M1344

Evaluation of the Effect of Food or Administration of a Proton Pump Inhibitor on the Single-Dose Plasma Pharmacokinetics of Cabozantinib in Healthy Adult Subjects

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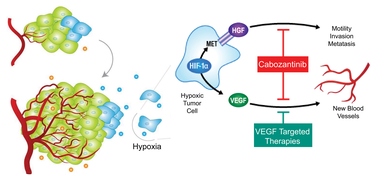
BACKGROUND

- Cabozantinib is indicated for the treatment of patients with progressive metastatic medullary thyroid cancer.[1] Additionally, cabozantinib is under development in other indications.[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.[1]

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**

- Following the single-dose administration of cabozantinib to fasting healthy subjects, median time to peak cabozantinib plasma concentrations (t_{max}) ranged from 2 to 5 hours post-dose and the terminal-phase half-life ($t_{1/2}$) value was approximately 5 days.
- Cabozantinib, a biopharmaceutical classification system (BCS) Class 2 drug, is weakly soluble in aqueous media and exhibits a pH-dependent solubility profile *in vitro* (0.11 mg/mL in 0.01 N HCl, and practically insoluble at pH values > 4).[1] Cabozantinib is a weak base tyrosine kinase inhibitor and other weak base tyrosine kinase inhibitors have shown decreased absorption under conditions of elevated gastric pH.[3]
- Food is known to impact the pharmacokinetics (PK) of drugs through several mechanisms such as changes in gastrointestinal pH, but for weak base drugs, food can enhance dissolution through increased intestinal and pancreatic enzyme secretion (e.g., lipase).[4]
- Coadministration with acid reducing agents (e.g., proton pump inhibitors, H_2 blockers) resulted in marked reductions in plasma drug exposures (AUC) for a variety of other BCS Class 2 small molecule kinase inhibitors, including dasatinib, erlotinib, gefitinib, lapatinib, and nilotinib.[3]
- The proton-pump inhibitor esomeprazole, the S-enantiomer of omeprazole, is a strong and widely used gastric pH modifying agent that inhibits gastric acid secretion. It suppresses H^+ ion formation by specific inhibition of the H^+/K^+ ATPase enzyme system at the secretory surface of gastric parietal cells.[5]

OBJECTIVES

The objectives of these two studies were as follows:

- To investigate the potential of a high fat diet (food effect study [Study 1]) and of gastric acid suppression (esomeprazole drug-drug interaction [DDI] study [Study 2]) to alter cabozantinib PK.
- To assess the safety and tolerability of cabozantinib when administered with and without food and with and without esomeprazole.

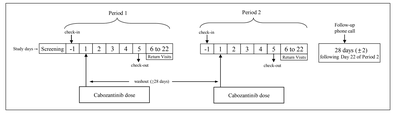
METHODS

Study Design

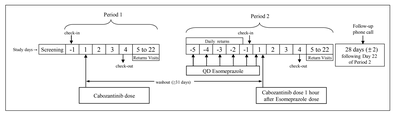
- Each study was designed as an open-label, single-center with healthy male and female subjects (18 - 55 years of age).
- In the 2-way crossover food effect study (Study 1), 56 subjects were randomly assigned to receive a single dose of 175 mg cabozantinib malate salt (140 mg free base equivalent [FBE]) capsule (1 x 100 mg and 3 x 25 mg) on Day 1. Dosing was under fasting or fed (30 minutes after administration of a high fat breakfast©) conditions, separated by a washout of 28 days. Subjects were confined from Day -1 through Day 5 with return visits to the clinical center for PK sampling or study procedures on Days 6, 7, 8, 11, 13, 15, 18, 21 (Period 2 only), and 22 during each period.
- In the fixed-sequence DDI study (Study 2), 22 subjects received a single dose of 100 mg cabozantinib FBE tablet (1 x 100 mg) under fasting conditions on Day 1 of Period 1. Subjects were confined from Day -1 through Day 4 with return visits to the clinical center for PK sampling on Days 6, 8, 11, 15, 18, and 22. There was a washout of 31 days between cabozantinib dosing in Period 1 and Period 2. In Period 2, subjects returned to the clinic on the morning of Days -5 to -1 to receive daily oral doses of 40 mg esomeprazole delayed-release capsule (1 x 40 mg delayed-release capsule) under fasting conditions. On Day 1, subjects received a single dose of 40 mg esomeprazole delayed-release capsule (1 x 40 mg delayed-release capsule) under fasting conditions followed by a single 100 mg FBE dose of cabozantinib tablet (1 x 100 mg) 1 hour after esomeprazole dosing on Day 1. Subjects were confined from the evening of Day -1 through Day 4 with return visits for PK sampling or study procedures on Days 6, 8, 11, 15, 18, 21, and 22.
- 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

Study 1 – Cabozantinib Food Effect



Study 2 – Cabozantinib and Esomeprazole DDI



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 post-dose in Study 1 and at 0.5, 1, 2, 3, 4, 5, 6, 8, 10, 14, 24, 48, 72, 120, 168, 240, 336, 408, and 504 hours post-dose in Study 2.
- 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.

Pharmacokinetic Parameters 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

Pharmacokinetic Parameters Statistical Analyses

- The food effect and the DDI were assessed by analyzing the natural log (ln)-transformed PK parameters AUC_{0-t}, AUC_{0-inf}, and C_{max} of cabozantinib under fed and fasting conditions (Study 1), and with and without esomeprazole (Study 2) using a 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-t}, AUC_{0-inf}, and C_{max} of cabozantinib under fed and fasting conditions or with and without esomeprazole fell within 80.00%-125.00%.

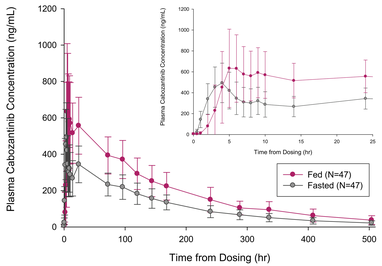
RESULTS

Pharmacokinetics

Study 1: Food effect study

- Fifty (50) of the 56 (89.3%) subjects enrolled completed both treatment periods. Three (3) participants had a plasma concentration of cabozantinib prior to dosing in Period 2 that was > 5% of their corresponding C_{max}. Therefore, data from 47 subjects were included in the calculation of mean plasma concentrations and the statistical analysis of PK parameters.
- Mean (standard deviation [SD]) plasma cabozantinib concentrations following single-administration of 140 mg FBE cabozantinib capsules under fed and fasting conditions are presented in Figure 2.

Figure 2: Mean (±SD) Plasma Cabozantinib Concentrations Versus Time Following Oral Administration of Cabozantinib 140 mg FBE Capsule Under Fed or Fasting Conditions



- Food delayed cabozantinib median T_{max} by 2 hours.
- The statistical comparisons of plasma cabozantinib PK parameters under fasting and fed conditions are presented in Table 1.

Table 1: Summary of the Statistical Comparisons of the Pharmacokinetic Parameters of Plasma Cabozantinib Under Fed and Fasting Conditions.

Pharmacokinetic Parameter	Geometric LSMs (Fed [Test]) (N=47*)	Geometric LSMs (Fasted [Reference]) (N=47*)	GMR (%) (Fed / Fasted)	90% Confidence Interval of the Ratio
C_{max} (ng/mL)	709	505	140.51	117.93 – 167.41
AUC_{0-t} (ng*hr/mL)	89800	57000	157.37	135.75 – 182.44
AUC_{0-inf} (ng*hr/mL)	95200	60700	156.95	135.13 – 182.31

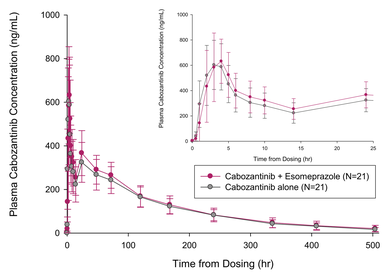
GMR: Geometric Mean Ratio, LSM: least square mean
* N=47, except for the AUC_{0-inf} parameter where N=46.
Test: 140 mg FBE cabozantinib dose administered 30 minutes after consuming a high fat breakfast
Reference: 140 mg FBE cabozantinib dose administered under fasting conditions

- The 90% CIs around the ratio of least-square means (LSMs) of C_{max}, AUC_{0-t}, and AUC_{0-inf} between Test (fed) and Reference (fasted) were not within the 80.00% to 125.00% boundary, demonstrating a positive food effect on cabozantinib PK. The rate of cabozantinib absorption, as measured by C_{max}, and the extent of absorption, as measured by AUCs, were moderately increased under high fat diet conditions, by 41% and 57%, respectively.

Study 2: Esomeprazole DDI study

- A total of 21 (95%) subjects completed both periods and were included in the PK and statistical analysis populations.
- Mean (SD) plasma cabozantinib concentrations following single-dose administration of 100 mg FBE cabozantinib tablets with and without multiple-dose administration of 40 mg esomeprazole once daily for 6 consecutive days are presented in Figure 3.

Figure 3: Mean (±SD) Plasma Cabozantinib Concentrations Versus Time Following Oral Administration of Cabozantinib 100 mg FBE Tablet With or Without Multiple Administrations of Esomeprazole.



- The statistical comparisons of plasma cabozantinib PK parameters with and without multiple-dose administration of esomeprazole are presented in Table 2.

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

Pharmacokinetic Parameter	Geometric LSM Cabozantinib + Esomeprazole (Test) (N=21)	Geometric LSM Cabozantinib Alone (Reference) (N=21)	GMR (%) (Test / Reference)	90% Confidence Interval of the Ratio
C_{max} (ng/mL)	679	614	110.50	97.61 – 125.10
AUC_{0-t} (ng*hr/mL)	58088	53962	107.65	96.92 – 119.57
AUC_{0-inf} (ng*hr/mL)	62033	56883	109.05	97.96 – 121.40

GMR: Geometric Mean Ratio, LSM: least square mean
Period 1 (Reference): 100 mg FBE cabozantinib tablet dose alone administered under fasting conditions
Period 2 (Test): multiple oral doses of 40 mg esomeprazole delayed-release capsules (Days -5 to Day 1) and coadministration with 100 mg FBE cabozantinib tablet dose (Day 1)

- The 90% CIs around the ratio of LSMs of AUC_{0-t} and AUC_{0-inf} parameters were within the limit of 80.00%-125.00% suggesting a lack of interaction. Although the upper 90% CI for C_{max} was determined to be 125.1% the small excursion above the upper standard bioequivalence limit of 125.00% does not appear to represent a clinically-relevant increased risk of treatment-emergent toxicity. The inter-subject variability in exposure at steady state (C_{max}: 37% - 43%) and exposure fluctuation at steady state (C_{min}/C_{max}: 0.64) are higher than the exposure differences of 25.1%. In addition, there has been no apparent correlation between relative plasma C_{max} values and adverse events (AEs) based on historical review of the clinical safety data in healthy subjects administered cabozantinib.

Safety

- In both studies, all AEs regardless of causality were of Grade 1 or 2. The most frequently occurring treatment-emergent adverse events (TEAEs) by MedDRA preferred term for the food effect study (Study 1) and the esomeprazole DDI study (Study 2) are summarized in Table 3 and 4 respectively.

Table 3: Food Effect Study Treatment-Emergent Adverse Events (>10%).

MedDRA Preferred Term	Overall N (%)	Related to Study Treatment N (%)
Headache	20 (36)	19 (34)
Back Pain	12 (21)	1 (2)
Somnolence	9 (16)	9 (16)
Abdominal pain	8 (14)	7 (13)
Diarrhea	7 (13)	7 (13)

Treatments: A single dose of 140 mg FBE of cabozantinib under fed and fasting conditions.

Table 4: Esomeprazole DDI Study Treatment-Emergent Adverse Events (>5%)a.

MedDRA Preferred Term	Overall N (%)	Related to Study Treatment N (%)
Headache	2 (9)	2 (9)
Constipation	2 (9)	2 (9)

[a]presenting adverse events >5% since the highest incidence is 9%.
Treatments: A single dose of 100 mg FBE of cabozantinib alone under fasting conditions and in combination with multiple daily doses of 40 mg esomeprazole under fasting conditions.

- In Study 1, one subject discontinued during Period 1 following treatment under fed conditions due to personal reasons (classified as 'subject request other than adverse event'). Five subjects were withdrawn during the washout period due to protocol-directed reasons (classified as 'other') including hemoglobin level below lower limit of normal (2 subjects in each treatment sequence) and out of range body mass index (1 subject following treatment under fasted conditions).
- In Study 2, Period 2 (cabozantinib + esomeprazole), one (1) subject experienced mild nausea and vomiting which was considered treatment-related and led to study discontinuation for that subject.
- In both studies, there were no clinically significant findings in the vital signs or ECG assessments and no indication of a clinically meaningful pattern of change for any hematology, serum chemistry, or urinalysis parameters.

CONCLUSIONS

- Cabozantinib should be taken on an empty stomach; patients should not eat for at least 2 hours before and at least 1 hour after cabozantinib administration.
- Concomitant use of cabozantinib with proton pump inhibitors or weaker gastric pH altering agents are not contraindicated due to the low risk of a clinically significant DDI.
- Single dose of cabozantinib was well tolerated in healthy normal adult subjects when administered fasted, with food, or with esomeprazole.

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