

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

22-187

MEDICAL REVIEW(S)

Team Leader's Memorandum

NDA: 22-187

Drug and Indication: INTELENCE™ (etravirine), in combination with other antiretroviral agents, is indicated for the treatment of HIV-1 infection in treatment-experienced adult patients who have evidence of viral replication and HIV-1 strains resistant to a non-nucleoside reverse transcriptase inhibitor and other antiretroviral agents.

Proposed Dose: 200 mg twice daily following a meal

Dosage Form: 100 mg tablet

Letter Date: July 17, 2007
Stamp Date: July 18, 2007

Date of Memorandum: January 17, 2008

Background

Etravirine (Intelex™) is a novel HIV-1 non-nucleoside reverse transcriptase inhibitor (NNRTI) under development by the applicant (Tibotec, Inc.) for the treatment of HIV-1 infection in treatment-experienced adult patients. This New Drug Application (NDA) was submitted in accordance with regulations and guidance for submission of drugs for accelerated approval; demonstration of efficacy of this drug is based on surrogate endpoint analyses of plasma HIV-1 RNA and CD4+ cell counts in antiretroviral heavily treatment-experienced HIV-infected subjects after 24 weeks of treatment.

The clinical development package submitted to support the efficacy of etravirine consists primarily of data from four clinical studies, two Phase 2 dose-finding studies and two Phase 3 studies, all conducted in treatment-experienced subjects. TMC125-C203 (C203) and TMC125-C223 (C223) are dose-finding studies that differ by study sites and evaluated doses. TMC125-206 (C206) and TMC125-C216 (C216) are identical Phase 3 studies initiated following dose selection. Notably, another study, TMC125-C227 (C227), a study comparing etravirine to lopinavir/r (LPV/r), each in combination with 2 investigator-selected sensitive nucleos(t)ide reverse transcriptase inhibitors (N(t)RTIs), in subjects failing a first-line NNRTI-containing regimen, was terminated due to the early identification of suboptimal virologic response in etravirine-treated subjects.

The Phase 3 studies C206 and C216 are international, multi-center, double-blind, randomized, placebo-controlled trials comparing etravirine in combination with optimized background therapy (OBT) to placebo in combination with OBT in highly treatment-experienced HIV-infected subjects. All study subjects received darunavir/ritonavir (DRV/r) as part of OBT. The studies were identical except for study site locations. Protocol C206 was conducted in the USA, France, Thailand and Latin

America, while Protocol C216 was conducted in the USA, Canada, Europe and Australia. Eligible subjects were HIV-1 infected patients failing antiretroviral therapy (ARV) as documented by HIV-1 RNA >5,000 copies/mL while on ARV for at least eight weeks. In addition, documented genotypic evidence of resistance to NNRTI(s) with at least one NNRTI resistance-associated-mutation and the presence of at least three primary protease inhibitor (PI) mutations were required.

In the etravirine development program, 1235 HIV-infected subjects and 1093 healthy subjects were exposed to etravirine. In Phase 2 and 3 studies, 861 HIV-1 infected subjects were exposed to etravirine at the to-be-marketed dose or its equivalent, either 200 mg twice daily as formulation F060 (to-be-marketed) or 800 mg twice daily as formulation TF035(dose equivalent) for 24 weeks. A total of 279 subjects received etravirine for at least 48 weeks. In addition, 2915 subjects were enrolled in the expanded access program as of July 2007.

Inclusion Criteria, Patient Demographics and Baseline Characteristics

Because Protocols C206 and C216 are identical, analyses were conducted using pooled data. Table 1 summarizes select patient demographics and baseline patient characteristics. Randomization was stratified by enfuvirtide (ENF) use (new use, re-use or no use), viral load and prior DRV/r use. As noted previously, all patients received DRV/r as part of their background regimen.

**APPEARS THIS WAY
ON ORIGINAL**

TABLE 1 – Selected Patient Demographics and Baseline Characteristics

	Etravirine N=599	Placebo N=604
Age, median (years)	45.0	45.0
Gender, n (%)		
Male	539 (90)	535 (89)
Female	60 (10)	69 (11)
Race, n (%)		
Caucasian	425 (70)	422 (70)
Black	78 (13)	79 (13)
Hispanic	66 (11)	74 (12)
Baseline log₁₀ VL		
Median (min, max)	4.83 (2.7-6.8)	4.83 (2.2-6.5)
Baseline CD4 count, cells/mm³		
Median (min, max)	99 (1-789)	109 (0-912)
CDC Stage of HIV infection		
Stage A	126 (21)	117 (19)
Stage B	127 (21)	130 (22)
Stage C	346 (58)	357 (59)
Baseline viral load category		
<30,000 copies/mL	165 (28)	174 (29)
≥ 30,000 and < 100,000 copies/mL	206 (34)	213 (35)
≥100,000 copies/mL	228 (38)	217 (36)
Baseline CD4 category		
≥ 200 cells/mm ³	177 (30)	186 (31)
≥ 50 and < 200 cells/mm ³	208 (35)	208 (34)
< 50 cells/mm ³	213 (36)	209 (35)
Median Duration HIV-1 infection		
Median (min, max)	14.3 (2.6, 25.5)	14.4 (4.7, 26.4)
Hep. B and/or C Co-infection - n (%)	72 (13)	68 (12)
Median FDA defined NNRTI mutations	2	2
Median etravirine fold change	1.6	1.6
Median efavirenz fold change	87	32
Median DRV fold change	5.9	6.8
Phenotypic Sensitivity Score (PSS)¹ – n (%)		
0	198 (17)	97 (16)
1	216 (36)	230 (39)
2	160 (27)	163 (27)
≥ 3	118 (20)	103 (17)
Enfuvirtide Use in OBT – n (%)		
Naïve Use	153 (26)	160 (26)
Experienced Use/ No Use	446 (74)	444 (74)

Source: Clinical Review – Charu Mullick, M.D.

Efficacy Analyses

A “snapshot” analysis of efficacy of pooled data from C206 and C216 at Week 24 is summarized in Table 2. A snapshot analysis differs from the “Time to Loss of Virologic Response (TLOVR)” analysis typically used by the Division of Antiviral Products (DAVP), primarily by not requiring that a subject have two consecutive viral loads below the assay threshold of 50 copies/mL in order to be considered a virologic responder. The TLOVR analysis was initially developed by the DAVP to evaluate Week 48 outcomes, although it has been used in recent years for Week 24 analyses as well.

At Week 24, 60% of etravirine-treated subjects achieved a viral load of <50 copies/mL as compared to 40% of placebo-treated subjects; the treatment difference was statistically significant for each protocol alone and when pooled. The most frequent reason for non-response was virologic failure, observed in 31.7% of etravirine recipients and 52.6% of placebo recipients. The mean change in CD4+ cell count from baseline was 86 cells/mm³ in etravirine-treated subjects and 67 cells/mm³ in placebo-treated subjects.

Table 2: Outcome of Randomized Treatment at Week 24 by Snapshot Classification of Pooled Phase 3 Protocols C206 and C216¹

Virologic Response Data Specification	Etravirine (%) N=599	Placebo (%) N=604
HIV VL < 50 copies/mL at Week 24	358 (59.8)	243 (40.2)
Non-Responders		
Virologic Failures at Week 24	190 (31.7)	318 (52.6)
Death	9 (1.5)	15 (2.5)
Discontinued due to VF before Week 24	2 (0.3)	4 (0.7)
Discontinuation due to AE	28 (4.7)	11 (1.8)
Discontinuation due to other reasons	12 (2.0)	13 (2.2)

¹Discontinuations include subjects who discontinued before Week 24 excluding deaths

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

Reprinted from Clinical Review – Charu Mullick, M.D.

Additional analyses were conducted to further evaluate the treatment effect of etravirine when combined with other ARV drugs, including treatment response by first-time (*de novo*) ENF use shown in Table 3. Within the etravirine-treated subject population, *de novo* ENF users had a better treatment response as compared to those who reused or did not use ENF. The impact of *de novo* ENF use on treatment response in placebo-treated subjects as compared to those who reused or did not use ENF was numerically greater, likely reflecting the impact of the addition of a second or third active drug to a placebo-containing regimen.

Table 3: Response (HIV VL < 50 copies/mL) by ENF Use in Combined Phase 3 Studies

ENF Use	Etravirine N=565	Placebo N=593
<i>De Novo</i> ENF	70% (102/145)	62% (99/159)
Re-Used/Not Used ENF	60% (251/420)	34% (149/434)

Source: Microbiology Review – Lisa Naeger, PhD

An analysis evaluating the effect of the phenotypic sensitivity score (PSS) score on the response rate showed that the magnitude of the treatment effect of etravirine as compared to placebo was greatest when the PSS score was 0 or 1, and diminished when the PSS score was 2 or more.

Table 4: Response (HIV VL < 50 copies/mL) by Baseline PSS Score in Combined Phase 3 Studies

PSS Score	Etravirine Arms N=565	Placebo Arms N=593
0	43% (40/93)	7% (7/95)
1	59% (120/205)	28% (63/225)
2	75% (112/150)	63% (102/162)
3	70% (63/90)	68% (52/76)
4	73% (16/22)	64% (14/22)
5		(3/3)
0-1	54% (160/298)	22% (70/320)
2+	73% (191/262)	65% (171/263)

*As-treated analysis

Source: Microbiology Review – Lisa Naeger, PhD

Clinical Resistance Analyses

In Protocols C206 and C216, response rates to etravirine decreased as the number of baseline NNRTI mutations increased. Subjects with two or more 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, the most prevalent NNRTI substitution at baseline in subjects enrolled in C206 and C216, did not affect virologic response in etravirine-treated subjects.

Response rates assessed by baseline etravirine phenotype showed that a ≤ 3 -fold change in etravirine susceptibility 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 these Phase 3 trials and are provided in the etravirine package insert 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 C206 and C216, the median baseline phenotype was 1.7. The median baseline phenotype was 1.4 (n=351) in responders and 3.4 (n=210) in non-responders.

Summary of Safety

In general, etravirine appeared to be well tolerated in Phase 3 studies, with 5.8% of etravirine-treated subjects discontinuing for adverse events. By preferred term, the most common adverse events reported in etravirine-treated subjects, at greater than 10% incidence and more frequently than in placebo-treated subjects, were rash and nausea. Rash and nausea were also the most common adverse events leading to treatment discontinuation. Other adverse events leading to treatment discontinuation and reported in at least two etravirine-treated subjects were pneumonia, diarrhea, anemia, congestive heart failure, cardiac arrest, renal failure and transaminase elevations. Review of these events indicates they are not likely related to etravirine use. A single case of hemolytic anemia was considered likely related to etravirine use.

Consistent with other drugs of the NNRTI class, rash emerged as the most common adverse event considered related to etravirine use. In general, rash was mild to moderate in severity, developed during the second week of therapy and resolved with continued etravirine use; however, 2% of etravirine-treated subjects required discontinuation for rash. In the overall development program, serious skin events such as Stevens-Johnson syndrome, erythema multiforme and atypical bullous dermatitis were reported uncommonly. Notably, erythema multiforme and atypical bullous dermatitis were only observed in one healthy volunteer study conducted at a single site using a different etravirine formulation; the significance of these events is not fully understood at this time. One subject experienced a hypersensitivity reaction, with rash, fever and seizure reported as components of the reaction. Rash appeared to be more common in females, although the number of female etravirine-treated subjects enrolled in Phase 3 studies was small (60/599). In addition, the incidence of rash appears to increase with increased exposures to etravirine, as assessed by pharmacokinetic sampling from Phase 3 study subjects.

Cardiac events were thoroughly reviewed due to the finding of hemorrhagic cardiomyopathy in male mice in preclinical studies. Findings in mice were attributed to inhibition of Vitamin K formation. These findings were not observed in female mice or in dogs. Nonetheless, cardiac events were examined for any potential imbalance between placebo and etravirine-treated subjects. In summary, no imbalance in the incidence of coronary artery disease was observed. Two cases of cardiomyopathy observed in etravirine-treated subjects appeared to be related to worsening of pre-existing disease or developed in a predisposing clinical setting. Coagulation parameters and bleeding events from Phase 3 studies were also reviewed. No imbalance in abnormalities of INR, PTT or in bleeding events was observed in etravirine-treated subjects as compared to placebo-treated subjects.

Although renal excretion is not a significant route of elimination of etravirine, a small, clinically insignificant increase in creatinine was observed in etravirine-treated subjects. Despite this observation, no imbalance in the incidence of renal insufficiency or renal failure was observed between etravirine and placebo arms. The most common risk factor for developing renal failure for etravirine-treated subjects was tenofovir use. Mean changes in creatinine at Week 24 are summarized in Table 5.

Table 5 - Mean Change in Creatinine at Week 24

Treatment Arm	Tenofovir Use (n)	Creatinine (g/dL) Mean Change from Baseline
Etravirine	No (119)	0.08
Etravirine	Yes (427)	0.12
Placebo	No (140)	0.04
Placebo	Yes (420)	0.07

A single case of biopsy confirmed drug-induced hepatotoxicity was reported from the expanded access program during the clinical development of etravirine. The patient was taking both darunavir and etravirine and causality at this time cannot be determined. The incidence of Grade 3-4 transaminase elevations in etravirine-treated subjects was slightly higher in etravirine-treated subjects (2.7%) as compared to placebo-treated subjects (1.8%); however, no Hy's law cases were identified in Phase 3 clinical trials.

Elevations in total cholesterol and low density lipoprotein (LDL) and initiation of lipid lowering therapy were more common in etravirine-treated subjects. Quantification of the increase in lipid parameters is difficult to assess in this patient population given the administration of multiple confounding medications, including lipid lowering agents and other lipid elevating HIV medications and differences in the duration of HIV therapy in study subjects.

Fewer etravirine-treated subjects died as compared to placebo-treated subjects. This has not been observed in other recent development programs of ARV developed primarily in highly treatment-experienced populations. This observation has been attributed to open-label study designs, unequal randomization (i.e. 2:1, 4:1), and shorter time on study for control subjects due to early discontinuation options for non-responders. The etravirine Phase 3 studies are the first studies in this patient population to eliminate these areas of potential bias. Etravirine Phase 3 studies were blinded, placebo-controlled and randomized 1:1. Time on study was similar for etravirine and placebo-treated subjects, likely due to receipt by all study subjects of a potent ARV drug, DRV/r, as part of the background regimen. At Week 24, deaths were reported in 1.5% of etravirine-treated subjects and 2.6% of placebo-treated subjects; AIDS-defining events were reported in 2.7% of etravirine-treated subjects and 4.5% of placebo-treated subjects.

In Phase 3 trials, etravirine was co-administered with DRV/r, a drug combination found to decrease etravirine exposure by about 37%. Because etravirine will be co-administered in clinical practice with drugs (i.e. LPV/r) that may increase etravirine exposure by as

much as 85% as compared to exposures observed in the Phase 3 trials, an analysis comparing the safety profile of subjects with higher etravirine exposures to subjects with lower etravirine exposures was performed. The mean AUC of the "higher exposure" sub-group is similar to the estimated exposure for etravirine when co-administered with lopinavir/ritonavir. When the higher exposure sub-group of subjects was compared to the other subjects, a small increase in the incidence of rash was observed, consistent with previous findings that the incidence of rash increases with increasing exposure. No other clear increase in the incidence of etravirine-related adverse events was observed. In a sponsor-conducted review of subjects with higher exposures, a higher incidence of Grade 3/4 abnormalities in triglycerides, total cholesterol and creatinine was observed. Review of clinical events of renal failure revealed other risks factors, in particular, tenofovir use. In order to provide flexibility in constructing treatment regimens, co-administration of etravirine with LPV/r will be allowed. The package insert states that this combination should be co-administered with caution.

Clinical Pharmacology and Drug-Drug Interactions

Following oral administration, etravirine is absorbed with a T_{max} of about 2.5- 4 hours. When administered with food, the mean systemic exposure (AUC) of etravirine is about 105% higher relative to the fasting state. The mean (\pm standard deviation) terminal elimination half-life of etravirine is about 41 (\pm 20) hours. Etravirine primarily undergoes metabolism by CYP3A4, CYP2C9, and CYP2C19 enzymes. In brief, etravirine is a substrate and weak inducer of CYP3A4, and a substrate and weak inhibitor of CYP2C9 and CYP2C19. Several clinically relevant drug-drug interactions stem from these effects. Please refer to the package insert for a complete description of clinical pharmacology and drug-drug interactions.

Because etravirine is an inducer of CYP3A4 and an inhibitor of CYP2C9 and CYP2C19, the co-administration of etravirine with drugs that are substrates of CYP3A4, CYP2C9, and CYP2C19 may alter the therapeutic effect or adverse event profile of the *co-administered drug(s)*. As a result, etravirine should not be co-administered with any unboosted protease inhibitors or with fosamprenavir/ritonavir. The increased generation of 14-hydroxy clarithromycin with concomitant etravirine may reduce activity against *Mycobacterium avium* complex (MAC), and therefore, alternatives to clarithromycin should be considered for treatment of MAC in subjects receiving etravirine. Dose adjustment of sildenafil, methadone, HMG-CoA reductase inhibitors, diazepam and antiarrhythmics may be required when co-administered with etravirine. Co-administration with warfarin should be accompanied by monitoring of international normalized ratio (INR).

As etravirine is a substrate of CYP3A4, CYP2C9 and CYP2C19, the co-administration of etravirine with drugs that are inducers or inhibitors of these enzymes may alter the therapeutic effect or adverse event profile of *etravirine*. Co-administration of etravirine with tipranavir/ritonavir, full-dose ritonavir (600 mg twice daily), phenytoin, phenobarbital, carbamazepine, rifampin, and rifapentin is not recommended. As previously noted, an 85% increase in etravirine exposure (relative to exposure observed in Phase 3 studies) is observed when etravirine is co-administered with LPV/r; co-

administration should be undertaken with caution. Co-administration of systemic corticosteroids or St. John's wort (*hypericum perforatum*) decreases etravirine plasma concentration and may result in loss of therapeutic effect.

Co-administration of etravirine with atazanavir/ritonavir (ATV/r) results in both a significant reduction in atazanavir systemic exposure and a significant increase in systemic exposure of etravirine; therefore, co-administration of etravirine with ATV/r is not recommended.

Conclusion

I agree with the primary reviewer's conclusion. Etravirine 200 mg twice daily is generally safe and effective in combination with other antiretroviral agents for the treatment of HIV-1 infection in antiretroviral treatment-experienced adult patients with limited treatment options. The risks associated with taking this medication are balanced by the efficacy observed in this population. Etravirine is not indicated for treatment-naïve patients or for pediatric patients. In addition, etravirine, in combination with dual N(t)RTIs, should not be used in patients failing first-line NNRTI therapy.

Kendall A. Marcus, M.D.

Medical Team Leader/Division of Antiviral Products

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

/s/

Kendall Marcus
1/17/2008 03:57:14 PM
MEDICAL OFFICER

Debra Birnkrant
1/17/2008 03:59:02 PM
MEDICAL OFFICER

CLINICAL REVIEW

Application Type NDA
Submission Number 22-187
Submission Code 000

Letter Date July 17, 2007
Stamp Date July 18, 2007
PDUFA Goal Date January 18, 2008

Reviewer Name Charu J. Mullick
Review Completion Date January 17, 2008

Established Name Etravirine
(Proposed) Trade Name INTELENCE™
Therapeutic Class Non-nucleotide Reverse Transcriptase Inhibitor
Applicant Tibotec Pharmaceuticals Inc.

Priority Designation P

Formulation Tablet (100 mg)
Dosing Regimen 200 mg twice daily
Indication Etravirine, in combination with other antiretroviral agents, is indicated for the treatment of human immunodeficiency virus (HIV) infection in treatment-experienced adults who have evidence of viral replication and HIV-1 strains resistant to

Intended Population HIV-1-infected treatment-experienced adults

Table of Contents

1	EXECUTIVE SUMMARY	5
1.1	RECOMMENDATION ON REGULATORY ACTION	5
1.2	RECOMMENDATION ON POSTMARKETING ACTIONS	6
1.2.1	Risk Management Activity	6
1.2.2	Required Phase 4 Commitments	6
1.2.3	Other Phase 4 Requests	7
1.3	SUMMARY OF CLINICAL FINDINGS	7
1.3.1	Brief Overview of Clinical Program	7
1.3.2	Efficacy	8
1.3.3	Safety	8
1.3.4	Dosing Regimen and Administration	9
1.3.5	Drug-Drug Interactions	9
1.3.6	Special Populations	10
2	INTRODUCTION AND BACKGROUND	11
2.1	PRODUCT INFORMATION	11
2.2	CURRENTLY AVAILABLE TREATMENT FOR INDICATIONS	11
2.3	AVAILABILITY OF PROPOSED ACTIVE INGREDIENT IN THE UNITED STATES	11
2.4	IMPORTANT ISSUES WITH PHARMACOLOGICALLY RELATED PRODUCTS	12
2.5	PRESUBMISSION REGULATORY ACTIVITY	12
3	SIGNIFICANT FINDINGS FROM OTHER REVIEW DISCIPLINES	13
3.1	CMC (AND PRODUCT MICROBIOLOGY, IF APPLICABLE)	13
3.2	ANIMAL PHARMACOLOGY/TOXICOLOGY	14
4	DATA SOURCES, REVIEW STRATEGY, AND DATA INTEGRITY	15
4.1	SOURCES OF CLINICAL DATA	15
4.2	REVIEW STRATEGY	18
4.3	DATA QUALITY AND INTEGRITY	18
4.4	COMPLIANCE WITH GOOD CLINICAL PRACTICES	18
4.5	FINANCIAL DISCLOSURES	18
5	CLINICAL PHARMACOLOGY	19
5.1	PHARMACOKINETICS	19
5.2	EXPOSURE-RESPONSE RELATIONSHIP	26
6	INTEGRATED REVIEW OF EFFICACY	29
6.1	INDICATION	29
6.1.1	Methods	29
6.1.2	General Discussion of Endpoints	29
6.1.3	Study Design	29
6.1.4	Efficacy Findings	30
6.1.5	Clinical Microbiology	40
6.1.6	Efficacy Conclusions	42
7	INTEGRATED REVIEW OF SAFETY	43
7.1	METHODS AND FINDINGS	43
7.1.1	Deaths	43

7.1.2	Serious Adverse Events	47
7.1.3	Dropouts and Other Significant Adverse Events	49
7.1.4	Other Search Strategies	81
7.1.5	Common Adverse Events	84
7.1.6	Less Common Adverse Events	87
7.1.7	Laboratory Findings	88
7.1.8	Vital Signs	101
7.1.9	Electrocardiograms (ECGs)	101
7.1.10	Immunogenicity	102
7.1.11	Human Carcinogenicity	102
7.1.12	Special Safety Studies	102
7.1.13	Withdrawal Phenomena and/or Abuse Potential	103
7.1.14	Human Reproduction and Pregnancy Data	103
7.1.15	Assessment of Effect on Growth	103
7.1.16	Overdose Experience	103
7.1.17	Postmarketing Experience	103
7.2	ADEQUACY OF PATIENT EXPOSURE AND SAFETY ASSESSMENTS	104
7.2.1	Description of Primary Clinical Data Sources (Populations Exposed and Extent of Exposure) Used to Evaluate Safety	104
7.2.2	Description of Secondary Clinical Data Sources Used to Evaluate Safety	104
7.2.3	Adequacy of Overall Clinical Experience	105
7.2.4	Adequacy of Special Animal and/or In Vitro Testing	106
7.2.5	Adequacy of Routine Clinical Testing	106
7.2.6	Adequacy of Metabolic, Clearance, and Interaction Workup	106
7.2.7	Adequacy of Evaluation for Potential Adverse Events for Any New Drug and Particularly for Drugs in the Class Represented by the New Drug; Recommendations for Further Study	106
7.2.8	Assessment of Quality and Completeness of Data	106
7.2.9	Additional Submissions, Including Safety Update	107
7.3	SUMMARY OF SELECTED DRUG-RELATED ADVERSE EVENTS, IMPORTANT LIMITATIONS OF DATA, AND CONCLUSIONS	107
7.4	GENERAL METHODOLOGY	108
7.4.1	Pooling Data Across Studies to Estimate and Compare Incidence	108
7.4.2	Explorations for Predictive Factors	108
7.4.3	Causality Determination	109
8	ADDITIONAL CLINICAL ISSUES	109
8.1	DOSING REGIMEN AND ADMINISTRATION	109
8.2	DRUG-DRUG INTERACTIONS	109
8.3	SPECIAL POPULATIONS	110
8.4	PEDIATRICS	111
8.5	ADVISORY COMMITTEE MEETING	111
8.6	LITERATURE REVIEW	111
8.7	POSTMARKETING RISK MANAGEMENT PLAN	111
8.8	OTHER RELEVANT MATERIALS	111
9	OVERALL ASSESSMENT	111
9.1	CONCLUSIONS	111
9.2	RECOMMENDATION ON REGULATORY ACTION	112
9.3	RECOMMENDATION ON POSTMARKETING ACTIONS	112
9.3.1	Risk Management Activity	112
9.3.2	Required Phase 4 Commitments	113

Clinical Review
Charu Mullick, M.D.
NDA 22-187
Etravirine

9.3.3	Other Phase 4 Requests.....	114
9.4	LABELING REVIEW.....	114
9.5	COMMENTS TO APPLICANT.....	115
10	APPENDICES.....	115
10.1	REVIEW OF INDIVIDUAL STUDY REPORTS.....	115
10.2	LINE-BY-LINE LABELING REVIEW.....	117
11	REFERENCES.....	147

1 EXECUTIVE SUMMARY

1.1 Recommendation on Regulatory Action

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

This recommendation is based on the antiviral superiority of etravirine over placebo demonstrated by Week 24 results of two large, double-blind, randomized placebo-controlled trials, TMC125-C206 (C206) and TMC126-C216 (C216). In these trials, 59.8% of subjects receiving etravirine achieved a plasma viral load reduction to less than 50 copies/mL compared to 40.2% in the placebo arm.

The safety concerns related to etravirine include skin reactions, gastrointestinal side effects and hyperlipidemia. Overall, 15.2% of subjects reported skin reactions such as rash with etravirine use compared to 8.1% reported in the placebo arm. Rash was typically mild to moderate in severity, manifested primarily in the second week of therapy. In general, rash was self-limited and resolved with continued etravirine use; however, 2% of etravirine-treated subjects discontinued treatment for rash. Serious dermatologic events including Stevens-Johnson syndrome were rare. A female predisposition to development of rash was observed, although the numbers of female subjects enrolled in C206 and C216 were small.

Gastrointestinal side effects attributed to etravirine are nausea and vomiting. A slight imbalance was observed in the frequency of elevations of serum alanine aminotransferase in the etravirine arm compared to placebo arm; however, no cases of hepatotoxicity were clearly attributable to etravirine use. A mild increase in nasopharyngitis, herpes zoster, herpes simplex, and oral candidiasis was noted in the etravirine subjects. A modest increase in serum low density lipoprotein cholesterol was observed in the etravirine arm compared to placebo; etravirine subjects were more likely to initiate lipid-lowering therapy when compared to placebo subjects. The attributability of adverse events including seizures, diabetes mellitus and anemia in remains questionable.

In summary, based on the demonstrated virologic efficacy of etravirine in HIV-infected treatment-experienced adults and the supportive safety data, accelerated approval under 21 CFR 312 subpart H is recommended.

1.2 Recommendation on Postmarketing Actions

1.2.1 Risk Management Activity

A risk management plan was not submitted with NDA 22-187. The Applicant states that risk assessments based on available data indicate routine monitoring of the safety profile in ongoing and planned clinical trials and routine pharmacovigilance activities suffice as tools to identify potential risks for etravirine. The FDA Office of Surveillance and Epidemiology (OSE) was briefed at an internal Pre-approval Safety Meeting regarding outstanding safety concerns and potential safety issues for etravirine. No additional risk minimization activities are required outside of Phase 4 commitments and requests.

1.2.2 Required Phase 4 Commitments

1. Submit study reports for Week 48 data analyses for the ongoing Phase 3 studies TMC125-C206 and TMC125-C216 to support the traditional approval of etravirine.
Final Report Submission by: January 2009
2. Deferred pediatric study under PREA for the treatment of HIV-1 infection in pediatric subjects from 6 to 18 years of age. Conduct a pediatric safety and activity study of etravirine with activity based on the results of virologic response over at least 24 weeks of dosing and safety monitored over 48 weeks.
Protocol submission by: June 2008
Final report submission by: June 2010
3. Deferred pediatric study under PREA for the treatment of HIV-1 infection in pediatric subjects from 2 months to 6 years of age. This study will determine the pharmacokinetic profile, safety, and activity of etravirine in pediatric subjects from 2 months to 6 years of age.
Protocol submission by: June 2010
Final report submission by: June 2013
4. Conduct a study of etravirine in treatment-experienced female patients to elucidate any potential gender differences in efficacy and safety.
Protocol Submission: Completed, cross referenced to IND 62,477 for TMC114 (PREZISTA); "*Gender, Race And Clinical Experience (GRACE)*" trial, TMC114HIV3004
Final Report Submission: December 2009 (TMC125 subgroup analysis report of TMC114HIV3004)
5. Conduct a 48-week clinical study of treatment-experienced patients enrolling at least 200 subjects to evaluate safety and pharmacokinetics of etravirine when given with drug combinations that do not contain darunavir/rtv. Submit an interim report including

analyses of 12-week safety data and supportive efficacy data with the Safety Update submission for the traditional approval supplemental new drug application for etravirine.

Protocol submission: July 2008

Final study report submission: July 2011

6. Complete ongoing carcinogenicity study in mice and submit the final report.

Protocol submission date: Completed

Final study report submission date: January 2009

7. Complete ongoing carcinogenicity study in rats and submit the final report.

Protocol submission date: Completed

Final study report submission date: January 2009

8. Conduct an *in vivo* drug-drug interaction study between etravirine and fluconazole.

Protocol submission date by: July 2008

Final Report Submission by: August 2009

9. Conduct an *in vivo* drug-drug interaction study between etravirine and buprenorphine/naloxone.

Protocol submission date by: July 2008

Final Report Submission by: August 2010

1.2.3 Other Phase 4 Requests

Other requests excluding postmarketing commitments are:

1. Please assess the combination activity relationships of etravirine with maraviroc and raltegravir.

Final Study Report submission date: by December 2008

1.3 Summary of Clinical Findings

1.3.1 Brief Overview of Clinical Program

Etravirine is a non-nucleoside reverse transcriptase inhibitor (NNRTI) of human immunodeficiency virus type 1 (HIV-1). Etravirine is a new molecular entity. The NDA was filed with a proposed indication for the treatment of HIV-1 infection in antiretroviral treatment-experienced adult patients with evidence of viral replication and HIV-1 strains resistant to

The Phase 3 trials C206 and C216 are the chief sources of data for efficacy and safety analyses. These trials were identical in design and enrolled treatment-experienced HIV-1 infected adults failing antiretroviral therapy with plasma HIV viral load > 5000 copies/mL and with at least 1

NNRTI mutation and at least 3 primary mutations to protease inhibitors. In trials, subjects received etravirine or placebo along with an optimized background regimen comprised of darunavir/ritonavir and at least 2 nucleoside or nucleotide reverse transcriptase inhibitors. Subjects also had the option of using enfuvirtide.

1.3.2 Efficacy

The results of Week 24 efficacy analysis demonstrate greater antiviral activity of etravirine as compared to placebo in treatment-experienced subjects with NNRTI resistance who were receiving a background regimen containing darunavir/ritonavir. Virologic response (subject achieved HIV viral load < 50 copies/mL) was observed more frequently in subjects receiving etravirine (59.8%) as compared to subjects receiving placebo (40.2%). A difference between the etravirine and placebo treatment response, favoring etravirine was noted in subjects using *de novo* enfuvirtide, as well as subjects re-using or not using enfuvirtide; this difference was statistically significant in the group re-using or not using enfuvirtide. The response rates in the two treatment arms were comparable when the antiretroviral regimen contained 3 or more active agents.

The presence of K103N, the most prevalent NNRTI substitution at baseline, did not affect the response in the etravirine arm. In the Phase 3 trials, substitutions that developed most commonly in subjects who experienced virologic failure at Week 24 to the etravirine-containing regimen were V179F, V179I, Y181C, and Y181I, which usually emerged in a background of multiple other NNRTI resistance-associated substitutions.

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.

1.3.3 Safety

The most common adverse events associated with etravirine use include rash and nausea. Rash was observed in 15.2% of etravirine recipients as compared to 8.1% of placebo recipients. Rash was typically mild to moderate in severity, manifested primarily in the second week of therapy. In general, rash was self-limited and resolved with continued etravirine use; however, 2% of etravirine-treated subjects discontinued treatment for rash. Overall, serious dermatologic entities including Stevens-Johnson syndrome, erythema multiforme and atypical bullous dermatitis were rare. A female predisposition to development of rash was observed, although the numbers of female subjects enrolled in clinical trials were small.

A mild increase in serum low density lipoprotein cholesterol was noted in the etravirine arm as compared to placebo arm, and a greater proportion of etravirine recipients initiated lipid-lowering agents.

A clear association between hepatotoxicity attributable to etravirine use was not established. Concerning hepatic adverse events and serum transaminase abnormalities in etravirine recipients were confounded by underlying viral hepatitis, the use of known hepatotoxic medications, or other plausible explanations for hepatic injury. A higher frequency of hepatic laboratory abnormalities was observed in etravirine subjects with Hepatitis B or C co-infection compared to placebo subjects.

In addition, a mild increase in nasopharyngitis, herpes zoster, herpes simplex, and oral candidiasis was noted in the etravirine subjects. The etravirine subjects who experienced renal failure of any type had risk factors and tenofovir use was the most prominent risk factor for renal disease.

Fewer subjects in the etravirine arm (1.8%) died as compared to placebo arm (3.3%). The most frequent cause of death in both treatment groups was an AIDS-defining illness or infection. The frequency of AIDS-defining illness was modestly decreased (3.0%) in the etravirine arm compared to the placebo arm (5.9%). Discontinuations due to adverse events were observed in 6.3% of etravirine subjects compared to 4.6% to placebo subjects. The most frequent event leading to etravirine discontinuation was rash.

With respect to cardiac safety, the frequency of coronary artery disease was comparable in the two treatment groups. In general, cases of cardiomyopathy in these trials occurred in subjects with pre-existing cardiac failure or developed in a predisposing clinical setting.

1.3.4 Dosing Regimen and Administration

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

1.3.5 Drug-Drug Interactions

The human cytochrome P450 enzymes (CYP) play a major role in the metabolism and biotransformation of etravirine. In brief, etravirine is a substrate and weak inducer of CYP3A4, and a substrate and weak inhibitor of CYP2C9 and CYP2C19. Several clinically relevant drug-drug interactions stem from these effects, notable being the interactions prohibiting concomitant use of etravirine with select protease inhibitors. The following provides an overview of etravirine drug interactions; refer to Table 2 in Section 5.1 for details.

As etravirine is a substrate of CYP3A4, CYP2C9 and CYP2C19, the co-administration of etravirine with drugs that are inducers or inhibitors of these enzymes may alter the therapeutic effect or adverse event profile of *etravirine*. Hence, co-administration of etravirine with **tipranavir/ritonavir**, and **full-dose ritonavir** (600 mg twice daily) is not recommended. An increase in etravirine exposure was observed when co-administered with **lopinavir/ritonavir**; caution is warranted when etravirine is co-administered with lopinavir/ritonavir as toxicity associated with increased plasma concentrations of etravirine may be observed. The co-

administration of etravirine with **phenytoin, phenobarbital, carbamazepine, rifampin, and rifapentin** is not recommended. **Systemic corticosteroids** and **St. John's wort (*hypericum perforatum*)** decrease etravirine plasma concentrations and may result in loss of therapeutic effect. On the other hand, **clarithromycin** and azole antifungal agents namely, **fluconazole, itraconazole, ketoconazole, posaconazole** may increase plasma concentration of etravirine resulting in etravirine toxicity. Additionally, an effect on exposure of itraconazole, ketoconazole and voriconazole is anticipated with etravirine co-administration. The increased generation of 14-hydroxy clarithromycin with concomitant etravirine may reduce activity against *Mycobacterium avium* complex (MAC), and therefore, alternatives to clarithromycin should be considered for treatment of MAC in subjects receiving etravirine.

In addition, since etravirine is an inducer of CYP3A4 and an inhibitor of CYP2C9 and CYP2C19, the co-administration of etravirine with drugs that are substrates of CYP3A4, CYP2C9, and CYP2C19 may alter the therapeutic effect or adverse event profile of the *co-administered drugs*. Etravirine should not be co-administered with **unboosted protease inhibitors** and **fosamprenavir/ritonavir**. The co-administration of etravirine and atazanavir/ritonavir reduces systemic exposures of atazanavir by approximately similar proportions as observed in the tenofovir-atazanavir interaction. The reduction in atazanavir exposure in that interaction was sufficient to recommend co-administration of tenofovir with atazanavir only in the presence of ritonavir, as ritonavir boosts atazanavir concentrations in plasma to acceptable levels. In light of this reduction of systemic exposure of atazanavir, the co-administration of **atazanavir/ritonavir** and etravirine is not recommended. Additionally, an increase in plasma etravirine concentrations to 100% of that observed in pivotal Phase 3 trials is anticipated when etravirine is combined with atazanavir/ritonavir. Dose adjustment of **sildenafil, vardenafil, tadalafil, methadone, HMG-CoA reductase inhibitors, diazepam** and antiarrhythmic agents such as **amiodarone, bepridil, disopyramide, flecainide, lidocaine (systemic), mexiletine, propafenone, quinidine** may be required when co-administered with etravirine. Similarly, co-administration with systemic immunosuppressants such as **cyclosporine, tacrolimus and sirolimus** should be done with caution, and co-administration with **warfarin** should be accompanied by monitoring of international normalized ratio (INR). The co-administration of etravirine with **rifabutin** does not require dose adjustment in the absence of protease inhibitor/ritonavir; however, rifabutin should not be co-administered with etravirine as part of a regimen containing a protease inhibitor/ritonavir combination.

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

1.3.6 Special Populations

In preclinical studies, no treatment-related effects on embryonic or fetal survival or fetal weights were observed. In addition, no treatment-related external, visceral, or skeletal malformations were observed. However, no adequate studies have been performed in pregnant women. Because animal reproduction studies are not necessarily predictive of human response, etravirine

2.4 Important Issues With Pharmacologically Related Products

The NNRTI class of compounds consists of three commercially available agents, namely efavirenz, nevirapine and delavirdine. Efavirenz and nevirapine are recommended as first-line regimen in antiretroviral-naïve patients with the primary goal of reducing HIV-related morbidity and mortality to restore and preserve immunologic function and maximally and durably suppress plasma HIV viral load (VL). They offer an advantage of lower pill burden, and allow preservation of PIs as future options thus delaying or reducing patient exposure to some adverse effects of PIs.

Efavirenz has demonstrated potent viral suppression and efavirenz containing regimens have been shown to be superior to some PI-based regimens.

Despite a robust impact on immunologic and virologic parameters and convenient dosing use of this class is limited for several reasons. A chief limitation is the emergence of resistance related to a single viral mutation that can lead to loss of activity. More importantly, this single mutation often leads to cross resistance with other drugs in this class.

The other disadvantage of this class is the toxicity profile. Efavirenz is associated with common side effects such as rash, central nervous system and psychiatric symptoms and teratogenicity. Nevirapine is an alternative NNRTI, however, variables such as gender and pre-treatment CD4 T cell count should be considered if the regimen will contain nevirapine. Serious and fatal hepatic events have been observed with nevirapine, often in association with a skin rash with or without fever or flu-like symptoms. Women with higher CD4 T cell counts appear to be at highest risk. In addition, serious and life-threatening skin reactions including Stevens-Johnson syndrome have been reported with nevirapine.

Lastly, NNRTIs are also substrates of CYP3A4 enzymes and these agents can interact with commonly prescribed drugs.

Delavirdine is currently not recommended due to unfavorable effects on lipid profile, relatively weak efficacy compared to different available antiretroviral drugs, and high pill burden.

2.5 Presubmission Regulatory Activity

The Investigational New Drug application (IND 63,646) for etravirine was submitted on November 6, 2001. The notable events throughout drug development are summarized below.

The etravirine development plan was temporarily halted due to a cluster of grade 3 rashes observed in 3 healthy volunteers (2 cases of erythema multiforme, 1 case of atypical bullous dermatitis) in a Phase I single-dose food interaction study TMC125-C137. Subjects were receiving a formulation of etravirine that is different from the to-be-marketed F060 formulation. All cases of rash including skin biopsy reports were reviewed; the Applicant decided to resume clinical development with implementation of measures for ensuring safety and minimizing undue risk with respect to rash. This included increased and systematic safety monitoring of skin adverse events, establishment of stopping rules and appropriate management strategies in the

event of occurrence of rash adverse events. A clinical drug development meeting with FDA was held on April 3, 2002. The principal issues discussed were assessment of adverse events and attributability with emphasis on reporting of dermatologic adverse events, the justification of selected dose for Phase 2 studies and formulation development. Additionally, the FDA restricted domestic drug development to studies involving only HIV-infected patients due to skin findings in Phase 1 trials.

The results of early analyses from Phase 2b studies C203 and C223, and designs of Phase 3 protocols were discussed at a meeting on May 11, 2005. The key issues addressed were FDA concern regarding potential risk of masking the efficacy of etravirine by concomitant use of potent agent darunavir in combination with low-dose ritonavir (DRV/rtv) and dose selection for Phase 3 studies.

The End of Phase 2 meeting was held on September 6, 2005 to discuss dose selection for the Phase 3 trials. The FDA agreed with the proposed dose based on exposure-response analysis. As data from Phase 2b studies demonstrated an added benefit of etravirine in treatment-experienced HIV-infected patients including those with NNRTI resistance, and addressed an unmet need in patients with a life-threatening condition, a Fast Track Designation was granted by FDA on August 11, 2005.

The Pre-NDA Meeting was held on June 1, 2007 to discuss content and format issues pertaining to submission of the NDA. The key points communicated by the FDA at this meeting include:

- The Phase 3 pivotal studies, C206 and C216, support the NDA submission for review for accelerated approval of etravirine
- Based on results of study TMC125-C227, etravirine has no role as part of a first-line regimen for treatment-naïve patients who are resistant to NNRTIs and susceptible to protease inhibitors, including those with primary NNRTI resistance.

3 SIGNIFICANT FINDINGS FROM OTHER REVIEW DISCIPLINES

3.1 CMC (and Product Microbiology, if Applicable)

The solubility properties of etravirine have predominated manufacturing issues of this drug. Etravirine is insoluble in aqueous medium. Several formulations of etravirine were developed in an effort to optimize solubility and increase the oral bioavailability, which in turn would lead to a lower pill burden for patients. Since the intended population in Phase 3 trials was treatment-experienced subjects who harbor resistant HIV, a lower daily pill burden would encourage adherence to an antiretroviral (ARV) regimen and assist the likelihood of viral suppression.

The key formulations of etravirine were TF035 and F060 used in Phase 2b/3 trials. In Phase 2b dose-finding studies, the TF035 formulation was administered. The dose of 800 mg b.i.d. of TF035 formulation (4 tablets b.i.d.) of etravirine was selected for further development. However, all subjects in Phase 3 trials received a newly developed formulation, F060 of etravirine. A biopharmaceutical comparability study TMC125-C228 revealed that 800 mg b.i.d.

of TF035 formulation was equivalent in exposure to 200 mg b.i.d. of the F060 formulation. The newer F060 formulation was manufactured using spray-drying technology instead of previously used _____ techniques, and is associated with a decreased pill burden of 2 tablets twice daily. All subjects in the Phase 3 trials received 200 mg b.i.d. of the F060-formulation; the Applicant is seeking approval for this dose and formulation.

The chemical name for etravirine is 4-[[6-amino-5-bromo-2-[(4-cyanophenyl)-amino]-4-pyrimidinyl] oxy]-3,5-dimethylbenzotrile. The molecular formula is $C_{20}H_{15}BrN_6O$ and the molecular weight is 435.28. For full details regarding review of the chemistry, manufacturing, and controls (CMC) data submitted in the NDA, please refer to FDA Chemistry Review conducted by Dr. Mark Seggel.

3.2 Animal Pharmacology/Toxicology

The etravirine non-clinical toxicity program is comprised of several single and repeated dose studies in rodent and dog species, longer-term studies of 3 months in mice, 6 months in rats and 12 months in dogs, genetic toxicity studies and reproductive and developmental toxicity studies covering fertility to postnatal development.

The outstanding findings in animal studies involved toxicity of the coagulation system, heart and liver. Additional abnormal findings were noted in thyroid and gall bladder.

Mortality due to hemorrhagic cardiomyopathy was observed in male mice. Hemorrhagic cardiomyopathy was accompanied by elevation of troponin, often associated with hemothorax at necropsy; myocarditis and pericarditis were observed in some animals. Macroscopic hemorrhages in other tissues such as testes or thymus were also noted in few animals. These findings prompted further evaluation in the form of two mechanistic toxicity studies in mice. These studies demonstrated an effect of etravirine on the metabolic pathway of Vitamin K resulting in abnormalities of clotting factors and coagulation time (3.9-fold increase prothrombin time, > 100 second increase activated plasma thromboplastin time); however, hemorrhagic cardiomyopathy was not observed in any animals in the mechanistic studies. No hemorrhage, cardiac changes or coagulation effects were seen in female mice or other species. Pathology of this nature has been previously reported in Vitamin-K deficient mice where the underlying mechanism is presumed to be myocardial interstitial hemorrhage that evolves into muscle degeneration. The mouse is a susceptible species due to thinner ventricular and atrial walls and higher heart rate. The Applicant concluded that in male mice, hemorrhagic cardiomyopathy was due to etravirine-mediated alterations in Vitamin K metabolism and the associated coagulation defects. The lack of clotting or cardiac abnormalities in female mice is not explained; the Applicant has hypothesized that female mice are less likely to develop Vitamin K deficiency and for this reason they did not manifest this toxicity. The margin of safety for cardiotoxicity is 0.3-fold compared to anticipated exposures in humans at the selected dose. There were no relevant effects on in vitro cardiovascular electrophysiological parameters in the safety pharmacology studies. Similarly, no relevant changes were observed on ECG or hemodynamic parameters in dogs at exposures higher than human exposures at the to-be-marketed dose. Based on these

preclinical findings, safety and toxicity monitoring with respect to ECG and coagulation factors was performed in clinical trials.

Liver abnormalities were observed in mouse, rat and dog. In mice, elevation of serum transaminase, hepatocellular hypertrophy and pathological fatty vacuolation were observed at exposures 0.14 to 0.28-fold below the anticipated human exposure. In dogs, increases in serum transaminase and microgranuloma formation were observed at exposures 7-fold greater than the anticipated exposure in humans. Bile inspissation in gall bladder accompanied liver enzyme and bilirubin elevations in dog.

Thyroid cellular hypertrophy and increase in organ weight observed in rat was attributed to effects of enzyme induction. Erythema and alopecia in dogs were the only dermatologic toxicities observed in the preclinical setting.

No mortality was noted in 6 month and 12 month animal studies. In vitro and in vivo genotoxicity tests showed no genotoxic potential of etravirine. Carcinogenicity studies are ongoing at the time of this review without indication of risk of carcinogenicity. Fertility and early embryonic development studies have shown that etravirine is not associated with relevant effects on fertility, and maternal or fetal toxicity. Etravirine is therefore considered not to be teratogenic in rat. Similarly, no adverse effects were observed in a pre- and postnatal development study. Note that due to poor solubility, etravirine was administered in 3 different formulations, namely as base, salt of hydrogen bromide and a spray-dried form during animal studies.

Please refer to Animal Pharmacology/Toxicology Review of NDA 22-187 by Dr. Kuei-Meng Wu for a detailed analysis of the etravirine pharmacology and toxicology data.

4 DATA SOURCES, REVIEW STRATEGY, AND DATA INTEGRITY

4.1 Sources of Clinical Data

The etravirine development program consists of 64 ongoing or completed clinical trials. All evaluations pertaining to drug efficacy are based on data from the Phase 3 trials; the evaluations for safety are based on the totality of the drug development program.

The assessment of efficacy includes analysis of individual study data from C206 and C216 (DUET-1 and DUET-2, respectively) as well as analysis of pooled data at Week 24. In addition, the results of one Phase 2b study, TMC125-C227 (C227), are described in this review as they provide important conclusions about the overall efficacy of etravirine.

As Phase 3 trials were double-blind, placebo-controlled with 1:1 randomization scheme, they allow for relative comparisons of safety data in subjects receiving etravirine or placebo. In addition to pooled data from C206 and C216, comprehensive analyses of deaths and select

Clinical Review
Charu Mullick, M.D.
NDA 22-187
Etravirine

adverse events such as rash, cardiac events and hepatic events required review of data from Phase 1 and 2 trials. In particular, the database for Phase 2b trials, TMC125-C203, TMC125-C213, TMC125-C229 and TMC125-C227 was utilized (Table 1). Additionally, serious adverse event (SAE) data was reviewed from pre-approval access programs, including early access program (EAP) and compassionate use/named patient program. Furthermore, data submitted in the Safety Update Report was incorporated in safety analyses.

The types of data reviewed include datasets, clinical narratives, subject case report forms, Medwatch reports, Applicant's summaries for efficacy, safety, non-clinical toxicology and product information, the Proposed Pediatric Study Request, and available source documents.

**APPEARS THIS WAY
ON ORIGINAL**

Table 1: Overview of Trials Providing Clinical Efficacy and Safety Data

Trial, Location	Design	Population	Treatment Groups (formulation) ¹	Duration, Status	Subjects ²
Phase 3 Studies					
C206 US France Thailand L America	Double blind	HIV-infected, ≥ 1 NNRTI and ≥ 3 primary PI mutations	200 mg BID F060 or placebo Background: DRV/rtv, at least 2 NRTI, option of ENF	48 wks/ongoing	612 (304/308)
C216 US Europe Canada Australia					591 (295/296)
Phase 2b Studies					
C203 Europe Canada	Two-stage	HIV-infected 3-class ARV-experienced	400 mg BID (TF035) 800 mg BID (TF035) placebo 800 mg BID (TF035) 1200 mg BID TF035) placebo	48 wks/ completed	240
C223 US	Active control	HIV-infected ≥ 1 NNRTI and ≥ 3 primary PI mutations	400 mg BID (TF035) 800 mg BID (TF035) Investigator selected ART	48 wks/ completed	199
C227 Thailand S Africa L America Europe	Active control	HIV-infected, NNRTI resistant, PI-naive	800 mg BID (TF035) or Protease inhibitor/RTV	Premature stop at Wk 12 ³	116
C209 Europe	Open-label, Single group	HIV-infected, 3-class ARV-experienced	800 mg BID (TF035)	48 weeks/ completed	7

¹Dose 200 mg b.i.d. of F060 formulation provides comparable steady-state exposure to 800 mg b.i.d. of TF035 formulation in HIV-infected subjects; F060 formulation used in Phase 3 trials

²Number of subjects who have received at least one dose of study medication

³Premature discontinuation of trial as suboptimal virologic response observed in the etravirine-treated group compared to the active control (protease inhibitor/ritonavir)

4.2 Review Strategy

Data from the two Phase 3 pivotal trials C206 and C216 forms the basis of the safety and efficacy analyses. Review of additional data from Phase 1 and 2 trials was performed for specific events including death, skin reactions and cardiac events. Data related to serious adverse events (SAE) was reviewed from pre-approval access programs, including early access program and compassionate use/named patient program. The Safety Update Report (SUR) providing updated safety information until the cut-off date July 17th, 2007 was also reviewed.

4.3 Data Quality and Integrity

Inspection of two clinical sites by Division of Scientific Investigations was performed. The medical records reviewed failed to disclose findings that would reflect negatively on the reliability of the data. In general, records reviewed were accurate and found no significant problems that would impact the results. There were no known limitations to the inspections. The data from these sites was considered acceptable in support of the etravirine NDA.

4.4 Compliance with Good Clinical Practices

The clinical trials were conducted according to guidelines prescribed by the Declaration of Helsinki. In addition, the trials were conducted in compliance with International Conference on Harmonization Good Clinical Practice guidelines. Inspection of select clinical sites was performed by FDA Division of Scientific Investigations; the data from sites inspected was considered acceptable. Refer to the Clinical Inspection Summary of NDA 22-187 for details.

4.5 Financial Disclosures

The majority of investigators who participated in Studies TMC125-C206, TMC125-C216, TMC125-C223 and TMC125-C178 did not hold any disclosable financial arrangements with Johnson & Johnson, the parent company of the Applicant, Tibotec Inc. as defined in 21 CFR 54.2 (a), (b), (c), and (f). The Applicant states that despite attempts, complete financial disclosure information was not available for some investigators. This includes 6 investigators (none were primary investigators) who enrolled subjects in C206, and 8 investigators (none were primary investigators) who enrolled subjects in C216. The remaining investigators of unknown status with respect to financial interests did not enroll subjects into these trials.

One investigator who enrolled 1 subject in _____ owns an equity interest in Johnson & Johnson with a value of \$200,000 as calculated on September 1, 2006. All case report forms and data were analyzed by the Applicant to minimize potential bias on the study; this investigator enrolled _____ in the trial.

One investigator who had previously received \$30,000 honoraria as a member of the Speaker's Bureau of Ortho-McNeill, a division of Johnson & Johnson enrolled _____. All case report forms and data were analyzed by the Applicant to minimize potential bias on the study.

The site where this investigator participated enrolled _____ patients in the trial.

5 CLINICAL PHARMACOLOGY

5.1 Pharmacokinetics

This section provides a brief summary of the pharmacokinetics and drug-drug interactions of etravirine. Please refer to FDA Clinical Pharmacology Review of NDA 22-187 by Dr. Vikram Arya for details.

Absorption

The absolute bioavailability of etravirine could not be investigated due to the inability to produce an acceptable intravenous formulation. A dose proportional increase in mean systemic exposure including AUC (area under the plasma concentration vs time curve) and C_{max} is observed between total daily doses of 200 and 400 mg of etravirine. Systemic exposures at steady-state were 3 to 8-fold higher than single dose of etravirine.

Distribution

The *in vitro* plasma protein binding of etravirine is approximately 99%. It is extensively bound to human albumin. Distribution into other compartments such as CSF or genital tract secretions is not known.

Metabolism

Metabolism of etravirine was studied in a clinical mass-balance study as well as *in vitro* in human hepatocytes. Approximately 94% of etravirine is excreted unchanged in feces, and only 1.2% recovered in urine. Data indicate that in humans hydroxylation was the predominant Phase I metabolic pathway. There is minimal renal metabolism of this drug.

Etravirine affects activity of CYP3A4, CYP2C9 and CYP2C19. It is an inducer of CYP3A4 and inhibitor of CYP2C9 and CYP2C19. In addition, it is also a substrate for these three enzymes. *In vitro*, etravirine was shown to inhibit P-glycoprotein (P-gp). The proposed *in vivo* digoxin study will also assess the effects on P-gp activity.

Elimination

Data from mass balance study showed that approximately 94% of etravirine was excreted unchanged in feces. The most important metabolic pathway of etravirine was hydroxylation.

Food Effect

The exposure was 51% lower than when a 100-mg dose of the to-be-marketed formulation of etravirine was administered under fasted conditions compared to after a standard meal. The type of meal or timing of meal with respect to administration of etravirine did not have an impact on drug exposure. In Phase 2b and 3 trials, subjects were instructed to take etravirine tablets following a meal.

Special Populations

The effects of HIV status, gender, age, weight and race on etravirine pharmacokinetics were assessed. No dose adjustment is required for mild and moderate hepatic impairment; the setting of severe hepatic impairment was not evaluated. Since etravirine elimination through renal pathway is minimal, a renal impairment study was not conducted. No differences in gender and race were observed; and the pharmacokinetics in pediatric population is under investigation at this time.

Drug-Drug Interactions

The human cytochrome P450 enzymes (CYP) play a major role in the metabolism and biotransformation of etravirine. Etravirine is a substrate and weak inducer of CYP3A4, and a substrate and weak inhibitor of CYP2C9 and CYP2C19; multiple drug-drug interactions have emerged because of these effects.

The drug-drug interaction studies were conducted using various doses and formulations of etravirine. However, the drug-drug interaction trials that provide information to be included in the package insert were conducted either with formulation TF035 (800 mg b.i.d.) or with the to-be-marketed formulation F060 (200 mg b.i.d.). The use of a different dose (800 mg b.i.d.) and different formulation (TF035) does not alter the interpretation of most drug interaction studies.

As etravirine is a substrate of CYP3A4, CYP2C9 and CYP2C19, the co-administration of etravirine with drugs that are inducers or inhibitors of these enzymes may alter the therapeutic effect or adverse event profile of *etravirine*. Hence, co-administration of etravirine with **tipranavir/ritonavir**, and **full-dose ritonavir** (600 mg twice daily) is not recommended. An increase in etravirine exposure was observed when co-administered with **lopinavir/ritonavir**; caution is warranted when etravirine is co-administered with lopinavir/ritonavir as toxicity associated with increased plasma concentrations of etravirine may be observed (Refer to Section 7.1.7.4 for related safety analysis). The co-administration of etravirine with **phenytoin**, **phenobarbital**, **carbamazepine**, **rifampin**, and **rifapentin** is not recommended. **Systemic corticosteroids** and **St. John's wort** (*hypericum perforatum*) decrease etravirine plasma concentration and may result in loss of therapeutic effect. On the other hand, **clarithromycin** and azole antifungal agents namely, **fluconazole**, **itraconazole**, **ketoconazole**, **posaconazole** may increase plasma concentration of etravirine resulting in etravirine toxicity. Additionally, an effect on exposure of itraconazole, ketoconazole and voriconazole is anticipated with etravirine co-administration. The increased generation of 14-hydroxy clarithromycin with concomitant etravirine may reduce activity of clarithromycin against *Mycobacterium avium* complex (MAC), and therefore, alternatives to clarithromycin should be considered for treatment of MAC in subjects receiving etravirine.

In addition, since etravirine is an inducer of CYP3A4 and an inhibitor of CYP2C9 and CYP2C19, the co-administration of etravirine with drugs that are substrates of CYP3A4, CYP2C9, and CYP2C19 may alter the therapeutic effect or adverse event profile of the *co-administered drugs*. Etravirine should not be co-administered with **unboosted protease**

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

Table 2 shows the established and other potentially significant drug interactions based on which, alterations in dose or regimen may be recommended. The interaction between etravirine (trade name, INTELENCE™) and the drug preceding the asterisk (*) sign was evaluated in a clinical study; the interactions between etravirine and other drugs are predicted.

Table 2. Established and Other Potentially Significant Drug Interactions: Alterations in Dose or Regimen may be Recommended Based on Drug Interactions Studies or Predicted Interaction

Concomitant Drug Class: Drug Name	Effect on Concentration of Etravirine Or Concomitant Drug	Clinical Comment
HIV-Antiviral Agents: Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTIs)		
efavirenz* nevirapine*	↓ etravirine	Combining two NNRTIs has not been shown to be beneficial. Concomitant use of INTELENCE™ with efavirenz or nevirapine may cause a significant decrease in the plasma concentrations of etravirine and loss of therapeutic effect of INTELENCE™. INTELENCE™ and other NNRTIs should not be co-administered.
delavirdine	↑ etravirine	Combining two NNRTIs has not been shown to be beneficial. INTELENCE™ and delavirdine should not be co-administered.
HIV-Antiviral Agents: Protease Inhibitors (PIs)—Unboosted (i.e., without co-		

administration of low-dose ritonavir)		
Atazanavir* fosamprenavir nelfinavir indinavir*	↓ atazanavir ↑ amprenavir ↑ nelfinavir ↓ indinavir	Concomitant use of INTELENCE™ with PIs without co-administration of low-dose ritonavir may cause a significant alteration in the plasma concentrations of the PI. INTELENCE™ should not be co-administered with PIs without low-dose ritonavir.
ritonavir*	↓ etravirine	Concomitant use of INTELENCE™ with ritonavir 600 mg b.i.d. may cause a significant decrease in the plasma concentration of etravirine and loss of therapeutic effect of INTELENCE™. INTELENCE™ and ritonavir 600 mg b.i.d. should not be co-administered.
HIV-Antiviral Agents: Protease Inhibitors (PIs)—Boosted (with co-administration of low-dose ritonavir)		
tipranavir/ritonavir*	↓ etravirine	Concomitant use of INTELENCE™ with tipranavir/ritonavir may cause a significant decrease in the plasma concentrations of etravirine and loss of therapeutic effect of INTELENCE™. INTELENCE™ and tipranavir/ritonavir should not be co-administered.
fosamprenavir/ritonavir*	↑ amprenavir	Due to a significant increase in the systemic exposure of amprenavir, the appropriate doses of the combination of INTELENCE™ and fosamprenavir/ritonavir have not been established. INTELENCE™ and fosamprenavir/ritonavir should not be co-administered.
atazanavir/ritonavir*	↓ atazanavir ↑ etravirine	Concomitant use of INTELENCE™ with atazanavir/ritonavir may cause a significant decrease in atazanavir C_{min} and loss of therapeutic effect of atazanavir. In addition, the mean systemic exposure (AUC) of etravirine after co-administration of INTELENCE™ with atazanavir/ritonavir is anticipated to be about 100% higher than the mean systemic exposure of etravirine observed in the Phase 3 trials. INTELENCE™ and atazanavir/ritonavir should not be co-administered.
darunavir/ritonavir	↓ etravirine	The mean systemic exposure (AUC) of

		etravirine was reduced by about 37% when INTELENCE™ was co-administered with darunavir/ritonavir. Because all subjects in the Phase 3 trials received darunavir/ritonavir as part of the background regimen and etravirine exposures from these trials were determined to be safe and effective, INTELENCE™ and darunavir/ritonavir can be co-administered without any dose adjustments.
lopinavir/ritonavir	↑ etravirine	The mean systemic exposure (AUC) of etravirine after co-administration of INTELENCE™ with lopinavir/ritonavir is anticipated to be about 85% higher than the mean systemic exposure of etravirine observed in the Phase 3 trials. The amount of safety data at these increased etravirine exposures is limited, therefore, INTELENCE™ and lopinavir/ritonavir should be co-administered with caution.
saquinavir/ritonavir	↓ etravirine	The mean systemic exposure (AUC) of etravirine was reduced by about 33% when INTELENCE™ was co-administered with saquinavir/ritonavir. Because the reduction in the mean systemic exposures of etravirine in the presence of saquinavir/ritonavir is similar to the reduction in mean systemic exposures of etravirine in the presence of darunavir/ritonavir, INTELENCE™ and saquinavir/ritonavir can be co-administered without any dose adjustments.
Other Agents		
Antiarrhythmics: amiodarone, bepidil, disopyramide, flecainide, lidocaine (systemic), mexiletine, propafenone, quinidine	↓ antiarrhythmics	Concentrations of these antiarrhythmics may be decreased when co-administered with INTELENCE™. INTELENCE™ and antiarrhythmics should be co-administered with caution. Drug concentration monitoring is recommended, if available.
Anticoagulants: warfarin	↑ anticoagulants	Warfarin concentrations may be increased when co-administered with INTELENCE™. The international normalized ratio (INR) should be monitored when warfarin is

		combined with INTELENCE™.
Anticonvulsants: carbamazepine, phenobarbital, phenytoin	↓ etravirine	Carbamazepine, phenobarbital and phenytoin are inducers of CYP450 enzymes. INTELENCE™ should not be used in combination with carbamazepine, phenobarbital, or phenytoin as co-administration may cause significant decreases in etravirine plasma concentrations and loss of therapeutic effect of INTELENCE™.
Antifungals: fluconazole, itraconazole, ketoconazole, posaconazole, voriconazole	↑ etravirine ↔ fluconazole ↓ itraconazole ↓ ketoconazole ↔ posaconazole ↑ voriconazole	Posaconazole is a potent inhibitor of CYP3A4 and fluconazole is a potent inhibitor of CYP2C9; both may increase plasma concentrations of etravirine. Itraconazole and ketoconazole are potent inhibitors as well as substrates of CYP3A4. Concomitant systemic use of itraconazole or ketoconazole and INTELENCE™ may increase plasma concentrations of etravirine. Simultaneously, plasma concentrations of itraconazole or ketoconazole may be decreased by INTELENCE™. Voriconazole is a CYP2C19 substrate and CYP3A4, CYP2C9 and CYP2C19 inhibitor. Concomitant use of voriconazole and INTELENCE™ may increase plasma concentrations of both drugs. Dose adjustments for itraconazole, ketoconazole or voriconazole may be necessary depending on other co-administered drugs.
Antiinfectives: clarithromycin*	↑ etravirine ↓ clarithromycin ↑ 14-OH-clarithromycin	Clarithromycin exposure was decreased by etravirine; however, concentrations of the active metabolite, 14-hydroxy-clarithromycin, were increased. Because 14-hydroxy-clarithromycin has reduced activity against <i>Mycobacterium avium</i> complex (MAC), overall activity against this pathogen may be altered; therefore, alternatives to clarithromycin, such as azithromycin, should be considered for the treatment of MAC.
Antimycobacterials: rifampin, rifapentine,	↓ etravirine	Rifampin and rifapentine are potent inducers of CYP450 enzymes. INTELENCE™ should not be used with rifampin or rifapentine as co-administration may cause

		significant decreases in etravirine plasma concentrations and loss of therapeutic effect of INTELENCE™.
Antimycobacterials: rifabutin*	↓ rifabutin ↓ 25-O-desacetyl-rifabutin	If INTELENCE™ is NOT co-administered with a protease inhibitor/ritonavir, then rifabutin at a dose of 300 mg q.d. is recommended. If INTELENCE™ is co-administered with darunavir/ritonavir or saquinavir/ritonavir, then rifabutin should not be co-administered due to the potential for significant reductions in etravirine exposure
Benzodiazepines: diazepam	↑ diazepam	Concomitant use of INTELENCE™ with diazepam may increase plasma concentrations of diazepam. A decrease in diazepam dose may be needed.
Corticosteroids: dexamethasone (systemic)	↓ etravirine	Systemic dexamethasone induces CYP3A4 and can decrease etravirine plasma concentrations. This may result in loss of therapeutic effect of INTELENCE™. Systemic dexamethasone should be used with caution or alternatives should be considered, particularly for long-term use.
Herbal Products: St. John's wort (<i>Hypericum perforatum</i>)	↓ etravirine	Concomitant use of INTELENCE™ with products containing St. John's wort may cause significant decreases in etravirine plasma concentrations and loss of therapeutic effect of INTELENCE™. INTELENCE™ and products containing St. John's wort should not be co-administered.
HMG-CoA Reductase Inhibitors: atorvastatin*	↔ etravirine ↓ atorvastatin ↑ 2-OH-atorvastatin	The combination of INTELENCE™ and atorvastatin can be given without any dose adjustments, however, the dose of atorvastatin may need to be altered based on clinical response.
fluvastatin, lovastatin, pravastatin, rosuvastatin,	↔ etravirine ↑ fluvastatin,	No interaction between pravastatin, rosuvastatin and INTELENCE™ is expected.

simvastatin	↓ lovastatin, ↔ pravastatin, ↔ rosuvastatin, ↓ simvastatin	Lovastatin and simvastatin are CYP3A4 substrates and co-administration with INTELENCE™ may result in lower plasma concentrations of the HMG-CoA reductase inhibitor. Fluvastatin is metabolized by CYP2C9 and co-administration with INTELENCE™ may result in higher plasma concentrations of the HMG-CoA reductase inhibitor. Dose adjustments for these HMG-CoA reductase inhibitors may be necessary.
Immunosuppressants: cyclosporine, - sirolimus, tacrolimus	↓ immunosuppressant	INTELENCE™ and systemic immunosuppressants should be co-administered with caution because plasma concentrations of cyclosporine, sirolimus, or tacrolimus may be affected.
Narcotic Analgesics: methadone*	↔ etravirine ↔ methadone	INTELENCE™ and methadone can be co-administered without dose adjustments, however, clinical monitoring for withdrawal symptoms is recommended as methadone maintenance therapy may need to be adjusted in some patients.
Phosphodiesterase Type 5 (PDE-5) Inhibitors: sildenafil, vardenafil, tadalafil*	↓ sildenafil, vardenafil, tadalafil ↓ N-desmethyl- sildenafil, vardenafil, tadalafil	INTELENCE™ and sildenafil can be co-administered without dose adjustments, however, the dose of sildenafil may need to be altered based on clinical effect.
↑ = increases, ↓ = decreases, ↔ = no change * The interaction between etravirine and the drug was evaluated in a clinical study. The other drug interactions shown are predicted.		

*As appears in etravirine package insert

Lastly, etravirine is a substrate of P-glycoprotein and results of the *in vitro* studies with radiolabeled paclitaxel showed that etravirine has weak P-gp inhibitory properties. Trial TMC125-C180, a drug-drug interaction study of etravirine with digoxin designed to assess the *in vivo* P-gp induction and inhibition properties of etravirine is ongoing.

5.2 Exposure-Response Relationship

This section provides a summary of the FDA Pharmacometric Review for NDA 22-187 by Dr. Pravin Jadhav. Refer to that review for details.

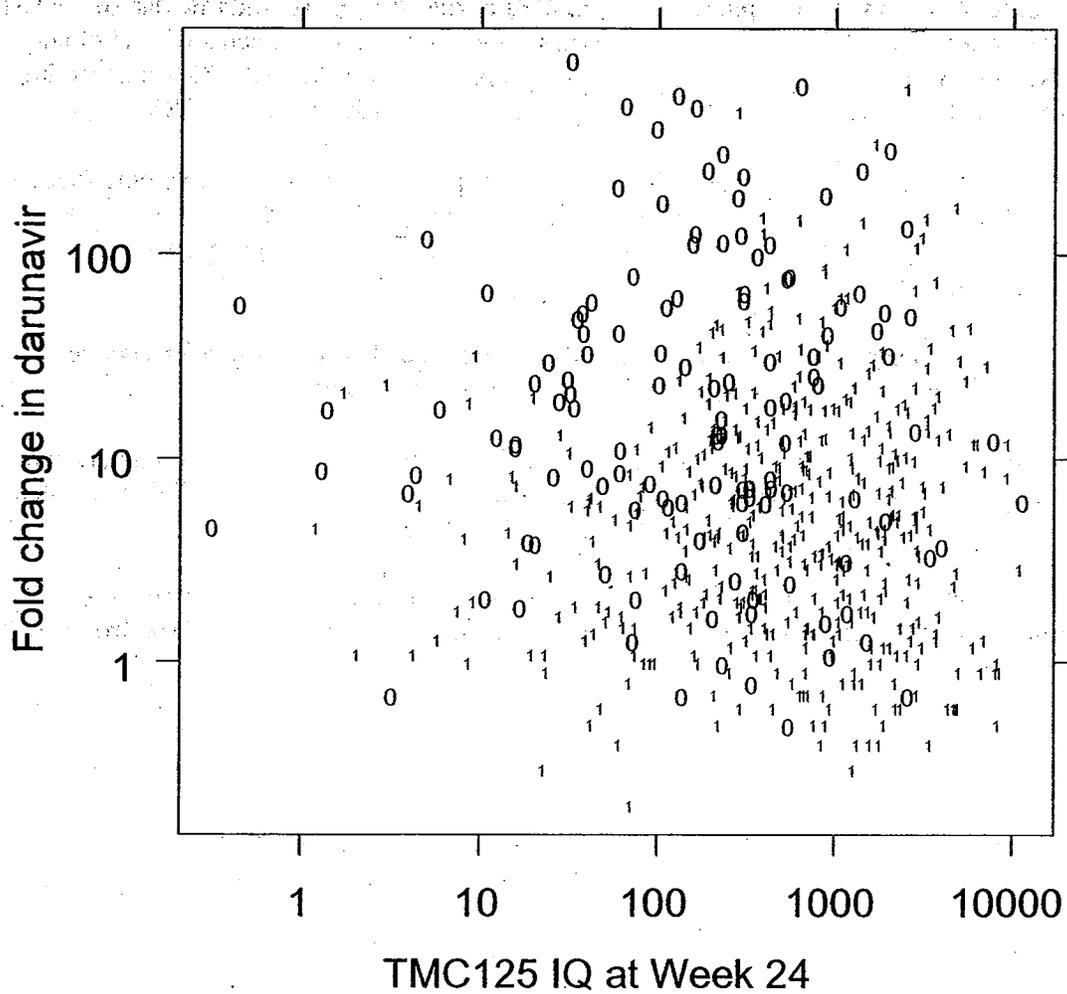
The relationship between plasma trough concentration of etravirine (C_{min}) and virologic response was evaluated. Key findings are summarized below:

- The fold change in darunavir (DRV) was noted to be the strongest predictor of success (response defined as HIV VL < 400 copies/mL). The proportion of patients with virologic success was lower (16% placebo arm, 52% etravirine arm) at 42-fold (median of the last quantile) change in DRV. On the other hand, the proportion of patients with virologic success (response defined as HIV VL < 400 copies/mL) was higher (~85% placebo arm, 85% etravirine arm) at 1.1-fold (median of the first quantile) change in DRV.
- Inhibitory quotient (IQ) appeared to be a more appropriate measure of virologic success than C_{min} or AUC, as the IQ takes into account C_{min} and fold change of etravirine. Analysis revealed an IQ of at least 400 was required to maximize the probability of virologic success.
- A modest dependency of virologic success on baseline HIV VL, baseline CD4+ cell count, compliance, phenotypic sensitivity score was observed.
- Etravirine pharmacokinetics were not affected by body weight, age, creatinine clearance, hepatitis B infection, hepatitis C infection, race, gender, enfuvirtide or TDF to an extent that would require dose adjustment.

Simulations conducted to assess the effect of doubling etravirine exposures in subjects with IQ < 400 showed the probability of virologic success increased only marginally by 2.5%, from 74.5% to 77% by doubling the exposure.

There were more failures in subjects with higher fold change in DRV even though they achieved relatively higher IQ. On the other hand, fewer failures were observed in subjects with a lower fold change in DRV and relatively low IQ (Figure 1). This finding suggests that to achieve the response rate seen in Phase 3 trials, it is essential that antiretroviral regimen have at least one fully active and potent agent, for example DRV/rtv, in addition to etravirine.

Figure 1: Relationship between Etravirine IQ and Fold Change in Darunavir with respect to Virologic Success¹



¹Virologic success is defined by viral load <400 copies/mL
Each symbol represents an individual patient, Success=1 and Failure=0

6 INTEGRATED REVIEW OF EFFICACY

6.1 Indication

The proposed indication for etravirine is for the treatment of HIV-1 infection in antiretroviral treatment-experienced adult patients, who have evidence of viral replication and HIV-1 strains resistant

6.1.1 Methods

The Phase 3 trials C206 and C216 are the chief sources of data for efficacy analyses in this review. The trial designs are identical and similar numbers of subjects were enrolled in the two treatment arms. For this reason, several efficacy analyses are based on pooled data. Data was analyzed when all subjects reached 24 weeks of treatment or discontinued earlier. In addition, the results from Phase 2b study C227 are reviewed in this section.

6.1.2 General Discussion of Endpoints

Viral load measurement of plasma HIV below the pre-specified threshold of 50 copies/mL was considered a surrogate marker of efficacy in the etravirine Phase 3 program. HIV VL is an established marker known to reflect the status of viral replication and HIV infection, and is endorsed by the FDA Guidance, "Antiretroviral Drugs Using Plasma HIV RNA Measurements-Clinical Considerations for Accelerated and Traditional Approval". All subjects in the Phase 3 trials received a viable background regimen including a potent protease inhibitor DRV/rtv. For this reason, a primary endpoint of the proportion of subjects achieving HIV VL < 50 copies/mL was selected; this treatment goal is consistent with the current Department of Health and Human Services (DHHS) HIV treatment guidelines. The secondary efficacy endpoints were proportion of subjects who achieved HIV VL < 400 copies/mL, a change in plasma VL by 1 log₁₀, the proportion of subjects with decrease in viral load of > 1.0 log₁₀ from baseline, increase in CD4 cell count and the incidence of clinical endpoints of AIDS-defining illness and death.

6.1.3 Study Design

Based on the resistance profile of etravirine, the Applicant chose to develop etravirine in the treatment-experienced HIV-infected population. The Phase 3 trials are ongoing, double-blind, placebo-controlled trials designed to investigate the efficacy, tolerability and safety of etravirine in treatment-experienced HIV-infected adults with evidence of NNRTI resistance. The Phase 3 trials were identical in design with the exception of geographical location of study sites; trial C206 was conducted in the USA, France, Thailand and Latin America, while trial C216 was conducted in the USA, Canada, Europe and Australia. Subjects were enrolled if they were on a failing antiretroviral regimen for at least 8 weeks with HIV VL > 5000 copies/mL and with ≥ 1 NNRTI mutation (at screening or archived resistance) and ≥ 3 primary PI mutations at the time of screening. Subjects received etravirine or placebo along with an optimized background

therapy (OBT) comprising of DRV/rtv and, at least, 2 NRTIs, and with the option of using enfuvirtide (ENF). At the time of trial enrollment, DRV/rtv was not approved but was known to have potent antiviral activity in combination with other antiretroviral agents. The Phase 3 trials were designed to assess whether addition of etravirine to a DRV/rtv-containing regimen would be beneficial compared to placebo in treatment-experienced HIV-infected patients. The use of *de novo* use ENF was limited to 40% of subjects in each Phase 3 trial to minimize the masking of benefit of etravirine by antiviral activity of ENF. This was based on estimates of anticipated contribution of ENF shown in DRV/rtv clinical trials. Subjects did not have the option of using another NNRTI, or a PI other than DRV/rtv. Stratification factors were use of ENF (*de novo* ENF use, not using ENF or re-using ENF), prior use of DRV, and screening HIV VL less than or greater than 30,000 copies/mL. Subjects who did not achieve a reduction of at least 1 log₁₀ from baseline at Week 24 or experienced viral rebound had the option to enroll into roll-over trial TMC125-217 after unblinding.

Each trial consisted of a screening period of up to 6 weeks, a 48-week treatment period, followed by a 4-week posttreatment follow-up period. At the screening visit, blood was collected for evaluation of plasma HIV VL, immunological parameters, pregnancy test, hepatitis serology, biochemistry and hematology. A 12-lead electrocardiogram (ECG) was obtained at screening. Eligible subjects were randomized to either etravirine or placebo in a 1:1 ratio. Subjects were also initiated on a background regimen consisting of DRV/rtv as the only PI and an optimized ARV regimen (at least 2 NRTIs with the option of ENF) based on investigator selected standard of care, prior ARV history, and results from genotypic and phenotypic testing. Evaluations for subject safety including safety laboratory test, physical examination, and ECG as well as assessment of drug efficacy such as HIV VL, CD4 count, HIV-1 genotype/phenotype were performed at scheduled visits. Protocol required visits were at Week 2, 4, 8, 12, 16, 20, 24, 32, 40, 48 and 52. Serious adverse events, all Grade 3 or 4 adverse events, and antiviral activity data were monitored by a Data and Safety Monitoring Board (DSMB).

Key inclusion criteria of Phase 3 protocols include:

- Subjects older than 18 years
- HIV VL > 5000 copies/mL at screening while on stable ART for at least 8 weeks
- Documented genotypic evidence of resistance to NNRTIs with at least 1 NNRTI resistance-associated-mutation (RAM) per IAS-USA list, update Nov 2005
- Presence of at least 3 primary PI mutations at screening

Key study stopping criteria includes lack or loss of virologic response in the trial. Lack of response was defined as HIV VL decline of < 0.5 log₁₀ from baseline by Week 8 or HIV VL decline of < 1.0 log₁₀ from baseline by Week 12. Loss of response was defined as 2 consecutive HIV VL > 0.5 log₁₀ above the nadir after at least 12 weeks of treatment.

6.1.4 Efficacy Findings

Characteristics of Study Population

The efficacy analysis was derived data from intention to treat population including 1203 subjects who received one or more doses of treatment. This consisted of 599 subjects who received etravirine and 604 subjects who received placebo. Subjects in the two arms were comparable in terms of age, gender and race (Table 3). The majority of the trial population was Caucasian (70%); Blacks and Hispanic groups accounted for 13% and 11.5% of the subjects. The trial was conducted in a predominantly male population with women representing 10 and 11% of subjects in the two arms.

The median HIV VL at baseline was 4.8 log₁₀ copies/mL and 36% of subjects had baseline HIV VL ≥ 100,000 copies/mL. These characteristics confirm the advanced stage of HIV infection in the heavily-treated trial population with at least 1 NNRTI mutation and at least 3 primary PI mutations. As expected, approximately 35% of subjects had CD4 count < 50 cells/mm³ at baseline, and 58% of subjects belonged to CDC Stage C of HIV infection. Overall, the treatment groups were comparable with respect to HIV disease markers at the time of study entry.

Table 3: Demographic and Baseline Disease Characteristics of Subjects in Phase 3 trials

	Etravirine (%) N=599	Placebo (%) N=604
Age, median (years)	45.0	45.0
Gender		
Male	539 (90)	535 (88.6)
Female	60 (10)	69 (11.4)
Race		
Caucasian	425 (70.1)	422 (69.8)
Black	78 (13)	79 (13)
Hispanic	66 (11)	74 (12.2)
Baseline viral load (log₁₀), median	4.83 (2.7-6.8)	4.83 (2.2-6.5)
Baseline CD4 count, (cells/mm³), median	99 (1-789)	109 (0-912)
CDC Stage of HIV infection		
Stage A	126 (21.0)	117 (19.5)
Stage B	127 (21.2)	130 (21.7)
Stage C	346 (57.8)	357 (59.5)
Baseline viral load category		
<30,000 copies/mL	165 (28)	174 (29)
≥ 30,000 and < 100,000 copies/mL	206 (34)	213 (35)
≥100,000 copies/mL	228 (38)	217 (36)
Baseline CD4 category		
≥ 200 cells/mm ³	177 (30)	186 (31)
≥ 50 and < 200 cells/mm ³	208 (35)	208 (34)

< 50 cells/mm ³	213 (36)	209 (35)
----------------------------	----------	----------

Source: Datasets DMAD for Studies C206 and C216

The median numbers of detectable NNRTI, NRTI and PI resistance-associated mutations present at baseline were comparable between Studies C206 and C216, and between the two treatment groups (Table 4). A high proportion of subjects in study C206 (53.6% in placebo arm, 53.8% in etravirine arm) and study C216 (55.5% in placebo arm, 53.2% in etravirine arm) had no sensitive NRTI in their OBT.

Table 4: Baseline Resistance Characteristics in Phase 3 Trials

	Study C206		Study C216		Pooled Data	
	Etravirine N=304	Placebo N=308	Etravirine N=295	Placebo N=296	Etravirine N=599	Placebo N=604
FDA-defined NNRTI Mutations	2	2	2	2	2	2
IAS-defined NNRTI Mutations	1	1	1	1	1	1
IAS-defined NRTI Mutations	6	6	6	6	6	6
IAS-defined Primary PI Mutations	4	4	4	4	5	4
Median TMC125 Fold Change	1.6	1.4	1.6	1.7	1.6	1.6
Median EFV Fold Change	102	73	40	28	87	32
Median DRV Fold Change	5.6	6.1	6.7	6.95	5.9	6.8

Source: Microbiology Reviewer's Analysis

In Phase 3 trials, subjects were stratified by ENF use as *de novo* ENF users, ENF re-users and ENF not used. In Studies C206 and C216, 25% and 27% of subjects, respectively, used ENF *de novo* (Table 5). The proportion of subjects reusing ENF was 16% in Study C206 and 25% in Study C216. The subjects reusing or having never used ENF before were comparable between the studies and treatment arms (approximately 74%). Note a greater proportion of ENF re-users in Study C216. Please refer to Microbiology Review of NDA 22-187 by Dr. Lisa Naeger for details.

Table 5: Enfuvirtide Use in Antiretroviral Therapy in Phase 3 Trials

ENF	Study C206		Study C216		Combined	
	TMC125 N=304	Placebo N=308	TMC125 N=295	Placebo N=296	TMC125 N=599	Placebo N=604
Total Use	40% (121)	41% (127)	52% (152)	53% (156)	46% (273)	47% (283)
De Novo	24% (74)	26% (79)	27% (79)	27% (81)	26% (153)	26% (160)
Re-Used/ Not Used	76% (230)	74% (229)	73% (216)	73% (215)	74% (446)	74% (444)

Source: Microbiology Reviewer's Analysis

The K103N mutation was the most prominent NNRTI-resistance associated mutation at baseline, present in 32% of all subjects in the Phase 3 trials. The baseline median numbers of detectable NNRTI-, NRTI-, and PI-resistance associated mutations were comparable between Studies C206 and C216 and the treatment groups within each trial (Table 6). The median baseline etravirine fold change values were 1.6 for both studies confirming that this was a highly treatment-experienced population and an NNRTI-resistant population. The applicant states that a high proportion of subjects in Study C206 (placebo: 53.6%; TMC125: 53.8%) and Study C216 (placebo: 55.5%; TMC125: 53.2%) had no sensitive NRTI in their OBT. Based on analyses performed by Microbiology Reviewer, Dr. Lisa Naeger, 16% of the subjects had no susceptible drugs in their OBT with a PSS of 0 and 38% of the subjects had a PSS of 1 in both trials. About 20% of subjects had 3 or more susceptible drugs in their OBT with phenotypic susceptibility score (PSS) ≥ 3 . The PSS was comparable between studies and arms.

Table 6: Percentage of Subjects in Phase 3 Studies by Baseline PSS Score

PSS Score	Study C206		Study C216		Combined	
	TMC125 N=299	Placebo N=303	TMC125 N=293	Placebo N=290	TMC125 N=592	Placebo N=593
0	50 (15%)	50 (17%)	48 (16%)	47 (16%)	17% (198)	16% (97)
1	114 (38%)	107 (35%)	102 (35%)	123 (42%)	36% (216)	39% (230)
2	71 (24%)	95 (31%)	89 (30%)	68 (23%)	27% (160)	27% (163)
3	50 (17%)	42 (14%)	45 (15%)	36 (12%)	16% (95)	13% (78)
4	14 (5%)	7 (2%)	9 (3%)	15 (5%)	4% (23)	4% (22)
5		2 (0.7%)		1 (0.3%)		0.5% (3)

Source: Microbiology Reviewer's Analysis

Efficacy

Virologic response (subject achieved HIV VL < 50 copies/mL) was observed more frequently in subjects receiving etravirine (58%) as compared to subjects receiving placebo (39%). The “snapshot” analysis was performed by selecting HIV VL values for all subjects at the Week 24 time-point. This analysis may not account for those subjects who have experience viral rebound during the initial weeks of therapy but subsequently achieved HIV VL < 50 copies/mL at the Week 24 time-point. In addition, subjects with only one VL value below 50 copies/mL at the Week 24 time-point in the absence of a second confirmatory reading were included. The most frequent reason for non-response was virologic failure observed in 31.7% of etravirine recipients and 52.6% of placebo recipients (Table 7); virologic failure could be either failure to respond or virologic rebound. Discontinuations due to adverse events (AE) were observed in 4.7% of etravirine recipients compared to 1.8% of placebo recipients. This analysis includes only deaths occurring prior to the Week 24 cut-off point, and differs from Table 15 in Safety Section 7.1.3. Table 15 describes all deaths during the treatment period including those that occurred after Week 24 of therapy.

Table 7: Outcome of Randomized Treatment at Week 24 by Snapshot Classification of Pooled Phase 3 trials¹

Virologic Response Data Specification	Etravirine (%) N=599	Placebo (%) N=604
HIV VL < 50 copies/mL at Week 24	358 (59.8)	243 (40.2)
Non-Responders		
Virologic Failures at Week 24	190 (31.7)	318 (52.6)
Death	9 (1.5)	15 (2.5)
Discontinued due to VF before Week 24	2 (0.3)	4 (0.7)
Discontinuation due to AE	28 (4.7)	11 (1.8)
Discontinuation due to other reasons	12 (2.0)	13 (2.2)

¹Discontinuations include subjects who discontinued before Week 24 excluding deaths

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

Further analyses of virologic responses were performed by FDA Statistical Reviewer, Dr. Fraser Smith. Refer to the Statistics Review of NDA 22-187 for more details.

As displayed in Tables 8 and 9, the efficacy results from the individual trials C206 and C216 were comparable, with only minor differences in the response rate (a slightly higher response rate in C216). Overall, more responders (HIV VL < 50 copies/mL) were observed in etravirine arm (59.8%) as compared to placebo arm (40.2%). Among subjects who did not achieve this endpoint, a greater proportion of subjects in etravirine arm achieved HIV VL < 400 copies/mL compared to placebo arm (16% etravirine vs. 11% placebo in C206; 13% etravirine vs. 11% placebo in C216) in Table 8. As expected, a higher proportion of subjects in the placebo arm did

not achieve even a 0.5 log₁₀ reduction in VL compared to placebo arm. A similar number of subjects discontinued treatment prior to Week 24 in both arms; the most frequent reason for discontinuation was virologic failure.

Table 8: Ordinal Categorical Responses using Snapshot Classification at Week 24, Study C206

Virologic Response Data, n (%)	Etravirine N = 304	Placebo N = 308
HIV VL < 50 copies/mL	176 (58)	121 (39)
VL ≥ 50 and < 400 copies/mL	48 (16)	34 (11)
VL > 400 copies/mL and reduction by 1 log ₁₀	16 (5)	20 (6)
0.5 to < 1 log ₁₀ drop	17 (6)	21 (7)
< 0.5 log ₁₀ drop	22 (7)	91 (30)
Discontinued prior to Week 24	25 (8)	21 (7)

N = number of subjects, n = number of observations

Note: The categories are mutually exclusive; no subject can be counted more than once.

Source: Statistical Reviewer's Analysis

Table 9: Ordinal Categorical Responses using Snapshot Classification at Week 24, Study C216

Virologic Response Data, n (%)	Etravirine N = 295	Placebo N = 296
HIV VL < 50 copies/mL	182 (62)	122 (41)
VL ≥ 50 and < 400 copies/mL	37 (13)	34 (11)
VL > 400 copies/mL and reduction by 1 log ₁₀	12 (4)	24 (8)
0.5 to < 1 log ₁₀ reduction	8 (3)	19 (6)
< 0.5 log ₁₀ reduction	31 (11)	81 (27)
Discontinued prior to Week 24	25 (8)	16 (5)

N = number of subjects, n = number of observations

Note: The categories are mutually exclusive; no subject can be counted more than once.

Source: Statistical Reviewer's Analysis

Primary Efficacy Variable

As stated previously, the primary efficacy parameter was the proportion of subjects who achieved HIV VL < 50 copies/mL at Week 24 and response rates were generally comparable between the studies (Table 10). The overall response rate was higher in etravirine subjects (59.8%) as compared to placebo subjects (40.2%).

Table 10: Response (HIV VL < 50 copies/mL) in Individual Phase 3 Trials and Pooled Data

	Study C206		Study C216		Pooled Data	
	TMC125 N=304	Placebo N=308	TMC125 N=295	Placebo N=296	TMC125 N=599	Placebo N=604
Proportion of Responders	176 (57.9)	121 (39.3)	182 (61.7)	122 (41.2)	358 (59.8)	243 (40.2)

Source: Statistical Reviewer's Analysis

In order to explore potential bias from use of ENF, an analysis was performed based on categorization of responders by 'de novo ENF users' and 'not de novo ENF users' for both studies (Table 11). In the etravirine arm, subjects with *de novo* ENF use had a better response (70%) than subjects without *de novo* ENF use (60%).

Table 11: Response (HIV VL < 50 copies/mL) by ENF Use in Combined Phase 3 Trials

ENF Use	Etravirine N=565	Placebo N=593
<i>De Novo</i> ENF	70% (102/145)	62% (99/159)
Re-Used/Not Used ENF	60% (251/420)	34% (149/434)

Source: Microbiology Reviewer's Analysis

An analysis evaluating the effect of PSS score on the response rate showed the response rates in the etravirine arm were greater than the placebo arm if subjects had PSS scores of 0-2, but the response rates were comparable between the arms if PSS scores were 3 or more (Table 12).

Table 12: Response (HIV VL < 50 copies/mL) by Baseline PSS Score in Combined Phase 3 Trials

PSS Score	Etravirine Arms N=565	Placebo Arms N=593
0	43% (40/93)	7% (7/95)
1	59% (120/205)	28% (63/225)
2	75% (112/150)	63% (102/162)
3	70% (63/90)	68% (52/76)
4	73% (16/22)	64% (14/22)
5		(3/3)
0-1	54% (160/298)	22% (70/320)
2+	73% (191/262)	65% (171/263)

*As-treated analysis

Source: Microbiology Reviewer's Analysis

In addition, an analysis was performed to evaluate the impact of ENF status and baseline PSS score on the response rate. Subjects in the placebo arm with PSS scores ≥ 3 had comparable response rates to the etravirine arms (Table 13). In the etravirine arms, subjects with De Novo ENF use had better response rates than subjects without De Novo ENF use if the baseline PSS score was 0-2, but response rates were comparable if the PSS score was ≥ 3 . These results re-emphasize that three or more active ARV drugs are required to obtain good response rates in treating HIV infection.

Table 13: Response (<50 copies/mL HIV-1 RNA) by Baseline PSS Score and ENF Use in Combined Studies C206 and C216

PSS Score	Etravirine Arms N=565		Placebo Arms N=593	
	De Novo ENF	Re-Used/Not Used ENF	De Novo ENF	Re-Used/Not Used ENF
0	-	43% (40/93)	-	7% (7/95)
1	59% (23/39)	58% (97/166)	37% (13/35)	26% (50/190)
2	76% (44/58)	74% (68/92)	67% (44/66)	60% (58/96)
3	71% (22/31)	69% (41/59)	74% (26/35)	63% (26/41)
4	76% (13/17)	60% (3/5)	65% (11/17)	60% (3/5)
5			3/3	
0-2	69% (67/97)	58% (205/351)	56% (57/101)	30% (115/381)
3+	73% (35/48)	69% (44/64)	73% (40/55)	63% (29/46)

* As-treated analysis

Source: Microbiology Reviewer's Analysis

Immunology

Overall, the mean change in CD4 cell count from baseline was 85.6 cells/mm³ in etravirine group and 66.8 cells/mm³ in placebo group (Table 14).

Table 14: Change from Baseline CD4 cell count in Pooled data from Phase 3 Trials

CD4 count, mean (cells/mm ³)	Etravirine N=599	Placebo N=604
Change from baseline at Week 24 (LOCF)	+85.6	+66.8
Change from baseline at Week 24 (NC=F)	+83.6	+65

Missing data imputed by LOCF=last observation carried forward

By Non completers = failures analysis, time points after discontinuation imputed by 0

Source: CDAD database for Studies C206, C216

Study TMC125-C227

Trial C227 was a Phase 2b study designed to assess the antiviral activity of etravirine 800 mg b.i.d. TF035 formulation (equivalent to the to-be-marketed dose 200 mg b.i.d. of F060 formulation) in HIV-infected subjects who were PI-naïve and with documented genotypic evidence of resistance to EFV, NVP and DLV after treatment with a first line NNRTI regimen. In brief,

suboptimal virologic response was observed in the etravirine treated group (59 subjects) compared to the active control group (57 subjects) who was receiving a PI-based therapy. Based on this data, the Applicant halted recruitment and prematurely discontinued the trial. The results of study C227 demonstrate no role for etravirine as part of a first-line regimen for treatment-naïve patients who are resistant to NNRTIs and susceptible to protease inhibitors, including those with primary NNRTI resistance. Details of design, trial population, efficacy results of C227 are described below.

C227 was a randomized, active-controlled, open-label, Phase 2b trial evaluating antiviral activity of etravirine 800 mg b.i.d. (TF035) at 24 weeks as part of an ARV regimen containing 2 NRTIs over 48 weeks of treatment. The trial was conducted in Thailand, South Africa, Latin America and Europe in PI-naïve subjects with documented genotypic evidence of resistance to EFV, NVP and DLV after treatment with a first line NNRTI regimen, or after treatment with an NNRTI, either alone or with other ARVs, for prevention of mother to child transmission. An initial design with sample size of 120 subjects was modified to show non-inferiority of etravirine by increasing the sample size to 300 subjects. Subjects were randomized 1:1 to receive etravirine 800 mg b.i.d. TF035 formulation (equivalent to to-be-marketed dose 200 mg b.i.d. of F060 formulation) or an active control. The control group received an investigator-selected PI in addition to 2 NRTIs. ENF use was not allowed; subjects had to be sensitive to the 2 selected NRTIs used in the regimen.

The study was conducted in PI-naïve HIV-1 infected subjects with evidence of NNRTI resistance from first-line NNRTI containing therapy. At the time recruitment was halted, 116 subjects had taken medication including 59 subjects in the etravirine group and 57 subjects in the control group. At baseline, the median number of NRTI mutations was 2 (range 0-6) in the etravirine group and 1 (range 0-6) in the control group (from Tibotec list of mutations). The most frequently used NRTIs in the underlying ART during the treatment period were zidovudine (55%), TDF (45%) and didanosine (31%). Nineteen (33%) subjects in the control group and 20 subjects (34%) in the etravirine group re-used an NRTI from the screening period. TDF was the most common new NRTI and was used by 51% and 37% of subjects in the etravirine and control groups, respectively. Initial sensitivity analysis to NRTIs by Antivirogram® and virco®TYPE HIV-1 demonstrated 85% of etravirine subjects and 87% of control subjects used 2 sensitive NRTIs. Further analysis of the baseline genotype using a more sensitive version of virco®TYPE HIV-1 showed only 37% of subjects using 2 sensitive NRTIs in the etravirine group. With respect to PI used in the control group, 63% of subjects used LPV/rtv and 32% used ATV/rtv.

The identification of a suboptimal virologic response in some of the etravirine-treated subjects prompted an early unplanned evaluation of the data in this trial at Week 12. Results showed

fewer subjects achieved plasma HIV VL < 50 copies/mL in the etravirine group (25.0%) compared to the control group (52.8%), and fewer subjects achieved a plasma VL < 400 copies/mL in the etravirine group (47.5%) compared to the control group (84.9%). An initial viral load decline of approximately 1.3 log₁₀ was not sustained past 8 weeks. The Applicant's analysis of efficacy data suggests that the combination of both NNRTI resistance and baseline NRTI resistance were associated with virologic response, and with increasing level of resistance to both of these classes, there was a lesser change in viral load at Week 12 (Figure 2).

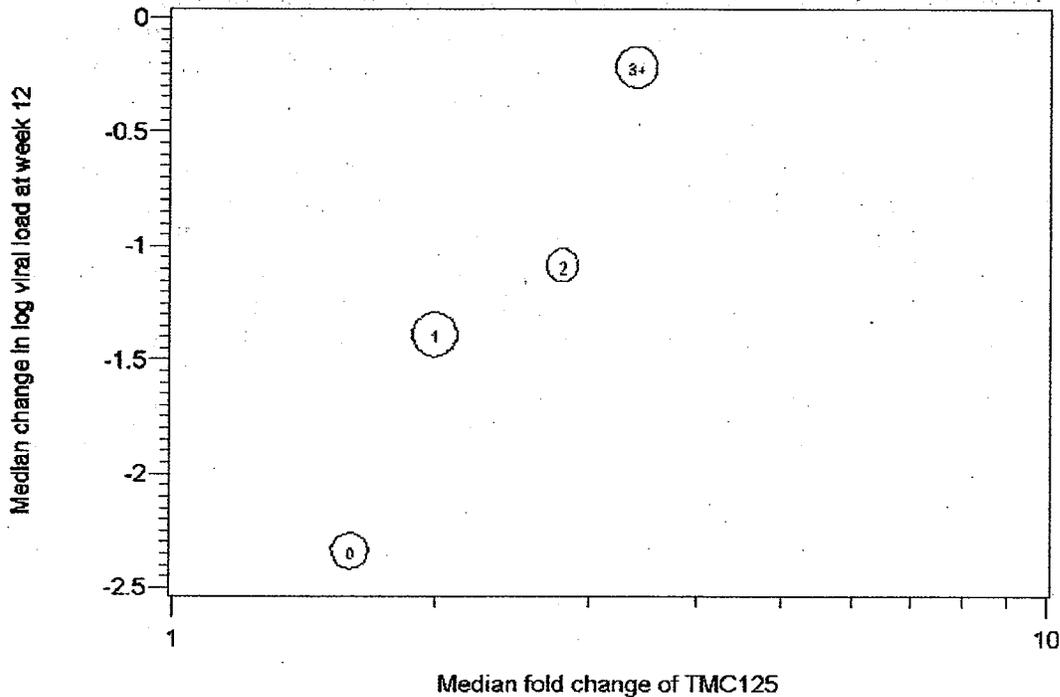
Based on these data, the Applicant halted recruitment and prematurely discontinued treatment with etravirine. This decision was endorsed by the independent DSMB for the trial. All subjects receiving etravirine were recommended to be switched to an investigator-selected PI-containing ARV regimen and followed for an additional 24 weeks after the treatment switch. Subjects in the control group who were still in the trial at the time recruitment was halted were followed for at least 24 weeks (with the same standard of care regimen) and then discontinued the trial.

In conclusion, the 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.

**APPEARS THIS WAY
ON ORIGINAL**

Figure 2: Applicant's Display of Effect of Baseline NNRTI and NRTI Resistance on the Change in Viral Load from Baseline at Week 12 in Study TMC125-C227

Tibotec Confidential Information



The size of the bubble is driven by the number of subjects.

The label inside the bubble denotes the number of mutations (TAM mutations + M184I, M184V, K65R).

Source: Post-hoc analysis

Source: Applicant's Summary of Clinical Efficacy

6.1.5 Clinical Microbiology

This section provides a brief summary of the FDA Microbiology Review of NDA 22-187. Please refer to the review by Dr. Lisa Naeger for details.

Mechanism of Action

Etravirine binds directly to RT and blocks the RNA-dependent and DNA-dependent DNA polymerase activities by causing a disruption of the enzyme's catalytic site.

Activity

Etravirine exhibits activity against laboratory strains and clinical isolates of wild-type HIV-1 in acutely infected T-cell lines, human peripheral blood mononuclear cells, and human monocytes/macrophages with median EC_{50} values ranging from 0.9 to 5.5 nM (i.e., 0.4 to 2.4