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Prescribing decisions should be made based on the approved package insert in the country of prescription.

Sponsor / Company: Sanofi Drug substance(s): SAR302503	Study Identifiers: NCT01763190, UTN U1111-1115-8416 Study code: POP13449
Title of the study: An open-label pharmacokinetic and tolerability study of SAR302503 given as a single 300 mg dose in subjects with mild, moderate and severe renal impairment, and in matched subjects with normal renal function	
Study center(s): 3 centers in the United States of America	
Study period: Date first subject enrolled: 30/Nov/2012 Date last subject completed: 02/Jul/2013	
Phase of development: Phase 1	
Objectives: Primary: To study the effect of mild, moderate, and severe renal impairment (RI) on the pharmacokinetics (PK) of SAR302503. Secondary: To assess the tolerability of SAR302503 given as a single 300 mg dose in subjects with mild, moderate, and severe RI and in matched subjects with normal renal function.	
Methodology: An open-label, nonrandomized, single oral dose study with 300 mg SAR302503 in subjects with mild, moderate, and severe RI and in matched subjects with normal renal function. The study was conducted in sequential cohorts; the severe RI cohort was studied first compared to healthy controls, and then the moderate RI cohort was studied compared to healthy controls.	
Number of subjects:	Planned: 32 Randomized: 32 Treated: 36
Evaluated:	Pharmacokinetics: 29 Safety: 36
Diagnosis and criteria for inclusion: Subjects (males and females) with mild, moderate, and severe RI and healthy subjects (males and females) with normal renal function (matched to renal impaired subjects on gender, age, and body weight) based on creatinine clearance (CLcr) calculated using Cockcroft-Gault formula: Normal: >80 mL/min; Mild: 50 to 80 mL/min; Moderate: 30 to 50 mL/min; Severe: <30 mL/min. The criteria used for matching healthy subjects with normal renal function to RI subjects were: same sex, age (≤50 years old or >50 years old), and body weight within 15% of the subject to be matched (males) or body weight within 15% of the average weight of the RI subjects (females).	

Study treatments

Investigational medicinal product(s):

Formulation: SAR302503 100 mg capsules

Route of administration: Oral, in fasted condition

Dose regimen: 300 mg single dose

Duration of treatment: 1 day of treatment

Duration of observation: Up to 35 days

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 quantification (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 ($R_{ac,pred}$), fraction unbound (fu), unbound C_{max}, and unbound AUC.

Safety: Adverse events (AEs) 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/Pharmacodynamics sampling times and bioanalytical methods:

Blood samples were collected for the measurement of 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 dialysate samples following equilibrium dialysis (unbound drug) were determined by validated liquid chromatography with tandem mass spectrometry methods with lower limits of quantification of 1.00 ng/mL and 0.100 ng/mL, respectively.

Statistical methods:

Pharmacokinetic

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

Primary analysis: The effect of RI on SAR302503 PK parameters was analyzed using a linear regression model for log transformed C_{max}, AUC_{last}, AUC, CL/F, unbound C_{max}, unbound AUC, V_{ss}/F, $t_{1/2z}$, and $t_{1/2eff}$, with log of CLcr (based on Cockcroft-Gault formula) as an explanatory variable. Estimate and 90% confidence intervals (CIs) for the geometric means ratio of PK parameters between each renal impaired group versus the pooled normal control group were provided for all parameters within the linear regression model. Additionally, estimates and 90% CIs for the geometric means of PK parameters for each population group were provided for all parameters. Scatter plots of individual PK parameter values versus CLcr values were provided with the geometric mean regression line and associated 90% confidence band from the regression model.

Secondary analysis: The estimates and 90% CIs for the geometric means ratio of severe and moderate renal impaired group versus the pooled normal control group (based on the Cockcroft-Gault formula) were provided respectively for each parameter, using a linear fixed effects model with fixed terms for population group and gender, and with age and body weight as covariates.

The effect of RI on SAR302503 PK was also analyzed using a classification of subjects according to the abbreviated Modification of Diet in Renal Disease Study (MDRD) equation instead of the Cockcroft-Gault formula, using a linear fixed effects model for log transformed parameters, taking into account all renal impaired subjects and pooled controls.

Safety

The safety analysis was based on the review of AEs, individual values (potentially clinically significant abnormalities [PCSAs]), and descriptive statistics by population group. Adverse events were coded according to the Medical Dictionary for Regulatory Activities, Version 16.0. The number of subjects with treatment-emergent AEs (TEAEs) was summarized by population group, system organ class, and preferred term. Potentially clinically significant abnormalities (definitions according to version dated 14 September 2009) for clinical laboratory, vital sign, and ECG data and out-of-normal range values for clinical laboratory data were flagged and summarized in frequency tables by population group. In addition, some study-specific PCSA criteria were also applied and analyzed as follows: alanine aminotransferase (ALT) ≥2x upper limit of normal (ULN), aspartate aminotransferase (AST) ≥2x ULN, lipase >2x ULN, lipase ≥3x ULN, amylase >2x ULN, amylase ≥3x ULN, and hemoglobin <100 g/L.

Summary:

Population characteristics:

Subject disposition: A total of 36 subjects were enrolled in the study including 8 with severe RI, 9 with moderate RI, and 19 healthy controls. One subject with moderate RI had postdose vomiting within 2 hours and was excluded for PK analysis. Fourteen healthy control subjects were enrolled in Cohort 1 to match the subjects with severe RI. Of those 14 subjects, 5 had postdose vomiting within 2 hours postdose and another subject did not match criteria for body weight; therefore, they were excluded for PK analysis. Five healthy controls were enrolled in Cohort 2 to match the subjects with moderate RI.

Three healthy subjects enrolled in Cohort 1 to match the subjects with severe RI also met the matching criteria for 3 subjects with moderate RI; therefore, they were also included (but not retreated) in Cohort 2 for the safety and PK analysis. A summary of the subject disposition is provided in the following table.

Analysis populations

	Cohort 1		Cohort 2		
	Severe RI	**Healthy**	**Moderate RI**	**Healthy**	**All**
Safety population	8	14	9	8	36
Pharmacokinetic population	8	8	8	8	29

RI = Renal Impairment
Five healthy subjects and moderate RI subject from Cohort 1 are excluded from PK analysis due to vomiting after IMP administration. One healthy subject from Cohort 1 is also being excluded since they did not match based on their weight.
Three subjects which are healthy matches from cohort 1 are also included for cohort 2.

Among the 8 subjects with severe RI: 4 males and 4 females between 50 to 78 years of age with body weight ranging from 49.6 to 87.1 kg, and CLcr between 14.0 to 28.5 mL/min.

Among the 14 healthy subjects used as controls for the severe RI group: 6 males and 8 females between 31 and 65 years of age with body weight ranging from 59.8 to 95.8 kg, and CLcr between 81.8 and 143.0 mL/min.

Among the 9 subjects with moderate RI: 4 males and 5 females between 55 to 75 years of age with body weight ranging from 66.2 to 100.8 kg, and CLcr between 31.2 and 47.9 mL/min.

Among the 8 healthy subjects used as controls for the moderate RI group: 4 males and 4 females between 53 and 72 years of age with body weight ranging from 64.3 to 95.3 kg, and CLcr between 85.5 and 150.0 mL/min.

Pharmacokinetic results:

The PK parameters of total SAR302503 are presented below.

Mean ± SD (Geometric Mean) [CV%] of SAR302503 Pharmacokinetic Parameters

	Severe RI	Moderate RI	Healthy
N	8	8	13
C_{max} (ng/mL)	1290 ± 439 (1230) [34.1]	1020 ± 584 (880) [57.0]	782 ± 211 (755) [27.0]
t_{max} [a] (h)	2.50 (1.00 - 4.00)	2.25 (1.50 - 3.07)	3.00 (1.00 - 3.05)
AUC_{last} (ng•h/mL)	16800 ± 9510 (15400) [56.5]	14500 ± 7320 (12700) [50.3]	9750 ± 2430 (9480) [24.9]
AUC (ng•h/mL)	19900 ± 12700 (17800) [64.0] [b]	16500 ± 8180 (14400) [49.7]	11200 ± 2920 (10900) [26.0] [c]
$t_{1/2z}$ (h)	136 ± 51.6 (127) [37.9]	112 ± 21.4 (110) [19.2]	126 ± 39.9 (122) [31.5]
CL/F (L/h)	18.1 ± 5.66 (16.9) [31.3] [b]	24.9 ± 18.2 (20.9) [73.3]	28.3 ± 7.03 (27.5) [24.8] [c]
V_{ss}/F (L)	1760 ± 673 (1640) [38.2] [b]	2220 ± 1060 (1980) [47.9]	2870 ± 1120 (2690) [38.9] [c]
$t_{1/2eff}$ (h)	26.6 ± 5.59 (26.1) [21.0] [b]	29.3 ± 5.63 (28.9) [19.2]	27.2 ±3.42 (27.0) [12.6] [c]
fu (%)	1.62 ± 0.257 (1.60) [15.9]	1.82 ± 0.754 (1.72) [40.9]	2.10 ± 0.468 (2.05) [22.3]
$C_{max,u}$ (ng/mL)	20.4 ± 5.87 (19.7) [28.8]	16.2 ± 5.62 (15.1) [34.7]	15.6 ± 1.98 (15.5) [12.7]
AUC_u (ng•h/mL)	318 ± 177 (287) [55.6] [b]	255 ± 65.7 (247) [25.8]	225 ± 20.9 (224 [9.28] [c]
R_{ac_pred}	2.15 ± 0.326 (2.13) [15.1] [b]	2.31 ± 0.329 (2.29) [14.2]	2.19 ± 0.199 (2.18) [9.10] [c]

RI = renal impairment

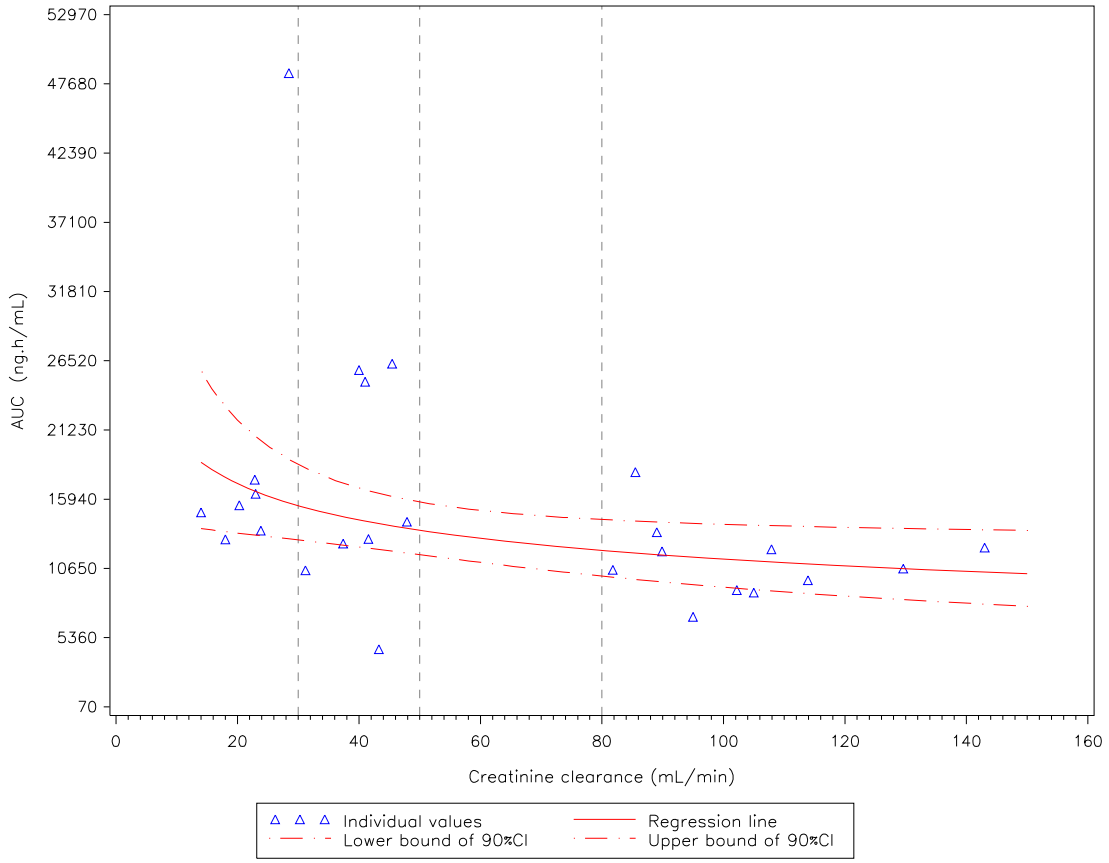
a Median (Min - Max)

b n=7, one subject was not included in summary statistics due to AUC_{ext} >20%

c n=11, two subjects were not included in summary statistics due to AUC_{ext} >20%

The primary linear regression analysis showed a significant increase in SAR302503 exposure, C_{max}, AUC_{last}, and AUC, with decrease in CLcr (based on Cockcroft-Gault formula) over the range of 150 to 14.0 mL/min. The relationship between CLcr and AUC is shown in figure below:

Scatter plot of individual AUC values versus individual creatinine clearance values with regression line



Regression model: AUC = exp(10.513-0.255Log[ClCr])

Note: 90%CI= 90% Confidence interval

Using 90 mL/min as a reference value of CLcr for healthy controls, estimates and 90% CIs for the geometric mean ratios of PK parameters between each renal impaired group versus the pooled normal control group are provided in the table below within the linear regression model. To provide conservative estimates for the effects of mild and moderate RI, the lower limits (50 mL/min and 30 mL/min respectively) of CLcr for those categories were used to compare to healthy controls. Similarly, 15 ml/min was selected to provide a conservative estimate of the effects of severe RI. Values below 15 mL/min are generally considered to be end-stage renal disease.

Treatment ratio estimates for SAR302503 with 90% CI from linear regression of log transformed PK parameters versus log transformed CLcr

PK Parameter	Label	Estimate	90% CI
C_{max} (ng/mL)			
	Mild(Creat.Clear.=50 mL/min) vs control	1.17	(1.05 to 1.30)
	Moderate(Creat.Clear.=30 mL/min) vs control	1.34	(1.10 to 1.64)
	Severe(Creat.Clear.=15 mL/min) vs control	1.62	(1.18 to 2.23)
Unbound Cmax (ng/mL)			
	Mild(Creat.Clear.=50 mL/min) vs control	1.07	(1.00 to 1.16)
	Moderate(Creat.Clear.=30 mL/min) vs control	1.14	(0.99 to 1.31)
	Severe(Creat.Clear.=15 mL/min) vs control	1.24	(0.99 to 1.56)
AUC_{last} (ng.h/mL)			
	Mild(Creat.Clear.=50 mL/min) vs control	1.17	(1.05 to 1.30)
	Moderate(Creat.Clear.=30 mL/min) vs control	1.33	(1.09 to 1.63)
	Severe(Creat.Clear.=15 mL/min) vs control	1.59	(1.15 to 2.21)
AUC (ng.h/mL)			
	Mild(Creat.Clear.=50 mL/min) vs control	1.16	(1.02 to 1.32)
	Moderate(Creat.Clear.=30 mL/min) vs control	1.32	(1.04 to 1.68)
	Severe(Creat.Clear.=15 mL/min) vs control	1.58	(1.07 to 2.33)
Unbound AUC (ng.h/mL)			
	Mild(Creat.Clear.=50 mL/min) vs control	1.07	(0.98 to 1.16)
	Moderate(Creat.Clear.=30 mL/min) vs control	1.13	(0.96 to 1.32)
	Severe(Creat.Clear.=15 mL/min) vs control	1.22	(0.94 to 1.57)

For the comparisons versus the control group, the creatinine clearance reference value of the control group is 90 mL/min.

Note: Point estimates and 90% CI= Ratios of geometric means for differences versus control.

Results of the secondary analysis based on analysis of variance (ANOVA) in the table below indicated that SAR302503 exposure, C_{max}, AUC_{last}, and AUC in subjects with moderate and severe RI was higher than in pooled healthy subjects (based on the Cockcroft-Gault formula).

Treatment ratio estimates with 90% CI for SAR302503 based on ANOVA

Comparison	Parameter	Estimate	90% CI
Severe RI vs Healthy	C_{max}	1.82	(1.30 to 2.56)
Moderate RI vs Healthy		1.31	(0.96 to 1.78)
Severe RI vs Healthy	Unbound C_{max}	1.35	(1.09 to 1.68)
Moderate RI vs Healthy		1.06	(0.87 to 1.30)
Severe RI vs Healthy	AUC_{last}	1.78	(1.23 to 2.58)
Moderate RI vs Healthy		1.44	(1.02 to 2.02)
Severe RI vs Healthy	AUC	1.94	(1.17 to 3.21)
Moderate RI vs Healthy		1.46	(0.97 to 2.21)
Severe RI vs Healthy	Unbound AUC	1.42	(1.03 to 1.96)
Moderate RI vs Healthy		1.18	(0.91 to 1.53)
Severe RI vs Healthy	CL/F	0.52	(0.31 to 0.85)
Moderate RI vs Healthy		0.68	(0.45 to 1.03)
Severe RI vs Healthy	Vss/F	0.49	(0.30 to 0.80)
Moderate RI vs Healthy		0.59	(0.40 to 0.88)
Severe RI vs Healthy	$t_{1/2z}$	1.11	(0.85 to 1.44)
Moderate RI vs Healthy		0.85	(0.67 to 1.09)
Severe RI vs Healthy	$t_{1/2eff}$	0.95	(0.79 to 1.14)
Moderate RI vs Healthy		0.99	(0.85 to 1.15)

Note: AUC, CL/F, V_{ss}/F and $t_{1/2eff}$ values were excluded from the analyses if AUC_{ext} > 20%.
Healthy subjects matched with Severe RI and Moderate RI are pooled together in the analysis.

The effect of RI on SAR302503 PK was also performed using a classification of subjects done according to the MDRD equation instead of the Cockcroft-Gault formula, and the results are presented below.

Treatment ratio estimates for SAR302503 with 90% CI (based on abbreviated MDRD equation)

Comparison	Parameter	Estimate	90% CI
Severe RI vs Healthy	C_{max}	1.84	(1.31 to 2.57)
Moderate RI vs Healthy		1.34	(0.92 to 1.94)
Mild RI vs Healthy		1.36	(0.80 to 2.33)
Severe RI vs Healthy	Unbound C_{max}	1.34	(1.07 to 1.66)
Moderate RI vs Healthy		1.08	(0.85 to 1.38)
Mild RI vs Healthy		1.23	(0.87 to 1.74)
Severe RI vs Healthy	AUC_{last}	1.82	(1.25 to 2.65)
Moderate RI vs Healthy		1.55	(1.03 to 2.35)
Mild RI vs Healthy		1.39	(0.76 to 2.53)
Severe RI vs Healthy	AUC	2.11	(1.25 to 3.56)
Moderate RI vs Healthy		1.73	(1.01 to 2.94)
Mild RI vs Healthy		1.58	(0.77 to 3.23)
Severe RI vs Healthy	Unbound AUC	1.48	(1.06 to 2.07)
Moderate RI vs Healthy		1.35	(0.96 to 1.90)
Mild RI vs Healthy		1.37	(0.86 to 2.17)

Note: AUC, CL/F, V_{ss}/F and $t_{1/2eff}$ values were excluded from the analyses if AUC_{ext} > 20%.
Healthy subjects matched with Severe RI and Moderate RI are pooled together in the analysis.

Safety results:

There were no deaths or serious AEs (SAEs) reported in the study. Treatment-emergent AEs were reported in 2/8 (25.0%) subjects with severe RI, 12/14 (85.7%) healthy controls to severe RI, 7/9 (77.8%) subjects with moderate RI, and 6/8 (75%) healthy controls to moderate RI. All TEAEs were recovered without sequelae.

The most frequently reported TEAE was gastrointestinal disorders reported in 2/8 subjects (25.0%) with severe RI, 12/14 healthy controls (85.7%) to severe RI, 6/9 subjects (66.7%) with moderate RI, and 5/8 healthy controls (62.5%) to moderate RI, and included: nausea (0/8 severe RI, 8/14 healthy control for severe RI, 3/9 moderate RI, and 3/8 healthy control for moderate RI), vomiting (0/8 severe RI, 5/14 healthy control for severe RI, 1/9 moderate RI, and 1/8 healthy control for moderate RI), diarrhea (2/8 severe RI, 6/14 healthy control for severe RI, 4/9 moderate RI, and 3/8 healthy control for moderate RI). Most gastrointestinal disorders were of mild intensity, a few cases were of moderate intensity.

One healthy subject experienced 2 severe TEAEs of cytomegalovirus (CMV) hepatitis and increased transaminases during the study. A 31-year old male vomited within 2 hours after a single dose of 300 mg SAR302503 administration on Day 1. The subject was discontinued from the study and was discharged from the clinic on Day 3. At the end-of-study visit on Day 15, the subject had increased transaminases with AST of 4.68 x ULN and ALT of 5.01 x ULN that was reported as an AE of transaminitis and increased alkaline phosphatase (1.40 x ULN) that was reported as an AE. His total bilirubin was within normal range. The subject had mild intermittent headache and mild upper respiratory infection and was treated with paracetamol on Days 11 and 14. A comprehensive laboratory investigation including biochemistry and serology showed positive CMV immunoglobulin M and deoxyribonucleic acid on polymerase chain reaction assay. The subject was seen by a hepatologist and was monitored until the AST and ALT values recovered to within normal range on Day 40. The increased transaminases and alkaline phosphatase were judged by the Investigator to be due to CMV hepatitis and not related to the investigational medicinal product. The CMV infection was considered by the Investigator as possibly related to investigational medicinal product.

There were few PCSAs in vital signs, laboratory, or ECG parameters, none of which were considered clinically significant except one case of above mentioned increased transaminases due to CMV infection in 1 healthy subject. There were no prolonged corrected QT intervals >500 ms or prolonged corrected QT interval increases from baseline >60 ms in the study.

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