2 SYNOPSIS

Sponsor:

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Individual Study Table Referring to Part of the Dossier

(For National Authority Use only)

Name of Finished Product:

Not applicable

Volume:

Name of Active Ingredient:

S-888711

Page:

Study Title:

A Phase 1 Study to Investigate the Absorption, Distribution, Metabolism, and Excretion of [^{14}C]-S-888711 Following Oral Dose Administration in Healthy Male Subjects

Investigator(s) and Study Center(s): [redacted]

Publication (reference): Not applicable.

Studied Period:

[redacted] August 2010 (first subject enrolled) to
September 2010 (last subject completed)

Phase of Development: 1

Objectives:

Primary: To assess the pharmacokinetics of S-888711 and its metabolites using [^{14}C]-S-888711; to determine the whole blood and plasma concentrations of total radioactivity; and to determine the urinary and fecal recovery of total radioactivity.

Secondary: To characterize and identify metabolites of S-888711 in plasma, urine, and feces and to assess the safety and tolerability of S-888711.

Methodology: This was an open-label, nonrandomized, absorption, distribution, metabolism, and excretion study conducted in 7 healthy male subjects at a single study center.

Potential subjects were screened to assess their eligibility to enter the study within 28 days prior to study entry and were confined at the clinical site from the time of Check-in (Day -1) until Clinic Discharge. Subjects were to be discharged no sooner than Day 8 and no later than Day 15, based on the subjects satisfying the study discharge criteria.

Throughout the study, plasma and urine samples were collected for the determination of S-888711 and metabolite concentrations and whole blood, plasma, urine, and feces were collected for the determination of radioactivity.

Safety assessments included adverse event inquiries, clinical laboratory evaluations, vital sign measurements, electrocardiograms, and physical examinations and were performed at Screening, Check-in, periodically throughout the study, and at Clinic Discharge/Study Completion.

Number of Subjects (Planned and Analyzed):

Seven subjects were planned to ensure 6 subjects completed the study. There were a total of 7 subjects who participated in the study with all 7 subjects included in the safety and pharmacokinetic analyses.

Diagnosis and Main Criteria for Inclusion:

Healthy males between 18 and 45 years of age, inclusive, with a body mass index between 18.5 and 30.0 kg/m^2 were eligible for study participation.

Test Product, Dose and Mode of Administration, Lot Number:

A single dose of 2 mg (approximately 100 μCi) of [^{14}C]-S-888711 as an oral solution was administered to all subjects. Lot number: [redacted].

Duration of Treatment: Following an up to 28-day screening period, each subject received a single dose of study medication on Day 1 and remained in the clinic for no longer than 15 days for collection of pharmacokinetic samples. The duration of the study from Screening until the last follow-up evaluation was approximately 1 month.

Reference Therapy, Dose and Mode of Administration, Lot Number:

Not applicable.

Criteria for Evaluation:

Pharmacokinetic:

For each subject, where possible, the following pharmacokinetic parameters were calculated:

- For plasma S-888711, S-888711 deshexyl, total radioactivity, and whole blood total radioactivity: maximum observed concentration (C_{max}), time to maximum observed concentration (T_{max}), area under the concentration-time curve from Hour 0 to the last measurable concentration (AUC_{0-t}), area under the concentration-time curve extrapolated to infinity ($AUC_{0-\infty}$), apparent terminal elimination half-life ($t_{1/2}$), apparent total clearance (unchanged S-888711 only) (CL/F), ratio of C_{max} of metabolite to C_{max} of unchanged S-888711 ($R_{M/D,Cmax}$), ratio of AUC of metabolite to AUC of unchanged S-888711 ($R_{M/D,AUC}$) based on the plasma concentrations of unchanged S-888711 and its metabolite (S-888711 deshexyl); pharmacokinetic parameters were not estimable for S-888711 5-keto as all concentrations were below the limit of quantitation;
- Percent contributions to total radioactivity from S-888711, S-888711 deshexyl, and S-888711 5-keto concentrations, and remaining radioactivity not accounted for as S-888711 and metabolites, ratios of whole blood to plasma radioactivity, and distribution to the red blood cells at shared sampling time points;
- $C_{max\ PL}/C_{max\ PR}$ (C_{max} ratio of plasma concentrations to plasma radioactivity), $C_{max\ WBR}/C_{max\ PR}$ (C_{max} ratio of whole blood radioactivity to plasma radioactivity concentrations, $AUC_{0-\infty PL}/AUC_{0-\infty PR}$ ($AUC_{0-\infty}$ ratio of plasma concentrations to plasma radioactivity concentrations), and $AUC_{0-\infty WBR}/AUC_{0-\infty PR}$ ($AUC_{0-\infty}$ ratio of whole blood radioactivity concentrations to plasma radioactivity concentrations);
- Amount of S-888711, S-888711 deshexyl, S-888711 5-keto, and total radioactivity excreted in the urine over the sampling interval (Ae_u), cumulative and overall amount; percent excreted in the urine ($\%Fe_u$) over the sampling interval, cumulatively and overall; and renal clearance (CL_R);

- Amount of drug (total radioactivity) excreted in the feces and toilet paper over the sampling interval (Ae_f), cumulative and overall amount, and percent excreted in the feces ($\%Fe_f$) over the sampling interval, cumulatively and overall;
- Mass balance calculations of recovery data (% dose) from urine, feces, and toilet paper over the sampling intervals, cumulatively, and total recovery.

Safety:

Safety variables included clinical laboratory tests (including chemistry panel, complete blood count, and complete urinalysis, which were collected at Screening, at Check-in, on Day 3, and at Clinic Discharge), electrocardiograms (Screening, Check-in, predose [0 hours], 4 hours postdose, and prior to Study Discharge), physical examinations (full examination at Screening and upon Check-in, abbreviated physical examination at Study Discharge), vital signs (Screening; Check-in; predose [0 hours]; at 2, 4, 8, and 12 hours postdose and continuing every 24 hours; and prior to Clinic Discharge/Study Completion), and adverse experience assessments.

Statistical Methods:

Pharmacokinetic Variables:

Descriptive statistics were calculated for the pharmacokinetic parameters. No formal statistical tests were performed.

Safety:

Adverse events were summarized using frequency counts and percentages. Clinical laboratory, vital sign, and electrocardiogram findings were summarized using descriptive statistics.

Summary of Results

Pharmacokinetic:

Following oral administration of [^{14}C]-S-888711 solution, the onset of absorption appeared to be immediate with radioactivity and S-888711 concentrations quantifiable at the first (0.5 hour) postdose time point. However the absorption process was slow with maximum plasma concentrations of radioactivity and S-888711 achieved approximately 5 hours after dosing. During the absorption phase, the concentration ratios of S-888711/[^{14}C]-S-888711 were high, at least 80%, suggesting most of the dose absorbed appeared in plasma as unchanged drug.

The ratios of radioactivity concentrations in whole blood to plasma radioactivity concentrations across all time points were stable with geometric mean values ranged from 52.9% to 56.9%. The distribution to the red blood cell was typically 0.0% for most samples.

A summary of key radioactivity and S-888711 parameters is presented below:

Parameters (N=7)	[^{14}C]-S-888711 Geometric Mean (GCV%)	S-888711 Geometric Mean (GCV%)
F_{eu} (%)	1.06 (15.1)	<0.1%[a]
F_{ef} (%)	83.00 (6.2)	NA
$F_{e, total}$ (%)	84.24 (6.1)	NA
$AUC_{0-\infty}$ (ng Eq·h/g or ng·h/mL)	3370 (24.7%)	1880 (30.1%)
C_{max} (ng Eq/g or ng/mL)	82.8 (22.6%)	66.2 (25.6%)
$t_{1/2}$ (h)	70.7 (20.2%)	25.7 (6.9%)
$C_{max\ PL}/C_{max\ PR}$	NA	0.800 (3.6%)
$AUC_{0-\infty PL}/AUC_{0-\infty PR}$	NA	0.559 (8.3%)

GCV% = geometric coefficient of variations, ND = not determined, NA = not applicable, F_{eu} = recovery in urine, F_{ef} = recovery in feces; $F_{e, total}$ = sum of urinary and fecal recovery (inclusive of recovery in from toilet paper)

[a] Based on arithmetic mean. S-888711, S-888711 deshexyl as well as S-888711 5-keto were not detected in most of the urine samples.

Circulating S-888711 deshexyl concentrations were less than 1% of the plasma radioactivity concentrations. S-888711 5-keto was not quantifiable in any of the subjects. During the first 24 hours postdose, unchanged S-888711 accounted for most of the radioactivity and the contributions from other analyte(s) not measured in the study were low (geometric means ranging from 14.0% to 27.1%). However, at later time points, the decline in radioactivity concentration was slower than S-888711, and the contributions of other analyte(s) became more pronounced, around 40.2% to 85.8%. The geometric mean $t_{1/2}$ of radioactivity in plasma was 70.7 hours compared to 25.7 hours for S-888711. The geometric mean $t_{1/2}$ of radioactivity in blood (collected over 336 hours) was 111 hours. These data suggests the presence of other metabolic product(s) whose elimination appeared to be longer than that of S-888711.

More than half of the dose (60%) was recovered in urine and feces (including toilet paper), within 5 days of dosing (approximately 4.5 times S-888711 $t_{1/2}$). The majority of the dose (80%) was recovered within 240 hours (10 days after dosing). Beyond that time, approximately 1% of the dose per day was recovered through the final scheduled study day (Day 15). By the end of the study, over the 336-hour collection period, the individual total recovery ranged from 75.21% to 89.62% with a geometric mean of 84.24%.

Metabolic Profiling:

Analytical Bio-Chemistry Laboratories, Inc. conducted the metabolic profiling and identification assessments and results are presented in a separate report.

In brief, the proposed metabolic pathway of S-888711 includes acyl glucuronidation, *O*-dealkylation, alkyl oxidation at different positions on the hexyl side chain, followed by taurine conjugation. Major metabolic reactions happened on the *O*-hexyl side chain, but not on the main structure of S-888711 except the acyl glucuronidation. The parent drug

S-888711, accounted for the dominant portion of the analyzed plasma sample radioactivity from 1 to 96 hours postdose. During this time period, the metabolites only accounted for a very minor portion (less than 3%) of the applied sample radioactivity.

Due to the extremely low radioactivity in the pooled urine samples and only approximately 1% of total dose excretion in urine, further efforts for metabolite identification were not pursued after initial attempts by mass spectrometry analysis. In the initial identification analysis, only the acyl glucuronide conjugate was detected at a trace level. No other known or unknown metabolites, or the parent drug, were detected. It is suggested S-888711 and all known metabolites are hydrophobic and not likely to be eliminated through renal excretion.

A total of 16 radioactive peaks (including parent S-888711) were observed in the pooled fecal homogenate radioprofile, of which Peaks 1, 2, 5, 6, 8, 9, 10, 11, and 12 were not identified. The tentatively identified radioactive components were: Peak 3, accounting for 17.93 ±4.18% of the total dose, as *O*-deshexyl derivative of S-888711 in coelution with S-888711 *O*-propanolic metabolite (or *O*-acetic acid [*β*-oxidated carboxylic acid] metabolite); Peak 4, accounting for 16.86 ±5.76% of the total dose, tentatively proposed to be a *O*-ethane-1,2-diol metabolite; Peak 7, accounting for 1.53 ±1.28% of the total dose, as S-888711 *β*-oxidated carboxylic acid metabolite; Peak 13, accounting for 2.04 ±0.44% of the total dose, as S-888711 5-keto metabolite; Peak 14, accounting for 0.66 ±0.42% of the total dose, as taurine conjugate of S-888711 *β*-oxidated carboxylic acid metabolite; and Peak 15, accounting for 1.59 ±0.32% of the total dose, as S-888711 acyl glucuronide. The parent S-888711 in fecal matrix accounted for 16.22 ±5.32% of the total dose among the 7 subjects.

Safety:

There were no deaths, serious adverse events, discontinuations from the study due to adverse events, or adverse events of severe intensity. Four of the 7 study participants (57.1%) had at least 1 treatment-emergent adverse event, including headache in 3 (42.9%) subjects and abnormal product taste and presyncope, reported in 1 (14.3%) subject each. All of the headache and abnormal product taste events were assessed by the Investigator as possibly related to study drug. All events were of mild intensity and resolved prior to study conclusion without concomitant medication.

There were no clinically relevant changes noted in clinical laboratory, vital sign, or electrocardiogram findings following dosing.

CONCLUSIONS

Pharmacokinetic Conclusions:

Excretion via feces was the primary elimination route with minimal contribution from renal elimination (1% of the dose). Each of the 3 measured analytes, S-888711, S-888711 deshexyl, and S-888711 5-keto, contributed less than 0.1% to urinary recovery.

Over the maximum allowable housing period (14 days postdose), the total dose recoveries ranged from 75.21% to 89.62% (geometric mean 84.24%); approximately 80% of the dose was attained within 10 days after dosing.

In blood, [^{14}C]-S-888711 was distributed mainly in the plasma with essentially no distribution to the red blood cells.

S-888711 accounted for approximately 80% of C_{max} and 56% of $AUC_{0-\infty}$ of the systemic radioactivity. S-888711 deshexyl was a minor circulating metabolite (less than 1% of the plasma radioactivity concentrations) and S-888711 S-keto was not quantifiable in plasma.

Metabolic profiling in plasma suggested that the metabolites only accounted for a very minor portion (less than 3%) of the applied sample radioactivity. These results suggested the presence of many undetectable minor circulating metabolites in plasma.

In feces, S-888711 accounted for 16.22% of the total dose. The *O*-deshexyl derivative of S-888711 in coelution with the S-888711 *O*-propanolic metabolite (or *O*-acetic acid [β-oxidated carboxylic acid] and the *O*-ethane-1,2-diol metabolite were the tentatively major metabolites and accounted for 17.93% and 16.86% of the total dose, respectively.

In urine, only the acyl glucuronide conjugate was detected at a trace level.

Safety Conclusions:

The single dose of 2 mg (approximately 100 μCi) of [^{14}C]-S-888711 as an oral solution administered in this study was well tolerated.

Final Report Date: Final 2 February 2012

Prepared in: Microsoft Word 2007