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Pharmacokinetic evaluation of non-nucleoside reverse transcriptase inhibitor TMC125 and integrase inhibitor raltegravir in healthy volunteers

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Abstract

Objectives: TMC125 (etravirine; ETR), a next generation non-nucleoside reverse transcriptase inhibitor (NNRTI), and raltegravir (RAL; MK-0518), a novel integrase strand transfer inhibitor (InSTI), have separately demonstrated potent activity in treatment-experienced HIV-infected patients. *In vitro*, RAL is primarily glucuronidated and TMC125 induces glucuronidation. The objective of this study was to assess the two-way interaction between TMC125 and RAL for potential co-administration in HIV-infected patients.

Methods: Nineteen healthy volunteers were enrolled in an open-label, sequential, three-period study. In Period 1, all volunteers were administered RAL 400mg every 12 hours for 4 days followed by a washout. In Period 2, all volunteers were administered TMC125 200mg every 12 hours for 8 days. In Period 3, all volunteers were administered RAL 400mg and TMC125 200mg every 12 hours for 4 days. There was no washout between Periods 2 and 3. Doses were administered with a meal. Plasma samples for RAL and/or TMC125 pharmacokinetics were collected over 12 hours after each period. Pharmacokinetic (PK) parameters were determined using non-compartmental analysis. Safety and tolerability were assessed throughout the study.

Results: RAL had no significant effect on TMC125 pharmacokinetics while TMC125 had only modest effects on RAL pharmacokinetics. The geometric mean ratio (GMR) (90% confidence interval [CI]) for TMC125 co-administered with RAL relative to TMC125 alone was 1.10 (1.03–1.16) for area under the plasma concentration versus time curve to 12 hours (AUC_{12h}), 1.04 (0.97–1.12) for maximum concentration of drug in the plasma (C_{max}) and 1.17 (1.10–1.26) for concentration of drug in plasma at 12 hours (C_{12h}); GMR (90% CI) for RAL co-administered with TMC125 relative to RAL alone was 0.90 (0.68–1.18) for AUC_{12h}, 0.89 (0.68–1.15) for C_{max} and 0.66 (0.34–1.26) for C_{12h}. Most adverse events (AEs) were mild and consisted of headache or gastrointestinal (GI)-related events. No grade 3/4 AEs or discontinuations due to AEs occurred.

Conclusions: RAL has no effect on TMC125 pharmacokinetics. TMC125 modestly decreased RAL pharmacokinetics, possibly via induction of glucuronidation. Co-administration of TMC125 and RAL was generally safe and well tolerated; no dose adjustment is necessary in HIV-infected patients.

Introduction

- TMC125 is an investigational NNRTI with potent in-vitro activity against both wild-type HIV-1 and HIV-1 resistant to current NNRTIs[1]
- Two randomised, double-blind, placebo-controlled, Phase III trials (DUET-1 and -2) demonstrated significant and sustained antiviral benefit after 24 weeks of treatment with TMC125 and background regimen including darunavir/ritonavir in treatment-experienced patients with NNRTI resistance. Treatment with TMC125 was generally safe and well tolerated[2,3]

Introduction (cont'd)

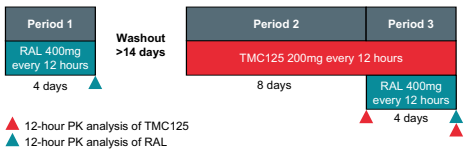
- RAL is an investigational InSTI with potent in-vitro activity against HIV-1 (IC_{95} = 31nM in 50% human serum)
- TMC125 is an inducer and substrate of CYP3A, and an inhibitor and substrate of CYP2C9 and CYP2C19; TMC125 is also metabolised by uridine diphosphate glucuronyl transferase (UDPGT); in vitro TMC125 induces UDPGT
- RAL is primarily metabolised by UDPGT
- This study was designed to assess the two-way PK interaction between TMC125 and RAL in healthy volunteers

Study objectives

- Primary objective
  - to evaluate the safety and tolerability of TMC125 alone, RAL alone, and TMC125 co-administered with RAL
- Secondary objective
  - to evaluate the effect of co-administration of TMC125 and RAL on the plasma PK profiles of RAL and TMC125 (AUC_{12h}, C_{max}, C_{12h}, and time to reach C_{max} [T_{max}])

Study design

- Open-label, sequential, three-period study in 20 healthy volunteers
- All doses were administered with food



Pharmacokinetic analysis

- Plasma samples for RAL and/or TMC125 PK were collected over 12 hours after each period
- Plasma concentrations of TMC125 and RAL were determined using validated liquid chromatographic-tandem mass spectrometric methods
  - lower limit of quantification was 2ng/mL for both drugs
- PK analyses were performed using WinNonlin Professional (version 5.1; Pharsight Corporation, Mountain View, California, USA)

Statistical analysis

- Model based analyses were performed for both TMC125 and RAL PK parameters (C_{12h}, AUC_{12h}, C_{max}) using a mixed effects linear model appropriate for a three-period, fixed design

Safety analysis

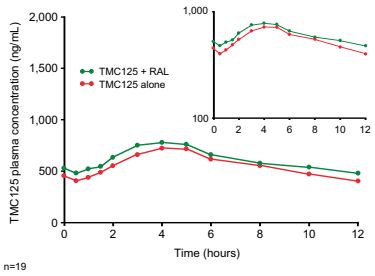
- Safety and tolerability were assessed by measurements of semi-recumbent heart rate and blood pressure, electrocardiogram, laboratory safety tests (haematology, chemistry, and urinalysis), and physical examinations
  - pregnancy tests were performed on female volunteers of childbearing potential
- AEs were evaluated as to their intensity, seriousness, and relationship to study drug

Volunteer demographics

	Overall (n=20)		Male (n=13)		Female (n=7)	
	Median	Range	Median	Range	Median	Range
Age (years)	29.8	19–45	29.5	19–41	30.4	23–45
Height (cm)	174.1	145–187	178.7	173–187	165.6	145–177
Weight (kg)	78.5	58.2–103.2	82.4	58.2–103.2	71.0	59.6–83.6

One volunteer discontinued the trial by withdrawing consent after the morning intake of RAL on Day 2 of Period 1 – this volunteer was not replaced

Mean plasma concentration-time profile* of TMC125 alone or co-administered with RAL



n=19

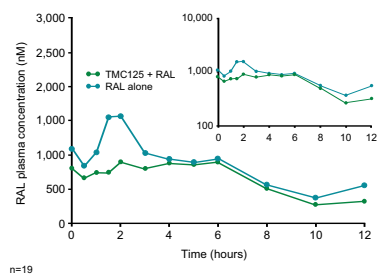
*Inset = semi-log scale

TMC125 plasma PK parameters alone or co-administered with RAL

	TMC125 + RAL			TMC125			RAL + TMC125/TMC125		
Parameter	N	GM*	95% CI	N	GM*	95% CI	GMR	90% CI	MSE†
C_{12h} (ng/mL)	19	439	359–536	19	373	306–457	1.17	1.10–1.26	0.015
AUC_{12h} (ng•h/mL)	19	6,813	5,633–8,240	19	6,216	5,139–7,518	1.10	1.03–1.16	0.011
C_{max} (ng/mL)	19	766	633–926	19	734	607–888	1.04	0.97–1.12	0.017
T_{max} (h)	19	4.0‡	–	19	4.0‡	–	–0.5§	–1.0–0.0	–

*Geometric mean (GM) computed from least squares estimate from an ANOVA performed on the natural-log transformed values
†Mean square error (MSE) on log-scale
‡Median reported for T_{max}
§Hodges-Lehman estimate of median difference with corresponding 90% CI for true median difference

Mean plasma concentration-time profile* of RAL alone or co-administered with TMC125



n=19

*Inset = semi-log scale

RAL plasma PK parameters alone or co-administered with TMC125

	TMC125 + RAL			RAL			RAL + TMC125/RAL		
Parameter	N	GM*	95% CI	N	GM*	95% CI	GMR	90% CI	MSE†
C_{12h} (nM)	19	141.6	77.2–259.6	19	216.0	117.8–396.0	0.66	0.34–1.26	1.347
AUC_{12h} (μM•h)	19	6.28	4.49–8.79	19	7.01	5.01–9.81	0.90	0.68–1.18	0.239
C_{max} (μM)	19	1.54	1.09–2.18	19	1.74	1.23–2.46	0.89	0.68–1.15	0.213
T_{max} (h)	19	3.0‡	–	19	1.5‡	–	1.8§	0.3–3.0	–

*Computed from least squares estimate from an ANOVA performed on the natural-log transformed values
†MSE on log-scale
‡Median reported for T_{max}
§Hodges-Lehman estimate of median difference with corresponding 90% CI for true median difference

Safety summary

- Co-administration of RAL with TMC125 was generally well tolerated
- No serious AEs were reported and no volunteer discontinued due to an adverse experience
- 16 volunteers reported a total of 44 AEs (grade 1 or 2)
  - three volunteers developed grade 1 rash, all of which were not classed as drug related by the investigator
  - 21 AEs were deemed by the investigator to be possibly related to either RAL or TMC125
  - the most common drug related AE was headache
  - there were no laboratory abnormalities reported in this study

Conclusions

- Co-administration of TMC125 and RAL at steady-state was generally safe and well tolerated
  - no volunteers discontinued the study due to an AE.
- RAL had no clinically relevant effect on TMC125 PK.
- TMC125 modestly reduced RAL C_{12h} (↓34%); AUC_{12h}, C_{max} and T_{max} were not altered to a clinically relevant extent.
- Based on the results of this study, TMC125 and RAL can be co-administered without dose adjustment in HIV-1-infected patients.

References

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3. Lazzarin A, et al. Lancet 2007;370:39–48.

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