Pharmacokinetics of fruquintinib in humans

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INTRODUCTION
Fruquintinib is a potent and highly selective oral small molecule kinase inhibitor targeting VEGFR and demonstrates promising activities against a broad-spectrum cancer types with a favorable pharmacokinetic/pharmacodynamic (PK/PD) profile. However, further investigation is warranted, and a series of human trials have been initiated. VEGFR plays a pivotal role in tumor-related angiogenesis.1

METHODS

Clinical trials included
One food effect trial (n=20) was carried out to test the effect of high-fat food on the pharmacokinetics at a single oral dose of 4 mg and to identify circulating metabolites in humans. A bioequivalence (BE) study (n=24) for two oral capsule-formulations of fruquintinib was conducted to quantify fruquintinib and its metabolites in plasma. Fourteen food effect trials were conducted in healthy volunteers to investigate the PK of fruquintinib in humans, including the effect of food on fruquintinib PK and the PK of the circulating metabolites.

Bio-analytical method for metabolite identification
The plasma was protein-precipitated by methanol/acetone (1:3, v/v). The supernatant was diluted with methanol/water (1:1, v/v) and then analyzed by the LC-MS system (Agilent LC instrument coupled to Thermo Fisher). The column used was an Agilent Zorbax SB C18 150×4.6 mm (5 µm). The chromatographic conditions were as follows: flow rate = 0.3 mL/min, column temperature = 40°C, injection volume = 5 µL. The MS parameter was as follows: ESI, positive MS3. The concentration of fruquintinib, M9 and M11 in human plasma was incubated at 37°C overnight.

Food effect
Food effect was investigated in several other phase I, I and II clinical trials for solid tumors, including two ongoing registration trials for lung cancer and gastric cancer. Favorable pharmacokinetic (PK) properties of fruquintinib, high oral absorption and low clearance, were observed in nonclinical PK studies. Following on studies in healthy volunteers were conducted to investigate the PK of fruquintinib in humans, including the effect of food on fruquintinib PK and the PK of the circulating metabolites.

RESULTS

Valuation of quantitative bio-analytical methods
A LC-MS/MS method was developed and validated for the determination of fruquintinib and its metabolites M9 and M11 in human plasma. The acceptable accuracy and precision demonstrated that this bioanalytical method was reliable and efficient. Quantification of the analytes was established in a linear range by simple sample processing and storage as indicated by the results of stability tests under the following conditions: 25 hours room temperature, 5 cycles of freeze-thaw -10°C to -80°C and -60°C to -80°C, 270 days at -10°C and 329 days at -80°C.

Food effect
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CONCLUSIONS
Fruquintinib showed rapid absorption, high exposure and long half-life in humans. No significant food effect was observed on the absorption extent of fruquintinib. Two major circulating metabolites M9 and M11 were derived from the amide bond hydrolysis and the N-demethylation of the parent fruquintinib, respectively. The analysis results showed that the amount of M10 decreased by 60% and M11 increased by over 69-fold. The amount of fruquintinib remained unchanged. The stability tests indicated that M10 was stable in the following scenarios: blood on ice for 3 hours, plasma on ice for 4 hours, and plasma at -80°C for 30 days. It was proposed that M10 was converted to M11 in the body but not during the blood collection and processing. The analysis results showed that the amount of M10 decreased by 60% and M11 increased by over 69-fold. The amount of fruquintinib remained unchanged. The stability tests indicated that M10 was stable in the following scenarios: blood on ice for 3 hours, plasma on ice for 4 hours, and plasma at -80°C for 30 days. It was proposed that M10 was converted to M11 in the body but not during the blood collection and processing.

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Pharmacokinetics of fruquintinib and metabolites

Table 3. Pharmacokinetic parameters for fruquintinib, M9 and M11 in healthy volunteers (n=24) following a single oral dose of 5 mg fruquintinib

Figure 1. Profiles of concentrations of fruquintinib, M9 and M11 in plasma versus time in healthy volunteers following a single oral dose of 5 mg fruquintinib (n=24)

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