SYNOPSIS

Name of Sponsor/Company	Janssen Research & Development*
Name of Finished Product	Intelence®
Name of Active Ingredient(s)	TMC125 (etravirine)

Status: Approved

Date: 9 November 2012

Prepared by: Janssen Infectious Diseases-Diagnostics BVBA

Protocol No.: TMC125-TiDP2-C238

Title of Study: A randomized, exploratory, open-label 48-week trial with a 2-week Pretreatment Phase to investigate the pharmacokinetics, safety, tolerability and antiviral activity of etravirine (ETR) in combination with ritonavir-boosted atazanavir (ATV/rtv) and 1 NRTI in treatment-experienced HIV-1 infected subjects.

EudraCT Number: 2009-010887-41

NCT No.: NCT00896051

Clinical Registry No.: CR016045

Principal Investigator: C. Orrell, Faculty of Health Sciences, [redacted] South Africa

Study Center(s): Argentina (2), South Africa (3), Thailand (3), US (9)

Publication (Reference): Kakuda T, Nijs S, Latham J, et al. Pharmacokinetics of atazanavir/ritonavir 300/100mg or 400/100mg qd when co-administered with etravirine 200mg bid in HIV-infected patients. 13th International Workshop on Clinical Pharmacology of HIV Therapy, Barcelona, Spain, 2012. Poster 0_24.

Study Period: 25 June 2009 - 10 April 2012

Phase of Development: 2

Objectives: The objectives of the main study were:

- to evaluate the pharmacokinetic interaction between ETR and ATV/rtv at 2 different doses;
- to assess the impact of cytochrome P450 (CYP) 2C9 and 2C19 genotypes on ETR pharmacokinetics;
- to evaluate safety and tolerability of ETR in combination with ATV/rtv and 1 nucleoside reverse transcriptase inhibitor (NRTI) over 48 weeks;
- to evaluate the antiviral activity of ETR in combination with ATV/rtv and 1 NRTI over 48 weeks;
- to evaluate the immunologic changes (as measured by CD4+ cells) with ETR and ATV/rtv with 1 NRTI over 48 weeks;

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- to evaluate changes in viral genotype and drug susceptibility over 48 weeks.

The objectives of an additional, exploratory substudy were:

- to evaluate the pharmacokinetics of ETR, ATV, and rtv with and without coadministration of tenofovir disoproxil fumarate (TDF);
- to evaluate short-term safety and tolerability of ETR + ATV/rtv + 1 investigator-selected NRTI + TDF.

Methodology: This was a randomized, exploratory, open-label, 2-arm 48-week Phase II study with a 2-week Pretreatment Period to investigate the pharmacokinetics, safety, tolerability and antiviral activity of ETR coadministered with 2 different doses of ATV/rtv each combined with 1 NRTI in treatment-experienced HIV-1 infected subjects.

The main study consisted of a Screening Period of a maximum of 4 weeks, a 2-week Pretreatment Period, a Baseline Visit, a 48-week Treatment Period, and a Final Visit (or Withdrawal Visit), followed by a 4 week Posttreatment Follow-up Period (not for subjects who continued treatment with ETR in another study or program).

A full pharmacokinetic profile was performed on Day -1 for ATV and rtv and at Week 2 for ATV, rtv, and ETR.

The study population consisted of early treatment-experienced HIV-1 infected subjects. Subjects were randomized in a 1:1 ratio to 1 of 2 ATV/rtv doses (300/100 mg q.d. or 400/100 mg q.d.). In the Pretreatment Period (2 weeks), all subjects initiated therapy with ATV/rtv 300/100 mg q.d. + 2 NRTIs. This was followed in the Treament Period (48 weeks) by treatment with 1 of the 2 ATV/rtv doses (300/100 mg q.d. or 400/100 mg q.d.) in combination with ETR 200 mg b.i.d. and 1 NRTI that had been used in the Pretreatment Period.

Forty-six subjects were to be included in the study, 23 on each ATV/rtv dose to ensure that there would be evaluable pharmacokinetic data from at least 19 subjects in each arm.

The first analysis was performed when all subjects had been treated with ETR for 12 weeks or discontinued earlier (reported in a Topline Results Report). The final analysis was performed when all subjects had been treated with ETR for 48 weeks or discontinued earlier (reported in a Clinical Study Report).

A substudy to explore the effect of adding TDF for 7 days on ATV and ETR pharmacokinetics was conducted in subjects with >24 weeks of treatment on ATV/rtv + 1 NRTI + ETR and at least the 2 most recent consecutive viral loads (VL) <50 copies/mL. Participation in this substudy was optional. Subjects participating in the substudy received TDF 300 mg q.d. for 7 days in addition to their ARV regimen. Pharmacokinetic sampling over 12 hours was performed for ETR and over 24 hours for ATV and rtv on Day -1, and for ETR over 12 hours and ATV, rtv and TDF over 24 hours on Day 7 of the substudy.

Enrollment in the substudy had to continue until TMC125-TiDP2-C238, hereafter referred to as TMC125-C238, was permanently discontinued or until 20 subjects were assigned to this substudy. Efforts had to be made to include a minimum of 8 subjects in each ATV/rtv dose group in this substudy.

Number of Subjects (planned and analyzed): 46 subjects planned; 50 subjects in the Pretreatment Period and 44 subjects in the Treatment Period were analyzed.

Diagnosis and Main Criteria for Inclusion:

Inclusion Criteria of the main study:

- Male or female, aged 18 years or above;

- Subject has signed the informed consent form (ICF) voluntarily;
- Subject can comply with the protocol requirements;
- Subject with documented HIV-1 infection;
- Subject had HIV-1 plasma VL at Screening >500 HIV-1 RNA copies/mL (assayed by [redacted] Amplicor HIV-1 VL assay);
- Subject had received at least 1 HAART regimen;
- Subject was on a stable antiretroviral therapy (ART) for at least 8 weeks at Screening and willing to stay on that treatment until the start of the Pretreatment Period;
- Presence of at least 1 of the following mutations (based upon the following list of NNRTI resistance-associated mutations (RAMs): V90I, A98G, L100I, K101E/H/P/Q, K103H/N/S/T, V106A/M, V108I, E138A/G/K/Q, V179E/G/I, Y181C, Y188C/H/L, V189I, G190A/C/E/Q, H221Y, P225H, F227C/L, M230I/L, P236L, K238N/T, Y318F) on the resistance test at Screening or from prior genotypic analysis;
- Demonstrated sensitivity to ATV, ETR and the selected NRTIs based on the resistance test at Screening. Subjects infected with HIV sensitive to only 1 of the selected NRTIs were only allowed if the second, nonactive NRTI selected was emtricitabine (FTC) or lamivudine (3TC);
- General medical condition, in the investigator's opinion, did not interfere with the assessments and completion of the main study.

Inclusion Criteria of the substudy:

- Currently enrolled in study TMC125-C238 for >24 weeks;
- ICF signed voluntarily;
- HIV-1 plasma VL <50 copies/mL on at least the 2 most recent consecutive study visits;
- General medical condition, in the investigator's opinion, does not interfere with the assessments and completion of the substudy.

Exclusion Criteria of the main study:

- Primary HIV-1 infection;
- Previously documented HIV-2 infection;
- Previously failed 2 or more HIV PI-containing regimens;
- Use of disallowed concomitant therapy;
- Previous diagnosis of hereditary hyperbilirubinemia;
- Any condition (including but not limited to alcohol and drug use) which, in the opinion of the investigator, could compromise the subject's safety or adherence to the protocol;
- Life expectancy less than 6 months according to the judgment of the investigator;
- Subject had any currently active AIDS-defining illness Category C conditions according to the Centers for Disease Control [CDC] Classification System for HIV Infection 1993, with the exception of stable cutaneous Kaposi's sarcoma, and wasting syndrome due to HIV infection;
- Any active clinically significant disease (eg, pancreatitis, cardiac dysfunction) or findings during screening of medical history, laboratory or physical examination that, in the investigator's opinion, could compromise the subject's safety or outcome of the study;
- Acute viral hepatitis including but not limited to A, B, or C;

- Chronic hepatitis B coinfection. Subjects with chronic hepatitis C (HCV) infection could be included as long as they were not currently treated with anti-HCV therapy, nor was it expected that they would require such treatment during the course of the study;
- Receipt of an investigational drug or investigational vaccine within 30 days prior to the study drug administration;
- Previously demonstrated clinically significant allergy or hypersensitivity to ETR or to any of the excipients of ETR;
- Pregnant or breastfeeding female subject;
- Female subject of childbearing potential not using effective birth control methods or not willing to continue practicing these birth control methods during the study and for at least 30 days after the end of the study;
- Non-vasectomized heterosexually active male subject not using effective birth control methods or not willing to continue practicing these birth control methods during the study and until 30 days after the end of the study;
- Any grade 3 or 4 laboratory abnormalities (according to the Division of AIDS [DAIDS] grading table, in aspartate aminotransferase (AST), alanine aminotransferase (ALT), amylase, lipase, hemoglobin or neutrophils;
- Subjects who previously received treatment with either ETR (TMC125), dapivirine (TMC120), rilpivirine (TMC278), maraviroc (MVC) or raltegravir (RAL);
- Presence of at least 1 of the following mutations: K103R, V106I, I167V, V179D/F/T, Y181I/V, and G190S.

Exclusion Criteria of the Substudy:

- Previously demonstrated clinically significant allergy or hypersensitivity to TDF or to any of the excipients of TDF;
- Any grade 3 or 4 serum creatinine abnormalities or a calculated creatinine clearance (CLcr) <50 mL/min;

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

ETR: commerical formulation F060, 200 mg b.i.d. administered as 2 x 100-mg oral tablets. Batch numbers: KL2900, 9AL1600, ALL2M00.

ATV: commercial formulation, 300 or 400 mg q.d. administered as 1 x 300-mg or 2 x 200-mg oral capsules, respectively. Batch numbers: 300 mg : 9D3057A, 0024, 9J50182, OL58188, 1D65089; 200 mg: 9D3102A, B017, OA59987, A082, OL61941.

Other Products:

rtv, TDF (in the substudy only), and NRTIs: all commercial formulations. Batch numbers rtv: 674372E23, 72649VA, 6005254, 923428D, 945518D; TDF: FDJ028D, 10VR043.

Dosing Schedule:

Pretreatment Period: ATV/rtv 300/100 mg q.d. + 2 investigator-selected NRTIs.

Treatment Period: ETR 200 mg b.i.d. + ATV/rtv 300/100 mg q.d. or ATV/rtv 400/100 mg q.d + 1 investigator-selected NRTI.

Substudy: ETR 200 mg b.i.d. + ATV/rtv 300/100 mg q.d. or ATV/rtv 400/100 mg q.d. + 1 investigator-selected NRTI + TDF 300 mg q.d.

Duration of Treatment: The study consisted of a Screening (maximum 4 weeks), Pretreatment Period (2 weeks), Treatment Period (48 weeks), Posttreatment Follow-up Period (4 weeks).

Criteria for Evaluation:

Pharmacokinetics:

Pharmacokinetic Analysis in the Main Study: On Day -1, 24-hour pharmacokinetics of ATV and rtv were performed (at Visits 3 and 4). At Week 2, 24-hour pharmacokinetics of ATV and rtv and 12-hour pharmacokinetics of ETR were performed. Blood samples were collected from the subjects at predose, 1, 2, 3, 4, 6, 9, 12 and 24 hours postdose.

Pharmacokinetic Analysis in the Substudy: On Day -1 and 7 of the Substudy, 24-hour pharmacokinetics of TDF, ATV, and rtv and 12-hour pharmacokinetics of ETR was performed. Blood samples were collected from the subjects at predose, 1, 2, 3, 4, 6, 9, 12, and 24 hours postdose.

Safety:

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

Laboratory Evaluations: Blood samples for serum chemistry and hematology and a urine sample for urinalysis were collected at most visits throughout the study. 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.

ECG: Twelve-lead ECGs were recorded at Screening, Day 1, and at several time points throughout the study. The different ECG intervals (RR if available, PR, QRS and QT) and heart rate (HR) were measured. In the statistical analysis, the QT-intervals were corrected for HR according to Bazett's (QTcB) and Fridericia's (QTcF) QT correction.

Vital Signs: Systolic and diastolic blood pressure (SBP, DBP) and pulse rate (sitting after at least 5 minutes rest) were recorded at Screening, Week -2 Day -1, and at several time points throughout the study.

Physical Examination: Height was measured at Screening Visit only. Weight was measured at Screening and at several time points.

Efficacy:

Plasma VL levels: Samples for the determination of plasma VL were taken at Screening, Week -2, Day 1 and most 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: Samples for the determination of plasma viral load were taken at Screening, Week -2, Day 1, and most visits 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, Day 1, and throughout the study. Samples collected at Baseline and Week 48 were processed in batches. 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 viral load 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, logistic regression, analysis of covariance (ANCOVA), Kaplan-Meier curves, and non-linear mixed effect model

Flowchart of the Main study

Type of Visit	Screening	Randomization/ Pretreatment Period		Baseline	Treatment Period											Final\ Withdrawal Visit	Post-Treatment Follow-up Period (30-35 days after Final/Withdrawal Visit)
Time of Visit	**Week -6**	**Week -2**	**Day -1**	**Day 1**	**Week 2**		**Week 4**	**Week 8**	**Week 12**	**Week 16**	**Week 20**	**Week 24**	**Week 30**	**Week 36**	**Week 42**	**Week 48**	**Week 52**
Visit	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17
Informed consent	X																
Demographic data, medical & surgical history, concomitant diseases and height	X																
Pregnancy test	X	X		X			X	X	X	X		X		X		X	X
Inclusion/exclusion criteria	X	X															
Physical examination	X			X					X			X				X	
PBMC sample				X												X	
Hematology & biochemistry (10 h fasting)	X	X	X	X	X		X	X	X	X		X		X		X	X
Vital signs (pulse, blood pressure)	X	X		X					X			X				X	
ECG	X			X	X			X				X				X	X
Framingham score				X												X	
Weight	X			X					X			X				X	X
CYP 2C9 and 2C19 genotyping			X														
Pharmacokinetic sampling			Xe		X		X	X	X	X		X		X		X	
Plasma VL	X	X		X	X		X	X	X	X	X	X	X	X	X	X	X

Type of Visit	Screening	Randomization/ Pretreatment Period		Baseline	Treatment Period											Final\ Withdrawal Visit	Post-Treatment Follow-up Period (30-35 days after Final/Withdrawal Visit)
Time of Visit	**Week -6**	**Week -2**	**Day -1**	**Day 1**	**Week 2**		**Week 4**	**Week 8**	**Week 12**	**Week 16**	**Week 20**	**Week 24**	**Week 30**	**Week 36**	**Week 42**	**Week 48**	**Week 52**
Visit	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17
Viral phenotyping/genotyping	X			X	X		X	X	X	X		X		X		X	X
CD4+ cell count	X	X		X	X		X	X	X	X	X	X	X	X	X	X	X
Hepatitis serology	X																
Dispensation of investigational medication		X		X	X		X	X	X	X		X		X			
Observe/Interview for AEs and HIV-1 related events & Concomitant therapy	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Pill count/Adherence		X	X	X	X	X	X	X	X	X		X		X		X	

Flowchart of the Substudy

Substudy Day	Time (hour)	Blood sample		Urine sample	Vital Signs	Other
		Drug	Safety[a]			
-1				X		Admission to unit, urine drug screening, physical examination, alcohol breath test
	- 2					Start water restriction
	Predose	X	X		X	Standardized breakfast
	0					Morning intake ETR (200 mg b.i.d.) + ATV/rtv (300/100 mg q.d. or 400/100 mg q.d.) + NRTI
	1	X				
	2	X				Resume water intake
	3	X				
	4	X			X	Resume food intake
	6	X				
	9	X				
	12	X				Evening intake ETR (200 mg b.i.d.) + NRTI (only if dosed b.i.d.)
1	24	X	X		X	Physical examination; Intake ETR (200 mg b.i.d.) + ATV/rtv (300/100 mg q.d. or 400/100 mg q.d.) + TDF (300 mg q.d.) + NRTI
2-6						Intake ETR (200 mg b.i.d.) + ATV/rtv (300/100 mg q.d. or 400/100 mg q.d.) + TDF (300 mg q.d.) + NRTI
7				X		Admission to unit, urine drug screening, physical examination, alcohol breath test
	-2					Start water restriction
	Predose	X	X		X	Standardized breakfast
	0					Morning intake ETR (200 mg b.i.d.) + ATV/rtv (300/100 mg q.d. or 400/100 mg q.d.) + TDF (300 mg q.d.) + NRTI
	1	X				
	2	X				Resume water intake
	3	X				
	4	X			X	Resume food intake
	6	X				
	9	X				
	12	X				Evening intake ETR (200 mg b.i.d.) + NRTI (only if dosed b.i.d.)
8	24	X	X		X	Intake ETR (200 mg b.i.d.) + ATV/rtv (300/100 mg q.d. or 400/100 mg q.d.) + NRTI

RESULTS:

Study Population:

Subject Disposition, Discontinuations and Treatment Duration	ATV/rtv 300/100 mg q.d.	ATV/rtv[a] 400/100 mg q.d.	All Subjects
Main Study			
Randomized and Treated with ATV/rtv + 2 NRTIs during the Pretreatment Period, n (%)	25 (100)	25 (100)	50 (100)[b]
Discontinued during Pretreatment Period, n (%)	3 (12.0)	3 (12.0)	6 (12.0)
Subject lost to follow-up	1 (4.0)	1 (4.0)	2 (4.0)
Subject withdrew consent	2 (8.0)	2 (8.0)	4 (8.0)
Randomized and Treated with ETR + ATV/rtv + 1 NRTI during Treatment Period, n (%)	22 (88.0)	22 (88.0)	44 (88.0)[c]
Discontinued during Treatment Period, n (%)	7 (28.0)	6 (24.0)	13 (26.0)
Adverse event	2 (8.0)	1 (4.0)	3 (6.0)
Subject lost to follow-up	2 (8.0)	1 (4.0)	3 (6.0)
Subject withdrew consent	1 (4.0)	0	1 (2.0)
Subject noncompliant	1 (4.0)	3 (12.0)	4 (8.0)
Other	1 (4.0)	1 (4.0)	2 (4.0)
Completed the study, n (%)	15 (60.0)	16 (64.0)	31 (62.0)
Treatment Duration			
Median (range), weeks	48.0 (1 - 56)	47.3 (4 - 55)	47.7 (1 - 56)
ETR Total patient years of exposure	16.8	16.6	33.3
Substudy			
Treated with ETR +ATV/rtv + TDF + 1 NRTI, n (%)	3 (100)	5 (100)[d]	8 (100)
Completed the substudy, n (%)	3 (100)	4 (80.0)[d]	7 (87.5)

N = number of subjects, n = number of subjects with observations

[a] During the Pretreatment Period all subjects of the main study received ATV/rtv 300/100 mg q.d.

[b] Safety intent to treat (ITT) population: including all randomized subjects with at least 1 ATV/rtv intake regardless of their compliance with the protocol.

[c] Efficacy ITT population: including all randomized subjects with at least 1 ETR intake regardless of their compliance with the protocol.

[d] 1 subject (CRF ID [redacted]) entered the substudy without being eligible (no VL < 50 copies/mL on at least the 2 most recent visits), and was withdrawn after 3 days of TDF administration.

Demographic Characteristics	ATV/rtv 300/100 mg q.d. N = 25	ATV/rtv 400/100 mg q.d. N = 25	All Subjects N = 50
Sex, n (%)			
Female	12 (48.0)	13 (52.0)	25 (50.0)
Male	13 (52.0)	12 (48.0)	25 (50.0)
Race, n (%)			
Asian	6 (24.0)	2 (8.0)	8 (16.0)
Black or African American	12 (48.0)	18 (72.0)	30 (60.0)
Multiple[a]	1 (4.0)	0	1 (2.0)
White	6 (24.0)	5 (20.0)	11 (22.0)
Ethnicity, n (%)			
Hispanic or Latino	2 (8.0)	2 (8.0)	4(8.0)
Not Hispanic or Latino	23 (92.0)	23 (92.0)	46 (92.0)
Age (years), median (range)	39.0 (26 - 63)	40.0 (18 - 56)	40.0 (18 - 63)
Weight (kg), median (range)	67.0 (47 - 153)	76.7 (46 - 98)	70.5 (46 - 153)
BMI (kg/m^2), median (range)	26.2 (17 - 51)	26.8 (17 - 35)	26.4 (17 - 51)

N = number of subjects; n = number of subjects with observations; BMI = body mass index
Note: height, weight and BMI were imputed with screening data if missing at Baseline
[a] Subject was White + Black or African American.

Baseline Disease Parameters, n (%)	ATV/rtv 300/100 mg q.d. N = 25	ATV/rtv 400/100 mg q.d. N = 25	All Subjects N = 50
Prebaseline[a] Viral Load, Copies/mL			
Median (Min - Max)	13400 (90 - 574000)	11500 (185 - 655000)	12800 (90 - 655000)
Prebaseline $\log_{10}$ Viral Load, Copies/mL			
Median (Min - Max)	4.1 (2 - 6)	4.1 (2 - 6)	4.1 (2 - 6)
Prebaseline CD4+ Cell Count (x10^6/L)			
Median (Min - Max)	186 (8 - 678)	238 (55 - 1061)	223 (8 - 1061)
Duration of Known HIV Infection, Years			
Median (Min - Max)	7.2 (2 - 16)	6.7 (1 - 26)	7.0 (1 - 26)
Clinical Stage of HIV Infection	**25 (100)**	**25 (100)**	**50 (100)**
A	10 (40.0)	9 (36.0)	19 (38.0)
B	7 (28.0)	7 (28.0)	14 (28.0)
C	8 (32.0)	9 (36.0)	17 (34.0)
Mode of HIV Infection	**25 (100)**	**25 (100)**	**50 (100)**
Heterosexual contact	15 (60.0)	12 (48.0)	27 (54.0)
Heterosexual contact/MSM	1 (4.0)	1 (4.0)	2 (4.0)
MSM	5 (20.0)	5 (20.0)	10 (20.0)
Other	4 (16.0)	7 (28.0)	11 (22.0)
HIV-1 Subtype[b]	**24 (100)**	**24 (100)**	**48 (100)**
A1	1 (4.0)	0	1 (2.1)
AE	4 (16.7)	1 (4.2)	5 (10.4)
B	11 (45.8)	10 (41.7)	21 (43.8)
C	6 (25.0)	11 (45.8)	17 (35.4)
Complex	2 (8.3)	2 (8.3)	4 (8.3)
Hepatitis B or C Coinfection Status	**25 (100)**	**24 (100)**	**49 (100)**
Negative	25 (100)	24 (100)[c]	49 (100)[c]

N = number of subjects; n = number of subjects with observations; MSM= men having sex with men
[a] Prebaseline = Day 1 of the Pretreatment Period
[b] As defined by Phenosense GT results provided by Monogram Biosciences
[c] For 1 subject in the ATV/rtv 400/100 mg q.d. group, hepatitis coinfection data were missing

Baseline Resistance, Median (Range)	**ATV/rtv 300/100 mg q.d.**	**ATV/rtv 400/100 mg q.d.**	**All Subjects**
Number of detectable mutations[a]	***22***	***22***	***44***
ETR RAMs [b,c]	1.0 (0 - 3)	0.0 (0 - 3)	0.0 (0 - 3)
NNRTI RAMs (extended list)[d]	2.0 (1 - 6)	2.0 (1 - 4)	2.0 (1 - 6)
IAS-USA NRTI RAMs[e]	1.0 (0 - 4)	1.0 (0 - 5)	1.0 (0 - 5)
IAS-USA PI RAMs[e]	5.0 (1 - 9)	4.0 (1 - 6)	4.5 (1 - 9)
IAS-USA Primary PI mutations[e]	0.0 (0 - 4)	0.0 (0 - 1)	0.0 (0 - 4)
ETR weighted genotypic score[b,c,f]	1.0 (0 - 3)	0.0 (0 - 3)	0.0 (0 - 3)
FC to NNRTI	***21***	***21***	***42***
ETR	1.1 (0.4 - 2.0)	0.8 (0.2 - 2.2)	0.9 (0.2 - 2.2)
Efavirenz	17.0 (0.4 - 125.0)	22.0 (0.6 - 154.6)	18.0 (0.4 - 154.6)
Nevirapine	173.0 (0.4 - 223.6)	120.0 (0.4 - 210.6)	141.0 (0.4 - 223.6)
FC to PI	***21***	***21***	***42***
Atazanavir	1.0 (0.5 - 3.1)	1.0 (0.5 - 1.9)	1.0 (0.5 - 3.1)

N= number of subjects, n= number of subjects with observations,

[a] Baseline resistance values contain all mutations present at any time point up to the first intake of study medication (Baseline and Prebaseline).

[b] Vingerhoets J, Tambuyzer L, Azijn H, et al. Resistance profile of etravirine: combined analysis of baseline genotypic and phenotypic data from the randomized controlled Phase III studies. AIDS 2010,24:503-514.

[c] Tambuyzer L, Nijs S, Daems B, Picchio G, Vingerhoets J. Effect of mutations at position E138 in HIV-1 reverse transcriptase on phenotypic susceptibility and virologic response to etravirine. J Acquir Immune Defic Syndr 2011;58(1):18-22.

[d] [redacted] List of non-nucleoside reverse transcriptase inhibitor resistance-associated mutations. Tibotec Virology Research Report NPR-TiDP-20060022-VRR, Version 7.0, January 2012.

[e] Johnson VA, Calvez V, Günthard HF, et al. Update of the drug resistance mutations in HIV-1. Topics in HIV Medicine 2011;19(4):156-164.

[f] The ETR weighted genotypic score was calculated at the Baseline time point only (not Prebaseline).

ARVs in the Background Regimen, n (%)	ATV/rtv 300/100 mg q.d.	ATV/rtv 400/100 mg q.d.	All Subjects
Pretreatment Period, N	25 (100)	24 (96.0)	49 (98.0)
NRTI	25 (100)	24 (96.0)	49 (98.0)
Lamivudine	17 (68.0)	15 (60.0)	32 (64.0)
Stavudine	9 (36.0)	11 (44.0)	20 (40.0)
Zidovudine	11 (44.0)	8 (32.0)	19 (38.0)
Didanosine	7 (28.0)	8 (32.0)	15 (30.0)
Abacavir	6 (24.0)	4 (16.0)	10 (20.0)
Emtricitabine	2 (8.0)	1 (4.0)	3 (6.0)
Tenofovir	1 (4.0)	1 (4.0)	2 (4.0)
PI	1 (4.0)	0	1 (2.0)
Darunavir[a]	1 (4.0)	0	1 (2.0)
Treatment Period, N	22 (100)	21 (95.5)	43 (97.7)
NRTI	22 (100)	21 (95.5)	43 (97.7)
Stavudine	7 (31.8)	9 (40.9)	16 (36.4)
Zidovudine	8 (36.4)	6 (27.3)	14 (31.8)
Abacavir	4 (18.2)	3 (13.6)	7 (15.9)
Lamivudine	3 (13.6)	3 (13.6)	6 (13.6)
Didanosine	2 (9.1)	0	2 (4.5)
Activity of ARVs Used in the Background Regimen All subjects except 2 used active NRTIs in the initial background regimen of the Treatment Period; 1 subject in each treatment group used 3TC as a resistant drug.			

N= number of subjects; n= number of subjects with observations.

Only the initial therapies (ie, as determined on Day 7 of the phase of treatment, or on the last day of treatment in case of dropout during this period.

Low-dose rtv was not counted as a PI. Combivir® was counted as 2 NRTIs; Trizivir® as 3 NRTIs; Truvada® as 2 NRTIs; Epzicom® / Kivexa® as 2 NRTIs; Kaletra® as 1 PI.

[a] Reported as protocol deviation (CRF ID [redacted])

Pharmacokinetic Results:

Main Study – Noncompartmental Pharmacokinetic Analysis:

Atazanavir: ATV/rtv 300/100 mg q.d. Dosing Arm

Pharmacokinetics of ATV (mean ± SD, t_{max}: median [range])	ATV/rtv 300/100 mg q.d. + 2 Investigator-Selected NRTIs (Reference)	ATV/rtv 300/100 mg q.d. + 1 Investigator-Selected NRTI + ETR 200 mg b.i.d. (Test)
n	20[a]	18[b]
C_{0h}, ng/mL	1339 ± 1728	845.7 ± 703.3
C_{min}, ng/mL	1104 ± 1511	758.6 ± 610.5
C_{max}, ng/mL	5652 ± 2735	5232 ± 2166
t_{max}, h	4.00 (1.98 - 6.00)	3.00 (1.00 - 4.17)
AUC_{24h}, ng.h/mL	60030 ± 39690	55070 ± 21860
$C_{ss,av}$, ng/mL	2496 ± 1659	2291 ± 909.4
FI, %	196.2 ± 60.54	214.0 ± 59.28
LS Mean Ratio (90% CI)		
	-	**Test vs Reference**
n	-	18[b] vs 20[a]
C_{min}	-	0.82 (0.55 - 1.22)
C_{max}	-	0.96 (0.80 - 1.16)
AUC_{24h}	-	0.96 (0.76 - 1.22)

[a] n=21 for C_{0h}, n=19 for AUC_{24h}, $C_{ss,av}$ and FI

[b] n=19 for C_{0h}, C_{max}, t_{max}

Atazanavir: ATV/rtv at 400/100 mg q.d. Dosing Arm

Pharmacokinetics of ATV (mean ± SD, t_{max}: median [range])	**ATV/rtv 300/100 mg q.d. + 2 Investigator-Selected NRTIs (Reference)**			**ATV/rtv 400/100 mg q.d. + 1 Investigator-Selected NRTI + 200 mg ETR b.i.d. (Test)**		
n	21[a]			20[b]		
C_{0h}, ng/mL	1898	±	2298	1545	±	1296
C_{min}, ng/mL	1671	±	2310	1107	±	866.8
C_{max}, ng/mL	6419	±	2853	6950	±	2693
t_{max}, h	3.04 (1.00 - 6.00)			3.21 (1.25 - 6.17)		
AUC_{24h}, ng.h/mL	74210	±	55480	72220	±	34600
$C_{ss,av}$, ng/mL	3085	±	2312	3005	±	1438
FI, %	188.6	±	73.02	213.0	±	44.23
LS Mean Ratio (90% CI)						
				Test vs Reference		
n	-			20[b] vs 21[a]		
C_{min}	-			0.91 (0.63 - 1.33)		
C_{max}	-			1.05 (0.86 - 1.27)		
AUC_{24h}	-			0.99 (0.81 - 1.21)		

[a] n=22 for C_{0h}, C_{max} and t_{max}

[b] n=18 for C_{min} and FI, n=19 for AUC_{24h} and $C_{ss,av}$

Based on the within dosing arm comparisons of Week 2 versus Day -1, addition of ETR to the ATV/rtv 300/100 mg q.d. regimen resulted in a decrease of 18% in ATV C_{min}, based on the LS means ratio. ATV C_{max}, and AUC_{24h} were relatively unchanged with LS means ratios of 96%. The addition of ETR to the ATV/rtv regimen along with a 100 mg increase in the ATV dose (ie, ATV//rtv 400/100 mg q.d.) resulted in an ATV C_{min} at Week 2 that was also lower compared to ATV/rtv 300/100 mg q.d. without ETR, however, the decrease was less pronounced. Based on the LS means ratio, ATV C_{min} was 9% lower. ATV C_{max} and AUC_{24h} were relatively unchanged when ATV/rtv 400/100 mg q.d. was administered in the presence of ETR (Week 2) compared to when ATV/rtv was dosed 300/100 mg, without ETR (Day -1). On Day -1 (ATV/rtv at 300/100 mg q.d. for both dosing arms) a difference was observed in ATV plasma concentrations between the ATV/rtv dosing arms; the mean ATV C_{max}, C_{min} and AUC_{24h} were slightly higher in those subjects randomized to receive ATV/rtv 400/100 mg q.d. Therefore, caution is needed when comparing the observed changes in ATV pharmacokinetics between the dosing arms.

Ritonavir: ATV/rtv at 300/100 mg q.d. Dosing Arm

Pharmacokinetics of rtv (mean ± SD, t_{max}: median [range])	**ATV/rtv 300/100 mg q.d. + 2 Investigator-Selected NRTIs (Reference)**	**ATV/rtv 300/100 mg q.d. + 1 Investigator-Selected NRTI + ETR 200 mg b.i.d. (Test)**
n	19[a]	18[b]
C_{0h}, ng/mL	143.4 ± 269.8	102.5 ± 157.2
C_{min}, ng/mL	60.42 ± 73.17	43.97 ± 36.29
C_{max}, ng/mL	1834 ± 1009	1740 ± 1149
t_{max}, h	4.00 (1.00 - 9.00)	4.00 (2.00 - 6.25)
AUC_{24h}, ng.h/mL	12560 ± 6643	11120 ± 6658
$C_{ss,av}$, ng/mL	521.4 ± 276.6	462.7 ± 276.4
FI, %	344.1 ± 117.4	347.6 ± 89.72
LS Mean Ratio (90% CI)		
	-	**Test vs Reference**
n	-	18[b] vs 19[a]
C_{min}	-	0.75 (0.46 - 1.21)
C_{max}	-	0.93 (0.77 - 1.13)
AUC_{24h}	-	0.88 (0.71 - 1.10)

[a] n=21 for C_{0h}, n=20 for C_{min}, C_{max} and t_{max}
[b] n=19 for C_{0h}, C_{max} and t_{max}

Ritonavir: ATV/rtv at 400/100 mg q.d. Dosing Arm

Pharmacokinetics of rtv (mean ± SD, t_{max}: median [range])	**ATV/rtv 300/100 mg q.d. + 2 Investigator-Selected NRTIs (Reference)**	**ATV/rtv 400/100 mg q.d. + 1 Investigator-Selected NRTI + ETR 200 mg b.i.d. (Test)**
n	20[a]	19[b]
C_{0h}, ng/mL	109.2 ± 94.50	163.4 ± 240.2
C_{min}, ng/mL	64.70 ± 51.80	75.68 ± 69.98
C_{max}, ng/mL	1882 ± 1026	1847 ± 859.9
t_{max}, h	4.00 (1.02 - 12.08)	4.17 (3.00 - 9.00)
AUC_{24h}, ng.h/mL	13880 ± 8198	13660 ± 6778
$C_{ss,av}$, ng/mL	577.1 ± 342.0	567.7 ± 279.8
FI, %	314.7 ± 62.33	323.8 ± 80.31
LS Mean Ratio (90% CI)		
	-	**Test vs Reference**
n	-	19[b] vs 20[a]
C_{min}	-	1.06 (0.62 - 1.83)
C_{max}	-	1.05 (0.82 - 1.35)
AUC_{24h}	-	1.02 (0.85 - 1.21)

[a] n=22 for C_{0h}, C_{max} and t_{max}
[b] n=20 for C_{0h}

Addition of ETR to the ATV/rtv 300/100 mg q.d. regimen resulted in a decrease of 25% in rtv C_{min}, based on the LS means ratio; rtv C_{max}, and AUC_{24h} were slightly lower, with LS means ratios of 0.93 and 0.88, respectively. For both rtv C_{max} and AUC_{24h}, the lower limits of the 90% CI of the LS means ratio were below 80.00%. When coadministered with ETR and the increased ATV dose of 400 mg (ie, ATV/rtv 400/100 mg q.d.), rtv C_{min} at Week 2 was slightly higher (LS means ratio 1.06) compared to Day -1; the lower and upper limits of the 90% CI were below 80.00% and above 125.00%, respectively. The C_{max} and AUC_{24h} of rtv were similar at Week 2 and Day -1, with LS means ratios of 1.05 and 1.02, respectively. For rtv C_{max}, the upper limit of the 90% CI of the LS means ratio was above 125.00%.

Etravirine

Pharmacokinetics of ETR (mean ± SD, t_{max}: median [range])	**TMC125-C206 + TMC125-C216: ETR 200 mg b.i.d. + DRV/rtv 600/100 mg b.i.d., Week 4 (Reference)**	**TMC125-C238: ATV/rtv 300/100 mg q.d. + 1 Investigator-Selected NRTI + ETR 200 mg b.i.d., Week 2 (Test 1)**	**TMC125-C238: ATV/rtv 400/100 mg q.d. + 1 Investigator-Selected NRTI + ETR 200 mg b.i.d., Week 2 (Test 2)**
n	25	18[a]	18[b]
C_{0h}, ng/mL	545.0 ± 818.6	422.2 ± 327.9	316.6 ± 215.4
C_{min}, ng/mL	452.6 ± 806.0	425.1 ± 328.1	286.5 ± 198.0
C_{max}, ng/mL	879.6 ± 1030	773.0 ± 360.5	628.7 ± 294.0
t_{max}, h	3.95 (0.08 - 6.08)	4.00 (3.00 - 9.00)	4.00 (2.00 - 6.07)
AUC_{12h}, ng.h/mL	7964 ± 11180	7629 ± 4213	5171 ± 2695
$C_{ss,av}$, ng/mL	663.9 ± 928.0	636.2 ± 350.9	431.9 ± 225.9
FI, %	85.15 ± 33.67	84.95 ± 37.66	86.92 ± 39.41
LS Mean ratio (90% CI)			
		Test 1 vs Reference	**Test 2 vs Reference**
n	-	18[a] vs 25	18[b] vs 25
C_{min}	-	1.07 (0.60 - 1.90)	0.83 (0.54 - 1.29)
C_{max}	-	1.06 (0.78 - 1.46)	0.87 (0.65 - 1.18)
AUC_{12h}	-	1.24 (0.88 - 1.76)	0.84 (0.60 - 1.18)

[a] n=19 for C_{0h}, n=16 for C_{min}, n=17 for AUC_{12h} and $C_{ss,av}$ and n=15 for FI

[b] n=19 for C_{0h}, n=20 for C_{max} and t_{max}

Based on the comparison of the 2 ATV/rtv dosing arms (ie, a between-subject comparison), ETR plasma concentrations were lower in the presence of ATV/rtv at 400/100 mg q.d. compared to in the presence of ATV/rtv at 300/100 mg. Based on statistical analysis, ETR C_{min}, C_{max} and AUC_{12h} values obtained in the ATV/rtv 300/100 mg dosing arm were 7%, 6%, and 24% higher, respectively, compared to historic control (ie, combined data from the TMC125-C206/C216 substudies [ETR in combination with DRV/rtv 600/100 mg b.i.d. and other ARVs])[*]. For the ATV/rtv 400/100 mg dosing arm, ETR C_{min}, C_{max} and AUC_{12h} values were 17%, 13% and 16% lower, respectively, compared to the combined TMC125-C206/C216 substudies at Week 4. The 90% CIs of the LS means ratios were wide.

[*] Kakuda TN, Wade JR, Snoeck E, et al. Pharmacokinetics and Pharmacodynamics of the Non-Nucleoside Reverse-Transcriptase Inhibitor Etravirine in Treatment-Experienced HIV-1-Infected Patients. Clin Pharmacol Ther 2010;88(5):695-703.

Main Study – Population Pharmacokinetic Analysis (Week 48):

Pharmacokinetic Parameter	ATV/rtv 300/100 mg q.d.	ATV/rtv 400/100 mg q.d.	All Subjects
Etravirine			
AUC_{12h} (ng.h/mL)			
n	18	17	35
Mean (SD)	6345 (4472)	5311 (3012)	5843 (3814)
Geometric mean	4926	4556	4743
Median (Min; Max)	6275 (962; 19600)	4780 (1280; 12900)	4950 (962; 19600)
C_{0h} (ng/mL)			
n	18	17	35
Mean (SD)	444 (363)	357.6 (255)	402 (313)
Geometric mean	304	266	285
Median (Min; Max)	401 (22; 1520)	318 (29; 981)	320 (22; 1520)
Atazanavir			
AUC_{24h} (ng.h/mL)			
n	18	17	35
Mean (SD)	54650 (21718.45)	73571 (37083)	63840 (31225)
Median (Min; Max)	50450 (24800; 94800)	68300 (24200; 140000)	56400 (24200; 140000)
C_{0h} (ng/mL)			
n	18	17	35
Mean (SD)	1038 (702.96)	1624 (1305.62)	1323 (1067)
Median (Min; Max)	863 (313; 3070)	1010 (550; 4790)	907 (313; 4790)
Ritonavir			
AUC_{24h} (ng.h/mL)			
n	19	18	37
Mean (SD)	10656 (5243)	13129 (6707)	11860 (6046)
Median (Min; Max)	10200 (3380; 20900)	11550 (6010; 29800)	11300 (3380; 29800)
C_{0h} (ng/mL)			
n	19	18	37
Mean (SD)	65 (49)	127 (146)	95 (111)
Median (Min; Max)	55 (14; 234)	72 (22; 613)	61 (14; 613)

Sex, race, region, or weight did not significantly influence the pharmacokinetics of ATV (AUC_{24h} or C_{0h}). A statistically significant effect was observed for age (both AUC_{24h} and C_{0h}). Higher ATV AUC_{24h} and C_{0h} values were observed in older subjects.

The geometric mean ETR AUC_{12h} in the ATV/rtv 300/100 mg q.d. group was 9% higher compared to results from the pooled Phase III studies TMC125-C206/C216, and in the ATV/rtv 400/100 mg q.d. group was comparable to the pooled Phase III studies[*]. The geometric mean ETR C_{0h} in the lower ATV/rtv dose group was comparable to the pooled Phase III studies, and in the higher ATV/rtv dose group was approximately 10% lower. There was no apparent difference in the ETR pharmacokinetics by sex or age. A trend towards higher exposures to ETR was observed in Asian subjects relative to White and Black subjects. Similarly, a trend towards higher ETR exposures was observed in subjects from the Asian region relative to other regions. Higher ETR exposures were observed in subjects with lower weights.

[*] 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.

Substudy – Noncompartmental Pharmacokinetic Analysis:

Atazanavir

Pharmacokinetics of ATV (mean ± SD, t_{max}: median [range])	**ATV/rtv 300/100 or 400/100 mg q.d. + 1 Investigator-Selected NRTI + ETR 200 mg b.i.d., Day -1 (Reference)**	**ATV/rtv 300/100 or 400/100 mg q.d. + 1 Investigator-Selected NRTI + ETR 200 mg b.i.d. + TDF 300 mg q.d., Day 7 (Test)**
n	7	6
C_{0h}, ng/mL	755 ± 488	688 ± 707
C_{min}, ng/mL	667 ± 404	677 ± 700
C_{max}, ng/mL	5859 ± 1205	5560 ± 1367
t_{max}, h	3.00 (2.00 - 4.00)	4.00 (3.00 - 4.00)
AUC_{24h}, ng.h/mL	58680 ± 12150	54390 ± 18060
$C_{ss,av}$, ng/mL	2446 ± 506	2266 ± 752
FI, %	217.2 ± 59.4	236.3 ± 84.3
LS Mean Ratio (90% CI)		
	-	**Test vs Reference**
n	-	6 vs 6
C_{min}	-	0.75 (0.41 - 1.36)
C_{max}	-	0.97 (0.75 - 1.25)
AUC_{24h}	-	0.91 (0.72 - 1.13)

Ritonavir

Pharmacokinetics of rtv (mean ± SD, t_{max}: median [range])	**ATV/rtv 300/100 or 400/100 mg q.d. + 1 Investigator-Selected NRTI + ETR 200 mg b.i.d., Day -1 (Reference)**	**ATV/rtv 300/100 or 400/100 mg q.d. + 1 Investigator-Selected NRTI + ETR 200 mg b.i.d. + TDF 300 mg q.d., Day 7 (Test)**
n	7	7
C_{0h}, ng/mL	64 ± 92	71 ± 81
C_{min}, ng/mL	53 ± 69	51 ± 52
C_{max}, ng/mL	1596 ± 796	1462 ± 714
t_{max}, h	3.98 (2.00 - 4.00)	4.00 (3.00 - 6.00)
AUC_{24h}, ng.h/mL	11270 ± 6489	10860 ± 5753
$C_{ss,av}$, ng/mL	470 ± 270	452 ± 240
FI, %	347.0 ± 67.7	323.3 ± 57.6
LS Mean Ratio (90% CI)		
	-	**Test vs Reference**
n	-	7 vs 7
C_{min}	-	0.87 (0.46 - 1.64)
C_{max}	-	0.91 (0.70 - 1.17)
AUC_{24h}	-	0.97 (0.85 - 1.10)

Etravirine

Pharmacokinetics of ETR (mean ± SD, t_{max}: median [range])	**ATV/rtv 300/100 or 400/100 mg q.d. + 1 Investigator-Selected NRTI + ETR 200 mg b.i.d., Day -1 (Reference)**			**ATV/rtv 300/100 or 400/100 mg q.d. + 1 Investigator-Selected NRTI + ETR 200 mg b.i.d. + TDF 300 mg q.d., Day 7 (Test)**		
n	7			7		
C_{0h}, ng/mL	672	±	449	637	±	426
C_{min}, ng/mL	634	±	423	581	±	371
C_{max}, ng/mL	1138	±	604	949	±	506
t_{max}, h	3.98 (2.75 - 6.17)			4.00 (2.75 - 5.75)		
AUC_{12h}, ng.h/mL	10590	±	6333	9090	±	5299
$C_{ss,av}$, ng/mL	889	±	529	762	±	443
FI, %	73.0	±	47.8	57.8	±	27.4
LS Mean Ratio (90% CI)						
				Test vs Reference		
n	-			7 vs 7		
C_{min}	-			0.97 (0.85 - 1.10)		
C_{max}	-			0.81 (0.72 - 0.91)		
AUC_{12h}	-			0.85 (0.79 - 0.92)		

Tenofovir Disoproxil Fumarate

Pharmacokinetics of TDF (mean ± SD, t_{max}: median [range])	**ATV/rtv 300/100 or 400/100 mg q.d. + 1 Investigator-Selected NRTI + ETR 200 mg b.i.d. + TDF 300 mg q.d., Day 7**		
n	7		
C_{0h}, ng/mL	81	±	39
C_{min}, ng/mL	76	±	38
C_{max}, ng/mL	372	±	87
t_{max}, h	2.00 (1.00 - 3.67)		
AUC_{24h}, ng.h/mL	4101	±	986
$C_{ss,av}$, ng/mL	172	±	41
FI, %	180.4	±	78.6

Overall, addition of TDF to ATV/rtv and ETR resulted in a modest effect on the pharmacokinetics of ATV, rtv, and ETR based on statistical analyses on paired data. Statistical analyses based on all data (ie, paired and unpaired) showed comparable results. Considering the limited number of subjects in the substudy, the extent of the observed effects have to be interpreted with caution. ATV C_{max} and AUC_{24h} were 3% and 9% lower, respectively, in the presence of additional TDF, compared to Day -1. The 90% CIs were wide and the lower limits fell below 80.00%. ATV C_{min} was 25% lower in the presence of TDF, with wide 90% CIs which contained 100%.

C_{min} and C_{max} for rtv were 13% and 9% lower, respectively, in the presence of additional TDF, compared to Day -1. The 90% CIs were wide, especially for C_{min}, and the lower limits fell below 80.00%. For C_{min} the upper limit of the 90% CI fell above 125.00% as well. The rtv AUC_{24h} was comparable with and without additional TDF (LS means ratio 97% and 90% CIs within 80.00% to 125.00%).

C_{max} and AUC_{12h} for ETR were 19% and 15% lower, respectively, in the presence of additional TDF, as compared to Day -1. The lower limits of the 90% CIs of the LS means ratio fell below 80.00% and the upper limits were below 100%. ETR C_{min} was comparable with and without additional TDF (LS means ratio 0.97 and 90% CIs within 80.00% to 125.00%).

Pharmacogenomic Results:

Based on the limited amount of available data, no obvious effect of CYP2C9 or CYP2C19 genotype on the pharmacokinetics of ETR was observed.

For CYP2C9, individual ETR AUC_{12h} values for subjects with a *1/*11 genotype (n=3), and a *2/*2 genotype (n=1) were within the ranges observed for the wild-type genotype (*1/*1). For one subject with a *1/*2 CYP2C9 genotype, the ETR AUC_{12h} value was just above the ranges observed for the wild-type genotype. For CYP2C19, individual ETR AUC_{12h} values for subjects with a *1/*2 genotype (n=3) and *1/*3 genotype (n=1) were within the ranges observed for the wild-type genotype. For the *1/*17 (n=6), the *17/*2 (n=3) and *17/*17 (n=2) CYP2C19 genotypes, ETR AUC_{12h} values tended to be below or towards the lower end of the ranges observed for the wild-type genotype, but this was not the case for all of these subjects.

Safety Results:

AEs

Treatment-emergent AEs during the Pretreatment Period occurred in 17 subjects (34.0%). The most common AE preferred terms were nausea, diarrhea, vomiting, and depression. Most AEs were grade 1 or 2 in severity. Grade 3 or 4 AEs occurred in 3 subjects (6.0%). Ten subjects (20%) had at least 1 AE considered possibly related to ATV/rtv. There were no deaths, 1 subject experienced an SAE (accidental overdose [grade 1, not related to ATV]), and no subjects permanently discontinued due to an AE. Skin events (rash [grouped term]) were the most frequent events of interest during the Pretreatment Period occurring in 5 subjects (10%), Other events of interest include hepatic and neuropsychiatric events occurring in 4 subjects (8%) and 2 subjects (4%), respectively.

Treatment-emergent AEs during the Treatment Period occurred in 90.9% of subjects in the ATV/rtv 300/100 mg q.d. group and 77.3% of subjects in the ATV/rtv 400/100 mg q.d. group. The most common AE preferred terms were influenza, sinusitis, cough, and headache. Most AEs were grade 1 or 2 in severity. Grade 3 or 4 AEs occurred in 4 subjects (18.2%) in both treatment groups. Three subjects had a grade 4 AE, all in the ATV/rtv 300/100 mg q.d. group; 2 of these grade 4 AEs were considered not related to ETR and 1 AE (hyperuricemia) was considered possibly related to ETR. One subject in the ATV/rtv 300/100 mg q.d. group died due to grade 4 metastatic malignant melanoma, considered not related to ETR. Four subjects (18.2%) in the ATV/rtv 300/100 mg q.d. group and 2 subjects (9.1%) in the ATV/rtv 400/100 mg q.d. group had at least 1 SAE, and all SAEs were considered not related to ETR. Each of the reported SAE preferred terms occurred in only 1 subject, except pneumonia (2 subjects). Two subjects in each treatment group permanently discontinued study treatment due to an AE (including 1 pregnancy).

Hepatic events were the most frequent events of interest, in both treatment groups occurring in 5 subjects (22.7%). The most common hepatic events by preferred term were blood bilirubin increased (4 subjects), and hyperbilirubinemia and jaundice (both reported in 2 subjects). Most hepatic events were grade 1 or 2 in severity. Overall, 3 subjects had hepatic events that were considered at least possibly related to ETR.

Skin events were reported in 5 subjects (22.7%) in the ATV/rtv 300/100 mg q.d. group and 2 subjects. (9.1%) in the ATV/rtv 400/100 mg q.d group. The most common skin event was rash (grouped term) reported in 5 subjects overall; 4 of these cases were considered at least possibly related to ETR. Other skin events of interest include 1 case of angioedema, and 1 case of conjunctivitis (grouped under severe cutaneous reactions) both in the ATV/rtv 300/100 mg q.d. group.

The incidence of neuropsychiatric events of interest (3 subjects in the ATV/rtv 300/100 mg q.d. group), and pancreatic events (1 subject in the ATV/rtv 400/100 mg q.d. group) was low. There were no cardiac, bleeding, or lipid-related events of interest reported.

In the substudy, there were no safety signals following the 7-day coadministration of ETR 200 mg b.i.d., ATV/rtv 300/100 or 400/100 mg q.d., TDF 300 mg q.d., and 1 NRTI.

AEs During Pretreatment Period, n (%)	ATV/rtv 300/100 mg q.d. N = 25	ATV/rtv 400/100 mg q.d.[a] N = 25	All Subjects N = 50
Any AE	12 (48.0)	5 (20.0)	17 (34.0)
Most frequent AEs (>1 subject)			
Nausea	3 (12.0)	0	3 (6.0)
Diarrhea	2 (8.0)	0	2 (4.0)
Vomiting	2 (8.0)	0	2 (4.0)
Depression	2 (8.0)	0	2 (4.0)
SAE	1 (4.0)	0	1 (2.0)
Fatal AE	0	0	0
Grade 3 or 4 AE	2 (8.0)	1 (4.0)	3 (6.0)
Leading to discontinuation	0	0	0
At least possibly related to ATV	6 (24.0)	4 (16.0)	10 (20.0)
AEs of Special Interest			
Skin Events of Interest	3 (12)	2 (8.0)	5 (10.0)
Rash	3 (12)	2 (8.0)	5 (10.0)
Neuropsychiatric Events of Interest	2 (8.0)	0	2 (4.0)
Hepatic Events of Interest	2 (8.0)	2 (8.0)	4 (8.0)
Cardiac Events of Interest	0	0	0
Bleeding Events of Interest	0	0	0
Pancreatic Events of Interest	0	0	0
Lipid-Related Events of Interest	0	0	0

N = number of subjects; n = number of subjects with observations

[a] During the Pretreatment Period all subjects received ATV/rtv 300/100 mg q.d.

AEs During Treatment Period, n (%)	ATV/rtv 300/100 mg q.d. N = 22	ATV/rtv 400/100 mg q.d. N = 22	All Subjects N = 44
Any AE	20 (90.9)	17 (77.3)	37 (84.1)
Most frequent AEs (>3 subjects)			
Cough	5 (22.7)	4 (18.2)	9 (20.5)
Headache	3 (13.6)	4 (18.2)	7 (15.9)
Influenza	2 (9.1)	3 (13.6)	5 (11.4)
Sinusitis	3 (13.6)	0	3 (6.8)
SAE	4 (18.2)	2 (9.1)	6 (13.6)
Fatal AE	1 (4.5)	0	1 (2.3)
Grade 3 or 4 AE	4 (18.2)	4 (18.2)	8 (18.2)
Leading to discontinuation	2 (9.1)	2 (9.1)	4 (9.1)
At least possibly related to ETR	5 (22.7)	5 (22.7)	10 (22.7)
At least possibly related to ETR or ATV	8 (36.4)	7 (31.8)	15 (34.1)
AEs of Special Interest			
Skin Events of Interest	5 (22.7)	2 (9.1)	7 (15.9)
Rash	3 (13.6)	2 (9.1)	5 (11.4)
Angioedema	1 (4.5)	0	1 (2.3)
Severe cutaneous reaction	1 (4.5)	0	1 (2.3)
Neuropsychiatric Events of Interest	3 (13.6)	0	3 (6.8)
Hepatic Events of Interest	5 (22.7)	5 (22.7)	10 (22.7)
Cardiac Events of Interest	0	0	0
Bleeding Events of Interest	0	0	0
Pancreatic Events of Interest	1 (4.5)	0	1 (2.3)
Lipid-Related Events of Interest	0	0	0

Clinical Laboratory Tests

Mean changes over time in the clinical laboratory parameters were generally small in both treatment groups and not considered clinically relevant, except for an increase in mean bilirubin values (direct, indirect, and total) during the Pretreatment period, which remained elevated throughout the Treatment Period up to Week 48.

During the Treatment Period, most treatment-emergent laboratory abnormalities reported were grade 1 or 2 in severity. The most common laboratory abnormalities were hepatic-related parameters, and mainly included hyperbilirubinemia (42.9% of subjects). Other abnormalities were related to lipid- and glucose-related parameters (total cholesterol in 31.0%, LDL cholesterol 21.4%, hyperglycemia in 26.2%). All individual grade 3 or 4 treatment-emergent abnormalities occurred in at most 1 subject, except hyperbilirubinemia, which occurred in 4 subjects (19.0%) in the ATV/rtv 300/100 mg q.d. group (all grade 3) and 2 subjects (9.5%) in the ATV/rtv 400/100 mg q.d. group (both grade 4). Direct bilirubin above normal occurred in 5 subjects (23.8%) in the ATV/rtv 300/100 mg q.d. group and 2 subjects (9.5%) in the ATV/rtv 400/100 mg q.d. group; indirect bilirubin above normal occurred in 4 (19.0%) and 7 (33.3%) subjects in the respective treatment groups. The incidence of AEs related to laboratory abnormalities was low in both treatment groups.

Cardiovascular Safety

No clinically relevant mean changes from Baseline in vital signs parameters were observed. There were no grade 3 abnormalities related to vital signs. One vital signs abnormality (grade 1 hypertension; not related) was reported as an AE during the Treatment Period.

Mean changes in ECG parameters from Baseline were generally small and comparable for the 2 treatment groups. The incidence of ECG abnormalities was low in both treatment groups. No subjects had QTcB >500 ms or QTcF ≥480ms. Both increased QTcB and QTcF by 30 to 60 ms were observed in 3 subjects in each treatment group. One ECG abnormality (grade 2 tachycardia; not related) was reported as an AE during the Treatment Period.

Other Safety Observations

No clinically relevant mean changes from Baseline in anthropometric measurements were observed. One AE related to anthropometric measurements (grade 1 weight decreased; possibly related) was reported during the Treatment Period.

Efficacy Results:

At Week 48, virologic response defined as plasma VL <50 copies/mL (NC=F, primary efficacy analysis) was achieved by 50.0% of subjects in the ATV/rtv 300/100 mg q.d. group and 45.5% in the ATV/rtv 400/100 mg q.d. group. Virologic response per the snapshot analysis demonstrated similar response rates. Five subjects (11.4%) discontinued the study for reasons not related to safety or efficacy (ie, discontinued due to other reason and last available HIV RNA <50 copies/mL).

An increase in absolute CD4+ cell count was observed at all time points in both treatment groups. At Week 48, the mean (SE) change in absolute CD4+ cell count from Prebaseline was +105 (31.1) x 10^6 cells/L in the ATV/rtv 300/100 mg q.d. group, and +132 (32.6) x 10^6 cells/L in the ATV/rtv 400/100 mg q.d. group.

Efficacy Parameters	ATV/rtv 300/100 mg q.d. N = 22	ATV/rtv 400/100 mg q.d. N = 22	All Subjects N = 44
Primary Analysis (Week 48)			
NC=F[a], n (%)			
Plasma VL <50 copies/mL	11 (50.0)	10 (45.5)	21 (47.7)
Secondary Analysis (Week 48)			
NC=F[a]			
Plasma VL <400 copies/mL, n (%)	11 (50.0)	13 (59.1)	24 (54.5)
Change in Plasma VL from Prebaseline (log_{10} copies/mL), mean (SE)	-1.4 (0.24)	-1.4 (0.29)	-1.4 (0.18)
Change in CD4+ cell count from Prebaseline (x 10^6 cells/L), mean (SE)	+105.4 (31.08)	+131.9 (32.62)	+118.3 (22.33)
TLOVR[b], n (%)			
Plasma VL <50 copies/mL	10 (45.5)	11 (50.0)	21 (47.7)
Plasma VL <400 copies/mL	13 (59.1)	12 (54.5)	25 (56.8)
Snapshot[c], n (%)			
Plasma VL <50 copies/mL	11 (50.0)	10 (45.5)	21 (47.7)
Virologic Failure[(A)]	7 (31.8)	8 (36.4)	15 (34.1)
HIV RNA ≥50 copies/mL at Week 48	4 (18.2)	6 (27.3)	10 (22.7)
Discontinued due to other reason[(B)] and last available HIV RNA ≥50 copies/mL	3 (13.6)	2 (9.1)	5 (11.4)
No VL data in Week-48 Window	4 (18.2)	4 (18.2)	8 (18.2)
Discontinued due to AE/death[(C)]	2 (9.1)	1 (4.5)	3 (6.8)
Discontinued due to other reason[(B)] and last available HIV RNA <50 copies/mL (or missing)	2 (9.1)	3 (13.6)	5 (11.4)

N = number of subjects; n = number of subjects with observations

[a] Noncompleter equals failure (NC=F) imputation method.

[b] Time to loss of virologic response (TLOVR) imputation method.

[c] Snapshot analysis:

[(A)] Includes i) subjects who had ≥50 copies in the Week-48 window, ii) subjects who discontinued prior to Week-48 for lack or loss of efficacy, iii) subjects who had a switch in their other background regimen (OBR) that was not permitted by the protocol (provided the switch occurred before the earliest onset of an AE leading to permanent stop of study medication), and iv) subjects who discontinued for reasons other than AEs/death and lack or loss of efficacy (provided their last available VL was detectable).

[(B)] Includes subjects who discontinued for reasons other than AEs/death and lack or loss of efficacy (provided their last available VL was undetectable).

[(C)] Includes subjects who discontinued due to AE or death at any time point from Day 1 through the Week-48 time window if this resulted in no virologic data on treatment during the specified window (provided the earliest AE leading to permanent stop was not preceeded by a switch in the OBR that was not permitted by the protocol).

Resistance Results:

Limited emergence of NNRTI RAMs was observed in the 13 virologic failures, with K101P and Y181C as the only ETR RAMs observed in more than 1 subject (n=2 and n=3, respectively). For the 12 virologic failures with available phenotype data, the median ETR FC increased from 0.73 (ranging from 0.4 to 1.7) at baseline to 2.99 (ranging from 0.6 to 40.0) at endpoint. No relevant development of resistance to ATV was observed in the group of virologic failures.

Study Limitations:

- Difficulty in retention of subjects in the study, as reflected in the high number of discontinuations due to noncompliance, loss to follow up, and withdrawal of consent.
- Enrollment in the substudy was planned until 20 subjects were assigned or until the main study was permanently discontinued; efforts were made to include a minimum of 8 subjects in each ATV/rtv dose group. Eventually, only 7 evaluable subjects were enrolled in the substudy, 1 subject entered while not being eligible and was withdrawn after 3 days of TDF administration.

Conclusion(s):

The noncompartmental pharmacokinetic analyses showed that the addition of ETR to ATV/rtv 300/100 mg q.d. or 400/100 mg q.d. resulted in ATV AUC_{24h} and C_{max} relatively unchanged. However, ATV C_{min} was decreased 18% when ETR was administered with ATV/rtv 300/100 mg q.d. and decreased 9% when ETR was administered with ATV/rtv 400/100 mg q.d. compared to when ATV/rtv was administered without ETR.

ETR plasma concentrations were lower in the presence of ATV/rtv at 400/100 mg q.d. compared to in the presence of ATV/rtv at 300/100 mg q.d.. Based on statistical analysis, ETR C_{min}, C_{max} and AUC_{12h} values obtained in the ATV/rtv 300/100 mg dosing arm were 7%, 6%, and 24% higher compared to historic control. For the ATV/rtv 400/100 mg dosing arm, ETR C_{min}, C_{max} and AUC_{12h} values were 17%, 13%, and 16% lower compared to historic control. The 90% CIs of the LS means ratios were wide.

The addition of TDF to ETR and ATV/rtv (in the pharmacokinetic substudy) showed a modest effect on the pharmacokinetics of ATV, rtv and ETR. In the presence of TDF, ATV C_{min}, C_{max} and AUC_{24h} were 25%, 3% and 9% lower, rtv C_{min} and C_{max} were 13% and 9% lower (AUC_{24h} was comparable), and ETR C_{max} and AUC_{12h} were 19% and 15% lower (C_{min} was comparable).

The population pharmacokinetic analyses showed lower ETR AUC_{12h} and C_{0h} relative to the results from the pooled Phase III studies TMC125-C206/C216 (where ETR was coadministered with DRV/rtv 600/100 mg b.i.d.) were observed when ETR was coadministered with ATV/rtv 400/100 mg q.d. In contrast, ETR pharmacokinetics were comparable when comparing ETR coadministered with ATV 300/100 mg q.d. ATV C_{min} was decreased in both dosing arms, 18% in the ATV 300/100 mg q.d. group versus 9% in the ATV/rtv 400/100 mg q.d. group. ATV AUC_{24h} and C_{max} on the other hand were relatively unchanged.

Based on the limited amount of available data, no obvious effect of CYP2C9 or CYP2C19 genotype on the pharmacokinetics of ETR was observed.

Coadministration of ETR 200 mg b.i.d. and ATV/rtv at 300/100 mg q.d. or 400/100 mg q.d. and 1 NRTI 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.

The only ETR RAMs that emerged in more than 1 subject experiencing virologic failure were K101P (n=2) and Y181C (n=3).

The efficacy results for this study showed that with combined treatment of ETR, ATV/rtv and 1 NRTI, 47.7% of subjects achieved a plasma viral load of < 50 copies/mL at Week 48 (NC=F): 50.0% in the lower and 45.5% in the higher ATV/rtv dose group. The overall mean change in CD4+ cell count from Prebaseline at Week 48 was +118 x 10^6 cells/L.

SIGNATURES

Signed by	Date	Justification
[redacted]	09Nov2012, 11:48:26 AM, UTC	Document Approval

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