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Sponsor / Company: Sanofi Drug substance: SAR236553/REGN727 (alirocumab)	Study Identifiers: NCT01670734, UTN U1111-1129-0248 EudraCT 2012-002292-33 Study code: POP12671
Title of the study: An open-label, pharmacokinetic and tolerability study of SAR236553/REGN727 given as a single subcutaneous dose in subjects with mild and moderate hepatic impairment, and in matched subjects with normal hepatic function	
Study center: 1 center in the Republic of Moldova and 1 center in France	
Study period: Date first subject enrolled: 12/Sep/2012 Date last subject completed: 17/May/2013	
Phase of development: Phase 1	
Objectives: Primary: • To study the effect of mild and moderate hepatic impairment (HI) on the pharmacokinetics (PK) of SAR236553 (referred to by the international nonproprietary name, alirocumab, hereafter). Secondary: • To assess the safety and tolerability of alirocumab given as a single subcutaneous (SC) dose in subjects with mild and moderate HI and in matched subjects with normal hepatic function. • To assess the pharmacodynamic (PD) profile of alirocumab in subjects with HI and in matched subjects with normal hepatic function.	
Methodology: Multicenter, open-label, single dose study	
Number of subjects: Planned: 24 Randomized: Not applicable Treated: 25 (1 moderate HI subject was replaced due to deviation in inclusion criteria) Evaluated: Pharmacokinetics: 24 (8 for each subject population group; 1 moderate HI subject was excluded due to deviation in inclusion criteria) Safety: 25 Pharmacodynamics: 24 (8 for each subject population group; 1 moderate HI subject was excluded due to deviation in inclusion criteria)	
Diagnosis and criteria for inclusion: Male or female subjects, between 18 and 75 years of age, inclusive, with mild or moderate HI based on the Child-Pugh score, and subjects with normal hepatic function (matched to HI subjects for gender, age, and body weight).	

Study treatments

Investigational medicinal product: Alirocumab

Formulation: 75 mg/mL solution for injection

Route of administration: Subcutaneous abdominal administration

Dose regimen: Single dose of 75 mg

Duration of treatment: Single dose administered on Day 1

Duration of observation: Approximately 12 weeks (excluding the screening period of 2 to 21 days) including 1 treatment period of 64 days (1 treatment day) and an end-of-study (EOS) visit 85 ± 2 days after the study drug administration.

Criteria for evaluation:

Pharmacokinetics: The following PK parameters were calculated for alirocumab, using noncompartmental methods: maximum serum concentration observed (C_{max}), time to reach C_{max} (t_{max}), serum concentration on Study Day 29 (C_{D29}), area under the serum concentration versus time curve calculated using the trapezoidal method from time zero to the real time (AUC_{last}), area under the serum concentration versus time curve extrapolated to infinity (AUC), area under the serum concentration versus time curve calculated using the trapezoidal method from time zero to Day 29 ($AUC_{0\text{-}D28}$), area under the serum concentration versus time curve calculated using the trapezoidal method from time zero to Day 14 ($AUC_{0\text{-}D14}$), time corresponding to the last concentration above the limit of quantification (t_{last}), terminal half-life associated with the terminal slope ($t_{1/2z}$), mean time a molecule resides in the body (MRT), distribution volume at steady-state (Vss/F), and apparent total body clearance of a drug from the serum (CL/F). Total serum alirocumab concentrations, total and free proprotein convertase subtilisin kexin type 9 (PCSK9) concentrations, and anti-drug antibodies (ADAs) were measured.

Safety: Subjects were monitored for safety via adverse events (AEs) spontaneously reported by the subjects or observed by the Investigator, clinical laboratory evaluations (biochemistry, hematology, coagulation, and urinalysis), vital sign assessments, physical examination, 12-lead electrocardiograms (ECGs), local tolerability and immunogenicity (ADA titer) assessments.

Pharmacodynamics: The percentage and absolute change from baseline in calculated serum low-density lipoprotein cholesterol (LDL C), and the percentage and absolute change from baseline in total cholesterol, high-density lipoprotein cholesterol (HDL-C), triglycerides, non-HDL-C, and apolipoprotein B, were analyzed. Time to maximum effect for calculated serum LDL-C was derived as an exploratory parameter.

Pharmacokinetic/Pharmacodynamics sampling times and bioanalytical methods:

Pharmacokinetic blood samples (including samples for assay of total and free PCSK9) were collected on Day 1 (predose and 4H and 8H postdose) and on Days 2 , 3, 4, 8, 11, 15, 22, 29, 43, 64 and 85 postdose. Additional samples for assay of total and free PCSK9 only were collected at screening and on Day -1.

Serum concentrations of alirocumab were determined using a validated enzyme-linked immunosorbent assay (ELISA) method with a lower limit of quantification (LLOQ) of 78 ng/mL in neat serum samples.

Total and free PCSK9 levels were determined using a validated ELISA with LLOQs in neat serum samples of 156 ng/mL and 31.2 ng/mL for the total PCSK9 assay and the free PCSK9 assay respectively.

Samples for the determination of ADA levels in serum were collected at predose and on Days 29, 64, and 85 postdose. Samples were analyzed using a validated bridging electrochemiluminescence assay for the determination of ADAs in acid-treated human serum. Based on the minimum dilution of the samples, the minimum titer for any ADA positive sample was 30. In neat serum samples, the validated lower limit of detection was approximately 1.7 ng/mL.

Pharmacodynamic blood samples were collected on Day 1 predose and on Days 2, 4, 8, 11, 15, 22, 29, 43, 64, and 85 postdose.

Statistical methods:

Pharmacokinetics: Pharmacokinetic parameters of alirocumab were summarized using descriptive statistics for each population group. For log-transformed C_{max}, AUC, AUC_{last}, $t_{1/2z}$, CL/F and Vss/F, the effect of population group on a single dose of alirocumab was analyzed using a linear fixed effects model with fixed terms for population group (subjects with HI or normal healthy subjects), gender, age, and body weight. Estimates and 90% confidence intervals (CIs) for the geometric means ratio of each HI group versus the normal hepatic function group were obtained within the linear fixed effects model framework.

Safety: For AEs, frequencies of treatment-emergent adverse events (TEAEs) were summarized by population group. All AEs were listed. Abnormalities in clinical laboratory, vital sign, and ECG parameters were assessed using potentially clinically significant abnormalities ([PCSA] list) criteria, and subjects with on-treatment PCSAs were summarized by population group. Frequencies for signs of local intolerance were documented and subjected to standard AE analyses. The number and percentage of subjects with ADAs (positive or negative) were also evaluated.

Pharmacodynamics: For all lipid parameters from Days 1 to 85, the raw data, the percentage and absolute change from baseline were summarized for each population group. Plots of the mean (± standard error of the mean [SEM]) raw data, the percentage and absolute change from baseline over days was provided for each population group.

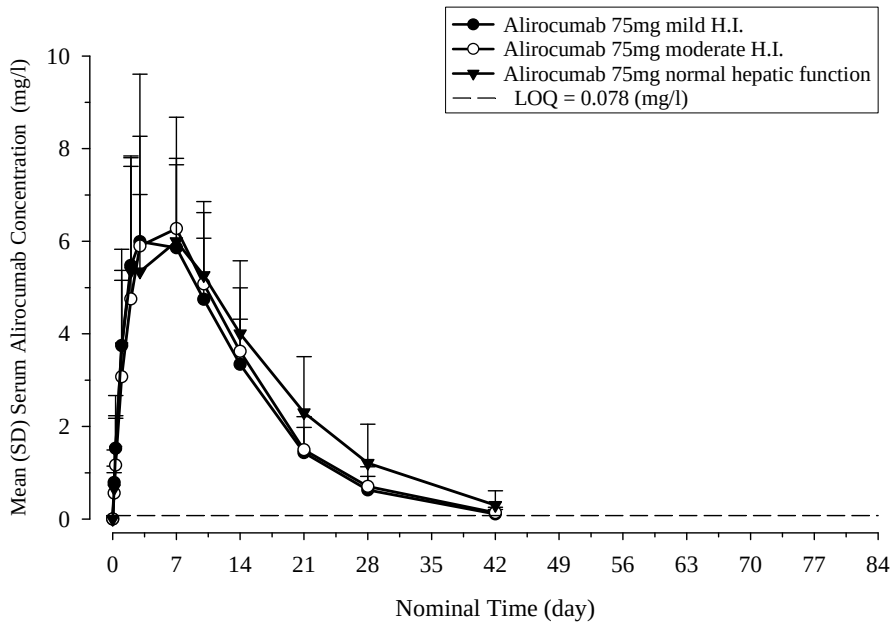
Pharmacokinetics/pharmacodynamics: A population group comparison of baseline PCSK9 levels (free and total) was performed and ratio estimates with associated confidence intervals were estimated within a fixed effect model. Time profile plots of mean (±SEM) free and total PCSK9 were performed by population group. Overlay of time profile plots of mean (±SEM) free and total PCSK9 and of mean (±SEM) percent change from baseline LDL-C were performed.

Summary:

Population characteristics: The study population included 25 subjects (8 and 9 subjects with mild and moderate HI respectively, and 8 healthy matched subjects); there were 20 male and 5 female subjects aged between 31 and 68 years.

Pharmacokinetic results:

Mean (±SD) concentrations of alirocumab in serum after a single SC dose of 75 mg alirocumab (linear scale)



Mean ± SD (geometric mean) [CV%] serum PK parameters of alirocumab

Mean ± SD (Geometric Mean) [CV%]	**Serum Alirocumab**		
	Alirocumab 75mg SC normal hepatic function	Alirocumab 75mg SC mild H.I.	Alirocumab 75mg SC moderate H.I.
N	8	8	8
C_{max}	6.47 ± 1.52	6.23 ± 2.09	6.45 ± 3.16
(mg/l)	(6.32) [23.5]	(5.90) [33.6]	(5.81) [49.1]
t_{max}[a]	5.00	3.00	7.00
(day)	(2.00 - 7.00)	(2.00 - 7.00)	(3.00 - 7.00)
C_{D29}*	1.21 ± 0.840	0.628 ± 0.295	0.628 ± 0.386
(mg/l)	(0.921) [69.6]	(0.571) [47.0]	(NA) [61.5]
t_{last}[a]	42.00	42.00	42.00
(day)	(28.00 - 63.00)	(28.00 - 42.06)	(21.00 - 42.00)
$t_{1/2z}$	6.06 ± 1.89	5.95 ± 0.977	5.64 ± 1.95
(day)	(5.80) [31.2]	(5.87) [16.4]	(5.30) [34.5]
AUC_{last}	117 ± 38.1	96.6 ± 29.9	93.3 ± 26.4
(mg•day/l)	(111) [32.6]	(92.4) [31.0]	(89.7) [28.4]
$AUC_{0\text{-}D14}$**	70.0 ± 20.4	68.2 ± 22.3	65.3 ± 27.1
(mg•day/l)	(66.2) [29.1]	(64.9) [32.6]	(60.3) [41.5]
$AUC_{0\text{-}D28}$**	104 ± 29.3	92.1 ± 27.9	88.7 ± 27.5
(mg•day/l)	(99.7) [28.1]	(88.3) [30.3]	(84.6) [31.0]
AUC	119 ± 38.1	98.4 ± 29.5	95.2 ± 26.2
(mg•day/l)	(112) [32.1]	(94.3) [30.0]	(91.8) [27.5]
CL/F	0.710 ± 0.298	0.831 ± 0.270	0.853 ± 0.292
(l/day)	(0.667) [41.9]	(0.795) [32.5]	(0.817) [34.3]
Vss/F	9.58 ± 4.87	9.55 ± 3.71	10.8 ± 6.30
(l)	(8.83) [41.9]	(8.98) [38.8]	(9.48) [58.4]
MRT	13.6 ± 3.36	11.4 ± 1.70	12.1 ± 3.49
(day)	(13.2) [24.6]	(11.3) [14.9]	(11.6) [28.9]

[a] Median (Min - Max)

* Concentration in serum on study day 29 (28 days after administration)

** Partial AUC calculated between Study Days 1 and 15 or 1 and 29 (PK time zero to Day 15 or Day 28)

Mild and moderate HI PK profiles compared to normal hepatic function PK profiles

The PK profiles of alirocumab after administration of a single 75 mg SC dose in normal hepatic function (control), mild HI, or moderate HI subjects were similar, with a non-significant shift towards faster clearance in HI groups. The study was not powered to show bioequivalence. The estimate of geometric mean ratios for mild HI subjects versus normal hepatic function subjects were 1.04 (90% CI = 0.74 to 1.48) and 0.91 (90% CI = 0.66 to 1.24) for C_{max} and AUC, respectively. For moderate HI subjects versus normal hepatic function subjects, C_{max} and AUC estimates were 0.90 (90% CI = 0.64 to 1.26) and 0.82 (90% CI = 0.61 to 1.12), respectively. Median t_{max} values were detectable between 3 and 7 days after administration.

Free and total PCSK9 concentrations in serum

A longer suppression of mean free PCSK9 concentrations and lower mean concentrations of total PCSK9 were observed in normal hepatic function (control) subjects compared to HI subjects.

Safety results:

There were no deaths reported during the study. Serious adverse events (SAEs) were reported by 3 subjects (2 subjects with normal hepatic function: of which 1 experienced transient acantholytic dermatosis [reported as Grover disease] and 1 had a transient ischemic attack [TIA]; and 1 subject with moderate HI who experienced acute renal impairment). Only The TIA was considered related to study treatment by the Investigator.

In the mild HI, moderate HI, and matched healthy subjects groups, 2/8, 6/9, and 5/8 subjects experienced treatment-emergent adverse events (TEAEs), respectively. The most frequently reported TEAEs (reported by at least 2 subjects in any group) were upper abdominal pain (3/9 subjects in the moderate HI group, and none in the other groups), nasopharyngitis (2/8 subjects in the normal hepatic function group, and none in the other groups), headache (2/9 subjects in the moderate HI group, 0/8 in the mild HI group, and 1/8 in the normal hepatic function group) and peripheral edema (2/9 subjects in the moderate HI group, and none in the other groups).

As expected, laboratory abnormalities were more frequent in the group of subjects with HI (hematology and biochemistry); these abnormal values were considered not clinically significant by the Investigator except for 2 subjects with (i) abnormal liver function tests (elevated alanine aminotransferase and bilirubin) reported as non-serious TEAEs and (ii) increased serum creatinine reported as a SAE. There were few potentially clinically significant abnormalities (PCSAs) in ECG parameters, but no QTc >500 ms was recorded. There were no increases from baseline >60 ms reported. None of these abnormalities were considered clinically significant.

Immunogenicity:

One subject in the mild HI group had a positive anti-drug antibodies (ADA) status (titer of 30) in the predose sample. At later time points no ADAs were detectable in this subject. This suggested that this subject exhibited a pretreatment immunoreactivity in the assay, and not a treatment-emergent ADA response to the administration of study drug.

During the postdose phase, a total of 7 out of 25 subjects had a positive ADA status (with negative ADA status at predose); 1/8 subjects in the normal hepatic function group, 2/8 subjects in the mild HI group, and 4/9 subjects in the moderate HI group tested ADA positive postdose, with titers ranging between 30 (minimum detectable titer) and 240. A single titer of 240 was detected in 1 subject in the moderate HI group on Day 29 declining to a titer of 120 on Day 64. On Days 1 (predose) and 85 (EOS visit), no ADAs were detectable in this subject. All other measured ADA titers were low and between 30 and 120 for all other ADA positive subjects.

Positive ADA status had no impact on the incidence or nature of TEAEs.

The effect on LDL-C was not impacted by the presence of ADAs.

Pharmacodynamic results:

Mean LDL-C baseline levels were much higher in the matched healthy control subjects (4.25 mmol/L) than in the mild and moderate HI groups (2.53 and 2.79 mmol/L, respectively). Levels of LDL-C declined in all groups, with a comparable time course through Day 11, but LDL-C continued to decline in healthy subjects but not HI subjects up to Day 15. As a result, the magnitude of peak percent decrease in the HI subjects (reaching 33.20% and 35.83% in mild and moderate HI subjects respectively), was somewhat less than in healthy subjects (peak decrease reaching 45.42%).

Pharmacokinetic/pharmacodynamic relationship:

Significant LDL-C reductions were observed across all groups, with a greater reduction of LDL-C observed in normal hepatic function (control) subjects compared to both HI subject population groups. This is in line with a longer suppression of mean free PCSK9 concentrations and lower mean concentrations of total PCSK9 in normal hepatic function (control) subjects compared to HI subjects.

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