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Effects of Itraconazole and Rifampin on the Pharmacokinetics of Mobocertinib (TAK-788), an Oral Epidermal Growth Factor Receptor Inhibitor, in Healthy Volunteers

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Abstract

Mobocertinib (TAK-788) is an investigational oral tyrosine kinase inhibitor targeting epidermal growth factor receptor and human epidermal growth factor 2. A phase 1 open-label, 2-period, fixed-sequence, 2-part study (NCT03928327) characterized effects of a strong CYP3A4 inhibitor (itraconazole) and inducer (rifampin) on the pharmacokinetics (PK) of mobocertinib and its active metabolites, AP32960 and AP32914. Healthy volunteers (n = 12 per part) received a single dose of mobocertinib alone (20 mg, part 1; 160 mg, part 2) and with multiple doses of itraconazole 200 mg once daily (part 1) or rifampin 600 mg once daily (part 2). Coadministration of itraconazole with mobocertinib increased the combined molar area under the plasma concentration-time curve from time 0 to infinity ($AUC_{0-\infty}$) of mobocertinib, AP32960, and AP32914 by 527% (geometric least-squares mean [LSM] ratio, 6.27; 90% confidence interval [CI], 5.20-7.56). Coadministration of rifampin with mobocertinib decreased the combined molar $AUC_{0-\infty}$ of mobocertinib, AP32960, and AP32914 by 95% (geometric LSM ratio, 0.05; 90%CI, 0.04-0.07). Based on these results, the strong CYP3A inhibitor itraconazole and inducer rifampin significantly influenced the PK of mobocertinib and its active metabolites. Coadministration of mobocertinib with moderate and strong CYP3A inhibitors or inducers is not recommended in ongoing clinical trials.

Keywords

mobocertinib, CYP3A4, drug-drug interaction, inhibition, induction, non-small cell lung cancer

Mobocertinib (TAK-788, AP32788) is a potent, selective orally administered inhibitor of epidermal growth factor receptor (EGFR) and human epidermal growth factor 2 including exon 20 insertion mutations,[1] for which there are no effective approved tyrosine kinase inhibitors (TKIs). It potently inhibits all activated forms of the *EGFR* gene, including those containing exon 20 activating insertion mutations, uncommon activating mutations, and the common activating mutations (exon 19 deletions and L858R) with or without the *T790M* resistance mutation.[1,2] An iterative, structure-guided design strategy was used to optimize affinity and selectivity for *EGFR* with exon 20 insertion mutations over wild-type *EGFR*, thereby differentiating it from available TKIs that are typically ineffective against *EGFR* exon 20 insertion mutations.[1] Accumulating preclinical data support that mobocertinib is neither mutagenic nor genotoxic, and clinical data indicate that generally mild adverse events have been reported within the single-dose range of 20-160 mg in clinical pharmacology studies conducted in healthy participants (data on file; Millennium Pharmaceuticals, Inc., Cambridge, Massachusetts).

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Mobocertinib is under clinical development as a treatment for non-small cell lung cancer (NSCLC) with *EGFR* exon 20 insertion mutations. Following single oral doses in healthy volunteers, mobocertinib was systemically absorbed and reached peak plasma concentrations after 4 to 6 hours, with a mean half-life of 20 hours.[3] Mobocertinib is metabolized by cytochrome P450 (CYP)-mediated dealkylation to 2 active metabolites, AP32960 and AP32914, which are approximately equally potent at inhibiting EGFR.[1] Mobocertinib is minimally eliminated renally (<1.2% excreted unchanged in urine). A low-fat meal had no apparent effect on mobocertinib absorption.[3] A 3-part phase 1/2 study (NCT02716116) was conducted to evaluate the safety, pharmacokinetics (PK), and antitumor activity of mobocertinib in patients with NSCLC.[4] In part 1, the dose-escalation phase, sequential dose escalation was employed using a standard 3 + 3 design, starting at 5 mg once daily orally and increasing in increments until the maximum tolerated dose was identified. From this study, the recommended phase 2 dose was identified as 160 mg once daily. In the phase 1/2 study, mobocertinib was readily absorbed following once-daily administration, with a median time to reach the maximum concentration (t_{max}) of 4 hours postdose. Mobocertinib maximum concentration (C_{max}) and area under the concentration-time curve from time 0 to 24 hours ($AUC_{0\text{-}24}$) increased in a dose-proportional manner over the dose range of 5 to 180 mg once daily. The combined molar exposure of mobocertinib, AP32960, and AP32914 is also dose proportional following single- and multiple-dose administration. After repeat dosing in patients with NSCLC, moderate accumulation of mobocertinib systemic exposure was observed in the dose range of 20 to 120 mg once daily. However, administration of mobocertinib 160 mg once daily resulted in similar cycle 1, day 1 and cycle 2, day 1 mobocertinib $AUC_{0\text{-}24}$, with a geometric mean accumulation ratio of 1.03, which is smaller than the calculated accumulation ratio based on its half-life and 24-hour dose interval. Negligible accumulation of mobocertinib exposure at 160 mg once daily and less than dose-proportional increases in mobocertinib exposure from 120 to 160 mg once daily suggest autoinduction of the apparent oral clearance of mobocertinib, likely via induction of CYP3A at 160 mg once daily (data on file; Millennium Pharmaceuticals, Inc.). Overall, metabolism appears to be the major route of elimination for mobocertinib. In vitro studies using recombinant human CYPs suggest that mobocertinib metabolism is primarily mediated by CYP3A4/5 as the percent contribution of this enzyme was >90%, with minor biotransformation via CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, and CYP2D6 pathways as the percent contributions of these enzymes are <2% each. After extensive metabolism of mobocertinib by CYP3A4/5, AP32960 was found to be a major active metabolite, and AP32914 was found to be a minor active metabolite (about 62% and 8% of parent exposure, respectively). Therefore, mobocertinib systemic exposure is expected to be impacted by concomitantly administered strong CYP3A4/5 inhibitors or inducers.

Given the role of CYP3A4 in the metabolism of mobocertinib, this study was conducted to assess the effect of coadministration of a strong CYP3A inhibitor (itraconazole) or a strong CYP3A inducer (rifampin) on the PK of mobocertinib and its 2 active metabolites, AP32960 and AP32914. The results reported here were intended to inform strategies for management of potential drug-drug interactions (DDIs) with moderate and strong CYP3A inhibitors or inducers in current and future clinical studies of mobocertinib.

Methods

Participants

The study was conducted at Celerion in Tempe, Arizona. The protocol and consent form were approved by an institutional review board (Advarra, Inc., Columbia, Maryland) before study initiation, and all participants provided written informed consent. The study was performed in accordance with the requirements of the Declaration of Helsinki, the International Council for Harmonisation Guideline for Good Clinical Practice, and other applicable regulatory requirements.

Eligible participants were nonsmoking healthy men or women 18-55 years of age with a body mass index of 18 to 32 kg/m^2 at screening, as well as normal baseline spirometry for forced vital capacity (FVC) and forced expiratory volume/FVC within 7 days prior to the first dosing. Healthy volunteers were excluded from study participation if they had a clinically significant abnormality as assessed by physical examination, medical history, electrocardiogram (ECG), vital signs, or laboratory test values; history of any clinically significant illness; or received treatment with an investigational drug within 30 days of the last blood collection or dosing, whichever was later.

Study Design

This was a phase 1 open-label, 2-period, fixed-sequence, 2-part study (NCT03928327) of mobocertinib, designed to characterize mobocertinib DDI with either itraconazole (part 1) or rifampin (part 2) in healthy adult volunteers. Volunteers participating in part 1 were different from those participating in part 2. Part 1 was a sequential design study conducted in 2 cohorts: cohort 1 enrolled 4 volunteers and assessed whether mobocertinib 20 mg was an appropriate dose for the mobocertinib/itraconazole DDI study; depending on

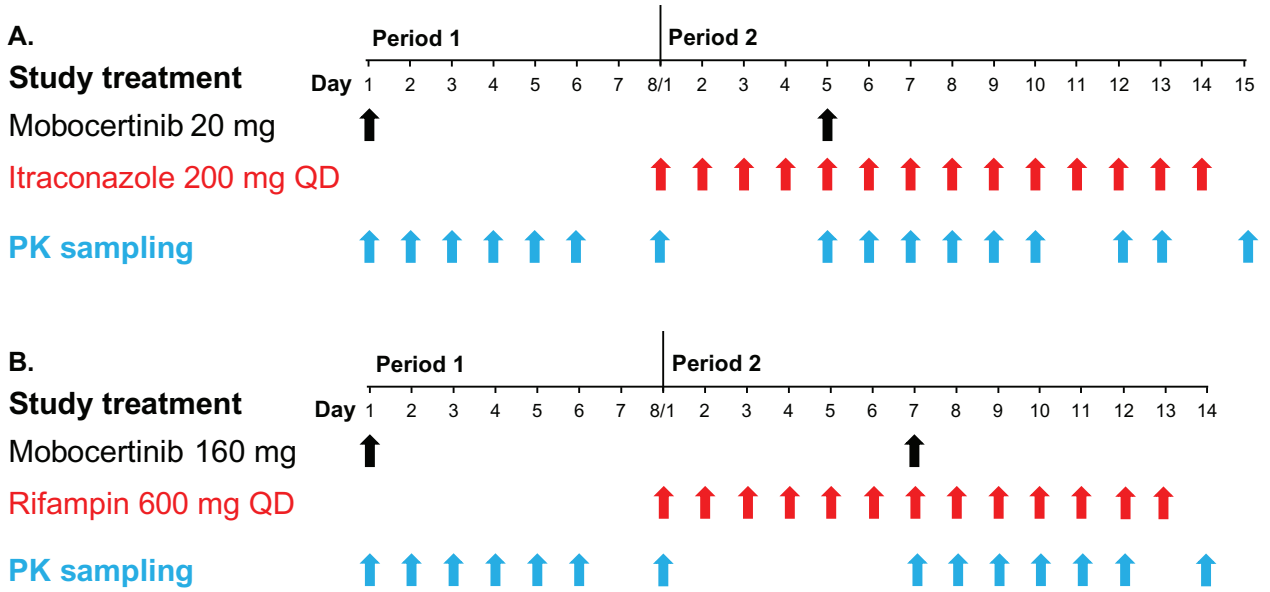

Figure 1. DDI study designs: study treatment and PK sampling for (A) the itraconazole study arm (n = 12) and (B) the rifampin study arm (n = 12). DDI, drug-drug interaction; PK, pharmacokinetics; QD, once daily.

the PK results; cohort 2 was to either continue to enroll 8 more volunteers at this same dose or enroll 12 more volunteers at a revised mobocertinib dose. Of note, following review of the cohort 1 PK data, the dose of mobocertinib for cohort 2 remained 20 mg.

In part 1, volunteers were admitted to the clinical research unit (CRU) on day 1 and received a single oral dose of mobocertinib 20 mg (capsules) on day 1 of period 1 (fasting). A standardized meal was provided at least 4 hours postdose. Volunteers were discharged after samples were collected on the morning of day 4. Subsequently, in period 2, volunteers received itraconazole 200 mg once daily alone as an oral solution on an empty stomach (no food from at least 1 hour before until at least 2 hours after dosing) for 14 consecutive days. Volunteers were admitted on day 4. In period 2 on day 5, volunteers received itraconazole 200 mg together with mobocertinib 20 mg (fasting; Figure 1A), followed by a standardized meal at least 4 hours postdose. Volunteers were discharged after the 72-hour PK sample was collected on the morning of day 8. Itraconazole dosing and PK sample collection were conducted during outpatient visits on days 1 to 3 and days 9 to 14.

In part 2, volunteers were admitted on day 1 and received a single oral dose of mobocertinib 160 mg in period 1 on day 1 (fasting). A standardized meal was provided at least 4 hours postdose. Volunteers were discharged after 72-hour PK samples were collected on the morning of day 4. In period 2, volunteers received rifampin 600 mg once daily (fasting) for 13 consecutive days. Volunteers were admitted to the CRU on day 6. On day 7, volunteers received a single oral dose of mobocertinib 160 mg together with 600 mg rifampin under fasted conditions (Figure 1B), followed by a standardized meal at least 4 hours postdose. Volunteers were discharged after the 72-hour PK sample was collected on the morning of day 10. Rifampin dosing and PK sample collection were conducted during outpatient visits to the CRU on days 1 to 5 and days 11 to 13.

All study drugs were orally administered with ≈240 mL of water. Itraconazole was supplied as a 10-mg/mL Sporanox oral solution (Janssen Pharmaceuticals, Inc., Titusville, New Jersey) and rifampin as 300-mg Rifadin capsules (sanofi-aventis US LLC, Bridgewater, New Jersey, a Sanofi company).

Assessments

For both treatment periods in parts 1 and 2, blood samples were collected at predose and 0.5, 1, 2, 4, 6, 8, 12, 24, 36, 48, 72, 96, 120, and 168 hours postdose to measure plasma concentrations of mobocertinib and its metabolites, AP32960 and AP32914 (Figure 1A,B). For treatment period 2 of part 1, additional samples were collected 192 and 240 hours postdose. Plasma concentrations of mobocertinib, AP32960, and AP32914 were measured using a liquid chromatography-tandem mass spectrometry assay at Charles River (Worcester, Massachusetts) per previously published methodology.[3] The lower limit of quantitation of the assay for mobocertinib and its metabolites in plasma was 0.100 ng/mL.

PK parameters of mobocertinib, AP32960, and AP32914 included C_{max}, AUC from time 0 to infinity ($AUC_{0-\infty}$), t_{max}, and elimination half-life ($t_{\frac{1}{2}}$). Molar

C_{max} was calculated as C_{max} × 1000/molecular weight (MW), and molar AUC_{∞} was calculated as AUC_{∞} × 1000/MW. The combined molar C_{max} = mobocertinib molar C_{max} + AP32960 molar C_{max} + AP32914 molar C_{max}. The combined molar $AUC_{0-\infty}$ = mobocertinib molar $AUC_{0-\infty}$ + AP32960 molar $AUC_{0-\infty}$ + AP32914 molar $AUC_{0-\infty}$.

Safety evaluations included treatment-emergent adverse events (TEAEs), vital signs, clinical laboratory assessments (hematology, chemistry, urinalysis), and 12-lead ECG. Adverse events (AEs) were evaluated throughout the study and up to 30 days after the last dose of mobocertinib. All AEs were coded using the Medical Dictionary for Regulatory Activities version 22.0, and AE severity was assessed by National Cancer Institute Common Toxicity Criteria for Adverse Events version 5.

Pharmacokinetic and Statistical Analysis

All volunteers who received at least 1 dose of study drug were included in the safety population. The PK-evaluable population was defined as all volunteers who complied with the protocol and had an evaluable PK profile (ie, no emesis within 8 hours of dosing, availability of measurements, and absence of major protocol violations). The plasma PK parameters were calculated using noncompartmental methods with Phoenix WinNonlin version 7.0 (Certara, Princeton, New Jersey). All safety parameters were summarized using descriptive statistics. Statistical analyses were performed using SAS (version 9.4; SAS Institute, Cary, North Carolina).

For evaluation of the potential effect of itraconazole and rifampin, a linear mixed-effects model was used for the analysis of the natural log (ln)-transformed $AUC_{0-\infty}$ and C_{max}. The model included treatment as a fixed effect and subject as a random effect. Each model included calculation of least-squares means (LSMs) as well as the difference between LSMs. Geometric mean ratio and 90% confidence interval (CI), consistent with the two 1-sided tests, were calculated using the exponentiation of the difference between treatment LSMs from the analyses on the ln-transformed and combined molar $AUC_{0-\infty}$ and C_{max}.

Results

Volunteers

A total of 12 volunteers entered and completed part 1 of the study, and 12 volunteers entered and completed part 2 of the study. Demographic and baseline characteristics of the populations are presented in Table 1. All 12 volunteers for part 1 and 12 volunteers for part 2 were included in the PK and statistical analyses for mobocertinib and AP32960. In part 1, 3 volunteers receiving mobocertinib alone and 4 volunteers receiving mobocertinib plus itraconazole did not show any quantifiable AP32914 concentration. These volunteers were not included in the PK and statistical analyses for AP32914. Likewise, 4 volunteers receiving mobocertinib plus rifampin in part 2 were not included in the PK and statistical analyses for AP32914. However, the molar C_{max} and $AUC_{0-\infty}$ of AP32914 were treated as zero in calculating the combined molar C_{max} and $AUC_{0-\infty}$ of mobocertinib, AP32960, and AP32914.

Table 1. Demographics and Baseline Characteristics

	Part 1, Combined,[a] n = 12	Part 2, n = 12
Age,[b] y		
Mean (SD)	37.7 (8.3)	40.3 (8.7)
Range	26-55	25-55
Sex, n (%)		
Male	8 (67)	4 (33)
Female	4 (33)	8 (67)
Race, n (%)		
White	10 (83)	12 (100)
American Indian or Alaska Native	1 (8)	0
Other	1 (8)	0
Ethnicity, n (%)		
Non-Hispanic/non-Latino	3 (25)	2 (17)
Hispanic or Latino	9 (75)	10 (83)
Weight, kg		
Mean (SD)	85.5 (10.0)	79.8 (11.5)
Range	69.9-99.0	65.1-98.9
BMI, kg/m^2		
Mean (SD)	28.6 (1.8)	29.0 (2.7)
Range	25.4-31.2	23.7-31.9

BMI, body mass index; DDI, drug-drug interaction; SD, standard deviation.
[a] The dose of mobocertinib is the same in cohorts 1 and 2 of part 1. Their results are combined.
[b] Age at the time of informed consent.

Pharmacokinetics

Effect of itraconazole. Mean plasma concentration-time profiles with and without coadministration of itraconazole are presented in Figure 2A-C. Following administration of itraconazole and mobocertinib 20 mg, the arithmetic and geometric mean systemic exposure to mobocertinib (C_{max} and $AUC_{0-\infty}$) was greater than with mobocertinib alone (Table 2). Median t_{max} was reached 2 hours later, and the geometric mean $t_{\frac{1}{2}}$ was increased by 154% following itraconazole plus mobocertinib compared with mobocertinib alone. Based on the statistical comparisons of ln-transformed PK parameters, the plasma mobocertinib C_{max} and $AUC_{0-\infty}$ following itraconazole and mobocertinib increased by ≈283% (geometric LSM ratio, 3.83; 90%CI, 3.25-4.50) and 743% (geometric LSM

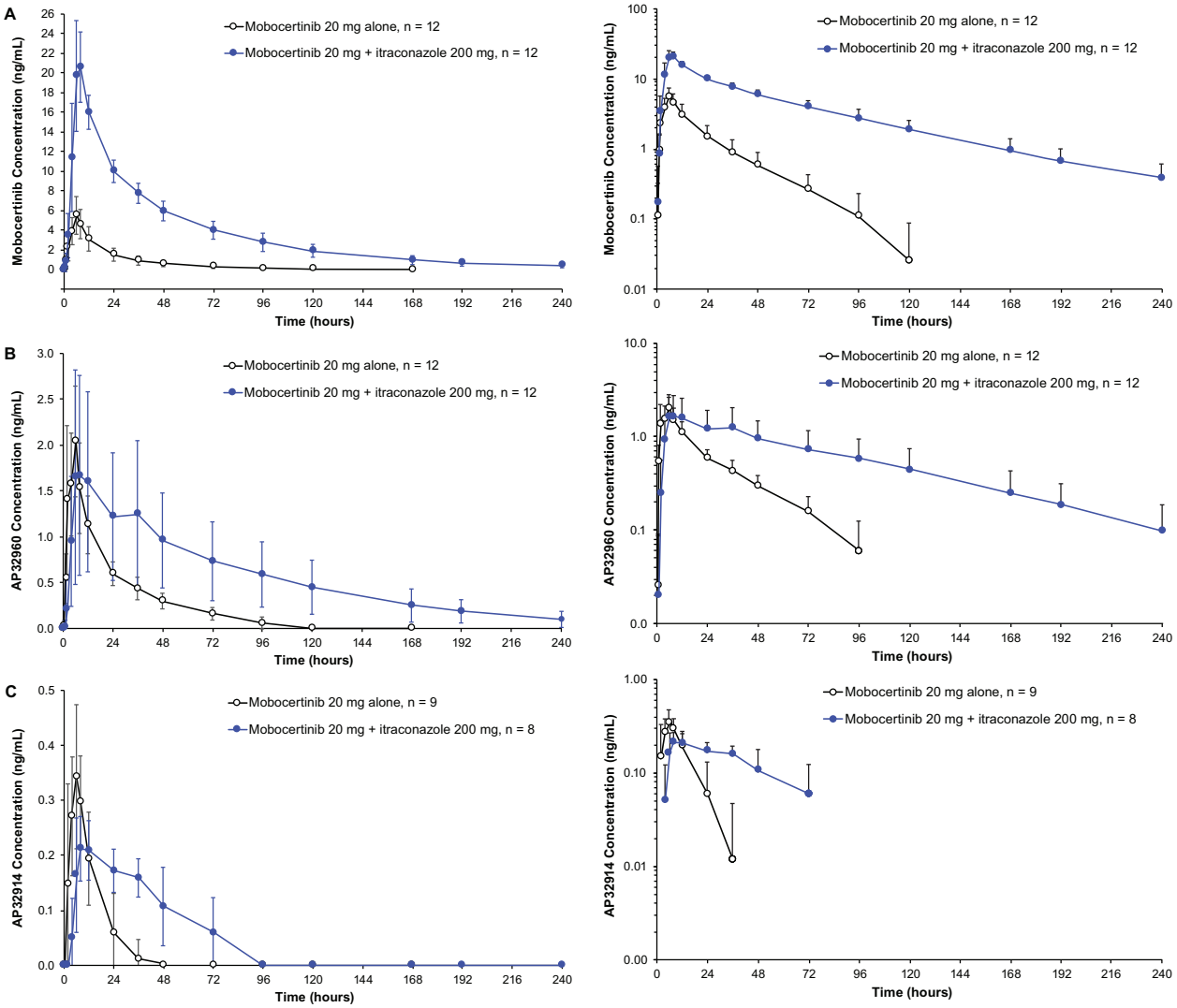

Figure 2. Mean ± SD plasma mobocertinib (A) and metabolites AP32960 (B) and AP32914 (C) concentration-time profiles (linear and semilog plots) with and without coadministration of itraconazole (PK-evaluable population). PK, pharmacokinetics; SD, standard deviation.

ratio, 8.43; 90%CI, 7.02-10.12) of the corresponding values obtained following mobocertinib alone. With combined molar exposure, the geometric LSM plasma C_{max} and $AUC_{0-\infty}$ were 2.86 (90%CI, 2.48-3.30) and 6.27 (90%CI, 5.20-7.56), respectively, which is considered a clinically significant DDI. For AP32960 and AP32914, the median t_{max} was reached 2 hours later, and the geometric mean $t_{\frac{1}{2}}$ was increased by 145% and 394%, respectively, following itraconazole plus mobocertinib compared with mobocertinib alone. The metabolite-to-parent ratios for molar $AUC_{0-\infty}$ following mobocertinib 20 mg alone and with 200 mg itraconazole were approximately 0.473 and 0.151, respectively, for AP32960 and 0.0615 and 0.0205, respectively, for AP32914, indicating inhibition of mobocertinib metabolism via these biotransformation pathways.

Effect of rifampin. Mean plasma concentration-time profiles with and without coadministration of rifampin are presented in Figure 3A-C. Following administration of rifampin plus mobocertinib, the arithmetic and geometric mean plasma mobocertinib C_{max} and $AUC_{0-\infty}$ were lower compared with the corresponding values following 160 mg mobocertinib alone (Table 3). The median t_{max} was reached 2 hours earlier and the geometric mean $t_{\frac{1}{2}}$ reduced by 29% following rifampin plus mobocertinib compared with mobocertinib alone. Per statistical comparisons of ln-transformed PK parameters, the plasma mobocertinib C_{max} and $AUC_{0-\infty}$ following rifampin plus mobocertinib were approximately 5%

Table 2. Plasma PK Parameters of Mobocertinib and Metabolites With (Test Condition) and Without (Reference Condition) Coadministration of Itraconazole

	Arithmetic Means (SD)		Geometric Means (%CV)		
Parameter (unit)	Mobocertinib (Reference)[a] n = 12	Mobocertinib + Itraconazole[a] (Test) n = 12	Mobocertinib (Reference)[a] n = 12	Mobocertinib + Itraconazole[a] (Test) n = 12	Geometric LS Mean Ratio (90%CI) (Test/Reference)[b]
Mobocertinib					
t_{max}, h, median	6.00 (2.00-8.00)	8.00 (5.99-12.00)	–	–	–
C_{max}, ng/mL	5.78 (29.4)	21.5 (19.9)	5.52 (34.1)	21.1 (19.0)	3.83 (3.25-4.50)
$AUC_{0-\infty}$, ng·h/mL	113 (40.8)	907 (19.3)	106 (40.0)	892 (20.0)	8.43 (7.02-10.12)
$t_{\frac{1}{2}}$, h	21.5 (16.4)	54.7 (17.6)	21.2 (16.7)	53.9 (18.2)	–
AP32960					
t_{max}, h, median	6.00 (2.00-6.01)	8.00 (6.00-12.00)	–	–	–
C_{max}, ng/mL	2.20 (28.2)	1.75 (65.4)	2.11 (32.4)	1.43 (75.9)	0.68 (0.51-0.91)
$AUC_{0-\infty}$, ng·h/mL	50.3 (26.3)	150 (55.2)	48.8 (26.9)	132 (56.6)	2.70 (2.16-3.38)
$t_{\frac{1}{2}}$, h	28.5 (15.0)	71.2 (26.0)	28.2 (14.9)	69.0 (26.7)	–
AP32914					
t_{max}, h, median	6.00 (2.00-8.00)[c]	8.00 (6.00-12.00)[d]	–	–	–
C_{max}, ng/mL	0.375 (38.5)[c]	0.222 (23.5)[d]	0.345 (49.2)[c]	0.215 (28.3)[d]	0.57 (0.46-0.70)
$AUC_{0-\infty}$, ng·h/mL	7.38 (26.1)[e]	19.2 (25.5)[f]	7.16 (28.6)[e]	18.7 (27.9)[f]	2.61 (1.76-3.86)
$t_{\frac{1}{2}}$, h	11.2 (30.2)	54.0 (17.1)[f]	10.8 (31.3)[e]	53.4 (17.8)[f]	–
Combined molar exposure					
C_{max}, nM	14.2 (25.7)	40.0 (22.0)	13.7 (30.7)	39.2 (21.1)	2.86 (2.48-3.30)
$AUC_{0-\infty}$, h·nM	314 (33.9)[d]	1850 (18)[g]	298 (35.2)[d]	1820 (18.0)[g]	6.27 (5.20-7.56)

$AUC_{0-\infty}$, area under the plasma concentration-time curve from time 0 to infinity; CI, confidence interval; C_{max}, peak plasma concentration; CV, coefficient of variation; LS, least squares; PK, pharmacokinetics; $t_{\frac{1}{2}}$, elimination half-life; t_{max}, time to peak plasma concentration.

[a] Parameters are presented as arithmetic mean (mean %CV) and geometric mean (geometric mean %CV), except for t_{max}, which is presented as median (range).

[b] The geometric LS mean ratio is calculated for C_{max} and $AUC_{0-\infty}$ parameters only.

[c] n = 9; 3 subjects had unreportable values.

[d] n = 8; 4 subjects had unreportable values.

[e] n = 5; 7 subjects had unreportable values.

[f] n = 6; 6 subjects had unreportable values.

[g] n = 10; 2 subjects had unreportable values.

(geometric LSM ratio, 0.05; 90%CI, 0.04-0.07) and 4% (geometric LSM ratio, 0.04; 90%CI, 0.03-0.05) of the corresponding values obtained following 160 mg mobocertinib alone, representing a clinically relevant DDI. With combined molar exposure, the geometric mean plasma C_{max} and $AUC_{0-\infty}$ were 0.08 (90%CI, 0.07-0.11) and 0.05 (90%CI, 0.04-0.07), respectively. Median t_{max} was reached 4 hours earlier for AP32960 and 2 hours earlier for AP32914, and the geometric mean $t_{\frac{1}{2}}$ was reduced by approximately 39% and 60%, respectively, following rifampin and mobocertinib compared with mobocertinib alone. The metabolite-to-parent ratios for molar $AUC_{0-\infty}$ following mobocertinib 160 mg alone and with 600 mg rifampin were approximately 0.514 and 1.00, respectively, for AP32960 and 0.0341 and 0.0437, respectively, for AP32914.

Safety

Table 4 summarizes the TEAEs by study part. Most TEAEs were mild in intensity, with no severe TEAEs reported. The most common TEAEs were diarrhea (17%) when mobocertinib was coadministered with itraconazole and diarrhea (25%) and nausea, pruritus, rash, headache, oropharyngeal pain, and chest discomfort (17% each) when mobocertinib was coadministered with rifampin. No deaths, serious TEAEs, or discontinuations were reported.

There were no apparent or consistent treatment-related changes in laboratory parameters, vital signs, or ECGs during the study.

Discussion

Incubations with recombinant human CYPs indicated that the metabolism of mobocertinib is primarily mediated by CYP3A4/5, forming 2 active metabolites, AP32960 and AP32914 (also metabolized via CYP3A4/5, per in vitro observations). Based on the in vitro studies, coadministration of mobocertinib with a strong CYP3A inhibitor or inducer, such as itraconazole or rifampin, respectively, may have a potential for

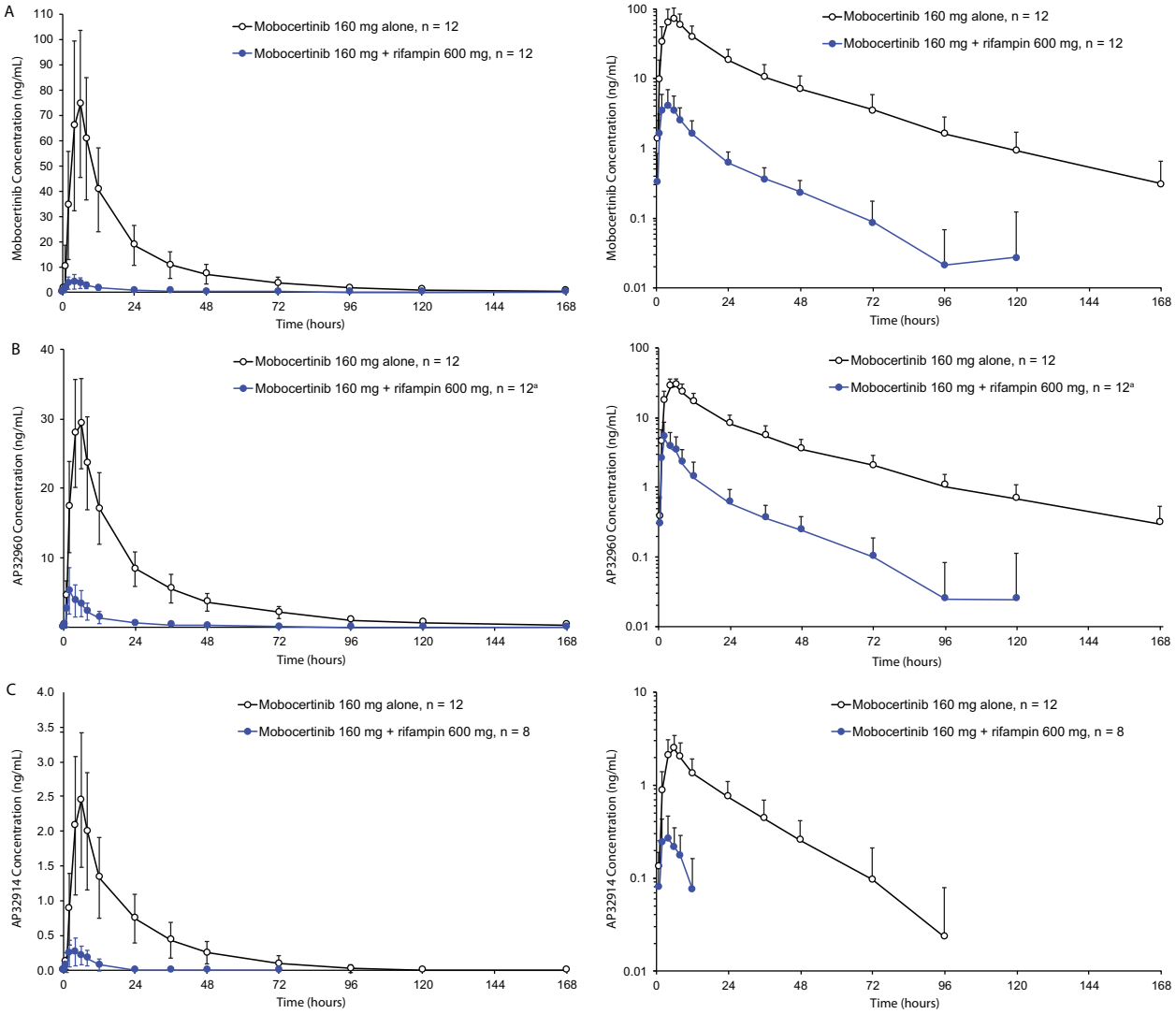

Figure 3. Mean ± SD plasma mobocertinib (A) and metabolites AP32960 (B) and AP32914 (C) concentration-time profiles (linear and semilog plots) with and without coadministration of rifampin (PK-evaluable population). PK, pharmacokinetics; SD, standard deviation. [a]n = 11 at 96 hours.

an increase or decrease in systemic exposure to mobocertinib, AP32960, and AP32914 because of the inhibition or induction of CYP3A-mediated intestinal and/or hepatic metabolism of mobocertinib. The purpose of this study was to assess the effect of coadministration of the strong CYP3A inhibitor itraconazole and the strong CYP3A inducer rifampin on the PK of mobocertinib and its 2 active metabolites.

Several EGFR TKIs, including erlotinib, gefitinib, and osimertinib, are known to have CYP3A4-mediated metabolism as a major mechanism of clearance, with varying effects on exposure.[5–11] Because mobocertinib is mainly metabolized by CYP3A, it was anticipated that mobocertinib exposure would increase significantly with coadministration of mobocertinib with itraconazole, a well-characterized inhibitor of CYP3A. Itraconazole 200-mg dosing for 3-5 days would be necessary to achieve maximum CYP3A inhibition to detect a DDI.[12,13] However, it should be noted that although itraconazole is classified as a strong CYP3A inhibitor, it does not induce maximal CYP3A inhibition in vivo compared with ketoconazole.[14] In the current study, itraconazole was administered as an oral solution on an empty stomach to ensure the highest oral absorption under fasting conditions and minimize gastrointestinal tract irritation during fasting. The 4-day lead-in ensured that CYP3A was maximally inhibited prior to coadministration with mobocertinib. Daily itraconazole coadministration resulted in higher plasma concentrations of mobocertinib throughout the 168-hour postdose interval and higher plasma concentrations of AP32960 and AP32914 after the absorption

Table 3. Plasma PK Parameters of Mobocertinib and Metabolites With (Test Condition) and Without (Reference Condition) Coadministration of Rifampin

Parameter, unit	Mobocertinib[a] (Reference) n = 12	Mobocertinib + Rifampin[a] (Test) n = 12	Mobocertinib[b] (Reference) n = 12	Mobocertinib + Rifampin[b] (Test) n = 12	Geometric LS Mean Ratio (90%CI) (Test/Reference)[c]
Mobocertinib					
t_{max}, h	6.00 (4.00-8.00)	4.00 (1.03-6.00)	–	–	
C_{max}, ng/mL	75.3 (39.0)	4.37 (66.0)	70.0 (42.5)	3.65 (68.6)	0.05 (0.04-0.07)
$AUC_{0-\infty}$, ng·h/mL	1510 (46.6)	64.8 (54.2)[d]	1360 (51.0)	56.9 (57.7)[d]	0.04 (0.03-0.05)
$t_{\frac{1}{2}}$, h	28 (17.7)	20.2 (28.0)[d]	27.6 (17.5)	19.5 (30.6)[d]	
AP32960					
t_{max}, h	6.00 (2.01-6.00)	2.00 (1.03-6.00)	–	–	
C_{max}, ng/mL	30.2 (20.3)	5.58 (55.1)	29.6 (20.3)	4.79 (66.4)	0.16 (0.12-0.21)
$AUC_{0-\infty}$, ng·h/mL	711 (31.3)	64.9 (57.3)[d]	681 (31.2)	55.8 (64.4)[d]	0.08 (0.07-0.10)
$t_{\frac{1}{2}}$, h	38.1 (22.3)	23.4 (19.6)[d]	37.3 (20.5)	22.9 (20.9)	
AP32914					
t_{max}, h	6.00 (4.00-6.01)	4.00 (1.03-119.92)[e]	–	–	
C_{max}, ng/mL	2.46 (39.1)	0.315 (55.7)[e]	2.29 (41.9)	0.279 (55.5)[e]	0.12 (0.09-0.16)
$AUC_{0-\infty}$, ng·h/mL	50.8 (50.8)	3.93 (45.2)[f]	45.2 (53.9)	3.59 (51.9)[f]	0.06 (0.04-0.08)
$t_{\frac{1}{2}}$, h	17.8 (33.2)	6.89 (21.1)[f]	16.9 (34.2)	6.76 (22.6)[f]	
Combined molar exposure					
C_{max}, nM	186 (32.9)	17.6 (60.2)	177 (34.1)	14.9 (68.0)	0.08 (0.07-0.11)
$AUC_{0-\infty}$, h·nM	3900 (41.4)	231 (61.7)[g]	3610 (43.2)	194 (70.2)[g]	0.05 (0.04-0.07)

$AUC_{0-\infty}$, area under the plasma concentration-time curve from time 0 to infinity; C_{max}, peak plasma concentration; CV, coefficient of variation; LS, least squares; PK, pharmacokinetics; $t_{\frac{1}{2}}$, elimination half-life; t_{max}, time to peak plasma concentration.

[a] Parameters are presented as geometric mean (geometric mean %CV), except for t_{max}, which is presented as median (range).

[b] Parameters are presented as arithmetic mean (%CV).

[c] The geometric LS mean ratio is calculated for C_{max} and $AUC_{0-\infty}$ parameters only.

[d] n = 11; 1 subject had unreportable values.

[e] n = 8; 4 subjects had unreportable values.

[f] n = 5; 7 subjects had unreportable values.

[g] n = 9; 3 subjects had unreportable values.

phase. The observed increase in mobocertinib $AUC_{0-\infty}$ with a corresponding increase in mobocertinib C_{max} and increase in $t_{\frac{1}{2}}$ further indicates that the interaction between itraconazole and mobocertinib is likely explained via a decrease in presystemic extraction by the intestine and/or liver and inhibition of systemic clearance. The formation and clearance of the 2 active metabolites are mediated by CYP3A4/5. The precise mechanism of the decrease in AP32960 and AP32914 C_{max} is unknown. The metabolite/parent ratios for both AP32960 and AP32914 were decreased by itraconazole, indicating inhibition of formation of both metabolites by itraconazole, consistent with their formation by CYP3A. Based on these collective findings, coadministration of mobocertinib with moderate and strong CYP3A inhibitors is not recommended in ongoing clinical trials.

Rifampin was administered as a 600-mg dose once daily with 7 days of lead-in dosing prior to concomitant administration with mobocertinib in this study, as it is well established in the literature that rifampin has maximum CYP3A induction after 5-7 days of lead-in dosing.[15,16] Because the half-life of AP32960 was ≈28 hours, the longest among mobocertinib and its active metabolites, oral administration of rifampin continued for 6 days after coadministration of mobocertinib for sustained induction of CYP3A enzymes. In contrast with part 1 with itraconazole, the dose of mobocertinib selected for the DDI study with rifampin (part 2) was 160 mg (recommended phase 2 dose), with a reduction in exposure anticipated. The geometric mean $t_{\frac{1}{2}}$ of mobocertinib and its metabolites following a single dose were all reduced in the presence of rifampin, reflecting CYP3A4 induction and an associated increase in apparent clearance. The reduced systemic exposure in terms of C_{max} and $AUC_{0-\infty}$ to mobocertinib and its 2 active metabolites and the shorter observed $t_{\frac{1}{2}}$ on coadministration with rifampin once daily indicate the contribution of pregnane X receptor (PXR)-inducible enzymes to the clearance of mobocertinib and its 2 active metabolites in humans. The metabolite-to-parent ratios for both AP32960 and AP32914 were increased

Table 4. Treatment-Emergent Adverse Events (≥10%) by Treatment

	Part 1, Combined[a]			Part 2		
	Treatment			Treatment		
	Mobocertinib 20 mg Alone	Mobocertinib 20 mg + Itraconazole	Overall	Mobocertinib 160 mg Alone	Mobocertinib 160 mg + Rifampin	Overall
Volunteers, n (%)						
Volunteers dosed	12 (100)	12 (100)	12 (100)	12 (100)	12 (100)	12 (100)
Volunteers with TEAEs	1 (8)	4 (33)	5 (42)	9 (75)	10 (83)	11 (92)
Volunteers without TEAEs	11 (92)	8 (67)	7 (58)	3 (25)	2 (17)	1 (8)
TEAEs,[b] n (%)						
Diarrhea	0	2 (17)	2 (17)	2 (17)	3 (25)	4 (33)
Dry skin	1 (8)	0	1 (8)	3 (25)	0	3 (25)
Headache	0	1 (8)	1 (8)	1 (8)	2 (17)	3 (25)
Nausea	0	0	0	1 (8)	2 (17)	3 (25)
Back pain	0	1 (8)	1 (8)	1 (8)	1 (8)	2 (17)
Chest discomfort	0	0	0	0	2 (17)	2 (17)
Dry throat	0	0	0	2 (17)	0	2 (17)
Oropharyngeal pain	0	0	0	0	2 (17)	2 (17)
Pruritus	0	0	0	0	2 (17)	2 (17)
Pruritus generalized	0	0	0	2 (17)	0	2 (17)
Rash	0	0	0	0	2 (17)	2 (17)

MedDRA, Medical Dictionary for Regulatory Activities; TEAE, treatment-emergent adverse event.
If a volunteer had ≥2 clinical adverse events, the volunteer was counted only once within a category. The same volunteer may appear in different categories.
[a] The dose of mobocertinib is the same in cohorts 1 and 2 of part 1; results are combined.
[b] Adverse events classified according to MedDRA version 22.0.

following rifampin administration, consistent with induction of CYP3A-mediated formation of both metabolites. These results support the conclusion that chronic use of concomitant moderate and strong inducers of PXR-inducible enzymes, including CYP3A, should be avoided in patients receiving mobocertinib.

Single oral doses of mobocertinib 20 mg with itraconazole and 160 mg with rifampin were generally well tolerated in this healthy volunteer population. Most TEAEs were of mild intensity, with no discontinuations because of TEAEs.

Conclusions

The strong CYP3A inhibitor itraconazole significantly increased systemic exposure of mobocertinib and its 2 active metabolites, whereas the strong CYP3A inducer rifampin significantly reduced the exposure of mobocertinib and its 2 active metabolites. Hence, coadministration of mobocertinib with moderate and strong CYP3A inhibitors and inducers is not recommended in ongoing clinical trials. Single-dose mobocertinib, administered with or without itraconazole or rifampin, appeared to be generally safe and well tolerated in these healthy adult volunteers.

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Conflicts of Interest

S.Z., S.J., C.G., Z.F., J.L., and N.G. are Takeda employees. K.V. is a prior employee of Millennium/Takeda and a current employee of EMD Serono Inc.

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Data-Sharing Statement

The data sets, including the redacted study protocol, redacted statistical analysis plan, and individual participant data supporting the results reported in this article, will be made

available within 3 months from initial request to researchers who provide a methodologically sound proposal. The data will be provided after deidentification, in compliance with applicable privacy laws, data protection, and requirements for consent and anonymization.

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