated exposures does not provide an acceptable way of assessing whether 100 mg daily dose in pediatrics ≥ 35 Kg provides safe and effective exposures in pediatrics. To assess the appropriateness of the 100 mg daily dose in pediatrics ≥ 35 Kg, the reviewer compared estimated exposures in adults with the 95% prediction intervals of exposures after 200 Monte-carlo simulations in 200 virtual pediatric samples of 5000 individuals each (See section 6.1.6.1)

6.1.5.1 Reviewer's independent analysis for appropriateness of 100 mg QD dose in pediatrics ≥ 35 Kg

The reviewer created virtual pediatric samples in the same way as the sponsor. The distribution of age and weight for one of the virtual pediatric samples is shown in Table 16. The relationship of weight vs age for the virtual population created by the reviewer is shown in Figure 17 where it is overlaid on the 3rd, 50th and 97th percentiles of the CDC growth chart.

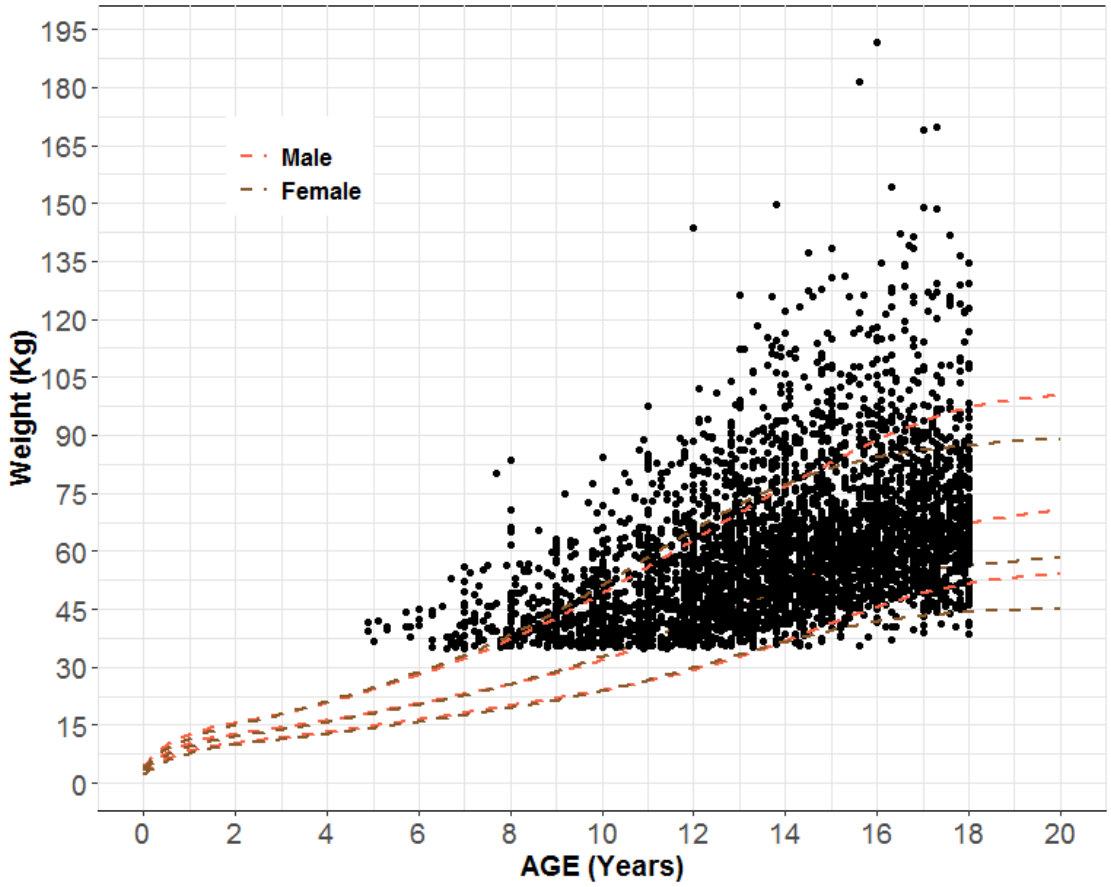


Figure 17. A scatter plot of weight versus age for a virtual pediatric sample (n=5000) overlaid on the 3rd, 50th, and 97.5th percentiles of the CDC growth charts (colored dashed lines)

Source: Reviewer's independent analysis

Table 16. Descriptive statistics for age and weight of a virtual pediatric sample

Covariate	N	Min	P05	P25	Median	P75	P95	Max	Mean	Std Dev	Geo Mean	Geo CV
Age (Yr)	5,000	4.9	9.0	12.0	14.0	16.0	17.8	18.0	13.8	2.8	13.5	22.2
Weight (Kg)		35.0	37.5	46.6	56.9	68.6	94.9	191.7	60.2	18.7	57.7	29.0

Source: Reviewer's independent analysis

Using the virtual pediatric samples and model parameters estimated by the applicant, the reviewer performed monte-carlo simulations to project steady state exposures. Steady state concentration -vs - time profiles were simulated for each virtual patient and used to calculate AUC0-24, Cmax and Cmin at steady state after 100 mg QD dosing. For each virtual pediatric sample, the following descriptive statistics of the exposures were calculated: mean, 2.5th percentile, and 97.5th percentiles. Population means and 95% prediction intervals were calculated as mean of the individual means, 2.5th percentiles, and 97.5th percentiles.

Figure 18 shows projected population mean and 95% prediction intervals of AUC0-24 in pediatrics (error-bars) compared to estimated AUC0-24 in treatment naive adult patients (boxplots and open points). The figure shows that compared to the estimated sample mean AUC0-24 in treatment naive adult subjects, the projected population mean AUC0-24 in pediatric subjects ≥ 45 Kg is comparable, but it is higher in pediatric subjects weighting < 45 Kg.

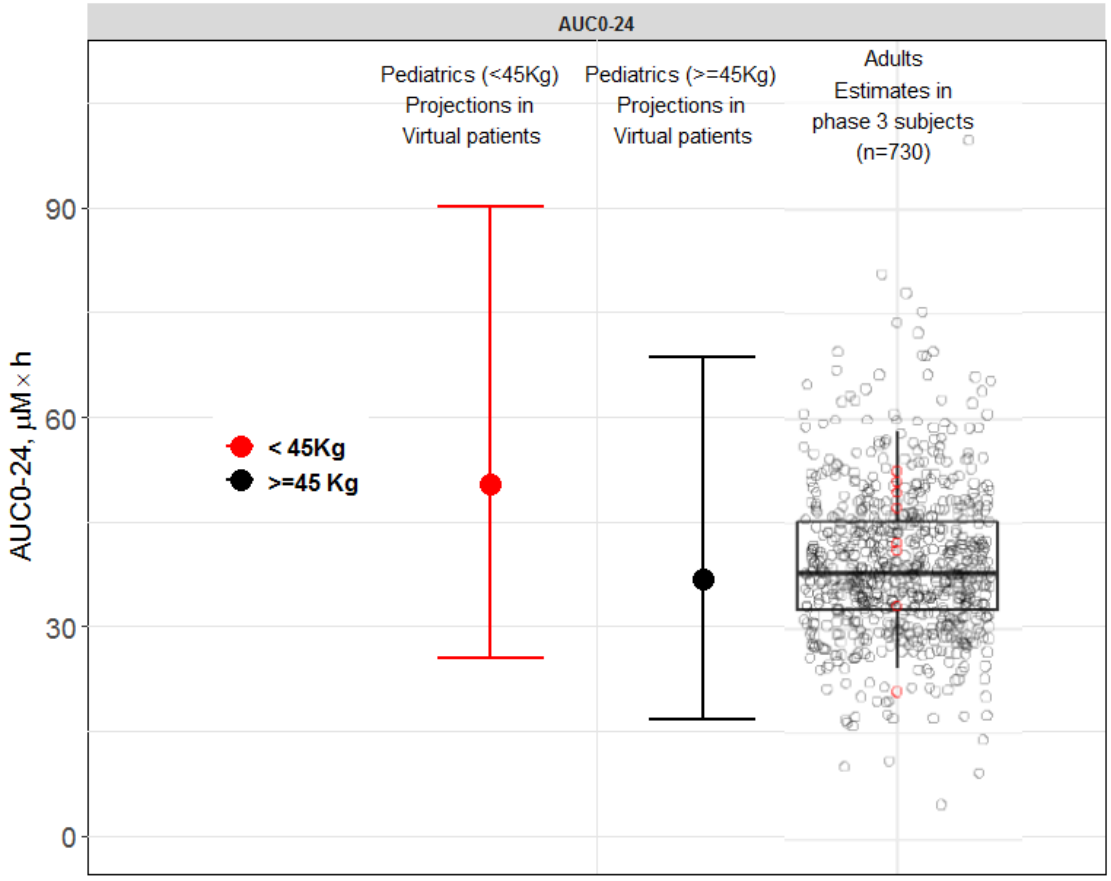


Figure 18. Comparisons of model predicted population mean and 95% prediction intervals (PI) of AUC0-24 in pediatric subjects compared to model estimated AUC0-24 in adult patients. Error-bar represent mean and 95% PI, while box plots represent mean and inter-quartile range.

Source: Reviewer's independent analysis

Figure 19 shows projected population mean and 95% prediction intervals of Cmax in pediatrics (error-bars) compared to estimated Cmax in treatment naive adult patients (boxplots and open points). The figure shows that compared to the estimated sample mean Cmax in treatment naive adult subjects, pediatric subjects weighting ≥ 45 Kg have comparable population mean Cmax while pediatric subjects weighting < 45 Kg have higher population mean Cmax.

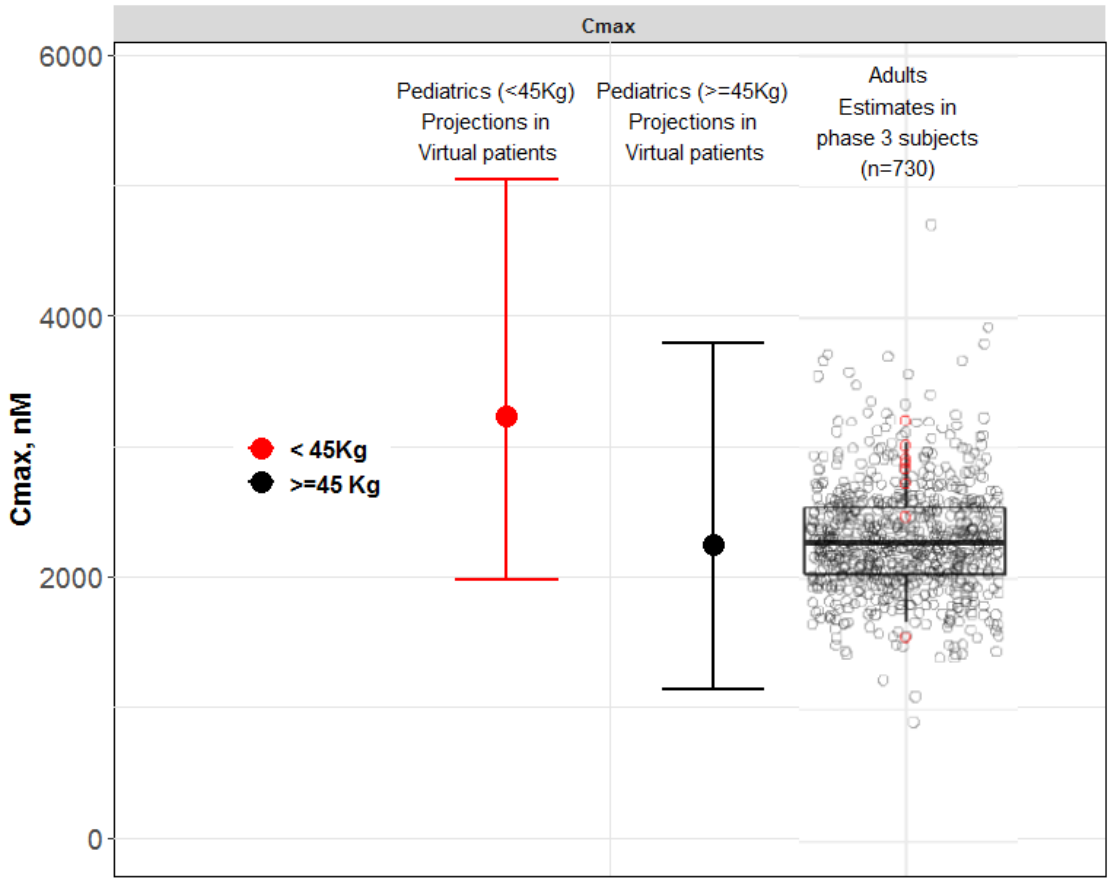


Figure 19. Comparisons of model predicted population mean and 95% prediction intervals (PI) of CMAX in pediatric subjects compared to model estimated CMAX in adult patients. Error-bar represent mean and 95% PI, while box plots represent mean and inter-quartile range

Source: Reviewer's independent analysis

Figure 20 shows projected population mean and 95% prediction intervals of Cmin in pediatrics (error-bars) compared to estimated Cmin in treatment naive adult patients (boxplots and open points). The figure shows that compared to the estimated sample mean Cmin in treatment naive adult subjects, pediatric subjects weighting ≥ 45 Kg have comparable population mean Cmin while pediatric subjects weighting < 45 Kg have higher population mean Cmin.

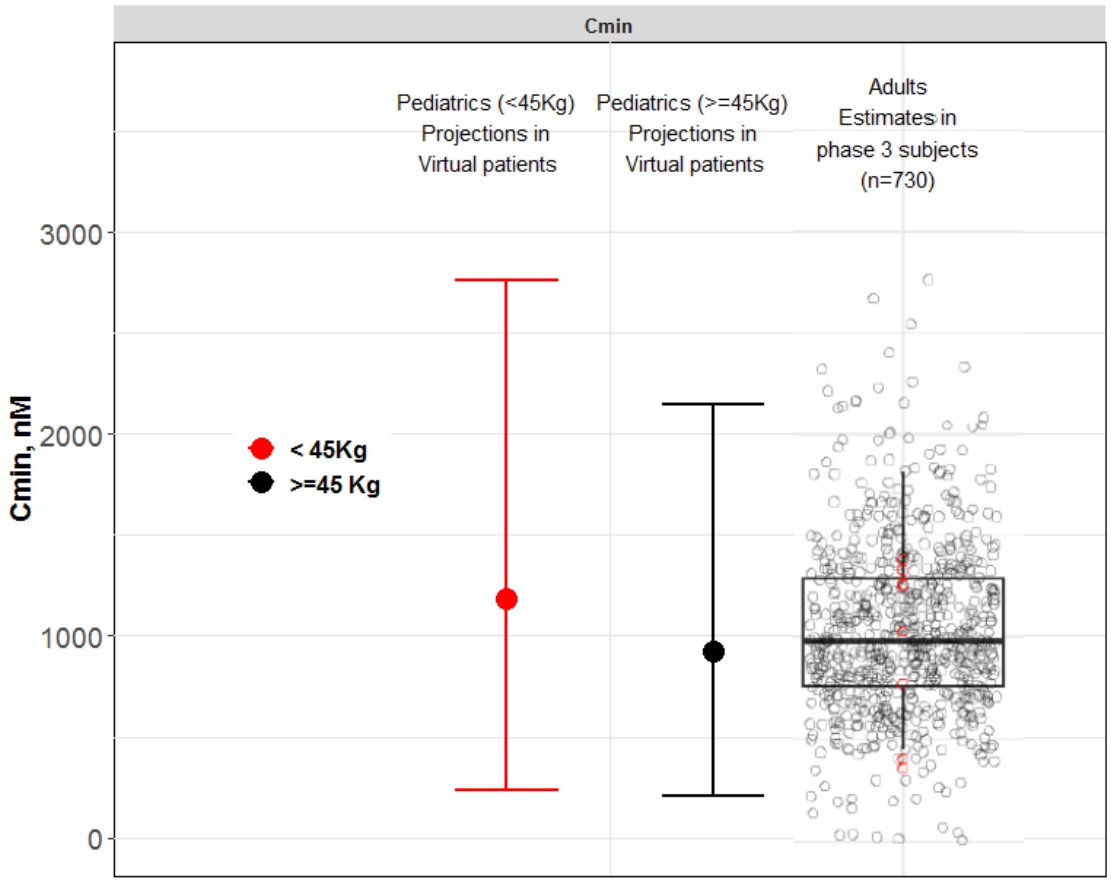


Figure 20. Comparisons of model predicted population mean and 95% prediction intervals (PI) of CMIN in pediatric subjects compared to model estimated CMIN in adult patients. Error-bar represent mean and 95% PI, while box plots represent mean and inter-quartile range

Source: Reviewer's independent analysis

The simulated pediatric Cmax and AUC0-24 were compared to the maximum Cmax and AUC0-24 in datasets used for exposure-vs-safety analysis among adult patients. In a dataset used to exposure-vs-neuropsychiatric adverse events analysis, the observed Cmax and AUC0-24 at week 48 in adult patients were 5215 nM and 98.6 $\mu M \times h$ respectively. Table 17 shows mean (95% prediction interval) of simulated Cmax and AUC0-24, it also shows the proportions of pediatric subjects with Cmax > 5215 nM and AUC0-24 > 98.6 $\mu M \times h$.

Table 17. Population means (95% CI) of projected Cmax and AUC0-24 in pediatric subjects, and corresponding proportions of pediatric subjects with exposures above adults maximum Cmax and AUC0-24

WEIGHT GROUPS	MEAN CMAX (95% PI) nM	MEAN AUC (95% PI) uM*h	PROPORTIONS (%) WITH CMAX > 5215 nM (95%CI)	PROPORTIONS (%) WITH AUC24 > 98.6 uM*h (95%CI)
< 45Kg	3229 (1973 - 5046)	50.5 (25.6 - 90.1)	1.9 (1 - 2.7)	1.3 (0.6 - 1.9)
>=45 Kg	2244 (1135 - 3785)	36.7 (16.6 - 68.7)	0.1 (0 - 0.2)	0.1 (0 - 0.2)

6.1.5.2 Sensitivity analysis for effect of age on doravirine exposure in pediatric patients.

One of the assumptions in the adolescent population PK model for doravirine was that clearance decreased with increasing age at the same rate as it was estimated in adults. It is not yet certain if the same situation applies for pediatric patients < 12 years. Due to this uncertainty, we compared the projected doravirine exposures with versus without the influence of age effect on clearance in pediatrics < 12 years old. Table 18 shows mean (95% prediction interval) of simulated Cmax and AUC0-24, it also shows the proportions of pediatric subjects with Cmax > 5215 nM and AUC0-24 > 98.6 $\mu M \times h$. Exposures in pediatrics < 12 years were projected without accounting for assumed influence of age on CL in this pediatric population. Projections of exposures in adolescents ≥ 12 years accounted for the estimated influence of age in this population as indicated in Table 18.

Table 18. Population means (95% CI) of projected Cmax and AUC0-24 in pediatric subjects (stratified by weight and age groups), and corresponding proportions of pediatric subjects with exposures above adults maximum Cmax and AUC0-24

WEIGHT GROUPS	AGEGRP	MEAN CMAX (95% PI) nM	MEAN AUC (95% PI) uM*h	PROPORTIONS (%) WITH CMAX > 5215 nM (95%CI)	PROPORTIONS (%) WITH AUC24 > 98.6 uM*h (95%CI)
< 45Kg	< 12 Yrs	3311 (2017 - 5151)	52.1 (26.4 - 92.6)	2.3 (1.3 - 3.6)	1.6 (0.8 - 2.4)
< 45Kg	>=12 Yrs	3178 (1961 - 4921)	50 (25.7 - 88.1)	1.5 (0.5 - 2.9)	1.2 (0.3 - 2.2)
>=45 Kg	< 12 Yrs	2494 (1391 - 4046)	40.4 (19.4 - 73.6)	0.2 (0 - 0.6)	0.2 (0 - 0.7)
>=45 Kg	>=12 Yrs	2209 (1115 - 3736)	36.2 (16.4 - 68)	0.1 (0 - 0.2)	0.1 (0 - 0.2)

Source: Reviewer's independent analysis

Figure 21 shows that the projected population mean (95%CI) Cmax in pediatric subjects < 12 years is slightly higher but comparable to that in pediatric patients ≥ 12 years.

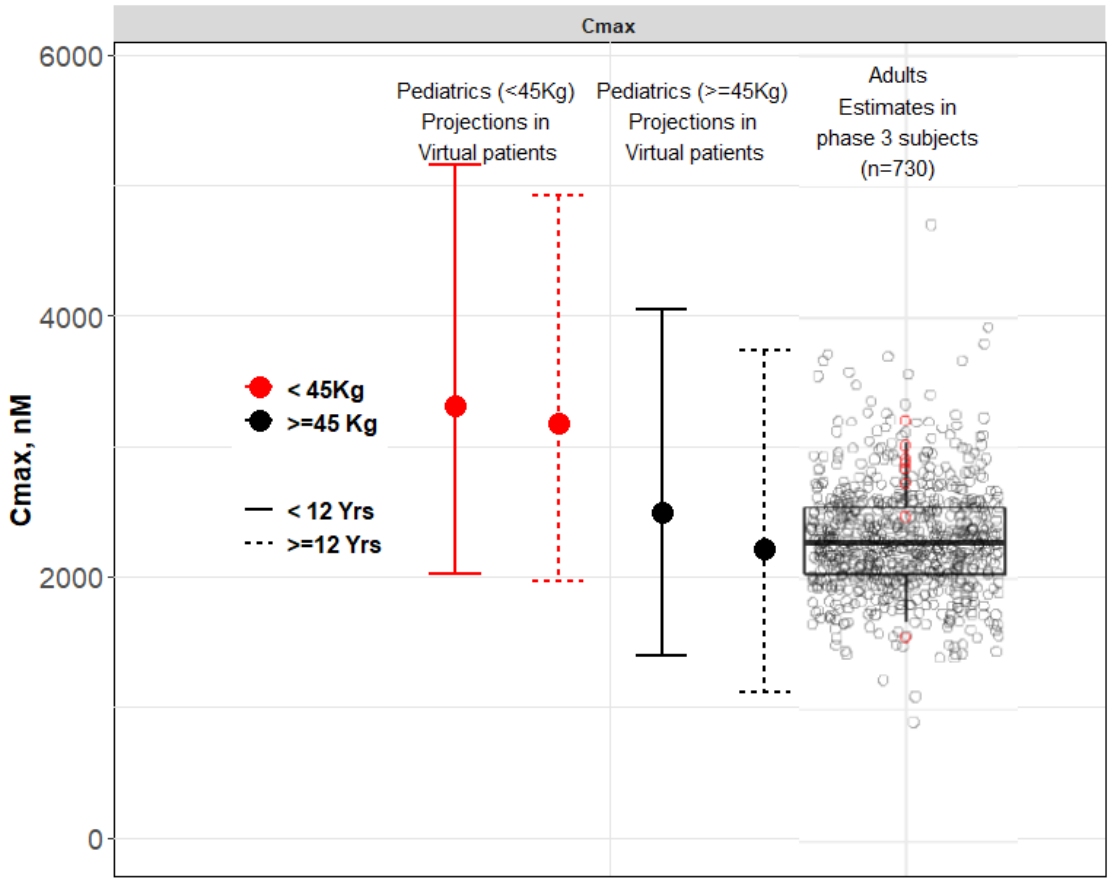


Figure 21. Comparisons of model predicted population mean and 95% prediction intervals (PI) of CMAX in pediatric subjects (stratified by weight and age groups) compared to model estimated CMAX in adult patients. Error-bar represent mean and 95% PI, while box plot represents mean and inter-quartile range

Source: Reviewer's independent analysis

Figure 22 shows that the projected population mean (95%CI) AUC0-24 in pediatric subjects < 12 years is slightly higher but comparable to that in pediatric patients ≥ 12 years.

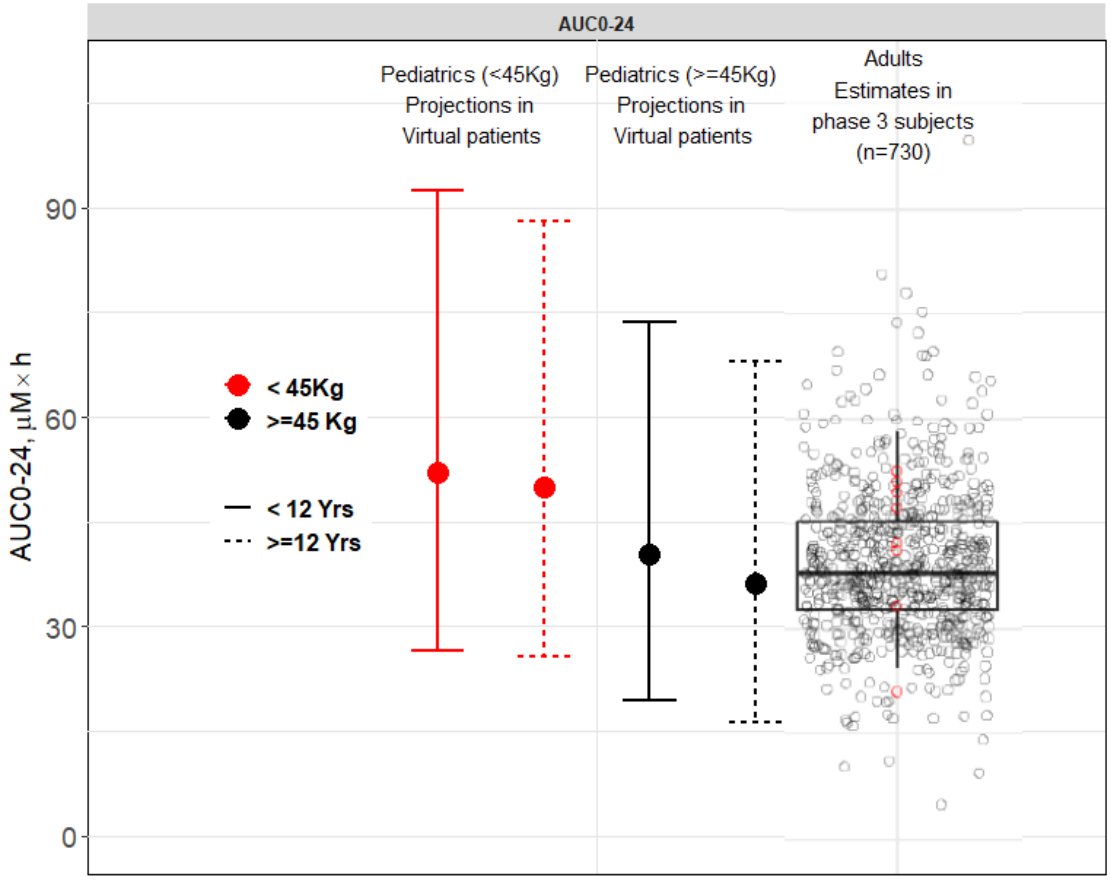


Figure 22. Comparisons of model predicted population mean and 95% prediction intervals (PI) of AUC0-24 in pediatric subjects (stratified by weight and age groups) compared to model estimated AUC0-24 in adult patients. Error-bar represent mean and 95% PI, while box plots represent mean and inter-quartile range

Source: Reviewer's independent analysis

6.1.5.3 Reviewer's conclusion

Pediatric subjects weighting ≥ 45 Kg have comparable exposures to treatment naive adult patients. This provides supportive evidence that 100 mg QD dosing will provide safe and effective exposures in pediatric subjects weighting ≥ 45 Kg.

Pediatric subjects weighting < 45 Kg have higher exposures compared to adult patients. There is no significant difference in exposures between pediatric subjects < 12 years compared to those ≥ 12 years. The clinical relevance of this higher exposure can be assessed by comparing these exposures to the clinical comparability bounds. As indicated in table 1.7 and table 1.6, the proportion of pediatric subjects weighting < 45 Kg and < 12 years old who have exposures that are higher than the highest exposures in adult patients is less than 2%. These results provide some assurance that doravirine exposures in pediatric patients ≥ 35 kg will have comparable safety and efficacy as that observed in adult patients.

6.2. Listing of Analyses Codes and Output Files

File Name	Description	Location in \\cdsnas\pharmacometrics\
Pharmacometrics_review.Rmd	A markdown file with analysis codes for the complete pharmacometrics review	\Reviews\Ongoing PM Reviews\Doravirine_NDA210806_S07_ENK\PPK Analyses\notebook
Run2.mod	Applicant's final pharmacometrics model that was repeated by the reviewer	\Reviews\Ongoing PM Reviews\Doravirine_NDA210806_S07_ENK\PPK Analyses\modeling\sponsor
Doravirine_poppk_model.Rmd, Doravirine_poppk_model_agelessthan12.Rmd, Doravirine_poppkPOSTHOC_model.Rmd	Population PK model mrgsolve simulation scripts	\Reviews\Ongoing PM Reviews\Doravirine_NDA210806_S07_ENK\PPK Analyses\scripts\models

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