2 SYNOPSIS

Sponsor: **Individual Study Table Referring to Part of the Dossier** **(For National Authority Use only)**

Name of Finished Product: **Volume:**

S-297995

Name of Active Ingredient: **Page:**

S-297995 monotosylate

Study Title:

A Phase 1 Study to Investigate the Absorption, Metabolism, and Excretion of [^{14}C]-S-297995 Following Oral Dose Administration in Healthy Male Subjects

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

Publication (reference): see Appendix 16.1.11

Studied Period:

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

Phase of Development: 1

Objectives:

Primary Objectives

The primary objectives of this study were:

- to assess the pharmacokinetics (PK) of a single dose of S-297995 and its metabolites using [^{14}C]-S-297995.
- to determine the whole blood and plasma concentrations of total radioactivity.
- to determine the urinary/fecal recovery of total radioactivity.

Secondary Objectives

The secondary objective of this study was to assess the safety and tolerability of S-297995.

Methodology: This was a Phase 1, open-label, single center, non-randomized, absorption, metabolism, and excretion study conducted in 12 healthy male subjects. The planned Enrollment/Screening duration for this study was approximately 28 days. Subjects were confined to the clinical research unit from approximately 24 hours prior to dose until discharge criteria had been satisfied (at least 120 hours postdose [Day 6]) or the maximum stay was reached (Day 15). The planned study conduct duration was approximately 6 weeks (including Screening).

Number of Subjects (Planned and Analyzed):

Twelve subjects (healthy men) were planned; 12 subjects were analyzed for safety; and 12 subjects were included in the analyses of pharmacokinetic variables.

Diagnosis and Main Criteria for Inclusion:

Subject was male; between 18 and 45 years of age (inclusive); with a body mass index between 18.5 and 29.9 kg/m^2, inclusive; a non-smoker; and in good health based upon results of medical history, physical examination, 12-lead electrocardiogram (ECG; within normal limits), and laboratory test results.

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

Twelve subjects (healthy men) were enrolled in the study (6 subjects for each cohort) and received a single 2-mg (free base form; approximately 140 μCi) oral dose of radiolabeled S-297995 tagged as follows:

- Cohort 1: [Oxadiazole-^{14}C]-S-297995 monotosylate
- Cohort 2: [Carbonyl-^{14}C]-S-297995 monotosylate

Duration of Treatment: The planned Study Conduct Duration was approximately 6 weeks (including Screening), with planned enrollment/screening duration of approximately 28 days and length of each confinement approximately 24 hours prior to dose until Discharge criteria were satisfied (at least 120 hours postdose [Day 6]) or the maximum stay was reached (Day 15).

Criteria for Evaluation:

Safety:

Safety procedures included adverse event (AE) assessments, 12-lead ECGs, vital signs, physical examinations, and laboratory assessments.

Statistical Methods:

General: Data listings are provided for PK and safety data. Summary statistics may be provided for data if applicable. Subject eligibility data collected only at Screening or Check-in may not be summarized in tables. Data analysis was performed using SAS® Version 9.1 or greater.

Pharmacokinetic: Descriptive statistics (arithmetic mean, standard deviation, median, minimum, and maximum, coefficient of variation [CV%], geometric mean, and coefficient of variation for geometric mean) were calculated for the PK parameters in each cohort, apart from T_{max} where geometric mean and geometric CV% are not presented. No formal statistical tests were planned. Data analysis was performed using SAS Version 9.1 or higher.

Safety: Descriptive statistics were calculated on the safety parameters. No formal statistical analyses were planned.

Pharmacokinetic Variables:

For each subject, the following PK parameters of S-297995 and its metabolites were calculated, whenever possible, based on the plasma concentrations of S-297995 and its metabolites and concentrations of total radioactivity in whole blood and plasma using the non-compartmental model[1] in WinNonlin ([redacted], Version 5.2):

C_{max}	Maximum observed concentration
T_{max}	Time to maximum concentration
AUC_{0-t}	Area under the concentration-time curve from Hour 0 to the last measurable concentration, calculated using the linear trapezoidal rule for increasing concentrations and the logarithmic rule for decreasing

	concentrations
$AUC_{0-\infty}$	Area under the concentration-time curve extrapolated to infinity, calculated using the formula: $AUC_{0-\infty} = AUC_{0-t} + C_t/\lambda_Z$ where Ct is the last measurable concentration and λ_Z is the apparent terminal elimination rate constant
$\%AUC_{extrap}$	Percentage of $AUC_{0-\infty}$ that is extrapolated from C_t to infinity
λ_Z	Apparent terminal elimination rate constant, where λ_Z is the magnitude of the slope of the linear regression of the log concentration versus time profile during the terminal phase
$t_{1/2,z}$	Apparent terminal elimination half-life (whenever possible), where $t_{1/2,z} = (\ln 2)/ \lambda_Z$
CL/F	Apparent total clearance, where $CL/F = Dose/AUC_{0-\infty}$ (unchanged S-297995 only)
V_z/F	Apparent volume of distribution (unchanged S-297995 only)
$MR_{M/U,Cmax}$	Molar Ratio of C_{max} of metabolites to C_{max} of unchanged S-297995
$MR_{M/U,AUC}$	Molar Ratio of AUC of metabolites to AUC of unchanged S-297995, calculated from $AUC_{0-\infty}$

In addition, the following ratios were calculated for each subject:

- blood: plasma concentrations for total radioactivity
- plasma concentrations of S-297995: plasma total radioactivity
- plasma concentrations of S-297995 + metabolites (corrected for molecular weight): plasma total radioactivity
- C_{max} and $AUC_{0-\infty}$ for S-297995: plasma total radioactivity
- C_{max} and $AUC_{0-\infty}$ for S-297995 + metabolites: plasma total radioactivity
- C_{max} and $AUC_{0-\infty}$ for whole blood total radioactivity: plasma total radioactivity

If $AUC_{0-\infty}$ could not have been determined for all subjects, an alternative AUC, such as AUC to a fixed time point, could have been used in the calculation of the molar ratios and the radioactivity ratios analysis.

The association of total radioactivity with red blood cells was calculated, whenever possible, for each subject based on the total radioactivity in whole blood (B), plasma (P) and Hct value (Ht: %) by the following equation:

The association of total radioactivity with red blood cells (%) = [B-P × (1-Ht/100)]/B × 100.

In addition, the following PK parameters of S-297995 and its metabolites were calculated, whenever possible, for each subject based on the concentrations and total radioactivity in urine:

A_{eu}	Amount of drug excreted in the urine over the sampling interval
CL_R	Renal clearance, where $CL_R = A_{eu}/AUC_{0-\infty}$
$\%F_{eu}$	Percent excreted in the urine, where % Excreted = 100 x (A_{eu}/dose)

The following PK parameters were calculated, whenever possible, for each subject based on the fecal total radioactivity concentrations:

A_{ef}	Amount of drug excreted in the feces over the sampling interval
$\%F_{ef}$	Percent excreted in the feces, where % Excreted = 100 x (A_{ef}/dose)

Safety:

Descriptive statistics were calculated on the safety parameters and summary statistical analyses were performed. No formal statistical tests were performed. All adverse events were coded using the Medical Dictionary for Regulatory Activities (MedDRA) Version 12.1 or higher and summarized using MedDRA terms.

Summary of Results

Pharmacokinetic:

The pharmacokinetics of S-297995 are similar to those seen in earlier studies, with rapid absorption resulting in median T_{max} values of approximately 1 hour postdose and a mean $t_{1/2,z}$ of approximately 11 hours. Metabolites Nor-S-297995 and S-297995-3-*O*-β-D-glucronide were markedly less abundant than parent compound, whilst metabolites S-297995-6-*O*-β-D-glucuronide, S-297995 carboxylic acid, and Benzamidine were not detected in the systemic circulation after a single oral dose of 2 mg S-297995.

The plasma total radioactivity concentration time profiles were similar for both [Oxadiazole-^{14}C]-S-297995 and [Carbonyl-^{14}C]-S-297995 and the rate of absorption was similar to that seen for S-297995. At the first sampling time of 0.25 hours postdose, the contribution of S-297995 accounted for approximately 95% of plasma total radioactivity, which suggests that S-297995 undergoes minor first pass metabolism. Furthermore, geometric mean total systemic exposure (based on AUC) of all drug related material analyzed by LC-MS/MS accounted for 65 to 74% of total radioactivity, which suggests the presence of additional metabolites not measured by LC-MS/MS. In addition, the rate of elimination of plasma total radioactivity was slower than that seen for parent compound (geometric mean plasma total radioactivity $t_{1/2,z}$ of approximately 20 and 16 hours, respectively, for [Oxadiazole-^{14}C]-S-297995 and [Carbonyl-^{14}C]-S-297995 compared to 11 hours for S-297995), and ratios of S-297995 + quantifiable metabolites: plasma total radioactivity decreased over time, both of which suggests the presence of drug-related moieties which are cleared more slowly than S-297995.

S-297995 related material was found to show some degree of binding to red blood cells, with up to 18% of radioactivity being associated with red blood cells after both [Oxadiazole-^{14}C]-S-297995 and [Carbonyl-^{14}C]-S-297995 administrations. However, this increased up to 34% at 48 hours postdose following [Oxadiazole-^{14}C]-S-297995 administration, which suggests that a slowly formed radiolabeled metabolite unique to this radiolabel position has a greater

binding affinity than all other metabolites.

S-297995 was found to undergo renal elimination with approximately 20% of dose being recovered in urine as parent compound. The metabolite Benzamidine, although not detected in the systemic circulation, was found in urine and accounted for approximately 30% of dose, whilst S-297995 3-*O*-β-D-glucuronide only accounted for up to 0.8% of dose. Other metabolites were either not detected or had very low levels present in urine. Total recovery of S-297995-related material as analyzed by LC-MS/MS did not account for the full amount of total radioactivity renally eliminated, demonstrating the formation and urinary excretion of additional metabolites. The degree of renal elimination was greater following administration of [Oxadiazole-^{14}C]-S-297995, which indicates the presence of a renally cleared radiolabeled metabolite unique to this radiolabel position. Conversely, the extent of fecal elimination of total radioactivity was greater following administration of [Carbonyl-^{14}C]-S-297995, suggesting the presence of a radiolabeled metabolite unique to this radiolabel position which undergoes biliary elimination.

Safety:

At total of 44 AEs were reported by 8 of the 12 subjects, with 11 AEs reported following administration of [Oxadiazole-^{14}C]-S-297995 and 33 AEs reported following administration of [Carbonyl-^{14}C]-S-297995. The AE with the highest reported incidence after administration of [Oxadiazole-^{14}C]-S-297995 was diarrhea (3 of 6 subjects; 50.0%). The AEs with the highest reported incidence after administration of [Carbonyl-^{14}C]-S-297995 were nausea (3 of 6 subjects; 50.0%) and vomiting (3 of 6 subjects; 50.0%).

All AEs were mild or moderate in severity and resolved by the end of the study. The relationship to study drug of the reported AEs was: 33 unrelated AEs and 11 possibly related AEs.

No clinically significant changes or findings were noted from clinical laboratory evaluations, vital sign measurements, or 12-lead ECGs for this study.

There were 3 physical examination findings that were also reported as AEs (mild bilateral clear rhinorrhea, bilateral erythema scleral conjunctiva, and a dry non-productive cough with lungs clear to percussion and auscultation).

Overall, the changes in the clinical safety assessments were unremarkable.

CONCLUSIONS

Pharmacokinetic Conclusions:

- Following a single oral dose of [^{14}C]-S-297995 (2 mg; 140 μCi), S-297995 was rapidly absorbed with maximum plasma concentrations being attained at 0.5 to 3 hours postdose, with median values of 0.75 hours for [Oxadiazole-^{14}C]-S-297995 and 0.875 hours for [Carbonyl-^{14}C]-S-297995. The mean $t_{1/2,z}$ of S-297995 in plasma was approximately 11 hours.
- S-297995 was rapidly metabolized to Nor-S-297995 and S-297995 3-*O*-β-D-glucuronide, with maximal plasma levels attained within 2.5 to 10 hours (median 4 hours) and 1.5 to 4 hours postdose (median 2 hours), respectively, for [Oxadiazole-^{14}C]-S-297995; and 4 hours (median 4 hours) and 2 to

4 hours postdose (median 2 hours), respectively, for [Carbonyl-^{14}C]-S-297995. Both metabolites were less abundant than the parent molecule with mean total systemic exposure of Nor-S-297995 (based on AUC_{0-t}) and S-297995 3-*O*-β-D-glucuronide (based on AUC_{0-t} for [Oxadiazole-^{14}C]-S-297995 and $AUC_{0-\infty}$ for [Carbonyl-^{14}C]-S-297995) being approximately 9% and 2%, respectively, for [Oxadiazole-^{14}C]-S-297995 and approximately 13% and 1%, respectively, for [Carbonyl-^{14}C]-S-297995 of those seen for parent drug.

- A proportion of S-297995 was renally cleared, with a mean of approximately 20% of administered dose of [Oxadiazole-^{14}C]-S-297995 and [Carbonyl-^{14}C]-S-297995 being recovered in urine as unchanged parent compound. Two metabolites, S-297995-3-*O*-β-D-glucuronide and Benzamidine were also shown to undergo renal elimination, with mean urinary recoveries of less than 1% and approximately 30%, respectively.
- The concentration time curves for total radioactivity in plasma and whole blood were similar following administration of [Oxadiazole-^{14}C]-S-297995 and [Carbonyl-^{14}C]-S-297995, with maximal level of radioactivity being attained within 0.5 to 3 hours for both matrices (median values in plasma and whole blood of 1 and 0.875 hours, respectively, for [Oxadiazole-^{14}C]-S-297995 and 0.75 hours for both matrices for [Carbonyl-^{14}C]-S-297995). The $t_{1/2,z}$ was slightly shorter for whole blood compared to plasma for both radiolabel positions, with geometric mean plasma total radioactivity terminal elimination half-lives of 16.2 to 20.4 hours being longer than those seen for parent compound (geometric mean values of approximately 11 hours, respectively).
- S-297995 accounted for approximately 50 to 64% of the plasma total radioactivity associated with $AUC_{0-\infty}$ following administration of either [Oxadiazole-^{14}C]S-297995 or [Carbonyl-^{14}C]-S-297995, and the ratio of S-297995: plasma total radioactivity was found to decrease over time. The sum of the parent compound plus metabolites accounted for a similar proportion of total radioactivity as for parent compound alone, with values of 59% to 71%, respectively, for [Oxadiazole-^{14}C]-S-297995 and 71% to 78%, respectively, for [Carbonyl-^{14}C]-S-297995.
- Geometric mean C_{max} and $AUC_{0-\infty}$ values for whole blood radioactivity were, respectively, approximately 39% and 35% lower than plasma radioactivity following dosing with [Oxadiazole-^{14}C]-S-297995 and were, respectively, approximately 38% and 41% lower than plasma radioactivity following dosing with [Carbonyl-^{14}C]-S-297995. The percentage of radioactivity associated with red blood cells was low following dosing with [Carbonyl-^{14}C]-S-297995, with geometric mean values generally ranging from 9 to 12%, although following dosing with [Oxadiazole-^{14}C]-S-297995, up to 34% of total radioactivity was associated with red blood cells at 48 hours postdose.
- Overall mean recoveries of total radioactivity of 92% and 85% were obtained following dosing with [Oxadiazole-^{14}C]-S-297995 and [Carbonyl-^{14}C]-S-297995, respectively. Renal excretion represented the main route of elimination following [Oxadiazole-^{14}C]-S-297995 administration, with a mean of 57.3% of total radioactivity excreted in urine, compared to a mean of 34.8% in feces. Following

[Carbonyl-^{14}C]-S-297995 administration, fecal excretion represented the main route of elimination with a mean of 64.3% of total dose being voided in feces and a mean of 20.4% recovered in urine

Safety Conclusions:

Overall, the changes in the clinical safety assessments were unremarkable.

Final Report Date: 05 Dec 2011

Prepared in: Microsoft Word 2003