CLINICAL REVIEW

Application Type	NDA 22-187
Submission Number	009
Submission Code	SE5
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Reviewer Name	Charu Mullick, M.D.
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Established Name	Etravirine
Trade Name	INTELENCE™
Therapeutic Class	Antiretroviral
Applicant	Janssen Products, L.P.
Priority Designation	P
Formulation	Oral Tablet (25, 100, 200 mg)
Dosing Regimen	Twice daily (BID)
Indication	Treatment of HIV-1 Infection in treatment-experienced patients
Intended Population	Pediatric ages 6 to <18 yrs

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1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

I recommend approval of supplemental NDA 22-187, submission 9 supporting use of etravirine (ETR) for the treatment of HIV-1 infection in pediatric patients above 6 years of age. In pediatric clinical trial TMC125-C213 (C213), antiretroviral experienced subjects ages 6 to 18 years received ETR in combination with an optimized background regimen (OBR). At week 24, ETR exposures in pediatric subjects were comparable to the exposures achieved in adult phase 3 trials. Etravirine, in combination with antiretroviral (ARV) drugs, resulted in reduction in plasma HIV viral load and increases in CD4 cell counts. The safety and tolerability profile in trial C213 was acceptable. In addition, data supporting a new 25 mg strength tablet was submitted to allow for proposed pediatric dosing. The 25 mg tablet is dispersible and compositionally proportional to the marketed 100 mg tablet. I concur with the CMC review and conclusions supporting approval of the new 25 mg tablet strength.

Etravirine was approved in 2008 for treatment of HIV infection in treatment-experienced adults. In an initial pediatric dose-finding trial TMC125-C126 (C126), two ETR doses were evaluated in subjects ages 6 to < 18 years. The 5.2 mg/kg twice daily dose was selected because it yielded drug exposures comparable to exposures observed in the adult phase 3 trials. Subsequently, the safety, efficacy, and pharmacokinetics of ETR in this pediatric age group were evaluated in the 48 week trial C213. In C213, a total 101 subjects ages 6 to < 18 years received 5.2 mg/kg ETR twice daily with an OBR. At week 24, 52% of subjects achieved virologic response defined as viral load < 50 copies/ml, and 65% of subjects achieved viral load < 400 copies/ml. This treatment response was comparable to the adult Week 24 response rate (60%) in phase 3 trials. The response rate was also comparable to outcomes observed in treatment-experienced pediatric trials of other ARVs. Importantly, pediatric ETR exposures matched adult drug exposures in pivotal phase 3 trials. Similar to adults, an exposure-response relationship was observed in pediatric subjects. The most frequent adverse events (AEs) in C213 include upper respiratory tract infection (27%), and rash of any type (25%). Rash due to ETR was observed in adult trials and postmarketing and is well-described in the package insert. Similar to adult rash, the majority of pediatric rash was mild to moderate in severity, self-limited, and more frequent in female subjects compared to male subjects. A higher rash frequency in trial C213 compared to adult trials is explained by the greater proportion of female subjects in C213 (60%) compared to adult trials (10%) following examination of other possible factors. Unlike adult trial observations, severe pediatric rash events including discontinuations were observed more frequently in female subjects compared to male subjects in C213.

1.2 Risk Benefit Assessment

Etravirine, in combination with other ARV drugs, was shown to be effective in treating HIV-1 infected treatment experienced adults in pivotal phase 3 trials TMC125-C206 and TMC125-C216. In the pediatric population, ETR exposures with (b) (4) 5.2

mg/kg dose were comparable to adult exposures in adult phase 3 trials. In addition, virologic response and immunologic benefit was demonstrated in ages 6 and above in trial C213. Treatment differences between children and adolescent age groups in this trial were likely due to more advanced HIV disease and greater previous ARV exposure in adolescents relative to children. These data support the pediatric efficacy of ETR when used in combination with other ARVs.

Rash due to ETR, identified in adult clinical trials, is well-described in the drug package insert. Skin reactions including serious events are displayed under Warnings and Precautions, and Adverse Drug Reactions section. The rash profile in C213 was similar to adults, as follows: majority of events were mild to moderate in severity, self-limited nature, median time to onset was 9 days, and female subjects were more likely to develop rash compared to male subjects. A higher rash frequency in the pediatric trial compared to adult phase 3 trials was explained by a greater proportion of female subjects in the pediatric trial compared to adult trials. Overall, the AE profile was similar to adults. No new safety concerns were identified in this supplement review.

Currently, only two NNRTIs, nevirapine and efavirenz, are approved for pediatric use. Because ETR is effective in NNRTI-resistant subjects, it will provide an additional treatment option for pediatric HIV-infected patients failing NNRTIs. The dispersible 25 mg tablet will provide a new strength to allow pediatric dosing. Overall, data in this sNDA provide a favorable risk-benefit assessment for pediatric use of ETR in ages 6 to < 18 years. The assessment is based on matching of pediatric ETR exposures to adult exposures in phase 3 trials, virologic response rates in pediatric subjects, and an acceptable safety profile demonstrated in trial C213.

1.3 Recommendations for Postmarketing Risk Management Activities

The Applicant will continue to follow subjects enrolled in pediatric trial C213 until 48 weeks trial duration. In addition, the Applicant will submit periodic safety reports for review. No additional pediatric postmarketing risk management activities are planned.

1.4 Recommendations for other Post Marketing Study Commitments

No new pediatric PMC or post marketing requirement (PMR) will be issued. With accelerated approval, a pediatric PMR was issued for the younger age population (see Section 2.5).

2 Introduction and Regulatory Background

2.1 Product Information

Etravirine is an NNRTI which binds to HIV-1 reverse transcriptase resulting in disruption of the enzyme's catalytic site. Etravirine was approved for treatment of HIV-1 infection in treatment-experienced adults in 2008.

Established name:	Etravirine (or TMC125)
Trade name:	Intelence™
Chemical:	4-[[6-amino-5-bromo-2-[(4-cyanophenyl)-amino]-4-pyrimidinyl]oxy]-3,5-dimethylbenzonitrile
Proposed indication:	Treatment of HIV-1 infection in treatment-experienced pediatric population age 6 to < 18 years of age
Dose and regimen:	Adult dose 200 mg twice daily (BID) Pediatric dosing for ages 6 years and older as follows, ≥ 16 kg to < 20 kg: 100 mg BID ≥ 20 kg to < 25 kg: 125 mg BID ≥ 25 kg to < 30 kg: 150 mg BID ≥ 30 kg: 200 mg BID
Dosage form:	25mg, 100mg, 200 mg tablet

2.2 Table of Currently Available Treatments for Proposed Indication

Treatment of HIV infection in the pediatric population relies on drugs available from six mechanistic classes namely, nucleoside reverse transcriptase inhibitors (NRTIs), protease inhibitors (PIs), NNRTIs, integrase inhibitor, CCR5 co-receptor antagonist, and fusion inhibitor. Drugs in the NNRTI class approved for pediatric use include nevirapine approved for all pediatric ages and efavirenz approved for ages 3 years and above.

Table 1: Currently approved pediatric antiretroviral drugs

Drug Class	Generic Name	Trade Name
NRTI	Zidovudine (AZT or ZDV)	Retrovir®
	Didanosine (ddI)	Videx®
	Stavudine (d4T)	Zerit®
	Lamivudine (3TC)	Epivir®
	Abacavir (ABC)	Ziagen®
	Tenofovir (TDF)	Viread®
	Emtricitabine (FTC)	Emtriva®
NNRTI	Nevirapine (NVP)	Viramune®
	Efavirenz (EFV)	Sustiva®
PI	Ritonavir (rtv)	Norvir®
	Nelfinavir	Viracept®
	Fosamprenavir	Lexiva®
	Lopinavir/ritonavir (LPVR/rtv)	Kaletra®
	Atazanavir (ATV)	Reyataz®
	Darunavir (DRV)	Prezista®
	Tipranavir	Aptivus®
Integrase Inhibitor	Raltegravir (RALT)	Isentress®
CCR5 inhibitor	Maraviroc (MVC)	Selzentry®
Fusion Inhibitor	Enfuvirtide (T-20)	Fuzeon®

2.3 Availability of Proposed Active Ingredient in the United States

Etravirine has been marketed in the United States since January 2008 as Intelence™. The proposed API for treating pediatric patients remains the same as the drug approved for adult use. The same 100 mg and 200 tablet formulations marketed currently will be applicable to pediatric patients. An additional dose-proportional 25 mg strength tablet has also been developed for use in pediatric patients.

2.4 Important Safety Issues with Consideration to Related Drugs

The NNRTI class comprises of four available agents, EFV, NVP, ETR, and rilpivirine. Both EFV and NVP are approved for pediatric use. Safety concerns with EFV include rash, teratogenicity, psychiatric and central nervous system symptoms. Nevirapine can cause hepatotoxicity including serious and fatal events. Nevirapine can also lead to rash including serious skin reactions. Another limitation with these two drugs is the emergence of resistance due to a single viral mutation resulting in loss of activity and cross-resistance among these drugs.

Rilpivirine, a recently approved NNRTI associated with neuropsychiatric events and rash, is not currently approved for pediatric use. Delavirdine an approved NNRTI is no longer marketed. The safety profile with ETR is discussed in Section 7.

2.5 Summary of Presubmission Regulatory Activity Related to Submission

The Investigational New Drug application (IND 63,646) was submitted in 2001. In 2005, the IND was granted Fast Track Designation. Etravirine was approved under accelerated approval regulations in January 2008. The label was revised for fatal cutaneous toxicity in September 2009. Traditional approval was granted in November 2009. Other key regulatory activities include labeling updates for drug interaction findings from completed studies (buprenorphine/naloxone drug interaction, fluconazole drug interaction, and LPV/rtv tablet drug interaction), and approval of the 200 mg tablet formulation.

The following PMRs related to Pediatric Research Equity Act (PREA) were issued with accelerated approval:

1. Pediatric study under PREA for the treatment of HIV-1 infection in pediatric subjects from 6 to 18 years of age. Conduct a pediatric safety and activity study of etravirine with activity based on the results of virologic response over at least 24 weeks of dosing and safety monitored over 48 weeks.
   Protocol submission: Completed
   Final report submission by: June 2010

2. Deferred pediatric study under PREA for the treatment of HIV-1 infection in pediatric subjects from 2 months to 6 years of age. This study will determine the pharmacokinetic profile, safety, and activity of etravirine in pediatric subjects from 2 months to 6 years of age.
   Protocol submission by: June 2010
   Final report submission by: June 2013

In addition to these PREA requirements, a Pediatric Written Request (PWR) was also issued in 2008 requiring studies to be conducted in pediatric subjects from 2 months of age to < 18 years.

The current pediatric application contains the interim study report for a pediatric trial intended to fulfill the pediatric PMR 387-2. Refer to sections 9.1 and attachment 1 for PREA and PWR details.

2.6 Other Relevant Background Information

There is no other background information relevant to this supplement.

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

The sNDA was submitted as an electronic document to the FDA electronic data room (EDR). The submission was organized and datasets were easy to access and navigate.

FDA's Office of Scientific Investigations (OSI) inspected three clinical sites in Thailand (two sites) and Brazil (one site). These sites were selected because they enrolled the highest number of subjects in the trial and had not been recently audited. Analytic site inspections were also performed. At the time of this review, the outcomes from clinical and analytical site inspections are pending. Refer to Dr. Yodit Belew's CDTL memo for findings and conclusions of FDA inspections.

3.2 Compliance with Good Clinical Practices

The Applicant has stated the pediatric clinical trials were conducted according to guidelines prescribed by the Declaration of Helsinki. The trials were also conducted in compliance with International Conference on Harmonization (ICH) Good Clinical Practice guidelines.

3.3 Financial Disclosures

No investigators participating in trial C213 had financial arrangements with Johnson & Johnson, the parent company of the Applicant, Janssen as defined in 21 CFR 54.2 (a), (b), (c), and (f).

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls (CMC)

This supplemental application provides support for approval of a 25 mg tablet formulation. The proposed 25 mg tablet (F066) is compositionally proportional to the approved 100 mg tablet (F060) and dispersible. Refer to CMC reviews by Drs. Jean Salemme and John Duan supporting strength approval including *in vitro* dissolution comparisons and results from bioequivalence study TMC125-C173.

The proposed 25 mg tablet is also scored for halving. Although proposed dosing for ages 6 to < 18 years does not require tablet halving, (b) (4) No significant CMC issues were identified to preclude approval of the 25 mg tablet strength.

4.2 Clinical Microbiology

In trial C213, 43% of subjects were classified as virologic failures (VF) including 33% who were non-responders and 10% who were rebounders. Among 10 rebounders, 6 subjects had a viral load < 400 copies/mL at Week 24. Higher mean baseline viral load and greater median number of NNRTI resistance associated mutations (RAMs) were observed in VF compared to non-VF subjects.

Resistance development to ETR was evaluated in 23 VF subjects with genotypic and phenotypic profiles available both at baseline and endpoint. In these subjects, median

ETR fold change (FC) increased from 0.9 at baseline to 2.8 at endpoint (an ETR FC < 3 was shown to confer full susceptibility in adult phase 3 trials). Additionally, the median number of ETR RAMs increased from 0 (at baseline) to 1 at treatment end. Frequent NNRTI RAMs emerging in at least 3 VF subjects included Y181C (n = 3), V90I (n = 3) and E138A (n = 3). Of note, these mutations were also identified as ETR RAMs in adult phase 3 trials. In 48% of VF subjects, no ETR resistance by either phenotype or genotype assays was observed. Refer to Dr. Patrick Harrington's Clinical Microbiology review for details.

4.3 Pharmacology/Toxicology

No new animal pharmacology/toxicology reports were submitted with this sNDA. Please refer to Dr. Kuei-Meng Wu's review of original and traditional approval of NDA 22-187.

4.4 Clinical Pharmacology

4.4.1 Mechanism of Action

Etravirine binds directly to HIV viral reverse transcriptase enzyme and blocks RNA-dependent and DNA-dependent DNA polymerase activities by disrupting the enzyme's catalytic site.

4.4.2 Pharmacodynamics

Key findings from clinical pharmacology/pharmacometrics review by Dr. Jenny Zheng are summarized here. The review focused on the following three key questions:

1. *Does the* (b) (4) *pediatric ETR exposure attain comparable exposure to that achieved in adults?*

The selected ETR dose of 5.2 mg/kg BID (up to 200 mg BID, the approved adult dose) provided pediatric exposures similar to adult exposures achieved with 200 mg BID. Etravirine phase 3 trials C206 and C216, also known as DUET trials, were the source of adult exposure data. Comparison of pediatric and adult exposures is displayed in Table 2.

Table 2: Comparison of etravirine pediatric exposure (C213) and adult exposure

	Pediatrics (6 - <12 years)	Pediatrics (12 - < 18 years)	Adults (DUET trials)
	N=41	N=60	N=575
AUC_{12h} (ng.h/mL) Mean (SD) Median (Min; Max)	 5764 (4404) 5289 (513; 24291)	 4956 (4480) 3786 (111; 28865)	 5506 (4710) 4380 (458; 59084)
C_{0h} (ng/mL) Mean (SD) Median (Min; Max)	 381 (320) 342 (33; 1879)	 329 (357) 251 (2; 2276)	 393 (391) 298 (2; 4852)

Source: NDA 22-187 S-009 Clinical pharmacology review

In adult DUET trials, ETR was co-administered with DRV/rtv. In pediatric trial C213, 52 subjects (51%) received DRV/rtv as part of their OBR. Etravirine exposures were comparable for pediatric subjects receiving DRV/rtv and adults (see Table 3).

Table 3: Comparison of etravirine pediatric exposure and adult exposure with DRV/RTV as background PI

	Pediatrics (6 - <12 years)	Pediatrics (12 - <18 years)	Adults (DUET trials)
	N=21	N=31	N=575
AUC_{12h} (ng.h/mL) Mean (SD) Median (Min; Max)	 6202 (4791) 4791 (819; 24291)	 5088 (5239) 3822 (111; 28865)	 5506 (4710) 4380 (458; 59084)
C_{0h} (ng/mL) Mean (SD) Median (Min; Max)	 412 (406) 322 (47; 1879)	 336 (420) 253 (4; 2276)	 393 (391) 298 (2; 4852)

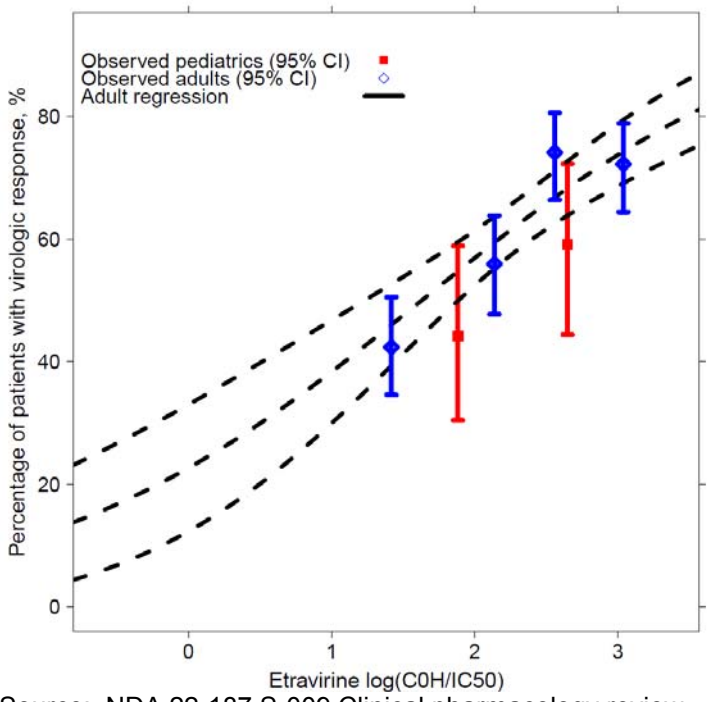
Source: NDA 22-187 S-009 Clinical pharmacology review

Based on drug interaction data for ETR-DRV/rtv and ETR-LPV/rtv tablet, both PIs result in a similar magnitude of decrease (approximately 35%) in ETR exposures. Although no adult clinical efficacy data is available for ETR co-administered with LPV/rtv tablet, the efficacy outcome of this combination is expected to be similar to that of ETR-DRV/rtv based on adult drug interaction data. In pediatric subjects receiving ETR with LPV/rtv tablet, median ETR AUC was 45% lower compared to pediatric subjects receiving ETR with DRV/rtv. It should be noted these exposures were obtained through sparse plasma sampling, and from a limited number of subjects (n=23). Additionally, information about the type of LPV/rtv formulation was not prospectively collected and was incomplete (four trial subjects received an unknown LPV/rtv formulation). In sum, LPV/rtv tablet subgroup data does not alter the conclusion of comparable pediatric-adult exposures.

2. *Does the exposure-response relationship for ETR antiviral activity support the proposed pediatric doses?*

An exposure-response relationship for efficacy was observed in pediatric subjects, similar to adult exposure-response observations. As shown in Figure 1, the exposure-antiviral activity relationship was comparable between children and adults.

Figure 1: Comparison of exposure-response relationship between pediatric subjects and adults at Week 24



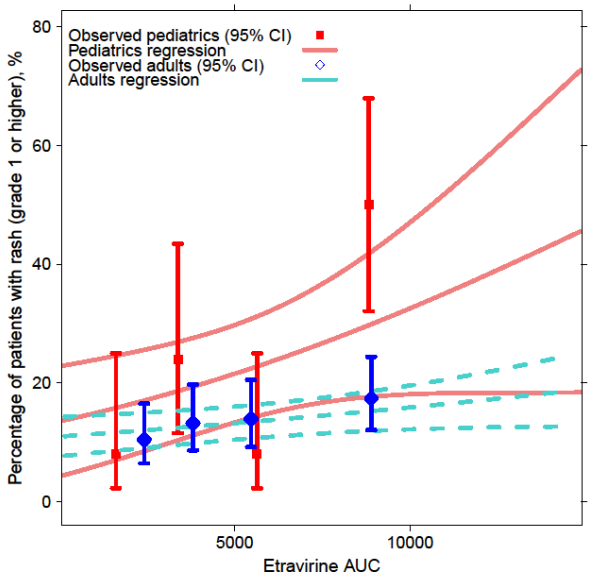
Source: NDA 22-187 S-009 Clinical pharmacology review

Response rate of 43% in subjects receiving LPV/rtv tablet (n=23) was slightly lower than the overall response rate of 52%. No dose adjustment for pediatric ETR co-administration with LPV/rtv tablets was recommended based on the following: in adults, no dose adjustment is recommended for ETR co-administered with LPV/rtv tablet; data obtained from a limited number of subjects in the pediatric LPV/rtv tablet subgroup; and the incomplete and post-hoc information for LPV/rtv formulation type.

3. Does the exposure-safety relationship for etravirine support the proposed dose?

The AE profile in pediatric trial C213 was generally comparable to adult phase 3 trial observations. Rash, well-characterized in adult trials, was observed in C213. A trend towards exposure-rash relationship was observed in trial C213 for all ETR exposure quartiles except the third AUC quartile (Figure 2).

Figure 2: Rash vs. AUC Relationship for Adults and Pediatrics



Source: NDA 22-187 S-009 Clinical pharmacology review

Rash was more frequent in the pediatric trial (23%) compared to adult phase 3 trials (15%). As shown in Figure 2, a steeper exposure-rash relationship was observed in C213 compared to the adult exposure-rash relationship. Based on this finding, it can be surmised that factors other than drug exposure alone contributed to the higher frequency of pediatric rash. Etravirine rash is observed more frequently in females, and a higher proportion of female subjects enrolled in C213 (63%) compared to adult phase 3 trials (10%) is a possible explanation for the higher rash rate in C213.

4.4.3 Pharmacokinetics

Please refer to clinical pharmacology/ pharmacometrics review by Dr. Jenny Zheng for details. Briefly, pediatric PK data were provided by two trials, C126 and C213.

Pediatric dose selection was based on results from phase 1 trial C126 conducted in pediatric subjects 6 to < 18 years age. The 25 mg and 100 mg ETR formulations were evaluated sequentially in two weight-based doses, 4 mg/kg BID and 5.2 mg/kg BID. Thirty-five treatment-experienced HIV-infected subjects suppressed on a LPV/rtv-containing regimen received ETR for 8 days. The adult reference for ETR exposures was pooled data from phase 3 DUET trials. With 4 mg/kg BID dosing, ETR exposures were lower than adult exposures (median pediatric AUC_{12h} 2979 ng.h/ml vs. DUET 4380 ng.h/ml). With 5.2 mg/kg BID dosing, exposures were comparable to adult DUET exposures (median pediatric AUC_{12h} 4407 ng.h/ml vs. DUET 4380 ng.h/ml) supporting selection of this dose for pediatric development.

Trial C213, is the pivotal pediatric trial in treatment-experienced subjects ages 6 to < 18 years. The protocol details are presented in Section 5.3.1. Briefly, C213 is an open-label, single-arm, 48 week trial evaluating the safety, PK, antiviral activity of ETR in 6 to < 18 years age group. Subjects received ETR 5.2 mg/kg BID in combination with an

OBR comprising of at least two ARVs including a boosted PI and NRTIs. The primary analysis was performed when all subjects were either treated for 24 weeks or discontinued from the trial. Sparse PK samples were obtained at weeks 4, 8, 12 and 24. A population PK model was created using adult and pediatric PK data.

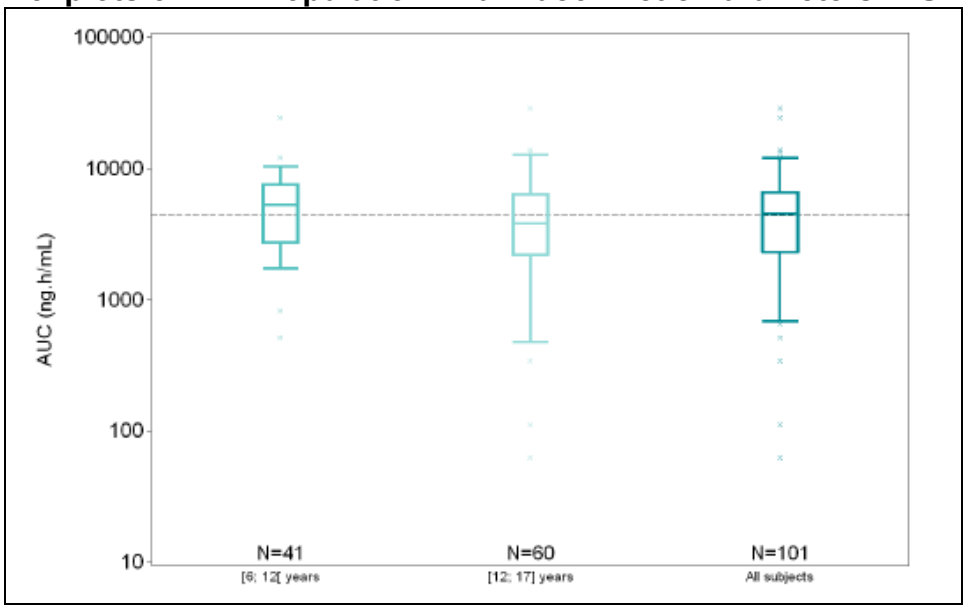
Clearance: Etravirine clearance was similar across the age ranges. Clearance was also similar across the background PI (e.g. DRV/rtv, LPV/rtv) administered in combination with ETR. In addition, ETR clearance was similar with different LPV/rtv formulations.

Exposure: As mentioned previously, ETR dose of 5.2 mg/kg BID up to 200 mg BID provided pediatric exposures similar to the adult exposures achieved with 200 mg BID.

A) Exposure in Adolescents

Slightly lower exposures were observed in adolescents compared to children (Figure 3). This finding is not uncommon in the adolescent age group and results from dose capping at 200 mg BID, the maximum adult recommended dose. Treatment adherence is another consideration in the adolescent age group.

Figure 3: Boxplots of ETR Population Pharmacokinetic Parameters: AUC_{12h}



Reference line indicates median AUC_{12h} (DUET data)
Source: NDA 22-187 S-009 Clinical Study Report TMC125-C213

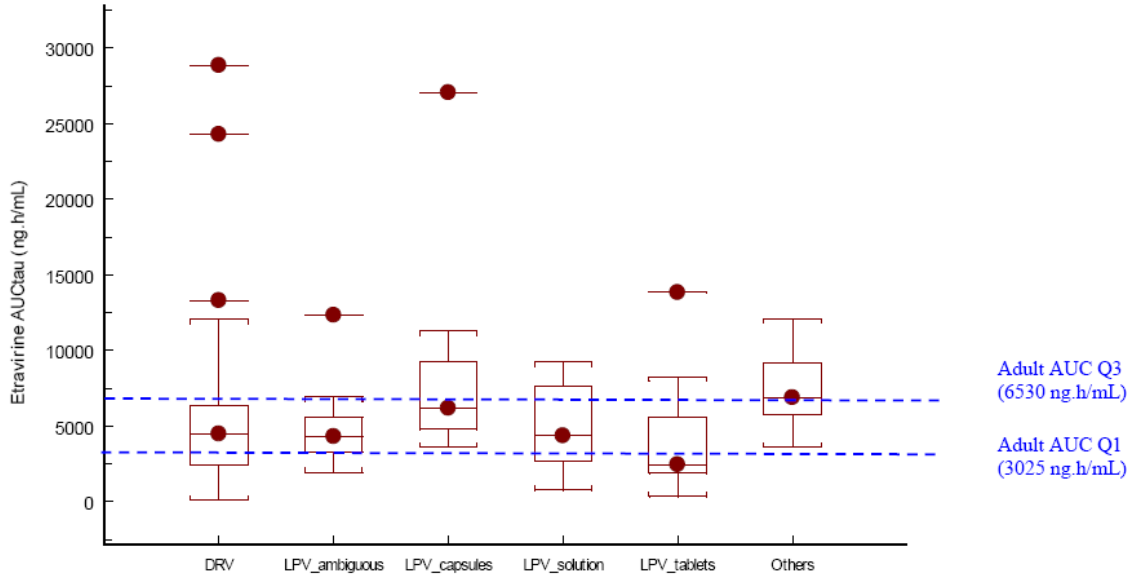
B) Exposure by background PI

As demonstrated in adult studies, PIs may have effects on ETR exposure. Based on the adult phase 3 clinical trials (ETR co-administered with DRV/rtv) and based on adult drug-drug interaction study (ETR administered with LPV/rtv tablet), both these PIs decrease ETR exposure by similar magnitude (about 35%).

Approximately 51% of pediatric subjects received DRV/rtv as part of their OBR. Etravirine exposure in these subjects was comparable to the ETR exposure observed in adult subjects who received ETR in combination with DRV/rtv.
Information about type of LPV/rtv formulation administered in C126 and C213 was not collected prospectively. In C213, a total of 39 pediatric subjects (39%) received LPV/rtv. Based on post-hoc data collection, the majority of subjects (n=23) received LPV/rtv tablet formulation (replaced LPV/rtv capsule in the US), while 7 and 5 subjects received suspension or capsule formulations, respectively. Specific LPV/rtv formulation information was not known for 4 subjects. In C126, 2 subjects received LPV/rtv tablet, 5 subjects received capsule, and 3 subjects received solution. Type of LPV/rtv formulation was not known for 10 subjects.

Etravirine AUC tended to be lower for subjects receiving ETR with LPV/rtv tablets compared to LPV/rtv capsule or LPV/rtv solution (Figure 4).

Figure 4: Box plot for Etravirine AUC when Different PIs were used as part of OBR in Combined Studies TMC125-C213 and TMC125-C126



Source: NDA 22-187 S-009 Clinical pharmacology review

In summary, the [redacted] (b) (4) ETR dose (5.2 mg/kg BID up to 200 mg BID) resulted in exposures similar to the adult exposures achieved with 200 mg BID. The AUCs observed for adult and pediatric subjects in C213 were generally overlapping. Lower exposures observed in adolescent age group are likely due to lower body-weight based ETR dose administered as 200 mg BID was the maximum allowed dose. However, although the adolescent subjects had lower exposure compared to the younger cohort (6 to <12 years old), the exposures observed in these adolescent subjects overlaps with the exposures observed in the adult trials at the marketed 200 mg BID dose.

Lower ETR exposures were also observed when ETR was co-administered with LPV/rtv tablet; a finding not supported by the adult drug interaction data. Data from adult drug interaction study and phase 3 trials demonstrate ETR exposures were decreased by a similar magnitude when ETR is co-administered with DRV/rtv or with LPV/rtv tablet. As

such, LPV/rtv tablet exposure findings are based on data from limited number of subjects. Further, information about the type of LPV/rtv formulation was not prospectively collected but gathered post-hoc, and information was missing for some subjects. Exposure data were based on sparse sampling in C213; and in the two subjects in C126 who received ETR 5.2 mg/kg BID with LPV/rtv tablet, ETR exposures (obtained by intensive PK sampling) were comparable to adult phase 3 exposures. Therefore, limited conclusions can be drawn from exposure data from LPV/rtv tablet subgroup. Refer to section 6.1.8 for further discussion with regards to exposure and response based on age and background PI administered.

5 Sources of Clinical Data

This submission contains data and results from two pediatric trials, C126 and C213 (Table 4). The electronic submission contains final study reports, datasets, Summary of Clinical Safety, Summary of Clinical Efficacy, and case report forms. A safety update report was also submitted during the review cycle.

5.1 Tables of Clinical Studies

Table 4: Summary of supporting clinical studies

Study	Description	Number of subjects enrolled	Number of subjects with ≥ 24 weeks data
TMC125-C126	Phase 1, open-label, dose-finding study in HIV-infected subjects ages 6 years to < 18 years age	20	0
TMC125-C213	Phase 2 open-label study to evaluate the safety, tolerability, pharmacokinetics and antiviral activity of etravirine in 48 week treatment period in HIV-infected subjects ages 6 to < 18 years	101	101

5.2 Review Strategy

Trial C213, the source of 24 week data, is the focus of this clinical review. Data from trial C213 were reviewed to assess safety, tolerability, efficacy and PK of ETR in subjects ages 6 to < 18 years. The Applicant's conclusions regarding safety and efficacy were confirmed by independent FDA analysis of data. I evaluated trial demographics, AE, laboratory abnormalities and efficacy outcomes using JMP Statistical software. Additional exposure-response analyses by background PI were undertaken by the clinical pharmacology review team. No formal statistical analyses confirming the endpoints were performed by FDA statistician because C213 is a single arm study. All tables and figures not created by me are indicated by a footnote referencing the information source.

5.3 Discussion of Studies

Trial C213 is a 48-week trial evaluating safety, efficacy, antiviral activity, and PK of ETR in treatment-experienced HIV-infected subjects ages 6 years to < 18 years of age. Primary analysis was performed when all enrolled subjects completed at least 24 weeks of treatment or had discontinued prematurely. The 24 week analysis forms the principal source of data supporting ETR dosing and use in pediatric ages 6 to < 18 years age. The multinational trial was conducted at 42 sites across 13 countries including USA, Thailand, Argentina, South Africa and Brazil.

Objectives
The primary objective was to evaluate the safety and tolerability of ETR in combination with other ARVs over a 24-week treatment period in children and adolescents aged 6 to < 18 years.

Secondary objectives include:

- Evaluation of long-term safety and tolerability of ETR in combination with other ARVs over a 48-week treatment period in children and adolescents aged 6 to < 18 years;
- Assessment of population pharmacokinetic parameters and PK/ pharmacodynamic relationships of ETR for antiviral activity and safety over 24 and 48 weeks of treatment in children and adolescents aged 6 to < 18 years;
- Evaluation of antiviral activity of ETR in combination with other ARVs over a 24-week and 48-week treatment period in children and adolescents aged 6 to < 18 years;

Dose regimen
Subjects received ETR in combination with an investigator-selected OBR comprising of at least two antiretroviral drugs including a boosted PI. Allowed boosted PIs include LPV, DRV, ATV, and saquinavir (SQV). Use of RALT and enfuvirtide was allowed.

Based on findings from study C126, ETR was dosed 5.2 mg/kg BID up to a maximum 200 mg bid which is the adult recommended dose. The following ETR doses were administered based on weight bands:

- 16 to < 20 kg: 100 mg BID (4 x 25-mg tablets or 1 x 100-mg tablets)
- 20 to < 25 kg: 125 mg BID (5 x 25-mg tablets or 1 x 100-mg + 1 x 25-mg tablets)
- 25 to < 30 kg: 150 mg BID (6 x 25-mg tablets or 1 x 100-mg + 2 x 25-mg tablets)
- ≥ 30 kg: 200 mg BID (8 x 25-mg tablets or 2 x 100-mg tablets)

Key eligibility criteria
Key inclusion criteria include:

- Male or female subjects ages between 6 and less than 18 years at study entry.
- Subjects with documented HIV-1 infection.
- Subject could comply with the protocol requirements.
- HIV-1 plasma viral load at screening visit ≥ 500 copies/mL.

Key exclusion criteria include:

- Evidence of resistance against ETR based on the resistance test performed at Screening.
- Any grade 3 or 4 toxicity according to the Division of AIDS (DAIDS) grading scale, except for: grade 3 absolute neutrophil count; grade 3 platelets; asymptomatic grade 3 pancreatic amylase elevation; asymptomatic grade 3 triglyceride / cholesterol / glucose elevation; and asymptomatic grade 4 triglyceride elevation.

Procedures and endpoints
Study endpoints included safety parameters (including AEs and laboratory abnormalities), efficacy parameters (HIV virologic response, change in CD4 count from baseline), and PK parameters (including C_{max} and AUC_{12h}), as well as population PK modeling. Safety parameters and HIV viral load were assessed at study visits at Week 2, 4, 8, 12, 16, 24, 32, 40, 48 and post-treatment follow-up visit. Virologic endpoints were defined as:

- Plasma viral load decline of < 0.5 $\log_{10}$ copies/mL from Baseline by Week 8,
- Plasma viral load decline of < 1.0 $\log_{10}$ copies/mL from Baseline by Week 12.

C126 was a phase 1, dose-finding trial to evaluate steady-state PK and short-term safety of ETR in pediatric subjects ages 6 to < 18 years age. The objective was to obtain pediatric doses that provided comparable exposures to adult approved dose. Thirty-five treatment-experienced HIV-infected subjects virologically suppressed on a LPV/rtv-containing regimen were enrolled. In stage 1, 21 subjects received ETR 4 m/kg BID for 8 days plus their ARV regimen. In stage 2, 21 subjects received ETR 5.2 mg/kg BID for 8 days plus their ARV regimen. In both stages, 12-hour intensive PK sampling was performed on Day 8. HIV viral load and CD4 counts were monitored on Day 8. Safety assessments were performed at scheduled intervals.

6 Review of Efficacy

Efficacy Summary

The 5.2 mg/kg BID ETR dose developed for pediatric use is supported by dose-finding trial C126. Exposures in pediatric subjects ages 6 years and older were comparable to adult phase 3 trial exposures in C126. Safety, tolerability, PK, and antiviral activity of 5.2 mg/kg BID dose at Week 24 were demonstrated in pediatric trial C213.

In C213, subjects ages 6 years to < 18 years received ETR in combination with an OBR comprising of a boosted PI. At Week 24, virologic response defined as proportion achieving viral load < 50 copies/ml was observed in 52% of subjects. Viral load < 400 copies/ml was observed in 65% of subjects. Other favorable trends were also observed including median increase in CD4 count from baseline of 112 cells/mm^3 and 4% median increase in CD4 percentage.

In subgroup analyses, a higher treatment response was observed in children ages 6 to < 12 years (59%) compared to adolescents older than 12 years (47%). At baseline, adolescents were more likely to have advanced HIV disease (greater duration since HIV

diagnosis, lower median baseline CD4 count and higher median viral load), and prior exposure to more ARVs relative to children. These baseline differences may explain the 12% treatment difference in children compared to adolescents. Of note, with the less stringent efficacy parameter of viral load < 400 copies/ml, the treatment difference between the two age cohorts was reduced to 6%. Other contributing factors may include slightly lower ETR exposures and lower adherence in adolescents relative to children.

A lower response rate was also observed in subjects co-administered LPV/rtv tablet (43%) compared to DRV/rtv (52%). Because adult LPV/rtv tablet drug interaction and phase 3 trials (DRV/rtv co-administration) demonstrate a similar magnitude of effect on ETR exposures with either LPV/rtv tablet or DRV/rtv co-administration, similar response rates are expected when ETR is co-administered with either of these boosted PIs. Findings of lower response rates with LPV/rtv tablets are therefore unexpected. As this finding is based on data are from a limited number of subjects in this subgroup (n=23), and because information for type of LPV/rtv formulation used was obtained post-hoc and was incomplete, firm efficacy conclusions cannot be drawn from the subgroup analysis.

Overall, the response rate in pediatric trial C213 (52%) was comparable to adult Week 24 response rates of 58% in adult phase 3 trials. The response rate is also comparable to outcomes observed in treatment-experienced pediatric trials with other ARVs.

6.1 Indication

INTELENCE, in combination with other antiretroviral agents, is indicated for the treatment of HIV-1 infection in antiretroviral treatment experienced pediatric patients 6 years to less than 18 years of age, including those with NNRTI resistance.

This indication is based on 24-week analyses of a single-arm, open-label trial TMC125-C213 in antiretroviral treatment-experienced pediatric subjects 6 years to less than 18 years of age.

6.1.1 Methods

I performed analyses for baseline demographic and HIV disease characteristics, subject disposition, and efficacy endpoints. A formal statistical review was not conducted by an FDA statistician for this single-arm trial without comparator. For the efficacy assessment, I analyzed the following virologic efficacy parameters:

- Proportion of subjects achieving HIV viral load < 50 copies/mL at Week 24 (primary efficacy parameter), and
- Proportion of subjects achieving HIV viral load < 400 copies/mL at Week 24.

Snapshot method was used to calculate proportion of virologic responders. By this analysis, subjects with viral load > 50 copies/ml or with missing viral load values at the Week 24 visit were assigned as non-responder. Analyses included all subjects who received at least one dose of study drug or Intent to Treat population (ITT).

Comparative analyses for the two age groups, children 6 to < 12 years and adolescents 12 to < 18 years age were also performed. Responder analysis by background PI was also performed. In addition to virologic parameters, resistance parameters, select immunologic parameters, and exposure-response were assessed as part of efficacy evaluation.

6.1.2 Demographics

Trial C213 enrolled 101 HIV-infected subjects including 41 children ages 6 to < 12 years and 60 adolescents ages 12 to < 18 years. As displayed in Table 5, the majority of trial subjects were female (63%). The median age of the trial population was 12 years. About 49% of subjects were White. Blacks or African Americans accounted for 30%, and Asians comprised 20% of the population. At least 10% of enrolled subjects were from the following countries: Thailand (20%), United States (15%), Argentina (15%), and South Africa (10%). Demographics parameters were generally comparable across children and adolescent age groups. An exception was a greater distribution of Black subjects in 6 to < 12 years age group relative to adolescents.

Table 5: Demographics of ITT population, C213

	Etravirine ≥6 to <12 yrs N=41	**Etravirine ≥12 years** N=60	**All subjects** N=101
Gender			
Female	27 (66%)	37 (62%)	64 (63%)
Male	14 (34%)	23 (38%)	37 (37%)
Age (median, yrs)	10	15	12
Race			
White	20 (49%)	29 (48%)	49 (49%)
Black	16 (39%)	14 (23%)	30 (30%)
Asian	4 (10%)	16 (27%)	20 (20%)
Country			
Thailand	4 (10%)	16 (27%)	20 (20%)
Argentina	9 (22%)	6 (10%)	15 (15%)
USA	3 (7%)	12 (20%)	15 (15%)
South Africa	8 (20%)	2 (3%)	10 (10%)

Source: NDA 22187 S-009 dm.xpt

6.1.3 Baseline HIV Characteristics

Although treatment-experienced, trial subjects were moderately advanced in terms of HIV disease as supported by median baseline CD4 count 387 cells/mm^3 and median baseline HIV viral load approximately 8000 copies/ml (Table 6). Only 11% had baseline viral load > 100,000 copies/ml, while the majority (63%) had baseline viral load < 20,000

copies/ml. About 55% of subjects had baseline CD4 count > 350 cells/mm^3. Only one subject was co-infected with HBV; three trial subjects with positive anti-HCV antibody had negative HCV PCR results. Majority (99%) of subjects acquired HIV infection through vertical or perinatal transmission.

HIV disease was more advanced in adolescents relative to children. This is based on the observation of lower median CD4 count and higher median viral load at baseline in adolescents. Further, fewer adolescents (48%) had baseline CD4 count ≥ 350 cells/mm^3 relative to children (63%). The findings are not unexpected because vertical transmission was the major HIV acquisition route in trial participants; therefore, older children were infected for a longer duration and more likely to have advanced disease.

Table 6: Baseline Disease Characteristics of ITT population C213

Parameter	Etravirine ≥6 to <12 yrs N=41	Etravirine ≥12 years N=60	All subjects N=101
Plasma viral load (median, copies/ml)	4955 (132-384000)	9660 (97-517000)	8110 (97-3840000)
Plasma viral load category			
< 20,000 copies/ml	28 (68%)	35 (58%)	63 (63%)
20,000-100,000 copies/ml	8 (20%)	19 (32%)	27 (27%)
≥ 100,000 copies/ml	5 (12%)	6 (10%)	11 (11%)
CD4 cell count (median, cells/mm^3)	446 (45-1441)	356 (7-1345)	387 (7-1441)
CD4 % (median)	26 (3-43)	20 (1-41)	22 (1-43)
CD4 category			
< 50	1 (2%)	3 (5%)	4 (4%)
50-350	13 (32%)	26 (43%)	39 (39%)
≥ 350	26 (63%)	29 (48%)	55 (55%)
Active HBV/HCV infection	0	1 (2%)	1 (1%)

Source: NDA 22187 S-009 dm.xpt and lb.xpt

Previous ARV Experience

At baseline, all subjects were treatment-experienced and used at least 2 ARV agents (see Table 7). About 75% of subjects had previous NNRTI exposure (not including PMTCT NNRTI use). About 80% subjects had previous PI exposure. Compared to children, adolescents were exposed to greater total number of ARVs.

Table 7: Previous ARV Experience in C213

Number of ARVs n (%)	Children ≥ 6 to < 12 years N = 41	Adolescents ≥ 12 to < 18 years N = 60	All subjects N = 101
Total No of ARVs			
2 - 5	25 (61.0)	17 (28.3)	42 (41.6)
6 - 9	16 (39.0)	33 (55.0)	49 (48.5)
10 - 14	0	10 (16.7)	10 (9.9)
NNRTI			
0	14 (34.1)	11 (18.3)	25 (24.8)
1	25 (61.0)	42 (70.0)	67 (66.3)
2	2 (4.9)	7 (11.7)	9 (8.9)
PI			
0	8 (19.5)	12 (20.0)	20 (19.8)
1	16 (39.0)	12 (20.0)	28 (27.7)
2	14 (34.1)	20 (33.3)	34 (33.7)
3	3 (7.3)	10 (16.7)	13 (12.9)
4	0	4 (6.7)	4 (4.0)
5	0	2 (3.3)	2 (2.0)
NRTI			
2	19 (46.3)	8 (13.3)	27 (26.7)
3	8 (19.5)	10 (16.7)	18 (17.8)
4	8 (19.5)	18 (30.0)	26 (25.7)
5	6 (14.6)	14 (23.3)	20 (19.8)
6	0	5 (8.3)	5 (5.0)
7	0	5 (8.3)	5 (5.0)
Fusion Inhibitor			
0	41 (100)	57 (95.0)	98 (97.0)
1	0	3 (5.0)	3 (3.0)

N = number of subjects; n = number of subjects with observations
Low dose ritonavir was not counted as a PI. Combivir® was counted as 2 NRTIs; Trizivir® as 3 NRTIs; Truvada® as 2 NRTIs; Epzicom® / Kivexa® as 2 NRTIs; Kaletra® as 1 PI.

Source: NDA 22-187 S-009 TMC125-C213 Clinical Study Report

Baseline resistance

At least one or more baseline NNRTI RAMs were observed in 70% of subjects (either IAS-USA or sponsor-defined NNRTI RAM). The most common ETR RAMs at baseline were G190A (13 subjects), K101E (9 subjects), A98G and V106I (8 subjects each). By the Antivirogram phenotypic assay, 10% subjects were not fully susceptible to ETR and 60% of subjects were not fully susceptible either to EFV or NVP. Median FC values for ETR, EFV and NVP were 0.9, 11.1 and 35.5, respectively. For ETR, FC < 3 was shown to confer full susceptibility in adult phase 3 trials. Full susceptibility to ≥ 1 NRTI and ≥ 1 PI was observed in 95.4% and 97.7% of subjects, respectively. Refer to Microbiology review by Dr. Patrick Harrington for details.

Phenotypic susceptibility scores (PSS) at baseline are presented in Table 8. About 80% of all subjects had a PSS of at least 2. More adolescent subjects (26%) had baseline PSS 0-1 compared to children (9%).

Table 8: Baseline phenotypic susceptibility scores (PSS) in C213

Number of Subjects With Active Drugs per Class, n (%)	Children ≥ 6 to < 12 years N = 41	Adolescents ≥ 12 to < 18 years N = 60	All subjects N = 101
N With Available Antivirogram Data	**34**	**53**	**87**
Total Number of Active Drugs (PSS*)	**34**	**53**	**87**
0-1	3 (8.8)	14 (26.4)	17 (19.5)
2	16 (47.1)	31 (58.5)	47 (54.0)
3+	15 (44.1)	8 (15.1)	23 (26.4)
Number of Active PIs	**34**	**53**	**87**
0	1 (2.9)	8 (15.1)	9 (10.3)
1	33 (97.1)	45 (84.9)	78 (89.7)
Number of Active NRTIs	**33**	**48**	**81**
0	3 (9.1)	14 (29.2)	17 (21.0)
1	15 (45.5)	25 (52.1)	40 (49.4)
2+	15 (45.5)	9 (18.8)	24 (29.6)

N = number of subjects; n = number of subjects with observations
*ETR was not included in the calculation of the phenotypic sensitivity score (PSS).
Only the initial therapies (i.e. as determined on Day 7) were considered.
Antivirogram data do not exist for ENF (fusion inhibitor) and RAL (InSTI). ENF and RAL were considered active if they were not previously used.

Source: NDA 22-187 S-009 TMC125-C213 Clinical Study Report

6.1.4 Patient Disposition

Among 178 subjects screened, 101 subjects were eligible for the trial and received at least one dose of ETR. Among these, 52% subjects completed 48 week trial duration, and 26% were continuing in the trial (data collected until cut-off date March 14, 2011). The remainder 22% subjects discontinued due to reasons outlined in Table 9. Discontinuations due to an AE or non-compliance were the most frequent reasons for premature discontinuation accounting for 8% of subjects each.

Table 9: Subject Disposition in TMC125-C213 Week 24 data

Subject Disposition	Subjects
Screened	**178**
Received at least one dose (ITT)	**101**
Completed trial	52 (52%)
Ongoing	26 (26%)
Discontinuations	
Due to AE or HIV-related	8 (8%)
Subject non-compliant	8 (8%)
Subject reached virologic endpoint	3 (3%)
Subject withdrew consent	2 (2%)
Subject ineligible to continue in trial	1 (1%)
Other	1 (1%)

Source: NDA 22-187 ds.xpt, lb.xpt, ae.xpt, dm.xpt

6.1.5 Analysis of Primary Endpoint

The primary efficacy parameter is proportion of subjects achieving viral load < 50 copies/ml at Week 24 visit. In trial 213, 52% of subjects met criteria for virologic response (Table 10), 42% subjects were classified as virologic failures, and 6% subjects had discontinued prior to Week 24 due to an AE. No viral load data were available at the Week 24 visit for one subject (missing data).

Table 10: Outcomes by Snapshot Analysis TMC125-C213 Week 24 data

Week 24 outcome	All subjects N=101
Virologic Response (VL < 50 copies/ml)	**52 (52%)**
Virologic Failure	**42 (42%)**
Plasma VL > 50 copies/ml at Wk 24	36 (36%)
Virologic failure discontinuation	3 (3%)
Discontinued due to other reason and last VL > 50 copies/ml[a]	3 (3%)
No data at Week 24 window	**7 (7%)**
Discontinuation due to AE	6 (6%)
Missing data	1 (1%)

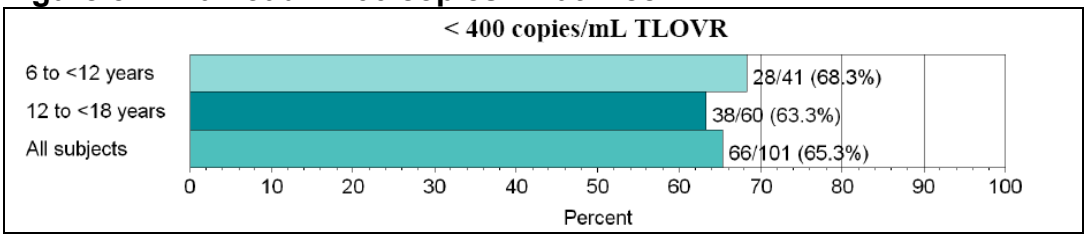
Source: NDA 22-187 lb.xpt, ae.xpt, dm.xpt
[a] Reason for discontinuation: non-compliant (n=2), ineligible to continue study (n=1)

6.1.6 Analysis of Secondary Endpoints

Viral load < 400 copies/ml at Week 24

Analysis by snapshot methodology demonstrated 67% subjects achieved viral load < 400 copies/ml at Week 24. Sponsor's analysis by TLOVR showed 65% subjects achieved this endpoint (Figure 5). Because primary efficacy endpoint viral load < 50 copies/ml computed by snapshot method is reported in the package insert, the reviewer recommends viral load < 400 copies/ml by snapshot method is included in the package insert. Of note, this difference in the reviewer's and sponsor's findings does not change the overall efficacy conclusion.

Figure 5: Viral load < 400 copies/ml at Week24

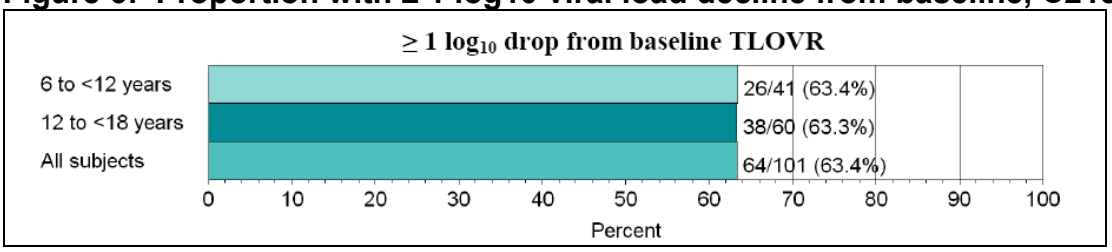


Source: NDA 22-187 TMC125-C213 Clinical Study Report

Proportion with ≥ 1 log_{10} viral load decline from baseline

About 63% of subjects experienced ≥ 1 log_{10} decline in viral load from baseline as depicted (Figure 6).

Figure 6: Proportion with ≥ 1 log10 viral load decline from baseline, C213

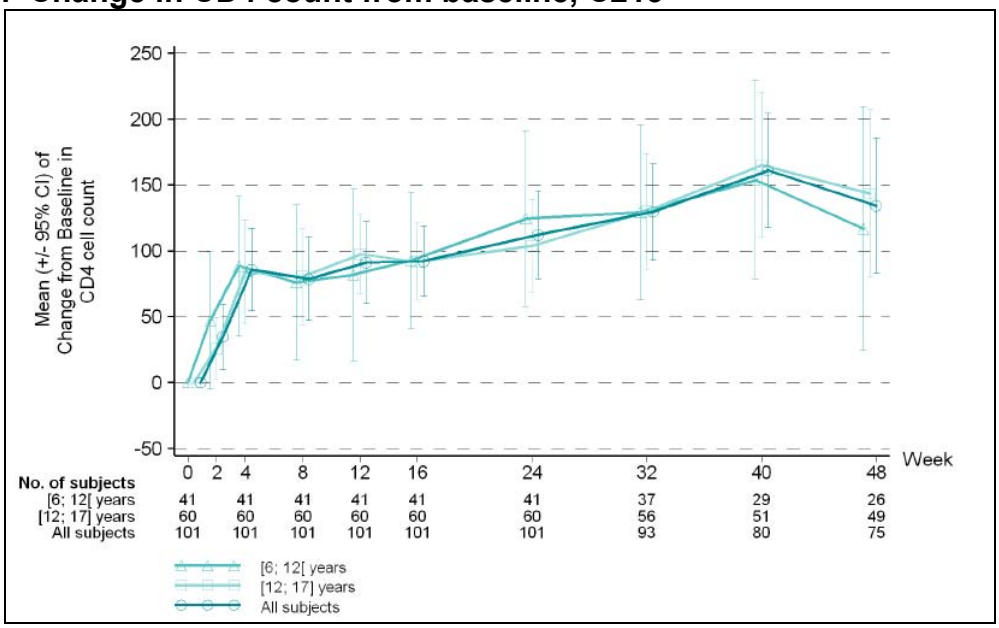


Source: TMC125-C213 Clinical Study Report

Change in CD4 count from baseline

The mean increase in CD4 count at Week 24 was 112 cells/mm^3, and mean increase in CD4% was 4% in all subjects (Figure 7).

Figure 7: Change in CD4 count from baseline, C213



Source: TMC125-C213 Clinical Study Report

6.1.7 Other Endpoints

Key secondary analysis endpoints also included determination of ETR pharmacokinetic parameters at steady-state (C_{max}, AUC_{0-10h}, AUC_{0-12h}, T_{max}, CL). Refer to section 4.4.3 and clinical pharmacology review for details.

6.1.8 Subanalysis

Analysis by Age Groups

The primary efficacy outcome, viral load < 50 copies/ml at Week 24, was analyzed by two age groups for children ages 6 to < 12 years and adolescents ages 12 to < 18 years. As depicted in Table 11 below, a greater proportion of children achieved virologic response (59%) compared to adolescents (47%). Although some adolescents failed due to non-compliance (4%), the chief reason for non-response was virologic failure. Differences in treatment response between age groups were less pronounced when virologic success was measured by VL < 400 copies/ml: this endpoint was achieved in 63% of adolescents and 68% of children. This implies several adolescents with VL > 50 copies/ml at Week 24 had achieved VL < 400 copies/ml.

Table 11: Virologic Outcome by Age Groups in C213, Week 24 data

Outcome	Etravirine ≥6 to <12 yrs N=41	Etravirine ≥12 years N=60	All subjects N=101
Virologic Response (VL < 50 copies/ml)	**24 (59%)**	**28 (47%)**	**52 (52%)**
Virologic Failure	**15 (36%)**	**27 (44%)**	**42 (42%)**
Plasma VL > 50 copies/ml at Wk 24	14 (34%)	22 (37%)	36 (36%)
Virologic failure discontinuation (met virologic endpoint)	1 (2%)	2 (3%)	3 (3%)
Discontinued due to other reason and last VL > 50 copies/ml[a]	0	3 (4%)	3 (3%)
No data at Week 24 window			
Discontinuation due to AE	2 (5%)	4 (7%)	6 (6%)
Missing data	0	1 (2%)	1 (1%)

Source: NDA 22-187 lb.xpt, ae.xpt, dm.xpt
[a]Reason for discontinuation: non-compliant (n=2), ineligible to continue study (n=1)

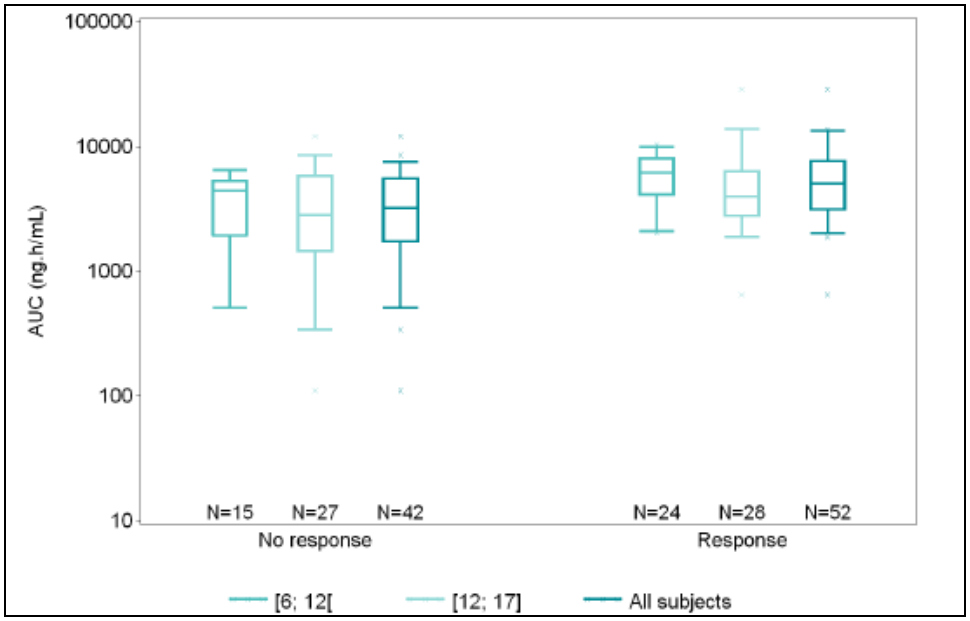
Lower response rates in adolescents relative to children can be explained by factors including baseline HIV disease, baseline resistance mutations, ETR exposures, and treatment compliance.

A) Baseline HIV disease, ARV exposure, and baseline resistance: At baseline, adolescents were more likely to have advanced HIV disease (greater duration since HIV diagnosis, lower median baseline CD4 count and higher median viral load) and longer prior exposure to more ARVs compared to children. Lower treatment responses in adolescent age group relative to children have been observed in other pediatric treatment trials. Because vertical transmission at birth is the major source of transmission, adolescent subjects are likely to have more advanced HIV disease. Adolescents are also more likely to harbor drug resistant virus than children due to

greater previous ARV exposure. Lastly, treatment non-compliance was observed in at least 2 adolescent subjects and not in children.

B) Exposure: Lower exposures were observed in adolescent subjects relative to children (Figure 11). As discussed previously, drug clearance per kg BW is similar among children, adolescent, and adult subjects. Therefore, for a given mg/kg dose, similar exposure should be observed across the age groups. However, due to capping of the maximum allowable dose at 200 mg BID, adolescent subjects may have received a lower mg/kg dose leading to lower exposures. Because data on dose-proportionality at doses higher than 200 mg BID are not available in adults, one cannot definitively assume doses higher than 200 mg in adolescents would have led to higher exposures. Further, even if the virologic failure rate is higher in adolescent subjects, it is not likely to be due to lower exposures because the observed exposure in adolescent subjects was still within the targeted adult exposure range. Compared to children, more adolescent subjects likely took the LPV/rtv tablet than LPV/rtv solution. Lower ETR exposures attained with LPV/rtv tablet co-administration (compared to solution) could also have contributed to lower exposures in adolescents.

Figure 11: Boxplots of ETR Pharmacokinetic Parameters by Virologic Response (< 50 copies/mL TLOVR non-VF Censored) at Week 24: AUC_{12h} – TMC125-C213 Week 24 Analysis



Source: NDA 22-187 S-009 Summary of Clinical Efficacy

Analysis by Background PI

In C213, 52 subjects (51%) were co-administered DRV/rtv and 39 subjects (39%) were co-administered LPV/rtv. Among LPV/rtv subjects, 23 received LPV/rtv tablet, 5 received capsule formulation, 7 received solution, and 4 subjects received an unknown LPV/rtv formulation based on post-hoc information. As mentioned previously, specific LPV/rtv formulation information was not collected prospectively.

As displayed in Table 12, lower virologic response was observed in subjects co-administered LPV/rtv tablets (43%) compared to other LPV/rtv formulation (57-67%) or

DRV/rtv (52%). Adult drug-drug interaction and phase 3 clinical trial data demonstrate similar decreases (about 35%) in ETR exposure when ETR is co-administered with LPV/rtv tablet, or if ETR is co-administered DRV/rtv. Although no adult clinical efficacy trial data are available with ETR co-administered with LPV/rtv, based on the PK data, it can be concluded that similar efficacy outcomes would be expected if ETR was co-administered with LPV/rtv tablet. Therefore in the pediatric trial C213, no differences in exposure (and thus response) should be expected between LPV/rtv tablet subgroup and DRV/rtv subgroup. Difference in response rates noted between these two subgroups may be related to other factors such as baseline disease characteristics or effects exerted by the individual PI/regimen. Further, there are limited numbers of subjects within each subgroup, and efficacy conclusions should be drawn with caution. Lastly, it should be noted the information for type of LPV/rtv formulation was collected post hoc and is incomplete (LPV/rtv formulation unknown for 4 subjects).

Table 12: Responders by Background PI (DRV/rtv or LPV/rtv) in C213

	Co-administered boosted PI			
	DRV/rtv N=52	LPV/rtv tablet N=23	LPV/rtv solution N=7	LPV/rtv capsule N=5
Response Rate (n,%)	27 (52%)	10 (43%)	4 (57%)	4 (67%)

Source: Clinical pharmacology reviewer's analysis

6.1.9 Analysis of Clinical Information Relevant to Dosing Recommendations

Dose selection and recommendations are based on the following:

1. The selected ETR 5.2 mg/kg BID dose provided ETR plasma concentrations similar to those obtained in adults receiving the approved 200 mg.
2. Virologic response at week 24 in pediatric trial C213 is comparable to the adult virologic response observed at week 24 in adult phase 3 trials. Two large clinical trials, TMC125-C206 and TMC125-C216, provided efficacy and safety data supporting adult approval. In these placebo-controlled and double-blind trials, HIV-infected treatment-experienced adults received ETR or placebo in combination with OBR comprising of DRV/rtv and NRTIs. In pooled analysis, virologic response (VL < 50 copies/ml) at Week 24 was observed in 60% of subjects in the ETR arm compared to 38% subjects in placebo arm. In comparison, 52% of pediatric subjects in C213 achieved VL < 50 copies/ml at Week 24. In my opinion, adult and pediatric efficacy findings are comparable and support proposed dosing recommendations.
3. Similar to adult findings, an exposure-rash relationship was observed in the pediatric trial. This finding does not impact body-weight based proposed dose recommendations.

In summary, the recommended ETR dose for pediatric patients ages 6 to < 18 years is as follows:

Table 13: Recommended dose of INTELENCE® for pediatric patients 6 years to less than 18 years of age

Body Weight (kilograms, kg)	**Dose**
≥ 16 kg to less than 20 kg	100 mg twice daily
≥ 20 kg to less than 25 kg	125 mg twice daily
≥ 25 kg to less than 30 kg	150 mg twice daily
≥ 30 kg	200 mg twice daily

6.1.10 Discussion of Persistence of Efficacy and/or Tolerance Effects

The study submitted is a 24 week interim study report. The full 48 week study report will be submitted as soon as the report (and data) is available.

6.1.11 Additional Efficacy Issues/Analyses

Etravirine efficacy demonstrated in pediatric trial C213 was comparable to the adult phase 3 trials (week 24 data). Extrapolation of efficacy for ARV drugs like ETR is based on the presumption that the course of HIV disease and the effects of the drug are sufficiently similar in adults and pediatric subjects (21 CFR 201.57 (f)(9)(iv), Sec. 505B 21 USC 355c)[4]. The Division agrees HIV disease in pediatric subjects is similar but not identical to adult HIV disease (Domachowske, JB; Pediatric Human Immunodeficiency Virus Infection; October 1996; Clin. Microbiol. Rev. 9(4) 448-468), noting routes of HIV transmission may be different. Vertical transmission from mother to child is the predominant means of infection for children less than 12 years of age in contrast to adolescent and adult subjects in whom sexual contact or injection drug use are the primary modes of transmission. The pathophysiology of immune system destruction by HIV is similar in adult and pediatric subjects. Consequently, infectious complications of pediatric HIV disease consist of both severe manifestations of common pediatric infections and also opportunistic infections like those seen in HIV-infected adults. In pediatric and adult subjects, treatment of HIV disease is monitored by the same two surrogate markers, CD4 count and plasma HIV VL. Antiretroviral drugs have been shown to lower HIV RNA, improve CD4 counts (or percentage), and improve general clinical outcome in adult and pediatric subjects and treatment recommendations are very similar across all age groups (see Working Group on Antiretroviral Therapy and Medical Management of HIV-Infected Children. Guidelines for the Use of Antiretroviral Agents in Pediatric HIV Infection. February 28, 2008 1-134. Available at http://aidsinfo.nih.gov/ContentFiles/PediatricGuidelines.pdf for a review of studies and references).

7 Review of Safety

Safety Summary

Etravirine in combination with other ARV drugs was safe and tolerable when administered to pediatric subjects ages 6 years and older. The types of AEs observed in C213 were similar to adults. The most frequent AEs regardless of causality include upper respiratory tract infection (27%), and rash of any type (25%).

Rash due to ETR was observed in adult clinical trials. Rash profile in pediatric subjects was similar to adults [majority of rash AEs were grade 1 or 2 in severity, AEs were more frequent in female subjects (30%) compared to males (16%), similar timing of rash onset, duration of rash, and exposure-rash relationship]. No fatalities or Grade 4 cutaneous events were observed in C213. A total of 4% subjects discontinued treatment due to rash. Rash frequency was higher in the pediatric trial (25%) compared to adult phase 3 trials (16%), a finding explained by the greater proportion of female subjects in the pediatric trial (63%) compared to adult trials (10%). Additionally, unlike adults, all pediatric serious cutaneous AEs and discontinuations due to AEs were in female subjects. The ETR package insert already carries a warning about rash and cutaneous toxicity which is based on adult data. Pediatric rash findings will be described under Adverse Reactions section 6.2.

No other safety concerns were identified. Note the study was not powered or designed to have an active comparator arm, nor was there a pre-specified number of subjects required for testing statistical differences in AE incidences. Descriptive statistics were applied to describe the observed findings. The results should be interpreted with caution.

7.1 Methods

7.1.1 Clinical Studies Used to Evaluate Safety

The safety profile of ETR has already been established in adult clinical trials in an adequate number of subjects. C213, an ongoing 48-week trial, represents the pivotal pediatric trial conducted to assess ETR safety and efficacy in subjects ages 6 years to < 18 years. The primary objective of the trial is to evaluate the safety and tolerability of ETR in combination with other ARV drugs over 24 weeks. Refer to Section 5.3.1 for study details.

7.1.2 Adequacy of Data

Data submitted support safety and tolerability of ETR in combination with other ARVs. The PWR required a minimum of 100 patients are followed for safety at the to-be-marketed dose or higher dose for 24 weeks. As this submission is an interim study report as well as a partial response to the PWR, more data (i.e. data on 48 week duration treatment as well as data on additional subjects between 2 months to < 6 years

of age) are expected in the future. The submitted data are adequate with respect to number of subjects exposed to ETR and duration of exposure. The data were submitted by SAS transport file for analysis using JMP software. Adverse events were presented using MedDRA preferred terms and by System Organ Class. All AEs were graded using the standard DAIDS Toxicity Table for Grading Severity of Pediatric (> 3 months of age) Adverse Events.

A trial in treatment-experienced pediatric subjects 2 months to < 6 years of age is planned. No studies will be conducted in subjects less than 2 months age. Please refer to Section 2.5 for expected timelines for submission of various pediatric studies.

7.2 Adequacy of Safety Assessments

7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

The Applicant has submitted safety data on 101 pediatric subjects with at least 24 week safety data. Overall, subjects were exposed to ETR for a median duration of 48.1 weeks.

7.2.2 Explorations for Dose Response

In trial C126, two ETR doses were 4 mg/kg BID and 5.2 mg/kg BID were sequentially evaluated in 21 subjects. Based on matching adult-pediatric exposures, 5.2 mg/kg BID dose was selected for pediatric dosing and further evaluated in the 48-week trial C213. Exposure-response relationships explored by the pharmacometrics review team are presented in section 4.4.2 of this review. Similar to adults, an exposure-response relationship was observed in C213. Virologic response (VL < 50 copies/ml) at Week 24 was observed in 21% subjects in the lowest AUC quartile compared to 78% subjects in the highest quartile. Refer to clinical pharmacology/ pharmacometrics review by Dr. Jenny Zheng for details.

7.2.3 Special Animal and/or In Vitro Testing

Refer to the original and traditional reviews NDA 22-187 for details. No new animal and/or *in vitro* testing was submitted with this sNDA.

7.2.4 Routine Clinical Testing

Protocol defined routine clinical and laboratory testing were conducted during the trial. Subjects were evaluated for AEs and laboratory tests were performed at appropriate frequencies (Week 2, 4, 8, 12, 16, 24, 32, 40, 48 and a post-treatment follow-up visit). The safety testing was adequate.

7.2.5 Metabolic, Clearance, and Interaction Workup

Refer to clinical pharmacology review for NDA 22-187 S009.

7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

Class-associated events such as cutaneous reactions, hepatic events, and hepatic laboratory abnormalities were monitored during the study period.

7.3 Major Safety Results

7.3.1 Deaths

No deaths occurred during the 24 week study period.

7.3.2 Nonfatal Serious Adverse Events (SAEs)

In the 24 week analysis, SAEs were reported by 6 (6%) subjects (Table 14). Among these, only one SAE of drug overdose was considered by the investigator as related to study treatment. The rest of SAEs were considered as not related to treatment. All SAEs were observed in the adolescent age group. One SAE, pneumonia, was observed in one subject during the screening period. After week 24, one SAE, pregnancy resulting in elective termination, was reported as an SAE.

Table 14: Treatment-emergent serious adverse events in C213

Preferred AE term	Etravirine Children ≥6 to <12 yrs N=41	Etravirine Adolescents ≥12 years N=60	All subjects N=101
Investigations			
Lymphocyte morphology abnormal	0	1 (1.7%)	1 (1%)
Immunoglobulin elevated	0	1 (1.7%)	1 (1%)
Weight decreased	0	1 (1.7%)	1 (1%)
Poisoning, Injury Complications			
Drug toxicity	0	1 (1.7%)	1 (1%)
Drug overdose	0	1 (1.7%)	1 (1%)
Eye Disorder			
Ulcerative keratitis	0	1 (1.7%)	1 (1%)
General Disorders			
Drug resistance	0	1 (1.7%)	1 (1%)
Social Circumstances			
Treatment noncompliance	0	1 (1.7%)	1 (1%)

Source: NDA 22187 S-009 ae.xpt and dm.xpt

7.3.3 Dropouts and/or Discontinuations

During the 24 week treatment period, 8 (8%) subjects discontinued treatment due to an AE (Table 15). The most frequent AE leading to discontinuation was rash (of any type) in 4% of subjects. Three of the four rash cases were considered by the investigator as at least possibly related to ETR. One subject (1%) discontinued due to hypersensitivity reaction. Please refer to Section 7.3.5 for detailed discussion of these five cases. Two trial participants discontinued treatment when pregnancy was diagnosed. One subject discontinued due to treatment failure secondary to drug resistance. Discontinuations were more frequently observed in the adolescent age group compared to children.

Table 15: Discontinuations due to Adverse Events C213

Preferred AE term	Etravirine Children ≥6 to <12 yrs N=41	Etravirine Adolescents ≥12 years N=60	All subjects N=101
Discontinuations due to AE	**2 (4%)**	**6 (10%)**	**8 (8%)**
Skin Disorders			
Rash	0	2 (3%)	2 (2%)
Maculopapular rash	1 (2%)	1 (2%)	2 (2%)
Immune System Disorders			
Hypersensitivity	1 (2%)	0	1 (1%)
Pregnancy			
Pregnancy	0	2 (3%)	2 (2%)
General Disorders			
Drug resistance	0	1 (2%)	1 (1%)

Source: NDA 22187 S-009 ae.xpt and dm.xpt

7.3.4 Significant (Grade 3 and/or 4) Adverse Events

A total of 14 subjects (14%) experienced 16 Grade 3 or 4 AE (Table 16). The most frequent AEs observed in at least 2 subjects were thrombocytopenia (2%) and hypertriglyceridemia (2%). Grade 3/4 rash was observed in two subjects. With the exception of Grade 4 thrombocytopenia, the rest of AEs were Grade 3 in severity.

Table 16: Treatment-emergent Grade 3 or 4 AEs

Preferred AE term	Etravirine Children ≥6 to <12 yrs N=41	Etravirine Adolescents ≥12 years N=60	All subjects N=101
Grade 3 or 4 AE	**8 (17%)**	**7 (15%)**	**14 (14%)**
Skin Disorders			
Rash	0	1 (2%)	1 (1%)
Maculopapular rash	1 (2%)	0	1 (1%)
Blood and Lymphatic System Disorders			
Thrombocytopenia	2 (5%)	0	2 (2%)
Anemia	0	1 (2%)	1 (1%)
Neutropenia	1 (2%)	0	1 (1%)
Immune System Disorders			
Hypersensitivity	1 (2%)	0	1 (1%)
Gastrointestinal Disorders			
Diarrhea	0	1 (2%)	1 (1%)
Inguinal hernia	0	1 (2%)	1 (1%)
Infections and Infestations			
Influenza	0	1 (2%)	1 (1%)
Otitis Media	1 (2%)	0	1 (1%)
Investigations			
Blood amylase increased	1 (2%)	0	1 (1%)
Lipase increased	1 (2%)	0	1 (1%)
Hypertriglyceridemia	0	2 (3%)	2 (2%)
Reproductive System Disorders			
Dysmenorrhea	0	1 (2%)	1 (1%)

Source: NDA 22187 S-009 ae.xpt and dm.xpt

Both AEs of thrombocytopenia were considered not related to study treatment. In both cases, platelet count abnormalities were observed at baseline visits. Worsening from baseline grade to Grade 4 severity was observed during treatment and resolved to Grade 2 severity or normal range despite continued ETR use. Of note, no clinical bleeding events were observed in these two subjects.

7.3.5 Submission Specific Primary Safety Concerns

Rash and Hypersensitivity Reactions

Rash is a known side-effect of ETR observed in adult clinical trials and postmarketing. In adult phase 3 trials, the frequency of skin events of interest (preferred AE terms representing cutaneous drug reaction) was 16% in the ETR arm compared to 8% in placebo arm. The majority (99%) of events were grade 1 or 2 events. Most subjects with rash were able to continue ETR therapy, and only 2% discontinued treatment. The median time to onset was 11 days. The median duration of these events was 13 days. Female subjects were more likely to develop rash (25%) compared to male subjects (14%). Hypersensitivity reactions were observed in clinical trials and identified in the postmarketing period. These findings warranted labeling for skin reactions and hypersensitivity reactions in the Warnings/Precautions section.

In this review, SEI refers to the following preferred AE terms: rash, rash of any type, erythema, hypersensitivity, urticaria, erythema multiforme, toxic epidermal necrolysis, and Stevens-Johnson syndrome. The definition was selected to facilitate comparison with adult phase 3 data using the same definition.

In trial C213, SEIs were observed in 25% of all subjects (Table 17). Events were more frequent in the adolescent age group (28%) compared to children (19%). Rash was the most preferred AE term observed in 11% of all subjects.

Table 17: Treatment-Emergent Skin Events of Interest Week 24 analysis

Preferred AE term	Etravirine ≥6 to <12 yrs N=41	Etravirine ≥12 years N=60	All subjects N=101
Any SEI	**8 (19%)**	**17 (28%)**	**25 (25%)**
Rash, any type	**6 (15%)**	**17 (28%)**	**23 (23%)**
Rash	2 (5%)	9 (15%)	11 (11%)
Rash maculo-papular	3 (7%)	6 (10%)	9 (9%)
Rash papular	2 (5%)	1 (2%)	3 (3%)
Rash pruritic	0	1 (2%)	1 (1%)
Rash erythematous	0	1 (2%)	1 (1%)
Rash generalized	0	1 (2%)	1 (1%)
Rash macular	1 (2%)	0	1 (1%)
Other			
Erythema multiforme	1 (2%)	0	1 (1%)
Hypersensitivity	1 (2%)	0	1 (1%)

Source: NDA 22187 S-009 ae.xpt and dm.xpt

Overall, the majority (22%) of SEIs were Grade 1 or 2 in severity (Table 18). No Grade 4 AEs were observed. Grade 3 AEs were observed in 3% subjects. Median duration of onset was 9 days after initiating treatment and median duration of episode was 8 days.

These findings are similar to adult rash/SEI observations. The majority of SEI cases (20%) in C213 were considered by the investigator as at least possibly related to ETR. A total of 5% subjects discontinued due to an SEI.

Table 18: Characteristics of Skin Events of Interest Week 24 analysis

Preferred AE term	Etravirine ≥6 to <12 yrs N=41	Etravirine ≥12 years N=60	All subjects N=101
SEI	**8 (19%)**	**17 (28%)**	**25 (25%)**
Grade 1	2 (5%)	6 (10%)	8 (8%)
Grade 2	4 (10%)	10 (17%)	14 (14%)
Grade 3	2 (5%)	1 (2%)	3 (3%)
Discontinuations	2 (5%)	3 (5%)	5 (5%)
Related AEs			
Possibly	4 (10%)	4 (7%)	8 (8%)
Probably	2 (5%)	9 (15%)	11 (11%)
Very Likely	0	1 (2%)	1 (1%)
Time to onset (Days, median/range)	8 (5-120)	10 (8-52)	9 (5-120)
Duration (Days, median/range)	9 (2-28)	7 (2-30)	8 (2-30)

Source: NDA 22187 S-009 ae.xpt and dm.xpt

Female subjects were more likely to develop SEI (30%) compared to male subjects (16%). All Grade 3 events and discontinuation events, a total of 8 cases, were observed in female subjects only (Table 19).

Table 19: Rash by gender Week 24 analysis

Preferred AE term	Female N=64	Male N=37	All subjects N=101
SEI	**19 (30%)**	**6 (16%)**	**25 (25%)**
Grade 1	4 (6%)	4 (11%)	8 (8%)
Grade 2	12 (19%)	2 (5%)	14 (27%)
Grade 3	3 (5%)	0	3 (7%)
Discontinuations	5 (8%)	0	5 (10%)
Related AEs			
Possibly	6 (9%)	2 (5%)	8 (17%)
Probably	9 (14%)	2 (5%)	11 (20%)
Very Likely	1 (2%)	0	1 (1%)

Source: NDA 22187 S-009 ae.xpt and dm.xpt

Analysis by clinical pharmacology/pharmacometrics review team demonstrated a trend of increased rash with baseline CD4 count in C213. However, this finding was confounded by higher CD4 counts in female pediatric subjects compared to male subjects. Refer to clinical pharmacology review for details.

Similar to adult findings, rash was observed frequently in pediatric subjects, the majority of pediatric cases were mild to moderate in severity, and female pediatric subjects were more likely than males o develop rash events. Notable differences in adult-pediatric rash characteristics include:

- A higher rash frequency observed in the pediatric trial (25%) compared to adult trials (16%). Because female subjects constitute a larger proportion of the pediatric trial population (63%) compared to adult phase 3 trials (10%), higher rash rates in the pediatric trial likely represents preponderance in females. Other factors influencing rash were explored. Although trends were observed with higher ETR exposure and higher baseline CD4 count, firm conclusions were not drawn due to weak correlations and limited number of subjects.
- Serious cutaneous AEs (grade 3-4) and discontinuations were observed only in female subjects in the pediatric trial.

In summary, pediatric rash profile in C213 is similar to the adult profile. The ETR label already describes rash and serious skin reactions including hypersensitivity reactions under Warnings and Precautions section and Adverse Reactions section. Additional information for pediatric rash is proposed in Adverse Reaction section. The proposed language is reasonable; however, it does not convey the higher event rate of serious rash in female pediatric subjects. The following excerpt includes proposed and recommended (underlined) labeling:

> **6.2 Clinical Trials Experience: Pediatric Patients (6 years to less than 18 years of age)**
>
> The frequency, type and severity of adverse drug reactions in pediatric subjects were comparable to those observed in adults, except for rash which was observed more frequently than in (b) (4) .**[26]** The most common adverse drug reactions in (b) (4) 2% pediatric subjects were rash and diarrhea. Rash (≥ grade 2) occurred in 15% of pediatric subjects.**[27]** In the majority of subjects, rash was mild to moderate, of macular/papular type, and occurred in the second week of therapy.**[28]** Rash was (b) (4) self-limiting and resolved within 1 week on continued therapy.**[29]** The discontinuation rate for rash was 4%. Rash events including serious (Grade 3 or 4) events and discontinuations were more frequently observed in female subjects compared to male subjects.

Other Safety Concerns

Safety events of interest selected based on class-related toxicity, preclinical safety concerns, or adult safety profile are discussed in this section. Events of concern include hepatic events, psychiatric events, lipid-related events, cardiac events related to coronary artery disease, bleeding events, and pancreatitis.

No AEs of pancreatitis, hepatic events, or cardiac events pertaining to coronary artery disease were observed. Psychiatric, lipid-related, and bleeding-related AEs are outlined in Table 20. All lipid AEs were considered not related to ETR. No abnormalities in coagulation parameters (PTT or INR) were observed in three subjects with bleeding

type events (hematochezia, hemoptysis, and metrorrhagia); these AEs were unrelated to a bleeding disorder.

Table 20: Select Adverse Events Analysis in C213 Week 24 analysis

Preferred AE term	Etravirine ≥6 to <12 yrs N=41	Etravirine ≥12 years N=60	All subjects N=101
Psychiatric disorders	**1 (2%)**	**2 (6%)**	**3 (3%)**
Nightmare	0	1 (2%)	1 (1%)
Adjustment Disorder	0	1 (2%)	1 (1%)
Anxiety	1 (2%)	0	1 (1%)
Bleeding-type events			
Hematochezia	0	1 (2%)	1 (1%)
Hemoptysis	0	1 (2%)	1 (1%)
Metrorrhagia	0	1 (2%)	1 (1%)
Lipid-related events			
Hypercholesterolemia	2 (5%)	1 (2%)	3 (3%)
Hypertriglyceridemia	0	2 (3%)	2 (2%)
Blood triglyceride increased	2 (5%)	2 (3%)	4 (4%)

Source: NDA 22187 S-009 ae.xpt and dm.xpt

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

A total of 92% of all subjects experienced at least 1 AE including 95% of adolescents and 85% of children (Table 19). The most frequent AEs regardless of causality in at least 10% of all subjects were upper respiratory tract infection (27%), diarrhea (17%), cough (12%), rash (11%), vomiting (10%), nausea (10%), and headache (10%). Refer to Table 21.

At Wk 24 analysis in adult phase 3 trials, frequent AEs in the ETR arm include diarrhea (15%), nausea (14%), rash (10%), headache (9%), nasopharyngitis (8%), vomiting (7%), cough (6%), bronchitis (6%), pyrexia (6%), and upper respiratory tract infection (4%).

Table 21: Treatment-emergent adverse events (all causality, ≥ 5% of all subjects)

Preferred AE term	Etravirine Children ≥6 to <12 yrs N=41	Etravirine Adolescents ≥12 years N=60	All subjects N=101
	35 (85%)	57 (95%)	92 (92%)
Upper respiratory tract infection	10 (24%)	17 (28%)	27 (27%)
Diarrhea	5 (12%)	12 (18%)	17 (17%)
Cough	5 (12%)	7 (12%)	12 (12%)
Rash	2 (5%)	9 (15%)	11 (11%)
Vomiting	4 (10%)	6 (10%)	10 (10%)
Nausea	3 (7%)	7 (12%)	10 (10%)
Headache	2 (5%)	8 (12%)	10 (10%)
Rash maculopapular	3 (7%)	6 (10%)	9 (9%)
Pyrexia	3 (7%)	6 (10%)	9 (9%)
Pharyngitis	2 (5%)	6 (10%)	8 (8%)
Bronchitis	0	8 (12%)	8 (8%)
Sinusitis	3 (7%)	4 (6%)	7 (7%)
Rhinitis	2 (5%)	5 (8%)	7 (7%)
Conjunctivitis	2 (5%)	5 (8%)	7 (7%)
Oropharyngeal pain	1 (2%)	5 (8%)	6 (6%)
Oral herpes	1 (2%)	5 (8%)	6 (6%)
Influenza	2 (5%)	4 (6%)	6 (6%)
Pneumonia	4 (10%)	1 (2%)	5 (5%)
Otitis media acute	1 (2%)	4 (6%)	5 (5%)
Nasopharyngitis	3 (7%)	2 (3%)	5 (5%)
Abdominal pain	2 (5%)	3 (5%)	5 (5%)

Source: NDA 22187 S-009 ae.xpt and dm.xpt

7.4.2 Laboratory Findings

Chemistry

Grades 1-4 abnormalities per DAIDS criteria are summarized in Table 22. Majority of the liver-related laboratory abnormalities were grade 1 or 2 in severity. No subjects met biochemical criteria for Hy's law for drug-induced liver injury, namely, ALT or AST value > 3 x ULN accompanied by total bilirubin value > 2 x ULN. Grade 3 creatinine elevations were observed in one subject at a single time point and improved to grade 1 severity with continued treatment. All serum lipase elevations were grade 1 in severity.

Table 22: Treatment-Emergent Laboratory Abnormalities[1] in C213, Week 24 analysis

Select Chemistry Parameters	Etravirine Children N=41	Etravirine Adolescents N=60	All subjects N=101
Serum ALT			
Grade 2	1 (2%)	0	1 (1%)
Grade 1	6 (15%)	8 (13%)	14 (14%)
Serum AST			
Grade 2	2 (5%)	2 (3%)	4 (2%)
Grade 1	4 (10%)	3 (5%)	7 (7%)
Total Serum Bilirubin			
Grade 3	0	2 (3%)	2 (2%)
Grade 2	0	1 (2%)	1 (1%)
Grade 1	1 (2%)	0	1 (1%)
Serum Alk Phosphatase			
Grade 2	1 (2%)	0	1 (1%)
Grade 1	4 (10%)	6 (10%)	10 (10%)
Serum Creatinine			
Grade 3	0	1 (2%)	1 (1%)
Grade 2	0	0	0
Grade 1	2 (5%)	4 (7%)	3 (3%)
Serum Lipase			
Grade 1	1 (2%)	1 (2%)	2 (2%)

[1]Worst-grade
Source: NDA 22187 S-009 lb.xpt, dm.xpt

Hematology

The most frequently observed hematological abnormality was low hemoglobin in 9% of all subjects (Table 23).

Table 23: Treatment-Emergent Hematology Abnormalities[1] in C213, Week 24 analysis

Parameter	Etravirine Children	Etravirine Adolescents	All subjects
	N=41	N=60	N=101
Hemoglobin			
Grade 3	0	1 (2%)	1 (1%)
Grade 2	1 (2%)	0	1 (1%)
Grade 1	4 (10%)	3 (5%)	7 (7%)
Decrease in WBC			
Grade 1	1 (2%)	2 (3%)	3 (3%)
Decrease in Platelet count			
Grade 4	1 (2%)	0	1 (1%)
Grade 1	1 (2%)	2 (3%)	2 (2%)

[1]Worst-grade; Source: NDA 22187 S-009 lb.xpt, dm.xpt

Majority of hematologic abnormalities were Grade 1 in severity. A case of grade 4 thrombocytopenia considered by the investigator as not related to ETR was previously discussed in 7.3.4.

Lipid Profile

The most frequent lipid related laboratory abnormality was an increase in total cholesterol observed in 34% of all subjects (Table 24). The majority of abnormalities were Grade 1 or 2 in severity.

Table 24: Treatment-Emergent Lipid Abnormalities in C213[1], Week 24 analysis

Parameter	Etravirine Children ≥6 to <12 yrs	Etravirine Adolescents ≥12 years	All subjects
	N=41	N=60	N=101
Triglycerides			
Grade 3	1 (2%)	0	1 (1%)
Grade 2	0	2 (3%)	2 (2%)
Total Cholesterol			
Grade 2	8 (20%)	12 (20%)	20 (20%)
Grade 1	9 (22%)	5 (8%)	14 (14%)
LDL Cholesterol			
Grade 3	0	1 (2%)	1 (1%)
Grade 2	5 (12%)	8 (13%)	13 (13%)
Grade 1	4 (10%)	2 (3%)	6 (6%)

[1]Worst-grade

Source: NDA 22187 S-009 lb.xpt, dm.xpt

7.4.3 Vital Signs

Vital signs (heart rate, blood pressure) were collected for all randomized subjects. No significant differences were noted when comparing baseline to on-treatment values.

7.4.4 Electrocardiograms

As reported in the original NDA approval, ETR is not associated with a risk of QT interval prolongation based on findings reported in trial TMC1215-178. No AEs of QT prolongation were observed in trial C213.

7.4.5 Immunogenicity

No new findings related to immunogenicity of ETR were reported in trial C213.

7.5 Other Safety Explorations

7.5.1 Dose Dependency for Adverse Events

The pharmacometrics team performed formal analyses for exposure-safety relationship. As discussed in section 4.4.2, exposure-safety analyses focused on rash AEs. An exposure-rash relationship was observed. Because of exposure-rash relationship, an evaluation of frequency and severity of rash AEs by exposure and body weight (≥ 16 to < 20kg, ≥ 20 to < 25 kg, ≥ 25 to < 30 kg, ≥ 30 kg) was performed by the clinical pharmacology/pharmacometrics review team. Specifically for 30-35 kg weight band, rash AEs were reviewed for possible consideration of a lower 175 mg dose. In this weight band, the majority of cutaneous AEs were grade 1 or 2 in severity. One case of grade 3 hypersensitivity reaction AE was confounded by concomitant drugs known to cause rash and hypersensitivity reactions like abacavir, DRV, and trimethoprim/sulfamethoxazole. In the absence of a compelling safety advantage, and keeping in mind greater pill burden associated with 175 mg dose (175 mg BID comprises of 4 tablets BID, and 200 mg BID comprises 1 or 2 tablets BID), the proposed 200 mg BID dose was considered acceptable for 30-35 kg weight band.

7.5.2 Time Dependency for Adverse Events

Evaluation of time dependency for AEs is integrated in the safety analyses. Refer to section 7.3.5 for detailed analysis for timing of onset of rash AEs.

7.5.3 Drug-Demographic Interactions

This sNDA evaluated use of ETR in the pediatric population 6 to < 18 years. Results were analyzed by children (6 to < 12 years) and adolescent age groups (12 to < 18 years). Rash events were more frequent in adolescents (28%) compared to children (19%), however, clear-cut conclusions cannot be drawn because of few subjects in each group. Refer to section 7.3.5 for details. The overall safety profile was similar in children and adolescent age groups.

7.5.4 Drug-Disease Interactions

Etravirine was not administered as monotherapy. However, similar to adults, administration of ETR in combination with other ARVs appears decrease the plasma HIV-1 viral load in the host. In addition, CD4 cell count and percentage improved across all age groups after initiation of treatment with etravirine in combination with other ARVs.

7.5.5 Drug-Drug Interactions

It is expected that the same types of drug interactions will be observed in pediatric subjects as those that have been observed in adult subjects taking ETR. Drug-Drug interactions are included in the label.

7.6 Additional Safety Explorations

7.6.1 Human Carcinogenicity

No association with malignant neoplasms was observed in adult phase 3 trials. Please refer to the original NDA reviews.

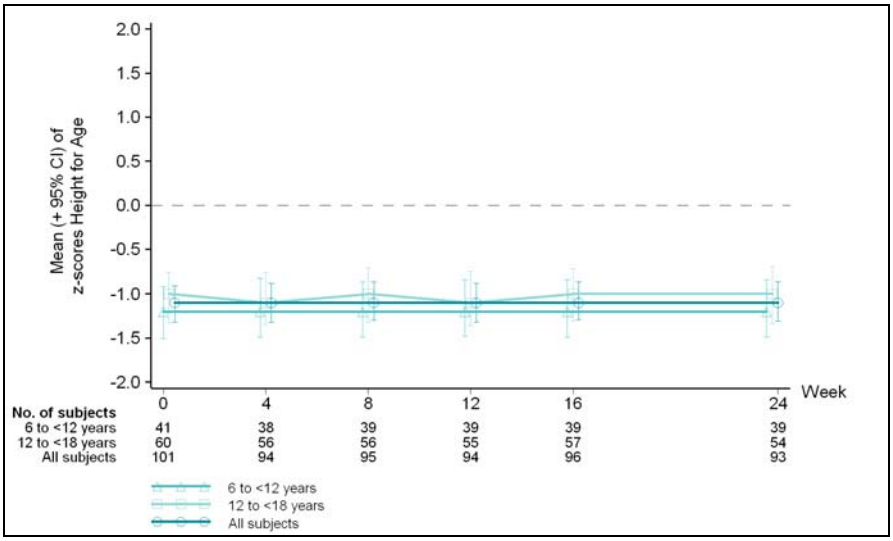
7.6.2 Human Reproduction and Pregnancy Data

In C213, two pregnancies were reported both resulting in elective termination of pregnancy. No adequate and well-controlled studies of ETR have been conducted in pregnant women. No pharmacokinetic studies have been conducted in pregnancy. Etravirine belongs to pregnancy Category B and should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. For details about animal reproductive toxicology findings, refer to the Pharmacology/toxicology review for the traditional NDA approval.

7.6.3 Pediatrics and Effect on Growth

According to Applicant's analysis, within-group comparison for changes from baseline for age-adjusted scores for height, weight and body mass index at Week 24 revealed no significant changes. Sponsor's analysis for effects on height is displayed in Figure 8.

Figure 8: Effect of Etravirine on Height



Source: NDA 22187 S-009 TMC125-C213 Clinical Research Report

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

There is no withdrawal or abuse potential with ETR. One adolescent subject in trial C213 was inadvertently dosed with 250 mg BID dose of ETR. This dose exceeds the maximum recommended adult dose (200 mg BID). The subject received the incorrect dose for 50 days and no safety consequences were reported for this case.

7.7 Additional Submissions

A safety update report (SUR) to this sNDA was submitted on December 16, 2011. This report contained updates for SAEs and discontinuations due to AEs in C213 after cut-off date for the Summary of Clinical Safety up to October 19, 2011. No new SAEs or AEs leading to permanent discontinuation were reported in the SUR. Findings in SUR do not alter the overall safety conclusion of this review.

8 Postmarketing Experience

Etravirine has not been previously approved for use in the pediatric population. The Applicant will continue to provide periodic safety updates in addition to providing full 48 week study report for trial C213.

9 Appendices

9.1 Literature Review/References

1. TITLE IV—PEDIATRIC RESEARCH EQUITY ACT OF 2007 ‘‘(B) SIMILAR COURSE OF DISEASE OR SIMILAR EFFECT OF DRUG OR BIOLOGICAL PRODUCT - (i) IN GENERAL.—If the course of the disease and the effects of the drug are sufficiently similar in adults and pediatric subjects, the Secretary may conclude that pediatric effectiveness can be extrapolated from adequate and well-controlled studies in adults, usually supplemented with other information obtained in pediatric subjects, such as pharmacokinetic studies. (ii) EXTRAPOLATION BETWEEN AGE GROUPS.—A study may not be needed in each pediatric age group if data from one age group can be extrapolated to another age group. (iii) INFORMATION ON EXTRAPOLATION.—A brief documentation of the scientific data supporting the conclusion under clauses (i) and (ii) shall be included in any pertinent reviews for the application under section 505 of this Act or section 351 of the Public Health Service Act (42 U.S.C. 262).

2. Pediatric Written Request. See Section 9.4 (Attachment 1)

9.2 Labeling Recommendations

Key recommendations by the review team are outlined here. Refer to CDTL memo by Dr. Yodit Belew for labeling changes recommended (if any) after this review was entered in DARRTS.

- Indication: Recommendation to include language about cross-resistance with rilpivirine, based on recent approval of EDURANT (rilpivirine). Language describing cross-resistance data were included in section 12.4 of the PI.

INTELENCE®*, in combination with other antiretroviral agents, is indicated for the treatment of human immunodeficiency virus type 1 (HIV-1) infection in antiretroviral treatment-experienced patients ages 6 years and older, who have evidence of viral replication and HIV-1 strains resistant to a non-nucleoside reverse transcriptase inhibitor (NNRTI) and other antiretroviral agents.

In treatment-experienced adult and pediatric patients, the following points should be considered when initiating therapy with INTELENCE®:[6]

- Treatment history and resistance testing should guide the use of INTELENCE®.
- (b) (4)
- In patients who have experienced virologic failure on an NNRTI-containing regimen, do not use INTELENCE® in combination with only N[t]RTIs [*see Clinical Studies (14)*].
- The use of other active antiretroviral agents with INTELENCE® is associated with an increased likelihood of treatment response.

The safety and efficacy of INTELENCE® have not been established in pediatric patients less than 6 years of age or in treatment-naïve adult or pediatric patients.[7]

- Dosing recommendation: Agree with sponsor's proposed dosing.

Recommended dose of INTELENCE® for pediatric patients 6 years to less than 18 years of age[16]	
Weight kilograms (kg)	**Dose**
greater than or equal to 16 kg to less than 20 kg	100 mg twice daily
greater than or equal to 20 kg to less than 25 kg	125 mg twice daily
greater than or equal to 25 kg to less than 30 kg	150 mg twice daily
greater than or equal to 30 kg	200 mg twice daily

- Adverse Drug Reactions – Pediatrics: Include common adverse reactions information. Also specify serious rash events and discontinuations were more frequent in female pediatric subjects compared to male subjects.

The safety assessment in children and adolescents is based on the Week 24 analysis of the single-arm, Phase 2 trial TMC125-C213 in which 101 antiretroviral treatment-experienced HIV-1 infected subjects 6 years to less than 18 years of age and weighing at least 16 kg received INTELENCE in combination with other antiretroviral agents [*see Clinical Studies (14.2)*].[25] The frequency, type and severity of adverse drug reactions in pediatric subjects were comparable to those observed in adult subjects, except for rash which was observed more frequently in pediatric subjects.[26] The most common adverse drug reactions in (b) (4) 2% pediatric subjects were rash and diarrhea. Rash (≥ grade 2) occurred in 15% of pediatric subjects.[27]In the majority of cases, rash was mild to moderate, of macular/papular type, and occurred in the second week of therapy.[28] Rash was self-limiting and generally resolved within 1 week on continued therapy.[29] The discontinuation rate for rash was 4%. Rash including serious (Grade 3 or 4) events and discontinuations were more frequently observed in female subjects compared to male subjects. [30]

9.3 Advisory Committee Meeting

No Advisory Committee meeting was convened for this application.

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/s/

CHARU J MULLICK
03/05/2012

YODIT BELEW
03/05/2012