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Relative bioavailability of a concept paediatric formulation of TMC278, an investigational NNRTI

THPE0158

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Introduction

- TMC278 (Figure 1), is a next-generation NNRTI that has demonstrated sustained efficacy and good tolerability in treatment-naïve, HIV-1-infected adults over 192 weeks in a Phase IIb trial.[1]
- TMC278 is currently being evaluated in two Phase III trials[2] in adults in a tablet formulation at a dose of 25 mg q.d., in combination with a backbone of two NRTIs.
- Available treatment options for HIV-infected children are limited compared with the broad range of effective therapies developed for HIV-infected adults.

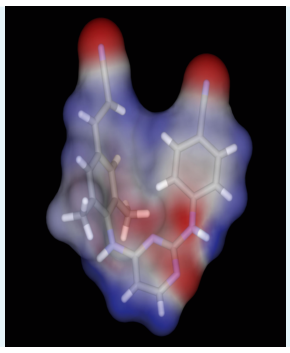

Figure 1. Three-dimensional chemical structure of TMC278.

- An important aspect to facilitate dosing in HIV-infected children is the availability of child-friendly oral formulations, such as granule formulations or crushable or dispersible tablets.[3]
- Such new formulations are needed to improve the long-term adherence and treatment success and help limit the emergence of drug resistance in HIV-infected children.[3,4]
- An appropriate oral paediatric formulation of TMC278 would allow flexibility in dosing, depending on age and/or bodyweight.
- It could also provide benefits to children unable to swallow pills or taking an unpalatable medication, as well as provide a once-daily treatment option for HIV-infected children in combination with a backbone regimen.
- This trial in adults evaluated the relative oral bioavailability of TMC278 when administered as a new granule formulation intended for use in paediatric patients, compared with the adult tablet formulation.

Methods

Study design

- Phase I, open-label, randomised, three-way, crossover trial in 12 healthy, HIV-negative adults (n=2 in each of groups 1–6, according to a Williams design) (Table 1).
- Participants received a single, oral 25 mg dose of TMC278 under fed or fasted conditions in the following dosage forms
  - Paediatric granule formulation within 10 minutes after completion of a standardised breakfast[5] (Treatment A)
  - Paediatric granule formulation after at least a 10-hour overnight fast (Treatment B)
  - Tablet (Phase III formulation used in ECHO [**E**fficacy **C**omparison in treatment-naive **H**IV-infected subjects **O**f TMC278 and EFV] and THRIVE [**T**MC278 against **H**IV, in a once daily **R**eg**I**men **V**ersus **E**favirenz; 25 mg q.d.]) within 10 minutes after completion of a standardised breakfast (Treatment C).
- The tablet and granules were administered together with approximately 240 mL of water; the granules were dispersed in the water before intake, and the glass rinsed until all granules had gone.
- The recommended use of the TMC278 tablet is with a meal, and is studied as such in the Phase III trials.[2] Apart from the de-bossing, the commercial tablet will be identical to the Phase III tablet.
- There was a washout period of at least 14 days between subsequent intakes of TMC278.
- The study protocol was reviewed and approved by the appropriate institutional ethics committee and health authority, and the study was conducted in accordance with the Declaration of Helsinki. Written informed consent was obtained from all participants.

Table 1. Schematic overview of study design.

	Treatment session				
	Session 1	Washout*	Session 2	Washout*	Session 3
Group 1 (n=2)	Treatment A	→	Treatment B	→	Treatment C
Group 2 (n=2)	Treatment B	→	Treatment C	→	Treatment A
Group 3 (n=2)	Treatment C	→	Treatment A	→	Treatment B
Group 4 (n=2)	Treatment C	→	Treatment B	→	Treatment A
Group 5 (n=2)	Treatment B	→	Treatment A	→	Treatment C
Group 6 (n=2)	Treatment A	→	Treatment C	→	Treatment B

*Washout period of at least 14 days between two intakes of TMC278; Treatment A = single 25 mg TMC278 dose of granules under fed conditions; Treatment B = single 25 mg TMC278 dose of granules under fasted conditions; Treatment C = single 25 mg TMC278 dose as tablet under fed conditions

Study assessments

- Blood samples for pharmacokinetic (PK) analysis were collected at regular timepoints in each treatment session, for the evaluation of a complete PK profile of TMC278
  - Predose, 0.5, 1, 2, 3, 4, 5, 6, 9, 12, 16, 24, 48, 72, 120 and 168 (Day 8) hours post-dose.
- Bioanalysis of TMC278 in plasma was performed using a validated liquid chromatography-mass spectrometry/mass spectrometry method, with a lower limit of quantification of 1.0 ng/mL.
- The palatability of the granule formulation was assessed under fasted conditions (Treatment B) using a taste questionnaire, and a five-point taste visual analogue scale.
- The type and incidence of adverse events (AEs) and laboratory abnormalities (haematology, biochemistry and urinalysis) were assessed throughout the treatment period and during follow-up (Days 30, 31 or 32). Events were examined by severity, possible relationship to drug and outcome.
- Vital signs and electrocardiogram (ECG) parameters were monitored throughout the study.

PK and statistical analysis

- PK parameters were calculated using non-compartmental analysis.
- The primary PK parameters for the statistical analysis were maximum plasma concentration (C_{max}), area under the plasma concentration-time curve from time of administration up to the last timepoint with a measurable concentration (AUC_{last}) and AUC extrapolated to infinity (AUC_{inf}), on the logarithmic scale.
- Statistical analyses for the primary PK parameters were performed for
  - Evaluation of the relative bioavailability of the granule formulation, by comparing Treatments A and B (test: granules fed and fasted states) with Treatment C (reference 1: tablet fed state)
  - Evaluation of the food effect for the granule formulation, by comparing Treatment B (test: granules fasted state) with Treatment A (reference 2: granules fed state).
- All observations for test and reference, paired and unpaired, were included in the statistical analysis.
- The least square means (LSM) of the primary PK parameters of TMC278 for each treatment were estimated using a linear mixed effect model with treatment, sequence and period as fixed effects and subject as random effect. A 90% confidence interval (CI) was constructed around the difference between the LSM of test and reference.

Results

Volunteer disposition and baseline characteristics

- Eleven of the volunteers completed the study and one was withdrawn (after Session 1, Treatment B) for non-compliance with the study protocol.
- Baseline demographics are shown in Table 2.

Table 2. Baseline demographics.

Characteristic	Value (n=12)
Age,* years	39.5 (20–54)
Sex, n (%)	
Male	11 (91.7)
Female	1 (8.3)
Height,* cm	182.3 (165–192)
Weight,* kg	75.4 (66–91)
Body mass index,* kg/m²	23.5 (19.7–28.8)
Race, n (%)	
Caucasian	9 (75.0)
Asian	1 (8.3)
Black	2 (16.7)

*Median and range

PK analyses

Plasma concentration-time profiles and PK parameters

- Evaluable PK parameters were available for 11 volunteers in each of the treatment sessions.
- TMC278 plasma concentrations were quantifiable from 0.5 hours post-dose for the granule formulation (fed and fasted conditions), indicating more rapid absorption than for the tablet formulation, for which TMC278 plasma concentrations were quantifiable as of 1 or 2 hours post-dose (Figure 2).
- The time to reach the maximum plasma concentrations (t_{max}) was comparable between the different treatments (Table 3).
- The mean TMC278 plasma concentration-time profile was higher after administration of the granule formulation (fed conditions) compared with the tablet (fed conditions) (Figure 2).

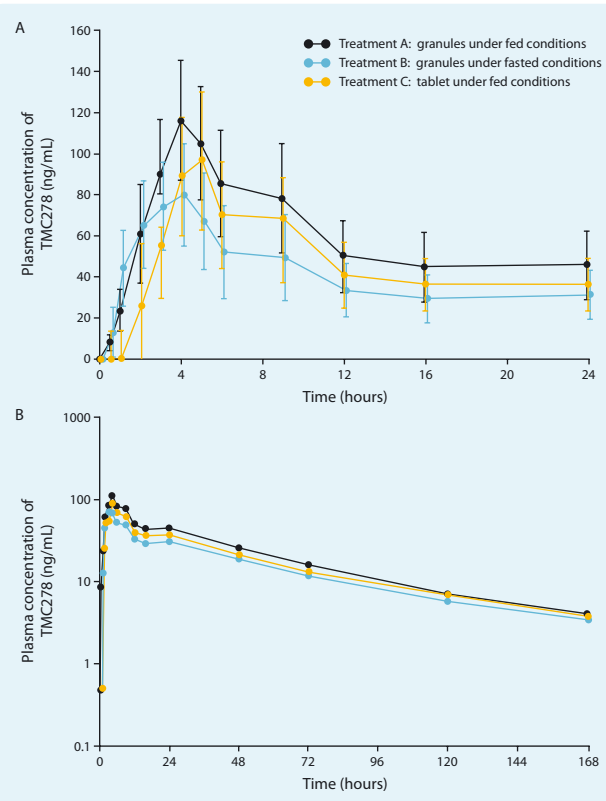

Figure 2. Mean (± standard deviation [SD]) A) 24-hour or B) 168-hour plasma concentration-time curves for Treatment A (granules, fed conditions), Treatment B (granules, fasted conditions) and Treatment C (tablet, fed conditions).

Statistical analyses

- The observed increases in TMC278 PK parameters for the granules compared with the tablet formulation, both under fed conditions, were: 18% increase in C_{max}, 28% increase in AUC_{last} and 26% increase in AUC_{inf} (Table 4).

Table 3. PK parameters for Treatment A (granules, fed conditions), Treatment B (granules, fasted conditions) and Treatment C (tablet, fed conditions).

PK parameter	Treatment A Granules fed (n=11)	Treatment B Granules fasted (n=11)	Treatment C Tablet fed (n=11)
C_{max}, ng/mL Mean (± SD)	119.3 ± 26.81	85.95 ± 22.07	102.9 ± 33.16
t_{max}, hour Median (range)	4.0 (3.0–5.0)	4.0 (2.0–5.0)	5.0 (2.0–5.0)
AUC_{last}, ng•h/mL Mean (± SD)	3665 ± 1273	2479 ± 1097	2922 ± 1220
AUC_{inf}, ng•h/mL Mean (± SD)	3990 ± 1425	2740 ± 1192	3263 ± 1467
$t_{1/2term}$, hour Mean (± SD)	40.00 ± 16.89	45.90 ± 22.98*	43.34 ± 23.23

*n=12; Treatment A = single 25 mg TMC278 dose of granules under fed conditions; Treatment B = single 25 mg TMC278 dose of granules under fasted conditions; Treatment C = single 25 mg TMC278 dose as tablet under fed conditions; $t_{1/2term}$ = terminal elimination half-life

- Granules administered in fasted conditions resulted in similar TMC278 exposure compared with the tablet formulation taken with a meal (Table 4).
- Evaluation of the effect of food on the pharmacokinetics of the granule formulation indicated a decrease of 30% (C_{max}), 29% (AUC_{last}), and 28% (AUC_{inf}) for the granules taken in fasted conditions compared with intake with a meal (Table 4).

Table 4. Statistical analysis comparing TMC278 granule and tablet formulations, and the effect of food on granule formulation: LSM (90% CI).

	Test	Reference 1	n/n	C_{max}	AUC_{last}	AUC_{inf}
Relative bioavailability	Granules fed	Tablet fed	11/11	1.18 (1.00–1.40)	1.28 (1.11–1.48)	1.26 (1.09–1.46)
	Granules fasted	Tablet fed	11/11	0.87 (0.79–0.96)	0.93 (0.85–1.00)	0.93 (0.86–1.00)
	Test	**Reference 2**	**n/n**	**C_{max}**	**AUC_{last}**	**AUC_{inf}**
Food effect	Granules fasted	Granules fed	11/11	0.70 (0.59–0.83)	0.71 (0.63–0.80)	0.72 (0.64–0.81)

LSM (90% CI) calculated as test/reference; n/n = number of volunteers in the test/reference; one volunteer dropped out before trial completion due to non-compliance with study procedures; PK parameters were not assessable for one volunteer receiving Treatment B

Taste questionnaire

- The overall palatability of the granules was rated as 'acceptable' or 'good' by 10 out of 12 (83.3%) volunteers.
- On the visual analogue scale, only two of 12 (16.7%) volunteers disliked the granule formulation 'a little'.

Safety and tolerability

- Administration of TMC278 as either the tablet or granule formulation was generally well tolerated.
- The number of volunteers reporting AEs during administration of each treatment were
  - Treatment A: granules (fed), seven (63.6%); one volunteer had at least one AE thought to be possibly related to treatment
  - Treatment B: granules (fasted), five (41.7%); three volunteers had at least one AE thought to be possibly related to treatment
  - Treatment C: tablet (fed), three (27.3%); one volunteer had at least one AE thought to be possibly related to treatment.
- The most frequently reported AEs (reported in ≥2 volunteers with any treatment) were headache, nasopharyngitis, myalgia and abnormal dreams.
- No cases of rash were seen.
- There were no treatment-emergent grade 3 (severe), grade 4 (life-threatening) or serious AEs.
- No consistent trends or clinically relevant changes in laboratory parameters, or clinically relevant abnormalities were observed for ECGs and vital signs.
- There were no discontinuations due to AEs.

Conclusions

- The exposure (AUC_{inf}) to TMC278 was 26% higher when administered as granules compared with the tablet, both taken with a meal.
- The exposure for the granule formulation administered in fasted conditions was comparable with that of the tablet formulation taken with a meal.
- The bioavailability of TMC278 administered as granules is affected by food intake, with a 28–30% lower exposure (C_{max}, AUC) when the granules were administered in the fasting state compared with intake with a meal. It will be recommended to take the granules with a meal.
- All treatments were generally well tolerated. No new safety signals for AEs, laboratory parameters, vital signs or ECGs were observed.
- The TMC278 granule formulation has good oral bioavailability and palatability, and will be further developed for use in paediatric trials.

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Acknowledgements and disclosures

- We would like to express gratitude to
  - The study volunteers
  - The investigator: F Cohen, MD, Kendle International BV, Utrecht, The Netherlands
  - Tibotec TMC278 team members, in particular D Anderson, S Fox, E Lefebvre, D Schaible, P Williams for their input into this poster
  - I Vanwelkenhuysen (J&J Pharmaceutical Research and Development, Beerse, Belgium)
  - T Stevens.
- This study was sponsored by Tibotec Pharmaceuticals.
- Editorial support was provided by I Woolveridge and C Waterhouse of Gardiner-Caldwell Communications, Macclesfield, UK; this support was funded by Tibotec.
- HMC, RPGVH, DFM, AB, KB and RMWH are full-time employees of Tibotec.
- RL and GS are full-time employees of Janssen Pharmaceutica NV.