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# Prediction of clinical benefits of TMC125 from treatment effects on CD4 counts and HIV RNA

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## Abstract

**Objective**
To predict the decrease in progression to AIDS or death based on the treatment benefit of TMC125 over active control on CD4 counts and HIV RNA.

**Methods**
In the TMC125-C223 trial, multidrug resistant patients (n=199, baseline median CD4 99, HIV RNA 4.7 $\log_{10}$) were randomized to receive optimized background treatment plus either TMC125 400mg bid, TMC125 800mg bid or best available treatment (control). Twenty-four-week CD4 and HIV RNA data from TMC125 800mg bid group (n=79), the selected dose, was used to predict clinical benefits (lower progression to AIDS or death) using a standard regression method and a new categorization method: 1) regression method – data from 14 randomized clinical endpoint trials (n>9,000) was used to correlate previous CD4 and HIV RNA treatment benefits with the relative hazard of clinical progression; 2) CD4 categorization method – data from 14,000 patient-years on highly active antiretroviral therapy (HAART) in the EuroSIDA cohort within CD4 count ranges was combined with the proportions of patients in the same ranges at Week 24 and used to predict rates of disease progression during TMC125 800mg bid and control treatment.

**Results**
At Week 24, CD4 counts rose by mean 48 cells/μL for TMC125 800mg bid versus 10 cells/μL for control; HIV RNA fell by mean –1.2 and –0.2 $\log_{10}$ at Week 24 in the two groups. The CD4 categorization method predicted 1-year rates of progression to AIDS and death of 12% for TMC125 versus 17% for control, a comparative reduction of 31%. The regression method predicted a 39% comparative reduction from the difference in HIV RNA levels, and a 33% comparative reduction in progression from the difference in CD4 counts.

**Conclusions**
Based on the 24-week results from the TMC125-C223 trial 800mg bid group, the benefits of TMC125 versus control in raising CD4 counts and suppressing HIV RNA are predicted to lower progression rates to AIDS/death by 31–39% for TMC125 treatment, using two independent methods. These methods could be used to estimate clinical benefits of other antiretrovirals.

### Introduction

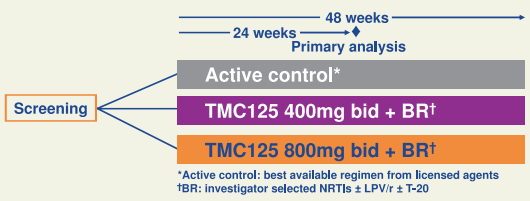
- TMC125 is a novel NNRTI, with proven clinical efficacy against HIV-1 strains resistant to currently available NNRTIs[1]
- In the TMC125-C223 trial, patients were randomized to receive optimized background (investigator selected NRTIs with or without T-20) plus either
  - one of two doses of TMC125
  - best available HAART regimen not including NNRTI (control arm)
- In the TMC125 arms, there were significant and sustained reductions in HIV RNA and rises in CD4 count compared with the control arm[1]

1. Cohen C, et al. 12th BHIVA 2006 (Poster 2)

### Introduction (cont'd)

- Patients with persistently low CD4 count and high HIV RNA levels on HAART are at higher risk of progressing to AIDS and death
- It is no longer feasible to conduct clinical endpoint trials of antiretrovirals, owing to the ethics of maintaining patients on treatment arms with weaker effects on HIV RNA suppression and CD4 counts
- Therefore, two independent methods were used to predict the likely effects of TMC125 treatment on progression to AIDS and death
- These methods were developed using data from a large cohort study (EuroSIDA), where CD4 counts during HAART treatment had been correlated with clinical progression rates, and from clinical endpoint trials conducted in the past

### TMC125-C223: study design




*Active control: best available regimen from licensed agents
†BR: investigator selected NRTIs ± LPV/r ± T-20

- Viral load (VL) >1,000 copies/mL
- Documented NNRTI resistance and ≥3 primary protease inhibitors mutations
- Randomized 1:2:2 (active control versus TMC125 400mg bid versus 800mg bid), partially blinded
- After 48 weeks, patients were enrolled into a long-term follow-up trial

BR = background regimen; LPV = lopinavir

### TMC125-C223: baseline disease characteristics

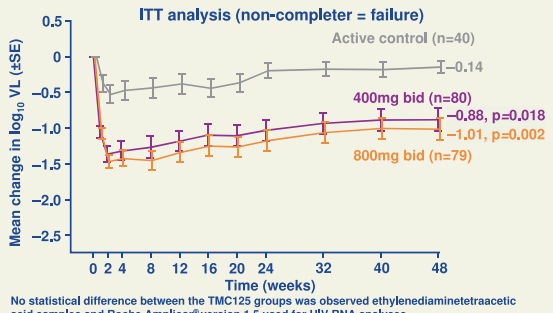
| | TMC125 400mg bid (n=80) | TMC125 800mg bid (n=79) | Active control (n=40) |
|---|---|---|---|
| VL ($\log_{10}$ copies/mL)* | 4.67 | 4.69 | 4.69 |
| CD4 count (cells/mm³)* | 91 | 102 | 100 |
| Duration HIV infection (years)* | 14.6 | 14.8 | 14.6 |
| CDC class C (%) | 64 | 67 | 68 |
| HBsAg positive (%) | 7 | 5 | 8 |
| HCV RNA positive (%) | 17 | 5 | 5 |

*Median values

- Highly treatment-experienced population

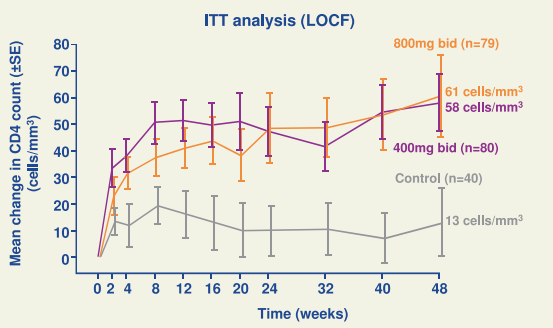
CDC = Centers for Disease Control and Prevention; HBsAG = hepatitis B surface antigen; HCV = hepatitis C virus

### TMC125-C223 primary endpoint: change in VL at 48 weeks




No statistical difference between the TMC125 groups was observed ethylenediaminetetraacetic acid samples and Roche Amplicor® version 1.5 used for HIV RNA analyses
P values versus active control
ITT = intent-to-treat; SE = standard error

### TMC125-C223: change in CD4 count



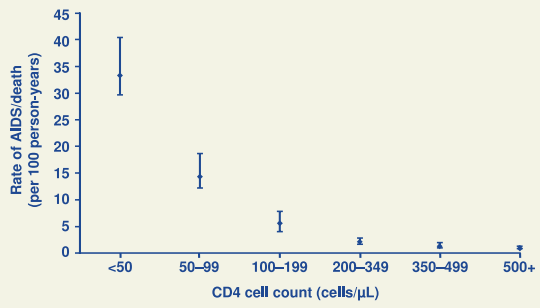

LOCF = last observation carried forward

### Prediction of progression to AIDS/death: CD4 categorization method

- Recent EuroSIDA cohort data on 6,814 patients taking HAART, with 22,766 patient-years of follow-up[1]
- Annual progression rate to AIDS/death categorized by mean CD4 counts over 1 year, in ranges
  - 0–49 cells/μL
  - 50–99 cells/μL
  - 100–199 cells/μL
  - 200–349 cells/μL
  - 350–499 cells/μL
  - 500+ cells/μL
- Data were from the C223 study on percentage of patients in each category at Week 24, for TMC125 and control groups
  - Week 24 CD4 data were used to estimate the 1-year effect (as an average of the 0–48 week CD4 data)
  - in the C223 trial, little change was observed in CD4 count between Week 24 and 48
- Proportion of patients in each CD4 category in C223 were used to predict 1-year rate of progression to AIDS/death for the two treatment arms

1. Olsen CH, et al. AIDS 2005;19:319–30

### Rate of AIDS or death (mean, 95% CI) according to CD4 cell count (EuroSIDA cohort)




CI = confidence interval

Olsen CH, et al. AIDS 2005;19:319–30

### Prediction of clinical progression rates for the C223 trial: CD4 categorization method

| CD4 count (cells/μL) | Progression rate (%) | Predicted progression rate n (%) TMC125 | CPI |
|---|---|---|---|
| <50 | 33.3 | 7.6 (23) | 14.2 (43) |
| 50–99 | 14.3 | 2.1 (15) | 1.1 (8) |
| 100–199 | 5.5 | 1.4 (25) | 1.1 (20) |
| 200–349 | 2.0 | 0.5 (24) | 0.5 (23) |
| >350 | 1.2 | 0.2 (13) | 0.1 (8) |
| Overall predicted progression rate (%) | | 11.7 | 17 |

From EuroSIDA HAART treated cohort

- Predicted reduction in progression rate, TMC125 versus CPI = (11.7–17)/17=31%

CPI = control protease inhibitor

### Prediction of progression to AIDS/death: regression method

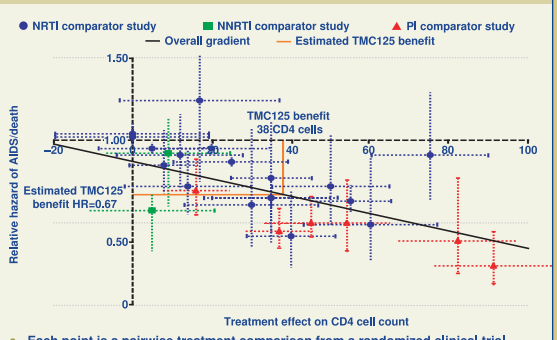
- Literature search for randomized controlled clinical trials with estimates of
  - progression to AIDS/death
  - CD4 change from baseline to Weeks 16–24
  - change in HIV RNA copies from baseline to Weeks 16–24
  - total sample size above 300
- For each clinical trial, the treatment effect of change in rates of progression to AIDS/death was correlated with the treatment effect on CD4 count and copies of HIV RNA[1]
- Main clinical trials used in the analysis (n>9,000 total)[1]
  - CAESAR, Delta 1 and 2, ACTG 116a, ACTG 116b/117, ACTG 175, ACTG 241, ACTG 320, Abbott 247, DLV-017, BW-034, Merck 028, Roche NV14256, VA-298

1. Hill AM, et al. Antivir Ther 1998;3:139–45

### Prediction of progression to AIDS/death: regression method (cont'd)

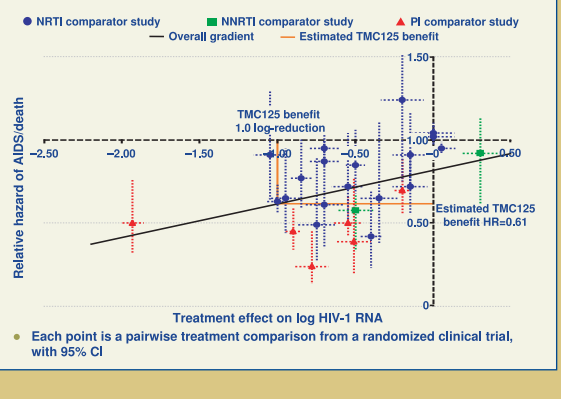
- Regression was carried out between CD4 benefit, HIV RNA benefit and reduced progression to AIDS and death, based on data from published trials
- Methodology
  - boot-strapping method
  - multivariate analysis
  - regression line established
- Regression model was applied to data from the TMC125-C223 trial
- The benefits of TMC125 on change in CD4 count and HIV RNA were used to predict potential reductions in progression to AIDS/death

### Prediction of progression to AIDS/death: CD4 count regression method




- Each point is a pairwise treatment comparison from a randomized clinical trial, with 95% CI

### Prediction of progression to AIDS/death: HIV RNA regression method




- Each point is a pairwise treatment comparison from a randomized clinical trial, with 95% CI

## Conclusions

- The predicted benefits of TMC125 on lowering rates of progression were consistent for all methods used, based on the Week 24 efficacy results (CD4 count increases, HIV RNA reductions) of the TMC125-C223 trial in treatment-experienced patients.
- According to this model and compared with control, TMC125 is anticipated to result in:
  - a 31% reduction in clinical progression to AIDS/death over 1 year, based on the CD4 categorization method
  - 33% reduction in clinical progression to AIDS/death over 1 year, based on the CD4 regression method
  - 39% reduction in clinical progression to AIDS/death over 1 year, based on the HIV RNA regression method.
- These predictions of clinical benefit can be reassessed using longer-term efficacy data in larger Phase III trials (DUET).
- These predictions apply for treatment-experienced patients where TMC125 is used as an additional antiretroviral treatment. Data on CD4 counts, HIV RNA and clinical progression from other cohort studies could be used to further validate these predictions.

This poster is available on-line at www.tibotec.com

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