## SYNOPSIS

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|---|---|
| Name of Sponsor/Company | Janssen Research & Development* |
| Name of Finished Product | INTELENCE |
| Name of Active Ingredient(s) | TMC125 (etravirine) |

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**Status:** Approved

**Date:** 6 June 2014

**Prepared by:** Janssen Infectious Diseases - Diagnostics BVBA

**Protocol No.:** TMC125IFD3002

**Title of Study:** An open-label study to evaluate the safety, tolerability and pharmacokinetics of etravirine (ETR) in combination with other antiretrovirals (ARVs) in antiretroviral treatment experienced HIV-1 infected subjects.

**Study Name:** VIOLIN (Week 48) Final Analysis

**EudraCT Number:** 2010-023532-16

**NCT No.:** NCT01422330

**Clinical Registry No.:** CR017860

**Coordinating Investigator:** E. Arathoon, Oficina Privada, 1a Avenida 11-19 Zona 1, Ciudad de Guatemala, Guatemala

**Study Center(s):** Argentina, France, Guatemala, Mexico, Peru, Puerto Rico, Romania, Russian Federation, South Africa, United States

**Publication (Reference):** None

**Study Period:** 26 August 2011 (FPI) - 11 November 2013 (LPO); Database lock: 13 December 2013

**Phase of Development:** 4

**Objectives:**

The primary objective of the main study was to evaluate the safety, tolerability and pharmacokinetics of an ETR-containing regimen without darunavir/ritonavir (DRV/rtv) over 48 weeks. The secondary objectives of the main study were to evaluate the maintenance or achievement of virologic suppression over 48 weeks, immunologic changes over 48 weeks, and changes in the genotype and in phenotypic susceptibility to ETR, to determine the relationship between ETR pharmacokinetics and safety, and to assess the impact of cytochrome P450 (CYP) 2C9 and CYP2C19 genotypes on ETR pharmacokinetics. No formal hypothesis was tested. The objective of the substudy was to obtain full pharmacokinetic profiles of ETR at steady-state when given together with ARVs other than DRV/rtv in ARV treatment-experienced human immunodeficiency virus type 1 (HIV-1) infected subjects. The plasma concentrations of lopinavir (LPV), atazanavir (ATV) and rtv in the optimized background regimen (OBR) were also analyzed.

**Methodology:**

This was an open-label, single arm, multicenter Phase 4 study.

The main study consisted of a screening period of maximum 6 weeks, a baseline visit and a 48-week treatment period. After the end of the treatment period, subjects with ongoing adverse events (AEs) were followed for an additional 4 weeks.

At least 200 ARV treatment-experienced HIV-1 infected subjects aged 18 years or older were planned to be enrolled in this study.

Subjects received ETR 200 mg twice daily (bid) in combination with an investigator-selected background regimen. Etravirine needed to be active based on resistance testing for subjects with a screening viral load (VL) ≥500 HIV-1 ribonucleic acid (RNA) copies/mL, or based on historical ARV resistance testing or ARV treatment history for subjects entering the study with a plasma VL <50 HIV-1 RNA copies/mL. The background regimen had to consist of at least 1 active ARV resulting in a treatment regimen with at least 2 active ARVs. Exceptions to this were: (1) if raltegravir (RAL) or ATV/rtv were part of the background regimen, the number of active ARVs in this background regimen had to be at least 2; (2) low-dose ritonavir was not to be counted as an active ARV. DRV/rtv was not allowed in the background regimen to allow evaluation of the safety and pharmacokinetics of ETR in combination with ARVs other than DRV/rtv. Furthermore, a background regimen consisting of nucleoside reverse transcripate inhibitors (NRTIs) only was not allowed.

The background regimen could not be modified until the end of the treatment period except for: switches within the same ARV class were allowed for well documented tolerability/toxicity reasons, and provided that the subject's virus showed sensitivity to the alternative ARV.

An interim safety analysis was performed once all subjects had been treated for 24 weeks or had discontinued earlier (cut-off 6 May 2013) and was described in a separate abbreviated report in order to comply with a postmarketing requirement of the US Food and Drug Administration (FDA). The primary analysis was performed once all subjects had completed the final (Week 48)/withdrawal visit, the follow-up visit or discontinued earlier, and is described in this report.

Subjects participating in the TMC125IFD3002 main study were invited to participate in the pharmacokinetic substudy if they were eligible. Participating subjects had a 12- or 24-hour pharmacokinetic sampling period at Week 4 or Week 8 (when ETR was at steady-state) in addition to the assessments conducted for the main study.

**Number of Subjects (planned and analyzed):** 200 subjects planned; 211 enrolled, treated, and analyzed.

**Diagnosis and Main Criteria for Inclusion:**

Subjects could be male or female, had to be at least 18 years of age, with documented HIV-1 infection, on treatment with stable highly active antiretroviral therapy (HAART) for at least 8 weeks prior to Screening and needing to switch their current HAART regimen: 1) because they experienced virologic failure (screening VL ≥500 copies/mL), or 2) to simplify their regimen or, 3) due to AEs and/or tolerability reasons (screening VL <50 copies/mL). Furthermore, subjects had to demonstrate sensitivity to ETR and to at least 1 ARV in the background regimen, based on the resistance test (PhenoSense GT™) for subjects with a screening VL ≥500 HIV-1 RNA copies/mL or based on historical ARV resistance testing or ARV treatment history for those subjects entering the study with a plasma VL <50 HIV-1 RNA copies/mL.

Subjects could not have any currently active acquired immunodeficiency syndrome (AIDS) defining illness (except from stable cutaneous Kaposi's Sarcoma and wasting syndrome), any clinical or laboratory evidence of significantly decreased hepatic function or decompensation, or any other active clinically significant diseases that, in the investigator's opinion, could compromise their safety or outcome of the study. The use of disallowed concomitant therapies was prohibited and female subjects could neither be pregnant nor breast-feeding. Subjects with grade 3 or 4 laboratory abnormalities as defined by Division of AIDS (DAIDS) grading scheme were excluded from the study, with the following exceptions: pre-existing diabetes or with asymptomatic glucose grade 3 or 4 elevations, asymptomatic triglyceride or

cholesterol elevations of grade 3 or 4, asymptomatic and isolated lactated dehydrogenase (LDH) and/or gamma-glutamyl transferase (GGT) elevations of grade 3 or 4 with all other liver function tests including bilirubin within normal ranges (≤3 x upper limit of laboratory normal range [ULN]), or pre-existing peripheral neuropathy of grade 3 or 4.

**Test Product, Dose and Mode of Administration, Batch No.:**

ETR: commerical formulation F060, 200 mg bid administered as 2 x 100-mg oral tablets; commercial formulation F068, 200 mg bid administered as 1 x 200-mg oral tablet.

Batch numbers: AFL1W00 (AFTK01L), AFL3W00 (AGTK01H), BBL1F00 (BBTK00L), BEL4M00 (BETK009), ALL1400 (BATK01J), ALL1400 (BAZS092), BIL3S00 (BJTK00K), CAL2300 (CATK00W), and CLL3S00 (DATK00F).

**Duration of Treatment:**

Screening: maximum 6 weeks

Treatment Period: 48 weeks of ETR 200 mg bid + at least 1 investigator-selected active ARV

Follow-up Period: 4 weeks for subjects with ongoing AEs after the end of the treatment period

Substudy: 12- or 24-hour pharmacokinetic sampling at Week 4 or 8 visit (when ETR was at steady-state)

**Criteria for Evaluation:**

**Pharmacokinetics:**

Pharmacokinetic Analysis in the Main Study: Sparse sampling was performed at the visits at Week 4, 8, 24 and 48 or at the Withdrawal visit.

Pharmacokinetic Analysis in the Substudy: At the Week 4 or 8 visit of the main study, 12-hour pharmacokinetics of ETR and 12- or 24-hour pharmacokinetics of other ARVs was performed. Blood samples were collected from the subjects at predose, 1, 2, 3, 4, 6, 9, 12, and 24 hours (if applicable) postdose.

**Safety:**

AEs: AEs were reported for the duration of the study.

Laboratory Evaluations: Blood samples for serum chemistry and hematology were collected at all visits throughout the study except follow-up. The subjects had to have fasted for at least 10 hours before the safety blood sample was taken. In case a grade 3 or grade 4 laboratory abnormality occurred, a confirmatory test had to be performed preferably within 48 hours after the results had become available, if feasible. A serum pregnancy test was performed for all female subjects of childbearing potential at Screening and a urine pregnancy test was performed at other time points during the study.

Electrocardiogram (ECG): A local ECG was taken at Screening only.

Vital Signs: Systolic and diastolic blood pressure (SBP, DBP) and pulse rate (PR) (supine after at least 5 minutes rest) were recorded at all time points throughout the study except follow-up.

Physical Examination: A physical examination was performed at all time points throughout the study except follow-up.

**Efficacy**:

Plasma VL levels: Samples for the determination of plasma VL were taken at all visits throughout the study. Changes in plasma VL, including rebound and incomplete virologic suppression, were part of the efficacy analysis and were not to be reported as (S)AEs.

Immunologic Change: Immunology assessments were done at all time points throughout the study. Changes in CD4+ cell count, either increases or decreases, were part of the efficacy analysis and were not to be reported as (S)AEs.

**Resistance Determinations**:

Samples for resistance determination were taken at Screening, Baseline, and throughout the study. Samples collected at other time points were stored and selected for testing only on request of the Clinical Virologist. Plasma samples were processed for resistance testing only if the plasma VL was ≥500 HIV-1 RNA copies/mL. Relevant changes in the phenotype and genotype of the virus, determined by the PhenoSense GT™ assay, were evaluated by the Virologist. These changes in phenotype and genotype were not to be regarded as AEs.

**Statistical Methods:** Intent-to-treat (ITT) analysis, descriptive statistics, frequency tabulations, analysis of (co)variance (AN[C]OVA), Kaplan-Meier curves.

**RESULTS:**

STUDY POPULATION:

**Subject Disposition and Study Termination; All Subjects (Study TMC125IFD3002)**

| | ETR 200 mg bid |
|---|---|
| Number of subjects screened | 528 (100.0%) |
| Number of subjects treated with ETR | 211 (40.0%) |
| Completed[a] | 165 (78.2%) |
| Discontinued[a] | 46 (21.8%) |
| Lost to follow-up | 11 (5.2%) |
| Subject reached a virologic endpoint | 11 (5.2%) |
| Adverse event | 9 (4.3%) |
| Withdrawal by subject | 8 (3.8%) |
| Other | 2 (0.9%) |
| Sponsor's decision | 2 (0.9%) |
| Subject non-compliant | 2 (0.9%) |
| Subject ineligible to continue the trial | 1 (0.5%) |

[a] Percentages of subjects for Completed and Discontinued (and for each of the discontinuation reasons) are based on the number of treated subjects

**Demographic Characteristics; ITT (Study TMC125IFD3002)**

| | ETR 200 mg bid (N=211) |
|---|---|
| Sex, n (%) | |
| Female | 116 (55.0%) |
| Male | 95 (45.0%) |
| Race, n (%) | |
| American Indian or Alaska Native | 17 (8.1%) |
| American Indian or Alaska Native + White | 10 (4.7%) |
| Black or African American | 129 (61.1%) |
| White | 53 (25.1%) |
| Not allowed to ask per local regulations | 2 (0.9%) |
| Ethnicity, n (%) | |
| Hispanic or Latino | 49 (23.2%) |
| Not Hispanic or Latino | 151 (71.6%) |
| Not allowed to ask per local regulations | 11 (5.2%) |
| Age at screening, years | |
| Median (min - max) | 41.0 (19 - 65) |
| Weight, kg | |
| Median (min - max) | 65.60 (42.7 - 149.0) |
| Body mass index, $kg/m^2$ | |
| Median (min - max) | 24.40 (16.5 - 58.2) |

N = number of subjects with data, n = number of subjects with that observation

**Baseline Disease Characteristics; ITT (Study TMC125IFD3002)**

| | ETR 200 mg bid (N=211) |
|---|---|
| Baseline HIV RNA, copies/mL | |
| Median (min - max) | 5530.0 (19 - 2880000) |
| Baseline $log_{10}$ HIV RNA | |
| Median (min - max) | 3.743 (1.28 - 6.46) |
| Baseline HIV RNA (categorical), n (%) | |
| N | 211 |
| <50 copies/mL | 56 (26.5%) |
| ≥50 - <500 copies/mL[a] | 19 (9.0%) |
| ≥500 copies/mL | 136 (64.5%) |
| Baseline CD4+ cell count, x $10^6$/L | |
| Median (min - max) | 270.0 (2 - 1059) |
| Known duration of HIV infection, years | |
| Median (min - max) | 7.30 (0.4 - 27.2) |
| Mode of HIV infection, n (%) | |
| Blood transfusion | 3 (1.4%) |
| Heterosexual contact | 162 (76.8%) |
| Heterosexual contact / MSM | 2 (0.9%) |
| Intravenously injectable drug use | 3 (1.4%) |
| MSM | 29 (13.7%) |
| Mother to child transmission | 2 (0.9%) |
| Other[b] | 10 (4.7%) |
| CDC Classification System Category of HIV infection at screening, n (%) | |
| Category A | 65 (30.8%) |
| Category B | 58 (27.5%) |
| Category C | 88 (41.7%) |
| HIV-1 subtype (clade), n (%) | |
| N | 151 |
| A | 1 (0.7%) |
| A1 | 2 (1.3%) |
| B | 61 (40.4%) |
| BF | 1 (0.7%) |
| C | 62 (41.1%) |
| Complex | 13 (8.6%) |
| F1 | 11 (7.3%) |
| Hepatitis B/C co-infection status, n (%) | |
| N | 211 |
| Yes | 12 (5.7%) |
| No | 193 (91.5%) |
| Unknown | 6 (2.8%) |

N = number of subjects with data, n = number of subjects with that observation

[a] Two subjects were included in the study, although the screening VL was ≥50 and < 500 copies/mL. A major protocol violation was assigned to both of them. At Baseline, an additional 3 subjects with a screening VL <50 copies/mL and 14 subjects with a screening VL ≥500 copies/mL had a baseline VL that was ≥50 and < 500 copies/mL.

[b] Other modes of HIV infection included homosexual contact, parenteral mode, traditional ritual of scarification, unknown mode, and wound contact.

**Baseline Resistance, Median (Range) - Tabulation; ITT (Study TMC125IFD3002)**

| | ETR 200 mg bid |
|---|---|
| No. of subjects with data | 151 |
| **Number of detectable mutations** | |
| IAS-USA NRTI RAMs at (pre)baseline | 1.0 (0 - 5) |
| IAS-USA NNRTI RAMs at (pre)baseline | 2.0 (0 - 6) |
| Extended NNRTI RAMs (pre)baseline | 2.0 (0 - 6) |
| ETR RAMs at (pre)baseline | 0.0 (0 - 4) |
| ETR Weighted Genotypic Score at (pre)baseline | 0.0 (0 - 9) |
| IAS-USA PI RAMs at (pre)baseline | 5.0 (0 - 14) |
| IAS-USA Primary PI mutations at (pre)baseline | 0.0 (0 - 6) |
| **Fold change to NNRTIs** | |
| Delavirdine | 8.450 (0.15 - 172.08) |
| Efavirenz | 17.000 (0.21 - 150.21) |
| Etravirine | 0.820 (0.16 - 39.00) |
| Nevirapine | 68.000 (0.23 - 235.41) |
| Rilpivirine | 0.850 (0.17 - 22.00) |

(Pre)baseline mutations are mutations observed at Screening and/or Baseline

**Concomitant Initial ARV Therapies - Individual ARVs; ITT (Study TMC125IFD3002)**

| | ETR 200 mg bid (N=211) |
|---|---|
| Number of patients with no concomitant ARV therapy | 0 |
| Number of patients with at least 1 concomitant ARV therapy | 211 |
| Number of NNRTIs | |
| 0 | 211 (100.0%) |
| Number of NRTIs[a] | |
| 0 | 46 (21.8%) |
| 1 | 81 (38.4%) |
| 2 | 83 (39.3%) |
| 3 | 1 (0.5%) |
| Number of PIs | |
| 0 | 36 (17.1%) |
| 1 | 175 (82.9%) |
| Number of fusion inhibitors | |
| 0 | 211 (100.0%) |
| Number of CCR5 inhibitors | |
| 0 | 210 (99.5%) |
| 1 | 1 (0.5%) |
| Number of integrase inhibitors | |
| 0 | 192 (91.0%) |
| 1 | 19 (9.0%) |
| NRTI | 165 (78.2%) |
| Tenofovir | 119 (56.4%) |
| Emtricitabine | 52 (24.6%) |
| Lamivudine | 32 (15.2%) |
| Zidovudine | 22 (10.4%) |
| Abacavir | 14 (6.6%) |
| Stavudine | 10 (4.7%) |
| Didanosine | 1 (0.5%) |
| Boosted PI | 161 (76.3%) |
| Lopinavir | 130 (61.6%) |
| Atazanavir | 19 (9.0%) |
| Saquinavir | 10 (4.7%) |
| Darunavir[b] | 1 (0.5%) |

| Concomitant Initial ARV Therapies - Individual ARVs; ITT (Study TMC125IFD3002) | |
|---|---|
| | ETR 200 mg bid (N=211) |
| Tipranavir[b] | 1 (0.5%) |
| Integrase inhibitor | 19 (9.0%) |
| Raltegravir | 19 (9.0%) |
| Unboosted PI[b] | 14 (6.6%) |
| Saquinavir | 7 (3.3%) |
| Atazanavir | 6 (2.8%) |
| Fosamprenavir | 1 (0.5%) |
| CCR5 inhibitor | 1 (0.5%) |
| Maraviroc | 1 (0.5%) |

Low-dose ritonavir (< 800 mg total daily dose) is not counted as a PI.
For the treatment phase, only the treatment phase initial therapies are considered.
Treatment phase initial therapies: therapies taken at Day 7; in case of dropout during this period: therapies taken at the last day of treatment.
[a] 18 subjects used a background regimen consisting of only NRTIs, which was not allowed per protocol and documented as major protocol deviation.
[b] Use of these ARVs was not allowed per protocol and documented as major protocol deviation.

***Adherence***

Adherence to Any Drug[*](as based on observed detectable/undetectable plasma concentrations of ETR, ATV or LPV) was 62.2% and when combined with adherence by ETR pill count it was 49.3%. There were more subjects classified as nonadherent in the subgroup with baseline VL ≥50 copies/mL compared to the group with baseline VL <50 copies/mL.

SAFETY RESULTS:

***AEs***

No substantial changes in the incidences of AEs were apparent at the Week 48 analysis compared to the Week 24 analysis[#].

In total 145 subjects (68.7%) experienced at least 1 AE. Most AEs were grade 1 or 2 in severity. Grade 3 or 4 AEs occurred in 28 subjects (13.3%). Grade 3 AEs were reported in 22 subjects (10.4%) (of which 3 AEs were reported as at least possibly related to ETR) and grade 4 AEs in 6 subjects (2.8%) (all not related to ETR). The number of subjects with at least 1 AE with an at least possible drug relationship to ETR, as reported by the investigator, was 49 (23.2%). By preferred term, the most common AEs (regardless of relatedness and in >5.0% of subjects) were diarrhea (16.6%), upper respiratory tract infection (8.1%), bronchitis (6.2%), influenza (5.7%), nasopharyngitis, and urinary tract infection (each 5.2%). There were no deaths in this study. Eleven subjects (5.2%) had at least 1 serious adverse event (SAE) during the Treatment Period. By preferred term, each SAE was reported in only 1 subject. None of the SAEs were reported as at least possibly related to ETR by the investigator and 1 case led to

[*] A subject was considered nonadherent when having a plasma concentration below the limit of detection for any of the respective ARVs on at least 1 time point with available pharmacokinetic data.

[#] Opsomer M, Vanveggel S. An open-label study to evaluate the safety, tolerability and pharmacokinetics of etravirine (ETR) in combination with other antiretrovirals (ARVs) in antiretroviral treatment experienced HIV-1 infected subjects. Johnson & Johnson Pharmaceutical Research & Development, Week 24 Interim Analysis Report, TMC125IFD3002, 9 December 2013.

discontinuation (grade 4 tuberculosis). Nine subjects (4.3%) permanently discontinued treatment due to an AE. By preferred term, each AE leading to discontinuation of ETR occurred in only 1 subject, except for pregnancy (5 subjects). Three AEs leading to discontinuation were reported as related to ETR: grade 2 weight decreased (preceded by the AE appendicitis and appendectomy), grade 1 paraesthesia, and grade 3 rash.

Taking into account treatment adherence as assessed by pill count, the percentage of subjects with at least 1 adverse event was slightly greater in nonadherent (78.9%) compared to adherent (65.3%) subjects (ad hoc analysis). The level of nonadherence observed in this study is not considered to have significantly impacted the safety results.

Fourteen subjects (6.6%) had skin events of interest. Rash and rash macular were reported in 7 (3.3%) and 2 (0.9%) subjects, respectively. These events were all grade 1 or 2 in severity, except for 1 subject with grade 3 rash (leading to discontinuation, see above), and reported as at least possibly related to ETR in 6 subjects (2.8%). One case of angioedema was reported as a grade 4 SAE 234 days after the first intake of ETR. The event was reported as not related to ETR.

Twelve subjects (5.7%) had hepatic events of interest, of which hyperbilirubinemia (5 subjects) and alanine aminotransferase (ALT) increased (3 subjects) were the most frequently reported. Four of the 5 subjects reported with hyperbilirubinemia were using boosted ATV as protease inhibitor (PI) and all 4 cases were at least possibly related to the background regimen. Grade 3 and 4 hepatic events of interest were reported in 8 subjects (3.8%), and in 1 subject taking ATV/rtv (hyperbilirubinemia), respectively (some subjects had more than 1 event). The grade 3 or 4 hepatic events of interest were not or doubtfully related to ETR, except for ALT increased (possibly related) in 1 subject.

Seven subjects (3.3%) had nervous system and psychiatric events of interest (all grade 1 or 2). Nervous system and psychiatric events were reported as at least possibly related to ETR in 4 subjects (1.9%). One nervous system and psychiatric event of interest led to permanent discontinuation of ETR (grade 1 paresthesia) and none were reported as an SAE.

Eight subjects (3.8%) had lipid-related events of interest, of which 6 subjects had hypertriglyceridemia and 3 subjects had hypercholesterolemia. Three subjects had a grade 3 and 1 subject had a grade 4 lipid-related event of interest. One lipid-related event of interest (grade 3 hypercholesterolemia) was reported as at least possibly related to ETR. None were reported as an SAE or led to permanent discontinuation of ETR.

Three subjects (1.4%) had a pancreatic event of interest. Two subjects had grade 2 blood amylase increased that was reported as possibly related to ETR and the background ARVs. One subject had grade 3 blood amylase increased that was reported as doubtfully related to ETR and the background ARVs.

No cardiac or bleeding events of interest were reported.

**Adverse Event Summary Table - Treatment Period; ITT (Study TMC125IFD3002)**

| | ETR 200 mg bid | | | | |
|---|---|---|---|---|---|
| Number (%) of subjects with at least one ... | ATV/r (N=19) | LPV/r (N=130) | Other PI (N=26) | No PI use (N=36) | All (N=211) |
| **AE** | 15 (78.9%) | 97 (74.6%) | 12 (46.2%) | 21 (58.3%) | 145 (68.7%) |
| Most frequent AEs (in >5.0% of subjects) | | | | | |
| Diarrhoea | 2 (10.5%) | 31 (23.8%) | 1 (3.8%) | 1 (2.8%) | 35 (16.6%) |
| Upper respiratory tract infection | 2 (10.5%) | 12 (9.2%) | 0 | 3 (8.3%) | 17 (8.1%) |
| Bronchitis | 3 (15.8%) | 10 (7.7%) | 0 | 0 | 13 (6.2%) |
| Influenza | 0 | 9 (6.9%) | 0 | 3 (8.3%) | 12 (5.7%) |
| Nasopharyngitis | 1 (5.3%) | 5 (3.8%) | 0 | 5 (13.9%) | 11 (5.2%) |
| Urinary tract infection | 0 | 10 (7.7%) | 0 | 1 (2.8%) | 11 (5.2%) |
| Worst Grade 1 or 2 AE[a] | 10 (52.6%) | 79 (60.8%) | 9 (34.6%) | 17 (47.2%) | 115 (54.5%) |
| Worst Grade 3 or 4 AE[a] | 4 (21.1%) | 17 (13.1%) | 3 (11.5%) | 4 (11.1%) | 28 (13.3%) |

**Adverse Event Summary Table - Treatment Period; ITT (Study TMC125IFD3002)**

| Number (%) of subjects with at least one ... | ETR 200 mg bid ATV/r (N=19) | LPV/r (N=130) | Other PI (N=26) | No PI use (N=36) | All (N=211) |
|---|---|---|---|---|---|
| AE at least possibly related to ETR | 4 (21.1%) | 39 (30.0%) | 0 | 6 (16.7%) | 49 (23.2%) |
| Fatal AE | 0 | 0 | 0 | 0 | 0 |
| SAE | 1 (5.3%) | 7 (5.4%) | 0 | 3 (8.3%) | 11 (5.2%) |
| AE leading to permanent stop of ETR | 2 (10.5%) | 5 (3.8%) | 0 | 2 (5.6%) | 9 (4.3%) |
| **AEs of Special Interest** | | | | | |
| Any skin event of interest | 0 | 13 (10.0%) | 0 | 1 (2.8%) | 14 (6.6%) |
| Rash | 0 | 8 (6.2%) | 0 | 1 (2.8%) | 9 (4.3%) |
| Severe cutaneous reactions | 0 | 4 (3.1%) | 0 | 0 | 4 (1.9%) |
| Angioedema | 0 | 1 (0.8%) | 0 | 0 | 1 (0.5%) |
| Any nervous system and psychiatric event of interest | 1 (5.3%) | 2 (1.5%) | 1 (3.8%) | 3 (8.3%) | 7 (3.3%) |
| Any hepatic event of interest | 3 (15.8%) | 4 (3.1%) | 4 (15.4%) | 1 (2.8%)[b] | 12 (5.7%) |
| Any lipid-related event of interest | 1 (5.3%) | 5 (3.8%) | 2 (7.7%) | 0 | 8 (3.8%) |
| Any cardiac event of interest | 0 | 0 | 0 | 0 | 0 |
| Any bleeding event of interest | 0 | 0 | 0 | 0 | 0 |
| Any pancreatic event of interest | 0 | 3 (2.3%) | 0 | 0 | 3 (1.4%) |

[a] Both the ATV/rtv and LPV/rtv subgroup included 1 subject with an ungraded pregnancy as the only AE.
[b] Subject 3002-0200 started on ATV/rtv after the start of ETR intake (Day 17) and is therefore not captured in the ATV/rtv subgroup but in the No PI subgroup. This subject experienced an additional hepatic event of interest (hyperbilirubinemia).

### *Clinical Laboratory Tests*

Mean changes over time in the clinical laboratory parameters were generally small and not considered clinically relevant. No unexpected mean changes over time were observed in laboratory parameters given the ARVs included in the background regimen.

The most frequently observed (>15% of subjects) graded laboratory abnormalities were increased total cholesterol (33.7%), hyperuricemia (27.4%), increased low density lipoprotein (LDL) cholesterol (23.1%), hyponatremia (21.2%), increased amylase (20.2%), increased ALT (17.8%), hypophosphatemia (17.3%), hyperglycemia (17.3%), and increased aspartate aminotransferase (AST) (16.3%). The majority of treatment-emergent graded laboratory abnormalities were grade 1 or 2. The most frequently observed (>5 subjects) grade 3 or 4 laboratory abnormalities were hyperbilirubinemia (10 subjects, 4.8%), hypophosphatemia (9 subjects, 4.3%), and LDL cholesterol (6 subjects; 2.9%). Hyperbilirubinemia was observed as a laboratory abnormality in 13.9% of subjects overall, and in 16 of the 19 subjects who were in the ATV/rtv subgroup (84.2%). Hyperbilirubinemia is a known adverse drug reaction of ATV.[*,#] Laboratory abnormalities were reported as a grade 3 or 4 AE in 17 subjects (at least possibly related to ETR in 2 cases; ALT increased and hypercholesterolemia), and reported as serious in 1 case (grade 2 anemia; doubtfully related to ETR).

### *Vital Signs*

Mean changes in vital signs parameters were generally small, and none were considered clinically relevant. Grade 3 vital signs abnormalities were observed in 6 subjects. Adverse events related to vital signs abnormalities were reported in 6 subjects. There was one grade 3 hypertension. One grade 1

[*] SmPC of atazanavir: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/000494/WC500056380.pdf.

[#] USPI of atazanavir: http://www.accessdata.fda.gov/drugsatfda_docs/label/2013/021567s032s033lbl.pdf.

bradycardia was reported as possibly related to ETR. None of the events were serious or led to permanent discontinuation of ETR.

PHARMACOKINETIC RESULTS:

**Noncompartmental Pharmacokinetic Analysis - Substudy**

| **Pharmacokinetics of etravirine (mean ± SD, $t_{max}$: median [range])** | **Overall: 200 mg etravirine bid in combination with an investigator-selected background regimen for 48 weeks** | **200 mg etravirine bid + LPV/rtv** | **200 mg etravirine bid + Other PI** | **200 mg etravirine bid + No PI** |
|---|---|---|---|---|
| N | 24 | 12 | 6 | 6 |
| $C_{0h}$, ng/mL | 420 ± 328 | 246 ± 191 | 457 ± 320 | 733 ± 344 |
| $C_{min}$, ng/mL | 338 ± 277 | 202 ± 158 | 339 ± 306 | 607 ± 271 |
| $C_{max}$, ng/mL | 662 ± 409 | 487 ± 263 | 630 ± 373 | 1044 ± 479 |
| $t_{max}$, h | 3.88 (0.00 - 6.00) | 3.88 (3.00 - 6.00) | 2.50 (0.00 - 5.97) | 4.72 (3.00 - 6.00) |
| $AUC_{12h}$, ng.h/mL | 5793 ± 3979 | 3923 ± 2287 | 5962 ± 4059 | 9364 ± 4597 |

Etravirine pharmacokinetics were evaluated overall, and by subgroups of background regimen: LPV/rtv, No PI, Other PI (including unboosted PI). It should be noted there was only 1 subject with ATV/rtv in the background regimen in the substudy, who was included in the Other PI subgroup.

Overall, the range of ETR PK parameters was largely comparable to the range of ETR PK parameters previously observed in the pooled pharmacokinetic substudies of the DUETa studies when ETR was combined with DRV/rtv. The overall mean $C_{min}$, $C_{max}$ and $AUC_{12h}$ values of ETR in the substudy were somewhat lower compared to those in the DUET* studies. This was mainly due to the lower mean ETR exposure when ETR was administered in combination with LPV/rtv.

Between the subgroups, the mean ETR PK parameters were lowest for the LPV/rtv subgroup and highest for the No PI subgroup.

**Population Pharmacokinetic Analysis - Main Study**

**ETR Population Pharmacokinetic Parameters - Descriptive Statistics; ITT (Study TMC125IFD3002)**

| | ETR 200 mg bid | | |
|---|---|---|---|
| | Baseline Viral Load (copies/mL) | | |
| | <50 | ≥50 | All |
| *Parameter = AUC12h (ng.h/ml)* | | | |
| ETR | | | |
| N | 53 | 146 | 199 |
| Geom. Mean | 5561.1 | 4637.8 | 4867.6 |
| Median (min - max) | 6530.0 (366 - 38200) | 5060.0 (216 - 29400) | 5390.0 (216 - 38200) |
| *Parameter = C0H (ng/ml)* | | | |
| ETR | | | |
| N | 53 | 146 | 199 |

* Kakuda TN, Wade JR, Snoeck E, et al. Pharmacokinetics and pharmacodynamics of the non-nucleoside reversetranscriptase inhibitor etravirine in treatment-experienced HIV-1-infected patients. Clin Pharmacol Ther 2010; 88(5): 695-703.

**ETR Population Pharmacokinetic Parameters - Descriptive Statistics; ITT (Study TMC125IFD3002)**

| | ETR 200 mg bid | | |
|---|---|---|---|
| | Baseline Viral Load (copies/mL) | | |
| | <50 | ≥50 | All |
| Geom. Mean | 333.5 | 279.8 | 293.2 |
| Median (min - max) | 436.0 (4 - 3080) | 341.5 (8 - 2330) | 353.0 (4 - 3080) |

N = number of subjects with data

The geometric mean ETR area under the plasma concentration-time curve over 12 hours ($AUC_{12h}$) and predose plasma concentration ($C_{0h}$) in the present study were comparable to results from the pooled Phase 3 studies TMC125-C206/C216[*].

PHARMACOGENOMIC RESULTS:

Overall, there was no indication for a clinically relevant difference in ETR pharmacokinetics by CYP2C9 or CYP2C19 genotype. However, as the number of subjects was limited, especially in certain subgroups, and the study was not powered for these comparisons, the results should be interpreted with caution and no firm conclusions can be drawn.

EFFICACY RESULTS:

The overall response rate (virologic success, VL <50 copies/mL, Snapshot) at Week 48 was 55.0% (116/211 subjects); 75.0% (42/56) of subjects with a baseline VL <50 copies/mL maintained their virologic response, and 47.7% (74/155) of subjects with a baseline VL ≥50 copies/mL achieved virologic response.Virologic response rates according to noncompleting equals failure (NC=F) and time to loss of virologic response (TLOVR) analysis were similar.

In the subgroup analyses for virologic response (<50 and <400 copies/mL; Snapshot) at Week 48, effects were noted for baseline VL, treatment adherence, and number of sensitive ARVs in the background.

Stratifying subjects with a baseline VL ≥50 copies/mL by baseline VL, 52.1%, 51.4%, and 38.8% of subjects within the baseline VL categories [50-20000], [20000-50000[, and ≥50000 copies/mL achieved a virologic response (<50 copies/mL) at Week 48, respectively.

Assessed by pill count, virologic response was greater in subjects adherent (>95%) to ETR intake compared to nonadherent subjects: with baseline VL ≥50 copies/mL, virologic response was 54.6% in adherent vs 34.1% in nonadherent subjects and with baseline VL <50 copies/mL, virologic response was 82.1% in adherent vs 76.9% in nonadherent subjects. When adherence to ETR, LPV and ATV was assessed by observed detectable/undetectable plasma concentrations[#], similar effects were observed on virologic response. For subjects with a baseline VL ≥50 copies/mL virologic response was 54.4%, 63.6%, and 63.8%, respectively in subjects adherent to ETR, Any Drug (defined as ETR, ATV or LPV), and Any Drug combined with adherence by ETR pill count and 26.1%, 30.0%, and 38.0%, respectively, in nonadherent subjects.

For subjects with baseline VL ≥50 copies/mL, virologic response was greater in subjects with a lower number of sensitive ARVs in the background regimen, the reverse from what would be expected. Note that, almost all subjects showed sensitivity to all ARVs in their OBR, hence the number of sensitive ARVs in their OBR was equal to the total number of ARVs in their OBR. There was also a clear correlation between the level of adherence to the OBR, as subjects taking 3 sensitive ARVs appeared to

[*] The 48-week Bayesian pharmacokinetic feedback of TMC125 for studies TMC125-C206 (DUET-1) and TMC125-C216 (DUET-2). Exprimo NV, TMC125-C930 PK report, December 2008.

[#] A subject was considered nonadherent when having a plasma concentration below the limit of detection for any of the respective ARVs on at least 1 time point with available pharmacokinetic data.

be less adherent based on observed plasma concentrations (32.4%) than subjects taking 1 (70.7%) or 2 (65.5%) sensitive ARVs. Thus, pill burden, and consequently suboptimal adherence to the OBR, may have played a role.

At Week 48, the mean (standard error [SE]) change in absolute CD4+ cell count from Baseline was +64.6 (11.4) x $10^6$ cells/L for subjects with a baseline VL ≥50 copies/mL. For subjects with a baseline VL <50 copies/mL this was +32.4 (17.0) x $10^6$ cells/L.

**Virologic Response (<50 Copies/mL) - Tabulation; ITT (Study TMC125IFD3002)**

| | ETR 200 mg bid | | |
|---|---|---|---|
| | Baseline Viral Load (copies/mL) | | |
| | <50 (N=56) | ≥50 (N=155) | All (N=211) |
| **Primary Analysis (Week 48)** | | | |
| *Snapshot Outcome, n(%)* | | | |
| Virologic success HIV RNA <50 copies/mL at Week 48 | 42 (75.0%) | 74 (47.7%) | 116 (55.0%) |
| Virologic failure | 7 (12.5%) | 65 (41.9%) | 72 (34.1%) |
| Virologic failure - at Week 48 | 4 (7.1%) | 45 (29.0%) | 49 (23.2%) |
| Virologic failure - last available HIV RNA ≥50 copies/mL | 2 (3.6%) | 11 (7.1%) | 13 (6.2%) |
| Virologic failure - leading to discontinuation before Week 48 | 1 (1.8%) | 9 (5.8%) | 10 (4.7%) |
| No viral load data in Week 48 window | 7 (12.5%) | 16 (10.3%) | 23 (10.9%) |
| Discontinued due to AE/death - before Week 48 | 1 (1.8%) | 8 (5.2%) | 9 (4.3%) |
| Discontinued due to other reason and last available HIV RNA <50 copies/mL - before Week 48 | 6 (10.7%) | 7 (4.5%) | 13 (6.2%) |
| Missing data during Week 48 window | 0 | 1 (0.6%) | 1 (0.5%) |
| **Secondary Analysis (Week 48)** | | | |
| *Virologic response, n(%)* | | | |
| Response (<50 copies/mL) NC=F | 42 (75.0%) | 75 (48.4%) | 117 (55.5%) |
| Confirmed response (<50 copies/mL) TLOVR | 42 (75.0%) | 69 (44.5%) | 111 (52.6%) |

N = number of subjects with data, n = number of subjects with that observation

RESISTANCE RESULTS:

In 29 of the 49 virologic failures with genotypic data in this study, emergence of non-nucleoside reverse transcriptase inhibitor (NNRTI) resistance-associated mutations (RAMs) was observed with Y181C, E138A, and M230L as the most frequent (in ≥5 subjects) ETR RAMs. Other ETR RAMs that emerged in more than 1 subject experiencing virologic failure were V90I, E138G, E138K, and E138Q. The median ETR fold change (FC) increased from 0.84 (ranging from 0.39 to 39.00) at Baseline to 5.76 (ranging from 0.50 to 276.72) at Endpoint.

PHARMACOKINETIC/PHARMACODYNAMIC RESULTS:

Overall, and when taking into account that sample sizes of the subgroups are small, there is no indication of a relationship between the ETR pharmacokinetics and the occurrence of 'Rash' (skin events of interest), hepatic, or lipid-related event of interest. The median ETR $AUC_{12h}$ and $C_{0h}$ were higher in subjects who achieved or maintained virologic response (Snapshot) compared to those who did not. It should however be noted that caution should be applied when interpreting the pharmacokinetic-pharmacodynamic relationships data. These results should be interpreted with caution, taking into account the low adherence levels observed in some subjects..

STUDY LIMITATIONS:

Study TMC125IFD3002 was an open-label, single-arm study for which results need to be interpreted with caution since there was no placebo or comparator as a control.

CONCLUSIONS:

Coadministration of ETR 200 mg bid in combination with ARVs other than DRV/rtv was generally safe and well tolerated in the studied treatment-experienced HIV-1 infected population. There were no newly identified clinically relevant safety findings compared with the known ETR safety profile in HIV-1 infected adults.

In general, the range of ETR pharmacokinetic parameters was comparable with that observed in historical studies in HIV-infected subjects. The median ETR pharmacokinetic parameters were somewhat lower in subjects with LPV/rtv in their background regimen compared to those for the rest of the population.

Overall, there was no indication for a clinically relevant difference in ETR pharmacokinetics by CYP2C9 or CYP2C19 genotype.

The overall response rate (virologic success, VL <50 copies/mL, Snapshot) at Week 48 was 55.0% (116/211 subjects); 75.0% (42/56) of subjects with a baseline VL <50 copies/mL maintained their virologic response and 47.7% (74/155) of subjects with a baseline VL ≥50 copies/mL achieved virologic response. At Week 48, for subjects with a baseline VL ≥50 and VL<50 copies/mL, the mean (SE) change in absolute CD4+ cell count from Baseline was +64.6 (11.4) x $10^6$ cells/L and +32.4 (17.0) x $10^6$ cells/L, respectively.

Virologic response was higher in adherent subjects vs nonadherent subjects for both adherence measures (assessed by pill count and/or pharmacokinetic sampling). The observed virologic response rates may therefore have been impacted by the relatively high level of nonadherence, particularly in subjects with a baseline VL ≥50 copies/mL.

The ETR RAMs that emerged most frequently in subjects experiencing virologic failure were Y181C, E138A, and M230L.

There is no indication of a relationship between the ETR pharmacokinetics and the occurrence of 'Rash' (skin events of interest), hepatic, or lipid-related event of interest. The median ETR $AUC_{12h}$ and $C_{0h}$ were higher in subjects who achieved or maintained virologic response (Snapshot) compared to those who did not. These results should be interpreted with caution, taking into account the low adherence levels observed in some subjects.