Clinical Review

Date	December 19, 2015
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Subject	Clinical Review
NDA/BLA # Supplement#	202123 Supplement 021
Applicant	Gilead
Date of Submission	April 23, 2015
PDUFA Goal Date	February 23, 2016
Proprietary Name / Established (USAN) names	Complera (emtricitabine/rilpivirine/tenofovir disoproxil fumarate)
Dosage forms / Strength	Fixed dose tablet (200mg/25mg/300mg)
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 data used to support Gilead's supplemental NDA seeking approval for Complera® (emtricitabine/rilpivirine/tenofovir DF) for treatment of HIV-1 infection in pediatric patients (adolescents) ages 12 of age and older. No clinical trial was conducted with Complera. Rather, the indication is supported by existing and previously FDA-reviewed data with the individual drug products, emtricitabine, tenofovir and rilpivirine. The pharmacokinetic, safety and efficacy (antiviral activity) data with the individual drug products support extension of the indication for Complera to include adolescents because the proposed doses for Complera are identical to the approved doses for the individual drug products. Complera contains 200mg/25mg/300mg of emtricitabine (FTC)/rilpivirine (RPV)/tenofovir (TDF); the approved doses for adolescent use are 200mg emtricitabine (FTC), 25mg rilpivirine (RPV) and 300mg tenofovir (TDF), all once daily.

This application allows for once daily, fixed dose, NNRTI-based regimen for adolescent 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-based regimen include fewer discontinuations due to adverse events compared to efavirenz; 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 adult 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. In August 2015, the indication for rilpivirine was expanded to include adolescent patients. Please refer to the reviews for the adult and adolescent NDAs and sNDAs for full details.

Based on the data from C209 and C215, Complera was approved for treatment of HIV infection in adults. In addition, the efficacy of Complera was established in certain virologically-suppressed (HIV-1 RNA <50 copies/mL) adult patients with no history of virologic failure and who had been on a stable PI-containing regimen for at least 6 months and switch their therapy to Complera.

This supplemental NDA extend the indication for Complera to include adolescent patient population.

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 the 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 virologic failure. Therefore, there is a need for continuous development of new ARTs for treatment of HIV infection. In addition, very few, if any FDC products are available for pediatric HIV patients, particularly for younger age groups. There are many benefits to having FDC products available. Most importantly, FDC products reduce pill-burden and thus increase the likelihood of adherence; adherence is an important factor in achieving HIV viral suppression, especially for adolescents.

Although the fixed dose combination product under review contains three antiretroviral agents, limited discussions are included for emtricitabine and tenofovir as these NRTIs have been approved for use in pediatric patients for several years. Emtricitabine was approved on 28 September 2005 for use in pediatric patients as young as neonates (Gilead's NDA 21-896 for an oral solution); tenofovir was approved on 24 March, 2010 for use in pediatric patients 12 years of age and older (Gilead's NDA 21-356 for tablet formulation). Emtricitabine and tenofovir were also approved on 11 July 2011 for the treatment of HIV-1 infection as an FDC product, Truvada® (Gilead's NDA 21-752). Prescribers are familiar with the adverse reactions associated with the

individual drugs. On the contrary, rilpivirine was approved for use in adolescents in August, 2015, where knowledge of rilpivirine among prescribers may be limited. Therefore, this clinical review focuses on the safety and efficacy of rilpivirine, when used in combination with 2-NRTIs; the efficacy of rilpivirine when used in combination specifically with tenofovir and emtricitabine is also included in this review. Please refer to the individual drug products reviews of tenofovir and emtricitabine for additional safety information.

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

> 2756-1: Conduct a pediatric trial to evaluate the safety and antiviral activity of COMPLERA (emtricitabine/rilpivirine/tenofovir disoproxil fumarate) FDC tablets in HIV infected pediatric subjects 12 to 18 years old. Safety and antiviral activity (efficacy) of emtricitabine/rilpivirine/tenofovir disoproxil fumarate FDC tablets in pediatric subjects should be evaluated for a minimum of 48 weeks

The applicant submitted the sNDA in accordance with FDA guidelines. The sponsor submitted no financial information pertinent to the application as no new clinical trial was conducted to support this sNDA submission.

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

Extensive programs of nonclinical studies with FTC, RPV, and TDF have been previously conducted. In view of the nonclinical safety profiles for each of these compounds, additional nonclinical combination safety studies with FTC, RPV and TDF are not considered necessary to support this application. Therefore, no new nonclinical pharmacology/toxicology data were submitted.

Emtricitabine and tenofovir DF have been marketed since 2003 and 2001, respectively. Please refer to the individual drugs' NDAs for further details.

Please refer to NDA 202022 for full details on the preclinical studies conducted. Of interest for this pediatric submission is the adrenal effect observed in pre-clinical studies across multiple species. One of the primary toxicity findings in nonclinical studies were adrenal effects generally characterized by increased serum progesterone and decreased cortisol levels. These effects are thought to be associated with an inhibition of steroidogenesis at the level of cytochrome P450 21-hydroxylase (CYP21) and 17-hydroxylase. In dogs, findings of premature activation and overstimulation of the ovaries may also be related to inhibition of steroidogenesis (at exposures 8 to 25 times higher than clinical exposures at 25 mg once daily).

5. Clinical Microbiology

Emtricitabine and tenofovir: Refer to the respective USPI and NDAs for details.

Rilpivirine: 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, specifically, 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 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).

6. Clinical Pharmacology/Biopharmaceutics

FDC product

Please refer to Clinical Pharmacology Review for Complera for full details. The bioequivalence of the FDC tablets containing emtricitabine (FTC) 200 mg, rilpivirine (RPV) 25 mg, and tenofovir disoproxil fumarate (TDF) 300 mg (FTC/RPV/TDF), compared to a 200-mg strength capsule of FTC, a 25-mg strength tablet of RPV, and a 300-mg strength tablet of TDF taken concurrently under fed conditions was evaluated by Gilead Sciences. The study demonstrated that the FTC/RPV/TDF FDC is bioequivalent to concurrent administration of the individual components under fed conditions. In addition, based on a relative BA study (fasted condition), Gilead concluded that the FDC tablet provided modestly higher exposures (~ 25% higher) of RPV compared to the individual components administered concurrently under fasted conditions; FTC and TFV exposures were comparable.

Individual drug products:

Emtricitabine and tenofovir: Please refer to the USPI and reviews from the original NDAs for full details on pharmacokinetics and pharmacodynamic information.

Rilpivirine: Please refer to the USPI and the original review for details on the pharmacokinetic profile of rilpivirine. The pharmacodynamic properties of rilpivirine have been explored previously in adult clinical trials. 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 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. The potential QTc prolongation due to hepatic impairment and/or 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.

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 weighing at least 32kg. 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. The approved 25mg rilpivirine tablet was administered. 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 ratio of geometric mean for AUC_{24h} in the range of >0.80 and <1.25 is generally accepted.

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

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)

	Least squares 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: Janssen's 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 (Janssen) 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. 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. Part 2 of the trial was for evaluation of the long-term safety and efficacy of rilpivirine over a 24- and 48- week treatment period. 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.

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
Thirty six adolescent subjects were enrolled. 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).

When the rilpivirine label was revised to restrict the indication to patients with baseline HIV RNA ≤100,000 copies/mL, the adolescent trial was already ongoing. The protocol was then amended to only enroll those with baseline HIV RNA ≤100,000 copies/mL. Overall 36 subjects were enrolled, of whom 8 had baseline HIV RNA >100,000 copies/mL .The median (range) baseline HIV RNA for the 36 subjects 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.

The median baseline plasma HIV-1 RNA for the 28 subjects with baseline ≤100,000 copies/mL 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).

The majority (24) of subjects received rilpivirine in combination with emtricitabine and tenofovir DF. Of these 24 subjects, 20 had baseline HIV RNA $\leq$100,000 copies/mL. Among the 20 subjects, the median baseline plasma HIV-1 RNA and CD4+ cell count were 49,550 (range 2,060 to 92,600 copies/mL) and 437.5 cells/mm^3 (range 123 to 983 cells/mm^3), respectively.

Efficacy Results at Week 48
The primary efficacy endpoint was plasma viral load < 50 copies/mL at Week 48, based on FDA's snapshot algorithm. Rilpivirine, in combination with other ARVs, demonstrated antiviral activity over the 48 week trial period. Similar to the adult Complera indication, the primary efficacy outcome evaluated to support the indication of Complera in pediatric patients is the

subset of subjects whose baseline HIV RNA is ≤100,000 copies/mL and received background regimen containing emtricitabine and tenofovir (*mITT, N=20*). In addition, efficacy analyses were also conducted for all subject enrolled (ITT1, N=36) and for subjects with baseline HIV RNA ≤100,000 copies/mL (ITT2, N=28).

Primary efficacy population (mITT)
At Week 48, among subjects with baseline HIV RNA ≤100,000 copies/mL and who received TDF/FTC as part of their background regimen, 80% (16/20) of the subjects had HIV RNA <50 copies/mL, 15% (3/20) had HIV RNA ≥50 copies/mL, and one subject discontinued therapy prior to Week 48 and before reaching virologic suppression (Table 4). The efficacy outcome at Week 48 in the adult pooled phase 3 trials among subjects with baseline HIV RNA ≤100,000 copies/mL and who received TDF/FTC as part of their background regimen copies/mL was 83%. Table 4 also summarizes the efficacy outcomes for the ITT1 and ITT2 populations. Please refer to the rilpivirine pediatric sNDA review for additional details.

Table 4: Efficacy Outcome at Week 48

Virologic outcome Week 48	**N=20 n(%)**	**N=36 n(%)**	**N=28** n(%)
Population	**mITT**	**ITT1**	**ITT2**
HIV RNA <50 copies/mL	**16(80)**	**26(72)**	**22(79)**
HIV RNA ≥ 50 copies/mL	**4(20)**	**9(25)**	**6(21)**
Data in window not below threshold	3(15)	3(8)	3(11)
Discontinued for lack of efficacy		5(17)	2(7)
Discontinued for other reason while not below threshold	1(5)	1(3)	1(4)
No Virologic Data		**1(3)**	
Discontinued due to AE or Death		1(3)	

mITT: subjects with baseline HIV RNA ≤100,000 copies/mL and received TDF/FTC as background regimen
ITT1: intent to treat population
ITT2: ITT with baseline HIV RNA ≤100,000 copies/mL
Source: Snapshot dataset for C213

Exposure-response
Please refer to the original rilpivirine NDA review and pediatric sNDA review for details. In summary, the inhibitory quotient (IQ) for rilpivirine correlates with efficacy outcome. The 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.

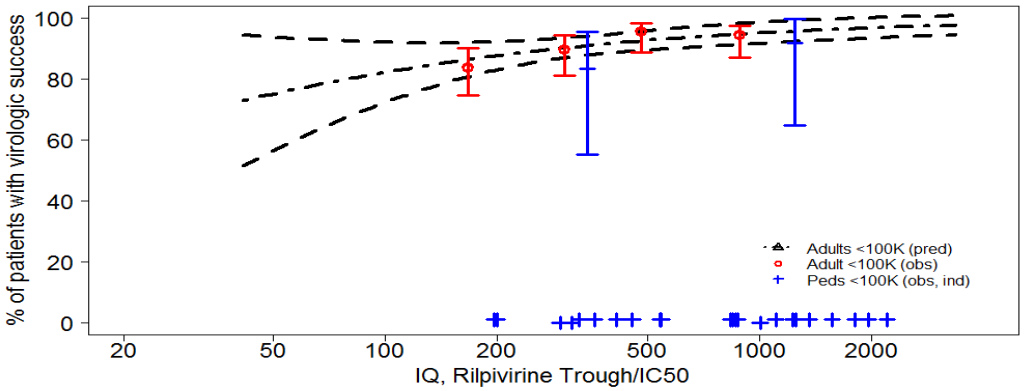
While rilpivirine exposures in adolescents (both AUC and Ctrough) and HIV-1 viral susceptibility were similar to adults, the efficacy outcomes (HIV RNA <50 copies/mL) for the ITT pediatric population were slightly lower in the pediatric age group than in adults (79% vs. 89%). A comparison of the virologic 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. Even after the exclusion of subjects with BLQ, the 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.

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 (Janssen) figures below (for AUC and Ctrough).

Figure 2: Rilpivirine Exposure (AUC) and Virologic Outcome

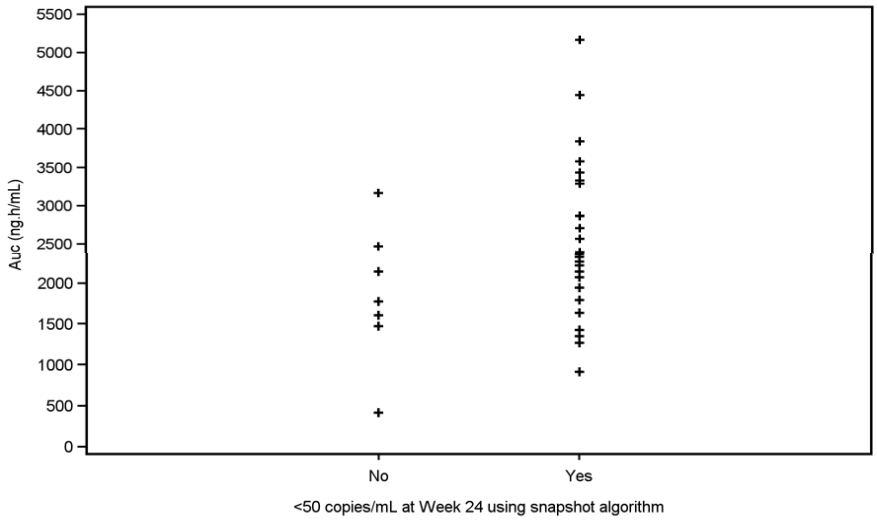
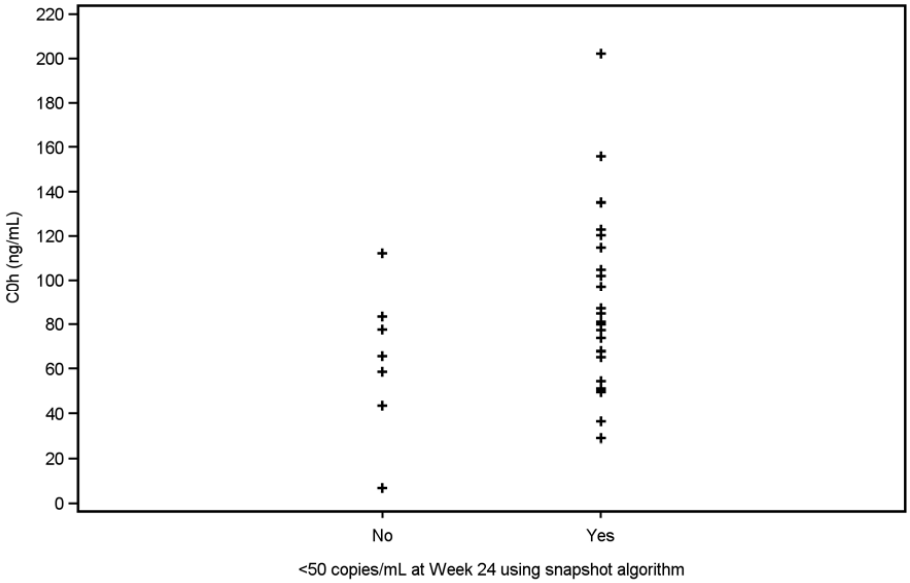


Figure 3: Rilpivirine Exposure (Ctrough) and Virologic Outcome



Efficacy summary and conclusions

The efficacy of rilpivirine 25mg once daily in treatment-naïve pediatric subjects was demonstrated in the single arm C213 trial. At Week 48, the efficacy outcome was best among the mITT subjects whose baseline HIV RNA was ≤100,000 copies/mL and received TDF/FTC as their background regimen. Rilpivirine in combination with ARVs resulted in virologic response in 72% of the ITT1 subjects. The response rate improves to 79% among the ITT2 subjects whose baseline HIV RNA is ≤100,000 copies/mL. Although the response rates in ITT1 and ITT2 are numerically lower than what were observed in the adult population, 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, the intensive PK analyses and the overall efficacy outcome for C213 are consistent with results observed during the adult trials and supported the approval of rilpivirine for adolescent patients.

8. Safety

The data submitted supported the safety and tolerability of rilpivirine when administered in combination with other ARVs. As mentioned in the introduction, no additional discussions on TDF and FTC are included in this review as these NRTs have been approved and used in pediatric patients for many years. Please refer to the USPIs and NDA reviews for the respective drugs for additional details.

The Applicant references the safety data from the 36 pediatric subjects enrolled in C213 and received at least 1 dose of rilpivirine. Although the supportive evidence for the efficacy of Complera relied primarily on subjects whose background ARV regimen included emtricitabine and tenofovir, the safety assessment relied on all enrolled adolescent subjects (n=36). This conservative approach of including all subjects exposed to rilpivirine was taken to maximize on the sample size when evaluating the safety profile of rilpivirine. Rilpivirine, in combination with other ARV drugs was safe and tolerable. 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.

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 agreed 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 agreed 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 AEs) 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 were consistent with the ADRs identified during the adult NDA review for rilpivirine.

Janssen relied on its own adjudication system to identify adverse events as ADR. This adjudication system was also used during the analyses of the adult clinical trial data and labeling. Per Janssen'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

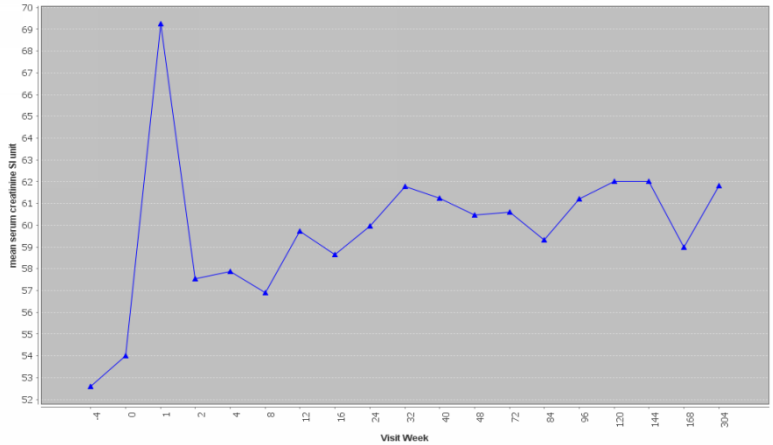
Depression, including suicidal ideations or attempts is known ADRs with use of rilpivirine. These events are described in the USPI under Warnings and Precautions. The events described during the pediatric trial are consistent with the events described during the original NDA review. No new terms were identified. Overall, eight subjects experienced *psychiatric-related* events, seven 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.

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 in adults, 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 rilpivirine sNDA for pediatric indication, 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			49

													8
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. The clinical significance of the increased number of abnormal ACTH stimulation tests observed during treatment with rilpivirine is unclear. 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. This information was included into the USPI for rilpivirine and is included in the Complera label.

Adverse Events with Severe or Life-threatening Intensity
Most AEs were Grade 1 or 2 in severity. Grade 3 or higher adverse events (regardless causality) were reported in 7 subjects (19%).Grade 4 events were reported in 2 subjects: one subject experienced depression, suicide attempt/ideation (all Grade 4) events while another subject experienced depression. None were considered treatment-related while the suicide attempt/ideation was considered serious. Among the Grade 3 events were pancreatitis, neutropenia and malaria. None were considered treatment-related.

Common AEs
Most subjects (97%; 35/36) experienced at least 1 AE. The most common AE (by preferred term, all grades, regardless of causality) with incidence reported in at least 10% of subjects include

headache (22%), depression (19%), somnolence (14%), dizziness (11%) and nausea (11%). 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 signal or significant changes in the frequency of previously described AEs were identified. Overall, the findings in this pediatric clinical trial are consistent with previously described events with use of rilpivirine in adults.

9. Advisory Committee Meeting
Not applicable.

10. Pediatrics
This application is in response to PREA PMR for the adolescent patient population. The pediatric assessment was presented to the PeRC. The PeRC agreed with the Division's proposed plans. Clinical trial in children less than 12 years of age has not yet been initiated. (b) (4) [redacted]. No studies are required in children under 6 years of age for this FDC drug product.

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 HIV infected children weighing at least 35 kg. Sections 6, 8, 12 and 14 have also been updated with pediatric information including safety, trial C213 description, PK and efficacy outcome. These labeling updates have been successfully negotiated with the Sponsor.

13. Recommendation for Postmarketing Risk Evaluation and Management strategies
DAVP and OSE are continuously monitoring post-marketing AEs and reviewing specific events as needed.

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

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