**Introduction**

**TMC435** is a macrocyclic CYP3A4 inhibitor currently in Phase IIa clinical development for the treatment of hepatic Cirrhosis (CYP) infection.

- This patient and volunteer database includes ethical approval for all study participants.
- Informed consent was obtained from all participants prior to the start of the study.
- Findings from Phase I studies have shown that TMC435 is well tolerated, has a pharmacokinetic (PK) profile that supports a single-dose (SQ) dosing regimen, and has demonstrated potent antiviral activity in both treatment-naive and experienced patients.

- As a consequence, realizations are made to better treat co-existing disease in HIV-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 these studies conducted in healthy volunteers (TMC435-C104, TMC435-C105 and TMC435-C106); here we report findings from these three studies.

**Study objectives**

**TMC435-C104**
- To determine the effects of TMC435 on the single-oral PK of midazolam and a cocktail of representative probes of CYP enzymes (CYP3A4, CYP2C9, CYP2C19 and CYP1A2).

**TMC435-C105**
- To determine the effect of the potent CYP1A2 inhibitor omeprazole on the PK of TMC435 following both oral and SQ dosing.

**Methods**

**TMC435-C104** Study design
- This was a Phase, non-blinded, single-arm, two-period, sequential crossover study comprising 12 healthy adults (Table 2).

**TMC435-C105** Study design
- This was a Phase, open-label, single-arm, two-period, sequential crossover study comprising 21 healthy adults.

**Screening**
- Group B (n=8):
  - CYP1A2: plasma concentrations of caffeine and its metabolite paraxanthine.
  - CYP2D6: plasma concentrations of dextromethorphan and its metabolite, dextromethorphan-glucuronide.

**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.**
- AUC was determined for all 3 CYP metabolic probes.
- The PK parameters for caffeine (C max and AUC 24h) and dextromethorphan were calculated for TMC435 alone or in combination with ritonavir.
- Safety and tolerability were assessed using the standard ITT population.

**Study population**
- Baseline demographics were generally well-balanced between treatment sequences.
- Baseline demographics were generally well-balanced between sequences.
- PK parameters for TMC435 were determined on Days 1 and 7 (in 9 subjects).
- Safety and tolerability were assessed both during and after the drug-cooled and in the presence of TMC435. (see Table 5).

**Primary endpoint**
- The effect of TMC435 on the PK of midazolam (C max and AUC 24h).

**Secondary endpoints**
- TMC435 plasma concentrations of various CYP enzymes.
- TMC435 plasma concentrations of various CYP enzymes.

**Supporting information**
- Baseline demographics were generally well-balanced between sequences.
- Safety and tolerability were assessed using the standard ITT population.

**Results**

**TMC435-C104**
- Subject disposition:
  - Twenty volunteers were randomized to receive treatment and completed the study.
  - Baseline demographics were generally well-balanced between sequences.
  - Plasma concentrations of TMC435 were determined on Days 1-7 (n=9).
  - Safety and tolerability were assessed both during and after the drug-cooled and in the presence of TMC435.

**Pharmacokinetics of TMC435**
- The PK profile of TMC435 was determined on Days 1 and 7 of session 1 and 6 and 12 of session 2 (see Table 5).

**Safety**
- 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 liver CYP3A4.

- TMC435 has no relevant effect on drugs that are primarily metabolised via CYP2D6, CYP2C9 or CYP2C19.

**References**

4. Available on request from the author. (See also: Br J Clin Pharmacol 2009; 68: 130-139)
5. Available on request from the author. (See also: Br J Clin Pharmacol 2009; 68: 130-139)