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Pharmacokinetics and safety of capmatinib with food in patients with MET-dysregulated advanced solid tumors

Victor Moreno, MD, PhD[1]; Richard Greil, MD[2]; Jeffrey Yachnin, MD, PhD[3]; Margarita Majem, MD, PhD[4]; Martin Wermke, MD[5]; Hendrik-Tobias Arkenau, MD, PhD[6,7]; Jean-Rene Basque, PhD[8]; Prasanna Kumar Nidamarthy, MSc[9]; Shruti Kapoor, MD[9]; Xiaoming Cui, PhD[10]; and Monica Giovannini, MD[11]

[1]START Madrid-FJD, Hospital Fundación Jímenez Díaz, Madrid, Spain; [2]IIIrd Medical Department, Paracelsus Medical University, Salzburg Cancer Research Institute, Salzburg, Austria; [3]Department of Oncology–Pathology, Karolinska Institutet and University Hospital, Stockholm, Sweden; [4]Medical Oncology Department, Hospital de la Santa Creu i Sant Pau, Barcelona, Spain; [5]Medical Clinic I, University Hospital Carl Gustav Carus, NCT/UCC Early Clinical Trial Unit, Dresden, Germany; [6]Medical Oncology, Sarah Cannon Research Institute UK, London, United Kingdom; [7]Cancer Institute, University College London, London, United Kingdom; [8]Novartis Pharma AG, Basel, Switzerland; [9]Novartis Healthcare Private Limited, Hyderabad, India; [10]Novartis Institutes for BioMedical Research, East Hanover, New Jersey; and [11]Novartis Pharmaceuticals Corporation, East Hanover, New Jersey

ABSTRACT

Purpose: In the Phase II GEOMETRY mono-1 study, the potent and selective mesenchymal-epithelial transition (MET) inhibitor capmatinib exhibited considerable efficacy in *MET* exon 14 skipping (*MET*ex14)–mutated metastatic non–small cell lung cancer at a dose of 400 mg BID. The current recommended dose is 400 mg BID in tablet formulation, with or without food. This article reports the pharmacokinetic (PK) profile, safety, and tolerability of capmatinib 300 and 400 mg BID given with food in MET-dysregulated advanced solid tumors.

Methods: This multicenter, open-label, Phase I study enrolled adult patients with MET-dysregulated advanced solid tumors. In the dose escalation phase, capmatinib tablets were orally administered at a dose of 300 mg BID with food; if tolerated, the dose escalation cohort of 400 mg BID was to be opened to enrollment. In the expansion phase, patients were to be enrolled at the higher of the tolerated doses. Tablets were taken within 30 minutes of an unrestricted meal type, except on cycle 1 day 1 (C1D1) and cycle 1 day 7 (C1D7), when they were given with a high-fat meal. The primary objectives were to determine the higher of the tolerated study doses and assess PK variables, with a secondary objective of safety.

Findings: Overall, 35 patients (300 mg BID, n = 8; 400 mg BID, n = 27) with MET-dysregulated advanced solid tumors were enrolled; all patients had received prior antineoplastic therapy, and the most common primary site was lung (45.7%). Among PK-evaluable patients, the median T_{max} for capmatinib after administration with a high-fat meal (on C1D1/C1D7) was 4.0 to 5.6 hours across doses. At steady state (C1D7), capmatinib accumulation was low across dose levels (geometric mean of accumulation ratios, 1.29–1.69), with an increase in exposure (AUC_{tau} and C_{max}) from 300 to 400 mg BID. There were no occurrences of dose-limiting toxicity. All patients experienced at least 1 adverse event, and treatment-related adverse events occurred in 28 patients (80%; 300 mg BID, n = 6; 400 mg BID, n = 22), the most frequent of which were fatigue (37.1%) and nausea (34.3%).

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Implications: Capmatinib tablet formulation at a dose of up to 400 mg BID with food is well tolerated in patients with MET-dysregulated advanced solid tumors, with safety observations consistent with the existing profile under fasted conditions. These findings support the capmatinib dosing recommendation of 400 mg BID with or without food. ClinicalTrials.gov identifier: NCT02925104. (*Clin Ther.* 2021;000:1–16.)

Key words: Capmatinib, Food, MET, Pharmacokinetics, Phase I.

INTRODUCTION

Upon binding of its high-affinity ligand hepatocyte growth factor (HGF), the receptor tyrosine kinase mesenchymal-epithelial transition (MET) orchestrates an invasive growth program through the unique coordination of signaling cascades involved in cell proliferation, survival, motility, and invasion, including the RAS–mitogen-activated protein kinase and phosphatidylinositol 3-kinase–protein kinase B pathways.[1–3] The MET–HGF pathway is frequently dysregulated in several solid tumors, notably non–small cell lung cancer (NSCLC)[4] and gastrointestinal cancers,[5] in which MET dysregulation is a biomarker of poor prognosis and constitutes an oncogenic driver implicated in metastatic progression and drug resistance.

MET can be aberrantly activated through a number of mechanisms, including overexpression (via gene amplification or transcriptional upregulation), genetic mutation, and autocrine/paracrine HGF signaling.[6] *MET* amplification, which leads to constitutive ligand-independent activation, correlates with response to MET inhibitors in vitro[7,8] and in patients with *MET*-amplified lung and gastric cancers,[9–13] and acquired *MET* amplification confers clinical resistance to epidermal growth factor receptor (EGFR)-targeted therapy in NSCLC.[14–16] *MET* exon 14 skipping (*MET*ex14) mutations, which lead to removal of the juxtamembrane domain and, consequently, stabilization and oncogenic activation of MET,[17] have been reported in NSCLC at a frequency of ~3% to 4%,[18] are predictive of response to MET inhibitors,[19–23] and are an independent prognostic factor that can predict poor outcomes.[24,25]

Capmatinib is an orally bioavailable, adenosine triphosphate (ATP)–competitive, reversible, highly potent, and selective inhibitor of the MET tyrosine kinase domain that inhibits downstream signaling and subsequent tumor growth and progression.[26] In preclinical studies, capmatinib exhibited high selectivity for MET relative to other kinases in large screening panels and had potent activity *in vitro* (50% inhibition, 0.13 nM) and against a range of MET-dependent lung cancer (50% inhibition, 0.3–0.7 nM) and *MET*ex14-mutated cancer (half maximal inhibitory concentration [IC_{50}], 0.6 nM) cell lines; it also induced tumor regression in MET-driven mouse models harboring *MET* amplification and/or overexpression at tolerable doses.[26–28] Preliminary efficacy signals were observed in a range of MET-dysregulated advanced solid tumors, including as a single agent in hepatocellular carcinoma[29] and NSCLC,[13,30] and in combination with gefitinib in EGFR-mutant, MET-dysregulated NSCLC harboring resistance to EGFR tyrosine kinase inhibitors.[31]

In the open-label, multicohort, Phase II GEOMETRY mono-1 study, capmatinib (400 mg BID tablet) exhibited a clinically meaningful overall response rate (ORR) when administered under fasting conditions in treatment-naive and previously treated patients with *MET*ex14-mutated advanced NSCLC, and had a manageable toxicity profile across all cohorts.[32] Importantly, deep and durable responses were observed in the majority of patients, irrespective of the line of therapy. On the basis of these findings, the US Food and Drug Administration (FDA) granted accelerated approval in May 2020 to capmatinib for treatment of adult patients with metastatic NSCLC whose tumors harbor a *MET*ex14 mutation (as determined by an FDA-approved test).[33] In June 2020, the Japanese Ministry of Health, Labor, and Welfare granted approval in the same indication.

In a global Phase I dose escalation study in patients with MET-dysregulated solid tumors, capmatinib was well tolerated with an acceptable safety profile at the recommended Phase II dose of 400 mg BID in tablet formulation under fasted conditions, and the maximum tolerable dose was not reached.[13,33] Furthermore, preliminary findings from cohort 6 of GEOMETRY mono-1, in which capmatinib was administered without fasting restrictions, showed that capmatinib at the dose of 400 mg BID had a manageable safety profile in patients with *MET*ex14-

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mutated advanced NSCLC after one line of treatment.[34] In an absorption, distribution, metabolism, and excretion study in healthy male volunteers, ^{14}C-labeled capmatinib (a single 600 mg oral dose, capsule formulation) had substantial systemic availability, was extensively metabolized, and was mainly distributed to the peripheral tissue, with a mean elimination $t_{1/2}$ of 7.84 hours.[35] The highest tested dose of capmatinib in tablet formulation reported in the literature is 400 mg BID,[13,32,36] and all published pharmacokinetic (PK) studies have been conducted under fasted conditions.

In the present study (NCT02925104; A Dose Escalation Study to Assess PK, Safety and Tolerability of INC280 When Taken With Food in cMET Dysregulated Advanced Solid Tumors), we present study, we evaluated the PK profile, safety, and tolerability of the 300 and 400 mg BID capmatinib tablet regimens administered with food in patients with MET-dysregulated advanced solid tumors.

PARTICIPANTS AND METHODS

Study Design and Treatment

This was a multicenter, open-label, Phase I study of capmatinib (tablet formulation) administered with food in patients with MET-dysregulated advanced solid tumors, comprising dose escalation and expansion phases. In the dose escalation part, capmatinib treatment was initiated in a minimum of 6 patients at a dose of 300 mg BID with food on a continuous dosing schedule. With the exception of the mornings of cycle 1 day 1 (C1D1) and cycle 1 day 7 (C1D7), when it was administered with a high-fat meal (to capture the maximum impact of food on PK exposure), capmatinib was taken within 30 minutes of an unrestricted meal type. If the 300 mg BID dose was tolerated during a minimum of the first 28 days of treatment (the minimum exposure criterion), the dose escalation cohort of 400 mg BID with food was to be opened to enroll a minimum of 6 patients. Dose escalation decisions were guided by the escalation with overdose control criteria based on the Bayesian logistic regression model,[37,38] as well as by clinical judgment regarding safety, tolerability, and PK variables. The dose escalation rules applied in this study are provided in the Supplemental Methods (see the online version at doi:10.1016/j.clinthera.2021.04.006), and the study criteria for dose-limiting toxicity (DLT) are provided in Supplemental Table I (see the online version at doi:10.1016/j.clinthera.2021.04.006). At the completion of the dose escalation phase, additional patients (a minimum of 15 PK-evaluable patients and 20 patients for safety considerations) were to be enrolled in the expansion phase at the higher of the tolerated doses.

Irrespective of the dose level, capmatinib tablets were administered orally on a continuous BID dosing schedule, on a flat scale of milligrams per day and not individually adjusted by weight or body surface area. The treatment period began on C1D1 and a treatment cycle was defined as 21 days. Patients were treated with capmatinib until investigator-determined disease progression (per Response Evaluation Criteria in Solid Tumors [RECIST] version 1.1); unacceptable toxicity precluding further treatment; death; or discontinuation. Patients were followed up for safety until 30 days after the last dose, regardless of the reason for discontinuation. If discontinuation occurred for reasons other than progression or withdrawal of consent, patients were followed up for tumor assessments until progression, start of new anticancer therapy, or death. Patients in ongoing study treatment at the end of the study could be enrolled into a rollover study. Details on dose modification, treatment interruption, and treatment discontinuation are provided in the Supplemental Methods (see the online version at doi:10.1016/j.clinthera.2021.04.006).

The primary objectives of the present study were to determine the higher of the tolerated doses (between the 300 mg and 400 mg BID tablet) and to assess the PK variables of capmatinib when administered with food. Accordingly, the related primary end points were the incidence, frequency, and category of DLT in the dose escalation phase during the first 28 days of treatment, and the plasma concentration and PK parameters for capmatinib. The secondary objective was to assess the safety of capmatinib tablet formulation when taken with food, with a related secondary end point of the frequency and severity of adverse events (AEs). The exploratory objective was to evaluate the preliminary antitumor activity of capmatinib when taken with food, with an exploratory end point of investigator-determined ORR (per RECIST 1.1).

Patients

Patients (aged ≥18 years) with MET-dysregulated advanced solid tumors whose disease had progressed despite standard therapy, or for whom no standard therapy existed, were included in this study. Eligible patients were required to have an Eastern Cooperative

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Oncology Group performance status of ≤1, at least one measurable lesion (per RECIST 1.1), and adequate organ function. Key exclusion criteria included: prior treatment with crizotinib or a MET/HGF-targeted agent; symptomatic central nervous system metastases that were neurologically unstable or required increasing doses of steroids within 2 weeks of study entry; clinically significant uncontrolled heart diseases; major surgery within 4 weeks of starting capmatinib (or within 2 weeks for resection of brain metastases); prior treatment with medications that strongly induce cytochrome P450 3A4 and that cannot be discontinued at least 1 week before starting capmatinib and for the duration of the study; pregnancy or breastfeeding (lactation); and childbearing potential.

At molecular prescreening, MET dysregulation was determined cytopathologically or histopathologically (either by local or central assessment) and was defined as at least one of the following criteria: *MET* amplification determined by fluorescent in situ hybridization, defined by a gene copy number (GCN) of ≥4; MET overexpression determined by MET immunohistochemistry (IHC), defined by intensity score of +3 in ≥50% of tumor cells; and *MET*ex14 mutation. Not all patients were screened for both amplification and overexpression if at least one criterion was met.

Clinical Assessments

Clinical assessments were conducted at the screening visit; on days 1, 7, and 15 of cycles 1 and 2; at every 21 days thereafter starting on cycle 3 day 1; and at the end of treatment (within 7 days of the last dose). Safety monitoring consisted of collecting DLTs, all AEs, and serious AEs (SAEs), along with their severity and relationship to capmatinib treatment. Patients were regularly monitored for hematology and blood chemistry, and assessed for vital signs and physical parameters. All safety and tolerability assessments were conducted at predose, unless otherwise specified. Tumor response and disease progression per RECIST 1.1 was assessed locally by the investigator. Archival or newly obtained biopsy specimens or slides were required as part of the molecular prescreening.

PK Assessments

To be considered PK evaluable, patients were required to have taken capmatinib according to the originally assigned dose with assigned prandial conditions on C1D1/C1D7; have taken 3 consecutive doses of capmatinib before steady-state PK collection on C1D7; and have not vomited within 4 hours of capmatinib administration on C1D1 and C1D7.

For the measurement of the capmatinib plasma concentrations, predose (0 h) and postdose (0.5, 1, 2, 4, 6, 8, and 12 hours) blood samples were collected on C1D1 and C1D7, and predose samples were collected on cycle 1 day 15, cycle 2 day 1, and cycle 3 day 1; unscheduled collection was permitted at any time thereafter. In addition, meal records were collected on C1D1 and C1D7.

Capmatinib plasma concentrations were determined by using a validated LC-MS/MS assay, which has been described elsewhere.[35] The assay used a lower limit of quantitation of ~1 ng/mL using 100 μL of plasma sample in di-potassium EDTA. Sample preparation in 96-well plates comprised addition of a 100 μL aliquot of the samples, a 50 μL aliquot of the internal standard working solution, and a 300 μL aliquot of 0.5% ammonium hydroxide solution to the designated wells. Determination of the capmatinib concentration comprised solid-phase extraction of the samples and evaporation of the extract to dryness; diluted samples (with 300 μL of 20% acetonitrile) were subsequently analyzed by injecting a 10 μL aliquot of each sample into the LC-MS/MS system in multiple reaction monitoring, positive ion mode using electrospray ionization as the ionization technique. The LC-MS/MS system consisted of a CAPCELL PAK MG C18 column (50 × 2 mm, 5 μm particle size; Osaka Soda Co, Ltd, Osaka, Japan) and an API 4000 mass spectrometer (Applied Biosystems/Sciex, Framingham, Massachusetts). Chromatographic elution was performed using 0.1% formic acid 1.0 mmol/L ammonium acetate in water (mobile phase A) and 0.1% formic acid 1.0 mmol/L ammonium acetate in 95% acetonitrile (mobile phase B). The MS transitions observed were m/z 413.1 to 354.2 for capmatinib and m/z 417.2 to 382.0 for the internal standard.

Key PK parameters assessed included area under the plasma concentration–time curve from time zero to the end of a dosing interval (AUC_{tau}), C_{max}, and T_{max}, with additional PK parameters of accumulation ratio (Racc), total body apparent clearance of drug from the plasma at steady state (CLss/F), and effective half life ($T_{1/2}$) ($t_{1/2,\,eff}$). Because the 12-hour

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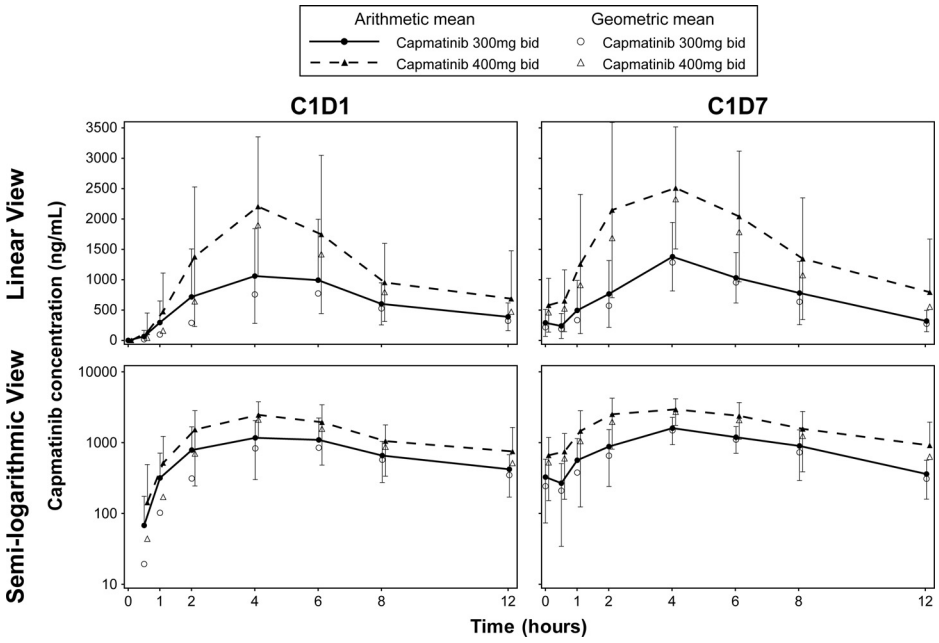

Figure 1. Geometric mean and arithmetic mean (SD) concentration–time profiles for capmatinib according to treatment (full pharmacokinetic analysis set). The graphs depict the arithmetic and geometric mean concentration–time profiles for capmatinib in the 300 mg BID (solid lines) and 400 mg BID (dotted lines) dose levels on cycle 1 day 1 (C1D1) and cycle 1 day 7 (C1D7). Error bars denote the mean (SD) for the arithmetic mean and the mean for the geometric mean at each time point. Both linear and semi-logarithmic views of the data are presented. The full pharmacokinetic analysis set was used for analysis. Zero concentrations at individual time points are excluded from geometric mean computation.

postdose PK sampling period was not long enough to capture the elimination phase of capmatinib for most patients (Figure 1), PK parameters derived from the elimination phase (terminal half life ($T_{1/2}$), elimination rate constant, and volume of distribution) were not reported. Instead, $t_{1/2,\,eff}$ was calculated based on Racc: $\tau \times \ln 2/\ln[\text{Racc}/(\text{Racc} - 1)]$.[39] In this study, Racc was calculated as $AUC_{tau,ss}/AUC_{tau,sd}$, where $AUC_{tau,ss}$ refers to AUC_{tau} at steady-state, $AUC_{tau,sd}$ refers to AUC_{tau} after single dosing, and tau refers to the dosing interval.

Statistical Analysis

For the final analysis, all available data from all patients at the end of the study (May 16, 2018) were used, with all dose escalation and expansion phase arms combined for the same dose level. SAS version 9.4 (SAS Institute, Inc, Cary, North Carolina) was used to perform all analyses.

Patients were classified into different analysis sets according to the assigned or received dose level. The full analysis set (FAS) comprised all patients who received at least 1 dose, with patients analyzed according to the planned treatment assigned. The safety set included all patients who received at least 1 dose, with patients analyzed according to the study drug they actually received. The dose-determining set consisted of all patients in the dose escalation phase from the FAS who had taken capmatinib for at least 21 days during the first 28 days (the minimum exposure criterion) and had sufficient safety evaluations, or experienced a DLT during the first 28 days of dosing. The full PK analysis set (full PAS) included all patients who provided an evaluable PK profile for at least 1 period (C1D1 or C1D7).

For the primary end point of probability of DLT in the first 28 days, the dose-determining set was used. For the primary PK end points, the full PAS was used, and PK parameters were estimated from each individual plasma concentration time profile using noncompartmental analysis (WinNonlin software

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version 6.4; Certara L.P. [Pharsight], Princeton, New Jersey). Descriptive statistics were presented at each scheduled time point and on C1D1 and C1D7 for all noncompartmental PK parameters (including AUC_{tau}, C_{max}, T_{max}, CLss/F, and Racc). Descriptive statistics for the secondary end points were presented according to dose group, and the safety set was used for analysis. For the exploratory objective, ORR, best overall response (BOR), and disease control rate (DCR) were described in the FAS, with the exact 95% CI.

For this study, no formal statistical power calculations were performed to determine sample size. A minimum of 6 patients were estimated to be enrolled at the starting dose level of capmatinib 300 mg BID with food. Pending the dose escalation decision, an arm of at least 6 patients would be enrolled at capmatinib 300 mg BID or 400 mg BID with food. For further assessment of safety and PK parameters, additional patients were to be enrolled to have ˜15 PK-evaluable patients at the higher of the tolerated dose levels assessed in this study with food. In addition, for safety considerations, a sample size of 20 patients who received at least one dose of the higher tolerated dose level was estimated to result in a 90% probability of detecting an AE with an incidence of >10%. This sample size of 20 patients for expansion at the higher tolerated dose level was selected on the basis of the consideration of acceptable safety signal detection and operational feasibility.

Ethics

This study was designed, conducted, and reported according to the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use Harmonized Tripartite Guidelines for Good Clinical Practice, with applicable local regulations (including European Directive 2001/20/EC and US Code of Federal Regulations Title 21), and with the ethical principles of the Declaration of Helsinki. The study protocol and all amendments were reviewed by the independent ethics committee or institutional review board for each center, and written informed consent was provided by all patients before conducting any molecular prescreening or protocol-defined study procedures. The study was designed by the sponsor (Novartis Pharmaceuticals Corporation, East Hanover, New Jersey); data were collected and analyzed by the sponsor in conjunction with the authors.

RESULTS

Recruitment and Patient Characteristics

At the conclusion of the study (May 16, 2018), a total of 35 patients (300 mg BID, n = 8; 400 mg BID, n = 27) with a median age of 63 years (range, 31–75 years) were enrolled; among the 27 patients in the 400 mg BID dose level, 12 were enrolled in the dose escalation phase and 15 were enrolled in the expansion phase.

Most patients had stage IV disease at initial diagnosis (n = 24 [68.6%]), and the most common primary site was the lung (n = 16 [45.7%]) (Table I). The majority of tumors were adenocarcinomas (n = 25 [71.4%]), and most were either poorly differentiated (n = 15 [42.9%]) or of unknown histologic grade (n = 13 [37.1%]). All 35 (100%) patients had received prior antineoplastic medication, 19 (54.3%) had prior radiotherapy, and 23 (65.7%) had prior surgery. The median time since initial diagnosis (of the primary site) was 27.6 months (range, 2.7–283.2 months), and the median time since the most recent recurrence/relapse was 1.8 months (range, 0.4–7.7 months). At baseline, all patients had measurable disease according to RECIST 1.1; most patients (n = 29 [82.9%]) had both target and nontarget lesions, and 6 (17.1%) had only target lesions. The extent of disease was consistent with that expected among patients with advanced solid tumors with metastasis, comprising liver (n = 21 [60%]), lung (n = 20 [57.1%]), and bone lesions (n = 8 [22.9%]).

All patients had met at least one confirmed MET dysregulation criterion (*MET*ex14 mutation, n = 1 [2.9%]; *MET* amplification with GCN ≥4, n = 23 [65.7%]; MET overexpression with IHC score +3 in ≥50% of tumor cells, n = 14 [40%]) at prescreening, with 3 patients having concurrent amplification and overexpression. At the 300 mg BID dose level, 5 (62.5%) and 4 (50%) patients had *MET* amplification and MET overexpression, respectively. At the 400 mg BID dose level, 18 (66.7%) and 10 (37%) patients had *MET* amplification and MET overexpression; the single patient (3.7%) with *MET*ex14 mutation was enrolled at the 400 mg BID dose level.

Exposure and Disposition

All patients received the planned dose of capmatinib, with a median relative dose intensity of 100% at both the 300- and 400 mg BID dose levels. Overall, the median duration of capmatinib exposure was

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Table I. Baseline demographic and disease characteristics (full analysis set).

Characteristic	Capmatinib 300 mg BID (n = 8)	Capmatinib 400 mg BID (n = 27)	All Patients (N = 35)
Age, y			
Mean (SD)	59.5 (9.56)	61.1 (11.16)	60.7 (10.70)
Median	61.5	64.0	63.0
Minimum–maximum	38–68	31–75	31–75
Age ≥65 y, no. (%)	2 (25.0)	11 (40.7)	13 (37.1)
Male sex, no. (%)	4 (50.0)	16 (59.3)	20 (57.1)
Race, no. (%)			
White	8 (100)	21 (77.8)	29 (82.9)
Unknown	0	6 (22.2)	6 (17.1)
ECOG PS, no. (%)			
0	5 (62.5)	9 (33.3)	14 (40.0)
1	3 (37.5)	18 (66.7)	21 (60.0)
Primary site of cancer, no. (%)			
Lung	5 (62.5)	11 (40.7)	16 (45.7)
Rectum	1 (12.5)	2 (7.4)	3 (8.6)
Colon	1 (12.5)	1 (3.7)	2 (5.7)
Esophagus	0	2 (7.4)	2 (5.7)
Pancreas	0	2 (7.4)	2 (5.7)
Other*	0	8 (29.6)	8 (22.9)
Adenocarcinoma of unknown primary	1 (12.5)	0	1 (2.9)
Unknown	0	1 (3.7)	1 (2.9)

ECOG PS = Eastern Cooperative Oncology Group performance status.
*Other organ sites (n = 1 each in the Capmatinib 400 mg BID and All Patients columns) include breast, cervix, gallbladder, gallbladder ducts, kidney, skin melanoma, small intestine, and thyroid.

11.8 weeks (range, 2–27 weeks) at the 300 mg BID dose level and 6 weeks (range, 0–36 weeks) at the 400 mg BID dose level. Three patients from the 400 mg BID dose level whose treatments were ongoing at the time of study completion continued on to the rollover study; the duration of exposure for these patients before rollover was 18.1, 25.6, and 36.1 weeks. A total of 3 patients (8.6%; 300 mg BID, n = 1 [12.5%]; 400 mg BID, n = 2 [7.4%]) required at least one dose reduction due to AEs, and 19 patients (54.3%; 300 mg BID, n = 5 [62.5%]; 400 mg BID, n = 14 [51.9%]) required at least one dose interruption, due to AEs (n = 16 [45.7%]; 300 mg BID, n = 3 [37.5%]; 400 mg BID, n = 13 [48.1%]), physician's decision (n = 4, 11.4%; 300 mg BID, n = 3 [37.5%]; 400 mg BID, n = 1 [3.7%]), or dosing errors (n = 1 [2.9%]; 300 mg BID, 0%; 400 mg BID, n = 1 [3.7%]). All patients discontinued capmatinib, mostly due to progressive disease (n = 23 [65.7%]; 300 mg BID, n = 6 [75%]; 400 mg BID, n = 17 [63%]), followed by AEs (n = 4, 11.4%), physician's decision (n = 3 [8.6%]), study termination (n = 3 [8.6%]), death due to study indication (n = 1 [2.9%]), or patient/guardian decision (n = 1 [2.9%]).

PK Variables

In total, 7 patients in the 300 mg BID dose level and 24 patients in the 400 mg BID dose level were evaluable for PK analysis. Fig. 1 depicts the geometric and arithmetic mean concentration–time profiles for capmatinib on C1D1 and C1D7 (steady state) by treatment dose level in the full PAS, with descriptive

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statistics for PK parameters shown in Table II. After administration with a high-fat meal, the median T_{max} for capmatinib ranged from 4.00 to 5.6 hours across dose levels (C1D1 300 mg BID, 5.6 hours; C1D1 400 mg BID, 4.01 hours; C1D7 300 mg BID, 4.04 hours; C1D7 400 mg BID, 4.0 hours), followed by a decline in concentration over time. The geometric mean of AUC_{tau} and C_{max} increased with capmatinib dose. At steady-state (C1D7), the geometric means of AUC_{tau} and C_{max} were 9370 ng × h/mL (%CV 24.3) and 1550 ng/mL (%CV 22.6) in the 300 mg BID dose level, and 16,800 ng × h/mL (%CV 26.7) and 3050 ng/mL (%CV 39.5) in the 400 mg BID dose level, respectively. On C1D7, the accumulation of capmatinib was low, with the geometric mean of Racc ranging from 1.29 (400 mg BID) to 1.69 (300 mg BID). Geometric means of CLss/F ranged from 23.8 to 32 L/h, and geometric means of $t_{1/2,\,eff}$ ranged from 5.97 to 10.7 hours across dose levels.

Safety

The 300- and 400 mg BID capmatinib tablets were well tolerated when administered with food, and there were no DLTs during the first 28 days of treatment in either the 300- or 400 mg BID dose cohort. On the basis of Bayesian logistic regression model considerations (posterior probability of excessive toxicity 0% for both dose levels) and an overall safety assessment, the dose escalation cohort for 400 mg BID with food was opened to enrollment. The 400 mg BID dose was selected as the higher of the tolerated doses evaluated in this study.

Table III provides a summary of AEs and treatment-related AEs (TRAEs). All 35 patients experienced at least one AE, and grade 3 or higher AEs occurred in 4 patients (50%) in the 300 mg BID dose level and 16 (59.3%) in the 400 mg BID dose level. The most frequently reported AEs (incidence of ≥20% across all grades) were fatigue (45.7%), nausea (40.0%), peripheral edema (28.6%), and dyspnea (20.0%) (see Supplemental Table II, as shown in the online version at doi:10.1016/j.clinthera.2021.04.006). A total of 28 patients (80%) experienced TRAEs, including 6 (75.0%) in the 300 mg BID dose level and 22 (81.5%) in the 400 mg BID dose level; the most frequent TRAEs (incidence of ≥10% across all grades) were fatigue (n = 13 [37.1%]), nausea (n = 12 [34.3%]), peripheral edema (n = 5 [14.3%]), vomiting (n = 5 [14.3%]), and decreased appetite and diarrhea (n = 4 [11.4%] each). No patients in the 300 mg BID dose level experienced grade 3 or higher TRAEs, whereas 6 patients (22.2%) in the 400 mg BID dose level experienced grade 3 or higher TRAEs. Overall, 13 patients (37.1%) experienced at least one SAE of any grade, the most frequent of which were general physical health deterioration, abdominal pain, and dyspnea (n = 2 [5.7%] each) (see Supplemental Table III, as shown in the online version at doi:10.1016/j.clinthera.2021.04.006). Twelve patients (34.3%) had at least one grade 3 or higher SAE, which were deemed treatment-related in 2 patients (7.4%) in the 400 mg BID arm. No fatal SAEs occurred.

Regarding AEs of special interest (AESIs), 5 patients (14.3%) experienced liver toxicity (grade 3, n = 1), 3 (8.6%) experienced central nervous system toxicity, 3 (8.6%) experienced renal toxicity, 2 (5.7%) experienced pancreatitis (grade 3, n = 2), 1 (2.9%) experienced pneumonitis (grade 3), and 1 (2.9%) experienced QT prolongation (grade 3). Among these AESIs, pneumonitis was the only AE reported as an SAE (n = 1 [2.9%]) (see Supplemental Table IV, as shown in the online version at doi:10.1016/j.clinthera.2021.04.006). AESIs were deemed to be related to treatment in a total of 5 patients (pancreatitis, n = 2 [5.7%]; liver toxicity, n = 2 [5.7%]; renal toxicity, n = 1 [2.9%]), all in the 400 mg BID dose level.

Five patients (14.3%) died during the study, including 2 patients (25.0%) at the 300 mg BID dose level and 3 patients (11.1%) at the 400 mg BID dose level. All of the deaths were due to the study indication (disease progression) and were unrelated to the study treatment.

Four patients (11.4%) experienced at least 1 AE leading to capmatinib discontinuation, including 1 patient (12.5%) at the 300 mg BID dose level (grade 4 general physical health deterioration) and 3 patients (11.1%) at the 400 mg BID dose level (grade 3 hypersensitivity, myocardial infarction, and thrombocytopenia) (Table III). TRAEs leading to discontinuation (grade 3 or higher hypersensitivity and myocardial infraction) occurred in only 2 patients (5.7%). A total of 15 patients (42.9%) experienced at least one AE leading to dose adjustment and/or interruption, including 2 patients (25.0%) at the 300 mg BID dose level and 13 patients (48.1%) at the 400 mg BID dose level.

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Table II. Capmatinib pharmacokinetic parameters according to treatment dose level (full pharmacokinetic analysis set).

Parameter	Cycle 1 Day 1		Cycle 1 Day 7	
	Capmatinib 300 mg BID (n = 7)	Capmatinib 400 mg BID (n = 24)	Capmatinib 300 mg BID (n = 7)	Capmatinib 400 mg BID (n = 24)
AUC_{tau}, ng × h/mL				
n*	3	14	4	15
Mean (SD)	6910 (1690)	14,000 (3880)	9580 (2350)	17,300 (4330)
%CV	24.5	27.7	24.5	24.9
Geometric mean	6760	13,500	9370	16,800
%CV	27.2	28.0	24.3	26.7
C_{max}, ng/mL				
n*	7	24	6	23
Mean (SD)	1330 (946)	2850 (1270)	1590 (382)	3260 (1130)
%CV	71.3	44.4	24.1	34.8
Geometric mean	1110	2580	1550	3050
%CV	66.9	49.8	22.6	39.5
T_{max}, h				
n*	7	24	6	23
Median	5.60	4.01	4.04	4.00
Minimum–maximum	1.87–8.00	0.5–8.17	1.17–6.12	1.07–8.28
Racc				
n*	NA	NA	6	19
Mean (SD)	NA	NA	1.78 (0.610)	1.33 (0.355)
%CV	NA	NA	34.3	26.6
Geometric mean	NA	NA	1.69	1.29
%CV	NA	NA	36.7	26.0
CLss/F, L/h				
n*	NA	NA	4	15
Mean (SD)	NA	NA	32.7 (7.47)	24.6 (6.78)
%CV	NA	NA	22.9	27.6
Geometric mean	NA	NA	32.0	23.8
%CV	NA	NA	24.3	26.7
Effective $t_{1/2}$, h				
n*	NA	NA	5	16
Mean (SD)	NA	NA	11.4 (4.57)	6.58 (3.07)
%CV	NA	NA	40.0	46.7
Geometric mean	NA	NA	10.7	5.97
%CV	NA	NA	42.1	47.4

AUC_{tau} = area under the plasma concentration–time curve from time zero to the end of a dosing interval; CLss/F = total body apparent clearance of drug from the plasma at steady state; NA = not applicable; Racc = accumulation ratio.
* Number of patients with corresponding evaluable pharmacokinetic parameters.

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Table III. Adverse event (AE) summary (safety set).

Category	Capmatinib 300 mg BID (n = 8)		Capmatinib 400 mg BID (n = 27)		All Patients (N = 35)	
	All Grades	Grade 3 or Higher	All Grades	Grade 3 or Higher	All Grades	Grade 3 or Higher
Summary of AEs, no. (%)						
AEs	8 (100)	4 (50.0)	27 (100)	16 (59.3)	35 (100)	20 (57.1)
TRAEs	6 (75.0)	0	22 (81.5)	6 (22.2)	28 (80.0)	6 (17.1)
SAEs	3 (37.5)	3 (37.5)	10 (37.0)	9 (33.3)	13 (37.1)	12 (34.3)
Treatment-related SAEs	0	0	2 (7.4)	2 (7.4)	2 (5.7)	2 (5.7)
AEs leading to discontinuation	1 (12.5)	1 (12.5)	3 (11.1)	3 (11.1)	4 (11.4)	4 (11.4)
TRAEs leading to discontinuation	0	0	2 (7.4)	2 (7.4)	2 (5.7)	2 (5.7)
AEs requiring additional therapy	7 (87.5)	4 (50.0)	26 (96.3)	12 (44.4)	33 (94.3)	16 (45.7)
AEs requiring dose adjustment/interruption	2 (25.0)	2 (25.0)	13 (48.1)	11 (40.7)	15 (42.9)	13 (37.1)
TRAEs by preferred term,* no. (%)						
Fatigue	5 (62.5)	0	8 (29.6)	1 (3.7)	13 (37.1)	1 (2.9)
Nausea	2 (25.0)	0	10 (37.0)	0	12 (34.3)	0
Peripheral edema	2 (25.0)	0	3 (11.1)	0	5 (14.3)	0
Vomiting	0	0	5 (18.5)	1 (3.7)	5 (14.3)	1 (2.9)
Decreased appetite	0	0	4 (14.8)	0	4 (11.4)	0
Diarrhea	0	0	4 (14.8)	0	4 (11.4)	0
Muscle spasms	1 (12.5)	0	2 (7.4)	0	3 (8.6)	0
Rash	1 (12.5)	0	2 (7.4)	0	3 (8.6)	0
Dyspnea	1 (12.5)	0	1 (3.7)	1 (3.7)	2 (5.7)	1 (2.9)
Pain	1 (12.5)	0	1 (3.7)	0	2 (5.7)	0
Chills	0	0	2 (7.4)	0	2 (5.7)	0
Constipation	0	0	2 (7.4)	0	2 (5.7)	0
Headache	0	0	2 (7.4)	0	2 (5.7)	0
Mucosal inflammation	0	0	2 (7.4)	0	2 (5.7)	0

SAE = serious adverse event; TRAE = treatment-related adverse event.
*TRAEs with incidence ≥5% of all grades are shown.

One patient met the laboratory criteria for drug-induced liver injury (Hy's Law), which was not deemed to be related to the study treatment, and the patient discontinued study treatment due to disease progression (including worsened target lesions in liver and new lesions in liver). Upon medical review, this case did not meet the clinical Hy's Law criteria; thus, no confirmed cases of drug-induced liver injury/Hy's Law were observed in this study. No other clinically significant hematology/clinical chemistry abnormalities or ECG/vital sign changes were observed.

Efficacy

Table IV illustrates the BOR, ORR, and DCR per investigator assessment (RECIST 1.1) in the FAS. No patients experienced a complete response. Two patients

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Table IV. Best overall response (BOR) per investigator assessment (full analysis set).

End point	Capmatinib 300 mg BID (n = 8)	Capmatinib 400 mg BID (n = 27)	All Patients (N = 35)
BOR, no. (%)			
Partial response*	2 (25.0)	0	2 (5.7)
Stable disease†	1 (12.5)	6 (22.2)	7 (20.0)
Progressive disease‡	4 (50.0)	16 (59.3)	20 (57.1)
Unknown	1 (12.5)	5 (18.5)	6 (17.1)
ORR,§ no. (%) [95% CI]	2 (25.0) [3.2–65.1]	0 [0.0–12.8]	2 (5.7) [0.7–19.2]
DCR,‖ no. (%) [95% CI]	3 (37.5) [8.5–75.5]	6 (22.2) [8.6–42.3]	9 (25.7) [12.5–43.3]

DCR = disease control rate; ORR = overall response rate.

* Defined (per Response Evaluation Criteria in Solid Tumors [RECIST] version 1.1,[40,41]) as a ≥30% decrease in the sum of target lesion diameters (taking the baseline sum diameters as a reference).

† Defined (per RECIST 1.1,[40,41]) as an insufficient shrinkage (compared with baseline) to qualify for partial or complete response or an insufficient increase (taking the smallest sum diameters at baseline or while on study, whichever is smallest, as a reference) to qualify for progressive disease.

‡ Defined (per RECIST 1.1,[40,41]) as a ≥20% increase in the sum of target lesion diameters (taking the smallest sum on study, including the baseline, as a reference); in addition, the sum must also demonstrate an absolute increase of ≥5 mm. The appearance of ≥1 new lesion is also considered progression.

§ Defined as the sum of complete responses and partial responses.

‖ Defined as the sum of complete responses, partial responses, and stable disease events.

had a BOR of partial response. The first patient had stage IVA NSCLC with MET overexpression (IHC score +3 in 90% of tumor cells) and experienced a partial response (as per assessments on days 41, 82, and 125); this patient was escalated to 400 mg BID (starting on day 85) but subsequently experienced progressive disease (as per assessment on day 163) and was permanently discontinued from the study on day 169. The second patient had stage IV adenocarcinoma of unknown primary with *MET* amplification (fluorescent in situ hybridization–determined GCN 24.51) and experienced a partial response (as per assessments on day 82 and 124); this patient was escalated to 400 mg BID (starting on day 127) but later experienced progressive disease (as per assessment on day 166) and was permanently discontinued from the study on day 168.

The investigator-determined ORR was 25% (95% CI, 3.2–65.1) at the 300 mg BID dose level owing to partial responses in 2 patients, and 0% at the 400 mg BID dose level. Accordingly, the ORR for all patients across both dose escalation and expansion phases was 5.7% (95% CI, 0.7–19.2). The DCR was 37.5% (95% CI, 8.5–75.5) at the 300 mg BID dose level, 22.2% (95% CI, 8.6–42.3) at the 400 mg BID dose level, and 25.7% (95% CI, 12.5–43.3) across all patients.

Three patients in the 300 mg BID dose level cohort had their dose escalated from 300 mg BID to 400 mg BID after cycle 4, two of whom had a BOR of partial response and one had a BOR of stable disease. The single patient in the study with recorded *MET*ex14 mutation (stage IV thyroid cancer with lung metastasis) had a BOR of stable disease at each assessment (on days 39, 84, 126, 168, 210, and 252).

DISCUSSION

In this study, capmatinib was well tolerated when given with food in patients with MET-dysregulated advanced solid tumors; no DLTs were observed at either the 300 mg BID or 400 mg BID dose levels, and an increase in capmatinib exposure was observed with a dose increase from 300 mg BID to 400 mg BID. Accordingly, the 400 mg BID dose was selected as the higher of the tolerated doses in this study. The 400 mg BID dose (tablet) was also used in the pivotal Phase II GEOMETRY mono-1 study.[32] The capmatinib tablet formulation currently has a recommended dose of 400 mg BID with or without food.[33]

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The observed increase in capmatinib exposure from 300 mg to 400 mg BID seems over dose-proportional in this study (geometric mean C_{max}, 1550 vs 3050 ng/mL; geometric mean AUC_{tau}, 9370 vs 16,800 ng × h/mL). However, we posit that this observation is largely due to the small sample size of the 300 mg BID cohort (n = 7). Indeed, capmatinib (tablet formulation) has previously shown a linear PK profile from 200 mg to 400 mg BID in a population PK analysis using pooled data from several studies (data on file, Novartis Pharmaceuticals Corporation).[33] Furthermore, dose proportionality has also been reported from 200 to 600 mg with the capmatinib tablet after single administration in healthy subjects (data on file, Novartis Pharmaceuticals Corporation).

Compared with the median steady-state T_{max} of 1.09 hours in GEOMETRY mono-1 cohorts 1 to 5, in which capmatinib 400 mg BID (tablet) was given under fasted conditions,[32] the median T_{max} for capmatinib 400 mg BID after administration with a high-fat meal in this study was delayed, with a value of 4.0 hours at steady-state (C1D7). At steady-state, accumulation of capmatinib 400 mg BID was low and numerically similar when administered with food in the current study (Racc geometric mean, 1.29) and under fasted conditions in GEOMETRY mono-1 cohorts 1 to 5 (Racc geometric mean 1.39).[32] Compared with the steady-state exposure for the 400 mg BID capmatinib tablet under fasted conditions, reported by Wolf et al[32] (geometric mean C_{max}, 4780 ng/mL; geometric mean $AUC_{0–12h}$, 20,200 ng × h/mL), the geometric mean C_{max} was ˜36% lower and the geometric mean $AUC_{0–12h}$ was ˜20% lower when administered with food in this study (geometric mean C_{max}, 3050 ng/mL; geometric mean $AUC_{0–12h}$, 16,800 ng × h/mL). Furthermore, at steady-state, accumulation of capmatinib 400 mg BID was low and numerically similar when administered with food in the current study (Racc geometric mean, 1.29) and under fasted conditions in GEOMETRY mono-1 cohorts 1 to 5 (Racc geometric mean, 1.39).[32] Overall, these PK data indicate that capmatinib administration with food affects the absorption rate; however, based on the similar steady-state AUC_{0-12h} when capmatinib was administered under fasted conditions or with food, it can be concluded that the extent of the absorption was similar. A key strength of this study was the collection of PK data for capmatinib when administered with a high-fat meal, which enabled assessment of the maximum impact of food on exposure.

In the present study, capmatinib was well tolerated when administered with food, and there were no occurrences of DLTs. Overall, safety observations were in line with the existing safety profile for capmatinib administered under fasted conditions in patients with advanced solid malignancies,[13,36] with no major or new observations. Indeed, Bang et al[13] observed no DLTs among patients with advanced MET-positive solid tumors who were treated with the capmatinib tablet at the 400 mg BID dose under fasted conditions. However, DLT (grade 3 depression) occurred in 1 patient receiving the 400 mg BID tablet in a Japanese Phase I dose escalation study in patients with advanced solid tumors not stratified according to MET status.[36]

When capmatinib was given with food in the present study, the most frequent AEs (any grade) were fatigue (45.7%), nausea (40.0%), peripheral edema (28.6%), and dyspnea (20.0%); the most common TRAEs (any grade) were fatigue (37.1%) and nausea (34.3%). These findings are generally consistent with the 400 mg BID tablet arms of other Phase I studies.[13,36] These findings are also concordant with those across all cohorts of the Phase II GEOMETRY mono-1 study (n = 364), in which capmatinib (400 mg BID tablet) had a manageable safety profile, with the most commonly reported AEs (any grade) as follows: peripheral edema (all cohorts, 51%; fasted cohorts, 51%; nonfasted cohorts, 53%), nausea (all cohorts, 45%; fasted cohorts, 46%; nonfasted cohorts, 37%), and vomiting (all cohorts, 28%; fasted cohorts, 29%; nonfasted cohorts, 21%). The most common TRAEs (any grade) across all cohorts were peripheral edema (42.9%), nausea (34.3%), vomiting (18.7%), and increased blood creatinine levels (18.4%).[32]

Capmatinib was recently granted accelerated approval by the FDA (May 2020) and subsequently received approval by the Japanese Ministry of Health, Labor, and Welfare (June 2020) for the treatment of *MET*ex14-mutated metastatic NSCLC on the basis of findings from GEOMETRY mono-1.[33] In this trial, patients received capmatinib 400 mg BID orally until disease progression or unacceptable toxicity. Capmatinib (fasted conditions) led to a clinically meaningful ORR benefit in patients with treatment-naive (n = 28; ORR, 68%; 95% CI, 48–84) and previously treated (n = 69; ORR, 41%; 95% CI, 29–53) *MET*ex14-mutated advanced NSCLC.[32] In

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addition, in cohort 6, capmatinib (without fasting restrictions) exhibited efficacy as second-line therapy in patients with *MET*ex14-mutated advanced NSCLC (n = 31; ORR, 48.4%; 95% CI, 30.2–66.9).[34] In the present study, in which preliminary evidence of capmatinib antitumor activity was an exploratory objective and MET selection criteria were broader than those in GEOMETRY mono-1,[33] the ORR was 5.7% (95% CI, 0.7–19.2) and the DCR was 25.7% (95% CI, 12.5–43.3) across all patients. However, as this study was not primarily designed or powered to evaluate antitumor activity, no conclusions or comparisons regarding efficacy can be made. Moreover, only one patient with a *MET*ex14 mutation, which is now recognized as an oncogenic driver, was enrolled in this study; the significance of *MET* amplification (with GCN ≥4) and MET overexpression (IHC score +3 in ≥50% of tumor cells) remain poorly understood.

CONCLUSIONS

Safety observations and capmatinib exposure data for the capmatinib tablet formulation (300 mg BID and 400 mg BID) administered with food were consistent with the published safety profile and PK data under fasted conditions in patients with advanced MET-positive solid tumors, with no DLTs observed in this study. Thus, based on a review of all safety and PK data, we conclude that the capmatinib tablet formulation at 400 mg BID was well tolerated with food in patients with MET-dysregulated advanced solid tumors. These findings support the current capmatinib dosing recommendation of 400 mg BID with or without food in patients with MET-dysregulated advanced solid tumors.[33]

DECLARATION OF COMPETING INTEREST

Dr. Moreno has received personal fees (advisory board honoraria) from Bristol Myers Squibb, Bayer, Pieris, Janssen, Roche and Basilea, outside of the current work. Dr. Greil has received personal fees from AstraZeneca, Novartis, Amgen, Bristol Myers Squibb, Merck Sharp & Dohme, Sandoz, AbbVie, Gilead, Daiichi Sankyo, and Janssen, outside of the current work. Dr. Arkenau is employed by the Sarah Cannon Research Institute, UK (part of HCA Healthcare UK); and has received personal fees (advisory board honoraria) from Pierre Fabre, Servier, BeiGene, Bicycle, BioNTech, iOnctura, Roche, Guardant and Taiho, outside of the current work. Dr. Majem has received grant support and personal fees from Bristol Myers Squibb; personal fees and non-financial support from Merck Sharp & Dohme and Boehringer Ingelheim; personal fees, non-financial support, and other support from AstraZeneca and Roche; and personal fees from Kyowa Kirin and Pierre Fabre, all of which are outside of the current work. Dr. Wermke has received grant support (research funding) and personal fees (honoraria) from Novartis, outside of the current work. Dr. Basque, Kapoor, and Giovannini and Mr. Nidamarthy are full-time employees of Novartis. Dr. Cui is a full-time employee and shareholder of Novartis. The authors have indicated that they have no other conflicts of interest regarding the content of this article.

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Drs. Cui, Basque, and Giovannini contributed to designing the study. Drs. Moreno, Basque, Arkenau, Majem, Giovannini, Yachnin, and Wermke contributed to patient accrual. Drs. Cui, Kapoor, Basque, and Giovannini, and Mr. Nidamarthy, contributed to data analysis. All authors contributed to data interpretation, writing and critical revision of the manuscript, and have read and approved the final version of this manuscript.

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 patients who have participated in the trial in line with applicable laws and regulations. The availability of this trial data is according to the criteria and process described on www.clinicalstudydatarequest.com.

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Address correspondence to: Victor Moreno, MD, PhD, START Madrid-FJD, Hospital Fundación Jímenez Díaz, Madrid, Spain.E-mail: Victor.Moreno@startmadrid.com.

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SUPPLEMENTARY MATERIALS

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