Executive summary

TMC125 (etavirine) is an HIV non-nucleoside reverse transcriptase inhibitor (NNRTI) currently being developed by Tibotec Inc., Yardley, PA for use in treatment-experienced HIV-1 infected individuals in combination with other antiretroviral agents. Approximately six hundred HIV-1 infected subjects on a stable but virologically failing regimen were enrolled in each of the Phase III trials: DUET-1 (TMC125-C206, N=612) and DUET-2 (TMC125-C216, N=591). Eligible subjects were randomized, in a double-blind manner, to either the TMC125 group or the placebo group in a 1:1 ratio. Subjects in the TMC125 groups received TMC125 200 mg BID together with darunavir/ritonavir (DRV/rtv) (600/100mg BID) and optimized background regimen (OBR; with at least 2 ARV drugs: NRTI(s) with optional use of ENF).

The review focused on the following major questions:

Is there an exposure response relationship for TMC125 to support evidence of effectiveness?

Based on the univariate graphical analyses and logistic regression analyses, the fold change (fold change in IC50 relative to wild type control) in DRV was found to be the strongest predictor of success. The proportion of subjects with virologic success (HIV-1 RNA <400 copies/mL) was lower (~16% in the placebo and ~52% in the TMC125 treated subjects) at 42 (median of the last quantile) fold change in DRV. On the other hand, the proportion of subjects with virologic success was higher (~85% in the placebo and ~85% in the TMC125 treated subjects) at 1.1 (median of the first quantile) fold change in DRV. There was a modest dependency of virologic success on baseline viral load, baseline CD4+ cell count, compliance, phenotypic sensitivity score, TMC125 Cmin, TMC125 AUC, TMC125 Inhibitory quotient (IQ; ratio of Cmin and IC50). The use of IQ seem to be more appropriate than Cmin or AUC as the IQ accounts for Cmin and fold change in TMC125. The predicted likelihood of response as a function of the Cmin and IQ of TMC125 showed an initial increase and seemed to reach a plateau. The proportion of subjects with virologic success (viral load <400 copies/mL) was 52% in the placebo treated subjects, 59% in the group with median IQ of 47 (range 0.3-161), 75% in the group with median IQ of 295 (range 161-487), 85% in the group with median IQ of 833 (range 487-1409) and 89% in the group with median IQ of 2583 (range 1409-11402).

The finding made in the end of phase II review was confirmed that an IQ of at least 400 is required to maximize the probability of virologic success.

Simulations were conducted to assess effect of doubling TMC125 exposures (Cmin) in subjects with IQ<400. This was accomplished by doubling Cmin in subjects with IQ<400 while keeping the rest of the data same. The new IQ was calculated. The probability of virologic success increased to 77% from 74.5% by doubling the exposure. The marginal increase of 2.5% was observed. The reasons for small increase (2.5%) were investigated. There were more failures in subjects with higher fold change in DRV even

if they achieved relatively higher IQ. On the other hand, less number of failures was seen in subjects with lower fold change in DRV and relatively low IQ (see Figure 5).

The implications of these findings on TMC125 clinically are more important. In order to achieve the response rate seen in phase III trials, it is important that patient's ART regimen should have at least one fully active and strong agent, for example DRV, when adding TMC125 to patient's optimized ART.

Is there an exposure safety relationship for TMC125?

Rash

A total of 167 records (from 141 subjects) of rash and rash type events were identified. In the pooled DUET analyses, the proportion of subjects with rash (any type) was higher in TMC125 group (15%) compared to the placebo group (8%). The trend was similar in individual studies, however, the proportion of subjects with rash (any type) was higher (18%) in DUET-1 compared to DUET-2 (12%). Rash with TMC125 treatment mostly emerged during the first weeks of treatment. In the TMC125 group, the median time to onset was 12 days (range 1 to 231 days) and the median duration was 11 days (range 1 to 171 days). The predicted likelihood of response (rash) as a function of TMC125 AUC showed an increase with increasing AUC. The proportion of subjects with rash was 8% in the placebo treated subjects, 10% in the lowest quantile of TMC125 AUC (median=2413, range=145-3026 hr•ng/mL), 13% in the 2nd quantile of TMC125 AUC (median=3805, range=3026-4525 hr•ng/mL), 14% in the 3rd quantile of TMC125 AUC (median=5462, range=4525-6530 hr•ng/mL) and 17% in the last quantile of TMC125 AUC (median=8882, range=6530-64164 hr•ng/mL).

Of the subjects who had rash or rash type event, 8.5% (12/141) subjects permanently discontinued TMC125 treatment and 8% (11/141) subjects temporarily discontinued TMC125 treatment. The pharmacokinetic data were available in only 2 subjects out of 12 before or at discontinuation. The median time to drop out was 11 days with a range of 2-27 days.

In conclusion, the likelihood of rash events appeared to increase with increasing TMC125 exposures. Higher frequency of rash AEs was observed in females compared to males. Also, higher frequency of rash AEs was observed in Caucasian subjects, event rate in Caucasians 17% compared to event rate 10% in minorities.

Serum creatinine

Mean creatinine levels tended to slightly increase over time with a trend to higher increases in the TMC125 arm. The effect of TMC125 on serum creatinine was, however, no worse than effect of TDF and/or placebo. A trend towards an additive effect on mean change in serum creatinine between TMC125 and TDF did not translate into higher number of subjects with Grade 3 or 4 changes in serum creatinine.

Benefit-risk assessment for rash

Based on exposure-virologic success relationship, TMC125 IQ of >400 does not lead to incremental benefit in virologic success, an IQ of 400 corresponds to Cmin of ~200 (400

multiplied by median IC50 (0.5)). It was also established that incidence of rash increases with increasing exposures.

A mean Cmin of 200 ng/mL corresponds to mean AUC~2300 hr•ng/mL. For IC50 equal to 1 and a target IQ of 400, the corresponding AUC would be ~6300 hr•ng/mL. Therefore, the risk-benefit in subjects with median IC50 is different than subjects with IC50 greater than median IC50. Therefore, the multivariate relationship does not allow a global rule controlling TMC125 exposures. If the exposures are reduced in overall population to control toxicity, such exposures could be subtherapeutic for some subjects. At the same time, if the exposures are increased in overall population to maximize benefit, such exposures could be toxic for some subjects.

In the DUET trials, no incidence of Stevens-Johnson syndrome was observed on TMC125. Most rash events appeared in the first few weeks of the treatment. In reviewer's opinion, the exposures of TMC125 should not exceed to the exposures achieved in DUET trials. Also, any PK intervention for rash management might not be useful. It will be beneficial to identify characteristics of subjects who might be susceptible to TMC125 induced rash.

Are the labeling claims based on population PK supported?

Based on population PK analyses, the sponsor concluded that no dose adjustment was needed based on hepatitis B &/or C co-infection, gender, race, age (age range 18-77 years) and use of T-20.

The sponsor's analyses were replicated and additional empirical evidence was used to validate the findings. There were no major pharmacokinetic differences by subgroups to the extent requiring dose adjustment.

Recommendations

1. The exposure response analyses support effectiveness of TMC125 in HIV-1 infected subjects.
2. The dose adjustment of TMC125 for drug-drug interaction should be carefully considered. The range of exposures of TMC125 should at least not exceed to the exposures achieved in DUET trials.
3. No adjustments for TMC125 are recommended based on hepatitis B &/or C co-infection, gender, race, age (age range 18-77 years) and use of T-20.

Introuduction

TMC125 (etravirine) is an HIV non-nucleoside reverse transcriptase inhibitor (NNRTI) currently being developed by Tibotec Inc., Yardley, PA for use in treatment-experienced HIV-1 infected individuals in combination with other antiretroviral agents. Two phase III clinical studies, protocols TMC125-C206 (DUET-1) and TMC125-C216 (DUET-2) have been conducted to investigate the efficacy, tolerability and safety of TMC125 as part of an antiretroviral treatment (ART) including darunavir/ritonavir (DRV/rtv) and an investigator-selected optimized background regimen (OBR) in HIV-1 infected subjects with limited to no treatment options.

Data

The data from two placebo controlled registration studies (DUET-1 and DUET-2) of TMC125 in addition to an ART containing DRV/rtv, nucleoside reverse transcriptase inhibitor(s) (NRTI[s]) and optional enfuvirtide (ENF, T20) in treatment-experienced HIV-1 infected subjects were used in the exposure-response analyses. The supportive or further exploratory analyses included 12 and 24 week data from two phase 2b trials, a dose escalation trial (TMC125-C203) and a dose finding trial (TMC125-C223), respectively. The results were confirmed at 24 week for TMC125-C203.

Protocol TMC125-C206 (DUET-1) [Registration study in HIV-1 infected subjects with limited to no treatment options; United States, Brazil, Argentina, France, Mexico, Panama, Chile, Thailand and Puerto Rico]

This is an ongoing Phase III, randomized, double-blind, placebo-controlled trial to evaluate the long-term efficacy, tolerability, and safety of TMC125 in addition to an antiretroviral therapy containing DRV/rtv, nucleoside reverse transcriptase inhibitor(s) and optional enfuvirtide in treatment-experienced HIV-1 infected subjects. In addition, immunologic changes, changes in the HIV-1 genotype, drug susceptibility, population pharmacokinetics, and pharmacokinetic/pharmacodynamic relationships were assessed. A pharmacokinetic substudy was performed at selected sites. Six hundred HIV-1 infected subjects on a stable but virologically failing regimen were to be included in the trial. Subjects with at least 1 documented NNRTI resistance-associated mutation (RAM) (either at Screening or from historical genotype reports), at least 3 documented primary protease inhibitor (PI) mutations, and an HIV-1 plasma viral load > 5000 RNA copies/mL at Screening were eligible. Subjects were randomized in a 1:1 ratio to either TMC125 (200 mg BID) or to matching placebo; both in combination with DRV/rtv (600/100 mg BID) and an investigator-selected OBR of at least 2 antiretrovirals (ARVs) consisting of NRTI(s) with or without ENF. The use of ENF was optional and de novo use of ENF was limited to a maximum of 40% of the overall trial population. The trial consists of a screening period of maximum 6 weeks, a 48-week treatment period, and a 4-week follow-up period. The data and report submitted to the agency describe the results of the primary analysis of the ongoing trial when all subjects reached Week 24 or discontinued earlier. The cut-off date for this analysis was 18-Jan-2007.

- Pharmacokinetic sampling: At a number of visits throughout the trial (Weeks 4, 8, 12, 24, 48, 72, 96/withdrawal visit), blood samples were taken to determine the TMC125, DRV (also known as TMC114) and ritonavir concentrations. At Week 4, 2 samples were taken. The first sample was to be a trough sample (taken immediately before intake of investigational medication). The second sample was taken at least 1 hour after intake of investigational medication. Sampling at the other time points was done at any given time point after intake of medication. Subjects from selected sites, willing to participate in the substudy and eligible to participate in main trial were asked to participate in a pharmacokinetic substudy.

These subjects had a 12-hour pharmacokinetic sampling period at Weeks 4 and 24 in addition to the assessments conducted for the main trial.

- Pharmacodynamic sampling: At each visit specified in the protocol through week 96, blood samples were collected to assess plasma HIV-RNA load, CD4+ cell count and samples for phenotype and genotype determinations.
- Virologic failure[†]: Unblinding after discontinuation for virological failure in case of urgent medical need was allowed under strict circumstances, i.e., only for subjects with very limited options for whom knowledge of the previous use of TMC125 in DUET trial was required to compose a new regimen. Unblinding was only possible after the primary time point (database lock Week 24 data) has been reached.
- Treatment: TMC125 200 mg BID (Formulation F060) was administered with food. TMC114/rtv 600/100 mg BID was administered with food.

Protocol TMC125-C216 (DUET-2) [Registration study in HIV-1 infected subjects with limited to no treatment options; United States, France, Italy, Germany, Canada, Spain, Australia, Belgium, United Kingdom, The Netherlands, Poland and Portugal]

This study was designed identical in most respects to DUET-1 except that it recruited subjects from different countries.

[†] Virologic failure '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. Virologic failure 'loss of response' is defined as 2 consecutive measurements of plasma viral load > 0.5 log10 above the nadir after a minimum of 12 weeks of treatment. Confirmation had to be done at the next planned visit or at an unscheduled visit. There was to be a minimum 2-week interval between plasma viral load assessments.

Exposure response analyses

Is there an exposure response relationship for TMC125 to support evidence of effectiveness?

Approximately six hundred HIV-1 infected subjects on a stable but virologically failing regimen were enrolled in each of the Phase III trials: DUET-1 (TMC125-C206, N=612) and DUET-2 (TMC125-C216, N=591). Eligible subjects were randomized, in a double-blind manner, to either the TMC125 group or the placebo group in a 1:1 ratio. Subjects in the TMC125 groups received TMC125 200 mg BID together with DRV/rtv (600/100mg BID) and OBR (at least 2 ARV drugs: NRTI(s) with optional use of ENF). The primary analysis of both DUET studies was done when all subjects completed 24 weeks of treatment.

In the present PK/PD analysis, the effect of TMC125 on viral load was analyzed as a binary variable (virologic success) and the effect of TMC125 exposure and various prognostic factors on viral load was evaluated using generalized additive logistic regression models. The sponsor also analyzed CD4 counts using generalized additive models (GAM) but as the continuous variable change from baseline.

Virologic response at week 24 was defined as confirmed viral load below 50 copies/mL (VL50) as the primary endpoint, as well as confirmed viral load below 400 copies/mL (VL400) as secondary endpoint. The pharmacokinetic exposure parameters of TMC125 that were investigated were the steady-state pre-dose concentration (Cmin) and the AUC during a dosing interval (AUCτ) obtained via Bayesian feedback.

The final analysis dataset up to week 24 consisted of 1203 subjects who received TMC125 or placebo. Pharmacokinetic exposure parameters of TMC125 were obtained in 294 subjects from DUET-1 and in 280 subjects from DUET-2. Table 1, Table 2 and Figure 1 summarizes categorical variables in the dataset used for the PKPD analyses.

Table 1: Description of the data used by the sponsor and reviewer

Parameter[1]	Number of subjects	Percentage
Study		
DUET-1 (TMC125-C206)	612	50.9%
DUET-2 (TMC125-C216)	591	49.1%
Race		
Caucasian/White	749	62.3%
Black	140	11.6%
Hispanic	126	10.5%
Oriental/Asian	10	0.8%
Other/Not allowed to ask	178	14.8%
Sex		
Male	1074	89.3%
Female	129	10.7%
ENF in background therapy		
No	647	53.8%
De novo use	313	26.0%
Re-use	243	20.2%
Tenofovir in background therapy		
No	323	26.8%
Yes and sensitive	291	24.2%
Yes and insensitive	589	49.0%
Number of sensitive NRTI's		
0	640	53.2%
1	359	29.8%
2	166	13.8%
3	19	1.6%
NA's	19	1.6%
Hepatitis B or C co-infection		
No	990	82.3%
Yes	139	11.6%
NA's	74	6.1%
Virologic response after placebo (total n = 604)		
VL < 50 copies/mL	248	41.1%
VL < 400 copies/mL	317	52.5%
Virologic response after TMC125 (total n = 599)		
VL < 50 copies/mL	353	58.9%
VL < 400 copies/mL	445	74.3%

(Source: Sponsor's table 1 from tmc125-c931-crr-pkpd.pdf; page 13/67)

Table 2: Description of the data used by the sponsor and reviewer (Table 1 data split by study)

Type	Pooled DUET	DUET-1		DUET-2	
		Placebo	TMC125	Placebo	TMC125
Total (N)	1203	308	304	296	295
Race					
Caucasian (N)	749	189	187	187	186
Black (N)	140	35	39	35	31
Hispanic (N)	126	42	41	24	19
Oriental/Asian (N)	10	3	2	NA	5
Other/Not allowed to ask (N)	178	39	35	50	54
Sex					
Male (N)	1074	264	263	271	276
ENF in background therapy					
No T20 use (N)	647	181	183	140	143
De novo T20 use (N)	313	79	74	81	79
De novo T20 use (N)	243	48	47	75	73
Tenofovir in background therapy					
No Tenofovir use (N)	323	66	65	106	86
Tenofovir use and sensitive (N)	291	77	79	63	72
Tenofovir use and insensitive (N)	589	165	160	127	137
Number of sensitive NRTIs					
0 (N)	640	162	161	161	156
1 (N)	359	96	82	90	91
2 (N)	166	41	50	34	41
3 (N)	19	3	6	5	5
Hepatitis B or C coninfection					
+ve (N)	139	31	34	36	38
-ve (N)	990	250	248	245	247

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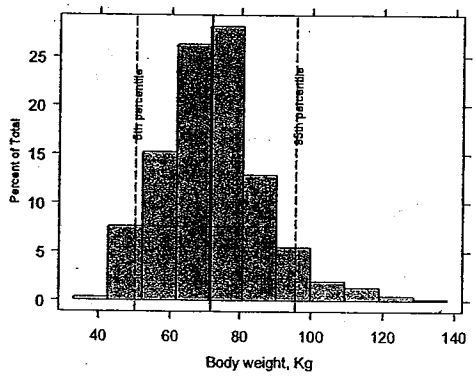
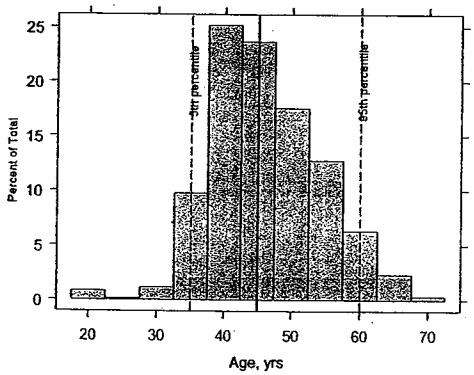
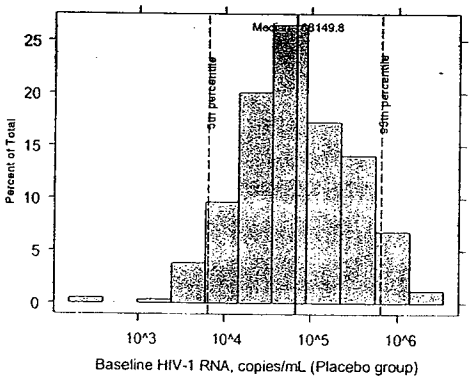
Figure 1: Description of the data (Pooled DUET) used by the sponsor and reviewer (continuous variables)

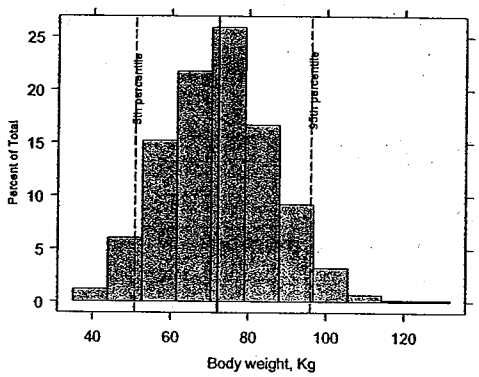
Placebo group

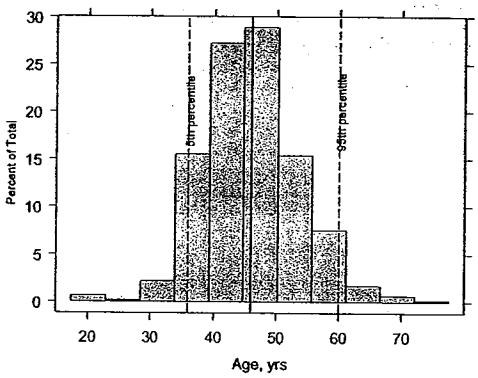


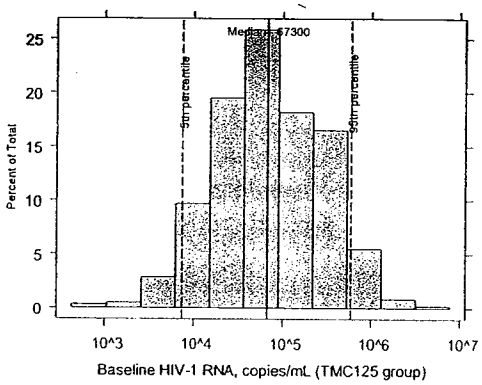


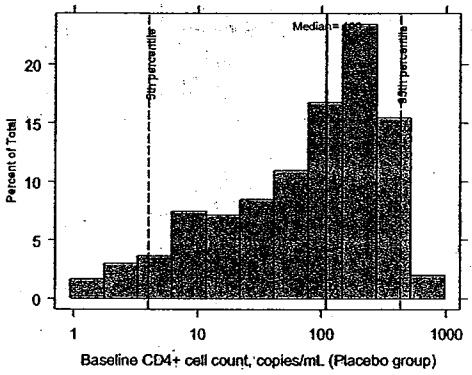


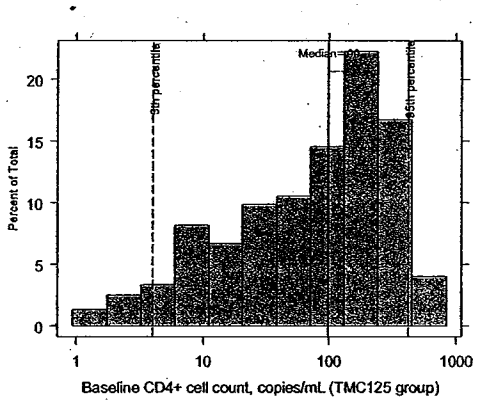
TMC125 group








Median=100
5th percentile
95th percentile
Percent of Total
0
5
10
15
20
1
10
100
1000
Baseline CD4+ cell count, copies/mL (Placebo group)


Median=90
5th percentile
95th percentile
Percent of Total
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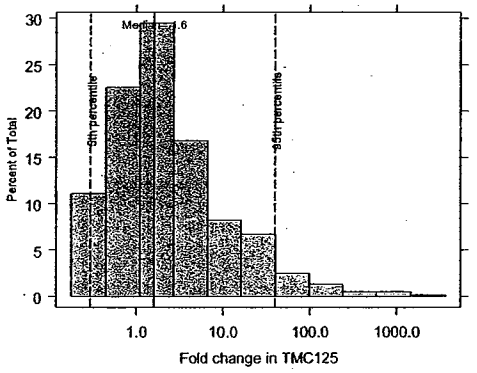
5
10
15
20
1
10
100
1000
Baseline CD4+ cell count, copies/mL (TMC125 group)

NA


Median=7.6
5th percentile
95th percentile
Percent of Total
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5
10
15
20
25
30
1.0
10.0
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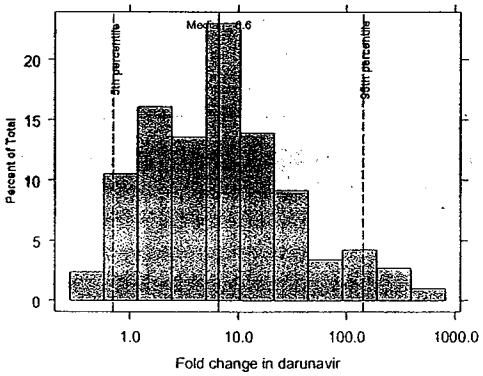
Fold change in TMC125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95th percentile
Percent of Total
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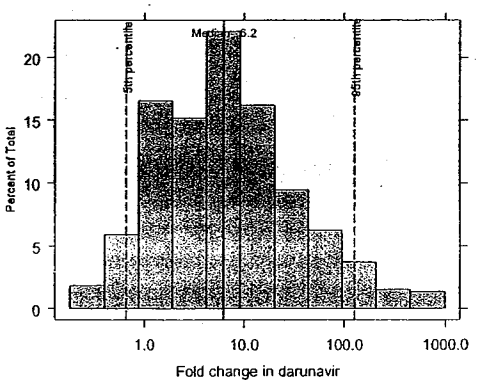
10.0
100.0
1000.0
Fold change in darunavir


Median=9.2
5th percentile
95th percentile
Percent of Total
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5
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10.0
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1000.0
Fold change in darunavir

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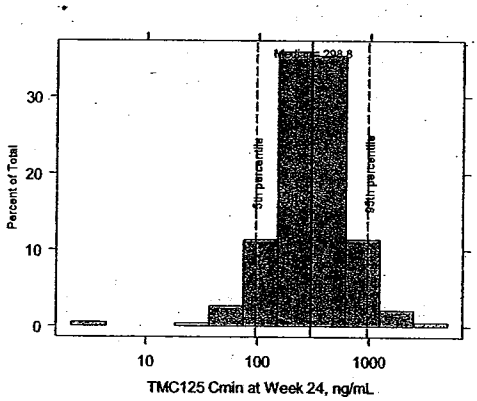

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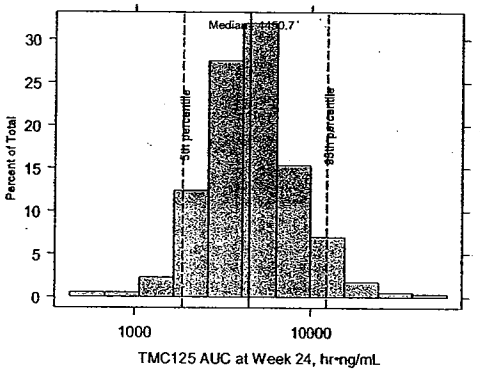
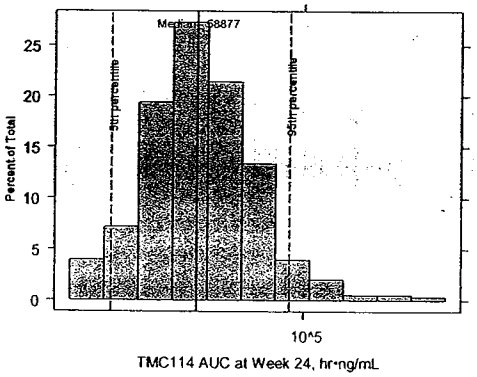
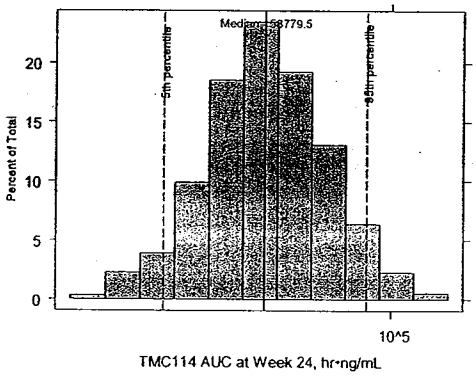






Sponsor's analyses

According to the sponsor, exposure to TMC125 was not a prognostic factor for the primary efficacy parameter at week 24 (i.e. virologic response defined as viral load < 50 copies/mL) and for CD4 count change from baseline, so that no exposure-effect relationship appeared to be present for these two efficacy parameters. This might be explained by reaching the plateau of the maximal effect for the evaluated exposure range of TMC125.

For virologic response defined as viral load below 400 copies/mL exposure to TMC125 was retained as a prognostic factor, in addition to the well known prognostic factors such as baseline viral load (BVL), baseline CD4 count (BCD4), Phenotypic Sensitivity Score (PSS), phenotypic fold change for DRV (FCDRV), phenotypic fold change for TMC125 (FC125), compliance based on pill-count (COMP) and de novo use of T20. As the correlation was high between C0H and AUCτ of TMC125, no particular exposure parameter of TMC125 was found to be markedly superior as prognostic factor for this clinical endpoint.

When the virologic response was defined as viral load below 400 copies/mL, the predicted likelihood of response showed an initial increase with an increasing C0h or AUCt of TMC125 and seemed to reach a plateau.

In summary, a PK/PD analysis using generalized additive models revealed that exposure to TMC125 was neither retained as prognostic factor for the primary efficacy parameter (i.e. virologic response defined as viral load < 50 copies/mL) nor for CD4 count change from baseline. The likelihood of virologic response defined as viral load below 400 copies/mL was predicted to slightly increase with increasing exposure to TMC125. Other factors such as baseline CD4 count, fold change of DRV, fold change of TMC125, baseline viral load and PSS are more important drivers of response to TMC125.

For more details refer study report (\\Cdsesub1\evsprod\NDA022187\0002\m5\53-clin-stud-rep\535-rep-effic-safety-stud\treatment-of-hiv-1-infection\5353-rep-analys-data-more-one-stud\tmc125-c931\ tmc125-c931-crr-pkpd.pdf)

Reviewer's assessment

The sponsor's analyses were replicated and the reviewer was in agreement with the sponsor's analyses.

The analyses were extended to assess:

1. the use of inhibitory quotient (Plasma trough concentration (Cmin, ng/mL) divided by the in vitro IC50 concentration in µM multiplied by the molecular weight of TMC125 (435.28)) as a predictor of virologic success.
    a. Inhibitory quotient (IQ) was used as a predictor in the end of phase II meeting review to decide on future development of TMC125.

b. The sponsor implicitly included IQ in the analyses by using Cmin and fold change in TMC125 as predictors in a multivariate model. However, the values of the phenotypic fold change for TMC125 (FC125) for all subjects in the placebo treated groups were replaced by the upper limit of quantification of the assay, i.e. 5000. According to the sponsor, the measured fold change for TMC125 after placebo should not have an additional contribution to the likelihood of response or CD4 count change from baseline as no TMC125 was administered. This situation was mimicked by assuming a very high resistance to TMC125 with placebo treatment and which is why the fold change for TMC125 after placebo was set to the upper limit of quantification of the fold change for TMC125.

2. a possibility of maximizing TMC125 effect for subjects with lower exposures who might have lower overall virologic success.

- **Univariate analyses of virologic success (<50 copies/mL and <400 copies/mL)**

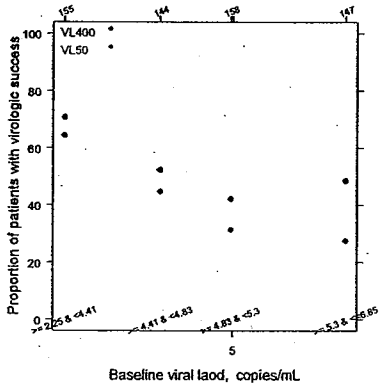
Figure 2 illustrates the relationship between various covariates (baseline HIV-1 RNA, baseline CD4+ count, age, body weight, compliance, race, sex, continuous phenotypic sensitivity score, DRV AUC, TMC125 Cmin, IQ, AUC and fold change in DRV) and proportion of subjects with virologic success. The virologic success was higher in subjects with lower baseline HIV RNA, higher CD4+ cell count.

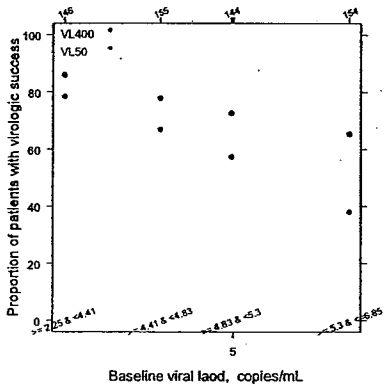
The fold change in DRV was found to be strongest predictor of success. The proportion of subjects with virologic success was lower (~16% in the placebo and ~52% in the TMC125 treated subjects) at 42 (median of the last quantile) fold change in DRV. On the other hand, the proportion of subjects with virologic success (<400 copies/mL) was higher (~85% in the placebo and ~85% in the TMC125 treated subjects) at 1.1 (median of the first quantile) fold change in DRV.

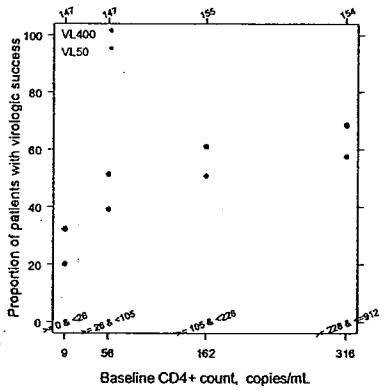
There was a modest dependency of virologic success on baseline viral load, baseline CD4+ cell count, compliance, phenotypic sensitivity score, Cmin, AUC, IQ. The use of IQ seem to be more appropriate than Cmin or AUC as the IQ accounts for Cmin and fold change in TMC125.

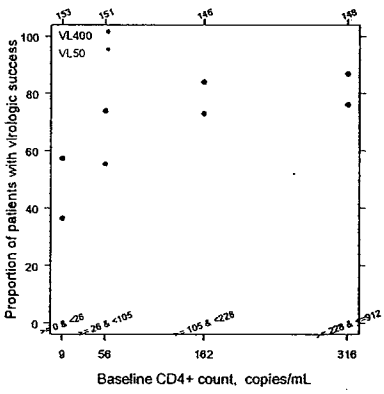
Figure 2: Relationship between virologic success and baseline HIV-1 RNA, baseline CD4+ cell count, age, body weight, compliance, race, sex, continuous phenotypic sensitivity score, DRV AUC, TMC125 Cmin, TMC125 IQ, TMC125 AUC, fold change in DRV. The mean response is plotted against the median for each quantile or group by dose groups. The sample size for each quantile or group is included at the top and the range for each quantile is indicated as appropriate.

Placebo group **TMC125 group**









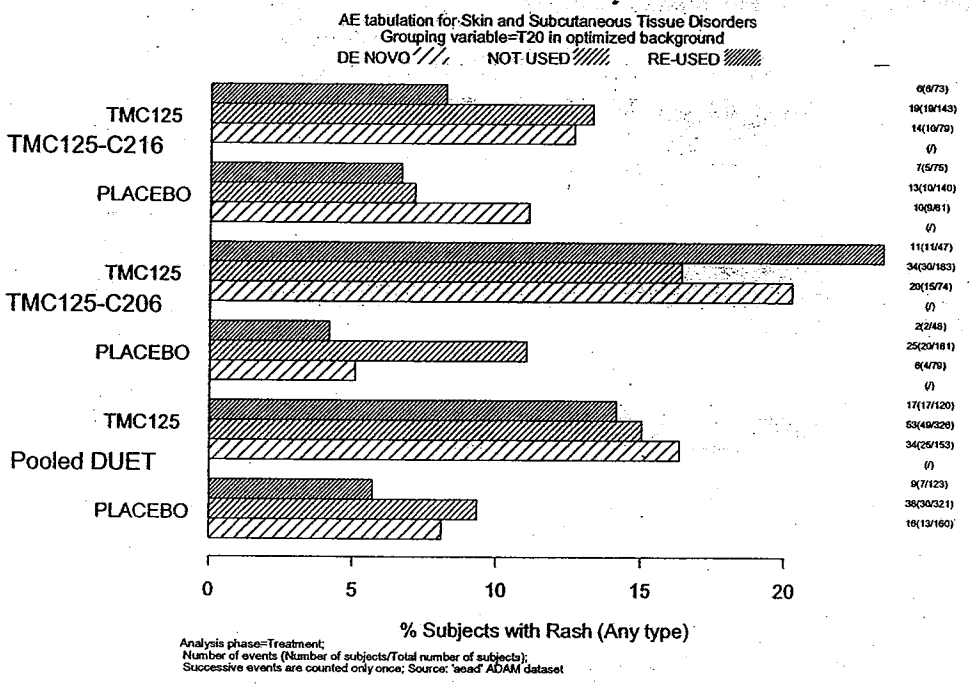


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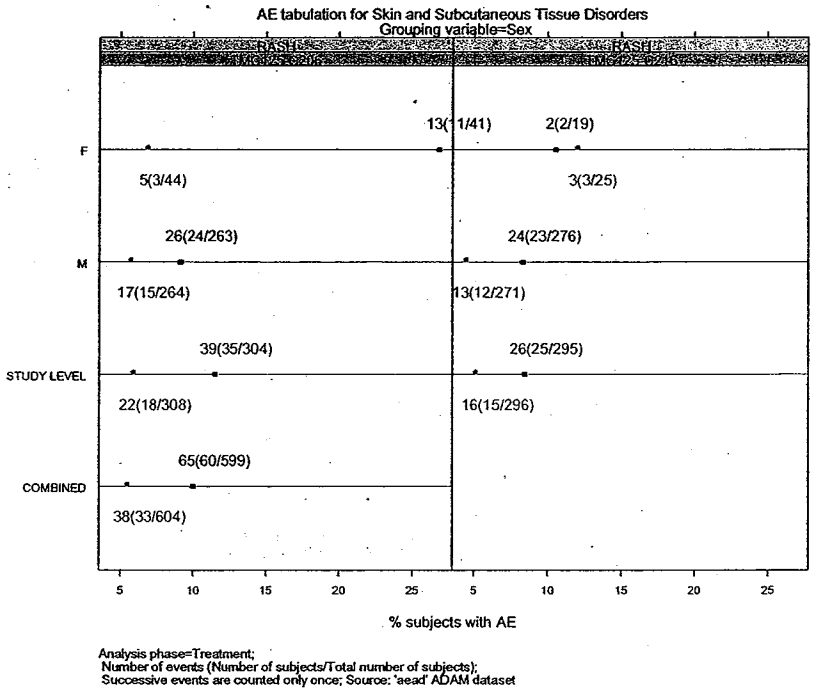
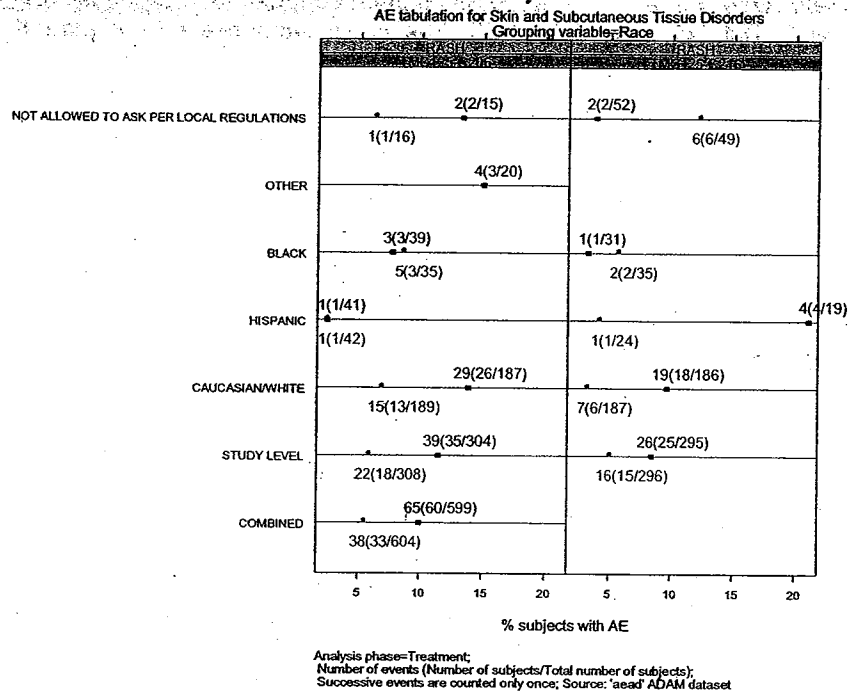
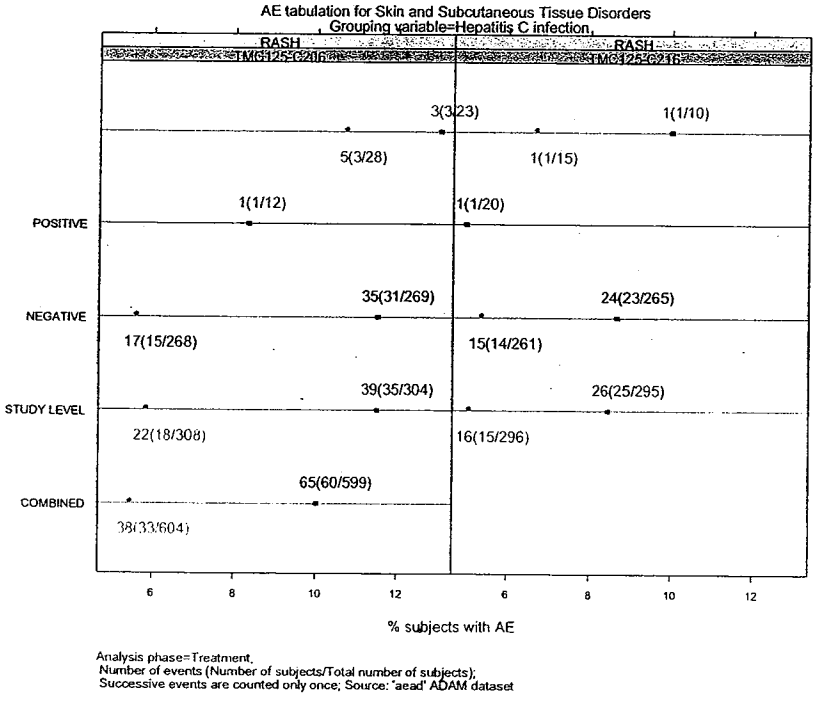
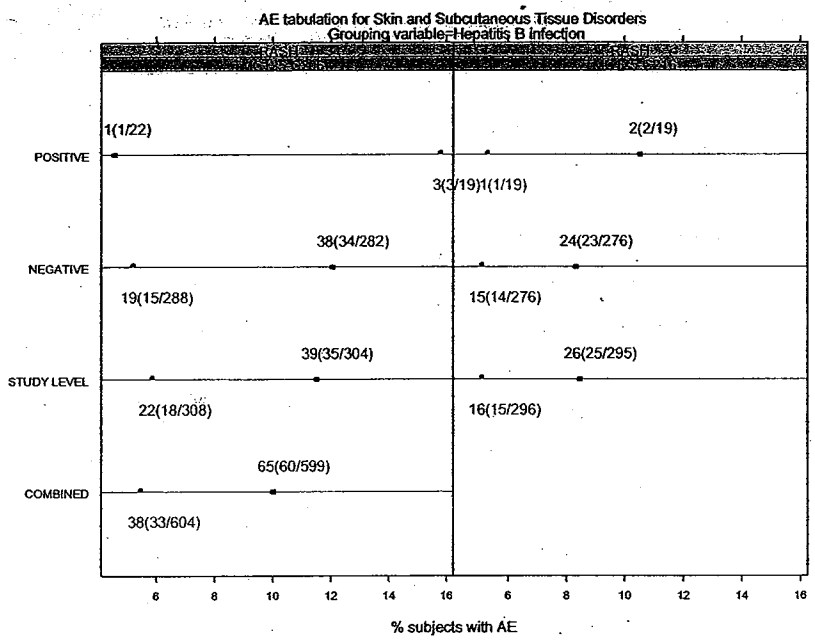
Figure 9: Relationship between proportion of subjects with rash (AEDECOD="RASH") and treatment arm, Sex, Race, Hepatitis C infection, Hepatitis B infection, Baseline CD4+ cell count, Baseline HIV-1 RNA, TMC125 AUC, DRV AUC. The mean incidence rate is plotted against the median for each quantile or group by dose groups.

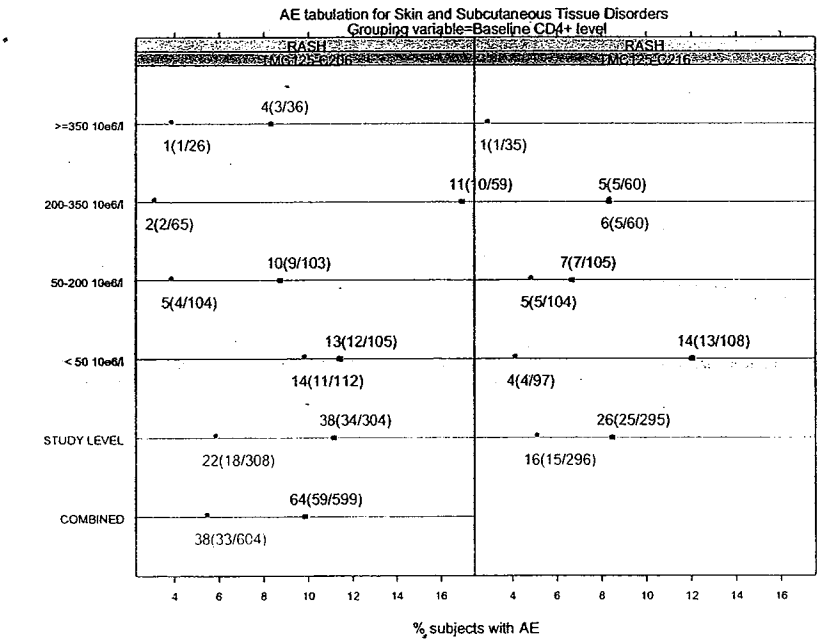



AE tabulation for Skin and Subcutaneous Tissue Disorders
Grouping variable=Race
RASH
TMC125-C216
RASH
TMC125-C216
NOT ALLOWED TO ASK PER LOCAL REGULATIONS
2(2/15)
1(1/16)
2(2/52)
6(6/49)
OTHER
4(3/20)
BLACK
3(3/39)
5(3/35)
1(1/31)
2(2/35)
HISPANIC
1(1/41)
1(1/42)
4(4/19)
1(1/24)
CAUCASIAN/WHITE
29(26/187)
15(13/189)
19(18/186)
7(6/187)
STUDY LEVEL
39(35/304)
22(18/308)
26(25/295)
16(15/296)
COMBINED
65(60/599)
38(33/604)
5
10
15
20
% subjects with AE
Analysis phase=Treatment;
Number of events (Number of subjects/Total number of subjects);
Successive events are counted only once; Source: 'aead' ADAM dataset

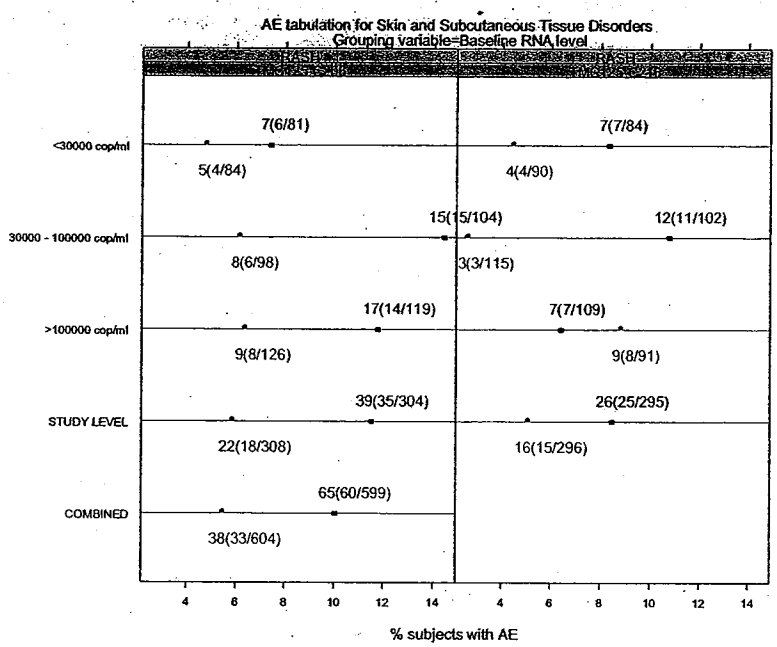

AE tabulation for Skin and Subcutaneous Tissue Disorders
Grouping variable=Hepatitis C infection
RASH
TMC125-C216
RASH
TMC125-C216
POSITIVE
3(3/23)
5(3/28)
1(1/10)
1(1/15)
1(1/12)
1(1/20)
NEGATIVE
35(31/269)
17(15/268)
24(23/265)
15(14/261)
STUDY LEVEL
39(35/304)
22(18/308)
26(25/295)
16(15/296)
COMBINED
65(60/599)
38(33/604)
6
8
10
12
% subjects with AE
Analysis phase=Treatment;
Number of events (Number of subjects/Total number of subjects);
Successive events are counted only once; Source: 'aead' ADAM dataset



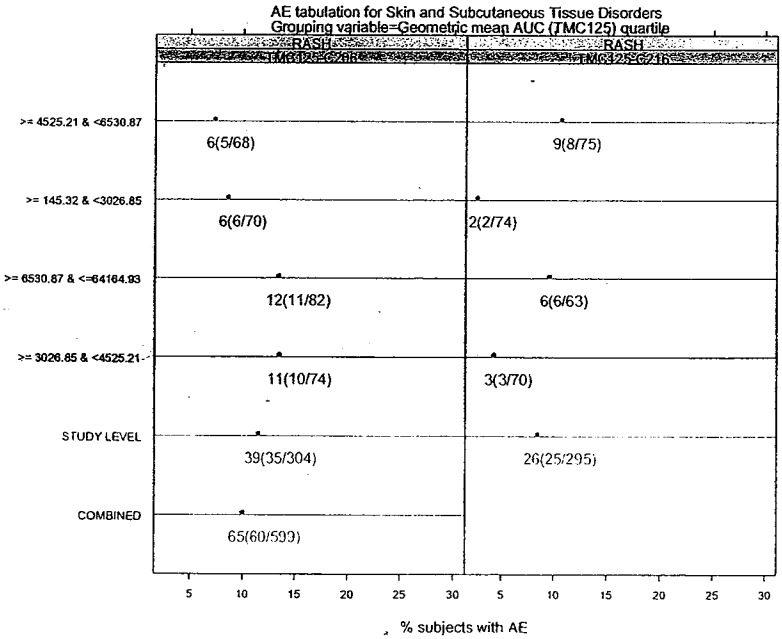
Analysis phase=Treatment;
Number of events (Number of subjects/Total number of subjects);
Successive events are counted only once; Source: 'aead' ADAM dataset



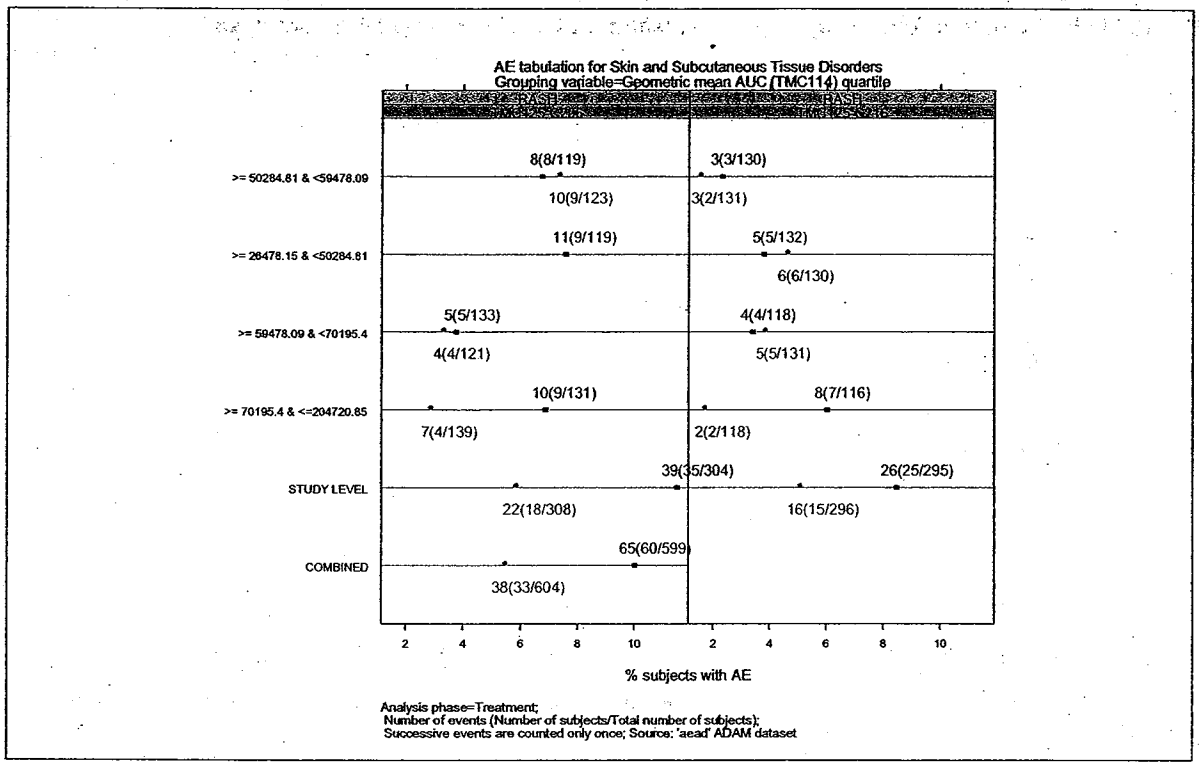
Analysis phase=Treatment;
Number of events (Number of subjects/Total number of subjects);
Successive events are counted only once; Source: 'aead' ADAM dataset



Analysis phase=Treatment;
Number of events (Number of subjects/Total number of subjects);
Successive events are counted only once; Source: 'aead' ADAM dataset



Analysis phase=Treatment;
Number of events (Number of subjects/Total number of subjects);
Successive events are counted only once; Source: 'aead' ADAM dataset

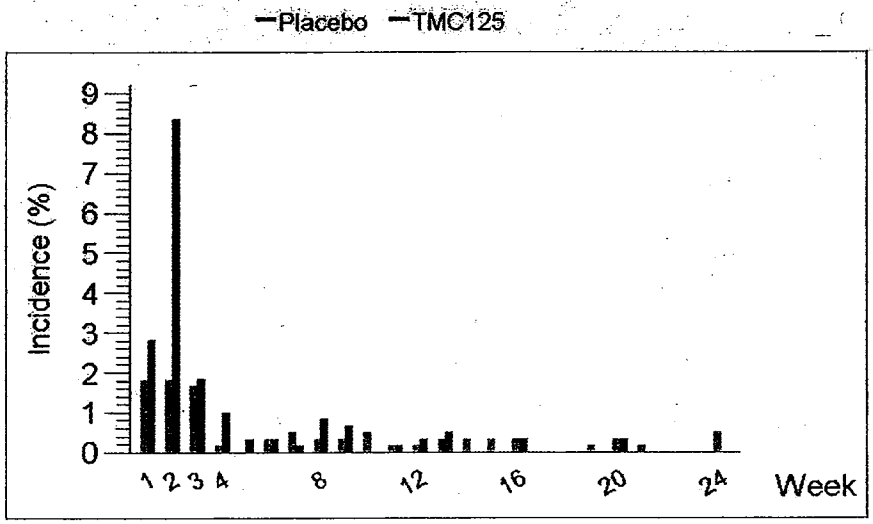


- **Time to rash event**

After analyzing effect of covariates on rash incidence, time to rash event was investigated. As shown in Figure 10, rash with TMC125 treatment mostly emerged during the first weeks of treatment. For the rashes in the TMC125 group, the median time to onset was 12 days (range 1 to 231 days) and the median duration was 11 days (range 1 to 171 days). In the placebo group, the median time to onset for rash was 45 days (range 1 to 225 days) and the median duration was 17 days (range 1 to 233 days).

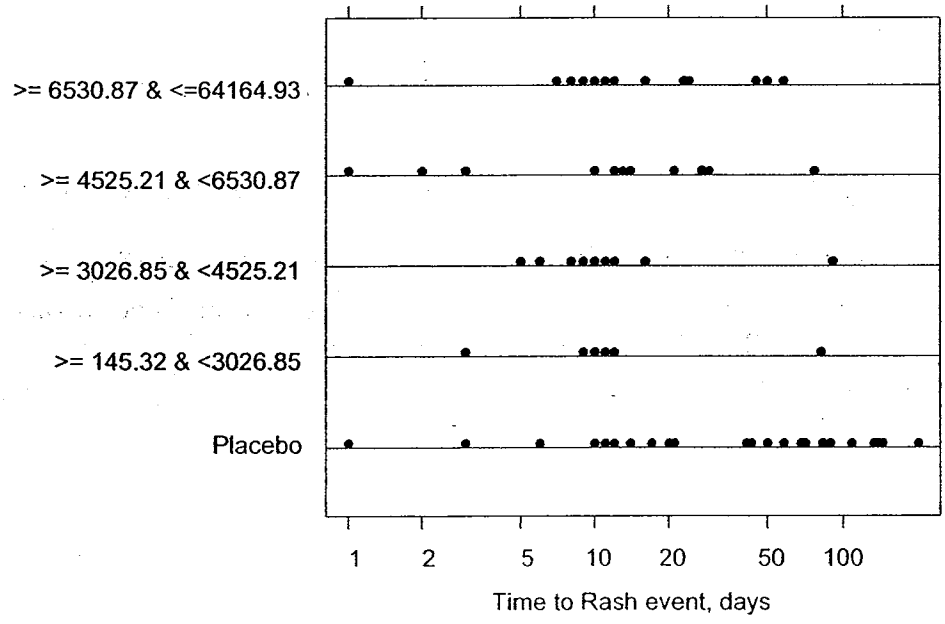
As most of the events happened in first few weeks of the treatment, the time to rash event was not related to TMC125 AUC (Figure 11).

Figure 10: Incidence of Rash (Any Type) by Treatment Group (Pooled DUET Analysis)



Source: Sponsor's figure 2; Page 77 of 418 of TMC125-20070600-cls-saf.pdf

Figure 11: Time to rash in the placebo treated subjects and TMC125 treated subjects divided according TMC125 AUC quantiles



- Generalized additive modeling

The effect of TMC125 exposure and several other predictors on rash events was analyzed as a binary variable (irrespective rash grade; most of the events were grade 1 or 2) using both logistic regression and generalized additive models (GAM). A GAM model was built using the automated step-wise search developed in S-PLUS. This automated step-wise search selects the best GAM using forward selection and backwards deletion given the range of models. A series of candidate relationships (e.g. linear, log-transformation, spline, Loess smooth) that describe how each particular predictor might enter the model was defined for every predictor and the final model was built up by evaluating all candidate forms for each predictor in a step-wise manner.

The GAM ready dataset was created by merging adverse event dataset (aead.xpt) for 141 subjects with rash and demographic datatset (dmad.xpt) for 1203 randomized subjects. For automated search, baseline viral load, baseline CD4+ cell count, sex, study number, weight, race, hepatitis C infection, hepatitis B infection, TMC125 AUC, TMC114 AUC, age, use of T20 was evaluated as predictors of rash events. The results of the automated step-wise searches for the prognostic factors of virologic success are given in Table 7 and Figure 12.

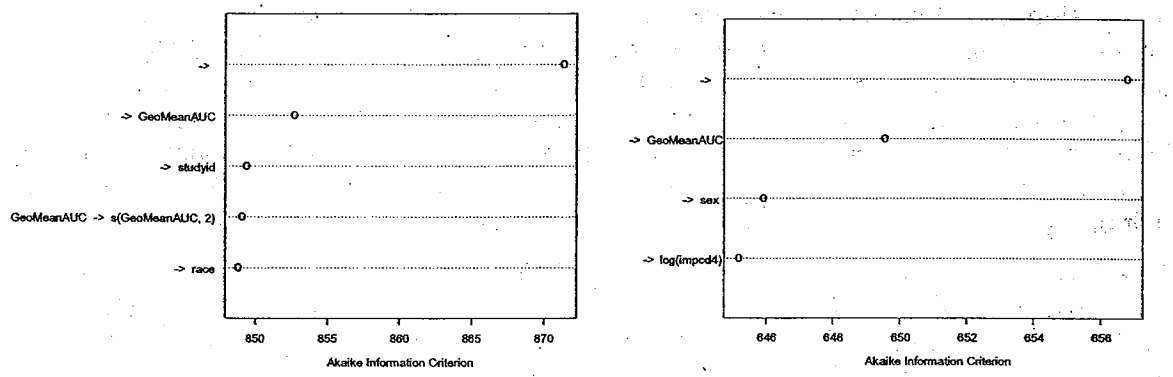
Table 7: GAM models at the end of automated step-wise searches for prognostic factors of rash events.

Model	Endpoint	Parameter included in the analysis	GAM model
1	Incidence of rash (any type)	TMC125 AUC (GeoMeanAUC)	
2	Incidence of rash (AEDECOD="RASH")	TMC125 AUC (GeoMeanAUC	

In model 1, race and study number and in model 2, sex and baseline CD4+ cell count were identified as the predictors of rash events in addition to TMC125 AUC, which was the strongest predictor (largest drop in AIC). Given the small differences with respect to race and sex, inconsistent effect of baseline CD4+ cell count across studies as revealed in the univariate analyses, the implications of these findings were not obvious.

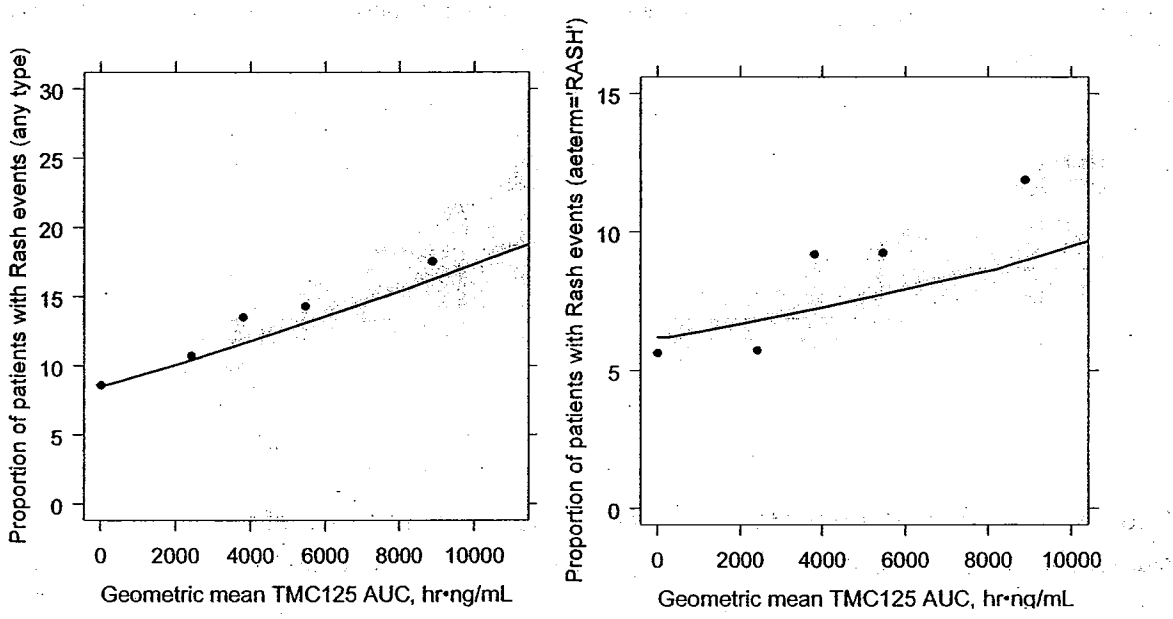
Most importantly, the TMC125 AUC was identified as predictor and the probability of rash increased with increasing TMC125 AUC.

Figure 12: Results of the automated step-wise GAM search for prognostic factors of rash events (Left: Any type- model 1; Right: AEDECOD="RASH"- model 2). On the y-axis, "-> a" indicates addition of variable "a"; "a->b" indicates the replacement of variable "b" with "a".



Simulations of exposure-rash event relationship including model uncertainty (but not the residual error) were performed. TMC125 pharmacokinetic exposure values covering the observed exposure range were assigned to each patient in the original database while keeping all other data as it was originally recorded. The likelihood of rash event was subsequently predicted based on the corresponding 500 sets of GAM parameters obtained in a bootstrap step. The calculated median and 95% confidence interval for the predictions from the replicates were presented graphically, as a function of TMC125 exposure. The predicted likelihood of response (rash) as a function of TMC125 AUC showed an increase (Figure 13) with increasing AUC. The proportion of subjects with rash was 8% in the placebo treated subjects, 10% in the lowest quantile of TMC125 AUC (median=2413, range=145-3026 hr•ng/mL), 13% in the 2nd quantile of TMC125 AUC (median=3805, range=3026-4525 hr•ng/mL), 14% in the 3rd quantile of TMC125 AUC (median=5462, range=4525-6530 hr•ng/mL) and 17% in the last quantile of TMC125 AUC (median=8882, range=6530-64164 hr•ng/mL). The uncertainty of the predicted likelihood of response increased substantially for higher TMC125 AUC (data not shown AUC >10000). This finding might be explained by the limited number of subjects having AUC of 10000 or more (Figure 2).

Figure 13: Median (95% CI) prediction of likelihood of response (rash event) as a function of TMC125 AUC (left panel-Model 1 and right panel-Model 2), based on the GAM models fitted to 500 bootstrap samples of the original data set. (circles: observed data, line and shaded area: model prediction)



In Figure 13, there was a good agreement between observed data and model predictions for rash events as far as the trend is considered. The GAM model underpredicts rash events at high TMC125 exposures. However, it is sufficient to conclude that rash events were related to TMC125 exposures.

For implications of these finding see - Understanding Exposure-virologic success and Exposure-safety relationship.

- Rash related Dropouts and exposure

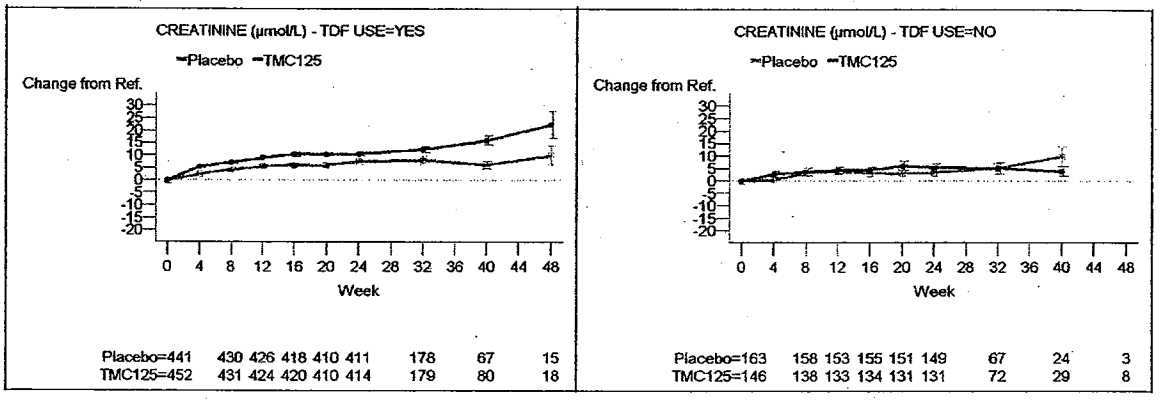
Rash was further investigated to explore exposures achieved in subjects who discontinued due to rash or rash type of events. Of the subjects who had rash or rash type event, 8.5% (12/141) subjects permanently discontinued TMC125 treatment and 8% (11/141) subjects temporarily discontinued TMC125 treatment. The pharmacokinetic data were available in only 2 subjects out of 12 before or at discontinuation. The median time to drop out was 11 days with a range of 2-27 days. Thus, any association between rash related dropouts and TMC125 exposure is difficult to interpret.

- Serum creatinine

According to the sponsor, creatinine levels tended to slightly increase over time in both treatment groups with a trend to higher increases in the TMC125 arm. This was further evaluated in subjects who were receiving or not receiving tenofovir (TDF). The

increased creatinine levels were observed only in the subgroup of subjects taking TDF. The increase was most apparent in subjects taking TDF in the TMC125 group. The difference with respect to placebo was small and not considered clinically relevant. Individual abnormalities in creatinine were infrequent.

Figure 14: Mean Change (±SE) from Baseline of Selected Laboratory Parameters Over Time (Pooled DUET Analysis)



Source: Sponsor's Figure 5; Page 111 of 418 Integrated summary of safety

Based on the input by Dr. Mullick, the sponsor's analysis was extended to understand relative contributions of TMC125 and TDF. From drug interaction studies, TDF decreases TMC125 exposures by 30% and TMC125 increases exposures of TDF by 30% (trial TMC125-C138). There was a slight increase in total urinary excretion of TDF when coadministered with TMC125. TDF levels were not available for subjects enrolled in the DUET trials.

From the laboratory data, 9078 records of creatinine measurements were identified. The missing data were ignored. The baseline or screening data were used for baseline correction. The comedication data were used to identify TDF administration during the randomized treatment period. Out of 919 subjects who received or were intended to receive TDF, a few number of subjects required discontinuations of TDF treatment for various reasons. There were 9 subjects who stopped TDF treatment on the baseline day. There is a slight discrepancy between the sponsor's and reviewer's assessment number of subjects receiving TDF. The reviewer used subjects who received or were intended to receive TDF based on "cmad.xpt" datasets. The following table illustrates number of subjects and the number of discontinuations in TDF treatment.

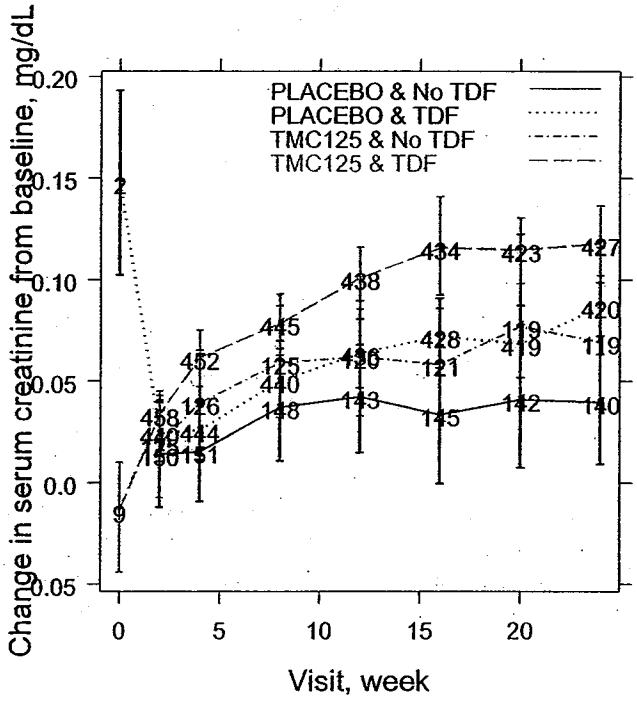
Table 8: Number of subjects and associated number of discontinuations in TDF treatment (pooled DUET analyses)

Number of discontinuations in TDF treatment	Number of subjects	
	Placebo group	TMC125 group
None	382	416
1	52	36
2	12	8
3	4	5
4	-	1
5	-	1
6	1	-
8	-	1

If multiple measurement were obtained within a short timeframe (identified as identical visit information), the worst observation was used in the analyses.

Figure 15 illustrates time course of change from baseline in serum creatinine for four groups based on randomized treatment (Placebo or TMC125) and the use of TDF (TDF or No TDF). Most subjects (~approx 400) on TMC125 and Placebo used TDF in the OBR. These were considered as non-clinically significant changes in serum creatinine for all the groups. However, the groups were ordered with TMC125 and TDF coadministration (TMC125 TDF) leading to highest change in serum creatinine over time. The changes in serum creatinine were similar in subjects using TDF in absence of TMC125 (Placebo TDF) and in subjects using TMC125 in absence of TDF (TMC125 No TDF). The Placebo group in absence of TDF demonstrated lowest change in serum creatinine. Therefore, an additive effect of TMC125 and TDF coadministration can be concluded.

Figure 15: Time course of change from baseline in serum creatinine for four groups based on randomized treatment (Placebo or TMC125) and the use of TDF (TDF or No TDF). The numbers at scheduled week represent the number of subjects. Limited data are available beyond week 24 visit (not shown).



The relative contribution of TMC125 and TDF was further investigated based on grade (grades 1-4) changes in serum creatinine, lab abnormality compared to the reference standard. As shown in Table 9, within a given grade, there are no significant differences between treatment groups. The placebo rate 19% (Grade 1), 9.8% (Grade 2) and 2.6% (Grade 3 or 4) are similar across all treatment groups. The discontinuations in TDF treatment might have contributed to lower incidence rate on TDF.

In conclusion, TMC125 effect on serum creatinine was no worse than effect of TDF and/or placebo. A trend towards an additive effect on mean change in serum creatinine between TMC125 and TDF did not translate into higher number of subjects with Grade 3 or 4 changes in serum creatinine.

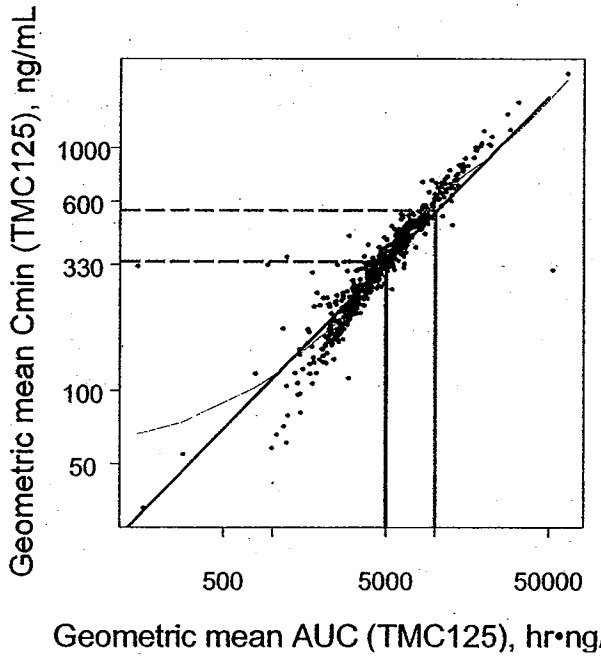
Table 9: Grade changes (compared to reference standard) in serum creatinine by randomized treatment groups and the use of TDF. All visit data were included and, for example, subjects with grade 1 change at one visit worsening to grade 3 change were included under grade 1 as well as grade 3 changes.

Changes in serum creatinine	Treatment group	Use of TDF	Number of events (any visit)	Number of subjects	Total N	% Subjects with event
Grade 1	PLACEBO	No	79	29	153	19.0
	TMC125		90	24	129	18.6
	PLACEBO	TDF	131	56	451	12.4
	TMC125		268	86	461	18.7
Grade 2	PLACEBO	No	32	15	153	9.8
	TMC125		30	14	129	10.9
	PLACEBO	TDF	51	19	451	4.2
	TMC125		87	31	461	6.7
Grade 3 or 4	PLACEBO	No	9	4	153	2.6
	TMC125		11	3	129	2.3
	PLACEBO	TDF	20	7	451	1.6
	TMC125		12	8	461	1.7

- Understanding Exposure-virologic success and Exposure-safety relationship

To consolidate exposure-virologic success and exposure-safety relationship that used Cmin and AUC, respectively, an approximate relationship between two measures of exposures was derived. Simple linear model after log transformation was used (log(TMC125 Cmin)=0.685*log(TMC125 AUC)). The model slightly overpredicts Cmin at low AUC and slightly underpredicts at high AUC.

Figure 16: Approximate Cmin-AUC relationship to understand benefit (virologic success)-risk (rash).



Based on exposure-virologic success relationship, TMC125 IQ of >400 does not lead to incremental benefit in virologic success (Figure 4), which corresponds to Cmin of ~200 (400 multiplied by median IC50 (0.5)). It was also established that incidence of rash increases with increasing exposures.

Using the relationship developed above, a mean Cmin of 200 ng/mL corresponds to mean AUC~2300 hr•ng/mL. For IC50 equal to 1 and a target IQ of 400, the corresponding AUC would be ~6300 hr•ng/mL. Therefore, the risk-benefit in subjects with median IC50 is different than subjects with IC50 greater than median IC50. Therefore, the multivariate relationship does not allow a global rule controlling TMC125 exposures. If the exposures are reduced in overall population to control toxicity, such exposures could be subtherapeutic for some subjects. At the same time, if the exposures are increased in overall population to maximize benefit, such exposures could be toxic for some subjects.

In the DUET trials no incidence of Stevens-Johnson syndrome was observed on TMC125 and rash events appeared in the first few weeks of the treatment. Therefore, in reviewer's opinion, the exposures of TMC125 should not exceed to the exposures achieved in DUET trials. Also, any PK intervention for rash management might not be useful. It will be beneficial to identify characteristics of subjects who might be susceptible to TMC125 induced rash.

In conclusion, these findings could be important under following situations:

1. Drug interactions
    a. Agents that were not administered with TMC125 in the pivotal trial and could increase exposures of TMC125.
    b. Agents that were not prospectively studied in drug-drug interaction studies or agents studied but yielded inconclusive results.
2. Overdose of TMC125 as the rash events appear in few days in some subjects.
3. Administration of TMC125 with other agents that could cause rash.

Population PK analyses

Are the labeling claims based on population PK supported?

Based on population PK analyses, the sponsor concluded that no dose adjustment was needed based on hepatitis B &/or C co-infection, gender, race, age (age range 18-77 years) and use of T-20.

Sponsor's analyses

The population pharmacokinetic model to describe the pharmacokinetics of TMC125 after administration as formulation F060 comprised of a lagtime followed by a sequential zero and first order absorption process and two compartment disposition; the model was parameterised as ALAG1, D1, KA, CL, V2, K23 and K32 (Run 75). Thus the structural form of the model remained the same but while inter-subject variability on K23 and D1 could no longer be estimated, the introduction of intra-subject variability on F1 clearly improved the model. As for the previous model, the residual error model was additive (data were Ln transformed).

Clearance was estimated to be 43.7 L/h (3.34 %CV); inter-subject variability in clearance was estimated to be 60.4%. IOV in F1 (fraction absorbed) was estimated to be 40.1%. The residual variability was 20.1%.

No covariates met the pre-defined selection criteria and so the final population pharmacokinetic model for TMC125 when administered as formulation F060 is the updated basic population pharmacokinetic model (Run 75). The parameter estimates for the final pharmacokinetic model are presented in Table 10.

Table 10: TMC125 parameter estimates for the updated population pharmacokinetic model (Run 75)

Parameter	Estimate	SE (%)
Structural model		
CL (L/h)	43.7	3.34
V2 (L)	422	35.8
K23 (/h)	0.390	46.4
K32 (/h)	0.0838	130
Ka (/h)	0.885	46.0
D1 (h)	2.47	13.9
ALAG1(h)	0.610	22.8
Statistical model		
	IIV (%)	SE (%)
CL	60.4	10.5
	IOV (%)	SE (%)
F1	40.1	12.5
Residual error (%)	20.1	14.7

Source: Sponsor's table 7 on page 27 of 138 of TMC125-C929-CRR-PK.pdf

For more details on the models and model building refer study reports (\\Cdsesub1\evsprod\NDA022187\0002\m5\53-clin-stud-rep\535-rep-effic-safety-stud\treatment-of-hiv-1-infection\5353-rep-analys-data-more-one-stud\tmc125-c929\ tmc125-c929-crr-pk.pdf AND \\Cdsesub1\evsprod\NDA022187\0002\m5\53-clin-stud-rep\535-rep-effic-safety-stud\treatment-of-hiv-1-infection\5353-rep-analys-data-more-one-stud\tmc125-c929\ tmc125-c929-crr-pk-add-1.pdf)

Reviewer's assessment

The sponsor's analyses were replicated and additional empirical evidence was used to validate the findings. There were no major pharmacokinetic differences by subgroups to the extent requiring TMC125 dose adjustment.

As supportive analyses, two time windows (2-6 hrs and 10-14 hrs) were selected with reference to reported time since the last dose. The rationale was to capture the differences, if any, around the Tmax (mean ~3 hrs) and around predose time (dosing interval 12 hrs). Table 11 summarizes demographics of subjects used in the analyses. Figure 17 illustrates distribution of TMC125 concentrations by body weight, age, creatinine clearance, hepatitis B infection, hepatitis C infection, race, sex, ENF and TDF.

Table 11: Demographics of the subjects used in the analyses

Type	Pooled	DUET-1	DUET-2
Total (N)	577	294	283
Male (N)	520	255	265
Caucasian (N)	361	181	180
Black (N)	67	39	28
Hispanic (N)	56	39	17
Oriental/Asian (N)	7	2	5
Other race (N)	20	18	2
Unknown race (N)	66	15	51
Subjects (N) age ≥60	33	12	21
Subjects (N) age ≥65	7	2	5
Hepatitis C +ve (N)	43	15	28
Hepatitis C -ve (N)	533	278	255

Hepatitis B +ve (N)	41	21	20
Hepatitis B -ve (N)	536	273	263
Hepatitis B -ve /C -ve (N)	495	257	238
Hepatitis B +ve /C +ve(N)	3	0	3
Hepatitis B -ve /C +ve(N)	40	15	25
Hepatitis B +ve /C -ve(N)	38	21	17
T20 Use (N)	252	112	140
Tenofovir Use (N)	270	166	104
All records (N)	7528	3863	3665
Observation records (N)	2880	1452	1428
Observation records (Window 1)	1258	574	684
Observation records (Window 2)	118	56	62
Subjects missing CrCL (N)	1	1	0

In conclusion, TMC125 pharmacokinetics were not affected by body weight, age, creatinine clearance, hepatitis B infection, hepatitis C infection, race, sex, ENF and TDF to an extent requiring dose adjustment.

6 Page(s) Withheld

✓ Trade Secret / Confidential

_____ Draft Labeling

_____ Deliberative Process

4.3 DCP 4 Division Directors Concurrence on PMCs

From: Lazor, John A
Sent: Wednesday, January 09, 2008 11:30 AM
To: Arya, Vikram
Cc: Reynolds, Kellie S
Subject: RE: NDA 22187-TMC125-List of Post Marketing Commitments-Request for Official Concurrence

Concur.

From: Arya, Vikram
Sent: Wednesday, January 09, 2008 11:27 AM
To: Lazor, John A
Cc: Reynolds, Kellie S; Arya, Vikram
Subject: NDA 22187-TMC125-List of Post Marketing Commitments-Request for Official Concurrence

John,

Your official concurrence is requested on the attached list of Post Marketing Commitments (PMCs) for Etravirine (TMC125).

Thanks,

Vikram
<< File: Post Marketing Commitments for Etravirine (TMC125).doc >>

APPEARS THIS WAY
ON ORIGINAL

4.4 OCP Filing/Review Form

General Information About the Submission			
	Information		Information
NDA Number	**22-187**	**Brand Name**	**INTELENCE**
OCP Division	**DCP 4**	**Generic Name**	**Etravirine**
Medical Division	**DAVP**	**Drug Class**	**Non Nucleoside Reverse Transcriptase Inhibitor**
OCP Reviewer	**Vikram Arya**	**Indication(s)**	**HIV-1 Infection**
OCP Team Leader	**Kellie Reynolds**	**Dosage Form**	**Tablet**
		Dosing Regimen	**200 mg b.i.d**
Date of Submission	**July 18, 2007**	**Route of Administration**	**Oral**
Estimated Due Date of OCP Review		**Sponsor**	**Tibotec Inc**
PDUFA Due Date	**January 18, 2008**	**Priority Classification**	**Priority Review**
Division Due Date			

Clin. Pharm. and Biopharm. Information				
	"X" if included at filing	**Number of studies submitted**	**Number of studies reviewed**	**Critical Comments If any**
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	**X**			
Tabular Listing of All Human Studies	**X**			
HPK Summary	**X**			
Labeling	**X**			
Reference Bioanalytical and Analytical Methods	**X**			
I. Clinical Pharmacology				
Mass balance:	**X**	1		
Isozyme characterization:	**X**	4		
Blood/plasma ratio:	**X**	1		
Plasma protein binding:	**X**	1		
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:				
multiple dose:	X	3		
Patients-				

single dose:				
multiple dose:	X	1		
Dose proportionality -				
fasting / non-fasting single dose:				
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				
In-vivo effects on primary drug:	X	16		
In-vivo effects of primary drug:	X	18		
In-vitro:	X	1		
Subpopulation studies -				
ethnicity:				
gender:				
pediatrics:				
geriatrics:				
renal impairment:				
hepatic impairment:	X	1		
PD:				
Phase 2:				
Phase 3:	X	1		
PK/PD:				
Phase 1 and/or 2, proof of concept:	X	3		
Phase 3 clinical trial:	X	2		
Population Analyses -				
Data rich:				
Data sparse:	X	2		
II. Biopharmaceutics				
Absolute bioavailability:				
Relative bioavailability -				
solution as reference:				
alternate formulation as reference:	X	10		
Bioequivalence studies -				
traditional design; single / multi dose:	X	1		
replicate design; single / multi dose:				
Food-drug interaction studies:				
Dissolution:				

(IVIVC):				
Bio-wavier request based on BCS				
BCS class				
III. Other CPB Studies				
Genotype/phenotype studies:				
Chronopharmacokinetics				
Pediatric development plan				
Literature References				
Total Number of Studies		66		

Filability and QBR comments		
	"X" if yes	Comments
Application filable ?	**X**	Reasons if the application is not filable (or an attachment if applicable) For example, is clinical formulation the same as the to-be-marketed one?
Comments sent to firm ?		Comments have been sent to firm (or attachment included). FDA letter date if applicable.
QBR questions (key issues to be considered)		
Other comments or information not included above		
Primary reviewer Signature and Date		
Secondary reviewer Signature and Date		

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

/s/

Vikram Arya
1/16/2008 04:30:16 PM
BIOPHARMACEUTICS

Pravin Jadhav
1/16/2008 04:39:14 PM
BIOPHARMACEUTICS
A memo on additional exposure-safety analyses covering high exposure patients will follow.

Jogarao Gobburu
1/16/2008 04:40:05 PM
BIOPHARMACEUTICS

Kellie Reynolds
1/17/2008 11:18:13 AM
BIOPHARMACEUTICS