Effect of Renal and Hepatic Impairment on the Pharmacokinetics of Cabozantinib

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BACKGROUND

- Cabozantinib is indicated for the treatment of patients with progressive metastatic medullary thyroid cancer and is under development in other indications.[1,2]
- 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 (see Figure 1).[1]
- Following the single-dose administration of cabozantinib to fasting healthy participants, median time to peak cabozantinib plasma concentrations (t_{max}) ranged from two to five hours post-dose and the terminal-phase half-life ($t_{1/2}$) was approximately five days. Cabozantinib is highly protein bound to human plasma (≥99.7%).
- Cabozantinib elimination is mainly non-renal. In a mass balance study where a single-dose of 140 mg cabozantinib free base weight containing 100 µCi [^{14}C] was administered in healthy participants, approximately 54% and 27% of the treatment-related radioactivity was recovered in the first 48 days in feces and urine, respectively.
- Hepatic and renal disease may affect the absorption, metabolism, disposition (e.g., protein binding), and elimination of compounds. Based on the metabolic and elimination profile of cabozantinib, it was important to evaluate if its pharmacokinetics (PK) are altered in these populations.
- The PK and safety of cabozantinib were therefore evaluated in two distinct studies of participants with different degrees of renal and hepatic impairment versus healthy control participants. The ultimate goal was to provide, if applicable, dosing recommendations to clinicians for future treatment of patients with these conditions.

OBJECTIVES

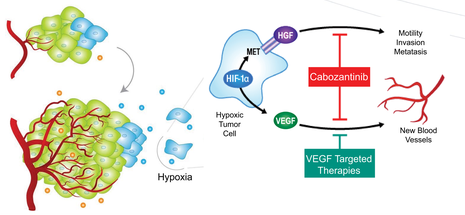
The objectives of the two studies were:

- To compare the PK of a single oral 60 mg [free base weight] capsule dose of cabozantinib in participants with impaired renal function to that of healthy control participants matched for age, gender, and body mass index (BMI).
- To compare the PK of a single oral 60 mg capsule dose of cabozantinib in participants with impaired hepatic function to that of healthy control participants matched for age, gender, BMI, and ethnicity.
- To assess safety and tolerability.

METHODS STUDY DESIGN

- Both studies were designed in accordance with the Food and Drug Agency guidances[3,4] and the European Medicines Agency guidelines.[5,6]
- Both studies were parallel and open-label. Participants received a single-dose of 60 mg cabozantinib. The renal study was conducted in three sites in the United States (USA), whereas the hepatic study was conducted in one site in the USA.
- The renal study enrolled 10 mild (eGFR ≥ 60 - ≤ 89 mL/min/1.73 m^2), 10 moderate renal impaired patients, (eGFR ≥ 30 - ≤ 59 mL/min/1.73 m^2), and 12 healthy participants (eGFR ≥ 90 mL/min/1.73 m^2); 29 participants completed the study. Participants were between 18 - 80 years old with a BMI ≤ 38 kg/m^2; healthy participants were enlisted to be matched 1:1 to a specific participant in the moderate renal impairment cohort by age (±10 years), gender, and BMI (±10%).
- The hepatic study, using Child-Pugh (C-P) Clinical Assessment Scoring, enrolled 8 mild (C-P score between 5 - 6), 8 moderate (C-P score between 7 - 9) hepatic impaired patients and 10 healthy participants. Participants were 18-70 years old (inclusive) with a BMI ≤ 36 kg/m^2; healthy participants were enlisted to match each hepatic patient by age (±10 years), gender, BMI (±5%), and ethnicity.
- In both studies, patients were allowed to continue their concomitant medication if on a stable dosage regimen for at least one month prior to dosing in the renal study and for at least 14 days for the hepatic study. Some concurrent medications were, however, restricted for a specific timeframe around dosing. All participants were restricted from using any drug known to be a moderate or strong inhibitor or inducer of CYP3A4 enzymes within 28 days from dosing and throughout the study.
- Safety (e.g., adverse events, vital signs, ECGs, clinical laboratory and concomitant medication) was assessed throughout the study and for 28 days following completion of the last study event or upon early withdrawal.

Figure 1. Cabozantinib Mechanism of Action.



⇨ **MET and VEGFR cooperate to promote tumor survival**
⇨ **Dual inhibition of MET and VEGFR2 by cabozantinib blocks major escape mechanisms used by tumors to overcome hypoxia**

PHARMACOKINETIC BLOOD SAMPLING & BIOANALYTICAL ASSAY

- Serial blood samples for determination of plasma cabozantinib concentrations were collected at the following times:

Renal Study Sampling Times (hours)	Predose	0.5	1	2	3	4	5	6	8	10	14	24	48	72	96	120	168	240	288	336	408	504
Hepatic Study Sampling Times (hours)	Predose	0.5	1	2	3	4	5		8		14	24	48	72	96	120	168	240	288	336	432	504

- Blood samples for plasma protein binding determination were collected at check-in, and at 4 and 24 hours post-dose in both studies.
- Plasma cabozantinib was assayed via a validated liquid chromatography-tandem mass spectrometry (LC-MS/MS) method. The analytical range for cabozantinib was of 0.500 - 500 ng/mL. Protein binding was measured using equilibrium dialysis.

PHARMACOKINETIC PARAMETER ESTIMATION

- In both studies, the following main PK parameters were calculated for plasma cabozantinib data using a noncompartmental approach:
  - AUC_{0-t} : Area under the plasma concentration versus time curve, from time 0 to the time of the last measurable concentration
  - AUC_{0-inf} : Area under the plasma concentration versus time curve, from time 0 to infinity
  - C_{max} : Maximum measured plasma concentration
  - Fu : Fraction of unbound cabozantinib

STATISTICAL ANALYSES OF PHARMACOKINETIC PARAMETERS

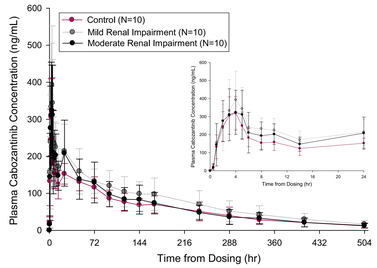
- The impact of renal or hepatic dysfunction on cabozantinib PK was assessed by analyzing the natural log (ln)-transformed PK parameters AUC_{0-t}, AUC_{0-inf}, and C_{max} of the impaired group cohort over the healthy control cohort, using a SAS mixed model procedure.

RESULTS PHARMACOKINETICS

Study 1: Renal Impairment Study

- 30 participants had evaluable PK data and were included in the PK analysis.
- Mean (SD) plasma cabozantinib concentration-time profiles following a cabozantinib oral dose of 60 mg FBE are shown in Figure 2 and the statistical analysis of PK parameters is shown in Table 1.

Figure 2:Mean (±SD) Plasma Cabozantinib Concentrations Versus Time - Renal Impairment Study



Results PK, Study 1, Renal Impairment

Table 1: Statistical Comparisons of Plasma Cabozantinib PK Parameters - Renal Impairment Versus Control

Parameter	Geometric LS Means: Mild Impairment N=10	Control N=10	Geometric LS Mean Ratio (%)	90% Confidence Intervals (CI)
C_{max} (ng/mL)	392	328	119	92, 156
AUC_{0-t} (ng*hr/mL)	37524	28777	130	101, 169
AUC_{0-inf} (ng*hr/mL)	40194	30901	130	99, 171
Parameter	**Geometric LS Means: Moderate Impairment N=10**	**Control N=10**	**Geometric LS Mean Ratio(%)**	**90% Confidence Intervals (CI)**
C_{max} (ng/mL)	336	328	102	79, 134
AUC_{0-t} (ng*hr/mL)	30698	28777	107	82, 138
AUC_{0-inf} (ng*hr/mL)	32635	30901	106	80, 140

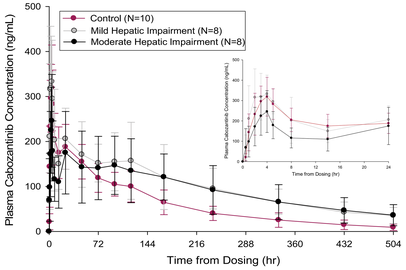
LS Mean: Least square mean

- The C_{max} and AUC values were 19% and 30% higher, respectively, for participants with mild renal impairment compared to control. These differences were not statistically significant.
- Both C_{max} and AUC were similar between the moderate impairment and control groups, with a less than 7% difference in exposure parameters.
- Approximately 0.28%, 0.24%, and 0.36% of the drug was unbound to plasma proteins (Fu, vivo) for the control, the mild, and the moderate impairment cohorts, respectively.

Study 2: Hepatic Impairment Study

- All 26 enrolled participants were included in the PK analyses.
- Mean (SD) plasma cabozantinib concentration-time profiles following a cabozantinib oral dose of 60 mg FBE are shown in Figure 3 and the statistical analysis of PK parameters is shown in Table 2.

Figure 3: Mean (±SD) Plasma Cabozantinib Concentrations Versus Time – Hepatic Impairment Study



Results PK, Study 2, Hepatic Impairment

Table 2: Statistical Comparisons of Plasma Cabozantinib PK Parameters – Hepatic Impairment Versus Control

Parameter	Geometric LS Means: Mild Impairment N=8	Control N=10	Geometric LS Mean Ratio (%)	90% Confidence Intervals (CI)
C_{max} (ng/mL)	383	347	110	82, 148
AUC_{0-t} (ng*hr/mL)	47370	30060	158	110, 227
AUC_{0-inf} (ng*hr/mL)	57061	31492	181	121, 270
Parameter	**Geometric LS Means: Moderate Impairment N=8**	**Control N=9**	**Geometric LS Mean Ratio(%)**	**90% Confidence Intervals (CI)**
C_{max} (ng/mL)	235	331	71	53, 95
AUC_{0-t} (ng*hr/mL)	41128	28952	142	98, 207
AUC_{0-inf} (ng*hr/mL)	49517	30426	163	107, 247

LS Mean: Least square mean

- Participants with mild and moderate hepatic impairment had an 81% and 63% higher plasma cabozantinib AUC_{0-inf}, respectively, in comparison to control. Because the upper bounds of 90% CI of the GLS mean ratio of AUCs are greater or equal to 200%, the possibility of observing double the exposure to cabozantinib could not be ruled out in participants with mild and moderate hepatic impairment.
- The mean %Fu in mild and healthy control groups was similar [approximately 0.33% and 0.35%, respectively] and was slightly higher in the moderate group [approximately 0.57%].

RESULTS - SAFETY

- In the renal impairment study, adverse events were reported in three (25%) healthy participants, two (20%) mild renal impairment participants, and three (30%) moderate renal impairment participants. The most common drug-related adverse events were arthralgia and diarrhea.
- In the hepatic impairment study, the most common drug-related adverse events were headache, back pain, thrombocytopenia, and sinus bradycardia.
- There was no indication of a clinically meaningful pattern of change for any laboratory results with respect to renal or hepatic status. There were no clinically significant findings in ECG assessments.
- There were no discontinuations due to AEs during these renal and hepatic impairment studies.

CONCLUSIONS

- Exposure to cabozantinib was not affected by mild or moderate renal impairment in a clinically significant manner, therefore, no dosage adjustment or special precaution is needed for cabozantinib administration in patients having mild or moderate renal impairment.
- Exposure to cabozantinib was increased by approximately 81% and 63% in participants with mild and moderate hepatic impairment, respectively. Therefore, a doubling in exposure could not be ruled out in those populations. Clinical use of cabozantinib needs to involve evaluation of possible dose reduction and monitoring of potential toxicity in patients with mild or moderate hepatic impairment.

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