

≥ 2.5-5 x ULN	72 (12)	57 (9.4)
≥ 1.25-2.5 x ULN	140 (23.4)	133 (22)
<b>Hyperlipidemias</b>		
≥ 10 x ULN	22 (3.7)	9 (1.5)
≥ 5-10 x ULN	30 (5)	28 (4.6)
≥ 2.5-5 x ULN	56 (9.4)	59 (9.8)
≥ 1.25-2.5 x ULN	0 -	0 -

Source: Datasets LBAD for Studies C206 and C216

Hyperlipidemia and hypertriglyceridemia are well-described metabolic complications of ARV agents, in particular protease inhibitors. Since the study population was highly treatment-experienced to multiple agents, further analyses were undertaken to evaluate changes in LDL cholesterol from baseline, and to assess proportion of subjects initiating new lipid-lowering agents (LLA).

Minimal differences in change in serum LDL cholesterol from baseline were observed between the two arms over 32-week period (Table 53). However, more etravirine recipients (16.5%) started a new LLA as compared to placebo recipients (12.9%) as shown in Table 54.

**Table 53: Calculated Serum LDL Cholesterol values over Time for Pooled data**

Treatment Timepoint (weeks)	Treatment Group	Number of Subjects	Mean LDL (mmol/L)	Mean Change from Baseline (mmol/L)	Standard Error of Change from Baseline
0	Placebo	531	92.3	0	0
	Etravirine	520	92.5	0	0
2	Placebo	494	98.3	+6.3	0.026
	Etravirine	473	99.2	+6.5	0.027
4	Placebo	509	100.1	+7.2	0.029
	Etravirine	470	102.8	+8.9	0.033
8	Placebo	489	101.3	+8.5	0.032
	Etravirine	460	105.6	+11.3	0.035
12	Placebo	472	102.4	+9.3	0.033
	Etravirine	441	106.6	+13.4	0.038
16	Placebo	469	104.9	+11.0	0.037
	Etravirine	446	107.0	+13.7	0.037
20	Placebo	462	103.8	+9.8	0.036
	Etravirine	423	108.3	+14.3	0.040
24	Placebo	474	103.8	+10.6	0.036
	Etravirine	441	108.3	+13.9	0.037
32	Placebo	203	110.7	+9.2	0.056
	Etravirine	202	116.7	+17.9	0.061

Source: Statistical Reviewer's Analysis (datasets LBAD for Studies C206 and C216)

**Table 54: Elevation of Serum LDL from Baseline and Initiation of Lipid Lowering Therapy<sup>1</sup>**

Subjects	Etravirine (%) N=599	Placebo (%) N=604
Subjects requiring initiation of new LLA <sup>2</sup>	99 (16.5)	78 (12.9)
Subjects with increase $\geq 10$ mg/dL from baseline up to Week 24 <sup>3</sup>	266 (44.4)	248 (41.0)
Subjects with increase LDL $\geq 10$ mg/dL up to Week 24 and requiring initiation of new LLA	26 (4.3)	18 (2.9)

<sup>1</sup>By Fisher's Exact Test

<sup>2</sup>LLA, lipid-lowering agent

<sup>3</sup>Values available for 479 and 502 subjects in etravirine and placebo arm, respectively

Source: Statistical Reviewer's Analysis (datasets LBAD, CMAD for Studies C206 and C216)

In summary, alterations in lipid profile were observed more frequently in the etravirine arm as compared to placebo arm. Highly treatment-experienced subjects taking protease inhibitors such as those enrolled in etravirine trials are at risk of developing hyperlipidemia. A greater proportion of etravirine subjects required initiation of new lipid-lowering therapy suggesting an association of etravirine with hyperlipidemia.

#### 7.1.7.3.1 Analyses focused on measures of central tendency

An analysis of mean changes from baseline was performed to explore trends of select laboratory parameters namely serum lipase and serum LDL cholesterol.

#### 7.1.7.3.2 Analyses focused on outliers or shifts from normal to abnormal

Clinically relevant laboratory abnormalities as judged by the site investigator were reported as AEs. Outliers with respect to laboratory abnormalities were captured as AEs or SAEs as per nature of severity, and were included in the discussion of AEs or SAEs.

#### 7.1.7.3.3 Marked outliers and dropouts for laboratory abnormalities

Study discontinuations for reasons of laboratory abnormalities were included in the discussion of AEs leading to study discontinuation in Section 7.1.3.

#### 7.1.7.4 Additional analyses and explorations

Subjects in the Phase 3 trials received the DRV/rtv as part of their OBT; data from these Phase 3 trials provide the majority of the safety data for etravirine. The use of DRV/rtv with etravirine decreases etravirine plasma AUC (area under the plasma concentration vs time curve), on average by 37%; the Phase 3 trials therefore reflect the safety profile of reduced etravirine exposure. Etravirine exposure in patients who take etravirine without DRV/rtv and without other

drugs that alter etravirine exposure is anticipated to be approximately 60% higher than exposure in subjects in the Phase 3 studies. If patients take etravirine without DRV/rtv, but with drugs that increase etravirine exposure, etravirine exposure may be more than 60% higher than exposure in subjects in the Phase 3 studies. An example is the drug interaction between etravirine and LPV/rtv which is discussed in this section. Data indicate LPV/rtv increases mean etravirine AUC by 17%. Thus, the mean AUC of etravirine after co-administration of etravirine with LPV/rtv is anticipated to be about 85% higher than the mean systemic exposure of etravirine observed in the Phase 3 trials. The evaluation of the acceptability of co-administration of etravirine with LPV/rtv includes assessment of safety in Phase 2b subjects receiving etravirine with LPV/rtv and evaluation of safety in subjects in the highest quartile of etravirine exposure in Phase 3 trials.

Analysis was performed to explore the anticipated distribution of etravirine exposure across a population that receives etravirine (formulation F060, 200 mg bid) with lopinavir/ritonavir, as compared to the distribution of exposure observed in phase 3. This analysis was achieved by multiplying the highest etravirine AUC value observed for each subject with pharmacokinetic data in Phase 3 by a factor of 1.85.

**Table 55: Analysis of Anticipated Distribution of Etravirine Exposure with LPV/rtv as compared to Exposure in Phase 3 trials**

	Observation from Phase 3 trials N= 582	Multiply each AUC by 1.85 to account for administration of LPV/rtv rather than DRV/rtv
AUC <sub>12</sub> (ng*hr/mL) range	145 - 69997	268 – 129,495
% subjects with AUC > 70,000	0	0.51%
% subjects with AUC between 50,000 to 70,000	0.34%	0.51%
% subjects with AUC between 30,000 to 50,000	0.69%	4.47%
% subjects with AUC between 10,000 to 30,000	16.67%	48.97%

Source: Clinical Pharmacology Team Leader Memo

As noted in the table above, AUC greater than 30,000 is not frequently observed when etravirine is administered with darunavir/ritonavir or with lopinavir/ritonavir. However, almost 50% of patients who receive etravirine with lopinavir/ritonavir may have etravirine AUC between 10,000 to 30,000, while AUCs in this range were observed for 17% of subjects in phase 3. The safety database for etravirine exposures that may be observed in approximately 50% of patients who receive etravirine with lopinavir/ritonavir is limited. However, due to variability in etravirine pharmacokinetics, the etravirine exposure in most patients who receive etravirine with lopinavir/ritonavir will be not higher than that observed in at least a small percentage of subjects in Phase 3. Refer to Clinical Pharmacology Team Leader Memo of NDA 22-187 by Dr. Kellie Reynolds for details.

Analyses were performed to evaluate the safety profile of etravirine in subjects achieving the highest exposure of etravirine in Phase 3 trials, as etravirine exposure in this subgroup would most closely mimic exposures in patients taking etravirine without DRV/rtv who may achieve etravirine exposure higher than that observed in Phase 3 trials. Subjects receiving etravirine in Phase 3 trials were categorized into quartiles based on etravirine exposure as displayed in the table below.

**Table 56: Categorization of Etravirine Exposure<sup>1</sup> In Phase 3 trials by Quartiles**

Etravirine Exposure	Mean±SD	Median	IQR	Range
<b>Highest Exposure Quartile</b>	10474.8±4988.4	8882.4	7417.7-12187.6	6530.9-64164.9
<b>Lower Three Exposure Quartiles</b>	3776.3±1474.1	3826.4	2717.4-4853.4	145.3-6528.2

<sup>1</sup>Geometric mean AUC, hr•ng/mL

Source: Pharmacometrics Review for NDA 22-187

Pharmacokinetic data was available for 576 of 599 etravirine-treated subjects; adverse events were compared between 145 subjects in the highest quartile and 431 subjects in the lower three quartiles (lower quartiles). Additional comparisons with placebo-treated subjects in the Phase 3 trials (604 subjects) and with subjects receiving etravirine with LPV/rtv in Phase 2b trials (147 subjects) were performed. Safety analyses of subjects in the highest quartile of etravirine exposures consist of comparisons of number of deaths, permanent discontinuations and subjects with Grade 3 or 4 adverse events, common adverse events and evaluation of select laboratory abnormalities.

Table 57 shows fewer deaths were observed in the group with highest quartile of etravirine exposure (0.7%) as compared to subjects in the lower three quartiles (1.4%). Similarly, fewer subjects in the highest quartile of etravirine exposure discontinued due to adverse events.

**Table 57: Summary of Death, Permanent Discontinuations and Grade 3 or 4 Rash Events in Subjects in the Highest Quartile of Etravirine Exposure in Phase 3 trials**

	Highest Quartile Etravirine Exposure N=145 (%)	Lower Quartiles Etravirine Exposure N=431 (%)
<b>Deaths<sup>1</sup></b>	1 (0.7)	6 (1.4)
<b>Permanent discontinuations</b>		
Discontinued due to adverse events	4 (2.8)	24 (5.5)
<b>Grade 3 or 4 rash (any type)</b>	0 -	7 (1.6)

<sup>1</sup>Pharmacokinetic data available for 7 deaths

Source: Datasets AEAD, PPAD, DMAD for Studies C206 and C216

Discontinuations in the highest quartile of etravirine exposure were reviewed (Table 58). No specific pattern or association with higher exposure of etravirine was appreciated.

**Table 58: Adverse Events leading to Permanent Discontinuation in Subjects in the Highest Quartile of Etravirine Exposure in Phase 3 trials**

CRF ID	Preferred AE term(s)	Etravirine AUC <sup>1</sup>	Pertinent findings	Relatedness
2060179	Anemia	8219.8	Anemia at baseline due to chronic renal insufficiency requiring erythropoietin; developed grade 2 anemia, drug stopped	Probably related
2060569	Rash	8624.2	Drug stopped	Probably related
2060569	Osteomyelitis Respiratory failure Respiratory tract infection	12489.5	History of TDF-induced renal insufficiency; died due to septic shock in setting of respiratory and renal failure	Doubtfully related
2060716	ALT increased AST increased Alkaline phosphatase increased Blood LDH increased Hepatitis B	9553.2	Diagnosed with Hepatitis elevation of serum ALT, AST, LDH and alkaline phosphatase were part of the presentation	Not related

<sup>1</sup>Geometric mean AUC, hr•ng/mL

Source: Datasets AEAD, PPAD, DMAD, case narratives for Studies C206 and C216

Because creatinine elevations were observed more frequently in the highest quartile group, the higher frequency of renal failure (grouped, 'renal failure', 'renal failure acute', 'renal impairment') also observed in the highest quartile group(3.5%) as compared to the lower quartiles (2.1%) and placebo (2.8%) was examined more closely. Renal failure of any type was observed in five subjects in the highest quartile group (Table 59). One subject with renal and respiratory failure died; in three subjects the AE resolved without treatment interruption. One subject (ID 2160012) with grade 1 elevation of serum creatinine at baseline developed worsening to grade 2 severity during treatment; drug was continued without further worsening. All subjects had at least 1 risk factors for nephrotoxicity; the most common risk factor was concomitant use of tenofovir. Analysis of elevations of serum creatinine are described in Table 60.

**Table 59: Renal Failure of any type in Subjects in the Highest Quartile of Etravirine Exposure in Phase 3 trials<sup>1</sup>**

CRF ID	Preferred AE term	Etravirine AUC <sup>2</sup>	Risk factor(s)	Relatedness
2060532	Renal failure <sup>3</sup>	8931.9	TDF, hypertension	Doubtfully related
2060569	Renal impairment	12489.5	TDF	Fatal <sup>4</sup>
2060742	Renal failure <sup>3</sup>	8468.8	TDF	Possibly related
2160012	Renal failure <sup>3</sup>	6961.8	TDF	Not related
2160281	Renal failure acute <sup>3</sup>	13694.6	TDF	Doubtfully related

<sup>1</sup>Includes preferred AE term, 'renal failure', 'renal failure acute', 'renal impairment'

<sup>2</sup>Geometric mean AUC, hr•ng/mL

<sup>3</sup>Subject did not interrupt etravirine

<sup>4</sup>History of tenofovir (TDF)-induced renal insufficiency; renal failure was considered doubtfully related to study medication and was accompanied by respiratory failure and osteomyelitis, death due to septic shock

Source: Datasets AEAD, PPAD, DMAD for Studies C206 and C216

Mild differences in the frequency of Grade 3 or 4 abnormalities of serum ALT were observed in the highest quartile compared to lower quartiles and placebo groups; however, no Hy's law cases were observed in Phase 3 clinical trials and subjects discontinuing etravirine for hepatitis had alternative etiologies, for example acute hepatitis B. One case of hepatotoxicity was identified in expanded access; while drug levels are not available, this subject was receiving DRV/r, a drug combination known to decrease etravirine levels.

A mild increase in the frequency of LDL cholesterol of Grade 2 or 3 severity was noted in subjects in the highest quartile as compared to lower quartiles and placebo groups. Regardless of exposure, a greater proportion of etravirine-treated subjects initiated lipid lowering agents in Phase 3 trials as compared to placebo-treated subjects. A relationship may exist between higher exposures of etravirine and likelihood of development of hyperlipidemia; dyslipidemia is noted as an adverse drug reaction due to etravirine in the etravirine package insert.

**Table 60: Treatment-Emergent Abnormalities of Select Laboratory Tests in Phase 3 Trials by Etravirine Exposure<sup>1</sup>**

	Highest Quartile Etravirine Exposure N=145 (%)	Lower Quartiles Etravirine Exposure N=431 (%)	Placebo Phase 3 N=604 (%)
<b>Serum Alanine Aminotransferase</b>			
≥ 10 x ULN	2 (1.4)	2 (0.5)	2 (0.3)
≥ 5-10 x ULN	3 (2.1)	8 (1.9)	8 (1.3)
≥ 2.5-5 x ULN	19 (13.5)	28 (6.5)	36 (6.0)
≥ 1.25-2.5 x ULN	38 (27)	90 (20.9)	129 (21.4)

Serum Creatinine			
≥ 10 x ULN	0 -	0 -	2 (0.3)
≥ 5-10 x ULN	7 (5)	4 (0.9)	9 (1.5)
≥ 2.5-5 x ULN	15 (10.6)	23 (5.3)	29 (4.8)
≥ 1.25-2.5 x ULN	22 (15.6)	48 (11.1)	60 (9.9)
Serum Hemoglobin			
≥ 10 x ULN	2 (1.4)	2 (0.5)	4 (0.7)
≥ 5-10 x ULN	3 (2.1)	4 (0.9)	4 (0.7)
≥ 2.5-5 x ULN	5 (3.5)	9 (2.1)	22 (3.6)
≥ 1.25-2.5 x ULN	7 (5)	19 (4.4)	50 (8.3)
Low Density Lipoprotein Cholesterol			
≥ 10 x ULN	0 -	0 -	0 -
≥ 5-10 x ULN	11 (7.8)	21 (4.9)	37 (6.1)
≥ 2.5-5 x ULN	23 (16.3)	48 (11.1)	57 (9.4)
≥ 1.25-2.5 x ULN	30 (21.3)	110 (25.5)	133 (22)

The categories are mutually exclusive; no subject is counted more than once  
 Source: Datasets LBAD, PPAD studies C206 and C216

Adverse events observed commonly in 3 or more subjects in the highest quartile are displayed in Table 61. Rash was the most frequent AE reported in the highest quartile group and a modest increase in rash (any type) in subjects in the highest quartile (21.4%) was noted as compared to subjects in lower quartiles (15.8%) and the placebo arm (13.5%). However, rash events in the high-exposure group were of mild to moderate severity and resulted in treatment discontinuation in only 1 subject.

Adverse events of hypersensitivity and drug hypersensitivity appeared more common in the highest quartile group, however, etiologies other than etravirine-related hypersensitivity in almost all cases.

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**Table 61: Common Adverse Events observed in > 2% of Subjects in the Highest Quartile of Etravirine Exposure in Phase 3 trials**

	Highest Quartile (Phase 3) N=145 (%)	Lower Quartiles (Phase 3) N=431 (%)	Placebo Subjects (Phase 3) N=604 (%)	Etravirine and LPV/r (Phase 2b) N=147 (%)
<b>Blood and lymphatic disorders</b>				
Anemia	5.5	3.9	4.5	0.7
Lymphadenopathy	4.1	3.9	4.8	10.9
Neutropenia	2.8	1.9	4.1	1.4
<b>Gastrointestinal disorders</b>				
Diarrhea	15.2	15.5	20.4	8.2
Nausea	11.7	13.2	11.1	21.1
Vomiting	4.8	6.3	5.5	2.7
Upper abdominal pain	4.1	2.8	2.3	1.4
Flatulence	2.8	3.7	3.5	10.2
Abdominal pain nos	-	-	-	14.3
<b>General disorders</b>				
Pyrexia	7.6	4.9	8.9	19
Fatigue	5.5	7.7	8.4	18.4
Peripheral edema	3.4	2.8	2.6	3.4
<b>Hepatobiliary disorders</b>				
Cytolytic hepatitis	0.7	0.2	0	-
Hepatic cirrhosis	0.7	0	0.2	-
<b>Immune system disorders</b>				
Hypersensitivity	2.8	0.2	0.2	0.7
Drug hypersensitivity	1.4	0	0.7	0.7
<b>Infections and Infestations</b>				
Herpes simplex	8.3	7.7	6.6	6.8
Oral candidiasis	7.6	5.6	5	8.2
Upper respiratory tract infection	6.9	3.7	6.6	2.7
Bronchitis	6.2	6	4.5	2
Influenza	6.2	3	2.6	4.8
Nasopharyngitis	5.5	9.3	7.5	12.2
Sinusitis	4.1	2.8	5	5.4
Pharyngitis	3.4	1.4	1.8	7.5
Urinary tract infection	2.8	1.9	2.3	2
Herpes zoster	2.1	3.5	2.2	4.8
<b>Metabolism and nutrition disorders</b>				
Hypertriglyceridemia	4.1	2.8	1.7	4.8
Hypercholesterolemia	3.4	2.1	0.7	2
Diabetes mellitus	2.1	0.7	0.3	-

	Highest Quartile (Phase 3) N=145 (%)	Lower Quarters (Phase 3) N=431 (%)	Placebo Subjects (Phase 3) N=604 (%)	Etravirine and LPV/r (Phase 2b) N=147 (%)
Dyslipidemia	2.1	0.7	0.8	-
<b>Musculoskeletal disorders</b>				
Back pain	4.8	2.8	4.3	8.8
Myalgia	3.4	1.9	3.8	3.4
Pain in extremity	2.8	3.7	3.1	2.7
<b>Nervous system disorders</b>				
Headache	6.2	10.7	12.3	21.1
Peripheral neuropathy	5.5	2.6	1.5	2.7
Anxiety	4.8	1.9	3	2
Neuropathy	2.8	1.4	1.8	1.4
Parasthesia	2.8	2.1	2.6	2
Depression	2.8	3.2	5	5.4
Dizziness	2.1	2.8	4.1	10.2
Somnolence	2.1	1.4	2	2
Tremor	2.1	0.5	0.7	0.7
Disturbance in attention	0.7	0	1	-
Neuralgia	0.7	0.2	0.5	-
Syncope	0.7	0.5	0.5	0.7
Vasovagal syncope	0.7	0	0	0.7
Convulsion	0	0.2	0.5	-
<b>Renal and urinary disorders</b>				
Renal failure, impairment (grouped)	3.5	2.1	2.8	
Renal failure	2.1	1.9	1	-
Renal failure acute	0.7	0.2	1	-
Renal impairment	0.7	0	0.5	-
Renal failure chronic	0	0	0.3	-
Renal insufficiency	-	-	-	2.7
<b>Respiratory, mediastinal and thoracic disorders</b>				
Cough	6.9	6.5	5.8	9.5
Nasal congestion	2.1	1.2	0.8	4.8
<b>Skin and subcutaneous disorders</b>				
Rash any type (grouped)	21.4	15.8	13.5	17.6
Rash	11.7	7.9	5.5	2
Pruritis	3.4	2.8	4.6	3.4
Rash papular	2.1	0.9	0.7	3.4
Rash generalized	1.4	0.5	0	-
Rash maculo-papular	1.4	1.4	0.8	3.4
Rash macular	0.7	0.9	1.3	1.4

	Highest Quartile (Phase 3) N=145 (%)	Lower Quartiles (Phase 3) N=431 (%)	Placebo Subjects (Phase 3) N=604 (%)	Etravirine and LPV/r (Phase 2b) N=147 (%)
Rash pruritic	0.7	1.2	0.2	0.7
Rash erythematous	0	0.2	0.3	0.7
Rash follicular	0	0	0.2	-
Rash nos	-	-	-	2
Rash scaly	-	--	-	0.7
Stevens-Johnson syndrome	0	0	0.2	-
<b>Vascular disorders</b>				
Hypertension	5.5	3.7	3	2.7
Hypertensive crisis	0	0.2	0	-
Hypertension nos	-	-	-	0.7

Adverse events in LPV/rtv and etravirine recipients in the available Phase 2b database were reviewed. However, the Phase 2b studies used formulation 035, rather than formulation 060 (Phase 3 and to-be-marketed formulation). Formulation 035 has lower bioavailability than formulation 060 and etravirine plasma concentrations for subjects who received etravirine and LPV/rtv in Phase 2b are not higher than the exposures observed in Phase 3 (etravirine plus DRV/rtv).

In conclusion, due to limited safety data, drugs that increase etravirine exposure should be co-administered with etravirine with caution. Users and prescribers are alerted to the drug interaction potential with etravirine use in the Highlights section of the package insert, with additional details about specific drug interactions in the Full Prescribing Information in the package insert. With regards to the interaction between etravirine and LPV/rtv, the label includes the following recommendation:

The mean systemic exposure (AUC) of etravirine after co-administration of INTELENCE™ with lopinavir/ritonavir is anticipated to be approximately 85% higher than the mean systemic exposure of etravirine observed in the Phase 3 trials.

Therefore, INTELENCE™ and lopinavir/ritonavir may be co-administered with caution.

Additionally, the safety of etravirine at higher exposures achieved in combination with other antiretroviral agents will be evaluated in a separate study by the Applicant as a post-marketing commitment and linked to traditional approval of etravirine.

#### 7.1.7.5 Special assessments

No additional special assessments were performed.

## **7.1.8 Vital Signs**

### **7.1.8.1 Overview of vital signs testing in the development program**

Vital signs including pulse and blood pressure (BP) were obtained at screening and at each visit. Systolic and diastolic BP was recorded in sitting position and after 5 minutes of rest. No clinically relevant or consistent changes over time in vital signs or ECG parameters were observed in Phase 3 trials.

### **7.1.8.2 Selection of studies and analyses for overall drug-control comparisons**

Blood pressure, pulse, respiratory rate, temperature and body weight were evaluated.

### **7.1.8.3 Standard analyses and explorations of vital signs data**

An assessment of vital signs did not demonstrate clinically relevant differences between the treatment groups. The results of the assessments did not raise safety concerns.

### **7.1.8.4 Additional analyses and explorations**

No additional analyses or explorations were conducted.

## **7.1.9 Electrocardiograms (ECGs).**

### **7.1.9.1 Overview of ECG testing in the development program, including brief review of preclinical results**

Testing of ECG parameters was performed in Study TMC125-C178, a thorough QT/QTc study and in Study TMC125-C153, a holter monitoring study.

In preclinical studies, no significant treatment-related effects were observed on ECG or cardio-hemodynamic parameters in dogs at exposure levels exceeding the human exposure at the to-be-marketed dose (margin of safety greater than 7-fold, refer to Toxicology Review of NDA for details). Mortality due to hemorrhagic cardiomyopathy observed in male mice was attributed to changes in clotting times due to inhibition of Vitamin K formation by etravirine. In light of concerns of cardiac toxicity, human studies were closely monitored for cardiovascular AEs. In Phase 3 studies, ECGs were obtained at screening, on the day of randomization and at Weeks 4, 12, 24, 48. In brief, no consistent or clinically relevant changes in ECG parameters of PR interval and QRS duration were observed over time during etravirine treatment.

Study TMC125-C178 was a double-blind, double-dummy Phase 1 study to evaluate the effect of etravirine on QT/QTc interval. Healthy subjects received 4 different 8-day treatments: 200 mg etravirine b.i.d., 400 mg etravirine q.d., 400 mg moxifloxacin q.d., and placebo. Moxifloxacin significantly prolonged QT interval and served as a positive control. The etravirine treated subjects were associated with small decreases in QTc duration. The upper bounds of time-matched mean changes in QTcF in etravirine group did not exceed the 10 msec boundary on Day 1 or Day 8. Based on the findings of this study, etravirine is not associated with a risk of QT interval prolongation.

Study TMC125-C153 evaluated the effect of 8-day once daily dosing of 400, 800, and 1600 mg etravirine (formulation TF035) on cardiac rhythm via holter monitoring. No relevant changes over time or between treatment groups were observed for ECG parameters QTcB and QTcF.

#### 7.1.10 Immunogenicity

Etravirine is a small molecule, not a peptide. As it is unlikely to have potential for immunogenicity, specific evaluation of this entity was not performed in clinical trials. In preclinical studies, immunotoxicity was evaluated and no relevant effect of etravirine treatment was observed on immune response measured by IgM production. Local tolerance was evaluated in guinea pig and rabbit. Etravirine was classified as "nonsensitizing" and "nonirritant" to skin. Refer to Pharmacology/Toxicology Review of NDA 22-187 for details.

#### 7.1.11 Human Carcinogenicity

Animal carcinogenicity studies of etravirine in rodents are ongoing. In Phase 3 clinical trials, 7.5% of subjects receiving etravirine reported at least 1 neoplasm-related AE as compared to 5.8% of subjects receiving placebo. Benign papilloma (preferred AE terms, buccal papilloma and skin papilloma) the most frequent benign neoplasm was observed in 4% of etravirine recipients compared to 2.8% of placebo recipients. Malignant neoplasms reported in at least 1 subject in etravirine arm include squamous cell carcinoma, basal cell carcinoma, lymphoma, Kaposi's sarcoma, meningioma, and anogenital carcinoma. There were no marked differences in the frequency of individual types of malignant neoplasms between the two treatment groups.

#### 7.1.12 Special Safety Studies

A hepatic impairment study, study TMC125-C125, demonstrated that steady state pharmacokinetic parameters of etravirine were similar after multiple dose administration of etravirine to subjects with normal hepatic function, mild hepatic impairment (Child-Pugh Class A), and moderate hepatic impairment (Child-Pugh Class B). The effect of severe hepatic impairment on the pharmacokinetics of etravirine has not been evaluated.

There is no data in renally impaired subjects as etravirine is minimally excreted by renal route. Study TMC125-C178 a thorough QT/QTc study is discussed in Section 7.1.9.1.

#### **7.1.13 Withdrawal Phenomena and/or Abuse Potential**

Etravirine has no known potential for drug withdrawal or abuse.

#### **7.1.14 Human Reproduction and Pregnancy Data**

Pregnancy was an exclusion criteria for all clinical trials of etravirine. Four women became pregnant during clinical trials. Three pregnancies were detected during the screening phase; these subjects were discontinued from the trials prior to drug intake. One pregnant subject exposed to etravirine experienced fetal demise with missed abortion. This subject had completed 48 weeks of therapy with etravirine and had enrolled into Phase 2b roll-over trial TMC125-C229. Ultrasound revealed an estimated fetal age of 6 weeks and slowing of fetal heart rate; a follow-up ultrasound 4 days later demonstrated no fetal cardiac activity.

No additional data on pregnancy was available from clinical trials. Etravirine belongs to pregnancy Category B and should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. No adequate and well-controlled studies have been conducted in pregnant women. In addition, no pharmacokinetic studies have been conducted in pregnant subjects.

#### **7.1.15 Assessment of Effect on Growth**

Etravirine has only been administered to adults; no clinical assessment on growth has been performed.

#### **7.1.16 Overdose Experience**

No cases of acute overdose with etravirine were reported during clinical trials. There is no specific antidote for overdose with etravirine. Since etravirine is highly protein bound, successful elimination by dialysis is unlikely.

#### **7.1.17 Postmarketing Experience**

Etravirine has not yet been approved in any country and therefore no postmarketing experience exists at this time.

## **7.2 Adequacy of Patient Exposure and Safety Assessments**

### **7.2.1 Description of Primary Clinical Data Sources (Populations Exposed and Extent of Exposure) Used to Evaluate Safety**

#### **7.2.1.1 Study type and design/patient enumeration**

The Phase 3 studies, C206 and C216, form the principal sources of data for the safety review. These are randomized, double-blind, placebo-controlled, international trials designed to evaluate the efficacy, tolerability, and safety of etravirine compared to placebo as part of an ART including DRV/rtv and an investigator selected optimized background regimen in treatment-experienced HIV-1 infected subjects.

In total, 599 subjects were exposed to etravirine treatment across the Phase 3 trials. At original NDA submission, the median duration of treatment was 30.0 weeks for etravirine treated subjects and 29.1 weeks for placebo control; total subject years of exposure was 357.7 for etravirine subjects and 359.5 for placebo treated subjects. The Safety Update Report submitted during the NDA review cycle provided data on 6 additional months of exposure to etravirine (cut-off date July 27, 2007).

#### **7.2.1.2 Demographics**

See section 6.1.4 for description of demographic characteristics of the population.

#### **7.2.1.3 Extent of exposure (dose/duration)**

In Phase 2b and Phase 3 trials, 861 subjects were exposed to etravirine at to-be-marketed dose either 200 mg b.i.d of F060 or 800 mg b.i.d. of TF035. In total, 1091 subjects were treated with etravirine in Phase 2b and Phase 3 trial. Overall, 861 and 279 subjects were treated with etravirine for at least 24 and 48 weeks, respectively. Inclusive of Phase 1 trials, 1235 HIV-infected subjects were exposed to etravirine and 1093 healthy subjects were exposed to etravirine.

### **7.2.2 Description of Secondary Clinical Data Sources Used to Evaluate Safety**

#### **7.2.2.1 Other studies**

##### TMC125-C203

This was a 48-week, randomized, placebo-controlled, dose-escalating Phase 2b study in HIV-infected subjects with 3-class antiretroviral therapy experience. In the first stage, 166 subjects

received either etravirine 400 mg b.i.d. or 800 mg b.i.d. or placebo. In the second stage, 74 subjects received either etravirine 800 mg b.i.d. or 1200 mg b.i.d. or placebo.

#### TMC125-C223

This was a randomized, controlled, partially blinded, dose-finding Phase 2b trial designed to evaluate dose-response relationship of antiviral activity at Week 24 in HIV-infected subjects with documented genotypic evidence of resistance to available NNRTIs. A total of 80, 79 and 40 subjects were randomized to etravirine 400 mg b.i.d., etravirine 800 mg b.i.d and control groups, respectively.

#### TMC125-C209

This was an open-label, single group Phase 2b trial in 7 HIV-infected, 3-class experienced subjects who had received at least 1 NRTI, 1 NNRTI and 1 PI each for at least 3 months prior to treatment, with the objective to assess safety and tolerability of etravirine 800 mg b.i.d. combined with optimized ARV regimen for 48 weeks. The original trial design investigated higher doses of etravirine, namely 1200 mg and 1600 mg b.i.d.; however, the findings of serious rash resulted in revision of this study to treat only with 800 mg dose of etravirine with discontinuation of new enrolment.

#### TMC125-C227

This was a randomized, active-controlled, open-label, Phase 2b trial evaluating antiviral activity of etravirine 800 mg b.i.d. in PI-naïve subjects with documented genotypic evidence of resistance to EFV, NVP and DLV. Suboptimal virologic response was observed in the etravirine treated group (59 subjects) compared to the active control group (57 subjects) who was receiving a PI-based therapy. Based on this data, the Applicant halted recruitment and prematurely discontinued the trial.

#### **7.2.2.2 Postmarketing experience**

At present, there are no post-marketing experiences with etravirine.

#### **7.2.3 Adequacy of Overall Clinical Experience**

The etravirine development program met requirements of International Conference of Harmonization with relation to size of the NDA package. Per the requirements, at least 100 HIV-infected subjects were exposed to the to-be-marketed dose (or equivalent dose of different drug formulation) for at least 12 months, and at least 600 HIV-infected subjects were exposed to the same for at least 6 months. Table 62 displays subject exposure to etravirine by duration. An adequate number of the target population was exposed for an adequate duration during the etravirine Phase 2b/3 trials.

**Table 62: Size of Etravirine NDA Package**

<b>Exposure to to-be-marketed or an Equivalent Dose</b>	<b>Duration</b>	<b>N</b>
HIV-infected subjects	6 months	719
HIV-infected subjects	12 months	161
HIV-infected subjects	>36 months	28
<b>Exposed to all doses of etravirine</b>		
Total subjects (includes healthy and HIV-infected)	Any	2328

As the majority of subjects in Phase 3 studies were males and of Caucasian ethnicity, the findings from the pivotal trials may not accurately reflect findings in women and minorities.

#### **7.2.4 Adequacy of Special Animal and/or In Vitro Testing**

The nonclinical toxicity program and design of the preclinical studies was consistent with acceptable scientific practices and international guidelines. The pivotal studies were conducted according to good laboratory practices (GLP) standards as per Organization for Economic Co-operation and Development (OECD) Principles of GLP, which concur with FDA GLP regulations.

#### **7.2.5 Adequacy of Routine Clinical Testing**

The routine clinical tests performed during Phase 3 trials are described in section 6.1.3, and were adequate.

#### **7.2.6 Adequacy of Metabolic, Clearance, and Interaction Workup**

The metabolic, clearance and interaction evaluation was adequate. Please refer to Section 5 and to Dr. Vikram Arya's review for details.

#### **7.2.7 Adequacy of Evaluation for Potential Adverse Events for Any New Drug and Particularly for Drugs in the Class Represented by the New Drug; Recommendations for Further Study**

The evaluation for potential adverse events associated with etravirine appears adequate based on limited data submitted for accelerated approval.

#### **7.2.8 Assessment of Quality and Completeness of Data**

The overall quality of clinical data was acceptable.

### **7.2.9 Additional Submissions, Including Safety Update**

The Safety Update Report was submitted three months after the original NDA was filed. The cut-off date for this update was 27 July 2007. Data related to select AE of interest has been incorporated into section 7.1.3 to provide a comprehensive assessment of all safety findings during the Phase 3 program.

### **7.3 Summary of Selected Drug-Related Adverse Events, Important Limitations of Data, and Conclusions**

A decrease in mortality and AIDS-defining illness was observed in the etravirine arm as compared to placebo arm in Phase 3 trials. The most frequent cause of death in both treatment groups was an AIDS-defining illness or infection. Discontinuations due to adverse events were observed in 6.3% of etravirine subjects compared to 4.6% to placebo subjects.

Rash and nausea were frequent adverse events associated with etravirine. Overall, 15.2% of subjects experienced rash with etravirine use compared to 8.1% in placebo arm. Rash was typically mild to moderate in severity, manifested primarily in the second week of therapy, and infrequently resulted in drug discontinuation. Serious dermatologic entities including Stevens-Johnson syndrome were rare. A female predisposition to development of rash was observed.

A mild increase in serum LDL cholesterol was observed in the etravirine arm compared to placebo arm; greater proportion of etravirine recipients initiated lipid-lowering therapy, suggesting an unfavorable effect of etravirine on lipid metabolism.

A clear association between hepatotoxicity attributable to etravirine use was not established. The etiology of concerning hepatic adverse events as well as serum transaminase abnormalities in etravirine recipients was confounded by underlying viral hepatitis, the use of known hepatotoxic medications, or other plausible explanations for liver enzyme elevations. In one case of confirmed drug-induced liver injury, etravirine was not clearly implicated as the offending agent. A higher frequency of hepatic laboratory abnormalities was observed in etravirine subjects with Hepatitis B or C co-infection compared to placebo subjects.

A mild increase in nasopharyngitis, herpes zoster, herpes simplex, and oral candidiasis was noted in the etravirine subjects. The etravirine subjects who experienced renal failure of any type had risk factors for renal disease; tenofovir use was the predominant risk factor. With respect to cardiac safety, the frequency of coronary artery disease was comparable in the two treatment arms. The majority of cases of cardiomyopathy were related to worsening of pre-existing cardiac failure or developed in a predisposing clinical setting.

The determination of drug-related adverse experiences was complicated by the presence of multiple antiretroviral agents in the background regimen with overlapping toxicity profiles and complex clinical scenarios given the advanced state of HIV infection in the trial population.

In conclusion, based on the limited data submitted for accelerated approval, the safety profile of etravirine appears acceptable for the proposed indication.

## **7.4 General Methodology**

### **7.4.1 Pooling Data Across Studies to Estimate and Compare Incidence**

The two Phase 3 studies, C206 and C216 were identical in design. This allowed pooling of data for safety and efficacy analyses. For key safety concerns, data from individual trials was analyzed to explore trends. Analysis of pooled data provided similar conclusions and only pooled results are described in section 6.1.3.

#### **7.4.1.1 Pooled data vs. individual study data**

Studies C206 and C216 have identical design including the same eligibility criteria. Hence, the safety data from these trials were pooled to increase the power to detect AEs potentially associated with the use of etravirine.

### **7.4.2 Explorations for Predictive Factors**

Exploration for predictive factors for select AEs was undertaken, and is discussed with specific AE in Section 7.1.3.

#### **7.4.2.1 Explorations for dose dependency for adverse findings**

Based on pharmacometric analyses, the predicted likelihood of rash (any type) as a function of etravirine AUC showed an increase with increasing AUC (refer to Section 7.1.3).

#### **7.4.2.2 Explorations for time dependency for adverse findings**

Time to onset analyses was performed for select AEs. Skin events of interest among etravirine recipients had a shorter time to onset from start of treatment (median time 11 days) compared to placebo (median time 17 days). Refer to Section 7.1.3 for details.

#### **7.4.2.3 Explorations for drug-demographic interactions**

Subgroup analyses of clinical AEs by gender, race and age were performed. A higher proportion of skin events of interest were observed in female subjects and Caucasian subjects in the etravirine treatment group. Refer to Section 7.1.3 for details.

#### **7.4.2.4 Explorations for drug-disease interactions**

No conclusive drug-disease interactions were observed.

#### 7.4.2.5 Explorations for drug-drug interactions

Please refer to Clinical Pharmacology Review of NDA 22-187 for explorations related to drug-drug interaction studies.

#### 7.4.3 Causality Determination

Adverse events potentially caused by etravirine are considered in Section 7.1.3 in detail.

### 8 ADDITIONAL CLINICAL ISSUES

#### 8.1 Dosing Regimen and Administration

The proposed dosing regimen for etravirine is 200 mg (two 100 mg tablets) twice daily in adults, following a meal.

#### 8.2 Drug-Drug Interactions

Etravirine is a substrate and weak inducer of CYP3A4, and a substrate and weak inhibitor of CYP2C9 and CYP2C19. Several clinically relevant drug-drug interactions stem from these effects, notable being the interactions prohibiting concomitant use of etravirine with select protease inhibitors.

As etravirine is a substrate of CYP3A4, CYP2C9 and CYP2C19, the co-administration of etravirine with drugs that are inducers or inhibitors of these enzymes may alter the therapeutic effect or adverse event profile of *etravirine*. Hence, co-administration of etravirine with **tipranavir/ritonavir**, and **full-dose ritonavir** (600 mg twice daily) is not recommended. An increase in etravirine exposure was observed when co-administered with **lopinavir/ritonavir**; caution is warranted when etravirine is co-administered with lopinavir/ritonavir as toxicity associated with increased plasma concentrations of etravirine may be observed. The co-administration of etravirine with **phenytoin**, **phenobarbital**, **carbamazepine**, **rifampin**, and **rifapentin** is not recommended. **Systemic corticosteroids** and **St. John's wort** (*hypericum perforatum*) decrease etravirine plasma concentration and may result in loss of therapeutic effect. On the other hand, **clarithromycin** and azole antifungal agents namely, **fluconazole**, **itraconazole**, **ketoconazole**, **posaconazole** may increase plasma concentration of etravirine resulting in etravirine toxicity. Additionally, an effect on exposure of itraconazole, ketoconazole and voriconazole is anticipated with etravirine co-administration. The increased generation of 14-hydroxy clarithromycin with concomitant etravirine may reduce activity against *Mycobacterium avium* complex (MAC), and therefore, alternatives to clarithromycin should be considered for treatment of MAC in subjects receiving etravirine.

In addition, since etravirine is an inducer of CYP3A4 and an inhibitor of CYP2C9 and CYP2C19, the co-administration of etravirine with drugs that are substrates of CYP3A4,

CYP2C9, and CYP2C19 may alter the therapeutic effect or adverse event profile of the *co-administered drugs*. Etravirine should not be co-administered with **unboosted protease inhibitors** and **fosamprenavir/ritonavir**. The co-administration of etravirine and atazanavir/ritonavir reduces systemic exposures of atazanavir by approximately similar proportions as observed in the tenofovir-atazanavir interaction. The reduction in atazanavir exposure in that interaction was sufficient to recommend co-administration of tenofovir with atazanavir only in the presence of ritonavir, as ritonavir boosts atazanavir concentrations in plasma to acceptable levels. In light of this reduction of systemic exposure of atazanavir, the co-administration of **atazanavir/ritonavir** and etravirine is not recommended. Additionally, an increase in plasma etravirine concentrations to 100% of that observed in pivotal Phase 3 trials is anticipated when etravirine is combined with atazanavir/ritonavir. Dose adjustment of **sildenafil, vardenafil, tadalafil, methadone, HMG-CoA reductase inhibitors, diazepam** and antiarrhythmic agents such as **amiodarone, bepridil, disopyramide, flecainide, lidocaine** (systemic), **mexiletine, propafenone, quinidine** may be required when co-administered with etravirine. Similarly, co-administration with systemic immunosuppressants such as **cyclosporine, tacrolimus and sirolimus** should be done with caution, and co-administration with **warfarin** should be accompanied by monitoring of international normalized ratio (INR). The co-administration of etravirine with **rifabutin** does not require dose adjustment in the absence of protease inhibitor/ritonavir; however, rifabutin should not be co-administered with etravirine as part of a regimen containing a protease inhibitor/ritonavir combination.

The combination of two NNRTIs has not been shown to be beneficial, and is not recommended. The concomitant use of etravirine with efavirenz or nevirapine may cause a significant decrease in plasma concentrations of etravirine and resultant loss of therapeutic effect of etravirine.

### 8.3 Special Populations

The highest doses of etravirine in reproductive and developmental toxicity studies produced systemic exposures in rats and rabbits respectively at approximately equivalent to those at the recommended human dose. In both rabbits and rats, no treatment-related effects on embryonic/fetal survival or fetal weights were observed. In addition, no treatment-related external, visceral, or skeletal malformations were observed. However, no adequate studies have been performed in pregnant women. Because animal reproduction studies are not necessarily predictive of human response, etravirine should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

A hepatic impairment study demonstrated similar steady state pharmacokinetic parameters of etravirine after multiple dose administration of etravirine to subjects with normal hepatic function (n = 16), mild hepatic impairment (Child-Pugh Class A, n = 8), and moderate hepatic impairment (Child-Pugh Class B, n = 8). The effect of severe hepatic impairment on the pharmacokinetics of etravirine has not been evaluated. The pharmacokinetics of etravirine has not been studied in renally impaired subjects as etravirine is minimally excreted by renal route.

Clinical studies of etravirine did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects.

#### **8.4 Pediatrics**

The safety and effectiveness of etravirine in pediatric subjects have not been established. The pediatric development program was initiated with a Phase 1 dose-finding study, C126 using the 100 mg adult tablet formulation as well as a compositionally proportional 25 mg tablet (bioequivalence was established in healthy adult volunteers) in subjects of ages 6 to  $\leq$  17 years.

Stage 1 of this study involved dosing 4 mg/kg twice daily of etravirine for 7 day to 20 subjects. In the absence of achievement of target etravirine exposure, Stage 2 consisting of dosing 5.2 mg/kg twice daily for 7 days will be initiated.

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#### **8.5 Advisory Committee Meeting**

An Advisory Committee meeting was not held, as etravirine is not the first agent in the class of NNRTIs. No unique safety or efficacy issues were identified during drug development, nor did issues requiring input from Advisory Committee members arise during the review process.

#### **8.6 Literature Review**

Literature citations are provided in the References Section.

#### **8.7 Postmarketing Risk Management Plan**

The Applicant has not proposed a postmarketing risk management plan. Please refer to Section 9.3 for a detailed description of all post-marketing commitments.

#### **8.8 Other Relevant Materials**

No other materials were used during this review.

### **9 OVERALL ASSESSMENT**

#### **9.1 Conclusions**

The antiviral superiority of etravirine over placebo was demonstrated by Week 24 results of two large double-blind randomized placebo-controlled trials, TMC125-C206 and TMC12-C216 in treatment-experienced HIV-1 infected subjects. In these trials, 59.8% of subjects, receiving etravirine achieved a plasma viral load reduction to less than 50 copies/mL compared to 40.2%

in the placebo arm. Both treatment groups received ART including DRV/rtv and an investigator selected optimized background regimen.

The safety concerns related to etravirine include skin reactions, gastrointestinal side effects and hyperlipidemia. Overall, 15.2% of subjects reported skin reactions such as rash with etravirine use compared to 8.1% reported in the placebo arm. Rash was typically mild to moderate in severity, manifested primarily in the second week of therapy, and infrequently resulted in drug discontinuation. Serious dermatologic events including Stevens-Johnson syndrome were observed less frequently. A female predisposition to development of rash was observed.

Gastrointestinal side effects attributed to etravirine are nausea and vomiting. A slight imbalance was observed in the frequency of elevations of serum alanine aminotransferase in the etravirine arm compared to placebo arm; however, no cases of hepatotoxicity were clearly attributable to etravirine use. A mild increase in nasopharyngitis, herpes zoster, herpes simplex, and oral candidiasis was noted in the etravirine subjects. The etravirine subjects who experienced renal failure of any type had risk factors for renal disease. A modest increase in serum low density lipoprotein cholesterol was observed in etravirine arm compared to placebo arm; etravirine subjects were more likely to initiate lipid-lowering therapy when compared to placebo subjects. A decrease in mortality and AIDS-defining illness was observed in the etravirine arm as compared to placebo arm in Phase 3 trials.

Several clinically relevant drug-drug interactions are associated with etravirine, notable are the interactions prohibiting concomitant use of etravirine with select protease inhibitors namely, atazanavir/ritonavir, tipranavir/ritonavir, fosamprenavir/ritonavir and any unboosted protease inhibitor.

Etravirine exerts antiviral activity and is well tolerated in treatment-experienced HIV-infected subjects with evidence of NNRTI resistance.

## **9.2 Recommendation on Regulatory Action**

Accelerated approval of etravirine is recommended for the management of HIV-1 infected treatment-experienced adults who have evidence of viral replication and HIV-1 strains resistant

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This recommendation is based on antiviral superiority of etravirine over placebo demonstrated by Week 24 results of two large double-blind randomized placebo-controlled trials in this population.

## **9.3 Recommendation on Postmarketing Actions**

### **9.3.1 Risk Management Activity**

A risk management plan was not submitted with NDA 22-187. The Applicant states that risk assessments based on available data indicate routine monitoring of the safety profile in ongoing

and planned clinical trials and routine pharmacovigilance activities suffice as tools to identify potential risks for etravirine. The FDA Office of Surveillance and Epidemiology (OSE) was briefed at an internal Pre-approval Safety Meeting regarding outstanding safety concerns and potential safety issues for etravirine. No additional risk minimization activities are required outside of Phase 4 commitments and requests.

### 9.3.2 Required Phase 4 Commitments

1. Submit study reports for Week 48 data analyses for the ongoing Phase 3 studies TMC125-C206 and TMC125-C216 to support the traditional approval of etravirine.  
Final Report Submission by: January 2009
2. Deferred pediatric study under PREA for the treatment of HIV-1 infection in pediatric subjects from 6 to 18 years of age. Conduct a pediatric safety and activity study of etravirine with activity based on the results of virologic response over at least 24 weeks of dosing and safety monitored over 48 weeks.  
Protocol submission by: June 2008  
Final report submission by: June 2010
3. Deferred pediatric study under PREA for the treatment of HIV-1 infection in pediatric subjects from 2 months to 6 years of age. This study will determine the pharmacokinetic profile, safety, and activity of etravirine in pediatric subjects from 2 months to 6 years of age.  
Protocol submission by: June 2010  
Final report submission by: June 2013
4. Conduct a study of etravirine in treatment-experienced female patients to elucidate any potential gender differences in efficacy and safety.

Protocol Submission: Completed, cross referenced to IND 62,477 for TMC114 (PREZISTA); "*Gender, Race And Clinical Experience (GRACE)*" trial, TMC114HIV3004

Final Report Submission: December 2009 (TMC125 subgroup analysis report of TMC114HIV3004)

5. Conduct a 48-week clinical study of treatment-experienced patients enrolling at least 200 subjects to evaluate safety and pharmacokinetics of etravirine when given with drug combinations that do not contain darunavir/rtv. Submit an interim report including analyses of 12-week safety data and supportive efficacy data with the Safety Update submission for the traditional approval supplemental new drug application for etravirine.

Protocol submission: July 2008

Final study report submission: July 2011

6. Complete ongoing carcinogenicity study in mice and submit the final report.  
Protocol submission date: Completed  
Final study report submission date: January 2009
7. Complete ongoing carcinogenicity study in rats and submit the final report.  
Protocol submission date: Completed  
Final study report submission date: January 2009
8. Conduct an *in vivo* drug-drug interaction study between etravirine and fluconazole.  
Protocol submission date by: July 2008  
Final Report Submission by: August 2009
9. Conduct an *in vivo* drug-drug interaction study between etravirine and buprenorphine/naloxone.  
Protocol submission date by: July 2008  
Final Report Submission by: August 2010

### 9.3.3 Other Phase 4 Requests

Other requests excluding postmarketing commitments are:

1. Please assess the combination activity relationships of etravirine with maraviroc and raltegravir.  
Final Study Report submission date: by December 2008

### 9.4 Labeling Review

The Package Insert (PI) and Patient Product Information (PPI) versions as of 15 January 2008 are attached in Section 10.2.

Key changes to the Applicant's proposed PI include:

- Addition of Stevens-Johnson syndrome and hypersensitivity in the Highlights section of package insert. Revision of description of rash events under 'skin reactions' in Warnings and Precautions section Full Prescribing Information.
- Recommendation to not co-administer etravirine with atazanavir/ritonavir due to significant decrease in plasma concentrations of atazanavir and loss of therapeutic effect of atazanavir.
- Recommendation to allow co-administration of etravirine with lopinavir/ritonavir with caution due to increase in plasma concentration of etravirine and the potential for etravirine toxicity.
- Inclusion of language reflecting virologic failure of etravirine in subjects with NNRTI resistance who are PI-naïve.

- Recommendation to not co-administer etravirine with fosamprenavir/ritonavir due to increase in plasma concentration of amprenavir and the potential for amprenavir toxicity.
- In the Section 6 Adverse Reactions in Full Prescribing Information, addition of anemia and hemolytic anemia to section pertaining to less common adverse reactions and addition of graded elevations of serum creatinine in the laboratory safety table.

## 9.5 Comments to Applicant

Comments were provided to the Applicant throughout the review, and there are no additional comments at this time.

## 10 APPENDICES

### 10.1 Review of Individual Study Reports

Data from relevant individual studies was incorporated into the review. Two Phase 2a studies are summarized.

#### Study TMC 125-C201

“A randomized, double-blind, monotherapy trial in 25 antiretroviral naïve, HIV-1 positive volunteers receiving either placebo, 100 or 400 mg of etravirine b.i.d. for 7 days” (TF002 formulation). Study TMC125-C201 was a dose-ranging monotherapy study to evaluate the efficacy, pharmacokinetics and safety of twice daily dosing of 100 mg or 400 mg of etravirine administered for 7 days. Twenty-five antiretroviral naïve, HIV-1 infected male subjects were randomly allocated to one of three treatment arms in a ratio of 1:2:2, placebo (5 subjects): 100 mg etravirine (10 subjects): 400 mg etravirine (10 subjects). Subjects greater than 18 years of age with plasma HIV RNA VL between 5000 and 150,000 copies/mL and CD4 cell count > 200 cells/mm<sup>3</sup> were enrolled.

Viral load was assessed twice daily. Viral genotype and drug susceptibility, CD4+ cell counts and safety were evaluated. Pharmacokinetic profiles were determined after the first dose and on Day 7. Twenty-five subjects enrolled and completed this study. Subjects were all male (100%), Caucasian (100%) with the median age of 23 years, mean HIV RNA 4.62 log<sub>10</sub> copies/mL and mean CD4 cell count 537 cells/mm<sup>3</sup>.

The plasma viral load decay rate estimates over 7 days were -0.141 and -0.187 log<sub>10</sub> HIV-1 RNA copies/mL/day in the 100 mg and 400 mg b.i.d. etravirine dose group, respectively (both p<0.001). The difference between the 100 mg and 400 mg b.i.d. etravirine dose groups was not statistically significant. There were no SAEs reported, and none of the subjects prematurely discontinued treatment because of AEs. Overall, AEs and laboratory abnormalities reported

during the trial are consistent with that observed in Phase 3 studies. Data regarding select AEs is summarized in Section 7.1.3.

#### Study TMC 125-C208

“A Phase 2a randomized, double-blind, placebo-controlled trial in antiretroviral naïve, HIV-1 positive volunteers receiving 900 mg b.i.d of etravirine as single-drug therapy for 7 days” (TF002 formulation). Study TMC125-C208 was a monotherapy study in anti-retroviral naïve, HIV-1 infected subjects to assess the antiviral efficacy, safety and pharmacokinetics of 900 mg of etravirine (TF002) administered twice daily for 7 days. Twelve male subjects greater than 18 years of age with plasma HIV RNA VL between 5000 and 125,000 copies/mL and CD4 cell count > 200 cells/mm<sup>3</sup> were enrolled. Safety parameters, HIV viral load, CD4 cell count, virologic resistance and pharmacokinetic profile were monitored.

Nineteen subjects were randomized, 7 to the placebo group and 12 subjects to etravirine treatment group (1:2 ratio). Eighteen subjects completed the trial, one subject in the placebo group discontinued due to gastroenteritis resulting in hypotension. Subjects were all male (100%), Caucasian (100%) with the median age of 23 years, mean HIV RNA 4.33 log<sub>10</sub> copies/mL and mean CD4 cell count 492 cells/mm<sup>3</sup>. The plasma viral load decay rate was -0.32 log<sub>10</sub> copies/mL/day after 7 days of treatment. The median change of HIV viral load from baseline after 7 days of treatment was -1.95 log<sub>10</sub> copies/mL, compared to placebo group -0.11 log<sub>10</sub> copies/mL (p ≤ 0.001).

One SAE of hospitalization for gastroenteritis in placebo subject is reported in this study. Overall, AEs and laboratory abnormalities reported during the trial are consistent with that observed in Phase 3 studies. Data regarding selected AEs is summarized in Section 7.1.3.

31 Page(s) Withheld

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Charu J Mullick  
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1/18/2008 09:40:59 AM  
MEDICAL OFFICER

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION		<b>REQUEST FOR CONSULTATION</b>		
TO (Division/Office): <b>Markham Luke, M.D., Medical Officer ODE3/DDDP</b>		FROM: Charu Mullick, M.D., clinical reviewer via Anne Marie Russell, Ph.D., Regulatory Project Manager Division of Antiviral Products Office of Antimicrobial Products Phone (301)796-2014		
DATE January 11, 2008	IND NO. 63,646	NDA NO. 22-187	TYPE OF DOCUMENT Stevens-Johnson syndrome case (see below)	DATE OF DOCUMENT
NAME OF DRUG Etravirine (TMC125) Proposed trade name: Intence		PRIORITY CONSIDERATION ASAP	CLASSIFICATION OF DRUG 7030240 antiretroviral/ systemic/HIV/ non-nucleoside reverse transcriptase inhibitor	DESIRED COMPLETION DATE <b>asap</b>
NAME OF FIRM: Tibotec, Inc.				
<b>REASON FOR REQUEST</b>				
<b>I. GENERAL</b>				
<input type="checkbox"/> NEW PROTOCOL <input type="checkbox"/> PROGRESS REPORT <input type="checkbox"/> NEW CORRESPONDENCE <input type="checkbox"/> DRUG ADVERTISING <input type="checkbox"/> ADVERSE REACTION REPORT <input type="checkbox"/> MANUFACTURING CHANGE/ADDITION <input type="checkbox"/> MEETING PLANNED BY				
<input type="checkbox"/> PRE-NDA MEETING <input type="checkbox"/> END OF PHASE II MEETING <input type="checkbox"/> RESUBMISSION <input checked="" type="checkbox"/> SAFETY/EFFICACY <input type="checkbox"/> PAPER NDA <input type="checkbox"/> CONTROL SUPPLEMENT				
<input type="checkbox"/> RESPONSE TO DEFICIENCY LETTER <input type="checkbox"/> FINAL PRINTED LABELING <input type="checkbox"/> LABELING REVISION <input type="checkbox"/> ORIGINAL NEW CORRESPONDENCE <input type="checkbox"/> FORMULATIVE REVIEW OTHER (SPECIFY BELOW):				
<b>II. BIOMETRICS</b>				
STATISTICAL EVALUATION BRANCH		STATISTICAL APPLICATION BRANCH		
<input type="checkbox"/> TYPE A OR B NDA REVIEW <input type="checkbox"/> END OF PHASE II MEETING <input type="checkbox"/> CONTROLLED STUDIES <input type="checkbox"/> PROTOCOL REVIEW <input type="checkbox"/> OTHER (SPECIFY BELOW):		<input type="checkbox"/> CHEMISTRY REVIEW <input type="checkbox"/> PHARMACOLOGY <input type="checkbox"/> BIOPHARMACEUTICS <input type="checkbox"/> OTHER (SPECIFY BELOW):		
<b>III. BIOPHARMACEUTICS</b>				
<input type="checkbox"/> DISSOLUTION <input type="checkbox"/> BIOAVAILABILITY STUDIES <input type="checkbox"/> PHASE IV STUDIES		<input type="checkbox"/> DEFICIENCY LETTER RESPONSE <input type="checkbox"/> PROTOCOL-BIOPHARMACEUTICS <input type="checkbox"/> IN-VIVO WAIVER REQUEST		
<b>IV. DRUG EXPERIENCE</b>				
<input type="checkbox"/> PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL <input type="checkbox"/> DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES <input type="checkbox"/> CASE REPORTS OF SPECIFIC REACTIONS (List below) <input type="checkbox"/> COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP		<input type="checkbox"/> REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY <input type="checkbox"/> SUMMARY OF ADVERSE EXPERIENCE <input type="checkbox"/> POISON RISK ANALYSIS		
<b>V. SCIENTIFIC INVESTIGATIONS</b>				
<input type="checkbox"/> CLINICAL		<input type="checkbox"/> PRECLINICAL		
<b>COMMENTS/SPECIAL INSTRUCTIONS:</b> See case narrative from Dr. Mullick below				
SIGNATURE OF REQUESTER Anne Marie Russell (x2014)		METHOD OF DELIVERY (Check one) <input checked="" type="checkbox"/> MAIL (DFS) <input type="checkbox"/> HAND		
SIGNATURE OF RECEIVER		SIGNATURE OF DELIVERER		

**NARRATIVE FOR STEVENS-JOHNSON SYMDROME CASE**  
**(by Charu Mullick, M.D., clinical reviewer, DAVP 1/11/08)**

Reason for consult: Please provide clinical input regarding the diagnosis of Stevens-Johnson syndrome in patient receiving etravirine.

Etravirine is a non-nucleoside reverse transcriptase inhibitor (NNRTI) of human immunodeficiency virus type 1 (HIV-1). In the etravirine Phase 3 trials, a marked increase in frequency of skin reactions was associated with etravirine compared to placebo. The majority of skin reactions due to etravirine were rash events of mild to moderate severity; few subjects discontinued due to rash. In the Phase 3 trials, no cases of Stevens-Johnson syndrome (SJS) were reported; however, 2 cases of SJS were noted in the etravirine early access program.

In general, rash due to etravirine was more frequent in women compared to men. An association of rash with higher baseline CD4 count was apparent among women in etravirine group, however, in light of small numbers in this subgroup these findings cannot be considered conclusive. The likelihood of rash events appeared to increase with increasing etravirine exposures. In comparison to nevirapine, skin reactions due to etravirine are less likely to be severe. Similar to NVP, the reactions due to etravirine were frequently seen within weeks of treatment onset and more frequently observed in women. Rash was infrequently accompanied by liver enzyme elevations or other laboratory abnormalities. Cases of serious skin reactions in the entire drug development program are summarized in Table 1.

**Table 1: Noteworthy Cutaneous Adverse Events in Etravirine Development Program**

CRF ID/ EAP ID	AE term	Trials <sup>1</sup>	Pertinent findings	Onset of AE (days)	Investigator Causality
20070202731	Stevens-Johnson Syndrome	EAP	Only etravirine stopped Improvement with steroids	15	Very likely related
20070507019	Stevens-Johnson Syndrome	EAP	Nausea and vomiting at presentation	35	Probably related
1092852	Stevens-Johnson Syndrome	Phase 1	Hepatotoxicity due to nevirapine, followed by SJS suspected due to NVP <sup>2</sup>	15	Not related
2232613	Erythema multiforme <sup>3</sup>	Phase 2b	EEM on skin biopsy, drug discontinued	261	Possibly related
137009 <sup>4</sup>	Erythema multiforme	Phase 1	EEM or PCT or PPCT differential diagnosis based on skin biopsy <sup>5</sup>	8	Related
137001 <sup>4</sup>	Erythema multiforme	Phase 1	Clinical diagnosis by dermatologist	10	Related
137022 <sup>4</sup>	Atypical bullous dermatitis	Phase 1	Clinical diagnosis by dermatologist	1	Related
2060712	Drug hypersensitivity syndrome	Phase 3	Worsening of pre- existing rash accompanied fever, convulsion; skin biopsy showed drug allergy	11	Probably related

<sup>1</sup>Phase 1 cases were healthy volunteers

<sup>2</sup>Onset of SJS on Day 9 of continuous NVP alone and 15 days after single dose of 900 mg of etravirine (TF035 formulation)

<sup>3</sup>Received 400 mg b.i.d. (TF035), less than to-be-marketed dose

<sup>4</sup>Received 1600 mg single dose etravirine (TF035 formulation)

<sup>5</sup>EEM, erythema exudativum multiforme; PCT, porphyria cutanea tarda; PPCT, pseudoporphyria cutanea tarda

An additional case of SJS diagnosed clinically was reported in the early access program, and is described below:

A 53-year old African American male with HIV receiving etravirine, raltegravir and tenofovir-emtricitabine for approximately 6 weeks was diagnosed with Stevens-Johnson syndrome. The patient was diagnosed with HIV infection in 1995, last CD4 count was 59 cells/mm<sup>3</sup> and VL<50 copies/mL on therapy, at the four week visit. The patient was hospitalized with nausea, vomiting, generalized rash, acute renal failure and diarrhea. On physical examination, patient had stable vital signs and appeared chronically ill. Exam was notable for desquamating, erythematous macular rash involving the entire body including palms, sole, face, trunk and extremities without vesicular lesions. No oropharyngeal lesions were observed. White blood cell count was elevated at 15.6/mm<sup>3</sup> with 38% neutrophils, 25% bands, 18% eosinophils, 15% lymphocytes, 3% atypical lymphocytes and 1% metamyelocytes. Serum creatinine was 4.2 mg/dL and liver enzymes were normal. Stool exam indicated colonization with methicillin-resistant staphylococcus aureus. A CT scan of chest showed bilateral apical scarring with ground-glass infiltrates with probable air-fluid levels, and an infiltrate in the right middle lobe. The infectious diseases consultant concluded that skin findings were due to drug eruption and recommended discontinuation of medications and performing a skin biopsy. It is reported that rash improved dramatically after discontinuation of ART and initiation of steroids. A skin biopsy was not performed. This subject had advanced HIV infection with HIV wasting syndrome, chronic hepatitis C, and was an intravenous drug abuser. In the preceding six months, he had several visits to the outpatient clinic for abdominal pain, one hospitalization for gallstones and one emergency room visit for Norwegian scabies. The patient had no known drug allergies. At the time of admission, he was also taking cotrimoxazole, valacyclovir, azithromycin, erythropoietin, protonix and merinol. The patient was re-hospitalized for altered mentation within 5 days of discharge. Exam at this time reported intact skin with residual lesions of SJS. Lumbar puncture was negative for meningitis. As subject had elected Do Not Resuscitate code status, palliative measures were instituted and subject died due to cardiac arrest. **In summary, this is case of Stevens-Johnson syndrome by clinical diagnosis that was possibly related to etravirine per the site investigator.** The subject subsequently died due to complications of end-stage AIDS.

Additional clinical information including hospital physician notes and discharge summaries have been forwarded by email.

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**This is a representation of an electronic record that was signed electronically and  
this page is the manifestation of the electronic signature.**  
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/s/

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Anne Marie Russell  
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