Clinical Review

Date	June 19, 2015
From	Yodit Belew, M.D.
Subject	Clinical Review
NDA/BLA # Supplement#	202022/E08
Applicant	Janssen
Date of Submission	February 27, 2015
PDUFA Goal Date	August 27, 2015
Proprietary Name / Established (USAN) names	Edurant/Rilpivirine (RPV)
Dosage forms / Strength	Tablet 25mg
Proposed Indication(s)	Treatment of HIV-1 infection To expand indication to include HIV infected children 12 years and older
Recommended:	Approval

1. Introduction

This review summarizes the findings from Janssen's supplemental NDA seeking approval of Edurant® (rilpivirine, RPV) for treatment of HIV-1 infection in treatment-naïve pediatric patients ages 12 to less than 18 years weighing at least 35kg and with HIV RNA ≤ 100,000 copies/mL. This review highlights the supporting pharmacokinetic, safety and efficacy (antiviral activity) data. The data supports extension of the indication to include pediatric population at least 12 years of age and weighing at least 35 kg. The 25mg strength tablets are approved (one tablet, once daily) for treatment of HIV infection in treatment-naive adults with HIV RNA ≤ 100,000 copies/mL at the start of therapy; the recommended dose of rilpivirine for adolescents is also 25mg once daily.

This application was granted a priority review because the data submitted fulfills a PREA PMR. This application allows for once daily NNRTI-based regimen for pediatric patients. Although efavirenz is also approved in adolescents, rilpivirine provides an alternative once daily NNRTI-based regimen. Additional benefits demonstrated during the adult clinical trial for rilpivirine include fewer discontinuations due to adverse events compared to efavirenz; and fewer subjects treated with rilpivirine discontinued due to adverse events compared to efavirenz-treated subjects. Furthermore, the nonclinical data for rilpivirine demonstrated that rilpivirine does not have reproductive toxicity.

2. Background

Edurant (rilpivirine), the fifth NNRTI approved by the Agency, was granted Traditional Approval on May 20, 2010. The approval was based on Week 48 efficacy and safety results from two Phase 3, active control, clinical trials (C209 and C215) and one Phase 2 dose finding trial (C204) in treatment-naive subjects. The trials demonstrated that rilpivirine is non-inferior to the comparator, efavirenz. However, more rilpivirine treated subjects with HIV RNA >100,000 copies/mL at the start of treatment experienced virologic failure compared to subjects with HIV

RNA ≤100,000 copies/mL at the start of therapy. Furthermore, the supplemental NDA for the Week 96 efficacy data demonstrated durability was a concern in subjects with baseline HIV RNA >100,000 copies/mL. Therefore, the indication for rilpivirine was limited to HIV infected treatment-naïve adult patients with HIV RNA ≤100,000 copies/mL. Please refer to the reviews for the original NDA for full details.

According to the UNAIDS, as of 2013, the estimated number of people infected with HIV or AIDS worldwide is approximately 35 million, 3.2 (9%) of whom are children 0 to 14 years old. Per CDC, in the United States, transmission of HIV-1 among adolescents is attributable primarily to sexual exposure and relatively little to illicit intravenous drug use. In 2009, young persons (age 13-29) accounted for 39% of all new HIV infections in the US. Therefore, it is important to have effective antiretroviral therapies (ART) for treatment of HIV infection in the pediatric population.

Currently available HIV treatment includes six different antiretroviral drug classes- comprised of over 27 approved single agents (not including FDC products). The drug classes include: nucleoside reverse transcriptase inhibitors (NRTI), non- nucleoside reverse transcriptase inhibitors (NNRTI), protease inhibitors (PI), fusion inhibitors, CCR5 receptor antagonists, and integrase strand transfer inhibitors (INSTI). Most approved ARVs have dosing recommendations in at least one subset of pediatric age range.

While there are approved NNRTI-, PI- and INSTI-based regimens available for the treatment of HIV infection in children, there continues to be challenges. For example, poor adherence, and short and long term toxicities may contribute to the development of drug resistance and failed therapy. Therefore, there is a need for continuous development of new ARTs for treatment of HIV infection. Rilpivirine was evaluated in a single Phase 1/2 open-label, non-comparative trial in pediatric subjects in 7 centers across five countries. Electronic materials submitted included the Clinical Study Report (CSR) for Week 48 data; datasets as SAS transport files; and case narratives for all subjects who experienced deaths, SAEs, and discontinuation due to AEs.

This pediatric supplement fulfills one of the two outstanding post-marketing requirements (PMR) under Pediatric Research Equity Act (PREA):

> 1982-2: Conduct a pediatric safety and antiviral activity study of rilpivirine with activity based on the results of virologic response over at least 48 weeks of dosing and safety monitored over 48 weeks in pediatric subjects from 12 to <18 years of age.

The applicant submitted the sNDA in accordance with FDA guidelines. The quality and integrity of the submission were adequate. Although a consult request was made to the Office of Scientific Investigations (OSI) for inspection of the bioanalytical data, the Division was notified that inspections of bioanalytical sites will not be conducted for this submission.

According to the applicant, the pivotal trial was conducted in conformance with Good Clinical Practice standards and applicable country and/or local statutes and regulations regarding ethical committee review, informed consent, and the protection of human subjects participating in biomedical research. (b) (4) [redacted] he data from these subjects were included for the safety analyses. For

efficacy analyses, a sensitivity analysis was conducted to assess if exclusion of the site would affect the efficacy outcome (see Clinical Efficacy section).

The sponsor also submitted financial information pertinent to the application. The statement specified that the sponsor had not entered into any financial arrangement with particular clinical investigators whereby the value of compensation to the investigators could be affected by the outcome of the study (as defined in 21 CFR 54.2(a)).

3. CMC

No new CMC data were submitted for review. The same adult formulation is proposed for use in children 12 years of age and older and weighing at least 35kg. Please refer to the original NDA for details.

4. Nonclinical Pharmacology/Toxicology

The preclinical evaluation of rilpivirine included over 55 trials to assess the safety pharmacology, pharmacokinetics, general toxicology, carcinogenicity, reproductive and developmental toxicology, genetic toxicology and local tolerance in mice, rats, rabbits, dogs and Cynomolgus monkeys. Please refer to NDA 202022 for full details.

Of interest for this pediatric submission is the adrenal effect observed in pre-clinical studies. According to Dr. Mark Seaton, toxicology reviewer, one of the primary toxicity findings in nonclinical studies were adrenal effects, generally characterized by increased serum progesterone and decreased cortisol levels, observed in rats, dogs, Cynomolgus monkeys, and possibly mice. These effects are thought to be associated with an inhibition of steroidogenesis at the level of cytochrome P450 21-hydroxylase (CYP21) and 17-hydroxylase (CYP17; inhibition of the latter was observed in Cynomolgus monkeys only). In dogs, findings of premature activation and overstimulation of the ovaries may also be related to inhibition of steroidogenesis. Those effects on dog ovaries were noted at exposures 8 to 25 times higher than clinical exposures at the recommended dose of 25 mg once daily. Premature ovulation, as was noted in immature dogs treated for four weeks, was not seen in immature Cynomolgus monkeys treated for eight weeks, although the lack of an early puberty effect in the monkeys may be related to the young age of the monkeys and the fact that the monkeys were still pre-pubertal at the end of the study.

Of note, extensive adrenal monitoring was included during the adult clinical trials. Similar adrenal function monitoring plans were also included for this adolescent trial, as further discussed in the Clinical safety section.

5. Clinical Microbiology

No new resistance pattern was identified during the pediatric clinical trial. Please see USPI and the Clinical Microbiology Review by Dr. Lisa Nagaer for the original NDA for further details. The following is a summary of the microbiology characteristics identified during the adult pivotal trials.

In addition to the important genotypic and phenotypic changes that emerged in rilpivirine treated subjects with virologic failure, cross-resistance to the NNRTI class is likely after virologic failure with rilpivirine. In adults, the emergence of resistance was greater in the rilpivirine group compared to the comparator group- 41% (38/92) of the virologic failures in the rilpivirine group

had genotypic and phenotypic evidence of rilpivirine resistance compared to 25% (15/60) of the virologic failures in the EFV group who developed efavirenz resistance. Cross-resistance to efavirenz, etravirine and/or nevirapine is likely after virologic failure with a rilpivirine- containing regimen. Of these patients, 89% (n=34) were resistant to etravirine and efavirenz, and 63% (n=24) were resistant to nevirapine. In the EFV group, none of the 15 EFV-resistant virologic failures were resistant to etravirine or rilpivirine at failure; all were resistant to nevirapine. In addition, phenotypic resistance to a background (BR) drug (emtricitabine, lamivudine, tenofovir, abacavir or zidovudine) emerged in 48% (44/92) of the subjects in the rilpivirine group compared to 15% (9/60) in the EFV group. These data suggest the ability to use a subsequent NNRTI, specifically etravirine whose indication is for subjects with HIV-1 strains resistant to an NNRTI and other ARVs, is limited. This significant information is included in the label (Use and Indication Section and Microbiology Section).

No new virologic information was identified with use of rilpivirine in the adolescent subjects. Therefore, no changes to the microbiologic section of the USPI are recommended.

6. Clinical Pharmacology/Biopharmaceutics

Overview
Refer to the USPI and reviews from the original NDA for full details.

Rilpivirine (rilpivirine hydrochloride, RPV), is a nonnucleoside reverse transcriptase inhibitor (NNRTI) of the human immunodeficiency virus type 1(HIV-1). Rilpivirine inhibits HIV-1 replication by non-competitive inhibition of HIV-1 reverse transcriptase (RT).

Pharmacodynamic properties of rilpivirine have been explored previously in adult clinical trials. Rilpivirine demonstrated antiviral activity in a 7-day monotherapy trial using rilpivirine at doses ranging from 25mg to 150mg, with mean viral load reduction of 1.29 log10 copies/mL with the 25mg QD dose. Furthermore, rilpivirine, in combination with other ARVs effectively suppressed HIV RNA replication, as demonstrated during the pivotal phase 3 clinical trials in adults.

Rilpivirine prolongs the QT interval at doses of 75 mg or higher. At the recommended dose of 25 mg once daily, the maximum mean time-matched difference in QTcF interval from placebo was 2.0 milliseconds, which is below the threshold of regulatory concern. At supratherapeutic doses of 75 mg and 300 mg once daily, the maximum mean time-matched differences in QTcF interval from placebo was 10.7 and 23.3 milliseconds, respectively. The potential QTc prolongation, hepatic impairment and drug- drug interaction issues with concomitantly administered drugs metabolized by CYP enzymes are reflected in the rilpivirine label.

The PK/PD (exposure-response analyses) from Phase 2b and 3 trials in adults identified inhibitory quotient (e.g. a ratio between an individual subject's HIV RNA susceptibility [IC50] and rilpivirine Ctrough) as the key PK parameter that correlated with efficacy outcome. During Phase 2b trial, rilpivirine 75 mg arm provided higher exposure compared to the rilpivirine 25mg arm; the efficacy outcome was higher in the rilpivirine 75mg arm compared to the rilpivirine 25mg arm. During the Phase 3 trial only the 25 mg dose was evaluated and subjects with higher Ct concentrations were less likely to have virologic failure, especially in subjects with HIV RNA >100,000 c/mL.

Pediatric trial C213

Protocol C213 is a Phase 1/2, multi-center, open-label, non-comparative trial to evaluate the safety and antiviral activity of rilpivirine in approximately 36 HIV-1 infected children 12 years through 18 years of age. Rilpivirine was administered with investigator selected background antiretrovirals. The investigator-selected N(t)RTIs were ABC or AZT plus 3TC or TDF/FTC, whichever are approved and marketed or considered local standard of care for children ages 12 to < 18 years in a particular country. Rilpivirine was administered orally using the the approved tablet formulation. The goal of the pediatric dose selection was to target the adult exposure from the 25 mg QD, which is known to be an effective dose. To conclude comparability in rilpivirine pharmacokinetics between adults and adolescents, the pre-specified ratio of geometric mean for AUC_{24h} was >0.80 and <1.25.

Twenty three subjects were enrolled into Part 1 of trial (intensive PK) which allowed for review of the PK and the short-term safety and tolerability of rilpivirine. Based on the Part 1 intensive pharmacokinetic data and the safety and antiviral activity results, enrollment for Part 2 of the study was initiated after IDMC review of the results.

The primary objective for Part 1 was to evaluate the steady-state PK, short-term safety and tolerability of rilpivirine 25mg QD in pediatric subjects. Pharmacokinetic parameters characterized included Cmax, Cmin, Tmax, and AUC.

During Part 2 of the trial, sparse rilpivirine PK samples were collected to further evaluate the rilpivirine pediatric exposure-response relationship.

Based on results from Part 1 of the trial, the mean Ctrough, Cmin, Cmax and AUC24h were 80.8 ng/mL, 57.1 ng/mL, 109 ng/mL and 1872 ng.h/mL, respectively; The statistical results comparing the geometric mean Ctrough, Cmin, Cmax and AUC24h of rilpivirine in adolescents with the geometric mean Ctrough, Cmin, Cmax and AUC24h of rilpivirine in adults obtained in the Phase 3 PK sub-studies are presented in Table 1. Based on the ratio of the least squares (LS) means for adolescents to adults, substantial differences in rilpivirine exposure were not observed.

In summary, for Part 1, the rilpivirine exposures in pediatric subjects administered 25mg QD were acceptable compared with the rilpivirine exposures from the adult trials using 25mg QD dosing regimen and support the selected 25mg dose in adolescents.

Table 1. Summary of Statistical Analysis of the Steady-state PK Parameters of Rilpivirine after Multiple Dose Administration of PRV 25mg QD in Adult and Adolescent (Part 1)

	LS means[a]			
Parameter (in geometric means)	**TMC278-C209 + TMC278-C215 (reference)**	**TMC278-C213 (Part 1a + 1b) (test)**	**LS means ratio, %**	**90% CI,% [b]**
C_{trough}, ng/mL	58.3	70.6	121.07	95.45 – 153.58
C_{min}, ng/mL	47.5	51.3	108.09	87.44 – 133.61
C_{max}, ng/mL	116	102	88.24	71.09 – 109.54
AUC_{24h}, ng.h/mL	1782	1750	98.19	80.53 - 119.73

a: 70.6/58.3= 1.21 (LS mean ratio); N=44 for reference and N=23 for test
b: 90% confidence intervals
Source: Sponsor analysis

Population Pharmacokinetics model was also utilized based on PK data from both the intensive and sparse PK sample (parts 1 and 2 of the pediatric trial). These analyses also support the use of 25mg in the adolescent population. The Sponsor's result tables are provided below. Refer to Clinical Efficacy section for discussion on the exposure-response assessments.

Table 2: Population Pharmacokinetics/model - AUC24h (ng.h/mL)*

Rilpivirine 25 mg qd	Week 24	Week 48
N	32	34
Mean (SD)	2374.7 (1069.76)	2390.9 (991.29)
Coefficient of Variation	0.45	0.41
Geom. Mean	2062.5	2174.9
Median (min - max)	2203.5 (110 - 5080)	2264.2 (417 - 5166)

*The adult pooled data for AUC24 mean (SD): 2397 (1032) ng.h/ml

Table 3: Population Pharmacokinetics/model - Ctrough (ng/mL)*

Rilpivirine 25 mg qd	Week 24	Week 48
N	26	34
Mean (SD)	86.8 (52.71)	83.5 (38.74)
Coefficient of Variation	0.61	0.46
Geom. Mean	71.6	73.3
Median (min - max)	79.0 (15 - 230)	78.7 (7 - 202)

*The adult pooled data for Ctrough mean (SD): 80.1 (36.5) ng/mL

7. Clinical/Statistical- Efficacy

This section summarizes Week 48 results for trial C213. Though cross-trial comparisons to the results from the adult trials should be done with caution, the general principal 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 rilpivirine 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[1], noting that the routes of transmissions 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 parameters, CD4 count and HIV RNA viral load. Antiretroviral drugs including nucleoside reverse transcriptase inhibitors (NRTIs), nonnucleoside reverse transcriptase inhibitors (NNRTIs), integrase strand transfer inhibitors (INSTIs) and protease inhibitors (PIs) are 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 US Department of Health and Human Services (DHHS) Guidelines for the Use of Antiretroviral

Agents in HIV-1-Infected Adults and Adolescents; Guidelines for the Use of Antiretroviral Agents in Pediatric HIV Infection]. Available at http://aidsinfo.nih.gov/guidelines

Overview of the Trial Designs
Trial C213 was the pivotal pediatric (adolescent) trial evaluating the use of rilpivirine. Rilpivirine was administered orally as the 25mg film-coated tablet. Twenty three subjects were enrolled into Part 1 of trial (intensive PK) which allowed for review of the PK and the short-term safety and tolerability of rilpivirine. Based on the Part 1 intensive pharmacokinetic data and the safety and antiviral activity results, enrollment for Part 2 of the study was initiated.

The primary objective was to evaluate the steady-state PK, short-term safety and tolerability of rilpivirine 25mg QD in pediatric subjects. The secondary objectives included evaluation of the long-term safety and efficacy of rilpivirine over a 24- and 48- week treatment period. Additional endpoints included evaluation of immunologic changes, evolution of viral genotype and phenotype during therapy, population PK and PK-PD relationships for safety and efficacy of rilpivirine and to evaluate treatment adherence. Subjects were followed for safety and tolerability as well as efficacy for a minimum of 48 weeks with additional planned 4 years-extension period. Resistance information was also collected from pediatric patients, particularly from those who experience loss of virologic response.

Trial C213 was reviewed for efficacy, 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 and Jreview software.

Disposition
Seventy-five subjects were screened and 36 were treated with at least 1 dose of rilpivirine 25mg. Of the 36 subjects, 24 (66.7%) subjects were ongoing at the Week 48 analysis cut-off date, and 8 (22.2%) had discontinued prematurely: 6 (16.7%) subjects reached a virologic endpoint, one (2.8%) was discontinued on Day 7 due to protocol violation, and another subject was discontinued due to pulmonary tuberculosis (protocol defined criterion for discontinuation).

Demographics and Baseline Characteristics
The intent to treat population (ITT) included 36 subjects. The majority of the participants were female (56%) and Black/African American (89%). The median age was 14.5 years (range: 12-17). Most of the female subjects were in Tanner stage was III (55%), while 3 subjects each were in II, IV and V. Most (70%) were past menarche. Most subjects (83%; 30/36) acquired HIV via mother-to-child transmission (MTCT).

As discussed earlier, the Week 96 efficacy data in adults demonstrated durability was a concern in subjects with high baseline HIV RNA (>100,000 copies/mL). Therefore, the indication for rilpivirine was limited to HIV infected treatment-naïve adult patients with HIV RNA ≤100,000 copies/mL. At the time of the change in the indication, the adolescent trial was already ongoing; of the subjects already enrolled, 8 had baseline HIV RNA >100,000 copies/mL . The protocol was then amended to only enroll those with baseline HIV RNA ≤100,000 copies/mL. The median (range) baseline HIV RNA was 57,150 (range 2,060-676,000) copies/mL. At baseline, 28 (78%) subjects had HIV RNA ≤100,000 copies/mL, 6 (16.7%) had HIV RNA >100,000 to ≤500,000 copies/mL and 2 (5.6%) had HIV RNA >500,000 copies/mL. Most, 89%, had CD4 cell counts > 200 cells/mm^3. The majority (74%) of subjects were CDC class A at baseline.

Of note, the primary efficacy analysis was also conducted for the 28 subjects with baseline HIV RNA ≤100,000 copies/mL. The median baseline plasma HIV-1 RNA for these 28 subjects was 44,250 (range: 2,060-92,600 copies/mL); the median baseline CD4+ cell count was 445.5 cells/mm3 (range: 123 to 983 cells/mm3).

Efficacy Results at Week 48

The primary efficacy endpoint was plasma viral load < 50 copies/mL at Week 48. Rilpivirine, in combination with other ARVs, demonstrated antiviral activity over the 48 week trial period. The proportion of subjects with plasma viral load < 50 copies/mL at Week 48 (based on FDA snapshot algorithm) was 71% (Table 4). The observed success trend in this pediatric population is generally comparable to that observed during the adult trials (C209 and C215) where the proportion of subjects with HIV RNA < 50 copies/mL at 48 was 83%. The lower rate of success in the adolescent population may be due decreased adherence to treatment. As described in the literature and further discussed in the Exposure-response section below, adherence to therapy in the adolescent population is lower than what is reported for adults.

Table 4: Efficacy Outcome at Week 48

Virologic outcome Week 48	**N=36 n(%)**
HIV RNA <50 copies/mL	**26(72.2)**
HIV RNA ≥ 50 copies/mL	**9 (25)**
Data in window not below threshold	3 (8.3)
Discontinued for lack of efficacy	5(17)
Discontinued for other reason while not below threshold	1 (2.8)
No Virologic Data	**1(2.8)**
Discontinued due to AE or Death	1(2.8)

Source: Snapshot dataset for C213

With regards to subgroup analyses, baseline HIV-RNA has been previously identified to have influence on response (and maintenance of response) to rilpivirine; adult subjects with baseline HIV-RNA >100,000 had higher rate of virologic failure compared to those with lower baseline HIV RNA. At week 48, the proportion of adult subjects with HIV RNA <50 copies/mL was 83% for the overall population and 89% among subjects with baseline HIV RNA ≤ 100,000 copies/mL. Similarly in the pediatric trial, the response rate increased to 79% after exclusion of the eight subjects with baseline HIV RNA >100,000 copies/mL, as summarized in Table 5.

Table 5: Efficacy Outcome by Baseline HIV RNA (≤100,000 copies/mL)

Virologic Outcome Week 48	**N=28** n(%)
HIV RNA <50 copies/mL	**22(79)**
HIV RNA ≥ 50 copies/mL	**6 (21)**
Data in window not below threshold	3 (11)
Discontinued for lack of efficacy	2(7)
Discontinued for other reason while not below threshold	1(4)

Source: Snapshot dataset for C213

Efficacy analysis was also conducted after exclusion of the four subjects (b) (4) . After the exclusion of this site, the overall virologic success rate at Week 48 was 78%; six subjects (19%) were considered virologic failure and 1 subject (4%) had no data in the Week 48 window due to discontinuation due to an adverse event.

Exposure-response

Based on previous analyses with the adult trial, the inhibitory quotient (IQ) was found to correlate with efficacy outcome. Therefore, IQ was also evaluated in the adolescent trial for exposure-response relationship. Specifically, exposure-response assessment was conducted for subjects with baseline HIV RNA ≤ 100,000 copies/mL and compared to adults with baseline HIV RNA ≤ 100,000 copies/mL. Sparse pharmacokinetic data collected during part 2 of the pediatric trial were used to evaluate the exposure response relationship.

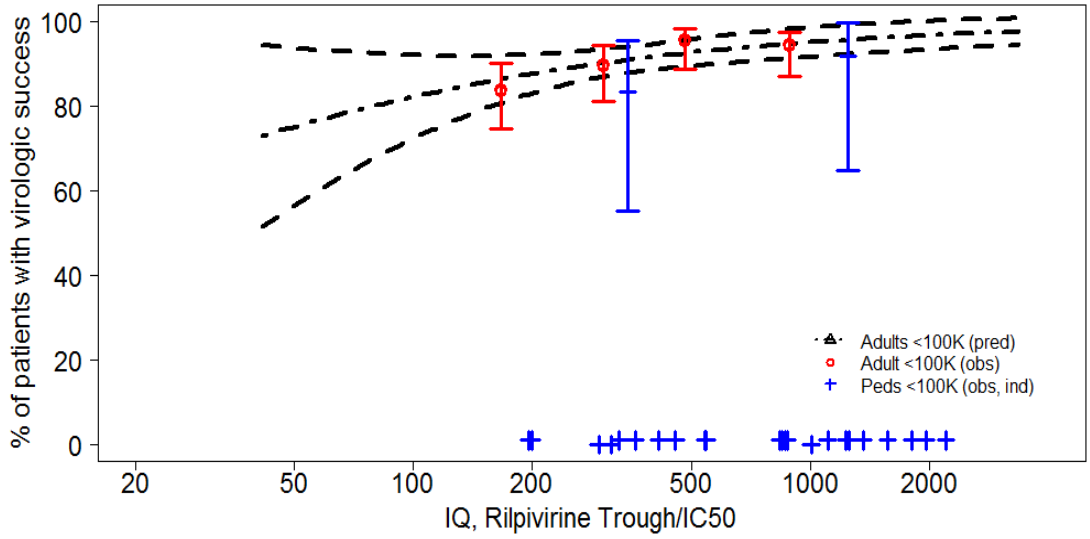
While rilpivirine exposures in adolescents (both AUC and Ctrough) and HIV-1 viral susceptibility were similar to adults, the efficacy outcomes (HIV RNA <50 copies/mL) were slightly lower in the pediatric age group than in adults (79% vs. 89%). A comparison of the virologic success and IQ relationship between adults and pediatrics suggested a more rapid drop-off in the relationship for pediatric subjects, especially at *lower IQ values*. A potential explanation for the discrepancy in the pediatric and adult exposure-response relationships is that samples from the pediatric subjects were disproportionately more likely to have rilpivirine concentration measurements that were below limit of quantification (BLQ) compared to adults (7% for pediatric subjects versus 4% in adults); given the half-life for rilpivirine (e.g. 50 hours), this would suggest that subjects missed multiple, consecutive doses, leading to a steeper exposure-response relationship than would be expected if these subjects had taken all their medication.

Exposure-response relationships were also assessed after excluding subjects with BLQ. Figure 1 demonstrates the exposure-response relationships, based 343 adult subjects with baseline viral load ≤100,000 copies/mL, IC50 values at baseline, and no BLQ measurements on treatment. Plotted along are two, IQ value groups for the 24 pediatric subjects with HIV RNA ≤100,000 copies/mL; the additional four pediatric subjects with baseline HIV RNA ≤100,000 copies/mL were excluded from the analysis due to no concentration data/BLQ concentration (n=3) and no IC50 value at baseline for IQ calculation (n=1). The virologic outcome for this subset of pediatric subjects was 88% (21/24) while among the 343 adult subjects, virologic success was 91% (311/343). Similarly, the exposure-response relationship based on IQ ratio improved in pediatric subjects after exclusion of subjects with BLQ or no IC50 data. In addition, the exposure-response relationship between adults and adolescents became more similar, especially at the higher IQ value. However, some differences remained between the adult and adolescent exposure-response relationship; among pediatric subjects with lower IQ value, a steeper exposure-response relationship was observed (i.e. more virologic failures). Multiple factors likely contributed to this outcome, including a smaller sample size and sub-optimal adherence. Even after the exclusion of subjects with BLQ, this analysis suggests that the exposure among pediatric subjects who were virologic failures remained slightly lower, likely due to adherence and unlikely due to suboptimal dosing selection, as the exposures observed during Part 1 (intensive PK) of the trial demonstrated the selected dose to be adequate.

Adherence is a known challenge in the adolescent age group, especially when medications are used for chronic health conditions[(2)]. Compared to adults, HIV infected youth have been reported to be less adherent to ART[(3)]. They face several barriers to adherence, including developmental

and/or cognitive immaturity [4,5]. Therefore, it is not unusual that adherence (thus efficacy) were lower in the adolescent subjects compared to adults. The lack of adherence appears to be more profound for some pediatric subjects, as they were found to have very low concentration or BLQ. For example, one subject with outlying AUC and Ct data had evidence suggestive of non-compliance [the AUC24h for this subject was much higher on the early visits with pharmacokinetic sampling (1128 ng.h/mL at Week 2, 3176 ng.h/mL at Week 4, 416 ng.h/mL at Week 8, 109 ng.h/mL at Week 12 and 379 ng.h/mL at the withdrawal visit). Virologic failure occurred at Week 16. There were no indications for factors such as concomitant medication which could explain this variability in pharmacokinetics during the study, and this is suggestive of suboptimal adherence to rilpivirine treatment, though the subject's reporting of compliance is on the contrary.

Figure 1: Exposure-Response Relationship- IQ and Percent of subjects with HIV RNA <50 copies/mL



Exposure-response analysis was also conducted to assess for exposure differences among pediatric subjects who were virologic success (HIV RNA <50 copies/mL) versus those who were virologic failures (HIV RNA ≥ 50copies/mL). No significant differences were observed between the two groups, as summarized by Sponsor's figures below (for AUC and Ctrough).

Figure 2: Rilpivirine Exposure (AUC) and Virologic Outcome

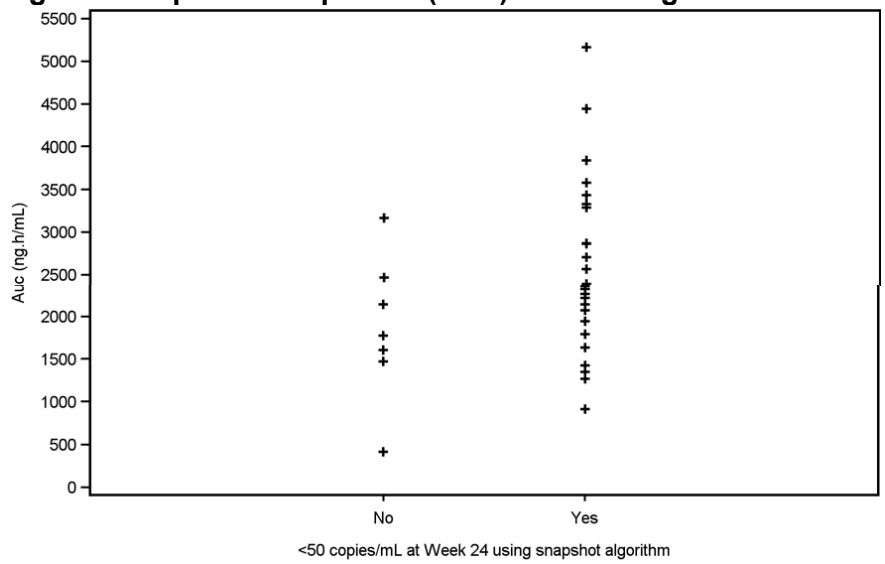
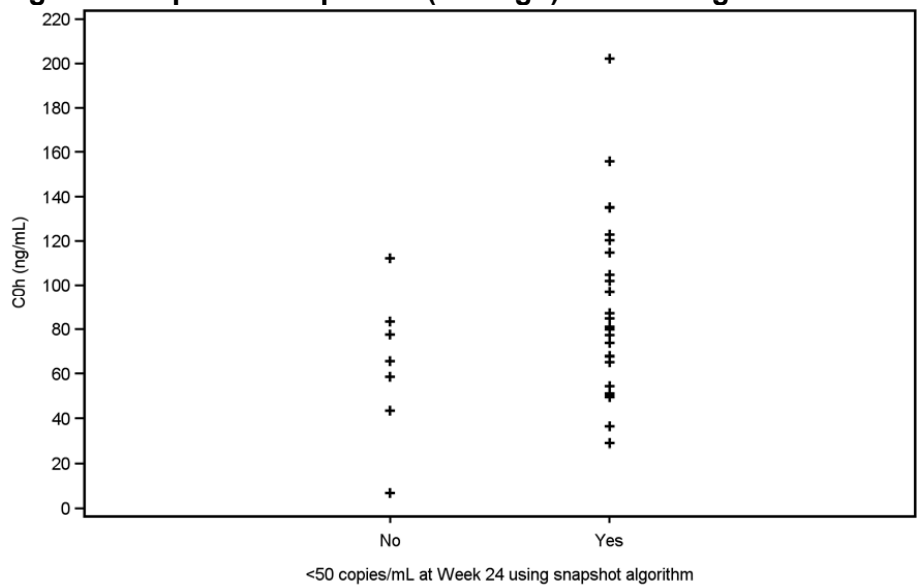


Figure 3: Rilpivirine Exposure (Ctrough) and Virologic Outcome



Efficacy summary and conclusions

The efficacy of rilpivirine 25mg once daily in treatment-naïve pediatric subjects was demonstrated in this single arm trial. At Week 48, rilpivirine in combination with other ARVs resulted in virologic response in 72% of subjects; the response rate is higher when considering the population in which rilpivirine is approved – treatment naïve patients with HIV RNA ≤100,000 copies/mL at the start of therapy. The efficacy outcome for adolescents with baseline HIV RNA ≤ 100,000 copies/mL was 79%. Although the response rate is numerically lower than what was observed in the adult population with HIV RNA ≤100,000 copies/mL, the difference in response between the two trials (~10%) is consistent with previous ARV trial observations between adolescent and adult subjects. The primary reason for the treatment difference in the two populations is likely related to adherence issues unique to the adolescent patient. The IQ-

response analysis support the hypothesis that adherence was low at least in some subjects, particularly in those with virologic failure. Importantly, the difference in the efficacy outcome between adults and adolescent is highly unlikely to be related to inadequate dose selection, as the exposures from Part 1 (intensive PK) phase of C213 trial were found to be similar to those observed in the adult trials.

In summary, because the exposure data from the intensive PK analyses supported the conclusion that an adequate dose was selected for evaluation, and because the overall efficacy outcome for C213 are consistent with results observed during the adult trials, this reviewer supports the approval of rilpivirine for adolescent patients.

8. Safety

The data submitted support safety and tolerability of rilpivirine when administered in combination with other ARVs. The Applicant has submitted safety data from 36 pediatric subjects enrolled in C213 and received at least 1 dose of rilpivirine. Rilpivirine in combination with other ARV drugs was safe and tolerable when administered to subjects ages 12 years and older. The types of AEs observed were similar to adults. No new safety concerns were identified. 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.

Deaths and other SAEs

There were no deaths reported. Non-fatal SAEs were reported in 6 subjects. The events were malaria (2 subjects), pneumonia (1 subject), suicide attempt/ideation (1 subject), hypersensitivity (1 subject) and abscess (1 subject). Only the hypersensitivity event (Grade 2) was considered treatment-related. The hypersensitivity case and the suicide attempt case are further discussed below, because these were events of interests during the original NDA review in adults based on NNRTI class events.

Hypersensitivity: Subject was a 12 year-old male from Uganda with history of a drug allergy to cotrimoxazole, and no history of rash. His concomitant medication included 3TC, TDF and Dapsone. On Day 5 of treatment, a Grade 2 AE of rash was reported, treated with cetirizine and prednisolone and resolved on Day 30. The investigator considered the AE to be very likely related to study medication. On Day 43, a second Grade 2 AE rash and Grade 2 hypersensitivity were reported, considered possibly or probably related to study medication. On Day 45, the subject was hospitalized for further investigation and treatment with cetirizine, prednisolone and topical hydrocortisone were initiated. Treatment with rilpivirine was not interrupted. The subject was discharged from the hospital after 2 days of hospitalization and hypersensitivity rash was resolved. I agree with the investigator's assessment that the drug hypersensitivity could be related to rilpivirine. Postmarketing events of hypersensitivity have been reported with use of rilpivirine and with other NNRTIs.

Suicide attempt/ideation: Subject was a 17 year-old female with history of depression and previous multiple suicide attempts (at least 10) and her psychiatric medication included sertraline. On Day 29 of treatment, Grade 2 depression (worsening depression) was reported, considered doubtfully related to study drug. On Day 106 of treatment, Grade 3 suicide attempt with a combination of 10 pills was reported, and the depression worsened to Grade 3. Subsequently, a Grade 4 suicide attempt with a combination of 30 to 40 pills was reported. The

subject was then hospitalized for suicide attempts and discharged at a later date after the depression improved to Grade 2. On Day 270, the subject experienced increasing suicidal ideation and depression, both reported as Grade 4 and subject was hospitalized again. At the last visit (Week 48), the depression was Grade 2. The investigator did not consider the suicidal ideation/attempts or depressions to be related to rilpivirine. Given the extensive medical history of depression and suicide attempts, I agree with the investigator that the events are unlikely related to study drug, although worsening of pre-existing depression due to rilpivirine cannot be ruled out.

Discontinuations due to AEs
No subject discontinued due to drug-related AE. The one subject who discontinued due to an AE experienced pulmonary TB, a pre-specified protocol criterion for treatment discontinuation.

Adverse Drug Reactions
Adverse drug reactions (ADRs) are defined as events considered treatment-related to study drug, as assessed by the investigator. In all, ADRs were reported in thirteen subjects (36%). Clinical events (i.e. excluding laboratory events reported as 'investigation') by preferred term reported in at least 2 subjects include nausea (n=2) and somnolence (n=5). All ADRs were Grade 1 or 2. Overall, the findings in the pediatric subjects are consistent with the ADRs identified during the adult NDA review for rilpivirine.

Sponsor relied on its own adjudication system to identify adverse events as ADR. This adjudication system was also used by the Sponsor during the analyses of the adult clinical trial data and labeling. Per Sponsor's analyses, most ADRs were Grade 1 or 2. The most common ADRs reported in at least 2 subjects (regardless of severity) include headache (19.4%), depression (19.4%), somnolence (13.9%), nausea (11.1%), dizziness (8.3%), abdominal pain (8.3), vomiting (5.6%) and rash (5.6%).

Adverse events of interest:
Based on signals from nonclinical toxicity studies or previously identified potential NNRTI-class effect, adverse of events of interest for further safety evaluation included hypersensitivity reactions and rash, neuropsychiatric events, hepatobiliary events, renal events and adrenal events.

Rash and hypersensitivity reactions
Overall, eight subjects (22%) experienced rash-related events, including 'hypersensitivity drug rash', 'allergic dermatitis', 'pruritic papular eruption', 'polymorphus eruption', 'rash', 'skin rash' and 'red itchy painful lesions'. While 'rash' and 'skin rash' were reported in 2 subjects each, the other preferred terms were reported in no more than one subject. No subject discontinued therapy due to the events. Treatment-related events occurred in one subject, who experienced 'hypersensitivity', 'rash', and 'skin rash'. The only serious event was hypersensitivity, as described previously. No Grade 3 or 4 events were reported. In summary, the overall findings for rash-related events were consistent with current USPI for rilpivirine.

Neuro-psychiatric events
Depression, including suicidal ideations or attempts is known ADRs with use of rilpivirine. To summarize the adult trial, during the Week 48 data review, 8% of rilpivirine-treated subjects experienced mood-related adverse events, regardless of causality or severity. The findings are described in the USPI under Warnings and Precautions. No new terms were identified during the

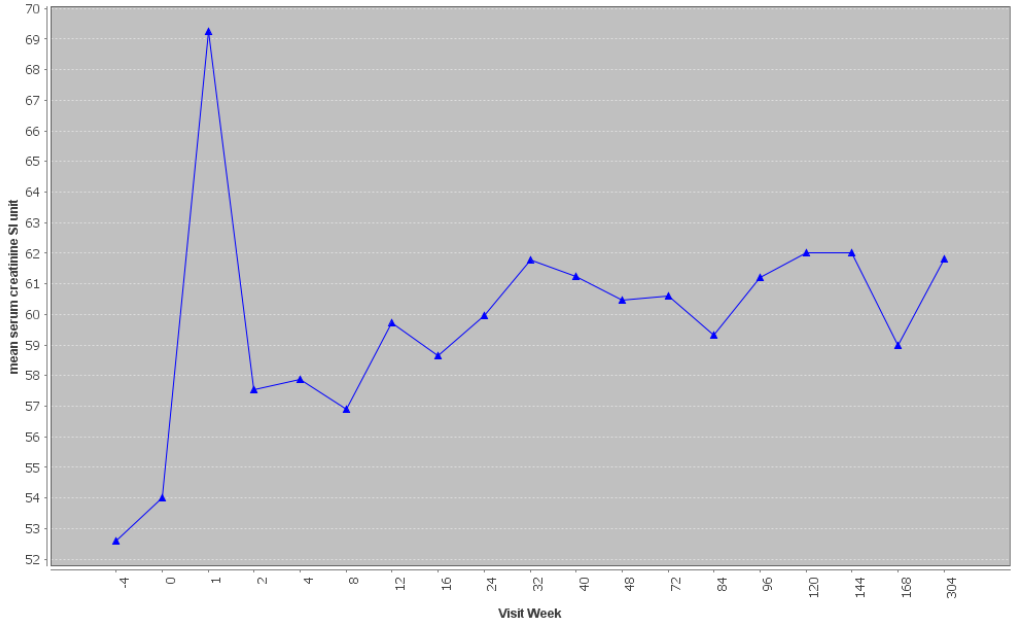
pediatric trial. Overall, eight pediatric subjects experienced *psychiatric-related* events, seven (19%) of whom reported mood-related events (e.g. depression) and one reported sleep disorder. The preferred terms include 'depression', 'worsening depression', 'suicidal ideation/intent' and 'insomnia'. One event was considered serious (suicide ideation/suicide attempt, Grade 4), as discussed previously. Among the seven subjects who reported depression, two experienced a severe (Grade 3) depression. None of the events were considered treatment-related by the investigator and none led to treatment discontinuation. Of the subjects who experienced depressive disorder, two were reported to have previous psychological history; the exact history was not reported for one subject while another subject had history of depression and suicide attempts. In summary, psychiatric events, in particular depressive disorders, described during the pediatric trial are consistent with the events described during the original NDA review. The higher rate of incidence in the pediatric trial should be interpreted in the context of small sample size and uncontrolled trial design.

Fourteen subjects (39%) experienced *neurologic* adverse events. The most commonly reported preferred terms, reported in at least 2 subjects (regardless of severity, causality) were headache (22%), somnolence (14%) and dizziness (11%). Treatment-related events reported in 5 subjects: dizziness (n=1), somnolence (n=3), headache (n=1). Most were mild or moderate in severity; none were serious or led to treatment discontinuation. These events are consistent with previous observations during the adult trials.

Hepatobiliary events
No hepatobiliary events were reported. Refer to the laboratory section for liver-related laboratory abnormalities (i.e. serum biochemistry).

Renal events
In the pooled Phase 3 trials, an increase in serum creatinine was observed during the treatment period over 96 weeks. Most of this increase occurred within the first four weeks of treatment. The increase in serum creatinine is believed to be an effect (inhibition) on transporters found on renal tubules, thereby no effect on GFR would be expected. An increase in serum creatinine, especially during the first 2 weeks of treatment was also observed in the adolescent trial, as summarized in the figure below. The mean serum creatinine then stabilizes over the treatment course period.

Figure 4: Serum Creatinine (SI unit) over time (Visit Week)



Source: Laboratory dataset for C213

During the adolescent trial, no renal-related clinical adverse events were reported (i.e. excluding laboratory-related events). Laboratory-related events included Grade 1 and 4 increase in serum creatinine (n=1), hematuria (n=2) and proteinuria (n=1).

Adrenal events

Due to the signal observed in the preclinical studies, monitoring and assessment of adrenal function has been part of the clinical development program for rilpivirine. DAVP has been in consultation with Division of Metabolic and Endocrine Products (DMEP) to provide recommendations regarding overall adrenal monitoring and assessment at the time of protocol development, dataset review at the time of the adult NDA submission, and labeling recommendations at the time of the original NDA approval. With the submission of the current pediatric sNDA, DMEP was again consulted to review the submitted pediatric data and provide labeling recommendations, if indicated. Please refer to the consult review by Dr. Smita Abraham for full details.

Adverse events

There were no discontinuations due to low serum cortisol level or due to signs and symptoms of adrenal insufficiency. Seven subjects had Grade 1 'blood cortisol decreased' (range: 149-204nmol/L). Although a decrease in blood cortisol level were reported in these seven subjects, comparison of the baseline cortisol value to the 'worse-toxicity grade' value reported during treatment for each subject revealed that their baseline cortisol values were lower than the reported Grade 1 cortisol values during treatment for all seven subjects.

Laboratory findings- mean cortisol values

During the pediatric trial, at Week 48, an increase of + 43.8 nmol/L in mean basal cortisol over

the mean baseline value was observed. The mean cortisol level post ACTH-stimulation also increased compared to baseline.

Laboratory findings- individual subject results to ACTH stimulation tests
With regards to cortisol values post ACTH stimulation tests, eleven (11) subjects had abnormal cortisol (<500nmol/L) results, as summarized in the Table below. Six of the eleven subjects also had abnormal baseline response to ACTH stimulation test (i.e. pre-treatment with rilpivirine); and four of the six subjects recovered while on treatment with rilpivirine. Of the remaining five of the eleven subjects, four responded appropriately at baseline but failed at Week 48; one responded appropriately at baseline, failed at Week 16, then recovered at Week 48. Table 6 summarizes the results for the eleven subjects; the four subjects highlighted are those who responded at baseline but failed at Week 48.

Table 6: Subjects with abnormal ACTH stimulation tests

	Cortisol levels (nmol/L)												
Patient ID	Wk 0	Wk 2	Wk 4	Wk 8	Wk 12	Wk 16	Wk 24	Wk 28	Wk 32	Wk 48	WK 60	Wk 84	Wk 96
213-0003	371				501		344	497					
213-0005	539	499		466	509					216			
213-0023	569					432				560			
213-0031	494					662				465		508	
213-0035	476	575			507					479	549		
213-0046	572				580				520	485			498
213-0047	350		499						446	507			
213-0048	467					502				479			491
213-0053	436	466								545			
213-0063	518				580					457			
213-0065	594				576					461			

To convert to µg/dL, divide by 27.6
The highlighted subjects are those with normal stimulation test at baseline but failed stimulation test without recovery during treatment period.
Abnormal peak stimulated cortisol levels are in red

Review of the adult and pediatric data is inconclusive in correlating use of rilpivirine with adrenal insufficiency. For example, although some pediatric subjects failed ACTH stimulation test during the trial, others recovered during therapy after failing the test at baseline (pre-treatment). Analyses of the controlled, larger adult data from the Phase 3 trials did not demonstrate use of

rilpivirine increases risks for adrenal insufficiency during the 96 weeks of therapy. In addition, both control (efavirenz-) and the rilpivirine-treated adult subjects with a normal ACTH stimulation test at baseline failed ACTH stimulation test during therapy, albeit more subjects failed in the rilpivirine arm compared to efavirenz arm (7% vs. 3%). Furthermore, at the end of therapy, the two treatment arms had similar proportion of subjects responding adequately to ACTH stimulation test-58% and 56% for the rilpivirine- and efavirenz- treatment arms, respectively. Finally, while biochemical evidence of adrenal insufficiency was observed during the adult and pediatric trials, no notable clinical adverse event related to adrenal insufficiency was identified in either population, despite continuing treatment with rilpivirine.

In summary, based on the review of the pediatric and adult data, DMEP concluded that overall, there is no conclusive evidence to recommend routine ACTH testing and monitoring during treatment with rilpivirine. Despite the preclinical data suggesting rilpivirine inhibits 21-hydroxylase enzyme leading to decrease in cortisol level, the clinical trial results are, at best, inconclusive. The primary observation during the adult and pediatric clinical trials has been limited biochemical evidence of adrenal insufficiency without development of clear signs and symptoms of clinical adrenal insufficiency. It is unclear to determine clinical significance of the increased number of abnormal ACTH stimulation tests observed during treatment with rilpivirine. There were no serious adverse events, deaths or treatment discontinuation that could be attributed to adrenal insufficiency.

In conclusion, the biochemical evidence of adrenal insufficiency seen in the adult and pediatric data does not appear to result in any clinical disease. As summarized by Dr. Abraham, there are several hypotheses to consider:

1. Rilpivirine might cause interference in the cortisol assay.
2. Rilpivirine might cause a mild 21-hydroxylase inhibition in humans resulting in slightly lower cortisol levels, but not clinical disease.
3. Abnormal ACTH stimulation test results are representative of the diagnostic limitation of the 250 µg ACTH stimulation test in this population.
4. Of the limited data available, this is the largest, prospective dataset of ACTH stimulation in an HIV infected population representing the natural history of adrenal function in this population.

Based on the totality of the data, DMEP also made additional recommendations (b) (4)

(b) (4)

With regards to labeling, DMEP has concluded that the current data do not warrant labeling of adrenal insufficiency in the Warnings and Precautions section; DMEP recommends including the laboratory results (e.g. change from baseline in mean cortisol) for the pediatric trial, similar to the adult labeling language. DMEP also recommends including the ACTH stimulation test for the subjects who failed during treatment with rilpivirine. DMEP does not recommend adding data regarding the group of subjects who had abnormal 250 µg ACTH stimulation tests at baseline and recovered during treatment with rilpivirine, as these subjects might have had a true

hypothalamic-pituitary-adrenal dysfunction at baseline. For consistency, DMEP also recommends modifying the language currently describing the adult results to include the ACTH stimulation test results for subjects who failed after start of treatment with either rilpivirine or efavirenz. Below are the recommended labeling language for both adult and pediatric subjects (under Clinical Trial Experiences; adrenal function) and for pediatric subjects (under Special Populations; Pediatrics).

Proposed (adult) language

Adrenal Function
In the pooled Phase 3 trials, at Week 96, there was an overall mean change from baseline in basal cortisol of (b) (4) in the EDURANT group and of (b) (4) in the efavirenz group.

In the EDURANT group, (b) (4) of subjects with a normal 250 µg ACTH stimulation test at baseline developed an abnormal 250 µg ACTH stimulation test (peak cortisol level (b) (4) during the trial compared to 18/ (b) (4) %) in the efavirenz group. (b) (4) Overall, there were no serious adverse events, deaths, or treatment discontinuations that could clearly be attributed to adrenal insufficiency. The clinical significance of the higher abnormal rate of ACTH stimulation tests in the EDURANT group is not known.

Proposed (pediatric) language

Adrenal Function
(b) (4) (b) (4) the overall mean change from baseline in basal cortisol showed an increase of (b) (4)

(b) (4) subjects with a normal 250 µg ACTH stimulation test at baseline developed an abnormal 250 µg ACTH stimulation test (peak cortisol level < (b) (4) during the trial. Three subjects had a (b) (4) 250 µg ACTH stimulation test (b) (4). Overall, there were no serious adverse events, deaths, or treatment discontinuations that could clearly be attributed to adrenal insufficiency. The clinical significance of the abnormal 250 µg ACTH stimulation tests is not known.

(b) (4)

These findings are consistent with previous findings during the original NDA review. The table below summarizes adverse events, by SOC, reported in at least 2 subjects.

Table 7: Common Adverse Events, by SOC

SOC	N=36 n(%)
Infections and infestations	30 (83)
Gastrointestinal disorders	15 (42)
Investigations	14 (39)
Nervous system disorders	14 (39)
Respiratory, thoracic and mediastinal disorders	10 (28)
Psychiatric disorders	8 (22)
Skin and subcutaneous tissue disorders	8 (22)
Blood and lymphatic system disorders	7 (19)
Eye disorders	5 (14)
General disorders and administration site conditions	4 (11)
Renal and urinary disorders	3 (8)
Reproductive system and breast disorders	3 (8)
Surgical and medical procedures	2 (6)

Source: AE dataset for C213

Laboratory Abnormalities

The following are selected laboratory toxicities selected based on previously described toxicities with use of rilpivirine. Overall, the laboratory toxicities reported during the pediatric trial are similar to the findings reported in adults. No Hy's law cases were reported. One subject, 17 year old female from South Africa, was reported to have pancreatitis (Grade 3, non-serious). The subjects had history of chronic pancreatitis believed to be related to HIV disease (baseline amylase Grade 1). On Day 8 of treatment, acute on chronic pancreatitis was reported (amylase Grade 3; lipase Grade 0); the acute event was considered not to be related to study drugs (rilpivirine, Truvada) and resolved after 21 days with continued treatment.

Table 8: Selected Laboratory Parameters, Maximum Treatment-emergent Toxicities

Laboratory Test	**N=36 n(%)**
ALT	
Grade 1	2(6)
Grade 2	1(3)
AST	
Grade 1	6(17)
Grade 2	2(6)
ALK Phos	
Grade 1	10(28)
Grade 2	1 (3)
Total Bilirubin	
Grade 1	2(6)
Amylase	
Grade 1	6(17)

Grade 2	5(14)
Grade 3	2(6)
Creatinine	
Grade 1	1(3)
Grade 4	1(3)

Source: laboratory analysis datasets C213

Safety summary

In summary, no new safety signals were identified. Overall, the findings in this pediatric clinical trial are consistent with previously described events with use of rilpivirine in adults. Although some adverse events appear to have higher incidence rate in pediatric subjects, it should be noted that C213 is a single-arm trial with significantly fewer number of subjects compared to the adult trials. The Clinical Adverse Events section (Section 6) will be updated to include ADRs, as identified by the Sponsor and regardless of severity and reported in at least 2 subjects. As discussed above, results related to adrenal function will also be included in the USPI.

9. Advisory Committee Meeting

Not applicable.

10. Pediatrics

This application contains pediatric data for adolescent subjects. The pediatric trial design, clinical outcome and prosed labeling for the adolescent age group were presented to the PeRC. The PeRC agreed with the Division's proposed plans. (b) (4) The PREA PMR for pediatric patients (b) (4) to less than 12 years of age remains outstanding. However, the PREA PMR submission due date is not until March, 2019. The Division plans to inquire with the Sponsor about the status of the trial.

11. Other Relevant Regulatory Issues

No additional regulatory issues have been identified.

12. Labeling

The labeling has been updated to reflect changes in the indication, extending the population to treatment-naïve HIV infected children weighing at least 35 kg and with HIV RNA ≤100,000 at start of therapy. In addition, the Indication and Usage section has been updated to reflect the currently recommended language when describing limitation of use. Lastly, the recently negotiated language highlighting skin and hypersensitivity reactions under Section 5 has also been included into this label. The changes with this efficacy supplement primarily affected the following sections. Note, while most of the labeling sections have been agreed upon, the adrenal labeling recommendation is currently under negotiation with the Sponsor.

1 INDICATIONS AND USAGE

EDURANT®, in combination with other antiretroviral agents, is indicated for the treatment of human immunodeficiency virus type 1 (HIV-1) infection in antiretroviral treatment-naïve patients with HIV-1 RNA less than or equal to 100,000 copies/mL at the start of therapy.

Limitations of Use:

- More EDURANT treated subjects with HIV-1 RNA greater than 100,000 copies/mL at the start of therapy experienced virologic failure (HIV-1 RNA ≥ 50 copies/mL) compared to EDURANT treated subjects with HIV-1 RNA less than or equal to 100,000 copies/mL *[see Clinical Studies (14.1)]*.

- Regardless of HIV-1 RNA at the start of therapy, more EDURANT treated subjects with CD4+ cell count less than 200 cells/mm^3 experienced virologic failure compared to EDURANT treated subjects with CD4+ cell count greater than or equal to 200 cells/mm^3 *[see Clinical Studies (14.1)]*.

- The observed virologic failure rate in EDURANT treated subjects conferred a higher rate of overall treatment resistance and cross-resistance to the NNRTI class compared to efavirenz *[see Microbiology (12.4)]*.

- More subjects treated with EDURANT developed tenofovir and lamivudine/emtricitabine associated resistance compared to efavirenz *[see Microbiology (12.4)]*.

2 DOSAGE AND ADMINISTRATION

The recommended dose of EDURANT in patients 12 years of age and older weighing at least 35kg is one 25 mg tablet once daily taken orally with a meal *[see Clinical Pharmacology (12.3)]*.

EDURANT is not recommended for patients less than 12 years of age *[see Use In Specific Populations (8.4)]*.

5.2 Skin and Hypersensitivity Reactions

Severe skin or hypersensitivity reactions have been reported during the postmarketing experience, including cases of Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS), with rilpivirine-containing regimens. While some skin reactions were accompanied by constitutional symptoms such as fever, other skin reactions were associated with organ dysfunctions, including elevations in hepatic serum biochemistries. During the Phase 3 clinical trials, treatment-related rashes with at least Grade 2 severity were reported in 3% of subjects receiving EDURANT. No grade 4 rash was reported. Overall, most rashes were Grade 1 or 2 and occurred in the first four to six weeks of therapy *[see Adverse Reactions (6 and 6.2)]*. Discontinue EDURANT immediately if signs or symptoms of severe skin or hypersensitivity reactions develop, including but not limited to, severe rash or rash accompanied by fever, blisters, mucosal involvement, conjunctivitis, facial edema, angioedema, hepatitis or eosinophilia. Clinical status including laboratory parameters should be monitored and appropriate therapy should be initiated.

5.3 Depressive Disorders

The adverse reaction depressive disorders (depressed mood, depression, dysphoria, major depression, mood altered, negative thoughts, suicide attempt, suicidal ideation) has been reported with EDURANT. Patients with severe depressive symptoms should seek immediate medical evaluation to assess the possibility that the symptoms are related to EDURANT, and if so, to determine whether the risks of continued therapy outweigh the benefits.

During the Phase 3 trials in adults (N = 1368) through 96 weeks, the incidence of depressive disorders (regardless of causality, severity) reported among EDURANT (n = 686) or efavirenz (n = 682) was 9% and 8%, respectively. Most events were mild or moderate in severity. The incidence of Grade 3 and 4 depressive disorders (regardless of causality) was 1% for both EDURANT and efavirenz. The incidence of discontinuation due to depressive disorders among EDURANT or efavirenz was 1% in each arm. Suicidal ideation was reported in 4 subjects in each arm while suicide attempt was reported in 2 subjects in the EDURANT arm.

During the Phase 2 trial in pediatric subjects 12 to less than 18 years of age (N = 36) receiving EDURANT through 48 weeks, the incidence of depressive disorders (regardless of causality, severity) was 19.4% (7/36). Most events were mild or moderate in severity. The incidence of Grade 3 and 4 depressive disorders (regardless of causality) was 5.6% (2/36). None of the subjects discontinued due to depressive disorders. Suicidal ideation and suicide attempt were reported in 1 subject.

(b) (4)

6.1 Clinical Trial Experience: Adult (b) (4)

Adrenal function

In the pooled Phase 3 trials, at Week 96, there was an overall mean change from baseline in basal cortisol of (b) (4) in the EDURANT group and of (b) (4) in the efavirenz group.

In the EDURANT group, (b) (4) of subjects with a normal 250 µg ACTH stimulation test at baseline developed an abnormal 250 µg ACTH stimulation test (peak cortisol level < (b) (4)) during the trial compared to 18/ (b) (4) in the efavirenz group. (b) (4)

Overall, there were no serious adverse events, deaths, or treatment discontinuations that could clearly be attributed to adrenal insufficiency. The clinical significance of the higher abnormal rate of ACTH stimulation tests in the EDURANT group is not known.

6.2 Clinical Trials Experience: Pediatric Patients

The safety assessment is based on the Week 48 analysis of the single-arm, open-label, Phase 2 trial, TMC278-C213, in which 36 antiretroviral treatment-naïve HIV-1 infected patients 12 to less than 18 years of age and weighing at least 32 kg received EDURANT (25 mg once daily) in combination with other antiretroviral agents *[see Clinical Studies (14.2)]*. The median duration of exposure was 63.5 weeks. There were no patients who discontinued treatment due to ADRs. No new ADRs were identified compared to those seen in adults.

Most ADRs were Grade 1 or 2. The most common ADRs (b) (4) were headache (19.4%), depression (19.4%), somnolence (13.9%), and nausea (11.1%). Observed laboratory abnormalities were comparable to those in adults.

Adrenal function

In a 48 week, (b) (4) the overall mean change from baseline in basal cortisol showed an increase of (b) (4)

(b) (4) of (b) (4) subjects with a normal 250 µg ACTH stimulation test at baseline developed an abnormal 250 µg ACTH stimulation test (peak cortisol level < (b) (4) during the trial. Three subjects had a (b) (4) 250 µg ACTH stimulation test (b) (4). Overall, there were no serious adverse events, deaths, or treatment discontinuations that could clearly be attributed to adrenal insufficiency. The clinical significance of the abnormal 250 µg ACTH stimulation tests is not known.

12.3 Pharmacokinetics

Pediatric Patients

The pharmacokinetics of rilpivirine in antiretroviral treatment-naïve HIV-1 infected pediatric subjects 12 to less than 18 years of age receiving EDURANT 25 mg once daily were comparable to those in treatment-naive HIV-1 infected adults receiving EDURANT 25 mg once daily. There was no clinically significant impact of body weight on rilpivirine pharmacokinetics in pediatric subjects in trial C213 (33 to 93 kg).

Table 6: Population Pharmacokinetic Estimates of Rilpivirine 25 mg once daily in Antiretroviral Treatment-Naïve HIV-1-Infected Pediatric Subjects aged 12 to less than 18 years (Data from Phase 2 Trial through Week 48)

Parameter	Rilpivirine 25 mg once daily N = 34
AUC_{24h} (ng•h/mL)	
Mean ± Standard Deviation	(b) (4)
Median (Range)	(b) (4) (417 - 5166)
C_{0h} (ng/mL)	
Mean ± Standard Deviation	85 ± 40
Median (Range)	(b) (4) (7 - 202)

14.2 Treatment-Naïve Pediatric Subjects (12 to less than 18 years of age)

The pharmacokinetics, safety, tolerability and efficacy of EDURANT 25 mg once daily, in combination with an investigator-selected background regimen (BR) containing two NRTIs, was evaluated in trial TMC278-C213, a single-arm, open-label Phase 2 trial in antiretroviral treatment-naïve HIV-1 infected pediatric subjects 12 to less than 18 years of age and weighing at least 32 kg. Thirty six (36) subjects were enrolled in the trial to complete at least 48 weeks of treatment. The 36 subjects had a median age of 14.5 years (range: 12 to 17 years), and were 55.6% female, 88.9% Black and 11.1% Asian.

In the efficacy analysis, most subjects (75%; 28/36) had baseline HIV RNA <100,000 copies/mL. For these 28 subjects the median baseline plasma HIV-1 RNA was 44,250 (range: 2,060-92,600 copies/mL) and the median baseline CD4+ cell count was 445.5 cells/mm^3 (range: 123 to 983 cells/mm^3).

Among the subjects who had baseline HIV RNA ≤ 100,000, the proportion with HIV-1 RNA <50 copies/mL at Week 48 was 79% (22/28), versus 50.0% (4/8) in those with >100,000 copies/mL. The proportion of virologic failures among subjects with a baseline viral load ≤100,000 copies/mL was 21.4% (6/28), versus 37.5% (3/8) in those with >100,000 copies/mL. At Week 48, the mean increase in CD4+ cell count from baseline was 201.2 cells/mm^3.

13. Outstanding Issues
None. However, labeling negotiations are currently ongoing.

14. Recommendations/Risk Benefit Assessment
Supplement to NDA 202022 (supporting document 217) containing week 48 data from the pediatric clinical trial C213 supports dosing recommendations for Edurant® (rilpivirine) in combination with other antiretroviral drugs for the treatment of HIV-1 infection in pediatric patients 12 years of age and older weighing at least 35kg and with HIV RNA ≤ 100,000 copies/mL at the start of therapy. This reviewer recommends the approval of this supplemental NDA (sNDA). Rilpivirine, in combination with other antiretroviral drugs, resulted in suppression of HIV-1 RNA.

Through the review of this sNDA, no deficiencies that would preclude the approval of this submission were identified. Rilpivirine was studied in a single Phase 1/2, open-label, non-comparative trial in which 36 pediatric subjects were enrolled, all of which received the to-be-marketed dose. The trial design comprised of two stages: Stage I was a dose-finding stage which also evaluated the short term safety and efficacy of rilpivirine in a limited number of subjects; Stage II evaluated the safety and efficacy of the selected dose (25mg), for a minimum of a 48-week treatment period.

Similar to other pediatric trials which evaluate 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 the findings.

Rilpivirine exposures during the intensive PK period in pediatric subjects approximated that in adult subjects, with the geometric mean (GM) AUC and Ctrough values falling in the pre-specified target AUC and Ctrough ranges. The results from the intensive PK period support the dose selection and approval of the 25mg PO QD in treatment naïve adolescent patients weighing at least 35 Kg and with HIV RNA ≤100,000 copies/mL at the start of therapy.

After establishing the PK primary endpoint, and after the completion of Part 2 of the trial, partial extrapolation of the antiviral activity of rilpivirine in adolescent subjects was made. The efficacy outcome (HIV RNA < 50 copies/mL) for the overall adolescent subjects enrolled was 72%; the response rate increased to 79% at Week 48 when outcome was assessed for the population for whom rilpivirine would be indicated – those with HIV RNA ≤100,000 copies/mL at the start of therapy. Although the efficacy outcome in adolescent subjects was lower than the adult subjects, the difference was not due to inadequate dose selection, as demonstrated by the intensive PK data. The outcome disparity may be related to smaller sample size and decreased adherence in the adolescent subjects; this was suggested by the disproportionate number of pediatric subjects whose rilpivirine concentrations were much lower (e.g. BLQ).

The applicant demonstrated an acceptable safety profile for rilpivirine in combination with other antiretroviral drugs. Rilpivirine was generally safe and tolerable in pediatric subjects enrolled in this trial. No deaths were reported and serious adverse events were limited. No adverse events led to trial drug discontinuation. Adverse events of special interest with the use of antiretroviral agents such as rilpivirine (hepatotoxicity or AST/ALT elevations, rash or hypersensitivity reactions, psychiatric disorders, renal or elevation is serum creatinine and endocrine disorders) occurred with low frequency, and no new safety signals were identified. The observed risks of

rilpivirine use have been described previously, and the rate and nature of the adverse events were similar to those in adults.

The Safety Update Report on the use of rilpivirine in pediatric patients was reviewed and no new safety signal was identified. Of note, as the size of the safety database is limited for pediatrics, the trial will continue to follow subjects beyond the Week 48 cut-off.

Recommendation for Postmarketing Risk Evaluation and Management strategies
The current submission partially fulfills the Pediatric Written Request, and no additional pediatric post marketing study commitments will be sought. The current submission also fulfills one of the Post Marketing Requirement under Pediatric Research Equity Act (PREA) (see Section 2.5). (b) (4)

Recommendation for other Postmarketing Requirements and Commitments
None. The applicant will continue to submit PAERS and annual reports (DSURs) for review.

References

1. Domachowske, JB; Pediatric Human Immunodeficiency Virus Infection; October 1996; Clin. Microbiol. Rev. 9(4) 448-468
2. Taddeo D, et al.; Adherence to Treatment in Adolescents; January 2008; Paediatric Child Health. 13(1): 19-24
3. Nachegra, Jean B, et al.; Antiretroviral Therapy Adherence, Virologic and Immunologic Outcomes in Adolescents Compared With Adults in Southern Africa; May 2009; JAIDS.51(1) 65-71
4. MacDonell K, Naar-King S, Huszti H, Belzer M. Barriers to medication adherence in behaviorally and perinatally infected youth living with HIV. AIDS Behav. Jan 2013;17(1):86-93. Available at http://www.ncbi.nlm.nih.gov/pubmed/23142855.
5. Rudy BJ, Murphy DA, Harris DR, Muenz L, Ellen J, Adolescent Trials Network for HIVAI. Prevalence and interactions of patient-related risks for nonadherence to antiretroviral therapy among perinatally infected youth in the United States. AIDS Patient Care STDS. Feb 2010;24(2):97-104. Available at http://www.ncbi.nlm.nih.gov/pubmed/20059354.

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