EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

26 March 2020
EMA/175628/2020
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

INTELENCE

International non-proprietary name: etravirine

Procedure No. EMEA/H/C/000900/II/0058

Note

Variation assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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List of abbreviations

abbreviation	description of abbreviated term
ADR	Adverse Drug Reaction
AE	adverse event
AEOI	Adverse event of interest
AIDS	acquired immune deficiency syndrome
ALT	Alanine aminotransferase
ART	antiretroviral treatment
ARV	antiretroviral
AST	Aspartate aminotransferase
AUC_{12h}	area under the plasma concentration time curve over a 12-hour dosing
CI	confidence interval
CSR	clinical study report
DRV	Darunavir
EFV	Efavirenz
EMA	European Medicines Agency
ERA	Environmental Risk Assessment
ETR	Etravirine
EU	European Union
FDA	Food and Drug Administration
GCP	Good Clinical Practices
HIV(-1)	human immunodeficiency virus (type 1)
ICH	International Council for Harmonisation
IMPAACT	International Maternal Paediatric Adolescent AIDS Clinical Trials Group
INI	Integrase inhibitor
ITT	Intent-to-treat
LDL	low-density lipoprotein
LPV	Lopinavir
M=F	missing equals failure
MAH	Marketing Authorization Holder
MedDRA	Medical Dictionary for Regulatory Activities
NC=F	non-completer equals failure
NNRTI	Non-nucleoside reverse transcriptase inhibitor
NVP	Nevirapine
OBR	optimized background regimen
OC	Observed case
PI	protease inhibitor
PIP	Paediatric investigation plan
PK	pharmacokinetic(s)
RAM	resistance-associated mutation
RMP	Risk Management Plan
rtv	ritonavir
SAE	serious adverse event
SmPC	Summary of Product Characteristics
SMQ	Standardised Medical Dictionary for Regulatory Activities Query
TLOVR	time to loss of virologic response
WGS	weighted genotypic score

1. Background information on the procedure

1.1. Type II variation

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, Janssen-Cilag International NV submitted to the European Medicines Agency on 16 October 2019 an application for a variation.

The following variation was requested:

Variation requested		**Type**	**Annexes affected**
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I and IIIB

To extend the approved therapeutic indication of Intelence in order to include patient population from 2 to 6 years of age based on the 48 week study results from study TMC125-C234/P1090 (A Phase I/II, Open-label Trial to Evaluate the Safety, Tolerability, Pharmacokinetics and Antiviral Activity of Etravirine (ETR) in Antiretroviral (ARV) Treatment-experienced HIV-1 Infected Infants and Children, Aged ≥2 Months to <6 Years). As a consequence, sections 4.1, 4.2, 4.8, 5.1 and 5.2 of the SmPC and sections 1, 2 and 3 of the PL are updated accordingly. The updated RMP version 13.1 has also been submitted.

The RMP (version 13.1) of the product has been updated to remove the completed additional pharmacovigilance activities (TMC125-C234/P1090 (Week 48) and TMC125-EPPICC) from the pharmacovigilance plan of the RMP). The RMP has also been updated to meet the requirements and updated definitions in the European Medicines Agency (EMA) Guideline on good pharmacovigilance practices (GVP) Module V Revision 2 (EMA/838713/2011; Rev 2) and Guidance on the format of the RMP in the European Union (EMA/164014/2018 Rev 2.0.1) including proposed removal of safety concerns.

The MAH took the opportunity to include some typographic changes in Annex II C and D.

Information on paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included (an) EMA Decision(s) P/0121/2019 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP P/0121/2019 was completed.

The PDCO issued an opinion on compliance for the PIP P/0121/2019. The PDCO considered that the measures are in compliance with the agreed above mentioned paediatric investigation plan and that the agreed timelines have been respected accordingly.

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the MAH did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

Scientific advice

The MAH did not seek Scientific Advice at the CHMP.

1.2. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Jean-Michel Race Co-Rapporteur: Bruno Sepodes

Timetable	Actual dates
Submission date	16 October 2019
Start of procedure:	2 November 2019
CHMP Co-Rapporteur Assessment Report	19 December 2019
CHMP Rapporteur Assessment Report	24 December 2019
PRAC Rapporteur Assessment Report	24 December 2019
PRAC members comments	8 January 2020
PRAC Outcome	16 January 2020
CHMP members comments	20 January 2020
Updated CHMP Rapporteur(s) (Joint) Assessment Report	27 January 2020
Request for supplementary information (RSI)	30 January 2020
CHMP Rapporteur Assessment Report	20 March 2020
CHMP members comments	23 March 2020
Updated CHMP Rapporteur Assessment Report	Not Applicable
Opinion	26 March 2020

2. Scientific discussion

2.1. Introduction

Etravirine (ETR) is a non-nucleoside transcriptase inhibitor (NNRTI) indicated, in combination with a boosted protease inhibitor (PI) and other antiretroviral medicinal products, for the treatment of HIV-1 infection in antiretroviral (ARV) treatment-experienced adult and paediatric patients from 6 years of age.

This extension of paediatric indication in subjects <6 years old is supported by the data from study TMC125-C234 (IMPAACT P1090). This study is part of the currently agreed Intelence Paediatric Investigation Plan (EMEA-000222-PIP01-08-M08, decision P/0163/2015 dated 7 August 2017). Week 48 results of this study were previously assessed in March 2019 as part of the procedure EMEA/H/C/000900/P46/053, without further action required.

For this extension of indication variation II/58, no new clinical study report of study TMC125-C234 was provided. In addition, a PopPK analysis report and an erratum of this study TMC125-C234 were submitted.

2.2. Non-clinical aspects

No new clinical data have been submitted in this application, which was considered acceptable by the CHMP.

2.2.1. Introduction

2.2.2. Pharmacology

No new non-clinical pharmacodynamic studies have been conducted to support the extension of indication in adolescent patient population, which was considered acceptable by the CHMP.

2.2.3. Pharmacokinetics

No new non-clinical pharmacokinetic studies have been conducted to support the extension of indication in adolescent patient population, which was considered acceptable by the CHMP.

2.2.4. Ecotoxicity/environmental risk assessment

The MAH did not submit an updated Environmental Risk Assessment in the initial submission for this variation, with the reason that this medicinal product is considered unlikely to result in any significant increase in the environmental concentration of the active substance.

It can be acknowledged that target population is only expected to be marginally increased. This is because ETR is to be used in ARV experienced children in combination with a boosted Protease Inhibitor (PI), while in the newly younger age strata, NNRTI and boosted PI are more expected to be sequentially introduced and that vertical transmission of viral strains harbouring resistance is limited.

However, the CHMP requested the MAH to calculate the new Predicted Environmental Concentrations (PEC) value for etravirine for the new target group and then, sum it to the previous PEC to reach the

total PEC and the environmental risk assessment updated based on new PEC value.

At the request of CHMP, the MAH provided an Environmental Risk Assessment for Etravirine paediatric indication (children ≥ 2 to < 6 years).

The MAH provided an updated ERA according to the Guideline on the Environmental Risk Assessment of Medicinal Products for Human Use (CHMP/SWP/4447/00). In this version, the market penetration factor for etravirine was recalculated using the prevalence data for the indication. This resulted in newly calculated PECs (surface water, ground water, sediment and soil) and risk characterization ratios (water, sediment and soil).

Phase I Screening for Persistence, Bioaccumulation, and Toxicity (PBT)

The $logP_{ow}$ calculated for etravirine in study TMC125 is 3.4, which is below 4.5, consequently, no screening for persistence, bioaccumulation and toxicity according to the European Chemicals Bureau (2003) Technical Guidance Document was performed. Etravirine does not exhibit potential for bioaccumulation based on $logP_{ow.}$

Phase I Calculation of the Predicted Environmental Concentration

An estimation of the PEC of TMC125 in surface waters receiving the discharge of sewage treatment facilities was obtained using the following formula:

$$PEC_{surfacewater} = \frac{DOSE_{ai} \times F_{pen}}{WASTEW_{inhab} \times DILUTION \times 100}$$

For TMC125: $DOSE_{ai}$: = 400 mg/day; $WASTEW_{inh}$: = 200 L (default); DILUTION: = 10 (default)

Current WHO/ECDC data indicate that the HIV prevalence in any single EU member state does not exceed 0.9% (highest being Estonia) [WHO Global Health Observatory data repository, updated September 11, 2019]. However, the INTELENCE population including paediatric population would be a small part of this group since patients need to have resistance to multiple antiretroviral therapy classes to be eligible. Less than 10% of the HIV infected population is "highly treatment-experienced" but sources on this are very difficult to get due to the small size of the population. Therefore, for the purpose of this ERA a prevalence of 0.1% was used ((F_{pen}: = 1% (default) (=0.01)) which is already an overestimation of the population.

$PEC_{surfacewater}$ of TMC125 in surface water is 0.2 µg/L.

And $PEC_{groundwater}$ = 0.25 × PECsurfacewater = 0.05 µg/L

Calculation of PNECwater, PNECmicroorganisms, PNECgroundwater

The $PNEC_{water}$ was based on the lowest NOEC result from the long-term toxicity tests; $PNEC_{microorganism}$ is based on the NOEC result of the microbial effect study and the $PNEC_{groundwater}$r is based on the NOEC result of the acute toxicity test with *Daphnia magna.*

The $PNEC_{sediment}$ for TMC125 is based on the NOEC from the 28 days toxicity test with *Chironomus riparius.* As the NOEC from the 28 days toxicity test with *Chironomus riparius* is > 20 µg/L, the $PNEC_{sediment}$ is > 0.2 µg/L.

For stuvy TMC125:

$PNEC_{water}$ = 0.49 µg/L

$PNEC_{groundwater}$ = 0.91 µg/L

$PNEC_{microorganisms}$ = 100 mg/L = 100000 µg/L

$PNEC_{sediment}$ > 0.2 µg/L

Calculation PEC/PNEC ratios

$PEC_{surfacewater}/PNEC_{water}$ = 0.2 µg/L / 0.49 µg/L= 0.41

Consequently, further testing in the aquatic compartment is not necessary and it can be concluded that TMC125 and/or its metabolites are unlikely to represent a risk to the aquatic environment.

$PEC_{groundwater}/PNEC_{groundwater}$ = 0.05 µg/L / 0.91 µg/L= 0.055

The ratio $PEC_{groundwater}/PNEC_{groundwater}$ is below 1. Consequently, further evaluation on the fate of TMC125 and/or its metabolites in the aquatic environment is not needed.

$PEC_{surfacewater}/PNEC_{microorganisms}$ = 0.2 µg/L / 100 mg/L= 0.2 x 10-5

The ratio $PEC_{surfacewater}/PNEC_{microorganisms}$ is below 0.1. Consequently, further evaluation of the fate and effects of TMC125 on microorganisms is not required.

$PEC_{surfacewater}/PNEC_{sediment}$ = 0.2 µg/L / > 0.2 µg/L < 1 The risk ratio $PEC_{sediment}/PNEC_{sediment}$ is below 1. Consequently, further testing in the sediment compartment is not necessary and it can be concluded that TMC125 and/or its metabolites are unlikely to represent a risk to the sediment compartment.

Table 1: ERA summary table with the updated data for TMC125:

Compartiment	PEC (µg/L)	PNEC (µg/L)	PEC/PNEC
Surfacewater	0.2	0.49	0.41
Groundwater	0.05	0.91	0.055
Microorganisms		100000	0.000002
Sediment		>0.2	<1

Potential to Bioaccumulate

The kinetic BCF values were 370.1 for the low dose and 530.9 for the high dose. These BCFk values are below 1000 indicating that TMC125 does not bioaccumulate in fish.

Affinity to Bind to Sewage Sludge

The adsorption/desorption coefficient (Koc) for TMC125 is 16617 kg/L, which is higher than the limit value of 10000 kg/L, indicating that ETR has a high affinity to bind to sewage sludge in the sewage treatment plant. Consequently, an environmental assessment in the terrestrial compartment was conducted.

For TMC125, PEC_{sludge} was calculated as:

Type (i) STP = 0.413 mg/kg dry sludge (combined sludge, i.e., primary + surplus sludge);
Type (ii) STP = 0.503 mg/kg dry sludge (surplus sludge).

PEC_{soil} of TMC125 in soil after the first sludge application is: PEC_{soil} (1) = = 0.00074 mg/kg soil.

According to the TGD, a realistic worst-case assumption for exposure should be considered assuming that sludge application takes place for ten consecutive years. For this calculation, the fraction of active substance that remains in the top soil layer at the end of each application year has to be calculated using the formula:

$F_{acc} = e^{-365\,k}$, where k is a first order rate constant for removal from top soil:

$$\text{i.e., } k = \frac{\ln 2}{DT_{50\,soil}} = \frac{0.693}{587} = 0.00118.$$

The yearly accumulation fraction of TMC125 in soil is $F_{acc} = 0.65$

Finally, the initial concentration of TMC125 in the top-soil layer after ten applications of sludge is given by:

$$PEC_{soil}(10) = PEC_{soil}(1) \times \left[1 + \sum_{n=1}^{9} F_{acc}{}^{n}\right]$$

And PECsoil (10) = 0.0021 mg/kg soil.

The calculation of PNECsoil is based on the lowest NOEC result from the long-term toxicity tests, i.e., 76 mg/kg dry soil for terrestrial plants.

PNECsoil = 7.6 mg/kg soil

Lastly, the PECsoil/PNECsoil = 0.0021 mg/kg / 7.6 mg/kg = 0.3 × 10-3

The ratio PECsoil/PNECsoil is below 1. Consequently, further testing in the terrestrial compartment is not necessary. In accordance with EMEA Guideline on the Environmental Risk Assessment of Medicinal Products for Human Use, TMC125 and/or its metabolites are considered unlikely to represent a risk to the terrestrial compartment following prescribed usage in patients.

2.2.5. Discussion on non-clinical aspects

The justification provided by the applicant for the ERA exemption was not acceptable by the CHMP, as no reliable data were included to show that an increase in the environmental concentration of the active substance was not expected.

At the request of the CHMP, the MAH submitted an updated Environmental Risk Assessment for this extension of indication. The PEC/PNEC ratios remain below 1.0 and 0.1 for surface water/ groundwater/ sediment and microorganism respectively.

Etravirine does not exhibit potential for bioaccumulation based on $logP_{ow}$. It doesn't bioaccumulate in fish.

The calculated adsorption/desorption coefficient (Koc) for TMC125 was 16617 kg/L, higher than the limit value of 10000 kg/L. the MAH conducted an environmental assessment of TMC125 in the terrestrial compartment.

The ratio PECsoil/PNECsoil remains below 1, therefore, etravirine and its metabolites are considered unlikely to represent a risk to the terrestrial compartment.

2.2.6. Conclusion on the non-clinical aspects

Based on the updated data submitted in this application, the extended indication does not lead to a significant increase in environmental exposure further to the use of Etravirine.

Considering the above data, etravirine is not expected to pose a risk to the environment.

2.3. Clinical aspects

2.3.1. Introduction

In the European Union (EU), INTELENCE, in combination with a boosted protease inhibitor (PI) and other antiretroviral (ARV) medicinal products, is indicated for the treatment of HIV infection in antiretroviral therapy (ART)-experienced adult patients and in ART-experienced paediatric patients from 6 years of age. The recommended dose of ETR for paediatric patients aged ≥6 years to <18 years and weighing ≥16 kg is based on body weight (see Table 2):

Table 2: Recommended Dose of Etravirine for Paediatric Patients Aged ≥6 to <18 Years

Body Weight	Dose	Tablets
≥16 to <20 kg	100 mg twice daily	Four 25 mg tablets twice daily or one 100 mg tablet twice daily
≥20 to <25 kg	125 mg twice daily	Five 25 mg tablets twice daily or one 100 mg tablet and one 25 mg tablet twice daily
≥25 to <30 kg	150 mg twice daily	Six 25 mg tablets twice daily or one 100 mg tablet and two 25 mg tablets twice daily
≥30 kg	200 mg twice daily	Eight 25 mg tablets twice daily or two 100 mg tablets twice daily or one 200 mg tablet twice daily

An application for the extension of the indication in HIV-1 infected paediatric subjects aged ≥2 to <6 years was approved by the Food and Drug Administration (FDA) in July 2018, based on the Week-24 analysis of Study TMC125-C234. Of note, the purpose of this EU type II variation is to extend to the same target population on the basis of the 48 weeks data of this study.

GCP

The clinical trial TMC125-C234 was performed in accordance with the ethical principles that have their origin in the Declaration of Helsinki and that are consistent with Good Clinical Practices and applicable regulatory requirements, as claimed by the applicant.

- Tabular overview of clinical studies:

Table 3: Tabular overview of clinical studies

Study phase	Study (Country and Number of Centres)	Design Study Objectives	Subjects: Total Number of Subjects	Dosage Regimen Route of Administration Duration of Treatment
1/2	TMC125-C234 (P1090) (Brzil:5. South Africa:2, United States:4)	Ongoing, open-label, study to evaluate the PK, safety, tolerability, and antiviral activity of ETR in combination with other ARV drugs, in treatment-experienced HIV-1 infected paediatric subjects < 6 years of age.	HIV-1 infected paediatric subjects < 6 years of age Total: 26: - 20 in Cohort I (aged ≥2 to <6 years) - 6 in Cohort II (aged ≥1 to <2 years)	At study start, subjects started on a 5.2 mg/kg ETR dose, together with an OBR consisting of ≥2 active ARVs. After analysis for the first mini-cohort of 6 subjects, the weight-based ETR recommended dose; to be taken together with an OBR consisting of ≥2 active ARVs, was adjusted as follows: - < 8 kg: 50 mg bid; - 8 to <10 kg: 75 mg bid; - 10 to <20 kg: 100 mg bid; - 20 to <25 kg: 125 mg bid; - 25 to <30 kg: 150 mg bid; - ≥ 30 kg: 200 mg bid; Oral 48 weeks treatment + long-term follow-up for a maximum of 5 years

2.3.2. Pharmacokinetics

Extensions of indication to include paediatric population for antiretroviral agents are primarily based on demonstration of comparable exposure in children vs. adults. As stated in the EMA Guideline on the clinical development of medicinal products for the treatment of HIV infection, a specific demonstration of antiviral efficacy in paediatric patients is not required. As it is assumed that the PK/PD relation for a direct acting antiviral is roughly similar regardless of the age of the patient, the efficacy of a dose that yields sufficiently similar exposure in children, compared to adults, would be inferred. The parameters that would be applied to conclude on similarity should be based on available data from the entire development programme, including PK and efficacy data in adults

Main study TMC125-C234 (P1090)

The clinical PK, efficacy and safety data in support of this younger age paediatric extension are derived from an open label phase 1/2 study TMC125-234 (IMPAACT 1090) enrolling 20 subjects in Cohort I (aged ≥2 to <6 years) and 6 subjects in Cohort II (aged ≥1 to <2 years). Subjects were on a virologically-failing regimen (containing at least 3 ARV). Of note, a Cohort III (< 1 y/o) was originally planned but did not enrol and was closed (See Table 4).

For more details about Clinical Efficacy of study TMC125, refer to section 2.4.1 - Main Study.

Study design

TMC125 is a Phase I/II, multicenter, open label 48 week study of ETR in combination with at least 2 active agents (a boosted PI and at least one additional active drug), for treatment experienced HIV-1-infected infants and children ≥ 2 months to < 6 years separated by age into three cohorts (see Table 4).

Table 4: Description of Cohorts

					Anticipated Accrual		
Cohort	**Description of Subject**	**Drug Regimen**	**Phenotyping / Genotyping Information**	**Comments**	**Mini Cohort**	**To complete a full cohort**	**Total cohort size**
I	≥ 2 year to < 6 years who are treatment experienced	ETR + OBR (1 active boosted PI+ at least 1 other active drug)	HIV genotype and phenotype assays should be performed in real time and results available prior to starting study drug	Subjects will be enrolled providing the phenotypic assay results indicate a < 10 fold change in sensitivity to ETR	6	6	Up to 18
II	≥ 1 year to < 2 years who are treatment experienced	ETR + OBR (1 active boosted PI+ at least 1 other active drug)	HIV genotype and phenotype assays should be performed in real time and results available prior to starting study drug	Subjects will be enrolled providing the phenotypic assay results indicate a < 10 fold change in sensitivity to ETR	6	6	12
III	≥ 2 months to < 1 year who are treatment experienced 1	ETR + OBR (1 active boosted PI+ at least 1 other active drug)	HIV genotype and phenotype assays should be performed in real time and results available prior to starting study drug	Subjects will be enrolled providing the phenotypic assay results indicate a < 10 fold change in sensitivity to ETR	6	6	12

1. Subjects below 6 months of age will only be enrolled upon availability of initial safety and PK data from subjects between 6 months and 1 year of age.

Results:

All PK analyses were based on subjects in the ITT population with at least 1 PK sample taken, with further analyses by subsets as indicated (Table 5):

Table 5: Overview of Subjects Included in PK Analyses Intensive PK (Study TMC125 C234)

	Cohort I ≥2 to <6 years	Cohort II ≥1 to <2 years	All Subjects
Subjects with intensive PK data in the first mini-cohort (ETR 5.2 mg/kg bid for all body weights)	6	0	6
Subjects on the recommended ETR dose (or higher) included in the PK statistical analyses			
• Subjects with intensive PK data on the recommended ETR dose	15	6	21
• Subjects with intensive PK data on a higher than the recommended ETR dose - PK data included for listings only	6	2	8
Subjects not included in the PK statistical analyses			
• From subset i+b, 1 subject (1 subjet aged ≥2 to <6 years) was excluded from the PK analyses (diarrhea before and on day of PK assessments).	1	0	1

- Mini-cohort I: non-compartmental PK analysis

At the start of the study, all subjects in the first mini-cohort (N=6, aged ≥2 to <6 years) were on an ETR dose of 5.2 mg/kg bid. The ETR PK parameters for this subgroup are as follows:

Table 6: Intensive Pharmacokinetics: Descriptive Statistics; ITT - Initial Dose (5.2 mg/kg Twice Daily) in Mini-cohort I (Study TMC125 C234; Age Group ≥2 to <6 years)

	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	7.855
Geom. Mean	2466.54	302.81	127.05	166.74
Median (min; max)	2359.50 (1151.0; 5776.0)	317.00 (128.7; 713.9)	134.85 (59.0; 397.3)	154.50 (102.0; 397.0)

N: number of subjects with data

Of the 6 subjects in this mini-cohort, 2 subjects had an individual dose adjustment, because their ETR AUC12h was below 2,350 ng•h/mL (i.e., below the 10th percentile of the adult ETR AUC12h in the DUET studies). Both subjects were adjusted to an ETR 200 mg bid dose and thereafter had an AUC12h above 2,350 ng•h/mL.

A comparison of the geometric mean ETR AUC12h in the mini-cohort with that in adults indicated that it was unlikely that, with this ETR dose, the geometric mean ETR exposure would be within target for the full cohort (see Table 7):

Table 7: Geometric Mean Ratio for ETR PK Parameters; ITT - Initial Dose (Study TMC125-C234

	≥2 to <6 years (N=6)	Adults[a] (N=575)	GMR (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)

[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.
N: number of subjects with data

A revision of the ETR dosing table was introduced for the remainder of the cohorts. For 2 subjects of the mini-cohort, based on their body weight, the newly recommended ETR dose was the same as their initial dose, and PK data for these subjects are included for the summary and analysis of data from subjects on the newly recommended dose.

- ETR Pharmacokinetics on the Recommended ETR Dose: Non-compartmental PK Analysis

The ETR PK parameters on the recommended ETR dose by age cohort are as follows:

Table 8: Intensive Pharmacokinetics: Descriptive Statistics; ITT - Recommended ETR Dose (Study TMC125 C234)

	≥2 to <6 years (Cohort I)			
	AUC_{12h} (h*ng/mL)	C_{max} (ng/mL)	C_{0h} (ng/mL)	C_{12h} (ng/mL)
N	15	15	15	15
Mean (SD)	4814.72 (3613.417)	564.63 (389.349)	296.50 (280.380)	327.56 (288.452)
CV%	75.049	68.957	94.563	88.061
Geom. Mean	3824.42	465.82	203.16	231.82
Median	3709.39	457.80	179.60	245.00
Min; Max	1220.5; 12998.6	199.0; 1494.0	54.0; 908.0	54.3; 962.0
	≥1 to <2 years (Cohort II)			
	AUC_{12h} (h*ng/mL)	C_{max} (ng/mL)	C_{0h} (ng/mL)	C_{12h} (ng/mL)
N	6	6	6	6
Mean (SD)	4158.56 (3137.787)	489.88 (349.349)	201.53 (185.599)	261.88 (234.589)
CV%	75.454	71.313	92.094	89.578
Geom. Mean	3328.14	390.38	192.93	197.70
Median	3389.69	379.35	146.95	175.50
Min; Max	1148.0; 9989.0	121.9; 1085.0	0.0[a]; 503.0	82.3; 706.0

N: number of subjects with data
[a] One subject in Cohort II with virologic failure had ETR pre-dose concentrations below the detection limit at the intensive PK visit; while the C_{12h} was 159 ng/mL, which is an indication of suboptimal adherence to ETR prior to the intensive PK visit, even though non-adherence was not reported.

The mean ETR PK parameters were lower in subjects in Cohort II, compared to Cohort I. Overall, the inter-subject variability was large in both age cohorts.

The statistical results comparing ETR PK parameters between children and adults (pooled DUET studies) are as follows (Table 9):

Table 9: Geometric Mean Ratio (Children/Adults) for ETR PK Parameters; ITT - Recommended ETR Dose (Study TMC125 C234)

	Geometric Mean			GMR (90% CI) [a,b]	
	≥2 to <6 years (N=15)	≥1 to <2 years (N=6)	Adults [b] (N=575)	≥2 to <6 years	≥1 to <2 years
AUC_{12h} (h*ng/mL)	3824	3328	4522	0.84 (0.61; 1.16)	0.73 (0.40; 1.35)
C_{0h} (ng/mL)	203	193	297	0.69 (0.46; 1.03)	0.65 (0.31; 1.35)
C_{12h} (ng/mL)	232	198	NA	0.78 (0.53; 1.17)	0.67 (0.35; 1.28)

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.

The geometric mean ETR AUC12h for subjects in Cohort I (aged ≥2 to <6 years, N=15) and Cohort II (aged ≥1 to <2 years, N=6) **was within the target of 60% to 150% of the geometric mean ETR AUC12h in adults.**

Subgroup analyses

A subgroup analysis was performed for subjects with intensive PK data on the ETR recommended dose:

Table 10: Intensive Pharmacokinetics - ETR AUC12h (ng*h/mL) by Subgroup; ITT - Recommended Dose (Study TMC125 C234)

	≥2 to <6 years (N=20)	≥1 to <2 years (N=6)	All Subjects (N=26)
Female			
N	7	3	10
CV%	45.670	68.916	61.259
Geom. mean	3060.75	4814.05	3506.17
Median (min; max)	3129.38 (1764.0; 6105.5)	3956.38 (2823.0; 9989.0)	3419.39 (1764.0; 9989.0)
Male			
N	8	3	11
CV%	73.166	69.886	79.983
Geom. mean	4647.41	2300.88	3836.56
Median (min; max)	4370.90 (1220.5; 12998.6)	2190.00 (1148.0; 4845.0)	3934.70 (1148.0; 12998.6)
Black or African American			
N	6	3	9
CV%	51.759	100.919	63.086
Geom. mean	6885.75	3187.07	5326.37
Median (min; max)	6708.80 (3934.7; 12998.6)	2823.00 (1148.0; 9989.0)	4807.09 (1148.0; 12998.6)
Other			
N	4	2	6
CV%	29.234	53.372	37.159
Geom. mean	2666.65	3257.38	2850.58
Median (min; max)	2618.59 (2066.7; 3709.4)	3517.50 (2190.0; 4845.0)	2659.69 (2066.7; 4845.0)
North America (US)			
N	3	1	4
CV%	58.015	-	46.861
Geom. mean	3336.60	3956.38	3481.79
Median (min; max)	3449.00 (1764.0; 6105.5)	-	3702.69 (1764.0; 6105.5)
South America (Brazil)			
N	6	2	8
CV%	36.413	53.372	42.672
Geom. mean	2274.10	3257.38	2487.85
Median (min; max)	2174.40 (1220.5; 3709.4)	3517.50 (2190.0; 4845.0)	2215.50 (1220.5; 4845.0)
Africa (South Africa)			
N	6	3	9
CV%	51.759	100.919	63.086
Geom. mean	6885.75	3187.07	5326.37
Median (min; max)	6708.80 (3934.7; 12998.6)	2823.00 (1148.0; 9989.0)	4807.09 (1148.0; 12998.6)
Boosted PI: ATV/rtv			
N	1		1
CV%	-		-
Geom. mean	6105.50		6105.50
Median (min; max)	-		-
Boosted PI: DRV/rtv			
N	6		6
CV%	75.629		75.629
Geom. mean	4061.24		4061.24
Median (min; max)	4534.20 (1220.5; 11815.4)		4534.20 (1220.5; 11815.4)

Table 10: Intensive Pharmacokinetics - ETR AUC12h (ng*h/mL) by Subgroup; ITT - Recommended Dose (Study TMC125 C234)

	≥2 to <6 years (N=20)	≥1 to <2 years (N=6)	All Subjects (N=26)
Boosted PI: LPV/rtv			
N	8		8
CV%	86.318		86.318
Geom. mean	3448.27		3448.27
Median (min; max)	3289.19 (2066.7; 12998.6)		3289.19 (2066.7; 12998.6)
Combination of both			
N	1		1
CV%			
Geom. mean	3129.38		3129.38
Median (min; max)			
Dispersed in liquid			
N	11	5	16
CV%	46.127	48.529	45.446
Geom. mean	2921.49	2671.39	2840.92
Median (min; max)	3449.00 (1220.5; 6105.5)	2823.00 (1148.0; 4845.0)	3136.00 (1148.0; 6105.5)
Swallowed whole			
N	3	1	4
CV%	20.377	-	17.886
Geom. mean	10976.33	9989.00	10720.71
Median (min; max)	11815.38 (8610.5; 12998.6)	-	10902.19 (8610.5; 12998.6)

N: number of subjects with data

The mean ETR PK parameters on the recommended dose were not different between males and females (p=0.773).

The mean ETR PK parameters on the recommended dose were numerically higher in black or African American children compared to the other race categories; however, this was not statistically significant (p=0.094). Similarly, by region, the mean ETR PK parameters were numerically highest in the children from Africa, followed by North America, and lowest in the children from South America; this was not statistically significant (p=0.066). The mean ETR PK parameters on the recommended dose were numerically higher in children with DRV/rtv as boosted PI in their regimen, compared with LPV/rtv, though not statistically different (p=0.612).

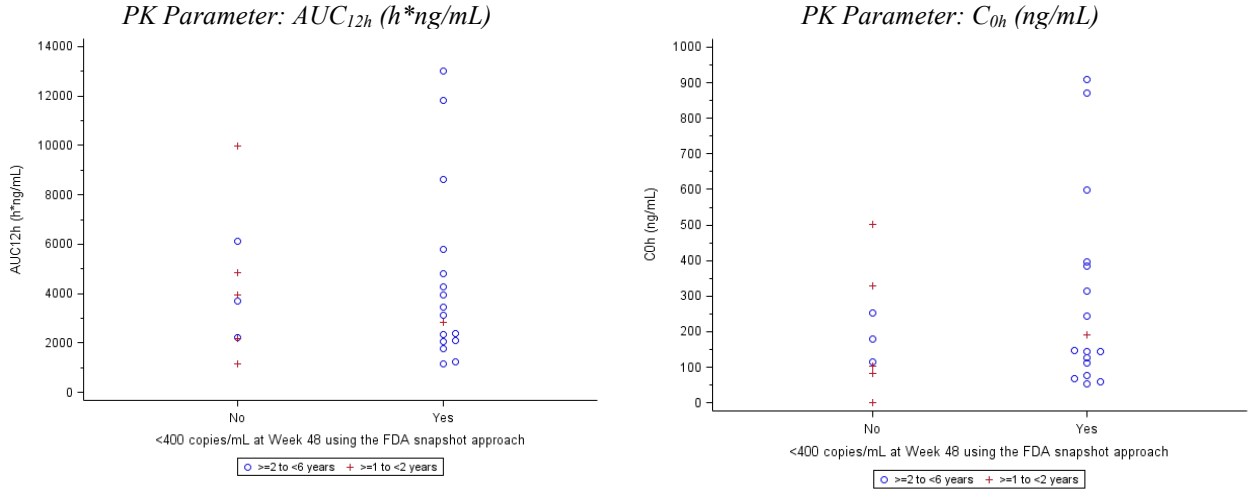
The mean ETR PK parameters on the recommended dose were statistically higher in children who swallowed the tablets whole compared to those who took the tablets dispersed in liquid (p<0.001). It should be noted that there were only 4 children with intensive PK on the recommended ETR dose who swallowed the tablet whole.

- PK/PD relationships

There was no clear relationship between the ETR PK (steady-state PK for each subject at the intensive PK visit) and virologic response (viral load <400 c/ml at Week 48 with FDA snapshot approach; PDVF). The ranges of ETR exposures in subjects with or without virologic response largely overlapped. Also for the ETR PK parameter quartile PK/PD analysis (FDA Snapshot, TLOVR), there was no clear trend for a PK/PD relationship.

Figure 1: Scatterplots of Selected PK Parameters (Intensive PK Visit) by Virologic Response (FDA Snapshot Approach, <400 HIV-1 RNA copies/mL at Week 48) (Study TMC125 C234)

ITT Population



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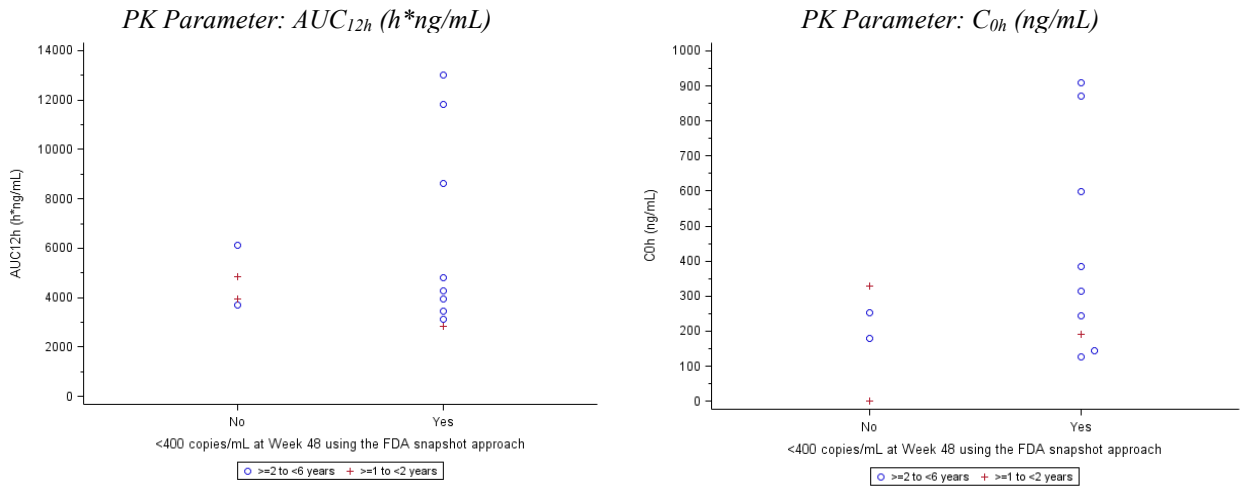
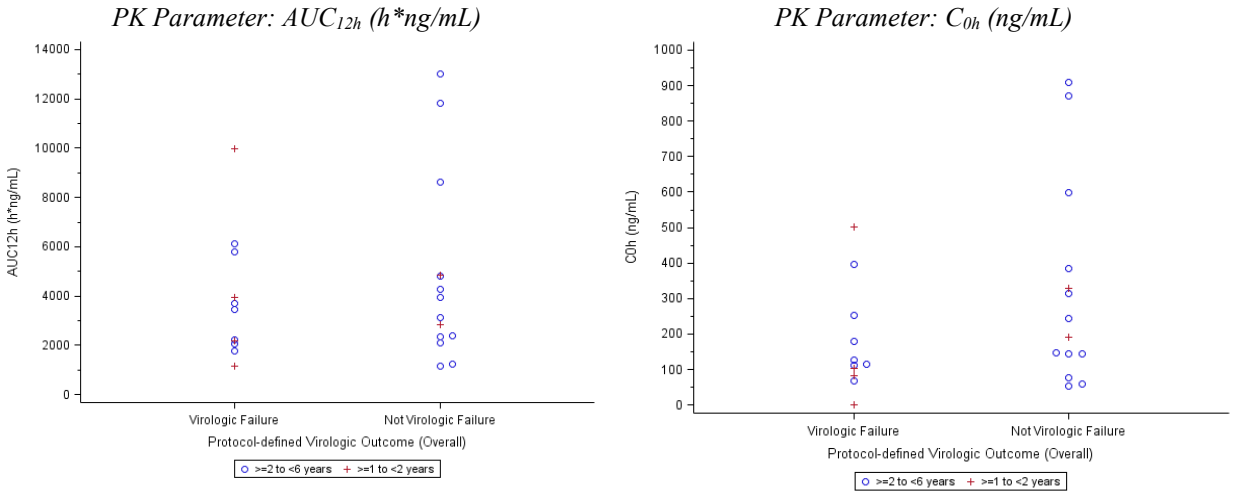


Subject [redacted] had diarrhea before and during PK assessments; excluded from PK analyses
For subjects with multiple PK parameters on different doses, the PK parameters on the recommended dose are used, and when not available, the PK parameters on the lowest dose.

Cross reference: GPK05a and GPK05b

Figure 2: Scatterplots of Selected PK Parameters (Intensive PK Visit) by Protocol-defined Virologic Failure (Overall Assessment) (Study TMC125-C234)

ITT Population



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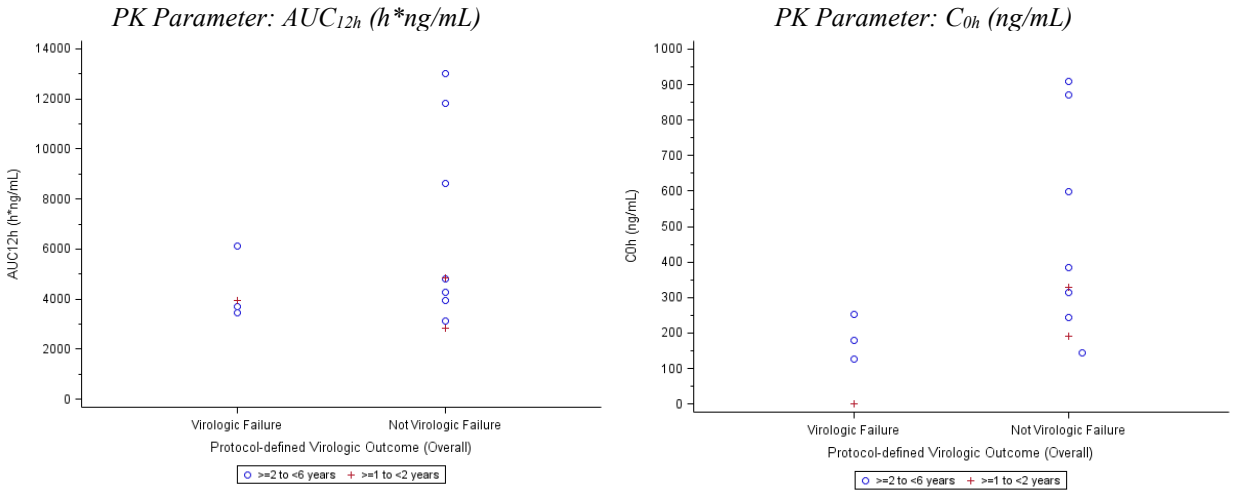


For the criteria of protocol-defined virologic failure (ie, lack of virologic response or virologic rebound), Subject [redacted] had diarrhea before and during PK assessments; excluded from PK analyses
For subjects with multiple PK parameters on different doses, the PK parameters on the recommended dose are used, and when not available, the PK parameters on the lowest dose.

Cross reference: GPK05c and GPK05d

Figure 3: Bar Charts of the Proportion of Virologic Response (Sanpshot) by ETR PK Quartiles; ITT (Study TMC125C234)

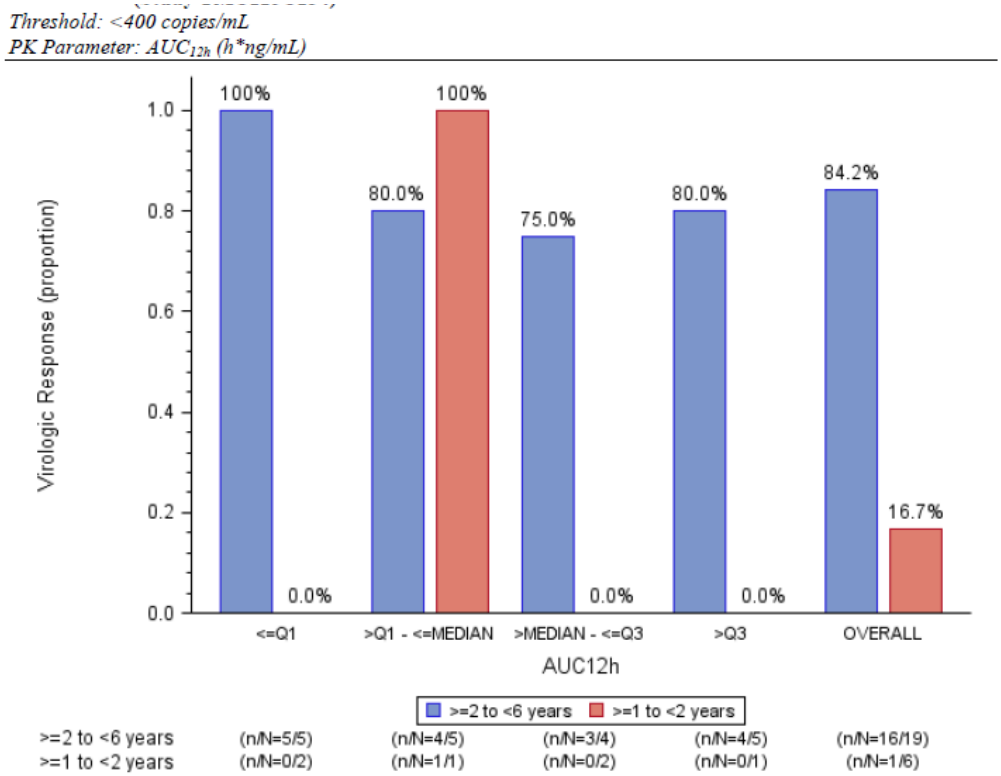
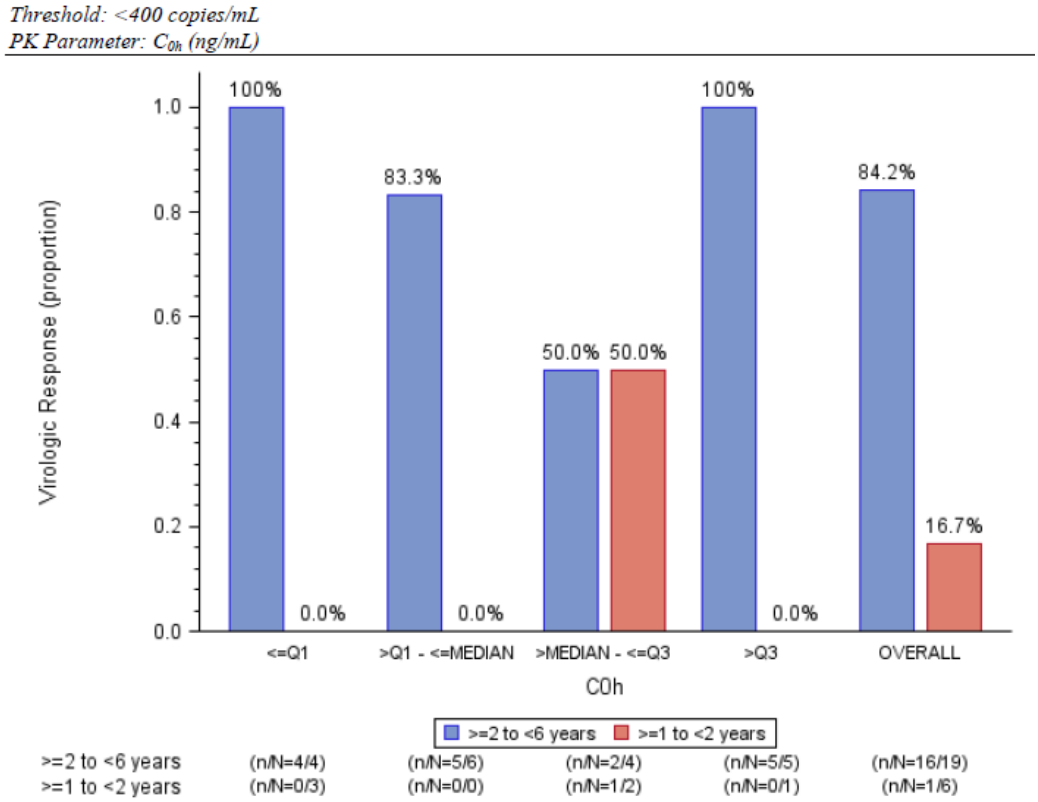


Figure 4: Bar Charts of the Proportion of Virologic Response (Sanpshot) by ETR PK Quartiles; ITT (Study TMC125C234)



N: number of subjects with data, n: number of subjects with that observation
Subject had diarrhea before and during PK assessments; excluded from PK analyses
For subjects with multiple PK parameters on different doses, the PK parameters on the recommended dose are used and when not available, the PK parameters on the lowest dose
C_{0h}(ng/mL): Q1=101.9; median=146; Q3=330

One subject in Cohort II with virologic failure had ETR pre-dose concentrations below the detection limit at the intensive PK visit; while the C12h was 159 ng/mL, which is an indication of suboptimal adherence to ETR prior to the intensive PK visit even though non-adherence was not reported.

No clear relationship was observed between ETR PK and the occurrence of selected AEs of interest.

- ETR population PK analysis

The main objective of the current analysis is to confirm that the dosing regimens selected for the administration of ETR to children below 6 years of age that would result in an exposure comparable to that observed in adults.

DATA

For this analysis, all the available rich and sparse PK data obtained from the P1090 study (Week 48 analysis cut-off date July 12, 2018) were added to existing data from historical paediatric studies. These historical data consisted of richly sampled PK data collected from children (≥6 to <18 years) in TMC125-C1262 and sparsely sampled PK data collected from children (≥6 to <18 years) in TMC125-C2133. The studies included in the NONMEM data file are summarized in Table 11.

Table 11: Overview of Studies Included in the Population PK Analysis

	Study 1 TMC125-C216	Study 2 TMC125-C213	Study 3 P1090
Type of subjects	**Paediatric**	**Paediatric**	**Paediatric**
	≥6-<18 y	**≥6-<18 y**	**≥6-<18 y**
No. of subjects with PK data available	41	101	26
Dose	100, 125, 150, 175 or 200 mg BID (based on weight)	100, 125, 150, or 200 mg BID (based on weight)	75, 100 or 200 mg BID (based on weight)
Route of administration	Oral	Oral	Oral
No of samples per subject	9 per (rich) sampling occasion	1 to 2 per (sparse) sampling occasion	7 per rich sampling occasion, 1 per sparse sampling occasion.
Sampling time (h)	Pre-dose, 1, 2, 3, 4, 6, 8, 10 and 12h post-dose	Week 4: 4h post dose; Week 48: pre-dose and at least 1h post-dose; Other visits: any time point	Rich sampling occasion: pre-dose, 1, 2, 4, 6, 8 and 12h post dose; Other visit: any time point
Limit of Quantification	2.00 ng/mL	2.00 ng/mL	5.00 ng/mL

After data exploration of the pooled dataset, selected complete subject's (ID) data were excluded as the data resulted in an incomplete pharmacokinetic-time profile. Additionally, some occasion data for several subjects (OID) were excluded from the pooled dataset as they were not in line with other data. In addition, some (4) subjects had inconsistent data across their entire concentration-time profile and were excluded. Individual data from one subject were excluded as the subject's data resulted in a very low exposure (~4% of target AUC), as this subject suffered from diarrhoea on the days before and the day of the pharmacokinetic sampling and, in addition, there were uncertainties regarding the conditions of collection/storage of PK samples for this subject.

A summary of the final dataset (number of patients, samples) and subject age and weight is presented in Table 12.

Table 12: Demographics and characteristics of Pooled Data

Study No	Pooled	P1090	TMC125-C126	TMC125-C213
N Individuals	127	26	41	60
Observations	947	362	368	304
Rich Profiles	78	37	41	0
Sparse samples	423	119	0	304
Age (years)				
Mean (SD)	10.6 (4.31)	3.9 (1.46)	12.0 (2.99)	12.5 (2.86)
Median	11.0	4.1	11.1	12.4
Range	1.5-18.0	1.5-6.0	6.9-18.0	6.4-17.6
Weight (kg)				
Mean (SD)	34.7 (16.01)	15.0 (3.95)	39.9 (13.64)	39.8 (14.11)
Median	32.0	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. Study C213 and C126 used screening values, P1090 used covariate values at
the first visit

METHODS

A paediatric population PK model for ETR was previously established and was used as a starting model for this analysis. This prior model consists of a one-compartment model with a zero-order input into the depot compartment, after a lag time, followed by a first-order absorption process from depot to central compartment, and a first order elimination. The parameter estimates are shown in Table 13. Inter-individual variability (IIV) was introduced on the apparent clearance CL/F, apparent central volume V/F and absorption rate KA. Weight (WT) was included as a covariate on both CL/F and V/F as presented in Table 13.

$$(CL/F)_i = TVCL \cdot \left(\frac{WT_i}{70}\right)^{\gamma CL} \cdot \exp \eta_i$$

$$(V/F)_i = TVV \cdot \left(\frac{WT_i}{70}\right)^{\gamma CL} \cdot \exp \eta_i$$

Table 13: Parameter Estimates of ETR for the Prior Model

Parameter (unite)	Population Mean Estimate	Relative Standard Error (%)	Interindividual Variability (%CV)	Relative Standard Error (%)
CL/F (L/h)	65	0.00044	62.2a	0.00014
V/F (L/h)	1660	0.0016	68.0a	0.0013
KA (h^{-1})	10.2	0.0029	149	0.00012
D1 (h)	2.05	0.00016	-	
ALAG1 (h)	0.954	0.0013	-	
Allometric exponent: WT on CL/F	0.75	Fixed	-	
Allometric exponent: WT on V/F	1	Fixed	-	
Residual error (CV%)	35	0.00016		

a: Correlation between the variance estimates of apparent clearance and apparent central volume estimated at 0.56

The prior population PK model was used as a starting point for the current analysis. Based on the empirical Bayesian estimates of pharmacokinetic model parameters, the P1090 subjects were estimated, the model was then to be reparametrized before further model development. All analyses were performed using NONMEM version 7.4.1 with an Intel® Fortran 64 compiler Version 11.1. Data handling, graphical evaluations and data simulations were done 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. During model selection, this estimation step was followed by the importance sampling IMP step to improve the estimations of the Objective Function Value (OFV). Graphical techniques were used to assess the fit of the model to the data.

Since the main objective is to confirm the recommended ETR dose selected for the paediatric population, the only additional continuous covariate investigated was AGE, as WT was already present in the model through the allometric scaling model. Age effects were empirically introduced using the function:

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

In addition, categorical covariates mode of drug administration (FORM: tablets swallowed whole or dispersed) and study (STU) were investigated by addition of the covariate to the model using additional fixed effects for the groups of interest.

To capture differences between the sparse sampling data and the multiple rich PK profiles of the P1090 subjects, inter-occasion variability (IOV) was introduced.

Evaluation of the proposed ETR dosing regimen was performed by estimating the probability that the typical exposure/AUC lies in the target range (80% to 150% of the geometric mean adult AUC). This was evaluated across the weight and dose range of interest, ie, 5 to 35 kg and 25 to 200 mg bid, respectively. To this end, the standard error (SE) of the AUC estimate (ie, the extent to which the AUC estimate is likely to deviate from the true AUC) had to be derived. Since the AUC is not directly estimated in the model, the SE of the AUC predictions were obtained as follows. First, a thousand parameter values are sampled form the parameter uncertainty distribution. Next, using the final model (Figures Section 4), the model predicted AUC at steady state for a given dose (DOSE) and weight (WT) is given by:

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

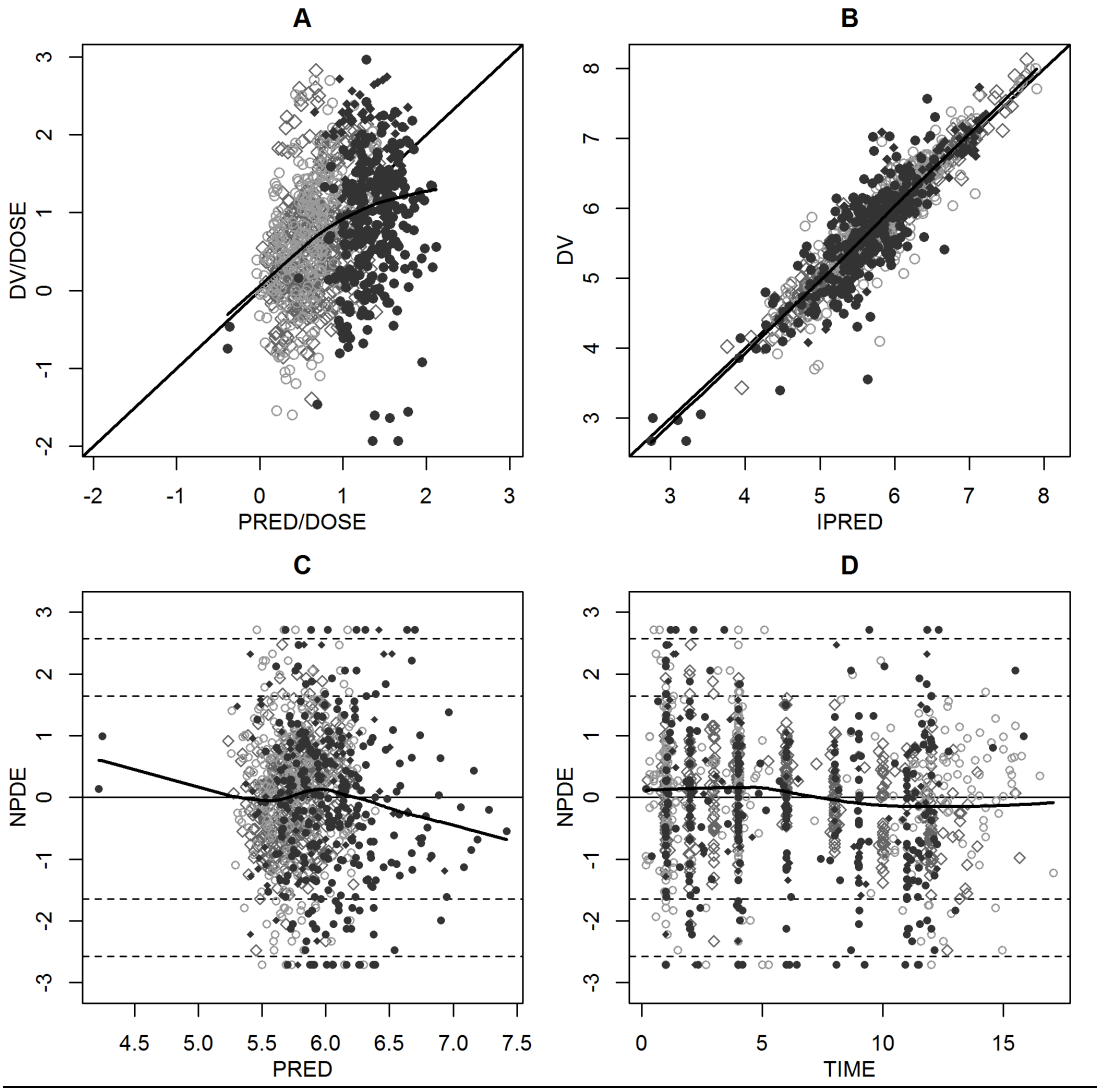
Finally, using these expected values and SEs the probability of the true AUC being in the target 80%-150% range of the adult AUC can be derived, for any dose and any weight, as:

$$P(.8\ AUC_a \leq AUC \leq 1.5\ AUC_a) = \Phi\left(1.50\ AUC_a \mid \mu_{D,W}, \lambda^2_{D,W}\right) - \Phi(.8\ AUC_a \mid \mu_{D,W}, \lambda^2_{D,W})$$

RESULTS

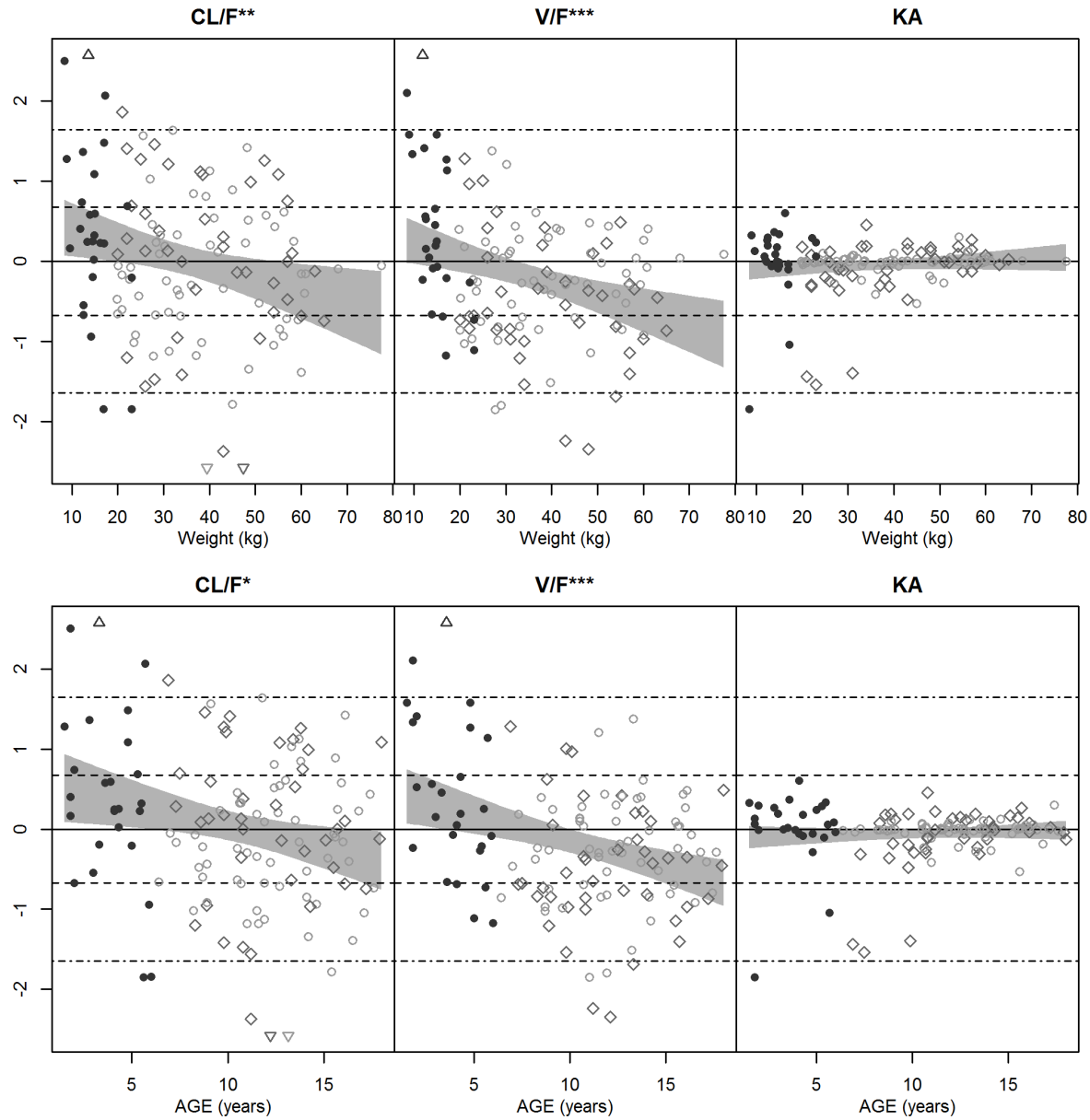
Graphical evaluation of the PRIOR model revealed significant bias in the population predicted exposures for P1090 data compared to data from the original dataset (TMC125-C213, TMC125-C126) and significant trends in the normalized random effects of both CL/F and V/F with respect to the covariates of interest, WT and AGE (nest Figures), suggesting a strong correlation between the covariate effect on CL/F and V/F.

Figure 5: Prior model: Goodness of fit plot



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.

Figure 6: Prior model: Normalized Random effects vs continuous covariates



Normalized random effects (η/√ω) on parameters (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 the 95% CI of the linear regression line. Apparent distortions are due to the log scaling of the x-axis.

To model this combined covariate effect on both CL/F and V/F the PRIOR model was reparametrized such that the IIV on V/F was moved to F1 while keeping the typical value of F1=1. It is important to note that, given the lack of IV data, the absolute oral bioavailability remains undetermined and the reported values of F1 should thus not be interpreted as such. Moreover, although intuitively attractive, the IIV on F1 is not a 'pure' estimate of IIV on the relative oral bioavailability as it also captures the correlations among apparent parameters CL/F and V/F.

The explored hypotheses around the trends observed on the random effects on F1 were that these could be due to differences in the mode of drug administration (tablets swallowed whole for nearly all subjects in TMC125-C213 and TMC125-C126, and dispersed tablets for the majority of subjects in the P1090 study), the subject's age, or the study itself. The model was thus refitted by including each covariate

separately, however, none of the models proved to be significantly better than the others (based on the OFV, in next table).

Table 14: Run Record for Development of the Base Model

Objective Function

RUN	*PROBLEM*	*OFV*	*DOFV*	*Success*	*nInd*	*nRec*
IOV_200f	BASE Model	-960.206	0.000	MINIMIZATION SUCCESSFUL	123	1001
IOV_201	Study Effect on F1	-971.956	-11.750	MINIMIZATION SUCCESSFUL	123	1001
IOV_211	Maturation/AGE effect on F1	-983.626	-23.420	NOT SUCCESSFUL	123	1001
IOV_202	**Final model: Administration Effect on F1**	**-975.790**	**-15.584**	**MINIMIZATION SUCCESSFUL**	**123**	**1001**
IOV_202b	Final model with extreme individuals	-978.389	-18.183	MINIMIZATION SUCCESSFUL	127	1034

Fixed Effects

RUN	*CL*	*V*	*KA*	*D1*	*TLAG*	*F1*	*nAGE*	*h*
IOV_200f	64.6 (-)	905 (-)	1.07 (-)	2.25 (-)	0.303 (-)			
IOV_201	59.7 (10%)	858 (17%)	1.21 (37%)	2.27 (11%)	0.303 (31%)	0.648 (13%)		
IOV_211	54.8 (55%)	793 (63%)	1.21 (40%)	2.27 (12%)	0.292 (33%)	0 (-)	3 (98%)	1.85 (163%)
IOV_202	**61.2 (5%)**	**879 (17%)**	**1.22 (44%)**	**2.29 (11%)**	**0.298 (33%)**	**0.634 (10%)**		
IOV_202b	58.9 (8%)	835 (19%)	1.32 (47%)	2.33 (10%)	0.321 (26%)	0.631 (12%)		

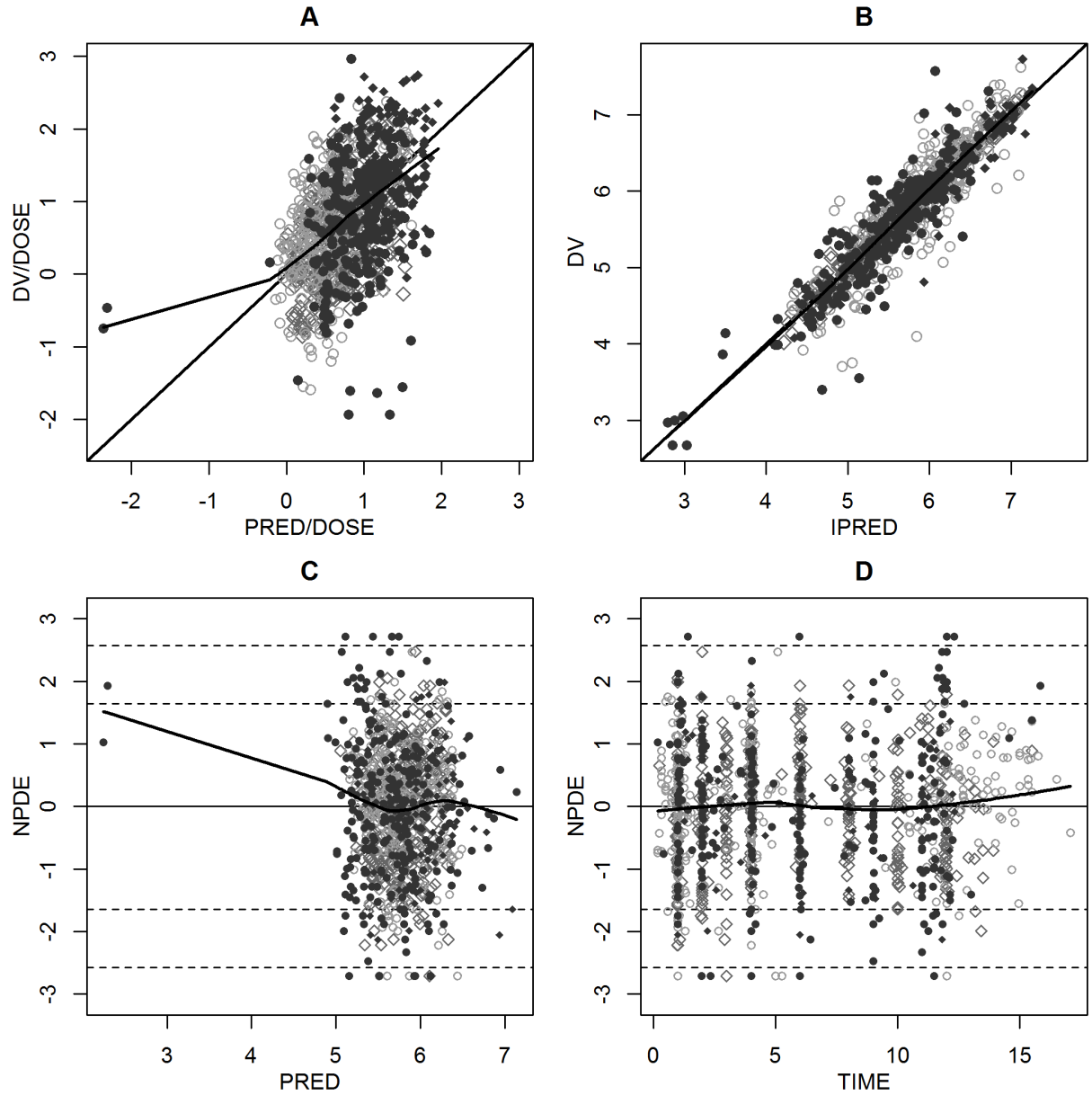
Random Effects and residual error

RUN	IIV CL	IIV KA	IIV F1	IOV F1	EPS1	EPS2
IOV_200f	0.0791 (-)	2 (-)	0.235 (-)	0.301 (-)	0.0387 (-)	0.2 (-)
IOV_201	0.122 (24%)	1.86 (42%)	0.216 (29%)	0.253 (65%)	0.0341 (14%)	0.194 (13%)
IOV_211	0.134 (23%)	1.69 (39%)	0.191 (28%)	0.248 (70%)	0.0339 (14%)	0.192 (13%)
IOV_202	**0.113 (21%)**	**1.81 (37%)**	**0.2 (25%)**	**0.268 (81%)**	**0.0344 (14%)**	**0.197 (13%)**
IOV_202b	0.129 (24%)	1.97 (44%)	0.274 (28%)	0.254 (79%)	0.035 (13%)	0.194 (13%)

The bolded line represents the selected base model.

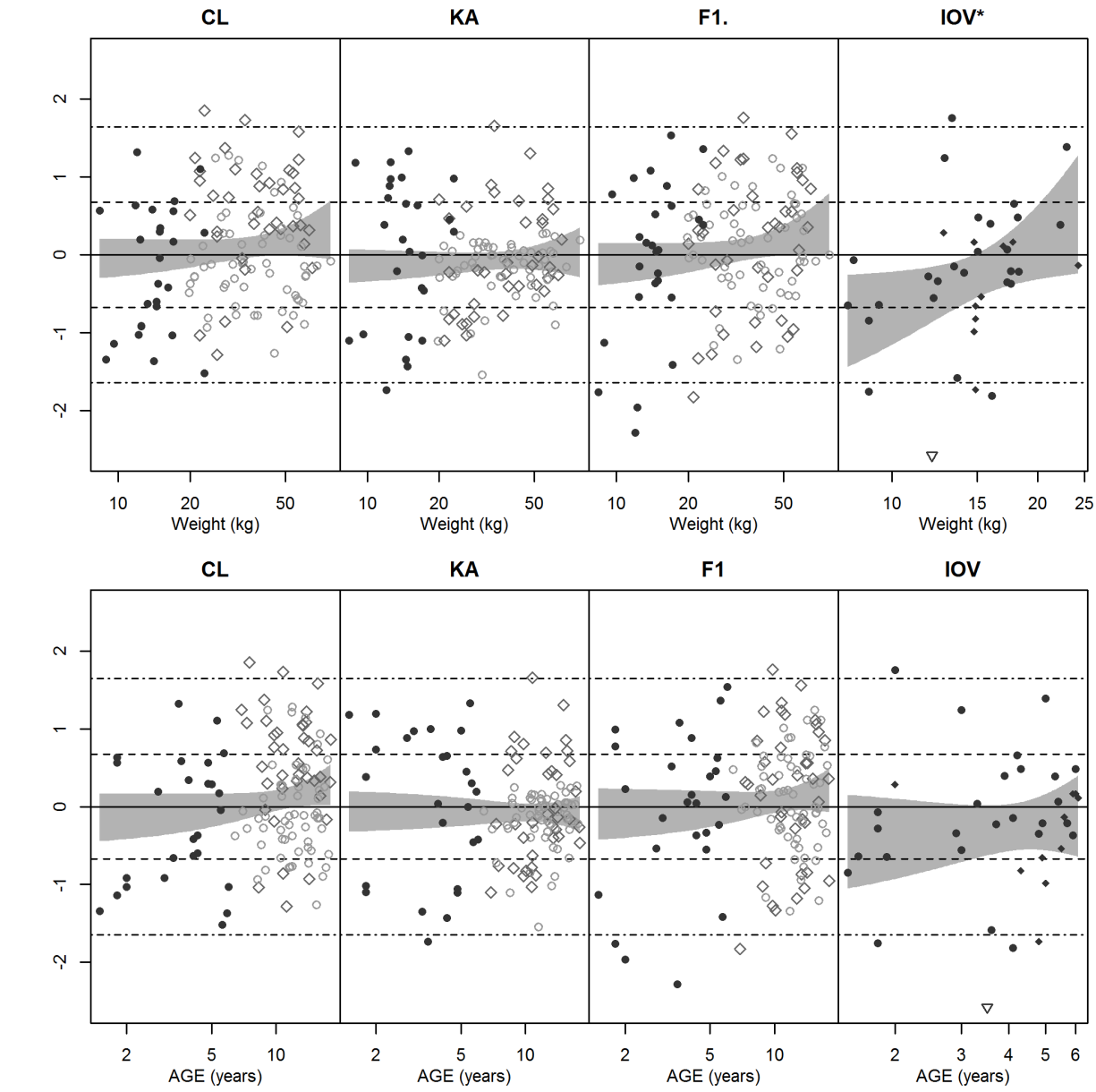
Since within the age range of the current analysis dataset, the potential age-related differences are not likely to be due to the maturation of CYP enzymes, the study or mode of administration are more plausible causes for the observed trends. A prior relative bioavailability study revealed no significant differences in the absorption of ETR when dispersed compared to swallowed whole (TMC125-C173). However, challenges associated with the administration of drugs to the younger age group suggest that they may not always ingest the full ETR dose. Consequently, the effect of mode of administration was incorporated in the model as it is more likely to explain the observed differences that were initially attributed to age. The final model thus includes mode of administration (as observed in the P1090 study) as an effect on F1. As a result (next Figures), no further significant age or weight effects could be detected on the random effects of the model parameters.

Figure 7: FINAL model: Goodness of fit plot



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.

Figure 8: FINAL model: Normalized Random effects vs continuous covariates



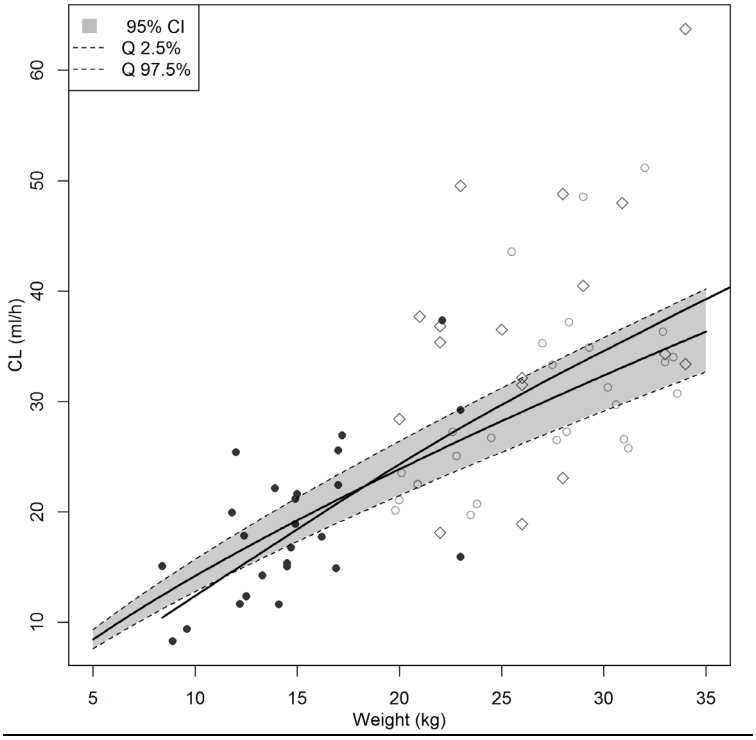
Normalized random effects ($\eta/\sqrt{\omega}$) on parameters (records form the P1090 study presented as dark grey dots, from the TMC125-C213 study as light grey circles and from the TMC125-C126 study as grey diamonds) along with the 95% CI of the linear regression line. Apparent distortions are due to the log scaling of the x-axis.

DOSE SELECTION AND REGIMEN

The goal of this analysis is to evaluate the proposed ETR dosing regimen in the context of population PK modelling, which was done in three steps. For this, it is assumed that the ETR dose is fully administered, i.e., F1=1.

First the model predicted typical clearance, along with the 95% confidence interval, is evaluated over the weight range of interest and overlaid with the individual (post-hoc) clearance estimates along a smoother through those. Although borderline at the lowest bodyweights (corresponding to data from the children with the lower ages <2 years), overall there do not seem to be any significant deviations between the population and post-hoc estimations of the expected (mean) clearance.

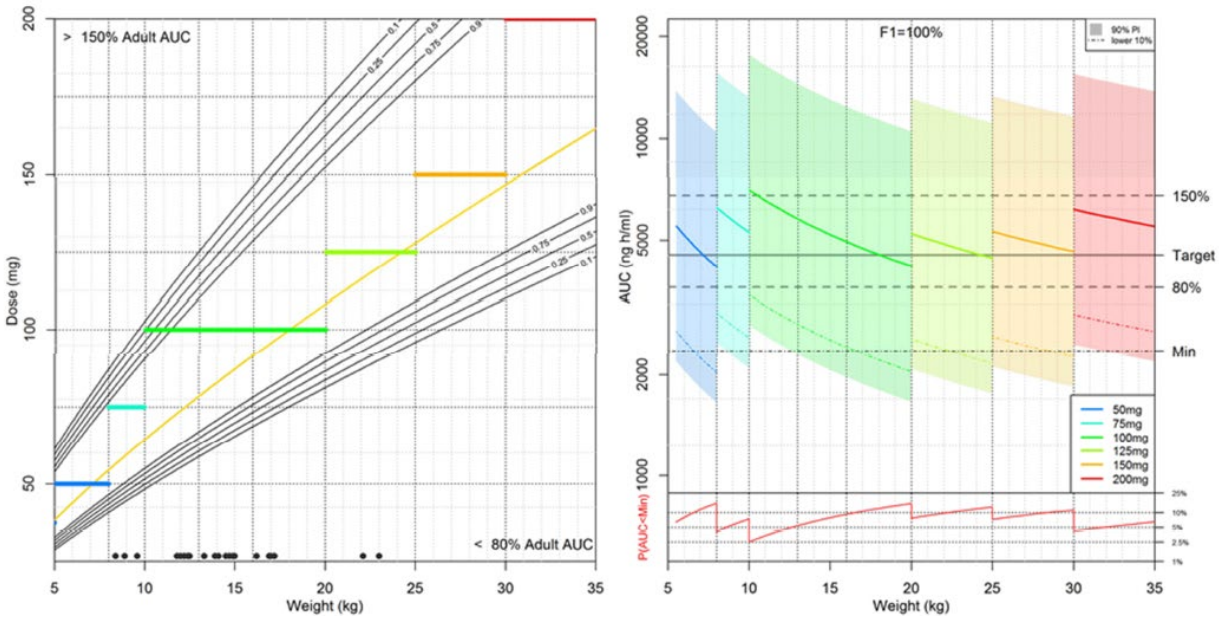
Figure 9: CL vs Weight with confidence interval



Individual estimates of CL vs WT, patients form the P1090 study are 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 the 95%CI of the model-predicted CL and the post-hoc estimate of expected CL as function of WT (loess smoother).

Second, as shown in Figure 4, for any DOSE and WT combination (assuming F1=1) one can derive the estimated AUC, evaluate the extent by which the true AUC is likely to deviate from the estimate and thus how likely the true AUC will fall in the target range (which is denoted as the confidence level as boils down to an integration over the same distribution used to derive the confidence interval).

Figure 10: CL vs Weight with confidence interval



Left Panel: Contour plot. Ranges in between the black solid lines represent the confidence level that the AUC12h for the given ETR dose (represented by the colored horizontal lines) would be within 80% to 150% of that in adults. The black dots represent observed WT for subjects in the TMC125-C234 study.
Right Panel: The solid colored lines represent the mean predicted AUC12h for the given ETR bid dose by body weight; the shaded area represents the 90% prediction interval. The horizontal lines represent the mean (solid line) AUC12h in adults with the 80% to 150% range (dotted lines) and the 'Min' represents the 10th percentile of the adult AUC12h. The red line in the lower part of the right panel represents the expected fraction of subjects below the 'Min'.

For doses already in the approved ETR prescribing information, the confidence level of e.g., 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. Evaluating the ETR recommended dose regimen as per P1090 study (Table 1) across the weight range indicates that confidence levels above 90% are reached across the entire weight range except between 10 and 11.5 kg (Table 15).

Table 15: ETR Dosing Schedule for Cohorts I and II (as of Version 4.0 of the Protocol)

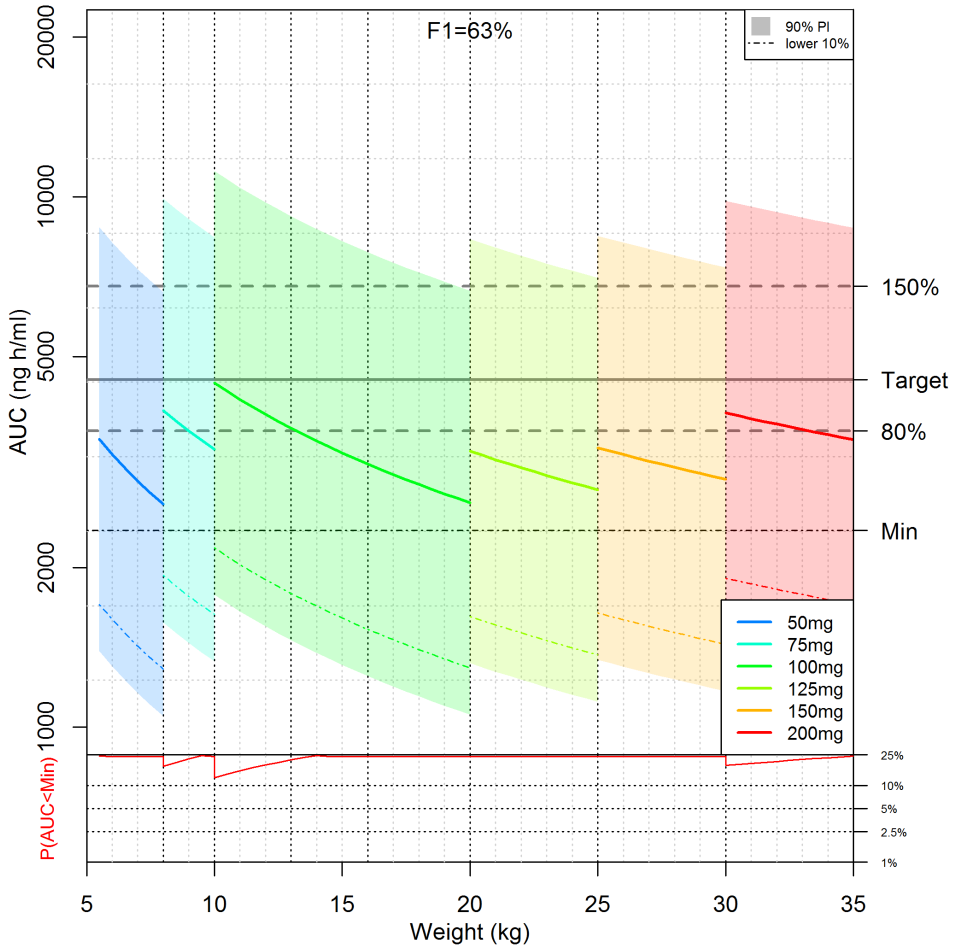
Age	Weight Band (kg)	Target Dose (mg/kg bid)	Actual Dose (mg bid)
≥1 year to <6 years (Cohorts I and II)	<8	8.8	50 mg
	8-<10	8.8	75 mg
	10-<13	8.8	100 mg
	13-<16	6.8	100 mg
	16-<20	5.2	100 mg
	20-<25	5.2	125 mg
	25-<30	5.2	150 mg
	≥30	5.2	200 mg

Available tablets were the 25 mg and 100 mg commercially available dispersible tablets

Finally, for the third step of the dose recommendation, i.e., evaluating the expected AUC range across the population including IIV, the 90% prediction interval as well as the 10th percentile of the AUC for the prosed ETR dose regimen was evaluated across the weight range of interest (Figure 4, right panel). From this, it is apparent that the likelihood of under-dosing becomes low as the doses selected were confirmed to provide an exposure similar or higher than the typical expo sure for adults and the 10% lower bound of the prediction interval rises well above the 10th percentile of the exposures observed in adults (2350 ng.h/mL). These simulations assumed full administration of the ETR dose (F1=1, i.e., no difference in bioavailability between dispersed or swallowed whole). Thus, seemingly omitting the

deviations in F1 (driven by mode of administration) included in the final model. A difference in bioavailability related to suboptimal or incomplete intake of the ETR dose should however not be accounted for by an increase in the recommended dose, as that would lead to higher than anticipated ETR exposures in children that do take the complete ETR dose. One could estimate the exposures of the (potentially incomplete) dispersed administration (assuming F1=63%, Figure 11). The exact F1 is however difficult to predict, and it is anticipated that incomplete dose intake is mostly a problem for younger children, which are on the low end of the body weight range.

Figure 11: AUC predictions including inter-individual variability (Dispersed: F1=63%).



The solid colored lines represent the mean predicted AUC12h (assuming F=63%) for the given ETR bid dose by body weight; the shaded area represents the 90% prediction interval. The horizontal lines represent the mean (solid line) AUC12h in adults with the 80% to 150% range (dotted lines) and the 'Min' represents the 10th percentile of the adult AUC12h. The red line in the lower part of the figure represents the expected fraction (25% indicates ≥25%) of subjects below the 'Min'.

CONCLUSION

The analysis confirms that the ETR recommended doses (as per P1090 protocol version 4.0) would result in comparable exposures to adults, and, therefore, no significant alterations to the dosing regimen described in the protocol are deemed necessary. Given the limited data for low weights, this analysis should be used with caution for the weight band <8 kg.

2.3.3. Discussion on clinical pharmacology

In order to propose an appropriate ETR dose for children aged ≥2 to <6 years, new clinical pharmacology data obtained on week 48 of an ongoing open-label Phase 1/2 clinical study (TMC125-C234) was provided. This study intended to evaluate the steady-state pharmacokinetics (PK) of ETR in combination with an optimized background regimen (OBR) in HIV-1 infected children aged from ≥2 months to <6 years.

A validated analytical method, with slight changes in the linearity limits over time, was used. At the request of the CHMP, the applicant provided the ISR analysis that was undertaken. The total number of analysed samples were 367. The ISR analysis included only 30 samples from Study P1090, slightly below the required 10% of study samples. However, results shown that 96% (29 of 30) of the reanalysis were within the acceptance value of 20%. In this case, even if extra 7 samples were included with negative results, the percentage of correct values would still be above the required ones.

The clinical study was divided in two cohorts. Initially, all subjects from 2 to <6 years of age were treated with ETR 5.2 mg/kg BID for all body weights. However, according to the protocol, a failure to meet the safety and/or PK criteria would result in an adjustment of the (starting) dose.

The mean ETR exposure (AUC and C_{min}) was significantly lower for the first 6 patients included in the mini-cohort I. Notably, 2 subjects required individual dose adjustment because their ETR AUC12h was below 2,350 ng.h/ml. Following the protocol, the evaluation of the mini cohort data resulted in improved dose adjustment with different target dose per weight band.

The MAH proposed to increase ETR dose for subjects weighing <16 kg (6.8 mg/kg BID for subjects 13-<16 kg, and 8.8 mg/kg BID for subjects <13 kg). This dose adjustment for the lower weight ranges was supported by the population PK analysis and intensive PK analysis in subjects receiving the recommended dose of ETR. After that, the geometric mean ETR AUC12h for subjects aged ≥2 to <6 years (Cohort I, N=15) was within the target of 60% to 150% of the geometric mean ETR AUC12h in adults. (See Table 16)

Table 16: Geometric Mean Ratio (Children/Adults) for ETR PK Parameters; ITT - Recommended ETR Dose (Study TMC125-C234)

	Geometric Mean			GMR (90% CI) [a,b]	
	≥2 to <6 years (N=15)	≥1 to <2 years (N=6)	Adults [b] (N=575)	≥2 to <6 years	≥1 to <2 years
AUC_{12h} (h*ng/mL)	3824	3328	4522	0.84 (0.61; 1.16)	0.73 (0.40; 1.35)
C_{0h} (ng/mL)	203	193	297	0.69 (0.46; 1.03)	0.65 (0.31; 1.35)
C_{12h} (ng/mL)	232	198	NA	0.78 (0.53; 1.17)	0.67 (0.35; 1.28)

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.

Table 17: Population pharmacokinetic estimates for etravirine (all doses combined) in treatment-experienced HIV-1 infected paediatric patients 6 years to less than 18 years of age (PIANO 48-week analysis)

Parameter	Etravirine N=101
AUC_{12h} (ng h/ml)	
Geometric Mean ± Standard Deviation	3,729 ± 4,305
Median (Range)	4,560 (62 – 28,865)
C_{0h} (ng h/ml)	
Geometric Mean ± Standard Deviation	205 ± 342
Median (Range)	287 (2 – 2,276)

Therefore, ETR exposure observed in subjects from 2 to 6 years old receiving the recommended doses are close to those observed in older paediatric subjects treated with the approved ETR dose. The same conclusion cannot apply for subjects <2 years old, based on these PK data but also from efficacy data.

As regards the PK values observed in Cohort I, the number of subjects is low, especially subjects in the lower weight range (3 subjects in the 10-<13kg weight range, see baseline data in Section 2.4.1 Main Study). This was considered more worrying that PK data in Cohort II, as it speaks in favour of a potential inadequate ETR dose, with subexposure and increased risk of virologic failure. In Cohort II, the 6 subjects weighted between 8 to 12 kg at baseline (including 3 subjects in the weight range 10-<13 kg). When focusing on the 3 subjects from Cohort II in this weight range (i.e. the heaviest children of this cohort), 2 of them had adequate ETR exposure and 1 subject had suboptimal adherence.

In Cohort I, it is noted that 6 subjects have received a higher-than-recommended ETR dose according to individual PK results, because the exposure (AUC12h) on their initial ETR dose was below the 10th percentile of the adult exposure. This dose adjustment was not well described in the report, and it was not clear how and how much were the dose increased for each individual case

Upon request of the CHMP, the MAH provided the links to the relevant parts of the report describing the dose adjustments on the 5 subjects of Cohort I. The dose adjustments and the reason for dose adjustment (i.e., change in body weight, low exposure or other) were clarified by the MAH, with the reason of being a Therapeutic Drug Monitoring (TDM) dose adjustment.

Table 18 summarizes the doses and corresponding exposures (AUC12h) for subjects in Cohort I and Cohort II who received a dose adjustment, because the exposure (AUC12h) on their initial ETR dose was below the 10th percentile of AUC12h in adults.

Table 18: Dose Adjustment for Subjects with AUC12h below Percentile of Adult AUC12h

Subject	Initial Dose, bid (mg) (AUC_{12h}) (ng h/mL) – Mode of Administration	Initial Dose, bid (mg) (AUC_{12h}) (ng h/mL) – Mode of Administration
Cohort I		
(Subject ID)	100 (1,764) - dispersed	200 (3,469) - dispersed
(Subject ID)	100 (2,241) – dispersed	150 (3,235) - dispersed
(Subject ID)	100 (2,067) – dispersed	150 (10,722) - dispersed
(Subject ID)	100 (1,221) - dispersed	200 (1,991) - dispersed 300 (4,149) - dispersed

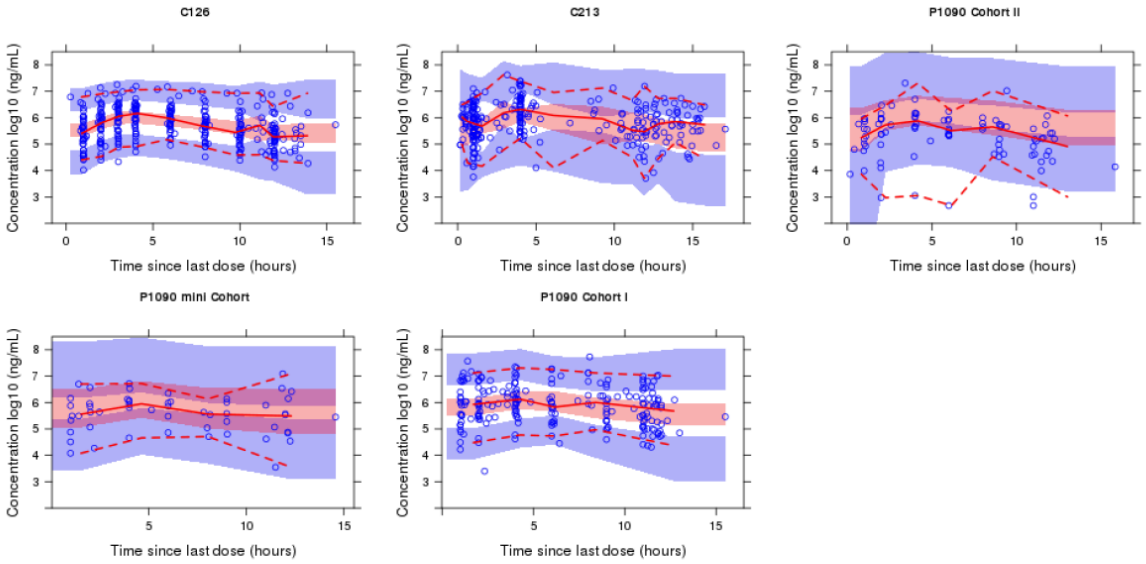
Subject	Initial Dose, bid (mg) (AUC_{12h}) (ng h/mL) – Mode of Administration	Initial Dose, bid (mg) (AUC_{12h}) (ng h/mL) – Mode of Administration
(Subject ID)	100 (2,108) – dispersed	150 (5,763) – dispersed
Cohort II		
(Subject ID)	75 (1,148) - dispersed	200 (2,844) – dispersed
(Subject ID)	75 (2,190) – dispersed	100 (2,828) - dispersed

Regarding the PopPK analysis, a prior model was initially used. However, graphical evaluation of the PRIOR model revealed significant bias in the population predicted exposures for P1090 data compared to data from the original dataset (TMC125-C213, TMC125-C126). As such, since weight was already included in the model, the effect of age, mode of administration and study were further investigated, and the final model included the mode of administration (as observed in the P1090 study) as an effect on Bioavailability.

This model seemed appropriate for the purpose, with acceptable goodness of fit plots and parameter estimates. However, the CHMP requested the applicant to provide visual predictive checks (VPCs) plots by study and cohort (in study P1090), as well as the parameters evaluation by bootstrapping for further assessment of the model quality.

Upon request of the CHMP, the MAH presented VPCs for studies TMS125-C234, TMC125-C213, and TMC125-C234 (Figure 12):

Figure 12: Visual Predictive Checks-Observed ETR Plasma Concentrations for Studies TMC125-C126, TMC125-C213 and TMC125-234 (Paediatrics)



The observed ETR plasma concentrations are represented by blue circles.
The solid red line represents the median observed ETR plasma concentration, and the semitransparent red area represents a simulation-based 95% confidence interval for the median.
The observed 5% and 95% percentiles are presented with dashed red lines, and the 95% confidence intervals for the corresponding model predicted percentiles are shown as semitransparent blue areas.

Figure 12 indicates that the observed ETR plasma concentrations for the three studies are within the predictions of the popPK model. For Cohort II of Study TMC12 5-C234, the observed ETR plasma concentrations are on the low side of the predictions. However, INTELENCE is not indicated for subjects aged ≥1 to <2 years or <10 kg. In addition, intake issues reported in Cohort II may have contributed to the lower observed values.

In addition, the bootstrap results also confirmed the adequacy of the estimated Theta's and Omega's (see tables in Figure 13) for the intended use and population.

Figure 13: Estimated THETA's and OMEGA's

1 THETA's

	EST	RSE	mean	SE	median	bias
CL	61.20	3.02	61.19	3.41	60.92	0.19
V	879.00	150.00	868.53	75.61	864.38	26.53
KA	1.22	0.54	1.23	0.36	1.22	0.10
D1	2.29	0.26	2.28	0.20	2.28	-0.10
TLAG	0.30	0.10	0.30	0.09	0.30	-0.02
F1	0.63	0.06	0.64	0.09	0.64	-0.13

Table 1.1: Fixed Effects: Model vs Bootstrap estimates

	0.05%	0.5%	2.5%	5%	95%	97.5%	99.5%	99.95%
CL	49.78	52.22	54.32	55.39	66.61	67.68	69.78	72.22
V	593.19	647.23	693.80	717.62	966.38	990.20	1036.77	1090.81
KA	-0.05	0.21	0.43	0.54	1.72	1.83	2.05	2.31
D1	1.73	1.87	1.99	2.06	2.70	2.77	2.89	3.03
TLAG	0.02	0.08	0.14	0.17	0.46	0.49	0.54	0.61
F1	0.47	0.54	0.59	0.62	0.92	0.95	1.01	1.07

Table 1.2: CI quantiles based on SE Bootstrap estimates

	0.5%	2.5%	5%	95%	97.5%	99.5%
CL	53.04	54.98	55.93	67.28	68.39	70.35
V	676.72	733.26	755.11	994.46	1030.49	1079.27
KA	0.48	0.63	0.70	1.84	2.01	2.29
D1	1.77	1.90	1.96	2.63	2.69	2.78
TLAG	0.03	0.09	0.14	0.43	0.46	0.51
F1	0.38	0.47	0.49	0.79	0.81	0.86

Table 1.3: Percentiles of Bootstrap estimates

2 OMEGA's

	EST	RSE	mean	SE	median	bias
CL	0.11	0.02	0.11	0.03	0.11	-0.01
KA	1.81	0.66	1.86	0.50	1.80	-0.03
F1	0.20	0.05	0.19	0.04	0.19	-0.09
IOV	0.27	0.22	0.29	0.17	0.25	0.08

Table 2.1: Random Effects: Model vs Bootstrap estimates

	0.05%	0.5%	2.5%	5%	95%	97.5%	99.5%	99.95%
CL	0.01	0.03	0.05	0.06	0.17	0.18	0.19	0.22
KA	0.24	0.60	0.91	1.06	2.72	2.87	3.18	3.54
F1	0.15	0.18	0.20	0.22	0.36	0.37	0.40	0.43
IOV	-0.34	-0.22	-0.12	-0.07	0.48	0.53	0.64	0.76

Table 2.2: CI quantiles based on SE Bootstrap estimates

	0.5%	2.5%	5%	95%	97.5%	99.5%
CL	0.02	0.05	0.06	0.16	0.17	0.19
KA	0.93	1.08	1.16	2.83	3.05	3.58
F1	0.10	0.12	0.13	0.27	0.29	0.32
IOV	0.06	0.09	0.11	0.60	0.77	1.06

Table 2.3: Percentiles of Bootstrap estimates

Based on this model, and assuming a F1 of 1, evaluation of 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. In addition, the likelihood of under-dosing becomes low as the doses selected were confirmed to provide an exposure similar or higher than the typical expo sure for adults and the 10% lower bound of the prediction interval rises well above the 10^{th} percentile of the exposures observed in adults (2350 ng.h/mL). However, this is not the case when considering a suboptimal or incomplete intake of the ETR dose. In this case, and assuming a F1=63% (related to the administration as dispersed tablets), the number of expected subjects below the 10^{th} percentile of the exposures observed in adults (2350 ng.h/mL) was higher than 25% in all weight classes.

Based on the popPK model, and after accounting for the allometric effect of weight for children, no significant effect of age could be identified. This seems acceptable, as no special maturation effect is expected for the ≥2 to <6 years age band. The ETR dose recommendations are, thus, specified by weight-band. The race and region effects on the PK of ETR were all non-significant, in line to what was already described for adults. Finally, no statistically significant differences were observed in the PK of ETR by different combinations of OBR (rtv-boosted atazanavir, rtv-boosted DRV or rtv-boosted LPV). This goes in line with the described lack of effect for adults in similar situation, as described in the SmPC.

The CHMP raised the issue that the mean ETR PK parameters on the recommended dose were statistically higher in children who swallowed the tablets whole compared to those who took the tablets dispersed in liquid ($p<0.001$). It should be noted that there were only 4 children with intensive PK on the recommended ETR dose who swallowed the tablet whole.

The CHMP requested the MAH to provide further analysis of the adequacy of the formulation for the younger population. This topic is discussed below in Section 2.4.2 – Discussion on clinical efficacy

2.3.4. Conclusions on clinical pharmacology

Overall, based on the available PK data, the proposed ETR may allow to achieve adequate ETR exposure for subjects between 2 to 6 years old and weighing at least 10 kg, having in mind that adherence is a crucial parameter.

The PopPK analysis confirmed that the ETR recommended doses (as per P1090 protocol version 4.0) would result in comparable exposures to adults, and, therefore, no significant alterations to the dosing regimen described in the protocol are deemed necessary. Given the limited data for low weights, this analysis should be used with caution for the weight band <8 kg.

2.4. Clinical efficacy

2.4.1. Main study

Study TMC125-C234 (IMPAACT P1090)

Study TMC125-C234 (IMPAACT P1090) is a Phase 1/2 study which evaluates the pharmacokinetics, safety, tolerability, and antiviral activity of ETR in HIV-1 infected paediatric subjects aged 2 months to <6 years who were on a virologically failing ARV regimen (containing ≥3 ARVs) for at least 8 weeks or on a treatment interruption of at least 4 weeks with a history of virologic failure while on a combination ARV regimen (containing ≥3 ARVs). The main results from the Week-48 of this study are summarized in this document.

Methods

Study design

This is a Phase I/II, multicenter, open label 48 week study of ETR in combination with at least 2 active agents (a boosted PI and at least one additional active drug), for treatment experienced HIV-1-

infected infants and children ≥ 2 months to < 6 years separated by age into three cohorts (see Table 19).

Table 19: Description of Cohorts

					Anticipated Accrual		
Cohort	**Description of Subject**	**Drug Regimen**	**Phenotyping / Genotyping Information**	**Comments**	**Mini Cohort**	**To complete a full cohort**	**Total cohort size**
I	≥ 2 year to < 6 years who are treatment experienced	ETR + OBR (1 active boosted PI+ at least 1 other active drug)	HIV genotype and phenotype assays should be performed in real time and results available prior to starting study drug	Subjects will be enrolled providing the phenotypic assay results indicate a < 10 fold change in sensitivity to ETR	6	6	Up to 18
II	≥ 1 year to < 2 years who are treatment experienced	ETR + OBR (1 active boosted PI+ at least 1 other active drug)	HIV genotype and phenotype assays should be performed in real time and results available prior to starting study drug	Subjects will be enrolled providing the phenotypic assay results indicate a < 10 fold change in sensitivity to ETR	6	6	12
III	≥ 2 months to < 1 year who are treatment experienced1	ETR + OBR (1 active boosted PI+ at least 1 other active drug)	HIV genotype and phenotype assays should be performed in real time and results available prior to starting study drug	Subjects will be enrolled providing the phenotypic assay results indicate a < 10 fold change in sensitivity to ETR	6	6	12

1. Subjects below 6 months of age will only be enrolled upon availability of initial safety and PK data from subjects between 6 months and 1 year of age.

Each cohort was to begin enrolment into an initial mini cohort of 6 subjects. Once the PK and safety data were found to be acceptable (as defined per protocol), enrolment was to be continued at the same ETR dose to complete enrolment of the remaining subjects in that age cohort (for Cohort I: at least 12 subjects), and the mini-cohort of the next age cohort was to be opened for enrolment. Subjects in the specific cohort were to continue their treatment at the selected dose, with the aim to have at least 12 evaluable subjects whose initial dose was the final recommended ETR dose for their age cohort according to PK and safety criteria.

A dose of ETR was considered acceptable if the dose was tolerated (based on the safety criteria) and if the geometric mean ETR AUC12h was between 60% and 150% of the geometric mean ETR AUC12h in HIV-1 infected, ART-experienced adults from the DUET studies (ie, between 2,713 and 6,783 ng*h/mL).

A failure to meet the safety and/or PK criteria would result in an adjustment of the (starting) dose. Subjects already in the (mini-)cohort were to be adjusted to the newly recommended ETR dose if the investigator and protocol team believed this was in the best interest of the subject.

In addition, subjects could have an individual ETR dose adjustment, based on their individual ETR exposure (AUC12h) compared with the adult AUC12h from the DUET studies (ie, the individual ETR AUC12h should be >2,350 ng*h/mL, the 10th percentile of the ETR AUC12h in HIV-1 infected adults).

At the start of the study, all subjects in the first mini cohort (n=6, aged ≥2 to <6 years) were on an ETR dose of 5.2 mg/kg bid. A comparison of the geometric mean ETR AUC12h in the mini cohort with that in adults indicated that it was unlikely that with this ETR dose (5.2 mg/kg bid for all bodyweights), the geometric mean ETR exposure would be within target for the full cohort. A revision of the ETR dosing table was therefore introduced for the remainder of the cohorts as presented below: (see Table 20).

Table 20: ETR Dosing Schedule for Cohorts I and II (as of Version 4.0 of the Protocol)

Age	Weight Band (kg)	Target Dose (mg/kg bid)	Actual Dose (mg bid)
≥1 year to <6 years (Cohorts I and II)	<8	8.8	50 mg
	8-<10	8.8	75 mg
	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

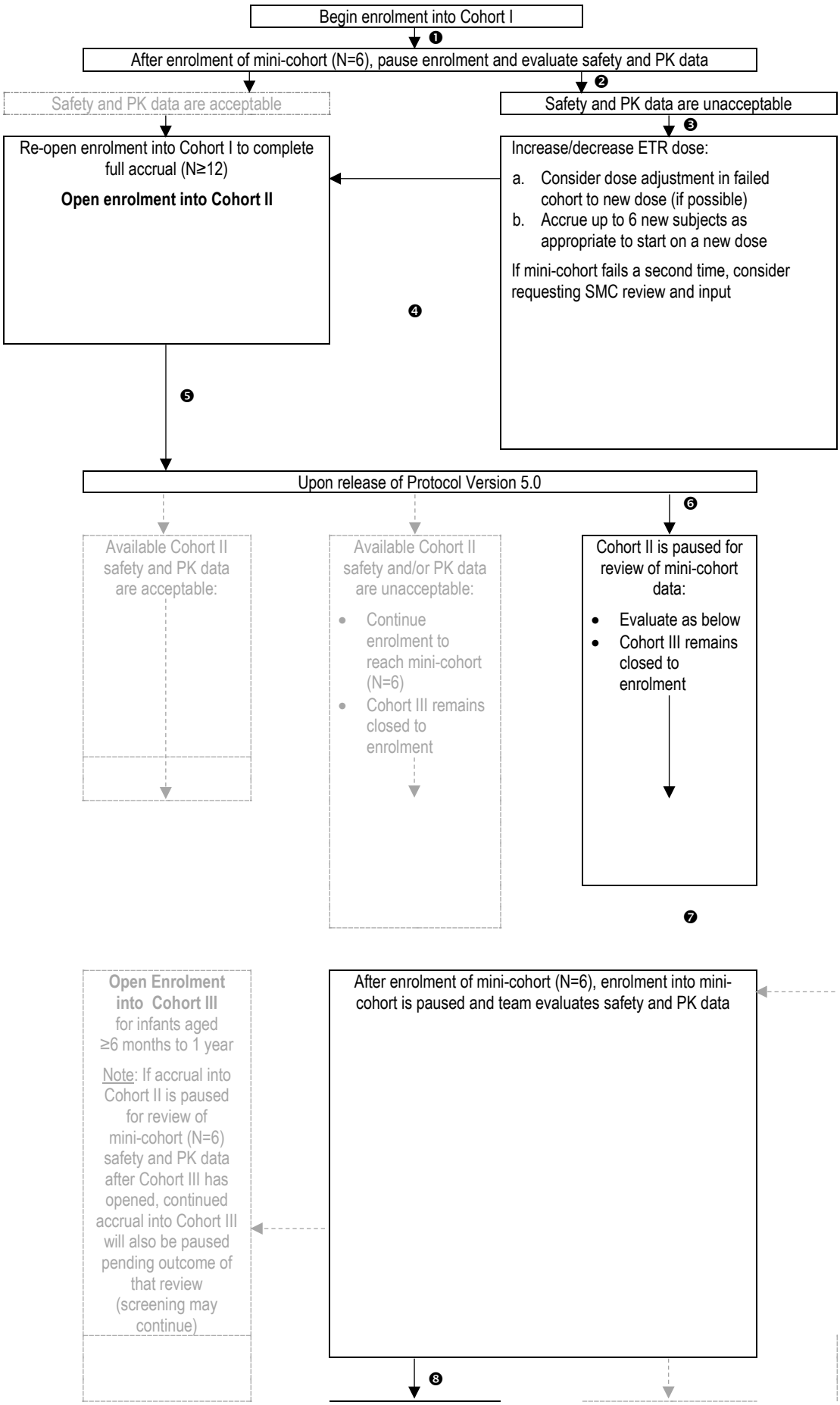
The study consists of a 48-week treatment period with an early study discontinuation visit for subjects who prematurely discontinued, a 4-week follow-up visit for the subjects who discontinued ETR, and a long-term safety follow-up of up to 5 years for the subjects continuing to receive study-provided ETR.

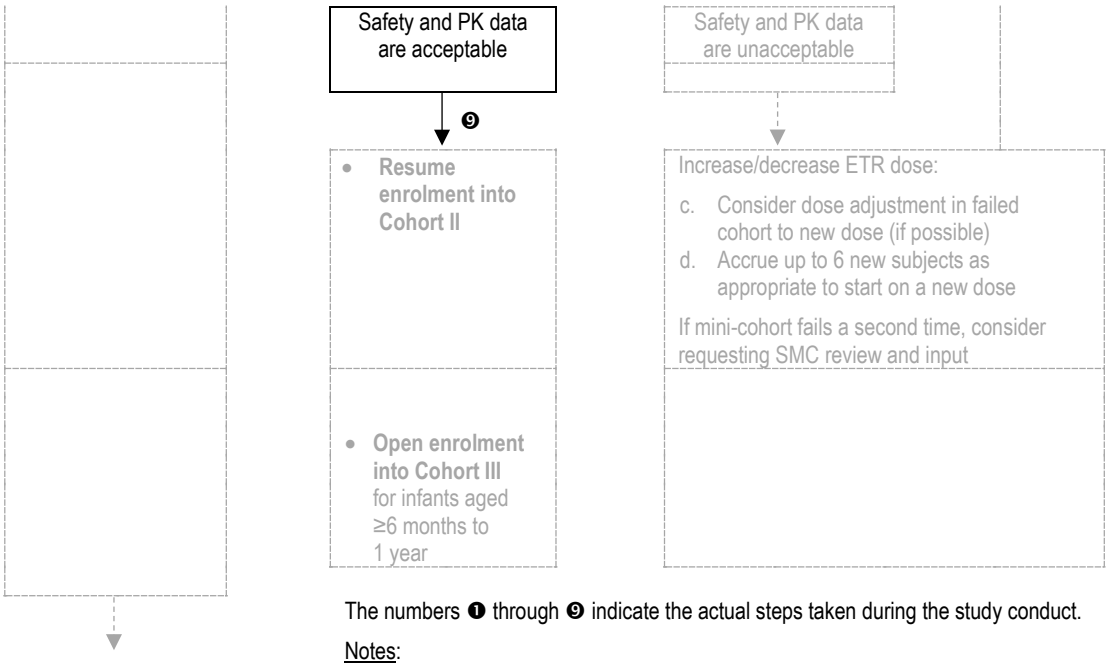
In March 2016 the study protocol was amended by IMPAACT to align with the requirements described in the paediatric investigation plan (PIP) (Decision P/0163/2015) and hence offer the possibility of opening of Cohort III, based on available PK and safety data to ongoing participants, while the first mini-cohort of Cohort II may still be enrolling. This amendment also included a study "go/no-go decision point" which was set 2 years after opening of Cohort II in order to determine whether, based on the examination of accrual rate and all of the relevant safety and pharmacokinetic data, it would be safe and worth to continue the study in an attempt to find an optimal dose for Cohorts II and III.

On 2 October 2017 (2 years after opening of Cohort II), in line with the study protocol, IMPAACT and the Marketing Authorization Holder (MAH) jointly decided to close enrolment in the study. Cohort I had been fully enrolled (N=20), as well as Cohort II (N=6 in the mini-cohort). No patients had been enrolled in Cohort III, as investigators preferred to continue to enroll sequentially. At the decision point, it was deemed unlikely to find subjects for mini-cohort III in a reasonable timeframe and the total of 26 subjects enrolled in the study was considered sufficient to fulfil the PIP requirements and allows a PK and clinical analysis to assess the dose of ETR to be used in HIV-1 infected children aged <6 years.

Results are available from the Week-48 analysis of Study TMC125-C234, which includes all available PK, safety, efficacy, and resistance data from Cohort I (N=20) and Cohort II (N=6) up to the cut-off date of 12 July 2018.

Figure 14: Algorithm for Cohort Management (as of Version 5.0 of the Protocol)


Begin enrolment into Cohort I
❶
After enrolment of mini-cohort (N=6), pause enrolment and evaluate safety and PK data
❷
Safety and PK data are acceptable
Safety and PK data are unacceptable
❸
Re-open enrolment into Cohort I to complete full accrual (N≥12)
Open enrolment into Cohort II
Increase/decrease ETR dose:
a. Consider dose adjustment in failed cohort to new dose (if possible)
b. Accrue up to 6 new subjects as appropriate to start on a new dose
If mini-cohort fails a second time, consider requesting SMC review and input
❹
❺
Upon release of Protocol Version 5.0
❻
Available Cohort II safety and PK data are acceptable:
Available Cohort II safety and/or PK data are unacceptable:
• Continue enrolment to reach mini-cohort (N=6)
• Cohort III remains closed to enrolment
Cohort II is paused for review of mini-cohort data:
• Evaluate as below
• Cohort III remains closed to enrolment
❼
Open Enrolment into Cohort III for infants aged ≥6 months to 1 year
Note: If accrual into Cohort II is paused for review of mini-cohort (N=6) safety and PK data after Cohort III has opened, continued accrual into Cohort III will also be paused pending outcome of that review (screening may continue)
After enrolment of mini-cohort (N=6), enrolment into mini-cohort is paused and team evaluates safety and PK data
❽



The numbers ❶ through ❾ indicate the actual steps taken during the study conduct.

Notes:

❸: Data review of the initial 6 subjects in Cohort I led to an increase in ETR dose (unacceptable PK, acceptable safety data).
❹: A total of 6 new subjects were recruited and started on the new (increased) dose.
❾: On 02 October 2017, enrolment into Cohort II was closed after enrolment of the 6th subject into mini-cohort II (which occurred after the cut-off date for the Week-24 analysis) and it was decided to not open Cohort III; see Section **Error! Reference source not found.**.

SMC: Study Monitoring Committee

Note that gray boxes with dotted lines show the options that were not applicable during the conduct

Study participants

Main inclusion criteria:

- Age ≥ 2 months to < 6 years old at study entry (For subjects who were born at ≤ 37 weeks gestational age, the subject must be at least 12 weeks of age, AND ≥ 46 weeks post-conceptual age at study entry)

- HIV-1 RNA viral load > 1,000 copies/mL

- Treatment experienced children on a failing combination antiretroviral regimen (containing at least 3 ARVs) for at least 8 weeks OR Treatment experienced children on a treatment interruption of at least 4

weeks with a history of virologic failure while on a combination antiretroviral regimen (containing at least 3 ARVs).

- Availability of sufficient active ARV drugs to create an OBR consistent with protocol requirements.

- Ability to swallow ETR whole or dispersed in an appropriate liquid.

Main exclusion criteria:

- Evidence of phenotypic resistance to ETR at screening. Phenotypic cutoffs of > 10 for loss of sensitivity for cohorts I, II, III.

- Diagnosis of a new CDC Stage C.

- Disallowed medications, including: Darunavir use in subjects < 3 years old, Fosamprenavir/ritonavir (etravirine increases fosamprenavir exposure posing a potential safety issue), Maraviroc, Saquinavir/ritonavir, Tipranavir/ritonavir (tipranavir/ritonavir significantly decreases etravirine), Ritonavir, used as sole PI therapy, Unboosted PIs including nelfinavir (drug interaction unknown – etravirine may increase nelfinavir), Other NNRTIs.

Treatments

Study treatment is defined as etravirine (ETR) 25 mg and 100 mg tablets. Both will be provided by the study. ETR will be dosed orally according to the dosing table (Table 21 and Table 22)

Table 21: Dosing Table 1: 1 year – 6 years

Weight Band (kg)	Dose (mg/kg)	Dose (mg)	Number of Tablet(s) to Administer Orally per Dose	Frequency
<8	8.8	50 mg	2 x 25 mg tablet	Twice Daily
8-<10	8.8	75 mg	3 x 25 mg tablet	Twice Daily
10-<13	8.8	100 mg	1 x 100 mg tablet	Twice Daily
13-<16	6.8	100 mg	1 x 100 mg tablet	Twice Daily
16-<20	5.2	100 mg	1 x 100 mg tablet	Twice Daily
20-<25	5.2	125 mg	1 x 100 mg tablet PLUS 1 x 25 mg OR 5 x 25 mg tablets	Twice Daily
25-<30	5.2	150 mg	1 x 100 mg tablet PLUS 2 x 25 mg OR 6 x 25 mg tablets	Twice Daily
≥30	5.2	200 mg	2 x 100 mg tablet OR 8 x 25 mg tablets	Twice Daily

Table 22: Dosing Table 2: 2 months to < 1 year

Weight Band (kg)	Dose (mg)	Number of Tablet(s) to Administer Orally per Dose	Frequency
<6	25 mg	1 x 25 mg tablet	Twice Daily
6<8	37.5 mg	1 and half scored 25 mg tablets	Twice Daily
8-<10	50 mg	2 x 25 mg tablet	Twice Daily
≥10	75 mg	3 x 25 mg tablets	Twice Daily

Note: as of the age of 1 year, doses should be adjusted according to the specific ETR dosing table for 1 year to 6 years (Dosing Table 1)

ETR tablets should be swallowed whole with enough water or other liquid within 30 minutes following a meal. Subjects unable to swallow the tablets whole may disperse the tablets in a container with a minimum of 5 mL (1 teaspoon) of water. One minute should be allowed for the tablet(s) to be dispersed, stirring will aid in the dispersion. The dispersed tablet(s) in water may be further diluted with a beverage (see list below) not to exceed 30 mL (2 tablespoons) total volume. The recommendation for administration to infants is to disperse the tablet in approximately 10 mL of liquid (e.g. formula or milk).

Darunavir 100 mg/mL suspension, darunavir 75 mg tablets, and darunavir 150 mg tablets, will be provided through the study if not reasonably available locally.

Objectives

Primary Objectives:

- To evaluate the steady state pharmacokinetics of ETR in combination with an OBR in HIV-infected children aged ≥ 2 months to < 6 years.

- To determine the safety and tolerability of ETR in combination with an OBR in children aged ≥ 2 months to < 6 years, through 48 weeks of therapy.

- To determine the appropriate dose of ETR in combination of an OBR for children aged ≥ 2 months to < 6 years.

Outcomes/endpoints

Primary Endpoints:

- *Toxicity Endpoints*: Termination from treatment due to a suspected adverse drug reaction (SADR); Adverse events of Grade 3 or higher severity; Death

- *Pharmacokinetic Endpoint*: Failure to meet PK targets: The target geometric mean ETR AUC12h for this study is between 60% and 150% of the geometric mean AUC12h observed in HIV-1-infected treatment-experienced adults from the DUET studies (i.e. between 2713 and 6783 ng•h/mL). For the individual subject management in this study, subjects with an individual AUC12h below the 10th percentile of adult exposure (i.e. <2350 ng•h/mL) will be dose-adjusted in order to meet an AUC12h ≥ 2350 ng•h/mL.

The key efficacy endpoint was defined as the number and percentage of subjects with plasma viral load <400 HIV-1 RNA copies/mL at Week 48 using the FDA Snapshot approach.

Sample size

The sample size for this study was estimated using a PK modelling and simulation approach. A minimum of 12 subjects in each age cohort was deemed sufficient to assess the ETR PK with sufficient precision and to evaluate the safety of ETR in paediatric subjects

Randomisation

Study TMC125-C234 was not a randomized study

Blinding (masking)

Study TMC125-C234 was an open-label study.

Statistical methods

The following analyses to be performed by Janssen R&D are planned in the protocol:

- When at least 12 evaluable subjects in Cohort I have completed the Week-24 assessments or discontinued earlier.

- When at least 12 evaluable subjects in Cohort I have completed the Week-48 assessments or discontinued earlier (current analysis).

- When at least 18 subjects across the age cohorts have completed the Week-48 assessments or discontinued earlier (current analysis).

In addition, a complete data analysis will be performed when the last subject has completed the 5-year follow-up period or discontinued earlier.

Considering the possibility to adjust ETR dose according to individual PK and safety data, the following analysis populations were considered:

- Intent-to-treat (ITT) population or population ii: All subjects who had taken at least 1 dose of ETR.

- Subset i: Subjects throughout on the recommended ETR dose. These subjects started on the recommended ETR dose and remained on this dose. These subjects had no individual PK-determined dose adjustment.

- Subset i+a: Subjects on the recommended ETR dose or lower. These subjects started on any ETR dose and had no subsequent individual PK-determined dose adjustment. This population includes subset i and subset a. Subset a consists of subjects who started on an ETR dose other than recommended, all of which had an ETR dose lower than the recommended dose.

- Subset i+b: Subjects on the recommended ETR dose or higher. These subjects started on the recommended ETR dose, with or without a subsequent individual PK-determined dose adjustment. This subset includes subset i and subset b, the latter consisting of subjects who started on the recommended ETR dose and had individual PK-determined dose adjustments, all of which resulted in a higher ETR dose.

Efficacy data were analysed for the ITT population and for subjects who received the recommended ETR dose throughout the study (subset i). Resistance data were analysed for the ITT population. Subgroup analyses for efficacy and resistance were performed on the ITT population.

Results

Participant flow/Recruitment

The study is being conducted at multiple sites in Brazil (5 sites; 9 subjects enrolled), the United States (US) (4 sites; 4 subjects enrolled), and South Africa (2 sites; 13 subjects enrolled). One site in Thailand screened subjects, however, none of these subjects were enrolled in the study.

At the time of the cut-off date for the Week-48 analysis (12 July 2018), 41 subjects had been screened and 26 subjects had been enrolled and received at least one dose of ETR (ITT population): 20 subjects

in Cohort I (⩾2 to <6 years) and 6 subjects in Cohort II (⩾1 to <2 years) (See Table 23). In total, 15 subjects (11 subjects in Cohort I, 4 subjects in Cohort II) received the recommended ETR dose throughout the study (subset i). The number of subjects in the other subsets is shown in Table 2. See Table 3 for a detailed breakdown of the different subject populations based on ETR dose.

Table 23: Subjects Disposition; All Subjects Screened (Study TMC125-C234)

	≥2 to <6 years	≥1 to <2 years	All Subjects
Screened, N	-	-	41
Screening Failures, n	-	-	15
Treated (ITT Set), n	20	6	26
ITT - Subset i[b]	11	4	15
ITT - Subset i + a[b]	14	4	18
ITT - Subset i + b[b]	16	6	22

[a] Subjects who received at least one dose of ETR.
[b] See Table 16 for an overview of the subsets (i, i+a, i+b)

Table 24: Overview of Subjects in Different Subject Populations Based on ETR Dose (Study TMC125 C234)

	≥2 to <6 years	≥1 to <2 years	All Subjects
Subjects enrolled who received at least 1 dose of ETR (ITT)			
• ITT (ie, population ii; all subjects treated)	20[a]	6	26[a]
Subjects throughout on the recommended ETR dose (subset i)			
• Subjects on the recommended ETR dose throughout the study	11	4	15
Subjects started on a lower dose than the recommended ETR dose (subset a)			
• Subjects who started on a lower ETR dose than the recommended dose and had no subsequent individual PK-determined dose adjustment	3	0	3
Subjects on the recommended ETR dose or lower (subset i+a):	***14***	***4***	***18***
Subjects started on the recommended ETR dose and then received a higher dose (subset b)			
• Subjects who started on the recommended ETR dose and had individual PK-determined dose increases	5[c]	2	7
Subjects on the recommended ETR dose or higher (subset i+b):	***16***	***6***	***22***

[a] In addition to the subjects included in the different subsets described in this table, 1 subject in the ITT population in the first mini-cohort) started on a lower ETR dose than the recommended dose and then received a higher ETR dose than the recommended dose, due to an individual PK-determined dose adjustment.
[b] Note that one of these subjects was included in the first mini-cohort I and, based on body weight, the initial dose was the same as the recommended ETR dose. Therefore, this subject is included in subset i.
[c] Note that one of these subjects was included in the first mini-cohort I and, based on body weight, the initial dose received was the same as the recommended ETR dose. This subject subsequently had a dose increase based on individual PK results. Therefore, this subject is included in subset b.

The rates reasons of ETR discontinuations in each cohorts are as follows (Table 25):

Table 25: Study Termination; ITT (Study TMC125-C234)

		≥2 to <6 years (N=20)	≥1 to <2 years (N=6)	All Subjects (N=26)
Drug Termination	Completed	0	0	0
	Discontinued	5 (25.0%)	3 (50.0%)	8 (30.8%)
	Up to Week 48	2 (10.0%)	2 (33.3%)	4 (15.4%)
	After Week 48	3 (15.0%)	1 (16.7%)	4 (15.4%)
	Clinical events or progression	2 (10.0%)	2 (33.3%)	4 (15.4%)
	Up to Week 48	1 (5.0%)	1 (16.7%)	2 (7.7%)
	After Week 48	1 (5.0%)	1 (16.7%)	2 (7.7%)
	Toxicity	1 (5.0%)	0	1 (3.8%)
	Up to Week 48	1 (5.0%)	0	1 (3.8%)
	Subject/parent/guardian/physician requests discontinuation of treatment	1 (5.0%)	1 (16.7%)	2 (7.7%)
	Up to Week 48	0	1 (16.7%)	1 (3.8%)
	After Week 48	1 (5.0%)	0	1 (3.8%)
	Protocol compliance	1 (5.0%)	0	1 (3.8%)
	After Week 48	1 (5.0%)	0	1 (3.8%)
	Ongoing	15 (75.0%)	3 (50.0%)	18 (69.2%)

N: number of subjects with data

Up to Week 48:

- Toxicity: 1 SAE (grade 4 lipase increase) (ETR discontinued on Day 16 [Analysis Time Point Week 2]; Cohort I).

- Clinical events or progression: 1 subject discontinued from the study due to virologic failure (ETR discontinued on Day 106 [Analysis Time Point Week 16]; Cohort II); and 1 subject had virologic failure and genotyping test revealing a high level of resistance to ETR (ETR discontinued on Day 170 [Analysis Time Point Week 24]; Cohort I).

- Subject/parent/guardian/physician requested discontinuation of treatment: 1 parent/legal guardian withdrew consent for all further study contact prior to completion of the protocol-defined study evaluations (ETR discontinued on Day 261 [Analysis Time Point Week 40]; Cohort II).

After Week 48:

- Clinical events or progression: for 1 subject the subject/parent/guardian/physician requested discontinuation because subject developed resistance (ETR discontinued on Day 400 [Analysis Time Point Week 60]; Cohort II); and 1 subject met protocol-defined objective (virologic failure due to non-adherence) requiring termination from the study (ETR discontinued on Day 770 [Analysis Time Point Week 108]; Cohort I).

- Protocol compliance: subject non-compliance with medication intake and clinic visits as defined by protocol (ETR discontinued on Day 479 [Analysis Time Point Week 72]; Cohort I).

- Subject/parent/guardian/physician requested discontinuation of treatment: 1 subject/parent/legal guardian withdrew consent for all further study contact prior to completion of the protocol-defined study evaluations through 5 years of follow-up (ETR discontinued on Day 1,518 [Analysis Time Point Week 216]; Cohort I).

Conduct of the study

The original protocol was issued on 17 October 2011. There were 4 amendments to the protocol:

- The first amendment (14 December 2012) **was issued to remove Cohorts IIB and IIIB (≥2-month to <2-year old treatment-naïve children, with or without exposure to ARVs as part of a regimen to prevent mother-to-child transmission).** Consequently, the number of cohorts was changed from 5 to 3, the sample size was updated from 80 to 50 subjects, and stratification by ARV exposure was deleted. This amendment was adopted before any study-related procedures had begun.

- The second amendment (04 October 2013) was issued **to revise the PK criteria for individual and cohort dose evaluations and adjustments.** In order to meet the PK criteria, at least 10 of 12 subjects per cohort were to have an AUC12h >2,350 ng*h/mL (>10th percentile of the adult AUC12h in the DUET studies) and a geometric mean AUC12h in the cohort **to fall within 80% to 130% of the geometric mean AUC12h in adults (ie, between 3,618 and 5,879 ng*h/mL).** For individual PK-determined dose adjustments, a stepwise approach was introduced aimed at obtaining an ETR AUC12h around the 20th percentile of the adult AUC12h (instead of the median adult AUC12h) and with a first dose adjustment capped at 200 mg twice daily (bid).

- The third amendment (05 December 2014) was issued to incorporate revisions related **to a change in the starting ETR dose (as per the new weight-banded ETR dosing table)** for the study cohorts and a change in the overall PK criteria for evaluation of the (mini-)cohorts.

- The fourth amendment (10 March 2016) was issued to revise the cohort management plan to allow early opening of the mini-cohort of Cohort III (while the first mini-cohort of Cohort II could still be enrolling) provided that the available Cohort II safety and PK were acceptable. Subjects <6 months of age could only be enrolled after initial safety and PK data from subjects between 6 months and 1 year of age were available. A go/no-go decision for further recruitment of study subjects was set approximately 2 years following the opening of Cohort II. **However, on 02 October 2017, the enrolment into Cohort II was closed after enrolment of the 6th subject into mini-cohort II (which occurred after the cut-off date for the Week-24 analysis) and it was decided to not open Cohort III.**

Baseline data

In the 2 cohorts combined, 53.8% (14/26) of subjects were male and 46.2% (12/26) were female. In the 2 cohorts combined, 50.0% (13/26) of the subjects were from South Africa, 34.6% (9/26) were from Brazil, and 15.4% (4/26) were from the US (See Table 26)

Table 26: Demographic Characteristics; ITT (Study TMC125-C234)

	≥2 to <6 years (N=20)	≥1 to <2 years (N=6)	All Subjects (N=26)
Sex, n (%)			
N	20	6	26
Female	9 (45.0%)	3 (50.0%)	12 (46.2%)
Male	11 (55.0%)	3 (50.0%)	14 (53.8%)
Age at baseline (years)			
N	20	6	26
Mean (SD)	3.9 (1.04)	1.0 (0.00)	3.2 (1.52)
Median (Min; Max)	4.0 (2; 5)	1.0 (1; 1)	3.0 (1; 5)
Age at baseline (months)			
N	20	6	26
Mean (SD)	52.2 (11.61)	19.2 (2.40)	44.6 (17.47)
Median (Min; Max)	52.5 (32.0; 69.0)	20.0 (15.0; 22.0)	46.5 (15.0; 69.0)
Race, n (%)			
Missing	4	1	5
Unknown	1	0	1
Not Reported	1	0	1
N	14	5	19
Black or African American	10 (71.4%)	3 (60.0%)	13 (68.4%)
Multiple	3 (21.4%)	1 (20.0%)	4 (21.1%)
Other	1 (7.1%)	1 (20.0%)	2 (10.5%)
Ethnicity, n (%)			
Unknown	8	3	11
N	12	3	15
Hispanic or Latino	8 (66.7%)	2 (66.7%)	10 (66.7%)
Not Hispanic or Latino	4 (33.3%)	1 (33.3%)	5 (33.3%)
Country/ study site identifier, n (%)			
N	20	6	26
Brazil	7 (35.0%)	2 (33.3%)	9 (34.6%)
5071	2 (10.0%)	0	2 (7.7%)
5072	2 (10.0%)	0	2 (7.7%)
5073	0	1 (16.7%)	1 (3.8%)
5074	1 (5.0%)	1 (16.7%)	2 (7.7%)
5097	2 (10.0%)	0	2 (7.7%)
South Africa	10 (50.0%)	3 (50.0%)	13 (50.0%)
30300	2 (10.0%)	0	2 (7.7%)
8051	8 (40.0%)	3 (50.0%)	11 (42.3%)
United States	3 (15.0%)	1 (16.7%)	4 (15.4%)
4001	1 (5.0%)	0	1 (3.8%)
4201	0	1 (16.7%)	1 (3.8%)
5003	1 (5.0%)	0	1 (3.8%)
5114	1 (5.0%)	0	1 (3.8%)
Height at baseline (cm)			
N	20	6	26
Mean (SD)	99.6 (6.94)	77.8 (4.62)	94.6 (11.32)
Median (Min; Max)	99.3 (86.4; 115.5)	78.0 (72.5; 82.5)	97.7 (72.5; 115.5)
Height for age (z-score)			
N	20	6	26
Mean (SD)	-1.18 (1.175)	-1.92 (1.180)	-1.35 (1.196)
Median (Min; Max)	-1.19 (-3.21; 1.21)	-2.22 (-3.10; -0.37)	-1.41 (-3.21; 1.21)

Table 26: Demographic Characteristics; ITT (Study TMC125-C234)

	≥2 to <6 years (N=20)	≥1 to <2 years (N=6)	All Subjects (N=26)
Height for age (percentile)			
N	20	6	26
Mean (SD)	22.30 (25.064)	10.71 (15.019)	19.63 (23.396)
Median (Min; Max)	11.93 (0.07; 88.62)	2.72 (0.10; 35.47)	7.99 (0.07; 88.62)
Weight at baseline (kg)			
N	20	6	26
Mean (SD)	16.0 (3.28)	10.5 (1.69)	14.7 (3.79)
Median (Min; Max)	14.9 (12.0; 23.0)	10.7 (8.4; 12.2)	14.5 (8.4; 23.0)
Weight for age (z-score)			
N	20	6	26
Mean (SD)	-0.79 (1.160)	-1.36 (1.526)	-0.92 (1.244)
Median (Min; Max)	-0.79 (-3.09; 1.56)	-1.15 (-3.57; 0.18)	-0.79 (-3.57; 1.56)
Weight for age (percentile)			
N	20	6	26
Mean (SD)	28.96 (29.605)	24.40 (26.366)	27.91 (28.442)
Median (Min; Max)	21.54 (0.10; 94.12)	19.55 (0.02; 57.19)	21.54 (0.02; 94.12)
Body mass index at baseline (kg/m^2)			
N	20	6	26
Mean (SD)	16.0 (1.81)	17.2 (1.11)	16.3 (1.73)
Median (Min; Max)	15.7 (13.6; 20.9)	17.5 (15.1; 18.4)	15.9 (13.6; 20.9)
Body mass index for age (z-score)			
N	20	NA	20
Mean (SD)	0.13 (1.156)		0.13 (1.156)
Median (Min; Max)	-0.03 (-2.21; 2.53)		-0.03 (-2.21; 2.53)
Body mass index for age (percentile)			
N	20	NA	20
Mean (SD)	52.47 (31.238)		52.47 (31.238)
Median (Min; Max)	49.01 (1.34; 99.43)		49.01 (1.34; 99.43)
Head circumference (cm)			
N	2	5	7
Mean (SD)	50.25 (0.354)	47.60 (0.834)	48.36 (1.468)
Median (Min; Max)	50.25 (50.00; 50.50)	47.20 (46.80; 48.50)	48.50 (46.80; 50.50)
Head circumference (z-score)			
N	2	5	7
Mean (SD)	-0.37 (2.461)	-0.15 (0.674)	-0.21 (1.151)
Median (Min; Max)	-0.37 (-2.11; 1.37)	-0.11 (-1.06; 0.83)	-0.11 (-2.11; 1.37)
Head circumference (percentile)			
N	2	5	7
Mean (SD)	46.60 (63.442)	44.80 (23.427)	45.31 (32.210)
Median (Min; Max)	46.60 (1.74; 91.46)	45.66 (14.40; 79.69)	45.66 (1.74; 91.46)

Table 26: Demographic Characteristics; ITT (Study TMC125-C234)			
	≥2 to <6 years (N=20)	≥1 to <2 years (N=6)	All Subjects (N=26)

N: number of subjects with data
NA: not applicable

In the 2 cohorts combined, the median baseline log10 viral load was 4.43 log10 copies/mL; the median baseline log10 viral load was 4.43 log10 copies/mL in Cohort I and 4.35 log10 copies/mL in Cohort II. Almost all subjects were infected with either HIV-1 Clade B virus (42.3% [11/26] in Cohorts I and II combined) or HIV-1 Clade C virus (50.0% [13/26] in Cohorts I and II combined). Two subjects (10.0% [2/20], both in Cohort I) were infected with HIV-1 Clade F virus.

In the 2 cohorts combined, the median baseline CD4+ percentage was 27.6%. The median baseline CD4+ absolute cell count was 863.0 cells/µL in the 2 cohorts combined, 817.5 cells/µL in Cohort I, and 1,491.5 cells/µL in Cohort II.

Table 27: Baseline HIV Disease Characteristics; ITT (Study TMC125-C234)			
	≥2 to <6 years (N=20)	≥1 to <2 years (N=6)	All Subjects (N=26)
HIV-1 Clade			
N	20	6	26
B	8 (40.0%)	3 (50.0%)	11 (42.3%)
C	10 (50.0%)	3 (50.0%)	13 (50.0%)
F	2 (10.0%)	0	2 (7.7%)
CDC clinical stage of HIV infection at baseline			
N	20	6	26
Category N (not symptomatic)	5 (25.0%)	1 (16.7%)	6 (23.1%)
Category A (mildly symptomatic)	2 (10.0%)	1 (16.7%)	3 (11.5%)
Category B (moderately symptomatic)	4 (20.0%)	1 (16.7%)	5 (19.2%)
Category C (severely symptomatic)	9 (45.0%)	3 (50.0%)	12 (46.2%)
Viral load at baseline (copies/mL)			
N	20	6	26
Mean (SD)	247296.3 (646652.49)	293679.7 (447657.99)	258000.1 (598563.19)
Median (Min; Max)	27144.0 (338; 2445733)	25792.0 (1732; 1040824)	27144.0 (338; 2445733)
Log_{10} viral load at baseline			
N	20	6	26
Mean (SD)	4.39 (1.001)	4.62 (1.096)	4.44 (1.006)
Median (Min; Max)	4.43 (2.5; 6.4)	4.35 (3.2; 6.0)	4.43 (2.5; 6.4)
CD4+ count at baseline (cells/µL)			
N	20	6	26
Mean (SD)	954.0 (643.80)	1455.8 (757.68)	1069.8 (690.16)
Median (Min; Max)	817.5 (179; 2936)	1491.5 (388; 2629)	863.0 (179; 2936)

Table 27: Baseline HIV Disease Characteristics; ITT (Study TMC125-C234)

	≥2 to <6 years (N=20)	≥1 to <2 years (N=6)	All Subjects (N=26)
CD4+ percentage at baseline			
N	20	6	26
Mean (SD)	25.97 (9.557)	25.38 (11.996)	25.83 (9.912)
Median (Min; Max)	27.60 (14.0; 41.0)	26.85 (7.0; 42.0)	27.60 (7.0; 42.0)
CD4+ count at baseline (categorical)			
N	20	6	26
<200 cells/µL	1 (5.0%)	0	1 (3.8%)
≥200 - <500 cells/µL	3 (15.0%)	1 (16.7%)	4 (15.4%)
≥500 - <1000 cells/µL	10 (50.0%)	1 (16.7%)	11 (42.3%)
≥1000 cells/µL	6 (30.0%)	4 (66.7%)	10 (38.5%)
CD4+ percentage at baseline (categorical)			
N	20	6	26
<25%	9 (45.0%)	3 (50.0%)	12 (46.2%)
≥25%	11 (55.0%)	3 (50.0%)	14 (53.8%)
CD8+ count at baseline (cells/µL)			
N	20	6	26
Mean (SD)	1491.8 (882.53)	2234.2 (867.83)	1663.1 (918.86)
Median (Min; Max)	1268.0 (491; 4097)	2124.0 (1038; 3641)	1424.5 (491; 4097)
CD8+ percentage at baseline			
N	20	6	26
Mean (SD)	41.47 (8.792)	38.97 (14.604)	40.89 (10.127)
Median (Min; Max)	40.65 (21.0; 57.0)	33.10 (30.0; 68.0)	38.60 (21.0; 68.0)
CD4+/CD8+ ratio at baseline			
N	20	6	26
Mean (SD)	0.6972 (0.40467)	0.7573 (0.42419)	0.7111 (0.40138)
Median (Min; Max)	0.6286 (0.245; 1.822)	0.7725 (0.107; 1.400)	0.6931 (0.107; 1.822)

N: number of subjects with data

Most subjects had previous experience with a NRTI and PI combination (80.8%, 21/26), an NRTI (53.8%, 14/26), or an NRTI and NNRTI combination (42.3%, 11/26). The most frequently used therapy at screening was an NRTI and PI combination (46.2%, 12/26). The following ARVs were previously used by ≥42.3% of subjects (≥11/26 subjects in the 2 cohorts combined): lamivudine (used by all subjects), lopinavir boosted with ritonavir (rtv), zidovudine, nevirapine, and abacavir. These ARVs were also the most frequently used ARVs at screening, with lamivudine as the most frequently used ARV (used by all but 1 subject):

Table 28: Previous and Screening ARV Therapies: Individual ARVs; ITT (Study TMC125-C234)

		≥2 to <6 years (N=20)		≥1 to <2 years (N=6)		All Subjects (N=26)	
Drug Class	Drug Name (Active Ingredients)	Previous[a]	Screening only[b]	Previous[a]	Screening only[b]	Previous[a]	Screening only[b]
Integrase Inhibitor	Raltegravir	1 (5.0%)	1 (5.0%)	0	0	1 (3.8%)	1 (3.8%)
NNRTI	Efavirenz	2 (10.0%)	1 (5.0%)	0	0	2 (7.7%)	1 (3.8%)
	Nevirapine	10 (50.0%)	4 (20.0%)	2 (33.3%)	1 (16.7%)	12 (46.2%)	5 (19.2%)
NRTI	Abacavir	8 (40.0%)	2 (10.0%)	3 (50.0%)	3 (50.0%)	11 (42.3%)	5 (19.2%)
	Lamivudine	20 (100.0%)	19 (95.0%)	6 (100.0%)	6 (100.0%)	26 (100.0%)	25 (96.2%)
	Stavudine	5 (25.0%)	1 (5.0%)	0	0	5 (19.2%)	1 (3.8%)
	Zidovudine	15 (75.0%)	11 (55.0%)	3 (50.0%)	3 (50.0%)	18 (69.2%)	14 (53.8%)
PI	Fosamprenavir	0	0	1 (16.7%)	0	1 (3.8%)	0
	Lopinavir	16 (80.0%)	7 (35.0%)	5 (83.3%)	4 (66.7%)	21 (80.8%)	11 (42.3%)
	Nelfinavir	0	0	1 (16.7%)	1 (16.7%)	1 (3.8%)	1 (3.8%)
	Ritonavir	16 (80.0%)	7 (35.0%)	5 (83.3%)	4 (66.7%)	21 (80.8%)	11 (42.3%)

Table 28: Previous and Screening ARV Therapies: Individual ARVs; ITT (Study TMC125-C234)

Drug Class	Drug Name (Active Ingredients)	≥2 to <6 years (N=20) Previous[a]	≥2 to <6 years (N=20) Screening only[b]	≥1 to <2 years (N=6) Previous[a]	≥1 to <2 years (N=6) Screening only[b]	All Subjects (N=26) Previous[a]	All Subjects (N=26) Screening only[b]

N: number of subjects with data
Note: specific ARV therapies may be counted in both columns
[a] Previous ARV therapy including ARV therapy taken at the time of the screening visit
[b] ARV therapy taken at the time of the screening visit

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Table 29: Previous and Screening ARV Therapies: Combinations of ARVs Classes; ITT (Study TMC125-C234)

Class Number	ARV Classes	≥2 to <6 years (N=20) Previous[a]	≥2 to <6 years (N=20) Screening only[b, c]	≥1 to <2 years (N=6) Previous[a]	≥1 to <2 years (N=6) Screening only[b]	All Subjects (N=26) Previous[a]	All Subjects (N=26) Screening only[b, c]
1	NNRTI	3 (15.0%)	0	0	0	3 (11.5%)	0
	NRTI	13 (65.0%)	6 (30.0%)	1 (16.7%)	0	14 (53.8%)	6 (23.1%)
2	NRTI + INSTI	1 (5.0%)	1 (5.0%)	0	0	1 (3.8%)	1 (3.8%)
	NRTI + NNRTI	9 (45.0%)	5 (25.0%)	2 (33.3%)	1 (16.7%)	11 (42.3%)	6 (23.1%)
	NRTI + PI	16 (80.0%)	7 (35.0%)	5 (83.3%)	5 (83.3%)	21 (80.8%)	12 (46.2%)
3	NNRTI + NRTI + PI	1 (5.0%)	0	0	0	1 (3.8%)	0

N: number of subjects with data
Note: specific ARV therapies may be counted in both columns
[a] Previous ARV therapy including ARV therapy taken at the time of the screening visit
[b] ARV therapy taken at the time of the screening visit
[c] One subject did not take ARV medication in the last 833 days prior to first ETR dose.

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Table 30: Initial OBR Therapies: Individual ARVs; ITT (Study TMC125-C234)

Drug Class	Drug Name (Active Ingredients)	≥2 to <6 years (N=20)	≥1 to <2 years (N=6)	All Subjects (N=26)
Integrase Inhibitor	Raltegravir	6 (30.0%)	0	6 (23.1%)
NRTI	Lamivudine	10 (50.0%)	6 (100.0%)	16 (61.5%)
	Stavudine	1 (5.0%)	0	1 (3.8%)
	Zidovudine	13 (65.0%)	6 (100.0%)	19 (73.1%)
PI	Atazanavir	1 (5.0%)	0	1 (3.8%)
	Darunavir	8 (40.0%)	0	8 (30.8%)
	Lopinavir	11 (55.0%)	6 (100.0%)	17 (65.4%)
	Ritonavir	20 (100.0%)	6 (100.0%)	26 (100.0%)

N: number of subjects with data

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Table 31: Initial OBR Therapies: Combinations of ARVs per Class; ITT (Study TMC125-C234)

ARVs Combinations	≥2 to <6 years (N=20)	≥1 to <2 years (N=6)	All Subjects (N=26)
DRV + rtv + RAL	2 (10.0%)	0	2 (7.7%)
LPV + rtv+ RAL	4 (20.0%)	0	4 (15.4%)
ATV + rtv + zidovudine	1 (5.0%)	0	1 (3.8%)
DRV + rtv + zidovudine	1 (5.0%)	0	1 (3.8%)
LPV + rtv + zidovudine	2 (10.0%)	0	2 (7.7%)
DRV + rtv + lamivudine + stavudine	1 (5.0%)	0	1 (3.8%)
DRV + rtv + lamivudine + zidovudine	4 (20.0%)	0	4 (15.4%)
LPV + rtv + lamivudine + zidovudine	5 (25.0%)	6 (100.0%)	11 (42.3%)

N: number of subjects with data

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Table 32: Initial OBR Therapies: Combinations of ARV Classes; ITT (Study TMC125-C234)

Class Number	ARV Classes	≥2 to <6 years (N=20)	≥1 to <2 years (N=6)	All Subjects (N=26)
2	PI + INSTI	6 (30.0%)	0	6 (23.1%)
	PI + NRTI	14 (70.0%)	6 (100.0%)	20 (76.9%)

N: number of subjects with data

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Outcomes and estimation

- HIV-1 RNA levels

Percentage of subjects with <400 HIV-1 RNA copies/mL at Week 48

The virologic response rate (ie, the percentage of subjects with <400 HIV-1 RNA copies/mL at Week 48 per the FDA Snapshot approach; key efficacy endpoint) was 80.0% (16/20) in Cohort I and 16.7% (1/6) in Cohort II.

Table 33: Outcome at Week 48 (FDA Snapshot Approach); ITT (Study TMC125-C234)

Snapshot Approach: (<400 copies/mL)

n (%)	≥2 to <6 years (N=20)	≥1 to <2 years (N=6)	All Subjects (N=26)
Week 48			
Virologic response	16 (80.0%)	1 (16.7%)	17 (65.4%)
HIV RNA <400 copies/mL at Week 48	16 (80.0%)	1 (16.7%)	17 (65.4%)
95% CI*	(56.3; 94.3)	(0.4; 64.1)	(44.3; 82.8)
Virologic failure	3 (15.0%)	5 (83.3%)	8 (30.8%)
HIV RNA ≥400 copies/mL at Week 48	2 (10.0%)	3 (50.0%)	5 (19.2%)
Virologic failure - leading to discontinuation	1 (5.0%)	1 (16.7%)	2 (7.7%)
Virologic failure - switched background regimen not permitted by the protocol	0	0	0
Virologic failure - discontinued due to other reason and last available HIV RNA ≥400 copies/mL	0	1 (16.7%)	1 (3.8%)
No viral load data in Week 48 window	1 (5.0%)	0	1 (3.8%)
Discontinued due to adverse event/death	1 (5.0%)	0	1 (3.8%)
Discontinued due to other reason and the last available HIV RNA <400 copies/mL (or missing)	0	0	0
Missing data during window but on study	0	0	0

* Two-sided Exact Clopper-Pearson 95% CI.

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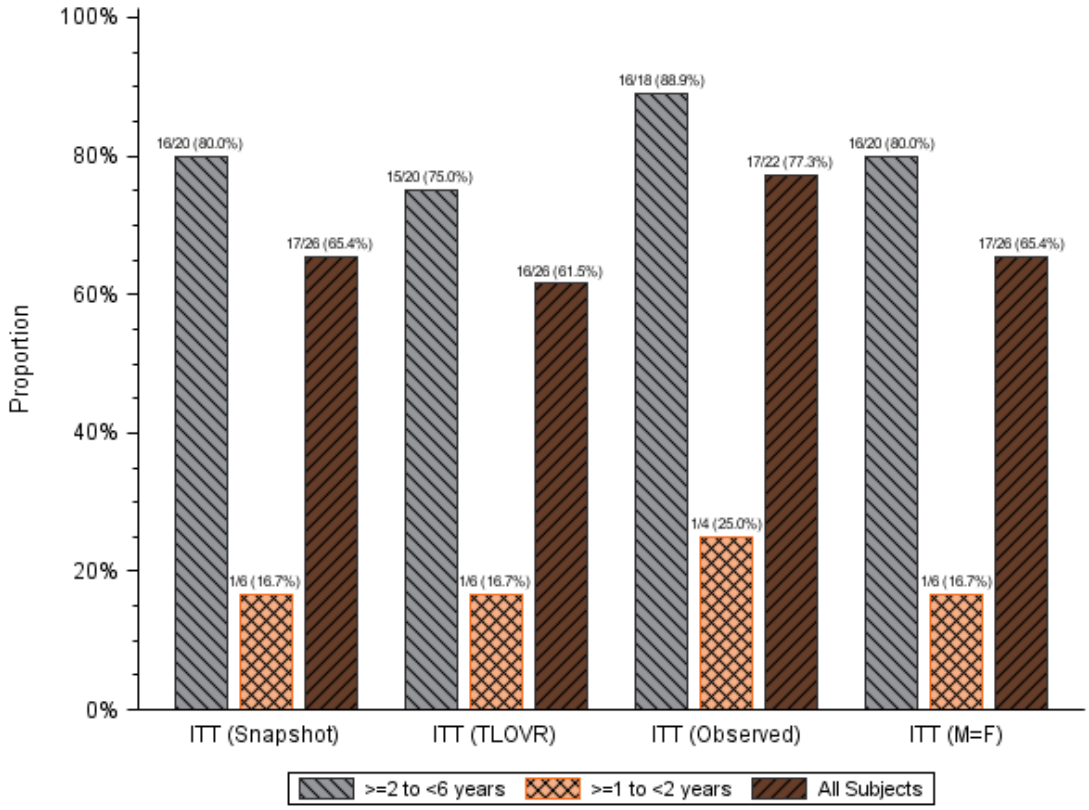
The results for virologic response (FDA Snapshot approach) were confirmed in the TLOVR (time to loss of virologic response), M=F (missing equals failure), and OC (observed case) analyses:

Figure 15: Bar Chart of Virologic Response (<400 copies/mL) According to Different Analyses at Week 48; ITT (Study TMC125-C234)



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Similar results were observed in subjects who received the recommended ETR dose throughout the study (subset i):

Table 34: Outcome at Week 48 (FDA Snapshot Approach); ITT, subset i (Study TMC125-C234)

Snapshot Approach: (<400 copies/mL)

n (%)	≥2 to <6 years (N=11)	≥1 to <2 years (N=4)	All Subjects (N=15)
Week 48			
Virologic response	8 (72.7%)	1 (25.0%)	9 (60.0%)
HIV RNA <400 copies/mL at Week 48	8 (72.7%)	1 (25.0%)	9 (60.0%)
95% CI*	(39.0; 94.0)	(0.6; 80.6)	(32.3; 83.7)
Virologic failure	2 (18.2%)	3 (75.0%)	5 (33.3%)
HIV RNA ≥400 copies/mL at Week 48	2 (18.2%)	2 (50.0%)	4 (26.7%)
Virologic failure - leading to discontinuation	0	0	0
Virologic failure - switched background regimen not permitted by the protocol	0	0	0
Virologic failure - discontinued due to other reason and last available HIV RNA ≥400 copies/mL	0	1 (25.0%)	1 (6.7%)
No viral load data in Week 48 window	1 (9.1%)	0	1 (6.7%)
Discontinued due to adverse event/death	1 (9.1%)	0	1 (6.7%)
Discontinued due to other reason and the last available HIV RNA <400 copies/mL (or missing)	0	0	0
Missing data during window but on study	0	0	0

* Two-sided Exact Clopper-Pearson 95% CI.

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Percentage of subjects with <200 and <50 HIV-1 RNA copies/mL at Week 48

Of the 17 subjects in the ITT population who achieved a virologic response of <400 HIV-1 RNA copies/mL at Week 48 (Cohorts I and II combined), 14 subjects in total (13/20 [65.0%] in Cohort I and 1/6 [16.7%] in Cohort II) reached a virologic response of <200 HIV-1 RNA copies/mL at Week 48 per the FDA Snapshot approach.

Of the 10 subjects in the ITT population (Cohorts I and II combined) with available data for the <50 HIV-1 RNA copies/mL threshold at Week 48 (ie, where the limit of quantification of the assay was 40 HIV-1 RNA copies/mL), 9 subjects (8/9 [88.9%] subjects in Cohort I and 1/1 [100%] subjects in Cohort II) achieved a viral load <50 HIV-1 RNA copies/mL at Week 48.

Table 35: Virologic Response (M=F); Tabulation by Analysis Timepoint; ITT (Study TMC125-C234)

n/N (%)	≥2 to <6 years (N=20)	≥1 to <2 years (N=6)	All Subjects (N=26)
Week 48			
Viral load <400 copies/mL	16/20 (80.0%)	1/6 (16.7%)	17/26 (65.4%)
Viral load <200 copies/mL	13/20 (65.0%)	1/6 (16.7%)	14/26 (53.8%)
Viral load assay limit <40 copies/mL*	9	1	10
Viral Load ≥ 50 -<200 copies/mL	1/9 (11.1%)	0/1	1/10 (10.0%)
Viral Load <50 copies/mL	8/9 (88.9%)	1/1 (100%)	9/10 (90.0%)

Table 35: Virologic Response (M=F); Tabulation by Analysis Timepoint; ITT (Study TMC125-C234)

n/N (%)	≥2 to <6 years (N=20)	≥1 to <2 years (N=6)	All Subjects (N=26)

* Due to low blood volumes for some samples, dilution was required for viral load testing, which returned values with limit of quantification of <200 copies/mL instead of <40 copies/mL for the respective viral load assay.

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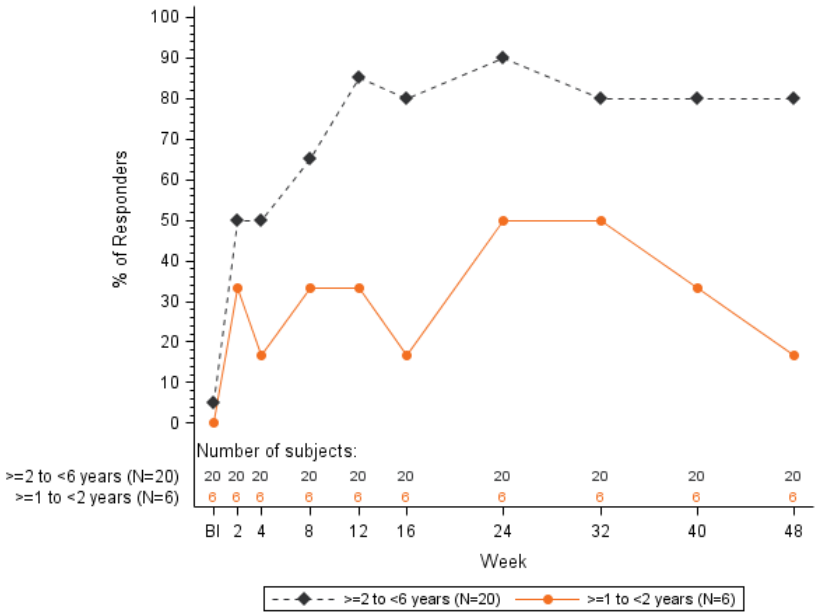
Change from baseline in HIV-1 RNA values

The virologic response rates over time is as follows:

Figure 16: Response (M=F) Over Time; ITT (Study TMC125-C234)

Parameter: Viral load <400 copies/mL



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At Week 48, the median (min; max) change in log10 HIV-1 RNA values from baseline was -2.308 (-4.04; 0.04) log10 copies/mL in Cohort I (N=20), -0.665 (-3.40; 0.45) log10 copies/mL in Cohort II (N=6), and -2.017 (-4.04; 0.45) log10 copies/mL in Cohorts I and II combined (N=26) (NC=F analysis).

Protocol-defined Virologic Outcome

The protocol-defined criteria for **success** were:

- either HIV-1 RNA <400 copies/mL or a ≥0.5 log10 reduction in HIV-1 RNA (copies/mL) at Week 8
- either HIV-1 RNA <400 copies/mL or a ≥1 log10 reduction in HIV-1 RNA (copies/mL) at Week 12
- either HIV-1 RNA <400 copies/mL or a ≥2 log10 reduction in HIV-1 RNA (copies/mL) at Week 24
- either HIV-1 RNA <400 copies/mL or a ≥2 log10 reduction in HIV-1 RNA (copies/mL) at Week 48

The protocol-defined criteria for **virologic failure** were:

- Lack of virologic response:

    - a confirmed HIV-1 RNA at Week 8 that was not ≥0.5 log10 lower than the HIV-1 RNA at baseline (unless the viral load at Week 8 was already <400 HIV-1 RNA copies/mL)
    - a confirmed HIV-1 RNA at or after Week 12 that was not ≥1 log10 lower than the HIV RNA at baseline (unless the viral load at Week 12 or later was already <400 HIV-1 RNA copies/mL)
    - a confirmed HIV-1 RNA ≥400 copies/mL and not ≥2 log10 reduction in HIV-1 RNA at Week 24
    - a confirmed HIV-1 RNA ≥400 copies/mL and not ≥2 log10 reduction in HIV-1 RNA at Week 48

- Virologic rebound:

    - for subjects whose nadir was <400 HIV-1 RNA copies/mL: a confirmed* HIV-1 RNA >1,000 copies/mL (on 2 consecutive measurements at least 1 week but no more than 4 weeks apart).

Among the subjects with data at the Week-48 timepoint, 88.9% (16/18) of the subjects in Cohort I, 25.0% (1/4) of the subjects in Cohort II, and 77.3% (17/22) of the subjects in Cohorts I and II combined met the criteria for protocol-defined virologic success.

Table 36: Virologic Response: Protocol-defined Virologic Outcome: Tabulation by Analysis Timepoint; ITT (Study TMC125-C234)

	Success				
	n/N	95% CI**	Virologic Failure n/N	Lack of Virologic Response* n/N	Virologic Rebound* n/N
≥2 to <6 years (N=20)					
Week 8	19/19 (100%)	(82.4; 100.0)	0/19 (0.0%)	0/19 (0.0%)	0/19 (0.0%)
Week 12	19/19 (100%)	(82.4; 100.0)	0/19 (0.0%)	0/19 (0.0%)	0/19 (0.0%)
Week 24	18/19 (94.7%)	(74.0; 99.9)	1/19 (5.3%)	0/19 (0.0%)	1/19 (5.3%)
Week 48	16/18 (88.9%)	(65.3; 98.6)	2/18 (11.1%)	2/18 (11.1%)	0/18 (0.0%)
Last available viral load			3/19 (15.8%)	1/19 (5.3%)	2/19 (10.5%)
≥1 to <2 years (N=6)					
Week 8	4/5 (80.0%)	(28.4; 99.5)	1/5 (20.0%)	0/5 (0.0%)	1/5 (20.0%)
Week 12	3/5 (60.0%)	(14.7; 94.7)	2/5 (40.0%)	1/5 (20.0%)	1/5 (20.0%)
Week 24	4/5 (80.0%)	(28.4; 99.5)	1/5 (20.0%)	1/5 (20.0%)	0/5 (0.0%)
Week 48	1/4 (25.0%)	(0.6; 80.6)	3/4 (75.0%)	0/4 (0.0%)	3/4 (75.0%)
Last available viral load			4/6 (66.7%)	0/6 (0.0%)	4/6 (66.7%)
All Subjects (N=26)					
Week 8	23/24 (95.8%)	(78.9; 99.9)	1/24 (4.2%)	0/24 (0.0%)	1/24 (4.2%)
Week 12	22/24 (91.7%)	(73.0; 99.0)	2/24 (8.3%)	1/24 (4.2%)	1/24 (4.2%)
Week 24	22/24 (91.7%)	(73.0; 99.0)	2/24 (8.3%)	1/24 (4.2%)	1/24 (4.2%)
Week 48	17/22 (77.3%)	(54.6; 92.2)	5/22 (22.7%)	2/22 (9.1%)	3/22 (13.6%)
Last available viral load			7/25 (28.0%)	1/25 (4.0%)	6/25 (24.0%)

N: Number of subjects with HIV-1 RNA data.
For the criteria of protocol-defined success and protocol-defined virologic failure (ie, lack of virologic response or virologic rebound)
Virologic rebound took precedence over the criteria for success and lack of virologic response.Last available viral load was defined as the last viral load measurement during treatment. For overall protocol-defined virologic outcome, a subject was classified as 'virologic failure' if the subject, over time, ever showed protocol-defined virologic failure (ie, lack of virologic response or virologic rebound).
Data from Week 8 onwards were used in the analysis. Subjects who discontinued prior to Week 8 were not included in the analysis. Subjects without HIV-1 viral load data (Abbott RealTime HIV-1 assay) at a visit (treatment phase), either due to missing data or due to discontinuation, whatever the reason, were not included in the analysis for that specific visit. For intermittent visits in between and beyond Weeks 8, 12, 24 and 48, definitions were carried forward. If no confirmatory HIV-1 RNA measurement was available (yet) within 1 to 4 weeks, the outcome assessment for 'virologic failure' was based on a single HIV-1 RNA measurement, ie, if that single value was higher than the threshold, it was classified as virologic failure.
Only HIV-1 RNA measurements from the Abbott RealTime HIV-1 assay were used in the efficacy analyses (at Weeks 12, 24 and 48 for Subject ID [redacted]; at Weeks 8 and 12 for Subject ID [redacted]; at Weeks 8 and 24 for Subject ID [redacted]; and at Week 8 for subject ID [redacted]).
* Part of the virologic failure category.
** Two-sided Exact Clopper-Pearson 95% CI.

Table 36: Virologic Response: Protocol-defined Virologic Outcome: Tabulation by Analysis Timepoint; ITT (Study TMC125-C234)

	Success				
	n/N	95% CI**	Virologic Failure n/N	Lack of Virologic Response* n/N	Virologic Rebound* n/N

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- CD4 levels

The observed antiviral activity of ETR in combination with an individualized OBR was mirrored in the increases in CD4+ cell counts:

Table 37: Descriptive Statistics of Actual CD4+ Values at Baseline and Change From Baseline at Week 48 (NC=F); ITT (Study TMC125-C234)

	Cohort I ≥2 to <6 years (N=20)	Cohort II ≥1 to <2 years (N=6)	All Subjects (N=26)
CD4 (%)			
Change from baseline at Week 48			
N	20	6	26
Mean (SE)	5.46 (1.710)	-0.58 (3.240)	4.06 (1.566)
Median (min – max)	5.15 (-8.0 – 26.0)	-2.20 (-8.0 – 14.3)	3.95 (-8.0 – 26.0)
CD4+ (cells/uL)			
Change from baseline at Week 48			
N	20	6	26
Mean (SE)	194.3 (94.82)	-56.3 (219.15)	136.4 (88.99)
Median (min – max)	298.5 (-722 – 871)	0.0 (-1058 – 545)	149.5 (-1058 – 871)

Ancillary analyses

- Subgroup analyses

Subgroup analyses shown a trend for a higher virologic response rate (according to the FDA Snapshot approach and the protocol-defined virologic outcome) for subjects:

- who were adherent to ETR and/or OBR versus subjects who were non-adherent per questionnaire (virologic response [HIV RNA <400 copies/mL] was 76.2% [16/21] for subjects adherent to ETR and 20.0% [1/5] for subjects non-adherent to ETR; and 75.0% [15/20] for subjects adherent to OBR and 40.0% [2/5] for subjects non-adherent to OBR), and

- who swallowed the ETR tablet whole versus subjects who took ETR dispersed (virologic response [HIV RNA <400 copies/mL] was 100.0% [6/6] for subject who swallowed the ETR tablet whole and 42.9% [6/14] for subjects who took ETR dispersed in liquid).

- Development of resistance

Paired resistance data (phenotype and/or genotype) at baseline and endpoint (defined as last viral load with available genotype and/or phenotype data within the treatment phase) were available for 9 subjects (4 in Cohort I and 5 in Cohort II) with confirmed virologic failure. For 2 subjects only paired phenotype data were available (both in Cohort II), and for 2 subjects only paired genotype data were available (1 in Cohort I and 1 in Cohort II).

Based on available paired phenotype and/or genotype data at baseline and endpoint, development of resistance to ETR (ie, ETR WGS≥4 and/or ETR FC>10) was observed for 2/9 subjects (for both during the Week-48 period): for 1 subject in Cohort I and for 1 subject in Cohort II (in both subjects determined by genotype and phenotype). Both subjects discontinued the study for this reason. In addition, 2 subjects (both in Cohort I) developed partial sensitivity to ETR by phenotype (2.9<FC≤10), of whom 1 also developed intermediate resistance to ETR by genotype (2.5≤ETR WGS≤3.5). Furthermore, 1 subject in Cohort II developed intermediate resistance to ETR by genotype (phenotype not available).

ETR RAMs emerging at endpoint were K101E, E138A, E138Q, V179F, V179T, Y181C, and M230L (all of which were observed in at most 1 subject, except for Y181C [3 subjects] and M230L [2 subjects]). The only other NNRTI RAMs observed were V179I and V189I (in a single subject in Cohort I). The respective OBRs remained sensitive at endpoint in all subjects with available phenotype data at endpoint.

Table 38: Summary of Individual Case Descriptions of Subjects with Virologic Failure

Snapshot Approach W48 (≥400 HIV-1 RNA Copies/mL)	Cohort	Protocol-defined Outcome		Genotype/Phenotype at EP		
		W48	LAV	EP[e]	ETR fold change (RC)	ETR WGS
VF	I	NA	VF/VR	W24	13 (R)[j]	4.0
VS	I	VS	VS	W40	3.89 (PS)	1
VF	I	VF/LR	VF/VR	W108	3.88 (PS)[g]	2.5
VF	I	VF/LR	VS	W40	1.08 (S)[h]	NA
VF	II	NA	VF/VR	W12	139 (R)[k]	5
VF	II	VF/VR	VF/VR	W16	0.52 (S)[f]	0
VF	II	NA	VS	W32	2.35 (S)[i]	NA
VF	II	VF/VR	VF/VR	W48	- (NA)	2.5
VF	II	VF/VR	VF/VR	W48	- (NA)	1

EP: endpoint; ETR: etravirine; NA: not applicable; LR: lack of virologic response; PS: partially sensitive; R: resistance; RC: resistance call; S: sensitive; VF: virologic failure; VR: virologic rebound; VS: virologic success; W: week; WGS: weighted genotypic score

[a] PK dose adjustment after intensive PK visit when the individual AUC_{12h} target of 2,350 ng•h/mL (10th percentile of adults).

[b] Worst and best outcome of assessments at different timepoints.

[c] From communication (10 June 2016) with the site it was noted that the child could not swallow the atazanavir (ATV) capsules, that adherence was reinforced, and that the ATV capsules (ATV/rtv total daily dose 250 mg/80 mg) was replaced by ATV powder (ATV/rtv 300 mg/80 mg) at Week 24.

[d] Adherence to ETR and OBR was assessed by the Paediatric Domestic or International Adherence Questionnaire's specific question was: "How many doses missed in the last 3 days?" "Adherent" for this question is defined as "never missed a dose".

[e] Endpoint is defined as the last viral load with available phenotype and/or genotype data.

[f] Subject [redacted] was discontinued from the study at Analysis Time Point Week 60, for development of resistance; no resistance data at the time of discontinuation are available.

[g] Subject [redacted] was discontinued from study at Analysis Time Point Week 108 for virologic failure and failure due to non-adherence.

[h] Subject [redacted] was discontinued from the study at Analysis Time Point Week 72 for lack of compliance.

[i] Subject [redacted] was discontinued from the study at Analysis Time Point Week 37 for consent withdrawal by parents.

[j] Subject [redacted] was discontinued from the study at Analysis Time Point Week 24 for virologic failure and resistance.

[k] Subject [redacted] was discontinued from the study at Analysis Time Point Week 16 for virologic failure.

Source: Attachment LVIRES01, Attachment LPK01, Attachment LPROADH01

2.4.2. Discussion on clinical efficacy

Extensions of indication to include paediatric patients for antiretroviral agents are primarily based on demonstration of comparable exposure in children vs. adults. A specific demonstration of antiviral efficacy in paediatric patients is not required, as it is stressed out in the EMA Guideline on the clinical development of medicinal products for the treatment of HIV infection.

Design and conduct of clinical studies

The clinical PK, efficacy and safety data in support of this younger age paediatric extension are derived from an open label phase 1/2 study TMC125-234 (IMPAACT 1090) enrolling 20 subjects in Cohort I (aged ≥2 to <6 years) and 6 subjects in Cohort II (aged ≥1 to <2 years). Subjects were on a virologically failing regimen (containing at least 3 ARV). Of note, a Cohort III (< 1 y/o) was originally planned but did not enrol and was closed.

This paediatric study TMC125-C234 including a research of the optimal dose (based on PK and safety criteria) and a sequential inclusion (with the use of mini-cohorts) was compliant with the PIP of Intelence (P/0121/2019). According to efficacy data and PK data, the inclusion of subjects from 1 to <2 years of age was stopped, which is endorsed. For these younger subjects on a failing ARV regimen, other medicines may be available (notably raltegravir), but efavirenz is the only NNRTI available for this population.

When focusing on subjects ≥2 years old (the cohort II was interrupted for efficacy concerns), only half of the subjects (11 subjects/20) have received the recommended ETR dose. Additionally:

- 3 subjects start with a lower ETR dose without further dose adjustment throughout the study,

- 1 subject start with a lower ETR dose and then received a higher-than-recommended ETR dose due to individual PK results,

- 5 subjects have received a higher ETR dose after dose adjustment based on individual PK results.

The 4 subjects who start with a lower ETR dose were subjects initially enrolled in the mini-cohort and who received the initial recommended ETR dose (which was 5.2 mg/kg bid for all body weights). Then, a revision of the ETR dose was introduced according to PK data from this mini-cohort, with an increased ETR recommended dose for subjects weighing 13-<16 kg (6.8 mg/kg/BID) and <13 kg (8.8 mg/kg/BID). According to individual PK dose-adjustments, one of these 4 subjects had an increase of its ETR dose according to the new recommended dosing schedule and, whereas the 3 other subjects remained with their original ETR dose (subset a).

Therefore, the efficacy and safety data of the proposed ETR dose in these subjects (i.e. 100 mg BID for subjects ≥10 kg to <20 kg, 125 mg BID for subjects ≥20 kg to <25 kg, 150 mg BID for subjects ≥25 kg to <30 kg and 200 mg BID for subjects ≥30 kg) were issued from only 11 subjects.

Among the 5 subjects (cohort I) who discontinued from study, 2 may be considered related to ETR (1 grade 4 lipase increase and 1 virologic failure due to ETR resistance).

The dose selection was established so that the geometric mean ETR AUC12h was between 60% and 150% of the geometric mean ETR AUC12h in HIV-1 infected, ART-experienced adults from the DUET studies (ie, between 2,713 and 6,783 ng*h/mL). Dose-adjustment may occur according to the individual PK data. Initially, all subjects from 2 to <6 years of age were treated with ETR 5.2 mg/kg BID, whatever their weight. However, the mean ETR exposure (AUC and Cmin) was significantly lower for the first 6 patients included in the mini-cohort I. Notably, 2 subjects required individual dose adjustment because their ETR AUC12h was below 2,350 ng.h/ml. Therefore, the Applicant has

proposed to increase ETR dose for subjects weighing <16 kg (6.8 mg/kg BID for subjects 13-<16 kg, and 8.8 mg/kg BID for subjects <13 kg).

This dose adjustment for the lower weight ranges was supported by the population PK analysis and intensive PK analysis in subjects receiving the recommended dose of ETR (Refer to section 2.3.2 Pharmacokinetics and 2.3.3 Discussion of clinical pharmacology). Consequently, among the 20 subjects above 2 years of age, only 11 children were treated with the recommended ETR dose according to their weight.

The design of the study targeting paediatric patients was acknowledged by the CHMP, with different age and/or weight cohorts, a sequential enrolment inter- and intra-cohort, and possible dose adjustments based on safety and PK data. The dose selection was established so that the geometric mean ETR AUC12h was between 60% and 150% of the geometric mean ETR AUC12h in HIV-1 infected, ART-experienced adults from the DUET studies (i.e., between 2,713 and 6,783 ng*h/mL).

The CHMP requested the MAH to discuss the adequacy of this PK objective. In general, the response does not add to the discussion in the first round. The ETR AUC12 target (60%-150% of the geometric mean ETR AUC12h in ART-experienced adults, i.e. between 2713 and 6783 ng.h/ml) was large to consider the high inter-individual variability in clearance of ETR (62% based on the popPK analysis).

As previously stated, the adequacy of this range may be debatable, notably as regards its lower limit. In addition to the proposed ETR doses, a dose adjustment was proposed for subjects with low ETR AUC12h (defined as <10th percentile of the adult AUC12h, i.e. 2350 ng.h/ml), which was endorsed. Overall, as previously stated, a relevant proportion of subjects (6/20 subjects ≥2 years old) required an increase of their ETR dose based on individual PK results, highlighting that the selection of paediatric ETR doses in younger subjects was challenging to obtain ETR exposure close to those observed in adults.

Regarding the conduct of the study and the amendments to the protocol, the CHMP signalled that it was unclear how the 2nd and 3rd amendments may have impacted the study outcome. The Applicant explained the main changes to the PK objectives in amendments 2 and 3 resulted in less strict criteria for dose adjustment throughout the study, allowing more extreme exposures in the final data set. Overall, most of the subjects were included in the versions 3 and 4 of the protocol, i.e. with the recommended ETR doses.

The included population could be regarded as representative for the target population in medical need, with mainly HIV-1 Clade B and C. Four subjects (20%) had viral load >100.000 c/ml and approximately half of subjects had mild to severe immunodeficiency. Of note, clinical data in subjects receiving ETR 100 mg BID in the weight group 10-<13 kg are very limited and the ETR dose in this weight group must be further supported by PK data. At screening, most subjects from Cohort I were treated with 2 NRTIs (mainly AZT/3TC) + a 3rd agent [LPV/rtv (n=7), NNRTIs (n=5) or RAL (n=1)]. In addition, 6 subjects were treated with monotherapy of lamivudine or zidovudine and one subject did not take ARVs at screening. When ETR was introduced in their failing regimen, subjects were rightly treated with ETR in combination with a boosted PI (mainly LPV/rtv or DRV/rtv) and at least one additional active drug (NRTI or RAL).

The enrolled subjects have mainly HIV-1 Clade B or C in line with the study centers notably clade C for a population mainly from South Africa. According to the baseline characteristics provided in the Annex of CSR, in cohort I (2-6 years old), subjects were rather 3 to 5 years old (only 2 subjects were 2 years of age at baseline). Enrolled subjects were at baseline in the weight bands 10 to <13 kg (n=3), 13 to <16 kg (n=9), 16 to <20 kg (n=5) and 20 to <25 kg (n=3), with a lower weight at 12 kg. Thus, clinical data in subjects receiving ETR 100 mg BID in the weight group 10-<13 kg are very limited, but PK data are in favor of an adequate ETR dose for these subjects. Four subjects (20%) had viral load

>100.000 c/ml. Considering the WHO classification in paediatric subjects, approximately half of subjects had mild to severe immunodeficiency, based on their CD4 cells count and percentage. In addition, 13 subjects (65%) were CDC class B or C.

At screening, the included subjects of cohort I (2-6 years old) were mainly treated with a backbone AZT/3TC (n=11) with few subjects treated with ABC/3TC (n=2) and d4T/3TC (n=1). A 3rd agent was used by 13 subjects (70%) and consisted in LPV/rtv (n=7), NNRTIs [nevirapine (n=4), efavirenz (n=1)] or RAL (n=1). Of note, 6 subjects were treated with monotherapy of lamivudine (n=5) or zidovudine (n=1) and one subject did not take ARVs at screening.

According to the protocol and the therapeutic indication of Intelence, subjects were rightly treated with ETR in combination with a boosted PI and at least one additional active drug. In cohort I, the boosted PI was mainly LPV/rtv (11 subjects) or DRV/rtv (8 subjects), with only 1 subject treated with ATV/rtv, and the 3rd agent was NRTI or RAL. No subjects were treated with more than 3 ARVs

The CHMP requested the MAH to display, for each subject from Cohort I, i) the number and composition of their previous ARV regimen and ii) whether there were modifications of their ARV regimen for efficacy and/or resistance concerns .

The MAH provided further information on the individual number and composition of the previous ARV regimen of each subject, which was acknowledged by the CHMP, and clarified that information on the reasons for modifications of the subjects' previous ARV regimen was not captured in the study. Considering the subjects from Cohort I (2-6 years old), the coadministration of ETR with a boosted PI and one additional active drug seems effective, with respectively 80% and 65% of subjects with viral load <400 c/ml and <200 c/ml at Week 48. As a matter of fact, it could be highlighted that this level of virologic suppression is achieved with 11 among the 20 subjects enrolled in the cohort, treated at the recommended ETR dose.

Efficacy data and additional analyses

ETR exposure with the recommended doses in this population is similar to that observed in older paediatric subjects (>6 years old, for which ETR is marketed) which was to be aligned to that of adult patients. In line with the EU guidelines for anti-HIV drug development, efficacy demonstration in HIV infected adults is not required to be duplicated for paediatric claim as soon as similar exposure to adults could be achieved to predict similar efficacy and safety.

Efficacy data although exploratory, can be regarded as reassuring in the cohort in subjects between 2 to 6 years old, 80% of the 20 subjects have achieved viral load <400 c/ml at Week 48. Therefore, a combination of 2 NRTIs + ETR recommended dose + another active ARV (usually PI or RAL) may be effective in ARV experienced paediatric subjects. These results were achieved while 11 on 20 subjects had required an adjusted dose so that finally be treated according to the recommended dose.

However, according to subgroup analyses, the mode of administration seems to have a significant impact on the efficacy result: across Cohorts I and II, 7/14 subjects who took ETR dispersed in liquid (including the 3 failing subjects from Cohort I) experienced virologic failure, vs none subject who swallowed the ETR tablet whole. PK data support this difference, with a statistically higher ETR exposure in children who swallowed the tablets whole compared to those who took the tablets dispersed in liquid. This may be the consequence of a partial intake of ETR when tablets are dispersed in liquid, possibly related to a bad taste.

Table 39: TEFVR02c: Outcome at Week 48 (FDA Snapshot Approach) by Subgroup – tablets dispersed; ITT (Study TNC125C234)

TEFVR02c: Outcome at Week 48 (FDA Snapshot Approach) by Subgroup; ITT (Study TMC125C234) *Snapshot Outcome: (<400 copies/mL)*			
	Etravirine		
n (%)	≥2 to <6 years (N=10)	≥1 to <2 years (N=4)	All Subjects (N=14)
Mode of Administration: Tablet Dispersed			
Week 48			
Virologic response	6 (60.0%)	0	6 (42.9%)
HIV RNA <400 copies/mL at Week 48	6 (60.0%)	0	6 (42.9%)
95% CI*	(26.2; 87.8)	(39.8; 100.0)	(17.7; 71.1)
Virologic failure	3 (30.0%)	4 (100%)	7 (50.0%)
HIV RNA ≥400 copies/mL at Week 48	2 (20.0%)	2 (50.0%)	4 (28.6%)
Virologic failure - leading to discontinuation	1 (10.0%)	1 (25.0%)	2 (14.3%)
Virologic failure - switched background regimen not permitted by the protocol	0	0	0
Virologic failure - discontinued due to other reason and last available HIV RNA ≥400 copies/mL	0	1 (25.0%)	1 (7.1%)
No viral load data in Week 48 window	1 (10.0%)	0	1 (7.1%)
Discontinued due to adverse event/death	1 (10.0%)	0	1 (7.1%)
Discontinued due to other reason and the last available HIV RNA <400 copies/mL (or missing)	0	0	0
Missing data during window but on study	0	0	0

Table 40: TEFVR02c: Outcome at Week 48 (FDA Snapshot Approach) by Subgroup - tablets swallowed; ITT (Study TNC125C234)

TEFVR02c: Outcome at Week 48 (FDA Snapshot Approach) by Subgroup; ITT (Study TMC125C234) *Snapshot Outcome: (<400 copies/mL)*		
	Etravirine	
n (%)	≥2 to <6 years (N=6)	All Subjects (N=6)
Mode of Administration: Tablet Swallowed		
Week 48		
Virologic response	6 (100%)	6 (100%)
HIV RNA <400 copies/mL at Week 48	6 (100%)	6 (100%)
95% CI*	(54.1; 100.0)	(54.1; 100.0)
Virologic failure	0	0
HIV RNA ≥400 copies/mL at Week 48	0	0
Virologic failure - leading to discontinuation	0	0
Virologic failure - switched background regimen not permitted by the protocol	0	0
Virologic failure - discontinued due to other reason and last available HIV RNA ≥400 copies/mL	0	0
No viral load data in Week 48 window	0	0
Discontinued due to adverse event/death	0	0
Discontinued due to other reason and the last available HIV RNA <400 copies/mL (or missing)	0	0
Missing data during window but on study	0	0

This may explain the inadequate rate of virologic response in the youngest subjects (Cohort II). Furthermore, PK data has reported a statistically higher ETR exposure in children who swallowed the tablets whole (mean ETR AUC12h: 10721 ng.h/ml) compared to those who took the tablets dispersed in liquid (mean ETR AUC12h: 2841 ng.h/ml, p<0.001).

Indeed, subgroups analyses highlighted that the mode of administration may have an impact the ETR exposure, with lower exposure (and consequently higher rate of virologic failure) in subjects who took the tablets dispersed in liquid vs ETR tablets swallowed whole. This trend is also observed with efficacy data. However, such administration is expected to be the main used method in younger subjects, especially under 6 years old. Notably, 5 of 6 subjects aged ≥2 to <6 years (Cohort I) who required an individual dose adjustment took the tablet dispersed in liquid.

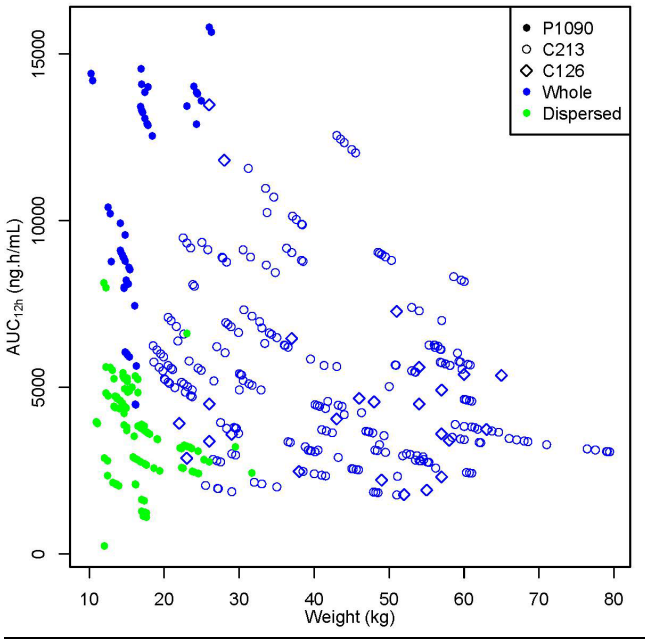
According to the protocol, the ETR tablets were to be swallowed whole with water or other liquid within 30 minutes following a meal. The tablets could also be dispersed in water or other liquid if the subject was unable to swallow the tablets whole. The ETR 25-mg and 100-mg tablets that are used in Study TMC125-C234 are the commercially available tablets. It was previously shown that, in healthy adults, the bioavailability of ETR was similar when the tablet was dispersed or swallowed whole (geometric mean (dispersed/whole) AUC ratio [90%CI]: 96.54% [90.48 – 103.0]). As such, it could be concluded that the bioavailability of ETR should be similar for dispersed tablets (taken correctly) compared to swallowed whole. However, since during study TMC125-C234 there were notifications of difficulties with dosing (refusing/vomiting/spitting up the dose and reporting bad taste).

This issue was signalled by the CHMP as a potential risks of formulation inadequacy. The formulation seems not appropriate for the younger population if not able to swallow whole.

At the request of the CHMP, the MAH analysed the impact of the mode of administration and the adequacy of the formulation. It should be noted that there were only 4 children with intensive PK on the recommended ETR dose who swallowed the tablet whole.

The MAH provided further data on the exposure of dispersed versus whole tablets and intake of entire dose. The popPK model, suggesting a formulation effect, was built based on PK data from Studies TMC125-C126, TMC125-C213, and TMC125-C234, including those obtained in children <2 years and/or <10 kg for whom intake issues were reported

Figure 17: AUC12h (Intensive and Population PK) of Whole and Dispersed Tablets for Children in



P1090: Study TMC125-C234
The low outlier for AUC12h of dispersed tablets was obtained for Subject [redacted] (12 kg) for which diarrhea was reported before and during the PK assessment

The popPK model suggests a lower ETR exposure in subjects taking ETR dispersed into liquid vs whole. However, the PK values are still within those observed in adults. In addition, there is no PK/PD relationship. Therefore, this lower ETR exposure might still be compatible with a virologic response.

Furthermore, the bioequivalence between ETR tablets administered dispersed vs swallowed whole was previously demonstrated in adults (study TMC125-C173). For children, the adequacy of the method for ETR administration by dispersion into liquid was verified in a study (*CMC Report DS-TEC-41719. In-use stability report of R165335 25mg oral tablets*). Thus, the bioavailability of ETR (and therefore ETR exposure) is expected to be similar whatever its method of administration, provided that i) the procedure for ETR tablets dispersion was rightly performed by the child caregiver, and ii) there was no intake issue by the child.

In children from 2 to <6 years of age, ETR sub-exposure was reported in subjects who took ETR tablets dispersed in liquid (which is expected to be the main method of administration in these subjects). This was due to intake issues (refusal by the child, notably because of bad taste), and low ETR dose (for subjects who had a body weight at the higher end (16-<20kg) of the range for which a dose a 100 mg was recommended (10-<20kg). This was predicted by the popPK analysis, where 10% to 20% of subjects weighing between 16-20 kg and receiving the recommended ETR dose (100 mg BID) are expected to have ETR AUC below the threshold of 2350 ng.h/ml. Of note, ETR is already indicated with this posology for children weighing 16 to 20 kg. For these subjects, no virological failure was reported.

In the case of children below 2 years of age, ETR sub-exposure and virological failure were associated to intake issues.

In addition, CHMP recommended the MAH to strongly advise in the SmPC that for children between 2 to 6 years of age who cannot swallow the tablet, a different drug can favourably be used instead of dispersing the tablet in liquid and potentially getting too low exposure. For the rare situations where

ETR is considered as the last option available and cannot be swallowed whole, CHMP recommended the MAH to reinforce the recommendation for an adequate handling of the dispersed tablet and discuss recommendation of Plasma Drug Monitoring (PDM) to ensure the adequacy of the ETR dose.

The MAH exposed that PDM, while not bearing major safety concerns, seemed unlikely to yield in improvements in treatment outcome. The CHMP agreed that a systematic TDM might not be an optimal tool, in view of the lack of PK/PD relationship and the fact that this might not always be locally feasible. Instead, the focus should stay on ensuring the adequate dispersion and complete intake of the ETR dose rather than the ETR plasma concentration.

In relation to the very low rate of virologic success in the younger cohort (1-<2 years old), with almost all included subjects (5/6) who have experienced virologic failure, the CHMP endorsed the MAH decision to stop inclusion of these subjects. However, CHMP requested the MAH to further scrutinize the reasons behind such a poor virologic response notably based on PK data and mode of administration and discuss the potential relevance for the claimed target paediatric extension.

Moreover, The CHMP requested the MAH to clarify if any condition (e.g. concomitant infection) has occurred in subjects with virologic failure which could have contributed to the observed increase in viral load in these cases. When focusing on the 3 subjects from Cohort II who experienced virologic failure, no common characteristic may be highlighted (notably as regards the weight or the subset group of ETR dose).

The MAH explored the potential reasons that could explain the inadequate response rate in subjects below 2 years of age. In Cohort II (⩾1 to <2 years), the MAH found that treatment adherence issues and infection episodes (mostly upper respiratory infections) seem to be the likely underlying reasons for the observed increase in viral load in these subjects.

In the case of Cohort I (⩾2 to <6 years), the MAH found that treatment adherence issues seem to be the likely underlying reasons for the observed increase in viral load in these subjects. Adherence/intake issues were not reported to the same extent as those reported in Cohort II.

The MAH's response was acknowledged by the CHMP. Even though infection episodes were occasionally identified, and in some cases temporally associated with a rise in viral load, the main driver for virologic failure was more likely related to treatment adherence issues (particularly in cohort I).

Again, the CHMP reinforced the concept that ensuring adequate administration is essential to obtain optimal virologic response.

Finally, regarding the development of resistance, the emergence of NNRTI RAMs is consistent with the known resistance profile of ETR.

2.4.3. Conclusions on the clinical efficacy

Overall, it is acknowledged that this study is not designed to substantiate clinical efficacy in subjects <6 years old. Nonetheless, the efficacy data in subjects between 2 to 6 years of age suggest that the recommended ETR doses, co-administered with boosted PI and another ARV, could be effective to obtain virologic success in ARV-experienced children between 2 to 6 years of age at the recommended dose. However, when integrating the PK and efficacy findings (notably the poor response rate in children from 1 to 2 years of age, with reasons of potential relevance for the claimed population) there is a need to better understand the situations under which ETR would not be adequate for achieving virologic response in the newly targeted younger paediatric age strata**.**

Concerns were raised on the fact that mode of administration may impact the ETR exposure, with lower exposure in subjects who took the tablets dispersed in liquid, even more when having in mind the

significant PK variability of ETR. Moreover, some patients have required higher than the ETR recommended dose. Inadequate method of dispersion and intake issues seem to be the more likely reasons for ETR sub-exposure and consequently for virologic failure. Therefore, the MAH proposed to reinforce the message in the SmPC and PL in response to CHMP recommendation. The MAH has included a warning in section 4.4 of the SmPC in regards to the potential risk of inadequate intake with potential virologic impact. It includes more explicit content, reflecting to some extent the recommendations given to the caregivers during the clinical trial (notably the methods of dilution of the tablets with the precision of the required volumes to be use).

2.5. Clinical safety

Patient exposure

At the cut-off date for the Week-48 analysis (12 July 2018), 26 subjects had been included in the study: 20 subjects aged ≥2 to <6 years (Cohort I) and 6 subjects aged ≥1 to <2 years (Cohort II). A total of 15 subjects received the recommended ETR dose throughout the study (subset i), 11 subjects in Cohort I and 4 subjects in Cohort II. A total of 22 subjects received the recommended ETR dose or higher (subset i+b), 16 subjects in Cohort I and 6 subjects in Cohort II.

- Cohort I (ITT population, N=20): Mean (SD) ETR exposure: 143.11 (82.88) weeks; Total patient-years of ETR exposure: 54.9 years

- Cohort II (ITT population, N=6): Mean (SD) ETR exposure: 53.48 (25.64) weeks; Total patient-years of ETR exposure: 6.1 years

Of these 26 subjects, 18 (69.2%) subjects (15 [75.0%] subjects in Cohort I and 3 [50.0%] subjects in Cohort II) were ongoing in the study at the time of analysis. Data beyond Week 48 were available for 17/26 (16/20 subjects in Cohort I and 1/6 subjects in Cohort II) subjects, with a maximum follow-up until Week 276.

Adverse events

All subjects in each cohort reported at least one adverse event (AE). The incidence of grade 3 or grade 4 AEs was 45.0% (9/20) and 83.3% (5/6) in Cohort I and Cohort II, respectively, and the incidence of serious adverse events (SAEs) at least possibly related to ETR was 10.0% (2/20) and 0% (0/6) of subjects in Cohort I and Cohort II, respectively. The majority of the AEs occurred between baseline and the Week 48 visit.

Table 41: Adverse Events: Summary Table; ITT (Study TMC125-C234)

Phase = Treatment

	≥2 to <6 years (N=20)	≥1 to <2 years (N=6)	All Subjects (N=26)
with at least one AE	20 (100.0%)	6 (100.0%)	26 (100.0%)
with at least one SAE	3 (15.0%)	3 (50.0%)	6 (23.1%)
with at least one fatal AE	0	0	0
with at least one worst grade 1 or 2 AE	11 (55.0%)	1 (16.7%)	12 (46.2%)
with at least one worst grade 3 or 4 AE	9 (45.0%)	5 (83.3%)	14 (53.8%)
with at least one AE for which study drug was permanently stopped	1 (5.0%)	0	1 (3.8%)
with at least one SAE which is at least possibly related to ETR	2 (10.0%)	0	2 (7.7%)

Table 41: Adverse Events: Summary Table; ITT (Study TMC125-C234)

Phase = Treatment

	≥2 to <6 years (N=20)	≥1 to <2 years (N=6)	All Subjects (N=26)
with at least one SAE which is at least possibly related to OBRa	3 (15.0%)	2 (33.3%)	5 (19.2%)
with at least one worst grade 3 or 4 AE at least possibly related to ETR	3 (15.0%)	1 (16.7%)	4 (15.4%)

a Relationship to OBR was only collected for serious AEs.

The most frequently reported AEs by preferred term were:

- In Cohort I: nasal congestion (70.0% [14/20] of subjects), cough (65.0% [13/20] of subjects), and pyrexia (50.0% [10/20] of subjects).

- In Cohort II: nasal congestion (100% [6/6] of subjects), cough (100% [6/6] of subjects), and rhinorrhea (83.3% [5/6] of subjects).

None of these most frequent AEs for which a causality assessment was available were considered related to ETR.

Table 42: Frequency (%) of Adverse Events at Least Possibly Related to ETR; ITT (Study TMC125-C234)

Phase = Treatment

	≥2 to <6 years (N=20)	≥1 to <2 years (N=6)	All Subjects (N=26)
Any adverse event	4 (20.0%)	1 (16.7%)	5 (19.2%)
Investigations	3 (15.0%)	1 (16.7%)	4 (15.4%)
Lipase increased	2 (10.0%)	0	2 (7.7%)
Alanine aminotransferase increased	0	1 (16.7%)	1 (3.8%)
Blood pressure diastolic increased	1 (5.0%)	0	1 (3.8%)
Gastrointestinal disorders	1 (5.0%)	0	1 (3.8%)
Vomiting	1 (5.0%)	0	1 (3.8%)

Serious adverse event/deaths/other significant events

There were no deaths during the study.

SAEs were reported in 15.0% (3/20) of subjects in Cohort I and 50.0% (3/6) of subjects in Cohort II:

- All SAEs by preferred term were reported in at most 1 subject within a cohort, except for lipase increased (reported in 2 subjects in Cohort I).

- Two subjects (1 in each cohort) had more than 1 SAE (Subject in Cohort I: lipase increased and platelet count decreased; Subject in Cohort II: platelet count decreased and ligament sprain).

- Three SAEs were grade 4 in severity (platelet count decreased and lipase increased in 1 subject in Cohort I, and anemia in 1 subject in Cohort II), and 1 was grade 2 in severity (ligament sprain); the other SAEs were grade 3 in severity.

- One SAE in Cohort I (lipase increased [reported in 2 subjects]) was considered to be at least possibly related to ETR. Both cases of lipase increased were considered to be at least possibly related to OBR, as well as 1 case of anemia (Cohort II), and 2 cases of neutrophil count decreased (1 in Cohort I and 1 in Cohort II).

- All SAEs occurred between baseline and the Week 48 visit.

Table 43: Frequency (%) of Serious Adverse Events; ITT (Study TMC125-C234)

Phase = Treatment

	≥2 to <6 years (N=20)	≥1 to <2 years (N=6)	All Subjects (N=26)
Any adverse event	3 (15.0%)	3 (50.0%)	6 (23.1%)
Investigations	3 (15.0%)	2 (33.3%)	5 (19.2%)
Lipase increased	2 (10.0%)	0	2 (7.7%)
Neutrophil count decreased	1 (5.0%)	1 (16.7%)	2 (7.7%)
Platelet count decreased	1 (5.0%)	1 (16.7%)	2 (7.7%)
Blood and lymphatic system disorders	0	1 (16.7%)	1 (3.8%)
Anaemia	0	1 (16.7%)	1 (3.8%)
Injury, poisoning and procedural complications	0	1 (16.7%)	1 (3.8%)
Ligament sprain	0	1 (16.7%)	1 (3.8%)

Note: Two subjects had more than 1 SAE (lipase increased and platelet count decreased [Subject [redacted]]; platelet count decreased and ligament sprain [Subject [redacted]]).

One subject in Cohort I had grade 4 lipase increased leading to permanent discontinuation of ETR at Week 2 (see Section 5.1.2.3). This grade 4 AE was reported as serious and considered related to ETR and OBR. No other (S)AEs led to permanent discontinuation of ETR.

Grade 3-4 AEs were reported in 45.0% (9/20) of subjects in Cohort I and 83.3% (5/6) of subjects in Cohort II:

- All grade 3-4 AEs concerned abnormalities in laboratory parameters or vital signs.

- All grade 3-4 AEs by preferred term occurred in at most 2 subjects within a cohort, except for blood pressure diastolic increased (reported in 3 subjects in each cohort) and blood pressure systolic increased (reported in 3 subjects in Cohort II).

- In Cohort I, 3 grade 3-4 AEs were reported as serious (lipase increased, neutrophil count decreased, and platelet count decreased).

- In Cohort II, 3 grade 3-4 AEs were reported as serious (neutrophil count decreased, platelet count decreased, and anemia).

- All Grade 3-4 AEs occurred between baseline and the Week 48 visit, except for 1 case of blood pressure diastolic increased in each cohort, 1 case of blood cholesterol increased, 1 case of blood pressure systolic increased, 1 case of low-density lipoprotein (LDL) increased, and 1 case of pyrexia.

Adverse events of interest

The AEs of interest (AEOI) for ETR included skin adverse events (rash cases, severe cutaneous reactions and angioedema), hepatic events (including liver enzyme elevations), pancreatic events and lipid-related events. A summary of the main AEOIs is provided in the Table 44 below:

Table 44: Adverse Events of Interest by Event of Interest Group; ITT (Study TMC125-C234)

Phase = Treatment

	≥2 to <6 years (N=20)	≥1 to <2 years (N=6)	All Subjects (N=26)
Any AEOI	14 (70.0%)	5 (83.3%)	19 (73.1%)
Skin events	13 (65.0%)	5 (83.3%)	18 (69.2%)
'(Serious) Rash Cases'*	11 (55.0%)	3 (50.0%)	14 (53.8%)
Rash	9 (45.0%)	2 (33.3%)	11 (42.3%)
Rash generalised	3 (15.0%)	1 (16.7%)	4 (15.4%)
Rash papular	2 (10.0%)	0	2 (7.7%)
Rash pruritic	2 (10.0%)	0	2 (7.7%)
Erythema	1 (5.0%)	0	1 (3.8%)
Rash erythematous	1 (5.0%)	0	1 (3.8%)
Rash pustular	1 (5.0%)	0	1 (3.8%)
'Angioedema'*	2 (10.0%)	2 (33.3%)	4 (15.4%)
Wheezing	1 (5.0%)	2 (33.3%)	3 (11.5%)
Urticaria	1 (5.0%)	0	1 (3.8%)
'(Severe) Cutaneous Reactions'*	2 (10.0%)	1 (16.7%)	3 (11.5%)
Mouth ulceration	2 (10.0%)	1 (16.7%)	3 (11.5%)
Hepatic events	0	2 (33.3%)	2 (7.7%)
Liver-related investigations, signs and symptoms	0	2 (33.3%)	2 (7.7%)
Alanine aminotransferase increased	0	1 (16.7%)	1 (3.8%)
Aspartate aminotransferase increased	0	1 (16.7%)	1 (3.8%)
Hepatomegaly	0	1 (16.7%)	1 (3.8%)
Pancreatic events	2 (10.0%)	0	2 (7.7%)
Pancreatitis	2 (10.0%)	0	2 (7.7%)
Lipase increased	2 (10.0%)	0	2 (7.7%)
Lipid-related events	1 (5.0%)	0	1 (3.8%)
Hyperlipidaemia	1 (5.0%)	0	1 (3.8%)
Blood cholesterol increased	1 (5.0%)	0	1 (3.8%)
Low density lipoprotein increased	1 (5.0%)	0	1 (3.8%)

* '(Serious) rash cases' are based on a predefined list of selected preferred terms used for the post-marketing safety monitoring; '(Severe) cutaneous reactions' are AEs grouped under the MedDRA SMQ of 'severe cutaneous adverse reactions', broad scope; and 'Angioedema' are AEs grouped under the MedDRA SMQ of 'angioedema', broad scope. Note:'Serious' does not refer to the seriousness criteria as outlined in ICH guideline E2A.

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- Skin events

Skin adverse events have been reported in 65% (13/20) of patients from cohort I and 83.3% (5/6) of patients from cohort II. All skin AEOI were grade 1 or 2 in severity. None led to ETR discontinuation. None of the skin adverse events for which a causality assessment is available was considered as related to ETR.

For the rash, the most frequent skin AEOI reported in 55% (11/20) of patients from cohort I and 50% (3/6) of patients from cohort II, all cases resolved while ETR treatment was continued and therefore none have been considered as related to ETR.

For (severe) cutaneous reactions, reported in 10% (2/20) of patients from cohort I and 16.7% (1/6) of patients from cohort II, one event in cohort I was considered as not related to ETR and the causal relationship to ETR for the other 2 AE was not reported.

For angioedema and related AE reported in 10% (2/20) of patients from cohort I (wheezing and urticarial) and 33% (2/6) of patients from cohort II (wheezing), all cases but one grade 2 were grade 1 in severity and the causal relationship was considered as not related or not reported. ARV therapies

have been continued in all cases. Overall none of the 4 cases have been considered as suggestive of angioneurotic syndrome.

- Hepatic events

Hepatic adverse events have been reported in 33% (2/6) patients from cohort II and in none patients from cohort I. Both AEs occurred before week 48 and none of them were serious or led to ETR discontinuation. There were:

-hepatomegaly reported in a [redacted] patient on day 1 which resolved on D106. HPM was considered as not related to ETR.

-one grade 4 ALT increased (possibly related to ETR and OBR) and grade 3 AST increased (considered as not related to ETR/OBT) reported at week 16 in a [redacted] patient which resolved at week 24. Both ETR and OBT have been temporarily suspended for 2 day at week 16.

Apart from the case described above, no other grade 3 or 4 hepatic laboratory abnormalities have been reported.

- Pancreatic events

Pancreatic adverse events occurred in 10% (2/20) of patients from cohort I and none from cohort II. Both patients from cohort I experienced serious lipase increase before week 48:

-a [redacted] patient experienced grade 4 lipase increased considered as definitely related to ETR and probably related to OBT at week 2. On day 16, ETR was permanently discontinued and OBT (LPV/rtv and RTG) temporarily suspended. The patient had no symptoms of pancreatitis and abdominal CT normal. At days 36 and 44, he had grade 2 lipase increase. The OBR was re-started.

-a [redacted] patient experienced grade 3 lipase increased at week 16. He had normal lipase at baseline and lipase returned to grade 2 at day 130 and to normal at the last assessment post-treatment. The AE was considered as possibly related to ETR and probably related to OBR (LPV/rtv and raltegravir).

Apart from these grade 3 and 4 lipase increase described above, no other grade 3 or 4 laboratory anomalies were reported.

- Lipid-related events:

Lipid-related adverse events have been reported in 5% (1/20) of patients from cohort I and none from cohort II. The only AE reported was a grade 3 blood cholesterol increased at week 120 and a grade 3 LDL cholesterol increased at week 156. Both AEs were not serious. ETR was not discontinued. The causality assessment for ETR was not specified. No other graded lipid-related laboratory abnormalities were reported in the paediatric population included in the study.

- Other AEOI:

As neuropsychiatric AEs, one grade 2 insomnia was reported on day 1303 in a [redacted] patient from cohort I. The duration of the AE is unknown. The AE was considered as not related to ETR and causality to OBR was not reported.

A neoplastic AEs, one skin papilloma (grade 1 not related to ETR) was reported in a patient from the cohort I.

Otherwise, no bleeding and cardiac AEs have been reported in the study.

Laboratory findings

The majority of treatment-emergent laboratory abnormalities reported are grade 1 or 2. Grade 3 and/or 4 disorders have been reported in 9 patients. Apart from the 5 reported described earlier, there have been 1 Hb decreased in a patient from cohort II, 1 platelet count decreased in 2 patients (1 in each cohort) and absolute neutrophils count decreased in 3 patients (1 in cohort II and 2 in cohort I). None led to ETR discontinuation.

Discontinuation due to adverse events

1 subject (5.0%) in Cohort I (and none in Cohort II) permanently discontinued ETR due to grade 4 lipase increased, which was reported as a grade 4 SAE that was considered to be related to ETR and the OBR.

Other safety assessments

The review of vital signs or electrocardiogram parameters did not identify any clinically relevant findings. Regarding growth parameters, the median height-for-age z-scores increased over time in both cohort I and II and the median weight-for-age z-scores increase was small notably in cohort I. Head circumferences have been measured in subjects aged <3 years. The median head circumference z-scores increased over time in cohort II and was available in only 1 patient from cohort I.

Overall, according to the MAH, no newly identified safety concerns have emerged from the review of safety data gathered in the study.

Post marketing experience

At the time of the finalization of this Summary of Clinical Safety Addendum, 16 Periodic Benefit Risk Evaluation Reports (PBRERs)/Periodic Safety Update Reports (PSURs) were available summarizing the safety data for ETR obtained by Global Medical Safety of Johnson & Johnson Pharmaceutical Research & Development during the period from 27 March 2008 to 27 September 2018, including data from paediatric patients. Additionally, postmarketing exposure data were requested for the period from 28 September 2018 to 31 July 2019.

There were 168,480 units of 25 mg ETR tablets distributed worldwide from launch to 31 July 2019. Based on the 313,187,880 tablets distributed worldwide from launch to 31 July 2019, the estimated exposure to 100 mg ETR is 217,491 person-years. Based on the 237,414,548 tablets distributed worldwide from launch to 31 July 2019, the estimated exposure to 200 mg ETR is 329,742 person-years.

The most recent PBRER/PSUR concluded that, no new risk or change in the risks characteristics were identified during the reporting period and that ETR continues to have a favourable benefit-risk profile for the treatment of patients with the approved indication.

2.5.1. Discussion on clinical safety

Overall, AEs considered related to ETR were lipase increase (n=2), ALT increase (n=1), vomiting (n=1) and platelet count decreased (n=1). As expected, rash and other skin events were commonly observed (69% of all subjects) although none was considered related to ETR. Two hepatic events were observed,

both in Cohort II (1-<2 years old). In Cohort I (2-<6 years old), 2 lipase increases, both considered related to ETR, were observed, including one Grade 4 leading to discontinuation. No symptoms of pancreatitis were observed.

Rash, ALT increase and lipase increase are known AEs observed with ETR. No new AEs was observed.

2.5.2. Conclusions on clinical safety

According to the Applicant, there were no newly identified clinically relevant safety findings in subjects from either Cohort I (aged ≥2 to <6 years) or Cohort II (aged ≥1 to <2 years) of this study, up to the safety cut-off date of 31 July 2019, compared with the known ETR safety profile in HIV-1 infected adults, adolescents and children aged ≥6 years. However, the number of subjects included in this study is too small to detect potential safety concern in this population.

2.5.3. PSUR cycle

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal. The PSUR cycle for the medicinal product should continue to follow a one-yearly cycle. The next data lock point will be 27 September 2020.

2.6. Risk management plan

The MAH submitted an updated RMP version (version 3, with a DLP 31 July 2019) with this application, in replacement of version 12.

The CHMP received the following PRAC Advice on the submitted Risk Management Plan:

The PRAC considered that the risk management plan version 3 is acceptable.

The CHMP endorsed the Risk Management Plan version 3 with the following content:

Safety concerns

The main proposed RMP changes were the revision of the safety specifications and PhV Plan due to the extended indication to children from 2 years of age instead of 6 years of age and the revision of the RMP in accordance with GVP Module V Rev 2.

The changes proposed are detailed below for each section

Epidemiology of the indications and Target Population

The figures concerning the target population (adults and children) have been revised accordingly based on the 2018 UNAIDS report.

Clinical trial exposure

The figures concerning children exposed to etravirine in clinical trials notably in studies TMC125-C234 and TMC125-C213 have been updated accordingly.

Safety specifications

Based on the extension of the submitted indication to paediatric patients from 2 years of age, the MAH has proposed :

- to change missing information "long-term safety data in children 6 years to less than 18 years of age" to "long-term safety data in children 2 years to less than 18 years of age",
- to remove the following important identified risks:

  -Rash/ severe cutaneous reactions

  -severe hypersensitivity including Drug Rash with Eosinophilia and Systemic Symptoms (DRESS),

  -hepatotoxicity

  -pancreatitis

  -hyperlipidemia

  -coronary artery disorders

  -development of drug resistance

  -drug-drug interactions

The justification provided by the applicant to remove from the safety specifications all these risks is that all these risks have been identified during the clinical development program. In post-marketing, no new signals have been raised. The applicant considers these risks to be fully characterized and appropriately managed. Moreover, there are no outstanding additional pharmacovigilance activities to evaluate these risks for Intelence and no further evaluation is considered as needed. Most risks are included in the European Guidelines as adverse reactions of individual ARV drugs. The information provided in the SmPC and Package Leaflet is considered as sufficient to inform on these risks.

- to remove the following important potential risks:
  - overdose due to medication error,

The Applicant justifies this removal stating that no cases of medication error and consequently no medication error resulting in overdose have been reported during the clinical development program. No new signals have been raised in post-marketing on this issue. There are also no outstanding additional pharmacovigilance activities to evaluate these risks for Intelence and no further evaluation is considered as needed.

  - immune reconstitution inflammatory syndrome

Cases of IRIS have been reported with etravirine-containing cART during its clinical development program. No new signals have been raised in post-marketing on this issue. There are also no outstanding additional pharmacovigilance activities to evaluate these risks for Intelence and no further evaluation is considered as needed. The diagnosis and management of this potential risk has been included into standard clinical practise. And the information provided in the SmPC and Package Leaflet is considered as sufficient to inform on these risks.

- to remove the following missing information:
  - children less than 6 years of age

The MAH justifies this removal by stating that children less than 6 years of age are no longer considered as missing information since indication of Intelence is proposed to be extended to children from 2 years of age based on results from the week 48 report of the TMC125-C234/IMPAACT study.

  - pregnant and breastfeeding women

The reason to justify this removal is according to the MAH that data from trial TMC114HIV3015 (PK and ETR during pregnancy) indicated that there is no clinically relevant impact of pregnancy on ETR PK (total exposure was generally higher during pregnancy but nevertheless in range with previously observed value in HIV-infected subjects). There have been no new clinically relevant safety findings in the mothers and in the newborns in this trial. Moreover, no signal i.e. no major teratogenic effect associated with etravirine have been identified in the APR. Data from an Investigator Initiated Study indicated that etravirine is excreted in human milk. The effect of etravirine on newborns/ infants is unknown. No other signal have been identified in post-marketing. There are no outstanding additional pharmacovigilance activities to evaluate the risks associated with the etravirine use during pregnancy and no need for it. The information provided in the PI (SmPC and PIL) is considered as sufficient (i.e. given the increased ETR exposure during pregnancy, caution should should be applied for pregnant patients that require concomitant medicinal products or have comorbidities that may further increase ETR exposure, HIV-infected women should be instructed not to breast-feed under any circumstances in order to avoid transmission of HIV).

- elderly (65 years of age and above)

Although limited information is available on the use of etravirine in elderly patients, the MAH states that evidence suggests that the safety profile of etravirine in this population is not different from that in the general population.

Overall, the list of safety specifications proposed by the MAH for Intelence is summarized in the table below:

Table 45: Summary of Safety Concerns from the annotated Risk Management Plan

Table SVIII.1: Summary of Safety Concerns

Important identified risks	None~~Rash/severe cutaneous reactions~~
	~~Severe hypersensitivity, including DRESS~~
	~~Hepatotoxicity~~
	~~Pancreatitis~~
	~~Hyperlipidaemia~~
	~~Coronary artery disorders~~
	~~Development of drug resistance~~
	~~Drug-drug interactions~~
Important potential risks	~~Overdose due to medication error~~None
	~~Immune reconstitution inflammatory syndrome~~
Missing information	Long-term safety data in children ~~6~~2 years to less than 18 years of age
	~~Children less than 6 years of age~~
	~~Pregnant and breast-feeding women~~
	~~Elderly (65 years of age and above)~~

Considering the rationale provided by the applicant and the revised GVP Module V Rev 2, the safety concerns listed above can be considered as appropriate.

Pharmacovigilance plan

No new additional pharmacovigilance activities have been proposed in the timeframe of the extension of indication in children from the age of 2 years. The study TMC125-EPPICC has been completed and has therefore it has been deleted. The ongoing and planned additional pharmacovigilance activities are summarized in the table below:

Table 46: Ongoing and Planned Additional Pharmacovigilance Activities from the annotated Risk Management Plan

Table Part III.1: Ongoing and Planned Additional Pharmacovigilance Activities

Study Status	Summary of Objectives	Safety Concerns Addressed	Milestones	Due Dates
Category 1 - Imposed mandatory additional pharmacovigilance activities which are conditions of the marketing ~~authorisation~~authorization				
Not applicable				
Category 2 - Imposed mandatory additional pharmacovigilance activities which are Specific Obligations in the context of a conditional marketing ~~authorisation~~authorization or a marketing ~~authorisation~~authorization under exceptional circumstances				
Not applicable				
Category 3 - Required additional pharmacovigilance activities				
Continued access to ETR~~etravirine~~ in treatment-experienced HIV-1-infected subjects~~children and adolescents~~ (study TMC125-C239) Ongoing	To ~~provide continued access to ETR for paediatric subjects completing 48 weeks of treatment in trial TMC125-C213 and~~ collect safety information ~~beyond 48 weeks~~ of ETR treatment in subjects >2 years of age who have completed another clinical trial with ETR~~children 6 years to less than 18 years of age~~.	Long-term safety data in children 2~~6~~ years to less than 18 years of age (missing information)	Final data	Open-ended
A Phase 1/2, open-label trial to evaluate the safety, tolerability, pharmacokinetics and antiviral activity of etravirine (ETR) in antiretroviral treatment-experienced HIV-1-infected infants and children, aged ~~>=~~2 months to <6 years (post	To determine the ~~appropriate dose of ETR in combination with an OBR and to determine the~~ safety and tolerability of ETR ~~in combination with an OBR through 48 weeks of therapy~~ in treatment-experienced HIV-1 infected infants and children aged 2 months to <~~less than~~ 6 years ~~of age~~, when they all either completed the Week-48 study visit, or discontinued earlier. For children who	~~Children less than 6 years of age~~ Long-term safety data in children 2 years to less than 18 years of age (missing information)	~~Week 48 study report~~ Final report	Q2~~4~~ 202~~19~~

Study Status	Summary of Objectives	Safety Concerns Addressed	Milestones	Due Dates
Week-48 follow-up period of study TMC125-C234/ IMPAACT P1090) Ongoing	successfully completed 48 weeks of ETR treatment and continue to receive ETR, long-term safety data will be collected for up to maximum 5 years. (Note that subjects ≥2 months to <1 year were not enrolled)			
~~A pharmacovigilance study to define the long-term safety profile of etravirine in HIV-1 infected children and adolescents in Europe (study TMC125-EPPICC)~~ ~~Ongoing~~	~~To monitor INTELENCE use in children and adolescents with HIV infection in a "real world" setting within EPPICC and to monitor patient safety in the short- to long-term.~~	~~Long-term safety data in children 6 years to less than 18 years of age (missing information)~~	~~Yearly report~~ ~~Final report~~	~~Starting Q3 2014~~ ~~Q3 2018~~

The final report of the study TMC125-EPPICC has been recently evaluated at the European level (EMA/H/C/900/P46) and led to reinforce the Intelence PI regarding the occurrence of Stevens-Johnson Syndrome in paediatric population with etravirine (type II variation II/055) . The revision of the additional pharmacovigilance activities planned for etravirine with additional follow-up of children enrolled in studies TMC125-C234/IMPAACT P1090 and TMC125-C239. Routine pharmacovigilance and the proposed post-authorisation PhV development plan are sufficient to identify and characterise the risks of the product.

Risk minimisation measures

No additional risk minimization measures have been proposed by the applicant in the timeframe of the extended indication for etravirine in children from the age of 2 years.

The risk minimization measures proposed for the missing information are summarized in the table below:

Missing information		
Long-term safety data in children ~~6~~2 years to less than 18 years of age	Routine risk ~~minimisation~~minimization measures: • ~~SmPC Section 4.1~~ • SmPC Section 4.8 • PL Section 2 • ~~~~ • Legal status: restricted medical prescription Additional risk minimization measures: • None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • None Additional pharmacovigilance activities: • Long-term safety study~~ies~~ TMC125-C239 ~~and TMC125-EPPICC~~Final data: Open-ended • Pediatric Phase 1/2 study TMC125-C234/IMPAACT P1090 (post Week-48 follow-up period) Final report: Q2 2021

Overall conclusions on risk minimisation measures

The proposed risk minimisation measures are sufficient to minimise the risks of the product in the proposed indication.

Elements for a public summary of the RMP

The elements for a public summary of the RMP do not require revision following the conclusion of the procedure.

The Annexes have been revised accordingly to the changes done previously. No additional information has been added.

2.7. Update of the Product information

As a consequence of this new indication, sections 4.1, 4.2, 4.4, 4.8, 5.1 and 5.2 of the SmPC have been updated. Sections 1, 2 and 3 of the Package Leaflet has been updated accordingly.

In addition, the MAH took the opportunity to update section 4.5 of the SmPC to remove the interactions with Nefinavir, Boceprevir and Simeprevir and to include some typographic changes in Annex II C and D.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

While untreated HIV-1 infection remains a life-threatening disease, it has become a chronic disease with combined antiretroviral therapy being early introduced to prevent pejorative impact of immune deficiency (notably including opportunistic infections in patients with CD4<200/mm3).

The goal of ARV therapy for HIV-1 infection is to delay disease progression and prolong survival by achieving maximal and durable suppression of HIV-1 replication. Thanks to combined antiretroviral therapies [mostly consisting in tri-therapy with one main agent [boosted protease inhibitor (PI), integrase inhibitor (INI) or non-nucleoside transcriptase inhibitor (NNRTI)] and a backbone regimen [with two nucleoside-reverse transcriptase inhibitors (NRTI)] nowadays available high level of viral suppression (>90% of patients with HIV RNA <50 copies/ml) can be achieved in HIV infected patients.

3.1.2. Available therapies and unmet medical need

Currently, the main ARV available for children below 6 years of age to be used as part of a multitherapy with NRTIs backbone are:

- NNRTIs: EFV (≥3 years old and ≥15 kg), NVP (≥2 months old)

- PIs: DRV/rtv (≥3 years old and ≥15 kg), LPV/rtv (≥14 days old)

- INI: raltegravir (from birth)

- other: maraviroc (≥2 years old and ≥10 kg)

Etravirine is a non-nucleoside analogue that, unlike others, can retain some level of activity against strains harbouring NNRTI resistance. Therefore, its pharmacodynamic properties confer some potential added value in children with NNRTI-RAM. While a medical need could be considered in Africa, given the use of nevirapine as part of prevention of vertical transmission and the concerning emergence of resistance, the situation is to be mitigated in EU/US and all the more given the availability of raltegravir. On a general point of view, the need for a triple class regimen with ETR **(NNRTI) plus a boosted PI** plus a third agent clearly limits the potential use in younger children, where NNRTI and boosted PI are preferably introduced sequentially to spare the subsequent lines of treatment in this chronic disease. However, still a medical need can be observed in EU given notably the migrant population from Africa.

In the European Union (EU), INTELENCE**, in combination with a boosted protease inhibitor (PI)** and other antiretroviral (ARV) medicinal products, is indicated for the treatment of HIV infection in antiretroviral therapy (ART)-experienced adult patients and in ART-experienced paediatric patients from 6 years of age.

An application for the extension of the indication in HIV-1 infected paediatric subjects aged ≥2 to <6 years was approved by the Food and Drug Administration (FDA) in July 2018, based on the Week-24 analysis of Study TMC125-C234. The purpose of the current EU type II variation is to extend the use of ETR to the same target population based on the 48 weeks data of this study.

3.1.3. Main clinical studies

3.2. Favourable effects

The clinical PK, efficacy and safety data in support of this younger age paediatric extension are derived from an open label phase 1/2 study TMC125-234 (IMPAACT 1090) enrolling 20 subjects in Cohort I (aged ≥2 to <6 years) and 6 subjects in Cohort II (aged ≥1 to <2 years). Subjects were on a virologically failing regimen (containing at least 3 ARV). Of note, a Cohort III (< 1 y/o) was originally planned but did not enrol and was closed.

Initially, all subjects from 2 to <6 years of age were treated with ETR 5.2 mg/kg BID, whatever their weight. However, the mean ETR exposure (AUC and Cmin) was significantly lower for the first 6 patients included in the mini-cohort I. Notably, 2 subjects required individual dose adjustment because their ETR AUC12h was below 2,350 ng.h/ml. Therefore, the Applicant proposed to increase ETR dose for subjects weighing <16 kg (6.8 mg/kg BID for subjects 13-<16 kg, and 8.8 mg/kg BID for subjects <13 kg). This dose adjustment for the lower weight ranges was supported by the population PK analysis and intensive PK analysis in subjects receiving the recommended dose of ETR.

ETR exposure with the recommended doses in this population is similar to that observed in older paediatric subjects (>6 years old, for which ETR is already authorized) which was to be aligned to that of adult patients. In line with the EU guidelines for anti-HIV drug development, efficacy demonstration in HIV infected adults is not required to be duplicated for paediatric claim as soon as similar exposure to adults could be achieved to predict similar efficacy and safety.

In subjects between 2 to 6 years old (Cohort I), 80% of the 20 subjects have achieved viral load <400 c/ml at Week 48. Therefore, a combination of 2 NRTIs + ETR recommended dose + another active ARV (usually PI or raltegravir) may be effective in ARV experienced paediatric subjects. These results were achieved while 11 on 20 subjects had required an adjusted dose so that finally be treated according to the recommended dose.

3.3. Uncertainties and limitations about favourable effects

It should be considered that conclusions on favourable effects were drawn from a very low number of subjects. In addition, the findings in some children shed some doubts on the adequate use of the drug in young children.

When having in mind that 11 children required dose adjustment to the recommended dose and 16 required dose adjustment to ETR dose or higher, this could indicate that 5 subjects in this cohort required a higher dose than the recommended dose for achieving adequate PK exposure.

While the PK parameters in the cohort II (1y/o to <2 y/o) were not that far from those in cohort I and 6 subjects in cohort II received the recommended ETR dose or higher, 5 on the 6 patients in cohort II did not achieve virologic success.

Table 47: Geometric Mean Ratio (Children/Adults) for ETR PK Parameters; ITT - Recommended ETR Dose (Study TMC125-C234)

	Geometric Mean			GMR (90% CI) [a,b]	
	≥2 to <6 years (N=15)	≥1 to <2 years (N=6)	Adults [b] (N=575)	≥2 to <6 years	≥1 to <2 years
AUC_{12h} (h*ng/mL)	3824	3328	4522	0.84 (0.61; 1.16)	0.73 (0.40; 1.35)
C_{0h} (ng/mL)	203	193	297	0.69 (0.46; 1.03)	0.65 (0.31; 1.35)
C_{12h} (ng/mL)	232	198	NA	0.78 (0.53; 1.17)	0.67 (0.35; 1.28)

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.

While the low response rate discouraged the applicant for any claim in the corresponding cohort II age strata, such finding needs to be scrutinized, since this shed doubts for the adequate use of the drug in children close to the lower age limit of the cohort I age strata.

The mode of administration seems to have a significant impact on the efficacy results: 7/14 subjects who took ETR dispersed in liquid (including 4 subjects aged between 1-2 years old) experienced virologic failure, vs 0/6 subjects who swallowed the ETR tablet whole. This may explain the inadequate rate of virologic response in the youngest subjects (Cohort II). Furthermore, PK data has reported a statistically higher ETR exposure in children who swallowed the tablets whole (mean ETR AUC12h: 10721 ng.h/ml) compared to those who took the tablets dispersed in liquid (mean ETR AUC12h: 2841 ng.h/ml, p<0.001).

The applicant discussed this issue and concluded that the lower ETR exposure might still be compatible with a virologic response.

3.4. Unfavourable effects

Overall, it is acknowledged that this study is not designed to substantiate clinical efficacy in subjects <6 years old.

Considering the PK data, no overexposure of ETR is expected is subjects <6 years of age receiving the recommended ETR doses.

AEs considered related to ETR were lipase increase (n=2), ALT increase (n=1), vomiting (n=1) and platelet count decreased (n=1). As expected, rash and other skin events were commonly observed (69% of all subjects) although none was considered related to ETR. Two hepatic events were observed, both in Cohort II (1-<2 years old). In Cohort I (2-<6 years old), 2 lipase increases, both considered

related to ETR, were observed, including one Grade 4 leading to discontinuation. No symptoms of pancreatitis were observed.

Rash, ALT increase and lipase increase are known AEs observed with ETR. No new AEs was observed.

3.5. Uncertainties and limitations about unfavourable effects

The number of subjects and the duration of ETR exposure are too limited to adequately substantiate the clinical safety of ETR in this paediatric population. At least no trend for a differential safety pattern seems to be identified.

3.6. Benefit-risk assessment and discussion

3.6.1. Importance of favourable and unfavourable effects

As above discussed, the need of a triple class regimen with ETR (NNRTI) plus a boosted PI plus a third agent clearly limits the potential use in younger children, where NNRTI and boosted PI are preferably introduced sequentially to spare the subsequent lines of treatment in this chronic disease. However, still a medical need can be observed in EU given notably the migrant population from Africa where nevirapine was used in vertical transmission with emergence of NNRTI resistance. Given that ETR is shown to maintain activity in presence of some NNRTI RAM, it is expected to be of potential interest in children.

Based on PK data, from intensive PK sampling and from POP PK modelling, ETR exposure is expected to be similar between the paediatric subjects 2-<6 years old and 6-<18 years old, and within the AUC range considered to be effective and safe (i.e. 60%-150% of the mean ETR AUC in adults).

AEs associated to Intelence are mainly gastrointestinal disorders and skin rash, with Stevens-Johnson Syndrome (SJS) which were reported at a higher incidence (1%) in paediatric subjects (6-18 years old) in a pos-tmarketing retrospective cohort than has been reported in adult clinical trials. Of note, no SJS were reported in the study TMC125-C234. Other severe cutaneous and hypersensitivity reactions were reported with Intelence. Transaminase and lipase increase were also reported.

However, the need for higher dose than the recommended in some children and the fact that the method of administration seems to significantly influence ETR PK parameters, with lower ETR exposure and consequently higher rate of virologic failure when ETR tablets are dispersed into liquid (main method of administration for subjects <6 years of age) is a source of concern. Also having in mind that the use of ETR in children from 1 to <2 years of age is considered inadequate so shedding also doubt for the use in the lower age limit of the claimed age strata.

3.6.2. Balance of benefits and risks

Considering that the targeted ETR exposure is obtained with the recommended ETR doses in paediatric subjects from 2 to 6 years old, the benefits provided by Intelence (i.e. to obtain a virologic suppression in ART-experienced subjects with virologic failure), coadministered with 2 NRTIs and a boosted PI, outweigh the potential risks associated to Intelence (i.e. mainly rash and severe hypersensitivity reactions, and also emergence of NNRTI-RAM).

3.7. Conclusions

The overall B/R of Intelence is positive.

4. Recommendations

Outcome

Based on the review of the submitted data, the CHMP considers the following variation acceptable and therefore recommends by consensus the variation to the terms of the Marketing Authorisation, concerning the following change:

Variation accepted		**Type**	**Annexes affected**
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I and IIIB

To extend the approved therapeutic indication of Intelence in order to include patient population from 2 to 6 years of age based on the 48 week study results from study TMC125-C234/P1090 (A Phase I/II, Open-label Trial to Evaluate the Safety, Tolerability, Pharmacokinetics and Antiviral Activity of Etravirine (ETR) in Antiretroviral (ARV) Treatment-experienced HIV-1 Infected Infants and Children, Aged ≥2 Months to <6 Years). As a consequence, sections 4.1, 4.2, 4.4, 4.8, 5.1 and 5.2 of the SmPC and sections 1, 2 and 3 of the PL are updated accordingly. The updated RMP version 13.1 has also been submitted.

The RMP (version 13.1) of the product has been updated to remove the completed additional pharmacovigilance activities (TMC125-C234/P1090 (Week 48) and TMC125-EPPICC) from the pharmacovigilance plan of the RMP). The RMP has also been updated to meet the requirements and updated definitions in the European Medicines Agency (EMA) Guideline on good pharmacovigilance practices (GVP) Module V Revision 2 (EMA/838713/2011; Rev 2) and Guidance on the format of the RMP in the European Union (EMA/164014/2018 Rev 2.0.1) including proposed removal of safety concerns. The PRAC agreed with version 13.1 of the RMP.

The MAH took the opportunity to update section 4.5 of the SmPC to remove the interactions with Nefinavir, Boceprevir and Simeprevir and to include some typographic changes in Annex II C and D.

Paediatric data

Furthermore, the CHMP reviewed the available paediatric data of studies subject to the agreed Paediatric Investigation Plan P/0121/2019 and the results of these studies are reflected in the Summary of Product Characteristics (SmPC) and, as appropriate, the Package Leaflet.

Amendments to the marketing authorisation

In view of the data submitted with the variation, amendments to Annex(es) I and IIIB and to the Risk Management Plan are recommended.