Poster 1076

Evaluation of metabolic interactions for TMC435 via cytochrome P450 (CYP) enzymes in healthy volunteers

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Introduction

- **TMC435 is a macrocyclic NS3/4A protease inhibitor currently in Phase IIb clinical development for the treatment of hepatitis C virus (HCV) infection.**
- **It is a potent and selective inhibitor of NS3/4A *in vitro*, with a 50% effective concentration (EC_{50}) of 8 nM in a genotype-1b replicon cell line.[1]**
- **Findings from Phase I and IIa studies have shown that TMC435 is well tolerated, has a pharmacokinetic (PK) profile that supports a once-daily (QD) dosing regimen, and has demonstrated potent antiviral activity in both treatment-naive and -experienced patients.[2-5]**
- **As concomitant medications are often used to treat co-existing diseases in HCV-infected patients, evaluating any potential interactions between TMC435 and other drugs is needed.**
- **CYP enzymes have been shown to play a role in the metabolism of TMC435 *in vitro*. As such, we evaluated a broad spectrum of potential metabolic interactions for TMC435 (via various CYP enzymes) in three studies conducted in healthy volunteers (TMC435-C107, TMC435-C104 and TMC435-C105); here we report findings from these three studies.**

Study objectives

TMC435-C107

- To determine the effects of TMC435 on the single-dose PK of oral midazolam and a cocktail of representative probes of CYP enzymes (CYP1A2, CYP2C9, CYP2D6, CYP3A4 and CYP2C19).

TMC435-C104

- To determine the effect of the potent CYP3A4 inhibitor, ritonavir, on the PK of TMC435 following 7 days of oral QD dosing.

TMC435-C105

- To determine the effect of the potent CYP3A4 inducer, rifampin, on the PK of TMC435 following 7 days of oral QD dosing.

Methods

TMC435-C107

Study design

- This was a Phase I, open-label, two-period, randomised, crossover study comprising 16 healthy adults.
- Following screening, eligible volunteers were randomised to one of two treatment sequences (Table 1).

Table 1. TMC435-C107: treatment plan.

Group A (n=8)						
	Treatment A		Washout	Treatment B		Follow-up
Screening	Day 1: Oral midazolam (0.075 mg/kg)	Day 2: Drug cocktail*	At least 14 days	11 days: TMC435 150 mg QD on Days 1–11; Day 10: Oral midazolam (0.075 mg/kg); Day 11: Drug cocktail*		30–32 days
Group B (n=8)						
	Treatment B		Washout	Treatment A		Follow-up
Screening	11 days: TMC435 150 mg QD on Days 1–11; Day 10: Oral midazolam (0.075 mg/kg); Day 11: Drug cocktail*		At least 14 days	Day 1: Oral midazolam (0.075 mg/kg)	Day 2: Drug cocktail*	30–32 days

*0.025 mg/kg midazolam (i.v. given slowly over a 1-minute period), dextromethorphan (30 mg p.o.), caffeine (150 mg p.o.), omeprazole (40 mg p.o.) and warfarin (10 mg p.o.) supplemented with vitamin K (10 mg p.o.)
QD, once daily

- Midazolam was given both orally and intravenously to enable differentiation between effect on intestinal and hepatic CYP3A4 activity.

Assessments

- CYP assessments:
  - CYP3A4: plasma concentrations of midazolam and its metabolite 1-OH-midazolam (measured on Days 1 and 2 [treatment A]; Days 10 and 11 [treatment B]).
  - CYP2D6: plasma concentrations of dextromethorphan and its metabolite, dextrorphan (measured on Day 2 [treatment A]; Day 11 [treatment B]).
  - CYP1A2: plasma concentrations of caffeine and its metabolite paraxanthine (measured on Day 2 [treatment A]; Day 11 [treatment B]).
  - CYP2C19: plasma concentrations of omeprazole and its metabolite 5-OH-omeprazole (measured on Day 2 [treatment A]; Day 11 [treatment B]).
  - CYP2C9: plasma concentrations of S-warfarin and its metabolite 7-OH-S-warfarin (measured on Days 2–6 [treatment A]; Days 11–15 [treatment B]).
- Plasma concentrations of TMC435 were determined on Days 9–15 (treatment B).
- Safety and tolerability were assessed throughout the study.

Statistical analysis

- Least squares means (LSM) ratios were calculated with a linear mixed-effects model, controlling for treatment, sequence and period as fixed effects, and subject as a random effect.
- The LSM and 90% confidence intervals (CIs) of the ratio of parent to metabolite (P/M) for individual area under the curve from time of administration to the last time point with a measurable concentration after dosing (AUC_{last}) was used to assess treatment differences between:
  - drug cocktail or oral midazolam alone (reference)
  - drug cocktail or oral midazolam co-administered with TMC435 (test).
- Safety and tolerability were analysed using the intent-to-treat (ITT) population.

TMC435-C104

Study design

- This was a Phase I, open-label, single-arm, two-period, sequential crossover study comprising 12 healthy adults (Table 2).

Table 2. TMC435-C104: treatment plan.

	Session 1 (7 days)	Washout	Session 2 (15 days)	Follow-up
Screening	TMC435 200 mg QD from Day 1 to Day 7	At least 7 days	TMC435 200 mg QD on Days 6–12 Ritonavir 100 mg BID on Days 1–15	30–35 days

BID, twice daily; QD, once daily

Assessments

- The PK profile of TMC435 was determined on Days 1 and 7 of session 1 and on Days 6 and 12 of session 2.
- PK parameters included: AUC from administration up to 24 hours post-dose (AUC_{tau}), pre-dose plasma concentrations (C_{pd}), minimum (C_{min}) and maximum (C_{max}) plasma concentrations, time to reach maximum concentration (t_{max}) and terminal elimination half-life ($t_{1/2term}$).
- Safety and tolerability were analysed throughout the study.

Statistical analysis

- The LSM of the primary outcome measures were calculated with a linear mixed-effects model, controlling for treatment period and sequence as fixed effects and subject as a random effect.
- The LSM and 90% CIs were used to assess treatment differences between:
  - TMC435 alone (reference)
  - TMC435 co-administered with ritonavir (test).
- Safety and tolerability were assessed using the ITT population.

TMC435-C105

Study design

- This was a Phase I, open-label, randomised, three-way crossover study comprising 18 healthy adults.
- Following screening, eligible volunteers were randomised to receive one of three treatments according to a classical six-sequence, three-period Williams design (Table 3).

Table 3. TMC435-C105: treatment plan.

	Group	Session 1	Washout	Session 2	Washout	Session 3	Follow-up
Screening	1 (n=3)	Treatment A	At least 10 days	Treatment B	At least 10 days	Treatment C	30–35 days
	2 (n=3)	Treatment B		Treatment C		Treatment A	
	3 (n=3)	Treatment C		Treatment A		Treatment B	
	4 (n=3)	Treatment C		Treatment B		Treatment A	
	5 (n=3)	Treatment B		Treatment A		Treatment C	
	6 (n=3)	Treatment A		Treatment C		Treatment B	

Treatment A: TMC435 200 mg QD for 7 days
Treatment B: rifampin 600 mg QD for 7 days
Treatment C: the combination of TMC435 200 mg + rifampin 600 mg both QD for 7 days
QD, once daily

Assessments

- The PK profile of TMC435 was determined on Day 7 of treatments A and C.
- The PK profiles of rifampin and its active metabolite, 25-desacetyl-rifampin, were determined on Day 7 of treatments B and C.
- PK parameters included: C_{pd}, C_{min}, C_{max}, t_{max} and AUC_{24h}.
- Safety and tolerability were analysed throughout the study.

Statistical analysis

- The LSM of the primary parameters were calculated with a linear mixed-effects model, controlling for treatment, period and sequence as fixed effects and subject as a random effect.
- The LSM and 90% CIs were used to assess treatment differences between:
  - TMC435 alone (reference) and TMC435 co-administered with rifampin (test) for TMC435
  - rifampin alone (reference) and rifampin co-administered with TMC435 (test) for rifampin and 25-desacetyl-rifampin.
- Safety and tolerability were assessed using the ITT population.

Results

TMC435-C107

Subject disposition

- Sixteen volunteers were randomised to receive treatment and completed the study.
- Baseline demographics were generally well balanced between sequences.
  - Median age: 47 years (range 21–56), median body mass index (BMI): 24.4 kg/m^2 (range 14.6–29.0), all volunteers were Caucasian, 5 (31.3%) were male.
- None of the volunteers displayed a poor metaboliser genotype for CYP2D6 (*3, *4, *5, *6), CYP2C9 (*2, *3) or CYP2C19 (*2, *3, *4, *8).

Effect of TMC435 on CYP probes

- The effect of TMC435 150 mg QD on the LSM AUC parent/metabolite ratios of CYP probes in the drug cocktail and oral midazolam are shown in Table 4.

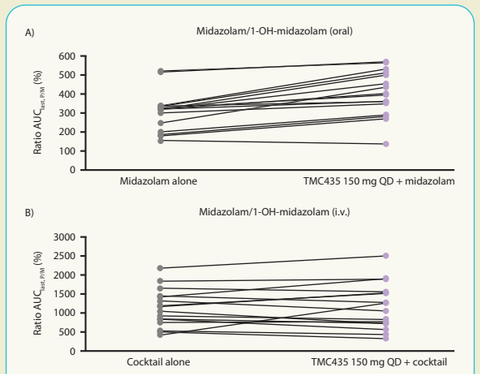
Table 4. TMC435-C107: Effect of TMC435 150 mg QD on the pharmacokinetics (least squares means ratios and associated 90% confidence intervals) of CYP probes in the drug cocktail and oral midazolam.

LS means ratio and 90% confidence interval ratio $AUC_{Parent/Metabolite}$					
CYP3A4 (intestinal) Midazolam/ 1-OH-midazolam (oral)	CYP3A4 (hepatic) Midazolam/- 1-OH-midazolam (i.v.)	CYP2C9 Warfarin/ S-warfarin	CYP1A2 Caffeine/ paraxanthine	CYP2C19 Omeprazole/ 5-OH-omeprazole	CYP2D6 Dextromethorphan/ dextrorphan
1.31 (1.21–1.42)	1.01 (0.86–1.18)	0.98 (0.86–1.12)	1.34 (1.26–1.42)	0.98 (0.85–1.12)	0.99 (0.80–1.23)

AUC, area under the concentration-time curve; i.v., intravenous; LS, least squares

- Co-administration of TMC435 with midazolam resulted in mild inhibition of intestinal CYP3A4 activity (Figure 1A) but did not affect hepatic CYP3A4 activity (Figure 1B).

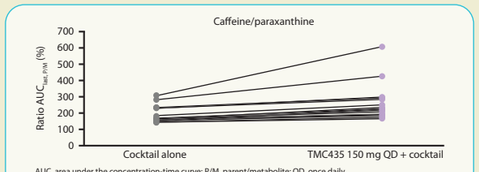
Figure 1. TMC435-C107: Individual midazolam/1-OH-midazolam ratios for AUC_{tau} (ratio $AUC_{tau,\ P/M}$) after (A) oral and (B) intravenous (i.v) administration of midazolam alone and in the presence of TMC435 (effect on intestinal [A] and hepatic [B] CYP3A4 activity).



AUC, area under the concentration-time curve; P/M, parent/metabolite; QD, once daily

- Co-administration of TMC435 with caffeine resulted in mild inhibition of CYP1A2 activity (Figure 2).
- CYP2C9 (Figure 3A), CYP2C19 (Figure 3B) and CYP2D6 (Figure 3C) activities were not significantly affected by TMC435.

Figure 2. TMC435-C107: Individual caffeine/paraxanthine ratios for AUC_{last} (ratio $AUC_{last,\ P/M}$) after intake of the drug cocktail alone and in the presence of TMC435 (effect on CYP1A2 activity).



AUC, area under the concentration-time curve; P/M, parent/metabolite; QD, once daily

Safety

- All volunteers reported at least one adverse event (AE), although most were grade 1 in severity. There were no grade-3 or -4 AEs, serious AEs (SAEs) or discontinuations due to AEs.
- The most frequent AEs were somnolence (n=16 [100%]; considered related to midazolam/cocktail) and headache (n=2 [12.5%]; considered related to TMC435).
- There were no relevant changes in laboratory tests, vital signs or echocardiogram (ECG) parameters.

TMC435-C104

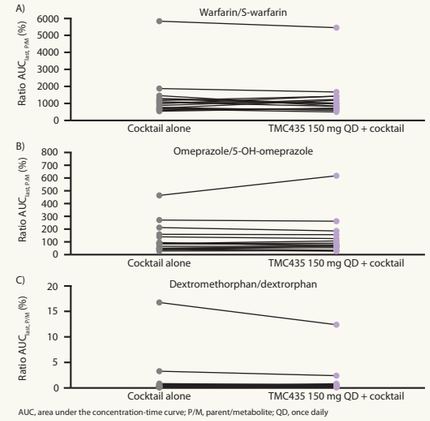
Subject disposition

- Twelve volunteers were randomised to receive treatment and completed the study.
- All volunteers were Caucasian males, median age: 35.5 years (range 18–54), median BMI: 24.8 kg/m^2 (range 20–28).

Pharmacokinetics of TMC435

- The PK profile of TMC435 alone (Days 1 and 7 of session 1) and in the presence of ritonavir (Days 6 and 12 of session 2) is shown in Table 5.

Figure 3. TMC435-C107: Individual ratios for AUC_{last} (ratio $AUC_{last,\ P/M}$) for (A) warfarin/S-warfarin, (B) omeprazole/5-OH-omeprazole, and (C) dextromethorphan/dextrorphan after intake of the drug cocktail alone and in the presence of TMC435 (effect on CYP2C9 [A], CYP2C19 [B] and CYP2D6 [C] activity).



AUC, area under the concentration-time curve; P/M, parent/metabolite; QD, once daily

Table 5. TMC435-C104: Pharmacokinetic profile of TMC435 200 mg QD alone (Days 1 and 7, session 1) and following co-administration with ritonavir 100 mg BID (Days 6 and 12, session 2).

Pharmacokinetics of TMC435 (mean ± SD, t_{max} median [range])	TMC435 alone Day 1 (reference 1)	TMC435 alone Day 7 (reference 2)	TMC435 + ritonavir Day 6 (test 1)	TMC435 + ritonavir Day 12 (test 2)
N	12	12	12	12[a]
C_{pd}, ng/mL	-	1140 ± 970.4	-	14050 ± 6987
C_{min}, ng/mL	-	1030 ± 971.6	-	11730 ± 5651
C_{max}, ng/mL	2194 ± 801.5	4617 ± 2788	2798 ± 1393	20150 ± 7861
t_{max}, h	6.0 (4.0-8.0)	6.0 (4.0-12.0)	6.0 (6.0-12.0)	6.0 (0.0-12.0)
AUC_{24h}, ng.h/mL	22510 ± 8236	60340 ± 41370	42180 ± 17670	391000 ± 151700
$t_{1/2term}$, h	-	11.39 ± 2.095	-	121.1[b] ± 119.7[b]
LS mean ratio (90% CI)				
	-	-	Test 1 vs reference 1	Test 2 vs reference 2
N	-	-	12 vs 12	12 vs 12
C_{pd}, ng/mL	-	-	-	14.78 (10.86–20.11)
C_{min}, ng/mL	-	-	-	14.35 (10.29–20.01)
C_{max}, ng/mL	-	-	1.30 (1.08–1.56)	4.70 (3.84–5.76)
AUC_{24h}, ng.h/mL	-	-	1.83 (1.64–2.04)	7.18 (5.63–9.15)

[a]n=10 for $t_{1/2term}$
[b]Accurate determination not possible
AUC_{24h}, area under the concentration-time curve from administration up to 24 hours post-dose; BID, twice daily; CI, confidence interval; C_{pd}, pre-dose plasma concentration; C_{max}, maximum plasma concentration; C_{min}, minimum plasma concentration; QD, once daily; $t_{1/2term}$, terminal elimination half-life; t_{max}, time to reach maximum concentration

- Compared with TMC435 alone, concomitant TMC435 and ritonavir administration resulted in:
  - higher mean plasma concentrations of TMC435
  - a 14.3-, 4.7- and 7.2-fold increase in TMC435 C_{min}, C_{max} and AUC_{24h}, respectively.

Safety

- Seven days of dosing with TMC435 was generally well tolerated, when administered alone or in combination with ritonavir.
- All volunteers reported at least one AE, although most were grade 1 in severity.
- The most common AEs were headache (7 volunteers [58.3%]) and nasopharyngitis (5 volunteers [41.7%]); there were no relevant differences in the incidence of AEs between treatment phases (treatment with TMC435 alone versus in combination with ritonavir).
- There were no grade-3 or -4 AEs, SAEs or discontinuations due to AEs.
- There were no relevant changes in laboratory tests, vital signs or ECG parameters.

TMC435-C105

Subject disposition

- Twenty-one volunteers were randomised to receive treatment and 16 completed the study.
  - Reasons for discontinuation were: grade-1 rash, grade-1 upper abdominal pain, positive urine drug screen, withdrawal of consent, non-compliance (n=1 for all).
- Baseline demographics were generally well balanced between treatment groups.
  - Median age: 39 years (range 24–52), median BMI: 28.1 kg (range 20–32), most were Caucasian (10 [47.6%]) or black (10 [47.6%]), and the majority (20 [95.2%]) were male.

Pharmacokinetics of TMC435

- The PK profiles of TMC435 alone (treatment A) and in the presence of rifampin (treatment C) are shown in Table 6.
- Compared with TMC435 alone, concomitant TMC435 and rifampin administration resulted in:
  - lower mean plasma concentrations of TMC435
  - a 31% increase and 48% decrease in TMC435 C_{max} and AUC_{24h}, respectively.

Table 6. TMC435-C105: Pharmacokinetic profile of TMC435 200 mg QD alone (treatment A) and following co-administration with rifampin 600 mg QD (treatment C).

Pharmacokinetics of TMC435 (mean ± SD, t_{max} median [range])	TMC435 200 mg QD (reference)	TMC435 200 mg QD + rifampin 600 mg QD + (test)
n	18[a]	17[b]
Day 1		
C_{pd}, ng/mL	NQ	NQ
Day 2		
C_{pd}, ng/mL	140.5 ± 103.5	255.0 ± 108.7
Day 4		
C_{pd}, ng/mL	340.2 ± 271.7	64.33 ± 21.03
Day 6		
C_{pd}, ng/mL	347.4 ± 324.0	31.75 ± 15.75
Day 7		
C_{pd}, ng/mL	434.7 ± 332.7	44.51 ± 37.52
C_{min}, ng/mL	363.5 ± 316.4	23.23 ± 10.10
C_{max}, ng/mL	2314 ± 1500	2623 ± 903.8
t_{max}, h	4.0 (2.0–12.0)	3.0 (2.0–4.0)
AUC_{24h}, ng.h/mL	28050 ± 19550	12690 ± 4802
LS mean ratio (90% CI)		
	-	Test vs reference
n	-	17 vs 18
C_{min}	-	0.08 (0.06–0.11)
C_{max}	-	1.31 (1.03–1.66)
AUC_{24h}	-	0.52 (0.41–0.67)

[a]n=17 for Day 1
[b]n=19 for Day 1 and 2, n=18 for Day 4
AUC_{24h}, area under the concentration-time curve from administration up to 24 hours post-dose; CI, confidence interval; C_{pd}, pre-dose plasma concentration; C_{max}, minimum plasma concentration; NQ, not quantifiable; LS, least squares; QD, once daily; t_{max}, time to reach maximum concentration

Pharmacokinetics of rifampin

- The PK profiles of rifampin alone (treatment B) and in the presence of TMC435 (treatment C) were comparable.
- The C_{max} of 25-desacetyl-rifampin was comparable when rifampin was administered alone or in the presence of TMC435, but the AUC_{24h} of 25-desacetyl-rifampin increased by 24% when rifampin was administered in the presence of TMC435 (data not shown).

Safety

- Seven days of dosing with TMC435 was generally well tolerated, when administered alone or in combination with rifampin.
- Thirteen volunteers (61.9%) reported at least one AE.
- The most common AEs were nausea, erythema and cough (3 volunteers each [14.3%]); there were no relevant differences in the incidence of AEs between treatment phases (treatment with TMC435 or rifampin alone, or co-administration of TMC435 and rifampin).
- Two volunteers experienced an AE that led to withdrawal from the study.
  - One volunteer discontinued during co-administration of TMC435 and rifampin due to upper abdominal pain, and one volunteer discontinued during rifampin treatment due to rash; both AEs leading to discontinuation were grade 1 in severity.
- There were no grade-3 or -4 AEs or SAEs.
- There were no relevant changes in laboratory tests, vital signs or ECG parameters.

Conclusions

- **The *in vivo* studies reported here confirm that TMC435 is a substrate for CYP3A4.**
- **Co-administration of TMC435 with potent inhibitors of CYP3A4, such as ritonavir, can increase plasma exposure to TMC435.**
- **Conversely, co-administration of TMC435 with potent inducers of CYP3A4, such as rifampin, can decrease plasma exposure to TMC435.**
- **Co-administration of TMC435 may lead to higher plasma exposure of drugs that undergo extensive first-pass metabolism by intestinal CYP3A4 and those that undergo metabolism primarily by CYP1A2.**
- **TMC435 has no relevant effect on drugs that are primarily metabolised via CYP2D6, CYP2C9 or CYP2C19.**

References

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