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ORIGINAL ARTICLE

Pharmacokinetics of capmatinib in participants with hepatic impairment: A phase 1, open-label, single-dose, parallel-group study

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Aims: Capmatinib, a mesenchymal–epithelial transition factor tyrosine kinase inhibitor, is metabolized by cytochrome P450 (CYP) 3A4 and aldehyde oxidase. In individuals with hepatic impairment, alterations in hepatobiliary excretion and metabolism could lead to higher capmatinib exposure. We compared the pharmacokinetics of a single oral dose of capmatinib 200 mg administered to participants with varying degrees of hepatic impairment *vs*. matched controls with normal hepatic function.

Methods: This phase 1, multicentre, open-label, parallel-group study enrolled adult participants with normal hepatic function and mild, moderate and severe hepatic impairments. Eligible participants received a single oral dose of 200 mg capmatinib. The pharmacokinetic parameters of capmatinib were analysed and compared across participants with impaired and normal hepatic function.

Results: Of 31 enrolled participants, 29 had an evaluable pharmacokinetic profile: normal ($n = 9$); mild ($n = 6$); moderate ($n = 8$); severe ($n = 6$). Compared with the normal group, geometric mean (GM) maximum (peak) observed plasma drug concentration after single-dose administration decreased by 27.6% in the mild group (GM ratio [GMR] = 0.724; 90% confidence interval [CI]: 0.476–1.10), by 17.2% in the moderate group (GMR = 0.828; 90% CI: 0.563–1.22) and remained unchanged in the severe group (GMR = 1.02; 90% CI: 0.669–1.55). Compared with the normal group, GM area under the plasma concentration–time curve from time zero to infinity decreased by 23.3% in the mild group (GMR = 0.767; 90% CI: 0.532–1.11), by 8.6% in the moderate group (GMR = 0.914; 90% CI: 0.652–1.28) and increased by 24% in the severe group (GMR = 1.24; 90% CI: 0.858–1.78).

Conclusion: Mild, moderate and severe hepatic impairment did not have a clinically relevant impact on capmatinib pharmacokinetics. No new safety findings are reported in this study.

Principal investigator: The authors confirm that the Principal Investigator for this paper is Dr Thomas C. Marbury and that he had direct clinical responsibility for participants.

Clinical Trial registration: ClinicalTrials.gov NCT02474537.

KEYWORDS
capmatinib, hepatic impairment, pharmacokinetics

1 | INTRODUCTION

Dysregulation of the mesenchymal–epithelial transition factor (MET) pathway via *MET* exon 14 skipping (*MET*ex14) mutations, *MET* gene copy number gain/amplification or MET protein overexpression is a known oncogenic driver that promotes cell–cell detachment and metastasis, epithelial–mesenchymal transition, invasion, angiogenesis, proliferation, and cell survival in many cancers.[1–6] Capmatinib is an orally bioavailable, highly selective and potent (IC_{50} 0.6 nM), ATP-competitive, small-molecule MET inhibitor (type 1b).[7–10] Several clinical studies have demonstrated promising efficacy and a manageable safety profile for capmatinib administered either as a single agent or in combination with other anticancer therapies in various solid tumors.[11–15] Capmatinib at a dose of 400 mg oral tablets twice daily (BID) with or without food was granted US Food and Drug Administration (FDA) accelerated approval in May 2020, followed by approval in Japan for the treatment of adult patients with metastatic non-small-cell lung cancer (NSCLC) whose tumours harbour *MET*ex14 mutations as detected by an FDA-approved test.[16] The approvals were based on the results from the phase 2, multicohort GEOMETRY mono-1 study in which capmatinib demonstrated clinically meaningful efficacy and a manageable safety profile in patients with advanced NSCLC harbouring *MET*ex14 mutations.[17]

Following oral administration, the capmatinib tablet (400 mg BID) was rapidly absorbed, with a median time to maximum observed plasma drug concentration (T_{max}) ranging from 1 to 2 hours.[17] The accumulation of capmatinib following repeated administration of 400-mg BID tablets was low, with a steady state geometric mean (GM) accumulation ratio of 1.4. The effective half-life ($t_{1/2}$) was 6.54 hours.[17] M16 (CMN288), the major pharmacologically inactive metabolite of capmatinib in circulation, does not accumulate after multiple dosing. No clinically significant differences have been observed in the pharmacokinetics (PK) of capmatinib based on race (White, Asian, Native American, Black).[16]

The PK of capmatinib tablets is linear following a single dose of 200–600 mg in healthy participants. Data from healthy participants indicate that capmatinib is tolerated when administered as a single dose of 600 mg in tablet formulation. Preliminary physiology-based PK modelling showed up to an ~3-fold decrease in CL/F in participants with mild, moderate and severe hepatic impairment *vs*. those with normal hepatic function. Therefore, a single dose of 200 mg capmatinib was considered tolerable in participants with hepatic impairment and was used in this study.

A human absorption, distribution, metabolism and excretion (ADME) study and in vitro phenotyping results showed that capmatinib is cleared via metabolism driven by cytochrome P450 (CYP) 3A4, with a significant contribution from aldehyde oxidase. ADME data suggest that absorbed capmatinib is eliminated from the systemic circulation primarily through liver metabolism and subsequent biliary/faecal excretion.[18] Results from several studies have indicated that the expression, levels and activity of drug-metabolizing enzymes, including CYP3A4, are altered in liver disease.[19–25] In individuals with hepatic impairment, alterations in hepatobiliary excretion and metabolism may lead to a higher exposure of capmatinib. Furthermore, hepatic impairment could also alter plasma protein binding (PPB) and consequently trigger changes in unbound concentrations of capmatinib, which is highly bound to plasma protein (96% bound).[16] In individuals with hepatic impairment, it is unknown whether changes in capmatinib PK would necessitate dose adjustments. The aim of this study was to compare the PK of a single oral dose of capmatinib administered to participants with varying degrees of hepatic impairment (by Child–Pugh classification) with that of demographically matched controls with normal hepatic function.

What is already known about this subject

- The MET inhibitor capmatinib is predominantly cleared via hepatic metabolism by CYP3A4 and aldehyde oxidase.
- Patients with non-small-cell lung cancer may have hepatic comorbidities.
- In individuals with hepatic impairment, it is unknown whether changes in capmatinib pharmacokinetics would necessitate dose adjustments.

What this study adds

- Capmatinib pharmacokinetics were not substantially changed in participants with mild, moderate and severe hepatic impairment *vs*. those with normal hepatic function.
- Single-dose capmatinib had a manageable safety profile in participants with hepatic impairment.
- Capmatinib starting dose adjustment is not required for individuals with mild, moderate or severe hepatic impairment classified according to Child–Pugh score.

2 | METHODS

2.1 | Participants

Adult participants (age 18–75 years) with normal or impaired hepatic function were enrolled in this study. Healthy participants were

determined by the absence of clinically significant findings in medical history, physical examination, vital signs and electrocardiograms (ECGs), unless consistent with known clinical disease for participants with hepatic impairment. The Child–Pugh classification was used to evaluate and score participants with hepatic impairment. Participants with hepatic impairment were required to have a clinically determined Child–Pugh score, no change in the Child–Pugh hepatic status at least 1 month prior to dosing and confirmed liver disease by at least 1 of the following criteria: history of hepatitis C, histologically by prior liver biopsy showing cirrhosis, clinically by physical examination, laboratory data, liver imaging or endoscopic findings. In addition, participants with hepatic impairment had to meet the following laboratory values: aspartate transaminase ≤5× upper limit of normal (ULN), alanine transaminase ≤5× ULN, total bilirubin ≤3× ULN (≤5× ULN for participants with severe hepatic impairment), calculated creatinine clearance (using Cockcroft–Gault formula) ≥45 mL/min and platelets >50 × 10^9/L (participants with severe hepatic impairment could be enrolled if platelet count >40 × 10^9/L).

Key exclusion criteria included the intake of prescription/nonprescription drugs, vitamins, supplements, or herbal remedies, use of proton-pump inhibitor medications, or the consumption of fruits known to influence the major CYP3A4 drug metabolism pathway of capmatinib within 1 week prior to dosing and until the end of treatment (EOT; day 4). Participants with hepatic impairment could have continued to receive medications required to treat their current disease (unless a CYP3A4 strong and moderate inhibitor). In addition, participants with normal hepatic function who had a positive hepatitis B surface antigen or hepatitis C test result (antibody-positive participants were allowed if nonviraemic) were excluded. Participants with hepatic impairment with an active grade 3 or 4 hepatic encephalopathy within 4 weeks of study entry, clinical evidence of severe ascites (grade ≥3 as per Common Terminology Criteria for Adverse Events v4.03), or ascites requiring paracentesis within 3 weeks prior to dosing were also excluded from the study.

This clinical study was designed and implemented in accordance with the principles of the Declaration of Helsinki and the Good Clinical Practice guidelines of the International Council for Harmonisation, with applicable local regulations. The study protocol and all amendments were reviewed by the independent ethics committee or institutional review board for each centre. Written informed consent was obtained from all participants before screening.

2.2 | Study design

This was a phase 1, multicentre, open-label, single-dose, parallel-group study conducted to evaluate the PK and safety of capmatinib in participants with impaired and normal hepatic function. A single dose of 200 mg capmatinib was administered to all participants in this study. A 2-stage study design was implemented (Figure 1). In stage 1, participants with mild hepatic impairment (mild group, Child–Pugh A [score 5–6]), moderate hepatic impairment (moderate group, Child–Pugh B [score 7–9]) and normal hepatic function (matched normal/control group) were enrolled. Upon completion of stage 1 (≥6 evaluable participants in the mild and moderate groups and matching control participants in the normal group), an interim analysis was conducted. The

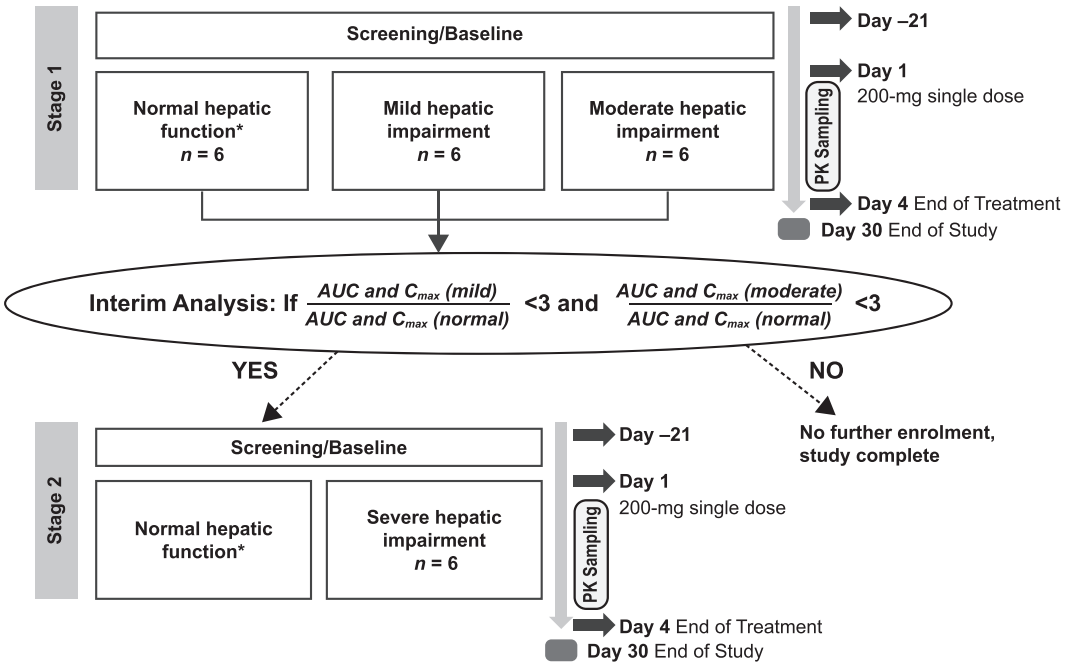

FIGURE 1 Study design. AUC, area under the plasma concentration–time curve; C_{max}, maximum (peak) observed plasma drug concentration after single-dose administration; PK, pharmacokinetics. *Enrolment of additional participants in the normal group could be required to ensure appropriate matches to the hepatic impairment groups

study was to be stopped if the estimated GM area under the plasma concentration–time curve (AUC) or maximum (peak) observed plasma drug concentration after single-dose administration (C_{max}) in the mild or moderate hepatic impairment groups was at least 3-fold higher *vs.* the normal group (exceeding the established safety margin). If not, stage 2 of the study could be started. In stage 2, participants with severe hepatic impairment (severe group, Child–Pugh C [score 10–15]) were enrolled, along with any additional matching controls (normal group), as needed. The matching criteria applied in stage 1 was implemented.

Enrolment of participants in the normal group was demographically matched to that in the hepatic impairment groups with respect to age (±10 years), body weight (±20%) and sex. Matching participants in the normal group were enrolled after 3 participants from the hepatic impairment groups (mild and moderate groups) were confirmed as evaluable. Sufficient male or female participants were enrolled to ensure that ≥6 evaluable participants in each hepatic impairment group as well as the matching normal group completed the study. Furthermore, enrolment in the normal group remained open until the enrolment in the hepatic impairment groups was complete and the number of matching controls had been achieved for comparison. In the final analysis, PK data from participants in the mild, moderate and severe groups were compared with data from participants in the normal group.

The study consisted of a 21-day screening/baseline period (day −21 to day −1; Figure 1). Participants who met the eligibility criteria at screening underwent baseline evaluations ∼24 hours prior to capmatinib dosing. Baseline safety evaluations were to be available prior to dosing. Participants were confined to the study centre from day −1 to day 4. On day 1, the participants received the study treatment. Between day 1 and day 4, PK samples were collected from participants, and safety assessments were performed. Participants then underwent EOT evaluations on day 4, following which they were discharged. Participants were instructed to contact the study staff during the safety follow-up period to report adverse events (AEs) and serious AEs (SAEs). Participants were contacted at the end of the study by phone for safety follow-up 30 days after dosing to collect and record AEs and SAEs that might have occurred following the dose administration and/or to follow-up on the resolution of ongoing AEs, if applicable. The planned total study duration was ∼8 weeks, from screening to the 30-day safety follow-up phone call.

2.3 | Treatment

All participants had to fast overnight (minimum 10 hours) prior to the administration of capmatinib. On the morning of dosing (day 1), they received a single oral dose of 200 mg capmatinib (2 × 100 mg tablets) taken with ∼240 mL of noncarbonated water. Participants continued to fast for at least 4 hours after dosing. Participants could consume water at any time, except for 1 hour before and 1 hour after the administration of capmatinib.

2.4 | Study objectives

The primary objective of the study was to compare the PK of a single oral dose of capmatinib 200 mg in participants with impaired and normal hepatic function. Secondary objectives included assessment of safety and PPB of capmatinib in participants with impaired and normal hepatic function. Exploratory objectives included PK assessment of the capmatinib metabolite M16 (CMN288) and PK assessment based on the National Cancer Institute (NCI) Organ Dysfunction Working Group classification of hepatic dysfunction in participants with impaired and normal hepatic function.

2.5 | Assessments

The PK parameters of capmatinib were calculated from individual concentration–time profiles by the noncompartmental method using Phoenix WinNonlin v6.4 (Pharsight, Mountain View, CA, USA). For PK evaluations, serial blood samples (4 mL) were collected from a forearm vein at the following time points: predose and 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 24, 36, 48 and 72 hours postdose. Plasma concentrations of capmatinib and its metabolite M16 (CMN288) were measured using a validated liquid chromatography tandem mass spectrometry assay with a lower limit of quantification (LLOQ) of ∼1.00 ng/mL (Supplementary Methods). Concentrations below the LLOQ were reported as 0.00 ng/mL, and missing samples were labelled accordingly. All sampling was relative to the administration of capmatinib.

A 7-mL blood draw was collected at 3 hours (±15 min) postdose on day 1 for PPB assessment of capmatinib using the ultrafiltration method.

Safety assessments included monitoring of haematology, blood chemistry, coagulation parameters, urinalysis, physical examinations, vital signs, weight, performance status, pregnancy tests and cardiac assessments. Haematology, blood chemistry, coagulation parameters and urinalysis assessments were performed at screening, baseline, day 1, day 2 and EOT. Vital signs were measured at screening, baseline, days 1, 2 and 3, and EOT. A complete physical examination, body weight measurements and serum pregnancy test were performed at screening, baseline and EOT. Standard 12-lead ECGs were performed in triplicate at screening, baseline, dosing visit (day 1) and at EOT. Unscheduled ECGs could also be performed at any time, if clinically indicated. In addition, all AEs and SAEs, with their severity and relationship to capmatinib, were collected.

2.6 | Statistical analysis

The full analysis set and safety set included all participants who received at least 1 dose of capmatinib. The PK analysis set (PAS) consisted of all participants who received capmatinib and had an evaluable PK profile.

A formal statistical analysis was performed using a linear model with study group as a fixed effect, which was fitted to the log-

transformed PK parameters (AUC_{last}, AUC_{inf} and C_{max}) to assess the effect of hepatic impairment on the PK of a single oral dose of capmatinib. The mild and moderate groups were the test study groups, and the normal group was the reference study group. Point estimates of differences between the study groups and the corresponding 90% confidence intervals (CIs) were calculated and anti-logged to obtain the point estimates and 90% CIs for the GM ratio (GMR) of the test *vs.* reference on the original scale. The effect of baseline covariates such as sex, age and weight on PK was investigated as appropriate. Difference in medians between study groups was provided for T_{max}. Individual participant values and GMs for AUC_{inf}, AUC_{last} and C_{max} were plotted. If the interim analysis results did not show a substantial increase in exposure for either the mild or moderate group (GMR for AUC [AUC_{inf} and AUC_{last}] and C_{max} [test: reference] < 3), stage 2 of the study was started. At the completion of stage 2, the above linear model was repeated to compare all hepatic impairment groups (including severe) with the normal group using all data from stages 1 and 2. In the event the study was closed with <6 participants in the severe group, the linear model did not include data from the severe group and the comparison between the severe and normal groups.

The statistical model described for the primary PK analysis was re-run on the unbound PK parameters ($C_{max,u}$, $AUC_{last,u}$ and $AUC_{inf,u}$) for capmatinib using PAS. The unbound parameters and concentrations were calculated by multiplying the respective capmatinib parameters and concentrations by the fraction unbound (fu) in the capmatinib concentration data set provided by Bioanalyst. The formulas CL,u/F = (CL/F)/fu and Vz,u/F = (Vz/F)/fu were used for unbound apparent clearance and volume of distribution, respectively.

As an exploratory analysis, descriptive statistics (mean [standard deviation], GM, GM coefficient of variation [CV] %) were presented for PK parameters (except T_{max}) by study group for the capmatinib metabolite. Median (minimum–maximum), GM and GM CV% were presented for T_{max}.

As an exploratory analysis, the classification of hepatic impairment was done according to the NCI Organ Dysfunction Working Group classification of hepatic dysfunction (NCI, Cancer Therapy Evaluation Program) based on screening visit hepatic parameters. NCI classification was not used for participant assignment. Descriptive statistics (mean [standard deviation], GM, GM CV%) were presented for the primary PK parameters by NCI classification (except T_{max}) at final analysis. Median (minimum–maximum), GM and GM CV% were presented for T_{max}. A model-based analysis was performed to assess the effect of hepatic impairment based on NCI classification on capmatinib PK parameters. If any impairment group had <6 participants by NCI classification, the linear model did not include data or comparisons from such groups.

3 | RESULTS

The interim PK analysis conducted at the end of stage 1 showed that the GMs of the exposures seen in the mild and moderate groups were

TABLE 1 Demographics by study group (full analysis set)

Demographic variable	Normal ($n = 10$)	Mild ($n = 7$)	Moderate ($n = 8$)	Severe ($n = 6$)	All participants ($N = 31$)
Median (range) age, y	54.5 (43.0–62.0)	57.0 (52.0–62.0)	56.5 (45.0–64.0)	49.0 (44.0–60.0)	55.0 (43.0–64.0)
Sex, *n* (%)					
Female	2 (20.0)	0	2 (25.0)	1 (16.7)	5 (16.1)
Male	8 (80.0)	7 (100)	6 (75.0)	5 (83.3)	26 (83.9)
Race, *n* (%)					
Caucasian	6 (60.0)	4 (57.1)	7 (87.5)	6 (100)	23 (74.2)
Black	4 (40.0)	2 (28.6)	1 (12.5)	0	7 (22.6)
Other	0	1 (14.3)	0	0	1 (3.2)
Ethnicity, *n* (%)					
Hispanic/Latino	4 (40.0)	1 (14.3)	6 (75.0)	5 (83.3)	16 (51.6)
Other	6 (60.0)	6 (85.7)	2 (25.0)	1 (16.7)	15 (48.4)
Median (range) weight, kg	83.6 (56.3–100.5)	82.4 (69.4–103.9)	82.2 (61.1–100.5)	88.7 (60.4–114.9)	83.7 (56.3–114.9)
Median (range) height, cm	173.8 (150.5–185.0)	180.0 (170.0–187.0)	166.6 (158.0–174.1)	176.5 (155.0–181.0)	174.0 (150.5–187.0)
Median (range) BMI, kg/m^2	27.9 (21.5–29.4)	24.2 (20.8–32.1)	28.3 (22.2–36.8)	30.2 (23.6–35.6)	27.4 (20.8–36.8)
Median (range) BSA, m^2	2.0 (1.6–2.3)	2.1 (1.8–2.3)	2.0 (1.7–2.2)	2.1 (1.7–2.4)	2.0 (1.6–2.4)

BMI, body mass index; BSA, body surface area.
BMI (kg/m^2) = weight (kg)/height $(m)^2$.
BSA (Gehan and George): BSA (m^2) = 234.94 × (height $[cm]^{0.422}$) × (weight $[kg]^{0.515}$)/10000.
BMI and BSA were calculated using the baseline weight and baseline height.

<3-fold higher than those in the normal group. Therefore, stage 2 was conducted as planned.

3.1 | Participant disposition

All 31 enrolled participants completed the study and treatment (normal group [$n = 10$], mild group [$n = 7$], moderate group [$n = 8$] and severe group [$n = 6$]). The full analysis set and safety set included all 31 enrolled participants. PAS included 29 participants; 1 participant in the normal group who did not fast overnight prior to capmatinib dosing and another in the mild group who took prohibited concomitant medication (omeprazole) during treatment were excluded from the PAS.

3.2 | Demographic and baseline characteristics

Table 1 summarizes the demographics by study group. The median age of all participants ($N = 31$) was 55 years (range, 43–64). The majority were male (83.9%) and Caucasian (74.2%); 51.6% had a Hispanic/Latino ethnicity. Demographics were similar across groups. All enrolled participants tested negative for an alcohol test, 4 tested positive for the drug screen test and 12 tested positive for the urine cotinine test. Table 2 provides a summary of the different liver function tests based on the Common Terminology Criteria grades by study group at baseline. The Child–Pugh scores were 5 (4 participants [57.1%]) or 6 (3 participants [42.9%]) in the mild group; 7 (6 participants [75%]), 8 (1 participant [12.5%]), or 9 (1 participant [12.5%]) in the moderate group; and 10 (4 participants [66.7%]), 11 (1 participant [16.7%]) or 12 (1 participant [16.7%]) in the severe group.

3.3 | PK parameters of capmatinib

The mean plasma concentration–time profiles of capmatinib were largely similar in the normal ($n = 9$), mild ($n = 6$) and moderate groups ($n = 8$) and numerically higher in the severe group ($n = 6$; Figures 2A and B). The individual participant values and GMs for

TABLE 2 Baseline liver function tests (CTC grade) by study group (safety set)

Parameter	Normal ($n = 10$)	Mild ($n = 7$)	Moderate ($n = 8$)	Severe ($n = 6$)
Increased ALP (serum), *n* (%)				
Grade 0	10 (100)	7 (100)	7 (87.5)	5 (83.3)
Grade 1	0	0	1 (12.5)	1 (16.7)
Grade 2	0	0	0	0
Grade 3	0	0	0	0
Grade 4	0	0	0	0
Increased bilirubin (total), *n* (%)				
Grade 0	10 (100)	7 (100)	6 (75.0)	0
Grade 1	0	0	1 (12.5)	2 (33.3)
Grade 2	0	0	1 (12.5)	4 (66.7)
Grade 3	0	0	0	0
Grade 4	0	0	0	0
Increased SGOT (AST), *n* (%)				
Grade 0	10 (100)	3 (42.9)	3 (37.5)	0
Grade 1	0	4 (57.1)	5 (62.5)	6 (100)
Grade 2	0	0	0	0
Grade 3	0	0	0	0
Grade 4	0	0	0	0
Increased SGPT (ALT), *n* (%)				
Grade 0	10 (100)	4 (57.1)	8 (100)	5 (83.3)
Grade 1	0	3 (42.9)	0	1 (16.7)
Grade 2	0	0	0	0
Grade 3	0	0	0	0
Grade 4	0	0	0	0

ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; CTC, Common Terminology Criteria; SGOT, serum glutamic-oxaloacetic transaminase; SGPT, serum glutamic-pyruvic transaminase.
Baseline was defined as the last nonmissing value prior to the first dose.
CTC version 4.03 was used.

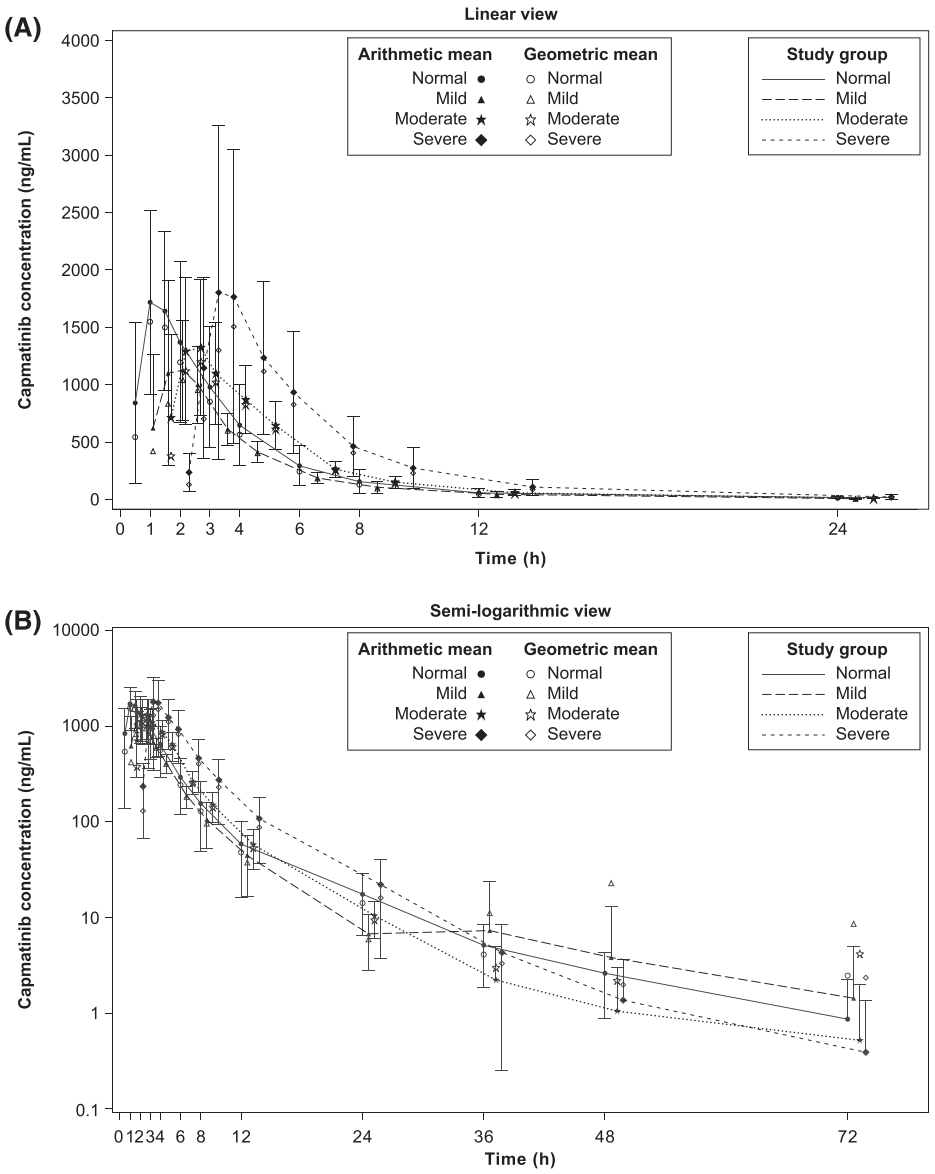

FIGURE 2 Geometric mean and arithmetic mean (standard deviation) concentration–time profiles for capmatinib by study group in (A) linear view and (B) semi-logarithmic view (pharmacokinetic analysis set). Zero concentrations at individual time points are excluded from geometric mean computation

C_{max}, AUC_{last} and AUC_{inf} by study group are presented in Figure 3. Except for 1 participant in the severe group, all individual AUC_{inf} and AUC_{last} values from the 3 hepatic impairment groups were within the ranges of individual values observed from the normal group. Compared with the normal group, GM C_{max} decreased by 27.6% in the mild group (GMR = 0.724; 90% CI: 0.476–1.10), by 17.2% in the moderate group (GMR = 0.828; 90% CI: 0.563–1.22) and remained similar in the severe group (GMR = 1.02; 90% CI: 0.669–1.55). Compared with the normal group, GM AUC_{inf} decreased by 23.3% in the mild group (GMR = 0.767; 90% CI: 0.532–1.11), decreased by 8.6% in the moderate group (GMR = 0.914; 90% CI: 0.652–1.28) and increased by 24% in the severe group (GMR = 1.24; 90% CI: 0.858–1.78). Similar results were observed for AUC_{last}. The model-based adjusted GMs for C_{max}, AUC_{last} and AUC_{inf} across groups are provided in Table 3. The interparticipant variability of C_{max}, AUC_{inf} and AUC_{last} values, as estimated by GM CV%s (Table 3), was 44.1–56.6, 21.4–54.6 and 20.7–55.2%, respectively, across all groups. Similar T_{max} was observed in the normal, mild, moderate and severe groups, with median T_{max} ranging from 1.0–1.5 hours (Table 3). Results using sex, age group (<65 and ≥65 y) and weight were similar and followed a similar trend for all comparisons. The effects of the 3 covariates were not clinically relevant across the primary PK variables (Table S1). Compared with the normal group, GM CL/F increased by 30.6 and 9.7% in the mild and moderate groups, respectively, while it decreased by 19.1% in the severe group, consistent with the changes in AUC; GM $t_{½}$ was shorter by 48.4, 44.5 and 41.5% in the mild, moderate and severe groups, respectively, *vs*. the normal group. GM Vz/F was lower by 32.9, 39.5 and 53.0% in the mild, moderate and severe groups, respectively, *vs*. the normal group (Table 3).

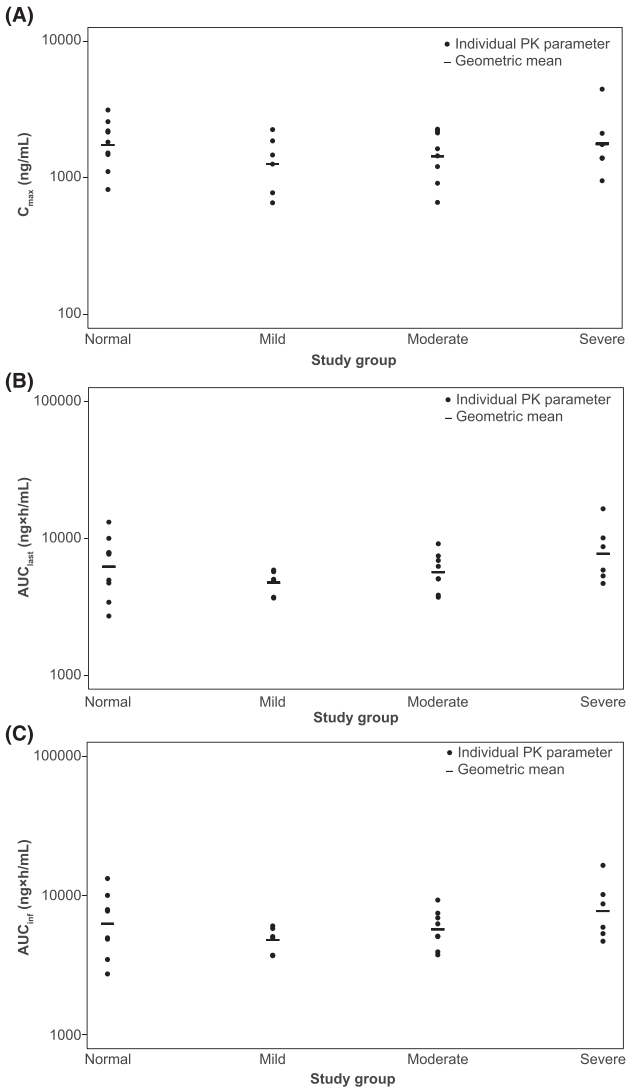

FIGURE 3 Individual participant values and geometric means for capmatinib PK parameters (A) C_{max}, (B) AUC_{last} and (C) AUC_{inf} by study group (pharmacokinetic analysis set). AUC, area under the plasma concentration–time curve; AUC_{inf}, AUC from time zero to infinity; AUC_{last}, AUC from time zero to last measurable concentration sampling time; C_{max}, maximum (peak) observed plasma drug concentration after single-dose administration; PK, pharmacokinetic

3.4 | PK parameters of unbound capmatinib

The PPB data of capmatinib from 3 hours postdose samples showed that capmatinib was highly bound (96.7%) to human plasma proteins across all participants. The GM unbound fraction of capmatinib across groups is presented in Table S2. The adjusted GMs for $C_{max,u}$, $AUC_{last,u}$ and $AUC_{inf,u}$ across all groups and the GMRs with 90% CIs for all comparisons are presented in Table S3. In the mild group *vs.* the normal group, GM $C_{max,u}$, $AUC_{last,u}$ and $AUC_{inf,u}$ decreased by 23.9, 19.6 and 19.3%, respectively. In the moderate group, GM $C_{max,u}$, $AUC_{last,u}$ and $AUC_{inf,u}$ were similar to that of the normal group. GM $C_{max,u}$, $AUC_{last,u}$ and $AUC_{inf,u}$ increased by 46, 78 and 78%, respectively, in the severe group *vs.* the normal group.

3.5 | PK of the capmatinib metabolite

A numerically lower GM AUC_{inf}, AUC_{last}, C_{max} and $t_{½}$ of CMN288 was observed in each of the hepatic impairment groups *vs.* the normal group. GM AUC_{inf} decreased by 52.0, 25.4 and 53.3%; GM AUC_{last} decreased by 52.4%, 25.4 and 53.3%; GM C_{max} decreased by 58.1, 41.9 and 74.1%; and GM $t_{1/2}$ decreased by 31.3, 35.5 and 41.1% in the mild, moderate and severe groups, respectively, *vs.* the normal group. The GMs and GM CV%s for AUC_{inf}, AUC_{last}, C_{max} and $t_{½}$ across groups are presented in Table 4. The median T_{max} was similar in the normal (1.5 h [1.0–2.0 h]), mild (1 h [1.0–2.0 h]) and moderate (1 h [1.0–3.0 h]) groups and numerically higher in the severe group (3 h [1.5–6.0 h]). The metabolite ratio GMs (CV%s) for AUC_{inf} and AUC_{last} were 0.704 (24.1) and 0.702 (24.0) in the normal group, 0.440 (23.8) and 0.437 (24.1) in the mild group, 0.573 (67.7) and 0.573 (68.0) in the moderate group, and 0.266 (32.2) and 0.264 (32.2) in the severe group (Table 4).

3.6 | PK of capmatinib based on NCI classification

There were differences in the classification of participants when using the NCI and Child–Pugh classification systems. A comparison of the classification of participants with hepatic impairment by NCI and Child–Pugh classification is shown in Table S4. The summary and statistical analysis of PK parameters of capmatinib by NCI classification are shown in Table S5; 14 participants were included in the normal group, 7 in the mild group, 7 in the moderate group and 1 in the severe group. In the mild *vs.* normal group, GM C_{max}, AUC_{last} and AUC_{inf} increased by 35, 27 and 26%. In the moderate *vs.* normal group, GM C_{max}, AUC_{last} and AUC_{inf} increased by 46, 39 and 38% (Table S5). The NCI severe group was not included in the analysis because there was only 1 participant in this group.

3.7 | Safety results

Most participants in the mild (7 [100%]), moderate (7 [87.5%]) and severe (4 [66.7%]) groups used some type of concomitant medication or significant nondrug therapy prior to or during the study. The medications most used were furosemide for ascites (7 participants), lisinopril for hypertension (5 participants), clonazepam for anxiety and insomnia (5 participants), and lactulose for hepatic encephalopathy (5 participants).

Overall ($N = 31$), 6 participants (19.4%) experienced AEs regardless of causality. The most frequently reported AEs were nausea and headache (each reported in 2 participants). Participants in the normal group ($n = 10$) did not experience any AE. Five participants, 2 each in the mild ($n = 7$) and moderate ($n = 8$) groups and 1 in the severe

TABLE 3 Summary and statistical analysis of pharmacokinetic parameters for capmatinib by study group (pharmacokinetic analysis set)

Parameter	Statistics	Normal ($n = 9$)	Mild ($n = 6$)	Moderate ($n = 8$)	Severe ($n = 6$)
AUC_{last} (ng × h/mL)	Mean (SD)	6930 (3350)	4810 (944)	5920 (1860)	8510 (4410)
	GM	6190	4730	5660	7710
	CV% GM	55.2	20.7	32.5	50.1
AUC_{inf} (ng × h/mL)	Mean (SD)	6970 (3340)	4870 (992)	5960 (1890)	8530 (4410)
	GM	6240	4790	5700	7720
	CV% GM	54.6	21.4	32.5	50.1
C_{max} (ng/mL)	Mean (SD)	1870 (732)	1380 (620)	1560 (613)	2020 (1270)
	GM	1740	1260	1440	1770
	CV% GM	44.1	51.5	47.3	56.6
T_{max} (h)	Median (range)	1.00 (0.500–2.00)	1.25 (0.500–2.00)	1.25 (0.500–3.00)	1.50 (1.00–3.00)
	GM	N/A	N/A	N/A	N/A
	CV% GM	N/A	N/A	N/A	N/A
$t_{½}$ (h)	Mean (SD)	12.0 (6.82)	6.38 (4.88)	7.62 (8.12)	6.80 (4.23)
	GM	10.4	5.37	5.77	6.08
	CV% GM	60.3	64.2	77.0	50.1
CL/F (L/h)	Mean (SD)	36.1 (19.1)	42.6 (9.23)	36.6 (11.4)	28.2 (11.7)
	GM	32.0	41.8	35.1	25.9
	CV% GM	54.6	21.4	32.5	50.1
Vz/F (L)	Mean (SD)	655 (504)	366 (218)	340 (227)	263 (128)
	GM	483	324	292	227
	CV% GM	104.3	55.6	61.1	74.4

	Adjusted GMs				GMR (90% CI)		
	Normal ($n = 9$)	Mild ($n = 6$)	Moderate ($n = 8$)	Severe ($n = 6$)	Mild/normal	Moderate/normal	Severe/normal
AUC_{inf} (ng × h/mL)	6240	4790	5700	7720	0.767 (0.532–1.11)	0.914 (0.652–1.28)	1.24 (0.858–1.78)
AUC_{last} (ng × h/mL)	6190	4730	5660	7710	0.764 (0.529–1.10)	0.915 (0.652–1.28)	1.24 (0.862–1.80)
C_{max} (ng/mL)	1740	1260	1440	1770	0.724 (0.476–1.10)	0.828 (0.563–1.22)	1.02 (0.669–1.55)

AUC, area under the plasma concentration–time curve; AUC_{inf}, AUC from time zero to infinity; AUC_{last}, AUC from time zero to last measurable concentration sampling time; CI, confidence interval; CL/F, the apparent total body clearance of drug from the plasma; C_{max}, maximum (peak) observed plasma drug concentration after single-dose administration; CV, coefficient of variation; GM, geometric mean; GMR, geometric mean ratio; SD, standard deviation; $t_{½}$, elimination half-life associated with terminal slope (λz) of a semi-logarithmic concentration–time curve (time); T_{max}, time to reach maximum (peak) plasma drug concentration after single-dose administration (time); Vz/F, apparent volume of distribution during terminal phase.
CV% GM = sqrt (exp [variance for log-transformed data]-1) × 100.
Model is a linear model of the log-transformed PK parameters. Study group was included in the model as a fixed effect. Results were back-transformed to obtain adjusted GM, GMR and 90% CI.

group ($n = 6$), experienced at least 1 grade 1 AE. One participant in the mild group had grade 2 hypoglycaemia (Table 5). No Grade 3 or 4 AEs were reported.

Three participants (9.7%) experienced AEs suspected to be capmatinib related; all AEs suspected to be capmatinib related were of grade 1 severity. In the moderate group, 1 participant had an AE of nausea and 1 had AEs of nausea and headache that were suspected to be drug related. In the severe group, 1 participant had AEs of diarrhoea and flatulence that were suspected to be drug related. No deaths and SAEs were reported during the study treatment and 30-day follow-up. Minimal changes in haematological parameters occurred. No clinically relevant changes in chemistry parameters, QTcF or other ECG parameters were observed.

4 | DISCUSSION

This phase 1, parallel-group study was conducted to compare the PK of a single oral dose of capmatinib 200 mg in participants with varying degrees of hepatic impairment *vs.* a demographically matched cohort with normal hepatic function. Administration of the same dose of capmatinib to all participants allowed for a direct comparison of PK

TABLE 4 Summary of pharmacokinetic parameters for M16 (CMN288) by study group (pharmacokinetic analysis set)

Parameter	Statistics	Normal ($n = 9$)	Mild ($n = 6$)	Moderate ($n = 8$)	Severe ($n = 6$)
AUC_{inf} (ng × h/mL)	Mean (SD)	4820 (1880)	2300 (691)	3850 (2490)	2350 (1200)
	GM	4560	2190	3400	2130
	CV% GM	35.2	37.4	52.0	49.5
AUC_{last} (ng × h/mL)	Mean (SD)	4780 (1880)	2250 (677)	3830 (2490)	2330 (1210)
	GM	4520	2150	3370	2110
	CV% GM	35.8	37.2	52.4	50.0
C_{max} (ng/mL)	Mean (SD)	1050 (328)	492 (272)	738 (645)	287 (130)
	GM	1010	423	587	262
	CV% GM	32.0	69.1	75.9	51.3
T_{max} (h)	Median (range)	1.50 (1.00–2.00)	1.00 (1.00–2.00)	1.00 (1.00–3.00)	3.00 (1.50–6.00)
	GM	N/A	N/A	N/A	N/A
	CV% GM	N/A	N/A	N/A	N/A
$t_{½}$ (h)	Mean (SD)	11.4 (6.92)	7.86 (5.49)	7.32 (5.16)	5.93 (0.907)
	GM	9.96	6.84	6.42	5.87
	CV% GM	57.9	55.6	50.8	14.8
Metabolite ratio of AUC_{inf} (fold)	Mean (SD)	0.722 (0.181)	0.450 (0.0988)	0.680 (0.443)	0.276 (0.0802)
	GM	0.704	0.440	0.573	0.266
	CV% GM	24.1	23.8	67.7	32.2
Metabolite ratio of AUC_{last} (fold)	Mean (SD)	0.720 (0.180)	0.447 (0.100)	0.680 (0.445)	0.274 (0.0795)
	GM	0.702	0.437	0.573	0.264
	CV% GM	24.0	24.1	68.0	32.2

AUC, area under the plasma concentration–time curve; AUC_{inf}, AUC from time zero to infinity; AUC_{last}, AUC from time zero to last measurable concentration sampling time; C_{max}, maximum (peak) observed plasma drug concentration after single-dose administration; CV, coefficient of variation; GM, geometric mean; SD, standard deviation; $t_{½}$, elimination half-life associated with terminal slope (λz) of a semilogarithmic concentration–time curve (time); T_{max}, time to reach maximum (peak) plasma drug concentration after single-dose administration (time).
CV% GM = sqrt (exp [variance for log-transformed data]-1) × 100.

profiles between the impairment groups and the normal group, attributing any observed differences in PK profiles to hepatic impairment (Child–Pugh class A, B or C). As per the NCI Organ Dysfunction Working Group classification of hepatic dysfunction, 1 participant was classified as having severe hepatic impairment. Consequently, the NCI severe group was not included in the PK analysis of capmatinib by NCI classification. This limited the statistical comparison of capmatinib PK parameters by NCI classification between the severe group ($n = 1$) and the normal group. Prior studies have reported on the effects of varying degrees of hepatic impairment on the PK of anticancer drugs metabolized by CYP3A4.[26–28]

A preliminary physiology-based PK model predicted up to an ~3-fold decrease in CL/F in all the hepatic impairment groups *vs*. the normal group. However, the results from this study showed that GM CL/F increased by 30.6 and 9.7% and decreased by 19.1% in the mild, moderate and severe hepatic impairment groups, respectively, *vs*. the normal group. Consistent with the CL/F results, in participants with mild, moderate and severe hepatic impairment, GM AUC_{inf} decreased by 23.3 and 8.6% and increased by 24%, respectively, *vs*. those with normal hepatic function. Compared with participants with normal hepatic function, GM C_{max} decreased in those with mild and moderate hepatic impairment by 27.6 and 17.2%, respectively, while it remained similar in participants with severe hepatic impairment. The inter-participant variability across all study groups indicated moderate variability for C_{max} and low to moderate variability for AUC_{inf}. It should be noted that the individual AUC_{inf} and AUC_{last} values from the 3 hepatic impairment groups were within the ranges of individual values observed from the normal group. Based on the NCI classification, for both the mild and moderate hepatic impairment groups, GM AUC_{inf}, AUC_{last} and C_{max} increased by 26–46% *vs*. the normal group and not decreased as observed from the Child–Pugh classification results. After adjusting for age, sex and body weight, the adjusted GMs of the PK parameters of the various hepatic impairment groups showed similar trends as obtained in the unadjusted primary analysis.

Mild, moderate or severe hepatic impairment did not have a clinically relevant effect on the PPB of capmatinib. Capmatinib was highly bound to plasma proteins (96.7%) across all hepatic groups. Unbound PK parameters largely followed similar trends to that of total capmatinib PK parameters for participants with mild and moderate hepatic impairment. Numerical increases in GM $C_{max,u}$, $AUC_{inf,u}$ and $AUC_{last,u}$ observed in participants with severe hepatic impairment *vs*. those with normal hepatic function could be related to the higher GM unbound fraction of capmatinib in the severe group (~44.8% higher *vs*. the normal group).

TABLE 5 Adverse events regardless of study drug relationship by primary system organ class, preferred term, maximum grade and study group (safety set)

Primary system organ class Preferred term	Normal ($n = 10$) *n* (%)	Mild ($n = 7$) *n* (%)	Moderate ($n = 8$) *n* (%)	Severe ($n = 6$) *n* (%)	All participants ($N = 31$) *n* (%)
Any primary system organ class	0	3 (42.9)	2 (25.0)	1 (16.7)	6 (19.4)
Grade 1	0	2 (28.6)	2 (25.0)	1 (16.7)	5 (16.1)
Grade 2	0	1 (14.3)	0	0	1 (3.2)
Ear and labyrinth disorders	0	1 (14.3)	0	0	1 (3.2)
Vertigo	0	1 (14.3)	0	0	1 (3.2)
Gastrointestinal disorders	0	0	2 (25.0)	1 (16.7)	3 (9.7)
Nausea	0	0	2 (25.0)	0	2 (6.5)
Diarrhoea	0	0	0	1 (16.7)	1 (3.2)
Flatulence	0	0	0	1 (16.7)	1 (3.2)
General disorders and administration site conditions	0	1 (14.3)	0	0	1 (3.2)
Medical device site dermatitis	0	1 (14.3)	0	0	1 (3.2)
Metabolism and nutrition disorders	0	1 (14.3)	0	0	1 (3.2)
Hypoglycaemia	0	1 (14.3)	0	0	1 (3.2)
Nervous system disorders	0	1 (14.3)	1 (12.5)	0	2 (6.5)
Headache	0	1 (14.3)	1 (12.5)	0	2 (6.5)
Dizziness	0	0	1 (12.5)	0	1 (3.2)

Primary system organ classes are presented alphabetically; preferred terms are sorted within primary system organ class in descending frequency, as reported in the *All participants* column. A participant with multiple occurrences of an adverse event (AE) under 1 study group is counted only once in the AE category for that study group. A participant with multiple severity ratings for an AE while on a study group is only counted under the maximum rating. A participant with multiple AEs within a primary system organ class is counted only once in the total row at maximum severity grade.

M16 (CMN288) is a major circulating, pharmacologically inactive metabolite of capmatinib. CMN288 is the metabolic product of aldehyde oxidase. The CYP3A enzyme does not contribute to the formation of CMN288. The exposure of CMN288 was monitored to explore potential impacts of hepatic impairment on the formation of CMN288 through the aldehyde oxidase pathway. Following a single oral dose of capmatinib 200 mg, CMN288 GM AUC_{inf} and AUC_{last} observed in participants from the 3 hepatic impairment groups decreased by 25–53% *vs*. those with normal hepatic function, indicating reduced metabolism of capmatinib to CMN288 in participants with hepatic impairment.

Therefore, based on the information above, the observed capmatinib PK differences in the mild, moderate and severe hepatic impairment groups *vs*. normal hepatic function are not considered clinically significant.

The results from this study suggest that capmatinib starting dose adjustment is not required for individuals with mild, moderate, or severe hepatic impairment classified as per the Child–Pugh score. Single-dose capmatinib was well tolerated and demonstrated a manageable safety profile in participants with mild, moderate and severe hepatic impairment and those with normal hepatic function. No new safety findings emerged from this study.

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COMPETING INTERESTS

Thomas C. Marbury is an employee and equity owner of Orlando Clinical Research Center. Xinhui Chen, Xiaoming Cui, Nathalie Pognan, Michelle Quinlan, Shruti Kapoor, Gholamreza Rahmanzadeh and Monica Giovannini are employees of Novartis. Xinhui Chen, Xiaoming Cui, Gholamreza Rahmanzadeh, Nathalie Pognan and Michelle Quinlan own Novartis stock.

CONTRIBUTORS

Xinhui Chen and Thomas C. Marbury contributed to patient accrual, data analysis, data interpretation, manuscript writing and approval. Xiaoming Cui and Monica Giovannini contributed to designing the study, patient accrual, data analysis, data interpretation, manuscript writing and approval. Michelle Quinlan and Gholamreza Rahmanzadeh contributed to data analysis, data interpretation, manuscript writing and approval. Shruti Kapoor and Nathalie Pognan contributed to data interpretation, manuscript writing and approval.

DATA AVAILABILITY STATEMENT

Novartis is committed to sharing with qualified external researchers, access to patient-level data and supporting clinical documents from eligible studies. These requests are reviewed and approved by an independent review panel on the basis of scientific merit. All data provided are anonymized to respect the privacy of participants who have participated in the trial in line with applicable laws and regulations. This trial data availability is according to the criteria and process described on www.clinicalstudydatarequest.com

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

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