sNDA 22,187/S-024: Etravirine
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Clinical and Cross-Discipline Team Leader Review / Addendum

Date	June 15, 2018 / Revised July 5, 2018
From	Melisse Baylor, M.D.
Subject	Clinical Review

Supplemental NDA #	22187 / Supplement 024
Applicant	Janssen Research and Development
Date of Submission	January 16, 2018
PDUFA Goal Date	July 16, 2018
Proprietary Name/ Established (USAN) names	INTELENCE® / etravirine (ETR)
Dosage forms / Strength	Oral tablets: 25 mg and 100 mg Tablets can be dispersed in water or other liquids in patients who cannot swallow tablets
Proposed indication(s)	Indicated for treatment of HIV-1 infection in treatment-experienced patients 2 years of age and older with viral strains resistant to an NNRTI and other antiretroviral agents
Recommendation on Regulatory Action	Approval

1. Introduction

This combined Clinical and Cross Discipline Team Leader (CDTL) Review provides an overview of the submitted clinical data, summarizes the findings of the FDA multi-disciplinary team of reviewers, describes the conclusions and recommendations presented by all disciplines, and provides an overall risk-benefit assessment of etravirine use in pediatric patients ≥ 2 to < 6 years of age. The data support extension of the etravirine indication to include pediatric patients 2 years of age and older.

The application was granted a priority review for several reasons. The data in the application are in response to the Pediatric Written Request issued under the Best Pharmaceuticals for Children Act. In addition, the application for etravirine allows for the use of etravirine, a non-nucleoside reverse transcriptase inhibitor (NNRTI), in HIV-1 infected children 2 years to < 6 years of age, who have resistance to other antiretroviral drugs, including the NNRTIs nevirapine and efavirenz. With the widespread use of nevirapine as a component of neonatal treatment regimens for the prevention of mother-to-child transmission, HIV-infected children are at risk of developing nevirapine resistance, and there is a need for additional treatment options for HIV-infected children.

2. Background

This supplemental NDA contains the results of a single study, TMC125-C234, a pharmacokinetic, safety, and antiviral activity study of etravirine in pediatric patients ≥ 2 years to < 6 years of age. Data from study TMC125-C234 support approval in pediatric patients ≥ 2

years to < 6 years of age based on evidence of safety and on comparable etravirine exposures in children and adults, allowing for extrapolation of efficacy data from adults to pediatric patients.

2.1 Etravirine

Etravirine, a non-nucleoside reverse transcriptase inhibitor, was granted Traditional Approval on November 25, 2009. Etravirine was the fourth NNRTI approved for the treatment of HIV-1 infection. Nevirapine, efavirenz, and delavirdine were approved for the treatment of HIV-1 infection regardless of treatment experience, however, use of delavirdine is not generally recommended because of high pill burden, suboptimal potency, and multiple drug interactions (https://aidsinfo.nih.gov/guidelines/html/1/adult-and-adolescent-arv/12/what-not-to-use, Accessed on April 25, 2018). Nevirapine and efavirenz are commonly used for the treatment of pediatric HIV infection. Nevirapine is used to prevent mother-to-child transmission during birth or during breast feeding and to treat neonates and infants who are HIV-infected (https://aidsinfo.nih.gov/guidelines/html/3/perinatal/187/antiretroviral-management-of-newborns-with-perinatal-hiv-exposure-or-perinatal-hiv, Accessed April 25, 2018). Efavirenz in combination with two NRTIs is recommended as an alternative initial regimen in HIV-1 infected children 3 years of age and older. (https://aidsinfo.nih.gov/guidelines/html/2/pediatric-arv/444/regimens-recommended-for-initial-therapy-of-antiretroviral-naive-children, Accessed May 7, 2018). However, a single amino acid substitution in viral reverse transcriptase, such as either K103N or Y181C mutations, can result in decreased viral susceptibility to both nevirapine and efavirenz (cross resistance). Etravirine is active against HIV-1 isolates with these two resistance mutations and treatment with etravirine provides a treatment option for subjects who have failed treatment with nevirapine and/or efavirenz.

The etravirine approval in HIV treatment-experienced adult patients was based on data from two Phase 3 trials (TMC125-C206 and TMC125-C216). These trials were randomized, double-blinded, placebo-controlled Phase 3 trials in HIV-experienced subjects. The trial designs for TMC125-C206 and TMC125-C216 were identical. Entry criteria included a HIV-1 RNA level > 5,000 copies/mL while on an antiretroviral regimen for at least 8 weeks, ≥ 1 NNRTI resistance-associated mutation, and ≥ 3 protease inhibitor resistance-associated mutations at screening. Subjects were randomized in a 1:1 ratio to receive either etravirine plus an optimized background regimen (OBR) or placebo + OBR. The percentage of subjects with HIV-1 RNA levels < 50 copies/mL at Week 48 in pooled results for both trials was 60% in the etravirine + OBR arm and 38% in the placebo + OBR arm. At week 48, 71% of subjects in the etravirine + OBR arm had HIV-1 RNA levels less than 400 cells/μL compared to 46% in the placebo + OBR arm. In combined data from the two studies, the mean increase in CD4 lymphocyte cells from baseline to Week 48 was 96 cells/μL in the etravirine + OBR arm and 68 cells/μL in the placebo + OBR arm. These efficacy data supported an indication for treatment of treatment-experienced adults with etravirine.

Etravirine is currently approved for use in treatment-experienced, HIV-1 infected children and adolescent patients from 6 to < 18 years of age weighing at least 16 kg. This approval was based on the results of two trials: TMC125-C126 and TMC125-C213. Study TMC125-C126 was a Phase 1 dose-finding study in HIV-infected subjects ≥ 6 years to < 18 years of age. In this study, subjects received etravirine for 8 days with intensive pharmacokinetic monitoring on Day 8; information on short-term safety was also collected. Study TMC125-C213 was a Phase 2, open-label, single-arm, safety, pharmacokinetic and antiviral activity study in HIV-infected, treatment-experienced subjects ≥ 6 years to < 18 years of age. A total of 101 antiretroviral experienced subjects with a plasma HIV-1 RNA level of ≥ 500 copies/mL and susceptibility to etravirine at screening were enrolled and treated with etravirine and an OBR through 48 weeks. After 24 weeks of etravirine, HIV RNA levels were less than 50 copies/ml in 52% of subjects.

The proportion of subjects with HIV RNA levels less than 400 copies/mL was 67% at week 24. The mean change in CD4 cell count was +112 cells/μL.

Currently available HIV treatment includes seven different antiretroviral drug classes and 28 individual antiretroviral drugs and 2 drugs used as pharmacokinetic enhancers with antiretrovirals, not including fixed drug combination products and different formulations. The drug classes include nucleoside reverse transcriptase inhibitors (NRTIs), non-nucleoside reverse transcriptase inhibitors (NNRTIs), protease inhibitors (PIs), fusion inhibitors, CCR5 receptor antagonists, integrase strand transfer inhibitors (INSTIs), and post-attachment inhibitors. Many approved ARVs have dosing recommendations in at least one subset of the pediatric age range.

While there are approved ARVs in multiple classes available for the treatment of HIV infection in children, there continue to be challenges. For example, poor adherence, and short and long term toxicities may contribute to the development of drug resistance and failed therapy. As a result, there is a need for continuous development of new ARVs for treatment of HIV infection. There are currently four NNRTIs approved for treatment of HIV-1 infection. While nevirapine is approved for use in patients from 15 days of age and older and efavirenz is approved for use in patients 3 months of age and older, a single genetic mutation can lead to high-level resistance to either or both drugs. The availability of etravirine in patients 2 years of age and older provides a treatment option for treatment-experienced patients including those with resistance to nevirapine or efavirenz.

This pediatric supplement provides a complete response to the Written Request for etravirine. Please see Pediatrics section of this review for a discussion of Pediatric Exclusivity Board meeting.

2.2 Study Conduct

The applicant submitted the sNDA in accordance with FDA guidelines. The quality and integrity of the submission were adequate, and the material was reviewable as submitted.

According to the applicant, the pivotal trial was conducted in conformance with Good Clinical Practice standards and applicable local regulatory requirements and laws regarding ethical committee review, informed consent, and the protection of human subjects participating in biomedical research. The Division did not consult the Office of Scientific Investigations for inspection of the clinical trial sites, but bioanalytical inspections were requested for validation of the pharmacokinetic data, which serve as pivotal data for the approvability of these applications. The bioanalytical inspections reviewer reported that the data from the audited site were reliable.

The applicant also submitted financial information pertinent to the application. The study was conducted by the IMPAACT (International Maternal Pediatric Adolescent AIDS Clinical Trials Group) network as Study P1090 and was sponsored by the Division of AIDS. There were 12 principal investigators and 144 sub-investigators; none were employees of Janssen Research and Development. None of the investigators received compensation where the value could have influenced the outcome of the study, none received payments greater than $25,000, none held proprietary interested in the study drug, and none held significant equity interest in Janssen Research and Development. Therefore, the conduct of this trial complied with the regulations as defined in 21 CFR 54.4(a)(3)(i), 54.2(a). Please see the Clinical Investigator Financial Disclosure Review Template in Section 16 of this review.

3. CMC

A new formulation was not developed for use in pediatric patients. As a result, no new product information regarding drug substance or manufacturing was submitted. Please refer to the original review of NDA 22187 for additional information on chemistry and manufacturing.

4. Nonclinical Pharmacology / Toxicology

No new Pharmacology/Toxicology data were submitted for review. Please refer to the original review of NDA 22187 for details.

5. Clinical Microbiology

Please refer to the USPI and reviews from the original NDA for details of adult clinical virology, including analysis of etravirine-resistant HIV-1 strains. Please see Dr. Colberg-Poley's review of this NDA supplement.

Study TMC-C234 was a single arm, open-label, pharmacokinetic, safety, and antiviral activity study. The study enrolled 20 subjects from 2 years to < 6 years age group and 6 from 1 year to < 2 years age group.

Antiviral activity was a secondary endpoint for this study. The key efficacy endpoint was the number and percentage of subjects with virologic success defined as plasma HIV RNA < 400 copies/mL at Week 24. Virologic failure was defined as either:

- Lack of virologic response was defined as a confirmed:
  - HIV-1 RNA that was not ≥ 0.5 $\log_{10}$ lower than baseline at Week 8,
  - HIV-1 RNA that was not ≥ 1 $\log_{10}$ lower than baseline at or after Week 12,
  - HIV-1 viral load ≥ 400 copies/mL and not ≥ 2 log10 reduction at Week 24, and
  - HIV-1 viral load ≥ 400 copies/mL and not ≥ 2 log10 reduction at Week 48
- Virologic rebound was defined as confirmed viral load of > 1,000 copies/mL for subjects whose nadir was < 400 copies/mL.

Efficacy results were provided for 17 of 20 subjects in the ≥ 2 year to < 6 year age group at Week 24; three subjects in the study had not reached Week 24 at the time of database lock. Efficacy results for these 3 subjects were not included in the Clinical Study Report and data for these subjects were not included in the proposed package insert. Data for these 3 subjects was requested during the review cycle, and submitted by the applicant. All three subjects had HIV RNA < 400 copies/mL at Week 24. The applicant calculated virologic response at Week 24 as 88% (15/17). However, DAVP virology reviewers censored results from one subject who discontinued the study on Day 14 due to an adverse event and calculated virologic response as 94% (15/16). One subject had virologic failure with a viral load greater than 400 copies/mL at Week 24.

Genotypic resistance data were provided for three subjects who had virologic failure at Week 48 (the subject with virologic failure at Week 24 plus two additional subjects who experienced virologic failure between Weeks 24 and 48). The majority of the resistance-associated substitutions observed were those known to occur in adult subjects who experienced virologic failure while on etravirine. Two additional resistance-associated substitutions that are not commonly associated with etravirine resistance were reported, and phenotypic characterization of these resistance-associated substitutions was requested.

Two subjects had partially etravirine sensitive virus (defined as a decrease between 2.9 and 10 fold in HIV growth compared to wild type virus in the PhenoSense™ assay) at baseline as

measured by screening phenotype. Both subjects had HIV RNA levels < 400 cells/mL at Week 24. All other subjects with screening phenotype available had sensitive virus, pre-defined in the study protocol as a fold change ≤ 2.9 using the PhenoSense assay. Both subjects with partially sensitive virus at baseline, and 13 of the 14 subjects (93%) with sensitive virus at baseline had HIV RNA levels < 400 copies/mL at Week 24.

In summary, the etravirine resistance-associated substitutions observed in subjects ≥ 2 years to < 6 years of age who failed treatment with an etravirine-containing regimen were similar to those observed in trials enrolling adults. The applicant has not proposed any changes in the microbiology section of the package insert.

6. Clinical Pharmacology / Biopharmaceutics

Please refer to the USPI and reviews from the original NDA for details of adult pharmacokinetics (PK). Please see Dr. Sun's Clinical Pharmacology review of this application for additional information regarding the pediatric PK results summarized below.

In Study TMC125-C234, the initial 6 subjects in each age group were enrolled as a mini-cohort; intensive pharmacokinetic (PK) evaluations were performed for subjects in the mini-cohort on Day 14, and safety was followed for 4 weeks. If an acceptable dose was identified and safety was demonstrated, additional subjects were to be enrolled to reach a minimum of 12 subjects in each age group. The PK parameters were compared to historical adult controls from TMC125-C206 and TMC125-C216, the randomized, double-blinded, placebo-controlled Phase 3 trials in HIV-experienced adults. Each PK parameter in pediatric subjects was compared to adult parameters and a geometric mean ratio and a corresponding 90% confidence interval (CI) were constructed. The primary PK parameter was the etravirine AUC_{12h} (area under the plasma concentration curve from time of administration up to 12 hours post dosing). The equivalency boundary for the ratio of AUC_{12h} in children to adults was 60% to 150%. Note that the original protocol-defined bioequivalence boundaries for AUC_{12h} were set at 80-130%, but were modified in protocol amendments due to high inter-individual variability (62%) for apparent etravirine clearance observed in population PK modelling. If an appropriate dose was not identified after analysis of the PK results for the first mini-cohort, a second mini-cohort would be enrolled. In addition, the etravirine dose could be increased for an individual subject if his/her AUC_{12h} was < 2,350 ng·h/mL (adult 10^{th} percentile).

The etravirine dose for the initial mini-cohort of subjects ≥ 2 years to < 6 years of age was 5.2 mg/kg administered twice daily. The geometric mean ratio comparing pediatric subjects in the mini-cohort to adult historical controls was 54%, below the lower equivalency boundary of 60%. The etravirine dosing was then changed to weight band dosing as shown in Table 1. Etravirine dosing was revised for 4 of the 6 subjects in the initial mini-cohort to use weight band dosing; since the newly recommended dose of etravirine was the same as the initial dose for 2 subjects, these 2 subjects in the mini-cohort remained on the same dose. Weight band dosing was also used for the additional subjects enrolled in the ≥ 2 year to < 6 year age group and for all subjects in the ≥ 1 year to < 2 year age group. Individual subjects also had dose adjustments, as appropriate.

Table 1: Revised Etravirine Dosing

Weight Band (kg)	Target Dose (mg/kg bid)	Actual Dose (mg/bid)
< 8	8.8	50 mg
8 -< 10	8.8	75 mg
10 -< 13	8.8	100 mg
13 -< 16	6.8	100 mg
16 -< 20	5.2	100 mg
20 -< 25	5.2	125 mg
25 -< 30	5.2	150 mg
≥ 30	5.2	200 mg

Source: Clinical Study Report TMC125-C234: Tables 1, page 42.

The etravirine package insert currently provides dosing recommendations for subjects ≥ 16 kg; the dosing used for subjects ≥ 16 kg in Study TMC125-C234 is identical to the dosing in the package insert.

The PK results and geometric least-square mean ratios for the subjects from 2 to 6 years of age dosed with weight-band dosing and for 5 subjects from 1 to 2 years of age enrolled in TMC125-C234 are shown in Table 2. This table does not include results for the initial 6 subjects included in the mini-cohort for PK and safety. PK and safety results are not available for 1 of the 6 subjects from 1 to 2 years of age; this subject was not enrolled until after database lock.

Table 2: Etravirine Pharmacokinetic Parameters and Geometric Mean Ratios (GMR) Comparing Pediatric to Historical Adult Controls in Subjects who Received Etravirine Using Weight-Band Dosing

	Subjects ≥ 2 to < 6 Years of Age N=14		Subjects ≥1 to <2 Years of Age N=5	
PK Parameter	**Mean Value**	**GMR (90% CI*)**	**Mean Value**	**GMR (90% CI*)**
AUC_{12h} (h·ng/mL)	3504.4	0.77(0.57, 1.04)	2671.4	0.59 (0.34, 1.01)
C_0 (ng/mL)	183.1	0.62 (0.42, 0.92)	151.8	0.51 (0.24, 1.07)
C_{12h} (ng/mL)	210.9	0.71 (0.48, 1.05)	153.3	0.52 (0.31, 0.87)

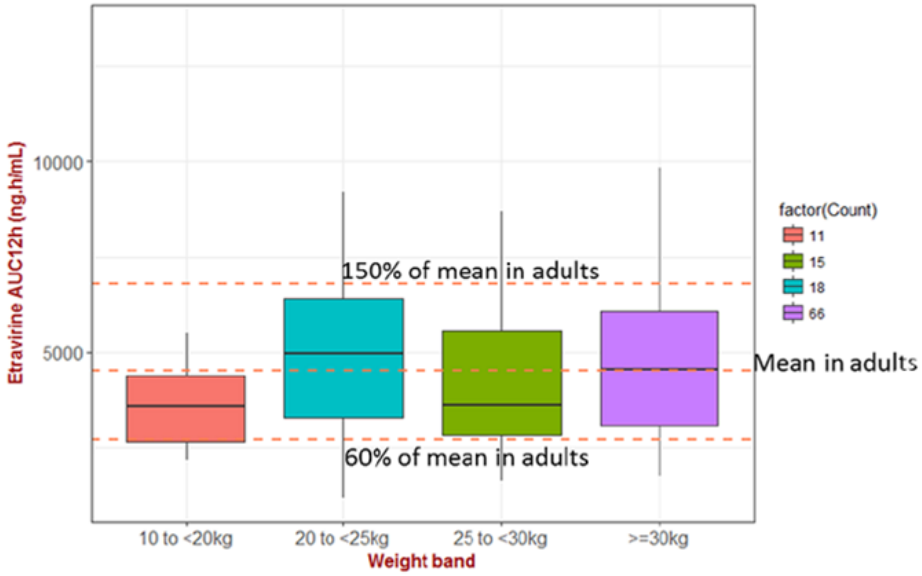
*CI=confidence interval

Source: Clinical Study Report TMC125-C234: Table 21, page 83.

As shown in Table 2, the geometric mean ratio for AUC_{12h} was 77%, well within the 60 to 150% boundary prespecified for PK matching in this study. Most pediatric patients ≥ 2 years to < 6 years of age had an AUC_{12h} well within the adult range (see Figure 1) and similar to that observed in older pediatric patients (≥ 6 years old).

There was considerable inter-subject variability in PK results. Five of the 14 subjects (36%) in the ≥ 2 year to < 6 year age cohort who received the recommended dose of etravirine had AUC_{12h} values less than the 10^{th} percentile for the adult AUC_{12h}. However, as shown in Figure 1, the AUC_{12h} for most patients aged 2 to < 6 years of age was well covered within the adult exposure range.

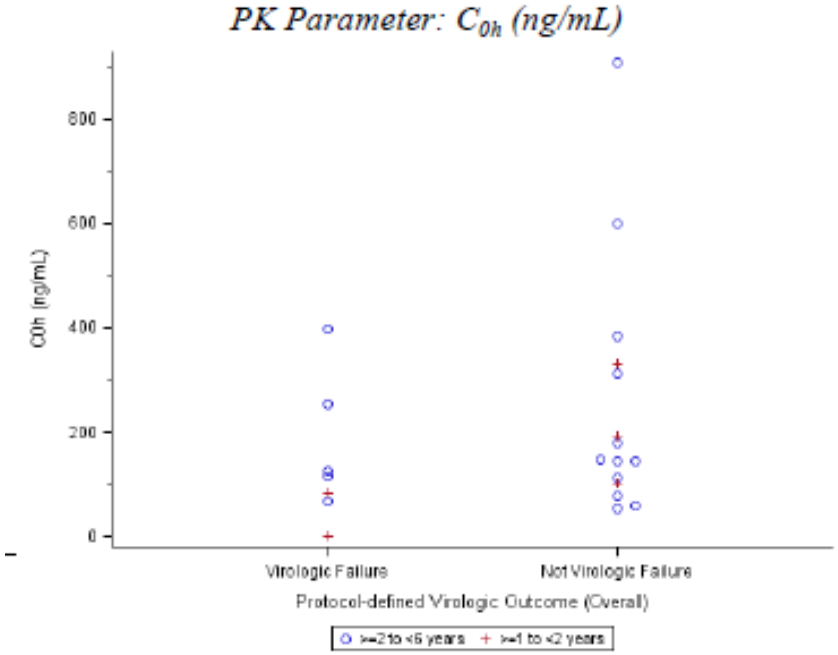
Figure 1: Comparison of Etravirine AUC_{12h} in Pediatric Subjects (by Weight) Compared to Adult Subjects



As shown in Figure 1, even with the inter-subject variability and low AUC_{12h} values in some subjects, the AUC_{12h} for all subjects were within 60% to 150% of adult values. In Dr. Sun's analysis, subjects from 2 to < 6 years of age with a low AUC_{12h} did not differ from subjects with a higher AUC_{12h} by weight, dose, or age. The reason for the low AUC_{12h} in these subjects is unclear but may be related to tolerability of the etravirine dosage form (tablet versus tablet dispersed in liquid). Please see the section in this review entitled Tolerability. Importantly, the AUC_{12h} levels did not correlate with efficacy. As a result, while the potential for low etravirine exposure in this age group exists and is concerning, the low exposure did not affect efficacy in this small study.

According to the Applicant, there was no correlation between any PK parameter and efficacy. As shown in the figure below, trough levels were generally similar in subjects who experienced virologic failure to that observed in those who did not.

Figure 2: Scatterplots of Observed Trough Levels (C_{0h}) by Protocol-Defined Virologic Failure



Source: Clinical Study Report TMC125-C234: Figure 24, page 157.

In Figure 2, subjects 2 to < 6 years of age are represented by circles. The geometric mean trough etravirine level was 183 ng/mL in subjects 2 to < 6 years of age.

As shown in Table 2 and in Figure 2, trough etravirine and AUC_{12h} levels were slightly lower in the subjects 1 to < 2 years of age compared to subjects from 2 to < 6 years of age. Subjects from 1 to < 2 years of age are represented by crosses in Figure 2, and the geometric mean trough etravirine level was 152 ng/mL. Although the trough levels were slightly lower than in older subjects, there was no clear correlation between trough levels and virologic failure. This may be related to the small number of subjects from 1 to < 2 years of age. The mean AUC_{12h} in the 1 year to < 2 year age group (2671.4 h*ng/mL) was lower than observed in subjects from 2 years to < 6 years of age (3504.4 h*ng/mL) and than that observed in adult studies (4522.4 h*ng/mL). The geometric mean ratio for AUC_{12h} of subjects 1 to < 2 years of age compared to adults was 59%, just outside the 60% criterion for demonstration of equivalency. (See Table 2). However, the 90% confidence interval was wide with a lower bound of 34%. Therefore, it is unclear if the appropriate dose of etravirine in subjects 1 to < 2 years of age was identified in this study. As described in efficacy results section of this review, 3 of the 5 subjects in the 1 to < 2 year age group experienced virologic failure. Isolates obtained from 2 subjects at the time of treatment failure were resistant to etravirine. Although the applicant did not request approval of etravirine for use in the age group from 1 to < 2 years of age, the lower exposure and high rate of virologic failure in this age group is concerning; and in the opinion of this reviewer, may be related to the lower AUC_{12h} in this age group. Therefore, this information will be included in Section 8.5 of the etravirine package insert. Of note, the Applicant received a PREA waiver for the study of etravirine in patients younger than 2 years of age, because etravirine was not likely to be used by a substantial number of patients < 2 years of age and did not represent a meaningful benefit over existing therapies in this age group.

Due to the study design with a mini-cohort enrolled for the initial PK and safety evaluation and the option to increase the etravirine dose in subjects with AUC_{12h} less than the adult 10th

percentile, the final dose used varied by study subjects. Of the 20 subjects from 2 to < 6 years of age, 11 received the recommended dose, 7 received a lower dose than the recommended dose, one received a higher than recommended dose, and one initially received a lower dose but the dose was changed to a higher than recommended dose. Therefore, the doses used in this study do not completely reflect the dosing recommendations for etravirine in this age group. However, efficacy did not appear to be dose-related, and all subjects who remained on the lower-than-recommended etravirine dose had HIV RNA < 400 copies/mL at Week 24.

In summary, etravirine exposure in subjects ≥ 2 years to < 6 years was demonstrated to be well within range of that observed in adults, and the geometric mean ratio comparing the AUC_{12h} in subjects ≥ 2 years to < 6 years of age to the AUC_{12h} in adult subjects in Phase 3 trials was 77%, (between the equivalency boundaries of 60% and 150%). Drs. Sun and Seo, Clinical Pharmacology reviewers, concluded that the etravirine doses proposed for 2 to < 6 year old pediatric patients were acceptable, and the primary PK endpoint was met in this age group, allowing for pharmacokinetic matching and extrapolation of efficacy.

7. Clinical / Statistical – Efficacy

As stated previously, this sNDA for etravirine was submitted to fulfill the outstanding study in the Pediatric Written Request, which required pharmacokinetic, safety, and antiviral activity data in pediatric patients from ≥ 2 to less than 18 years of age. The Written Request states that clinical study data for pediatric subjects must include data for at least 24 weeks of treatment. The clinical study report focused on the 24-week safety and efficacy analyses. Therefore, the efficacy section of this review summarizes the Week 24 efficacy results for Trial TMC125-C234, which is ongoing. Post Week 24 efficacy analyses were not presented by the applicant in the body of the clinical trial report and were not required for approval or labeling. As a result, efficacy data through Week 24 are presented in labeling. In addition, 24-week safety data were submitted to fulfill the etravirine Pediatric Written Request, and the safety section focuses on the Week 24 safety results. A limited discussion of 48-week data is included in this review.

Though cross-trial comparisons to the results from the adult trials should be done with caution, the general principle of comparing effectiveness of an ARV drug in children to adults is supported, as further discussed below.

The extrapolation of efficacy for antiretroviral drugs like etravirine 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]. DAVP agrees that HIV disease in pediatric subjects is similar but not identical to adult HIV disease, noting that the routes of 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 opportunistic infections like those seen in HIV-infected adults.

In pediatric and adult subjects, treatment of HIV disease is monitored by the same two parameters, HIV RNA viral load and CD4 count. Antiretroviral drugs including NRTIs, NNRTIs, PIs, and INSTIs are shown to lower HIV RNA, improve CD4 counts (or percentages) and improve general clinical outcome in adult and pediatric subjects. Treatment recommendations are very similar across all age groups [see US Department of Health and Human Services (DHHS) Guidelines for the Use of Antiretroviral Agents in HIV-1 Infected Adults and Adolescents

and Guidelines for the Use of Antiretroviral Agents in Pediatric HIV Infection, available at http://aidsinfo.nih.gov/guidelines].

Overview of Trial Design

Study TMC125-C234 is the pivotal pediatric trial for evaluating the use of etravirine in subjects ≥ 2 years to < 6 years of age. TMC125-C234 was an open-label, pharmacokinetic, safety and antiviral activity study in 25 treatment-experienced HIV-1 infected children ≥ 1 years to < 6 years of age. The study was originally designed to enroll subjects ≥ 2 months to < 6 years old; however, after the enrollment of 6 subjects in the ≥ 1 year to < 2 year old age cohort, enrollment was stopped because of extremely slow enrollment. In this review, the study protocol design will be limited to a description of the study as it relates to subjects ≥ 1 years to < 6 years of age. The description of study results will include both the ≥ 2 years to < 6 years age cohort and the ≥ 1 years to < 2 years cohort.

A mini-cohort of 6 subjects was enrolled in each age subgroup. Intensive PK sampling was conducted on Day 14 for this mini-cohort and safety was followed for 4 weeks. The goal of the pediatric dose selection was to achieve a geometric mean AUC_{12h} ratio (pediatric/adult) between 60% and 150% for the mini-cohort. If the dose was identified after analysis of PK and safety data from the initial mini-cohort, an additional 12 subjects were to be enrolled in the age subgroup. If a dose was not identified, a second mini-cohort of 6 subjects was to be enrolled. The second mini-cohort would have intensive PK sampling 7 to 14 days after starting their etravirine-containing antiretroviral regimen. Subjects would be enrolled into each age group until at least 12 subjects in total received the recommended etravirine dose.

The primary objectives were to evaluate the steady-state PK of etravirine in combination with an optimized background regimen (OBR), to determine the appropriate dose of etravirine for use in combination with an OBR, and to determine the safety and tolerability of etravirine in combination with OBR. The primary PK parameter for PK evaluation was AUC_{12h} at steady state. AUC_{12h} was used to determine the acceptability of the ETR dose. The target geometric mean etravirine AUC_{12h} was between 60% and 150% of the geometric AUC_{12h} in HIV-1-infected, treatment-experienced adult subjects in the two pivotal trials. See Section 6 of this review and Dr. Sun's Clinical Pharmacology review for a discussion of the PK results. Safety and tolerability were assessed from adverse events, laboratory results, physical examination findings, and changes in vital signs. Tolerability was also measured by the results of parent/ caregiver questionnaires. Assessment of antiviral activity was a secondary objective. The key efficacy endpoint was the number and percentage of subjects with plasma viral load < 400 copies/mL at Week 24. Other efficacy endpoints were change in $CD4^+$ absolute count and percentage, and changes in viral drug resistance during treatment. See the Clinical Microbiology section of this review for a discussion of the results for viral drug resistance analyses.

The trial enrolled treatment-experienced children from 1 year to < 6 years of age. Subjects were infected with HIV-1 with a HIV-1 viral load >1,000 copies/mL at screening. Subjects had to be antiretroviral (ART)-experienced and on a failing antiretroviral (ARV) regimen containing ≥ 3 ARVs for at least 8 weeks *or* be ART-experienced on a treatment interruption ≥ 4 weeks with a history of virologic failure on an ARV regimen of ≥ 3 ARVs. Patients with phenotypic resistance to etravirine at screening were not allowed to participate in the trial. Patients with a new diagnosis of a CDC Stage C criterion, an opportunistic infection, or a bacterial infection within 30 days of screening were also excluded from study participation. Patients were excluded from participation in the trial for a Grade 3 or higher laboratory abnormality for absolute neutrophil count (ANC), hemoglobin, platelet count, ALT, AST, lipase or creatinine value at screening.

Patients with a Grade 3 or higher QTc or PR interval prolongation on electrocardiogram (ECG) at screening were also excluded from study participation.

Etravirine was provided as 25 mg and 100 mg tablets. Subjects could swallow the tablet whole, could break tablets in half and swallow each half individually, or tablets could be dispersed in water or other liquids to a maximum volume of 30 mL for subjects who could not swallow tablets. The dose of etravirine in the initial mini-cohort was 5.2 mg/kg administered twice daily. When low plasma exposures were observed for subjects in the mini-cohort, etravirine dose was changed to dosing by weight band (see Table 1). As shown in Table 1, the same 5.2 mg/kg dose as used in the mini-cohort was used in subjects weighing ≥ 16 kg. However, with weight based, dosing, a higher dose was used in subjects weighing < 13 kg (8.8 mg/kg) and in subjects weighing 16 to < 20 kg (6.8 mg/kg).

The study was designed to follow antiviral activity and safety for 48 weeks; however, this supplement includes results for the first 24 weeks of the study as agreed upon in Pediatric Written Request for etravirine. Efficacy was assessed at Week 24 and Week 48 by evaluation of immunologic changes and changes in HIV RNA viral load. Resistance information was evaluated in subjects with virologic failure. See Section 5, Clinical Microbiology, of this review. Subjects will be followed on-study for long-term safety follow-up every 12 weeks for a maximum of up to 5 years.

Study TMC125-C234 was reviewed for antiviral activity, safety and tolerability, and pharmacokinetics. Subject demographics and baseline characteristics, clinical and laboratory adverse events, as well as safety and efficacy results were reviewed using JMP Statistical software.

Disposition

The study was conducted at 11 study centers in 3 countries: United States, Brazil, and South Africa. A total of 40 subjects were screened for study participation, 20 subjects from 2 to < 6 years of age received at least one dose of etravirine, and 5 subjects from 1 year to < 2 years received at least one dose of etravirine. The first subject was enrolled on November 30, 2012 and the cut-off for the Week 24 analysis was June 12, 2017. An additional subject in the 1 year to < 2 year age group was enrolled after the database was closed; the results for this subject were not included in the Clinical Study Report.

Of the 25 total subjects, 21 (84%) were ongoing at the Week 24 analysis cut-off date for the Clinical Study Report. This includes 18 (90%) of subjects in the ≥ 2 to < 6 year old age cohort and 3 of 5 (60%) in the ≥ 1 year to < 2 year age group. There were 2 premature study discontinuations in each age group at the time of study database closure. One subject in each age group discontinued prematurely due to virologic failure, one subject in the ≥ 2 year to < 6 year age group discontinued the study on Day 16 due to a serious adverse event (increased lipase), and one subject in the ≥ 1 year to < 2 year age group discontinued prematurely due to withdrawn consent. At the time of database closure, 3 subjects in the ≥ 2 to < 6 year old age cohort and 1 in the ≥ 1 year to < 2 year age group were still receiving their etravirine-containing ARV regimen but had yet reached 24 weeks. The Applicant provided additional information about these four subjects in an amendment received Mary 24, 2018; all four subjects completed 24 weeks of an etravirine-containing regimen.

Because of the study design, some subjects received a lower etravirine dose than the dose recommended after the study was revised to use weight band dosing. Other subjects, who had their dose increased because of an AUC_{12h} lower than the adult 10 [h] percentile, received higher

doses than the dose recommended in the revised study protocol. As a result, 14 (56%) subjects received the dose recommended in the revised weight band dosing and recommended in the proposed package insert. See Table 3 for subject disposition by dose and time on study.

Table 3: Subject Disposition by Dose and by Length of Treatment

Etravirine Dose	Subjects ≥ 2 to < 6 Years of Age	Subjects ≥ 1 to < 2 Years of Age	All Subjects
Subjects who received at least 1 dose of etravirine	20	5	25
Subjects who received the recommended dose of ETR for 24 weeks	8	3	11
Subjects who received the recommended dose for < 24 weeks	3	0	3
Subjects who received less than the recommended dose for 24 weeks	3	0	3
Subjects who received higher than the recommended dose for 24 weeks	4	0	4
Subjects who received higher than the recommended dose for < 24 weeks	1	2	1
Subjects who received both lower and higher doses than the recommended dose for 24 weeks	1	0	1

Source: Clinical Study Report TMC125-C234: Tables 2-3, page 61.

A substantial proportion of subjects aged 2 to < 6 years of age (N=9 or 45%) were not started at the recommended dose of etravirine during the study. However, analysis of efficacy by exposure did not reveal a dose-response relationship. Therefore, the differences in dosing did not appear to affect efficacy (see Dr. Sun's Clinical Pharmacology review). In addition, safety was examined for subjects by dose and there was no dose-relationship to safety. Therefore, the differences in etravirine doses did not appear to affect efficacy or safety.

Demographics and Baseline Characteristics

The Intent-to-Treat population included all 25 subjects. The majority of subjects were male (56%) and Black/African American (67%). In the group of subjects ≥ 2 to < 6 years of age, the mean age of subjects was 52.3 months with an age range of 31.7 to 68.4 months, and the mean weight was 16 kg with a weight range of 12.0 to 23.0 kg. Therefore, an acceptable distribution of subjects across the age and weight range for subjects 2 to 6 years of age was studied. In the group of subjects ≥ 1 to < 2 years of age, the mean age of subjects was 18.5 months and the mean weight was 10.2 kg.

Baseline HIV disease characteristics are shown in the following table.

Table 4: Baseline Disease Characteristics

	Subjects ≥ 2 to < 6 Years of Age	Subjects ≥ 1 to < 2 Years of Age	All Subjects
Mean viral load (copies/mL)	247,296.3	352,069.2	268,250.8
Mean $CD4^+$ cell count (cells/µL)	954.0	1555.4	1074.2
Mean $CD4^+$ percentage	25.97%	24.24%	25.62%
CDC clinical stage of HIV infection			
Asymptomatic (Category N)	5	0	5
Mildly symptomatic (Category A)	2	2	4
Moderately symptomatic (Category B)	4	0	4
Severely symptomatic	9	3	12

Source: Clinical Study Report TMC125-C234: Tables 6, pages 66-67.

One of the inclusion criteria was a baseline HIV RNA level >1000 copies/mL and the mean baseline viral load for all subjects in the study (268,250copies/mL) was considerably higher. $CD4^+$ counts and percentages are higher in children ≤ 5 years of age than in older children and adults. According to Denny et al. [Lymphocyte subsets in healthy children during the first five years of life, JAMA, 1992;267(23):3154], the 5^{th} and 95^{th} percentile for $CD4^+$ cell counts in healthy children from 2 to 5 years of age are 900 and 2,860 cells/µL and the percentage ranges from 35% to 51%. The values are higher in healthy children from 1 to 2 years of age with 5^{th} to 95^{th} percentile for $CD4^+$ cell counts of 1020 and 3600 cells/µ/L and $CD4^+$ percentages from 31% to 54%. The mean baseline $CD4^+$ cell count for HIV-infected children in this study was slightly above the 5^{th} percentile for healthy children in both age groups. The $CD4^+$ percentage for HIV-infected children in this study was below the 5^{th} percentile for healthy children. More than one-half of the study subjects were here moderately or severely symptomatic at baseline, as shown in Table 4. In conclusion, the baseline HIV disease characteristics are consistent with a population of children with advanced HIV disease.

The antiretroviral medications received in more than 2 subjects prior to study enrollment is shown in the following table.

Table 5: Antiretroviral Medication Received in > 2 Subjects Prior to Study Enrollment

Antiretroviral Class and Medication	Number of Subjects		
	Subjects ≥ 2 to < 6 Years of Age	Subjects ≥ 1 to < 2 Years of Age	All Subjects
Nucleoside reverse transcriptase inhibitors			
Lamivudine	20 (100%)	5 (100%)	25 (100%)
Zidovudine	15 (75%)	3 (60%)	18 (72%)
Abacavir	8 (40%)	2 (40%)	10 (40%)
Stavudine	5 (25%)	0	5 (20%)
Nonnucleoside reverse transcriptase inhibitors			
Nevirapine	10 (50%)	2 (40%)	12 (48%)
Efavirenz	2 (10%)	0	2 (8%)
Protease inhibitors			
Lopinavir/ritonavir	16 (80%)	4 (80%)	20 (80%)

Source: Clinical Study Report TMC-C234: Table 7, page 68.

A total of 14 subjects (56-2%) had received a NNRTI with 12 (48%) subjects previously receiving nevirapine and 2 (8%) efavirenz. The most commonly previously used ARV regimen was a regimen of two NRTIs plus a protease inhibitor, which was reported in 80% of subjects.

Efficacy Results at Week 24

Efficacy was a secondary endpoint for this study and the key efficacy endpoint was the number and percentage of subjects with HIV-1 RNA < 400 copies/mL at Week 24. Etravirine with an optimized background regimen demonstrated antiviral activity over the 24 week trial period. The proportion of subjects in the ≥ 2 to < 6 year age group with plasma viral load < 400 copies/mL at Week 24 was 88% (15/17), as calculated by the applicant. The proportion of subjects with viral load < 400 copies/mL was calculated as 94% (15/16) by DAVP Clinical Virology reviewers. See Dr. Colberg-Poley's Clinical Virology review. The difference was due to censoring of one subject who prematurely discontinued the study on Day 16 due to a serious adverse event (increased lipase). One subject had a viral load > 400 copies/mL at the Week 24 visit and was a virologic failure. There were no missing data at Week 24 therefore, the endpoint using missing as failure or excluded was not performed. These results are consistent with antiviral activity results in the pivotal trials of adults, TMC125-C206 and TMC-C216, in which HIV-treatment experienced adults were randomized to either etravirine + OBR or to placebo + OBR. In pooled results from TMC125-C206 and TMC-C216, the percentage of adult subjects with HIV RNA < 50 copies/mL at Week 24 was 59% and at Week 48 was 60%. The percentage of adult subjects with HIV RNA < 400 copies/mL at Week 24 was 74% and at Week 48 was 71%. In addition, the percentage of subjects with HIV RNA < 400 copies/mL at Week 24 was higher than in treatment-experienced pediatric subjects 6 to < 18 years of age (67%).

The proportion of subjects in the ≥ 1 year to < 2 year age group with HIV RNA < 400 copies at Week 24 was (1/4) 25%. Two subjects had viral loads > 400 copies/mL at the Week 24 visit, and one subject prematurely discontinued the study due to virologic failure. One of the 5 subjects in this age group had not reached Week 24 at the time of database cut–off and was not included in the efficacy analysis. The results in this age group differ for those in the age group of subjects ≥ 2 years to < 6 years. The reason for the difference is unclear. All subjects in the ≥ 1 year to < 2 year age group received the recommended dose. Although individual PK exposure was not demonstrated to correlate with efficacy in subjects in the ≥ 2 years to < 6 year age group, the geometric mean AUC_{12h} was lower in the ≥1 year to < 2 year age group (2671 h·ng/mL) compared to the ≥ 2 year to < 6 year age group (3504 h·ng/mL). Two of the 5 subjects in the ≥ 1 year to < 2 year age group had AUC_{12h} levels that were less than the 10^{th} percentile for adult subjects. It is possible that the lower plasma exposure contributed to lower efficacy in younger subjects. All five subjects in the ≥ 1 year to < 2 year age group received the tablet dispersed in liquid, and all five had adherence issues. This may also have contributed to the poor virologic success rate in this age group. Please see the section on tolerability in this review.

The percentage of subjects ≥ 2 years to < 6 years of age with HIV RNA < 50 copies/mL at Week 24 was 41% (7/17). The reason for the lower percentage of subjects with a viral load < 50 copies/mL in subjects ≥ 2 years to < 6 years in this study compared to the adult Phase 3 studies is unclear. It may be related to the small number of subjects in the pediatric study. It could also be related to the advanced HIV disease reported in pediatric subjects. Finally, it also could be related to poor adherence with the tablet dispersed in liquid.

Since only one subject in the ≥ 2 years to < 6 year age group experienced virologic failure, meaningful subgroup analyses could not be performed. The one subject with virologic failure

was a 2 year old female from Brazil with a HIV RNA of 1018 copies/mL at the Week 24 visit. This subject had a low etravirine AUC_{12h} at Day 14, and her etravirine dose was increased to a dose higher than the recommended dose.

The $CD4^+$ cell count at baseline in subjects from 2 to < 6 years of age was 954 cells/μL; the mean increase at Week 24 was 242cells/μL. The mean $CD4^+$ percentage at baseline was 26%, and the mean increase at Week 24 was 4%. In the age group of subjects from 1 to < 2 years of age the mean baseline $CD4^+$ cell count was 1554 cells/μL, and the mean increase at Week 24 was 17cells/μL. The mean baseline $CD4^+$ percentage for subjects in the ≥1 year to < 2 year age group was 24%, and the mean increase at Week 24 was 5%.

Efficacy Summary and Conclusions
The antiviral activity of etravirine in the treatment of treatment-experienced HIV-1 infected pediatric patients from 2 to < 6 years of age was demonstrated in this single arm, uncontrolled trial. At Week 24, etravirine in combination with other ARVs resulted in virologic response (HIV-1 RNA < 400 copies/mL) in 15 of 16 subjects (94%); the response rate is consistent with the antiviral response observed in the study of pediatric subjects from 6 to < 18 years of age and in studies of treatment-experienced adults. These results demonstrate the antiviral activity of etravirine in treatment-experienced pediatric patients 2 to < 6 years of age.

The virologic response rate in a small number of subjects (N=5) from 1 to < 2 years of age was only 25%. The reason for this low response rate is unclear; however, the applicant does not plan to seek an indication for use in this age group.

In summary, the etravirine exposure data from the intensive PK analyses support weight-band dosing and the efficacy outcomes as measured by HIV RNA and CD4+ cell count, in Study TMC125-C234 are consistent with results observed during trials of treatment-experienced adults, supporting extrapolation of efficacy from adults to pediatric patients 2 to < 6 years of age, and the antiviral activity of etravirine shown in this age group provides support for approval.

8. Safety

The data submitted support the safety and tolerability of etravirine in HIV-infected pediatric patients weighing from 2 years to < 6 years of age. The applicant has submitted safety data from 20 subjects from 2 to < 6 years of age who received at least one dose of etravirine in Study TMC125-C234. Additional safety data was also submitted for 5 subjects aged 1 year to < 2 years of age. The duration of follow-up was 24 weeks for 19 of the 25 subjects. Three of the 19 subjects received etravirine doses that were lower than the recommended dose. Since there are no known dose-dependent adverse events associated with etravirine use, the small number of subjects receiving a lower dose of etravirine should not have affected the safety results of this study.

The types of adverse events observed were similar to conditions or illnesses commonly observed during childhood and with the types of AEs observed in HIV-infected, treatment-experienced children and adults. 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 therefore applied to describe the observed findings.

Duration of Treatment
Subjects enrolled in Study TMC125-C234 are to be followed for at least 48 weeks. The Clinical Study Report summarized the safety data for the first 24 weeks. However, information on serious adverse events after Week 24 was included in the Clinical Study Report.

Deaths and Other Serious Adverse Events
There were no deaths. Non-fatal serious adverse events (SAEs) were reported in 5 of 20 subjects (25%) from 2 to < 6 years of age and in 2 of 5 subjects from 1 to < 2 years of age (40%). The SAEs are listed by study subject below:

- Subject (b) (6) was a 5 year old female with perinatally acquired HIV who was begun on etravirine at the recommended dose. She was also started on lamivudine, zidovudine, and lopinavir/ritonavir at study entry. Her lipase at screening was normal but increased to a Grade 2 level (79 U/L) by Week 2. The lipase remained elevated and increased to Grade 3 (140 U/L) at Week 16 but decreased to Grade 2 (72 U/L) when rechecked. The increased lipase was not treated. The subject was asymptomatic and was not hospitalized. The Grade 3 increase in lipase was judged as possibly related to etravirine and probably related to the OBR. The Grade 3 lipase was categorized as a SAE because it was an adverse event of special interest.
- Subject (b) (6) was a 3 year old female who began the study on etravirine at the recommended dose with an OBR of lopinavir/ritonavir and raltegravir. The subject had a Grade 2 decrease in platelet count (95,000 cells/μ/L) at screening which worsened to Grade 3 (48,000 cells/μ/L) at baseline. The subject was hospitalized for a Grade 4 decrease in platelet count on Day 13 (23,000 cells/μ/L); at that time, she was diagnosed with thrombocytopenia, which was judged as related to etravirine. At Week 4 her platelet count had increased to 149,000 cells/μL. Her treatment with etravirine was not interrupted during the time she was thrombocytopenic. The same subject had a Grade 2 lipase (78.6 U/L) at screening. The lipase increased to Grade 4 (158 U/L) on Day 15, and etravirine was stopped on Day 16. When a repeat lipase at Week 4 (167.9 U/L) was elevated after 2 weeks off etravirine, the subject was prematurely discontinued from the study due to the SAE. Four weeks after discontinuing etravirine, the lipase had decreased to Grade 2. The increase in lipase was judged as definitely related to etravirine and probably related to the OBR.
- Subject (b) (6) was a 2 year old male who was placed on a lower than recommended dose of etravirine and also began zidovudine, lamivudine, and lopinavir/ritonavir at study entry. At Week 55, he presented to clinic with cough, fever, vomiting, and pharyngitis. At the time, his ANC was 730 cells/μL (Grade 3). The subject's neutrophil count had been within normal limits at all visits prior to this visit. At the time, his hemoglobin, leukocyte, and platelet counts were within normal limits. His ANC was within normal limits when rechecked. The SAE was judged as possibly related to etravirine and probably related to OBR. In the opinion of this reviewer, the neutropenia was most likely related to the intercurrent infection.
- Subject (b) (6) was a 1 year old female who was placed on the recommended dose of etravirine on study entry. She had an isolated episode of Grade 3 decrease (31,000 cells/μL) in platelet count on Day 55 that was attributed to prolonged tourniquet use and manual compression of blood draw area during a difficult blood draw. Her platelet count was within normal limits at all previous study visits and within normal limits when rechecked two days after the Grade 3 event.
- Subject (b) (6) was a 1 year old female with a history of iron deficiency anemia, which was attributed to her underlying disease. She was started on etravirine at the recommended dose and was also started on an OBR of zidovudine, lamivudine, and

lopinavir/ritonavir. At screening her hemoglobin was within normal limits. She was diagnosed with Grade 1 decreased hemoglobin levels at the Week 8 visit. She then presented one month later with severe mucosal pallor, tachycardia, and a Grade 4 decrease in hemoglobin (5.4 g/dL) and was hospitalized. Ferrous gluconate treatment was started. Etravirine was interrupted for one day. The anemia was attributed to underlying disease and zidovudine, and was not attributed to etravirine.

- Two subjects were reported with the SAE of increased diastolic blood pressure. In both cases, the study subject was anxious or agitated, there was no treatment for the increased blood pressure, the increase in blood pressure was not observed at other visits, and all other vital signs were within normal limits. In addition, both incidents of increased diastolic blood pressure occurred at the same study site. On review, the protocol team determined that these events should not have been reported as SAEs; this reviewer agrees.

All SAEs were reported in subjects who received either the recommended dose or a lower dose of etravirine and none were reported in subjects receiving a higher than recommended dose of etravirine. It does not appear that use of the higher dose correlated with an increase in severity of adverse events.

In the opinion of this reviewer, the use of etravirine may have contributed to the increased lipase levels observed in two subjects. Etravirine was unlikely to have contributed to the SAE of thrombocytopenia for Subject (b) (6) since the subject had a Grade 2 decrease in platelet count at study entry and developed thrombocytopenia within 13 days of treatment with etravirine. In addition, there are other more likely explanations for the SAEs of decreased platelet count in Subject (b) (6), iron deficiency anemia, decreased neutrophil count, and increased diastolic blood pressure.

Discontinuations due to Adverse Events
There was one discontinuation due to adverse events. A 3 year old patient discontinued etravirine on Day 16 due to a Grade 4 increase in lipase. Please see the description of this SAE in the previous section of this review.

Adverse Events of Interest
Based on adverse events observed in animal toxicity studies and previous clinical use of etravirine, adverse events of interest were evaluated regardless of AE causality: the AEs of interest were skin adverse events, hepatic adverse events, pancreatic adverse events, and lipid-related adverse events.

Skin Adverse Events
The etravirine package insert includes severe skin and hypersensitivity reactions as a Warning and Precaution. Severe, potentially life threatening skin reactions such as Stevens-Johnson Syndrome, toxic epidermal necrolysis, and erythema multiforme, have been reported in <1% of subjects who have received etravirine. Hypersensitivity reactions such as DRESS syndrome (drug rash with eosinophilia and systemic symptoms) have also been reported. In the Phase 3 trials of etravirine in adults, Grade 3 and 4 rashes were reported in 1.3% of etravirine subjects compared to 0.2% of placebo subjects. Premature discontinuation due to rash was reported in 2.2% of subjects in the etravirine arm. Rash was the most frequently reported adverse drug reaction in the Phase 3 trials, and rash of Grade 2 severity or higher was reported in 10% of subjects who received etravirine compared to 3% of subjects who received placebo. The incidence of rash (Grade 2 or higher) was higher in women who received etravirine (15%) than in men (9.5%), and more women (5%) discontinued the study prematurely due to rash than men

(1.9%). Rash was typically mild to moderate and occurred in the first week of treatment. Rash was infrequent after Week 4. Most adult subjects continued etravirine despite the rash, and the rash resolved within one to two weeks.

In Study TMC125-C234, skin adverse events were monitored prospectively as one of three types: (serious) rash cases, (severe) cutaneous reactions, and angioedema. (Serious) rash cases were types of adverse events identified from a predefined list of 26 MedDRA preferred terms that are also used for post-marketing safety monitoring. The preferred terms include erythema, drug eruption, and rash +/- a description such as papular, morbilliform or vesicular. Although the term serious cutaneous reaction was used for these adverse events, the term serious in this context was different from the regulatory definition of serious when used for identification of serious adverse events. (Severe) cutaneous reactions were adverse events grouped under the MedDRA standardized query of "severe cutaneous reactions" and included Stevens-Johnson Syndrome. The term "severe" used for these types of skin adverse events was not related to actual severity. Angioedema adverse events were those grouped under the MedDRA standardized query of angioedema. There were a total of 17 subjects with skin adverse events: 13 (65%) in the ≥ 2 to < 6 year age group and 4 (80%) in the ≥ 1 to < 2 year age group. Of the 13 in the ≥ 2 to < 6 year age group, 11 were (serious) rash cases, 2 were (severe) cutaneous reactions, and 2 were angioedema. In the ≥ 1 to < 2 year age group, 3 were (serious) rash cases, 1 was a (severe) cutaneous reaction, and none were angioedema. The 11 (serious) rash cases in children 2 to < 6 years of age included rash (N=9), generalized rash (N=3), rash papular (N=2), rash pruritic (N=2) and one each of erythema, rash erythematous, and rash pustular. In the 2 to < 6 year age group, (serious) cutaneous reactions included 2 AEs of mouth ulceration, and angioedema cases included 1 AE of urticaria and one of wheezing. In the 1 to < 2 year age group, (serious) rash cases included 2 AEs of rash and one of generalized rash; the one (severe) cutaneous reaction was mouth ulceration.

All skin adverse events were either Grade 1 or 2 in severity and none resulted in premature study discontinuation. No skin AEs resulted in interruption of etravirine treatment.

Nine subjects had rashes within 4 weeks of starting etravirine. None of the rashes were judged as related to etravirine, and either the etiology of the rash was identified or the rash was specifically labeled as "non-allergic" in the AE datasets. None of the rashes that were reported after Week 4 were judged as related to etravirine.

The percentage of females with a rash was 6%; the percentage of males with a rash was 7%.

Mouth ulcerations were reported in 2 subjects in the 2 to < 6 year age group on study Days 24 and 1422 and in one subject in the 1 to < 2 year age group on Day 125. All mouth ulcerations were Grade 1 in severity and none were judged as related to etravirine.

The AEs of wheezing and urticaria were both reported after Week 24 and therefore, unlikely to be related to etravirine.

Hepatic Adverse Events

Hepatic adverse events including increased liver function tests (LFTs) were followed because of a NNRTI class effect. No increases in hepatic adverse events and LFTs were observed in the Phase 3 studies of etravirine in adults except in patients co-infected with hepatitis B or C. No hepatic related adverse events or increase in LFTs were reported in subjects in the ≥ 2 year to < 6 year age cohort. There were two hepatic AEs in the ≥ 1 year to < 2 year age group. One subject, a 1 year old male, had hepatomegaly at study baseline. Another subject, also a 1 year

old male had a Grade 4 increase in ALT and Grade 3 increase in AST at Week 16. This subject had Grade 0 ALT and AST at baseline and at Weeks 2, 4, and 8. Treatment with etravirine and the OBR (zidovudine, lamivudine, and lopinavir/ritonavir) was stopped for two days. Repeat ALT and AST values were Grade 0. At the time of elevated LFTs, the subject also had oral candidiasis, mouth ulcers, and vomiting. The increased ALT was judged as possibly related to ETR and the OBR; the increased AST was judged as not related to etravirine. In the opinion of this reviewer, the etiology of the increased LFTs is unclear and may be related to etravirine, to zidovudine or to lopinavir/ritonavir which have both been associated with hepatic toxicity, or to an intercurrent illness.

A total of 2 subjects (11 %) in the 2 to < 6 year age cohort had increased LFTs during treatment with etravirine. All increased values were Grade 1 or Grade 2 in severity. Two subjects in the ≥ 2 to < 6 year age group had increased bilirubin: one had a Grade 1 increase at Day 14 that resolved without treatment by Week 4, and the other with a Grade 2 bilirubin at baseline also had a Grade 2 increase in bilirubin at Week 48. Two subjects (40%) in the 1 to < 2 year age cohort had increases in LFTs. All increased LFTs, except in the subject described previously, were Grade 1 or 2. No subjects in the 1 to < 2 year age group had an increased bilirubin. No subjects had increases in ALT or AST at the same time as an increase in bilirubin; i.e., no adverse events met the criteria for Hy's Law.

Pancreatic Adverse Events

Only two pancreatic AEs were reported. One subject was asymptomatic and one had recurrent abdominal pain not attributed to pancreatitis or elevated lipase. Both of these AEs were SAEs in subjects in the ≥ 2 year to < 6 year age group, and both are described in the Serious Adverse Event section of this review. On analysis of lipase laboratory values, an additional subject had a Grade 1 lipase value reported, and another subject had a Grade 2 lipase.

Lipid-Related Adverse Events

Lipid-related adverse events of special interest were reported in one subject, a 4 year old female with Grade 3 blood cholesterol at Week 120 and Grade 3 LDL at Week 156. Both values were obtained after the subject fasted. The cholesterol level decreased to Grade 2 at Week 156. The LDL level decreased to Grade 2 at Week 132 but was Grade 3 again at Week 156. The investigator did not comment on the causality of the increased lipid levels, but the subject was also on lopinavir and ritonavir, which have been associated with increased lipid levels. Treatment was not interrupted or discontinued because of the increased lipid levels. No other study subjects had Grade 1 or higher increases in cholesterol or LDL.

Adverse Events with Severe or Life-threatening Intensity

Most AEs were Grade 1 or 2 in severity. Grade 3 or 4 adverse events (regardless of causality) were reported in 6 of 20 (30%) subjects in the 2 to < 6 year age group and in 4 of 5 (80%) subjects in the 1 to < 2 year age group. Grade 3 and 4 AEs in the 2 to < 6 year age group were: increased diastolic blood pressure in 2 subjects, increased lipase in 2 subjects, and decreased platelet count, thrombocytopenia, increased cholesterol, increased LDL, and decreased neutrophil count in one subject each. Grade 3 and 4 AEs in the 1 to < 2 year old group all were reported in one subject each and were increased diastolic blood pressure, increased systolic blood pressure, decreased platelet count, increased ALT, increased AST, and iron deficiency anemia. Eight of these Grade 3 and 4 AEs were reported as serious adverse events and were previously discussed in this review. A total of 6 Grade 3 and 4 AEs were considered related to etravirine: Grade 4 increase in lipase, Grade 3 increase in lipase, Grade 4 increase in ALT, Grade 3 decrease in platelet count, Grade 3 decrease in neutrophil count, and Grade 3 increase

in diastolic blood pressure. One subject discontinued prematurely due to a Grade 3 or 4 AE; this subject had a Grade 4 increase in lipase.

Common Adverse Events
A total of 12 adverse drug reactions (ADRs), e.g., adverse events considered etravirine-related, as assessed by the investigator, were reported in 6 subjects (24%). The most commonly reported ADR were increased lipase and rash. ADRs are shown in Table 7.

Table 6: Number (Percentage) of Subjects with Adverse Drug Reactions Reported Through Week 24

	Subjects ≥ 2 to < 6 Years of Age	**Subjects ≥ 1 to < 2 Years of Age**	**All Subjects**
Total Number of Subjects	20	5	25
Subjects with at least one ADR	3 (15%)	3 (60%)	6 (24%)
Increased lipase	2 (10%)	0	2 (8%)
Rash	0	2 (40%)	2 (8%)
Cough	1 (5%)	0	1 (4%)
Eczema	0	1 (20%)	1 (4%)
Tongue lesion	0	1 (20%)	1 (4%)
Diarrhea	0	1 (20%)	1 (4%)
Upper respiratory tract infection	0	1 (20%)	1 (4%)
Increased ALT	0	1 (20%)	1 (4%)

Source: Clinical Study Report TMC125-C234: AE Dataset.

The only ADRs reported in more than a single subject were increased lipase and rash, which were each reported in two subjects. Except for the ADRs of increased lipase and increased ALT, the ADRs in Table 6 were all Grade 1 in intensity. The subjects with increased lipase and ALT were discussed previously in this review.

The types of ADRs were varied and consistent with illness commonly observed in children, underlying HIV disease, and with previous studies of etravirine in children.

Adverse events of any causality
Most subjects [24/25 (96%)] experienced at least one adverse event (AE). The most common AEs (by Preferred Term, all grades, regardless of causality) with incidence reported in at least 10% of subjects are shown in Table 12. Some subjects in Table 7 were followed for more than 24 weeks.

Table 7: Number and Percentage of Subjects with Adverse Events (AEs) (Reported in ≥10% of Subjects)

	Subjects ≥ 2 to < 6 Years of Age	Subjects ≥ 1 to < 2 Years of Age	All Subjects
Total Number of Subjects	20	5	25
Subjects with at least one AE	19 (95%)	5 (100%)	24 (96%)
Cough	13 (65%)	5 (100%)	18 (72%)
Rhinorrhea	9 (45%)	4 (80%)	13 (52%)
Nasal congestion	9 (45%)	2 (40%)	11 (44%)
Rash	9 (45%)	2 (40%)	11 (44%)
Pyrexia	10 (50%)	1 (20%)	11 (44%)
Lymphadenopathy	6 (30%)	2 (40%)	8 (32%)
Pharyngitis	6 (30%)	1 (20%)	7 (28%)
Diarrhea	5 (25%)	2 (40%)	7 (28%)
Otorrhea	2 (10%)	3 (60%)	5 (20%)
Decreased appetite	3 (15%)	2 (40%)	5 (20%)
Impetigo	3 (15%)	1 (20%)	4 (16%)
Acute otitis media	2 (10%)	2 (40%)	4 (16%)
Dry skin	4 (20%)	0	4 (16%)
Eczema	3 (15%)	1 (20%)	4 (16%)
Rash generalized	3 (15%)	1 (20%)	4 (16%)
Increased diastolic BP	3 (15%)	1 (20%)	4 (16%)
Lice infestation	3 (15%)	0	3 (12%)
Tinea capitis	3 (15%)	0	3 (12%)
Upper respiratory tract infection	2 (10%)	1 (20%)	3 (12%)
Papule	2 (10%)	1 (20%)	3 (12%)
Mouth ulceration	2 (10%)	1 (20%)	3 (12%)
Vomiting	2 (10%)	1 (20%)	3 (12%)
Decreased weight	1 (5%)	2 (40%)	3 (12%)
Iron deficiency anemia	2 (10%)	1 (20%)	3 (12%)
Ear pain	2 (10%)	1 (20%)	3 (12%)
Headache	3 (15%)	0	3 (12%)

Source: Clinical Study Report TMC125-C234: Table 23, page 89 and Table 28, pages 92-94.

The most commonly reported adverse events were cough, rhinorrhea, and nasal congestion. These AEs and most other adverse events reported were consistent with common disease or conditions of childhood as well as conditions commonly reported in HIV-1 infected children, such as lymphadenopathy and decreased weight gain. However, rash and generalized rash were both reported in more than 10% of subjects. Please see the section of this review discussing skin adverse events. The adverse events reported were consistent with those reported in the study of older children and adolescent subjects.

Laboratory Abnormalities

A total of 9 Grade 3 or 4 laboratory abnormalities were reported in 4 (16%) subjects through Week 24. The Grade 3 abnormalities included two subjects with decreased platelet counts, two with increased lipase, and one with increased AST. The Grade 4 laboratory abnormalities included one subject with increased lipase and one with increased ALT. Etravirine was permanently stopped in the subject with a Grade 4 lipase. The types of Grade 3 and 4

laboratory abnormalities were varied and are consistent with the trial population of treatment-experienced subjects.

Tolerability
Tolerability of etravirine was measured by subject adherence and by questionnaires about the palatability (taste and texture) of the etravirine. Adherence was measured by pill count and by study personnel asking the subject's parent/guardian at each study visit, "How many missed doses in the last 3 days?" Adherence was defined as the subject taking greater than 95% of their etravirine doses. When both methods of measuring adherence were used, 71% of subjects (68% of those 2 to < 6 years of age and 80% of those 1 to < 2 years of age) were considered adherent. When treatment adherence was assessed by drug accountability (pill count) only, adherence to etravirine was observed for 71% of subjects who took the etravirine tablet dispersed in liquid compared to 80% for subjects who swallowed the etravirine tablet as a whole. However, only 5 subjects swallowed the tablet whole, so comparisons between taking the tablet dispersed in liquid and taking the tablet whole are difficult to make.

Palatability was assessed by a questionnaire that was administered on Day 14 and Week 4. Subjects were asked to separately rank the overall taste and the texture of etravirine using a 5-point scale as very good, good, average, bad, and very bad. The questionnaire used was not validated, and it is unclear how well children younger than 6 years of age could describe taste and texture using this instrument. Only four subjects rated the taste or texture as bad or very bad. This included 3 of the 5 (60%) subjects in the 1 to < 2 year age cohort and 1 subject in the 2 to < 6 year age cohort. All 4 subjects were receiving the dispersed tablet presentation of etravirine. The questionnaire and comments datasets were analyzed to determine how etravirine palatability may have affected adherence and/or outcome. In this analysis, there were 6 subjects (5 or 25% of subjects in 2 to < 6 year age group and 1 or 20% of subjects in 1 to < 2 year age group) who vomited or spit up after dosing with etravirine. All 6 subjects received the etravirine tablet dispersed in liquid. One subject (Subject (b) (6) vomited after dosing more than 3 times each week, but most subjects only had infrequent problems with vomiting after dosing. Nine of the 25 subjects (45%) refused etravirine at times or spit etravirine out periodically. Five of these were in the 1 to < 2 year age group, and 4 were in the 2 to < 6 year age group. However, one 5 year old subject who would refuse etravirine was receiving the tablet whole, not the tablet dispersed in liquid. One subject (Subject (b) (6)) who sometimes refused etravirine, prematurely discontinued from the study. This subject would refuse or spit out etravirine dispersed in liquid three or more times a week; the difficulties administering etravirine dispersed in a liquid may have contributed to the withdrawal of consent. There was one subject in TMC125-C234 with virologic failure prior to Week 24. This subject rated the taste and texture of etravirine as bad and very bad. This subject usually received the etravirine dispersed in liquid but sometimes took the tablet whole. This subject would refuse etravirine and vomited etravirine on several occasions. It is unclear, if the tolerability issues contributed to virologic failure in this subject. It should be noted that the reliability of the questionnaire results is not known given the difficulties of parent/caregiver reporting on palatability in young children.

In summary, it appears that the etravirine when dispersed in liquid may be difficult to tolerate because of the poor taste and texture. A substantial number of subjects refused to take etravirine in liquid or spit it out. The problems with etravirine dispersed in liquid were worse in the 1 to < 2 year age group, in which 1 of the 5 subjects vomited after etravirine dosing and 5 of 5 refused etravirine or spit it out at some time during the study. This may have contributed to the lower efficacy in the younger age group. However, there were only 5 subjects in the study who swallowed the etravirine tablet whole for the entire length of the study and there were only

5 subjects in the younger age group; therefore, it is difficult to make any definitive conclusions regarding differences in responses for the tablet and the tablet dispersed in liquid.

Safety and Tolerability Summary
In summary, no new safety signal or changes in the frequency of previously described AEs were identified for etravirine. Overall, the findings in this pediatric clinical trial are consistent with previously described adverse events observed with the use of etravirine in HIV-infected subjects. However, the etravirine tablet dispersed in liquid was difficult to tolerate with multiple subjects refusing to take their etravirine or spitting out their etravirine. This appeared to especially affect study subjects in the 1 to < 2 year old cohort. However, due to small numbers it is difficult to determine if the poor tolerability influenced the study outcome.

9. Advisory Committee Meeting
Not applicable.

10. Pediatrics
This application contains pediatric data for subjects from 2 to < 6 years of age. The pediatric trial design, clinical outcome, and proposed labeling for pediatric patients from 2 to < 18 years of age was presented to the Pediatric Review Committee (PeRC). The PeRC agreed with the Division's proposed plans for labeling.

Data included in this submission represent a response to the Pediatric Written Request for etravirine. The request for extended patient exclusivity through fulfillment of the Pediatric Written Request was reviewed by the Pediatric Exclusivity Board. The Board agreed with that the etravirine Written Request had been fulfilled.

11. Other Relevant Regulatory Issues
No additional regulatory issues have been identified.

12. Etravirine Labeling
The etravirine labeling has been updated to reflect changes in the indication, extending the population to HIV-1 infected pediatric patients 2 years to < 6 years of age (previously indicated in pediatric patients 6 years of age and older). The changes with this efficacy supplement primarily affected the following sections. Note that while most of the labeling sections have been agreed upon, the addition of wording related to decreased tolerability and of wording related to decreased efficacy in the ≥ 1 to < 2 years of age are currently being negotiated with the applicant.

1 INDICATIONS AND USAGE
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 2 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.

The following paragraph was deleted from this section:
The indication for adult use is based on Week 48 analyses from 2 randomized, double-blind, placebo-controlled trials of INTELENCE®. Both studies were conducted in clinically advanced, 3-class antiretroviral (NNRTI, N[t]RTI, PI) treatment-experienced adults. The indication for pediatric use is based on 24-week analyses of a single-arm, Phase 2 trial in antiretroviral

treatment-experienced pediatric subjects 6 years to less than 18 years of age [*see Use in Specific Populations (8.4)*].

2.2 Recommended Dosage
In this section of the package insert, the lower age limit for use was revised to 2 years of age, the lower weight limit was revised to 10 kg, and the first row of the dosing table was revised.

The recommended dose of INTELENCE for pediatric patients 2 years to less than 18 years of age and weighing at least 10 kg is based on body weight (see Table 1 below) not exceeding the recommended adult dose. INTELENCE tablet(s) should be taken orally, following a meal *[see Clinical Pharmacology (12.3)]*. The type of food does not affect the exposure to etravirine.

Table1: Recommended Dose of INTELENCE for Pediatric Patients 2 Years to Less Than 18 Years of Age

Body Weight kilograms (kg)	**Dose**
greater than or equal to 10 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	200mg twice daily

(b) (4)

2.3 Method of Administration
The instructions on how to disperse the tablet in water were revised for clarity and to encourage mixing the dispersed tablet in orange juice or milk to improve palatability.

The patient should be instructed to do the following:

- place the tablet(s) in 5 mL (1 teaspoon) of water, or at least enough liquid to cover the medication,
- stir well until the water looks milky,
- add approximately 15 mL (1 tablespoon) of liquid. Water may be used, but other liquids, such as orange juice or milk, may improve taste. The use of warm milk (with temperature greater than 104°F [greater than 40°C]) or carbonated beverages should be avoided.
- drink the mixture immediately,
- rinse the glass several times with orange juice, milk or water and completely swallow the rinse each time to make sure the patient takes the entire dose.

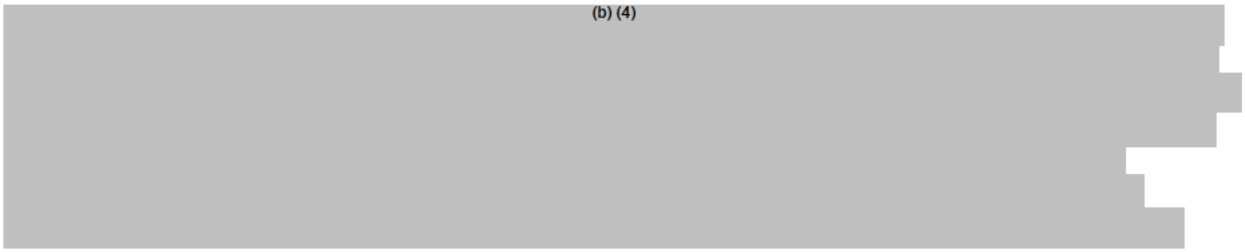
6.1 Clinical Trials Experience
This section was revised to include safety data from TMC125-C234.

Clinical Trials Experience in Pediatric Subjects (2 Years to Less Than 18 years of age)
The safety assessment in children and adolescents is based on two single-arm trials. TMC125 C213 is a Phase 2 trial in which 101 antiretroviral treatment experienced HIV 1 infected pediatric subjects 6 years to less than 18 years of age received INTELENCE® in combination with other antiretroviral agents (Week 24 analysis). TMC125-C234/IMPAACT P1090 is a Phase 1/2 trial in which 20 antiretroviral treatment-experienced HIV-1 infected pediatric subjects 2 years to less than 6 years of age received INTELENCE in combination with other antiretroviral agents (Week 24 analysis) [see Clinical Studies (14.2)].

In TMC125-C213, the frequency, type and severity of adverse drug reactions in pediatric subjects 6 years to less than 18 years of age were comparable to those observed in adult subjects, except for rash which was observed more frequently in pediatric subjects. The most common adverse drug reactions in at least 2% of pediatric subjects were rash and diarrhea. Rash was reported more frequently in female subjects than in male subjects (rash ≥ Grade 2 was reported in 13/64 [20.3%] females versus 2/37 [5.4%] males; discontinuations due to rash were reported in 4/64 [6.3%] females versus 0/37 [0%] males). Rash (greater than or equal to Grade 2) occurred in 15% of pediatric subjects from 6 years to less than 18 years of age. In the majority of cases, rash was mild to moderate, of macular/papular type, and occurred in the second week of therapy. Rash was self-limiting and generally resolved within 1 week on continued therapy. The safety profile for subjects who completed 48 weeks of treatment was similar to the safety profile for subjects who completed 24 weeks of treatment.

In TMC125-C234/IMPAACT P1090, the frequency, type and severity of adverse drug reactions in pediatric subjects 2 years to less than 6 years of age through Week 24 were comparable to those observed in adults. The most common adverse drug reactions (any grade) of pediatric subjects were rash (50% [10/20]) and diarrhea (25% [5/20]). In this age group, no subjects had Grade 3 or Grade 4 rash and no subjects discontinued prematurely due to rash. One subject discontinued etravirine due to asymptomatic lipase elevation.

8.4 Pediatric Use
This section was revised to include results for pediatric subjects from 1 year to < 2 years of age in TMC125-C234:



This section was also revised to reflect the new age indication and to clarify that the frequency and severity of rash in subjects 6 years to 18 years of age differed from what was observed in adults in Phase 3 studies.

12.3 Pharmacokinetics
Pediatric Patients
This section was revised to include the PK results from Study TMC125-C234.

The pharmacokinetics of etravirine in 115 treatment-experienced HIV-1-infected pediatric subjects, 2 years to less than 18 years of age showed that the administered weight-based dosages resulted in etravirine exposure comparable to that in adults receiving INTELENCE 200 mg twice daily *[see Dosage and Administration (2.2)]*. The pharmacokinetic parameters for etravirine (AUC_{12h} and C_{0h}) are summarized in Table 6 below.

Table 6: Pharmacokinetic Parameters for Etravirine in Treatment-Experienced HIV-1-Infected Pediatric Subjects 2 Years to Less Than 18 Years of Age (TMC125-C213 [Population PK] and TMC125-C234/P1090)

Study	**TMC125-C213**	**TMC125-C234/ IMPAACT P1090**
Age Range (years)	**(6 years to less than 18 years)**	**(2 years to less than 6 years)**
Parameter	N=101	N=14
AUC_{12h} (ng•h/mL)		
Geometric mean±standard deviation	3742±4314	3504±2923
Median (range)	4499 (62-28865)	3579 (1221-11815)
C_{0h} (ng/mL)		
Geometric mean±standard deviation	205±342	183±240
Median (range)	287 (2-2276)	162 (54-908)

The pharmacokinetics and dose of etravirine in pediatric subjects less than 2 years of age have not been established.

14 Clinical Studies
The Clinical Trials section of the package insert was revised to include the efficacy results for subjects from 2 to < 6 years of age in Study TMC125-C234.

14.2 Treatment-Experienced Pediatric Subjects (2 Years to Less Than 18 Years of Age)
The following sentence was added after the 14.2 subheading:
The evidence of efficacy of etravirine is based on two Phase 2 trials in antiretroviral treatment experienced pediatric patients.

This section was added to 14.2.
Pediatric Subjects (2 Years to Less Than 6 Years of Age [TMC125-C234/IMPAACT P1090])
TMC125-C234/IMPAACT P1090 is a Phase 1/2 trial evaluating the pharmacokinetics, safety, tolerability, and efficacy of INTELENCE in 20 antiretroviral treatment-experienced HIV-1 infected pediatric patients 2 years to less than 6 years of age. The study enrolled patients who had virologic failure on an antiretroviral treatment regimen for at least 8 weeks or on a treatment interruption of at least 4 weeks with a history of virologic failure while on an antiretroviral regimen, with a confirmed HIV-1 RNA plasma viral load greater than 1,000 copies/mL and with no evidence of phenotypic resistance to etravirine at screening.

The median baseline plasma HIV-1 RNA was 4.4 $\log_{10}$ copies/mL, the median baseline CD4+ cell count was 817.5 x 10^6cells/mm^3, and the median baseline CD4+percentage was 28%. Study treatment included etravirine plus an optimized background regimen (antiretroviral drugs). (b) (4)

Virologic response, defined as achieving plasma viral load less than 400 HIV-1 RNA copies/mL was evaluated.

At the time of the Week 24 analysis, seventeen patients had completed at least 24 weeks of treatment or discontinued earlier. At Week 24, the proportion of patients reaching less than 400

HIV-1 RNA copies/mL was 88% (15/17), and the proportion of patients with less than 50 HIV-1 RNA copies/mL was 50% (7/14), for those with available data. The median change in plasma HIV-1 RNA from baseline to Week 24 was -2.14 log_{10} copies/mL. The median CD4+ cell count increase and the median CD4+ percentage increase from baseline was 298 x 10^6 cells/mm^3 and 5%, respectively.

13. Outstanding Issues

Labeling negotiations are currently ongoing.

14. Recommendations / Risk Benefit Assessment

Based on the totality of the data presented and input from each of the review disciplines, the clinical review team recommends approval of etravirine for the treatment of HIV-1 infection in patients 2 years of age and older.

Throughout the review of this sNDA, no deficiencies that would preclude the approval were identified. Etravirine was studied in a multicenter, open-label, non-comparative trial, in which 20 pediatric subjects from 2 to less than 6 years of age were enrolled, and 16 were followed for 24 weeks. Intensive pharmacokinetic assessment was performed at Day 14 while the safety and efficacy of etravirine were evaluated through Week 24.

Similar to other pediatric trials which evaluate the safety and effectiveness of ARVs, this trial was not powered for true statistical analysis of safety or efficacy. Descriptive statistical methods were used to describe findings.

The first six subjects received a 5.2 mg/kg twice daily dose of etravirine but the geometric mean AUC_{12h} ratio comparing results for these subjects to those for adults were less than the pre-defined 60% lower limit for demonstration of equivalency to the adult dose of etravirine. Etravirine dosing was then revised to weight-band dosing, which is the recommended dosing described in the package insert. With weight-band etravirine dosing, the AUC_{12h} for etravirine in pediatric subjects from 2 to < 6 years of age met the criteria for demonstration of equivalency to the approved adult etravirine dose. The results support the use of the weight-band dosing of etravirine in pediatric patients 2 years of age and older. However, the geometric mean ratio comparing the AUC12h in subjects from 1 to < 2 years of age did not meet the criteria for demonstration of equivalency. This is reflected in the etravirine package insert, which states that the etravirine dose in subjects less than 2 years of age has not been established.

The trial was not powered for true statistical analysis of efficacy. The efficacy outcome, as measured by HIV RNA < 400 copies/mL, for the overall study population was 94%. The results were compared to the efficacy results of the Phase 3 trials of etravirine in treatment-experienced adults. The efficacy outcome was similar to that observed in treatment-experienced adults who were failing their current antiretroviral regimen and changed to an antiretroviral regimen of etravirine and an optimized background regimen. In addition, the proportion of subjects in this 2 to < 6 year age group with HIV RNA < 400 copies/mL at Week 24 was higher than observed in pediatric subjects 6 to < 18 years of age (67%).

The applicant demonstrated an acceptable safety profile for etravirine in pediatric patients weighing from 2 to < 6 years of age. Etravirine was generally safe and well tolerated in pediatric subjects enrolled in this trial. No deaths were reported and serious adverse events were uncommon. No new safety concerns were identified. However, the relatively poor palatability of the etravirine tablet when dispersed in liquid may have resulted in problems with adherence, especially in the youngest patients (1 to < 2 years old). The observed risks of etravirine use

have been described previously, and the rate and nature of adverse events were similar to those in HIV-1 infected children and in treatment-experienced adults and older pediatric patients, except for a higher percentage of subjects with ≥ Grade 2 rash in subjects 6 to < 18 years of age compared to subjects 2 to < 6 years of age.

Of note, the size of the safety database in pediatric patients is limited. Five subjects in both cohorts had not reached Week 24 at the time of the study database cutoff, and this trial has continued to follow subjects beyond the Week 24 cutoff.

Recommendation for Postmarketing Risk Evaluation and Management Strategies
None

Recommendation for Other Postmarketing Requirements and Commitments
None. The applicant will continue to submit PADERS and annual reports (DSURs) for review. The current submission fulfills the Etravirine Pediatric Written Request, and no additional pediatric post-marketing study commitments will be sought for etravirine.

15. Clinical Investigator Disclosure Review Template for sNDA 22187/S-024

Submission Date(s): January 16, 2018
Applicant: Janssen Research and Development
Product: Intelence (etravirine)

Reviewer: Melisse Baylor, MD
Date of Review: May 1, 2018
Covered Clinical Trial (Name and/or Number): TMC125-C234

Was a list of clinical investigators provided:	**Yes** ☒	No ☐ (Request list from applicant)
Total number of investigators identified: **156**		
Number of investigators who are sponsor employees (including both full-time and part-time employees): **0**		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): **0**		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: **0** Significant payments of other sorts: **0** Proprietary interest in the product tested held by investigator: **0** Significant equity interest held by investigator in sponsor of covered study: **0**		
Is an attachment provided with details of the disclosable financial interests/arrangements:	**Yes** ☐	No ☐ (Request details from applicant)
Is a description of the steps taken to minimize potential bias provided:	**Yes** ☐	No ☐ (Request information from applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) **0**		
Is an attachment provided with the reason: N/A	**Yes** ☐	No ☐ (Request explanation from applicant)

The Applicant has adequately disclosed financial interests/arrangements with clinical investigators as recommended in the Guidance for Industry: *Financial Disclosure by Clinical Investigators*.

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

MELISSE S BAYLOR
07/12/2018

MARY E SINGER
07/12/2018
I concur with Dr. Baylor's recommendations in this joint primary/CDTL review.