SYNOPSIS

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

Status: Approved

Date: 8 February 2013

Prepared by: Janssen Infectious Diseases - Diagnostics BVBA

Protocol No.: TMC125-C214

Title of Study: Early Access of TMC125 in combination with other antiretrovirals in treatment-experienced HIV-1 infected subjects with limited treatment options

EudraCT Number: 2006-002499-16

NCT No.: NCT00354627

Clinical Registry No.: CR002743

Principal Investigator: A. Lazzarin - Ospedale San Raffaele, via Stamira D'Ancona 20, 20132 Milano, Italy

Study Center(s): Multicenter

Publication (References):

Florence E et al. Antiretroviral treatment use and HIV RNA suppression rates for 941 European patients in the etravirine early access programme. 9th International Congress on Drug Therapy, Glasgow, UK, 9-13 November 2008.

Florence E at al. HIV RNA suppression rates after 24 weeks of treatment with etravirine, darunavir/ritonavir and raltegravir in the etravirine early access programme. Int. J STD & AIDS, 2010:1-2.

Loutfy M et al. Sustained HIV RNA suppression after switiching from enfuvirtide to etravirine in the early access programme. J Antimicrob Chemother, Advance Access Publication, 16 September 2009.

Ribera E et al. Switching from enfuvirtide to etravirine – efficacy results from the etravirine early access programme. 9th International Congress on Drug Therapy, Glasgow, UK, 9-13 November 2008.

Towner W et al. Efficacy, safety, and tolerability of etravirine with and without darunavir/ritonavir or raltegravir in treatment-experienced patients: analysis of the etravirine early access program in the United States. J Acquir Immune Defic Syndr, 2010;53(5):614-8.

* Janssen Research & Development is a global organization that operates through different legal entities in various countries. Therefore, the legal entity acting as the sponsor for Janssen Research & Development studies may vary, such as, but not limited to Janssen Biotech, Inc.; Janssen Products, LP; Janssen Biologics, BV; Janssen-Cilag International NV; Janssen, Inc; Janssen Infectious Diseases BVBA; Janssen R&D Ireland (formerly known as Tibotec Pharmaceuticals); or Janssen Research & Development, LLC. The term "sponsor" is used to represent these various legal entities.

Study Period: 24 January 2006 to 1 March 2012

Phase of Development: Not applicable

Objectives: The primary objective of this study was to provide early access to etravirine (ETR, formerly known as TMC125) for treatment-experienced human immunodeficiency virus type-1 (HIV-1) infected subjects who had failed multiple antiretroviral (ARV) regimens and had limited treatment options with currently approved ARVs.

The secondary objective of this study was to gather information on the safety and tolerability aspects of ETR in combination with other ARVs. Available efficacy data were also to be collected.

Methodology: This was a study to provide early access to ETR to HIV-1 infected subjects who had failed multiple ARV regimens and who had limited treatment options. Information on safety and tolerability aspects of ETR in combination with other ARVs in treatment-experienced HIV-1 infected subjects were assessed. Available data on antiviral activity and immunology were also collected.

The subject's eligibility to enter the study was assessed based on the need to use ETR to construct a viable regimen as determined by prior ARV treatment experience and selected laboratory parameters (results obtained within the 12 weeks prior to Screening could be used). Safety and tolerability of the entire ARV regimen, including ETR, were monitored by the investigator as per standard clinical practice.

Once treatment with ETR in combination with other ARVs was initiated, subjects were instructed to follow the Visit schedule based on routine clinical care. It was recommended that visits be scheduled 4 and 12 weeks after initiation of treatment, and every 12 weeks thereafter while on therapy. Treatment continued until virologic failure, treatment-limiting toxicity, subject lost to follow-up, withdrawal, pregnancy, discontinuation of ETR development, or when ETR became commercially available to the subject.

Number of Subjects (Planned and Analyzed):

Planned: No fixed number of subjects was planned. All eligible subjects who had signed the informed consent form (ICF) and willing to participate in the study could be enrolled.

Analyzed: In total, 5834 subjects were screened. The intent-to-treat (ITT) population and AE specific population included 5178 and 5208 subjects, respectively. See the Statistical methods section for the definitions of ITT and AE specific populations.

Diagnosis and Main Criteria for Inclusion: Subjects enrolled in this study were required to meet the following inclusion/exclusion criteria:

Inclusion Criteria:

- Subject or Legal Authorized Representative had voluntarily given informed consent before initiation of study procedures.
- Subject had documented HIV-1 infection.
- Adult male or female subject (lower age limit 16 or 18 years of age, depending on local regulations).
- Subject had limited treatment options due to virologic failure or intolerance to multiple ARV regimens.
- Subject was at least 3-class experienced (3 classes of licensed oral ARVs: nucleoside/nucleotide reverse transcriptase inhibitors [N{t}RTIs], protease inhibitors [PIs], non-nucleoside reverse transcriptase inhibitors [NNRTIs]).
- Subject had previously received at least 1 PI-based regimen.

- Subject was unable to use the concurrently approved NNRTIs due to resistance (primary or acquired) and/or intolerance.
- If receiving an ARV regimen and not achieving adequate virologic suppression on his/her current regimen (defined as a confirmed plasma viral load result ≥50 copies/mL on the current treatment). A subject who did achieve adequate virologic suppression was only eligible if:
  - Subject had a treatment-limiting toxicity to an agent in his/her regimen that required substitution of this agent,
  - Subject was at risk of viral rebound and in the opinion of the investigator an intensification of the ARV regimen was appropriate,
  - Subject previously participated in another ETR clinical study or program.

Exclusion Criteria:

- Primary HIV-1 infection.
- Any condition (including but not limited to alcohol and drug use) that, in the opinion of the investigator, could compromise the subject's safety or adherence to the study protocol.
- Use of disallowed concomitant therapy, including disallowed ARVs.
- Use of non-ARV investigational medications within the 30 days prior to Baseline Visit.
- Use of investigational ARVs (other than ETR), unless stated as an exception.
- Any active clinically significant disease (eg, cardiac dysfunction, pancreatitis, acute viral infection) or findings during the screening of medical history or physical examination that is not either resolved or stabilized for at least 30 days before the Screening Period of the study.
- Acute viral hepatitis, including but not restricted to A, B or C.
- Pregnant or breast-feeding female, and female subject of childbearing potential not using effective non-hormonal birth control or not willing to continue practicing these birth-control methods from Screening until the last study related activity.

  Note: Hormonal based contraception may not be reliable when taking ETR, therefore to be eligible for this study, females of childbearing potential who might have vaginal intercourse had to either:

  - use a double-barrier method to prevent pregnancy (ie, using a condom without spermicide, with either diaphragm or cervical cap); or
  - use hormonal-based contraceptives in combination with a barrier contraceptive (ie, male condom without spermicide, diaphragm or cervical cap or female condom); or
  - use an intra-uterine device (IUD) in combination with a barrier contraceptive (ie., male condom without spermicide, diaphragm or cervical cap or female condom); or
  - be non-heterosexually active, practice sexual abstinence, or have a vasectomized partner (confirmed sterile).

  Note: Females who were postmenopausal for at least 2 years, females with total hysterectomy, and females with tubular ligation were considered of non-childbearing potential.
- Subjects with the following laboratory abnormalities as defined by a standardized grading scheme based on Division of AIDS (DAIDS) grading table:
  - Hemoglobin <7.4 g/dL (4.5mmol/L);
  - Absolute neutrophil count <500/mm^3 (0.5 x 10^9/L);

- Platelets <25000/mm^3 (25 x 10^9/L);
- Prothrombin time (PT) >1.5 x upper limit of laboratory normal range (ULN);

  Note: Subjects on anticoagulant therapy with elevated PT >1.5 x ULN required approval of the sponsor prior to enrollment.
- Alkaline phosphatase >5 x ULN
- Aspartate aminotransferase (AST)/alanine aminotransferase (ALT) >5 x ULN
- Bilirubin >5 x ULN

  Note: Subjects with elevated bilirubin >5 x ULN assessed as related to a component of ARV therapy could be enrolled with prior approval of the sponsor.
- Lipase >3 x ULN;
- Amylase >5 x ULN, if lipase >2 x ULN;
- Creatinine >1.8 x ULN;
- Subjects with clinical or laboratory evidence of significantly decreased hepatic function or decompensation, irrespective of liver enzyme levels.

- Previously demonstrated clinically significant allergy or hypersensitivity to any of the excipients of ETR.

Test Product, Dose and Mode of Administration, Batch No.: ETR; formulation F060; 200 mg b.i.d. (administered as 2 x 100-mg oral tablets); Batch numbers: PO62001532; PO62001548; PO62001261; PO62001605; PO62001260; 5KL35; 5KL8I; 5KL62; 6BL3M02; 6ELB201; 6CL3M00; 6FL6Z00; 7BL8I00; 7BL8J00; 7BL8Q00; 7BL8Y00; 7BL9000; 7BL9900; 7CL9H01; 7DL8A00; 7EL7L00; 7EL7N00; 7EL7K00.

Duration of Treatment: Treatment with study medication was continued until virologic failure, treatment-limiting toxicity, loss to follow-up, subject's withdrawal, pregnancy, discontinuation of ETR development or when the study drug became commercially available to the subject.

Criteria for Evaluation:

Safety:

Safety evaluations were based upon reports of adverse events (AEs), AIDS-defining illnesses and serious adverse events (SAEs), and clinical laboratory tests. Viral load and CD4+ cell count, as collected by the local laboratory according to the local standard of care, were analyzed as part of the safety evaluation.

From signing the ICF onwards until 30 days after the Final/Withdrawal Visit, AEs leading to discontinuation or treatment interruption, or all AEs if applicable as per local regulations, and SAEs (with the exception of AIDS-defining illnesses [CDC class C]; non-fatal and not related to ETR) were collected. AEs judged at least possibly related to ETR by the investigator, and still ongoing at the end of study had to be followed until satisfactory clinical resolution or stabilization.

Clinical laboratory tests included analysis of biochemistry (ALT, AST, amylase [if available], lipase [if available]), serum pregnancy test, and urine pregnancy test. Laboratory assessments were recommended at Baseline, Week 4, Week 12 and subsequently at 12 week intervals, or more frequently as per local standard of care taking into account the subject's concomitant medications and his/her clinical condition. In case of grade 3 or 4 laboratory abnormalities, it was recommended to retest for confirmation within 48 hours.

Plasma viral load and immunology (CD4+ cell analysis) assessments were performed by a local laboratory. Information on resistance testing could be entered in the electronic case report form (eCRF) if locally available.

Statistical Methods:

The 2 analysis populations included:

- ITT analysis: All subjects enrolled and treated with at least 1 dose of ETR or had a Baseline Visit, and a signed ICF.
- AE specific population: All subjects included in the ITT population or with an SAE or fatal AE reported in the database.

All safety analyses were performed on both populations. The AE specific population was the primary population for the AEs with fatal outcome. The ITT population was the primary population for all other analyses.

Statistical methods included frequency tabulations, descriptive statistics including 95% confidence intervals (CIs).

As critical good clinical practice (GCP) issues were identified during a US FDA inspection at Site 10023 and a Warning Letter was issued, the subjects from this site (N=5) were excluded from all analyses. There were no safety signals from the data of these 5 excluded subjects.

RESULTS:

Study Population:

Subject Disposition, Termination and Treatment Duration	**ETR**
Subject Disposition	
Number of subjects screened	5834
Number of subjects not enrolled	650
Number of subjects enrolled but not treated	6
Number of subjects enrolled and treated with ETR (ITT population)[a]	5178
Study Termination	
Number of subjects with study termination data	**5082**
Switch to commercially available ETR, n (%)	**4189 (82.4)**
Prematurely discontinued, n (%)[b]	**893 (17.6)**
Adverse event/HIV related	312 (6.1)
Subject lost to follow-up	186 (3.7)
Other	163 (3.2)
Subject noncompliant	90 (1.8)
Subject withdrew consent	82 (1.6)
Subject reached a virologic endpoint	29 (0.6)
Subject ineligible to continue the study	15 (0.3)
Subject did not fulfill all inclusion/exclusion criteria	8 (0.2)
Sponsor's decision	5 (0.1)
Pregnancy	3 (0.1)
ETR Treatment Duration (Weeks), n	**4956**
Median (1st Quartile - 3rd Quartile)	41.8 (24 – 60)
ETR Total Patient Years of Exposure	**4438**

n = number of subjects with observations

[a] Thirty additional subjects were included in the AE specific population, which comprised of 5208 subjects.

[b] Percentages are calculated versus the number of subjects with data

Demographic Parameters	ETR N = 5178
Sex, n (%)	**5178 (100)**
Male	4460 (86.1)
Female	718 (13.9)
Race, n (%)[a]	**5151 (100)**
White	3566 (69.2)
Black	810 (15.7)
Hispanic	591 (11.5)
Asian	107 (2.1)
Demographic Parameters	**ETR N = 5178**
Other	77 (1.5)
Age (years), n	**5167**
Median (1st Quartile - 3rd Quartile)	46.0 (42 - 52)

N = number of subjects, n = number of subjects with observations
[a] Percentages are calculated versus the number of subjects with racial data.

Baseline Disease Parameters	ETR N = 5178
Baseline log_{10} Viral Load (Copies/mL), n	**4767**
Median (1st Quartile - 3rd Quartile)	4.3 (3.1 - 5.0)
Baseline CD4 cell Count (x 10^6 cells/L), n	**4710**
Median (1st Quartile - 3rd Quartile)	201.0 (79 - 349)
Clinical Stage of HIV Infection, n (%)[a]	**5175 (100)**
A	996 (19.2)
B	1045 (20.2)
C	3134 (60.6)
Hepatitis B Coinfection Status, n (%)[a]	**4947 (100)**
No	4507 (91.1)
Yes	440 (8.9)
Hepatitis C Coinfection Status, n (%)[a]	**4934 (100)**
No	4313 (87.4)
Yes	621 (12.6)
Hepatitis B and/or C Coinfection Status, n (%)[a]	**4928 (100)**
No	3936 (79.9)
Yes	992 (20.1)

N = number of subjects, n = number of subjects with observations
[a] Percentages are calculated versus the number of subjects with data

Safety Results:

AEs

In total, 119 of 5208 subjects (2.3%) died during the study. By preferred term, the majority of the fatal AEs was reported in at most 2 subjects. The most common fatal AE was pneumonia (11 subjects, 0.2%), followed by sepsis and death (no further information available at the time of database lock) (9 subjects, 0.2% each). In 9 cases, at least 1 fatal AE was at least possibly related to ETR (as determined by the investigator).

The incidence of SAEs was 12.8% (661 subjects). The most common SAE preferred terms were pneumonia (63 subjects, 1.2%) and pyrexia (25 subjects, 0.5%). The incidence of SAEs considered at least possibly related to ETR by the investigator was 1.7% (90 subjects). By preferred term, the most commonly reported SAEs considered at least possibly related to ETR were rash (9 subjects, 0.2%), and immune reconstitution syndrome (5 subjects, 0.1%).

According to the study discontinuation data (see previous page), 312 subjects (6.1%) discontinued due to an AE/HIV related event. The safety analysis showed that 274 subjects (5.3%) reported an AE for which ETR treatment was discontinued. By preferred term, the most common AE leading to permanent discontinuation of ETR was rash (60 subjects, 1.2%).

Safety	**ETR N = 5178**	
***Adverse Events* n (%)**		
AEs with fatal outcome[a]	119 (2.3)	
Other SAEs	661 (12.8)	
SAEs related to ETR	90 (1.7)	
AEs leading to ETR discontinuation	274 (5.3)	
Clinical Laboratory Tests		
At worst grade 3 or 4 ALT elevation, n (%)[b]	98 (2.1)	
At worst grade 3 or 4 AST elevation, n (%)[b]	76 (1.6)	
By hepatitis coinfection status:	**Hepatitis B and/or C Coinfection n' = 992**	**No Hepatitis B and/or C Coinfection n' = 3936**
At worst grade 3 or 4 ALT elevation, n (%)[b]	49 (5.3)	46 (1.2)
At worst grade 3 or 4 AST elevation, n (%)[b]	37 (4.1)	36 (1.0)

N = number of subjects, n = number of subjects with observations, n' = number of subjects with hepatitis coinfection data

[a] The AE specific population (N = 5208) was used for analysis of AEs with fatal outcome

[b] Percentage was calculated relative to the total number of subjects with the indicated test

Clinical Laboratory Tests

The mean and median changes from Baseline in ALT and AST over time were generally small and occurred both in subjects with and without hepatitis B and/or C coinfection. Grade 3 or 4 elevations in ALT and AST were recorded in 2.1% (98 subjects) and 1.6% (76 subjects), respectively. The incidence of abnormal ALT and AST values was higher in subjects with hepatitis B and/or C coinfection. In hepatitis B and/or C coinfected subjects, grade 3 or 4 elevations for ALT and AST were recorded in 5.3% (49 subjects) and 4.1% (37 subjects), respectively, as compared to 1.2% (46 subjects) and 1.0% (36 subjects) in subjects not coinfected with hepatitis B and/or C.

Viral Load and CD4+ Cell Count

The viral load and immunology data showed a sustained virologic response in most subjects, accompanied by a steady increase over time in median CD4+ cell count. The viral load showed a median decrease of -1.9 $\log_{10}$ copies/mL at Week 4, which was sustained during the rest of the observation period (-2.3 $\log_{10}$ copies/mL at Week 108). Because some local laboratories had a lower limit of detection of 75 copies/mL, an additional virologic response rate was defined as the proportion of subjects with a viral load <75 copies/mL. Following this definition, 50.6% of subjects responded to ETR treatment at Week 4, 68.9% at Week 12, and at least 75.6% of subjects from Week 24 onwards. A median increase in CD4+ cell count of more than 100 x 10^6 cells/L was observed from Week 36 onwards.

Median Change From Baseline Over Time in $\log_{10}$ Viral Load (Copies/mL)		
Time Point	**N**	**Median (1st Quartile; 3rd Quartile)**
Week 4	4018	-1.9 (-2.6; -0.8)
Week 24	3115	-2.2 (-3.0; -0.8)
Week 48	1673	-2.2 (-3.0; -0.9)
Week 96	138	-2.3 (-3.2; -1.1)
Week 108	65	-2.3 (-3.1; -0.4)
Week 120	30	-1.7 (-2.9; -0.3)

N = number of subjects at each time point

	Virologic Response							
	<50 Copies/mL		<75 Copies/mL		<400 Copies/mL		1.0 log_{10} Decrease	
Time Point	N	n (%)	N	n (%)	N	n (%)	N	n (%)
Baseline	4694	490 (10.4)	4736	604 (12.8)	4756	936 (19.7)	0	0
Week 4	3566	1432 (40.2)	3860	1955 (50.6)	4038	3041 (75.3)	4018	2878 (71.6)
Week 24	2833	1931 (68.2)	3118	2357 (75.6)	3186	2776 (87.1)	3115	2276 (73.1)
Week 48	1662	1191 (71.7)	1768	1381 (78.1)	1800	1588 (88.2)	1673	1228 (73.4)
Week 96	259	216 (83.4)	264	227 (86.0)	264	237 (89.8)	138	104 (75.4)
Week 108	167	139 (83.2)	170	151 (88.8)	173	164 (94.8)	65	44 (67.7)
Week 120	124	104 (83.9)	124	106 (85.5)	125	114 (91.2)	30	21 (70.0)

N = number of subjects at each time point, n = number of subjects with observations

Median Change From Baseline Over Time in CD4+ Cell Count (x 10^6 Cells/L)		
Time Point	N	Median (1st Quartile; 3rd Quartile)
Week 4	3928	36.0 (-3.0; 90.0)
Week 24	3063	80.0 (18.0; 154.0)
Week 48	1640	110.0 (31.0; 196.0)
Week 96	152	134.5 (35.5; 268.5)
Week 108	66	151.0 (57.0; 299.0)
Week 120	32	108.5 (27.5; 281.0)

N = number of subjects at each time point

Conclusions:

In study TMC125-C214, early access to ETR was provided to 5178 treatment-experienced HIV-1 infected subjects who had failed multiple ARV regimens and had limited treatment options with currently approved ARVs.

The safety results of the final analysis of study TMC125-C214 are consistent with the known safety profile of ETR. No clinically relevant safety issues associated with ETR treatment, which would affect the benefit/risk assessment for the use of ETR in treatment-experienced HIV-1 infected subjects were reported.