2 SYNOPSIS

Sponsor:
Shionogi USA, Inc.

Individual Study Table Referring to Part of the Dossier

(For National Authority Use only)

Name of Finished Product:
S-888711

Volume:

Name of Active Ingredient:
S-888711

Page:

Study Title:

A Phase 1, Open-Label, Case-Matched Cohort Design, Non-Randomized Pharmacokinetic and Safety Study of a Single Oral Dose of 0.75 mg S-888711 in Healthy Subjects and in Subjects with Mild or Moderate Hepatic Impairment

Investigator and Study Center:

Publication (reference): see Appendix 16.1.11

Studied Period:

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

Phase of Development: 1

Objectives:

Primary objective:

- To compare the pharmacokinetic (PK) parameters of a single 0.75 mg oral dose of S-888711 between subjects with mild or moderate hepatic impairment and healthy subjects (matched to the moderate group).

Secondary objective:

- To assess the safety and tolerability of a single 0.75 mg oral dose of S-888711 in subjects with mild or moderate hepatic impairment.

Methodology: Single-center, United States, open-label, single-dose, non-randomized, case-matched cohort design.

Number of Subjects (Planned and Analyzed):

A total of 24 subjects were planned for this study, including 8 healthy subjects, 8 subjects with mild hepatic impairment, and 8 subjects with moderate hepatic impairment. These 3 groups were enrolled as planned. All 24 enrolled subjects completed the study and were included in the analyses of PK variables and safety.

Diagnosis and Main Criteria for Inclusion:

Males and females aged 18 to 70 years (at informed consent), inclusive, with a body mass index (BMI) between 18.5 and 36.0 kg/m^2, inclusive. Healthy subjects had no relevant medical history. Subjects with hepatic impairment had a confirmed and documented diagnosis of liver cirrhosis with mild or moderate impairment defined by Child-Pugh Class A or B, respectively.

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

Subjects received a single dose of 0.75 mg S-888711 (three 0.25 mg tablets), Almac Lot No: [redacted] administered orally with 240 mL of water on Day 1 following a fast of at least 10 hours.

Duration of Treatment:

Screening duration: approximately 3 weeks

Length of each confinement: approximately 1 week

Study conduct duration: approximately 7 weeks (including Screening and Follow-up visit)

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

There was no reference therapy.

Criteria for Evaluation:

Pharmacokinetic Variables:

The PK parameters were calculated, where applicable, from the plasma concentration data of S-888711 and its metabolites (S-888711 deshexyl and S-888711 5-keto) using standard non-compartmental methods. Comparisons of the PK parameters of S-888711, including the maximum observed concentration (C_{max}), the area under the plasma concentration time curve from time 0 to the last measurable concentration (AUC_{0-t}), the area under the plasma concentration time curve from time 0 to infinity ($AUC_{0-\infty}$), the apparent terminal phase elimination rate constant (λ_Z), the apparent terminal elimination half-life ($t_{1/2,Z}$), and the apparent total clearance (CL/F) were made between subjects with mild and moderate hepatic impairment and healthy subjects.

Safety:

Safety variables included clinical laboratory evaluations (a comprehensive serum metabolic panel, as well as hematology panel, and urinalysis), 12-lead electrocardiograms (ECGs), physical examinations, vital signs assessments, and adverse event (AE) reports.

Statistical Methods:

Descriptive statistics (number of subjects, arithmetic mean, standard deviation [SD], minimum, median, maximum, coefficient of variation [CV%] for arithmetic mean, geometric mean, and CV for geometric mean) were calculated for the PK parameters. Pharmacokinetic parameters (C_{max}, AUC_{0-t}, $AUC_{0-\infty}$, λ_Z, $t_{1/2,Z}$ and CL/F) of S-888711 were compared between subjects with mild and moderate hepatic impairment and healthy subjects by an analysis of variance (ANOVA).

Safety and tolerability data were summarized descriptively. Change and/or shift from baseline were presented for clinical laboratory parameters, vital signs and ECG. Adverse events (AEs) were coded using MedDRA®. The number and percent of subjects reporting the treatment-emergent AE and the number of treatment-emergent AEs reported were presented by hepatic impairment group, system organ class, and preferred term and for serverity and

relationship to study drug.

Summary of Results

Pharmacokinetics Summary:

Pharmacokinetic Parameters	Geometric Means (Geometric CV%) (N=8)			%MR (90% CI)*	
	Healthy	Mild	Moderate	Mild vs Healthy	Moderate vs Healthy
C_{max} (ng/mL)	14.9 (30.9)	15.4 (29.8)	14.9 (29.8)	102.79 (79.73, 132.52)	99.86 (77.45, 128.73)
T_{max} (hr)†	4.00 (4.00, 5.00)	5.00 (4.00, 5.00)	4.00 (3.00, 5.00)	-	-
AUC_{0-t} (ng*hr/mL)	322.1 (21.3)	336.8 (25.8)	379.0 (27.3)	104.57 (84.64, 129.19)	117.66 (95.24, 145.37)
$AUC_{0-\infty}$ (ng*hr/mL)	328.4 (20.6)	344.1 (25.6)	395.6 (28.7)	104.78 (84.62, 129.74)	120.47 (97.29, 149.17)
$t_{1/2,Z}$ (hr)	25.0 (6.7)	25.4 (12.7)	31.3 (17.5)	101.80 (91.02, 113.85)	125.45 (112.17, 140.31)
λ_Z (1/hr)	0.0278 (6.7)	0.0273 (12.7)	0.0221 (17.5)	98.24 (87.83, 109.87)	79.71 (71.27, 89.15)
CL/F (L/hr)	2.28 (20.7)	2.18 (25.6)	1.90 (28.8)	95.44 (77.08, 118.18)	83.01 (67.04, 102.78)

* = 90% CI and % Mean Ratios (%MR) were calculated based on ln-transformed parameters
† = T_{max} is presented as Median (Minimum, Maximum)
Healthy = Healthy subjects matched to moderate hepatic impairment subjects
Moderate = Subjects with moderate hepatic impairment
Mild = Subjects with mild hepatic impairment
Source: Tables 14.2.2.1, 14.2.2.2, 14.2.2.3, 14.2.3, and 14.2.4

Pharmacokinetics Conclusion:

The following conclusions are based on the results of PK analyses at a single 0.75 mg oral dose of S-888711.

The differences in PK parameters were relatively small for the comparison of hepatic impairment (mild or moderate) groups to the healthy matched control group. However, a trend of increased exposure compared to healthy subjects increased with the degree of hepatic impairment. The lower or upper boundaries of the 90% CIs for %MRs of C_{max}, $AUC_{0-\infty}$, and AUC_{0-t} were outside of the 80% to 125% equivalence interval in the hepatic impairment (mild or moderate) groups, indicating that the exposure parameters cannot be considered equivalent between the hepatic impairment (mild or moderate) groups and the healthy matched control group. The upper bounds of the 90% CIs for the S-888711 concentrations were not meaningfully higher than 125% suggesting that S-888711 dose adjustments for subjects with hepatic impairment are unnecessary.

For both the metabolites (S-888711 deshexyl and S-888711 5-keto) majority of concentrations were BLQ or near BLQ, such that meaningful measures of exposure could not be estimated robustly.

Safety Summary:

There were no deaths, severe, or serious AEs reported in this study and the Investigator did not discontinue any subject due to an AE.

A total of 12 AEs were reported in 29% (7 of 24) of the subjects dosed. The number of subjects reporting AEs was 25% (2 of 8) for the healthy subjects, 25% (2 of 8) for the subjects with mild hepatic impairment and 38% (3 of 8) for the subjects with moderate hepatic impairment. The incidence of AEs was similar for all groups. The total number of AE episodes reported was 6 in the healthy subjects, 2 in the subjects with mild hepatic impairment, and 4 in the subjects with moderate hepatic impairment. Of these AEs, 2 AEs (facial rash in a healthy subject and headache in a subject with moderate hepatic impairment) were considered possibly or probably related to the study drug and the remaining 10 AEs were considered unrelated to the study drug.

Clinical laboratory, vital signs, physical examination, and ECG results were generally unremarkable. There was an increase from baseline in platelet count at end of study (Day 14), ranging from 13% – 16% by group, consistent with the mechanism of action of the study drug.

Safety Conclusion:

The incidence of AEs was comparable between the subjects with hepatic impairment and healthy volunteers and no serious or severe adverse events were reported. Additionally, no relevant changes in laboratory values, vital signs, ECGs or physical exam were noted during the study. The increases in platelet count observed were expected based on the mechanism of S-888711. These findings suggest that administration of a single, oral dose of 0.75 mg S-888711 to male and female subjects who were healthy or who exhibited mild or moderate hepatic impairment appeared to be generally safe and well tolerated.

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