Clinical Pharmacology Review

NDA/SDN	22187/584 (S-24)
Submission Date	1/16/2018
Submission Type	Efficacy supplement - pediatric
Drug	Intelence® (etravirine)
Sponsor	Janssen
Indication	Treatment of HIV-1 infection in treatment experienced patients 6 years of age and older with viral strains resistant to an NNRTI and other antiretroviral agents
Formulation	Tablet: 25, 100, and 200 mg
Dosage and Administration	Adult: 200 mg twice daily following a meal Pediatric (6 to 18 years of age and weighing at least 16 kg): based on body weight and should not exceed the recommended adult dose
OCP division	DCPIV
OND division	DAVP
Review team	Qin Sun, Ph.D., Simbarashe Zvada, Ph.D., Ada Zhuang, Ph.D., Shirley Seo, Ph.D.

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1. Executive Summary

Intelence® (etravirine [ETR]) is a human immunodeficiency virus type 1 (HIV-1) specific, non-nucleoside reverse transcriptase inhibitor (NNRTI), indicated in combination with other antiretroviral (ARV) agents for the treatment of HIV-1 infection in treatment experienced patients aged ≥6 years with viral strains resistant to an NNRTI and other ARV agents. The recommended dosage for adults is 200 mg taken twice daily following a meal. For pediatric patients aged 6 to 18 years and weighing at least 16 kg, the dosage is based on body weight and should not exceed the recommended adult dose.

The sponsor submitted an efficacy supplement to support the use of ETR in pediatric patients aged ≥2 to <6 years, and the submission consists of study TMC125-C234 (IMPAACT P1090) and a population pharmacokinetic (PK) analysis report. Study P1090 is a Phase I/II, open-label trial that evaluated the safety/tolerability, steady-state PK, and antiviral activity of ETR in combination with an optimized background regimen (OBR) in HIV-1 infected children aged ≥2 to <6 years (cohort I). The dose was determined by an exposure-matching approach using the steady-state PK data, with supportive antiviral activity and safety data from Study P1090.

In this submission, the sponsor concluded that the proposed pediatric dosage based on body weight band (**Table 1**) support the use of ETR in pediatrics aged 2 to <18 years and weighing ≥10 kg. Upon review of the data, the review team concluded the following:

- The ETR exposures in children aged ≥2 to <6 years using the ETR recommended dose (as per the TMC125-C234 study and confirmed by population PK modeling and simulation) were comparable to the ETR exposure observed in children greater than 6 years of age and adults.
- ETR on the recommended dosage was generally safe and well tolerated in treatment-experienced HIV-1 infected pediatric patients aged ≥2 to <6 years.
- The supportive antiviral activity data was acceptable, with only 1 of the 9 subjects on the recommended dose up to Week 24 had viral load >400 copies/mL (key efficacy endpoint, FDA snapshot approach).

Table 1: Recommended dosage of Intelence for pediatrics 2 to <18 years of age

Body Weight (kg)	Dose (mg)
≥10 to <20	100 BID
≥20 to <25	125 BID
≥25 to <30	150 BID
≥30	200 BID

2. Recommendations

The office of Clinical Pharmacology (OCP) has reviewed the submission and the review team agrees the proposed pediatric dosage based on body weight band can be recommended for approval in pediatric patients aged 2 to <18 years and weighing ≥10 kg with changes to the

Dosage and Administration section of labeling to increase palatability of the dispersion preparation for dosing.

3. Labeling Updates

Changes to clinical pharmacology-related labeling are summarized in **Table 2**:

Table 2: Clinical pharmacology-related labeling updates

Section/heading	Sponsor's proposal	Reviewer's recommendation
Highlights/Dosage and administration	Pediatric patients: Pediatric patients (2 ~~6~~years to less than 18 years of age and weighing at least ~~16~~ 10 kg): dosage of Intelence is based on body weight and should not exceed the recommended adult dose.	Acceptable
Section 2.2/ Dosage and Administration/Pediatric Patients (2 ~~6~~ Years to less than 18 years of age)	Body weight ≥~~16~~ 10 to <20 kg for 100 mg dosage	Acceptable
Section 2.3/ Dosage and Administration/Method of Administration		Patients should be instructed to swallow the INTELENCE tablet(s) whole with a liquid such as water. Patients who are unable to swallow the INTELENCE tablet(s) whole may disperse the tablet(s) in a glass of water. The patient should be instructed to do the following: • place the tablet(s) in 5 mL (1 teaspoon) of water, or at least enough liquid to cover the medication, • stir well until the water looks milky, (b) (4)

Section 12.3/ Pharmacokinetics/Special populations/Pediatric Patients	Add PK results for pediatrics aged 2 to 6 years	Acceptable

4. Key Clinical Pharmacology Findings

Study TMC125-C234 (P1090) Cohort I enrolled totally 20 HIV-1 infected, ARV agents experienced pediatric subjects aged ≥2 to <6 years with viral load >1000 copies/mL. The study cohort began enrollment into an initial mini-cohort of 6 subjects with starting dose at 5.2 mg/kg BID after a meal. The mini-cohort PK results indicated that it was unlikely that with ETR dose at 5.2 mg/kg BID for all body weights in this age group, the geometric mean ETR exposure would be within the sponsor's pre-defined target (60 to 150% of geometric mean exposure of adults) for the full cohort. A revision of the ETR dosing table was introduced for the remainder of the cohort (**Table 3**). An additional 14 subjects were enrolled in the full cohort starting at the final recommended doses, and Week 2 PK results were summarized (**Table 4**) for subjects starting on the final recommended doses (12 newly enrolled and 2 from mini-cohort). The ETR geometric mean PK parameters were within the target of 60 to 150% of the geometric mean ETR PK parameters in adults.

The PK data obtained in study P1090 cohort I for pediatric subjects aged ≥2 to <6 years have been incorporated into a population PK model for ETR, which also includes historical ETR data in children ≥6 years of age. The population PK analysis confirmed that the ETR exposures of the proposed pediatric dosage based on body weight band were comparable to the ETR exposure observed in adults (**Figure 1**).

In the study, 5/14 (36%) of children (Cohort I, aged ≥2 to <6 years) on the final proposed ETR dosage had AUC_{12h} values below the 10^{th} percentile of the adult exposure, necessitating an individual dose increase after Week 2. The lower exposures were mostly observed in children (aged ≥2 to <6 years) who took the ETR tablets dispersed in liquid, with no other unique characteristics associated with those kids who had lower exposures (e.g., body weight, age, country/clinical site). For 1 of these 5 subjects, there were reports of infrequently refusing drug intake. In Cohort II (aged ≥1 to <2 years), drug adherence or intake issues (refusing/vomiting/spitting up, and reporting bad taste/texture) were found for all 5 subjects.

Although palatability questionnaires in this study suggested it was overall good or average, the majority results were provided by the primary caregiver. In Study TMC125-C213 for subjects aged 6 to 18 years, the questionnaires suggested 40 to 60% of subjects reported unfavorable taste/texture for the dispersed form in water. The palatability issue may cause higher risk of lower exposures in real world conditions without close clinical monitoring for drug intake, and adherence could be an issue for chronic dosing. The lower exposure (potentially due to incomplete drug intake, per the sponsor) should not be compensated for by an increase in the recommended dose, as that would lead to higher than anticipated exposures in children that do take the complete dose. Rather, a strategy to ensure complete drug intake should be developed to avoid lower exposure.

An IR was sent to the sponsor to request the tablet samples at 25 and 100 mg, and the review team evaluated and confirmed the unfavorable texture of the tablets if dispersed in water. However, add juice or milk can help to mitigate the issue. Thus, the method of administration for the **dispersed form** in the labeling is revised to the following (b) (4)

Table 3: Revised/final recommended dosage for pediatric patients aged ≥2 to <6 years

Weight Band (kg)	Target Dose (mg/kg bid)	Actual Dose (mg bid)
10-<13	8.8	100 mg
13-<16	6.8	100 mg
16-<20	5.2	100 mg
20-<25	5.2	125 mg
25-<30	5.2	150 mg
≥30	5.2	200 mg

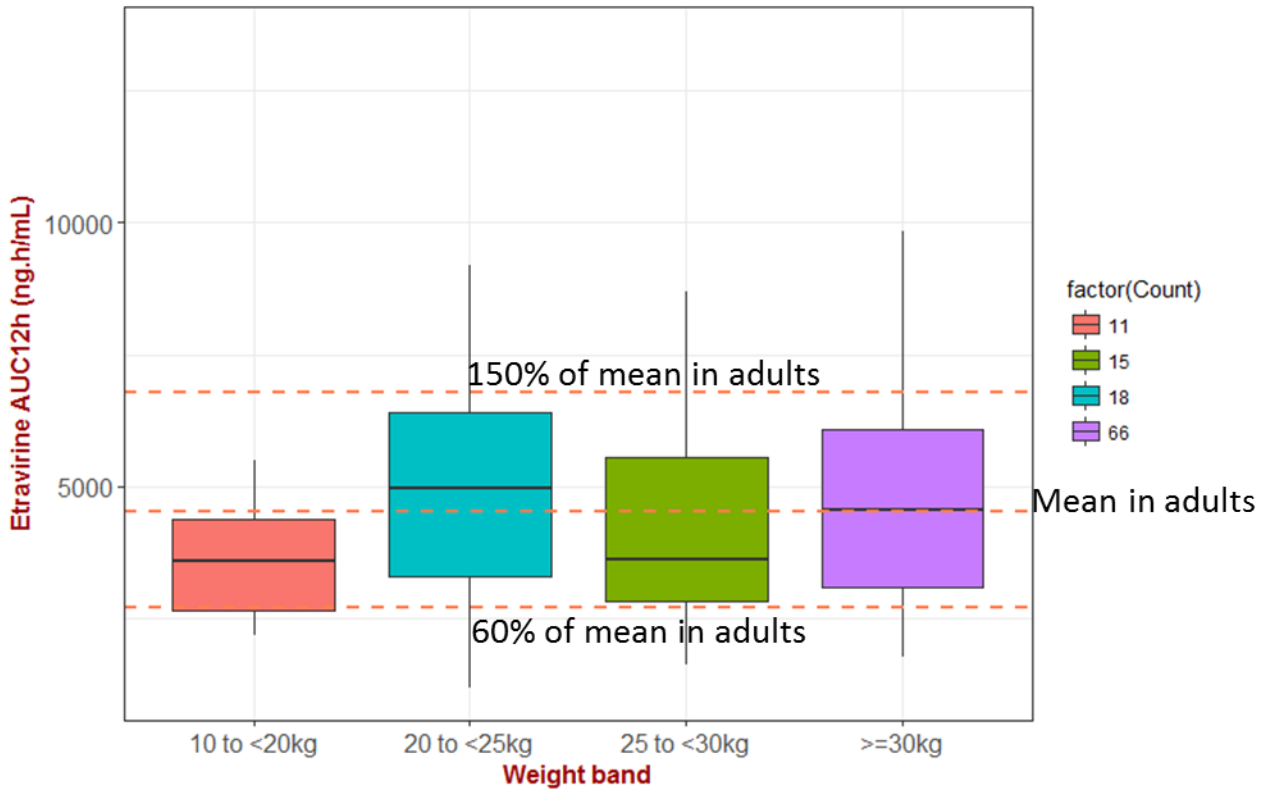
Table 4: Full cohort PK results and statistical analysis on the recommended dosage for pediatric patients aged ≥2 to <6 years

	≥2 to <6 years (Cohort I)			
	AUC_{12h} (h*ng/mL)	C_{max} (ng/mL)	C_{0h} (ng/mL)	C_{12h} (ng/mL)
N	14	14	14	14
Mean (SD)	4230.16 (2922.533)	498.24 (303.425)	255.46 (239.705)	288.74 (255.470)
CV%	69.088	60.899	93.831	88.477
Geom. Mean	3504.40	428.61	183.10	210.90
Median	3579.19	441.95	161.80	211.00
Min; Max	1220.5; 11815.4	199.0; 1236.0	54.0; 908.0	54.3; 962.0

	Geometric Mean		GMR (90% CI) [a,b]
	≥2 to <6 years (N=14)	Adults [b] (N=575)	≥2 to <6 years
AUC_{12h} (h*ng/mL)	3504.40	4522.39	0.77 (0.57; 1.04)
C_{0h} (ng/mL)	183.10	297.12	0.62 (0.42; 0.92)
C_{12h} (ng/mL)	210.90	NA	0.71 (0.48; 1.05)

N: number of subjects with data
[a] Geometric mean ratio (GMR), relative to adult data (90% confidence interval [CI])
[b] Pooled DUET population PK parameters; the GMR (90% CI) for C_{12h} was derived using the adults C_{0h} data.

Figure 1: Population PK predicted AUC_{12h} for the proposed dosage based on body weight



5. Individual Study Review

5.1 Title

A Phase I/II, Open-label Trial to Evaluate the Safety, Tolerability, Pharmacokinetics (PK) and Antiviral Activity of Etravirine (ETR) in Antiretroviral (ARV) Treatment-experienced HIV-1 Infected Infants and Children, Aged ≥2 Months to <6 Years - ***Results for Cohort I (aged ≥2 to <6 years)***

5.2 Information Regarding the Clinical Trial Site and Duration of the Trial

Twenty subjects aged ≥2 to <6 years were enrolled at sites in Brazil (4 sites, 7 subjects), South Africa (2 sites, 10 subjects), and the United Sites (3 sites, 3 subjects) from November 30, 2012 to June 12, 2017 (cut-off date for the Week-24 analysis).

5.3 Objectives

Primary objective:
- To evaluate the safety and tolerability, the steady-state PK, and the appropriate dose of ETR in combination with an optimized background regimen (OBR) in HIV-1 infected children aged ≥2 months to <6 years

Secondary objectives:
- To assess the antiviral activity, immunologic changes, drug resistance, and exposure-response (E-R) relationship for antiviral activity and safety of ETR-containing regimens

Exploratory objectives:
- To explore relationships between PK and CYP enzyme pharmacogenomics (not available in this submission), sex, age, weight, race, ARV regimen (e.g., boosted PI), and HIV response markers

5.4 Trial Design

This is an ongoing Phase 1/2, open-label, multicenter study with ETR in combination with an OBR consisting of at least 2 active ARVs (a boosted PI and at least 1 additional active ARV) in HIV-1 infected, ART-experienced pediatric subjects. The study was planned to be conducted in the following 3 age cohorts in subjects who are ART-experienced, and ***the current clinical study report only describes the results of Cohort I: ≥2 to <6 years of age.***

Cohort I: ≥2 to <6 years of age
Cohort II: ≥1 to <2 years of age
Cohort III: ≥2 months to <1 year

Each age cohort began enrollment into an initial mini-cohort of 6 subjects, and intensive PK was performed on Day 14 (±4 days). Once the PK and safety data were found to be acceptable, enrollment continued at the same dose to complete enrollment of the remaining subjects in that cohort. All subjects in the specific cohort continued their treatment at the selected dose, with the aim to have at least 12 subjects whose initial dose was the final recommended ETR dose per PK

and safety criteria for their age cohort. A dose of ETR was considered acceptable if the dose was tolerated and if the geometric mean ETR AUC_{12h} was between 60% and 150% of the geometric mean ETR AUC_{12h} in HIV-1 infected, ART-experienced adults from the DUET studies.

A failure to meet the safety and/or PK criteria would result in an adjustment of the (starting) dose. For the individual subject management in this study, subjects with an individual AUC_{12h} below the 10th percentile of adult exposure (ie, <2,350 ng•h/mL) were dose-adjusted to achieve an AUC_{12h} ≥2,350 ng•h/mL. For the full cohort analysis, subjects from an initial mini-cohort receiving the same dose as that recommended in the new dosing schedule would be included in the PK and safety analysis of the newly recommended ETR dose. The other subjects from the initial mini-cohort (either dose adjusted to the newly recommended ETR dose or not) were to be followed on study but not considered for the full cohort pass/fail criteria.

The ETR tablet(s) were to be swallowed whole with a sufficient amount of water or other liquid within 30 minutes following a meal. The tablet(s) could also be dispersed in water or other liquid in case the subject was unable to swallow the tablet(s) whole, and further diluted with a beverage (water, orange juice, milk, infant formula) not to exceed 30 mL (2 tablespoons) total volume (to ensure the full dose could be taken).

Inclusion criteria:

- Confirmed HIV-1 infection
- Age ≥2 to <6 years old at study entry
- HIV-1 RNA viral load >1,000 copies/mL (within the previous 90 days prior to screening) AND an HIV-1 RNA viral load >1,000 copies/mL at screening
- ART-experienced children on a failing combination ARV regimen (containing ≥3 ARVs) for at least 8 weeks, OR ART-experienced children on a treatment interruption of at least 4 weeks with a history of virologic failure while on a combination ARV regimen (containing ≥3 ARVs)
- Ability to swallow ETR whole or dispersed in an appropriate liquid

5.5 Excluded Medications and Restrictions

- Any drugs not recommended or contraindicated in the package insert under concomitant medications
- ARVs: darunavir use in subjects <3 years old; fosamprenavir/ritonavir; maraviroc; saquinavir/ritonavir; tipranavir/ritonavir; ritonavir, used as sole PI therapy; unboosted PIs including nelfinavir; other NNRTIs

5.6 Rationale for Doses Used in the Trial

ETR: starting dose at 5.2 mg/kg bid after a meal for all body weights is reasonable, and it is similar as the approved dosage for pediatric patients aged 6 to 18 years old. The dose has been adjusted based on mini-cohort PK results, and the final recommended dose has been confirmed in the full cohort with ≥12 subjects and ensured to meet the PK criteria.

5.7 Drugs Used in the Trial

ETR 25 mg tablets lot numbers: 4373757, 4372731, 4371357, 4367681, and 365798
ETR 100 mg tablets lot numbers: 364692, 4373807, 4372730, 4371935, 4370925, 4367645, 365799, 364692, and 65799

Table 5: Individual ARVs in OBR:

Drug Class	Drug Name (Active Ingredients)	≥2 to <6 years (N=20)
Integrase Inhibitor	raltegravir	6 (30.0%)
NRTI	lamivudine	10 (50.0%)
	stavudine	1 (5.0%)
	zidovudine	13 (65.0%)
PI	atazanavir/rtv	1 (5.0%)
	darunavir/rtv	8 (40.0%)
	lopinavir/rtv	11 (55.0%)

Combination of ARV Classes in OBR:

Class Number	ARV Classes	≥2 to <6 years (N=20)
2	Integrase Inhibitor + PI	6 (30.0%)
	NRTI + PI	14 (70.0%)

5.8 Sample Collection and Bioanalysis

Sample Collection
All subjects had 12-hour intensive PK sampling (pre-dose, 1, 2, 4, 6, 9, 12 h) on Day 14 (±4 days) of ETR administration as well as 7 to 14 days after a PK-determined dose adjustment (if applicable). In addition, sparse PK samples were to be taken at Weeks 4, 8, 12, 24, and 48, and at the determination of virologic failure.

Bioanalytical method
The precision and accuracy were acceptable for standard curve and QC runs. All samples were analyzed within the long-term storage stability duration of 3.5 years at -80°C for ETR.

Request for bioanalytical inspection: The Division of New Drug Bioequivalence Evaluation (DNDBE) within the Office of Study Integrity and Surveillance (OSIS) recommends accepting data after an on-site inspection. (Refer to Dr. Shila S Nkah's summary for details).

5.9 Results

5.9.1 Pharmacokinetic Analysis
No major protocol deviations were reported. At the time of data cut-off, 20 subjects aged ≥2 to 6 years old had been enrolled in Cohort I.

Six subjects were enrolled in the original mini-cohort (Subjects (b) (6)) with starting dose at 5.2 mg/kg BID after a meal. The mini-cohort PK results based on sponsor's analysis was summarized in **Table 6**. The results indicated that it was unlikely that with ETR dose at 5.2 mg/kg for all body weights in this age group, the geometric mean ETR exposure would be within target for the full cohort. A revision of the ETR dosing table was introduced for the remainder of the cohort (**Table 7**). The lower body weight cut-off of 10 kg is proposed as this is within the bodyweight range observed in this study, and a minimum bodyweight of 10 kg represents 97% of the children aged at least 2 years, as per the CDC growth chart. For Subjects (b) (6) , the newly recommended ETR dose was the same as their initial dose, and PK data for these 2 subjects are included in the full cohort analysis.

An additional 14 subjects were enrolled in the full cohort I starting at the final recommended doses, while Subject (b) (6) was still at baseline at the time of data cut-off (thus no Week 2 PK data), and Subject (b) (6) was excluded from PK analysis due to diarrhea before and on day of PK assessments. Totally 14 subjects (12 newly enrolled and 2 from mini-cohort [Subjects (b) (6)]) were administered at the final recommended doses with PK data available at Week 2 and the results were summarized in **Table 8**. The ETR geometric mean PK parameters for subjects in Cohort I (aged ≥2 to <6 years, N=14) were within the target of 60% to 150% of the geometric mean ETR PK parameters in adults.

Reviewer's comments: *The PK parameters for those 14 subjects administered at the final recommended doses at Week 2 have been validated by reviewer's analysis (**Table 9**).*

During the study, 5/14 (36%) of children (aged ≥2 to <6 years) on the recommended ETR dosage had AUC_{12h} below the 10th percentile of the adult exposure, necessitating a PK-determined individual dose increase after Week 2. The lower exposures were mostly observed in children (aged ≥2 to <6 years) who took the ETR tablets dispersed in liquid, and no other unique characteristics were associated with those kids who had lower exposures (e.g., body weight, age, country/clinical site). For 1 of these 5 subjects, there were reports of infrequently refusing drug intake. In Cohort II (aged ≥1 to <2 years), drug adherence or intake issues (refusing/vomiting/spitting up, and reporting bad taste/texture) were found for all 5 subjects.

Although palatability questionnaires in this study suggested it was overall good or average, the majority results were provided by the primary caregiver. In Study TMC125-C213 for subjects aged 6 to 18 years, the questionnaires suggested 40 to 60% of subjects reported unfavorable taste/texture for the dispersed form. The palatability issue may cause higher risk (>36%) of lower exposures in real world conditions without close clinical monitoring for drug intake, and adherence could be an issue for chronic dosing.

*An IR was sent to the sponsor to request the tablet samples at 25 and 100 mg, and the review team evaluated and confirmed the unfavorable texture of the tablets if dispersed in water. However, add juice or milk can help to mitigate the issue. Thus, the method of administration for **dispersed form** in the labeling is revised to the following* (b) (4) .

(b) (4)

Sponsor's analysis:

Table 6: Mini cohort PK results and statistical analysis at 5.2 mg/kg BID dosage

	AUC_{12h} (h*ng/mL)	C_{max} (ng/mL)	C_{0h} (ng/mL)	C_{12h} (ng/mL)
N	6	6	6	6
Mean (SD)	2809.83 (1640.609)	349.45 (205.986)	156.65 (123.738)	185.17 (107.129)
CV%	58.388	58.946	78.990	57.855
Geom. Mean	2466.54	302.81	127.05	166.74
Range (min; max)	1151.0; 5776.0	128.7; 713.9	59.0; 397.3	102.0; 397.0

	≥2 to <6 years (N=6)	Adults (N=575) [b]	GMR (90% CI) [a,b]
AUC_{12h} (h*ng/mL)	2466.54	4522.39	0.54 (0.34; 0.86)
C_{0h} (ng/mL)	127.05	297.12	0.43 (0.25; 0.75)
C_{12h} (ng/mL)	166.74	NA	0.56 (0.38; 0.83)

N: number of subjects with data

[a] Geometric mean ratio (GMR), relative to adult data (90% confidence interval [CI]).

[b] Pooled DUET population PK parameters; the GMR (CI) for C_{12h} was derived using the adults C_{0h} data.

Table 7: revised/final recommended dosage for pediatric patients at ≥2 to 6 years

Weight Band (kg)	Target Dose (mg/kg bid)	Actual Dose (mg bid)
10-<13	8.8	100 mg
13-<16	6.8	100 mg
16-<20	5.2	100 mg
20-<25	5.2	125 mg
25-<30	5.2	150 mg
≥30	5.2	200 mg

Table 8: Full cohort PK results and statistical analysis at final recommended dosage

	≥2 to <6 years (Cohort I)			
	AUC_{12h} (h*ng/mL)	C_{max} (ng/mL)	C_{0h} (ng/mL)	C_{12h} (ng/mL)
N	14	14	14	14
Mean (SD)	4230.16 (2922.533)	498.24 (303.425)	255.46 (239.705)	288.74 (255.470)
CV%	69.088	60.899	93.831	88.477
Geom. Mean	3504.40	428.61	183.10	210.90
Median	3579.19	441.95	161.80	211.00
Min; Max	1220.5; 11815.4	199.0; 1236.0	54.0; 908.0	54.3; 962.0

	Geometric Mean		GMR (90% CI) [a,b]
	≥2 to <6 years (N=14)	Adults [b] (N=575)	≥2 to <6 years
AUC_{12h} (h*ng/mL)	3504.40	4522.39	0.77 (0.57; 1.04)
C_{0h} (ng/mL)	183.10	297.12	0.62 (0.42; 0.92)
C_{12h} (ng/mL)	210.90	NA	0.71 (0.48; 1.05)

N: number of subjects with data
[a] Geometric mean ratio (GMR), relative to adult data (90% confidence interval [CI])
[b] Pooled DUET population PK parameters; the GMR (90% CI) for C_{12h} was derived using the adults C_{0h} data.

Reviewer's analysis:

Table 9: Full cohort PK results at final recommended dosage

	≥2 to 6 years (Cohort I)			
	AUC12h (h*ng/mL)	Cmax (ng/mL)	C0h (ng/mL)	C12h (ng/mL)
N	14	14	14	14
Mean (SD)	4455 (3179)	498 (303)	333 (269)	289 (255)
CV%	71	61	81	89
Geom Mean	3640	429	240	211
Median	3709	442	222	211
Min; Max	1258; 12696	199;1236	76; 908	54; 962

5.9.2 Viral Suppression

Although 14 subjects were administered the recommended dose at Week 2 for PK evaluation, the dose for 5 subjects were adjusted higher due to the observed low exposure (below the 10th percentile of the adult exposure). Thus, the efficacy for those 5 subjects were not tied to the recommended dosage. The efficacy results for the other 9 subjects who were at the recommended dosage up to Week 24 were summarized in **Table 10**, and Only 1 subject had viral load >400 copies/mL (key efficacy endpoint, FDA snapshot approach).

Table 10: Viral load results for subjects at recommended dosage up to Week 24

	Subject #	BW (kg)	Recommended dose BID (mg)	AUC12h (h*ng/mL)	Reach W24	W24 VL (c/mL)
1	(b) (6)	15	100	3449	Y	147
2		23	125	11815	Y	<40
3		23	125	6105	Y	1214
4		14.3	100	8610	Y	275
5		14.7	100	4261	Y	<200
6		14.5	100	4807	Y	40
7		*13.3*	*100*	*3935*	*no, W4*	*no data*
8		22.1	125	3129	Y	<40
9		17	100	3709	Y	42

5.9.3 Safety

ETR administered at the recommended dose in combination with an OBR consisting of at least 2 active ARVs (a boosted PI and ≥1 additional active ARV) was generally safe and well tolerated in the treatment-experienced HIV-1 infected pediatric population (aged ≥2 to <6 years). There were no newly identified clinically relevant safety findings compared with the known ETR safety profile in HIV-1 infected adults, adolescents and children aged ≥6 years.

5.10 Conclusions

The Week 24 analysis from study TMC125-C234 demonstrated that ETR administered at the recommended dose in combination with an OBR consisting of at least 2 active ARVs (a boosted PI and at least 1 additional active ARV) resulted in similar ETR exposure (AUC_{12h}) compared to adults (within 60% to 150% of the geometric mean), and was generally safe and well tolerated in the studied treatment-experienced HIV-1 infected pediatric population aged ≥2 to <6 years. Only 1 of the 9 subjects who were at the final recommended dosage up to Week 24 had viral load >400 copies/mL (key efficacy endpoint, FDA snapshot approach).

5.11 Reviewer's Assessment

- The study design is reasonable and the conclusions are acceptable.
- Due to the unfavorable taste/texture of the dispersed form in water, the risk of lower exposures could be more significant in real world conditions without close clinical monitoring for drug intake. Furthermore, adherence could be an issue for chronic dosing.
- The lower exposure (potentially due to incomplete drug intake, per the sponsor) should not be compensated for by an increase in the recommended dose, as that would lead to higher than anticipated exposures in children that do take the complete dose. Rather, a strategy to ensure complete drug intake should be developed to avoid lower exposure.
- Adding juice or milk can help to mitigate the unfavorable taste/texture of the dispersed form in water, thus the method of administration for the dispersed form in the labeling is revised to the

following: "(b) (4)".

6. Population Pharmacokinetic Analysis

The Applicant performed a population PK analysis to evaluate if the proposed dosing regimens of ETR in children 2 to <6 years of age would result in comparable exposure with that in adults. To carry out the population PK analysis, the Applicant combined PK data from historical studies (Study TMC125-C126 and TMC125-C213) with rich and sparsely sampled PK data from study P1090. The sampling schemes and regimens for each study is summarized in Table 11.

Table 11: Summary of pediatric ETR studies included in the population PK analysis (Source: Applicant's population PK report, page 8, Table 2)

	Study 1 TMC125-C126	**Study 2 TMC125-C213**	**Study 3 P1090**
Type of subjects	Pediatric ≥6 - <18 y	Pediatric ≥6 - <18 y	Pediatric ≥1 - <6 y
No. of subjects with PK data available	41	101	24[b]
Dose	100, 125, 150, 175 or 200mg BID (based on weight)[a]	100, 125, 150 or 200mg BID (based on weight)[a]	75, 100, 150, 200mg BID (based on weight)[a]
Route of administration	Oral	Oral	Oral
No. of samples per subject	9 per sampling occasion (rich sampling)	1 to 2 per (sparse) sampling occasion	7 per rich sampling occasion, 1 per sparse sampling occasion
Sampling times (h)	Pre-dose, 1, 2, 3, 4, 6, 8, 10 and 12 hours post-dose	Week 4: 4 hours post-dose; Week 24: pre-dose and at least 1 hour post-dose Other visits: any time point	Rich sampling visit: pre-dose, 1, 2, 4, 6, 9 and 12 hours post dose; Sparse sampling visits: Weeks 4 and 24: 1 to 4 hours post-dose; Week 8: 4 to 8 hours post-dose; Weeks 12 and 48: 8 to 12 hours post dose.
Limit of quantification (unit)	2.00 ng/mL	2.00 ng/mL	5.00 ng/mL

[a] Available tablets were the 25-mg and 100-mg commercially available dispersible tablets, F066 and F060

[b] 1 subject was excluded from the PK analysis (diarrhea before and on day of PK assessments)

The demographics of subjects from all the 3 studies (Study TMC125-C126, TMC125-C213 P1090) included for the population PK analysis are summarized in Table 12.

Table 12: Summary of demographics and characteristics of subjects included in the population PK analysis (Source: Applicant's population PK report, page 9, Table 3)

Study No		Pooled P1090, C126 & C213	P1090 TMC125-C234	Original dataset TMC125-C126	Original dataset TMC125-C213
N	Individuals	124	23	41	60
	Observations	980	308	368	304
	Rich Profiles	74	33	41	0
	Sparse samples	396	92	0	304
Age (years)					
	Mean (SD)	10.8 (4.14)	4.2 (1.54)	12.0 (2.99)	12.5 (2.86)
	Median	11.1	4.4	11.2	12.4
	Range	1.6-18.0	1.6-6.3	6.9-18.0	6.4-17.6
Weight (kg)					
	Mean (SD)	35.2 (15.87)	15.1 (4.10)	39.9 (13.64)	39.8 (14.11)
	Median	33.0	14.9	38.5	37.7
	Range	8.3-77.5	8.3-24.3	20.0-65.0	19.8-77.5

Key: N=number of subjects; SD=standard deviation.
For Study C213 and C126 screening demographic values are used, for P1090 demographic values at the first visit are used.

Methods

The Applicant performed population PK analysis using NONMEM version 7.4.1 with an Intel® Fortran 64 compiler Version 11.1, while graphical evaluations, data handling and simulation were performed using R version 3.3.3. All models were fitted on the logarithmically transformed data with the additive residual error model, using the First Order Conditional Estimation (FOCE) method. The estimation step was followed by the importance sampling IMP step to improve the estimations of the Objective Function Value (OFV). A 10.83 points reduction of the OFV for one additional parameter (either structural or random) in nested models, corresponding to $p<0.001$ in a corresponding Chi-Square test, was deemed significant during model development.

In terms of covariate evaluation, the only covariate evaluated was age given that body weight (WT) was included through allometric scaling. The effect of age was as shown in the function below:

$$f(AGE) = \frac{AGE^h}{nAGE^h + AGE^h}$$

where *h* is the parameter regulating the shape of the model fit.

AUC confidence and prediction interval

The Applicant evaluated the proposed ETR dosing regimen by estimating the probability that the typical exposure (AUC) lies in the target range (80%-150% of the geometric mean adult AUC). This was evaluated by the Applicant across the weight and dose ranges: 5-35 kg and 25-200 mg bid, respectively.

The standard error (SE) of the AUC predictions were obtained following sampling a thousand parameter values from the parameter uncertainty distribution and then using the final model, the predicted AUC at steady state dose (DOSE) and WT, is given by the following equation which also considers random effects, (η_F) for relative bioavailability and (η_{CL}) for clearance:

$$AUC = \frac{F1(FORM) \times DOSE}{CL \times (WT/70)^{0.75}} \frac{\exp(\eta_F)}{\exp(\eta_{CL})}$$

Results

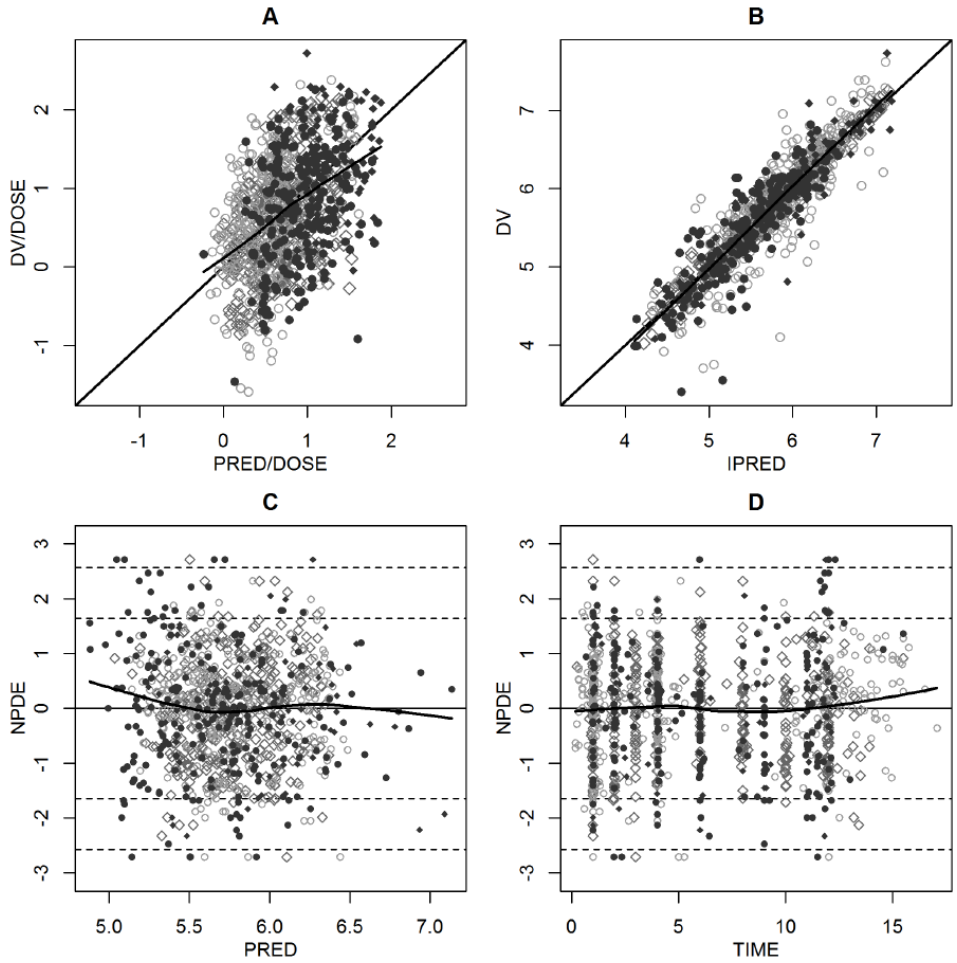
The final population PK estimates are shown in Table 13 together with their corresponding percent relative standard error (%RSE). The goodness-of-fit plots for the final model are shown in

Figure **2**. The plots show that the final model adequately described the population PK of ETR.

Table 13: Population PK parameter estimates for the final ETR model (FDA analysis)

Parameter	Population Mean Estimate (RSE)
CL/F (L/h)	61.6 (5.60)
V/F (L)	867 (19.9)
KA (h^{-1})	1.2 (41.3)
D1 (h)	2.29 (12.1)
TLAG (h)	0.292 (41.4)
Allometric exponent: WT on CL/F	0.75 (fixed)
Allometric exponent: WT on V/F	1 (fixed)
Dispersed F1 relative to swallowed whole (%)	63 (12.4)
Interindividual variability of parameters	
CL/F (%)	31.4 (8.1)
KA (%)	125.7 (69.0)
F1 (%)	42.3 (9.6)
Interoccasion variability of parameters	
F1 (%)	44.4 (40.0)
Additive residual error	
Rich sampling (ng/ml)	0.0348 (15.8)
Sparse sampling (ng/ml)	0.19 (14.0)

Figure 2: Goodness-of-fit plot for the final model (Source: Applicant's population PK report, page 33, Figure 15)



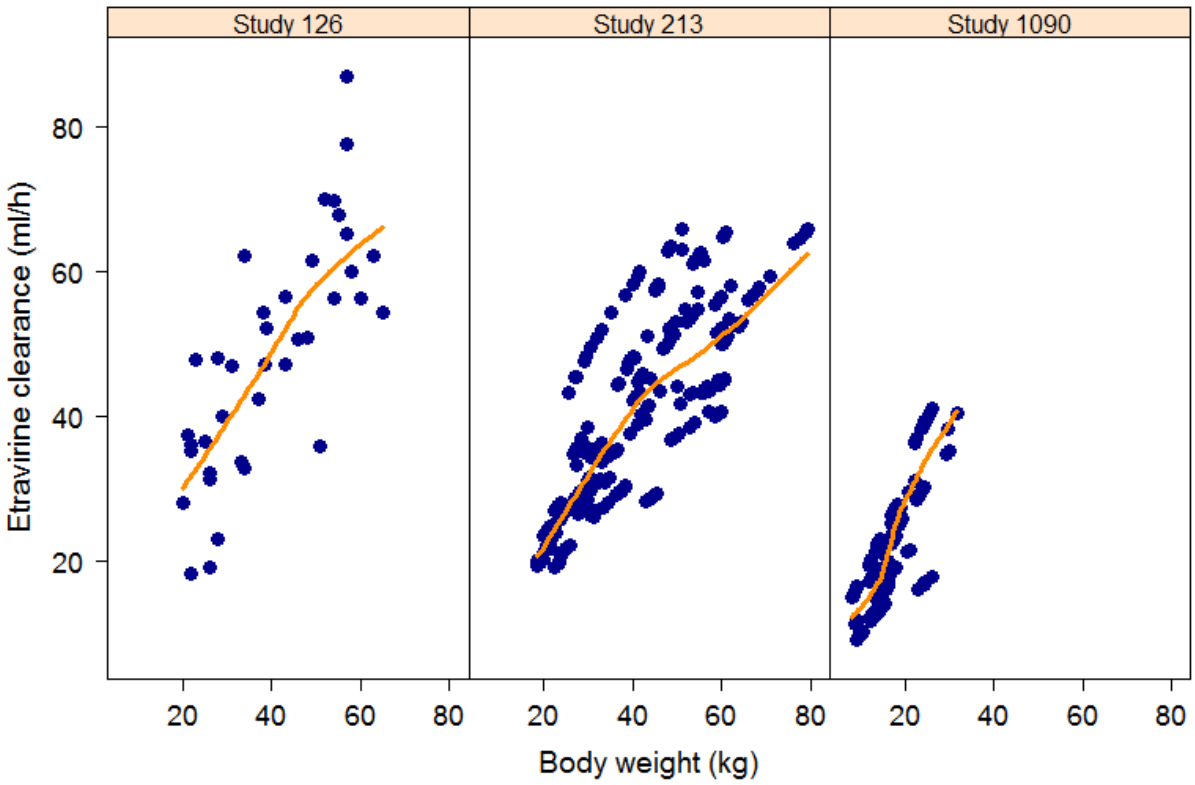
Goodness of fit plots, records form the P1090 study presented as dark grey dots, from the TMC125-C213 study as light grey circles and from the TMC125-C126 study as grey diamonds along with (loess) smoother through all points. Panel A: log of dose normalized observed concentration vs log of dose normalized population prediction. Panel B: log observed concentration vs log individual concentration, Panel C and D: Normalized prediction distribution errors (NPDE) vs population prediction and Time (since last dose) respectively.

Dose and Regimen Selection

The Applicant evaluated the proposed ETR dose selection in 3 steps. First, potential deviations between the typical (population) and mean post-hoc (individual) estimates of the clearance were evaluated. In this step, the Applicant evaluated the predicted typical clearance, along with the 95% confidence interval, over the weight range of interest and overlaid with the individual (post-hoc) clearance estimates. The Applicant could not find any significant deviations between the

population and post-hoc estimations of the expected (mean) clearance which we confirmed in our analysis (Figure 3) where we performed a similar analysis for different studies. Similar findings were obtained when the studies were pooled together.

Figure 3: Exploratory plot of ETR clearance versus body weight, stratified by study (FDA analysis)

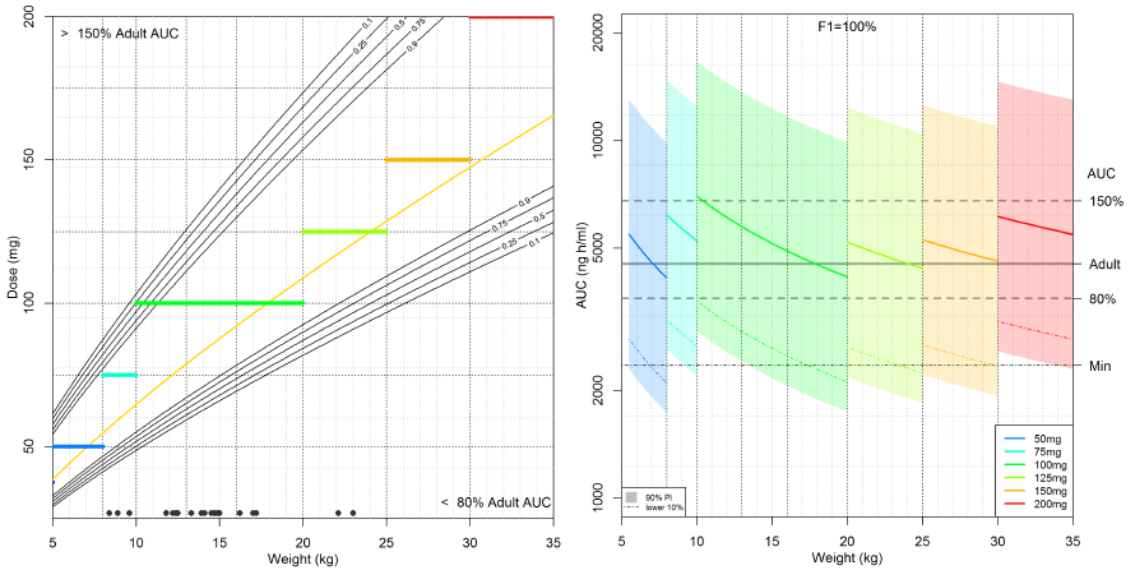


The blue dots are observed data, while the orange line is the smoothing line.

As a second step, the Applicant evaluated the likelihood that the true median AUC will be within the target AUC range. As the true median AUC is unknown, the Applicant estimated the extent by which the true AUC is likely to deviate from the estimated AUC. The applicant assumed a bioavailability of 1 for different combinations of dose and body weight when deriving the AUC. In the Applicant's illustration, three points on the Figure 4 (left panel) were chosen: the first is a DOSE of 150 mg to be administered to patients weighing 10 kg. The confidence level is below 0.1 (or 10%) so it is very unlikely that the selected dose would result in an average AUC within the confidence band. Similarly, the confidence level of a dose of 50 mg to be administered to patients weighing 25 kg is below 10% and will thus likely result in underexposure as it falls below the idealized regimen. Finally, for doses already in the approved ETR, the confidence level of a 150 mg dose given to patients between 25 kg and 30 kg is above 90% so it is very likely that the average AUC will fall within the target range with values slightly higher than the

geometric mean adult AUC. Using the left panel of Figure 4, it can be deduced that the ETR recommended dose regimen as per P1090 study across the weight range indicates that confidence levels above 90% are reached across the entire weight range except between 10 and 11.5 kg.

Figure 4: Applicant's dose selection plot (assuming F1=1) (Source: Applicant's population PK report, page 19, Figure 4)

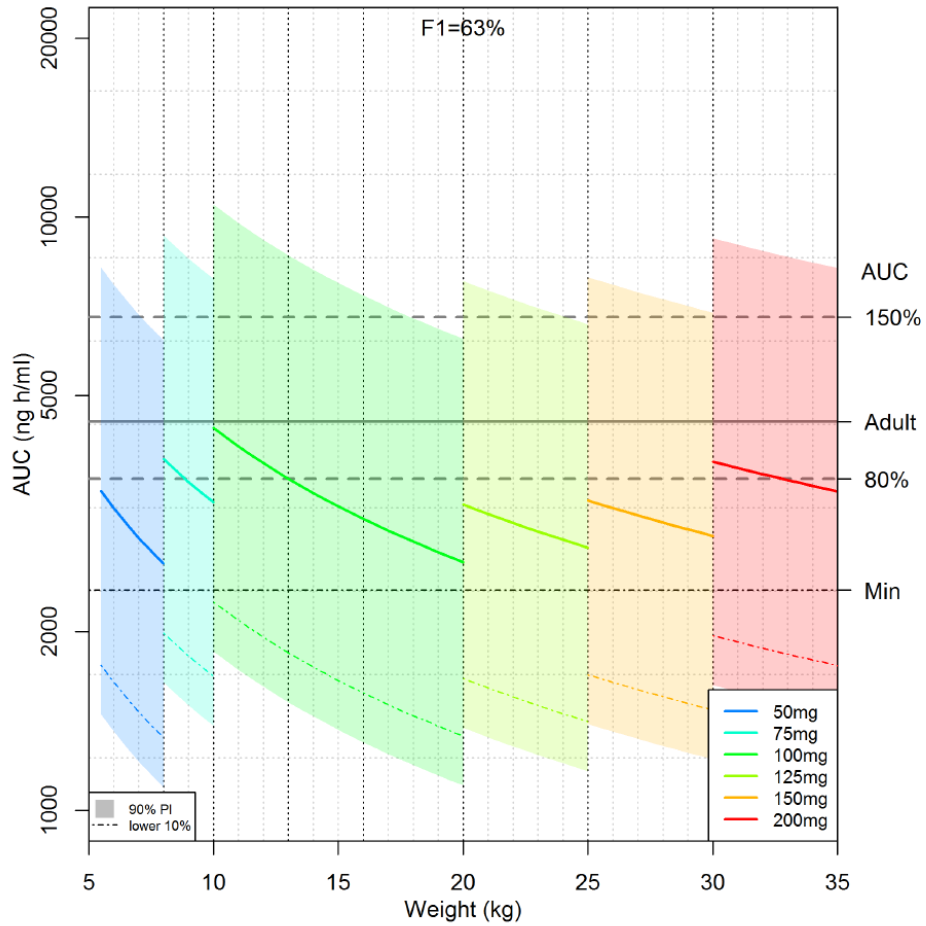


Left panel: contour of 10%, 25%, 75% and 90% confidence levels (for AUC being within 80-150% of the target adult AUC) as function of ETR Dose and Weight, overlaid by the proposed dose regimen (colored lines). Dots indicate the actual observed weight of the subjects included in the P1090 study. Right panel: mean expected AUC as a function of weight for the proposed regimen (colored lines) along with 90% prediction interval (shaded areas) and the 10% lower AUC (dashed lines). Min represents the 10th percentile of the adult AUC (pooled DUET trials).

As a last step, the Applicant evaluated the expected AUC range across the population including variability between individuals. The 90% prediction interval as well as the 10th percentile of the AUC for the proposed ETR dose regimen were evaluated across the weight range of interest as shown in Figure 4 (right panel). This indicated that the likelihood of under-dosing becomes low as the doses selected were confirmed to provide an exposure similar or higher than the typical exposure for adults and the 10% lower bound of the prediction interval rises well above the 10th percentile of the exposures observed in adults. The Applicant further performed a similar analysis for dispersed formulation which suggested that the mean AUC would be lower than 80% of the adult exposure for bodyweights >12kg (

Figure **5**).

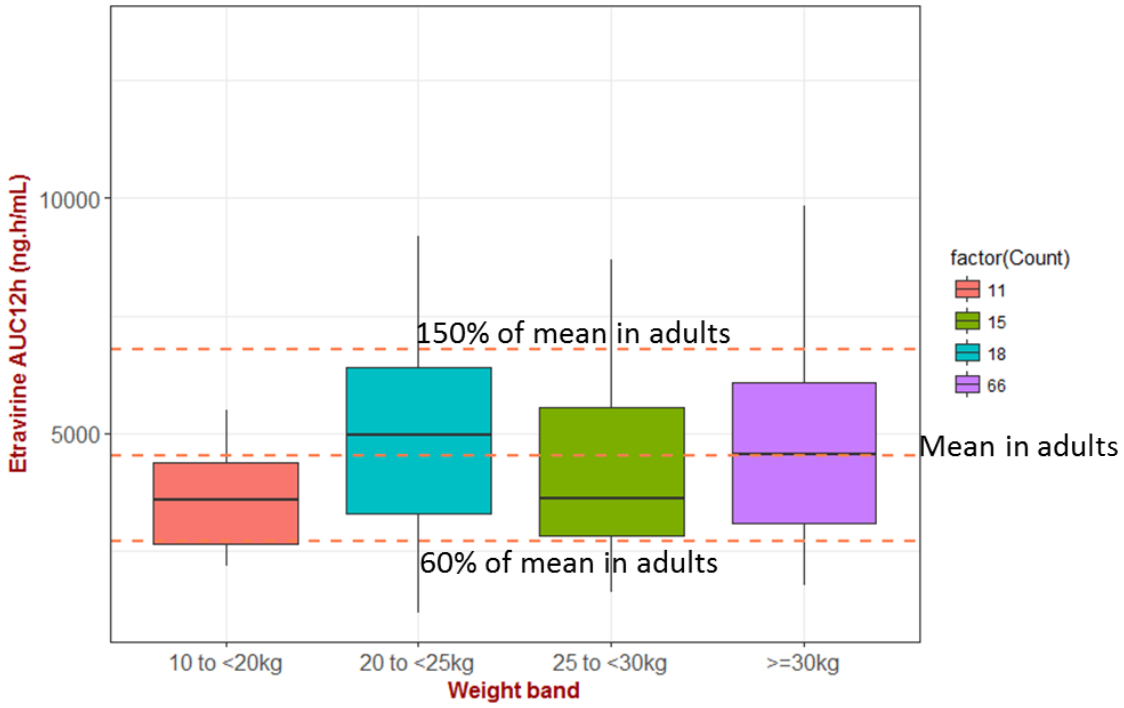
Figure 5: AUC predictions including inter-individual variability (Dispersed: F1=63%) (Source: Applicant's population PK report, page 40, Figure 20)



Mean expected AUC (assuming F1=63%) as a function of weight for the proposed regimen (colored lines) along with 90% Prediction interval (shaded areas) and the 10% lower AUC (dashed lines). Min represents the 10th percentile of the adult AUC (pooled DUET trials).

Reviewer's comments: *Applicant's population PK analysis reasonably described the PK of ETR as shown in the goodness-of-fit plots. The submitted final population PK model was reproducible and FDA reviewer agreed that it was appropriate to use the model for dose selection. We also confirmed that the exposures proposed by the Applicant were adequate as shown in* ***Error! Reference source not found.****.*

Figure 6: Population PK predicted AUC_{12h} for ETR based on the proposed dosage stratified on body weight



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/s/

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