R6332

Impact of CYP3A4 Inhibition and Induction on the Single-Dose Pharmacokinetics of Cabozantinib in Healthy Volunteers

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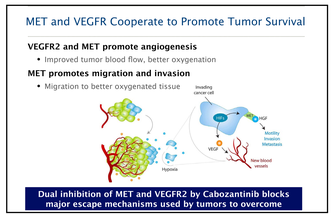
BACKGROUND

- Cabozantinib is a recently approved compound indicated for the treatment of patients with progressive, metastatic medullary thyroid cancer.
- Cabozantinib acts by inhibiting tyrosine kinase receptors, including the receptor for hepatocyte growth factor (MET) and vascular endothelial growth factor receptor 2 (VEGFR2), which are well known to play an important role in cancer biology.[1]
- Figure 1 represents the mechanism of action of cabozantinib

Figure1. Cabozantinib's (XL184) Mechanism of Action



- Following the single-dose administration of cabozantinib to healthy volunteers, the peak plasma concentration occurred around 4 hours, and the terminal-phase half-life ($t_{1/2}$, z) value was approximately 5 days. Cabozantinib was shown to have an approximately 4- to 6-fold accumulation based on C_{max} and $AUC_{0\text{-}24}$ values after multiple daily dose administration in cancer patients.[1]
- Cabozantinib was shown to be a substrate for cytochrome P450 (CYP) 3A4 mediated metabolism in *in vitro* testing. The formation of the cabozantinib N-oxide metabolite was inhibited by >80% when a neutralizing antibody targeting CYP3A4 was used.[1]
- Ketoconazole and rifampin are among the most potent modulators of CYP3A4 activity. Both compounds have been shown to significantly change the oxidative metabolism of a wide range of clinically used drugs and the FDA has classified ketoconazole and rifampin as the preferred compounds for use as an inhibitor or inducer, respectively, in *in vivo* drug-drug interaction studies.[2]

OBJECTIVES

The objectives of these two studies were as follows:

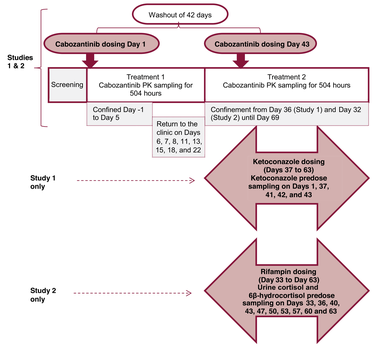
- To investigate the potential of a strong inhibitor (Study 1, ketoconazole) and inducer (Study 2, rifampin) of CYP3A4 to alter the single-dose pharmacokinetics (PK) of cabozantinib in healthy normal adult volunteers.
- To assess the safety and tolerability of cabozantinib when administered with and without ketoconazole (Study 1) and when administered with and without rifampin (Study 2).

METHODS

Study Design

- Study 1 and Study 2 were each designed as an open-label, single-center, two-treatment, single-sequence drug-drug interaction study in 28 healthy male and female volunteers (18 - 55 years of age).
- In Studies 1 and 2, volunteers received a single oral dose of 175 mg (1 x 100 mg capsule and 3 x 25 mg capsules) equivalent to 140 mg cabozantinib freebase weight on Day 1 (Period 1) and on Day 43 (Period 2), separated by a washout period of 42 days between doses.
- In Study 1, Period 2, volunteers received one daily dose of 400 mg ketoconazole for 27 days.
- In Study 2, Period 2, volunteers received one daily dose of 600 mg rifampin for 31 days.
- Safety (e.g., adverse events, vital signs, ECGs, clinical laboratory and concomitant medication) was assessed throughout the study and for 28 days (±2 days) following completion of the last study event or upon early withdrawal.

Study Design Diagram



Pharmacokinetic Blood Sampling and Bioanalytical Assay

- Serial blood samples for determination of plasma cabozantinib concentrations were collected prior to each cabozantinib dosing and at 0.5, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 14, 24, 72, 96, 120, 144, 168, 240, 288, 336, 408, and 504 hours postdose for Periods 1 and 2 for both studies.
- In Study 1, predose blood samples for determination of trough levels of ketoconazole were obtained on Day 1 (prior to cabozantinib dosing) and on Days 37 (prior to ketoconazole dosing), 41, 42, and 43.
- In Study 2, urine morning samples were collected to measure free cortisol and 6β-hydrocortisol at baseline (prior to rifampin dosing on Day 33) and prior to dosing on Days 36, 40, 43, 47, 50, 53, 57, 60, and 63. These measures were used to calculate the ratio of 6β-hydrocortisol/cortisol, a marker of CYP3A4 induction.[3]
- Plasma cabozantinib, plasma ketoconazole and urine cortisol and 6β-hydroxycortisol were assayed using validated liquid chromatography with mass spectrometric detection methods. Analytical ranges for cabozantinib, ketoconazole, cortisol and 6β-hydroxycortisol were of 0.5-500 ng/mL, 0.100 – 20.0 ng/mL, 2.0 – 500.0 ng/mL, and 30.0 – 2000.0 ng/mL respectively.

Pharmacokinetic Parameters Estimation

- In Study 1 and Study 2, PK parameters were calculated for plasma cabozantinib data using noncompartmental approach, including the following:
  - $AUC_{0\text{-}t}$: Area under the plasma concentration versus time curve, from time 0 to the time of the last measurable concentration
  - $AUC_{0\text{-}inf}$: Area under the plasma concentration versus time curve, from time 0 to infinity
  - C_{max} : Maximum measured plasma concentration
- In Study 1, the steady-state for plasma ketoconazole concentrations was assessed by visual inspection of the trough concentrations on Days 41, 42 and 43.

Pharmacokinetic Parameters Statistical Analyses

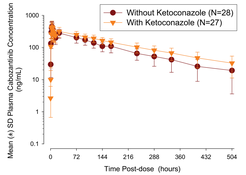
- Drug-Drug Interaction Assessment
  - The drug-drug interaction was assessed by analyzing the natural log (ln)-transformed PK parameters $AUC_{0\text{-}t}$, $AUC_{0\text{-}inf}$, and C_{max} of cabozantinib with and without ketoconazole (Study 1) and with and without rifampin (Study 2) using the SAS® mixed model procedure.
  - No interaction was to be claimed if the 90% confidence intervals (CIs) for the geometric mean ratios (GMRs) of the back-transformed PK parameters $AUC_{0\text{-}t}$, $AUC_{0\text{-}inf}$, and C_{max} of cabozantinib with and without ketoconazole (Study 1) or with and without rifampin (Study 2) fell within 80%-125%.

RESULTS

Pharmacokinetics

- In Study 1 (with ketoconazole), 28 volunteers [100%] completed Period 1 and 27 volunteers [96.4%] completed Period 2; all 28 volunteers were included in the PK and statistical analysis populations.
- Based on a visual inspection of ketoconazole predose concentrations, steady-state appeared to be achieved within 5 days after daily administration of 400 mg ketoconazole.
- Mean (standard deviation [SD]) plasma cabozantinib concentrations following single-dose administration of 140 mg cabozantinib with or without multiple-dose administration of 400 mg ketoconazole once daily for 27 consecutive days are presented in Figure 2.

Figure 2: Mean (SD) Plasma Cabozantinib Concentrations Versus Time With or Without Multiple Administrations of Ketoconazole.



- The statistical comparisons of plasma cabozantinib PK parameters with and without multiple-dose administrations of ketoconazole are presented in Table 1. The 90% CIs for the GMRs (with vs. without ketoconazole) of C_{max} of cabozantinib were within the 80–125% boundary demonstrating that the peak systemic exposure of cabozantinib was not affected by ketoconazole coadministration. However, the 90% CIs for the GMRs (with vs. without ketoconazole) of $AUC_{0\text{-}t}$ and $AUC_{0\text{-}inf}$ of cabozantinib were not within the 80-125% boundary; ketoconazole increases the mean overall systemic exposure of cabozantinib by approximately 34% - 38%.

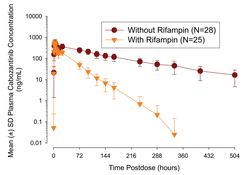
Table 1: Summary of the Statistical Comparisons of the Pharmacokinetic Parameters of Plasma Cabozantinib With and Without Multiple Administrations of Ketoconazole.

Pharmacokinetic Parameter	Geometric Mean with Ketoconazole (N=27)	Geometric Mean without Ketoconazole (N=28)	GMR (%) (with Ketoconazole/ without Ketoconazole)	90% CI of Ratio
C_{max} (ng/mL)	438	449	97.37	83.07-114.11
$AUC_{0\text{-}t}$ (ng*hr/mL)	61400	45700	134.30	122.45-147.30
$AUC_{0\text{-}inf}$ (ng*hr/mL)	66200	48000	138.05	124.51-153.07

GMR – Geometric Mean Ratio

- In Study 2 (with rifampin), 28 volunteers [100%] completed Period 1 and 25 (82.1%) completed Period 2; all 28 volunteers were included in the PK and statistical analysis populations.
- The ratios of urine 6β-hydroxycortisol to free cortisol concentrations during rifampin multiple-dose administration were 5.3 to 14.0-fold higher when compared to Day 33 (baseline day), confirming effective induction of CYP3A4.
- Mean (SD) plasma cabozantinib concentrations following single-dose administration of 140 mg cabozantinib with or without multiple-dose administration of 600 mg rifampin once daily for 31 consecutive days are presented in Figure 3.

Figure 3: Mean (SD) Plasma Cabozantinib Concentrations Versus Time With or Without Multiple Administrations of Rifampin.



- The statistical comparisons of plasma cabozantinib PK parameters with and without multiple-dose administrations of rifampin are presented in Table 2. The 90% CIs for the GMRs (with vs. without rifampin) of C_{max} of cabozantinib were within the 80–125% boundary, demonstrating that the peak systemic exposure (C_{max}) of cabozantinib was not affected by rifampin. However, the 90% CIs for the GMRs (with vs. without rifampin) of $AUC_{0\text{-}t}$ and $AUC_{0\text{-}inf}$ of cabozantinib were not within the 80–125% boundary; rifampin reduced the mean overall systemic exposure by approximately 76-77%.

Table 2: Summary of the Statistical Comparisons of the Pharmacokinetic Parameters of Plasma Cabozantinib With and Without Multiple Administrations of Rifampin

Pharmacokinetic Parameter	Geometric Mean with Rifampin (N=25)	Geometric Mean without Rifampin (N=28)	GMR (%) (with Rifampin/ without Rifampin)	90% CI of Ratio
C_{max} (ng/mL)	574	532	107.84	94.39-123.23
$AUC_{0\text{-}t}$ (ng*hr/mL)	13000	53500	24.25	22.11-26.59
$AUC_{0\text{-}inf}$ (ng*hr/mL)	13000	56500	23.03	20.89-25.40

GMR – Geometric Mean Ratio

Safety

- In Study 1, all adverse events (AEs) regardless of causality were of Grade 1 or 2. The most frequently occurring (reported in > 3 volunteers) Treatment Emergent Adverse Events (TEAEs) by MedDRA preferred term are summarized in Table 3:

Table 3: Study 1 Adverse Events

MedDRA Preferred Term	Overall n (%)	Related to Study Treatment n (%)	Not Related to Study Treatment n (%)
Weight Decreased	10 (35.7)	10 (35.7)	0 (0)
Headache	4 (14.3)	4 (14.3)	0 (0)
Nausea	4 (14.3)	4 (14.3)	0 (0)

One volunteer was withdrawn from the study during the washout period due to elevated BP

- Noteworthy clinical laboratory findings were confined to one transient elevation in white blood cells and absolute neutrophil counts (no CTCAE grade reported) that resolved without intervention or sequelae.
- In Study 2, all AEs regardless of causality were of Grade 1 or 2 except for one volunteer with a Grade 3 (allergic reaction/ hypersensitivity) causally related to rifampin. The most frequently occurring (reported in > 3 volunteers) TEAEs by MedDRA preferred term are summarized in Table 4:

Table 4: Study 2 Adverse Events

MedDRA Preferred Term	Overall n (%)	Related to Study Treatment n (%)	Not Related to Study Treatment n (%)
Headache	13 (43.4)	12 (42.9)	1 (3.6)
Constipation	12 (42.9)	0 (0)	12 (42.9)
Weight Decreased	11 (39.3)	11 (39.3)	0 (0)
Chromaturia	10 (35.7)	10 (35.7)	0 (0)
Nausea	7 (25.0)	7 (25.0)	0 (0)
Somnolence	6 (21.4)	5 (17.9)	1 (3.6)
Abdominal Pain Lower	5 (17.9)	3 (10.7)	2 (7.1)
Feces Discolored	5 (17.9)	5 (17.9)	0 (0)
Dyspepsia	4 (14.3)	4 (14.3)	0 (0)

- Noteworthy clinical laboratory findings included 3 volunteers who experienced neutropenia (Grade 2), one volunteer who experience elevated lipase level (Grade 3), and one volunteer who was withdrawn from the study due to hemoglobin levels below the lower limits of normal prior to Period 2.

CONCLUSIONS

- Concomitant use of cabozantinib and strong inhibitors or inducers of CYP3A4 results in altered oxidative metabolism of cabozantinib, with a marked change in systemic exposure.
- Patients taking cabozantinib should avoid chronic coadministration of strong inhibitors or inducers of CYP3A4. Alternatively, cabozantinib should be dose-adjusted if strong inhibitors or inducers of CYP3A4 are required for co-existing medical indications.
- Cabozantinib was well tolerated in healthy normal adult volunteers when administered alone or with ketoconazole or rifampin.

REFERENCE

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ACKNOWLEDGMENT

The authors are grateful for the contributions of QPS, Bih Hsu (Exelixis), Soraya Kebir (Celerion) and Elliot Offman (Celerion).

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