SYNOPSIS

Study Title: Open-Label Study with Rilpivirine in Treatment-naïve Indian Subjects With HIV-1 Infection to Determine Safety and Efficacy

Study Number: TMC278HTX3001

Study Phase: 3b

Name of Study Intervention: TMC278 (rilpivirine)

Trade Name: EDURANT®

Name of Sponsor/Company: Janssen-Cilag Limited

Status:	Approved
Date:	17 May 2022
Prepared by:	Janssen-Cilag Limited

NCT No.: NCT03563742

Clinical Registry No: CR108402

Study Name: RISE

Number of Study Centers and Countries: This study was conducted at 5 centers that enrolled participants in India.

Publications (if any): None.

Study Period: 24 September 2018 to 28 June 2021

Rationale: The 2 pivotal Phase 3 studies (ECHO and THRIVE) established the efficacy and safety of rilpivirine (RPV) for the treatment of human immunodeficiency virus type 1 (HIV-1) infection. These studies were used as the basis for EUDRANT's' approvals for the treatment of HIV-1 infection in treatment-naïve adult patients by the United States (US) Food and Drug Administration (FDA), European Medicines Agency (EMA), and in other countries worldwide. However, the ECHO and THRIVE studies enrolled few Indian participants and local clinical data were required to obtain approval for oral RPV from the Indian regulatory agency. The current study therefore aimed to evaluate safety, tolerability and efficacy of RPV in combination with other antiretroviral (ARV) agents in Indian adult HIV-1 infected participants who were treatment-naïve to ARV treatment and had plasma HIV-1 RNA <100,000 copies/mL.

Objectives and Endpoints:

Objectives	Endpoints
Primary	
• To evaluate the efficacy of RPV-based regimen in HIV-1 infected, ARV treatment-naïve participants, as determined by the proportion of virologic responders defined as having HIV-1 RNA <400 copies/mL at Week 24 (FDA-defined snapshot analysis)	• Proportion of virologic responders defined as having HIV-1 RNA <400 copies/mL at Week 24 (FDA-defined snapshot analysis)
Secondary	
• To evaluate the efficacy of RPV-based regimen in HIV-1 infected, ARV treatment-naïve adult participants, as determined by the proportion of virologic responders defined as having HIV-1 RNA <50 copies/mL at Week 24 (FDA-defined snapshot analysis)	• Proportion of virologic responders defined as having HIV-1 RNA <50 copies/mL at Week 24 (FDA-defined snapshot analysis)
• To evaluate the efficacy of RPV-based regimen in HIV-1 infected, ARV treatment-naïve adult participants, as determined by the proportion of virologic responders defined as having HIV-1 RNA <50, and <400 copies/mL at Week 48 (FDA-defined snapshot analysis)	• Proportion of virologic responders defined as having HIV-1 RNA <50, and <400 copies/mL at Week 48 (FDA-defined snapshot analysis)
• To evaluate the immunologic response (CD4+ T-cell count) through Week 48	• CD4+ T-cell count at Weeks 24 and 48 • Change from baseline in CD4+ T-cell count at Weeks 24 and 48
• To evaluate the incidence of Grade 3 and 4 AEs, SAEs, laboratory abnormalities and premature discontinuations due to AEs through Week 48	• Proportion of participants experiencing Grade 3 and 4 AEs, SAEs, and premature discontinuations due to AEs through Weeks 24 and 48 • Proportion of participants with laboratory abnormalities • Change from baseline in laboratory parameters
• To assess the development of viral resistance through Week 48	• Viral resistance through Weeks 24 and 48
• To examine adherence to treatment over the 48 weeks of study intervention using tablet counts	• Percentage of adherent (95% adherence) participants based on tablet count at each time point up to Weeks 24 and 48

Abbreviations: AE=adverse event, ARV=antiretroviral, CD4+= cluster of differentiation 4 positive, FDA=Food and Drug Administration, HIV-1=human immunodeficiency virus type 1, RNA=ribonucleic acid, RPV=rilpivirine, SAE=serious adverse event.

Methodology: This was a single-arm, multicenter, phase 3b, open-label, interventional study conducted in India that evaluated the efficacy, safety, and tolerability of oral RPV in adult participants infected with

HIV-1, who were naïve to ARV treatment and had a baseline viral load <100,000 copies/mL. The planned sample size was approximately 100 participants.

The study was conducted in 3 phases: a screening period of a maximum of 6 weeks, a 48-week open-label treatment phase, and a post-treatment follow-up visit (30 to 35 days after last dose of study intervention). The total duration of individual participation was approximately 58 weeks.

During the open-label treatment phase, all participants received ARV treatment of RPV 25 mg once daily, and background therapy of tenofovir disoproxil fumarate (TDF)/lamivudine (3TC) as the nucleo(t)side reverse transcriptase inhibitor (N[t]RTI) regimen administered as 1 tablet once daily containing 300 mg TDF and 300 mg 3TC.

For the participants who had plasma HIV-1 RNA levels of ≥50 copies/mL at any visit after 24 weeks of study treatment, blood samples were collected and retested at 4 to 8 weeks intervals until the plasma HIV-1 RNA levels were <50 copies/mL, or virologic failure (VF) was confirmed (ie, 2 consecutive plasma HIV-1 RNA levels of ≥400 copies/mL after 24 weeks of study treatment).

For participants with confirmed VF (2 consecutive plasma HIV-1 RNA levels ≥400 copies/mL), resistance testing was performed on the second confirmatory plasma sample with HIV-1 RNA levels ≥400 copies/mL, and treatment with RPV was discontinued for these participants. The participants were then treated for first-line non-nucleoside reverse transcriptase inhibitor (NNRTI) treatment failure per local guideline recommendations.

Key efficacy assessments during the study included HIV-1 RNA viral load levels and CD4+ T-cell count. Key safety assessments included monitoring of AEs, physical examinations, measurement of body weight, vital sign measurements, clinical laboratory tests and pregnancy testing.

Participants who discontinued study intervention before Week 48 had a treatment discontinuation visit within 72 hours of the last dose of study intervention, and a post-treatment follow-up visit performed 30 to 35 days after the last dose of study intervention. The participants who discontinued study intervention during the treatment phase for reasons other than treatment failure received investigator-selected treatment according to local guideline recommendations.

COVID-19 Impact: The sponsor proposed changes to the protocol-specific procedures in case a site visit was not possible under the restrictions and limitations due to the COVID-19 pandemic. Discontinuations of study intervention and withdrawals from the study due to COVID-19-related reasons were documented with the prefix "COVID-19-related" in the CRF. Missed assessments/visits and laboratory assessments (efficacy) were recorded as protocol deviations.

Number of Participants (Planned and analyzed): Planned: Approximately 100 participants.

Analyzed: 56 participants ie, those enrolled and who received at least one dose of study intervention (intent-to-treat [ITT]). The study was prematurely terminated due to slow recruitment.

Diagnosis and Main Criteria for Inclusion and Exclusion: The target population consisted of treatment-naïve adult men or women with documented HIV-1 infection. At the screening visit (performed within 6 weeks before RPV administration), eligible participants who were naive to ARV therapy were to have plasma HIV-1 RNA <100,000 copies/mL and CD4+ T-cell count >200/mm^3.

Participants with a history of any primary N(t)RTI or NNRTI mutation as defined by the guidelines of current International AIDS Society-USA (IAS-USA) 2017, clinical or laboratory evidence of hepatic insufficiency, diagnosed with acute viral hepatitis at screening or before baseline, infected with *Mycobacterium tuberculosis* requiring rifampicin-based treatment during the study, Grade 3 or 4 laboratory

abnormality as defined by the Division of Acquired Immunodeficiency Syndrome (DAIDS) or any currently active AIDS defining illness were excluded from the study.

Duration of Study Intervention: RPV (25 mg) tablets once daily and TDF/3TC (300 mg/300 mg) tablets once daily orally starting Day 1, for a total of 48 weeks. The study intervention was to be taken with a meal to improve absorption.

Statistical Methods

Sample Size Justification: This was an open-label study to evaluate safety, tolerability and efficacy of RPV in the Indian patient population. Based on the 2 pivotal clinical trials (ECHO, THRIVE), the expected virologic response (defined as plasma HIV-1 RNA <400 copies/mL) was in the range of 89% to 92% at Week 24. A sample size of 100 participants would provide the exact 95% confidence interval (CI, Clopper-Pearson) of (81.2%, 94.4%) for a response rate of 89%, and (84.8%, 96.5%) for a response rate of 92%. The half-width of the exact corresponding 2-sided 95% CI was 5.9% and 6.6%, respectively. Additionally, with a sample size of 100 participants, the probability to observe an AE with an incidence of 1%, 2%, 3%, and 4% was 63%, 86%, and 95%, respectively. Based on these estimations, a sample size of 100 participants was considered sufficient for this study.

Due to the limited availability of eligible participants and the impact of the COVID-19 pandemic, the study was prematurely terminated. The total sample size was reduced to 56, with a potential sample size of 29 to 56 participants at Week 24 with available data. With a sample size of 56 participants, the estimated virologic response precision decreased, for virologic response rates of 89% and 92%, the half-width of the exact corresponding 2-sided 95% CI increased to 7.7% and 9.0%, respectively, less than 10% across the range of expected outcomes, which was the desired precision.

Primary Efficacy Analysis: The primary efficacy analysis at Week 24 was conducted on the ITT population. The FDA-defined snapshot algorithm was used to define treatment success or failure for individual participants.

The proportion of participants with HIV-1 RNA<400 copies/mL at Week 24 was calculated along with the 95% CIs. The Clopper-Pearson method was used for calculating the 95% CIs of the proportions. The <400 copies/mL threshold was used in the study as it allowed for the reporting of transient low-level viremia per the consolidated WHO guidelines applicable at the time the Protocol was approved.

Secondary Efficacy Analysis:

The proportion of participants with HIV-1 RNA <50 copies/mL at Week 24 and Week 48 and <400 copies/mL at Week 48 as defined by the FDA snapshot analysis was analyzed using the same method as for the primary efficacy endpoint.

Actual values and changes from baseline values in CD4+ cell count at each analysis time point were summarized using descriptive statistics (n, mean [SE], median, min, and max). For the change from baseline values in CD4+ cell count, the observed method was used.

Safety: The incidence of Grade 3 and 4 AEs, SAEs, and premature discontinuations due to AEs through Weeks 24 and 48 was summarized descriptively. Descriptive statistics were calculated for each laboratory analyte at baseline and changes from baseline at each scheduled time point. HIV-related events or outcomes were recorded per the classification list of DAIDS Grading Table. The medical assessment of the safety data was performed according to a pre-specified algorithm and led to the final list of adverse drug reactions (ADRs).

Summary of events and incidence tabulations for individual adverse events were provided for adverse events of interest (AEoI) and for ADRs. AIDS defining illnesses based on World Health Organization

(WHO) clinical staging were tabulated. AE listings were provided for participants who had SAEs, AEs leading to discontinuation of study intervention, Grade 3 or 4 AE, or who had each AEoI category.

SUMMARY OF RESULTS AND CONCLUSIONS:

Demographic and Other Baseline Characteristics:

The study was terminated by the sponsor due to high screen failure (SF) rate (40%), and recruitment challenges following the COVID-19 pandemic. The availability of treatment-naïve participants especially those with viral load <100,000 copies/mL was low. In addition, recruitment was extended by almost 1.5 years, and only 50% of target recruitment was reached over the extended recruitment period. The decision was therefore taken to stop recruitment and terminate the study.

A total of 56 participants were enrolled across 5 centers in India (Asia). Of the 56 enrolled participants, 36 (64.3%) participants completed the study, and 20 (35.7%) participants were discontinued. The most common reasons for discontinuations were study termination by the sponsor (5 [25.0%)] participants) and withdrawal from the study (4 [20.0%] participants).

At time of study termination, 20 participants who were still on study drug were switched to the post trial access program (TMC278HTX3003). These 20 participants were listed as "Discontinued" in the analysis.

Overall, 1 (1.8%) participant with VF at Week 24 discontinued due to 'other' reasons and had HIV-1 RNA ≥400 copies/mL at the last available measurement.

None of the participant discontinuations were due to lack of efficacy or due to reaching the virologic endpoint.

The mean (SD) age of the study participants was 38 (10.446) years, and the majority of the participants (82.1% [n=46]) were aged between 26-50 years. The mean (SD) body mass index (BMI) of the population was 24.48 (5.213) kg/m^2. Half of the participants (50% [n=28]) had normal BMI, and 28.6% (n=16) were overweight. Females constituted 66.1% (n=37) of the study population.

At baseline, the Log_{10} Mean (SD) for HIV viral load was 3.90 (1.024) and the mean (SD) CD4 +T-cell count was 503.55 (239.081) cells/mm^3. The majority of the participants (87.5%) reported a HIV viral load of <100,000 copies/mL and 96.4% of the participants had ≥200 cells/mm^3 CD4+T-cells, at baseline. The mean (SD) time since diagnosis of HIV infection to study enrolment was 20.21 (36.588) months.

Exposure: A total of 56 participants included in the ITT analysis set received 25 mg RPV tablets once daily along with background therapy of TDF/3TC once daily.

Efficacy Results:

- Primary Analysis (based on the FDA-defined snapshot algorithm):
  - At Week 24, 75% (n=42) of the participants achieved virologic success at a threshold of HIV-1 RNA <400 copies/mL, whereas VF (HIV-1 RNA ≥400 copies/mL) was reported for 3.6% (n=2) of the participants. Overall, 21.4% (n=12) participants reported no viral load data in the week window.
- Secondary Analysis (based on the FDA-defined snapshot algorithm):
  - At Week 24, 67.9% (n=38) of the participants achieved virologic success at a threshold of HIV-1 RNA <50 copies/mL, whereas VF (HIV-1 RNA ≥50 copies/mL) was reported for 16.1% (n=9) of the participants. Overall, 16.1% (n=9) participants reported no viral load data in the week window.
  - At Week 48, 62.5% (n=35) of participants achieved virologic success at a threshold of HIV-1 RNA <400 copies/mL, whereas VF (HIV-1 RNA ≥400 copies/mL) was reported for 3.6% (n=2)

of participants. Overall, 33.9% (n=19) participants reported no viral load data in the week window.

– At Week 48, 62.5% (n=35) of participants achieved virologic success at a threshold of HIV-1 RNA <50 copies/mL, whereas VF (HIV-1 RNA ≥50 copies/mL) was reported for 12.5% (n=7) of participants. Overall, 25.0% (n=14) participants reported no viral load data in the week window.

- In terms of CD4+ T-cell levels, the mean (SE) change from baseline (observed) was 125.97 (24.494) cells/mm^3 at Week 24 and 149.91 (24.888) cells/mm^3 at Week 48, indicating an increase in CD4+ T-cell count through Week 48.
- The analysis for CD4+ T-cell count at Weeks 24 and 48 was not available at the time of this report.
- The analysis for viral resistance through Weeks 24 and 48 and percentage of adherent (95% adherence) participants based on tablet count at each time point up to Weeks 24 and 48, were not performed at the time of this report.

Safety Results:

- Overall, 41 (73.2%) participants experienced at least 1 treatment-emergent adverse events (TEAE). Of these, 8 (14.3%) participants reported AEs related to the study intervention. None of the related AEs were Grade 3 or Grade 4 in severity.
- No Grade 4 events were reported in the study. A total of 9 (16.1%) participants experienced Grade 3 AEs which were assessed to be unrelated to the study intervention. The most frequently (≥2% of participants) reported Grade 3 AEs, by PT were decreased levels of blood bicarbonate, decreased creatinine renal clearance and anemia, (2 [3.6%] participants each).
- A total of 13 participants experienced AEoI of mild, moderate and severe intensity. Except for an occurrence of Grade 1 headache in 2 participants (PPD and PPD and Grade 1 head discomfort (verbatim: heaviness of head) in 1 participant (PPD that were considered possibly related to study intervention by the investigator, all the other AEoI were considered unrelated to the study intervention.
- Overall, 2 (3.6%) participants reported SAEs of Grade 3 acute coronary syndrome and Grade 2 urinary tract infection. None of the SAEs were considered related to the study intervention.
- A non-related Grade 2 (moderate) AE (extrapulmonary tuberculosis) was reported by 1 (1.8%) participant, which resulted in the study intervention being permanently stopped.
- No deaths were reported during the conduct of the study.
- No major change from baseline was observed for the laboratory parameters and vital signs, through to Week 48.

Conclusions:

- In this phase 3, single-arm, multicenter, phase 3b, open-label, local interventional study in India, the efficacy and safety of RPV was evaluated in a total of 56 HIV-1 infected participants. Of the 56 enrolled participants, 36 (64.3%) completed the study (a subject was considered to have completed the study if he/she had completed 48 weeks of treatment with study drug and assessments at Week 48 of the open label treatment phase was performed) and 20 (35.7%) participants were discontinued. The most common reasons for discontinuations were study termination, by the sponsor (5 [25.0%] participants), and withdrawal from the study (4 [20.0%] participants). At time of study termination, 20 participants who were still on study drug were switched to the post trial access program (TMC278HTX3003). These 20 participants were listed as “Discontinued” in the analysis.

- The study was terminated by sponsor due to low recruitment rates, high rate of screen failures and significant challenges in recruitment due to the COVID-19 pandemic.
- Based on the FDA snapshot algorithm and using the HIV-1 RNA <400 copies/mL threshold, 75% and 62.5% of the participants achieved virologic success at Week 24 and Week 48, respectively. Using the HIV-1 RNA <50 copies/mL threshold, 67.9% and 62.5% of the participants achieved virologic success at Week 24 and Week 48, respectively.
- Based on the FDA snapshot algorithm and using the HIV-1 RNA ≥400 copies/mL threshold, VF (HIV-1 RNA ≥400 copies/mL) was reported for 3.6% and 3.6% of participants at Week 24 and Week 48, respectively. Using the HIV-1 RNA ≥50 copies/mL threshold, confirmed VF (HIV-1 RNA ≥50 copies/mL) was reported for 16.1% and 12.5% of participants at Week 24 and Week 48, respectively.
- At Week 24, for 400 copies/mL threshold, overall, 12 (21.4%) participants reported no viral load data in week window and for 50 copies/mL threshold, overall, 9 (16.1%) participants reported no viral load data in week window.
- At Week 48, for 400 copies/mL threshold, overall, 19 (33.9%) participants reported no viral load data in week window and for 50 copies/ml threshold, overall, 14 (25.0%) participants reported no viral load data in week window.
- In terms of CD4+ T-cell levels, incremental improvements were observed at each study time point: the mean (SE) increase from baseline was 125.97 (24.494) cells/mm^3 at Week 24, and 149.91 (24.888) cells/mm^3 at Week 48.
- A total of 41 (73.2%) participants experienced at least 1 TEAE, of whom 8 (14.3%) reported AEs that were related to the study intervention. None of the related AEs were Grade 3 or Grade 4 severity.
- No Grade 4 AEs or deaths were reported during the study. Grade 3 AEs were reported by 9 (16.1%) participants all of which were assessed as unrelated to the study intervention. The most frequently (≥2% of participants) reported Grade 3 AEs, by PT were decreased levels of blood bicarbonate, decreased creatinine renal clearance and anemia, (2 [3.6%] participants each).
- Overall, 2 (3.6%) participants reported SAEs of Grade 3 acute coronary syndrome and Grade 2 urinary tract infection, which were assessed as unrelated to the study intervention.
- There were no reports of related AEs leading to discontinuations.
- Overall, the study intervention was well tolerated, and no new safety findings were observed during the conduct of this study.

Disclaimer

Information in this posting shall not be considered to be a claim for any product, whether marketed or under development. In case of a marketed product, some of the information in this posting may differ from, or not be included in, the approved labeling for the product. Please refer to the full prescribing information for indications and proper use of the product.