EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

24 June 2021
EMA/CHMP/298507/2021
Human Medicines Division

Assessment report for paediatric studies submitted according to Article 46 of the Regulation (EC) No 1901/2006

INTELENCE

etravirine

Procedure no: EMEA/H/C/000900/P46/053.1

Note

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

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1. Introduction

On 24/02/2021, the MAH submitted a completed paediatric study (TMC125-C234 - IMPAACT P1090 study) for Intelence, in accordance with Article 46 of Regulation (EC) No1901/2006, as amended.

The main results from the Week 48 of this study have been submitted to EMA in January 2019 (procedure EMEA/H/C/00900/P46/053). The results of the post Week 48 follow-up period are described in the clinical study report, which is included in this submission and a summary of the results is also described in the short critical expert overview.

2. Scientific discussion

2.1. Information on the development program

This study was part of the Intelence Paediatric Investigation Plan (EMEA-000222-PIP01-08-M09, decision P/0121/2019), for which a full PIP compliance check has been performed (compliance statement EMEA-C-000222-PIP01-08-M09). The extension of the indication in HIV-1 infected pediatric subjects aged ≥2 to <6 years (procedure EMEA/H/C/000900/II/0058) was approved by the European Medicines Agency (EMA) in April 2020, based on the Week 48 analysis of Study TMC125-C234/P1090.

2.2. Information on the pharmaceutical formulation used in the study

Three tablet formulations are registered in EU, which can be either swallowed whole or dispersed:

- A scored 25-mg tablet (F066).

- A 100-mg tablet (F060).

- A 200-mg tablet (F068).

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 human immunodeficiency virus (HIV) infection in antiretroviral therapy (ART)-experienced adult patients and in antiretroviral therapy (ART)-experienced pediatric patients beginning at 2 years of age. The recommended dose of ETR for paediatric patients aged ≥2 years to <18 years and weighing ≥10 kg is based on body weight:

Body Weight	Dose	Tablets
≥10 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

The extension of the indication in HIV-1 infected pediatric subjects ≥2 to <6 years of age was based on the Week-48 analysis of Study TMC125-C234/P1090. The MAH submitted a final report of this study, including the long-term follow-up period after the week 48 endpoint.

2.3.2. Clinical study

Study TMC125-C234 (IMPAACT P1090)

The design and W48 results of this study were already detailed and discussed within the PAM P46/053 and the variation II/058.

Description

Study TMC125-C234 (IMPAACT P1090) is an ongoing Phase 1/2 study which evaluates the pharmacokinetics, safety, tolerability, and antiviral activity of ETR in HIV-1 infected pediatric 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

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.

Secondary Objectives

- To assess the antiretroviral activity of ETR containing regimens through 48 weeks of therapy.

- To determine the immunological changes (change in CD4 percent and absolute count;

CD4/CD8 ratio and percent) through 48 weeks of ETR therapy in combination with an OBR.

- To determine changes in viral drug resistance during 48 weeks of ETR therapy in combination with an OBR.

- To assess the relationship between ETR pharmacokinetics and the antiviral activity and safety of ETR containing regimens.

- To explore the relationship between subject-specific gene CYP profile, sex, age, weight, race, HIV regimen (e.g., boosted PI) and HIV response markers and pharmacokinetics of ETR.

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.

The study was planned to be conducted in the following 3 age cohorts:

Cohort	Description of Subject	Drug Regimen	Phenotyping / Genotyping Information	Comments	Anticipated Accrual		
					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.

Each cohort was to begin enrollment into an initial mini-cohort of 6 subjects. Once the PK and safety data were found to be acceptable (as defined per protocol), enrollment was to be continued at the same ETR dose to complete enrollment 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 enrollment. 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:

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

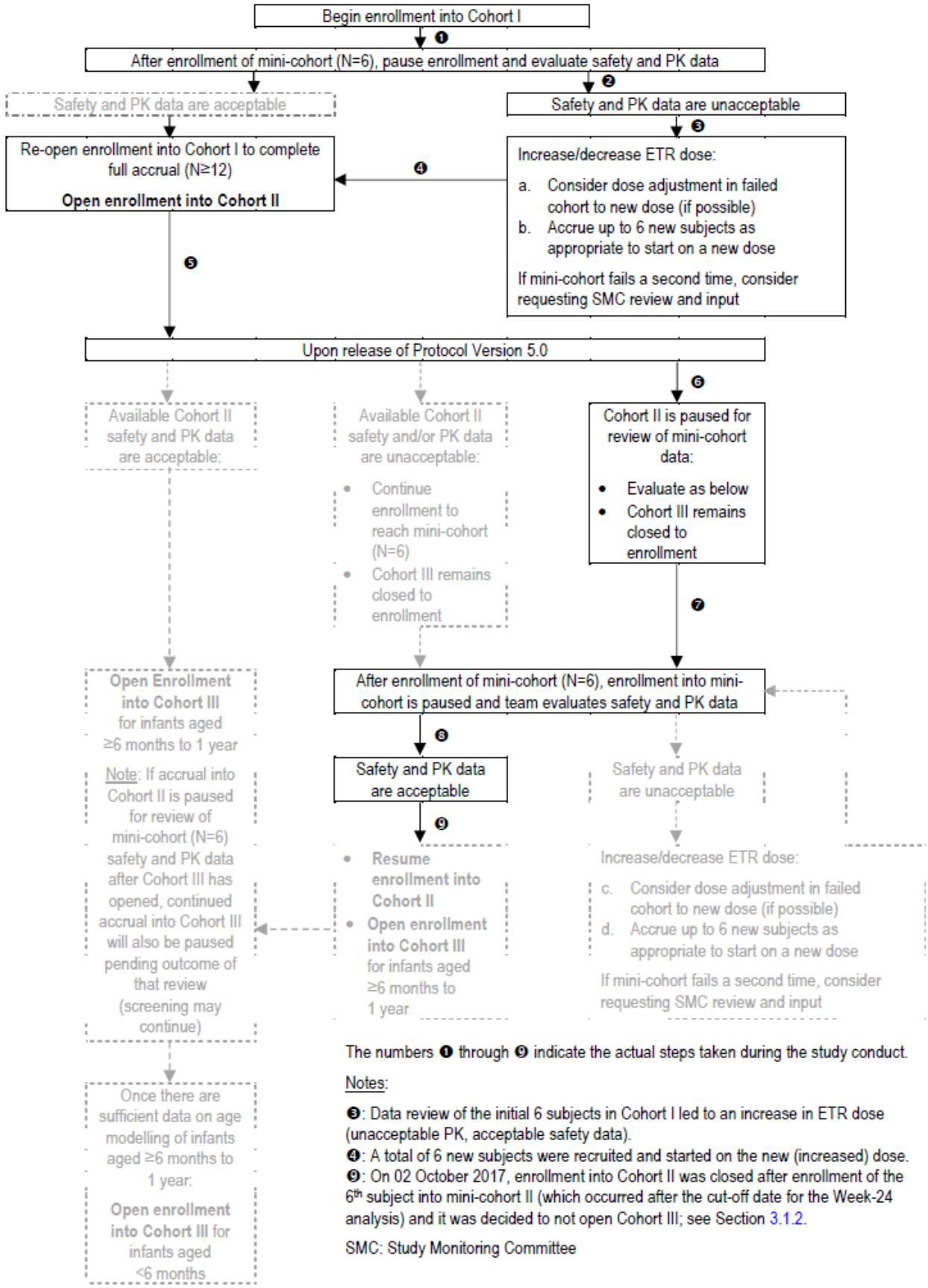
The study consists of a 48-week treatment period with an early study discontinuation visit for subjects who prematurely discontinued, a 4-week follow-up visit for the subjects who discontinued ETR, and a long-term safety follow-up of up to 5 years for the subjects continuing to receive study-provided 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 enrollment 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 enrol 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 1: Algorithm for Cohort Management (as of Version 5.0 of the Protocol)



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, enrollment into Cohort II was closed after enrollment 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 3.1.2.

SMC: Study Monitoring Committee

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

Study population/Sample size

A minimum of 12 subjects will be enrolled into each cohort of the study. Up to 18 subjects may be enrolled into Cohort 1. The total sample will include at least 36 evaluable subjects who have been treated exclusively at the doses judged to be optimal for their age cohorts.

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:

DOSING TABLE 1: 1 year – 6 years

Etravirine (ETR) dose per weight band				
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 tablets	Twice Daily
8-<10	8.8	75 mg	3 x 25 mg tablets	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 tablet OR 5 x 25 mg tablets	Twice Daily
25-<30	5.2	150 mg	1 x 100 mg tablet PLUS 2 x 25 mg tablets OR 6 x 25 mg tablets	Twice Daily
>=30	5.2	200 mg	2 x 100 mg tablets OR 8 x 25 mg tablets	Twice Daily

DOSING TABLE 2: 2 months to < 1 year

Etravirine (ETR) dose per weight band			
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 a half scored 25 mg tablets	Twice Daily
8-<10	50 mg	2 x 25 mg tablets	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 a sufficient amount of 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.

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 meanETR 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.

Results

The W48 results (including baseline characteristics, efficacy, PK and safety results) were already detailed and discussed within the PAM P46/053 and the variation II/058. Only the long-term follow-up period results are provided.

Recruitment/ Number analysed

Twenty-six subjects (20 subjects from Cohort I [≥2 to <6 years age group] and 6 subjects from Cohort II [≥1 to <2 years age group]) had been enrolled and received at least one dose of ETR. Seventeen subjects (75.0% [15/20] in Cohort I and 33.3% [2/6] in Cohort II) completed the study. A total of 9 subjects (25.0% [5/20] in Cohort I and 66.7% [4/6] in Cohort II) had discontinued ETR and the study. In total, 4 subjects discontinued the study prior to Week 48 (2 subjects in each cohort) and 5 subjects discontinued the study after Week 48 (3 subjects in Cohort I and 2 subjects in Cohort II).

Table 1: Study Termination; ITT (Study TMC125-C234)

		Etravirine ≥2 to <6 years (N=20)	Etravirine ≥1 to <2 years (N=6)	All Subjects (N=26)
Drug Termination	Completed	15 (75.0%)	2 (33.3%)	17 (65.4%)
	Completion of treatment	15 (75.0%)	2 (33.3%)	17 (65.4%)
	After Week 48	15 (75.0%)	2 (33.3%)	17 (65.4%)
	Discontinued	5 (25.0%)	4 (66.7%)	9 (34.6%)
	Clinical events or progression	2 (10.0%)	3 (50.0%)	5 (19.2%)
	Up to Week 48	1 (5.0%)	1 (16.7%)	2 (7.7%)
	After Week 48	1 (5.0%)	2 (33.3%)	3 (11.5%)
	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%)
Trial Termination	Completed	15 (75.0%)	2 (33.3%)	17 (65.4%)
	Completion of protocol	15 (75.0%)	2 (33.3%)	17 (65.4%)
	After Week 48	15 (75.0%)	2 (33.3%)	17 (65.4%)
	Discontinued	5 (25.0%)	4 (66.7%)	9 (34.6%)
	Subject withdraws or is withdrawn from study	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%)
	Completion of protocol	4 (20.0%)	3 (50.0%)	7 (26.9%)
	Up to Week 48	2 (10.0%)	1 (16.7%)	3 (11.5%)
	After Week 48	2 (10.0%)	2 (33.3%)	4 (15.4%)

N: number of subjects with data
Drug termination=permanent discontinuation of study intervention
Trial termination=subject withdrawal from the study.
Drug termination can be different from trial termination in cases when a subject discontinues study intervention intake but still returns for safety follow up. The study intervention termination will be before safety follow visit (ie, prior to trial termination date).

Efficacy results

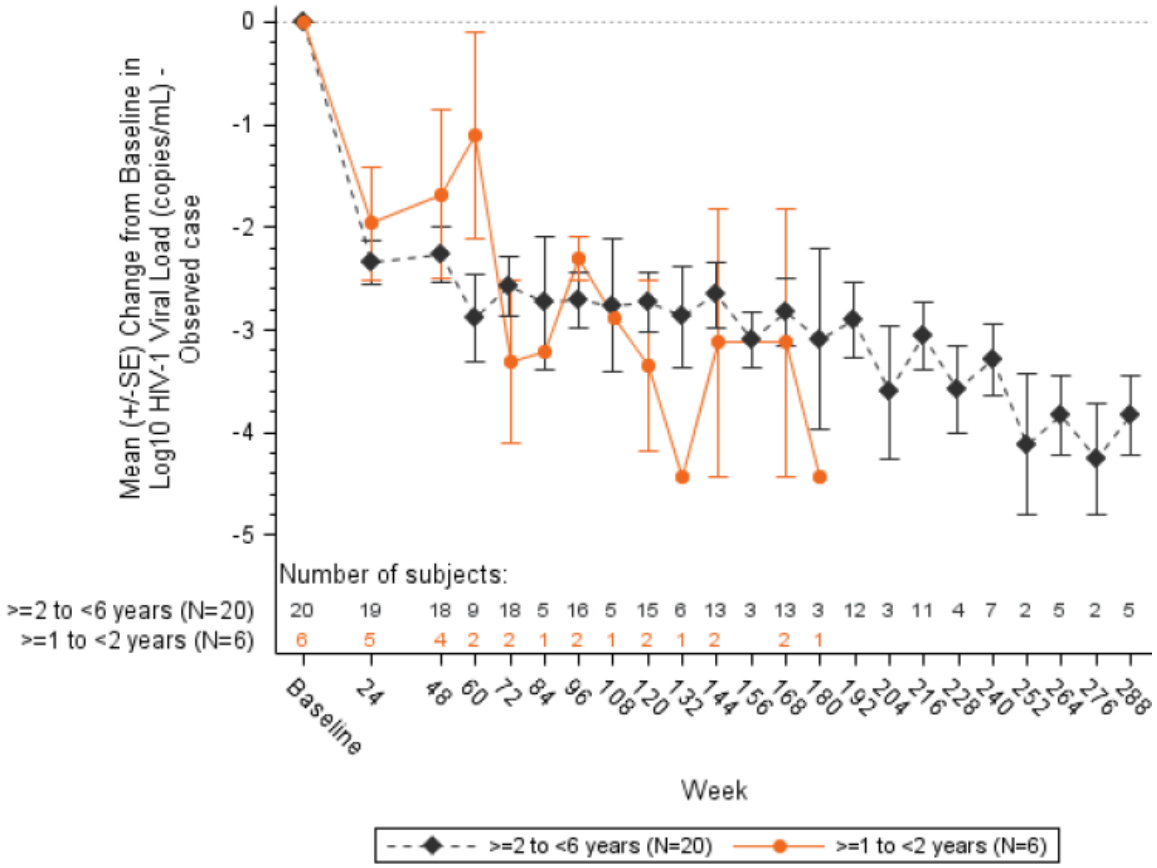
Virologic response and failures were not assessed during the long-term follow-up period.

Plasma Viral Load Over Time

The overall plasma viral load as assessed by $\log_{10}$ HIV-1 RNA (copies/mL) showed a gradual decrease postbaseline for both age groups and was maintained below the baseline values until the end of the study.

Figure 1: Mean (±SE) Changes From Baseline in Log_{10} HIV-1 RNA Values Over Time; ITT (Study TMC125-C234)

Parameter: Log_{10} HIV-1 RNA (copies/mL) - Observed case



Abbreviations: HIV=human immunodeficiency virus, ITT=intent-to-treat, RNA=ribonucleic acid.
Note: Only data on Weeks 24 and 48 since first intake are shown for the first 48 weeks, all data thereafter.
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Immunology

The CD4+ counts and percentages showed an increase from baseline over time for Cohort I (≥2 to <6 years age group), while no consistent trend was observed overtime in Cohort II. However, the CD8+ counts and percentages showed a consistent decrease from baseline over time in both cohorts. Furthermore, for both cohorts the resulting change from baseline in CD4/CD8 ratio over time was positive and maintained above the baseline throughout the study.

Table 2: Summary of Change from Baseline in CD4+ and CD8+ Cell Counts (cells/uL) for Selected Analysis Timepoints; ITT (Study TMC125-C234)

	Etravirine		
	≥2 to <6 years (N=20)	≥1 to <2 years (N=6)	All Subjects (N=26)
CD4+ (cells/uL) - Observed case			
End of treatment (Change from baseline)			
N	19	6	25
Mean (SE)	82.6 (111.01)	-36.2 (262.50)	54.1 (102.84)
95% C.I. *	(-150.65; 315.80)	(-710.94; 638.61)	(-158.18; 266.34)
Median (min – max)	98.0 (-1226 – 880)	112.5 (-1058 – 701)	98.0 (-1226 – 880)
CD4 (%) - Observed case			
End of treatment (Change from baseline)			
N	19	6	25
Mean (SE)	9.52 (1.857)	4.27 (3.816)	8.26 (1.704)
95% C.I. *	(5.615; 13.417)	(-5.542; 14.076)	(4.740; 11.772)
Median (min – max)	6.80 (1.0 – 24.7)	5.70 (-8.0 – 15.9)	6.80 (-8.0 – 24.7)
CD8+ (cells/uL) - Observed case			
End of treatment (Change from baseline)			
N	19	6	25
Mean (SE)	-571.7 (165.82)	-591.2 (224.53)	-576.4 (134.90)
95% C.I. *	(-920.06; -223.30)	(-1168.34; -13.99)	(-854.77; -297.95)
Median (min – max)	-382.0 (-2501 – 364)	-547.5 (-1546 – -45)	-399.0 (-2501 – 364)
CD8 (%) - Observed case			
End of treatment (Change from baseline)			
N	19	6	25
Mean (SE)	-10.44 (2.137)	-3.22 (2.806)	-8.71 (1.842)
95% C.I. *	(-14.931; -5.953)	(-10.429; 3.995)	(-12.510; -4.906)
Median (min – max)	-9.50 (-30.0 – 6.2)	-0.90 (-14.8 – 2.7)	-8.00 (-30.0 – 6.2)
CD4/CD8 ratio - Observed case			
End of treatment (Change from baseline)			
N	19	6	25
Mean (SE)	0.5171 (0.10223)	0.1323 (0.12798)	0.4248 (0.08889)
95% C.I. *	(0.30237; 0.73191)	(-0.19669; 0.46129)	(0.24132; 0.60823)
Median (min – max)	0.4328 (-0.186 – 1.403)	0.1126 (-0.338 – 0.609)	0.3228 (-0.338 – 1.403)

Resistance

There was no genotype/phenotype evaluation performed in the follow-up period since there was no early discontinuation for any subject during this period.

Safety results

The long-term safety data from the follow-up phase, which lasted 577 days was similar to that observed in the 48-Week Phase of the study. No new safety signals were observed; furthermore, changes in clinical laboratory values, vital signs and physical examination finding were consistent with those observed in the 48-week study phase.

Table 3: Adverse Events: Summary Table; ITT (Study TMC125-C234)

Phase: Treatment

	Etravirine		
	≥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	5 (25.0%)	3 (50.0%)	8 (30.8%)
with at least one fatal AE	0	0	0
with at least one worst grade 1 or 2 AE	10 (50.0%)	1 (16.7%)	11 (42.3%)
with at least one worst grade 3 or 4 AE	10 (50.0%)	5 (83.3%)	15 (57.7%)
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%)
with at least one SAE which is at least possibly related to OBR[a]	4 (20.0%)	2 (33.3%)	6 (23.1%)
with at least one worst grade 3 or 4 AE at least possibly related to ETR	3 (15.0%)	0	3 (11.5%)

Abbreviations: AE=adverse event, ETR=etravirine, ITT=intent-to-treat, OBR=optimized background regimen, SAE=serious adverse event.

[a] Relationship to OBR was only collected for serious AEs.

Common AEs

During the entire treatment phase including data up to Week 48, all 26 (100.0%) subjects reported at least 1 AE. The most frequently reported AEs (≥50%) in the combined group by PTs were nasal congestion (20 [76.9%] subjects), cough (19 [73.1%] subjects), rhinorrhea (15 [57.7%] subjects), pyrexia (14[53.8%] subjects), and rash (13 [50.0%] subjects).

Drug-related AEs

During the entire treatment phase including data up to Week 48, there were 5 (19.2%) subjects (4/20 [20.0%] subjects from Cohort I [≥2 to <6 years age group] and 1/6 [16.7%] subject from Cohort II [≥1 to <2 years age group]) who reported AEs that were considered at least possibly related to ETR as assessed by the investigator Adverse events which were considered at least possibly related to ETR were blood pressure diastolic increased and vomiting in 1 subject and lipase increased in 2 subjects from Cohort I (≥2 to <6 years age group) and rash in 1 subject from Cohort II (≥1 to <2 years age group).

SAEs

During the entire treatment phase including data up to Week 48, eight (30.8%) subjects total reported 10 SAEs; 5/20 (25.0%) from Cohort I (≥2 to <6 years age group) and 3/6 (50.0%) subjects from Cohort II (≥1 to <2 years age group). All SAEs occurred between baseline and the Week 48 visit, except for 1 event each of Grade 3 neutrophil count decreased and Grade 3 forearm fracture, which occurred post Week 48 analysis treatment phase; both these events were in subjects from Cohort I (≥2 to <6 years age group). Two subjects had more than 1 SAE (lipase increased and platelet count decreased platelet count decreased and ligament sprain). Three SAEs were Grade 4 in severity (platelet count decreased, lipase increased, and anemia) and 1 SAE was Grade 2 in severity (ligament sprain); all other events were Grade 3 in severity. There were no deaths during the study.

Two SAEs of lipase increased in 2 subjects from Cohort I (≥2 to <6 years age group) were considered to be at least possibly related to ETR. Six SAEs were considered at least possibly related to the Optimized Background Regimen (OBR): lipase increase (n=2; Cohort I [≥2 to <6 years age group]), neutrophil count decreased (n=2; Cohort I [≥2 to <6 years age group] and n=1; in Cohort II [≥1 to <2 years age group]), and anemia (n=1; Cohort II [≥1 to <2 years age group]).

AEs of interest

During the entire treatment phase including data up to Week 48, there were 20 (76.9%) subjects (15 [75.0%] subjects from Cohort I [≥2 to <6 years age group] and 5 [83.3%] subjects from Cohort II [≥1 to <2 years age group]) with at least 1 AEOI. The AEOIs reported were related to skin, hepatic, pancreatic, lipid-related, neuropsychiatric, and neoplasm events.

Post Week 48, there were 2 additional subjects with skin-related AEOIs. One subject from Cohort I (≥2 to <6 years age group) experienced AEOI of the category 'rash cases' and 1 subject from Cohort II (≥1 to <2 years age group) experienced AEOI of the category 'cutaneous reactions'. Both events were Grade 2 in severity, not reported as serious, and considered as not related to treatment with ETR.

No other AEOIs (hepatic, pancreatic, lipid-related, neuropsychiatric, and neoplasm events) were reported post Week 48. There were no cardiac or bleeding events reported during the entire study period.

Laboratory parameters

The majority of the treatment-emergent laboratory abnormalities were Grade 1 or Grade 2.

Grade 3 or Grade 4 laboratory abnormalities were observed in a total of 9 subjects, 25.0% (5/20) of subjects in Cohort I and 66.6% (4/6) of subjects in Cohort II; all were reported as AEs. Apart from the earlier described Grade 4 alanine aminotransferase (ALT), Grade 3 aspartate aminotransferase (AST), Grade 3 and Grade 4 lipase, and Grade 3 cholesterol abnormalities, the following Grade 3 and 4 hematologic abnormalities were reported:

- Lipase: One subject from Cohort I with Grade 0 at baseline had Grade 3 toxicity postbaseline and 1 subject from Cohort I with Grade 2 at baseline had Grade 4 toxicity postbaseline.

- ALT: One subject from Cohort II with Grade 0 at baseline had Grade 4 toxicity postbaseline

- AST: One subject from Cohort II with Grade 0 at baseline had Grade 3 toxicity postbaseline

- Hemoglobin: One subject from Cohort II with Grade 0 at baseline had Grade 4 toxicity postbaseline

- Platelets: One subject from Cohort II with Grade 0 at baseline had Grade 3 toxicity postbaseline

- Neutrophils: Three subjects from Cohort I with Grade 0 at baseline had Grade 3 toxicity postbaseline and 1 subject from Cohort II with Grade 1 at baseline had Grade 3 toxicity postbaseline

Other safety observations

None of the AEs relating to vital signs (increases in blood pressure and pulse) during the entire treatment phase were considered clinically significant. No Grade 4 increases in systolic blood pressure or diastolic blood pressure were observed.

Vital sign results for the entire treatment period were the same as the results up to Week 48. There were no additional changes in the vital sign evaluation post Week 48 analysis.

2.3.3. Discussion on clinical aspects

The Week 48 results of study TMC125-C234 were already assessed for the extension of indication of Intelence in HIV-1 infected pediatric subjects aged ≥2 to <6 years. The long-term follow-up data of this study, above the Week 48 endpoint, did not identify new efficacy nor safety concerns. However, the number of subjects is very limited, with only 17 subjects who have continued their ETR-based

treatment above 48 weeks. Only a few additional AEs have been reported after 48 weeks. Overall, all the AEs possibly related to ETR reported during the whole study are already listed in the Intelence SmPC. Of note, since the last Week 48 report, there was no new resistance data.

In conclusion, the data from this paediatric study are consistent with the known efficacy and safety data of ETR in adult subjects and did not impact the current indication in paediatric subjects ≥2 years old. No revision of the currently approved SmPC is considered warranted.

3. Rapporteur's overall conclusion and recommendation

☒ Fulfilled:

No regulatory action required.