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ARTICLE

Pharmacokinetics of RP5063 Following Single Doses to Normal Healthy Volunteers and Multiple Doses Over 10 Days to Stable Schizophrenic Patients

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RP5063, a multimodal dopamine (D)–serotonin (5-HT) stabilizer, possesses high affinity for $D_{2/3/4}$ and $5\text{-}HT_{1A/2A/2B/2C/6/7}$ receptors and moderate affinity for the serotonin transporter. Two phase I studies characterized the pharmacokinetics of a single dose (10 and 15 mg fasting, 15 mg fed/fasting) in healthy volunteers and multiple doses (10, 20, 50, and 100 mg fed) over 10 days in patients with stable schizophrenia. RP5063 displayed a dose-dependent C_{max} at 4 to 6 h, linear dose proportionality for both C_{max} and AUC, and a half-life between 40 and 71 h. In the single-dose study, food slightly increased the extent of drug absorption. In the multiple-dose study, steady-state was approached after 120 h of daily dosing. Pooled data in the single-dose study indicate that the pharmacokinetic profile appears to be comparable between Japanese and Caucasians. RP5063 appears to have a straightforward pharmacokinetic profile that supports for phase II and III evaluation as a once-daily oral administered agent.

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Study Highlights

WHAT IS THE CURRENT KNOWLEDGE ON THE TOPIC?
✔ RP5063 has no prior data on its pharmacokinetics in humans.

WHAT QUESTION DID THIS STUDY ADDRESS?
✔ The basic human pharmacokinetics of RP5063 and some of the variables that could affect its pharmacokinetics clinically in schizophrenia.

WHAT THIS STUDY ADDS TO OUR KNOWLEDGE
✔ RP5063 is well absorbed, has linear pharmacokinetics over the anticipated clinical range, and possesses a relatively long half-life allowing once-a-day dosing appropriate for the treatment of schizophrenia where the compliance is poor.

HOW THIS MIGHT CHANGE CLINICAL PHARMACOLOGY OR TRANSLATIONAL SCIENCE
✔ The pharmacokinetics of RP5063 are defined and the half-life is commensurate with once-daily dosing. The oral data are used to gain an understanding of the extent of bioavailability and any impact of first-pass metabolism on the bioavailability of RP5063.

Schizophrenia is a complex, chronic, and debilitating psychiatric syndrome that affects 1% of the world's population.[1] It is characterized by a complex mix of positive, negative and mood symptoms, along with cognitive impairment.[2,3] While typical and atypical antipsychotic agents, taken chronically, have been the cornerstone for treatment, 30% of patients remain refractory to treatment.[4] Furthermore, these treatments exhibit significant side effects affecting patient adherence or morbidity and mortality risk.[4–7] Unmet medical needs include the desire for a well-tolerated, nontitratable, once-daily agent.

RP5063, a dopamine (D)–serotonin (5-HT) stabilizer, represents a promising candidate for schizophrenia. It possesses partial agonist activity for $D_{2/3/4}$ and $5\text{-}HT_{1A/2A}$, antagonist activity for $5\text{-}HT_{1A/2A/2B/2C/6/7,}$ and moderate binding affinity for the serotonin transporter, SERT.[8] In rodent models of psychosis and schizophrenia, RP5063 was active in limiting symptoms.[9] Extensive preclinical studies have demonstrated an encouraging pharmacokinetic and toxicological profile (unpublished data).

As part of clinical development for schizophrenia, two separate phase I studies, the first in normal healthy volunteers, and the second in stable patients with schizophrenia, were undertaken. This article reports the pharmacokinetics of RP5063 obtained from these first-time-in-human (FTIH) and first-time-in-patient (FTIP) studies, as secondary objectives to guide future dosing decisions. The first study examined i) single-dose pharmacokinetics, and (1) ii) the effect of food on single-dose pharmacokinetics in normal healthy males. The second study evaluated the pharmacokinetics of multiple doses over 10 days in stable schizophrenia patients.

METHODS

Study conduct

Both studies were Institutional Review Board (IRB)–approved investigations. Informed consent was obtained per the

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requirements of the study IRB and the Helsinki Declaration of 1975. A Data Safety Committee (DSC) had established *a priori* stopping criteria, which was used to ensure safety, and evaluated study data after each cohort to make go-forward, dosing, sampling, and monitoring recommendations for the next cohort.

Single-dose study in healthy males (fasting and food effect)

This study involved a single-dose escalation fasting with food-effect phases to evaluate RP5063 in normal healthy males, who were either Caucasian or Japanese, and 20 to 45 years of age (45 years is a standard age limit in FTIH studies).

The fasting phase utilized a randomized, double-blind, placebo-controlled, ascending-dose design. The implemented dose-escalation portion involved two cohorts (10 and 15 mg) that recruited eight volunteers each, for a total of 16 study participants. The participants were randomized 3:1 (active:placebo), resulting in 12 participants receiving RP5063. A sentinel pair of participants, randomized 1:1 (active:placebo), were entered first, followed by the remaining participants in the cohort randomized 5:1 (active:placebo) after a 2-day safety evaluation.

The food-effect cohort involved a randomized, single-dose, open-label, two-period (fed and fasting) crossover design. This cohort involved eight volunteers, randomized so that four volunteers per group started in either a fed or fasting state and then proceeded to the other state after a 14-day washout period. Those assigned to the meal cohort received a standardized, US Food and Drug Administration (FDA)–approved high-fat meal 30 min before oral administration of RP5063.

The study schedule involved: i) screening (Day -28 to Day -2); ii) admission (Day 1); iii) in-house days (Days 1–3 for fasting cohorts or Days 1–5 food-effect cohort). Study duration ranged from 31 to 33 days, depending on the cohort. Blood samples for the preparation of plasma and subsequent pharmacokinetic analysis were collected at predose and at 0.5, 1, 1.5, 2, 4, 6, 8, 12, 16, 24, 36, and 48 h after the 10-mg dose (Cohort 1), and then with additional samples at 30, 42, 60, 72, 84, and 96 h for the 15-mg dose (Cohort 2) since a preliminary pharmacokinetic analysis by the DSC of the Cohort 1 indicated a relatively long half-life. Sampling was further extended by the DSC to 144 h postdose for Cohort 3.

Multiple-dose study in stable patients with schizophrenia

This study involved four cohorts (10, 20, 50, and 100 mg/day), each comprised of eight patients with stable schizophrenia (chronic, all types, age 18–65 years), totaling 32 participants. It proceeded through the dose-ascension cohorts as planned. Each cohort was randomized 6:2 (active:placebo). The participants remained within the clinic for the duration of study and were administered RP5063 30 min following a standardized, FDA–approved high-fat meal once daily for 10 days.

The study schedule involved: i) screening (Day -35 to Day -6); ii) admission (Day -5); iii) antipsychotic washout (Day -5 to Day 1); and iv) in-house days (Days 1–17). The study duration ranged between 31 and 33 days, depending on cohort. Blood samples of pharmacokinetic analysis were collected from predose to 24 h for Day 1 and from predose Day 10 until 144 h for Cohorts 1 and 2 and until 264 h for Cohorts 3 and 4 for a full evaluation of the terminal half-life. This extension out to 264 h for Cohorts 3 and 4 followed the decision by the DSC following Cohort 2.

Study drug

Participants took capsules of RP5063 orally, based on the prescribed dose and the randomization schedule. Both studies used RP5063 5 mg (batch 150002) and 10 mg (batch 150004) capsules, and the multiple-dose study used RP5063 25-mg (batch 150003) capsules.

Bioanalytical method

RP5063 concentrations were determined in human sodium heparin plasma samples using a liquid chromatography coupled with tandem mass spectrometry (LC/MS/MS) method. An aliquot of 50% methanol (20 μL) and a 100 ng/mL 50% methanolic solution of RP5063-d8 stable label, internal standard (50 μL) was added to an aliquot (100 μL) of the respective plasma sample, extracted by protein precipitation using an aliquot (250 μL) of acetonitrile:methanol (4:1 v/v). Following centrifugation, the supernatant (100 μL) was transferred into a solution (400 μL) of 0.1% aqueous formic acid of which an aliquot (50 μL) was used for LC-MS/MS analysis. Analytes of interest were separated using a Phenomenex (Torrance, CA) Luna 5 μ PFP 50 $\times$ 2.0 mm column with isocratic chromatography using a mobile phase of acetonitrile (35%), methanol (25%), and formic acid (0.1%), made up with water, at a flow rate of 0.20 mL/min. Detection was with an API 4000 or equivalent mass spectrometer (Applied Biosystems, Foster City, CA) using electrospray with multiple reaction monitoring in positive ion mode. The transitions were 449.91-285.10 for RP5063 and 458.11-293.10 for RP5063-d8 internal standard. Data were collected and processed by an Analyst 1.4.2 automated data acquisition system (Applied Biosystems) using linear calibration curves fitted by the least-squares method with a 1/x weighting. The run time was 2.0 min with a lower limit of quantification of 1 ng/mL. Analysis methods met the acceptance criteria per the FDA Guidance, Bioanalytical Method Validation.[10]

Pharmacokinetic analysis

Only patients who received RP5063 were included in this analysis. For the single-dose study, each RP5063 plasma profile was analyzed using a noncompartmental approach with WinNonlin v. 5.1 or higher (Certara, San Diego, CA). Pharmacokinetic parameters included: C_{max}, T_{max}, area under the curve $(AUC)_{last}$, $AUC_{0\text{-}48}$, $AUC_{0\text{-}96}$, $AUC_{0\text{-}144}$, AUC_{inf}, $AUC_{\%extrap}$, $T_{1/2}$, CL/F, and Vz/F. The parameters of most interest were C_{max}, T_{max}, AUC_{tau}, AUC_{inf}, AUC_{last}, and $T_{1/2}$.

For the multiple-dose study, pharmacokinetic parameters, C_{max}, C_{min}, T_{max}, and $AUC_{0\text{-}24}$, were calculated for the first and last dose together with AUC_{inf} and $t_{1/2}$ for the last dose only, using the noncompartmental approach with WinNonlin v. 5.2. The accumulation of RP5063 over a 10-day period was determined from the ratio of C_{max} and AUC for a dosing interval ($AUC_{0\text{-}24}$) of the last dose to those of the first dose.

For both studies, descriptive statistics were obtained for each parameter of interest, dose proportionality was examined, and 90% confidence intervals (CIs) for each treatment ratio were calculated. For the single-dose study, dose proportionality was explored for C_{max} and AUC. The natural logarithm of the pharmacokinetic parameters was compared between the fed and fasted participants using a 4-factor mixed model analysis of variance (ANOVA with SAS PROC REG (SAS, Cary, NC), and ANOVA for C_{max} and AUC on the food-effect cohort.

For the multiple-dose study, dose proportionality was assessed using the "power model" approach, in which C_{max} and $AUC_{0\text{-}24}$ were fitted to a power equation with a 2-sided 90% CI with SAS PROC REG to test if the power function was equivalent to unity as the indicator. A simple linear regression of the natural logarithm of C_{max} and AUC on the natural logarithm of the dose was used to assess the linear relationship with RP5063 dose administered.

RESULTS

Study populations

Twenty-four individuals were recruited, and 23 completed the single-dose evaluation. Cohorts 1 and 2 included six participants each assigned to the RP5063 10-mg and 15-mg cohorts. In Cohort 3, eight participants were enrolled, with seven completing both fed and fasting phases (one participant voluntarily withdrew and did not receive the RP5063 under fed conditions).

Demographics (**Table 1**) were similar across all cohorts in the single-dose study. Study participants were males with a mean age of 28 years (range, 20–36), either Caucasian ($N = 15$; 75%) or Japanese ($N = 5$; 25%) and were distributed by Cohort as follows: i) Caucasian (Cohort 1–5, Cohort 2–4, and Cohort 3–6) and ii) Japanese (Cohort 1–1, Cohort 2–2, and Cohort 3–2). Participants had a mean body weight of 74.44 kg (range, 53.9–91.8 kg) and mean body mass index (BMI) of 24.1 kg/m^2 (range, 18.7–29.8 kg/m^2). Differences were observed between Caucasian and Japanese participants in body weight (76.35 + 2.29 kg vs. 68.72 + 3.89 kg, respectively). No participants enrolled were poor CYP2D6 metabolizers.

All 32 randomized patients completed the multidose study, with 24 receiving treatment ($N = 6$ per cohort). Demographics (**Table 2**) were similar across all cohorts. Mean age ranged between 38.8 and 47.7 years, mean height between 173.78 and 179.47 cm, mean weight between 83.12 and 100.75 kg, and mean BMI between 27.1 and 31.1 kg/m^2. 81.25% of the patients were Black and 18.75% Caucasian.

Bioanalytic analysis

The LC/MS/MS method for the analysis of RP5063 was validated over the concentration range of 1.00–500 ng/mL using 100 μL of human sodium heparin plasma. No significant interfering peaks due to endogenous compounds or chemical reagents used were observed in the chromatograms of the six individual lots of human sodium heparin plasma. The six blank human sodium heparin plasma spiked lots reflected a mean concentration of 1.0 ng/mL, with an interassay accuracy for each lot at the lower limit of quantification range of 97.6–103%.

The interassay accuracy range was 97.6–102% (Acceptance Criteria (AC): percent nominal, 80–120% (lowest calibration standard); 85–115% (all other standards)). Nominal concentrations for lower limit, low, low-to-mid, medium, and high quality-control points were 1.0, 2.0, 20.0, 250, and 400 ng/mL, respectively. The intra- and interassay precision (and accuracy) ranges for the low-high QC samples were 1.19–4.56% (99.0–113%) and 3.39–5.59% (105-110%), respectively (AC: percent coefficient of variation (%CV) $\pm$15%; % recovery 80–120%). The lower limit sample intra- and interassay precision (and accuracy) ranges were 1.61–10.8% (88.2–102%) and 9.49% (96.2%), respectively (AC: %CV $\pm$ 20%; % recovery 85–115%). The linear range, linearity, slope, and intercept translated as follows: $y = 0.0301\ x + -0.00671$ ($r_2 = 0.9988$; AC > 0.99).

Stability was observed at room temperature for plasma extract for a minimum of 61 h and human sodium heparin plasma for a minimum of 5 h. Human sodium heparin plasma was stable after three freeze–thaw cycles (AC: % recovery 85–115%). Under room temperature conditions, RP5063 stock solution at 10.0 μg/mL and internal standard, RP5063-d8 was observed for 5 h and the spiking solution at 5.00 ng/mL for 4 h (AC: percent recovery 90.0–100%). Mean procedural recovery for RP5063 range was 92.5–105% (mean: 98.1%) and internal standard was 92.3–99.2% (mean: 95.6%).

Safety summary

In each study, RP5063 displayed an encouraging safety profile. Detailed review of these data are discussed in a separate publication evaluating the safety and pharmacodynamics of this compound. In the single-dose study evaluating RP5063 ($\leq$15 mg), no treatment-emergent adverse events (TEAEs) leading to withdrawal or deaths were observed. While one serious adverse event (SAE) was reported, it was discovered later that this patient had a prior history of seizures (an exclusion criteria) and should have been excluded. The most frequent TEAEs from this study included orthostatic hypotension, nausea, and dizziness.

In the multiple-dose study in patients with stable schizophrenia, RP5063 was well tolerated at doses from 10 to 100 mg, with no SAEs up to and including the 50-mg dose, despite two SAEs at the 100-mg dose. The most frequent TEAEs included akathisia and somnolence. No treatment-related changes were seen in glucose or prolactin levels or in lipid profiles.

Single-dose study: Dose escalation, Cohorts 1 and 2 (10 and 15 mg, fasting)

Figure 1 describes the RP5063 concentration–time data (linear and semi-log) and shows an increase in plasma concentrations with it peaking at about 5 h after dosing. A decline in plasma concentration followed in a biphasic manner with a terminal half-life of $\sim$40–50 h based on Cohort 3 data at 15 mg (**Figure 1c,d**), which included samples out to 144 h ($\approx$3 half-lives) since the shorter sampling periods in Cohort 1 and 2 could have led to an underestimate of the half-life. **Table 3** presents individual pharmacokinetic parameters for the single-dose study dose-escalation cohorts under fasting conditions. After a single oral administration of RP5063,

Table 1 Single-dose study population demographics

Parameter	Cohort 1: 10 mg RP5063 ($n = 6$)	Cohort 2: 15 mg RP5063 ($n = 6$)	Cohort 3 (food effect): 15 mg RP5063 ($n = 8$)
Age (Years) Mean (SD)	31.2 (5.74)	26.2 (4.26)	26.1 (5.99)
Height (cm) Mean (SD)	179.3 (6.70)	171.6 (7.83)	175.8 (3.19)
Weight (kg) Mean (SD)	81.78 (9.902)	68.97 (11.008)	73.04 (6.719)
Body Mass Index Mean (SD)	25.43 (2.839)	23.53 (4.408)	23.63 (2.197)
CYP2D6 Poor Metabolizer	–	–	–
Race			
Caucasian, *n* (%)	5 (83.33)	4 (66.67)	6 (75.00)
Japanese, *n* (%)	1 (16.67)	2 (33.33)	2 (25.00)
Black (%)	–	–	–
Ethnicity			
Hispanic, *n* (%)	1 (16.67)	1 (16.67)	–
Non-Hispanic *n* (%)	5 (83.33)	5 (83.33)	8 (100.00)
Sex			
Male, *n* (%)	6 (100.00)	6 (100.00)	8 (100.00)

Kg: kilograms; *n*: number; NP: not performed.

Table 2 Multidose study population demographics

Parameter	Cohort 1: 10 mg RP5063 ($n = 6$)	Cohort 2: 20 mg RP5063 ($n = 6$)	Cohort 3: 50 mg RP5063 ($n = 6$)	Cohort 4: 100 mg RP5063 ($n = 6$)
Age (Years) Mean (SD)	40.7 (12.5)	47.7 (7.61)	38.8 (12.3)	47.3 ((4.37)
Height (cm) Mean (SD)	176.78 (6.00)	173.78 (6.86)	179.47 (9.52)	175.23 (6.34)
Weight (kg) Mean (SD)	87.67 (19.69)	85.57 (14.84)	100.75 (20.44)	83.12 (11.97)
Body Mass Index Mean (SD)	28.25 (7.06)	28.33 (4.58)	31.13 (4.72)	27.07 (3.75)
CYP2D6 Poor Metabolizer	NP	NP	NP	NP
Race				
Caucasian, *n* (%)	2 (33.33)	1 (16.67)	–	1 (16.67)
Japanese, *n* (%)	–	–	–	–
Black (%)	4 (66.67)	5 (83.33)	6 (100.00)	5 (83.33)
Ethnicity				
Hispanic, *n* (%)	–	–	–	–
Non-Hispanic *n* (%)	6 (100.00)	6 (100.00)	6 (100.00)	6 (100.00)
Sex				
Male, n (%)	6 (100.00)	6 (100.00)	6 (100.00)	6 (100.00)

Kg: kilograms; *n*: number; NP: not performed.

both mean (coefficient of variation, CV%) C_{max}, and AUC increased from 10 mg to 15 mg: C_{max}: 27.9 ng/mL (34.0%) to 36.6 ng/mL (25.2%); and AUC_{inf}: 1,040 ng*h/mL (39.1%) to 1,448 ng*h/mL (35.2%). The results suggest that C_{max} and AUC_{inf} increased proportionally over this dose range, albeit narrow. However, the $AUC_{\%extrap}$ ranged from 31% to 52% (mean, 43.5%) for the participants administered the 10-mg dose and from 8% to 28% (mean, 18.5%) for the participants administered the 15-mg single dose. These findings indicate that the terminal half-life was probably not adequately characterized at the lower dose.

Single-dose study: Food effect, Cohort 3 (15 mg, fed and fasting)

Figure 1 also provides the concentration–time profile (linear and semi-log) for the food effect cohort and **Table 3** summarizes key pharmacokinetic parameters. The C_{max} was similar for both the fed and fasted state with a mean (CV%) of 37.0 ng/mL (33.0%) for the 15-mg dose fed and 34.0 ng/mL (29.1%) for the 15-mg dose fasted. This concentration was reached at a median time of 6 h postdose for both states. The mean (CV%) half-life was 56 h (52.6%) for the 15-mg dose fed and 53 h (36.1%) for the 15-mg dose fasted. The AUC measurements appear to reflect higher exposures in the fed state compared with fasted with the mean (CV%) AUC_{last} of 1848 ng*h/mL (51.3%) for the 15-mg dose fed and 1544 ng*h/mL (55.7%) for the 15-mg dose fasted. Mean (CV%) AUC_{inf} was 2,441 ng*h/mL (71.2%) for the 15-mg dose fed and 1,898 ng*h/mL (67.8%) for the 15-mg dose fasted.

Analysis of the effect of food on RP5063 bioavailability showed a slight increase in C_{max} with the ingestion of food, since the 90% CI surrounding the ratio of least-square means (LSMs) fell just above the usual boundary of bioequivalence (80–125%), but still encompassed 100%. The effect of food was more pronounced for AUC with the respective AUC_{last} and AUC_{inf} LSM values for the fed condition (1,728 hour*ng/mL and 2,113 hour*ng/mL, respectively) representing a greater than 20% increase in exposure, vs. LSM

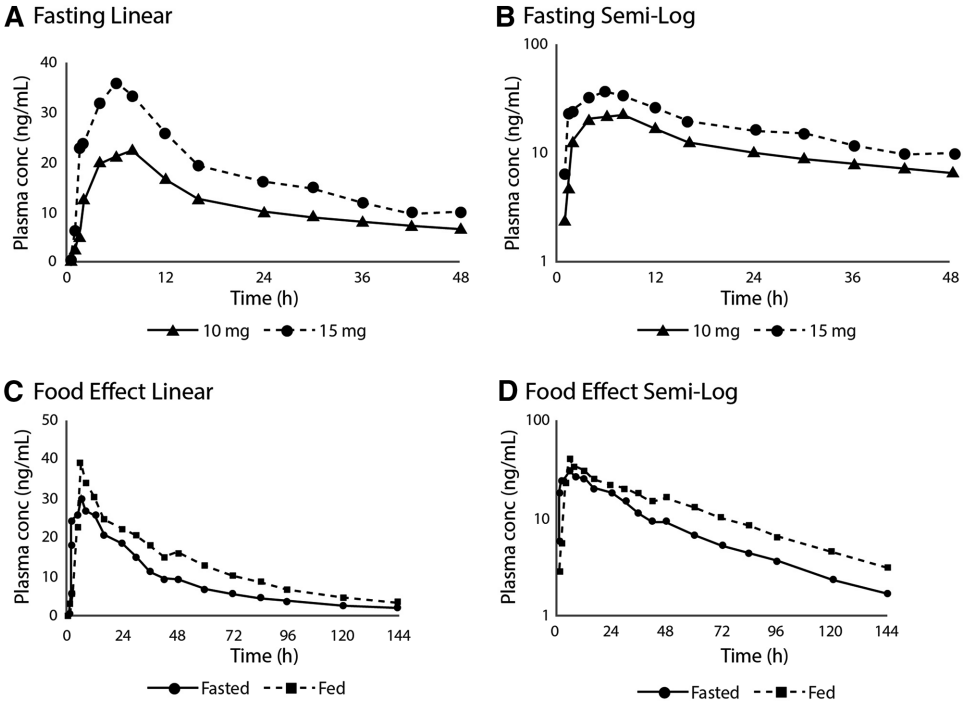

Figure 1 Concentration–time profiles for fasting (**a**) linear and (**b**) semi-log, and food effect (**c**) linear and (**d**) semi-log.

values for the fasting condition (421 hour*ng/mL and 1,676 hour*ng/mL, respectively). The 90% CI surrounding the ratio of LSMs was well above the usual boundary of bioequivalence (80–125%) and did not encompass 100%.

Effect of ethnicity

Table 4 compares RP5063 pharmacokinetic parameters for Japanese and Caucasian populations (Cohorts 1, 2, and Fasting 3). No statistically significant differences were found between these subpopulations across all the cohorts and in the pooled fasting data. However, these data need to be interpreted accordingly based on the small size of the Japanese group.

Multiple-dose study: Cohorts 1 through 4 (10, 20, 50, and 100 mg)

Figure 2 summarizes RP5063 concentration–time data. **Table 5** presents individual pharmacokinetic parameters. Following initial and 10 days of dosing at 10, 20, 50, and 100 mg, RP5063 had a median T_{max} occurring at ≈4–6 h postdose after both the first and last doses. Moreover, a visual examination of mean C_{trough} concentrations suggested that steady-state accumulation was approached by 120 h of daily dosing of RP5063 (**Figure 2**).

After the first dose of RP5063, C_{max} and AUC_{24} increased in a dose-proportional manner from 10–100 mg. Mean (CV%) C_{max} and AUC_{24} increased from 20.2 ng/mL (18.8%) to 195.0 ng/mL (26.7%) and from 314.0 hour*ng/mL (11.2%) to 3,538.0 hour*ng/mL (33.5%) across the 10- to 100-mg dose levels, respectively.

After daily administration for 10 days, mean C_{max}, AUC_{tau} (equivalent to AUC_{24}), and AUC_{inf} increased in a dose-proportional manner from 10–100 mg RP5063. Mean (CV%) C_{max} and AUC_{tau} increased from 70.1 ng/mL (25.4%) to 696.0 ng/mL (43.3%) and from 1361 hour*ng/mL (34.8%) to 12,526 hour*ng/mL (44.37%) across the 10- to 100-mg dose levels, respectively. Mean C_{max} was reached at a median time of 4–5 h postdose across all dose levels.

Linear regression of the natural logarithm of C_{max} and AUC on the natural logarithm of the dose suggests that C_{max} and AUC_{last} for Day 1 and C_{max} and AUC_{tau} for Day 10 are dose-proportional, since the point estimate of the slope was close to 1.0 for each parameter (range, 0.88–1.02) and 1.0 was contained within the 90% CI for the slope estimates at all dose levels.

The mean $AUC\%_{extrap}$, the percentage of AUC_{inf} that is due to extrapolation beyond T_{last} (Day 10), ranged from 4.6% for the 100-mg dose to 24.3% for the 10-mg dose, indicating that the exposure profile was adequately characterized for all dose levels. Plasma accumulation data of RP5063 for each dosage after 10 days of administration reflected the following: i) The mean ratio of the last vs. the first dose for C_{max} was 3.69, 3.39, 2.69, and 3.56 for the 10-, 20-, 50-, and 100-mg doses, respectively; and ii) mean ratio for AUC_{tau} was 4.43, 3.59, 3.15, and 3.58 for the 10-, 20-, 50-, and 100-mg doses, respectively.

The half-life was similar across all the dose levels studied and ranged from 55–71 h after completion of dosing. The span ratio (defined as, half-life time:overall sampling time) ranged from 1:3.5–1:4.4, which exceeds requirements for three half-lives or a ratio of 1:3.

DISCUSSION

These two studies characterize the pharmacokinetic profile of RP5063 in normal volunteers and stable patients with

Table 3 Single-dose study pharmacokinetic parameters

Pharmacokinetic parameter Unit	statistic	Cohort 1: 10 mg ($n = 6$)	Cohort 2: 15 mg ($n = 6$)	Cohort 3: (food effect) 15 mg Fed ($n = 7$)	Cohort 3: (food effect) 15 mg Fast ($n = 8$)
C_{max} (ng/mL)	Mean	27.9	36.6	37.0	34.0
	CV%	34.0	25.2	33.0	29.1
RaC_{max}	–	–	–	–	–
	–	–	–	–	–
T_{max} (hr)	Median	5.0	5.0	6.0	6.0
	Minimum	2.0	2.0	4.0	1.5
	Maximum	6.0	6.0	30.0	8.0
	–	–	–	–	–
	–	–	–	–	–
	–	–	–	–	–
AUC_{last} (hr*ng/mL)	Mean	565.4	1170.1	1848.2	1544.1
	CV%	27.0	32.7	51.3	55.7
	–	–	–	–	–
	–	–	–	–	–
	–	–	–	–	–
AUC_{inf} (hr*ng/mL)	Mean	1040.100	1447.791	2441.140	1897.794
	CV%	39.067	35.206	71.198	67.759
AUC_{tau} (hr*ng/mL)	–	–	–	–	–
	–	–	–	–	–
	–	–	–	–	–
	–	–	–	–	–
RaAUC	–	–	–	–	–
	–	–	–	–	–
Cl/F (mL/hr)	Mean	10713.1	11496.2	8886.2	11118.7
	CV%	33.4	34.2	60.9	58.0
Vz/F (mL)	Mean	649332.1	685400.9	549247.85	742628.7
	CV%	22.7	39.4	17.7	43.2
λz (1/hr)	Mean	0.02	0.02	0.02	0.01
	CV%	28.9	25.4	50.4	30.2
T½ (hr)	Mean	44.8	41.9	56.4	52.9
	CV%	28.8	24.4	52.6	36.1

AUC: area under the curve; C_{max}: maximum concentration; CV: coefficient of variation as a percentage. CL/F: Clearance; Hr: Hours; T_{max}: time of maximum concentration; T½ = half-life.; Vz/F = volume of distribution. T_{max} is summarized by median and range.

Table 4 Comparison of Japanese and Caucasian pharmacokinetic parameters from the single-dose study

	1 10 mg		2 15 mg		3 Fed 15 mg		3 Fast 15 mg		Pooled (Fast) 10 mg / 15 mg	
Cohort	**Japanese**	**Caucasian**	**Japanese**	**Caucasian**	**Japanese**	**Caucasian**	**Japanese**	**Caucasian**	**Japanese**	**Caucasian**
Dose	***N* = 1**	***N* = 5**	***N* = 2**	***N* = 4**	***N* = 1**	***N* = 6**	***N* = 2**	***N* = 6**	***N* = 4**	***N* = 10**
C_{max} (ng/mL) Mean (CV%)	43.8 (0)	24.7 (.24)	37.5 (.02)	36.1 (.33)	32.4 (0)	36.6 (.36)	36.95 (.17)	33 (.33)	38.5 (.11)	31.06 (.33)
T_{max} (hr) Mean (CV%)	6.0 (0)	4.4 (.38)	5.0(.28)	4.5 (.43)	4.0 (0)	9.7 (1.03)	3.75 (.85)	5.7 (.18)	4.7 (.42)	4.9 (.33)
λz (1/hr) Mean (CV%)	0.01 (0)	0.2 (.28)	0.02 (.50)	0.01 (.12)	0.02 (0)	0.01 (.57)	0.02 (.09)	0.01 (.36)	0.02 (.33)	0.02 (.27)
$T_{1/2}$ (hr) Mean (CV%)	58.8 (0)	42.1 (.29)	42.75 (.49)	41.6 (.12)	36.6(0)	59.7 (.52)	42.16 (.19)	55.9 (.41)	45.7 (.29)	47.5 (.34)
AUCLast (hr-ng/mL) Mean (CV%)	844.1 (0)	509.7 (.15)	1276.2 (.25)	1117.0 (.40)	1178.1 (0)	1959.9 (.50)	1203.6 (.12)	1657.5 (.57)	1160.8 (.22)	1130.8 (.71)

CV%: percent coefficient of variation.

schizophrenia. These results build on the *in vivo* preclinical experience with this compound and offer a valuable insight to drive dosing regimen design for future clinical studies.

Dose selection for the single-dose study was calculated based on the FDA's guidance document.[11] The no-observed-adverse-effect-level in the 4-week GLP toxicology study in the most sensitive species (rat) was 30 mg/kg/day and the corresponding human equivalent dose is 4.8 mg/kg/day. A safety factor of 50 was applied to yield 0.096 mg/kg/day. For a 60-kg human

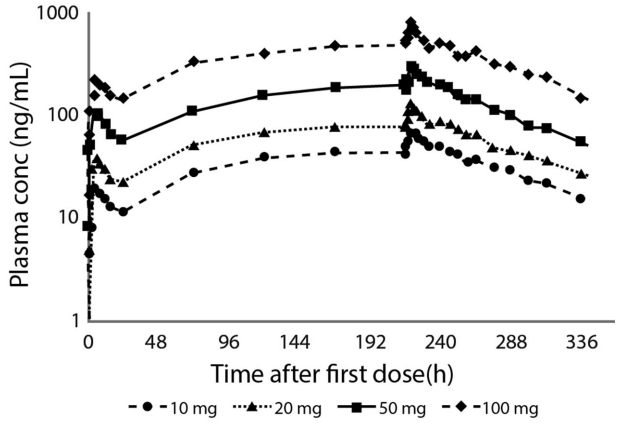

Figure 2 Mean plasma profiles of RP5063 when administered daily at increasing oral doses for 10 days to stable patients with schizophrenia

volunteer a dose of 0.096 mg/kg/day is 5.76 mg/day total or ≈10 mg/day.

Based on preclinical data, a somewhat shorter half-life was anticipated (unpublished data). The relatively short sampling time used initially for Cohorts 1 and 2 could have led to an underestimate of the half-life. Thus, the DSC reviewed and adjusted the duration of sampling for the next cohort based on data from a previously reviewed cohort, as the study progressed. This effort was undertaken to ensure that the terminal half-life and all the parameters depending on it were being adequately defined. Hence, additional samples for the 15-mg dose were made at 30, 42, 60, 72, 84, and 96 h since a preliminary pharmacokinetic analysis of the first cohort indicated a relatively long half-life. Sampling was further extended to 144 h postdose for the food-effect cohort. In examination of the AUC data from the multidose study that had sampling out to 264 h, it appeared that 144 h of collection sampling was

Table 5 Multiple-dose study pharmacokinetic parameters

Pharmacokinetic parameter unit	Day	Statistic	Cohort 1: 10 mg ($n = 6$)	Cohort 2: 20 mg ($n = 6$)	Cohort 3: 50 mg ($n = 6$)	Cohort 4: 100 mg ($n = 6$)
Cmax (ng/mL)	1	Mean	20.2	43.0	106.5	195.3
		CV%	18.87	31.2	20.70	26.7
	10	Mean	70.1	140.7	292.2	696.4
		CV%	25.41	27.5	414	43.3
RaC_{max}	10/1	Mean	3.7	3.7	2.7	3.6
		CV%	40.9	26.3	32.2	27.6
T_{max} (hr)	1	Median	6.0	6.0	6.0	6.0
		Minimum	4.0	1.5	4.0	4.0
		Maximum	12.0	8.0	16.0	12.0
	10	Median	4.0	4.0	4.0	4.0
		Minimum	1.5	4.0	4.0	1.5
		Maximum	8.0	6.0	8.0	8.0
AUC_{last} (hr*ng/mL)	1	Mean	314.5	682.5	1631.1	3537.7
		CV%	11.2	31.0	28.5	33.5
	10	N	6	6	6	5
		Mean	4576.2	7991.5	21337.7	48805.6
		CV%	50.9	43.5	57.8	58.12
AUC_{inf} (hr*ng/mL)	–	–	–	–	–	–
	–	–	–	–	–	–
AUC_{tau} (hr*ng/mL)	1	Mean	314.9	684.5	1635.3	3548.2
		CV%	11.2	31.0	28.6	33.5
	10	Mean	1360.7	2472.9	5317.9	12525.9
		CV%	34.8	35.4	44.0	44.4
RaAUC	10/1	Mean	4.431	3.587	3.146	3.584
		CV%	40.2	8.88	24.2	23.0
Cl/F (mL/hr)	–	–	–	–	–	–
	–	–	–	–	–	–
Vz/F (mL)	–	–	–	–	–	–
	–	–	–	–	–	–
λz (1/hr)	–	–	–	–	–	–
	–	–	–	–	–	–
T½ (hr)	10	Mean	68.1	55.1	70.9	58.8
		CV%	47.0	22.4	23.9	35.2

AUC: area under the curve; C_{max}: maximum concentration; CV: coefficient of variation as a percentage. CL/F: clearance; Hr: Hours; T_{max}: time of maximum concentration; T½ = half-life.; Vz/F = volume of distribution. T_{max} is summarized by median and range.

adequate, as at this point as three half-lives appeared to be reached.

The oral absorption was relatively rapid, achieving maximum plasma concentrations between 5 and 6 h when administered in the fasted state. Since RP5063 has only been administered orally to humans, it is not possible to definitively establish the absolute oral bioavailability. The oral Cl/F, which is ~10% of hepatic blood flow, is low and represents the maximum value for these subjects, since any increase in bioavailability (F) will only decrease the oral clearance further. A small increase in exposure (AUC_{inf}) was observed in Cohort 3 when food was given 30 min prior to RP5063. This observation would suggest that absorption, hence bioavailability, was not quite complete when RP5063 was administered fasted. While conclusions regarding the effect of food may be tempered by the coefficient of variation in the 50% range (related to sample size, population characteristics, sampling out to 144 h vs. 48 and 96 h in the prior cohorts, and that one participant did not participate in the fed state), it is important to recognize that the 90% CI surrounding the ratio of LSMs was well above the usual boundary of bioequivalence (80.0–125.0%). Finally, the similar C_{max} and half-life between the fed and fasted states would also be consistent with a low clearance hypothesis.

The half-life of RP5063 both in the single and multiple dose studies is relatively long, averaging ≈60 h (range, 40–71 h). The calculated accumulation index[12] based on a half-life of 60 h with a 24-h dosing interval (Equation (1)) is 4.1, which corresponds closely to that found when calculating the ratio of AUC_{tau} for the 10th dose with that of the first from the multiple dose study (≈3.7).

$$R_{acc} = \frac{1}{(1 - e^{-(0.693/t_{1/2})\tau}} \quad (1)$$

where R_{acc} is the accumulation index, and τ (tau) is the dosing interval.

The agreement between predicted and observed accumulation is likely due to the long half-life rather than a nonlinear phenomenon.

The relatively long half-life, however, is advantageous in schizophrenia, where compliance tends to be poor. It translates into a once-daily dose and can enable exposure to be maintained even if a dose or two is missed.

The pharmacokinetic profiles from the first and 10th dose of orally administered RP5063 were comparable to those found following a single dose, with a relatively rapid and good absorption achieving C_{max} values between 4 and 6 h. By the 10th day of dosing, steady state was achieved (as this time span easily surpassed three half-lives) with linear pharmacokinetics, and AUC_{tau} should be equivalent to the AUC_{inf} of a single dose. This observation was confirmed when comparing the AUC_{tau} for an equivalent situation such as for the 10th day of the 20-mg daily dose after food (2,473 ng*h/mL) with that of AUC_{inf} for the single 15-mg dose fed after normalizing for dose differences (2,817 ng*h/mL for a 20-mg equivalent dose). Demonstrates linear pharmacokinetics with respect to both dose and time.

Although the dose range evaluated in the single-dose study was comparatively narrow (10–15 mg), the pharmacokinetics did appear to be dose-dependent and dose-proportional. These findings were confirmed in the multiple dose study over a far wider dose range (10–100 mg) both for the AUC_{tau} of the first and last dose of the 10-day dosage regimen. Moreover, since RP5063 appears to be a low clearance compound (Cl/F ≈10% of hepatic blood flow), the similarity of the half-life between a single dose and after the 10th dose of a daily dosage regimen confirmed a lack of time dependency of the pharmacokinetics of RP5063.

CONCLUSIONS

These two phase I studies characterized the pharmacokinetics of a single dose (10-mg fasting, 15-mg fasting, 15-mg postmeal) in healthy volunteers and multiple doses (10-, 20-, 50-, and 100-mg doses postmeal) over 10 days in stable schizophrenia patients. Both studies demonstrated that RP5063 was rapidly and well absorbed, with a C_{max} at 4–6 h following dosing. The single-dose study found that food slightly increased the extent of RP5063 absorption and that the pharmacokinetics between Japanese and Caucasian subpopulations appeared comparable. Both studies showed that RP5063 exposure, as measured by C_{max}, $AUC_{inf,}$ or AUC_{tau}, increased in direct proportion to dose in a linear fashion. They found that the half-life, from 40–71 h, given patient variability and the small numbers, was reasonably long and similar among the healthy and stable schizophrenia populations. In the multiple-dose study, steady state was approached after 120 h of daily dosing. Finally, both studies showed that RP5063 possesses a predictable pharmacokinetic profile with daily doses up to 100 mg and would allow for once-daily dosing.

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Conflict of Interest. Laxminarayan Bhat, PhD, and Marc Cantillon, MD, are employees of Reviva Pharmaceuticals, Inc.
Robert Ings, PhD, is a DMPK consultant to Reviva Pharmaceuticals, Inc.

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