

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
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STATISTICAL REVIEW(S)



U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Pharmacoepidemiology and Statistical Science
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION CLINICAL STUDIES

NDA/Serial Number: 22187 / N000

Drug Name: Intelence® (TMC125; etravirine) F060 200 mg tablets, administered twice daily (200 mg b.i.d.)

Indication(s): Treatment of HIV-1 infection in combination with other antiretroviral agents in treatment-experienced patients

Applicant: Tibotec Research & Development

Date(s):

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Biometrics Division: DBIV

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1: EXECUTIVE SUMMARY

1.1 Conclusions and Recommendations

On July 17, 2007, Tibotec submitted the NDA to seek the Agency's accelerated approval of TMC125 (Intelence[®]; etravirine), a non-nucleoside reverse transcriptase inhibitor (NNRTI) for the treatment of HIV-1 infection in treatment-experienced adults. The dosage was TMC125 200 mg administered orally, twice daily (bid) following a meal.

The statistical reviewer evaluated efficacy results based on all 24-week data from two pivotal Phase III trials in treatment-experienced [i.e., Studies TMC125-C206 (DUET-1) and TMC125-C216 (DUET-2)] in the original submission which included the data up to database cutoff dates of February 9, 2007 for DUET-1 and January 18, 2007 for DUET-2.

The statistical reviewer concluded that TMC125 200 mg bid in combination of the background regimen (BR) had superior efficacy over the placebo in combination of BR for the treatment of HIV treatment-experienced adults who had previously taken or were retaking enfuvirtide. Among the non de-novo ENF subjects, 56% of the TMC125 subjects had HIV viral loads <50 copies/mL at Week 24 compared to only 34% of the placebo subjects.

In contrast, TMC125 200 mg bid appeared to offer less benefit compared to placebo in de novo enfuvirtide subjects. Among the de-novo ENF subgroup, 67% of the TMC125 subjects had HIV RNA viral loads <50 copies/mL at Week 24 compared to 62% of the placebo subjects.

The overall percentage of subjects with any adverse events was comparable in TMC125 and placebo treatment groups. However, rashes were more prevalent in TMC125 subjects than placebo subjects. Compared to placebo, the statistical reviewer also found somewhat higher increases in LDL cholesterol from baseline in TMC125 subjects.

1.2 Brief Overview of Clinical Studies

TMC125 is a non-nucleoside reverse transcriptase inhibitor (NNRTI) whose efficacy, according to the applicant was established in vitro in MT4 cells.

Tibotec conducted two pivotal Phase III, randomized, double-blind, placebo-controlled trials to evaluate the long-term efficacy, tolerability, and safety of TMC125 as part of an antiretroviral therapy (ART) containing TMC114/ritonavir (RTV) as an investigator-selected optimized background regimen (OBR) in treatment-experienced HIV-1 infected subjects. In addition, changes in the HIV-1 genotype, drug susceptibility, and the population pharmacokinetics of TMC125 will be assessed. A pharmacokinetic substudy was to be performed at selected sites in each trial. Safety and tolerability were to be documented throughout the two trials.

Six hundred HIV-1 infected subjects on a stable but virologically failing regimen were to be included in each trial. Subjects should have had at least one documented NNRTI resistance-associated mutation (either at screening or from historical genotype reports), an HIV-1 plasma viral load > 5000 RNA copies/mL at screening, and at least 3 documented primary protease inhibitor (PI) mutations. Subjects were randomized in a 1:1 ratio to either TMC125 (200 mg b.i.d.) or to matching placebo; both in combination with TMC114/RTV (600/200 mg b.i.d.) and an investigator-selected OBR of at least 2 antiretrovirals (ARVs) consisting of nucleoside reverse transcriptase inhibitor(s) (NRI[s]) with or without enfuvirtide (ENF). The use of ENF is optional and de novo use of ENF was to be limited to 40% of the overall trial population in each study. Each trial had a screening period of a maximum of 6 weeks, a 48-week treatment period, and a 4-week follow-up period.

The possibility to extend the treatment period will be provided for subjects, who in the opinion of their investigators are deriving clinical benefit from their ART. For each subject, the optional extension will immediately follow the 48-week treatment period and will continue until the subject has been treated for 96 weeks. As long as subjects continue to participate in the trial they were to remain on the same ART as started during the initial 48 weeks of treatment. Initially, the optional extension phase is to continue in a blinded manner; however, once the database for the 48-week analysis has been locked, the treatment code will be broken and subjects can continue treatment within the trial in an open-label fashion.

Table 1: Summary of Reviewed Studies

Study ID	Study Design	Treatment Arms and Number of Randomized Patients	Geographic Region
DUET-1 (Study TMC125-C206)	Phase III, multicenter, double-blind, randomized, placebo-controlled study to evaluate the safety and antiretroviral activity of TMC125 200 mg bid in combination with an OBT vs. OBT alone in HIV-infected treatment-experienced patients	TMC125 200 mg b.i.d.: n=304 Placebo: n=308	Primarily USA, Latin America, France, Thailand.
DUET-2 (Study TMC125-C216)	Phase III, multicenter, double-blind, randomized, placebo-controlled study to evaluate the safety and antiretroviral activity of TMC125 200 mg bid in combination with an OBT vs. OBT alone in HIV-infected treatment-experienced patients	TMC125 200 mg b.i.d.: n=295 Placebo: n=296	USA, Western Europe, Canada, Australia.

1.3 Statistical Issues and Findings

Overall, based on the data submitted, the following results were observed:

- In the two pivotal Phase III studies (TMC125-C206 and TMC125-C216), approximately 60% of the patients in the TMC125 treatment group had HIV RNA viral load <50 copies/mL at Week 24 compared to 40% of the placebo patients.

- TMC125 efficacy compared to placebo was more impressive for patients who never used or were re-using enfuvirtide than for de-novo enfuvirtide patients. Among the de-novo ENF subgroup, 67% of the TMC125 subjects had HIV RNA viral loads <50 copies/mL at Week 24 compared to 62% of the placebo subjects (p=0.427) while among the non de-novo ENF subjects, 56% of the TMC125 subjects had HIV viral loads <50 copies/mL at Week 24 compared to only 34% of the placebo subjects (p<0.0001).

To evaluate the robustness of the efficacy results of the two Phase III trials in the treatment-experienced patients, the applicant used different approaches to impute missing data and the statistical reviewer used a snapshot approach instead of the TLOVR algorithm and different rules of counting non-responders who discontinued early as virologic failures. The statistical reviewer's results were quite similar to the applicant's.

With regards to the mortality, there were 15 placebo deaths and 9 TMC125 deaths based on the database lock for the NDA submission.

Rash (any type) combining all rash-related terms reported during treatment and/or follow-up was reported in 17% of the subjects in the TMC125 treatment group compared to only 9% of the placebo group. AEs with at least grade 2 severity, determined by the investigator to be at least possibly related to the investigational medication occurring in at least 2.0% of subjects in the TMC125 group that appeared to be higher in TMC125 patients included rash (individual preferred term, 4.8% vs. 1.0% in the placebo group), nausea (3.2% vs. 1.3%) and metabolism and nutrition disorders (4.7% vs. 1.8%). None of the placebo subjects and 6 (1%) of the TMC125 subjects had grade 3 or 4 rashes.

After 24 weeks, mean calculated LDL levels increased from baseline by 11 mg/dL to 104 mg/dL in the placebo treatment group and by 14 mg/dL to 108 mg/dL in the TMC125 treatment group. At week 32, when less than half the randomized subjects remained, mean calculated LDL levels increased by 9 mg/dL in the placebo treatment group to 111 mg/dL and increased by 18 mg/dL in the TMC125 treatment group to 117 mg/dL.

After 24 weeks, the proportion of patients with increases in calculated LDL levels from baseline exceeding 10 mg/dL was 48% in the placebo treatment group and 56% in the TMC125 treatment group. This difference was statistically significant (p=0.02).

Statistically significant differences between TMC125 and placebo were also observed at Week 20 and 32 with non-significant statistical trends favoring placebo at Weeks 12 and 16:

An additional analysis used the last calculated LDL value up to and including Week 24 but prior to use of any new lipid lowering agents. In this analysis, the proportion of patients with increases in calculated LDL levels from baseline exceeding 10 mg/dL was 49% in the placebo treatment group and 56% in the TMC125 treatment group. These results were quite similar to the Week 24 results except they were not quite statistically significant (p=0.06).

As part of the review process, the FDA requested the copies of original source documents for treatment randomization schedules generated for each patient in the two DUET trials. In addition, the review team requested Tibotec's standard operating procedures for randomization schedule generation, unblinding and release of randomization codes along with corresponding flow charts.

The FDA asked the applicant to provide the address and phone number of the central laboratory used for the two DUET trials. The FDA asked the applicant if external vendors were used to generate randomization codes for the two studies, and if so, to provide their addresses and telephone numbers and to disclose to the FDA any financial or partnering agreements between Tibotec and the external vendors. If external vendors were used to generate the treatment allocation codes for the two DUET trials, the FDA asked to have the external vendors send the treatment allocation codes directly to the FDA along with information on when the vendors received/generated the original codes. The FDA also requested certification (from the external vendors, if they were used to generate treatment allocation codes for studies TMC125-C206 and TMC125-C216) that the documents of the treatment allocation codes were the original source documents and that the treatment allocation codes were generated prior to study initiations.

In addition, the FDA requested all other source documents of treatment allocation codes. (e.g., from the applicant's Clinical Pharmaceutical Operations or drug packaging group).

2. INTRODUCTION

2.1 Overview

TMC125 is a non-nucleoside reverse transcriptase inhibitor (NNRTI) whose efficacy, according to the applicant was established in vitro in MT4 cells.

Tibotec conducted two pivotal Phase III, randomized, double-blind, placebo-controlled trials to evaluate the long-term efficacy, tolerability, and safety of TMC125 as part of an antiretroviral therapy (ART) containing TMC114/ritonavir (RTV) as an investigator-selected optimized background regimen (OBR) in treatment-experienced HIV-1 infected subjects.

Six hundred HIV-1 infected subjects on a stable but virologically failing regimen were to be included in each trial. Subjects should have had at least one documented NNRTI resistance-associated mutation (either at screening or from historical genotype reports), an HIV-1 plasma viral load > 5000 RNA copies/mL at screening, and at least 3 documented primary protease inhibitor (PI) mutations. Subjects were randomized in a 1:1 ratio to either TMC125 (200 mg b.i.d.) or to matching placebo; both in combination with TMC114/RTV (600/100 mg b.i.d.) and an investigator-selected OBR of at least 2 antiretrovirals (ARVs) consisting of nucleoside reverse transcriptase inhibitor(s) (NRI[s]) with or without enfuvirtide (ENF). The use of ENF is optional and de novo use of ENF was to be limited to 40% of the overall trial population in each study. Each trial had a

screening period of a maximum of 6 weeks, a 48-week treatment period, and a 4-week follow-up period.

The possibility to extend the treatment period will be provided for subjects, who in the opinion of their investigators are deriving clinical benefit from their ART. For each subject, the optional extension will immediately follow the 48-week treatment period and will continue until the subject has been treated for 96 weeks. As long as subjects continue to participate in the trial they were to remain on the same ART as started during the initial 48 weeks of treatment. Initially, the optional extension phase is to continue in a blinded manner; however, once the database for the 48-week analysis has been locked, the treatment code will be broken and subjects can continue treatment within the trial in an open-label fashion.

Table 1 below summarizes the studies reviewed in this report.

Table 2: Summary of Reviewed Studies

Study ID	Study Design	Treatment Arms and Number of Randomized Patients	Geographic Region
Study C206	Phase III, multicenter, double-blind, randomized, placebo-controlled study to evaluate the safety and antiretroviral activity of TMC125 200 mg bid in combination with an OBT vs. OBT alone in HIV-infected treatment-experienced patients	TMC125 200 mg: n=304 placebo: n=308	Primarily United States, South America, and France plus a few subjects from Central America, Puerto Rico and Thailand.
Study C216	Phase III, multicenter, double-blind, randomized, placebo-controlled study to evaluate the safety and antiretroviral activity of TMC125 200 mg bid in combination with an OBT vs. OBT alone in HIV-infected treatment-experienced patients	TMC125 200 mg: n=295 placebo: n=296	United States, Western Europe, Canada, and Australia.

2.2 Data Sources

The application was electronic and can be found in FDA internal network drive of \\Cdsub1\evsprod\NDA022187.

The applicant informed FDA that copies of laboratory source documents of HIV RNA-Amplicor and HIV RNA-Ultrasensitive assay results and CD4+ cell counts data were available at the sites.

The central laboratory used for the two pivotal DUET studies was _____
 _____ The applicant provided _____ addresses and phone numbers in the United States, Europe, Singapore and Australia.

3. STATISTICAL EVALUATION

3.1 Evaluation of Efficacy Results in Studies TMC125-C206 and TMC125-C216

3.1.1 Study Design and the Dynamic Randomization Process

Studies C206 and C216 were identical in study design with the only difference arising in that Study C206 was conducted primarily in the United States and Latin America while Study C216 was conducted primarily in the United States and Europe. Both studies were multi-center, double-blind, randomized, placebo-controlled trials in heavily pretreated HIV populations who had limited or no treatment options available. These patients had screening HIV RNA > 5000 copies/mL and documented genotypic resistance to currently available NNRTIs by having at least 1 NNRTI resistance-associated mutation present and 3 or more documented primary protease inhibitor (PI) mutations.

The primary objective of the studies was to show superiority of TMC125 compared to placebo as part of an ART containing TMC114/RTV and an investigator-selected OBT for the primary endpoint [the proportion of subjects with undetectable plasma viral load values (< 50 copies/mL) at Week 24] in treatment-experienced HIV-1 infected subjects.

Subjects were randomized 1:1 according to a central randomization schedule, to either TMC125 (200 mg b.i.d.) or a placebo group, both in combination with TMC114/RTV (600/100 mg b.i.d.) and investigator-selected OBR of at least two antiretrovirals (ARVs) consisting of nucleoside reverse transcriptase inhibitors (NRTIs) with or without enfuvirtide (ENF). The randomization was stratified by the intended use of ENF in the underlying ART (not using ENF, using ENF de novo, or re-using ENF; i.e., experienced or using), previous use of TMC114 [durinavir (DRV)] (yes/no) and screening plasma viral load (< or \geq 30,000).

Randomization was performed at baseline using a central Interactive Voice Response System (IVRS), using an adaptive minimization technique with biased coin assignment to ensure balance across treatment groups in each stratum and random treatment assignment. Since the two DUET studies were double-blinded trials, treatment codes were not to be distributed to the investigator or patients. The applicant stated that neither they nor the investigators knew which treatment group the subjects were randomized to. In the primary analysis, treatment codes were to be revealed by Tibotec after the database lock.

In Section 5.4.8 of the protocols for the two DUET trials, the sponsor mentioned that the code should only be broken in case of an emergency if further treatment of the subject is dependent on the investigational medication he/she had been receiving. Only in those cases may the investigator call the IVRS to break the treatment code and the sponsor was to have been notified when a site broke the code.

In response to an FDA query about whether external vendors were used to generate or manage the treatment allocation codes for the two DUET trials, Tibotec informed FDA that _____ was the vendor used to generate and manage the treatment codes for both DUET trials.

In response to the FDA query about disclosing any financial or partnering agreements between Tibotec and the external vendor, the applicant provided FDA with a work order for _____. According to this document, the _____ toll-free telephone Voice System operates 24 hours/day, 7 days/week from all locations operating in the study and prompts callers to identify themselves by entering a user identification number and numeric password. These two identifying numbers serve to verify the caller represents a valid and active site/investigator or Project Team member.

_____ generated and sent confirmation faxes to the site and /or Tibotec (typically reports including patient enrollment and inventory summaries). The confirmation faxes include relevant patient information such as date of randomization and medication assigned. Site members are able to review their patients via an audio report. Upon entering a patient's ID into the IVRS/IWRS (Interactive Voice Response System / Interactive Web Response system), users at the sites can receive all pertinent patient information, including date of last visit and last medication assigned.

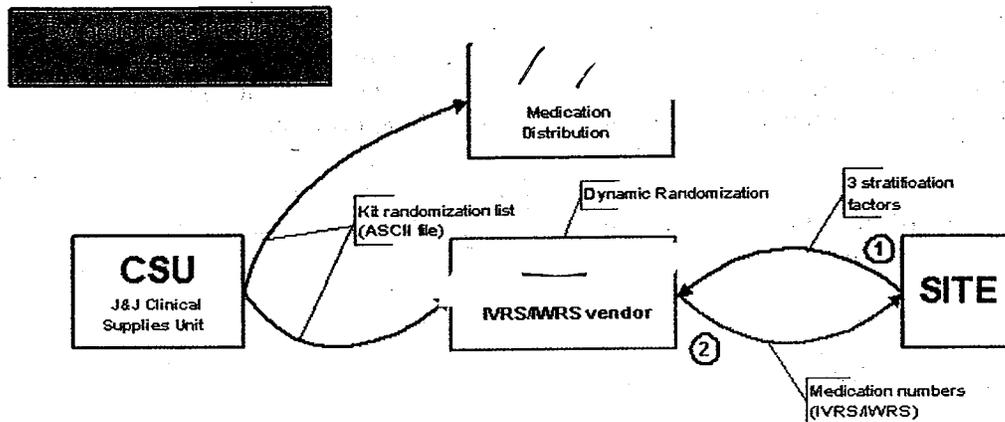
The applicant informed the FDA that a dynamic randomization system using a minimization technique was used in the DUET trials for the three pre-specified stratification variables. As a consequence of this randomization technique, there were no fixed randomization lists available prior to enrollment of the patients in either study. The external vendor _____ was used to generate and manage the treatment allocation codes for both DUET studies via their IVRS/IWRS.

The duet trials used a Pocock and Simon minimization randomization process that is designed to target a 1:1 treatment arm randomization balance. Unlike a list-based randomization scheme, there was no set treatment randomization schedule pre-determined and pre-loaded into the IVRS/IWRS. Rather, the algorithm evaluated previous treatment assignments across the different strata of the stratification factors to determine the probability of treatment assignment.

The source document for this IVRS/IWRS randomization algorithm is Section 13.1 of the Requirements Specification from _____ entitled 'IVRS Requirement Specifications.' This document was signed on 23 September 2005, prior to the first randomization in the study.

Once a subject was found to be eligible for the trial, the investigator contacted the IVRS/IWRS and provided the subjects details including the patient's data of the 3 stratification factors (step 1 in dynamic randomization process, Flowchart 1). After assignment of the treatment group, the IVRS/IWRS provided the numbers of the allocated medication bottles to the investigator (step 2 in the dynamic randomization process, Flowchart 1).

For each packaging order, Johnson & Johnson Clinical Supplies Unit (CSU) provided medication kit randomization lists to _____ and the distribution contractor _____ in ASCII file format. These lists did not provide individual patient treatment codes, but had information for unblinding the medication bottles (see Flowchart 1).



Flowchart 1: Dynamic Randomization Process

Source: Tibotec's Responses to FDA Statistics Questions in Filing Letter
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In response to our request for certification that the documents were the original source documents and that the treatment allocation codes were generated/received prior to study initiation, the applicant informed us that the Requirements Specification defined the randomization algorithm and was generated and approved prior to the first patient randomization on 8 December 2005. The testing of the randomization algorithm specified in Section 13.1 of the Requirement Specification was completed successfully and the associated functionality was released prior to the first patient randomization. The applicant attached PDF copies of the two validation test grids for the IVRS that verified the randomization algorithm of the Requirements Specification (signed and dated by employees of _____, as well as a PDF copy of the initial release notice for protocols TMC125-C206 and TMC125-C216 by _____ dated Dec 7, 2005.

In response to our request for standard operating procedures for randomization treatment code generation, unblinding and release of randomization codes, along with corresponding flow charts the applicant had the following responses:

The release of the randomization codes is described below along with a corresponding flowchart (Flowchart 2).

The parties with access to treatment codes included

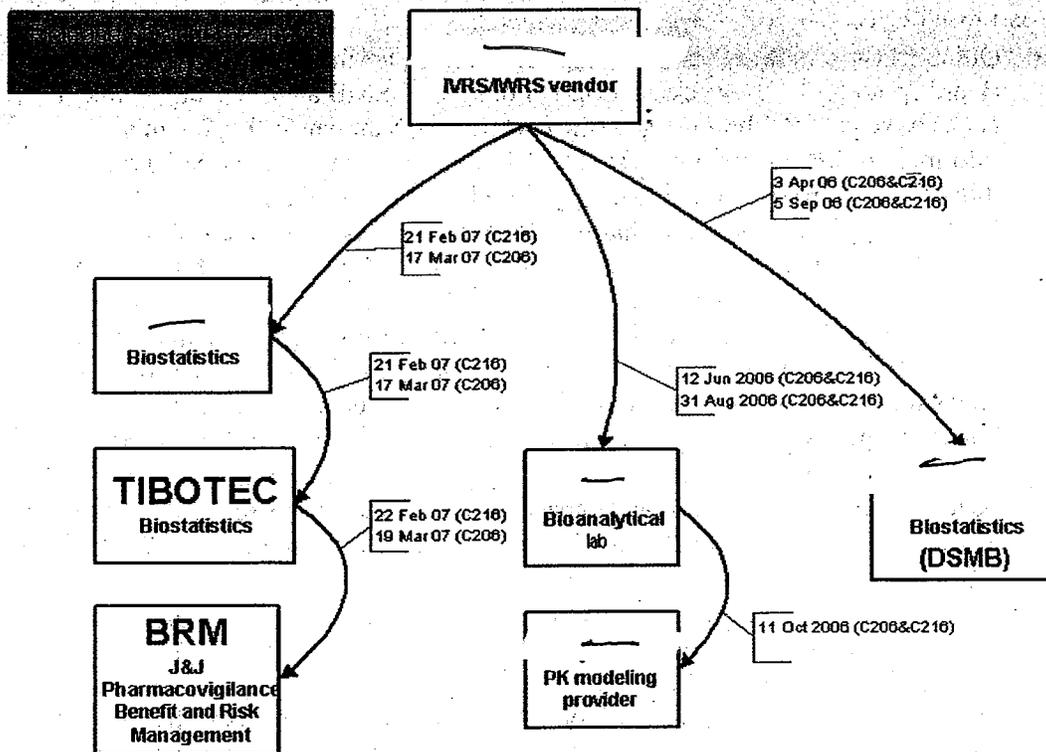
- _____ for conducting the analyses for the Data Safety Monitor Board (prior to the 24-week analysis). For Open DSMB analyses the treatment codes were partially broken up to the code level (treatment A, B), but this information was not communicated to Tibotec. The chair of the DSMB did not think it was necessary to completely unblind the treatment codes
- _____ for the bioanalysis of TMC125 plasma concentrations (prior to the 24-week analysis). _____ was allowed to be unblinded prior to the 24-week analysis in order to allow bioanalysis of TMC125 plasma concentrations in patients randomized to TMC125 and not placebo. _____ provided the randomization codes for both trials to _____ (first transfer for patients on 12 Jun 2006, second transfer when all patients were randomized on 31 Aug 2006).
- _____ PK modeling (prior to the 24-week analysis). _____ was allowed to be unblinded before the formal database lock in order to prepare the PK modeling analysis. _____ was provided with the randomization code through the data transfers received from _____
- _____, the CRO who performed the primary Week 24 analyses of both DUET studies and received the randomization codes after the official 24-week analysis database lock. Randomization codes were received by _____ on 21 Feb 2007 and 17 Mar 2007 for studies C216 and C206, respectively. _____ provided the codes to Tibotec Biostatistics on the same day for both studies.
- Johnson & Johnson Pharmacovigilance Benefit and Risk Management (BRM). Single cases in the BRM Worldwide Safety Database were to be unblinded if a serious adverse event (SAE) met expedited reporting requirements. The R&D Unit/Operating Company was to fully disclose treatment assignment information once a blinded study reached an analysis time point at which the blind needed to be broken and where the results of the unblinded data was to be shared with either investigators, Tibotec staff, or external personnel.

Note: Database Lock dates for DUET-trials for the 24-week Analyses were:

- 16 Mar 2007 for TMC125-C206
- 20 Feb 2007 for TMC125-C216

Access to emergency unblinding via the IVRS/IWRS for safety reasons was restricted to the following designees:

- Principal investigator
- BRM
- DSMB chair



Flowchart 2: Release of randomization codes

Source: Tibotec's Responses to FDA Statistics Questions in Filing Letter

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3.1.2 Efficacy and Safety Assessments

Viral load testing was performed using 2 methods: the standard (lower limit of quantitation=400 copies/mL) and the ultra-sensitive (lower limit of quantitation = 50 copies/mL) method. The ultra-sensitive method was used for the primary endpoint for subjects with different samples on the same sample date, unless the sample was right censored (above the upper limit of quantitation).

Missing baseline viral load data were imputed with screening data, if available.

Imputation of left-censored values: values below the detection limit (lower limit of quantitation) were scored at 49 in the analysis, unless explicitly specified differently.

Imputation of right-censored values occurred using diluted retests in cases where HIV RNA viral loads were above the upper limit of quantitation. In cases where no absolute value could be obtained from this diluted retesting, the viral load was scored at 750,001 copies/mL in the analysis, unless explicitly specified differently.

During the double-blind phase, HIV RNA and CD4 cell counts were to be determined at Randomization (Day 1), Weeks 2, 4, 8, 12, 16, 20, 24, 32, 40, and 48 with a Week 52 post-treatment follow-up period 30-35 days after the final/withdrawal visit. Unscheduled visits may have been performed for safety / tolerability reasons.

Virologic failure due to a lack of response was defined as:

- Plasma viral load decline of 0.5 log₁₀ from baseline by Week 8
- Plasma viral load decline of <1.0 log₁₀ from baseline by Week 12

Virological failure due to a loss of response was defined as 2 consecutive measurements of plasma viral load > 0.5 log₁₀ above the nadir after a minimum of 12 weeks of treatment.

Confirmation of virologic failures should have been done at the next planned visit or at an unscheduled visit. There should be a minimum 2-week time interval between such plasma viral load assessments.

There is an optional extended treatment period lasting up to Week 96. All subjects who are prematurely withdrawn from the trial will be followed for survival until the last follow-up visit of the last subjects in the trial, unless they withdraw consent.

Investigators will be asked to provide minimal information about the survival of the subjects every 6 months. For any fatal event, investigators will be asked to provide information about the cause of death.

Subjects from either treatment arm not achieving a 1 log decline from baseline in plasma viral load at Week 24 or subjects experiencing a viral rebound as evidenced by 2 consecutive plasma viral measurements at least 0.5 log above nadir at Week 24 or later

will have the opportunity to receive TMC125 in combination with TMC14/RTV in an open-label rollover trial (TMC125-C217).

Subjects who have been treated for at least 48 weeks in the trial and are in the opinion of the investigator not responding well to the therapy will have the possibility to enroll in the open-label rollover trial TMC125-C217 after having performed the 48-week visit. For these subjects, the treatment code can be individually unblinded before entering the rollover trial, if requested by the investigator and after approval of the sponsor.

The following time windows were allowed:

- For visits at Week 2: ± 2 days;
- For visits at Weeks 4, 8, 12, 16, 20 and 24: ± 4 days;
- For visits from Week 32 onwards: ± 7 days;
- Follow-up visit: 30-35 days after the Final/Withdrawal visit.

Unscheduled visits could be performed for safety / tolerability reasons or for confirmation of virologic failure. However there should have been a minimum 2-week time interval between such assessments.

The following time windows were to be used for the analyses:

Phase	Visit	Target day	Analysis time point	Time interval (days)
Screening	1		Screening	$\rightarrow -42$
Treatment	2	1	Baseline	Day -5 \rightarrow 1
	3	15	Week 2	Day 2 – Day 21
	4	29	Week 4	Day 22 – Day 42
	5	57	Week 8	Day 43 – Day 70
	6	85	Week 12	Day 71 – Day 98
	7	113	Week 16	Day 99 – Day 126
	8	141	Week 20	Day 127 – Day 154
	9	169	Week 24	Day 155 – Day 196
	10	225	Week 32	Day 197 – Day 252
	11	281	Week 40	Day 253 – Day 308
	12	337	Week 48	Day 309 – Day 364
	13 ^a	393	Week 56	Day 365 – Day 420
	14	449	Week 64	Day 421 – Day 476
15	505	Week 72	Day 477 – Day 546	
16	589	Week 84	Day 547 – Day 630	
17	673	Week 96	\geq Day 631	
Follow-up	13/18	32	30-35 days after Final / Withdrawal Visit	

^a A 48-week extension treatment period is optional (Protocol Amendment IV). The visit numbering after visit 12 depends on whether a subject will enter the extension period or not.

If 2 visits fell within the same interval, the one closest to the target day was used in the analysis. If the distances of 2 visits were equally close to the target day, the latest visit was used.

The applicant counted the end date of treatment as $\min(\max[\text{last TMC125/Placebo intake date} + 2 \text{ days}, \text{last TMC114 intake date} + 2 \text{ days}], \text{date of last contact})$.

If the subject died, the applicant counted the end date of treatment as $\min(\max[\text{last TMC125/Placebo intake date} + 2 \text{ days}, \text{last TMC114 intake date} + 2 \text{ days}], \text{date of death})$.

The statistical reviewer did not add 2 days to the end of treatment to compute discontinuation days.

3.1.3 Efficacy Endpoints

The primary efficacy endpoint in the two TMC125 DUET studies was the proportion of patients achieving HIV RNA <50 copies/mL at Week 24.

The secondary efficacy endpoints included the following variables.

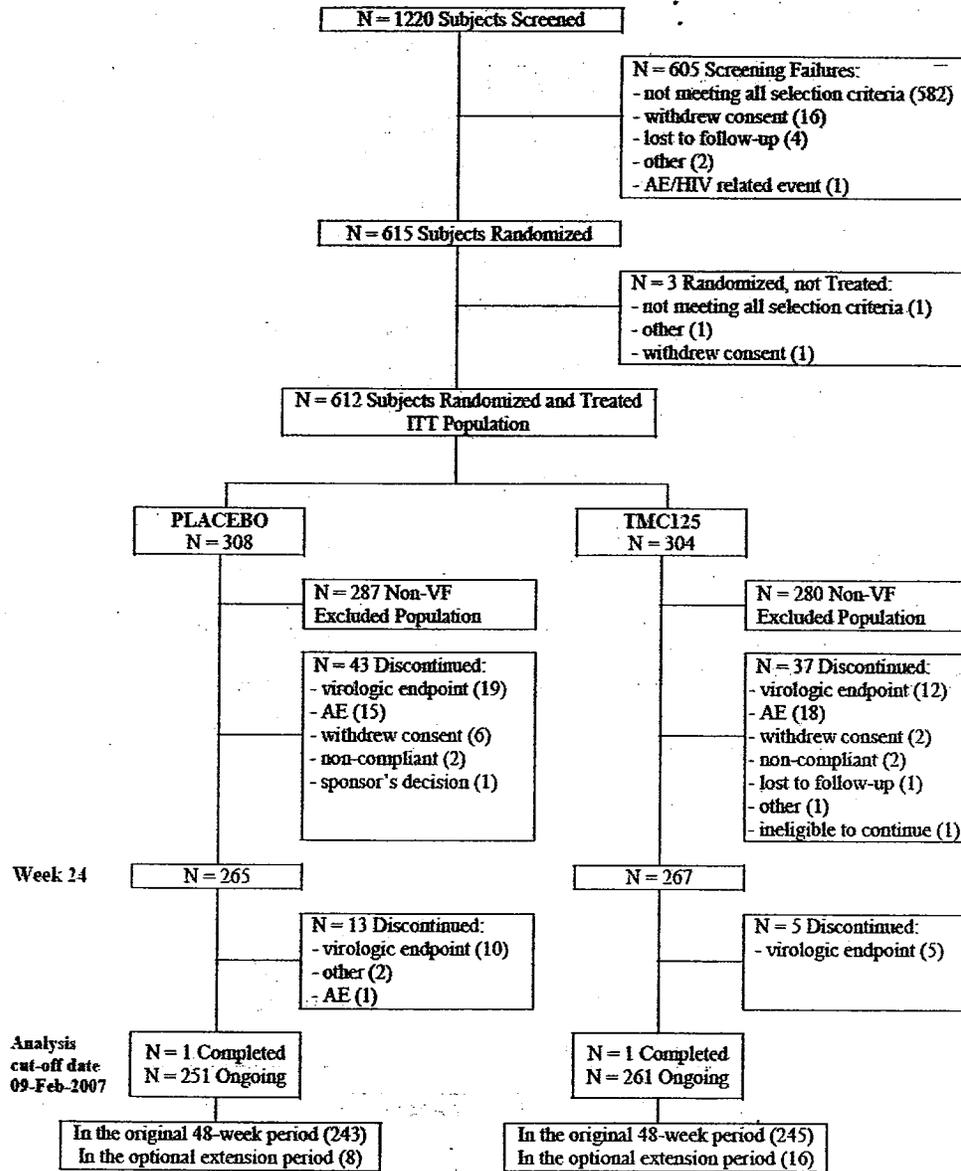
- 1) Virologic response defined as:
 - % of subjects with plasma viral load < 50 copies/mL at all other time points other than the Week 24 time point,
 - % of subjects with plasma viral load < 400 copies/mL at all time points,
 - % of subjects with at least a 1 \log_{10} decrease in viral load compared to baseline at all time points;
- 2) Time to reach first virologic response for the definitions of viral load < 50 or < 400 copies/mL or a 1.0 \log_{10} drop in plasma viral load from baseline. Subjects who never reached plasma HIV-1 RNA levels < 50 or 400 copies/mL or a 1.0 \log_{10} drop in plasma viral load from baseline were censored at their last available time point;
- 3) Time to loss of virologic response for the definitions of viral load < 50 and < 400 copies/mL or a 1.0 \log_{10} drop in plasma viral load from baseline. Only subjects who achieved the virologic response were included in these analyses. Subjects who did not lose the virologic response were censored at their last available time point;
- 4) Time to virologic failure for the definitions of viral load < 50 and < 400 copies/mL. Subjects who never achieved the virologic response were counted as failures as of Day 1;
- 5) change in \log_{10} plasma viral load from baseline at all time points;
- 6) Time-averaged difference (DAVG) over 24 weeks;
- 7) Change in CD4⁺ cell count (absolute and %);

8) Phenotype and genotype determinations including effects on plasma viral load response.

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3.1.4 Patient Disposition, Demographic and Baseline Characteristics

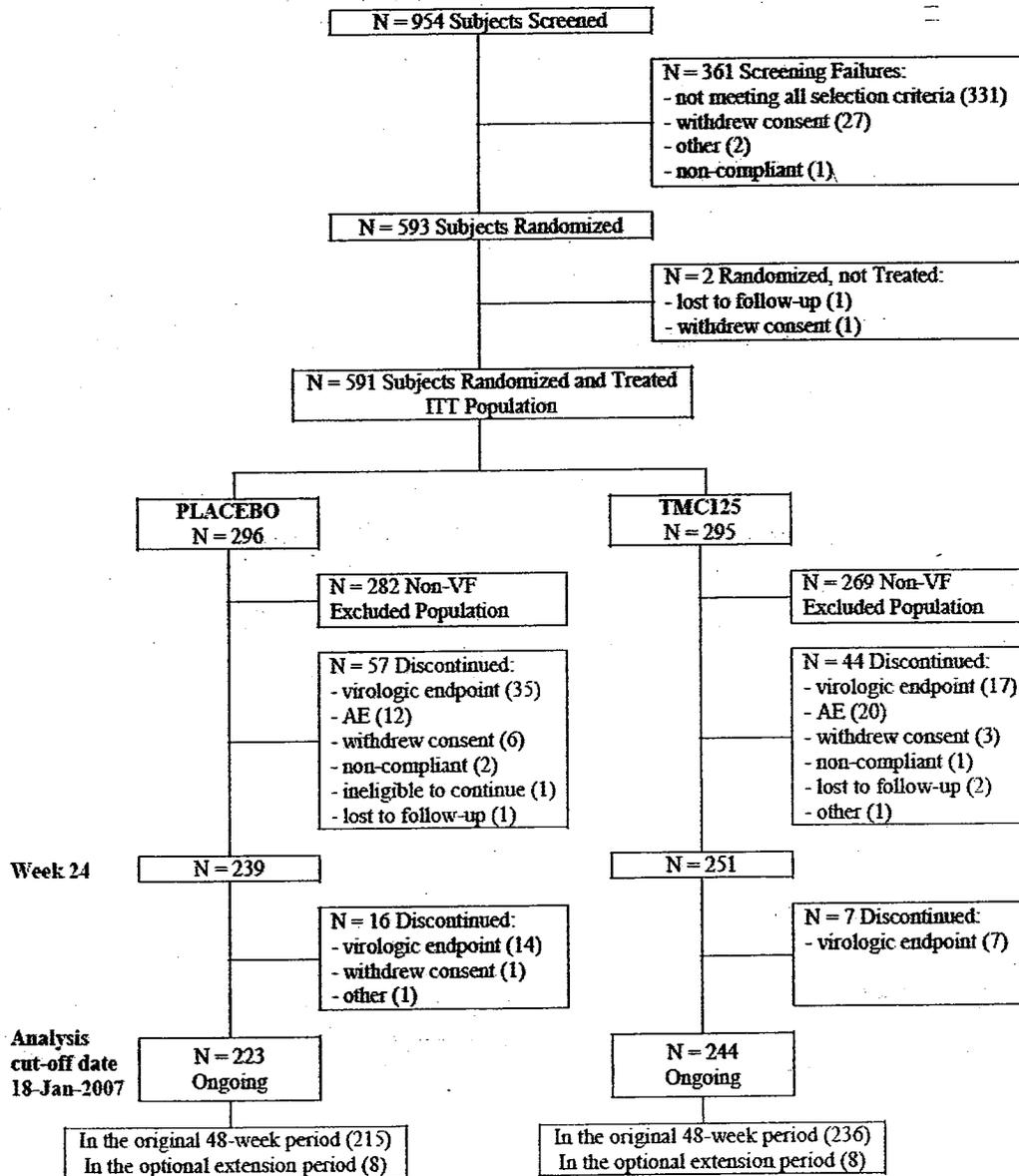


Subject Disposition in Trial TMC125-C206
Source: Figure 1 in Clinical Study Report for study TMC125-C206

Figure 1 displays patient disposition for each DUET trial.

In study TMC125-C206, almost half of the 1220 subjects screened were screening failures, leaving only 615 randomized subjects. Of the 605 screening failures, 582 (96%) did not fulfill all selection criteria, mostly because the inclusion criterion 8 (having 3 or more documented

primary PI mutations at screening) was not met. There were a total of 612 subjects in the ITT population (i.e., subjects who were randomized and treated) with 308 subjects in the placebo treatment group and 304 subjects in the TMC125 treatment group.



Subject Disposition in Trial TMC125-C216
Source: Figure 1 in Clinical Study Report for study TMC125-C216

In study TMC125-C216, 361 of the 954 screened subjects were screening failures, leaving 593 randomized subjects. Of the 361 screening failures, 331 (92%) did not fulfill all selection

criteria, mostly because the inclusion criterion 8 (having 3 or more documented primary PI mutations at screening) was not met. There were a total of 591 subjects in the ITT population (i.e., subjects who were randomized and treated) with 296 subjects in the placebo treatment group and 295 subjects in the TMC125 treatment group.

Number of Randomized and Treated Subjects per Country

Trial TMC125-C206

Country n (%)	Placebo N = 308	TMC125 N = 304	All Subjects N = 612
United States	118 (38.3)	119 (39.1)	237 (38.7)
Brazil	118 (38.3)	118 (38.8)	236 (38.6)
Argentina	37 (12.0)	29 (9.5)	66 (10.8)
France	21 (6.8)	21 (6.9)	42 (6.9)
Mexico	7 (2.3)	7 (2.3)	14 (2.3)
Panama	2 (0.6)	4 (1.3)	6 (1.0)
Chile	1 (0.3)	3 (1.0)	4 (0.7)
Thailand	2 (0.6)	2 (0.7)	4 (0.7)
Puerto Rico	2 (0.6)	1 (0.3)	3 (0.5)

N = number of subjects, n = number of subjects per country

Note: all subjects in Costa Rica were screening failures.

Source: Table 6 of the TMC125-C206 Clinical Report.

Trial TMC125-C216

Country n (%)	Placebo N = 296	TMC125 N = 295	All Subjects N = 591
United States	118 (39.9)	127 (43.1)	245 (41.5)
France	49 (16.6)	53 (18.0)	102 (17.3)
Italy	39 (13.2)	31 (10.5)	70 (11.8)
Germany	26 (8.8)	35 (11.9)	61 (10.3)
Canada	22 (7.4)	20 (6.8)	42 (7.1)
Spain	14 (4.7)	9 (3.1)	23 (3.9)
Australia	8 (2.7)	7 (2.4)	15 (2.5)
Belgium	8 (2.7)	6 (2.0)	14 (2.4)
United Kingdom	6 (2.0)	4 (1.4)	10 (1.7)
The Netherlands	4 (1.4)	2 (0.7)	6 (1.0)
Poland	1 (0.3)	1 (0.3)	2 (0.3)
Portugal	1 (0.3)	0	1 (0.2)

N = number of subjects, n = number of subjects per country

Source: Table 6 of the TMC125-C216 Clinical Report.

Study C206 was conducted primarily in the United States and Latin America (39% of the subjects were from the United States and 39% of the subjects were from Brazil) while Study C216 was conducted primarily in the United States and Europe (42% from the U.S., 17% from France, 12% from Italy, and 10% from Germany).

Reasons for Trial Termination, Trial TMC125-C206

Trial Termination Reason, n (%)	Placebo N = 308	TMC125 N = 304	All Subjects N = 612
<i>Up to Week 24 (inclusive)</i>	43 (14.0)	37 (12.2)	80 (13.1)
AE/HIV related event	15 (4.9)	18 (5.9)	33 (5.4)
Reached virologic endpoint	19 (6.2)	12 (3.9)	31 (5.1)
Withdrew consent	6 (1.9)	2 (0.7)	8 (1.3)
Non-compliant	2 (0.6)	2 (0.7)	4 (0.7)
Ineligible to continue the trial	0	1 (0.3)	1 (0.2)
Lost to follow-up	0	1 (0.3)	1 (0.2)
Other	0	1 (0.3)	1 (0.2)
Sponsor's decision	1 (0.3)	0	1 (0.2)
<i>At the Analysis Cut-Off Date^a</i>	56 (18.2)	42 (13.8)	98 (16.0)
Reached virologic endpoint	29 (9.4)	17 (5.6)	46 (7.5)
AE/HIV related event	16 (5.2)	18 (5.9)	34 (5.6)
Withdrew consent	6 (1.9)	2 (0.7)	8 (1.3)
Non-compliant	2 (0.6)	2 (0.7)	4 (0.7)
Other	2 (0.6)	1 (0.3)	3 (0.5)
Ineligible to continue the trial	0	1 (0.3)	1 (0.2)
Lost to follow-up	0	1 (0.3)	1 (0.2)
Sponsor's decision	1 (0.3)	0	1 (0.2)

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

^a Including terminations after Week 24 for subjects that had visits after Week 24.

Source: Table 7 of the TMC125-C206 Clinical Report.

In study TMC125-C206, 14% of the placebo subjects and 12% of the TMC125 subjects terminated the trial on or before Week 24. Subjects were counted as discontinuing if no data was present beyond the Week 24 analysis time point. At the time of the analysis cut-off date, 18% of the placebo subjects and 14% of the TMC125 subjects prematurely terminated from the trial. The majority of subjects discontinued from the trial because they reached a virologic endpoint or had AE/HIV related events.

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Reasons for Trial Termination, Trial TMC125-C216

Trial Termination Reason, n (%)	Placebo N = 296	TMC125 N = 295	All Subjects N = 591
<i>Up to Week 24 (inclusive)</i>	57 (19.3)	44 (14.9)	101 (17.1)
Reached virologic endpoint	35 (11.8)	17 (5.8)	52 (8.8)
AE/HIV related event	12 (4.1)	20 (6.8)	32 (5.4)
Withdrew consent	6 (2.0)	3 (1.0)	9 (1.5)
Lost to follow-up	1 (0.3)	2 (0.7)	3 (0.5)
Non-compliant	2 (0.7)	1 (0.3)	3 (0.5)
Other	0	1 (0.3)	1 (0.2)
Ineligible to continue the trial	1 (0.3)	0	1 (0.2)
<i>At the Analysis Cut-Off Date^a</i>	73 (24.7)	51 (17.3)	124 (21.0)
Reached virologic endpoint	49 (16.6)	24 (8.1)	73 (12.4)
AE/HIV related event	12 (4.1)	20 (6.8)	32 (5.4)
Withdrew consent	7 (2.4)	3 (1.0)	10 (1.7)
Lost to follow-up	1 (0.3)	2 (0.7)	3 (0.5)
Non-compliant	2 (0.7)	1 (0.3)	3 (0.5)
Other	1 (0.3)	1 (0.3)	2 (0.3)
Ineligible to continue the trial	1 (0.3)	0	1 (0.2)

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

^a Including terminations after Week 24 for subjects that had visits after Week 24.

Source: Table 7 of the TMC125-C216 Clinical Report.

In study TMC125-C216, 19% of the placebo subjects and 15% of the TMC125 subjects terminated the trial on or before Week 24. Subjects were counted as discontinuing if no data was present beyond the Week 24 analysis time point. At the time of the analysis cut-off date, 25% of the placebo subjects and 17% of the TMC125 subjects prematurely terminated from the trial. The majority of subjects discontinued from the trial because they reached a virologic endpoint or due to AE/HIV related events.

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**Treatment Allocation for different Stratification Factors (IVRS/IWRS Data)
Trial TMC125-C206**

Treatment Allocation Stratification Factors Specification, n (%)	Placebo N = 308	TMC125 N = 304	All Subjects N = 612
<i>Use of ENF in Underlying ART</i>			
Using de novo	88 (28.6)	86 (28.3)	174 (28.4)
Re-using	42 (13.6)	44 (14.5)	86 (14.1)
Not using	178 (57.8)	174 (57.2)	352 (57.5)
<i>Screening Plasma Viral Load</i>			
≥ 30000 copies/mL	220 (71.4)	214 (70.4)	434 (70.9)
< 30000 copies/mL	88 (28.6)	90 (29.6)	178 (29.1)
<i>Previous Use of DRV</i>			
No	291 (94.5)	286 (94.1)	577 (94.3)
Yes	17 (5.5)	18 (5.9)	35 (5.7)

N = number of subjects, n = number of subjects with observations
Source: Table 8 of the TMC125-C206 Clinical Report.

In study TMC125-C206, between 25-30% of the subjects in both treatment groups were using de novo ENF, while slightly less than 15% were re-using ENF and nearly 60% were not using ENF. Approximately 70% of the subjects in both treatment groups in study C206 and 65% of the subjects in study C216 had screening plasma viral loads of 30,000 copies/mL or higher. Approximately 5% of the subjects had previously used DRV.

**Treatment Allocation for different Stratification Factors (IVRS/IWRS Data)
Trial TMC125-C216**

Treatment Allocation Stratification Factors Specification, n (%)	Placebo N = 296	TMC125 N = 295	All Subjects N = 591
<i>Use of ENF in Underlying ART</i>			
Using de novo	79 (26.7)	80 (27.1)	159 (26.9)
Re-using	70 (23.6)	72 (24.4)	142 (24.0)
Not using	147 (49.7)	143 (48.5)	290 (49.1)
<i>Screening Plasma Viral Load</i>			
≥ 30000 copies/mL	193 (65.2)	191 (64.7)	384 (65.0)
< 30000 copies/mL	103 (34.8)	104 (35.3)	207 (35.0)
<i>Previous Use of DRV</i>			
No	281 (94.9)	283 (95.9)	564 (95.4)
Yes	15 (5.1)	12 (4.1)	27 (4.6)

N = number of subjects, n = number of subjects with observations
Source: Table 8 of the TMC125-C216 Clinical Report.

In study TMC125-C216, between 25-30% of the subjects in both treatment groups were using de novo ENF, while slightly less than 25% were re-using ENF and nearly 50% were not using ENF. Approximately 65% of the subjects in both treatment groups had screening plasma viral loads of 30,000 copies/mL or higher. Approximately 5% of the subjects in both treatment groups had previously used DRV.

**Duration of Investigational Medication Intake During the Treatment Period
Trial TMC125-C206**

Investigational Medication Intake^a Total Duration, Weeks	Placebo N = 308	TMC125 N = 304	All Subjects N = 612
N	308	304	612
Median (range)	26.6 (3-55)	26.6 (1-60)	26.6 (1-60)
Total patient-years of exposure	171.5	173.1	344.6

N = number of subjects

^a For the Primary Analysis, the 'latest available date of intake' was used, i.e., the last date that the subject was indicated as taking TMC125/placebo up to and including the analysis cut-off date.

Source: Table 9 of the TMC125-C206 Clinical Report.

The median duration of either treatment was 27 weeks in study TMC125-C206 and 33 weeks in study C216.

**Duration of Investigational Medication Intake During the Treatment Period
Trial TMC125-C216**

Investigational Medication Intake^a Total Duration, Weeks	Placebo N = 296	TMC125 N = 295	All Subjects N = 591
N	296	295	591
Median (range)	32.2 (3-55)	33.1 (2-56)	32.6 (2-56)
Total patient-years of exposure	187.7	184.4	372.1

N = number of subjects

^a For the Primary Analysis, the 'latest available date of intake' was used, i.e., the last date that the subject was indicated as taking TMC125/placebo up to and including the analysis cut-off date.

Source: Table 9 of the TMC125-C216 Clinical Report.

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**Number of Subjects per Visit
Trial TMC125-C206**

Number of Subjects Visit, n (%)	Placebo N = 308	TMC125 N = 304	All Subjects N = 612
Baseline	297 (96.4)	299 (98.4)	596 (97.4)
Week 2	301 (97.7)	300 (98.7)	601 (98.2)
Week 4	305 (99.0)	295 (97.0)	600 (98.0)
Week 12	294 (95.5)	287 (94.4)	581 (94.9)
Week 24	285 (92.5)	278 (91.4)	563 (92.0)
Week 32	92 (29.9)	99 (32.6)	191 (31.2)
Week 40	30 (9.7)	44 (14.5)	74 (12.1)
Week 48	11 (3.6)	17 (5.6)	28 (4.6)
Week 56	1 (0.3)	3 (1.0)	4 (0.7)

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

Note: Screening, Baseline (imputed), Weeks 8, 16, and 20 were not included in this table.

Source: Table 10 of the TMC125-C206 Clinical Report.

Over 90% of the subjects in the ITT population remained in the DUET studies for 24 weeks, while only 30% of the DUET-1 study subjects and slightly over 50% of the DUET-2 study subjects remained in the trials for at least 32 weeks. The percentage of subjects at each visit was similar in the two treatment groups up to Week 24 in study C206 and up to Week 48 in study C216. A higher percentage of TMC125 subjects than placebo subjects remained in study C206 after Week 24.

**Number of Subjects per Visit
Trial TMC125-C216**

Number of Subjects Visit, n (%)	Placebo N = 296	TMC125 N = 295	All Subjects N = 591
Baseline	293 (99.0)	293 (99.3)	586 (99.2)
Week 2	291 (98.3)	287 (97.3)	578 (97.8)
Week 4	291 (98.3)	285 (96.6)	576 (97.5)
Week 12	283 (95.6)	274 (92.9)	557 (94.2)
Week 24	276 (93.2)	268 (90.8)	544 (92.0)
Week 32	155 (52.4)	154 (52.2)	309 (52.3)
Week 40	63 (21.3)	67 (22.7)	130 (22.0)
Week 48	8 (2.7)	9 (3.1)	17 (2.9)

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

Note: Screening, Baseline (imputed), Weeks 8, 16, and 20 were not included in this table.

Source: Table 10 of the TMC125-C216 Clinical Report.

**Type and Incidence of Major Protocol Deviations
Trial TMC125-C206**

Protocol Deviations Deviation Class Deviation, n (%)	Placebo N = 308	TMC125 N = 304	All Subjects N = 612
Any Major Protocol Deviation	30 (9.7)	27 (8.9)	57 (9.3)
Treatment Deviation of Investigational Medication			
Non-compliance with investigational medication intake	10 (3.2)	9 (3.0)	19 (3.1)
Forbidden non-ARV Therapy	15 (4.9)	12 (3.9)	27 (4.4)
Disallowed drug in the treatment period	15 (4.9)	12 (3.9)	27 (4.4)
Selection Criteria not met	3 (1.0)	3 (1.0)	6 (1.0)
Selection criteria not met	3 (1.0)	3 (1.0)	6 (1.0)
Treatment Deviation of Underlying ART	4 (1.3)	4 (1.3)	8 (1.3)
Deviation of underlying ARV intake	3 (1.0)	3 (1.0)	6 (1.0)
Disallowed underlying ARV intake	1 (0.3)	1 (0.3)	2 (0.3)
Disallowed underlying ARV changes	1 (0.3)	0	1 (0.2)

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

Source: Table 11 of the TMC125-C206 Clinical Report.

Slightly less than 10% of the subjects in each treatment group in study C206 had major protocol deviations. In study C216, 9% of the placebo subjects and 5% of the TMC125 subjects had major protocol deviations. The most frequent major protocol deviations were the use of a disallowed drug in the treatment period, non-compliance with investigational medication intake, selection criteria not met and deviation of underlying ART intake.

**Type and Incidence of Major Protocol Deviations
Trial TMC125-C216**

Protocol Deviations Deviation Class Deviation, n (%)	Placebo N = 296	TMC125 N = 295	All Subjects N = 591
Any Major Protocol Deviation	27 (9.1)	15 (5.1)	42 (7.1)
Treatment Deviation of Investigational Medication			
Non-compliance with investigational medication intake	5 (1.7)	8 (2.7)	13 (2.2)
Forbidden non-ARV Therapy	8 (2.7)	4 (1.4)	12 (2.0)
Disallowed drug in the treatment period	8 (2.7)	4 (1.4)	12 (2.0)
Selection Criteria not met	10 (3.4)	1 (0.3)	11 (1.9)
Selection criteria not met	10 (3.4)	1 (0.3)	11 (1.9)
Treatment Deviation of Underlying ART	5 (1.7)	3 (1.0)	8 (1.4)
Deviation of underlying ARV intake	4 (1.4)	1 (0.3)	5 (0.8)
Disallowed underlying ARV intake	1 (0.3)	2 (0.7)	3 (0.5)

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

Source: Table 11 of the TMC125-C216 Clinical Report.

**Demographic Parameters
Trial TMC125-C206**

Demographic Parameters Specification	Placebo N = 308	TMC125 N = 304	All Subjects N = 612
<i>Gender, n (%)</i>			
Female	44 (14.3)	41 (13.5)	85 (13.9)
Male	264 (85.7)	263 (86.5)	527 (86.1)
<i>Age^a, years</i>	45.0	45.0	45.0
Median (range)	(18-72)	(18-67)	(18-72)
<i>Height^b, cm</i>	173.0	175.0	174.0
Median (range)	(146-196)	(140-203)	(140-203)
<i>Weight^b, kg</i>	70.0	71.0	70.6
Median (range)	(34-123)	(36-131)	(34-131)
<i>BMI^b, kg/m²</i>	23.0	23.1	23.1
Median (range)	(13-40)	(15-40)	(13-40)
<i>Ethnic Origin^c, n (%)</i>			
Caucasian	189 (64.7)	187 (64.7)	376 (64.7)
Hispanic	42 (14.4)	41 (14.2)	83 (14.3)
Black	35 (12.0)	39 (13.5)	74 (12.7)
Other	23 (7.9)	20 (6.9)	43 (7.4)
Asian	3 (1.0)	2 (0.7)	5 (0.9)

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

^a Age is calculated at Baseline (start intake investigational medication).

^b Height, weight and BMI are imputed with screening data if missing at Baseline.

^c In total, 31 subjects are not included in the denominator for race percentages due to local regulations in some countries prohibiting collection of racial information and are not in this table.

Source: Table 12 of the TMC125-C206 Clinical Report.

In the DUET-1 study 14% of the subjects were female, the median age was 45 years old, 65% of the subjects were Caucasian, 14% of the subjects were Hispanic, 13% were black, 1% were Asian and 7% were other races.

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**Demographic Parameters
Trial TMC125-C216**

Demographic Parameters Specification	Placebo N = 296	TMC125 N = 295	All Subjects N = 591
<i>Gender, n (%)</i>			
Female	25 (8.4)	19 (6.4)	44 (7.4)
Male	271 (91.6)	276 (93.6)	547 (92.6)
<i>Age^a, years</i>	45.0	46.0	46.0
Median (range)	(20-69)	(31-77)	(20-77)
<i>Height^b, cm</i>	176.0	177.0	176.5
Median (range)	(140-195)	(154-196)	(140-196)
<i>Weight^b, kg</i>	72.0	74.0	72.5
Median (range)	(45-137)	(41-115)	(41-137)
<i>BMI^b, kg/m²</i>	22.9	23.4	23.2
Median (range)	(15-47)	(14-34)	(14-47)
<i>Ethnic Origin^c, n (%)</i>			
Caucasian	187 (75.7)	186 (76.5)	373 (76.1)
Black	35 (14.2)	31 (12.8)	66 (13.5)
Hispanic	24 (9.7)	19 (7.8)	43 (8.8)
Asian	0	5 (2.1)	5 (0.8)
Other	1 (0.4)	2 (0.8)	3 (0.6)

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

^a Age is calculated at Baseline (start intake investigational medication).

^b Height, weight and BMI are imputed with screening data if missing at Baseline.

^c In total, 31 subjects are not included in the denominator for race percentages due to local regulations in some countries prohibiting collection of racial information and are not in this table.

Source: Table 12 of the TMC125-C216 Clinical Report.

In the DUET-2 study 7% of the subjects were female, the median age was 46 years old, 76% of the subjects were Caucasian, 9% of the subjects were Hispanic, 13% were black, and 1% were Asian and other races.

Demographic characteristics appeared to be very balanced across treatment groups in both studies.

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**Baseline Disease Characteristics
Trial TMC125-C206**

Baseline Disease Parameters Specification	Placebo N = 308	TMC125 N = 304	All Subjects N = 612
<i>Viral Load, copies/mL</i>			
Median	77000.0	67850.0	75200.0
(range)	(227-3,030,000)	(479-1,740,000)	(227-3,030,000)
<i>Log10 Viral Load, copies/mL</i>			
Median	4.9	4.8	4.9
(range)	(2-7)	(3-6)	(2-7)
<i>CD4 Cell Count, 10⁶ cells/L Median</i>			
Median	109.0	99.0	106.0
(range)	(1-694)	(1-789)	(1-789)
<i>CD4 Cell Count, %</i>			
Median	7.5	8.2	8.1
(range)	(0-40)	(0-37)	(0-40)
<i>Duration of Known HIV Infection at Screening, years</i>			
Median	13.3	13.4	13.3
(range)	(5-26)	(4-25)	(4-26)
<i>Clinical Stage of HIV Infection^a, n (%)</i>			
CDC Category A	59 (19.2)	69 (22.7)	128 (20.9)
CDC Category B	54 (17.5)	51 (16.8)	105 (17.2)
CDC Category C	195 (63.3)	184 (60.5)	379 (61.9)

N = number of subjects, n = number of observations

Note: Baseline values were imputed with screening values if no data at Baseline were available.

^a 1993 revised classification system for HIV infection and expanded surveillance case definition for AIDS among adolescents and adults. MMWR Recomm Rep. 1992 Dec 18;41(RR-17):1-19.

Source: Table 13 of the TMC125-C206 Clinical Report.

The subjects in the two DUET trials had advanced HIV disease, as was apparent from the high baseline viral loads, low CD4 cell counts and the long duration of HIV infection.

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**Baseline Disease Characteristics
Trial TMC125-C216**

Baseline Disease Parameters Specification	Placebo N = 296	TMC125 N = 295	All Subjects N = 591
<i>Viral Load, copies/mL</i>			
Median	61450.0	65300.0	64500.0
(range)	(177-2,110,000)	(977-7,030,000)	(177-7,030,000)
<i>Log₁₀ Viral Load, copies/mL</i>			
Median	4.8	4.8	4.8
(range)	(2-6)	(3-7)	(2-7)
<i>CD4 Cell Count, 10⁶ cells/L Median</i>			
Median	108.0	100.0	105.0
(range)	(0-912)	(1-708)	(0-912)
<i>CD4 Cell Count, %</i>			
Median	8.6	7.8	8.3
(range)	(0-35)	(0-35)	(0-35)
<i>Duration of Known HIV Infection at Screening, years</i>			
Median	15.1	14.5	14.9
(range)	(5-26)	(3-25)	(3-26)
<i>Clinical Stage of HIV Infection^a, n (%)</i>			
CDC Category A	71 (24.0)	57 (19.3)	128 (21.7)
CDC Category B	63 (21.3)	76 (25.8)	139 (23.5)
CDC Category C	162 (54.7)	162 (54.9)	324 (54.8)

N = number of subjects, n = number of observations

Note: Baseline values were imputed with screening values if no data at Baseline were available.

^a 1993 revised classification system for HIV infection and expanded surveillance case definition for AIDS among adolescents and adults. MMWR Recomm Rep. 1992 Dec 18;41(RR-17):1-19.

Source: Table 13 of the TMC125-C216 Clinical Report.

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**Specific Individual Previously Used ARVs (up to Baseline)
Trial TMC125-C206**

ARVs Previously Used^a Individual ARV, n (%)	Placebo N = 308	TMC125 N = 304	All Subjects N = 612
NNRTIs	288 (93.5)	283 (93.1)	571 (93.3)
EFV	227 (73.7)	220 (72.4)	447 (73.0)
NVP	180 (58.4)	173 (56.9)	353 (57.7)
DLV	40 (13.0)	25 (8.2)	65 (10.6)
Other	1 (0.3)	3 (1.0)	4 (0.7)
DRV	16 (5.2)	16 (5.3)	32 (5.2)
ENF	105 (34.1)	93 (30.6)	198 (32.4)

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

^a Specific individual ARVs up to Baseline were included.

Source: Table 16 of the TMC125-C206 Clinical Report.

In both DUET trials, the most frequently used ARV prior to the treatment period was EFV, which was used by approximately 70% of the subjects in each treatment group followed by NVP which was used by 60% of the subjects in each treatment arm and ENF which was used by 32% of the DUET-1 trial and 49% of the subjects in the DUET-2 trial. Other ARVs that were previously used by a much smaller proportion of subjects included DLV (8-19% use, depending on study and treatment group) and DRV (3-5% use).

**Specific Individual Previously Used ARVs (up to Baseline)
Trial TMC125-C216**

ARVs Previously Used^a Individual ARV, n (%)	Placebo N = 296	TMC125 N = 295	All Subjects N = 591
NNRTIs	268 (90.5)	267 (90.5)	535 (90.5)
EFV	211 (71.3)	201 (68.1)	412 (69.7)
NVP	174 (58.8)	169 (57.3)	343 (58.0)
DLV	37 (12.5)	57 (19.3)	94 (15.9)
Other	2 (0.7)	2 (0.7)	4 (0.7)
DRV	14 (4.7)	9 (3.1)	23 (3.9)
ENF	148 (50.0)	144 (48.8)	292 (49.4)

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

^a Specific individual ARVs up to Baseline were included.

Source: Table 16 of the TMC125-C216 Clinical Report.

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ARVs During the Screening Period (Other than NRTIs)
Trial TMC125-C206

ARVs During Screening Period Number of ARVs, n (%)	Placebo N = 308	TMC125 N = 304	All-Subjects N = 612
NNRTIs	42 (13.6)	42 (13.8)	84 (13.7)
EFV	34 (11.0)	28 (9.2)	62 (10.1)
NVP	8 (2.6)	12 (3.9)	20 (3.3)
DLV	1 (0.3)	2 (0.7)	3 (0.5)
Boosted PIs	268 (87.0)	267 (87.8)	535 (87.4)
DRV	12 (3.9)	13 (4.3)	25 (4.1)
Unboosted PIs	17 (5.5)	21 (6.9)	38 (6.2)
Fusion Inhibitor	62 (20.1)	54 (17.8)	116 (19.0)
ENF	62 (20.1)	54 (17.8)	116 (19.0)
Experimental ARVs^a	2 (0.6)	0	2 (0.3)

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

Low-dose ritonavir (< 800 mg/day) was not counted as a PI; and LPV/r as 1 PI.

^a Experimental ARVs: CCR5 and other entry inhibitors and integrase inhibitor

Source: Table 17 of the TMC125-C206 Clinical Report.

At screening subjects were required to be on a stable ART for at least 8 weeks and were to stay on this ART up to baseline.

14% of the DUET-1 subjects in each treatment group and 9% of the DUET-2 subjects in each treatment group were taking NNRTIs (mostly EFV). In both DUET trials, 87% of the subjects were taking boosted PIs, 6% of the subjects were taking unboosted PIs, 20% were taking fusion inhibitors (ENF), and <1% were taking experimental ARV drugs.

ARVs During the Screening Period (Other than NRTIs)
Trial TMC125-C216

ARVs During Screening Period Number of ARVs, n (%)	Placebo N = 296	TMC125 N = 295	All Subjects N = 591
NNRTIs	28 (9.5)	28 (9.5)	56 (9.5)
EFV	18 (6.1)	16 (5.4)	34 (5.8)
NVP	8 (2.7)	7 (2.4)	15 (2.5)
DLV	2 (0.7)	5 (1.7)	7 (1.2)
Boosted PIs	263 (88.9)	254 (86.1)	517 (87.5)
DRV	13 (4.4)	2 (0.7)	15 (2.5)
Unboosted PIs	13 (4.4)	23 (7.8)	36 (6.1)
Fusion Inhibitor	63 (21.3)	57 (19.3)	120 (20.3)
ENF	63 (21.3)	57 (19.3)	120 (20.3)
Experimental ARVs^a	1 (0.3)	2 (0.7)	3 (0.5)

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

Low-dose ritonavir (< 800 mg/day) was not counted as a PI; and LPV/r as 1 PI.

^a Experimental ARVs: CCR5 and other entry inhibitors and integrase inhibitor

Source: Table 17 of the TMC125-C216 Clinical Report.

3.1.5 Statistical Methodologies

The primary efficacy measure in this study was:

- The proportion of subjects with virologic response based on plasma HIV-1 RNA levels ≤ 50 copies/mL at Week 24. A responder at 24 weeks was defined as a subject who had achieved confirmed plasma HIV-1 RNA ≤ 50 copies/mL and had not yet lost the virological response by Week 24 as defined by the TLOVR algorithm, a composite endpoint of safety and virologic activity.

The primary population for analyses of clinical efficacy data was the Intent-to-Treat (ITT) Population and included all subjects who were randomized and exposed to at least one dose of any study medication.

Since the population with major protocol deviations was less than 10% in each DUET trial, no on-protocol analyses for efficacy and/or pharmacokinetics were performed. (The applicant said they had pre-specified this in the protocol).

The applicant anticipated in their sample size assumptions of the trial that there would be a significant statistical interaction effect between ENF use and the TMC125 treatment effect relative to placebo. In the presence of such an interaction, CMH tests for comparisons of TMC125 with placebo were to be run separately in each of the two ENF strata controlling for previous use of DRV (yes, no) and plasma viral load (<30000 , ≥ 30000 HIV-1 RNA copies).

To determine the sample size, trial simulations were performed based on the results of the TMC114 Phase IIb trials; and different assumptions of use of ENF in the OBR ranging from 20% to 80%. The following assumptions were made in all simulations:

- The expected response at Week 24 in the placebo group was 60% when ENF was used as a new drug; 35% when ENF was not used as a new drug. These were the results obtained in the combined TMC114 b.i.d. treatment groups at Week 24 in the combined efficacy analysis of the Phase IIb trials.
- The expected response at Week 24 in active TMC125 group was 60% when ENF was used as a new drug; 55% when ENF was not used.
- The significant level was 5% (two-sided).

The power to detect a statistically significant difference between TMC125 and placebo based on 1000 simulations with different sample size was presented in the following table.

Three hundreds subjects per treatment group were to be randomized in each DUET trial.

Table 1: Power Simulation

Expected used of ENF	Number of subjects/group	Power
20%	200 / 300/ 400	94% / 99% /99%
30%	200 / 300/ 400	91% / 98% /99%
40%	200 / 300/ 400	85% / 95% /99%
50%	200 / 300/ 400	80% / 93% / 98%
60%	200 / 300/ 400	66% / 84% / 94%
70%	200 / 300/ 400	54% / 72% / 85%
80%	200 / 300/ 400	39% / 55% / 68%

To evaluate the robustness of the efficacy results of the two Phase III trials in the treatment-experienced patients, the applicant used different approaches to impute missing data including Observed Cases consisting of patients with observations at a given visit, imputation of noncompleters as failures, and imputing missing data as failures. The statistical reviewer used a snapshot approach instead of the TLOVR algorithm and different rules of counting non-responders who discontinued early as virologic failures.

The applicant plotted the proportion of subjects with confirmed viral load < 50 and <400 copies/mL at all time points up to Week 24, in the overall population and by the ENF strata according to the TLOVR algorithm. Plasma viral load below the detection limit (< 50 copies/mL) was imputed with 49.

The applicant also used Kaplan-Meier plots to graphically compare the time to reach confirmed virologic response in TMC125 vs. placebo treatment groups. Proportional hazards models were used by the applicant to statistically test for differences between the time to confirmed virologic response in the two treatment groups. Treatment, baseline log viral load, use of ENF and the interaction between treatment and ENF use were used in these analyses.

The applicant also compared TMC125 with placebo for change from baseline with respect to log₁₀ plasma viral loads and CD4 cell counts. Subjects who discontinued early or who had ENF introduced in their OBR after Week 12, had their viral load values after discontinuation/change imputed with their baseline value, thus resulting in a 0 change from baseline (NC=F). To test the robustness of this imputation method, additional analyses were performed for the subsets of subjects who reached at least 24 weeks of treatment (observed data) or by using different imputation methods (e.g., M=F).

The statistical reviewer used a cross-sectional Week 24 'snapshot' approach for the primary analysis and compared his results with the applicant's TLOVR results. Using the snapshot approach, the statistical reviewer also performed sensitivity analyses that made different assumptions about whether certain discontinuations should be counted as virologic failures. The statistical reviewer also compared TMC125 to placebo using ordinal categories of viral load responses and analyzed LDL cholesterol data.

3.1.6 Applicant's Primary Efficacy Results

**TLOVR Classification at Week 24
Trial TMC125-C206**

Virologic Response Data (TLOVR) Specification, n (%)	Placebo N = 308	TMC125 N = 304
Viral Load < 50 copies/mL	119 (38.6)	170 (55.9)
Non-Response Reason:		
Virologic failure:	168 (54.5)	110 (36.2)
- Rebound (Loss of Response)	12 (3.9)	14 (4.6)
Viral load < 400 copies/mL at Week 24	8 (2.6)	11 (3.6)
Viral load ≥ 400 copies/mL at Week 24	3 (1.0)	3 (1.0)
Discontinued due to VF before Week 24	1 (0.3)	0
- Never suppressed (Not Responding)	156 (50.6)	96 (31.6)
Viral load < 400 copies/mL at Week 24	31 (10.1)	44 (14.5)
Viral load ≥ 400 copies/mL at Week 24	124 (40.3)	51 (16.8)
Discontinued due to VF before Week 24	1 (0.3)	1 (0.3)
Death	6 (1.9)	4 (1.3)
Discontinuation due to AE	7 (2.3)	13 (4.3)
Discontinuation due to other reasons	8 (2.6)	7 (2.3)

N = number of subjects, n = number of observations, VF = virologic failure

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

Source: Table 32 of the TMC125-C206 Clinical Report.

**TLOVR Classification at Week 24
Trial TMC125-C216**

Virologic Response Data (TLOVR) Specification, n (%)	Placebo N = 296	TMC125 N = 295
Viral Load < 50 copies/mL	129 (43.6)	183 (62.0)
Non-Response Reason:		
Virologic failure:	153 (51.7)	86 (29.2)
- Rebound (Loss of Response)	9 (3.0)	7 (2.4)
Viral load < 400 copies/mL at Week 24	4 (1.4)	7 (2.4)
Viral load ≥ 400 copies/mL at Week 24	5 (1.7)	0
Discontinued due to VF before Week 24	0	0
- Never suppressed (Not Responding)	144 (48.6)	79 (26.8)
Viral load < 400 copies/mL at Week 24	26 (8.8)	31 (10.5)
Viral load ≥ 400 copies/mL at Week 24	113 (38.2)	47 (15.9)
Discontinued due to VF before Week 24	5 (1.7)	1 (0.3)
Death	4 (1.4)	4 (1.4)
Discontinuation due to AE	4 (1.4)	17 (5.8)
Discontinuation due to other reasons	6 (2.0)	5 (1.7)

N = number of subjects, n = number of observations, VF = virologic failure

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

Source: Table 32 of the TMC125-C216 Clinical Report.

The applicant's distribution of virologic responses and failures along with reasons for discontinuation of treatment are summarized above using the TLOVR algorithm for studies C206 and C216. In the primary analysis, patients who discontinued for any reason were considered to be non-responders.

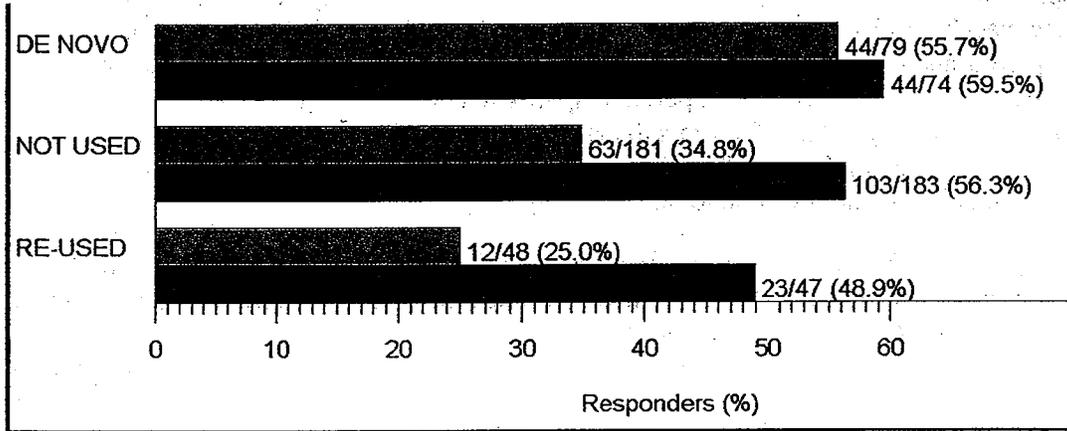
Approximately sixty percent (60%) of the TMC125 subjects compared to only about 40% of the placebo subjects had viral loads <50 copies/mL with slightly higher response rates observed in the study TMC125-C216. A little more than 50% of the placebo subjects were virologic failures at Week 24 compared to approximately 30% of the TMC125 subjects. Approximately 5% of the TMC125 subjects discontinued due to AEs compared to approximately 2% of the placebo subjects. Approximately 2% of the patients in each treatment arm discontinued due to other reasons.

The applicant performed the subgroup analyses for the primary efficacy endpoint with respect to Enfuvirtide (ENF) use (de novo, not used, re-used) as shown in Figure 14 of the Clinical Study Report. Since the percentage of patients with an SVR appeared similar in the subjects who had not used ENF and those who re-used it, these two categories were combined for treatment comparisons.

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Virologic Response (Viral Load < 50 copies/mL TLOVR) at Week 24 by ENF Use (3 Categories)

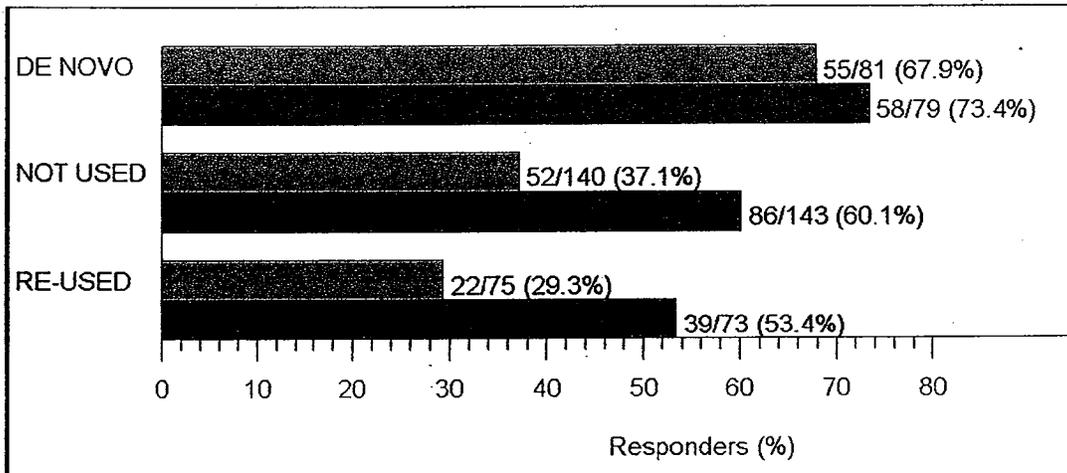
Trial TMC125-C206



■ Placebo ■ TMC125

Source: Figure 14 of the TMC125-C206 Clinical Report.

Trial TMC125-C216



■ Placebo ■ TMC125

Source: Figure 14 of the TMC125-C216 Clinical Report.

**Virologic Response Rate (Viral Load < 50 copies/mL TLOVR) at Week 24:
Primary Statistical Analysis for Trial TMC125-C206**

Primary Statistical Analysis	<i>De novo ENF</i>		Not de novo ENF	
	Placebo N = 79	TMC125 N = 74	Placebo N = 229	TMC125 N = 230
Response rate, n (%)	44 (55.7)	44 (59.5)	75 (32.8)	126 (54.8)
P-value vs. placebo ^a	0.7935		< 0.0001	

^a p-value for comparisons with placebo (Hochberg adjusted p-value)
p-value for Breslow-Day test of treatment by ENF interaction was 0.046
Source: Table 33 of the TMC125-C206 Clinical Report.

**Virologic Response Rate (Viral Load < 50 copies/mL TLOVR) at Week 24:
Primary Statistical Analysis for Trial TMC125-C216**

Primary Statistical Analysis	<i>De novo ENF</i>		Not de novo ENF	
	Placebo N = 81	TMC125 N = 79	Placebo N = 215	TMC125 N = 216
Response rate, n (%)	55 (67.9)	58 (73.4)	74 (34.4)	125 (57.9)
P-value vs. placebo ^a	0.3838		< 0.0001	

^a p-value for comparisons with placebo (Hochberg adjusted p-value)
p-value for Breslow-Day test of treatment by ENF interaction was 0.082
Source: Table 33 of the TMC125-C216 Clinical Report.

CMH tests for comparisons of TMC125 with placebo were run separately in each of the two ENF strata controlling for previous use of DRV (yes, no) and plasma viral load (<30000, ≥30000 HIV-1 RNA copies).

The sponsor anticipated in the sample size assumptions of the trial that there would be a significant statistical interaction effect between ENF use and treatment effects. As shown in Table 33 of the Clinical Study Report, there was no statistically significant benefit of adding TMC125 to the treatment regimen of de novo ENF subjects. However TMC125 was clearly superior compared to placebo in subjects who did not use ENF as a de novo drug (p<0.0001 in both studies). Therefore the applicant divided the primary statistical analysis into de novo ENF users and non de novo ENF users.

**Viral Load < 50 Copies/mL (TLOVR): Primary Statistical Analysis –
Pooled DUET Trials**

	Pooled DUET Trials			
	<i>de novo</i> ENF		Not <i>de novo</i> ENF	
	Placebo N = 160	TMC125 N = 153	Placebo N = 444	TMC125 N = 446
Observed response rates	61.9%	66.7%	33.6%	56.3%
p-value vs. placebo Hochberg adjusted p-value*	0.427		< 0.0001	

*CMH test controlling for baseline viral load and previous DRV use
Source: Module 2.7.3 Summary of Clinical Efficacy, Table 43

Results from the pooled analysis were similar to results for each individual study, with no statistically significant difference between TMC125 and placebo subjects in the *de novo* ENF subgroup and a highly significant difference in favor of TMC125 compared to placebo in non *de novo* ENF subjects.

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3.1.7 Applicant's Assessment of Robustness of Primary Efficacy Analysis

Virologic Response Rate (Viral Load < 50 copies/mL TLOVR) at Week 24: Sensitivity Analysis for the Imputation Methods Trial TMC125-C206

Sensitivity Analysis Imputation Method	<i>De novo ENF</i>				Not de novo ENF			
	Placebo		TMC125		Placebo		TMC125	
	N	n (%)	N	n (%)	N	n (%)	N	n (%)
Observed	75	45 (60.0)	69	47 (68.1)	208	76 (36.5)	208	129 (62.0)
NC = F	79	45 (57.0)	74	47 (63.5)	229	76 (33.2)	230	130 (56.5)
M = F	79	45 (57.0)	74	47 (63.5)	229	76 (33.2)	230	129 (56.1)
TLOVR	79	44 (55.7)	74	44 (59.5)	229	75 (32.8)	230	126 (54.8)

N = number of subjects, n = number of observations

Source: Table 36 of the TMC125-C206 Clinical Report.

The sponsor performed the sensitivity analyses separately for de novo ENF and not de novo ENF subjects. The primary analysis using the TLOVR algorithm is shown in the last row of the two tables of sensitivity analyses using different imputation schemes.

The Observed Cases Imputation Method was the most liberal imputation method both in terms of giving the highest estimates of the percentage of patients with a SVR and in terms of the magnitude of treatment effects in favor of TMC125 compared to placebo. Conversely, the TLOVR was the most conservative imputation method. However all of the approaches estimated larger treatment differences in favor of TMC125 compared to placebo for subjects who were not using de novo ENF.

Virologic Response Rate (Viral Load < 50 copies/mL TLOVR) at Week 24: Sensitivity Analysis for the Imputation Methods Trial TMC125-C216

Sensitivity Analysis Imputation Method	<i>De novo ENF</i>				Not de novo ENF			
	Placebo		TMC125		Placebo		TMC125	
	N	n (%)	N	n (%)	N	n (%)	N	n (%)
Observed	78	53 (67.9)	74	58 (78.4)	198	69 (34.8)	194	124 (63.9)
NC = F	81	53 (65.4)	79	58 (73.4)	215	69 (32.1)	216	124 (57.4)
M = F	81	53 (65.4)	79	58 (73.4)	215	69 (32.1)	216	124 (57.4)
TLOVR	81	55 (67.9)	79	58 (73.4)	215	74 (34.4)	216	125 (57.9)

N = number of subjects, n = number of observations

Source: Table 36 of the TMC125-C216 Clinical Report.

3.1.8 Applicant's Secondary Efficacy Results

Statistical Analysis of the Virologic Response (TLOVR) at Week 24: Pooled DUET Data

Grouping, Specification, %	Pooled DUET Trials			
	<i>de novo</i> ENF		Not <i>de novo</i> ENF	
	Placebo N = 160	TMC125 N = 153	Placebo N = 444	TMC125 N = 446
Viral load < 400 copies/mL				
Observed response rate	75.6	86.9	44.1	70.6
p-value vs placebo*	0.047		< 0.0001	
p-value vs placebo**	0.035		< 0.0001	
Overall p-value vs placebo**	< 0.0001			
Viral load > 1 log drop from baseline				
Observed response rate	84.4	88.2	49.1	76.9
p-value vs placebo*	0.402		< 0.0001	
p-value vs placebo**	0.316		< 0.0001	
Overall p-value vs placebo**	< 0.0001			

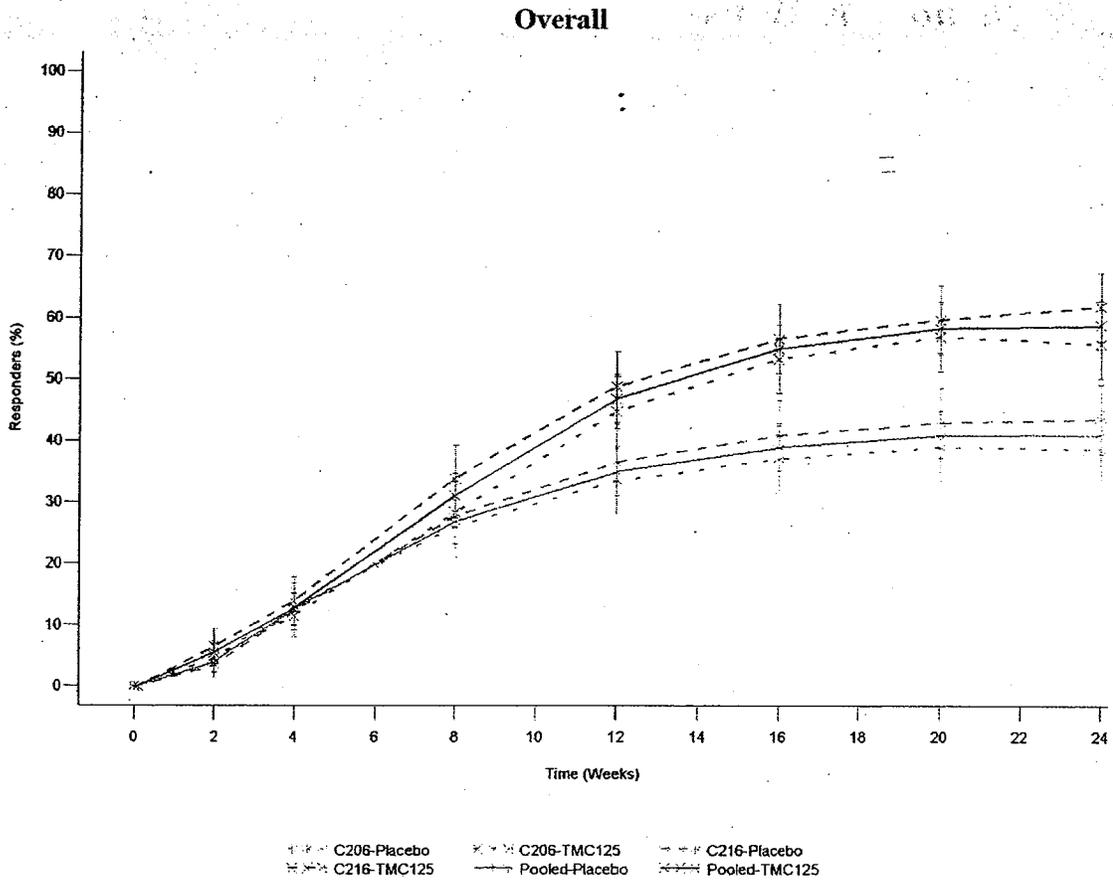
*p-value from CMH test controlling for previous DRV use and baseline viral load

**p-value from logistic regression model with covariates baseline viral load and factors ENF and treatment and interaction term ENF*treatment

Source: Module 2.7.3 Summary of Clinical Efficacy, Table 46

Similar trends that were apparent for the primary efficacy analysis were also apparent for the percentage of subjects with viral loads <400 copies/mL and the percentage of subjects with more than a 1 log drop from baseline.

Although p-values for treatment differences between the percentage of TMC125 and placebo subjects with viral load < 400 copies/mL were slightly under 0.05, these results were not statistically significant since this is a pooled analysis using data from the two DUET trials. The significance level for two pooled studies should be approximately 0.001 instead of 0.05.

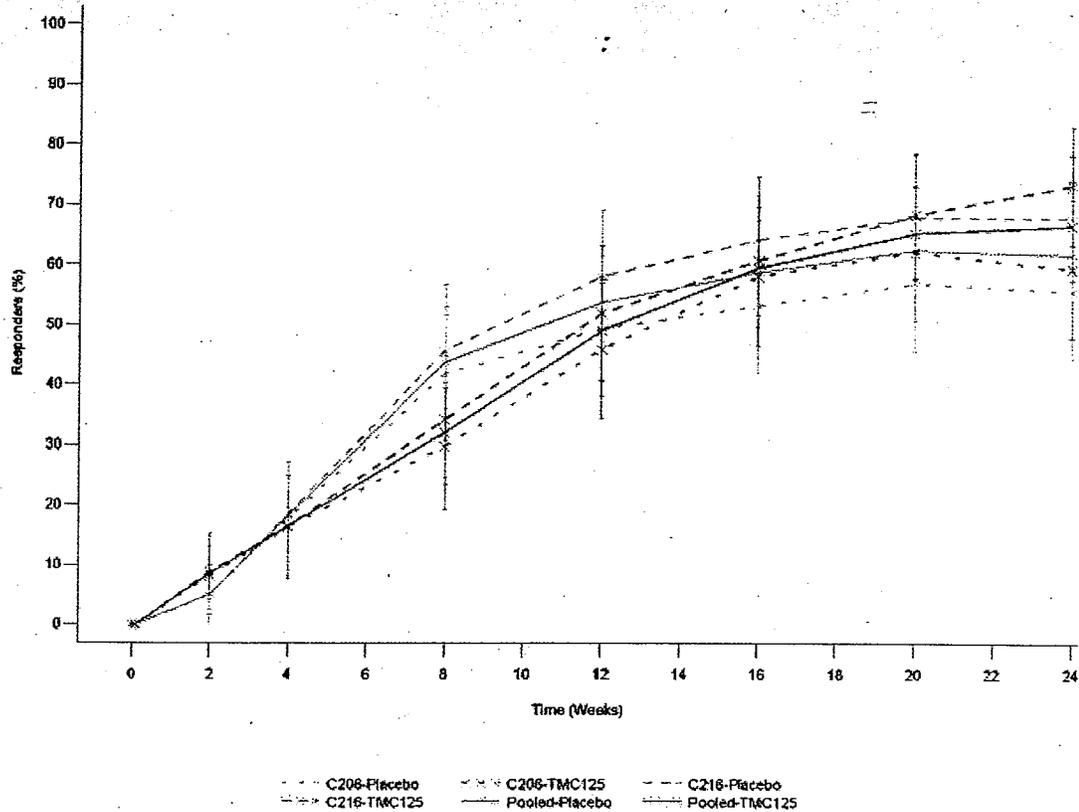


Proportion of Virologic Responders (< 50 Copies/mL; TLOVR Imputed), Overall in the DUET-1 and DUET-2 Trials

Source: Module 2.7.3 Summary of Clinical Efficacy, Figure 26

The proportion of virologic responders with HIV RNA viral loads < 50 copies/mL were plotted against time in Figure 26 of the Summary of Clinical Efficacy. Compared to placebo, there were a higher percentage of TMC125 subjects who were virologic responders (<50 copies/mL, TLOVR imputed) at later time points.

De novo ENF use

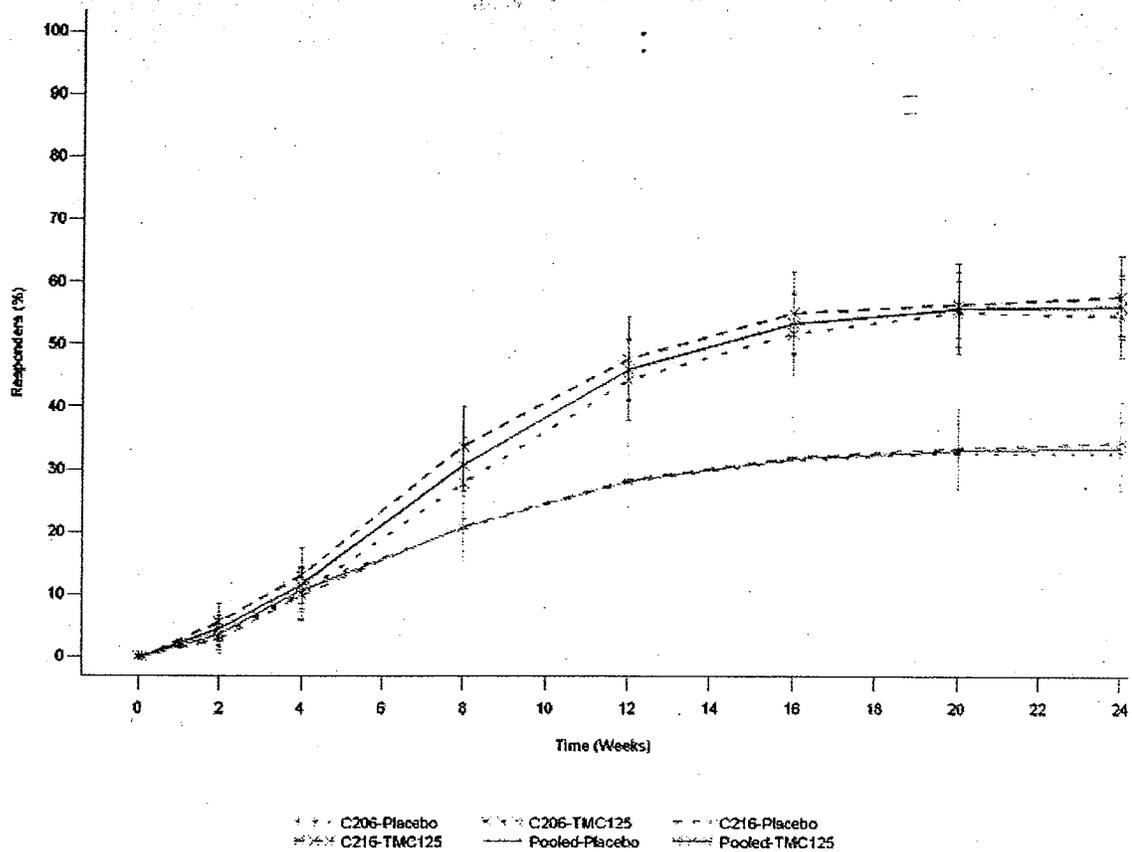


**Proportion of Virologic Responders (< 50 Copies/mL; TLOVR Imputed),
For De Novo ENF Subjects in the DUET-1 and DUET-2 Trials**

Source: Module 2.7.3 Summary of Clinical Efficacy, Figure 26

Compared to placebo, there were a similar percentage of TMC125 subjects who were virologic responders (<50 copies/mL, TLOVR imputed) in de novo ENF subjects.

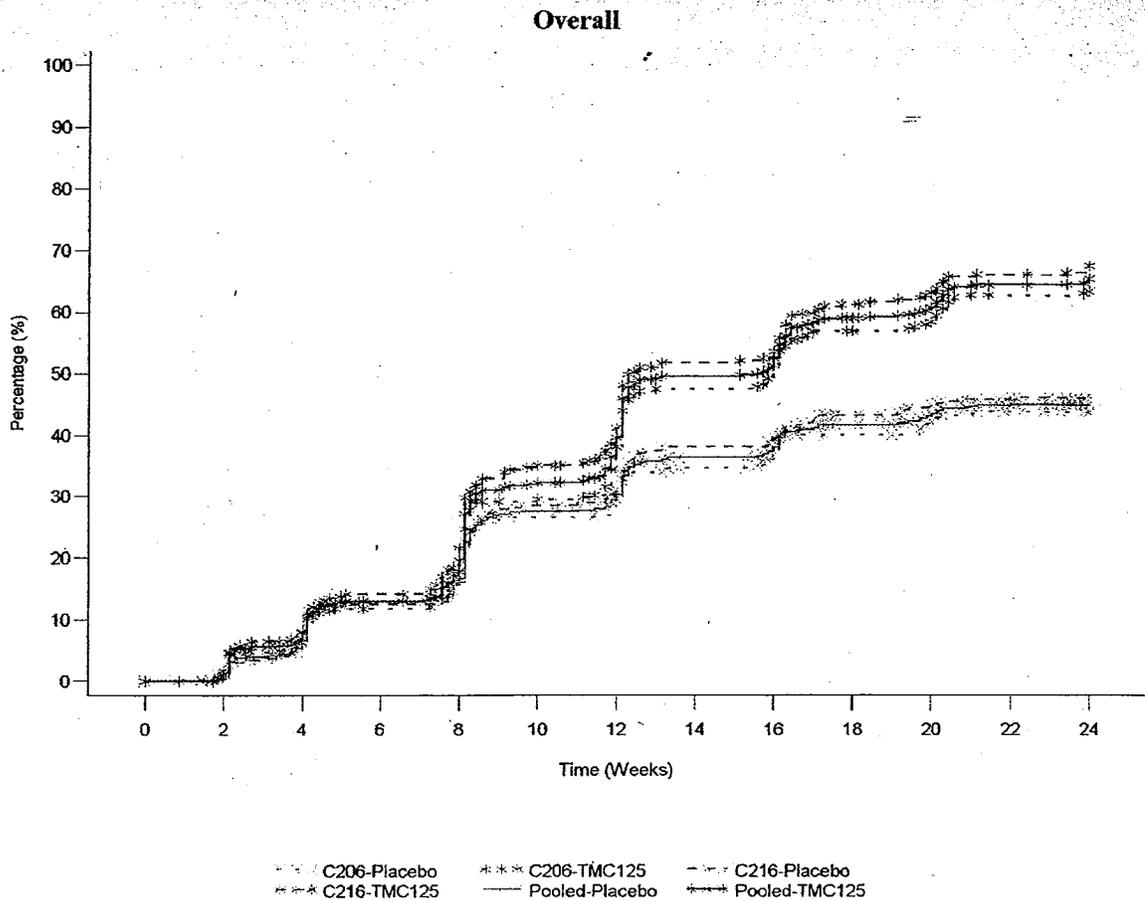
Not de novo ENF use



Proportion of Virologic Responders (< 50 Copies/mL; TLOVR Imputed), For Non De Novo ENF Subjects in the DUET-1 and DUET-2 Trials

Source: Module 2.7.3 Summary of Clinical Efficacy, Figure 26

Compared to placebo, there were a higher percentage of TMC125 subjects who were virologic responders (<50 copies/mL, TLOVR imputed) in non de novo ENF subjects.



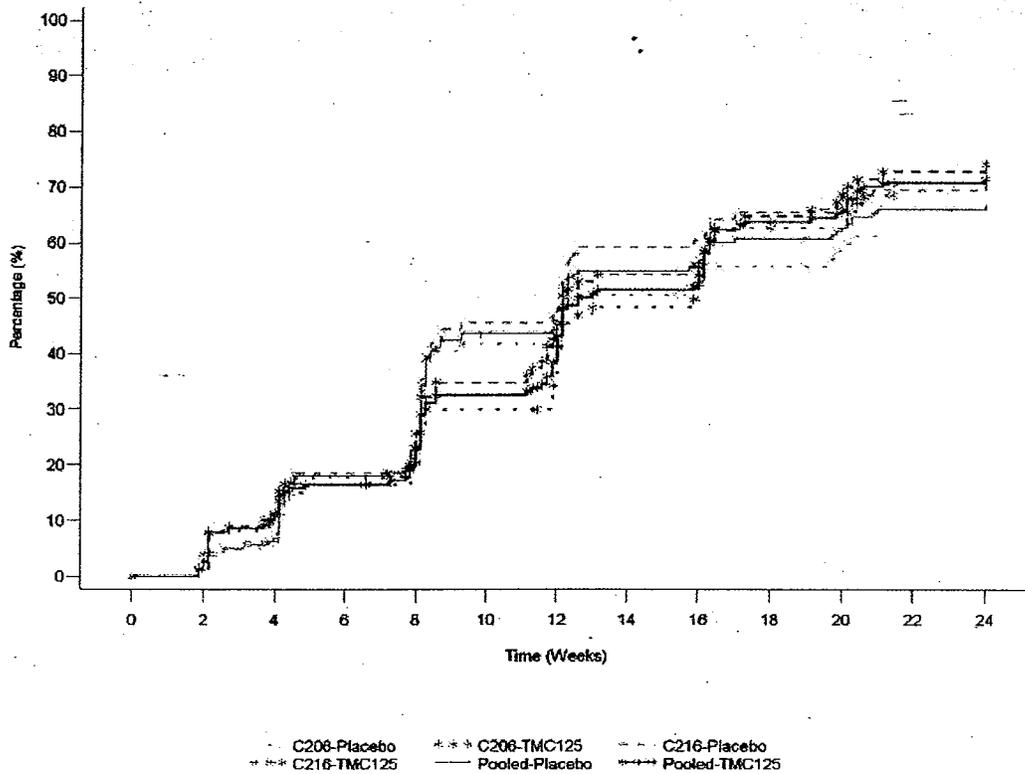
Kaplan Meier Curves for the Time to Confirmed Virologic Response (< 50 copies/mL, TLOVR), Overall in the DUET-1 and DUET-2 Trials

Source: Module 2.7.3 Summary of Clinical Efficacy, Figure 29

Similar trends were observed using Kaplan Meier Curves for the time to confirmed virologic response (< 50 copies/mL using the TLOVR algorithm). Using proportional hazards regressions to compare the time to confirmed virologic response in TMC125 and placebo subjects, the overall p-value for the effect of TMC125 vs. placebo was <0.0001.

Similar results were obtained for proportional hazards analyses of time to confirmed virologic response of <400 copies/mL.

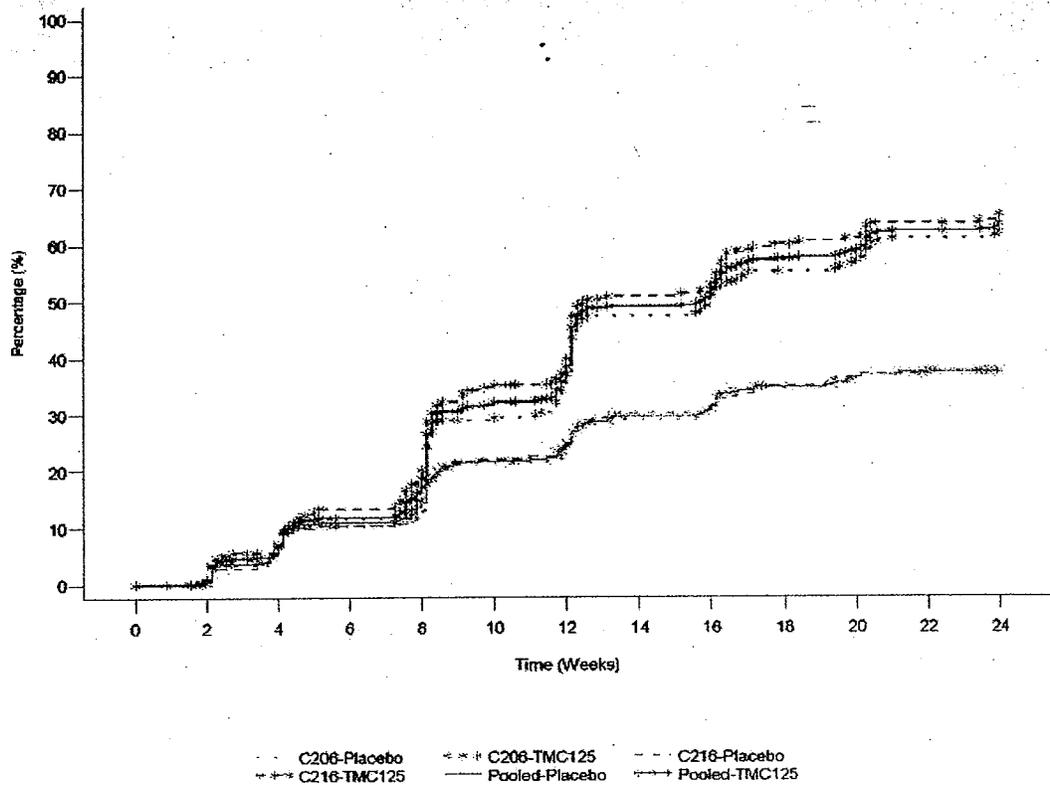
De novo ENF use



Kaplan Meier Curves for the Time to Confirmed Virologic Response (< 50 copies/mL, TLOVR), for De Novo ENF Subjects in the DUET-1 and DUET-2 Trials
Source: Module 2.7.3 Summary of Clinical Efficacy, Figure 29

When the proportional hazards model was fitted separately per ENF use stratum (excluding ENF use and its interaction with treatment as covariates), there was no statistically significant difference between TMC125 and placebo for the de novo ENF group ($p=0.375$).

Not de novo ENF use



Kaplan Meier Curves for the Time to Confirmed Virologic Response (< 50 copies/mL, TLOVR), for Non De Novo ENF subjects in the DUET-1 and DUET-2 Trials
 Source: Module 2.7.3 Summary of Clinical Efficacy, Figure 29

There was a statistically significant effect of TMC125 vs. placebo in the non de novo ENF group ($p < 0.0001$).

Change from Baseline in Log₁₀ Plasma Viral Load at Week 24 in the DUET-1 and DUET-2 Trials

Mean (SE)	DUET-1		DUET-2		Pooled DUET Trials	
	Placebo	TMC125	Placebo	TMC125	Placebo	TMC125
Overall	N = 308	N = 304	N = 296	N = 295	N = 604	N = 599
Baseline log ₁₀ viral load	4.90 (0.04)	4.87 (0.04)	4.75 (0.04)	4.81 (0.03)	4.83 (0.03)	4.84 (0.03)
Change in log ₁₀ viral load from baseline at Week 24	-1.70 (0.08)	-2.41 (0.07) ^a	-1.68 (0.08)	-2.34 (0.08) ^a	-1.69 (0.06)	-2.37 (0.05) ^a
de novo ENF	N = 79	N = 74	N = 81	N = 79	N = 160	N = 153
Baseline log ₁₀ viral load	4.96 (0.07)	4.92 (0.07)	4.77 (0.06)	4.83 (0.06)	4.86 (0.05)	4.87 (0.05)
Change in log ₁₀ viral load from baseline at Week 24	-2.47 (0.14)	-2.73 (0.13)	-2.49 (0.13)	-2.72 (0.13)	-2.48 (0.10)	-2.72 (0.09)
Not de novo ENF	N = 229	N = 230	N = 215	N = 216	N = 444	N = 446
Baseline log ₁₀ viral load	4.88 (0.04)	4.86 (0.04)	4.74 (0.05)	4.81 (0.04)	4.81 (0.03)	4.83 (0.03)
Change in log ₁₀ viral load from baseline at Week 24	-1.44 (0.10)	-2.30 (0.09) ^a	-1.37 (0.09)	-2.20 (0.09) ^a	-1.41 (0.07)	-2.25 (0.06) ^a

^a p-value < 0.0001 vs placebo

Missing data imputed by LOCF up until the time point that the subject is calculated to have reached in the trial at the cut-off date, and time points after dropout imputed by 0 in NC = F analysis up to the time point that the subject would have been in the trial at the cut-off date.

Source: Module 2.7.3 Summary of Clinical Efficacy, Table 47

Decrease from baseline at Week 24 in log₁₀ plasma viral load was higher in the TMC125 subjects than in placebo subjects. The use of de novo ENF increased the magnitude of the decrease from baseline in log₁₀ plasma viral load in placebo subjects, so the treatment group differences were not as impressive in the de novo ENF subgroup.

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**Change from Baseline in CD4 Cell Count ($\times 10^6/L$, Imputed [NC = F]),
Overall and by ENF Strata in the DUET-1 and DUET-2 Trials**

Mean (SE)	DUET-1		DUET-2		Pooled DUET Trials	
	Placebo	TMC125	Placebo	TMC125	Placebo	TMC125
Overall	N = 307	N = 303	N = 296	N = 295	N = 603	N = 598
Baseline	138.55 (7.65)	153.69 (9.03)	156.72 (9.04)	136.24 (7.85)	147.47 (5.91)	145.08 (6.00)
Change from baseline at Week 24	66.4 (5.25)	91.5 (5.44)	67.2 (4.70)	79.5 (4.86)	66.8 (3.53)	85.6 (3.66)
de novo ENF	N = 78	N = 74	N = 81	N = 79	N = 159	N = 153
Baseline	123.24 (13.07)	164.08 (17.68)	180.72 (17.23)	152.91 (13.94)	152.52 (11.08)	158.31 (11.15)
Change from baseline at Week 24	86.7 (9.59)	126.8 (10.82)	95.0 (10.30)	97.1 (9.03)	90.9 (7.03)	111.5 (7.09)
Not de novo ENF	N = 229	N = 229	N = 215	N = 216	N = 444	N = 445
Baseline	143.77 (9.23)	150.34 (10.50)	147.67 (10.58)	130.14 (9.41)	145.66 (6.99)	140.53 (7.08)
Change from baseline at Week 24	59.4 (6.18)	80.1 (6.11)	56.8 (5.01)	73.1 (5.71)	58.1 (4.00)	76.7 (4.19)

Missing data imputed by LOCF up until the time point that the subject was calculated to have reached in the trial at the cut-off date, and time points after dropout imputed by 0 in NC = F analysis up to the time point that the subject would have been in the trial at the cut-off date.

Source: Module 2.7.3 Summary of Clinical Efficacy, Table 48

Increase from baseline at Week 24 in CD4 cell counts was higher in the TMC125 subjects than in placebo subjects. The use of de novo ENF increased the magnitude of the increase from baseline in CD4 cell counts in both treatment groups. In the de novo ENF subjects in the DUET-2 study, the increase in CD4 cell counts from baseline was almost the same in placebo and TMC125 treatment groups.

**APPEARS THIS WAY
ON ORIGINAL**

3.1.9 Reviewer's Efficacy Analyses

Snapshot Classification at Week 24 Trial TMC125-C206

All patients who discontinued before Week 24 except deaths were counted as discontinuations

Virologic Response Data Specification, n (%)	Placebo N = 308	TMC125 N = 304
<i>Viral Load < 50 copies/mL</i>	121 (39.3)	176 (57.9)
Non-Response Reason:		
Virologic failures at Week 24	165 (53.6)	103 (33.9)
Death¹	8 (2.6)	5 (1.6)
Discontinued due to VF before Week 24	0	1 (0.3)
Discontinuation due to AE	7 (2.3)	12 (3.9)
Discontinuation due to other reasons	7 (2.3)	7 (2.3)

N = number of subjects, n = number of observations, VF = virologic failure

¹All deaths except placebo subject 206-0193

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

Source: Statistical Reviewer's Analysis

Snapshot Classification at Week 24 Trial TMC125-C216

All patients who discontinued before Week 24 except deaths were counted as discontinuations

Virologic Response Data Specification, n (%)	Placebo N = 296	TMC125 N = 295
<i>Viral Load < 50 copies/mL</i>	122 (41.2)	182 (61.7)
Non-Response Reason:		
Virologic failures at Week 24	153 (51.7)	87 (29.5)
Death¹	7 (2.5)	4 (1.4)
Discontinued due to VF before Week 24	4 (1.4)	1 (0.3)
Discontinuation due to AE	4 (1.4)	16 (5.4)
Discontinuation due to other reasons	6 (2.0)	5 (1.7)

N = number of subjects, n = number of observations, VF = virologic failure

¹All deaths

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

Source: Statistical Reviewer's Analysis