Abstract: 760

# A Randomized, Crossover, Phase 1 Study to Evaluate the Effect of a Strong CYP3A4 Inhibitor on Tivantinib (ARQ 197) Pharmacokinetics in Healthy Subjects

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## ABSTRACT

**Background:** Tivantinib is a selective, oral, non–ATP-competitive, small-molecule inhibitor of c-MET. In vitro data suggest that CYP2C19 and CYP3A4 are the major enzymes involved in tivantinib metabolism. Therefore, there is potential that CYP3A4 inhibitors may affect tivantinib pharmacokinetics (PK) leading to increased exposure. During the course of their disease, cancer patients receive multiple drugs, some of which may be strong CYP3A4 inhibitors. This open-label, 2-stage study evaluated the effect of ketoconazole, a strong inhibitor of CYP3A4, on tivantinib metabolism in adults with different CYP2C19 activity.

**Methods:** Healthy adults (age 18 to 45 years) with no clinical conditions were eligible. In stage 1, healthy subjects who were either an extensive metabolizer (EM) or intermediate metabolizer (IM) based on CYP2C19 activity were randomized to 1 of 2 sequences, each consisting of two 8-day treatment periods under fed conditions with a 14-day washout between periods. In sequence 1, tivantinib (120 mg) was administered alone on day 4 of period 1 followed by ketoconazole (400 mg/day) with concomitant tivantinib (120 mg) on day 4 of period 2. The treatments were reversed in sequence 2. If there was no interaction, poor metabolizer (PM) subjects were to be analyzed in stage 2. Serial blood samples were collected for 96 hours after tivantinib administration, and area under the curve (AUC), maximum concentration ($C_{max}$), and time to peak concentration ($t_{max}$) were calculated and statistically compared.

**Results:** Sixteen subjects were randomized equally to 1 of 2 treatment sequences. When tivantinib was combined with ketoconazole, total exposure to tivantinib (AUC) was increased 2.1-fold and $C_{max}$ was increased 1.4-fold compared with tivantinib alone. Median $t_{max}$ was similar for ketoconazole + tivantinib and tivantinib alone (4.75 vs 4.50 hours, respectively). Exposure to tivantinib was 2- to 3-fold higher in CYP2C19 IM subjects compared with CYP2C19 EM subjects, with or without ketoconazole. The median $t_{max}$ for tivantinib was comparable for IM and EM subjects with or without ketoconazole (tivantinib, 4.50 vs 4.49 hours, respectively, and ketoconazole + tivantinib, 5.00 vs 4.50 hours, respectively). A total of 10 adverse events (AEs) were reported in 5 subjects (31%); 4 AEs were considered related to ketoconazole and the remaining AEs were unrelated to study treatment. Two subjects discontinued the study because of elevated creatinine (related to ketoconazole) and elevated neutrophils (unrelated to treatment), respectively. Stage 2 assessment in CYP2C19 PM subjects was not performed.

**Conclusions:** Concurrent administration of ketoconazole substantially increased tivantinib exposure. Therefore, caution should be exercised when strong CYP3A4 inhibitors are coadministered with tivantinib.

## BACKGROUND

- Tivantinib is a selective, oral, small-molecule inhibitor of c-MET
  - In vitro data have suggested that tivantinib is metabolized primarily by CYP2C19 and CYP3A4
    - In the recombinant human isozyme system, CYP2C19 contributes to ~79% of tivantinib metabolism and CYP3A4 contributes to ~20%
    - In the human liver microsome system, contributions of CYP2C19 and CYP3A4 were similar (31% and 39%, respectively)
- It is possible that tivantinib exposure may be affected by concomitant medications that inhibit CYP3A4[1]
  - Inhibition of CYP3A4 could result in up to a 3-fold increase in tivantinib exposure
    - In CYP2C19 poor metabolizers (PM), CYP3A4 isozyme may be the dominant pathway for tivantinib metabolism. Therefore, CYP3A4 inhibitors may have greater effect on tivantinib pharmacokinetics (PK) in these subjects
  - Ketoconazole is a potent CYP3A4 inhibitor and is also a commonly used antifungal agent in cancer patients
  - The current study investigates the effect of ketoconazole on tivantinib PK

## OBJECTIVES

### Primary

- Effect of ketoconazole on tivantinib PK parameters by CYP2C19 phenotype

### Secondary

- Safety and tolerability of tivantinib when administered alone and concurrently with ketoconazole
- Comparison of PK parameters between extensive CYP2C19 metabolizers (EM) and intermediate metabolizers (IM)
- Effect of ketoconazole on tivantinib metabolite PK parameters

## METHODS

### Study Design

- Phase 1, single-center, open-label, crossover study in healthy subjects
  - Study was designed to enroll subjects in 2 stages
    - Stage 1: CYP2C19 EM and IM subjects
    - Stage 2: if no drug-drug interaction observed in stage 1, CYP2C19 PM subjects
  - Subjects were randomized to 1 of 2 treatment sequences under fed conditions (**Figure 1**)
    - Subjects fasted overnight (≥ 10 hours) and received a standardized high-fat breakfast
    - Dosing occurred 5 minutes after completion of the meal
    - Tivantinib (120 mg) was administered on day 4 with or without ketoconazole (400 mg)
  - Ketoconazole was administered on days 1 to 7
    - The second sequence was at least 14 days after completing the first

## METHODS

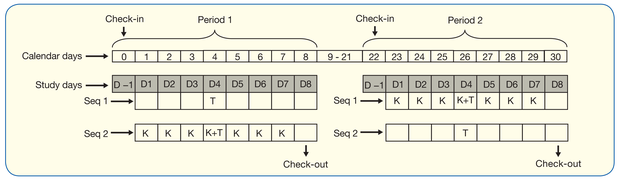


**Figure 1: Study schema.** Abbreviations: K, single oral 400 mg dose of ketoconazole; T, single oral 120 mg dose of tivantinib.

### Patient Eligibility

- Key inclusion criteria
  - Adults (age, 18 to 45 years; body mass index, 18 to 30 kg/m$^2$) in good health assessed by medical history and physical examination (including electrocardiogram)
  - For stage 1, EM or IM for tivantinib based on CYP2C19 activity assessed at screening
  - Abstinence from grapefruits or juice, Seville oranges, tobacco products, alcohol, and caffeinated products from 2 days to 3 months before (depending on item) and during study
- Key exclusion criteria
  - Adults who received any medications or herbal supplements within 14 days of study entry (for St. John's Wort, 30 days before study entry)
  - Adults with a history of conditions or treatment that would impair oral absorption
  - Adults who had significant blood loss within 56 days of study entry or donated plasma within 7 days of study entry
  - Adults who received a blood product transfusion within 30 days of study entry

### Study Assessments

- Blood samples for PK analysis were collected within 1 hour before dosing, every 30 minutes for 5 hours, and at 6, 7, 8, 10, 12, 18, 24, 36, 48, 60, 72, and 96 hours after dosing
- Adverse events were monitored continuously

### Statistical Analysis

- Geometric mean and geometric coefficient of variation (CV) were calculated for the PK parameters of area under the curve (AUC) and maximum concentrations ($C_{max}$)
- Mixed-effect analysis of variance (ANOVA) was performed on *ln*-transformed AUC and $C_{max}$ for the effect of ketoconazole on tivantinib PK
  - Treatment and sequence were fixed effects
  - Subjects within sequence were random effects
  - Absence of effect was concluded if the ANOVA 90% confidence intervals (CI) were entirely within the bioequivalence interval (80% to 125%)
- All statistical analyses were performed in SAS, version 9.1.3

## RESULTS—Baseline Characteristics

- 16 subjects were randomized: 8 to each sequence
  - 13 subjects completed the study; 1 withdrew consent and 2 discontinued due to adverse events (AEs)
- The majority of subjects were men (**Table 1**)

**Table 1. Subject Baseline Characteristics and Demographics**

| | (N = 16) |
|---|---|
| Gender, n (%) | |
| Female | 1 (6.3) |
| Male | 15 (93.8) |
| Race, n (%) | |
| Asian | 1 (6.3) |
| Black | 9 (56.3) |
| White | 5 (31.3) |
| Other | 1 (6.3) |
| Mean age, y (SD) | 32.9 (7) |
| Mean height, cm (SD) | 176.3 (7.1) |
| Mean weight, kg (SD) | 82.54 (10.4) |
| Mean BMI, kg/m$^2$ (SD) | 26.53 (2.7) |

Abbreviations: BMI, body mass index; SD, standard deviation.

## Pharmacokinetics

### Plasma Concentration

- Mean tivantinib concentrations were greater when ketoconazole was co-administered, as compared with tivantinib alone (**Figure 2**)
  - Similar increases in tivantinib concentrations were observed in IM and EM subjects

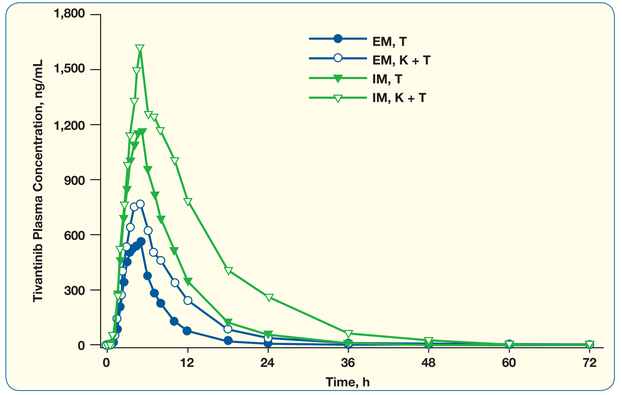


**Figure 2: Mean tivantinib concentration over time for extensive metabolizers (EM) and intermediate metabolizers (IM) by treatment sequence.** Abbreviations: K + T, single oral 400 mg dose of ketoconazole on days 1 to 7 and single oral 120 mg dose of tivantinib on day 4; T, single oral 120 mg dose of tivantinib.

### Effect of Metabolizer Status and Ketoconazole on Tivantinib PK Parameters

- Tivantinib total exposure in IM subjects was 3 times the exposure in EM subjects (**Table 2**)
  - Peak exposure in IM subjects was 2 times the exposure in EM subjects, and median half-life was 84% higher
  - Apparent oral clearance was decreased ~2.8-fold
- In the presence of ketoconazole, similar effects on tivantinib PK parameters were observed in EMs and IMs (**Table 2**)
  - Tivantinib total exposure and maximum concentration were increased ~2-fold and ~1.4-fold, respectively
  - Tivantinib apparent oral clearance was decreased ~2-fold
- There was a significant interaction between ketoconazole and tivantinib resulting in increased tivantinib exposure

**Table 2. Tivantinib Pharmacokinetic Parameters With and Without Ketoconazole**

| | Tivantinib Alone | | Tivantinib + Ketoconazole | |
|---|---|---|---|---|
| | EM | IM | EM | IM |
| $AUC_{0\text{-}last}$, ng•h/mL[a] | 3214.1 (45.0) | 9258.5 (57.5) | 6953.5 (37.4) | 18826 (42.8) |
| $C_{max}$, ng/mL[a] | 558.3 (34.0) | 1179.4 (37.7) | 769.3 (45.7) | 1603.6 (20.1) |
| Median $t_{max}$, h (min, max) | 4.492 (3.03, 5.03) | 4.500 (3.50, 5.02) | 4.500 (3.08,12.0) | 5.000 (4.00,10.0) |
| Median $t_{1/2}$, h (min, max) | 2.520 (1.91, 13.1) | 4.634 (2.36, 7.18) | 5.020 (2.55, 36.7) | 5.535 (3.32, 8.78) |
| CL/F, L/h[b] | 40.13 (14.613) | 14.38 (7.192) | 18.14 (5.268) | 6.836 (2.782) |
| V/F, L[b] | 218.5 (172.91) | 85.47 (30.762) | 260.2 (297.94) | 52.72 (7.876) |

Abbreviations: AUC, area under the curve; C, concentration; CL/F, apparent total body clearance; EM, extensive metabolizers; IM, intermediate metabolizers; $t_{1/2}$, terminal half-life; V/F, apparent volume of distribution.
[a] Geometric means (percentage coefficient of variance). [b] Arithmetic mean (standard deviation).

## Adverse Events

- A total of 10 treatment-emergent AEs (TEAEs) were reported in 5 subjects (**Table 3**)
  - All TEAEs were mild in severity and resolved during the study
  - 2 subjects discontinued because of TEAEs: 1 with mild creatinine level increase and 1 with mild white blood cell count increase
- During administration of tivantinib alone, 1 subject experienced dry skin
- During ketoconazole monotherapy (days 1 to 3), 4 TEAEs were reported
- Following ketoconazole plus tivantinib, 1 subject reported 5 TEAEs (oropharyngeal pain, pyrexia, increased white blood cell and neutrophil counts, and false positive laboratory result [pseudothrombocytopenia])

**Table 3. Incidence of Treatment-Emergent Adverse Events**

| | Subjects, n (%) | |
|---|---|---|
| | Tivantinib Alone (N = 14) | Tivantinib + Ketoconazole (N = 16) |
| Abdominal pain | 0 | 1 (6.3) |
| Diarrhea | 0 | 1 (6.3) |
| Pyrexia | 0 | 1 (6.3) |
| Creatinine level increase | 0 | 1 (6.3) |
| False positive laboratory level | 0 | 1 (6.3) |
| Neutrophil count increase | 0 | 1 (6.3) |
| White blood cell count increase | 0 | 1 (6.3) |
| Headache | 0 | 1 (6.3) |
| Oropharyngeal pain | 0 | 1 (6.3) |
| Dry skin | 1 (7.1) | 0 |

## CONCLUSIONS

- Concomitant tivantinib and ketoconazole administration resulted in increased tivantinib total exposure
  - There were no differences in the extent of changes between EM and IM subjects
  - Caution should be exercised when strong CYP3A4 inhibitors are administered with tivantinib
- During tivantinib monotherapy, IM subjects had increased tivantinib exposure compared with EM subjects
- Tivantinib as monotherapy or in combination with ketoconazole was well tolerated in healthy subjects
- Because there was a ketoconazole-tivantinib interaction in CYP2C19 EM and IM subjects, stage 2 of the study was not conducted
- This investigation was conducted after a single dose of tivantinib in healthy subjects
  - At steady state in cancer patients, the effects could be different; therefore, the data should be interpreted with caution

### Reference

1. Horn JR and Hansten PD. Get to know an enzyme: CYP3A4. *Pharmacy Times*. September 1, 2008. Available at: http://www.pharmacytimes.com/publications/issue/2008/2008-09/2008-09-8687.

### Acknowledgments

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