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Impact of baseline K103N or Y181C on the virological response to the NNRTI TMC125: analysis of study TMC125-C223

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Abstract

Background
TMC125 is a novel NNRTI with a high genetic barrier to the development of resistance and in-vitro and in-vivo activity against NNRTI-resistant HIV. TMC125-C223 is a randomised controlled phase IIb dose-finding study of TMC125 in heavily pretreated patients with documented NNRTI resistance and ≥3 primary protease inhibitor (PI) mutations at baseline. In this study, TMC125 showed significant antiviral efficacy at 24 weeks with a mean change in viral load (VL) of –1.18 $\log_{10}$ copies/mL vs –0.19 $\log_{10}$ in control ($p<0.05$). In a previous intent-to-treat (ITT) analysis, an association between a higher number of NNRTI mutations, the baseline fold change (FC) for TMC125 and virological response at 24 weeks was observed.

Methods
The effect of the NNRTI mutations K103N and Y181C on the virological response at 24 weeks in patients receiving TMC125 800mg twice-daily (n=79) was determined on observed data.

Results
Both K103N and Y181C were each present at baseline in 29 out of 79 patients, and always observed in combination with one to four other NNRTI mutations. Ten of these 48 patients carried both K103N and Y181C. The number of additional NNRTI mutations was similarly distributed for the samples with K103N or Y181C. The median TMC125 FC for all patients was 1.95. The median TMC125 FC for patients with and without K103N or with and without Y181C was 1.70 and 1.95 or 4.50 and 1.10, respectively. In an unadjusted analysis, patients with K103N at baseline achieved a mean reduction in VL of 1.43 $\log_{10}$ copies/mL, similar to the 1.40 $\log_{10}$ reduction in patients without K103N, and similar to the overall response of –1.41 $\log_{10}$ in all patients. Patients with Y181C at baseline achieved a mean 0.86 $\log_{10}$ reduction, which was lower than the 1.70 $\log_{10}$ reduction in patients without Y181C.

Conclusions
These data showed that TMC125 retained activity in the presence of multiple NNRTI mutations, including K103N and Y181C, where current NNRTIs were not expected to be active. The presence of Y181C, in combination with other NNRTI mutations, seemed to be associated with higher FC values for TMC125. Although the presence of Y181C, but not K103N, appeared to be associated with decreased virologic response, the observed analysis presented in the abstract was confounded by other factors, including a higher number of NNRTI mutations in the group with Y181C. In an adjusted analysis, there were no marked differences between responses with or without K103N or Y181C. Additional data are required to confirm these findings.

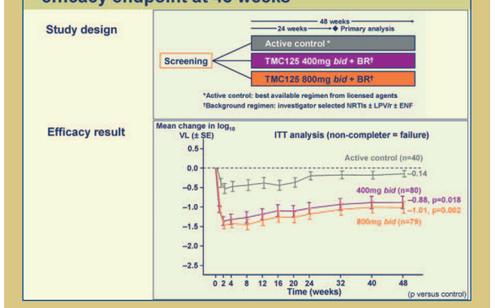
Abstract updated to reflect recent analysis

Introduction

- TMC125 is an NNRTI designed to have a high genetic barrier to the development of resistance[1,2]
- TMC125 showed significant and sustained efficacy at 24 and 48 weeks in heavily pretreated patients with substantial NNRTI and PI resistance in study TMC125-C223[3,4,5]
  - additional 1 $\log_{10}$ VL decline compared with control

1. Andries K, et al. Antimicrob Agents Chemother 2004;48:4680–6
2. Vingerhoets J, et al. J Vir 2005;79:12773–82
3. Nadler J, et al. 10th EACS 2006 (Abstract LBPS3/7A)
4. Grossman H, et al. 45th ICAAC 2005 (Abstract H-416c)
5. Cohen C, et al. 12th BHIVA 2006 (Abstract 2)

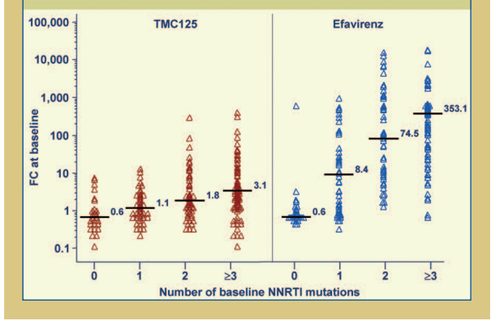
TMC125-C223: study design and primary efficacy endpoint at 48 weeks



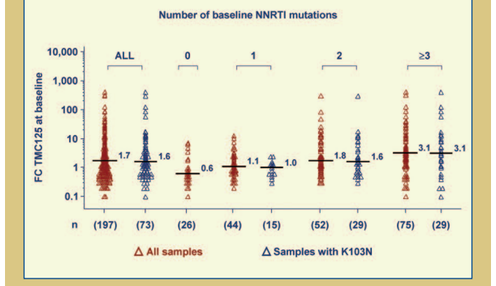
Objectives of the current analyses

- From previous analyses
  - the presence of K101P, Y181I, Y181V or the combination of Y181C with V179E, V179F, G190S or M230L was associated with a high TMC125 FC
  - K103N and Y181C: most prevalent mutations in TMC125-C223
- To determine and compare, retrospectively, the impact of baseline K103N or Y181C, with or without other NNRTI mutations, on the
  - TMC125 FC in EC_{50}
  - virologic response at 24 weeks in patients receiving TMC125 800mg twice-daily

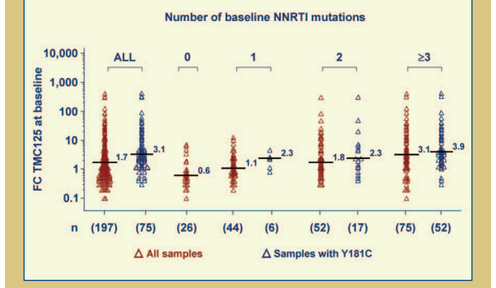
TMC125-C223: baseline resistance – phenotype



TMC125-C223: baseline resistance – phenotype (cont'd)



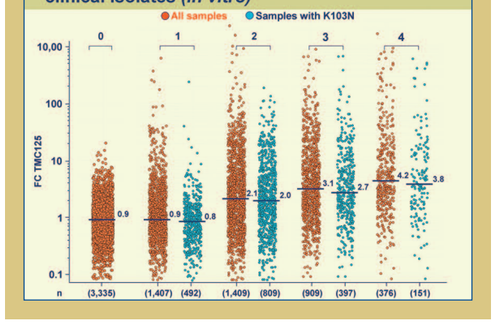
TMC125-C223: baseline resistance – phenotype (cont'd)



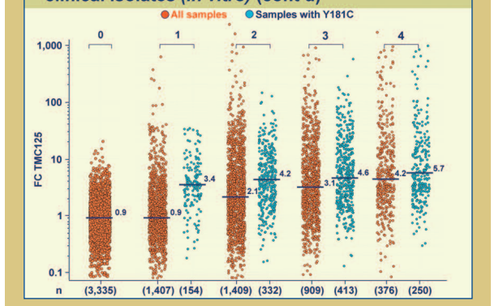
In-vitro analysis of clinical isolates to confirm the effect of K103N vs Y181C seen in TMC125-C223

- An analysis of a random panel of clinical isolates (Virco) was conducted, separate from TMC125-C223
- FC for TMC125 was determined in
  - all isolates (n=7,582)
  - isolates with K103N, with or without other NNRTI mutations (n=1,895 or 25%)
  - isolates with Y181C, with or without other NNRTI mutations (n=1,277 or 17%)

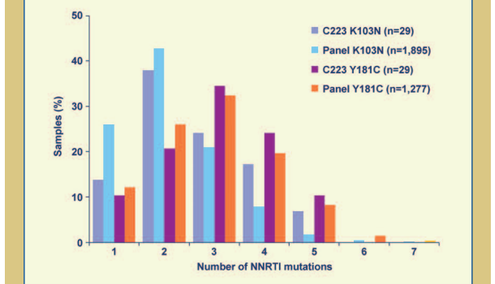
Effect of NNRTI mutations on TMC125 FC in clinical isolates *(in vitro)*



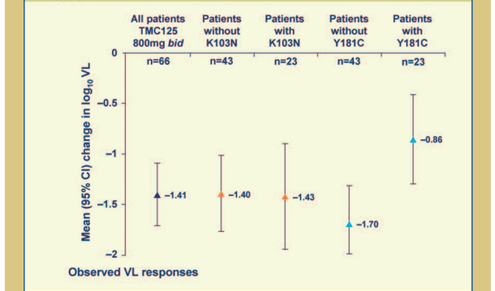
Effect of NNRTI mutations on TMC125 FC in clinical isolates *(in vitro)* (cont'd)



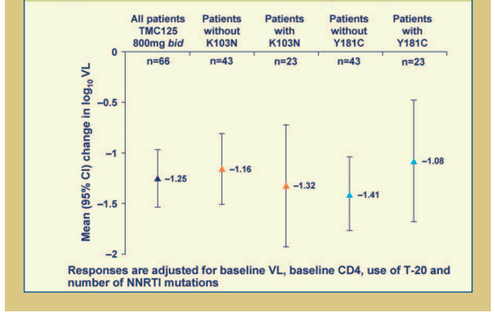
Distribution of the number of NNRTI mutations in samples with K103N or Y181C



TMC125-C223: virologic response at week 24 by presence of K103N or Y181C



TMC125-C223: virologic response at week 24 by presence of K103N or Y181C (cont'd)



Conclusions

- Baseline FC to TMC125 in this highly treatment-experienced population increased with a higher number of NNRTI mutations.
- The presence of Y181C, but not K103N, appears to be associated with a slightly higher FC value for TMC125, at baseline
  - a possible confounding factor is the higher number of NNRTI mutations in samples with Y181C – however, it is observed with Y181C alone as well
  - confirmed by in-vitro data using a panel of 7,582 clinical isolates (Virco).
- Although the presence of Y181C, but not K103N, appeared to be associated with decreased virologic response, the analysis is confounded by other factors, including a higher number of NNRTI mutations in the group with Y181C.
- In an adjusted analysis, there were no marked differences between responses with or without K103N or Y181C.
- Larger sample sizes, needed to identify key baseline combinations of mutations associated with decreased virologic response, will be obtained from the DUET trials.

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