



Characterization of the Pharmacokinetics of Samidorphan in Healthy Volunteers: Absolute Bioavailability and the Effect of Food and Age

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Abstract

Background and Objectives Samidorphan (SAM) is a novel μ -opioid receptor antagonist. We report clinical pharmacokinetic (PK) properties of SAM following different routes of administration, and the effects of food and age on the PK of SAM following oral administration in healthy volunteers.

Methods An open-label, fixed-sequence study (study 1, $N=10$) examined the PK parameters following intravenous, sublingual, and oral exposure to SAM to determine absolute bioavailability. A double-blind, placebo-controlled study (study 2, $N=45$) compared the PK in participants aged 18–40 years (cohort 1, $n=30$) and ≥ 65 years (cohort 2, $n=15$) who received a single oral dose of SAM 10 mg under fed (cohort 1 only) or fasted conditions.

Results In study 1, intravenous SAM had a plasma clearance of 33.7 L/h, volume of distribution of 341 L, and elimination half-life of 7–8 h. SAM was well-absorbed following sublingual or oral administration and reached peak concentrations (C_{max}) within 2 h, with absolute bioavailability of 71% (sublingual) and 69% (oral). In study 2, concentration–time profiles were similar under fed and fasted conditions (cohort 1) and for young and elderly participants from both cohorts; 90% confidence intervals for the geometric least squares mean ratios for C_{max} and area under the concentration–time curve from time zero extrapolated to infinity indicated equivalence.

Conclusions SAM has high bioavailability that is comparable following sublingual and oral administration and is not subject to extensive first-pass metabolism. The PK of orally administered SAM are not affected by food or age.

Key Points

When taken sublingually or orally, samidorphan (SAM) has high bioavailability.

When taken orally, the pharmacokinetics of SAM are not affected by food or age.

1 Introduction

Samidorphan (3-carboxamido-4-hydroxynaltrexone; ALKS 33; SAM), a naltrexone derivative, is a new chemical entity that binds with high specificity and selectivity to μ -, δ -, and κ -opioid receptors [1–4]. SAM acts primarily as a potent μ -opioid receptor antagonist, blocking the miotic and ‘drug-like’ effects of the μ -opioid receptor agonists buprenorphine and remifentanyl following sublingual and oral administration, respectively [5–7]. Oral administration of SAM has been associated with rapid and sustained blockade of opioid agonist challenge, with physiological and subjective effects blocked within 15 min of dosing and persisting for up to 48 h postdose [7]. The use of SAM monotherapy in binge-eating and alcohol dependence disorders has also been investigated [8, 9]. SAM is currently under clinical development as part of two combination therapies: with buprenorphine (buprenorphine/SAM; ALKS 5461) as a sublingual therapy for major depressive disorder [5, 6] and with olanzapine (olanzapine/SAM; ALKS 3831) as an oral therapy for schizophrenia [10, 11].

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The pharmacokinetic (PK) profile of SAM after oral administration was characterized in a first-in-human study [1]. SAM was rapidly absorbed, with a time to maximum concentration (t_{\max}) of 1 h and an increasing area under the curve (AUC) with increasing dose. The half-life of SAM after oral administration was approximately 7–9 h. With repeated daily oral dosing, steady state was approached after 5–7 days, with low accumulation (accumulation ratios < 1.65) [1]. SAM was well tolerated after single oral doses of up to 55.7 mg and multiple daily doses of up to 20 mg/day, and exhibited a PK profile suitable for a once-daily dosing regimen [1]. An N-dealkylation primary metabolite of SAM, RDC-9986, was identified in liver microsomes from all species (mouse, rat, dog, and human) and in *in vivo* PK studies in animals [12].

SAM demonstrates increased exposure following oral and sublingual administration compared with other orally available opioid antagonists, including naloxone and naltrexone (both with oral bioavailability $\leq 5\%$), and exhibits potent and sustained blockade of opioid agonism, which may result in antagonist activity at lower doses relative to naltrexone [1, 5, 13, 14]. However, there is currently no published information on the bioavailability of SAM. Given its sublingual/oral administrative route, determination of absolute bioavailability, i.e. the rate and extent to which a drug reaches the systemic circulation, is of particular importance. Low absolute bioavailability increases the interindividual variability of exposure to a drug, and can indicate poor performance of the formulation and/or poor absorption, as well as extensive first-pass metabolism [15, 16].

Co-administration with food can result in drug–food interactions, which may impact bioavailability by altering the rate and extent of drug absorption in the gastrointestinal tract [17, 18]. Given that all PK evaluations of SAM to date have been conducted in the fasted state, it is important to determine whether a food effect is of potential clinical relevance to SAM. Furthermore, age and gender are also factors recognized to influence bioavailability, and thus an investigation into the impact of age and gender on drug exposure will help inform decisions on the appropriateness of SAM in a wide range of patients [1, 19, 20].

We describe two phase I PK studies of SAM in healthy volunteers. The first study (ALK33-B107; ClinicalTrials.gov identifier: NCT02504463) compared the PK of SAM following single sublingual, oral, and intravenous doses in fasted male adults. The 2 mg dose of SAM selected for sublingual and oral use in this trial is the dose of SAM in the sublingual co-formulation with buprenorphine for major depressive disorder. The second study (ALK33-009) investigated safety, tolerability, and the effects of food, gender, and age on the PK of a single oral dose of SAM. The 10 mg dose of SAM selected in this second trial is the dose of SAM in the oral co-formulation with olanzapine for schizophrenia.

2 Methods

2.1 Materials

SAM preparations were manufactured by Alkermes, Inc. for both studies (study 1: Irix Manufacturing, Inc., Greenville, SC, USA; study 2: Cambridge Major Laboratories, Inc., Germantown, WI, USA). In study 1, the intravenous dose was 1 mg SAM in 5 mL saline without [^{14}C] label, administered as a slow bolus injection over approximately 1 min (at a rate of approximately 0.07 mL/min/kg for an average participant weighing 70 kg). The sublingual dose was 2 mg SAM combined with approximately 50 μCi [^{14}C]-labeled SAM pipetted onto a sublingual placebo, and the oral dose was 2 mg SAM combined with approximately 50 μCi [^{14}C]-labeled SAM in a 10 mL solution. In study 2, SAM was administered as a 10 mg oral capsule and placebo treatment was a matched lactose-containing capsule.

2.2 Study Design and Conduct

Study 1 was a single-center, open-label, fixed-sequence design trial conducted between 25 June and 12 September 2015. Following an initial screening visit (visit 1), healthy male volunteers were admitted to a research unit for a series of three single doses of SAM that were administered during consecutive visits as follows: visit 2, intravenous (1 mg for slow bolus injection over approximately 1 min); visit 3, sublingual (2 mg); and visit 4, oral (2 mg). All doses were administered following an overnight fast of ≥ 10 h, with fasting continuing for ≥ 4 h postdose. The sublingual and oral doses of SAM were labeled with [^{14}C]-SAM (see Sect. 2.1). Each dose period (visits 2, 3, and 4) included at least 8, 14, and 14 days for intravenous, sublingual, and oral administration, respectively. A final follow-up visit (visit 5) occurred approximately 2 weeks after the third dose visit (visit 4).

Plasma samples were collected to determine the PK profiles of SAM and its metabolite (RDC-9986) by liquid chromatography-tandem mass spectrometry (LC-MS/MS) at predose (0 h), immediately following administration (intravenous dose only), and at 0.25, 0.5, 1, 2, 4, 8, 12, 24, 36, and 48 h postdose, with the collection period extending to 72, 96, and 120 h postdose for the sublingual and oral doses, primarily for the measurement of total radioactivity in blood samples. Urine samples for LC-MS/MS analysis were collected up to 312 h postdose during the sublingual and oral dose periods. Urine was not collected during the intravenous dose period.

Data collected for measurement of radioactivity by liquid scintillation [not qualified for Good Laboratory

Practice (GLP)] and determination of the PK of [^{14}C]-SAM (whole blood, plasma, urine, and feces during the sublingual and oral dose periods), as well as collection of additional blood samples for plasma metabolite profiling and identification, are outside the scope of this article and will be described in a separate report.

Study 2 was a single-center, randomized, double-blind, placebo-controlled, crossover trial in young (aged 18–40 years; cohort 1) and elderly (aged ≥ 65 years; cohort 2) healthy adults, with each cohort stratified equally by gender. The study was conducted between 19 July and 23 November 2010.

Following screening procedures, participants were admitted to a research unit the day before dosing. Participants in cohort 1 were randomized 1:1 to ‘fed then fasted’ or ‘fasted then fed’ food sequences to be carried out in two dosing periods, separated by a washout period of at least 7 days. Cohort 2 consisted of one dosing period in the fasted state. For both sequences of cohort 1 and for cohort 2, randomization to oral SAM (10 mg) or placebo treatment in a 4:1 fashion occurred on the day of dosing. Study treatment was administered following an overnight fast of ≥ 10 h (fasted state) or 30 min following a high-calorie, high-fat breakfast (fed state; cohort 1 only). All participants fasted for 4 h post-dose. Blood plasma samples were collected predose (0 h) and 0.25, 0.5, 1, 2, 4, 8, 12, 24, and 36 h postdose. All participants returned for a follow-up visit approximately 7 days after their last dosing visit.

2.3 Study Populations

In study 1, male participants were aged 18–55 years, with a body mass index (BMI) ≥ 19 and ≤ 32 kg/m², and a minimum weight of 50 kg at screening. Participants were considered to be in good health on the basis of their medical history, physical examination, clinical laboratory tests, vital signs, and electrocardiogram (ECG). Participants who had participated in a clinical study with a [^{14}C]-labeled drug or with cumulative radiation exposure > 5 mSv within the past 12 months, or > 10 mSv within the past 5 years, were excluded. The target sample size was 10 (with the goal of eight participants completing the study) and was intended to provide reasonable point estimates for mean PK parameters.

In study 2, male and female adults were aged 18–40 and ≥ 65 years, with a BMI ≥ 19 and ≤ 30 kg/m², and were in good health at screening. Women of reproductive potential were required to use an approved method of contraception for the study duration. A target sample size of 30 young and 15 elderly participants was considered sufficient to provide an adequate number of participants completing the study (22 young and 11 elderly) with PK data for evaluation within prespecified equivalent exposure limits. For each portion of the study, the targeted number of evaluable subjects would

provide 80% probability that the 90% confidence interval (CI) for each parameter of interest would fall within the prespecified equivalency limits, provided that the true geometric mean ratio was 1.00.

In both studies, current or historical drug dependence [as assessed in *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision* (DSM-IV-TR) criteria] or a positive urine toxicology screen for cocaine, amphetamines, opioids, or benzodiazepines precluded study participation.¹

2.4 Assessments of Safety and Tolerability

The safety population included all participants who received at least one dose of study drug. Safety monitoring during both studies included the assessment of adverse events, standard clinical laboratory tests, vital signs, ECG results, and physical examination findings.

2.5 Bioanalysis

Plasma samples were assayed for SAM and its metabolite, RDC-9986, by LC–MS/MS according to validated GLP methodology as described previously for SAM [1]. The assay had a linear range of 0.250–100 ng/mL, with a lower limit of quantitation of 0.250 ng/mL.

2.6 Pharmacokinetic (PK) Analysis

The PK population for each study included participants in the safety population who had at least one plasma sample with a quantifiable concentration of SAM or RDC-9986. Standard PK parameters for SAM and RDC-9986 were calculated from individual concentration–time data by non-compartmental analysis using Phoenix[®] WinNonlin[®] software (version 6.1 or 6.2; Certara USA, Inc., Princeton, NJ, USA). The maximum plasma concentration (C_{max}) and t_{max} were obtained directly from concentration data. The AUC from time zero to the time of the last quantifiable concentration (AUC_{last}) was calculated by the mixed linear/logarithmic trapezoidal rule.

The AUC from time zero to infinity (AUC_{∞}) was calculated as $\text{AUC}_{\text{last}} + (C_{\text{last}}/\lambda_z)$, where C_{last} was the last measurable plasma concentration, and λ_z was the terminal elimination rate constant estimated by log-linear regression analysis of the measured concentrations on the terminal phase of the concentration–time curve. The extrapolated fraction of an individual AUC value had to be below 30% to be evaluable, which is standard practice in our laboratory for single- and

¹ In study 1, urine toxicology screen also included marijuana and barbiturates.

Table 1 Demographics and baseline characteristics (study 1 and study 2)

Characteristic	Study 1	Study 2		
	All participants [<i>N</i> = 10]	Cohort 1 SAM [<i>n</i> = 24]	Cohort 2 SAM [<i>n</i> = 12]	Pooled placebo ^a [<i>n</i> = 9]
Age, years				
Mean (SD)	36.5 (9.8)	26.6 (6.4)	71.2 (4.5)	41.4 (22.0)
Minimum, maximum	24, 54	18, 39	66, 80	19, 74
Race [<i>n</i> (%)]				
White	6 (60.0)	18 (75.0)	12 (100.0)	9 (100.0)
Black or African American	3 (30.0)	5 (20.8)	0	0
American Indian or Alaska native	1 (10.0)	0	0	0
Asian	0	1 (4.2)	0	0
Gender [<i>n</i> (%)]				
Male	10 (100.0)	12 (50.0)	6 (50.0)	5 (55.6)
Female	0	12 (50.0)	6 (50.0)	4 (44.4)
Weight (kg)				
Mean (SD)	83.53 (10.5)	71.1 (9.6)	75.8 (11.6)	74.9 (10.4)
Minimum, maximum	63.6, 100.6	49.5, 93.0	61.4, 99.1	53.2, 89.1
BMI (kg/m ²)				
Mean (SD)	27.1 (2.1)	25.2 (2.5)	26.4 (1.7)	25.6 (3.5)
Minimum, maximum	23.8, 30.3	19.8, 29.4	24.0, 28.7	20.1, 30.1

BMI body mass index, SAM samidorphan, SD standard deviation

^aPooled from cohorts 1 and 2

repeated-dose PK studies. The apparent terminal elimination half-life ($t_{1/2}$) was calculated as $\ln 2/\lambda_z$, and absolute bioavailability (F) was calculated as $(AUC_{\infty SL}/Dose_{SL})/(AUC_{\infty IV}/Dose_{IV})$ for the sublingual dose and $(AUC_{\infty PO}/Dose_{PO})/(AUC_{\infty IV}/Dose_{IV})$ for the oral dose of SAM. Apparent plasma clearance (CL/F) was calculated as $dose/AUC_{\infty}$. Renal clearance (CL_r) was determined from urine samples (study 1 only) following oral and sublingual administration and was calculated as $X_{last,urine}/AUC_{last}$, where $X_{last,urine}$ was the total amount of drug excreted in urine from time zero to the time of C_{last} . The metabolite to parent AUC ratio (R_{AUC}) was calculated as $RDC-9986 AUC_{\infty}/SAM AUC_{\infty}$ and was adjusted for molecular weight [370.44 and 316.35 (free base) for SAM and RDC-9986, respectively].

2.7 Statistical Analysis

All data were evaluated by descriptive statistics. In study 2, food and age effects were examined using a linear mixed model on log-transformed PK values. Covariates were not applicable. Two-sided 90% CIs for the geometric least squares mean (GLSM) ratios of C_{max} and AUC of SAM for the fed/fasted states within the limits of 0.80–1.25 were taken to indicate the absence of a significant food effect, and CIs for elderly/young participants within the limits of 0.70–1.43 were taken to indicate the absence of a significant age effect. We determined that a less strict standard would

be more appropriate for the age comparison because of the greater variability of the data, and because the age-effect study could only be conducted using a parallel comparison design, whereas the food-effect study used a crossover design. No criteria were used for evaluation of the gender effect; the GLSM ratios and CIs of C_{max} and AUC of SAM for male to female were reported.

3 Results

3.1 Study Population Characteristics

In study 1, a total of 10 participants were enrolled and included in the PK and safety populations. Nine participants completed the study and one participant withdrew consent.

In study 2, a total of 45 participants were enrolled, with 15 in each treatment sequence of cohort 1 and 15 in cohort 2. Within each group of 15, 12 were randomized to receive SAM and three were randomized to placebo; all were included in the safety population, with the three participants randomized to placebo in both treatment sequences of cohort 1 and in cohort 2 pooled (i.e. pooled placebo, $n = 9$). Only those participants randomized to SAM were included in the PK population. Overall, 39 participants completed the study and six discontinued: four participants withdrew consent, one was lost to follow-up, and one had a protocol violation.

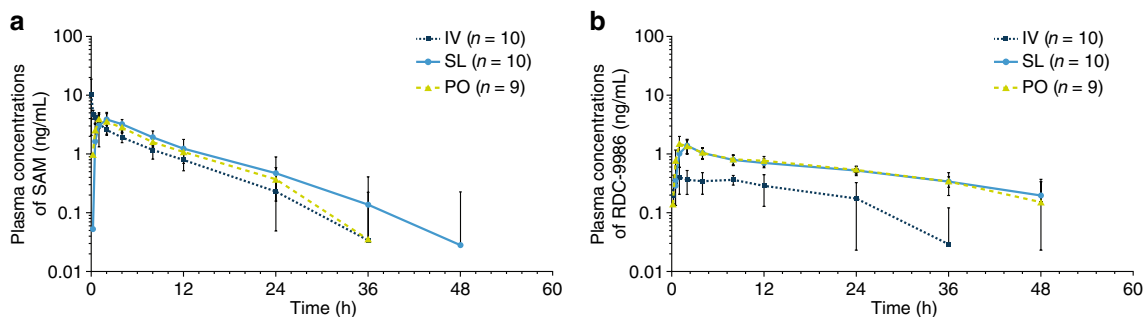


Fig. 1 Mean plasma concentrations of **a** SAM and **b** RDC-9986 over time following single IV administration of SAM 1 mg, and SL and PO administrations of SAM 2 mg (semi-logarithmic scale). Error bars represent standard deviations of the mean (semi-logarithmic scale). Note: For PL and SL administration, values at 72, 96, and 120 h were

all below the LLOQ. In these graphs, mean values could be below the LLOQ because measurements below the LLOQ occurring before the first measurable value and after the last measurable value were included and assigned a value of 0. SAM samidorphan, IV intravenous, LLOQ lower limit of quantification, PO oral, SL sublingual

Demographics and baseline characteristics for both studies are summarized in Table 1.

3.2 PK of Samidorphan (SAM) Following Sublingual, Oral, and Intravenous Administration (Study 1)

Mean plasma concentrations of SAM and RDC-9986 after a single intravenous, sublingual, or oral dose are shown in Fig. 1. Mean plasma and urine PK parameters, which were determined using non-compartmental methods, are listed in Table 2.

The PK profiles for both SAM and RDC-9986 were comparable after oral and sublingual administration. Mean plasma concentrations of SAM and RDC-9986 reached maximum levels within 2 h of a single 2 mg sublingual administration and within 1 h of a single 2 mg oral administration (Fig. 1). Subsequently, plasma concentrations decreased mono-exponentially for SAM (Fig. 1a) and bi-exponentially for RDC-9986 (Fig. 1b), with a rapid distribution phase and a slow elimination phase.

Following a single intravenous bolus injection of SAM (1 mg), mean plasma concentrations of SAM declined in a manner similar to that seen with the oral and sublingual routes of administration. Maximum plasma levels of RDC-9986 were reached within a median of 2.5 h after intravenous administration of SAM (Table 2), and declined slowly thereafter, although a terminal elimination phase could not be clearly defined.

Mean values for key PK parameters, including t_{\max} , C_{\max} , apparent plasma clearances, and $t_{1/2}$, were similar following oral and sublingual administration. The elimination half-life of SAM by the intravenous route was similar to the sublingual and oral elimination half-lives, with a mean value ranging from 7 to 9 h. The elimination half-lives for RDC-9986 were longer than that of SAM; the mean value was 26 h by the sublingual route and 23 h by the oral route. Mean R_{AUC}

values for RDC-9986/SAM were 0.314, 0.818, and 0.981 following intravenous, sublingual, and oral administration of SAM, respectively.

SAM was well-absorbed, with 20.4% (sublingual) and 18.8% (oral) excreted unchanged in urine following administration (Table 2). Average CL_r for SAM and RDC-9986 was approximately 11 L/h (183 mL/min) and 18 L/h (300 mL/min), which approximates or exceeds normal glomerular filtration rate. For both SAM and RDC-9986, mean CL_r was similar following sublingual and oral exposure (Table 2).

3.3 Absolute Bioavailability of SAM Following Sublingual and Oral Administration (Study 1)

Mean AUC values were similar following sublingual and oral administration of 2 mg SAM (Table 2), and hence the average absolute bioavailability for the sublingual route of administration (mean 71.2%; range 62.9–80.3%; $n = 10$) was similar to that observed for the oral route of administration (mean 68.6%; range 60.3–82.6%; $n = 9$).

3.4 Effect of Food, Age, and Gender on SAM PK (Study 2)

Mean PK profiles for SAM and RDC-9986 following a 10 mg oral dose of SAM, according to food, age, and gender, are shown in Fig. 2, and the PK parameter estimates are shown in Tables 3 and 4.

Concentration–time profiles following oral administration of SAM (10 mg) in cohort 1 were similar under fed and fasted conditions (Fig. 2a). One female participant vomited within 3 h of administration of SAM during the fed regimen and was excluded from the overall analysis. SAM was rapidly absorbed, with median t_{\max} reached at 2 h in the fasted state and 4 h in the fed state (Table 3). Despite a slight delay in t_{\max} under the fed state, the systemic exposure and

Table 2 Mean (CV%) plasma and urine PK parameters of SAM and RDC-9986 (study 1 PK population)

PK parameter	Intravenous [n=10]		Sublingual [n=10]		Oral [n=9]	
	SAM	RDC-9986	SAM	RDC-9986	SAM	RDC-9986
Plasma						
AUC _{last} [h-ng/mL]	27.7 (35.3)	6.7 (52.8)	41.3 (34.5)	25.5 (25.2)	35.1 (17.3)	26.3 (20.1)
AUC _∞ [h-ng/mL]	32.0 (31.2)	ND	45.4 (32.1)	36.3 (12.8) ^a	39.9 (16.8)	33.1 (10.8) ^b
C _{max} [ng/mL]	11.2 (66.0)	0.448 (30.5)	4.06 (19.5)	1.41 (28.0)	4.07 (28.7)	1.52 (30.8)
t _{max} [h] ^c	0.0167 (0.02, 0.25)	2.50 (0.50, 12.08)	2.00 (0.50, 4.00)	2.00 (1.00, 2.07)	1.08 (1.00, 2.00)	1.03 (1.00, 2.00)
t _{1/2} [h] ^d	7.45 (28.6)	ND	8.49 (31.4)	26.0 (22.8)	7.92 (23.7)	23.2 (25.9)
CL _r [L/h] ^e	33.7 (29.1)	ND	47.5 (27.1)	NA	51.5 (17.5)	NA
V [L] ^f	341 (17.9)	NA	543 (17.7)	NA	570 (13.6)	NA
F [%]	NA	NA	71.2 (9.1)	NA	68.6 (11.9)	NA
R _{AUC}	NA	0.314 (50.8)	NA	0.818 (34.6)	NA	0.981 (24.2)
Urine						
X _{last,urine} [mg]	NA	NA	0.409 (19.6)	0.422 (13.8)	0.377 (27.4)	0.380 (14.2)
Fe% _{last,urine} [%]	NA	NA	20.4 (19.6)	NA	18.8 (27.4)	NA
CL _r [L/h]	NA	NA	10.6 (32.2)	17.7 (32.3)	11.0 (29.6)	15.2 (30.1)

AUC_{last} area under concentration–time curve from time zero to the time of the last quantifiable concentration, AUC_∞ AUC from time zero extrapolated to infinity, CL clearance, CL/F apparent plasma clearance, C_{max} maximum observed concentration, CL_r renal clearance, CV% percentage coefficient of variation, F absolute bioavailability, Fe%_{last,urine} fraction of radioactivity excreted in urine from time zero to the time of the last quantifiable concentration, NA not available, ND not done, PK pharmacokinetic, R_{AUC} metabolite/parent ratio based on AUC corrected for molecular weight, t_{1/2} apparent terminal half-life, SAM samidorphan, t_{max} time to maximum observed concentration, V volume of distribution, V/F apparent volume of distribution, X_{last,urine} total amount of radioactivity excreted in urine from time zero to the time of the last quantifiable concentration

^an=3

^bn=5

^cMedian (minimum, maximum) values are presented for t_{max}

^dt_{1/2} for RDC-9986 following intravenous injection was not calculated because the terminal elimination phase could not be characterized

^eCL/F [L/h] presented for the sublingual and oral treatment groups

^fV/F [L] presented for the sublingual and oral treatment groups

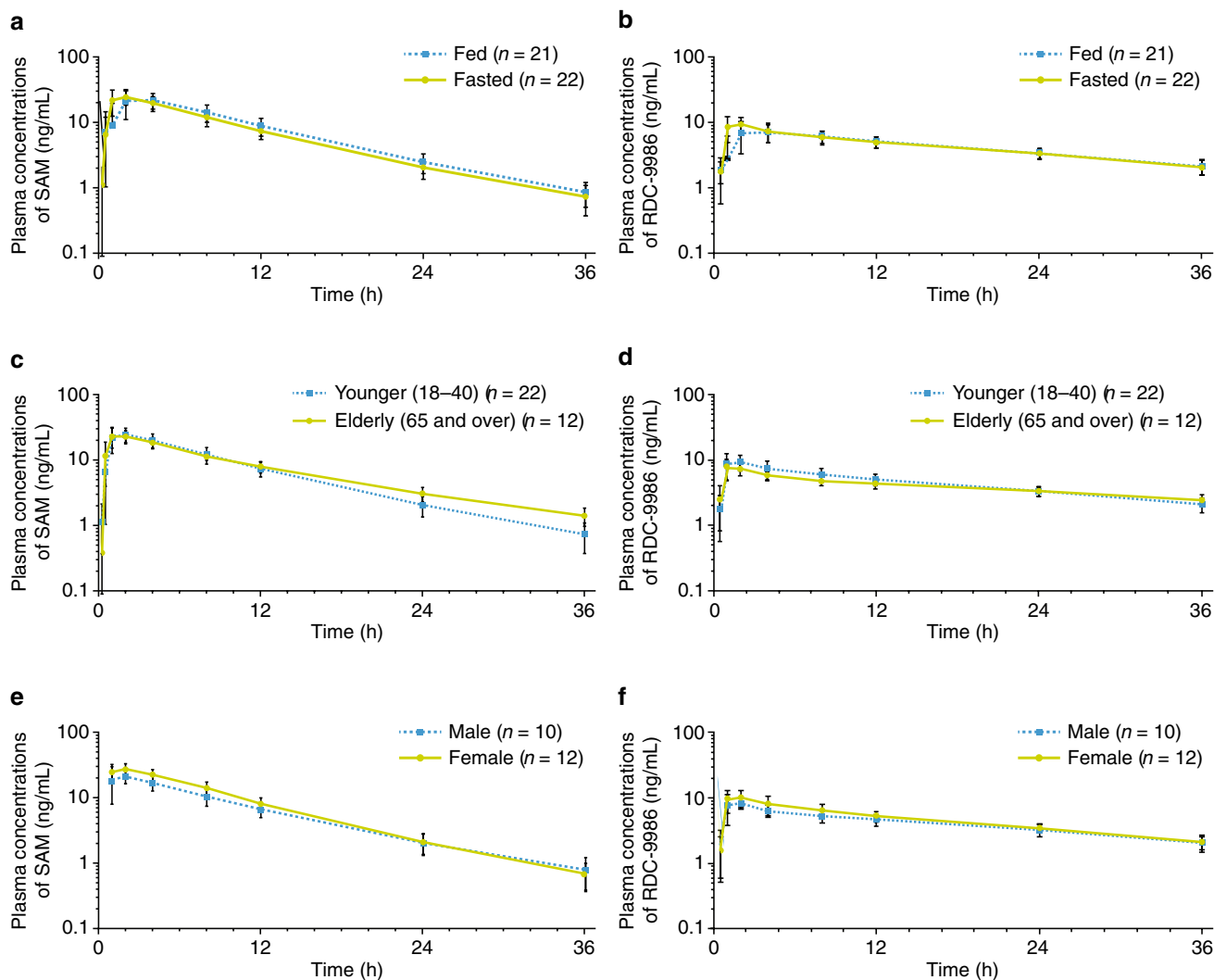


Fig. 2 Mean plasma concentration time course of SAM and RDC-9986 following single oral administration of SAM 10 mg. Effect of food on **a** SAM and **b** RDC-9986; effect of age under fasting conditions on **c** SAM and **d** RDC-9986; and effect of gender under fasting conditions on **e** SAM and **f** RDC-9986. Error bars represent standard deviations of the mean (semi-logarithmic scale). SAM samidorphan

elimination $t_{1/2}$ remained similar. In each food state, SAM concentrations decreased linearly when plotted using log-transformed concentration data, with measurable concentrations present through 36 h postdose. The 90% CIs for the GLSM ratios of C_{\max} and AUC_{∞} for the fed/fasted states fell within the prespecified 0.80–1.25 window of equivalence (Table 5), thereby excluding a significant effect of food on the PK of SAM.

When the young participants in cohort 1 and elderly participants in cohort 2 were compared in the fasted state, the 90% CIs for the GLSM ratios of C_{\max} , AUC_{last} , and AUC_{∞} fell within the prespecified interval of 0.70–1.43 (Table 5), indicating the absence of a significant effect of age on the systemic exposure of SAM. Based on a direct comparison of the median values for t_{\max} , no notable difference by age group was evident (Table 3). As shown in Fig. 2c, the

terminal elimination phase was longer in the elderly participants, resulting in a slightly increased half-life and reduced CL/F compared with the young participants.

Cohort 1 had 10 males and 12 females and cohort 2 had 6 males and 6 females who were dosed under fasted conditions. For young and elderly adults from both cohorts, systemic exposure appeared to be slightly higher in females than in males (Table 3). Within the pooled data across cohorts 1 and 2, the GLSM ratios for systemic exposure of SAM (C_{\max} , AUC_{last} , and AUC_{∞}) were approximately 1.2-fold higher in female participants than male participants (Table 5).

Mean PK profiles for RDC-9986 following a 10 mg oral dose of SAM were similar with respect to food, age, and gender (Fig. 2b, d, and f). A descriptive comparison of mean systemic exposures to RDC-9986 showed no apparent

Table 3 Descriptive statistics for plasma PK parameters of SAM according to food, age, and gender

PK parameter ^a	Cohort 1: Young		Cohort 2: Elderly	Cohort 1: Female	Cohort 1: Male	Cohort 2: Female	Cohort 2: Male
	Fed [n = 20]	Fasted [n = 22]	Fasted [n = 12]	Fasted [n = 12]	Fasted [n = 10]	Fasted [n = 6]	Fasted [n = 6]
C_{max} [ng/mL]	25.26 (8.16)	26.24 (6.83)	25.28 (6.16)	28.83 (5.19)	23.13 (7.50)	26.88 (6.33)	23.68 (6.11)
t_{max} [h; median (range)]	4.00 (1.0–4.02)	2.00 (1.00–4.00)	1.00 (1.00–2.00)	2.00 (1.00–4.00)	2.00 (1.00–4.00)	2.00 (1.00–2.00)	1.00 (1.00–2.00)
AUC_{last} [h·ng/mL]	266.64 (66.46)	244.94 (61.87)	262.80 (41.06)	265.06 (64.75)	220.79 (51.18)	280.66 (37.22)	244.93 (39.46)
AUC_{∞} [h·ng/mL]	275.41 (69.16)	258.88 (58.18)	282.47 (45.53)	285.40 (47.94)	229.71 (56.24)	299.00 (44.44)	265.95 (43.94)
$t_{1/2}$ [h]	6.95 (0.75)	6.95 (1.01)	9.50 (1.51)	6.47 (0.69)	7.47 (1.08)	8.96 (1.56)	10.05 (1.37)
Vz/F [L]	386.56 (106.22)	407.95 (115.77)	495.58 (110.28)	336.59 (75.42)	486.45 (101.93)	433.56 (54.77)	557.60 (120.51)
CL/F [L/h]	38.78 (10.68)	40.91 (10.97)	36.31 (6.23)	36.22 (7.95)	46.07 (11.87)	34.10 (5.36)	38.52 (6.72)

AUC_{last} area under concentration–time curve from time zero to the time of the last quantifiable concentration, AUC_{∞} AUC from time zero extrapolated to infinity, CL/F apparent plasma clearance, C_{max} maximum observed concentration, PK pharmacokinetic, SAM samidorphan, $t_{1/2}$ apparent terminal half-life, t_{max} time to maximum observed concentration, Vz/F apparent volume of distribution

^aAll values are presented as mean (standard deviation) except where noted

Table 4 Descriptive statistics for plasma PK parameters of RCD-9986 according to food, age, and gender

PK parameter ^a	Cohort 1: Young		Cohort 2: Elderly	Cohort 1: Female	Cohort 1: Male	Cohort 2: Female	Cohort 2: Male
	Fed [n = 20]	Fasted [n = 22]	Fasted [n = 12]	Fasted [n = 12]	Fasted [n = 10]	Fasted [n = 6]	Fasted [n = 6]
C_{max} [ng/mL]	8.14 (2.71)	10.19 (2.76)	8.32 (2.17)	11.02 (2.99)	9.19 (2.21)	8.52 (1.72)	8.13 (2.70)
t_{max} [h; median (range)]	4.00 (1.00–12.03)	2.00 (1.00–4.00)	1.00 (1.00–2.00)	1.50 (1.00–2.00)	2.00 (1.00–4.00)	1.50 (1.00–2.00)	1.00 (1.00–2.00)
AUC_{last} [h·ng/mL]	151.69 (29.58)	154.42 (37.11)	143.40 (21.76)	160.32 (45.45)	147.33 (24.21)	150.96 (9.48)	135.83 (28.55)
AUC_{∞} ^b [h·ng/mL]	207.34 (37.92)	211.77 (44.93)	200.02 (NA)	225.79 (49.98)	195.74 (35.13)	200.02 (NA)	NA (n = 0)
$t_{1/2}$ [h]	16.90 (1.90)	17.42 (2.31)	17.75 (NA)	16.50 (2.38)	18.48 (1.83)	17.75 (NA)	NA (n = 0)

AUC_{last} area under concentration–time curve from time zero to the time of the last quantifiable concentration, AUC_{∞} AUC from time zero extrapolated to infinity, $\%AUC_{ex}$ percentage of AUC_{∞} due to extrapolation from the time of the last measurable concentration, C_{max} maximum observed concentration, PK pharmacokinetic, Rsq goodness-of-fit statistic for the terminal elimination phase, $t_{1/2}$ apparent terminal half-life, t_{max} time to maximum observed concentration

^aAll values are presented as mean (standard deviation) except where noted

^bA minimum of three data points were used for each terminal phase determination. If the Rsq value was <0.80 or the $\%AUC_{ex}$ was >30, AUC_{∞} was set to missing

differences with respect to the effect of food, age, and gender (Table 4).

3.5 Safety

SAM was generally well tolerated across both studies, and no deaths, serious adverse events, or adverse events leading to treatment discontinuation were reported (Table 6). Adverse events were generally gastrointestinal or neurological in nature and predominantly mild or moderate in intensity (Table 6). The adverse events reported in two or more participants of study 1 included infrequent bowel

movements, nausea, abdominal pain, and headache. In study 2, adverse events in three or more participants receiving SAM in either cohort 1 or cohort 2 were nausea, dizziness, somnolence, headache, vomiting, and hot flush (Table 6). No adverse events were reported in two or more participants of the pooled placebo group ($N = 9$). The incidence and pattern of adverse events in participants receiving SAM did not appear to be influenced by food, age, or gender. Mean changes from baseline in laboratory parameters (hematology, chemistry, and urinalysis), vital signs, and 12-lead ECG parameters were not clinically meaningful between treatment groups in either study.

Table 5 Evaluation of food, age, and gender on the PK parameters of SAM following single oral administration of SAM 10 mg (study 2 PK population)

PK parameter	Geometric least squares mean		Geometric least squares mean ratio (90% CI)
Food^a	Fed: Cohort 1 [n = 20]	Fasted: Cohort 1 [n = 22]	Fed/fasted
C_{max} [ng/mL]	24.25	25.32	0.96 (0.83–1.11)
AUC_{last} [h·ng/mL]	251.13	234.61	1.07 (1.02–1.12)
AUC_{∞} [h·ng/mL] ^b	266.94	249.74 ^c	1.07 (1.02–1.12)
Age^d	Elderly: Cohort 2 [n = 12]	Young: Cohort 1 [n = 22]	Elderly/Young
C_{max} [ng/mL]	24.60	25.35	0.97 (0.83–1.14)
AUC_{last} [h·ng/mL]	259.73	236.26	1.10 (0.94–1.28)
AUC_{∞} [h·ng/mL] ^b	278.99	251.98 ^c	1.11 (0.97–1.27)
Gender^e	Female: Cohorts 1 and 2 [n = 18]	Male: Cohorts 1 and 2 [n = 16]	Female/Male
C_{max} [ng/mL]	27.67	22.46	1.23 (1.07–1.42)
AUC_{last} [h·ng/mL]	262.80	225.02	1.17 (1.01–1.35)
AUC_{∞} [h·ng/mL] ^b	286.33 ^f	237.45	1.21 (1.07–1.36)

ANOVA analysis of variance, AUC_{last} area under concentration–time curve from time zero to the time of the last quantifiable concentration, AUC_{∞} AUC from time zero extrapolated to infinity, *CI* confidence interval, C_{max} maximum observed concentration, $\%AUC_{ex}$ percentage of AUC_{∞} due to extrapolation from the time of the last measurable concentration, *PK* pharmacokinetic, *Rsq* goodness-of-fit statistic for the terminal elimination phase, *SAM* samidorphan

^aCalculated from the ANOVA model with food category as the main effect using only cohort 1. The effect of food on SAM PK was studied in cohort 1 (fed) and cohort 1 (fasted). Twenty participants were analyzed in cohort 1 (fed), and 22 participants were analyzed in cohort 1 (fasted)

^bA minimum of three data points were used for each terminal phase determination. If the *Rsq* value was <0.80 or the $\%AUC_{ex}$ was >30, AUC_{∞} was set to missing

^c*n* = 21

^dCalculated from the ANOVA model with age as the main effect using only fasting regimens. The effect of age on SAM PK was studied in cohort 1 (young; age 18–40 years) and cohort 2 (elderly; age ≥ 65 years) under fasting conditions. Twenty-two participants were analyzed in cohort 1, and 12 participants were analyzed in cohort 2

^eCalculated from the ANOVA model with gender as the main effect using only the fasting regimens. Cohort 1 had 10 males and 12 females who were dosed under fasting conditions; cohort 2 had six males and six females dosed under fasting conditions. For statistical analysis, the participants were pooled across the two cohorts by gender for an exploratory analysis

^f*n* = 17

4 Discussion

These phase I studies provide additional data on the PK profile of single sublingual, oral, and intravenous administrations of the novel μ -opioid receptor antagonist SAM. Following a single intravenous bolus dose of 1 mg SAM, the PK of SAM was characterized by a plasma clearance of 33.7 L/h, a volume of distribution of 341 L, and an elimination half-life of 7–8 h (study 1). Following a single sublingual or oral administration of 2 mg SAM, SAM was well-absorbed and reached peak concentrations within 2 h and had similar absolute sublingual and oral bioavailability of 71% and 69%, respectively. Approximately 20% of the sublingual or oral dose was excreted as SAM in urine. The elimination half-life was similar for the three routes of administration. For SAM and its metabolite, RDC-9986, there were no large differences in AUC, C_{max} , and t_{max}

between the sublingual and oral routes of administration (Table 2).

The high and comparable absolute bioavailability of SAM following sublingual and oral administration indicated that SAM has good permeability and is not subject to extensive first-pass metabolism, in contrast to other available opioid receptor antagonists, including naloxone and naltrexone [1, 13, 14, 21, 22]. The relatively low (<5%) oral and sublingual bioavailability of naloxone limits its clinical utility when administered via these routes [14, 21, 22]. Naltrexone undergoes rapid and extensive first-pass metabolism after oral administration, with large variation in bioavailability (from 5 to 60%) [23]. Due to physicochemical limitations, it is not feasible to administer the dose of naltrexone required for μ -opioid receptor blockade sublingually [24].

Food is known to impact the bioavailability of selected drugs when consumed concurrently, by altering the rate

Table 6 Summary of treatment-emergent AEs of the safety population (studies 1 and 2)

AE [n (%)]	Study 1		Study 2			
	Intravenous SAM [n = 10]	Sublingual SAM [n = 10]	Oral SAM [n = 9]	Cohort 1 Active [n = 24]	Cohort 2 Active [n = 12]	Pooled Placebo [n = 9]
Any AE	2 (20)	5 (50)	4 (44)	22 (92)	10 (83)	3 (33)
Any severe AE	0	0	0	4 (17)	1 (8)	0
Any SAE	0	0	0	0	0	0
AE leading to discontinuation	0	0	0	0	0	0
AEs occurring in two or more patients						
Infrequent bowel movements	0	2 (20)	2 (22)	0	2 (17)	0
Constipation	0	0	0	0	2 (17)	0
Nausea	1 (10)	2 (20)	1 (11)	15 (63)	6 (50)	0
Abdominal pain	0	0	2 (22)	1 (4)	1 (8)	0
Abdominal discomfort	0	0	0	1 (4)	1 (8)	0
Diarrhea	0	0	0	1 (4)	1 (8)	0
Headache	1 (10)	2 (20)	1 (11)	5 (21)	5 (42)	1 (11)
Dizziness	0	0	0	7 (29)	6 (50)	0
Somnolence	0	0	0	9 (38)	3 (25)	0
Vomiting	1 (10)	0	0	8 (33)	1 (8)	0
Hot flush	0	0	0	3 (13)	1 (8)	0
Dry mouth	0	0	0	0	2 (17)	0
Decreased appetite	0	0	0	2 (8)	0	0

AEs adverse events, SAE serious AE, SAM samidorphan

and extent of drug absorption [17, 18]. In the current study, equivalence between the fed and fasted states was established for orally administered SAM in healthy volunteers, indicating that the extent of absorption is not affected by the presence of food in the gastrointestinal tract.

PK studies published to date have focused on oral administration of SAM in healthy, predominantly younger, male participants [1]. The inclusion of elderly participants (age ≥ 65 years) in the current investigation provides important data confirming the lack of an age effect on the oral dose of SAM. Although the slightly higher systemic exposure of oral SAM in females than males is of potential interest, this study was not powered to detect gender differences. Moreover, the high degree of collinearity of body weight, BMI, and gender complicate the interpretation of these data.

The major metabolite of SAM, RDC-9986, was measurable in the plasma following intravenous, sublingual, and oral administration of SAM, with a mean exposure ratio to SAM of approximately 1 after molecular weight adjustment, and a longer $t_{1/2}$ (mean: 17–23 h vs. 7–9 h for SAM) with no overlap in ranges. However, RDC-9986 is not expected to contribute to the pharmacologic effects of SAM based on the known in vitro and in vivo pharmacology. In vitro, SAM acts as an antagonist at μ -opioid receptors with relatively high binding affinity (K_i value of 0.052 nM) and as a partial agonist at κ -opioid receptors with relatively lower binding

affinity (K_i value of 0.23 nM), whereas RDC-9986 functions as an agonist with relatively low binding to μ -opioid receptors (K_i value of 0.26 nM) and much lower binding to κ -opioid receptors (data on file, Alkermes). No μ - or κ -agonist activity of RDC-9986 has been observed to date in any of the preclinical or clinical evaluations [25–27].

5 Conclusions

Overall, these PK studies indicate that SAM has high permeability and bioavailability that are comparable following sublingual and oral administration, and SAM is not subjected to extensive first-pass metabolism. Equivalence between the fed and fasted states shows that the extent of absorption of orally administered SAM is not affected by food. SAM was generally well tolerated, and no new safety signals were detected.

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Compliance with Ethical Standards

Conflict of interest Vipul Kumar, Hong Lu, Marjie Hard, and Lisa von Moltke were all employees of Alkermes Inc. at the time the study was conducted and at the time the manuscript was written and submitted.

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