**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 renal cell carcinoma and is under development in several other tumor types. 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 (Figure 1).

Following the single-dose administration of cabozantinib to fasting healthy participants, maximal plasma concentrations were reached approximately five days. Cabozantinib is highly protein bound to human plasma proteins (approximately 98%).

Cabozantinib elimination is linear non-renal. In a mass balance study where a single-dose of 11 mg/kg cabozantinib free base weight containing 100 μCi [14C] was administered in healthy participants, approximately 50% and 50% of the administered radioactivity were recovered in the first 48 hours in feces and urine, respectively.

Hepatic and renal disease may affect the absorption, disposition, distribution (e.g., protein binding, and elimination) of compounds. Based on the metabolic and elimination profile of cabozantinib, it is important to evaluate its pharmacokinetics in patients with impaired hepatic and renal function.

The PK and safety of cabozantinib were therefore evaluated in two distinct studies of participants with different degrees of hepatic and renal impairment versus healthy control participants. The ultimate goal was to provide, applicable, dosage recommendations for future treatment of patients with these conditions.

**OBJECTIVES**

- To determine the impact of renal and hepatic impairment on the pharmacokinetics of cabozantinib in patients with impaired renal or hepatic function.
- To establish dosage recommendations for future treatment of patients with these conditions.

**Methods**

**Study 1: Renal Impairment Study**

The renal study enrolled 10 mild (eGFR ≥ 60 - ≤ 89 mL/min/1.73 m²), 10 moderate (eGFR ≥ 30 - ≤ 59 mL/min/1.73 m²) impaired patients and 10 healthy participants. Participants were 18-70 years old matched for age, gender, BMI, and ethnicity.

In participants with impaired hepatic function to that of healthy control participants with a doubling in exposure could not be ruled out in those populations. Clinical use of cabozantinib needs to involve evaluation of standard dose escalation and monitoring of potential toxicity in patients with mild or moderate hepatic impairment.

**RESULTS: SAFETY**

- In the renal impairment study, adverse events were reported in three (30%) healthy participants, two (30%) moderate impairment patients and none of the mild renal impairment participants. The most common drug-related adverse event was hypertension.

**RESULTS - PHARMACOKINETICS**

**PHARMACOKINETIC BLOOD SAMPLING & BIOANALYTICAL ASSAY**

- Serial blood samples for determination of plasma cabozantinib concentrations were collected at the following time points:
  - Predose
  - 1, 3, 5, 8, 24, 48, 72, 120, 168, 288, 360, 504 hours after dosing.

**PHARMACOKINETIC PARAMETER ESTIMATION**

- Blood samples for plasma protein binding determination were collected at check-in and at 1 and 2 hours post-dose in both studies.

**RESULTS - PHARMACOKINETICS**

**STATISTICAL ANALYSIS OF PHARMACOKINETIC PARAMETERS**

- The impact of renal or hepatic dysfunction on cabozantinib PK was assessed by comparing the PK parameters to a reference population (healthy control participants).

**RESULTS - SAFETY**

- In the renal impairment study, adverse events were reported in three (30%) healthy participants, two (30%) moderate impairment patients and none of the mild renal impairment participants. The most common drug-related adverse event was hypertension.

**REFERENCES**

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