Original Article

Phase 1, Single-Center, Double-Blind, Randomized, Placebo-Controlled Studies of the Safety, Tolerability, and Pharmacokinetics of Single and Multiple Ascending Oral Doses of the Sirtuin 6 Activator SP-624 in Healthy Adults

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Abstract

Sirtuin 6 activation is a novel epigenetic mechanism proposed for treatment of depression. Two Phase 1 studies, SP-624-101 and SP-624-102, examined the pharmacokinetics and safety of SP-624, an orally active sirtuin 6 activator, in healthy adults. SP-624-101 was a single-ascending-dose study. In Part A, participants were randomized 6:2 to SP-624 (single oral doses of 3, 10, or 30 mg) or placebo. Part B compared results in 8 participants receiving SP-624 while fasting or after a high-fat, high-calorie breakfast. In SP-624-102, a multiple-ascending-dose study, participants were randomized 6:2 to SP-624 (3 or 10 mg SP-624 daily) or placebo for 5 days and 5:2 to SP-624 20 mg daily or placebo for 10 days. At all doses, maximum concentration (C_{max}) exceeded predicted target plasma concentrations of 3.28 ng/mL. Area under the concentration-time curve and C_{max} increased dose proportionally. A food effect resulted in significantly lower C_{max}, later time to maximum concentration, and comparable AUC for fed versus fasting participants. No serious adverse events were observed. In SP-624-101 and SP-624-102, respectively, 3 (12%) and 5 (29%) SP-624–treated participants experienced treatment-emergent adverse events. SP-624 was well tolerated and reached target concentrations in healthy adults, supporting progression of SP-624 20 mg daily into Phase 2 studies of major depressive disorder.

Keywords

healthy volunteers, Phase 1, SIRT6, sirtuin 6, SP-624

There is substantial unmet need associated with the treatment of people living with depression. In 2019, depressive disorders were the 4th-largest contributor to global disease burden.[1] Only one third of patients respond to initial antidepressant drug treatment, and one third of patients may not achieve remission even after 4 different treatments.[2] Moreover, estimates indicate that up to 56% of people receiving antidepressant treatment may have treatment-resistant depression, which is generally characterized by lack of response to adequate dose and treatment duration of 2 or more antidepressant medications.[3] Relapse of depressive symptoms is also common; 1 recent study found that 39% of patients continuing antidepressant treatment had relapse of depressive symptoms in a 1-year period, compared with 56% of patients who discontinued antidepressant treatments at the start of the 1-year period.[4] At present, selective serotonin reuptake inhibitors are first-line treatment of major depres-

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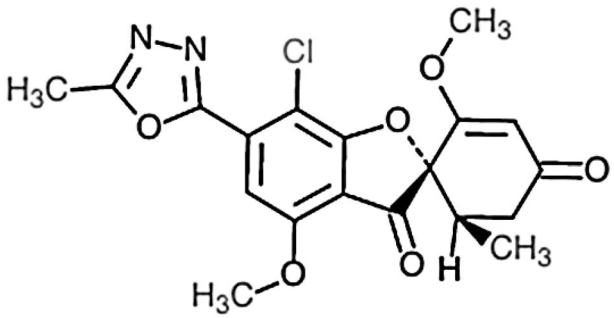

Figure 1. Structure of SP-624. Stereochemistry: (2S,6′R)-7-chloro-2′,4-dimethoxy-6′-methyl-6-(5-methyl-1,3,4-oxadiazol-2-yl)-3H- spiro[1-benzofuran-2,1′-cyclohex[2]ene]-3,4′-dione; molecular formula: C19H17ClN2O6; relative molecular mass: 404.80 Da.

sive disorder (MDD). Other mechanisms of action for older antidepressant medications are monoamine oxidase inhibition, norepinephrine reuptake inhibition, and dopamine uptake inhibition. Over the past decade, only 2 new antidepressants have been approved, esketamine and a dextromethorphan-bupropion combination, both N-methyl-D-aspartate receptor antagonists.[5]

Sirtuin 6 (SIRT6) is a nicotinamide adenine dinucleotide+ dependent histone deacetylase that acts as a chromatin regulatory protein.[6] Because of this epigenetic regulatory activity, SIRT6 has effects on gene expression in multiple physiological and pathological pathways.[7] SIRT6 plays a key role in repair of damaged DNA[8,9] and also mediates mitochondrial quality and health.[10,11] Enhanced DNA repair and maintenance of mitochondrial health may be novel mechanisms for treating MDD.[12,13]

SP-624 (Figure 1) is an orally active, selective activator of SIRT6 intended for the treatment of MDD and potentially for a broad range of indications including but not limited to other psychiatric disorders and neurodegenerative and metabolic disorders. SP-624 activates SIRT6 deacetylation of histone peptides and deacetylation of H3K9 and H3K18 in intact nucleosomes. SP-624 was active in multiple animal models used to predict efficacy for depression in humans, including tests in adrenocorticotropic hormone-treated mice and olfactory bulbectomized rats. Models of treatment-resistant depression included the forced swim test in Wistar Kyoto rats and, in an inflammation-induced model, lipopolysaccharide-induced depression. SP-624 also prevented cognitive deficits induced by scopolamine (anticholinergic) or phencyclidine (N-methyl-D-aspartate antagonist) in the novel object recognition test and suppressed excessive cytokine release in animal models (data on file, 2024).

Nonclinical absorption, distribution, metabolism, and excretion studies showed that SP-624 was well absorbed following oral administration in rats and cynomolgus monkeys and exhibited good brain penetration in rats. In vitro studies using human biomaterials indicated that SP-624 did not significantly affect human transporters (including P-glycoprotein and breast cancer resistance protein), and in vitro protein binding using human plasma indicated a range of binding of 81.9%-83.1% (data on file).

Tests using human cytochrome P450 (CYP)-expressing microsomes were used to show that SP-624 is metabolized by a variety of CYP enzymes including CYP2B6, CYP2C8, CYP2C9, CYP2C19, and CYP2D6. The variety of CYP enzymes involved suggests that no single CYP isoform provides a major pathway for clearance of SP-624. In addition, no significant inhibitory effects were identified on the marker activities of CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, or CYP3A. Finally, SP-624 had no significant induction effects on CYP3A4, CYP1A2, and CYP2B6 mRNA expression levels in fresh human hepatocytes.

We present here the results of 2 Phase 1 clinical studies of SP-624. The double-blind, placebo- controlled, first-in-human SP-624-101 study was designed to assess the safety and pharmacokinetics (PK) of single oral doses of SP-624 in healthy volunteers to guide selection of dose levels and the recommended dosing conditions (fasted or fed) for future multiple-dose studies. The double-blind, placebo-controlled SP-624-102 study was designed to assess the safety and PK of multiple oral doses of SP-624 in healthy volunteers.

Methods

Study Ethics

The SP-624-101 and SP-624-102 studies were performed in accordance with ethical principles that have their origin in the Declaration of Helsinki and are consistent with International Conference on Harmonization Good Clinical Practice and applicable regulatory requirements. Each study was conducted at a single site in the United States. The protocols were approved by Advarra Institutional Review Board for the study site. All participants in both studies provided written informed consent.

Study Designs

Both SP-624-101 and SP-624-102 were Phase 1, double-blind, randomized, placebo-controlled studies of orally administered SP-624 in healthy adults. Participants were randomized to all cohorts in both studies in a 6:2 ratio to SP-624 and placebo. End points in both studies include PK assessments and safety end points including

adverse events (AEs), laboratory tests, vital signs, body weight, and electrocardiograms.

SP-624-101 was a single-ascending-dose (SAD) study. The primary study objective was to evaluate the safety and tolerability of single oral doses of SP-624 in healthy adults. The secondary objectives of the study were to characterize the single-dose PK profile of SP-624 in the plasma of healthy adults and to evaluate the effect of food intake on the single-dose PK, safety, and tolerability of SP-624. The study was conducted in 2 parts (Figure S1). In SP-624-101 Study Part A, up to 4 sequential SAD cohorts of healthy adults were planned (Cohorts SAD-A1 to SAD-A4). The first dose evaluated was 10 mg of SP-624; subsequent doses were planned to be 30, 100, and 300 mg of SP-624, dependent on safety and PK data from the previous cohort(s).

Dose escalation in this study could be stopped for PK or safety reasons. If dose escalation was stopped, other lower doses could be considered. PK analyses were performed for each cohort after all members of the cohort completed the study; dose escalation would be stopped if more than 1 participant in the cohort had maximum concentration ($C_{max)}$ of 512 ng/mL or greater and/or area under the concentration-time curve (AUC) extrapolated to infinity (AUC_{inf}) of 1130 ng•h/mL or greater. These C_{max} and AUC_{inf} criteria were based on exposures seen at the no-observed-AEs level (NOAEL) in a study of SP-624 in adult male cynomolgus monkeys. The mean AUC_{inf} for the 30-mg group (Cohort SAD-A2) was 1447 ng•h/mL, exceeding the a priori limit of 1130 ng•h/mL (the AUC_{inf} at the NOAEL in the most sensitive species). Since the target plasma concentration of SP-624 was predicted based on results in the forced swim test in Wistar Kyoto rats (a model of treatment-resistant depression) to be active at substantially lower plasma concentrations (3.28 ng/mL), the planned dose escalation was stopped, cohort SAD-A3 received a single dose of 3 mg of SP-624 or placebo and cohort SAD-A4 was canceled.

A sentinel strategy was used for dose administration to the first 2 participants in cohorts SAD-A1 and SAD-A2 (1 active and 1 placebo). After a satisfactory review of the 24-hour safety data from these participants, the remainder of the cohort was dosed, no sooner than 48 hour after the sentinel dosing. In SP-624-101 Study Part B, a separate cohort of 8 healthy adults (Cohort SAD-B) received oral doses of SP-624 10 mg on 2 separate treatment days (Days 1 and 8), once following a 10-hour fast and once following a high-fat, high-calorie breakfast consisting of 2 eggs fried in butter, 2 slices of bacon, 4 ounces of hashbrown potatoes, 2 slices of white bread, 1 pat of butter, and 8 ounces of whole milk. Participants were randomly assigned to fed/fasted or fasted/fed sequences.

SP-624-102 was a multiple-ascending-dose (MAD) study with a primary objective to evaluate the safety and tolerability of multiple ascending oral doses of SP-624 in healthy adults and a secondary objective to characterize the multiple-dose PK profile of orally administered SP-624 in the plasma of healthy adults. Three sequential, multiple-dose cohorts of healthy adult participants were enrolled (Figure S1). Oral SP-624 doses for cohorts MAD-1 and MAD-2 were 3 mg and 10 mg, respectively, daily for 5 days. The oral SP-624 dose for cohort MAD-3 was 20 mg daily for 10 days.

Participants consumed a low-fat breakfast in the morning 2 hours before dosing. No food was allowed for 1 hour after dose administration. Two weeks elapsed between the completion of 1 cohort and initiation of the next to allow examination of safety and PK data by the safety review team.

Participants

Participants in both SP-624-101 and SP-624-102 were healthy adults aged 18-55 years with body mass index between 18.0 and 32.0 kg/m^2. Women could not be pregnant or breastfeeding and were required to be physiologically incapable of becoming pregnant. Men were required to be surgically sterile or to use a double-barrier method of contraception.

Key exclusion criteria included daily intake of caffeine more than 400 mg within 2 weeks of Day –1 or consumption or use of any of the following during the study: caffeine-containing or quinine-containing products, tobacco or nicotine-containing products, alcohol, prescription or over-the-counter medications, vitamins, or herbal remedies. Participants were required to have total cholesterol of 240 mg/dL or less and hemoglobin greater than 12.0 g/dL for women or greater than 13.5 g/dL for men. Participants could not have clinically significant cardiovascular disorders, unexplained syncope, hematological disorders, suicidal behavior or ideations within 1 year prior to screening or any lifetime history of a suicide attempt, or malignancy within the past 5 years (other than successfully treated basal cell carcinoma).

Pharmacokinetics

For the single-dose study, blood samples were collected before dosing and at 10, 20, 30, and 45 minutes and at 1, 1.5, 2, 3, 4, 6, 8, 10, 12, 24, and 48 hours after dosing. In the multiple-dose study, blood samples were obtained before dosing and 0.5, 0.75, 1, 1.25, 1.5, 2.5, 3, 4, 6, 8, 10, 12, and 24 hours after dosing on Days 1, 5, and 10 (20-mg dose only) as well as trough samples during intervening days and a postdose sample at 48 hours after the last dose. Plasma SP-624 concentrations were measured using a validated liquid chromatography-tandem mass spectrometry method over a range of 0.10-100 ng/mL

(Intertek Pharmaceutical Services). Additional details regarding the PK methods are presented in the supplemental digital content.

Noncompartmental PK analysis was conducted using WinNonlin version 7.0 (Pharsight). Plasma concentrations that were below the lower limit of quantification of 0.1 ng/mL were imputed to 0 and included as such in the calculation of the mean values. PK parameters assessed in SP-624-101 included the AUC from time 0 to the last quantifiable concentration (AUC_{last}), $AUC_{inf,}$ C_{max}, time to maximum concentration (t_{max}), terminal phase half-life, and apparent total clearance (CL/F). PK parameters assessed in SP-624-102 included $t_{max,}$ AUC from time 0 to the end of the dosing period, C_{max} at steady state, terminal phase half-life, CL/F at steady state, and the trough drug concentration at steady state.

Statistical Analyses

Continuous variables were summarized descriptively (actual value and change from baseline) by dose level and overall, tabulating sample size, mean, standard deviation, minimum, and maximum. Categorical variables were summarized by the number and percentage of participants in each category and 95% confidence intervals. No formal statistical tests were performed on the safety data. PK concentration and parameter data were summarized descriptively. Summary statistics for plasma concentrations of SP-624 included sample size; mean and standard deviation; and minimum, median, and maximum values. Dose proportionality was assessed with the power model using C_{max}, AUC_{last}, and AUC_{inf}. The effect of food on the bioavailability of SP-624 was assessed using an analysis of variance performed on the natural logarithm-transformed AUC_{last}, AUC_{inf}, and C_{max} values following a single oral dose of 10 mg SP-624 under fed versus fasting conditions. The analysis of variance model included sequence, period, and food effect as the fixed effects and participant nested within sequence as a random effect.

Results

Dosing cohorts for SP-624-101 were planned to be 10, 30, 100, and 300 mg. Cohort 1 and Cohort 2 received single oral doses of 10 and 30 mg of SP-624, respectively, as planned, and no treatment-emergent AEs (TEAEs) were observed in these 2 cohorts (Table S1). However, because the mean AUC_{inf} for the 30-mg group (Cohort SAD-A2) was 1447 ng•h/mL, which exceeded the a priori limit of 1130 ng•h/mL set in the PK stopping rule, and because plasma concentrations were well in excess of the target plasma concentration of approximately 3 ng/mL, the planned dose escalation was considered unnecessary and cohort SAD-A3 received a single 3-mg dose of SP-624.

In study SP-624-101, 32 participants were enrolled and randomized into treatment cohorts with 26 participants receiving SP-624 and 6 receiving placebo. In SP-624-102, 23 participants were enrolled. These participants were randomized to 3 treatment cohorts with 17 participants receiving SP-624 and 6 receiving placebo. All participants in both studies completed the trial (Figure S2). In both studies overall, participants were primarily male, White, and Hispanic; however, most participants in SP-624-101 Part B were women (Table S2). Across cohorts, mean age ranged from 30.3 to 43.8 years in SP-624-101 and 32.2 to 43.8 years in SP-624-102.

Pharmacokinetics in SP-624-101

In Part A, the mean half-life of SP-624 was 6.77-7.10 hours across cohorts (Table 1), and median t_{max} was 2.01-2.75 hours. The mean C_{max} was 22.0, 66.7, and 201 ng/mL, respectively, for participants who received 1 dose of 3, 10, and 30 mg of SP-624 (Table 1, Figure 2A). Half-life and CL/F were similar whether participants received 3 mg, 10 mg SP-624 while fasting or fed, or 30 mg (Table 1). In Part B, mean C_{max} was significantly lower (33%) among participants who received SP-624 after eating a high-fat, high-calorie breakfast than in participants who were fasting; however, AUC_{last} and AUC_{inf} were not significantly different (7% increase) between the fed and fasting groups (Table 1, Figure 2B). Coefficients of variation were relatively low for most PK parameters including CL/F (percent coefficient of variation ranging from 16.7% to 28.4%), indicating that SP-624 displays low intersubject variability across study participants.

Pharmacokinetics in SP-624-102

Day 1 PK parameters in SP-624-102 were similar to values from SP-624-101. Mean C_{max} was 20.4 ng/mL for the 3-mg SP-624 cohort, 69.6 ng/mL for the 10-mg SP-624 cohort, and 146.4 ng/mL for the 20-mg SP-624 cohort (Table 2, Figure 2C). After all doses were received (Day 5 or 10), mean half-life of SP-624 ranged from 6.11 to 6.89 hours across the MAD cohorts (Table 2). Median t_{max} was 1.5-3 hours. Mean C_{max} values were 20.8, 74.8, and 175.2 ng/mL, respectively, for participants in MAD-1, MAD-2, and MAD-3 cohorts. Steady state was achieved by Day 3 in all MAD cohorts. There was little or no accumulation during 5 days of dosing at 3 or 10 mg of SP-624 or 10 days of dosing at 20 mg of SP-624. In SP-624-102, coefficients of variation were also relatively low for most PK parameters, further supporting the general consistency across participants.

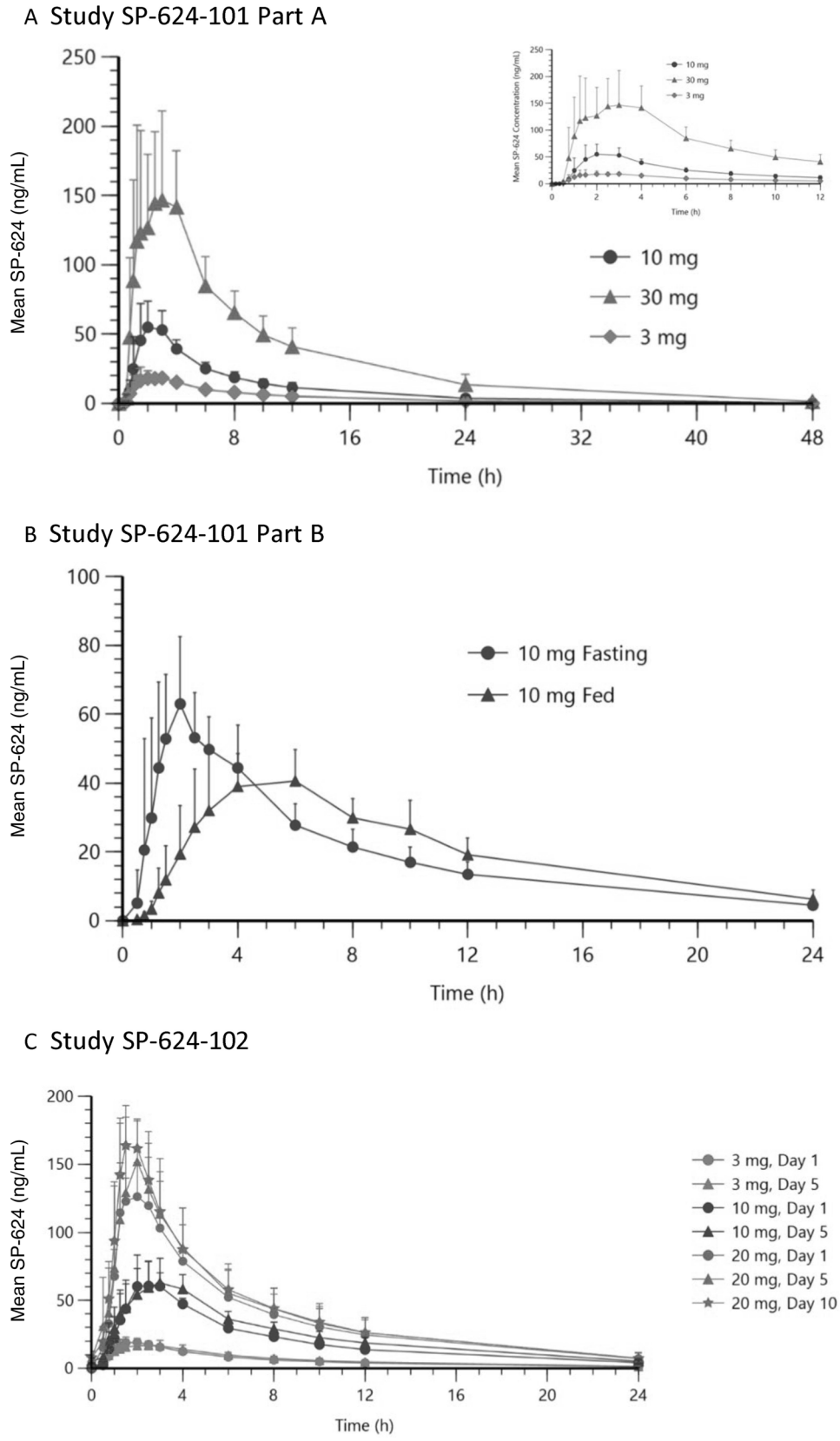

Figure 2. Mean SP-624 concentration from time of administration. Bars indicate standard deviation. (A) SP-624-101 Cohorts received single doses of 3-, 10-, and 30-mg SP-. The inset graph shows an expanded view of 1-12 hours following administration. (B) SP-624-101 Fed versus fasting participants. (C) SP-624-102 cohorts received 3 mg once daily for 5 days, 10 mg once daily for 5 days, or 20 mg once daily for 10 days. Data are shown following administration of the first and last dose in each cohort.

Table 1. Summary of PK Parameters for the SP-624-101 Single-Ascending-Dose Study

		Part A		Part B (10 mg)	
PK parameters	3 mg (n = 6)	10 mg (n = 6)	30 mg (n = 6)	Fasting (n = 8)	Fed (n = 8)
AUC_{last} (ng•h/mL)	170.2 (19.9)	427.5 (23.9)	1432 (23.0)	492.3 (19.9)	523.9 (18.1)
AUC_{inf} (ng•h/mL)	177.6 (17.4)	433.5 (24.1)	1447 (23.6)	497.5 (20.6)	532.1 (19.1)
C_{max} (ng/mL)	22.0 (19.8)	66.7 (25.2)	201 (19.7)	74.7 (30.2)	49.8 (12.6)
$t_{\frac{1}{2}}$ (hour)	7.10 (14.7)	6.77 (18.3)	6.97 (17.6)	7.08 (13.6)	7.31 (16.6)
CL/F (L/h)	17.3 (16.7)	24.0 (19.5)	21.9 (28.4)	20.8 (18.8)	19.3 (16.8)
t_{max} (hour), median (range)	2.50 (1.50-3.01)	2.01 (1.50-3.00)	2.75 (1.06-4.00)	2.00 (1.05-4.00)	5.00 (3.00-10.01)

Values are mean (% coefficient of variation) unless otherwise indicated. AUC_{last}, area under the concentration-time curve from time 0 to the time of the last quantifiable concentration; AUC_{inf}, area under the concentration-time curve from time 0 extrapolated to infinity; C_{max}, maximum observed concentration; $t_{\frac{1}{2}}$, terminal phase half-life; CL/F, apparent total plasma clearance after a single oral dose; PK, pharmacokinetic; t_{max}, time to maximum concentration.

Table 2. Summary of PK Parameters for the SP-624-102 Multiple-Ascending-Dose Study

	Day 1			Day 5		Day 10
PK parameters	3 mg once daily for 5 days (n = 6)	10 mg once daily for 5 days (n = 6)	20 mg once daily for 10 days (n = 5)	3 mg once daily for 5 days (n = 6)	10 mg once daily for 5 days (n = 6)	20 mg once daily for 10 days (n = 5)
C_{max} (ng/mL)	20.4 (16.9)	69.6 (26.7)	146.4 (21.2)	20.8 (23.6)	74.8 (11.3)	175.2 (13.6)
AUC_{tau} (ng•h/mL)	136.2 (15.9)	459.2 (10.3)	877.4 (30.2)	146.4 (16.3)	553.2 (8.5)	982.2 (28.5)
CL_{ss}/F (L/h)	NC	NC	NC	20.9 (15.8)	18.2 (8.5)	21.8 (29.4)
$t_{\frac{1}{2}}$ (hour)	NC	NC	NC	6.89 (15.9)	6.79 (12.2)	6.11 (14.2)
$C_{min,ss}$ (ng/mL)	NC	NC	NC	1.46 (38.3)	7.81 (35.6)	13.8 (46.2)
t_{max} (hour), median (range)	2.00 (1.50-2.50)	2.75 (1.51-4.00)	2.02 (1.00-2.50)	3.00 (1.00-4.00)	3.00 (2.00-4.01)	1.50 (1.25-2.50)

Values are mean (% coefficient of variation) unless otherwise indicated. AUC_{tau}, area under the concentration-time curve during the 24-hour dosing interval; CL_{ss}/F, apparent total plasma clearance at steady state; C_{max}, maximum observed concentration; $C_{min,ss}$, minimum concentration during a dosing interval at steady state; NC, not calculated (24-hour data available at Day 1 were not considered long enough to calculate a good estimate for these values); PK, pharmacokinetic; $t_{\frac{1}{2}}$, terminal phase half-life; t_{max}, time to maximum concentration.

Safety

No serious AEs were observed for any participant in either study, and no participants who received placebo experienced TEAEs in either study. In SP-624-101, 1 (17%) participant who received a single dose of 3 mg of SP-624 experienced headache and insomnia. In SP-624-101 Part B, a fed participant reported vessel puncture site pain and a fasting participant reported headache (Table S1). All TEAEs in SP-624-101 were mild and not considered related to the study drug. In SP-624-102, 2 participants (33%) who received 3 mg of SP-624 daily for 5 days experienced TEAEs: procedural dizziness and pallor in 1 participant and arthralgia in the other (Table S1). Participants who received 10 mg of SP-624 daily for 5 days reported no TEAEs. Three participants (60%) who received 20 mg of SP-624 for 10 days experienced a total of 8 TEAEs. These were defecation urgency, diarrhea, and rash macular in 1 participant; glucose intolerance, oropharyngeal discomfort, tongue blistering, and tongue discomfort in 1 participant and melanocytic nevus in 1 participant. Among these adverse events, rash macular, glucose intolerance, and arthralgia were considered unrelated to SP-624. The others were considered possibly related. No clinically meaningful changes in laboratory values were observed in either study.

Discussion

Following single oral doses of 3, 10, and 30 mg, SP-624 appeared to have a distinct absorption profile with slow absorption occurring over the first 2 hours followed by a spike to the C_{max}. At all doses, C_{max} exceeded target plasma concentrations of 3.28 ng/mL. Based on dose proportionality analysis, AUC and C_{max} values increased in relation to SP-624 oral doses following sin-

gle doses of 3, 10, and 30 mg of SP-624. AUC and C_{max} also appeared proportional during multiple daily doses of 3, 10, and 20 mg daily. Half-life and CL/F at steady state remained constant as the dose was increased. A food effect was observed in study SP-624-101 for 10 mg of SP-624, resulting in a significantly lower C_{max} and later t_{max} for participants who ate a high-fat, high-calorie meal compared with those who fasted. Although C_{max} was 31% lower for fed participants, it was still 15-fold above the target plasma concentration of 3.28 ng/mL. In addition, AUC was comparable for fed and fasted participants. These results imply a modest effect on plasma SP-624 concentrations, with minimal effects on exposure when a study participant consumes a high-fat, high-calorie meal prior to SP-624 administration. Based on this observation, participants in study SP-624-102 were allowed a low-fat breakfast 2 hours before taking SP-624. Although cross-study comparisons are problematic, mean C_{max} and median t_{max} appear comparable for the fasting participants in SP-624-101 and the participants who received a low-fat breakfast before dosing with 10 mg of SP-624 after 1 dose in SP-624-102.

SP-624 was well tolerated by study participants, and no notable safety signals were detected. In SP-624-101, 3 participants who received a single dose of SP-624 experienced 4 TEAEs; all were mild and considered not related to SP-624. Among participants who received multiple doses in study SP-624-102, 5 (29%) SP-624-treated participants experienced a total of 11 TEAEs, 8 of which were considered possibly related to SP-624. No serious AEs were observed in either study.

Limitations of studies SP-624-101 and SP-624-102, consistent with other Phase 1 studies, are the small sample size and short follow-up period. The emphasis on participant safety was a strength of these studies.

Together, the results of SP-624-101 and SP-624-102 indicate that SP-624 at single- and multiple-dose regimens was safe and well tolerated. PK parameters showed dose proportionality and reached target concentrations in healthy adults. These Phase 1 data, along with encouraging preclinical data, support the continued study of SP-624, a small molecule with a novel epigenetic mechanism of action. SP-624 20 mg daily is currently in Phase 2 studies for the treatment of MDD.

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Conflicts of Interest

All authors are consultants to Sirtsei Pharmaceuticals, a wholly owned subsidiary of Arrivo BioVentures, and all hold minority equity interests in Arrivo BioVentures.

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Supplemental Information

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