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Original Manuscript

Clinical Pharmacology
in Drug Development
2020, 9(7) 855–866

DOI: 10.1002/cpdd.853

Evaluation of Absolute Oral Bioavailability and Bioequivalence of Ribociclib, a Cyclin-Dependent Kinase 4/6 Inhibitor, in Healthy Subjects

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Abstract

Ribociclib, a selective and potent cyclin-dependent kinase 4/6 inhibitor, has demonstrated safety and efficacy in combination with endocrine therapy in hormone receptor-positive, human epidermal growth factor receptor-2-negative advanced breast cancer. In 2 open-label crossover studies in healthy participants, the absolute bioavailability of a single oral dose of a ribociclib 600-mg tablet (n = 16) was compared with a single intravenous ribociclib infusion of 150 mg (n = 16), and the bioequivalence of a ribociclib 600-mg tablet (n = 31) and a ribociclib 600-mg capsule (n = 31) was evaluated. The pharmacokinetics of ribociclib and its major metabolite, LEQ803, were assessed in both studies. The oral bioavailability of the 600-mg ribociclib tablet was 65.8% (90% confidence interval [CI], 59.1-73.2%). The geometric mean systemic clearance of ribociclib was moderate (40.2 L/h; 27.4% intersubject variability [CV%]) compared with hepatic blood flow, and the geometric mean volume of distribution was high (979 L; 25.2 CV%). LEQ803-to-ribociclib metabolic ratios were 0.198 for the oral administration and 0.125 for intravenous infusion. Bioequivalence of the tablet and capsule formulations was demonstrated for ribociclib. The geometric mean ratios of maximum concentration and area under the curve from time 0 to last quantifiable concentration and to infinity were 1.01, 1.00, and 0.937, respectively, within the predefined bioequivalence range of 0.80 to 1.25. The median time to reach maximum concentration was 3 hours with both formulations. No serious adverse events were observed in either study.

Keywords

clinical pharmacology, clinical trials, oncology, pharmacokinetics and drug metabolism, pharmacology

Cyclin-dependent kinase 4 and 6 (CDK4/6) inhibition is an effective mechanism of action that, in combination with endocrine therapy (ET), has become the standard of care for patients with hormone receptor-positive (HR+), human epidermal growth factor receptor-2-negative (HER2–) advanced or metastatic breast cancer (ABC).[1] Ribociclib (LEE011, molecular structure as published in James et al, 2020)[2,3] is an orally bioavailable, selective, and potent[4,5] small-molecule dual inhibitor of CDK4/cyclin-D1 and CDK6/cyclin-D3 enzyme complexes, which are upregulated by estrogen receptors and are required for estrogen-dependent cell proliferation.[6] It interferes with G1- to S-phase cell-cycle progression and inhibits pRb phosphorylation, which, with cyclin D1 deregulation, is associated with endocrine resistance.[7]

Ribociclib has been recently approved worldwide for use in combination with an aromatase inhibitor for the treatment of pre-/perimenopausal or postmenopausal women with HR+, HER2– ABC, as initial endocrine-based therapy; or in combination with fulvestrant for the treatment of postmenopausal women with HR+, HER2– ABC, as initial endocrine-based therapy or after disease progression on ET. The approval was based on 3 pivotal phase 3 trials (MONALEESA-2, MONALEESA-3, and MONALEESA-7), in which ribociclib in combination with ET was demonstrated to significantly improve progression-free survival,

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Submitted for publication 8 November 2019; accepted 18 June 2020.

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reducing progression or death by 40.7%-45% compared with ET alone.[8-10] The indication expansion based on MONALEESA-3 and MONALEESA-7 was approved by the US Food and Drug Administration and was the first cancer drug to be approved using the real-time oncology review.[11] In 2 trials to date, ribociclib has demonstrated a statistically significant overall survival (OS) benefit. In MONALEESA-7, estimated OS at 42 months was 70.2% (95% confidence interval [CI], 63.5-76.0%) with ribociclib versus 46.0% (95%CI, 32.0-58.9%) with placebo (hazard ratio [HR], 0.71; 95%CI, 0.54-0.95; $P < .05$).[12] In MONALEESA-3, estimated OS at 42 months was 57.8% (95%CI, 52.0-63.2%) with ribociclib versus 45.9% (95%CI, 36.9-54.5%) with placebo (HR, 0.72; 95%CI, 0.57-0.92; $P = .00455$).[13] Neutropenia, nausea, and fatigue were among the most prevalent adverse events (AEs) across studies.[8-10]

Ribociclib is a weak base formulated as a succinate salt, which exhibits high solubility (>2.4 mg/mL) in aqueous buffer at or below pH 4.5. However, in biorelevant media for fasted and fed states, ribociclib retains its high solubility regardless of pH; physiologically based pharmacokinetic (PBPK) modeling predicted high absorption for ribociclib at 600 mg, with the majority of absorption occurring in the small intestine.[14] Ribociclib also showed moderate permeability in Caco-2 cell monolayers and high passive permeability in human hepatocytes (data on file). Ribociclib is transported by human ABCB1 (P-gp), but not by human ABCG2[15,16]; it has a human plasma protein binding of approximately 70% and is extensively distributed.[3] Ribociclib is excreted predominantly via hepatic elimination in humans and is primarily metabolized by cytochrome P450 (CYP) 3A4.[3,17] LEQ803 (molecular structure published in James et al, 2020) is a major circulating metabolite of ribociclib formed via CYP3A4 and has no clinically relevant contribution to the pharmacological activity in vivo.[3,18]

Clinical studies in patients with retinoblastoma-positive advanced solid tumors or lymphomas found ribociclib to be rapidly absorbed, with a time to maximum concentration (T_{max}) of 1-5 hours and a half-life ($T_{1/2}$) of 33-54 hours; according to trough concentrations following repeated daily dosing, steady state was generally reached by day 8.[18,19] Plasma exposure increases were slightly higher than dose proportional across the dosage range of 50 to 1200 mg.[18] The recommended dosage of ribociclib is 600 mg once daily, in three 200-mg film-coated tablets, 3 weeks on/1 week off in 28-day cycles, with no restrictions on food intake or on concomitant proton pump inhibitors.[14]

The absolute bioavailability (F) of ribociclib has not been previously studied and was evaluated in healthy participants after the administration of single doses of an experimental intravenous formulation and the oral tablet formulation. The objectives of the absolute bioavailability study were to determine the fraction of ribociclib absorbed after oral administration and to characterize the absorption, distribution, and elimination of ribociclib in humans. In a separate study, the bioequivalence of 2 formulations of ribociclib was investigated to support the use of ribociclib in the market: a capsule formulation used during clinical development as the clinical service formulation and a tablet formulation that was developed for commercial use.

Methods

Absolute Bioavailability Study CLEE011A2117

Study Design and Treatment Schedule. Bioavailability was assessed through a phase 1 single-center, 2-period, 2-treatment, open-label crossover study (CLEE011A2117, referred to henceforth as A2117; Figure 1A). The study was conducted at a single early-phase clinic (PAREXEL International GmbH, Berlin, Germany), between May 31 and September 10, 2018; the research protocol was approved by the Landesamt für Gesundheit und Soziales (State Office for Health and Social Affairs, Berlin, Germany). The study protocol and all amendments were reviewed by the Independent Ethics ethical principles of the Declaration of Helsinki. Participants were healthy adult male and sterile or postmenopausal female volunteers screened by medical history, physical examination, vital signs, electrocardiogram (ECG), and laboratory tests. Written consent was obtained from all participants prior to the initiation of the study. The treatments were a single oral dose of 600 mg ribociclib succinate, formulated as three 200-mg film-coated tablets and a single intravenous infusion of 150 mg ribociclib over 4 hours. Treatment sequences were tablet followed by intravenous infusion (sequence 1) and intravenous infusion followed by tablet (sequence 2), both separated with a washout period of at least 12 days. Sixteen participants were randomized in a 1:1 ratio. Participants received a single dose of the study treatment on day 1 of period 1 and day 1 of period 2. Blood samples (2 mL) were collected after each ribociclib administration on day 1 of period 1 and day 1 of period 2 at predose (0 hours) and 0.5, 1, 2, 3, 4, 6, 8, 10, 12, 24, 48, 72, 96, 120, 144, and 168 hours after oral administration. In participants receiving intravenous administration, blood samples were collected at predose (0 hours) and 0.5, 1, 2, 3, 4, 4.25, 4.5, 5, 5.5, 6, 8, 10, 12, 16, 24, 36, 48, 60, 72, 96, 120, 144, and 168 hours after start of infusion. Blood samples were collected by either direct venipuncture or through an indwelling cannula into tubes containing K_3 ethylenediaminetetraacetic acid (EDTA). The end of study treatment was on day 8 of period 2 after the

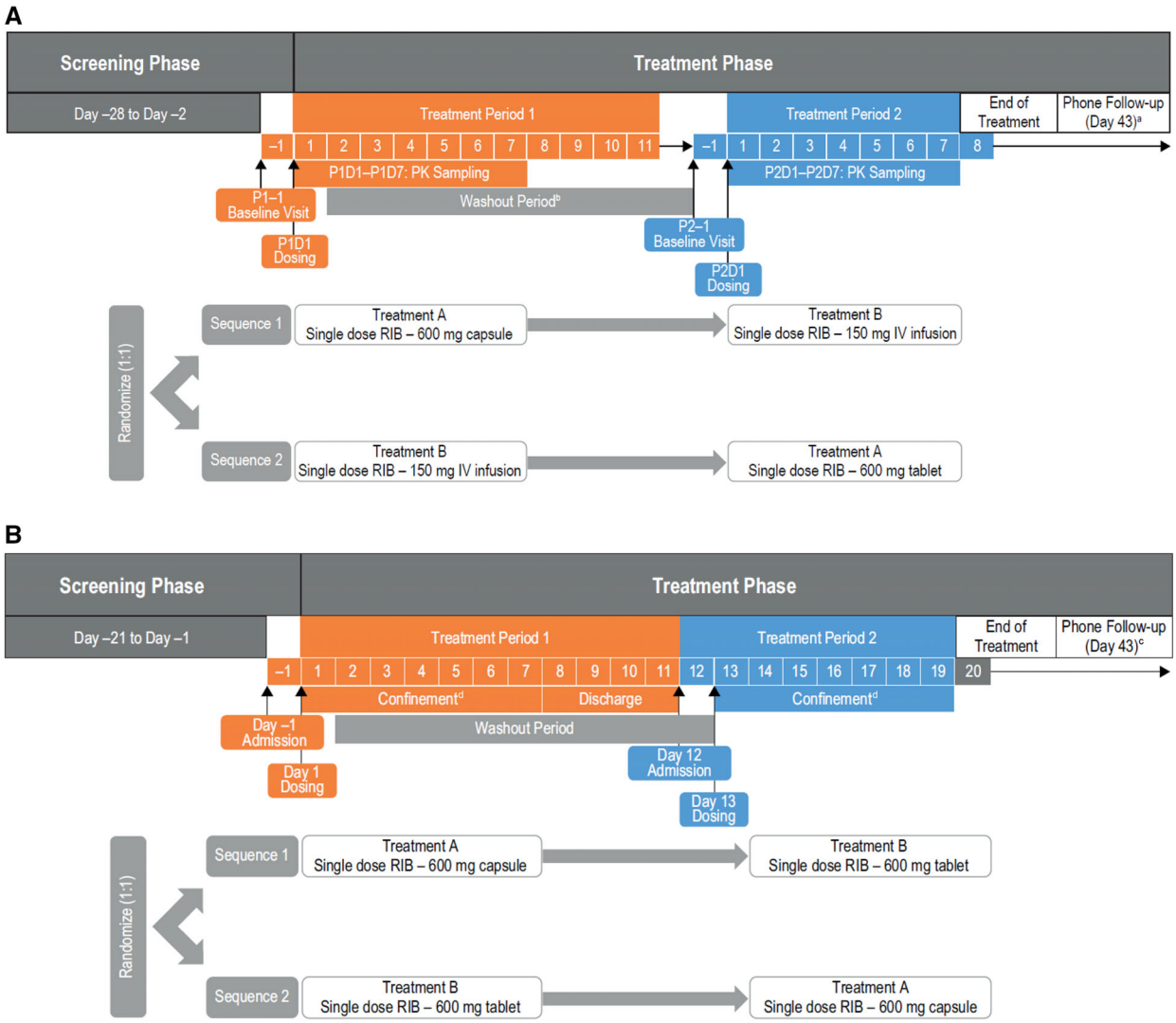

Figure 1. (A) Absolute bioavailability study A2117 design. (B) Bioequivalence study A2103 design. D, day; IV, intravenous; P, period; PK, pharmacokinetics; RIB, ribociclib.

[a]Safety follow-up phone call was 30 days after final dosing on period 2 day 1 (+5-day time window).

[b]The period between each ribociclib administration was at least 12 days (+18-day time window).

[c]Safety follow-up phone call was 30 days after final dosing on day 13.

[d]Subjects were confined to the study facility from days 1-8 and days 12-20 during treatment periods 1 and 2, respectively; subjects were discharged from the study center after the completion of PK sampling (168 h postdose) on days 8 and 20.

end of the final pharmacokinetic (PK) sampling. A follow-up phone call to assess safety was made on day 43.

The extent of drug absorption was compared between a single dose of 600 mg ribociclib administered as film-coated tablets and 150 mg ribociclib administered as a 4-hour intravenous infusion in fasted healthy participants, as measured by the F. The PK of ribociclib and LEQ803 were characterized after administration of either an oral or intravenous dose of ribociclib.

Pharmacokinetics and Statistical Analysis. Ribociclib PK parameters for the bioavailability study were derived from noncompartmental methods using Phoenix v6.4 (Certara, Princeton, New Jersey). A linear mixed model was fitted to the log-transformed dose-normalized area under the curve from time 0 to infinity (AUC_{inf}), with treatment, period, and sequence as fixed factors, and participants nested within sequences as a random factor. A point estimate and the corresponding 2-sided 90%CI for the difference between means of tablet formulation and solution for intravenous infusion was calculated. The point estimate and CI were anti-log-transformed to obtain the point estimate and the 90%CI for the geometric mean ratio (GMR) on the original scale. F of ribociclib was the ratio of geometric means from the model for dose-normalized AUC. Data

analysis was performed using SAS v9.4 (SAS, Cary, North Carolina).

Bioequivalence Study CLEE011A2103

Study Design and Treatment Schedule. Bioequivalence was assessed through a phase 1 randomized, 2-period, 2-sequence crossover study (CLEE011A2103, referred to henceforth as A2103; Figure 1B). The study was conducted at a single study center (Pharmaceutical Product Development, LLC, Austin, Texas) between August 1, 2014, and October 22, 2015; the research protocol was approved by IntegReview Institutional Review Board (Austin, Texas). The study protocol and amendment were reviewed by the independent ethics committee or institutional review board for each center. The study was conducted according to the ethical principles of the Declaration of Helsinki. Participants were healthy adult male and sterile or postmenopausal female volunteers screened by medical history, physical examination, vital signs, ECG, and laboratory tests. Written consent was obtained from all participants prior to the initiation of the study. The treatments were ribociclib succinate in either a capsule formulation (reference therapy) or a tablet formulation (test therapy); both were administered in single doses of 600 mg (3 × 200 mg). Participants were randomized 1:1 into 1 of the 2 sequences: capsule followed by tablet and tablet followed by capsule; treatment periods were separated by a 12-day washout period. Both sequences of the study included a 21-day screening period, 2 baseline periods, and 2 treatment periods; participants were confined to the study facility between days 1 and 8 during treatment period 1 and between days 12 and 20 during treatment period 2 and were discharged after completion of PK sampling on days 8 and 20. Blood samples (2 mL) were collected at predose (0 hours) and 0.5, 1, 2, 3, 4, 6, 8, 10, 12, 24, 48, 72, 96, 120, 144, and 168 hours after dose administration on days 1 and 13. Blood samples were collected by either direct venipuncture or through an indwelling cannula into tubes containing K_3EDTA. On day 43, a follow-up call to assess safety was made.

Pharmacokinetics and Statistical Analysis. The bioequivalence of 600 mg ribociclib administered as a tablet formulation compared with capsule was evaluated under fasted conditions in participants. PK parameters analyzed were derived by noncompartmental analysis using Phoenix WinNonlin v6.2.0.495 (Pharsight, Mountain View, California).

A linear mixed model was fitted to the log-transformed primary ribociclib PK parameters to assess the bioequivalence of the tablet (test) to capsule (reference). Included in the model were treatment, sequence, and period as fixed factors and participants nested within sequences as a random factor. A claim of bioequivalence was assessed based on the corresponding PK parameters (maximum observed plasma drug concentration after drug administration [C_{max}], area under the curve from time 0 to time of last quantifiable concentration [AUC_{last}], and AUC_{inf}). If the 90%CIs of the GMR for the 3 parameters were all completely contained within the range of 0.80-1.25, then bioequivalence was concluded. Data analysis was performed using SAS v9.4 (SAS, Cary, North Carolina).

Analytical Methods

The bioanalytical method to determine ribociclib and its metabolite LEQ803 plasma concentrations consisted of a protein precipitation of the human plasma samples using a TELOS PPT Protein Precipitation 96-Well Plate (Kinesis, Vernon Hills, Illinois), followed by liquid chromatography-electrospray ionization-tandem mass spectrometry. Stable labeled internal standards for ribociclib and LEQ803, [$_2H_6$]LEE011 and [$_{13}CD_3$]LEQ803, respectively, were used for quantification in plasma samples. For study A2117, plasma samples were chromatographed on a Shimadzu LC-30AD (Shimadzu Corporation, Kyoto, Japan). Mobile phase A was a solution of 10 mM ammonium acetate (pH 3.0 ± 0.10), and mobile phase B was acetonitrile. The column was an XSelect CSH C18 4.6 × 100 mm, 2.5 μm (Waters Corporation, Milford, Massachusetts), and the column temperature was set at 40°C. For study A2103, plasma samples were chromatographed on an ACQUITY UPLC System (Waters Corporation, Milford, Massachusetts). The column was a YMC-Triart C18, 2.0 × 30 mm, 1.9 μm, 12 nm (YMC Co. Ltd., Kyoto, Japan), and the column temperature was set at 50°C. Mobile phase A was an aqueous solution of 0.1% formic acid, and mobile phase B was acetonitrile, containing 0.1% formic acid.

Ribociclib and LEQ803 were detected and quantified by tandem mass spectrometry in positive ion mode with electrospray, following multiple reaction monitoring using a mass spectrometer 8050 (Shimadzu Corporation) for study A2117, and an API 4000 mass spectrometer (Applied Biosystems/Sciex, Concord, Ontario, Canada) for study A2103. The m/z transitions were 435.2→322.2 and 421.2→322.2 for ribociclib and LEQ803, respectively. For the internal standards, the m/z transitions were 441.3→322.2 and 425.2→322.2 for [$_2H_6$]LEE011 and [$_{13}CD_3$]LEQ803, respectively. Calibration curves of ribociclib and LEQ803 ranged from 1.00 to 1,000 ng/mL using 0.050 mL plasma. The lower limit of quantification for both analytes was 1.00 ng/mL. For both studies, the precision and accuracy of the analytical method were within ±15%. For study A2117, the method performance had accuracy in terms of bias ranging from –1.1% to 2.5% and precision ranging from 0.9% to 7.6% for ribociclib, and

Table 1. Subject Demographics

	Bioavailability Study A2117 (n = 16)	Bioequivalence Study A2103 (n = 32)
Age (years)		
Mean (SD)	39.4 (9.6)	36.7 (8.6)
Median (range)	39.5 (24-55)	36.0 (22-55)
Sex, n (%)		
Male	14 (87.5)	27 (84.4)
Female	2 (12.5)	5 (15.6)
Race, n (%)		
Caucasian	15 (93.8)	18 (56.3)
Black	1 (6.3)	10 (31.3)
Asian	0	1 (3.1)
Other	0	3 (9.4)
Weight (kg)		
Mean (SD)	76.0 (8.8)	78.5 (10.6)
Median (range)	77.9 (56.8-88.7)	80.4 (55.5-98.5)
Height (cm)		
Mean (SD)	176.3 (7.8)	175.0 (9.4)
Median (range)	178.5 (159-189)	175.8 (154.8-193.7)
BMI (kg/m^2)		
Mean (SD)	24.5 (2.3)	25.6 (2.9)
Median (range)	24.3 (19.0-28.4)	25.78 (18.8-29.5)

BMI, body mass index; SD, standard deviation.

accuracy ranging from –4.4% to 2.8% and precision ranging from 0.5% to 5.2% for LEQ803. For study A2103, the method performance had accuracy in terms of bias ranging from –6.0% to 4.4% and precision ranging from 1.9% to 5.9% for ribociclib, and accuracy ranging from –4.8% to 3.4% and precision from 3.1% to 4.9% for LEQ803.

Values below the limit of quantitation (BLQ) were set to 0 in the concentration data set for data analysis. Zero concentrations (including BLQ values, which were set to 0) at individual times were excluded from geometric mean and geometric coefficient of variance (CV%) computations. Missing concentration values were not imputed.

Safety Assessment

In studies A2117 and A2103, the safety and tolerability of ribociclib were characterized as assessed by the incidence of AEs and serious adverse events (SAEs), by changes in vital signs and ECGs, and by laboratory results (hematology, coagulation, blood chemistry, and urine) throughout the study. AEs were graded based on the Common Terminology Criteria for Adverse Events v4.03.

Results

Subject Demographics

Subject demographic characteristics for both studies are shown in Table 1. Participants in bioavailability study A2117 were between 24 and 55 years of age, with a similar median age across treatment groups; most participants were male and Caucasian.

In bioequivalence study A2103, participants were between 22 and 55 years of age; the median age was 34.0 years in the capsule-tablet group and 38.5 years in the tablet-capsule group. Most participants were male and Caucasian, with a substantial minority of Black participants. Participants in the sequence 1 group had lower median height and higher median body weight than those in the sequence 2 group, resulting in a higher median body mass index in the former group. One participant had a positive test for cotinine at baseline 2 and was subsequently discontinued from the study and excluded from the PK analysis set.

Bioavailability

Ribociclib and LEQ803 plasma concentration profiles exhibited biexponential disposition, and the elimination phases were parallel after intravenous or oral administration of ribociclib (Figure 2). After a single intravenous infusion of 150 mg, geometric mean systemic clearance (Cl) was 40.2 L/h (27.4 CV%), and volume of distribution (V_{ss}) was 979 L (25.2 CV%) for ribociclib (Table 2). The geometric mean of the elimination $T_{1/2}$ was 35.0 hours (20.3 CV%).

After administration of a single oral dose of 600 mg, ribociclib plasma concentration profiles showed rapid absorption (Figure 2), with a median T_{max} of 2.99 hours (range, 1-4 hours; Table 2). The $T_{1/2}$ of ribociclib was 32.9 hours (20.4 CV%); F of the 600-mg

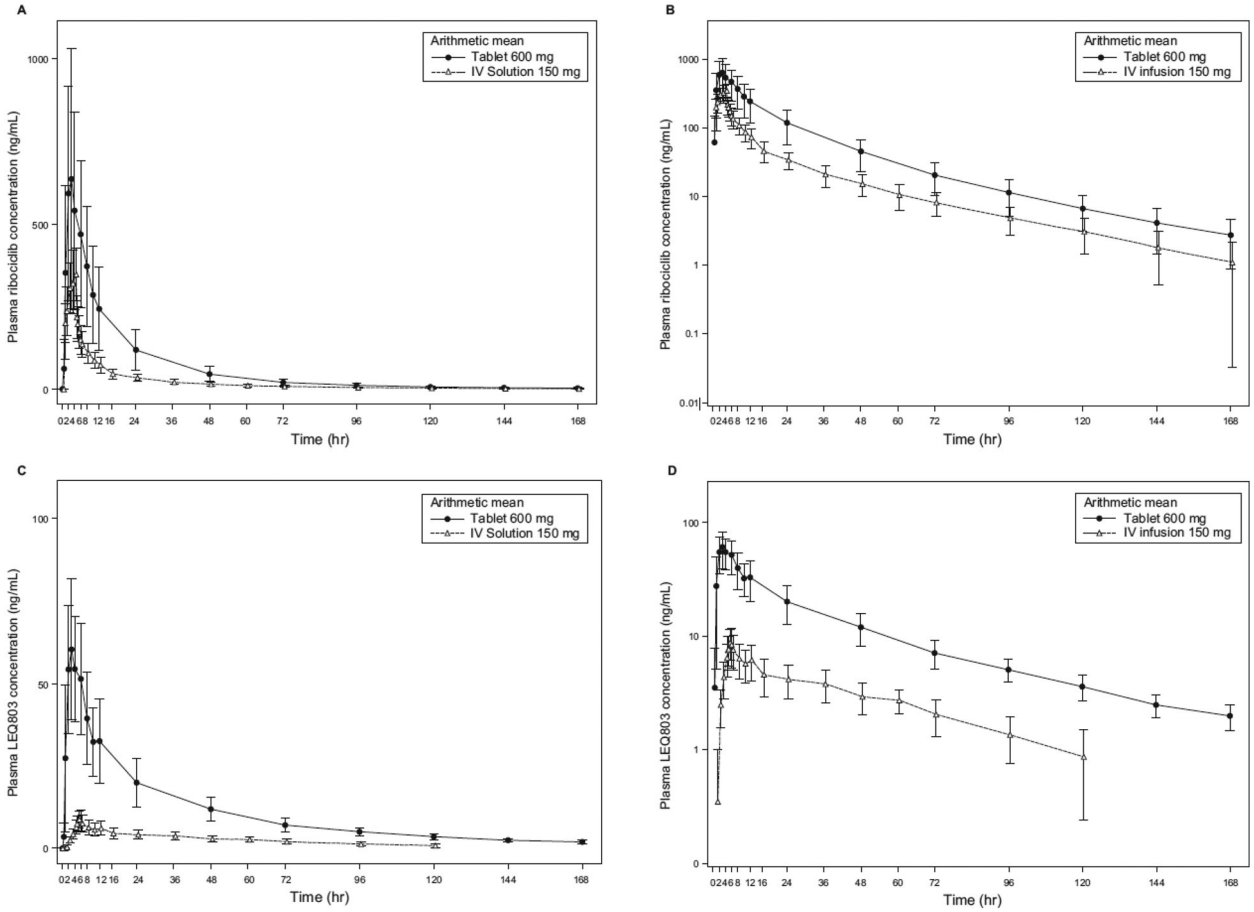

Figure 2. PK profiles of ribociclib and metabolite LEQ803 in the bioavailability study A2117 following a single oral dose of a 600-mg ribociclib tablet or a single intravenous infusion of ribociclib 150 mg. Symbols represent arithmetic mean; error bars represent standard deviation. Values below the BLQ (1.0 ng/mL) were set to 0 and are not represented. All 0 values were included in the calculation of arithmetic mean and SD. Ribociclib concentration for tablet versus intravenously in a linear and semilogarithmic view (A and B); LEQ803 concentration for tablet versus intravenously in a linear and semilogarithmic view (C and D). BLQ, below the limit of quantitation; PK, pharmacokinetics; SD, standard deviation.

ribociclib tablet, measured by the GMR of dose-normalized AUC between the intravenous and oral groups, was 65.8% (90%CI, 59.1-73.2%). One participant was observed to have a much higher dose-normalized AUC relative to other participants after oral administration of a ribociclib tablet; however, a sensitivity analysis showed that exclusion of the participant had no effect on the overall conclusion and resulted in a GMR of 62.8% (90%CI, 58.4-67.4%); hence, this participant was included in the final analysis and all the reported results.

Bioequivalence

Bioequivalence was demonstrated between the tablet and capsule formulations; 90%CIs of the primary PK parameters of ribociclib were all within the predefined bioequivalence boundary of 0.80-1.25 (Table 3). In addition, the mean ribociclib PK profiles following administration of tablet and capsule formulations are almost superimposable (Figure 3). After a single oral dose of tablet or capsule formulations, the geometric means of C_{max} were 598 and 596 ng/mL, respectively (Table 3), with a GMR of 1.01 (90%CI, 0.869-1.17). The geometric mean for AUC_{last} was 10,600 ng·h/mL for both formulations (GMR, 1.00; 90%CI, 0.881-1.14); the geometric means for AUC_{inf} for the tablet and capsule formulations were 10,700 and 11,400 ng·h/mL (GMR, 0.937; 90%CI, 0.885-0.991 ng·h/mL), respectively. No difference was observed in median T_{max} (3.00 hours) between the 2 formulations.

LEQ803 Pharmacokinetic Parameters

In bioavailability study A2117, the metabolic ratio (MR) of LEQ803 was 0.198 after oral administration, which was greater than the 0.125 after intravenous infusion (Table 4). The $T_{1/2}$ of LEQ803 was similar for oral and intravenous administration, at

Table 2. PK Parameters of Ribociclib in the Bioavailability Study A2117

		Oral Tablet 600 mg (n = 16)	Intravenous Infusion 150 mg (n = 16)
F (%)	Mean (SD)	67.7 (18.8)	Reference
	Geo. mean (90%CI)	65.8 (59.1-73.2)	Reference
C_{max} (ng/mL)	Mean (SD)	686 (376)	356 (80.6)
	Geo. mean (Geo. mean CV%)	625 (42.5)	347 (22.8)
T_{max} (h)	Median (range)	2.99 (0.998-3.99)	3.52 (2.00-4.06)
AUC_{last} (ng·h/mL)	Mean (SD)	10 600 (5170)	3770 (1030)
	Geo. mean (Geo. mean CV%)	9680 (44.2)	3650 (27.3)
AUC_{inf} (ng·h/mL)	Mean (SD)	10 700 (5240)	3860 (1060)
	Geo. mean (Geo. mean CV%)	9810 (44.4)	3730 (27.4)
$T_{1/2}$ (h)	Mean (SD)	33.6 (7.5)	35.6 (6.6)
	Geo. mean (Geo. mean CV%)	32.9 (20.4)	35.0 (20.3)
Cl (L/h)	Mean (SD)	N/A	41.6 (10.9)
	Geo. mean (Geo. mean CV%)	N/A	40.2 (27.4)
Cl/F (L/h)	Mean (SD)	66.0 (25.0)	N/A
	Geo. mean (Geo. mean CV%)	61.1 (44.4)	N/A
V_{ss} (L)	Mean (SD)	N/A	1010 (243)
	Geo. mean (Geo. mean CV%)	N/A	979 (25.2)
V_z (L)	Mean (SD)	N/A	2090 (486)
	Geo. mean (Geo. mean CV%)	N/A	2030 (26.2)

AUC_{inf}, area under the curve from time 0 to infinity; AUC_{last}, area under the curve from time 0 to time of last quantifiable concentration; CI, confidence interval; Cl, systemic (total body) clearance from plasma after intravenous administration; Cl/F, apparent total body clearance from plasma after oral administration; C_{max}, maximum observed plasma drug concentration after drug administration; F, absolute bioavailability; Geo. mean CV%, geometric mean of coefficient of variance; Geo. mean, geometric mean; N/A, not applicable; PK, pharmacokinetic; SD, standard deviation; $T_{1/2}$, elimination half-life associated with terminal slope (λ_z) of a semilogarithmic plasma concentration-time curve; T_{max}, time to reach maximum plasma concentration after drug administration; V_{ss}, apparent volume of distribution at steady state after intravenous administration; V_z, apparent volume of distribution during terminal phase (associated with λ_z) after intravenous administration.

Table 3. PK Parameters of Ribociclib in Bioequivalence Study A2103

Parameter	Treatment	n	Geo. Mean, Adjusted (Geo. Mean CV%)	Comparison	Geo. Mean, Ratio (90%CI)
AUC_{inf} (ng·h/mL)	Capsule	30	11 400 (41.8)	Tablet:capsule	0.937 (0.885-0.991)
	Tablet	31	10 700 (35.2)		
AUC_{last} (ng·h/mL)	Capsule	31	10 600 (55.5)	Tablet:capsule	1.00 (0.881-1.14)
	Tablet	31	10 600 (35.2)		
C_{max} (ng/mL)	Capsule	31	596 (66.3)	Tablet:capsule	1.01 (0.869-1.17)
	Tablet	31	598 (36.3)		
T_{max} (h)	Capsule	31	3.00	Tablet:capsule	0 (−4.0 to 3.0)
	Tablet	31	3.00		

AUC_{inf}, area under the curve from time 0 to infinity; AUC_{last}, area under the curve from time 0 to time of last quantifiable concentration; CI, confidence interval; C_{max}, maximum observed plasma drug concentration after drug administration; Geo. mean CV%, geometric mean of coefficient of variance; Geo. mean, geometric mean; PK, pharmacokinetics; T_{max}, time to reach maximum plasma concentration after drug administration.

48.4 hours (21.8 CV%) and 42.6 hours (12.6 CV%), respectively.

The MR of LEQ803 was 0.267 for the tablet formulation, which was similar to that of the capsule formulation, which had an MR of 0.255 in bioequivalence study A2103 (Table 4). The mean LEQ803 profiles following administration of tablet and capsule formulations of ribociclib are also almost superimposable (Figure 3). The $T_{1/2}$ of LEQ803 was similar for both the tablet and capsule formulations, at 49.6 hours (26.0 CV%) and 46.2 hours (24.2 CV%), respectively.

Safety and Tolerability

In bioavailability study A2117, 6 of 16 participants (37.5%) experienced at least 1 AE, with the majority being grade 1 or 2 and none being treatment related (Table 5). Increased aspartate aminotransferase (grade 3) and blood creatine phosphokinase (grade 4) were observed in 1 patient, but this was likely because of an intense physical workout prior to assessment. No participants died during the assessment, nor were any SAEs reported.

Eleven participants (34.4%) experienced at least 1 AE during bioequivalence study A2103; all AEs were

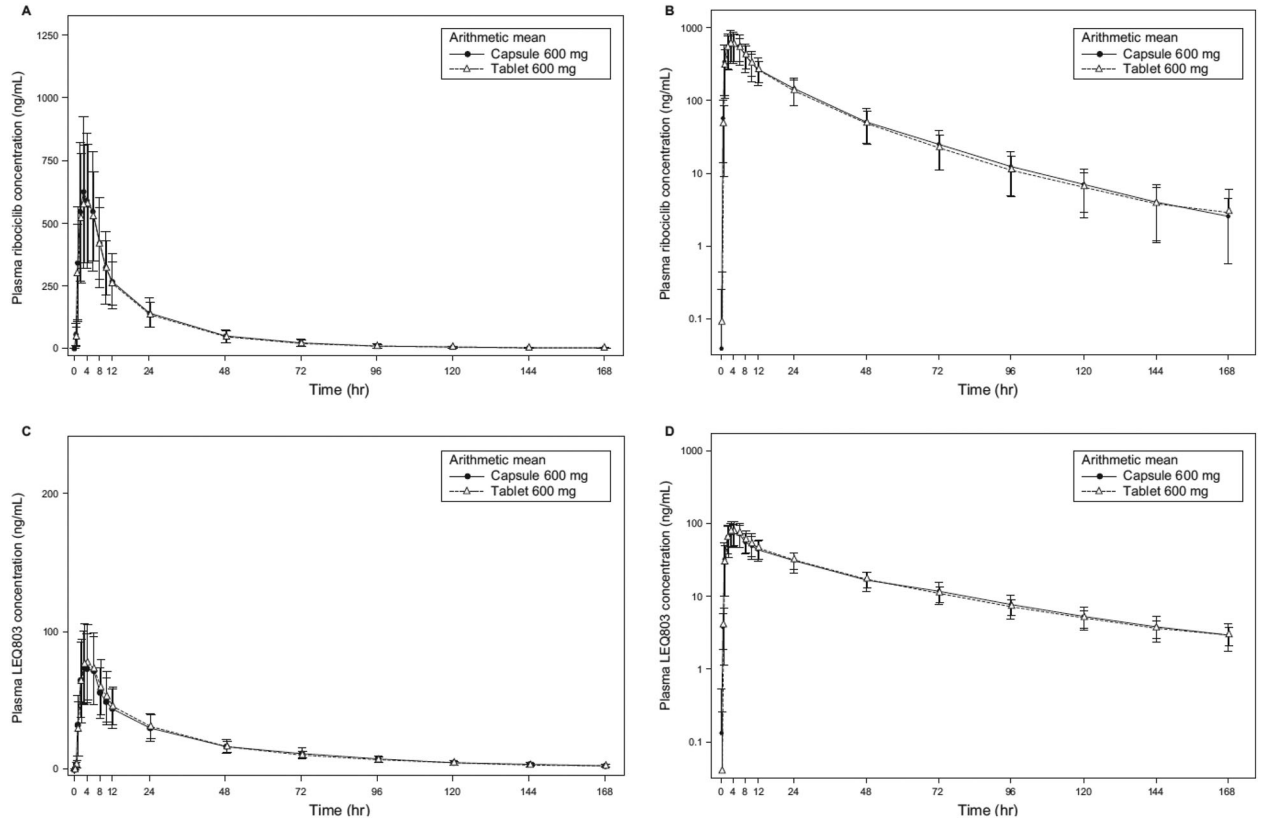

Figure 3. PK profiles of ribociclib and metabolite LEQ803 in the bioequivalence study A2103 following a single oral dose of a 600-mg ribociclib capsule or tablet. Symbols represent arithmetic mean; error bars represent standard deviation. Values below the BLQ (1.0 ng/mL) were set to 0 and are not represented. All 0 values were included in the calculation of arithmetic mean and SD. Ribociclib concentration for capsule versus tablet in a linear and semilogarithmic view (A and B); LEQ803 concentration for capsule versus tablet in a linear and semilogarithmic view (C and D). BLQ, below the limit of quantitation; PK, pharmacokinetics; SD, standard deviation.

grade ≤ 2 (Table 6). Most common AEs were gastrointestinal disorders, which affected 8 participants (25%) and included nausea and vomiting. Nervous system AEs were observed in 4 participants (12.5%), and respiratory, thoracic, and mediastinal disorders were observed in 3 participants (9.4%).

Discussion

Ribociclib is a selective and potent CDK4/6 inhibitor used for the treatment of patients with HR+, HER2– ABC in combination with ET.[4,5] Bioavailability study A2117 was conducted to determine the absolute oral bioavailability of ribociclib. Bioequivalence study A2103 was conducted to support formulation development.

In preclinical species, ribociclib showed a moderate first-pass effect in rats, with 66% absorption and an F of 37%; F was higher in dogs, ranging from 64% to 87%.[3] In vitro, ribociclib showed pH-dependent solubility in aqueous buffer and exhibited moderate permeability in Caco-2-cell monolayers and high passive permeability in human hepatocytes (data on file). As CYP3A4 contributes substantially to the systemic clearance of ribociclib, the first-pass effect was expected to be significant in humans, with the predicted gut metabolism having a minor contribution relative to hepatic metabolism. In healthy male volunteers who were administered a single oral dose of 600 mg ^{14}C-ribociclib, oral absorption of ribociclib was estimated to be moderate, at approximately 58.8% based on the mean percentage of the total radiolabeled dose recovered in the excreta.[3] The PBPK model-estimated oral absorption was 0.94, and F was calculated to be approximately 55% (data on file); the F of 65.8% reported here is in line with these estimated values.

In bioavailability study A2117, ribociclib exhibited biexponential disposition after both intravenous and oral administration (Figure 2A). The elimination phase of concentration-time profiles after oral and intravenous administration was parallel with similar elimination $T_{1/2}$ (35.0 hours [20.3 CV%] for intravenous administration and 32.9 hours [20.4 CV%] for oral administration; Figure 2A, Table 2). Ribociclib

Table 4. PK Parameters of LEQ803 in the Bioavailability and Bioequivalence Studies A2117 and A2103

Parameter		Bioavailability Study A2117 (n = 16/8[a])		Bioequivalence Study A2103 (n = 31[b])	
		Oral Tablet 600 mg	Intravenous Infusion[c] 150 mg	Oral Capsule 600 mg	Oral Tablet 600 mg
C_{max} (ng/mL)	Mean (SD)	64.8 (18.6)	8.97 (3.07)	80.1 (25.9)	83.7 (30.8)
	Geo. mean (Geo. mean CV%)	62.7 (26.2)	8.52 (33.2)	74.3 (48.5)	79.0 (35.0)
T_{max} (h)	Median	2.99	5.02	3.00	4.00
AUC_{last} (ng·h/mL)	Mean (SD)	1800 (533)	337 (116)	2600 (765)	2630 (658)
	Geo. mean (Geo. mean CV%)	1730 (27.8)	318 (37.9)	2470 (36.7)	2550 (24.7)
AUC_{inf} (ng·h/mL)	Mean (SD)	1940 (544)	472 (109)	2820 (822)	2850 (677)
	Geo. mean (Geo. mean CV%)	1880 (26.6)	461 (23.4)	2680 (35.5)	2770 (23.7)
$T_{1/2}$ (h)	Mean (SD)	49.5 (11.4)	42.9 (5.59)	47.6 (13.2)	51.3 (14.5)
	Geo. mean (Geo. mean CV%)	48.4 (21.8)	42.6 (12.6)	46.2 (24.2)	49.6 (26.0)
MR	Mean (SD)	0.210 (0.0764)	0.128 (0.0364)	0.276 (0.124)	0.287 (0.121)
	Geo. mean (Geo. mean CV%)	0.198 (38.4)	0.125 (26.6)	0.255 (41.0)	0.267 (39.6)

AUC_{inf}, area under the curve from time 0 to infinity; AUC_{last}, area under the curve from time 0 to time of last quantifiable concentration; C_{max}, maximum observed plasma drug concentration after drug administration; Geo. mean CV%, geometric mean of coefficient of variance; Geo. mean, geometric mean; MR, metabolic ratio of LEQ803 to ribociclib; PK, pharmacokinetics; SD, standard deviation; $T_{1/2}$, elimination half-life associated with the terminal slope (λ_z) of a semilogarithmic plasma concentration-time curve; T_{max}, time to reach maximum plasma concentration after drug administration.

[a]n = 8 for the intravneous infusion group for AUC_{inf}, MR, and $T_{1/2}$ parameters.

[b]One subject tested positive for cotinine at the baseline 2 visit and was discontinued from the study per physician decision.

[c]150 mg of ribociclib solution was administered via intravenous infusion over a period of 4 hours.

Table 5. AEs by Preferred Term (Safety Set; Bioavailability Study A2117)

	All Participants (n = 16)	
Preferred Term	All Grades, n (%)	Grade ≥ 3, n (%)
Participants with at least 1 event	6 (37.5)	1 (6.3)
Back pain	2 (12.5)	0
Abdominal pain	1 (6.3)	0
Alanine aminotransferase increased	1 (6.3)	0
Aspartate aminotransferase increased	1 (6.3)	1 (6.3)
Blood creatine phosphokinase increased	1 (6.3)	1 (6.3)
Catheter site-related reaction	1 (6.3)	0
Diarrhea	1 (6.3)	0
Headache	1 (6.3)	0

AE, adverse event; CTCAE, Common Terminology Criteria for Adverse Events; MedDRA, Medical Dictionary for Regulatory Activities; n, counts of subjects.
A participant with multiple severity grades for an AE is counted only under the maximum grade. AEs were coded using MedDRA version 21.0; grades were based on CTCAE version 4.03.

Table 6. AEs, Regardless of Study Drug Relationship by Primary System Organ Class, Preferred Term, and Maximum Grade, Reported in ≥5% of Patients (Safety Set; Bioequivalence Study A2103)

	All Participants (n = 32)	
Primary System Organ Class Preferred Term	All Grades, n (%)	Grade ≥ 3, n (%)
Any primary system organ class	11 (34.4)	0
Gastrointestinal disorders	8 (25.0)	0
Nausea	6 (18.8)	0
Vomiting	3 (9.4)	0
Nervous system disorders	4 (12.5)	0
Headache	2 (6.3)	0
Respiratory, thoracic, and mediastinal disorders	3 (9.4)	0
Nasal congestion	2 (6.3)	0
Rhinorrhea	2 (6.3)	0

AE, adverse event.
Primary system organ classes are presented alphabetically; preferred terms are sorted within primary system organ class in descending frequency of all grades column. A participant with multiple occurrences of an AE is counted only once in the AE category. A participant with multiple AEs within a primary system organ class is counted only once in the total row at maximum severity grade.

demonstrated moderate systemic clearance (61.1 L/h, 44.4 CV%) compared with hepatic blood flow. The V_{ss} was high (979 L, 25.2 CV%) relative to total body water volume, suggesting that ribociclib is extensively distributed to tissues. This is consistent with the apparent V_{ss} (V_{ss}/F) in patients with cancer estimated by population PK analysis.[20] A radiolabeled study in rats also indicated that ribociclib had extensive distribution into the extravascular compartment after intravenous or oral administration.[3]

Ribociclib undergoes extensive hepatic metabolism in humans via CYP3A4.[3] The elimination $T_{1/2}$ of LEQ803 was similar to that of ribociclib, suggesting that the metabolism to LEQ803 is formation rate limited. As expected, the ratio of ribociclib to its metabolite LEQ803 was lower after intravenous infusion than after oral administration because of the escape of first-pass metabolism when ribociclib was administered intravenously. Compared with intravenous administration, the CV% of ribociclib was greater after oral administration, which was expected because of the variability in absorption and first-pass metabolism after oral administration.

Ribociclib was rapidly absorbed and quickly reached C_{max} approximately 1-4 hours after oral administration (Tables 2 and 3). For the other 2 approved CDK4/6 inhibitors, palbociclib reached C_{max} between 6 and 12 hours after administration,[21] and the median T_{max} of abemaciclib ranged from 4 to 6 hours after oral administration.[22] The mean F of ribociclib after an oral dose of 600 mg was 65.8% (23.8 CV%), which is higher than the mean F of 46.0% for palbociclib after an oral dose of 125 mg[21] and 45.0% (19.0 CV%) for abemaciclib after an oral dose of 200 mg.[23]

Although ribociclib has pH-dependent solubility in an aqueous buffer, it retains its high solubility regardless of pH in biorelevant media for fasted and fed states, and clinical data have demonstrated that food and proton pump inhibitors have no effect on ribociclib PK.[14] A capsule formulation of ribociclib was used in most clinical trials during clinical development. Bioequivalence study A2103 is a key component in the development of a film-coated tablet formulation, bridging PK data between capsule and tablet formulations for ribociclib. Consistent with comparable PK of tablet and capsule formulations, simulations based on a biopharmaceutical PBPK data model showed that the absorption kinetics of ribociclib at a dose of 600 mg is not limited by its solubility or dissolution in the gut, but rather is driven by its permeability. This study demonstrated the bioequivalence of the tablet and capsule formulations and supports the commercial use of the tablet as well as its use in future clinical studies.

Ribociclib was generally well tolerated by all participants in both studies after a single dose through intravenous or oral administration. No AEs reported in bioavailability study A2117 were related to treatment, including the 2 grade 3 AEs observed; 6 patients in bioequivalence study A2103 experienced treatment-related AEs, but none were grade > 2. No severe AEs or SAEs were observed.

Conclusions

In summary, ribociclib is an orally available CDK4/6 inhibitor for ABC treatment that showed moderate systemic clearance (40.2 L/h [CV% 27.4]), high distribution (979 L [CV% 25.2]), and an F of 65.8% (90%CI, 59.1-73.2%). Bioequivalence was established between ribociclib capsule and tablet formulations, supporting the commercial use and future use in clinical trials of the tablet formulation. Finally, ribociclib has been demonstrated to be well tolerated in healthy subjects, with no new safety signals observed.

Acknowledgments

The authors thank the participants who enrolled in these studies and their families, the operational and clinical teams that supported the studies, clinical trial managers Priya Deshpande and Rahul Tyagi, bioanalytical chemist Serge Winter, and ADME scientist Hilmar Schiller, PhD, for their technical support and scientific discussions. Medical editorial assistance was provided by Robert M. Camp, PhD, of Healthcare Consultancy Group LLC, funded by Novartis Pharmaceuticals Corporation.

Conflicts of Interest

All authors are employees of Novartis; Yan Ji owns stock in Novartis.

Funding

This study was supported by Novartis Pharmaceuticals, which also funded medical writing assistance.

Data Accessibility

The data presented here were obtained through a clinical study, and the raw data are not publicly available.

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