

ng/mL). Etravirine demonstrates antiviral activity in cell culture against a broad panel of HIV-1 group M (subtype A, B, C, D, E, F, G) with EC₅₀ values ranging from 0.29 to 1.65 nM. Less activity was displayed against group O primary isolates with EC₅₀ values ranging from 11.5 to 21.7 nM. Etravirine shows antiviral activity against 55 of 65 HIV-1 strains (85%) with single amino acid substitutions at reverse transcriptase positions associated with NNRTI resistance, including the most commonly found K103N.

Resistance to etravirine

Development of reduced susceptibility to etravirine typically required more than one substitution in reverse transcriptase. The following mutations were observed most frequently: L100I, E138K, E138G, V179I, Y181C, and M230I. In the Phase 3 trials, substitutions that developed most commonly in subjects with virologic failure at Week 24 who were receiving an etravirine-containing regimen were V179F, V179I, Y181C, and Y181I. These mutations usually emerged in a background of multiple other NNRTI resistance-associated substitutions. In all the trials conducted with etravirine in HIV-1 infected subjects, the following substitutions emerged most commonly: L100I, E138G, V179F, V179I, Y181C and H221Y. NNRTI-resistance associated substitutions that emerged during etravirine treatment in <10% of the virologic failure isolates included K101E, K103N, V106I/M, V108I, Y188L, V189I, G190S/C, and R356K.

The single amino acid substitutions associated with an etravirine reduction in susceptibility > 3 fold were K101A, K101P, K101Q, E138G, E138Q, Y181C, Y181I, Y181T, and Y181V, and of these, the greatest reductions were Y181I (13-fold reduction in EC₅₀ value) and Y181V (17-fold reduction in EC₅₀ value). Mutant strains containing a single NNRTI resistance-associated substitution (K101P, K101Q, E138Q, or M230L) had cross-resistance between etravirine and efavirenz.

The highest levels of resistance to etravirine were observed for HIV-1 harboring a combination of substitutions V179F+Y181C (187 fold-change), V179F+Y181I (123 fold-change), V179F+Y181C +F227C (888 fold-change). In Studies C206 and C216, 35% of the baseline isolates had decreased susceptibility to etravirine (>3-fold change from reference) and >93% of these isolates were cross-resistant to delavirdine, efavirenz, and nevirapine. Cross-resistance to delavirdine, efavirenz and/or nevirapine is expected after virologic failure with an etravirine-containing regimen for the virologic failure isolates.

Impact of Baseline Mutations and ENF on Response Rate

In Phase 3 trials, response rates to etravirine decreased as the number of baseline NNRTI mutations increased. Subjects with two or more IAS-USA-defined NNRTI mutations at baseline had lower response rates than the overall response rate of 60% for subjects who were taking etravirine and not using or re-using enfuvirtide. The presence at baseline of the substitutions V179F, V179T, V179D, Y181V, or G190S resulted in a decreased virologic response to etravirine. The presence of K103N, which was the most prevalent NNRTI substitution in DUET-1 and DUET-2 at baseline, did not affect the response in the etravirine arm.

Etravirine Fold Change Cut-off

Response rates assessed by baseline etravirine phenotype showed that a ≤ 3 -fold change in etravirine susceptibility at baseline was associated with $> 60\%$ response rates. Response rates decreased when baseline etravirine susceptibility was >3 -fold. Response rates were 70%, 47% and 34% when baseline etravirine phenotype was 0-3, >3 -13, and >13 , respectively. These baseline phenotype groups are based on the select subject populations in Phase 3 trials and are provided to give clinicians information on the likelihood of virologic success based on pre-treatment susceptibility to etravirine in treatment-experienced subjects. Overall, in the etravirine arms of Studies C206 and C216, the median baseline phenotype was 1.7. The baseline phenotype of responders was 1.4 (n=351) and the median baseline phenotype of virologic failures was 3.4 (n=210).

6.1.6 Efficacy Conclusions

The etravirine Phase 3 trials demonstrated greater antiviral activity of etravirine as compared to placebo in treatment-experienced subjects with NNRTI resistance who were receiving a background regimen containing DRV/rvtv. Subjects with one or more active antiretroviral drugs in their background regimen had a greater probability of achieving virologic response. Thus, use of etravirine in combination with other antiretroviral drugs will provide an additional treatment option for treatment-experienced patients.

The likelihood of virologic success is related to etravirine susceptibility; etravirine fold change greater than 3-fold may be associated with decreased virologic success. The presence at baseline of the substitutions V179F, V179T, V179D, Y181V, or G190S resulted in a decreased virologic response to etravirine. The presence of K103N, which was the most prevalent NNRTI mutation at baseline, did not affect the response in the etravirine arm. Substitutions that developed most commonly in subjects who experienced virologic failure to the etravirine-containing regimen were V179F, V179I, Y181C, and Y181I, which usually emerged in a background of multiple other NNRTI resistance-associated substitutions. The emergence of NNRTI substitutions on etravirine treatment contributed to decreased susceptibility to etravirine with a median fold-reduction in etravirine susceptibility of 40-fold from reference and a median fold-reduction of 6-fold from baseline.

Suboptimal virologic response was observed in the etravirine-treated group compared to the PI-treated group in HIV-infected subjects who were PI-naive and with evidence of NNRTI resistance. These results of study C227 demonstrate no role for etravirine as part of a first-line regimen for treatment-naive patients who are resistant to NNRTIs and susceptible to protease inhibitors, including those with primary NNRTI resistance.

7 INTEGRATED REVIEW OF SAFETY

7.1 Methods and Findings

The Phase 3 trials of etravirine, C206 and C216, are identical, double-blind, placebo-controlled with a 1:1 randomization scheme. Pooled AE data was reviewed from 1203 subjects who received at least 1 dose of treatment, to identify clinical and laboratory side effects associated with etravirine use. To further evaluate the safety of etravirine, data from Phase 2b trials C203, C213, C227, C229, and the Phase 3 roll-over trial C217 were reviewed. The analysis of specific adverse events (AE) required review of Applicant's Summary of Clinical Safety for identification of additional events in Phase 1 and Phase 2a studies, and the Expanded Access Program.

The original NDA included safety data from trials with a cut-off date of 12 January 2007. This review also incorporates data submitted in the Safety Update Report (SUR) with a clinical cut-off date of 27 July 2007. The SUR includes SAE reports for ongoing trials including C206, C216, the Expanded Access Program, and TMC114HIV3004 [GRACE].

All deaths in the treatment or follow-up period were reviewed; serious adverse events (SAE) and AEs were included in review if they occurred within 30 days and 7 days, respectively, of drug discontinuation. Deaths in Phase 3 studies were captured as AEs; the immediate, contributing and underlying causes of death submitted by the investigator were reviewed by an independent expert panel. Similarly, all cardiovascular events in Phase 3 studies were reviewed by an adjudication panel and validated.

7.1.1 Deaths

In Phase 3 trials, 31 deaths were reported during the treatment period including additional data provided in the Safety Update Report (Table 15). Deaths occurred less frequently in subjects receiving etravirine (1.8%) compared to subjects receiving placebo (3.3%).

Causes of death were adjudicated by an independent panel for all but two subjects. I concur with all of the Applicant's attributions of cause of death based on the provided case narratives. The most frequent cause of death in both treatment groups was an AIDS-defining illness or infection (1.0% in etravirine group compared to 3.3% in placebo group), as would be expected in a study population with advanced HIV infection and considerable immunosuppression. Death was attributed to a cardiovascular etiology in 0.7% of etravirine recipients compared to 0.5% of placebo recipients. Malignancy, renal failure, bronchial hemorrhage and respiratory failure were other AEs leading to death. The demographics and baseline HIV disease characteristics of subjects who died were balanced between the two treatment groups. No relevant differences in the last CD4 count and last HIV VL prior to death were noted in subjects who died, between the two treatment groups.

Table 15: Overview of Deaths in Phase 3 Studies and Baseline HIV disease Characteristics

	Etravirine (%) N=599	Placebo (%) N=604
Treatment duration (median, weeks)	29.1	30
Deaths		
Treatment phase ¹	11 (1.8)	20 (3.3)
Cause of Death²		
AIDS-defining illness or infection	6 (1.0)	13 (2.2)
Cardiovascular event	4 (0.7)	3 (0.5)
Malignancy	1 (0.2)	1 (0.2)
Other ³	1 (0.2)	3 (0.5)
Baseline HIV disease characteristics		
Baseline CD4 count (median, cells/mm ³)	26 (5-760)	14 (1-106)
Baseline viral load (median, log ₁₀)	4.9	5.0

¹ Does not include 8 deaths in screening period and 2 deaths in follow-up phase of Phase 3 studies

² A subject may have two AEs assigned as the cause of death

³ Preferred AE term with fatal outcome: renal failure (2), bronchial hemorrhage (1), respiratory failure (2)

Source: Datasets AEAD, DMAD for Studies C206 and C216; SUR

A cumulative summary of treatment-emergent deaths including the primary cause of death and day of onset of AE leading to death in Phase 3 trials, including the Phase 3 roll-over trial are provided in Table 16.

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Table 16: Summary of AE leading to Death in the Treatment Period of all Phase 3 Trials

CRF ID	Treatment	Cause of Death	Onset of AE (days)	Duration of Therapy (days)
Phase 3 trials, C206 and C216				
2060190	Etravirine	Sudden death due to atherosclerosis, hypertension	151	151
2060424	Etravirine	Septic shock due to central line infection	62	76
2060569	Etravirine	Respiratory and renal failure, septic shock	131	150
2060587	Etravirine	Cerebral toxoplasmosis	302	319
2060594	Etravirine	Tumor lysis syndrome (Burkitt's lymphoma)	120	286
2060649	Etravirine	Cardiogenic shock	125	125
2160073	Etravirine	Sepsis related to <i>Mycobacterium avium</i> complex	16	19
2160222	Etravirine	HIV wasting syndrome	56	74
2160238	Etravirine	Sudden death due to cardiorespiratory failure	392	392
2160409	Etravirine	Myocardial infarction, cardiac arrest	57	58
2160489	Etravirine	Progressive multifocal leukoencephalopathy	142	180
2060103	Placebo	Pneumonia	61	63
2060145	Placebo	Progression of AIDS	92	92
2060152	Placebo	Herpes encephalitis	148	212
2060156	Placebo	Multi-organ failure, Non-Hodgkin's lymphoma	76	116
2060174	Placebo	Acute renal failure	19	73
2060212	Placebo	CMV, cryptosporidiosis	329	349
2060551	Placebo	Cardiopulmonary arrest	255	258
2060623	Placebo	<i>Mycobacterium avium</i> complex infection	73	144
2060646	Placebo	Cardiac arrest, shock	105	107
2060927	Placebo	<i>Pneumocystis jiroveci</i> pneumonia	158	160
2060944	Placebo	Progressive multifocal leukoencephalopathy	77	133
2160147	Placebo	Bacterial sepsis	170	195
2160285	Placebo	Central nervous system lymphoma	133	134
2160490	Placebo	Sepsis related to intestinal perforation	153	155
2160525	Placebo	Progression of malignant basalioma	31	225
2160584	Placebo	Cardiorespiratory failure (due to bronchial hemorrhage)	138	214
2160671	Placebo	Sepsis, AIDS	164	216
2160730	Placebo	Sepsis	122	122
2160737	Placebo	Respiratory failure	256	270
2160815	Placebo	Pulmonary hemorrhage (pre-existing vasculitis)	165	165
Roll-over Phase 3 trial TMC125-C217				
2170035	Etravirine	Progression of AIDS	90	-
2170105	Etravirine	Sepsis	120	-
2170148	Etravirine	Cardiorespiratory arrest, MRSA sepsis	80	-

Source: Datasets AFAD, DMAD for Studies C206 and C216; SUR

Among all deaths in etravirine-treated subjects in Phase 3 trials, three deaths were considered doubtfully or possibly related to etravirine by the investigator and the remaining deaths were considered unrelated to etravirine by the investigator. Death due to respiratory failure and renal failure in one subject was considered doubtfully related to etravirine; in this subject, renal failure was considered very likely related to tenofovir in the background regimen. In another subject, death due to sepsis was considered doubtfully related to etravirine; sepsis was due confirmed *Mycobacterium avium* complex infection. The third subject with Type 2 diabetes mellitus and electrocardiographic evidence of prior coronary artery disease experienced myocardial infarction leading to death; this death was considered doubtfully related to etravirine by investigator. Based on review of individual narratives for these 3 cases, the deaths do not appear to be attributable to etravirine. In short, deaths in etravirine-treated subjects do not appear to be plausibly attributable to etravirine.

In addition, deaths in Phase 2b studies were reviewed (Table 17). Similar to Phase 3 studies, an infectious illness or AIDS-defining illness was the leading causes of death.

Table 17: Treatment-emergent Deaths in Phase 2b trials¹

CRF ID	Treatment	Cause of Death	Onset of AE (days)	Treatment Duration (days)
2112001	Etravirine	Dehydration in setting of dysphagia, esophagitis	99	99
2113101	Etravirine	Upper GI hemorrhage	456	460
2114001	Etravirine	Pneumonia	362	362
2232002	Etravirine	Myocardial infarction, cardiopulmonary failure	136	136
2230710	Etravirine	Central nervous system lymphoma	78	102
2235506	Etravirine	Pseudomonal sepsis	279	282
2290108	Etravirine	Malignant hepatic neoplasm	420	420
2290116	Etravirine	Sudden death, possible arrhythmia ²	540	540
2290122	Etravirine	Progression of Kaposi's sarcoma, AIDS	540	540
2232709	Control ³	Cardiac arrest	74	74

¹ Includes subjects who received to-be-marketed or higher dose of etravirine

² Per provided narrative, investigator deemed cardiovascular myopathy as probable cause of death in subject with pre-existing cardiomyopathy

³ Active control arm

Source: Datasets AEAD, DMAD for Studies TMC125-C211, TMC125-C223, TMC125-C229

Additionally, deaths in the Expanded Access Program (EAP) were reviewed. In total, 21 deaths were reported among 2915 subjects enrolled in the EAP until 27 July 2007, the cut-off date for the SUR. Notable causes leading to death are tabulated in Table 18.

Table 18: Noteworthy Cases of Death in Etravirine Expanded Access Program¹

EAP Reference Number	Cause of Death	Risk factor for CAD	Onset of AE (Month)	Investigator Causality
AT-NJFOC-20070702813	Cerebral hemorrhage	Hypertriglyceridemia	8	Possibly related
US-JNJFOC-20070702584	Cardiac arrest	Diabetes mellitus, hypercholesterolemia	1	Doubtfully related
US-JNJFOC-20070601463	Coronary artery disease, pneumonia	Hypertension	3	Not related

¹Includes data submitted in SUR

In summary,

- Fewer deaths were observed in the subjects receiving etravirine compared to subjects receiving placebo in controlled clinical trials.
- The primary cause of deaths were verified and appear appropriate. The most frequent AEs leading to death were infection or an AIDS-defining illness. No pattern was observed among deaths between etravirine and placebo groups with respect to the primary cause of death or subject demographic and baseline HIV characteristics.
- Per my assessment, no deaths in Phase 3 studies were plausibly attributable to etravirine.

7.1.2 Serious Adverse Events

In Phase 3 studies, 195 subjects reported at least one SAE. Overall, fewer SAEs were observed in subjects receiving etravirine (13.1%) compared to subjects receiving placebo (19.2%). Table 19 lists SAEs reported in at least 2 subjects receiving etravirine; the prominent events observed more frequently with etravirine use appear in bold. The events myocardial infarction, renal failure, alanine aminotransferase (ALT) increase and pancytopenia are discussed in detail in Section 7.1.3.

Table 19: Serious Adverse Events in at least 2 subjects receiving Etravirine in Phase 3 Trials¹

Preferred AE term	Etravirine (%) N=599	Placebo (%) N=604
Pyrexia	7 (1.2)	11 (1.8)
Pneumonia	6 (1.0)	9 (1.5)
Anemia	5 (0.8)	6 (1.0)
<i>Pneumocystis jiroveci</i> pneumonia	4 (0.7)	5 (0.8)
Myocardial infarction	3 (0.5)	1 (0.2)
Cellulitis	3 (0.5)	4 (0.7)
Renal failure	3 (0.5)	2 (0.3)
Sepsis	3 (0.5)	5 (0.8)
Alanine aminotransferase increased	2 (0.3)	1 (0.2)
Asthenia	2 (0.3)	0 -
Blood glucose increased	2 (0.3)	1 (0.2)
Diabetes mellitus	2 (0.3)	0 -
Diarrhea	2 (0.3)	8 (1.3)
Dyspnea	2 (0.3)	3 (0.5)
Neutropenia	2 (0.3)	3 (0.5)
Esophageal candidiasis	2 (0.3)	5 (0.8)
Pancytopenia	2 (0.3)	1 (0.2)
Perianal abscess	2 (0.3)	0 -
Pneumonia bacterial	2 (0.3)	0 -
Renal failure acute	2 (0.3)	4 (0.7)
Septic shock	2 (0.3)	0 -
Thrombocytopenia	2 (0.3)	4 (0.7)

¹SAEs in bold print were observed more frequently in etravirine-treated subjects compared to placebo
Source: Datasets AEAD, DMAD for Studies C206 and C216

In Phase 3 trials, SAEs observed in 2 or more etravirine-treated subjects and considered doubtfully, possibly, probably or very likely related to etravirine were diabetes mellitus, increase in serum ALT and pyrexia. Diabetes mellitus considered possibly related to etravirine developed on day 160 of treatment in one subject with risk factors including family history of diabetes, prior use of PIs and obesity. Another subject with hepatitis C infection and chronic hepatic encephalopathy was diagnosed with diabetes mellitus; the AE diabetes mellitus was considered doubtfully related to etravirine. Neither subject with diabetes mellitus discontinued etravirine. Subjects who experienced SAE due to preferred AE term, 'blood glucose increased' were also reviewed as this AE reflects a clinical entity that is closely comparable to the AE 'diabetes mellitus'. In one of the two etravirine-treated subjects with SAE 'blood glucose increased', the AE was considered not related to etravirine by the site investigator. In the second subject, the AE was considered doubtfully related to etravirine; the abnormality resolved and the subject was able to continue etravirine treatment. The SAEs of serum ALT elevations are discussed in Section 7.1.3. The adverse event pyrexia was observed less frequently in the etravirine arm compared to the placebo arm.

7.1.3 Dropouts and Other Significant Adverse Events

7.1.3.1 Overall profile of dropouts

In Phase 3 studies, 1203 subjects were randomized, 599 subjects to etravirine and 604 subjects to placebo. At the time of submission of the original NDA, 84.3% of subjects receiving etravirine and 78.5% of subjects receiving placebo were continuing treatment. The most frequent reason for study discontinuation was realization of virologic endpoint (6.8% etravirine vs. 12.9% placebo). Discontinuations due to adverse events were observed in 6.3% of etravirine subjects compared to 4.6% to placebo subjects. Other reasons for study drop-out are provided in Table 20.

Table 20: Subject Disposition and Reasons for Study Discontinuation in Phase 3 Trials

Disposition Status	Etravirine (%) N=599	Placebo (%) N=604
Ongoing	505 (84.3)	474 (78.5)
Discontinuations		
Subject reached virologic endpoint	41 (6.8)	78 (12.9)
Adverse event/HIV related	38 (6.3)	28 (4.6)
Subject withdrew consent	6 (1)	14 (2.3)
Subject lost to follow-up	4 (0.7)	1 (0.2)
Subject non-compliant	3 (0.5)	3 (0.5)
Subject ineligible to continue trial	1 (0.2)	1 (0.2)
Sponsor's decision	0 -	1 (0.2)
Subject did not fulfill all eligibility criteria	0	1 (0.2)
Other	3 (0.5)	3 (0.5)

Source: Datasets AEAD, DMAD for Studies C206 and C216

7.1.3.2 Adverse events associated with dropouts

Discontinuation from Phase 3 studies due to at least one AE was observed in 6.3% of subjects in etravirine arm compared to 4.6% of subjects in placebo arm (Table 21). The majority of AEs leading to discontinuation in the etravirine arm were non-fatal; fewer fatalities were observed in the etravirine arm compared to placebo arm. Table 21 provides AEs by preferred term that led to discontinuation, reported in at least 2 etravirine subjects. Rash of any type was the most frequently observed AE resulting in treatment discontinuation, in total 2.0% of subjects receiving etravirine. In the pooled data, AEs related to discontinuations in ≥ 2 subjects and considered related to etravirine include rash, nausea, increase in serum ALT, increase in serum aspartate aminotransferase and anemia. Anemia considered possibly related to etravirine and requiring blood transfusion was diagnosed on day 56 of therapy in one subject. Another subject with

anemia due to chronic kidney disease who required erythropoietin developed worsening anemia that resolved after treatment discontinuation.

Analysis of rash, increase in serum transaminase enzymes, congestive cardiac failure, renal failure, diarrhea and nausea are presented in Section 7.1.3.3. Pneumonia, sepsis, cardiac arrest, thrombocytopenia and hepatitis were frequent AEs leading to discontinuation in the placebo arm.

Table 21: Adverse Events leading to Permanent Discontinuation in at Least 2 Subjects receiving Etravirine in Phase 3 Trials

Preferred AE term	Etravirine (%) N=599	Placebo (%) N=604
Rash ¹	11 (1.9)	0 -
Nausea	4 (0.7)	0 -
Alanine aminotransferase increased	2 (0.3)	0 -
Anemia	2 (0.3)	1 (0.2)
Aspartate aminotransferase increased	2 (0.3)	0 -
Congestive cardiac failure	2 (0.3)	0 -
Diarrhea	2 (0.3)	0 -
Pneumonia	2 (0.3)	2 (0.3)
Renal failure	2 (0.3)	0 -

¹Denotes preferred AE terms, 'rash', 'rash macular', 'rash maculo-papular', 'rash generalized'

Source: Datasets AEAD, DMAD for Studies C206 and C216

7.1.3.3 Other significant adverse events

This section presents detailed analyses of AEs of interest. The AEs were selected based on preclinical concerns, or to explore classic drug-related adverse events or known class-associated adverse events, or to understand AE trends observed in Phase 3 trials.

Skin Events of Interest

Dermatologic reactions including serious skin events such as Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis are known side effects of the NNRTI class. Rash was noted during etravirine Phase 1 trials in healthy volunteers: two cases of erythema multiforme (erythema exudativum multiforme) and 1 case of atypical bullous dermatitis were of concern. Skin biopsies were obtained in 2 of these subjects; a convened panel of experts from the fields of immunology, HIV, dermatology and allergy concluded that close monitoring for cutaneous adverse events was required in all future clinical trials.

All dermatologic AEs in the etravirine drug development program were reviewed to assess an association with etravirine and to characterize their nature and severity.

Definition of Skin Event of Interest (SEI): Within the category of AEs belonging to skin and subcutaneous tissue (by system organ class), AEs containing the term 'rash' were most

frequently reported with drug discontinuation as well as Grade 3/4 events. Hence, the definition of SEI included preferred AE terms, 'rash', 'rash erythematous', 'rash follicular', 'rash macular', 'rash generalized', 'rash maculo-papular', 'rash papular', 'rash pruritic', 'rash pustular'. In this review, the term 'rash, any type' represents above rash terms. Additionally, concerning cutaneous AEs including AEs from Phase 1 trials such 'Stevens-Johnson syndrome', 'drug eruption', 'vesicular lesion', 'bullous dermatitis', 'erythema multiforme' were included. Lastly, one subject in the Phase 3 program experienced rash as part of drug hypersensitivity syndrome. All subjects with preferred AE term 'drug hypersensitivity' were reviewed to confirm presence of a cutaneous component.

An imbalance in the frequency of SEI was noted in subjects receiving etravirine (15.5%) compared to subjects receiving placebo (8.4%) in Phase 3 trials, as displayed in Table 22. Rash of any type was the most frequent SEI observed in 15.2% of etravirine recipients; one etravirine-treated subject each experienced drug eruption and drug hypersensitivity. No cases of vesicular rash or Stevens-Johnson syndrome were reported in the Phase 3 trials. In etravirine recipients, the majority of SEI were Grade 1 or 2 in severity (14.3%) with fewer subjects experiencing Grade 3 or 4 events (1.2%). SEI resulted in discontinuations in 2% of subjects, and required treatment with systemic steroids in 0.5% of subjects. In the etravirine arm, SEI were observed in 15 female subjects out of a total of 599 subjects (2.5%) receiving etravirine (Table 22). In the placebo arm, SEI were observed in 6 female subjects out of a total of 604 subjects (1.0%) receiving placebo. A direct comparison of SEI observations between women and men within the etravirine arm is presented subsequently in Table 23.

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Table 22: Skin Events of Interest during the Treatment Period in Phase 3 Trials

	Etravirine (%) N=599	Placebo (%) N=604
Subjects with SEI	93 (15.5)	51 (8.4)
Rash, any type ¹	91 (15.2)	49 (8.1)
Drug eruption	1 (0.2)	1 (0.2)
Drug hypersensitivity	1 (0.2)	0 -
Stevens-Johnson syndrome	0 -	1 (0.2)
Discontinuations due to SEI	12 (2.0)	0 -
Death related to SEI	0 -	0 -
SAE	2 (0.3)	1 (0.2)
Grade 3 or 4 AE	7 (1.2)	1 (0.2)
Grade 1 or 2 AE	86 (14.3)	50 (8.3)
Systemic steroid treatment	3 (0.5)	0 -
Temporary interruption	10 (1.6)	1 (0.2)
History of any drug allergy	52 (8.7)	27 (4.5)
History of NNRTI allergy	9 (1.5)	6 (1.0)
SEI with constitutional symptoms²	6 (1.0)	0 -
SEI with abnormal liver enzymes³	4 (0.7)	0 -
Time to onset (median, days)	11 (1-225)	17 (1-199)
Duration (median, days)	13	19
Gender		
Female	15 (2.5)	6 (1.0)
Race		
Caucasian	68 (11.3)	32 (5.3)
Black	6 (1.0)	6 (1.0)
Hispanic	7 (1.2)	3 (0.5)

¹Includes preferred AE terms 'rash', 'rash erythematous', 'rash follicular', 'rash macular', 'rash generalized', 'rash maculo-papular', 'rash papular', 'rash pruritic', 'rash pustular'

²Includes fever, myalgia, fatigue, nausea, diarrhea, headache, night sweats

³Toxicity severity serum ALT: grade 2 (3), grade 1 (1)

Source: Datasets AEAD, DMAD, CMAD, CDAD for Studies C206 and C216

The median time to onset of SEI was 11 days in etravirine recipients compared to 17 days in placebo (Figure 3); events lasted for a shorter duration in etravirine recipients (median 13 days) compared to placebo (median 19 days).

Figure 3: Days to Onset of Rash (Any Type) by Treatment Group in Phase 3 trials

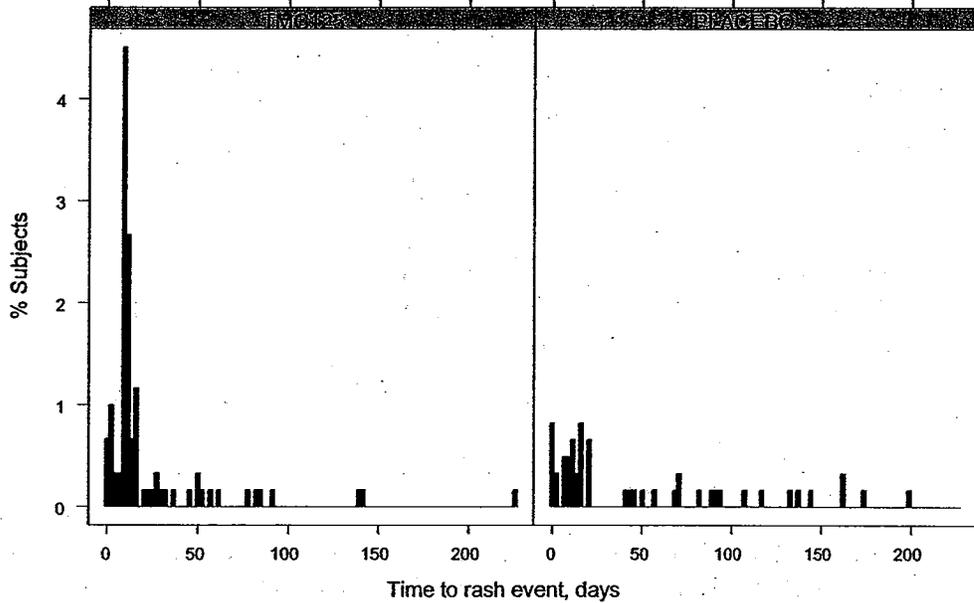


Table 23 provides a direct comparison of SEI between women and men within the etravirine arm in Phase 3 trials. Among the subjects receiving etravirine, 15 of 60 women experienced a SEI (25%), whereas 78 of 539 men experienced a SEI (14.5%); SEI was observed more frequently in the female subjects (25%) compared to male subjects (14.5%). SEI in women were more likely to result in permanent discontinuation of treatment or be of Grade 3 or 4 severity, compared to men. Women who develop SEI appear to have higher CD4 counts compared to men (median, 229 cells/mm³ in women compared to 77 cells/mm³ in men) at baseline. The interpretation of these analyses is limited by the small numbers of women enrolled in Phase 3 trials.

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Table 23: Skin Events of Interest by Gender in Subjects receiving Etravirine in Phase 3 trials

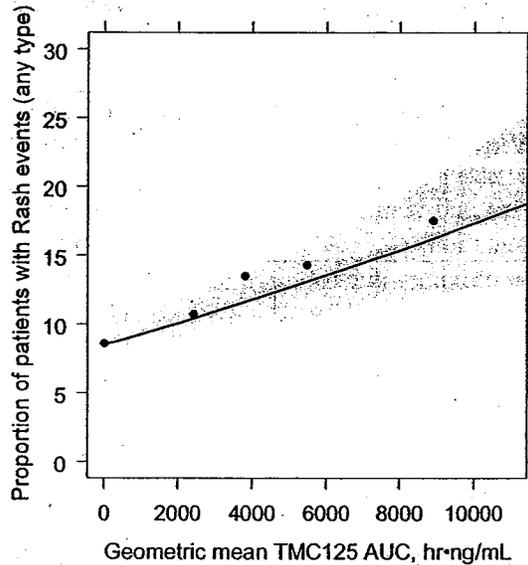
	Women (%) N=60	Men (%) N=539
Subjects with SEI	15 (25)	78 (14.5)
Discontinuations	2 (3.3)	10 (1.8)
Grade 3 or 4 AE	1 (1.7)	3 (0.5)
Baseline CD4 count (cells/mm ³ , mean)	275 (3-789)	125 (1-554)
Baseline CD4 count (cells/mm ³ , median)	229 (3-789)	77 (1-554)
Baseline viral load (median, log ₁₀)	4.78 (3.6-5.7)	4.8 (3.5-6.0)
Time to onset (median, days)	10	11
Duration (median, days)	12	13.5

Source: Datasets AEAD, DMAD for Studies C206 and C216

The relationship between rash and other covariates including race, baseline CD4 count, baseline HIV VL, darunavir exposure, enfuvirtide use, co-infection with Hepatitis B or C was explored. The results of analyses confirmed a higher frequency of rash (any type) in female subjects. Additionally, a higher frequency of rash AEs was observed in Caucasian subjects with an event rate of 17%, compared to the event rate of 10% in minority subjects. Refer to FDA Pharmacometrics review for NDA 22-187 for details.

An analysis was performed to understand the relationship between etravirine exposure (AUC) and the frequency of rash (any type). The likelihood of rash as a function of etravirine AUC increased with increasing AUC. Figure 4 displays 10% of etravirine subjects with any type of rash in the lowest quartile of etravirine AUC (median=2413, range=145-3026 hr•ng/mL), 13% in the 2nd quartile of etravirine AUC (median=3805, range=3026-4525 hr•ng/mL), 14% in the 3rd quartile of etravirine AUC (median=5462, range=4525-6530 hr•ng/mL) and 17% in the last quartile of etravirine AUC (median=8882, range=6530-64164 hr•ng/mL). Approximately 8% of placebo subjects developed rash providing a background frequency.

Figure 4: Median prediction of the Likelihood of Rash Event as a Function of Etravirine AUC (95% confidence)



Panel-Model 1 based on the GAM models fitted to 500 bootstrap samples of the original data set.
Circles: observed data, line and shaded area: model prediction

An analysis was undertaken to investigate the relationship of etravirine exposure in 12 subjects who discontinued due to SEI. As most SEI leading to discontinuation manifested in the first two weeks of treatment, pharmacokinetic data was available for only 2 subjects and was considered insufficient for meaningful interpretation. The time to onset of rash AE did not appear to be related to etravirine AUC. Please refer to Pharmacometrics Review of NDA 22-187 for details.

Additional data related to relevant cutaneous AEs in the Phase 1 and 2 trials, Phase 3 roll-over trial and the EAP were reviewed. Similar to observations in Phase 3 studies, a higher frequency of rash with etravirine use and preponderance in female subgroup was noted. Cases of prominence in these trials are presented in Table 24.

Table 24: Noteworthy Cutaneous Adverse Events in Etravirine Development Program

CRF ID/ EAP ID	AE	Trials or EAP ¹	Pertinent findings	Onset of AE (days)	Investigator Causality
EAP0202731	Stevens-Johnson syndrome	EAP	Only etravirine stopped Improvement with steroids	15	Very likely related
EAP1100471	Stevens-Johnson syndrome	EAP	Fatality; not taking DRV/rtv (case narrative below table)	39	Possibly related
EAP0507019	Stevens-Johnson syndrome	EAP ¹	Nausea and vomiting at presentation	35	Probably related
1092852	Stevens-Johnson syndrome	Phase 1	Hepatotoxicity due to NVP was followed by SJS that was also suspected to be due to NVP ²	15	Not related
2232613	Erythema multiforme ³	Phase 2b	Diagnosis based on skin biopsy, drug discontinued	261	Possibly related
137009 ⁴	Erythema multiforme	Phase 1	EEM, PCT, PPCT differential diagnoses based on skin biopsy ⁵	8	Related
137001 ⁴	Erythema multiforme	Phase 1	Clinical diagnosis by dermatologist	10	Related
137022 ⁴	Atypical bullous dermatitis	Phase 1	Clinical diagnosis by dermatologist	1	Related
EAP0704917	Rash and drug-induced liver injury ⁶	EAP	Subject recovered with drug discontinuation; a second episode of rash observed with re-imitation of etravirine-containing ART resolved with etravirine discontinuation	30; 1	Very likely related
2060712	Drug hypersensitivity syndrome	Phase 3	Worsening of pre-existing rash accompanied fever, convulsion; skin biopsy showed drug allergy	11	Probably related

¹Phase 1 cases were healthy volunteers

²Onset of SJS on Day 9 of continuous NVP alone and 15 days after single dose of 900 mg of etravirine (TF002)

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

⁴Received 1600 mg single dose etravirine (TF035)

⁵EEM, erythema exudativum multiforme; PCT, porphyria cutanea tarda; PPCT, pseudoporphyria cutanea tarda

⁶Full narrative presented in discussion of hepatic AE

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/mm³ 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/mm³ 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.

Rash and other skin reactions are well-described side-effects of the NNRTIs nevirapine (NVP) and efavirenz (EFV). The overall incidence of rash with NVP is 15%, with a discontinuation rate of 4.3%. A total of 1.5% of NVP recipients developed Grade 3 or 4 rash in NVP clinical trials, regardless of causality. Rash due to efavirenz is associated with a lower discontinuation rate of 1.7%; Grade 3 or 4 events were noted in 1.8% of EFV recipients in EFV clinical trials. In comparison to nevirapine, skin reactions due to etravirine are less likely to be severe. Similar to NVP, the reactions due to etravirine are frequently seen within weeks of treatment onset and more frequently observed in women. Unlike NVP, skin reactions are infrequently accompanied by liver enzyme elevations or other laboratory abnormalities and generally do not appear to be a component of hypersensitivity reaction. Note that these cross-study comparisons do not account for variability in definition of rash, observation periods, background regimen, and toxicity grading scale in these trials.

In summary,

- 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. Serious entities, namely, Stevens-Johnson syndrome, erythema multiforme and bullous dermatitis were rarely reported.
- 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.

Relevant findings associated with skin events in etravirine subjects are included in the Highlights section, Warnings and Precautions section, and Adverse Reactions section of the etravirine package insert.

Cardiac Events

In preclinical studies of etravirine, hemorrhagic cardiomyopathy associated with troponin elevation was observed in male mice. Further mechanistic studies revealed clotting abnormalities induced by inhibition of Vitamin K formation by etravirine. The Applicant has attributed fatal cardiomyopathy to hemorrhage from abnormal coagulation. Similar findings have been reported in Vitamin K deficient mice, the species in which the hemorrhagic cardiomyopathy was observed. In light of this finding, special attention was paid to cardiac adverse events in human studies in particular AEs affiliated with coronary artery disease (CAD) and cardiomyopathy. In addition, atrial fibrillation was selected as an AE of interest as one healthy volunteer was diagnosed with Grade 3 atrial fibrillation in a Phase 1 study after receiving a single dose of etravirine.

Cardiovascular events in Phase 3 studies were coded in a standardized manner by a blinded cardiac adjudication panel. For purpose of this review, the following preferred AE terms were used to evaluate cardiac events: 'Coronary artery disease and myocardial infarction': 'myocardial ischemia', 'myocardial infarction', 'acute myocardial infarction', 'angina pectoris' and interventions such as 'coronary angioplasty', 'coronary arterial stent insertion'. Because the most common etiology of cardiac arrest is cardiac ischemia or infarction, the preferred AE terms 'cardiac arrest' and 'sudden death' were also included in this definition. One case of sudden death was attributed to cardiovascular disease by autopsy examination.

Twenty-five cardiac AEs of interest were reported in 19 subjects in Phase 3 studies. Cardiac events of interest were observed in 1.9% of subjects receiving etravirine compared to 1.5% of

subjects receiving placebo (Table 25). The majority of these events were supported by objective evidence such as elevated cardiac enzymes or angiographic evidence of significant coronary occlusion. The frequency of CAD was comparable between etravirine and placebo subjects.

Table 25: Cardiac Events of Interest in Subjects in Phase 3 Trials

	Etravirine (%) N=599	Placebo (%) N=604
Subjects with at least 1 cardiac AE of interest	12 (1.9)	9 (1.5)
Death	4 (0.6)	1 (0.2)
SAE	10 (1.7)	6 (0.9)
Permanent discontinuations	3 (0.5)	2 (0.3)
Temporary discontinuations	2 (0.3)	-
Type of Cardiac AE		
Coronary artery disease and myocardial infarction¹	9 (1.5)	8 (1.3)
Confirmed by troponin elevation or angiographic evidence of coronary occlusion:		
Acute myocardial infarction	3 (0.5)	-
Myocardial infarction	3 (0.5)	1 (0.2)
Coronary angioplasty	1 (0.2)	0 -
Coronary arterial stent insertion	1 (0.2)	0 -
Coronary artery stenosis	0 -	0 -
Myocardial ischemia	0 -	3 (0.6)
Coronary artery disease	0 -	1 (0.2)
Cardiac arrest	0 -	2 ² (0.3)
Troponin elevation not reported or not observed ³		
Angina pectoris	0 -	1 (0.2)
Sudden death ⁴	1 (0.2)	0 -
Atrial fibrillation	1 (0.2)	0 -
Cardiac Myopathy	4 (0.6)	1 (0.2)
Congestive cardiac failure ⁵	1 (0.2)	0 -
Cardiogenic shock ⁶	1 (0.2)	0 -
Right ventricular failure	1 (0.2)	0 -
Cardiomyopathy	0 -	1 (0.2)
Diastolic dysfunction	1 (0.2)	0 -

¹ Defined as preferred AE term 'myocardial ischemia', 'myocardial infarction', 'acute myocardial infarction', 'cardiac arrest', 'angina pectoris' and interventions such as 'coronary angioplasty', 'coronary arterial stent insertion'

² Subject 2160172 experienced cardiac arrest and ventricular tachycardia; Subject 2060646 developed cardiac arrest during an episode of generalized seizures that was presumably related to ongoing cryptococcal meningitis

³ Classic symptoms of angina reported without laboratory or angiographic evidence of coronary event

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⁴Atherosclerotic and hypertensive cardiovascular disease determined as cause of death by autopsy

⁵Congestive cardiac failure developed in the setting of prolonged hospitalization for severe *pneumocystis jiroveci* pneumonia requiring mechanical ventilation leading to pulmonary fibrosis; death due to septic shock from central line infection (subject 2060424)

⁶Subject with pre-existing cardiomyopathy was admitted for pneumonia; subject developed cardiac arrest followed by worsening of cardiac failure and eventually succumbed to cardiogenic shock (subject 2060649)

Source: Datasets AEAD, DMAD for Studies C206 and C216

In general, subjects who suffered coronary events had either risk factors for CAD or a pre-existing cardiovascular condition (Table 26).

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Table 26: Descriptive Summary of Subjects with Coronary AEs in Phase 3 Trials

CRF ID	Preferred AE term and Pertinent data	Onset (day)	CAD risk factor or History of CAD
Etravirine			
2060040	Acute Myocardial Infarction	66	Smoker
2060217	Myocardial Infarction	258	Hyperlipidemia, hypertriglyceridemia, baseline ECG abnormality suggesting prior ischemic event
2060532	Acute Myocardial Infarction; angina	17; 28	Hypercholesterolemia
2160332	Myocardial infarction	251	DM ¹ , hypertension, hyperlipidemia, smoker
2160889	Acute coronary syndrome, cardiac bypass surgery; Angina, coronary angioplasty	29; 126	Strong family history, history of CAD had angioplasty and coronary stent placement procedures
2160409	Myocardial infarction followed by cardiac arrest ²	57	DM, history of CAD
2160463	Acute myocardial infarction, coronary artery stent placement	168	Hypertriglyceridemia
2160049	Angina pectoris, coronary artery stent placement	146	History of CAD had coronary stent placement, hypercholesterolemia, DM, family history of CAD
Placebo			
2160183	Myocardial ischemia	29	Peripheral vascular disease, history of lower extremity thrombosis
2160259	Myocardial ischemia; Coronary artery insufficiency, coronary artery stent placement	36; 79	History of CAD, DM, hypertension, Hypertriglyceridemia, history of stroke
2160413	Myocardial ischemia	1	Hypertension, hyperlipidemia, history of cerebral aneurysm
2160735	Myocardial ischemia; myocardial infarction, coronary artery stent placement	1, 8	Smoker
2160172	Cardiac arrest, ventricular tachycardia ³	36, 36	Smoker, cardiomegaly
2060646	Cardiac arrest ²	105	none
2060368	Coronary artery disease, coronary artery angioplasty	186	Hypertension, DM
2160339	Angina pectoris, coronary artery stent placement	251	History of CAD had coronary stent placement, hypercholesterolemia, DM, hypertension, smoker

¹DM, diabetes mellitus

²Fatal outcome

³Permanent discontinuation

Cardiac Myopathy:

Preclinical finding of hemorrhagic cardiomyopathy formed the basis of exploration of the Phase 3 database for cardiac myopathy defined by the following preferred AE terms: 'cardiomyopathy', 'cardiac failure', 'congestive cardiac failure', 'diastolic dysfunction' and 'heart failure'. Cardiac myopathy AEs were reported in 0.6% of etravirine recipients compared to 0.2% of placebo recipients. Among etravirine recipients, this AE was associated with death in 2 subjects and temporary discontinuation in 1 subject (Table 27). Pre-existing cardiomyopathy or risk factors for cardiovascular disease were present in most subjects. Echocardiogram results or other objective evidence of heart failure were not available for review.

Table 27: Descriptive Summary of Subjects with Cardiac Myopathy AEs in Phase 3 Trials

CRF ID	Preferred AE Term	Onset (day)	Outcome	Pre-existing cardiac disease or risk factor for CAD
2060649	Congestive cardiac failure, cardiac arrest, cardiogenic shock	116	Fatal	History of cardiomyopathy
2060424	Congestive cardiac failure	60	Fatal	Hypercholesterolemia, smoker
2060694	Diastolic dysfunction (mild)	31	Unknown	None
2160616	Right ventricular failure	10	Resolved	History of cardiac failure, DM

Source: Datasets AEAD, DMAD for Studies C206 and C216

Two cases of cardiomyopathy associated with fatality are described:

Subject 2060649 with pre-existing cardiomyopathy was admitted for pneumonia; subject developed cardiac arrest followed by worsening of cardiac failure and eventually succumbed to cardiogenic shock.

Subject 2060424 required mechanical ventilation for severe *pneumocystis jiroveci* pneumonia complicated by pulmonary fibrosis, and subsequently developed congestive cardiac failure. Death was due to septic shock from central line infection.

Because hemorrhagic cardiomyopathy in animal studies was thought to be related to disturbances in Vitamin K dependent coagulation pathway induced by etravirine, an analysis was performed to assess bleeding events and abnormalities in coagulation parameters in Phase 3 trials. The treatment groups were comparable with respect to the frequency of bleeding events; no specific pattern was observed with regards to type or site of bleeding (Table 28).

Table 28: Bleeding Events during the Treatment Period in Phase 3 Trials

	Etravirine (%) N=599	Placebo (%) N=604
Subjects experienced bleeding events	25 (4.2)	29 (4.8)
Death	0 -	2 (0.3)
Permanent discontinuation	0 -	0 -
SAE	0 -	5 (0.8)
Grade 3 or 4 AE	0	5 (0.8)
Preferred AE term		
Anal hemorrhage	4 (0.7)	1 (0.2)
Hematuria	3 (0.5)	8 (1.3)
Rectal hemorrhage	3 (0.5)	4 (0.7)
Contusion	2 (0.3)	1 (0.2)
Epistaxis	2 (0.3)	2 (0.3)
Hematemesis	2 (0.3)	0 -
Abdominal hematoma	1 (0.2)	0
Conjunctival hemorrhage	1 (0.2)	0
Hemarthrosis	1 (0.2)	0
Hemospermia	1 (0.2)	0
Hemoptysis	1 (0.2)	2 (0.3)
Injection site hematoma	1 (0.2)	1 (0.2)
Traumatic hematoma	1 (0.2)	0 -
Gastrointestinal hemorrhage	0 -	2 (0.3)
Hematochezia	0 -	2 (0.3)
Hemorrhage	0 -	1 (0.2)
Menorrhagia	0 -	1 (0.2)
Esophageal varices hemorrhage	0 -	1 (0.2)
Pulmonary hemorrhage	0 -	1 (0.2)
Retinal hemorrhage	0 -	1 (0.2)
Investigations ¹	1 (0.2)	1 (0.2)

¹Related laboratory abnormalities in Table 29

Source: Datasets AEAD, DMAD for Studies C206 and C216

Evaluation of tests of coagulation including INR and PTT did not reveal relevant difference between the two treatment groups (Table 29).

Table 29: Treatment-Emergent Abnormalities in Select Coagulation Parameters in Phase 3 Trials

	Etravirine (%) N=599	Placebo (%) N=604
INR		
≥ 10 x ULN	1 (0.2)	3 (0.5)
≥ 5-10 x ULN	3 (0.5)	2 (0.3)
≥ 2.5-5 x ULN	4 (0.7)	11 (1.8)
≥ 1.25-2.5 x ULN	27 (4.5)	32 (5.3)
PPT		
≥ 10 x ULN	5 (0.8)	7 (1.2)
≥ 5-10 x ULN	2 (0.3)	4 (0.7)
≥ 2.5-5 x ULN	11 (1.8)	8 (1.3)
≥ 1.25-2.5 x ULN	15 (2.5)	21 (3.5)

Source: Datasets LBAD for Studies C206 and C216

Atrial Fibrillation:

One subject in etravirine arm with a past history of myocardial infarction developed atrial fibrillation in the setting of pyrexia. Arrhythmia was reverted by DC cardioversion; causality was considered possible by site investigator.

Cardiac events of interest in Phase 2b trials:

The findings of Phase 2b studies appear similar to Phase 3 results, with respect to CAD events. Eleven subjects receiving etravirine experienced at least 1 coronary event (includes clinical diagnoses of angina pectoris not supported by objective findings); the majority of these subjects (10 of 11 subjects) had risk factors for CAD or prior history of CAD. Death due to cardiac arrest (myocardial infarction observed on ECG preceding arrest) was reported in one subject.

Cardiac events of interest in Phase 1 and Phase 2a trials:

No events of CAD were reported in the Phase 1 or 2 studies. Cardiac AE reported in these studies were non-cardiac chest pain (1), first degree atrio-ventricular block (2), atrial fibrillation (1) and tachycardia (1).

In summary,

- The frequency of CAD in subjects receiving etravirine appears comparable to subjects receiving placebo in double-blind Phase 3 studies. In general, underlying risk factors for coronary artery disease or pre-existing cardiac disease were observed in subjects whose deaths were attributed to cardiovascular causes.
- Cardiomyopathy observed in Phase 3 studies was apparently related to worsening of pre-existing disease or developed in a predisposing clinical setting, and appears less likely to be due to etravirine

Hepatic Events

Analysis of hepatic events was performed for Phase 3 studies. The following preferred AE terms were combined to define 'hepatic event': 'hepatomegaly', 'hepatitis', 'cirrhosis', 'hepatic encephalopathy', 'hepatosplenomegaly', 'hepatic steatosis', 'esophageal varices', 'esophageal variceal hemorrhage', 'hepatic enzyme elevation', 'alkaline phosphatase elevation', 'blood bilirubin elevation', 'urine bilirubin elevation', 'conjugated bilirubin elevation', 'jaundice', 'hyperbilirubinemia', 'bilirubinuria', 'cholecystitis', 'cholangitis', 'cholelithiasis', 'hepatic neoplasm', 'hepatic cyst', and 'upper abdominal pain'.

Overall, 88 subjects experienced hepatic events, 47 subjects receiving etravirine (7.8%) and 41 subjects in placebo arm (7.1%). The majority of hepatic-related AEs were Grade 1 or 2 in severity (Table 30). No apparent increase in frequency of hepatic SAEs or Grade 3/4 hepatic events was observed in etravirine-treated subjects. AEs associated with laboratory investigations were the most frequent category in both treatment groups; abnormalities of serum ALT and serum AST were analysed from data in the laboratory safety database and is presented in Table 31. Upper abdominal pain the most frequent clinical AE was reported more frequently in the etravirine group than placebo; all cases were grade 1 or 2 in severity, none were associated with hospitalization or study discontinuation. Analysis of AEs related to gall bladder and bilirubin metabolism did not reveal meaningful differences between the two arms.

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Table 30: Hepatic Events during the Treatment Period in Phase 3 Trials

	Etravirine (%) N=599	Placebo (%) N=604
Subjects experiencing hepatic events	47 (7.8)	41 (7.1)
Permanent discontinuation	4 (0.6)	3 (0.5)
SAE	4 (0.6)	6 (1.0)
Grade 3 or 4 AE	13 (2.2)	13 (2.2)
Temporary discontinuation	7 (1.2)	6 (1.0)
Preferred AE term		
Upper abdominal pain	18 (3)	14 (2.3)
Hepatitis events (grouped)	4 (0.6)	2 (0.3)
Hepatitis (due to Hepatitis B)	1 (0.2)	0 -
Cytolytic hepatitis	2 (0.3)	0 -
Hepatitis	1 (0.2)	2 (0.3)
Investigations¹	29 (4.8)	26 (4.3)
Hepatic cyst	1 (0.2)	0 -
Hepatic encephalopathy	1 (0.2)	0 -
Hepatic neoplasm	1 (0.2)	0 -
Hepatomegaly or hepatosplenomegaly	4 (0.6)	7 (1.2)
Hepatic cirrhosis	1 (0.2)	1 (0.2)
Hepatic steatosis	1 (0.2)	0 -
Jaundice	2 (0.3)	2 (0.3)
Cholecystitis	1 (0.2)	2 (0.3)
Cholangitis	0 -	2 (0.3)
Cholelithiasis	0 -	3 (0.5)

¹Captured in laboratory safety Table 31

Source: Datasets AEAD, DMAD for Studies C206 and C216

AEs linked to preferred term 'hepatitis' were grouped to identify cases reflecting primary hepatocellular damage that may potentially represent drug-induced liver injury.

An analysis of laboratory data (source: LBAD datasets C206, C216) pertaining to serum transaminase enzymes was performed (Table 31). Evaluation of serum alanine aminotransferase (ALT) in Phase 3 studies revealed a higher frequency of Grade 3 or 4 elevations in etravirine recipients (2.7%) compared to placebo recipients (1.8%). A similar imbalance with respect to Grade 3 or 4 elevation of serum aspartate aminotransferase (AST) was observed in etravirine subjects (2.7%) compared to placebo subjects (1.8%).

Table 31: Elevations of Serum ALT and AST during Treatment Period in Phase 3 Trials¹

	Etravirine (%) N=599	Placebo (%) N=604
Serum Alanine Aminotransferase, ALT		
≥ 10 x ULN	4 (0.7)	2 (0.3)
≥ 5-10 x ULN	12 (2)	9 (1.5)
≥ 2.5-5 x ULN	49 (8)	37 (6.1)
≥ 1.25-2.5 x ULN	132 (22)	133 (22)
Serum Aspartate Aminotransferase, AST		
≥ 10 x ULN	3 (0.5)	2 (0.3)
≥ 5-10 x ULN	13 (2.2)	9 (1.5)
≥ 2.5-5 x ULN	45 (7.5)	49 (8.1)
≥ 1.25-2.5 x ULN	166 (28)	164 (27)

¹Derived from pooled data; Source: Datasets LBAD Studies C206 and C216

To further assess the risk of hepatotoxicity with etravirine, all hepatic-related SAEs in the etravirine group were reviewed. All SAEs in this category were associated with hepatitis (cytolytic hepatitis, hepatitis B, hepatitis) and these cases were evaluated. Similarly, subjects who experienced Grade 3 or 4 elevation of serum ALT were evaluated. The pertinent clinical findings in 17 subjects with hepatitis AE or Grade 3/4 elevation of serum ALT are illustrated in Table 32. An alternative explanation for liver enzyme elevations was apparent in 11 subjects, namely viral hepatitis B or C (6 subjects), history of drug-induced hepatitis (2 subjects), use of known hepatotoxic medication such as didanosine, stavudine, valproic acid (2 subjects), and fatty liver (1 subject). Abnormal elevation of transaminase enzymes was observed at baseline in 3 subjects with subsequent worsening during treatment; the presence of baseline abnormalities suggests confounding conditions/medications prior to intake of etravirine. One subject with cytolytic hepatitis developed Grade 4 elevation of serum ALT that subsided with discontinuation of etravirine-containing regimen but returned upon initiation of non-etravirine containing antiretroviral regimen with possible implication of lamivudine. No data indicating prior hepatic damage was reported and no alternative explanation for liver enzyme elevation was apparent, for two subjects. However, in both subjects, liver enzymes normalized despite continuation of therapy.

Table 32: Case Summary of Hepatic-related Serious Adverse Events and Subjects with Grade 3 or 4 Elevation of Serum ALT during Treatment Period in Phase 3 Trials¹

CRF ID	Preferred AE term	Peak Serum ALT	Peak Serum AST	Underlying hepatic disease or pertinent data	Resolution
2060716	Hepatitis B ²	>1000	>1000	Hepatitis B infection diagnosed at time of this abnormality	No
2160206	Hepatitis ^{2,3}	>1000		Hepatitis C	Yes
2160235	Cytolytic hepatitis ²	456	320	New ALT rise after start of new ARV (non-etravirine) regimen	Yes
2160092	ALT increase ^{2,4}	314	232	History of drug-induced hepatitis	Yes
2060694	ALT increase	346	232	History of drug-induced hepatitis	Improved
2060968	ALT increase	522	218	Taking valproate	Improved
2060620	-	568	530	At baseline ALT Grade 2 and AST Grade 3; etiology unknown	No
2060023	-	230	146	History of Hepatitis B	Improved
2060181	-	267	128	History of fatty liver, at baseline ALT Grade 2 elevation	Yes
2060604	-	245	116	At baseline ALT elevated Grade 2, history of hepatic enzyme elevation related to atazanavir	No
2061046	ALT increased	243	158	-	Yes
2160182	ALT increased	227	128	-	Improved
2160324	ALT increased	265	191	Hepatitis C co-infection	Yes
2160464	-	361	167	History of non-Hodgkin's lymphoma, baseline ALT Grade 1	No
2160515	Hepatic enzyme increased	339	229	Taking didanosine and stavudine	Yes
2160882	-	328	141	History of chronic Hepatitis B infection	Yes
2160780	Cytolytic hepatitis	86	171	Hepatitis C	Yes

¹All laboratory abnormalities were not captured as AEs; lab values expressed as U/L.

²Drug discontinuation

³Symptomatic: nausea, vomiting, chills

⁴Grade 3 elevation of serum ALT, AST resolved with treatment interruption, returned with resumption of ARV regimen

Source: Datasets AEAD, CMAD, LBAD for Studies C206, C216; clinical narratives for Studies C206, C216

Two subjects receiving etravirine met the criteria for Hy's law for identification of drug-induced liver injury i.e. ALT or AST \geq 3 times upper limit of normal and total bilirubin \geq 3 times upper limit of normal. These cases were further evaluated:

One subject diagnosed with lymphoma was receiving chemotherapy with doxorubicin, cyclophosphamide and rituximab at the time liver enzyme abnormalities developed. The subject was withdrawn from the study and blind was broken, however, he was reported as continuing to tolerate etravirine-containing regimen. Hepatic enzyme abnormalities may be attributed to effect of chemotherapy; etravirine hepatotoxicity appears less likely as subject continued to tolerate ARV regimen.

The second subject had underlying Hepatitis C infection and elevated serum ALT and AST values at baseline.

In conclusion, no cases fulfilled the criteria for Hy's Law for identification of drug-induced liver injury.

Additionally, one subject in the EAP (ID 20070704917) diagnosed with drug-induced liver injury based on liver biopsy is described:

A 58-year-old HIV-infected male complained of nausea, fatigue, skin rash, abdominal discomfort and low mood approximately 4 weeks after starting regimen containing tenofovir, emtricitabine, etravirine, darunavir/rty, raltegravir. The subject was taking cotrimoxazole since October 2006. Liver function tests were reported as normal at time of start of treatment. At presentation, blood work demonstrated serum ALT 244 U/L, serum AST 169 U/L, serum alkaline phosphatase 533 U/L; cotrimoxazole was stopped on 3 June 2007. Further deterioration of liver function tests prompted the discontinuation of etravirine on 12 June 2007. An evaluation for common causes of hepatitis and chronic liver disease was non-revealing. Liver biopsy performed on — demonstrated severe acute hepatitis with bridging necrosis likely related to drug-induced injury. Peak serum ALT was 268 U/L and serum AST 294 U/L on — (Table 33). The rest of ARV regimen was discontinued; lamivudine monotherapy was started on 18 June 2007. Serum ALT and AST returned to normal over the next 3 weeks.

Table 33: Serial Liver Function Tests available for EAP Subject 20070704917

ALT (U/L)	<41	211	183	209	233	266	276	268	258	254	217	208	178	164	131	139	135	92	68
AST (U/L)	< 37	159	195	226	258	289	256	294	255	229	200	189	169	158	-	162	146	74	48
Total Bili (umol/L)	< 19	48	47	45	43	46	53	54	66	71	60	53	50	46	123	64	56	39	28
Direct Bili (umol/L)	< 5	-	-	-	31	-	-	-	-	-	-	-	-	21	-	-	-	-	-
Alk phos (U/L)	35-129	569	698	715	739	756	753	728	784	797	764	734	666	470	341	313	295	245	217
GGT (U/L)	8-61	538	535	532	546	565	565	-	-	571	545	534	516	388	286	274	251	-	192

The cause of hepatotoxicity was reported as likely related to drug and proposed consensus was that darunavir was the most likely candidate. Patient recommenced antiretroviral therapy on August 28 2007 with etravirine, enfuvirtide, raltegravir, tenofovir/emtricitabine. He developed a generalized, erythematous rash within 24 hours; liver enzymes tested on the following day were normal. Rash was deemed to be very likely due to etravirine. Rash resolved after drug discontinuation.

In summary, this is case of histologically confirmed drug-induced liver injury. Resolution of clinical and laboratory features occurred after discontinuation of medications including darunavir and etravirine. The timing of discontinuation of etravirine and darunavir does not lend clear evidence as to which drug is the offending agent, as decline in liver enzymes may be a delayed effect of etravirine discontinuation or an immediate effect of darunavir discontinuation. It is notable that hepatitis was accompanied by rash at initial presentation. A second episode of rash was reported when etravirine-containing ARV regimen was recommenced; this episode of rash was attributed to etravirine and resolved with etravirine discontinuation. As rash is more commonly associated with etravirine than darunavir, the cutaneous component may suggest etravirine as culprit. On the other hand, the postmarketing safety reports of darunavir available to FDA indicate a likely association of darunavir with hepatocellular injury; evaluation of potential darunavir-associated hepatotoxicity is ongoing. In conclusion, this case of hepatotoxicity cannot be clearly attributed to etravirine.

Analysis of hepatic AEs and hepatic laboratory abnormalities in subjects co-infected with Hepatitis B or C virus (HBV/HCV) was performed. In general, hepatic AEs and laboratory abnormalities were observed more frequently in the co-infected subjects compared to all subjects. Among co-infected subjects, the frequency of hepatic AEs was balanced between the two treatment arms (Table 34). An imbalance with respect to Grade 3 or 4 elevations of serum ALT was observed between the treatment groups (etravirine 8.3% compared to placebo 6.0%). Similarly, imbalances were observed with respect to serum AST and total bilirubin (Table 35).

Table 34: Hepatic Adverse Events in Subjects Co-infected with Hepatitis B or C

	Etravirine (%) N=72	Placebo (%) N=67
Subjects experiencing hepatic events	15 (20.8)	13 (19.4)
Discontinuation	5 (6.9)	5 (7.5)
SAE	13 (18.1)	15 (22.4)
Grade 3 or 4 AE	17 (23.6)	24 (35.8)
Types of AE		
Upper abdominal pain	4 (5.5)	1 (1.5)
Cytolytic hepatitis	1 (1.4)	0 -
Hepatic cirrhosis	1 (1.4)	0 -
Hepatic cyst	1 (1.4)	0 -
Hepatic encephalopathy	1 (1.4)	0 -
Hepatic neoplasm	1 (1.4)	0 -
Hepatitis	1 (1.4)	1 (1.5)
Jaundice	1 (1.4)	0 -
Blood alkaline phosphatase increased	0 -	1 (1.5)

Source: Datasets AEAD for Studies C206 and C216

Table 35: Elevations of Hepatic Enzymes in Subjects Co-infected with Hepatitis B or C¹

	Etravirine (%)		Placebo (%)	
	Co-infected Subjects N=72	All Subjects N=599	Co-infected Subjects N=67	All Subjects N=604
Serum Alanine Aminotransferase				
≥ 10 x ULN	1 (1.4)	4 (0.7)	1 (1.5)	2 (0.3)
≥ 5-10 x ULN	5 (6.9)	12 (2)	3 (4.5)	9 (1.5)
Serum Aspartate Aminotransferase				
≥ 10 x ULN	1 (1.4)	3 (0.5)	1 (1.5)	2 (0.3)
≥ 5-10 x ULN	3 (4.2)	13 (2.2)	2 (3.0)	9 (1.5)
Total Bilirubin				
≥ 10 x ULN	1 (1.4)	1 (0.3)	1 (1.5)	1 (0.2)
≥ 5-10 x ULN	4 (5.5)	7 (1.2)	0 -	3 (0.5)

¹Derived from pooled data; Source: Datasets LBAD for Studies C206 and C216

In conclusion,

- A minimal increase in frequency of hepatic AEs was observed in the etravirine recipients. The etiology of concerning hepatic AEs and transaminase abnormalities in etravirine recipients was confounded by underlying viral hepatitis, the use of known hepatotoxic medications, and other plausible explanations for enzyme elevations.
- Etravirine was not clearly implicated as the offending agent in a single case of confirmed drug-induced hepatotoxicity. No cases fulfilled the criteria of Hy's law for identification of drug-induced liver injury.
- A higher frequency of hepatic laboratory abnormalities was observed in etravirine subjects co-infected with HBV/HCV compared to placebo subjects.
- A clear association between hepatotoxicity and etravirine use cannot be established based on available data.

Renal Events

Evaluation of renal and urinary AEs was performed by selecting all preferred AE terms in system organ class 'renal or urinary disorders' in Phase 3 trials. Renal AEs were the focus of further analysis based on preferred AE terms, 'renal failure', 'acute renal failure', 'chronic renal failure', 'glomerulonephritis', 'renal impairment', 'increase blood creatinine', 'renal colic', 'renal disease', 'hematuria', 'azotemia', 'proteinuria', 'renal tubular disease' and 'chronic renal insufficiency'.

The frequency of renal AEs was comparable between the two treatment groups; events of death and discontinuations due to renal AEs were balanced as well (Table 36). The categorization of types of AEs based on nature of injury revealed renal failure as the most frequent AE; renal failure AEs were balanced (2.3%) in the two treatment groups (includes acute and chronic renal failure).

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Table 36: Summary of Renal AE during Treatment period in Phase 3 Trials

	Etravirine (%) N=599	Placebo (%) N=604
Subjects with at least one AE	37 (6.2)	45 (7.5)
Death	2 (0.3)	1 (0.2)
SAE	5 (0.8)	8 (1.3)
Permanent discontinuations	3 (0.5)	1 (0.2)
Grade 3 or 4 AE	9 (1.5)	12 (2.0)
Temporary discontinuations	0 -	5 (0.8)
Types of AE		
Renal failure	11 (1.8)	6 (1.0)
Renal failure acute	3 (0.5)	6 (1.0)
Renal failure chronic	0 -	2 (0.3)
Nephrolithiasis	4 (0.6)	5 (0.8)
Renal tubular disorder	2 (0.3)	0 -
Azotemia	1 (0.2)	0 -
Glomerulonephritis membranous	1 (0.2)	0 -
Renal colic	1 (0.2)	2 (0.3)
Renal impairment	1 (0.2)	3 (0.5)
Renal disorder	0 -	1 (0.2)
Blood creatinine increase	9 (1.5)	11 (1.8)
Proteinuria	5 (0.8)	8 (1.3)

Source: Datasets AEAD for C206 and C216

Renal toxicity observed in animal studies of etravirine consisted of focal renal tubular basophilia and high urinary electrolyte excretion observed only in rodent species. Seven etravirine-treated subjects who developed any type of renal failure revealed alternative risk factors for nephrotoxicity (Table 37). The risk factor most frequently associated with any type of renal failure was concomitant use of tenofovir. The remaining subjects with renal failure AEs experienced events of Grade 1 or 2 severity with normalization of serum creatinine in 5 subjects. Although resolution of AE was not observed in 2 subjects, the severity of AE and toxicity grade of serum creatinine elevation did not worsen in these two subjects.

Table 37: Adverse Events of Renal Failure of any type in Etravirine-treated Subjects in Pooled Phase 3 Trials

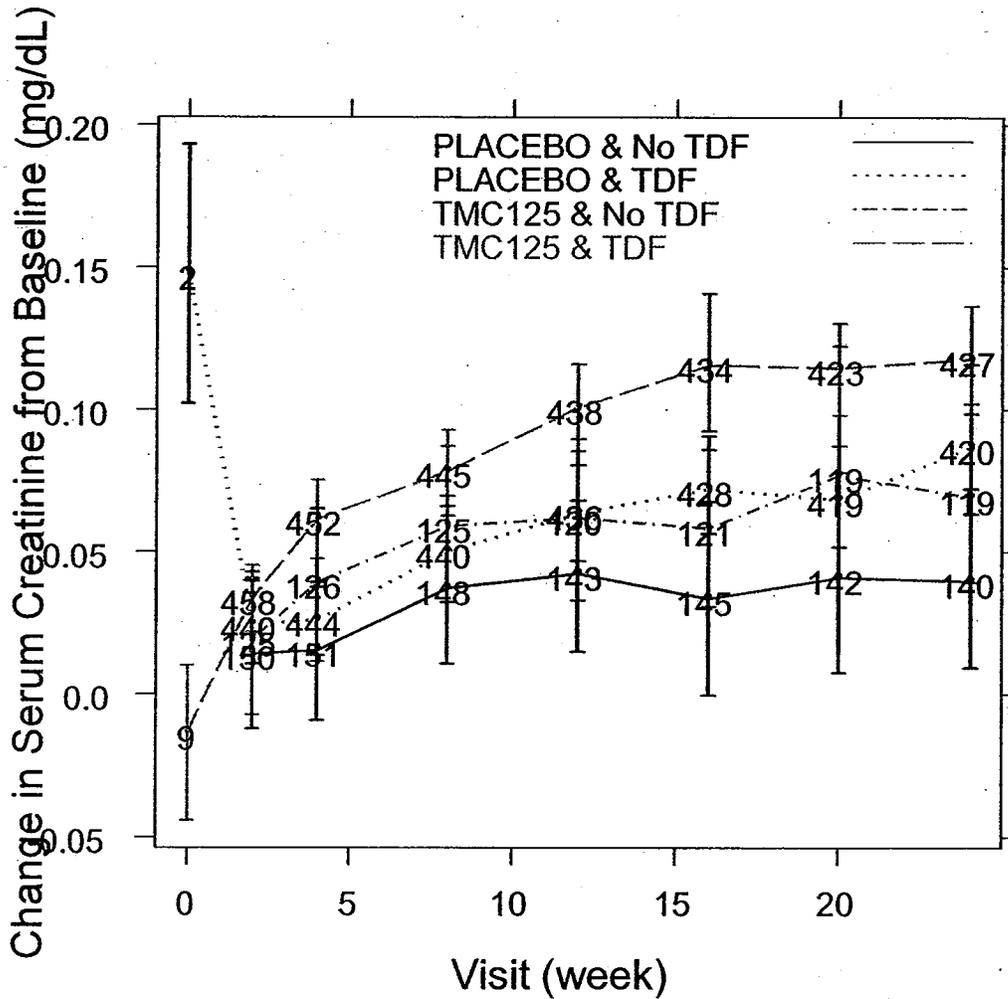
CRF ID	Onset (days)	Risk factor for renal disease	Outcome	Grade
2060569	131	TDF, h/o TDF-related renal insufficiency	Death	3
2060087	116	DM, h/o hematuria	Discontinued	4
2060940	121	TDF, sulfadiazine, amphotericin B	Death	3
2160363	109	TDF	Permanent stop	3
2060312	17	TDF	Recovered	3
2060424	13	TDF	Recovered	3
2060532	88	TDF, hypertension	Not recovered	3

Source: Datasets AEAD, DMAD, CMAD, LBAD for Studies C206 and C216

Renal dysfunction including Fanconi's syndrome is a known side effect of TDF. Cases described in the literature suggest an association with prolonged use of TDF co-administered with a ritonavir-containing ARV regimen. An increase in mean C_{min}, C_{max} and AUC of TDF by 20%, 15% and 15% was observed when TDF was co-administered with etravirine as compared to when TDF was administered alone. It should be noted, however, that concomitant use of DRV/rtv and etravirine results in approximately 37% decrease in exposure of etravirine. The combined impact of DRV/rtv and etravirine, the combination used in Phase 3 trials, on pharmacokinetics of TDF is not known. In an effort to clarify these pharmacodynamic effects, further analysis was undertaken.

Figure 5 illustrates change from baseline in serum creatinine over 24 weeks and the impact of tenofovir use. Subjects were categorized into groups based on the treatment arm (etravirine or placebo) and the use of TDF (taking TDF or not taking TDF). The mean change in serum creatinine from baseline was 0.12 mg/dL in subjects taking etravirine and TDF. Comparitively smaller increases in serum creatinine from baseline were observed in subjects taking placebo and TDF (mean change 0.07 mg/dL), subjects taking etravirine without TDF (mean change 0.08 mg/dL), and subjects taking placebo without TDF (mean change 0.04 mg/dL). Hence, subjects taking etravirine and tenofovir had the greatest change in serum creatinine from baseline. Based on this finding, it may be concluded that concomitant use of etravirine and TDF appears to have additive effect on serum creatinine, however the increase is minimal and of unclear clinical significance at this time.

Figure 5: Change in Serum Creatinine from Baseline by Treatment Group and Concomitant Use of Tenofovir¹



¹Analysis limited to Week 24 as data from fewer subjects was available for successive visits
 Numbers denote subjects contributing data at specified time-point
 Source: Pharmacometrics Review NDA-22817

The relative contribution of etravirine and TDF was further investigated by the severity of elevation of serum creatinine. As shown in Table 38, no significant differences within each treatment group were observed with respect to worsening toxicity grades of serum creatinine by TDF use.

Table 38: Comparison of Elevations of Serum Creatinine in Treatment Groups by Concomitant Use of Tenofovir in Phase 3 trials¹

Serum Creatinine	Treatment	Use of TDF	Total number of episodes	Total Subjects in category	Subjects with abnormality (n, %)
Grade 1	Placebo	No	79	153	29 (19.0)
	Etravirine		90	129	24 (18.6)
	Placebo	Yes	131	451	56 (12.4)
	Etravirine		268	461	86 (18.7)
Grade 2	Placebo	No	32	153	15 (9.8)
	Etravirine		30	129	14 (10.9)
	Placebo	Yes	51	451	19 (4.2)
	Etravirine		87	461	31 (6.7)
Grade 3 or 4	Placebo	No	9	153	4 (2.6)
	Etravirine		11	129	3 (2.3)
	Placebo	Yes	20	451	7 (1.6)
	Etravirine		12	461	8 (1.7)

¹Includes all grades of toxicity observed in a patient i.e. same subject may be counted more than once if abnormality was reported as different toxicity grade

In conclusion, the overall frequency of renal AEs was balanced between the two treatment groups. The most frequent renal AE by group, renal failure of any type was balanced between the two treatment groups. Etravirine subjects who experienced renal failure of any type had risk factors; tenofovir use was the most prominent risk factor. Further explorations to evaluate the etravirine/tenofovir combination and potential nephrotoxicity revealed an additive effect of tenofovir/etravirine on change in serum creatinine from baseline, of a magnitude that does not appear to be clinically relevant at this time. This adverse event is reflected in the etravirine package insert, in the section pertaining to less common adverse drug reactions in less than 2% of subjects.

Pancreatitis

Cases of pancreatitis and elevations of serum amylase and lipase were reported in Phase 2b studies. Data from Phase 3 studies were evaluated to detect potential pancreatic toxicity due to etravirine. All clinical pancreatic events are addressed in this section; pancreatic laboratory abnormalities that were not associated with clinical diagnoses are discussed in the section pertaining to laboratory safety data. A comparable frequency of all clinical pancreatic AEs was observed in the two treatment groups (0.8% etravirine compared to 0.7% placebo) (Table 39). More subjects in the etravirine arm reported pancreatitis (0.7%) compared to placebo arm (0.3%).

Table 39: Clinical Pancreatic Adverse Events in Phase 3 Trials

	Etravirine (%) N=599	Placebo (%) N=604
Subjects with clinical pancreatic event	5 (0.8)	4 (0.7)
Death	0 -	0 -
Permanent discontinuations	0 -	0 -
SAE	1 (0.2)	2 (0.3)
Grade 3 or 4 AE	4 (0.7)	2 (0.3)
Temporary discontinuations	1 (0.2)	0 -
Types of AE		
Pancreatitis	4 (0.7)	2 (0.3)
Pancreatic mass	1 (0.2)	0 -
Pancreatic pseudocyst	0 -	1 (0.2)
Pancreatic insufficiency	0 -	1 (0.2)

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

Four subjects receiving etravirine were diagnosed with pancreatitis compared to 2 subjects receiving placebo. Risk factors for pancreatitis and relevant clinical findings for these subjects are summarized in Table 40.

Table 40: Summary of Etravirine Recipients with Pancreatitis in Phase 3 Trials

CRF ID	Onset (days)	Risk Factor or Pertinent Finding	Toxicity Grade
2060023	184	Hypertriglyceridemia , amylase elevation at baseline	3
2160422 ¹	71	History of pancreatitis, ddi ² use, hypertriglyceridemia	3
2060424	15	Pentamidine use, history of alcohol abuse	3
2160511	14	ddi ² , lipase elevation at baseline	4

¹SAE

²didanosine

Source: Datasets AEAD, MHAD for Studies C206 and C216

Pancreatitis events in etravirine arm were associated with known risk factors such as past history of pancreatitis, alcoholism, use of didanosine or pentamidine. As an alternative etiology for pancreatitis is reported in these cases, it appears less likely that pancreatitis was induced by etravirine. Although causality remains in question, the AE pancreatitis is included in the label in section pertaining less frequently seen adverse drug reactions.

AIDS-defining Illness

An analysis was performed to assess the frequency and pattern of AIDS-defining illness in Phase 3 studies. Based on the currently accepted definition of AIDS-defining illnesses (1993 AIDS surveillance Case Definition for AIDS by Center of Disease Control), this review does not consider AE 'cytomegalovirus viremia' as an AIDS-defining illness and is in disagreement with the Applicant's assignment in the study dataset. Overall, the frequency of these AIDS-defining illnesses was modestly decreased (3.0%) in the etravirine arm compared to the placebo arm (5.9%). Overall, 12 types of AIDS-defining illnesses were reported in 54 subjects during the treatment phase. The most frequently reported AIDS-defining illness, esophageal candidiasis was observed in 13 subjects (Table 41).

Table 41: AIDS Defining Illness in Pooled data in Phase 3 Trials

	Etravirine (%) N=599	Placebo (%) N=604
Subjects with AIDS-defining Illness	18 (3.0)	36 (5.9)
Preferred AE term		
<i>Pneumocystis jirovecii</i> pneumonia	4 (0.7)	6 (0.9)
Esophageal candidiasis	3 (0.5)	10 (1.7)
CMV chorioretinitis	2 (0.3)	8 (1.3)
Kaposi's sarcoma	2 (0.3)	3 (0.5)
<i>Mycobacterium avium</i> complex infection	2 (0.3)	6 (0.9)
Cytomegalovirus infection	1 (0.2)	1 (0.2)
Diffuse large B-cell lymphoma	1 (0.2)	0 -
HIV wasting syndrome	1 (0.2)	4 (0.7)
Meningitis cryptococcal	1 (0.2)	2 (0.3)
Progressive multifocal leukoencephalopathy	1 (0.2)	1 (0.2)
Coccidioidomycosis	0 -	1 (0.2)
Lymph node tuberculosis	0 -	1 (0.2)

Source: Datasets AEAD for Studies C206 and C216

Neuropsychiatric Events

In Phase 3 trials, fewer subjects in etravirine arm experienced neuropsychiatric AEs (25.4%) compared to subjects in placebo arm (30.1%). Headache was the most frequent AE in both treatment groups and observed more frequently in the placebo-treated subjects (Table 42).

Table 42: Summary of all Neuropsychiatric Adverse Events and Events observed in the Etravirine-treated Subjects in Phase 3 Trials

	Etravirine (%) N=599	Placebo (%) N=604
Subjects who experienced neuropsychiatric event	152 (25.4)	182 (30.1)
Discontinuation	1 (0.2)	3 (0.5)
SAE	2 (0.3)	10 (1.7)
Grade 3 or 4 AE	2 (0.3)	13 (2.2)
Preferred AE term		
Headache	56 (9.3)	74 (12.3)
Insomnia	33 (5.5)	40 (6.6)
Depression	18 (3)	30 (5)
Dizziness	16 (2.7)	25 (4.1)
Anxiety	15 (2.5)	18 (3)
Somnolence	10 (1.7)	12 (2)
Sleep disorder	7 (1.2)	4 (0.7)
Vision blurred	5 (0.8)	3 (0.5)
Amnesia	4 (0.7)	3 (0.5)
Memory impairment	4 (0.7)	3 (0.5)
Abnormal dreams	3 (0.5)	4 (0.7)
Irritability	2 (0.3)	0 -
Libido decreased	2 (0.3)	3 (0.5)
Nightmare	2 (0.3)	1 (0.2)
Panic attack	2 (0.3)	0 -
Photophobia	2 (0.3)	0 -
Vertigo	2 (0.3)	6 (1)
Visual disturbance	2 (0.3)	0 -
Confusional state	1 (0.2)	1 (0.2)
Depressed mood	1 (0.2)	1 (0.2)
Disorientation	1 (0.2)	2 (0.3)
Distractibility	1 (0.2)	0 -
Disturbance in attention	1 (0.2)	6 (1)
Hypersomnia	1 (0.2)	2 (0.3)
Major depression	1 (0.2)	0 -
Mental impairment	1 (0.2)	0 -
Mood swings	1 (0.2)	1 (0.2)
Nervousness	1 (0.2)	1 (0.2)
Poor quality sleep	1 (0.2)	0 -
Restless legs syndrome	1 (0.2)	2 (0.3)
Sleep phase rhythm disturbance	1 (0.2)	1 (0.2)
Sluggishness	1 (0.2)	0 -
Stress	1 (0.2)	0 -

Thyroid disease

Follicular cell hypertrophy and hyperplasia secondary to enhanced hepatic clearance of T3 and T4 hormones were observed in rodent studies. In Phase 3 clinical trials, thyroid AEs by preferred term appeared balanced in the two treatment groups (Table 43).

Table 43: Adverse Events related to Thyroid in Phase 3 Trials

Preferred AE term	Etravirine (%) N=599	Placebo (%) N=604
Subject with at least 1 AE	7 (1.3)	6 (1.0)
Investigations		
Blood TSH increased	2 (0.3)	2 (0.3)
Tri-iodothyronine decreased	0 -	1 (0.2)
Tri-iodothyronine increased	0 -	1 (0.2)
Hyperthyroidism	1 (0.2)	0
Hypothyroidism	1 (0.2)	2 (0.3)
Secondary hyperthyroidism	1 (0.2)	0 -
Subacute thyroiditis	1 (0.2)	0 -
Thyroid neoplasm	1 (0.2)	0 -

Source: Datasets AEAD for Studies C206 and C216

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7.1.4 Other Search Strategies

Designated Medical Events

An analysis was performed to identify subjects in Phase 3 trials who experienced one of the following designated medical events: acute pancreatitis, acute respiratory failure, agranulocytosis, anaphylaxis or anaphylactoid reaction, aplastic anemia, blindness, bone marrow depression, deafness, disseminated intravascular coagulation, hemolytic anemia, liver failure, liver necrosis, liver transplant, pancytopenia, renal failure, seizure, Stevens-Johnson syndrome, torsades de pointes, toxic epidermal necrolysis, thrombotic thrombocytopenic purpura, and ventricular fibrillation. Table 44 lists AEs in this category. Detailed analyses for most events are described in the respective safety section; other AEs such as pancytopenia, seizure, blindness and hemolytic anemia are further discussed below.

Table 44: Designated Medical Events in Treatment Period in Phase 3 Trials

Preferred AE term	Etravirine (%) N=599	Placebo (%) N=604
Renal failure ¹	14 (2.3)	14 (2.3)
Pancreatitis	4 (0.7)	2 (0.3)
Pancytopenia	2 (0.3)	1 (0.2)
Seizure ²	4 (0.7)	4 (0.7)
Blindness	1 (0.2)	0 -
Hemolytic Anemia	1 (0.2)	0 -
Respiratory failure	1 (0.2)	0 -
Sudden death	1 (0.2)	0 -
Stevens-Johnson Syndrome	0 -	1 (0.2)

¹Renal failure includes preferred AE terms 'renal failure', 'renal failure acute', 'renal failure chronic'

²Seizure includes preferred AE terms 'seizure', 'partial seizures', 'seizure anoxic', 'complex partial seizures', 'convulsion'

Source: Datasets AEAD, DMAD for Studies C206 and C216

Pancytopenia

Three subjects developed pancytopenia in Phase 3 studies, 2 subjects in etravirine arm and 1 subject in placebo arm (Table 45). All events were Grade 3 or 4 in severity and reported as SAE. Clinical descriptions were available for two subjects. Pancytopenia may be attributed to disseminated *Mycobacterium avium* complex infection in one subject.

Table 45: Summary of Adverse Event Pancytopenia in Phase 3 Trials

CRF ID	Treatment	Pertinent History	Outcome
2160073	Etravirine	Disseminated <i>Mycobacterium avium</i> complex	Fatal
2060924	Etravirine	Narrative not available	Recovered
2160244	Placebo	Low platelet, WBC count at baseline, anemia due to variceal bleeding	Permanent stop

Source: Datasets AEAD for Studies C206 and C216

Seizures

For the purpose of this review, the term ‘seizures’ includes preferred AE terms ‘seizure’, ‘partial seizures’, ‘seizure anoxic’, ‘complex partial seizures’, ‘convulsion’. Eight subjects developed seizures during the treatment period in Phase 3 trials; the 4 cases reported as SAEs are summarized in Table 46.

Table 46: Adverse Events related to Seizure in Treatment period of Phase 3 Trials

CRF ID	Treatment	Preferred AE term	Pertinent History	Outcome	Causality
2060649	Etravirine	Anoxic seizure	Seizure occurred in the setting of cardiac arrest on Day 125	Fatal	Not related
2060712	Etravirine	Convulsion	Convulsions occurred in the setting of fever and rash on Day 11	Permanent stop	Probably related
2060968	Etravirine	Partial seizure	Seizures attributed to immune reconstitution in subject with prior CNS toxoplasmosis (Day 48)	Recovered	Possibly related
2060646	Placebo	Convulsion	Convulsions occurred in setting of cryptococcal meningitis on Day 79	Permanent stop	Doubtful related

Source: Datasets AEAD for Studies C206 and C216

The etiology of seizure can be explained by underlying clinical conditions in two subjects, namely cryptococcal meningitis and cardiac arrest; in both cases these AE were considered not or doubtfully related to etravirine. Two cases of particular concern are discussed below.

Subject 2060646 with a history of central nervous system (CNS) toxoplasmosis developed seizure AE considered possibly related to etravirine. Following initiation of ARV regimen, immune reconstitution inflammatory syndrome (IRS) associated with prior CNS toxoplasmosis was diagnosed. IRS and IRS-related seizure episode were the result of effective combination ARV therapy, and not induced by etravirine.

A 52-year-old male (subject 2060712) experienced convulsions as part of drug hypersensitivity syndrome 11 days after initiation of ARV regimen. Prior to enrollment, a generalized erythematous-petechial rash was noted and attributed to azithromycin or ganciclovir. The subject was hospitalized with fever greater than 38°C, worsening of skin rash and an episode of convulsion. Seizure evaluation was non-revealing. The rash was diagnosed as drug-induced based on results of a skin biopsy. Resolution of fever and improvement of rash were noted 13 days after drug discontinuation. The investigator considered the hypersensitivity syndrome including convulsion to be probably related to etravirine.

Overall, the frequency of seizure AEs was balanced in the two treatment groups. In most cases, an alternative etiology of seizure were present. A singular case of convulsions as a component of drug hypersensitivity syndrome raises concern. However, analysis of the available data does not offer substantial conclusions with respect to the relevance of etravirine use and seizure experiences. In addition, CNS penetration of etravirine in humans is not characterized at this time.

Other designated medical events:

- Subject 2160235 receiving etravirine was reported to develop Grade 2 **blindness** and photophobia on day 9 of study. This subject had a history of CMV retinitis. Photophobia resolved after 4 days, the subject apparently did not recover from loss of vision. In the absence of other clinical findings, it is plausible that visual changes are likely related to prior damage from CMV retinitis and less likely to be induced by etravirine.
- Subject 2060569 receiving etravirine developed respiratory failure on day 148. This subject with a history of pulmonary tuberculosis was diagnosed with pulmonary infiltrates and lumbar osteomyelitis. Acute worsening of respiratory status progressed to fatal **respiratory failure** despite therapy with broad-spectrum antibiotics and empiric therapy for tuberculosis. Respiratory failure in this scenario is without evidence supporting relatedness to etravirine.
- Subject 2061109 receiving etravirine experienced **hemolytic anemia** of Grade 2 severity that lasted for 44 days duration and resolved in the absence of treatment discontinuation.
- An additional case of **hemolytic anemia** was observed in the EAP. A 58-year-old subject was diagnosed with autoimmune hemolytic anemia approximately 8 weeks after starting ARV therapy. Improvement was noted after initiation of oral steroid therapy. Hemolytic anemia was considered likely to be drug-related due to etravirine. This subject had experienced drug-induced hepatitis in the 4 weeks preceding diagnosis of hemolytic anemia.

The accumulation of certain precursors of Vitamin K has been associated with hemolytic anemia; studies in mice showed effects of etravirine on Vitamin K dependent coagulation factors. However, based on evaluations of bleeding events and coagulation profile, there is no evidence that etravirine causes alteration in Vitamin K metabolism in humans. Hence, an association of

etravirine with hemolytic anemia involving the Vitamin K pathway is only speculative at this time.

The causality of seizures and hemolytic anemia is not clear and attributability to etravirine is questionable in the absence of cases with positive-rechallenge. The adverse events, convulsion and anemia are reflected in the etravirine package insert, in the section pertaining to less common adverse drug reactions in less than 2% of subjects.

7.1.5 Common Adverse Events

7.1.5.1 Eliciting adverse events data in the development program

In the clinical trials, AEs were elicited by investigator at each visit by inquiring about untoward medical occurrences. AEs were recorded in the Case Report Form according to Good Clinical Practices guidelines.

7.1.5.2 Appropriateness of adverse event categorization and preferred terms

The severity of AE was assessed by referring to Division of AIDS (DAIDS) grading scale for trials starting after December 2004 or AIDS Clinical Trials Group (ACTG) grading scale for trials starting before December 2004. The reported AEs were categorized using Medical Dictionary for Drug Regulatory Affairs (MedDRA) preferred terms versions 9.0 and 9.1 for Phase 1/2a and Phase 2b/3 trials, respectively. Overall, AEs in Phase 3 studies appear to be classified appropriately.

7.1.5.3 Incidence of common adverse events

In Phase 3 studies, AEs were observed in at least 92.5% of subjects in both treatment groups. The prominent AEs reported more frequently in etravirine recipients and in greater than 5% of subjects include nausea (13.9%), rash (10%), nasopharyngitis (8%), herpes simplex (7.8%), vomiting (6.8%), cough (6.5%), oral candidiasis (6%), bronchitis (5.8%). Overall, the most frequent AE in Phase 3 studies was diarrhea, observed in 15% of etravirine recipients and 20% of placebo recipients.

7.1.5.4 Common adverse event table

The most common AEs, by preferred term, reported in at least 2% of subjects regardless of causality are listed in Table 47. Common AEs observed more frequently in the etravirine arm include nausea, rash, nasopharyngitis, herpes simplex, and vomiting. Among etravirine recipients, the majority of AEs of nausea and vomiting were Grade 1 or 2 in severity, and discontinuations were infrequent (4 subjects). Peripheral neuropathy was observed more frequently in the etravirine arm (3.2%) as compared to placebo arm (1.5%). Six subjects

experienced a Grade 3 event. A prior history of neuropathy was reported in 3 subjects, and none discontinued treatment.

Table 47: Common Adverse Events observed in $\geq 2\%$ Subjects in Phase 3 Trials, regardless of Causality or Severity¹

Preferred AE term	Etravirine (%) N=599	Placebo (%) N=604
Diarrhea	90 (15)	124 (20.5)
Nausea	83 (13.9)	68 (11.3)
Rash	60 (10.0)	33 (5.5)
Injection site reaction	58 (9.7)	66 (10.9)
Headache	56 (9.3)	75 (12.4)
Nasopharyngitis	48 (8.0)	45 (7.5)
Herpes simplex	47 (7.8)	40 (6.6)
Fatigue	42 (7.0)	51 (8.4)
Vomiting	41 (6.8)	33 (5.5)
Cough	39 (6.5)	35 (5.8)
Oral candidiasis	36 (6.0)	30 (5.0)
Bronchitis	35 (5.8)	27 (4.5)
Pyrexia	35 (5.8)	54 (8.9)
Insomnia	33 (5.5)	40 (6.6)
Anemia	27 (4.5)	27 (4.5)
Upper respiratory tract infection	26 (4.3)	40 (6.6)
Hypertension	24 (4.0)	18 (3.0)
Abdominal pain	23 (3.8)	19 (3.1)
Lymphadenopathy	23 (3.8)	29 (4.8)
Influenza	22 (3.7)	16 (2.6)
Pain in extremity	22 (3.7)	19 (3.1)
Arthralgia	20 (3.3)	32 (5.3)
Asthenia	20 (3.3)	27 (4.5)
Flatulence	20 (3.3)	21 (3.5)
Back pain	19 (3.2)	26 (4.3)
Hypertriglyceridemia	19 (3.2)	10 (1.7)
Peripheral neuropathy	19 (3.2)	9 (1.5)
Sinusitis	19 (3.2)	30 (5.0)
Abdominal pain upper	18 (3.0)	14 (2.3)
Depression	18 (3.0)	30 (5.0)
Herpes zoster	18 (3.0)	13 (2.2)
Peripheral edema	17 (2.8)	16 (2.6)
Pruritis	17 (2.8)	28 (4.6)
Anogenital warts	16 (2.7)	18 (3.0)
Dizziness	16 (2.7)	25 (4.1)

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Anxiety	15 (2.5)	18 (3.0)
Myalgia	15 (2.5)	23 (3.8)
Night sweats	15 (2.5)	16 (2.6)
Onychomycosis	15 (2.5)	13 (2.2)
Blood amylase increased	14 (2.3)	16 (2.6)
Blood triglycerides increased	14 (2.3)	10 (1.7)
Hypercholesterolemia	14 (2.3)	4 (0.7)
Abdominal distension	13 (2.2)	14 (2.3)
Alanine aminotransferase increased	13 (2.2)	9 (1.5)
Muscle spasm	13 (2.2)	12 (2.0)
Neutropenia	13 (2.2)	25 (4.1)
Parasthesia	13 (2.2)	16 (2.6)
Hemorrhoids	12 (2.0)	6 (1.0)
Renal failure	12 (2.0)	6 (1.0)
Urinary tract infection	12 (2.0)	14 (2.3)
Constipation	10 (1.7)	13 (2.2)
Dyspepsia	10 (1.7)	22 (3.6)
Folliculitis	10 (1.7)	20 (3.3)
Somnolence	10 (1.7)	12 (2.0)
Lipase increased	9 (1.5)	13 (2.2)
Pneumonia	8 (1.3)	16 (2.6)
Weight decreased	5 (0.8)	18 (3.0)

¹ AE in bold were observed more frequently in etravirine treatment group

Source: Datasets AEAD for Studies C206 and C216

Among the common adverse events, preferred AE term 'rash' was outstanding and observed twice as frequently in etravirine arm (10%) compared to placebo arm (5.5%). In an effort to highlight prominent common AEs in Phase 3 trials independent of causality or severity, the etravirine package insert displays common AEs in $\geq 10\%$ of etravirine subjects, namely, rash and nausea. A wider range of AEs captured in Table 2 of etravirine package insert is presented as Table 48. This tabulates all adverse drug reactions of at least moderate intensity in $\geq 2\%$ of subjects in the etravirine group.

Table 48: Table 2 Package Insert - Adverse Drug Reactions of at least Moderate Intensity in $\geq 2\%$ of Subjects in the Etravirine Group¹

Table 2: Treatment-Emergent Adverse Reactions* of at least Moderate Intensity[†] (Grades 2-4) in $\geq 2\%$ of Adult Subjects in the INTELENCE™ Treatment Groups		
System Organ Class, Preferred Term, %	Pooled DUET-1 and DUET-2 Trials	
	INTELENCE™ + BR N=599	Placebo + BR N=604
Gastrointestinal Disorders		
Diarrhea	5.2%	9.6%
Nausea	4.7%	3.5%
Abdominal pain	3.0%	2.5%
Vomiting	2.3%	2.0%
General Disorders and Administration Site Conditions		
Fatigue	3.3%	4.0%
Nervous System Disorders		
Peripheral neuropathy	2.8%	1.8%
Headache	2.7%	4.1%
Skin and Subcutaneous Tissue Disorders		
Rash	9.0%	3.1%
Vascular Disorders		
Hypertension	2.8%	2.2%

N=total number of subjects per treatment group
* Includes adverse reactions at least possibly, probably, or very likely related to the drug.
[†] Intensities are defined as follows: Moderate (discomfort enough to cause interference with usual activity); Severe (incapacitating with inability to work or do usual activity).

¹Table 2 as appears in etravirine package insert

7.1.6 Less Common Adverse Events

Less common AEs observed in less than 2% of etravirine recipients were myocardial infarction, angina pectoris, atrial fibrillation, vertigo, blurred vision, gastroesophageal reflux disease, flatulence, gastritis, abdominal distension, pancreatitis, constipation, dry mouth, hematemesis, retching, stomatitis, sluggishness, cytolytic hepatitis, hepatic steatosis, hepatitis, hepatomegaly, drug hypersensitivity, immune reconstitution syndrome, diabetes mellitus, dyslipidemia, anorexia, paraesthesia, somnolence, convulsion, hypoesthesia, syncope, amnesia, hypersomnia,

tremor, insomnia, anxiety, sleep disorders, abnormal dreams, confusional state, disorientation, nervousness, nightmares, renal failure, gynaecomastia, exertional dyspnea, bronchospasm, night sweats, hyperhidrosis, prurigo, dry skin, lipohypertrophy, swelling face.

7.1.7 Laboratory Findings

7.1.7.1 Overview of laboratory testing in the development program

In Phase 3 trials, blood samples for standard laboratory safety monitoring were collected at specific time points described in Section 6.1.3. In light of preclinical data, tests of coagulation profile were included to standard laboratory parameters. A similar laboratory testing profile was used in other clinical trials. Characterization and grading of abnormalities was based on DAIDS grading scale (after 2004) or ACTG grading scale (before December 2004).

7.1.7.2 Selection of studies and analyses for drug-control comparisons of laboratory values

Data from the two pivotal Phase 3 trials, C206 and C216, form the basis of laboratory analyses. Parameters associated with notable preclinical findings such as tests of thyroid function and coagulation profile were analyzed. Additionally, laboratory tests were selected to assess relationship of etravirine with known side effects of antiretroviral therapy, such as hepatotoxicity (serum ALT, AST) nephrotoxicity (serum creatinine), pancreatitis (serum amylase, lipase), hyperglycemia (serum glucose), and hyperlipidemia (serum total cholesterol, serum low density lipoprotein or LDL cholesterol, serum triglyceride).

In this review, analysis of abnormal laboratory values are described as deviations from upper limit of normal (ULN) as per the DAIDS Table for Grading of the Severity of Adult and Pediatric Adverse Events, December 2004. Values ranging 1.25 – 2.5 x ULN, 2.6 – 5.0 x ULN, 5.1 – 10.0 x ULN, and > 10.0 x ULN are reflected as Grade 1, 2, 3 and 4, respectively. In the following tables, the categories of severity are mutually exclusive; subjects are counted only once reflecting the worst severity grade.

7.1.7.3 Standard analyses and explorations of laboratory data

A higher frequency of subjects in the etravirine group experienced Grade 3 or 4 ALT elevations (2.7%) compared to placebo group (1.8%) as shown in Table 49. A detailed review of individual case narratives is described in Section 7.1.3.

Table 49: Treatment-Emergent Abnormalities of Serum Aminotransferase Enzymes¹ in Phase 3 Trials

	Etravirine (%) N=599	Placebo (%) N=604
Serum Alanine Aminotransferase		
≥ 10 x ULN	4 (0.7)	2 (0.3)
≥ 5-10 x ULN	12 (2)	9 (1.5)
≥ 2.5-5 x ULN	49 (8)	37 (6.1)
≥ 1.25-2.5 x ULN	132 (22)	133 (22)
Serum Aspartate Aminotransferase		
≥ 10 x ULN	3 (0.5)	2 (0.3)
≥ 5-10 x ULN	13 (2.2)	9 (1.5)
≥ 2.5-5 x ULN	45 (7.5)	49 (8.1)
≥ 1.25-2.5 x ULN	166 (28)	164 (27)

¹The categories are mutually exclusive; no subject can be counted more than once

Source: Datasets LBAD for Studies C206 and C216

Elevations in serum creatinine were observed more frequently in etravirine-treated subjects (Table 50); however, the frequency of Grade 3 or 4 elevations of serum creatinine were comparable in the two treatment groups. This observation may be explained by the minimal increase in creatinine observed in etravirine/tenofovir-treated patients.

Table 50: Treatment-Emergent Abnormalities of Serum Creatinine in Phase 3 Trials

Serum Creatinine	Etravirine (%) N=599	Placebo (%) N=604
Any elevation serum creatinine	122 (20.4)	102 (16.9)
≥ 10 x ULN	0	2 (0.3)
≥ 5-10 x ULN	11 (1.8)	9 (1.5)
≥ 2.5-5 x ULN	41 (6.8)	31 (5)
≥ 1.25-2.5 x ULN	70 (11.6)	60 (9.9)

Source: Datasets LBAD for Studies C206 and C216

Although a greater frequency of pancreatitis was observed in the etravirine arm compared to placebo arm, analysis of serum lipase and serum amylase did not reveal substantial trends (Table 51). A proportion of these subjects in both treatment groups were using didanosine (ddI) or stavudine (D4T) as part of ARV regimen. NRTIs in general, and ddI and D4T in particular are associated with pancreatitis. Asymptomatic pancreatic enzyme elevation may reflect subclinical pancreatic injury and these subjects may have a greater propensity to develop pancreatitis. However, the frequency of abnormalities appears balanced in the two treatment groups and a specific association with etravirine use was not demonstrable.

Table 51: Treatment-Emergent Pancreatic Abnormalities in Phase 3 Trials

	Etravirine (%) N=599	Placebo (%) N=604
Serum lipase		
Any elevation of serum lipase	63 (10.5)	73 (12)
≥ 10 x ULN	6 (1)	4 (0.7)
≥ 5-10 x ULN	10 (1.7)	7 (1.2)
≥ 2.5-5 x ULN	23 (3.8)	34 (5.6)
≥ 1.25-2.5 x ULN	25 (4.2)	28 (4.6)
Worsening of parameter from baseline	60 (10)	67 (11.1)
Worsening from baseline and taking ddI or d4T	28 (4.7)	37 (6)
Serum amylase		
≥ 10 x ULN	9 (1.5)	7 (1.2)
≥ 5-10 x ULN	51 (8.5)	50 (8.3)
≥ 2.5-5 x ULN	47 (7.8)	51 (8.4)
≥ 1.25-2.5 x ULN	125 (21)	117 (19.4)

Source: Datasets LBAD, CMAD for Studies C206 and C216

Select lipid markers were analyzed for differences between the treatment groups (Table 52). Notable findings include a difference in the frequency of Grade 1 and 2 elevations of serum LDL cholesterol between the two arms. An increase in frequency of Grade 2 and 3 elevations of serum total cholesterol and serum triglyceride was observed in etravirine arm as compared to placebo arm.

Table 52: Treatment-Emergent Lipid Abnormalities in Phase 3 Trials

	Etravirine (%) N=599	Placebo (%) N=604
Total Cholesterol		
≥ 10 x ULN	0 -	0 -
≥ 5-10 x ULN	46 (7.7)	26 (4.3)
≥ 2.5-5 x ULN	124 (20.7)	96 (15.9)
≥ 1.25-2.5 x ULN	180 (30.0)	191 (31.6)
LDL Cholesterol		
≥ 10 x ULN	0 -	0 -
≥ 5-10 x ULN	32 (5.3)	37 (6.1)