SYNOPSIS

Trial Identification and Protocol Summary

Company: Tibotec Pharmaceuticals Ltd. (now Tibotec Pharmaceuticals) **Trade Name**: INTELENCE™ **Indication**: HIV-1	**Drug Substance**: etravirine **Trial no**.: TMC125-C229, CR002731 **Clinical Phase**: II
Title: An open-label trial with TMC125 in HIV-1 infected subjects, who were randomized to a TMC125 treatment arm in a sponsor-selected TMC125 trial and were treated for at least 48 weeks.	
Investigator: P. J. Ruane MD, 5901 W. Olympic Blvd., Suite 401, Los Angeles, CA 90036, USA.	**Countries**: United States, Canada, Italy, Belgium, Spain, France, Poland, Portugal, United Kingdom, The Netherlands, Switzerland, Germany
Trial Period: Start: 27-Jun-2005 End: 29-Aug-2008	**No. of Investigators**: 69 **No. of Subjects**: 211
Objectives: The primary objective of this study was to evaluate the long-term safety and tolerability of etravirine (ETR, formerly known as TMC125). Secondary objectives were to evaluate the antiviral activity of ETR as part of an antiretroviral therapy (ART) over time, to evaluate the immunological effect of ETR as part of an ART over time, and to evaluate genotypic and phenotypic changes over time.	
Design: This was a Phase II, open-label, roll-over trial to evaluate the long term safety and tolerability of etravirine (ETR, formerly known as TMC125), administered as part of an individually optimized antiretroviral therapy (ART), in HIV-1 infected subjects. In addition, the antiviral activity and immunologic effect of ETR as part of an ART regimen over time, and the genotypic and phenotypic changes over time were evaluated. Subjects who were randomized to an ETR treatment arm in a sponsor-selected ETR trial, were treated for at least 48 weeks with ETR, and who may have derived continued benefit from ETR therapy as judged by the investigator could be enrolled. Based on the selected trials it was estimated that approximately 300 subjects would be enrolled in the current trial. ETR at 800 mg b.i.d. (formulation TF035) and, after formulation switch, at 200 mg b.i.d. (formulation F060) was given in combination with an investigator-selected, optimized underlying therapy (NRTIs and/or allowed PIs and/or enfuvirtide [ENF]). Tolerability and safety were assessed throughout the trial and efficacy parameters were determined at defined timepoints during the trial. A pharmacokinetic substudy was performed to determine the steady-state pharmacokinetics of ETR administered as 800 mg b.i.d. (TF035) and after switching to 200 mg b.i.d. (F060). Participation in this substudy was optional.	
Subject Selection Inclusion Criteria 1. Subject voluntarily signed the informed consent; 2. Subject was previously randomized to an ETR treatment arm and completed at least 48 weeks of treatment with ETR. 3. Subject was able to comply with the protocol requirements; 4. Subject's general medical condition, in the investigator's opinion, did not interfere with the assessments and the completion of the trial. Exclusion Criteria 1. Use of disallowed concomitant therapy unless a prior exemption had been granted; 2. Any treatment-emergent condition or exacerbation of underlying condition during original Phase II trial, which in the investigator's opinion would likely have compromised the subject's safety or compliance with the study procedures;	

Exclusion Criteria (Cont'd.)

3. Female of childbearing potential without the use of effective birth control methods or not willing to continue practicing these birth control methods during the trial and for at least 14 days after the end of the trial (or after the last intake of ART);
   Note: Hormone-based contraception may not be reliable when taking ETR, therefore to be eligible for this study women of childbearing potential had to either:
   (1) use a double barrier method to prevent pregnancy (i.e., using a condom with diaphragm or cervical cap); or
   (2) use hormone-based contraceptives in combination with a barrier contraceptive (i.e. male condom, diaphragm or cervical cap or female condom); or
   (3) use an intrauterine device (IUD) in combination with a barrier contraceptive (i.e., male condom, diaphragm or cervical cap or female condom); or
   (4) be non-heterosexually active, practice sexual abstinence or have a vasectomized partner.
   Note: Women who were postmenopausal for at least 2 years, women with total hysterectomy and women who had had a tubal ligation were considered to be of non-childbearing potential.
4. A grade 3 elevation of amylase and/or lipase except for isolated grade 3 increases of amylase with lipase in normal range and no history of pancreatitis;
5. Any grade 4 toxicity according to the Division of AIDS (DAIDS) grading table; with the exception of grade 4 elevations of triglycerides or glucose asymptomatic or under non-fasting conditions; grade 4 elevation of glucose in subjects with pre-existing diabetes.
6. Subjects with clinical or laboratory evidence of significantly decreased hepatic function or decompensation, irrespective of liver enzyme levels (International Normalized Ratio [INR] > 1.5 or albumin < 30 g/L or bilirubin > 2.5 x ULN).

Treatment	ETR	
Concentration	800 mg b.i.d. or, after formulation switch, 200 mg b.i.d.	
Dosage Form (formulation)	200 mg tablets (TF035); 100 mg tablets (F060)	
Usage	Oral	
Batch Number	**Formulation TF035** D04255, D04256	**Formulation F060** 06A16, 06A12, 06A11, 05K24, 05J18, 05H18, 05H23, 05E2, 05H25, 05E23, 05E09, 05E03, 05E11, 05E10, 05E02, 05D27, 05D26, 05D25, 05D23, 05D08, 05D07, 05D06
Dose Regimen	TMC125 800 mg b.i.d. (4 tablets TF035 b.i.d.) or after formulation switch, TMC125 200 mg b.i.d. (2 tablets F060 b.i.d.) + Underlying ART consisting of optimized background regimen (OBR): at least 2 ARV drugs: NRTI(s) and/or allowed PI(s) and/or ENF	
Duration of Treatment	Until subjects no longer benefited from the ETR therapy, until ETR was commercially available, or until stopping the trial after the approval of the TMC125-C229-CTPA-GEN-III amendment by applicable IRB/IEC, upon which subjects could enroll in another Tibotec-sponsored program.	
Duration of Trial (Median; range)	122.9 weeks (0.6 - 149.7 weeks)	

Disallowed Medication	**Disallowed Antiretroviral Therapy** The following ARV drugs were not allowed from Visit 1 and throughout the trial: - PIs: use of a combination of PIs other than DRV/rtv 600/100 mg b.i.d., LPV/rtv 400/100 mg b.i.d., SQV/rtv 1000/100 mg b.i.d., ATV/rtv 300/100 mg q.d. and SQV/LPV/rtv 1000/400/100 mg b.i.d. SQV could be administered as Fortovase or Invirase. SQV or ATV was not to be used without low-dose ritonavir when combined with ETR. - NNRTIs: use of any other than ETR. **Disallowed Concomitant Therapy** The following medications were not allowed from enrollment until completion or withdrawal visit: • Therapeutic HIV vaccines; • Other approved vaccines were allowed as long as they were given outside the 4-week time frame preceding a plasma viral load measurement; • All investigational drugs were disallowed throughout the trial (except for tenofovir (TDF), emtricitabine (FTC), ENF where these were not yet licensed in a participating country); • Cytochrome P450 3A4 inducers: ➢ rifamycins: rifabutin, rifampicin/rifampin, rifapentin ➢ anticonvulsants: phenobarbital, phenytoin, carbamazepine, ➢ systemic dexamethasone, ➢ all products containing *Hypericum perforatum* (St John's Wort); • Cytochrome P450 3A4 inhibitors and inhibitors of transporting proteins: ➢ Systemic azole antifungals: ketoconazole and voriconazole were not allowed; itraconazole if not exceeding 200 mg/day and fluconazole were allowed, ➢ Macrolide antibiotics: erythromycin, clarithromycin and troleandomycin. In case there was a need to introduce these drugs during the trial, dosage and regimen had to be discussed in advance with the sponsor; • Cytochrome P450 3A4 substrates with a small therapeutic index: ➢ Terfenadine, astemizole, cisapride, triazolam, and midazolam; • The antiarrhythmics amiodarone and quinidine; • The antimigraine ergotamines, dihydroergotamine, ergonovine, methylergonovine, ergotaminetartrate and other ergot derivates; • The lipid lowering agents simvastatin and lovastatin; • Cyclosporin, tacrolimus, warfarin, digoxin; • Bone marrow suppressants used in oncology treatment. In case there was a need to introduce these drugs during the trial, this had to be discussed in advance with the sponsor.
Statistical Methods	Intent to treat (ITT) analysis, descriptive statistics, frequency tabulations Wilcoxon matched-pairs signed-ranks test, Kaplan-Meier curves.

Type of Visit	**Last visit original CR002731 trial / First visit CR002731 trial[1]**	**Treatment Period[2]**					**Final/ Withdrawal – Visit**	**Post-Treatment Follow-up Period**	
Time of Visit		**Week 8**	**Week 16**	**Week 24**	**Week 36**	**Week 48[3]**		**Week 1 Follow-up Visit**	**Week 4 Follow-up Visit**
Visit	**1**	**2**	**3**	**4**	**5**	**6**	**X**	**Y**	**Z**
Informed consent	X								
Urinary pregnancy test if applicable	X	X	X	X	X	X	X		X
Inclusion/exclusion criteria	X								
Complete physical examination	X			X		X	X		X
Brief physical examination		X	X		X				
PBMC sample	X			X		X	X		
T_3, T_4 and TSH testing	X			X		X	X		
Hematology and biochemistry (10h fasting), urinalysis	X	X	X	X	X	X	X	X	X
Vital signs	X	X	X	X	X	X	X	X	X
ECG (central reading)	X			X		X	X		
Weight	X	X	X	X	X	X	X		X
TMC125 pharmacokinetics[4]	X			X		X	X		
Samples for pheno-and genotypic determinations[5]	X	X	X	X	X	X	X	X	X
Plasma viral load	X	X	X	X	X	X	X	X	X
Immunology	X	X	X	X	X	X	X		X
Dispensation of investigational medication	X	X	X	X	X	X			
Concomitant therapy	X	X	X	X	X	X	X	X	X
Observe/Interview for AEs and HIV-related events	X	X	X	X	X	X	X	X	X

[1] The last visit of the original Phase II CR002731 trial was used as baseline for this trial. Overlapping assessments from the original trial to the CR002731 trial were only conducted once.

[2] Unscheduled visits could be performed for safety / tolerability reasons and for a confirmatory plasma viral load.

[3] Visits each 12 weeks beyond 48 weeks until ETR was commercially available alternating Visit 5 (starting with Week 60) and Visit 6 (Week72) assessments. Subjects were to be withdrawn from the trial at their next visit following the approval of the TMC125-C229-CTPA-GEN-III amendment by applicable IRB/IEC. Subjects could enroll in another Tibotec-sponsored program, in which case the final/withdrawal visit of this trial was to coincide with the baseline visit of that program. For these subjects the post-treatment follow-up period was not applicable.

[4] Pharmacokinetic samples were only analyzed upon sponsor specific request. Samples could be taken at any given time point before or after intake of study medication.

[5] Samples collected at the first visit of this trial were tested in real time for the determination of the virco®TYPE HIV-1 and results were provided to the investigator. Samples collected at the final/withdrawal visit and other intervals could be selected for testing by the Protocol Virologist based on viral load; reports were not provided.

Main Features of the Subject Sample and Summary of the Results

Subject dispostion **Discontinuations and Treatment Duration**	**ETR** **N = 211**
Discontinuations – Reason, n (%)	
Any reason	***72 (34.1)***
Subject reached a virologic endpoint	29 (13.7)
Subject withdrew consent	14 (6.6)
Adverse event/HIV related event	10 (4.7)
Subject lost to follow-up	4 (1.9)
Subject noncompliant	4 (1.9)
Subject ineligible to continue the trial	2 (0.9)
Other	9 (4.3)
Completed, n (%)	***139 (65.9)***
Duration of Treatment in CR002731	
Median (range), weeks	120.4 (0 - 149)
Total subject-years of exposure	411.1

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

Baseline Characteristics	**ETR** **N = 211**
Demographic Data*	
Gender, n (%)	
Female	21 (10.0)
Male	190 (90.0)
Age: median (range), years	46.0 (32 – 70)
Weight: median (range), kg	76.2 (47 – 130)
BMI: median (range), kg/m^2	24.6 (17 – 44)
Ethnic Origin, n (%)	
Caucasian	164 (77.7)
Black	24 (11.4)
Hispanic	16 (7.6)
Other	7 (3.3)
Baseline Disease Characteristics*	
Viral load: median (range), copies/mL	51 (49 – 661,765)
Log_{10} viral load: median (range), copies/mL	1.71 (1.7 – 5.8)
CD4+ cell count: median (range), 10^6 cells/L	309.0 (2.0 – 1266.0)
Duration of known HIV infection: median (range), years	14.61 (3.8 – 23.8)
CDC Category, n (%)	
Category A	45 (21.3)
Category B	51 (24.2)
Category C	115 (54.5)
HBV – HBsAg Positive, n (%)	9 (4.3)
Active HCV infection, n (%)	16 (7.6)
Hepatitis B and/or C co-infection	25 (11.8)

N = number of subjects; n = number of subjects with observations
* at Baseline of CR002731 trial

Previous* ARV experience, n (%)	**ETR N = 211**
NNRTI	
≥ 1	204 (96.7)
NRTI	
≥ 3	208 (98.6)
PI	
≥ 3	152 (72.0)
Fusion Inhibitor	
1	30 (14.2)

N = number of subjects; n = number of subjects with observations
* at Baseline of CR002731 feeder trial (trials TMC125-C203, TMC125-C209, TMC125-C223 or TMC125-C211)

Baseline* Resistance Data	**ETR N = 211**
Baseline RT Mutations, median (range)	
Tibotec NNRTI RAMs[a]	2 (0 – 8)
ETR RAMs[b]	1 (0 – 6)
IAS – USA NNRTI RAMs[c]	1 (0 – 6)
IAS – USA NRTI RAMs[c]	5 (0 – 8)
Baseline FC NNRTIs, median (range)	
Nevirapine (NVP)	66.8 (0.2 – 186.2)
Efavirenz (EFV)	15.3 (0.3 – 25445.3)
ETR	1.9 (0.0 – 2794.4)

N = number of subjects; n = number of subjects with observations.
*Baseline resistance data were imputed from the most recent on-treatment resistance tests in the CR002731 feeder trials
[a] Tambuyzer L, et al. NPR-20060022-VRR v5.0.
[b] Vingerhoets J, et al. Antiviral Therapy 2008; 13: Suppl 3, A26 (Abstract 24).
[c] Johnson VA, et al. Topics in HIV Medicine 2007; 15(4): 119-125.

Underlying ART During the CR002731 Treatment Period	**ETR N = 211**
Number of ARVs in Underlying ART, n (%)	
Any ARV	
1	1 (0.5)
2	34 (16.1)
3	95 (45.0)
4	65 (30.8)
5	13 (6.2)
6	3 (1.4)
NRTI	
0	3 (1.4)
1	34 (16.1)
2	117 (55.5)
3	52 (24.6)
4	5 (2.4)
PI (boosted)	
0	59 (28.0)
1	147 (69.7)
2	5 (2.4)
Fusion Inhibitor	
0	115 (54.5)
1	96 (45.5)
Individual ARVs in Underlying ART, n (%)	
PI (boosted)	
Lopinavir (LPV/rtv)	123 (58.3)
Saquinavir (SQV/rtv)	26 (12.3)
Atazanavir (ATV/rtv)	3 (1.4)
Darunavir (DRV/rtv)	2 (0.9)
Fosamprenavir (FPV/rtv)	2 (0.9)
Indinavir (IDV/rtv)	1 (0.5)
NRTI	
Tenofovir disoproxil fumarate (TDF)	146 (69.2)
Lamivudine (3TC)	86 (40.8)
Didanosine (ddI)	65 (30.8)
Emtricitabine (FTC)	57 (27.0)
Stavudine (d4T)	39 (18.5)
Zidovudine (AZT)	27 (12.8)
Abacavir (ABC)	24 (11.4)
Fusion Inhibitor	
Enfuvirtide (ENF)	96 (45.5)

N = number of subjects; n = number of subjects with observations
Only the initial therapies (i.e., as determined on Day 7) were considered

Sensitivity of Underlying ARVs During the CR002731 Treatment Period [a,b]	**ETR N = 211**
Number of Sensitive ARVs (Antivirogram®) in Underlying ART, n (%)	
Any ARV	210
0	31 (14.8)
1	66 (31.4)
2	59 (28.1)
3	45 (21.4)
4	8 (3.8)
5	0
6	1 (0.5)
NRTI	206
0	70 (34.0)
1	70 (34.0)
2	60 (29.1)
3	5 (2.4)
4	1 (0.5)
PI	150
0	79 (52.7)
1	70 (46.7)
2	1 (0.7)
Fusion Inhibitor	96
0	20 (20.8)
1	76 (79.2)

N = number of subjects; n = number of subjects with observations
Tabulation includes ARVs in the CR002731 underlying ART where CR002731 baseline Antivirogram® data were available for that ARV, and the ARV was sensitive.

[a] ETR was not included in the calculation. Sensitivity was based on Antivirogram®. The definition of sensitivity to ENF was based on previous use up to Baseline in the respective CR002731 feeder trial. However, all 96 subjects who used ENF during CR002731 had used ENF in the feeder trial prior to CR002731 Baseline.

[b] Only the initial therapies (i.e., as determined on Day 7) in the underlying ART in CR002731 were considered.

Efficacy (Observed Case)			
Virologic Response Rate[a] (< 50 copies/mL) (%)	**VL ≥ 50 copies/mL at CR002731 Baseline N = 107**	**VL < 50 copies/mL at CR002731 Baseline N = 104**	**All Subjects N = 211**
Week 48	22/80 (27.5%)	80/93 (86.0%)	102/173 (59.0)
Week 96	28/62 (45.2%)	72/83 (86.7%)	100/145 (69.0)
Week 144	4/8 (50.0%)	10/11 (90.9%)	14/19 (73.7)

Mean (SE)change[a] from CR002731 Baseline in CD4 + cell count (x^6 10 cells/L)		
All Subjects	**n**	**N = 211**
Week 48	172	+30.44 (11.364)
Week 96	142	+18.70 (11.395)
Week 144	18	+30.44 (60.607)

In subjects with a viral load ≥ 50 copies/mL at entry into CR002731, 22/80 (27.5%) subjects had undetectable viral load (< 50 copies/mL) at Week 48. By Week 144, 4/8 (50.0%) subjects had undetectable viral load. In subjects with a viral load < 50 copies/mL at entry into CR002731, at Week 48, 80/93 (86.0%) subjects had an undetectable viral load. By Week 144, 10/11 (90.9%) subjects had a viral load < 50 copies/mL. During the trial, a small positive mean change from CR002731 Baseline was observed in CD4+ cell counts. The mean change from CR002731 Baseline to Week 144 was +30.44 x 10^6 cells/L.

N = number of subjects; n = number of observations; SE = standard error

[a] Observed.

Long-Term Efficacy Responses Relative to First Intake of ETR (Feeder Trial Baseline)				
Virologic Parameter				**ETR All subjects**
Log_{10} viral load: mean change (SE) from Baseline (copies/mL)[a]				**n**	**N = 211**
Week 24				174	-1.870 (0.0938)
Week 48				186	-1.753 (0.0981)
Week 96				181	-1.815 (0.1021)
Week 144				148	-2.018 (0.1047)
Week 192				98	-2.262 (0.1086)
Week 240				26	-1.818 (0.1839)
Week 288				9	-1.869 (0.3113)
Endpoint[b]				211	-1.616 (0.0968)
Virologic Response Rate, n (%)					
Parameter		**VL < 50 copies/mL**	**VL < 400 copies/mL**	**> 1 log_{10} Decrease from Baseline[a]**
Responders n (%)	**n**			
Week 4	156	35 (22.4)	103 (66.0)	129 (82.7)
Week 12	165	70 (42.4)	117 (70.9)	120 (72.7)
Week 24	174	76 (43.7)	122 (70.1)	126 (72.4)
Week 48	186	86 (46.2)	120 (64.5)	120 (64.5)
Week 96	181	105 (58.0)	124 (68.5)	132 (72.9)
Week 144	148	95 (64.2)	104 (70.3)	118 (79.7)
Week 192	98	69 (70.4)	81 (82.7)	83 (84.7)
Week 240	26	19 (73.1)	22 (84.6)	21 (80.8)
Week 288	9	7 (77.8)	8 (88.9)	7 (77.8)

Immunologic change[a]: mean change (SE)	**n**	**ETR All subjects**
CD4+ cell count (x 10^6 cells/L)		
Week 24	194	+82.73 (8.948)
Week 48	200	+113.87 (10.470)
Week 96	181	+148.43 (14.697)
Week 144	147	+159.27 (17.369)
Week 192	96	+175.90 (26.720)
Week 216	48	+183.83 (26.418)
Week 240	26	+146.96 (36.964)
Week 288	9	+152.11 (63.230)
Endpoint[b]	211	+130.87 (15.658)

The mean change in log_{10} viral load from CR002731 feeder trial Baseline was approximately -1.81 log copies/mL at Week 4, and remained at a similar level throughout. Maximal suppression was achieved at Week 192 (-2.26 log_{10} copies/mL). At endpoint for all subjects the mean change from CR002731 feeder trial Baseline was -1.62 log_{10} copies/mL.

During the trial, a gradual increase in mean change from Baseline in observed CD4+ cell counts up to a level of approximately +183 x 10^6 cells/L at Week 216 was seen, after which a small downward trend was observed. At Endpoint, the mean change from CR002731 feeder trial Baseline was +130.87 x 10^6 cells/L.

N = number of subjects; n = number of observations; SE = standard error

[a] Observed.

[b] Endpoint was defined as the last available on treatment measurement for each individual subject.

Safety	**ETR N = 211**
Treatment duration (weeks)	
Median (Min - Max)	120.4 (0 - 149)
Treatment-Emergent AEs (Treatment Period)	
Most frequently reported AEs[a], n (%)	
Diarrhea	37 (17.5)
Upper respiratory tract infection	36 (17.1)
Sinusitis	24 (11.4)
Arthralgia	23 (10.9)
Nasopharyngitis	23 (10.9)
Fatigue	23 (10.9)
Lymphadenopathy	22 (10.4)
Headache	21 (10.0)
n (%) with 1 or more AEs	195 (92.4)
n (%) of deaths during treatment	5 (2.4)
n (%) with one or more serious AEs	46 (21.8)
n (%) of treatment discontinued due to AEs	9 (4.3)
n (%) with one or more grade 3 or 4 AEs	76 (36.0)
Treatment-Emergent AEs of Interest	
n (%) with any neuropsychiatric event of interest	61 (28.9)
n (%) with nervous system event of interest	32 (15.2)
n (%) with psychiatric event	36 (17.1)
n (%) with any skin event of interest	44 (20.9)
n (%) with rash (any type)	30 (14.2)
n (%) with any cardiac event	31 (14.7)
n (%) with any hepatic event of interest	19 (9.0)
n (%) with hepatobiliary disorders	12 (5.7)
n (%) with any bleeding event	14 (6.6)
n (%) with any pancreatic event	7 (3.3)
n (%) with pancreatitis	3 (1.4)

N = number of subjects; n = number of patients with observations.
[a] Individual preferred terms in at least 10% (rounded %) of subjects.

During the treatment period, 92.4% of subjects reported at least 1 adverse event (AE), with the most common AEs (individual preferred terms at least 10.0%) being diarrhea, upper respiratory tract infection, sinusitis, nasopharyngitis, fatigue, lymphadenopathy and headache. Most AEs were grade 1 or 2 in severity. No consistent pattern of individual grade 3 or 4 AEs was seen. Five subjects died during the treatment period. None of the deaths were considered related to ETR. SAEs were reported in 46 subjects (21.8%) during ETR treatment. The most common SAEs were pneumonia (5 subjects) and cellulitis (3 subjects). Other SAEs occurred in no more than 2 subjects each. The incidence of SAEs considered by the investigator at least possibly related to investigational medication was 1.4% (3 subjects). These SAEs were acute myocardial infarction (1 subject), femur fracture (1 subject) and osteoarthritis (1 subject). Nine subjects (4.3%) permanently discontinued trial treatment due to AEs. No individual AE leading to discontinuation was reported in > 1 subject. Rash (any type, grouped term) was reported in 30 subjects (14.2%). All rashes were grade 1 or 2 in severity. Neuropsychiatric events of interest occurred in 61 subjects (28.9%), hepatic events in 19 subjects (9.0%), cardiac events in 31 subjects (14.7%), bleeding events in 14 subjects (6.6%) and pancreatic events in 7 subjects (3.3%).

Clinical Laboratory Tests	***ETR N = 211***
Treatment emergent laboratory data	
n (%) with any grade 1 abnormality	193 (91.5)
n (%) with any grade 2 abnormality	151 (71.6)
n (%) with any grade 3/4 abnormality	66 (31.3)
n (%) with any grade 3 abnormality	61 (28.9)
n (%) with any grade 4 abnormality	18 (8.5)

There were no clinically relevant mean changes from CR002731 Baseline observed for any laboratory test parameter. The majority of graded laboratory abnormalities was grade 1 or 2 in severity. Treatment-emergent grade 3 laboratory abnormalities occurred in 61 (28.9%) subjects and 18 (8.5%) subjects had a treatment-emergent grade 4 laboratory abnormality. The most common treatment-emergent grade 3 or 4 laboratory abnormalities were increases in amylase experienced in 15 subjects (7.3%), increased LDL cholesterol in 11 subjects (5.3%) and increased total cholesterol in 10 subjects (4.9%). The most common treatment-emergent grade 4 laboratory abnormalities were increases in triglycerides in 7 (3.4%) subjects, increased partial thromboplastin time (PTT) in 4 (1.9%) subjects, decreased WBC count in 3 (1.5%) subjects and decreased neutrophil count in 3 (1.5%) subjects.

Cardiovascular Safety

Small mean changes from CR002731 Baseline were observed for vital signs and ECG parameters. None of the changes over time or treatment-emergent individual abnormalities were considered clinically relevant.

Other Safety Parameters

There were no clinically relevant changes over time in physical examination findings.

Pharmacokinetic substudy

Parameter (mean ± SD, t_{max}: median [range])	**800 mg b.i.d. ETR (TF035) (reference)**	**200 mg b.i.d. ETR (F060) (test)**
n	15	15
C_{0h}, ng/mL	346.3 ± 278.5	557.0 ± 421.9
C_{12h}, ng/mL	378.4 ± 363.1	422.6 ± 327.7
C_{min}, ng/mL	309.7 ± 256.8	418.2 ± 325.2
C_{max}, ng/mL	629.0 ± 426.4	805.6 ± 524.2
t_{max}, h	4.00 (2.00 - 9.00)	3.00 (0.00 - 6.00)
AUC_{12h}, ng.h/mL	5513 ± 3844	7115 ± 5018
$C_{ss,av}$, ng/mL	469.3 ± 336.3	594.8 ± 418.5
Fluctuation Index (FI), %	78.59 ± 35.15	82.77 ± 45.70
LSmean ratio (90% CI), %		
		Test vs reference
n	-	15 vs 15
C_{min}	-	132.2 (100.4 - 174.2)
C_{max}	-	132.2 (103.8 - 168.3)
AUC_{12h}	-	128.0 (99.94 - 163.9)

Fifteen subjects participated in a substudy to determine the steady-state pharmacokinetics of ETR administered as 800 mg b.i.d. (TF035) and after switching to 200 mg b.i.d. (F060). The results demonstrated that exposure to ETR, as expressed by the ratios of the LSmeans on C_{min}, C_{max} and AUC_{12h}, was increased by 28 to 32% when ETR was given 200 mg b.i.d. as formulation F060 compared to 800 mg b.i.d. as formulation TF035. The ranges in C_{min}, C_{max} and AUC_{12h} were comparable between both formulations. The 90% CIs of the LSmeans ratios were generally wide and above the upper limits of the 80 to 125% interval.

Conclusions

CR002731 was an open-label, rollover trial in HIV-1 infected subjects who were randomized to an ETR treatment arm in other sponsor-selected ETR trials, who were treated for at least 48 weeks, and who were considered, in the opinion of the investigator, to benefit from continued ETR therapy. All subjects had high levels of ARV resistance at trial entry. Results confirmed the long-term safety and tolerability of the ETR 800 mg b.i.d. (TF035) or 200 mg b.i.d (F060) treatment regimens in this patient population. The safety profile was consistent with the safety profile observed in other trials. Most AEs were grade 1 or 2 in severity and infrequently led to discontinuation. No safety signals were identified. No consistent or clinically relevant changes in laboratory, vital signs or ECG parameters were observed. The durability of the antiviral activity of ETR in this population was demonstrated by a sustained suppression of plasma viral load. The immunological status of subjects improved over the duration of CR002731 (median treatment duration 120.4 weeks) with mean increases from Baseline in the mean CD4+ cell count observed.

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