CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

219016Orig1s000

CLINICAL MICROBIOLOGY/VIROLOGY REVIEW(S)

DIVISION OF ANTIVIRAL PRODUCTS (HFD-530)
VIROLOGY REVIEW

NDA#: 202022 S-20 and (b) (4) **SDN:**536 **DATE REVIEWED:** 02/09/2024

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NDA-219016

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011	11/14/2023	11/14/2023	12/1/2023
016	1/5/2024	1/5/2024	1/9/2024
018	2/6/2024	2/6/2024	2/27/2024
019	2/22/2024	2/22/2024	2/27/2024

Related/Supporting Documents: IND67699

Product Name(s)

Proprietary: EDURANT

Non-Proprietary/USAN: rilpivirine

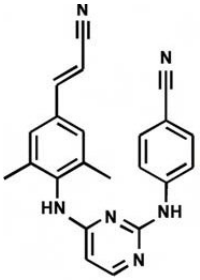
Code Name/Number: TMC278

Chemical Name: 4-[[4-[[4-[(1*E*)-2-cyanoethenyl]-2,6-dimethylphenyl]amino]-2-pyrimidinyl]amino]benzonitrile,

Molecular Weight: 366.42 Daltons

Molecular Formula: $C_{22}H_{18}N_6$

Structural Formula:



Rilpivirine

Dosage Form(s):
Route(s) of Administration: Oral
Indication(s): Treatment of HIV-1 infection in ARV treatment-naive adult patients, (b) (4) (b) (4) co-administered with other antiretroviral (ARV) agents.

These supplements to NDA 202022 (sNDA S-020 and S-022), contain pharmacokinetic (PK), safety, and Week 48 efficacy (antiviral activity) data from the pediatric clinical study TMC278-TiDP38-C213 (C213) and support dosing recommendations for EDURANT (rilpivirine [RPV]; 25 mg tablet) in combination with other antiretroviral (ARV) drugs for the treatment of HIV-1 infection in treatment-naïve pediatric patients weighing at least 25 kg and with HIV-1 RNA ≤100,000 copies/mL at the start of therapy. EDURANT, in combination with other antiretroviral drugs, resulted in suppression of HIV-1 RNA.

NDA 219016 (Original-1), contains PK, safety, and Week 48 efficacy (antiviral activity) data from the pediatric clinical study C213 and supports dosing recommendations for EDURANT PED (RPV; 2.5 mg tablet for oral suspension) in combination with other ARV drugs for the treatment of HIV-1 infection in treatment-naïve pediatric patients at least 2 years of age and weighing at least 14 kg and with HIV-1 RNA ≤100,000 copies/mL at the start of therapy. The review team concluded that the dosing recommendation is only acceptable for pediatric patients at least 2 years of age and weighing at least 14 kg.

The Clinical Virology Review is complete and has been added to the NDA-202022 S-20 and (b) (4) and NDA-219016 Integrated Review and Evaluation. Our recommendation for this application is approval.

Below is a summary of the clinical virology findings:

RESISTANCE ASSESSMENTS OF VIROLOGIC FAILURES
STUDY C213 COHORT 2:
ARV Treatment-naïve, HIV-1-infected Adolescents Aged 6 to <12 Years

Genotypic and Phenotypic Analysis at Screening/Baseline
Plasma-based deep sequencing analysis was planned at screening or baseline for all 18 participants and was successful for 17/18 participants. A whole blood sample was available for eight subjects at screening and retrospective archived resistance testing data were available for all of them. Four of these eight subjects carried the archived NNRTI polymorphism V179I; this substitution was also observed through standard plasma-based resistance testing in each of these subjects. Two out of four subjects with archived V179I had undetectable HIV-1 viral load at Week 48 while one subject had 55 copies/mL at Week 48 and one subject had missing data in window. In addition, one subject had archived NNRTI resistance substitution K101K/Q, and one subject had archived NRTI resistance substitution M184M/I at screening. The subject with pre-existing K101K/Q did not reach undetectable plasma viral load (<50 copies/mL) and withdrew from the study at Week 32. The subject with archived M184I/M at screening had undetectable HIV-1 viral load from Week 12 onwards.

According to the phenotypic analysis at screening and baseline, all 18 subjects were susceptible to rilpivirine and all were susceptible to their NRTI backbone regimen.

Analysis of Virologic Failures

Definition of Virologic Failure

Subjects were to be classified according to the below definitions. Viral load cut-offs of 200 or 400 copies/mL were used instead of 50 copies/mL, as these viral loads are associated with the minimum level of circulating virus needed for successful plasma-based standard resistance testing.

- Virologic failure
  - lack of response: confirmed decrease in plasma viral load of <1.0 $\log_{10}$ at Week 12 from the baseline viral load
  - loss of response: 2 consecutive measurements of ≥400 copies/mL after having been confirmed virologic responder; confirmed responder is defined as 2 consecutive measurements of <50 copies/mL
- Suspected virologic failure: ≥200 copies/mL after confirmed plasma viral load of <50 copies/mL

Post-baseline Genotypic and Phenotypic Data

Six out of 18 (33%) subjects had at least one visit with post-baseline standard genotypic data within the treatment phase; two of these visits occurred within the first 48 weeks and four occurred post-Week 48. Of these six subjects, five subjects had phenotypic data available at the first and last time point with post-baseline genotypic data. Five of these subjects had available viral load data at baseline, two of whom had a baseline viral load ≥100,000 copies/mL. There were two other subjects, Subjects (b) (6) and (b) (6) with >100,000 copies/mL at Baseline who achieved and remained <20 copies/mL out to Week 192 and Week 60, respectively.

In the FDA resistance analysis, six subjects were considered virologic failures (Table 1). Three subjects were <25kg and three were >25 kg. Of the six virologic failures, five had treatment-emergent RPV resistance-associated substitutions [K101E (n=3), E138Q or K (n=3), Y181C (n=1), H221Y (n=2), P225P/L (n=1), M230M/L (n=1)], four of whom also had decreased RPV susceptibility phenotypically. These emergent RPV resistance-associated substitutions in pediatric patients are consistent with those seen in adults failing on an RPV-containing regimen. In addition to RPV resistance, four of the virologic failure subjects also had treatment-emergent resistance substitutions to other drugs in the regimen [M184V (n=3) and M184M/I (n=1) conferring decreased susceptibility to 3TC; M41L (n=1) conferring decreased susceptibility to AZT; and K65R/Y115F (n=1) conferring decreased susceptibility to ABC].

Two subjects (b) (6) and (b) (6) with reported suboptimal adherence and post-baseline genotypic data experienced virologic failure at Week 72 (**Error! Reference source not found.**

Table 1. Resistance Emergence in Virologic Failures, Study C213 (n=6/18, 33%)

PID	Screening/ Baseline Viral Load	Wt/Dose QD	Failure Timepoint/HIV-1 RNA copies/mL	Emergent Genotypic RAS	Fold Change at Failure
(b) (6)	55400/57800	<25 kg/25 mg	WK48/703	K101K/E E138Q V179V/I M184V P225P/L	**RPV 4.1** AZT 0.7 **3TC 109**
	22600/32500	<25 kg/25 mg	WK132/15200	none	RPV 0.83 AZT 0.68 3TC 0.96
	85300/121000	>25 kg/25 mg	WK120/303	M41L E138K M184V H221Y	**RPV 7.6** AZT 1.5 **3TC 145**
	56600/33900	>25 kg/25 mg	WK72/1710	V90V/I E138E/K/A/G M184V M230M/L	**RPV 14** AZT 1.4 **3TC 145**
	52700/133000	<25 kg/25 mg	WK72/11800	K101K/E E138K/E/Q H221H/Y	RPV 2 TDF 0.8 3TC 1.3
	-/34500	>25 kg/25 mg	WK24/1150 WK32/2690	K65R K101E Y115F Y181I M184M/I	**RPV 41, 115** **ABC** 2.6**, 8.4** **3TC 141**

[a] Baseline HIV-1 RNA>100,000 copies/mL
[b] Suboptimal adherence (>95% pill count)
Bolded = decreased susceptibility
PID, participant identification number; RAS, resistance-associated substitutions; QD, once daily

The available adherence information together with population pharmacokinetic (popPK) parameters for each of the 6 patients requested are summarized in **Error! Reference source not found.**.

Table 2. Adherence and PK for C213 Virologic Failures

Participant ID	RPV Pill count at Week 48 (%)	RPV Pill count using all data (%)	Adherence Questionnaires Summary	RPV AUC_{24h} (ng.h/mL)	RPV C_{trough} (ng/mL)
(b) (6)	96.4	96.9	RPV: No doses missed	2667	94.0
	94.9	98.1	RPV: No doses missed	4704	161
	93.2	98.8	RPV: 1 dose missed at Week 12, Combivir: 6 doses missed at Week 12	2567	88.8
	98.8	89.6	RPV: No doses missed	2318	82.5
	79.9	88.4	RPV: No doses missed	4749	162
	99.6	99.6	RPV: No doses missed, ABC/3TC: 1.5 doses missed at Week 24	4394	150

Source: Listings lsiadh01 and lsiadh02, PopPK report - Appendix 20 (EDMS-RIM-928244)

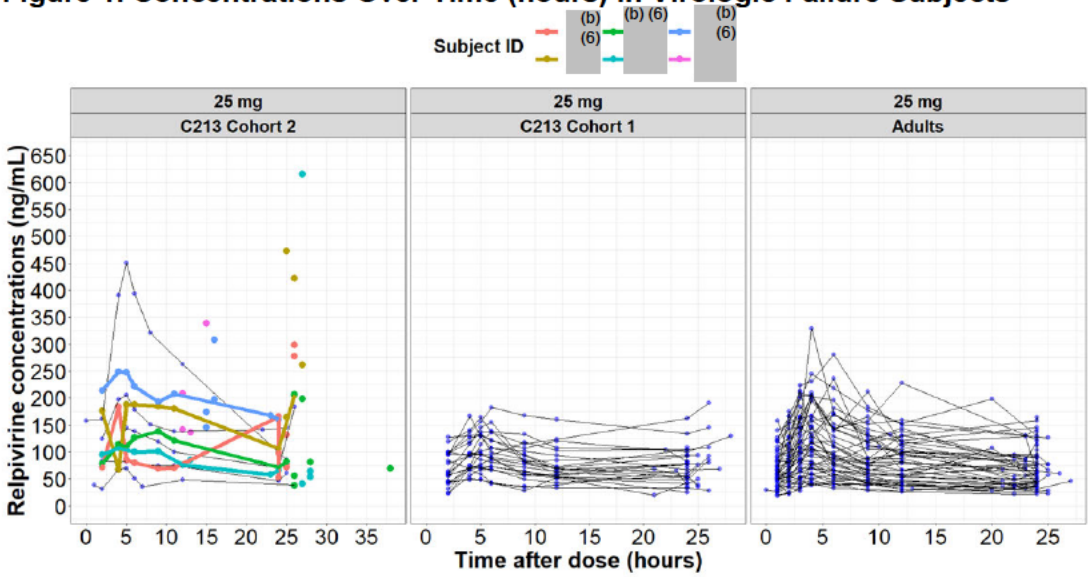
Pharmacokinetics (PK) of Virologic Failures

In study C213, the six patients who were virologic failures had exposures comparable to adults at the approved dose. The concentrations over time in the six virologic failure subjects were higher or comparable to the adult cohort (Table 2 and Figure 1).

Concentrations versus time graphs, after the inclusion of the Sparse PK samples (dots not linked with a solid line) from the six subjects with VF in C213 cohort 2 are shown in Figure 1.

The PK data cannot exclude virologic failure due to lack of adherence. For the C213 cohort 2, the rich PK sampling was performed at Week 2 and 3, as indicated in the protocol (Week 2). In the PK data, sparse PK was collected between 4 to 48 for most subject with virologic failure.

Figure 1. Concentrations Over Time (hours) in Virologic Failure Subjects



Bold solid lines are the rich PK profile per day (Week 2 to 3) in subjects with VF.
Thin solid lines are the rich PK profile per day for all other subjects.

STUDY C213 COHORT 1:
ARV Treatment-Naïve, HIV-1-infected Adolescents Aged ≥12 to <18 Years

Data on Cohort 1 were previously submitted in NDA202022 SDN217 (sequence 106). The applicant agreed to add resistance information on Cohort 2 (reviewed above) in Section 12.4 of the USPI but proposed to also include a summary of adolescent Cohort 1 resistance data. At the time of the C213 Cohort 1 analysis reviewed in 2015, resistance data were not included in the USPI because no new resistance substitutions were identified and the adult resistance data were deemed adequate to inform the prescriber. However, the Division is now including resistance data from Cohort 2 in Section 12.4 of USPI, because of the high rate of virologic failure and resistance emergence. Thus, Cohort 1 resistance information will also be included in Section 12.4 of the USPI for completeness.

The Cohort 1 resistance information is summarized below:

For subjects in the baseline viral load category ≤100,000 copies/mL (N=28), at Week 48, 5/28 (18%) subjects were considered virologic failures. For subjects in the baseline viral load category >100,000 copies/mL (N=8), at Week 48, 3/8 (38%) subjects were considered virologic failures.

Baseline Resistance Analysis
For all 36 subjects, genotypic data were available at baseline and/or screening. Phenotypic data were available for 34/36 (94%) subjects at baseline. None of the subjects carried RPV resistance-associated substitutions or NRTI resistance-associated substitutions at baseline. While 32/34 (94%) subjects were susceptible to RPV according to phenotypic analysis at baseline, 2/34 (6%) subjects had a baseline RPV fold change value ≥2.5-fold. One of these 2 subjects experienced virologic failure. The majority of subjects (64%) were infected with HIV-1 clade C.

Analysis of Virologic Failures
Eight of 36 (22%) subjects experienced virologic failure in the first 48 weeks (four subjects 'never suppressed' and four subjects rebounded); two subjects discontinued due to other reasons than virologic failure (1 due to an AE and 1 due to other reasons). Four additional subjects experienced virologic failure (rebound) after their Week 48 visit.

Genotypic Analysis
Of the eight subjects with virologic failure and post-baseline genotypic data, five (63%) had at least one treatment-emergent RPV resistance-associated substitution. The RPV resistance-associated substitutions detected in these five subjects were E138K (n=4), K101E (n=2), M230L (n=2), E138G (n=1), E138R (n=1), Y181I (n=1), and H221Y (n=1). In four of these five with treatment-emergent RPV resistance-associated substitutions, at least one treatment-emergent NRTI resistance-associated substitution was also observed at failure. These substitutions were M184V (n=3), K65R (n=1), and Y115F (n=1). The two subjects who discontinued due to other reasons than virologic failure did not have treatment-emergent NNRTI or NRTI resistance-

associated substitutions. Finally, none of the four subjects with virologic failure after their Week 48 visit had treatment-emergent NNRTI or NRTI resistance-associated substitutions.

Phenotypic Analysis

For three of five (60%) subjects experiencing virologic failure with treatment-emergent RPV resistance-associated substitutions, the RPV fold change value was >2.5-fold at the last post-baseline visit. Cross-resistance between RPV and other NNRTIs was shown for EFV, ETR, and NVP in these three subjects. The subjects with treatment-emergent NRTI resistance-associated substitutions showed phenotypic resistance to 3TC and FTC.

CONCLUSION

A high rate of virologic failure and resistance emergence to RPV and other drugs in the regimen was seen in Study C213. Virologic failure in this population is most likely associated with nonadherence.

In Study TMC278-C213 Cohort 1, a single-arm, open-label phase 2 trial in antiretroviral treatment-naïve HIV-1-infected pediatric subjects ≥12 to less than 18 years, RPV resistance-associated substitutions were observed in 63% (5/8) of subjects with virologic failure and post-baseline genotypic data at 48 weeks. The RPV resistance-associated substitutions detected in these five subjects were E138K (n=4), K101E (n=2), M230L (n=2), E138G (n=1), E138R (n=1), Y181I (n=1), and H221Y (n=1) consistent with substitutions seen in adults failing on a RPV-containing regimen. Four of the five virologic failure subjects with RPV substitutions had ≥2.5-fold decrease in susceptibility to RPV. In addition, four of the five virologic failure subjects with RPV resistance substitutions also had at least one treatment-emergent resistance substitution to nucleos(t)ide reverse transcriptase inhibitors.

In study TMC278-C213 Cohort 2, a single-arm, open-label phase 2 study in antiretroviral treatment-naïve HIV-1-infected pediatric subjects ≥6 to less than 12 years of age, six subjects experienced virologic failure on RPV-containing regimens (6/18, 33%) (three subjects failed ≤48 weeks and three subjects failed after 48 weeks). Additionally, three of the virologic failures were <25 kg and three were >25 kg in weight. Of the six virologic failures, five (83%) had treatment-emergent RPV resistance-associated substitutions [K101E (n=3), E138Q or K (n=3), Y181C (n=1), H221Y (n=2), P225P/L (n=1), M230M/L (n=1)], with four also showing reduced RPV susceptibility phenotypically (2- to 115-fold). The emergent RPV resistance-associated substitutions in pediatric patients are consistent with those seen in adults failing on a RPV-containing regimen.

In addition to RPV resistance emergence, four of the virologic failures also had treatment-emergent resistance substitutions to other drugs in their antiretroviral regimen [M184V (n=3) and M184M/I (n=1) conferring decreased susceptibility to lamivudine; K65R/Y115F (n=1) conferring decreased susceptibility to abacavir, and M41L (n=1), a zidovudine resistance-associated substitution].

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Section 12.4

Treatment--Naïve HIV-1-Infected Pediatric Subjects
In trial TMC278-C213 Cohort 1, a single-arm, open-label Phase 2 trial in antiretroviral treatment-naïve HIV-1-infected pediatric subjects ≥12 to less than 18 years *[see Clinical Studies (14.3)]*, rilpivirine resistance-associated substitutions were observed in 62.5% (5/8) of subjects with virologic failure and post-baseline genotypic data at 48 weeks with 4 of 5 having ≥2.5-fold decrease in susceptibility to rilpivirine. In addition, 4 of the 5 subjects with rilpivirine resistance substitutions also had at least 1 treatment-emergent resistance substitution to nucleos(t)ide reverse transcriptase inhibitors.

In trial TMC278-C213 Cohort 2, a single-arm, open-label Phase 2 trial in antiretroviral treatment-naïve HIV-1-infected pediatric subjects 6 to less than 12 years of age *[see Clinical Studies (14.4)]*, 83% (5/6) of subjects with virologic failure (3 subjects failed ≤48 weeks and 3 subjects failed after 48 weeks) had treatment-emergent rilpivirine resistance-associated substitutions with 4 showing reduced rilpivirine susceptibility. Additionally, 4 of the virologic failures also had treatment-emergent resistance substitutions to nucleos(t)ide reverse transcriptase inhibitors.

The emergent rilpivirine resistance-associated substitutions in pediatric patients are consistent with those seen in adults failing on a rilpivirine-containing regimen (see Table 13).

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