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Sponsor / Company: Sanofi Drug substance(s): SAR302503	Study Identifiers: NCT01762462, UTN U1111-1118-5554 Study code: POP13450
Title of the study: An open-label, pharmacokinetic and tolerability study of SAR302503 given as a single 300 mg dose in subjects with mild and moderate hepatic impairment, and in matched subjects with normal hepatic function (POP13450) This document reports the pharmacokinetic and safety findings for cohort 1 (mild hepatic impaired subjects [Group 1] and matched healthy subjects [Group 2]) only	
Study center(s): 3 centers in the United States of America	
Study period: Date first subject enrolled: 03/Jan/2013 Date last subject completed: 28/Mar/2013	
Phase of development: Phase 1	
Objectives: Primary: To study the effect of mild and moderate hepatic impairment on the pharmacokinetics (PK) of SAR302503. Secondary: To assess the tolerability of SAR302503 given as a single dose up to 300 mg in subjects with mild and moderate hepatic impairment and in matched subjects with normal hepatic function.	
Methodology: An open-label, nonrandomized, single oral dose study with 300 mg SAR302503 in subjects with mild (Group 1) and moderate (Group 3) hepatic impairment and in matched subjects (Group 2 [matched to Group 1] and Group 4 [matched to Group 3]) with normal hepatic function.	
Number of subjects: Planned (study/Group 1 + 2): 32/16 Randomized: 17 Treated: 17 Evaluated: Safety: 17 Pharmacokinetics: 16	
Diagnosis and criteria for inclusion: Male or female subjects 18 to 75 years of age, inclusive, with mild (defined as a Child-Pugh classification score of 5 to 6) or moderate (defined as a Child-Pugh rating score of 7 to 9) hepatic impairment, and healthy matched (by age, gender, and weight) subjects.	

Study treatments

Investigational medicinal product(s): SAR302503

Formulation: 100-mg capsule

Route(s) of administration: Oral, under fasted condition

Dose regimen: 300-mg single dose for mild hepatic impaired subjects and matching healthy subjects

Duration of treatment: 1 day of treatment

Duration of observation: 14 to 16 days after treatment, including 4 days institution stay and 5 days clinical visit

Criteria for evaluation:

Pharmacokinetics: The following PK parameters were calculated for SAR302503 using noncompartmental methods:

Primary endpoints: Maximum plasma concentration observed (C_{max}), area under the plasma concentration versus time curve extrapolated to infinity (AUC), and area under the plasma concentration versus time curve calculated using the trapezoidal method from time zero to the real time corresponding to the last plasma concentration above the limit of quantitation (AUC_{last}).

Secondary endpoints: First time to reach C_{max} (t_{max}), apparent total body clearance of a drug from the plasma (CL/F), apparent volume of distribution at steady state (V_{ss}/F), terminal half-life associated with the terminal slope ($t_{1/2z}$), effective half-life ($t_{1/2eff}$), predicted accumulation ratio ($R_{ac,pred}$), and unbound C_{max} and unbound AUC calculated based on fraction unbound (fu).

Safety: Adverse events reported by the subject or noted by the Investigator, physical examination, standard clinical laboratory evaluations (hematology, biochemistry, and urinalysis), vital signs (blood pressure and heart rate), and 12-lead electrocardiograms (ECGs).

Pharmacokinetic sampling times and bioanalytical methods:

Blood samples were collected for SAR302503 concentrations (ie, total drug) at predose and at 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 24, 48, 72, 96, 120, 168, 216, and 264 hours postdose.

Additional blood samples were collected for protein binding assessment by equilibrium dialysis for the determination of SAR302503 unbound concentrations at predose and at 1, 2, 3, 8, 24, and 48 hours postdose.

Concentrations of SAR302503 in plasma (total drug) and in the retentate samples from equilibrium dialysis were determined by a validated liquid chromatography tandem mass spectrometry method with a lower limit of quantification of 1.00 ng/mL. The concentrations of SAR302503 in the dialysate samples following equilibrium dialysis (unbound drug) were determined by a validated liquid chromatography tandem mass spectrometry method with a lower limit of quantification of 0.100 ng/mL.

Statistical methods:

Pharmacokinetics

Pharmacokinetic parameters of SAR302503 were summarized using descriptive statistics for each population group and listed.

For the mild and moderate hepatic impairment cohorts (cohorts 1 and 2, respectively), log-transformed C_{max}, AUC_{last}, AUC, $t_{1/2z}$, CL/F, V_{ss}/F, $t_{1/2eff}$, unbound C_{max}, and unbound AUC were analyzed by a linear fixed effects model, with population group as a fixed term and gender, weight, and age as covariates. An estimate and 90% confidence interval (CI) for the geometric mean ratio of the hepatic impaired group versus the normal control group were provided for C_{max}, AUC_{last}, AUC, CL/F, V_{ss}/F, unbound C_{max}, and unbound AUC. Also, for $t_{1/2z}$ and $t_{1/2eff}$, an estimate and 90% CI for the geometric mean of each hepatic impairment cohort and population group was provided.

Safety

The safety analysis was based on the review of individual values (clinically significant abnormalities) and descriptive statistics by population group. For laboratory tests, vital sign, and ECG data, potentially clinically significant abnormalities (PCSAs) were analyzed using the 14 September 2009 version of the PCSA list. Additionally, some study-specific PCSA criteria were applied as follows: alanine aminotransferase (ALT) ≥2 x upper limit of normal (ULN), aspartate aminotransferase (AST) ≥2 x ULN, lipase >2 x ULN, lipase ≥3 x ULN, amylase >2 x ULN, amylase ≥3 x ULN, and hemoglobin <100 g/L. Adverse events were coded according to the Medical Dictionary for Regulatory Activities, Version 15.1. Safety data were summarized by hepatic impairment cohort and population group. The number of subjects with treatment-emergent adverse events (TEAEs) was summarized by population group, system organ class, and preferred term.

For all parameters, raw data and changes from baseline were summarized using descriptive statistics by parameter, hepatic impairment cohort, and population group.

Summary: The current report is for mild hepatic impaired subjects (Group 1) and matched healthy subjects (Group 2) only.

Population characteristics:

Sixteen of 17 completed subjects were included in the PK analysis including 8 subjects with mild hepatic impairment in Group 1 and 8 healthy subjects matched to Group 1 (in Group 2). One healthy subject was excluded from the PK analysis due to vomiting within 2 hours of dosing. A total of 17 subjects who were enrolled and treated in the study were included in the safety population: 8 out of 17 with mild hepatic impairment and 9 out of 17 were healthy subjects with normal hepatic function. Hepatic impairment was assessed according to the Child-Pugh classification as shown below.

Clinical and biochemical measurements	Points scored and observed findings		
	1	2	3
Encephalopathy grade*	none	1 to 2	3 to 4
Ascites	absent	slight	moderate
Serum bilirubin, mg/dL	<2	2 to 3	>3
Serum albumin, g/dL	>3.5	2.8 to 3.5	<2.8
Prothrombin time, sec prolonged (internationalized normalized ratio)	<4 (<1.7)	4 to 6 (1.7 - 2.2)	>6 (>2.2)

* Grade 0: normal consciousness, personality, neurological examination, electroencephalogram
Grade 1: restless, sleep disturbed, irritable/agitated, tremor, impaired handwriting, 5 cps waves
Grade 2: lethargic, time-disoriented, inappropriate, asterixis, ataxia, slow triphasic waves
Grade 3: somnolent, stuporous, place-disoriented, hyperactive reflexes, rigidity, slower waves
Grade 4: unarousable coma, no personality/behavior, decerebrate, slow 2 to 3 cps delta activity
Subjects taking lactulose will have one (1) point added to their encephalopathy grade unless already graded a 3.

The 8 subjects enrolled in the mild hepatic impairment group had a total score (equal to the sum of the points for each of the 5 items above) of 5 or 6 at inclusion (Day -1).

The criteria used for healthy subjects with normal renal function to match mild hepatic impairment were same sex, age (≤50 years old or >50 years old), and body weight within 15%.

Pharmacokinetics:

Pharmacokinetic parameters of total and unbound SAR302503 and results of statistical analyses of PK data are presented below:

Mean ± SD (Geometric Mean) [CV%] plasma pharmacokinetic parameters of SAR302503

	Mild HI	**Healthy**
N	8	8
C_{max}	840 ± 248	687 ± 243
(ng/mL)	(807) [29.6]	(650) [35.3]
t_{max}[a]	2.00	2.00
(h)	(0.50 - 3.00)	(1.00 - 3.00)
AUC_{last}	10200 ± 2750	9260 ± 4120
(ng•h/mL)	(9830) [26.9]	(8580) [44.5]
AUC	11300 ± 2930	10100 ± 4780
(ng•h/mL)	(10900) [25.9]	(9320) [47.3][b]
$t_{1/2z}$	105 ± 20.3	126 ± 39.4
(h)	(103) [19.3]	(121) [31.3]
CL/F	28.7 ± 9.45	34.5 ± 12.8
(L/h)	(27.5) [33.0]	(32.2) [37.1][b]
V_{ss}/F	2560 ± 1280	3400 ± 1300
(L)	(2330) [50.2]	(3160) [38.1][b]
fu	2.74 ± 0.780	2.49 ± 0.704
(%)	(2.64) [28.4]	(2.41) [28.2]
Unbound C_{max}	22.2 ± 7.02	16.5 ± 5.92
(ng/mL)	(21.3) [31.6]	(15.7) [35.9]
Unbound AUC	298 ± 85.5	261 ± 125
(ng•h/mL)	(288) [28.7]	(236) [48.1][b]
$t_{1/2eff}$	25.1 ± 4.61	29.7 ± 5.72
(h)	(24.8) [18.3]	(29.3) [19.3][b]
$R_{ac,pred}$	2.07 ± 0.267	2.33 ± 0.337
	(2.05) [12.9]	(2.32) [14.4][b]

a Median (Min - Max)

b N=7; One subject was not included in calculation of summary statistics due to AUC_{ext} >20%

HI = hepatic impairment.

Treatment ratio estimates for SAR302503 with 90% CI			
Comparison	Parameter	Estimate	90% CI
Mild HI vs. Healthy	C_{max}	1.14	(0.89 to 1.46)
	AUC_{last}	1.06	(0.76 to 1.49)
	AUC	1.07	(0.74 to 1.54)
	CL/F	0.94	(0.65 to 1.36)
	V_{ss}/F	0.78	(0.48 to 1.26)
	unbound C_{max}	1.22	(0.96 to 1.56)
	unbound AUC	1.03	(0.73 to 1.46)

Note: For one subject, AUC was extrapolated by more than 20%. Therefore, the subject's AUC, CL/F, V_{ss}/F, and unbound AUC values were excluded from the analyses.

CI = confidence interval; HI = hepatic impairment.

Safety:

There were no deaths or severe adverse events reported in the study. Five out of the 8 (62.5%) mild hepatic impairment subjects and 4 out of 9 (44.4%) healthy matching subjects reported TEAEs. All TEAEs were of mild intensity and all subjects recovered without sequelae. The most frequently reported TEAEs were gastrointestinal disorders reported in 4 out of 8 mild hepatic impairment subjects and 4 out of 9 healthy subjects. One healthy subject experienced vomiting within 2 hours postdose and was excluded for PK analysis.

There were no clinically relevant PCSAs in vital sign, laboratory, or ECG parameters in healthy matching subjects with normal hepatic function.

One mild hepatic impairment subject with a white blood cell (WBC) count of 4.10 Giga/L and neutrophil count of 1.40 Giga/L at baseline had asymptomatic decreasing WBC count (2.90 Giga/L) and neutrophil count (0.70 Giga/L) on Day 3 of the study that were judged by the Investigator as not clinically significant. Both WBC and neutrophil counts were recovered at the end-of-study with values of 3.70 Giga/L for WBC and 1.30 Giga/L for neutrophil count.

Increased ALT and AST were reported in 3 mild hepatic impairment subjects at baseline. No changes of ALT and AST were reported during the study.

There were no prolonged QT intervals corrected for heart rate >450 ms (male), >470 ms (female), or prolonged QT interval corrected for heart rate increases from baseline >60 ms for any subjects.

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