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No frequent reporting of neurological or psychiatric events during TMC125 treatment

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Poster No. P146

Abstract

Background
TMC125 is a novel NNRTI active against wild-type HIV-1 and HIV-1 resistant to current NNRTIs.

Methods
TMC125-C203 is a 48-week, randomised, blinded, placebo-controlled, dose-escalation trial in three-class-experienced, HIV-1-infected patients. Patients received placebo or TMC125 400mg, 800mg or 1,200mg bid (Phase II formulation), added to an optimised background regimen (OBR) containing at least two other antiretrovirals. The primary objective was to determine the safety and tolerability of TMC125. This analysis focuses on the nervous system and psychiatric events when all patients had been treated for at least 24 weeks.

Results
The trial included 240 patients (66, 57, 74 and 43 patients received placebo, 400mg, 800mg and 1,200mg TMC125 bid respectively). The median age was 42 years and 11% were female. Median treatment duration was 32 weeks. The incidence of all nervous system events was similar between TMC125 doses and comparable with placebo: 38% with TMC125 vs 35% with placebo. A grade 3 nervous system event was reported by 1% of TMC125 vs 2% of placebo patients. The most frequently reported nervous system events with TMC125 vs placebo were headache (19% vs 17% respectively), dizziness (10% vs 5% respectively) and insomnia (6% vs 5% respectively). For the 400mg, 800mg and 1,200mg doses of TMC125, the median onset of these events was 16, 30, and 28 days respectively and the median duration was 7, 29 and 29 days respectively. The incidence of psychiatric disorders was similar between TMC125 (13%) and placebo patients (11%). No grade 3 or 4 psychiatric events were reported and only one patient, in the 400mg group, discontinued for a psychiatric event (confusional state). The most frequent psychiatric event was depression (4% of TMC125 vs 8% of placebo patients).

Conclusions
The incidence and severity of neuropsychiatric events observed with the 800mg dose of TMC125 was similar to that seen with placebo in this study. Phase III trials with a new formulation of TMC125 with comparable exposure to the 800mg bid Phase II formulation are ongoing.

Abstract updated with recent analysis

Introduction

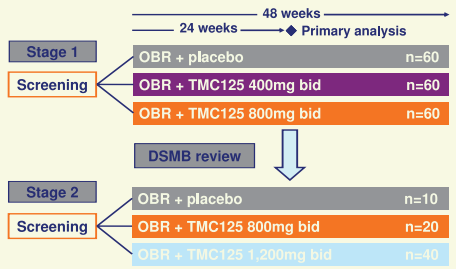
- TMC125 is a next-generation NNRTI designed to have a high genetic barrier to the development of resistance[1,2]
  - TMC125 was selected as it maintains activity despite common NNRTI mutations
- Data from TMC125-C207, a 7-day, Phase IIa, proof of principle trial with functional monotherapy in NNRTI-resistant patients, showed a mean change in $\log_{10}$ viral load of –0.9[3]
- Data from the 48-week efficacy analysis of the Phase IIb trial TMC125-C223 in heavily treatment-experienced patients with substantial NNRTI and PI resistance demonstrated significant and durable efficacy[4]

1. Andries K, et al. Antimicrob Agents Chemother 2004;48:4680–6
2. Vingerhoets J, et al. J Virol 2005;79:12773–82
3. Gazzard BG, et al. AIDS 2003;17:F49–54
4. Cohen C, et al. 16th IAC 2006 (TUPE0061)

TMC125-C203: study design

- TMC125-C203 was a Phase II, dose-escalation, double-blind, placebo-controlled trial conducted at 52 sites in Canada and Europe
  - patients were three-class experienced, each class for at least 3 months
  - patients had viral load >1,000 copies/mL
  - the study protocol was reviewed and approved by the appropriate institutional ethics committee and health authorities, and was conducted in accordance with the Declaration of Helsinki
- Primary objective: Assess the safety and tolerability of TMC125
- TMC125 or placebo plus an OBR consisting of
  - 3–4 antiretrovirals (1–4 NRTIs ± 1 ritonavir-boosted lopinavir or saquinavir ± enfuvirtide)
  - use of at least two active drugs (excluding TMC125)
- Phase II formulation of TMC125 was administered in this trial
  - a new formulation with a lower pill burden and smaller pill size is being administered in the ongoing Phase III (DUET) trials
- This sub-analysis focuses on the reported nervous system and psychiatric adverse events (AEs)

TMC125-C203: study design (cont'd)



- In this analysis, data for the same dose group in both stages were combined

n = enrolment target; DSMB = Data and Safety Monitoring Board

TMC125-C203: baseline characteristics

	TMC125 400mg bid (n=57)	TMC125 800mg bid (n=74)	TMC125 1,200mg bid (n=43)	Placebo (n=66)	All patients (N=240)
Male (%)	93	82	93	91	89
Caucasian (%)	90	89	86	88	88
Median viral load ($\log_{10}$ copies/mL)	4.23	4.37	4.50	4.09	4.25
Median CD4 count (cells/mm^3)	217	201	200	230	211
Median duration HIV infection (years)	10.8	10.9	10.9	11.0	10.9
History of psychiatric disorder (%)	25	39	56	35	38

Most common nervous system AEs*

AEs	TMC125 400mg bid (n=57)	TMC125 800mg bid (n=74)	TMC125 1,200mg bid (n=43)	TMC125 All TMC125 (N=174)	Placebo (n=66)	All TMC125 vs placebo 95% CI
Median treatment duration (weeks)	47	32	24	29	4	–
Any nervous system disorder (%)	44	38	40	40	35	–
Headache (%)	28	18	9	19	17	–8.4 to 13.0
Dizziness (%)	12	10	9	10	5	–0.9 to 12.5
Insomnia (%)	4	7	7	6	5	–4.9 to 7.3
Hypoaesthesia (%)	2	4	7	4	0	1.1 to 6.9
Paraesthesia (%)	0	0	2	1	8	– 3.5 to –0.5
Hypoaesthesia oral (%)	4	0	2	2	3	–5.8 to 3.2
Hyporeflexia (%)	0	1	5	2	3	–5.8 to 3.2

*Treatment-emergent AEs, regardless of severity or causality, which occurred in >2% in either the all TMC125 or placebo groups

Onset and duration of most common nervous system AEs

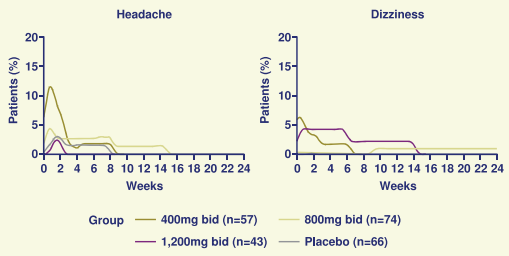
AEs	TMC125 (all doses) (n=174) Number patients	Onset*	Duration*	Placebo (n=66) Number patients	Onset*	Duration*
Headache	33 (19%)	16 (1–421)	7 (1–102)	11 (17%)	16 (1–111)	6 (1–369)
Dizziness	18 (10%)	30 (1–177)	29 (1–219)	3 (5%)	26 (12–294)	10 (2–18)
Insomnia	10 (6%)	28 (1–491)	29 (4–316)	3 (5%)	19 (14–168)	119 (1–236)

*Median (range) in days

- All events are included in the incidence and calculation of onset. However, as the trial was ongoing at the time of this analysis, end dates were not available for all AEs. Therefore, duration of AEs has been calculated based only on events with a reported end date.

Prevalence of headache and dizziness

- The majority of events of headache and dizziness occurred early during TMC125 treatment and were transient.



Most common psychiatric AEs*

AEs	TMC125 400mg bid (n=57)	TMC125 800mg bid (n=74)	TMC125 1,200mg bid (n=43)	TMC125 All TMC125 (N=174)	Placebo (n=66)	All TMC125 vs placebo 95% CI
Median treatment duration (weeks)	47	32	24	29	40	–
Any psychiatric disorder (%)	11	10	23	13	11	–
Depression (%)	4	4	5	4	6	–8.6 to 4.4
Anxiety (%)	2	1	2	2	2	–3.3 to 3.7
Sleep disorder (%)	0	3	2	2	2	–3.3 to 3.7
Abnormal dreams (%)	0	1	2	1	2	–3.7 to 2.9
Depressed mood (%)	0	0	0	0	2	–4.4 to 1.4

*Treatment-emergent AEs, regardless of severity or causality, which occurred in >2% in the all TMC125 or placebo groups

Onset and duration of most common psychiatric AEs

AEs	TMC125 (all doses) (n=174) No.*	Onset†	Duration†	Placebo (n=66) No.*	Onset†	Duration†
Depression	7 (4%)	225 (140–582)	109 (7–211)	4 (6%)	232 (102–393)	165 (57–272)
Anxiety	3 (2%)	52 (32–730)	NA‡	1 (2%)	43	NA‡
Sleep disorder	3 (2%)	22 (1–225)	39 (16–48)	1 (2%)	2	98

*Number of patients
†Median (range), days
‡No end date available for the majority of events

- All events are included in the incidence and calculation of onset. However, as the trial was ongoing at the time of this analysis, end dates were not available for all AEs. Therefore, duration of AEs has been calculated based only on events with a reported end date.

Grade 3, 4 and serious nervous system and psychiatric AEs*

AEs	TMC125 400mg bid (n=57)	TMC125 800mg bid (n=74)	TMC125 1,200mg bid (n=43)	TMC125 All TMC125 (N=174)	Placebo (n=66)
Grade 3 or 4 AEs†					
Dizziness (%)	2	0	0	1	0
Tension headache (%)	0	0	2	1	0
Loss of consciousness (%)	0	0	0	0	2
Serious AEs†					
Neuralgia (%)	0	1	0	1	0

*Treatment-emergent AEs
†No psychiatric grade 3 or 4 AEs or serious AEs were reported

Nervous system and psychiatric AEs* leading to treatment discontinuation

- Three (2%) patients treated with TMC125 discontinued treatment due to neuropsychiatric AEs
- One 53-year-old male patient after 6 days' treatment, due to grade 1 headache (probably related to study medication) with grade 2 diarrhoea (400mg bid group)
- One 38-year-old male patient after 9 months' treatment, due to grade 1 dizziness (possibly related to study medication) with grade 1 diarrhoea and dyspepsia (800mg bid group)
- One 56-year-old male patient after 5 days' treatment, due to grade 2 confusional state, dizziness, abnormal gait, headache, sweating, hot flushes, increased heart rate and tremor. All events were considered possibly related to study medication; the effect of a ritonavir-boosted PI on the levels of psychotropic medication may also have been causal
  - the patient was not receiving antiretrovirals at baseline, but was taking other medication including venlafaxine, alprazolam, amitriptyline and prochlorperazine
  - the dose of venlafaxine was increased just before the start of antiretroviral therapy with lopinavir/ritonavir, TMC125 400mg bid, NRTIs and enfuvirtide

*Treatment-emergent AEs, regardless of severity or causality

TMC125-C203: neuropsychiatric summary

- Nervous system disorders occurred in 40% of TMC125-treated patients and 35% of placebo-treated patients
  - the most common nervous system AEs were headache, dizziness and insomnia. Only dizziness was more common compared with placebo
  - headache, dizziness and insomnia generally occurred within the first month of TMC125 administration
  - there was no association between TMC125 dose and incidence or severity of nervous system events
- Psychiatric AEs occurred in 13% of TMC125-treated patients and 11% of placebo-treated patients
  - the most common psychiatric AEs were depression, anxiety and sleep disorder; the incidence was low and not different from placebo
  - there was no pattern in the time of onset for the most common psychiatric events
  - for TMC125-treated patients, there was an overall trend for increased incidence with the highest dose (1,200mg bid). A pre-trial history of psychiatric disorder(s) was also most frequent in the TMC125 1,200mg bid group

Conclusions

- Neuropsychiatric AEs in TMC125-treated patients:
  - were overall not more frequent than placebo
  - were generally mild to moderate in severity (ACTG grade 1 or 2)
  - generally resolved without intervention
  - infrequently led to treatment discontinuation.
- These results suggest that the addition of TMC125 to antiretroviral therapy is not associated with an increase in neuropsychiatric adverse events compared with placebo.

Acknowledgements

The authors would like to express their gratitude to the patients and their families, study centre staff, the DSMB and Tibotec study personnel. We also acknowledge the following principal investigators, listed by country:

Belgium: Dr N Clumeck, Dr F van Wanzeele.
Canada: Dr J Gill, Dr P Junod, Dr D Kilby, Dr J MacLeod, Dr J Montaner, Dr A Rachlis, Dr B Trottier, Dr C Tsoukas, Dr S Walmsley.
France: Dr L Cotte, Dr P Dellamonica, Dr C Katlama, Dr Y Mouton, Dr P Yeni.
Germany: Dr K Arastéh, Dr G Fätkenheuer, Dr H Knechten, Dr S Staszewski, Dr L Weitner.
Italy: Dr A Antinori, Dr G Filice, Dr A Lazzarin, Dr G Pagano, Dr E Raise, Dr S Rusconi, Dr L Sighinolfi, Dr ML Soranzo.
The Netherlands: Dr J Lange.
Poland: Dr M Beniowski, Dr A Boron-Kaczmarska, Dr A Horban.
Portugal: Dr F Antunes, Dr K Mansinho, Dr AM Miranda.
Spain: Dr JR Arribas, Dr MA Berdún, Dr JL Casado, Dr B Clotet, Dr P Domingo, Dr JM Gatell, Dr D Podzamczer, Dr F Pulido, Dr E Ribera, Dr R Rubio, Dr P Viciana.
Switzerland: Dr M Opravil, Dr A Telenti.
UK: Dr M Fisher, Dr P Hay, Dr M Johnson, Dr A Pozniak.

Supported by Tibotec

Presented at the 8th International Congress on Drug Therapy in HIV Infection, Glasgow, UK, 12–16 November 2006.

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