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Sponsor: Sanofi **Drug substance(s):** SAR247799	**Study Identifiers:** U1111-1197-8124, NCT03462017, 2017-002592-26 **Study code:** PDY15286
Title of the study: Study to assess the pharmacodynamic effects of repeated oral doses of SAR247799 on endothelial function in male and female patients with type 2 diabetes mellitus	
Study center(s): 2 centers in Germany	
Study period: Date first patient enrolled: 13/May/2017 Date last patient completed: 22/Dec/2018	
Phase of development: Phase 1	
Objectives: The primary objective was to assess the pharmacodynamic (PD) effects of SAR247799 on macrovascular endothelial function of the brachial artery using flow-mediated dilation (FMD) in patients with Type 2 diabetes mellitus (T2DM). The secondary objectives were: • To assess the PD effects of SAR247799 on microvascular endothelial function using laser Doppler perfusion monitoring in patients with T2DM. • To assess the safety profile of SAR247799 in patients with T2DM. • To assess the plasma pharmacokinetic (PK) profile of SAR247799 in patients with T2DM. The exploratory objectives were: • To assess the PD effect of SAR247799 on lymphocyte subsets, biomarkers of endothelial function (including but not limited to soluble intercellular adhesion molecule-1 [sICAM-1], endothelin 1 [ET-1; optional], circulating endothelial cells [CEC], endothelial progenitor cells [EPC], and nitrate/nitrite) in whole blood and serum in patients with T2DM. • Sphingosine 1-phosphate (S1P), and S1P-high density lipoprotein (S1P-HDL) were measured at baseline to establish potential relationships with improvement of the endothelial dysfunction. • To assess the effect of SAR247799 on 24-hour albuminuria in patients with T2DM. • To assess the potential relationship between gene polymorphisms, including but not limited to, endothelial nitric oxide synthase (eNOS) gene polymorphism and PD response to SAR247799. • To assess PK/PD relationships, if relevant.	
Methodology: A multi-center, randomized, double-blind, double-dummy, placebo- and positive-controlled, sequential 4-week study investigating the effects of repeated oral doses of SAR247799 in T2DM patients.	

Number of patients:	Planned: Up to 108 patients (27 per cohort; 15 treated with SAR247799, 6 treated with sildenafil, and 6 treated with placebo), including 2 fixed cohorts and 2 optional cohorts Randomized: 54 (including 2 fixed cohorts) Treated: 54
Evaluated:	
	Pharmacodynamics: 53 Safety: 54 Pharmacokinetics: 30

Diagnosis and criteria for inclusion: Male and female stable T2DM patients aged between 18 and 64 years, inclusive, with a body mass index (BMI) between 18 and 35 kg/m^2, inclusive. The following inclusion criteria also applied: hemoglobin A1c <8.5%, FMD ≤7%, estimated glomerular filtration rate >60 mL/min/1.73 m^2.

Study treatments

Investigational medicinal products (1): SAR247799 and placebo

Formulation: SAR247799 0.5-mg capsules (Size 3) and 2.5-mg capsules (Size 0) and identical matching placebo capsules (Size 0 and Size 3)

Route(s) of administration: Oral

Dose regimen: 2 SAR247799 doses of 1 mg (in Cohort 1) and 5 mg (in Cohort 2) or placebo, once daily in the morning under fasting conditions

Study treatments

Investigational medicinal products (2): Sildenafil and placebo

Formulation: 25 mg encapsulated tablets (Size 0) and identical matching placebo capsules (Size 0)

Route(s) of administration: Oral

Dose regimen: 50 mg sildenafil or placebo once daily in the morning under fasting conditions

Study treatments

Investigational medicinal product (3): Acetylcholine (challenge agent)

Formulation: 0.2 mL aqueous solution of 10 mg/mL of acetylcholine chloride

Route(s) of administration: Transdermally by iontophoresis

Dose regimen: Days -1, 14, 21, 28, 35, and 42 (at the same time points as laser Doppler perfusion monitoring)

Duration of treatment: 28 days

Duration of observation: Approximately 10 weeks including screening (Days -28 to -3), a treatment period from Days -2 to 28 (IMP administrations from Day 1 to Day 28 inclusive), a post-treatment visit (institutionalization from Days 34 to 35), and an end-of-study visit (institutionalization from Days 41 to 42)

Criteria for evaluation:

Pharmacodynamics: Macrovascular function (primary endpoint): Absolute change from baseline in the percentage FMD (%) index of the brachial artery during and after treatment (FMD is the percentage change from resting in brachial artery diameter in response to reactive hyperemia).

Microvascular function (secondary endpoint): Change from baseline in peak flow induced by acetylcholine iontophoresis, measured using laser Doppler perfusion monitoring.

Exploratory endpoints: 24-hour urinary albumin excretion; serum and whole blood biomarkers (lymphocyte subsets: T regulatory cells; T-CD4 and T-CD8 cells and their subsets [such as naïve, effector, effector memory, and central memory], B cells [naïve and memory], and natural killer cells); serum endothelial biomarkers (including sICAM-1, ET-1, nitrites/nitrates); CEC and EPC; serum S1P and HDL-bound S1P; high sensitivity C-reactive protein; gene polymorphisms (eNOS).

Safety (secondary endpoint): Adverse events (AEs) spontaneously reported by the patient or observed by the Investigator, clinical laboratory evaluations (including hematology, biochemistry, and urinalysis), lymphocyte count included in white blood cell count with differential count, physical examination findings, vital signs (supine and standing heart rate, systolic blood pressure, and diastolic blood pressure), body weight, body temperature, standard 12-lead electrocardiogram (ECG), and ECG telemetry.

Pharmacokinetics (secondary endpoint): The following PK parameters were calculated from plasma concentrations of SAR247799 using non-compartmental methods: Maximum plasma concentration observed (C_{max}), time to reach C_{max} (t_{max}), plasma concentration observed just before treatment administration during repeated dosing (C_{trough}), and area under the plasma concentration versus time curve (AUC) calculated using the trapezoidal method over the dosing interval (24 hours; AUC_{0-24}).

Statistical methods:

Pharmacodynamics

Descriptive statistics for FMD in raw data and in change from baseline, and for laser Doppler's absolute change from baseline in mean and median percentage change from baseline after the acetylcholine stimulations were provided by treatment group (SAR247799 doses, Sildenafil or placebo) for assessment from Day -1 to Day 42 and summary plots were provided.

Safety

The safety analyses were conducted on the safety population and were based on the review of descriptive statistics and individual data for AEs, clinical laboratory evaluations, vital signs, and ECG parameters.

Adverse events were coded using Medical Dictionary for Regulatory Activities (Version 21.1), and treatment-emergent AEs (TEAEs) were listed by primary system-organ-class (SOC) and preferred term (PT) and treatment group. Potentially clinically significant abnormalities (PCSAs, version dated 24-May-2014) for clinical laboratory, vital signs, and ECG data were flagged and listed. Out-of-normal range definitions for clinical laboratory data were listed.

Pharmacokinetics

Descriptive statistics for SAR247799 plasma concentrations were calculated. The PK parameters were calculated with a Bayesian approach using the population PK model developed for SAR247799 in healthy subjects after a single dose (study TDU14288) and repeated once daily doses study (study TDR14289).

Summary:

An abbreviated clinical study report (CSR) has been produced as Sanofi have decided to terminate the development of the SAR247799 compound. Therefore, not all the planned statistical analyses as per the statistical analysis plan were performed and/or presented in the CSR.

Population characteristics:

A total of 54 patients (39 males and 15 females) were randomized and treated. One patient who was receiving sildenafil was discontinued from the treatment and did not complete the study due to a TEAE of ventricular extrasystoles.

A total of 30 patients were exposed to SAR247799: 15 patients (13 males + 2 females) were treated with SAR247799 at 1 mg, 15 patients (9 males + 6 females) with SAR247799 at 5 mg. A total of 12 patients (8 males + 4 females) were exposed to sildenafil 50 mg and 12 patients (9 males + 3 females) received placebo.

The study was conducted in 2 successive cohorts:

- Cohort 1: SAR247799 1 mg (n=15), sildenafil 50 mg (n=6), placebo (n=6) followed by
- Cohort 2: SAR247799 5 mg (n=15), sildenafil 50 mg (n=6), placebo (n=6).

All 54 patients randomized were included in the safety population. Fifty-three patients were included in the PD population, with the patient who was discontinued from treatment due to a TEAE not included. Thirty patients were included in the PK population (1 and 5 mg SAR247799).

The mean age of patients was similar between treatment groups, with overall individual values ranging from 39 to 64 years of age. In each treatment group, the majority of patients were male. The mean BMI of patients was similar between treatment groups, with individual values ranging overall from 22.80 to 35.00 kg/m^2.

Pharmacodynamic results:

Flow-mediated dilation (primary endpoint)

One patient (sildenafil treatment group) of the PD population was excluded from the FMD analyses because the FMD curves during hyperemia for this patient did not show the typical shape of a brachial diameter curve and, therefore, interpretation was not possible.

Plots of raw data and changes from baseline for FMD (%) are presented in Figures 1 and 2 below.

At baseline, the mean FMD in the 4 groups ranged from 3.8% to 4.3% and were indistinguishable between groups.

The placebo group showed mean increases compared to baseline of 0.74%, 0.59%, and 0.68% at D14, D21, and D28, respectively. No changes were observed at D35 and D42 (EOS) compared to baseline.

The 50 mg sildenafil (positive control) group showed sustained mean increases of approximately 1.0% to 1.1% compared to baseline at Days 14, 21, and 28. Days 35 and 42 showed mean increases compared to baseline of approximately 0.77% and 0.39%, respectively.

The 1 mg SAR247799 group showed mean increases of approximately 0.47%, 0.67%, and 0.96%, compared to baseline at Days 14, 21, and 28, respectively. Days 35 and 42 showed mean increases compared to baseline of approximately 0.48% and 0.41%, respectively.

The 5 mg SAR247799 group showed mean increases of approximately 0.88%, 1.0%, and 1.1%, compared to baseline at Days 14, 21, and 28, respectively. Days 35 and 42 showed mean increases compared to baseline of approximately 1.1% and 0.45%, respectively.

Figure 1: Summary plot of FMD (%) following SAR247799 1 and 5 mg, sildenafil 50 mg and placebo measured at screening, baseline, Days 14, 21, 28, 35 and 42 (EoS); raw data – PD population

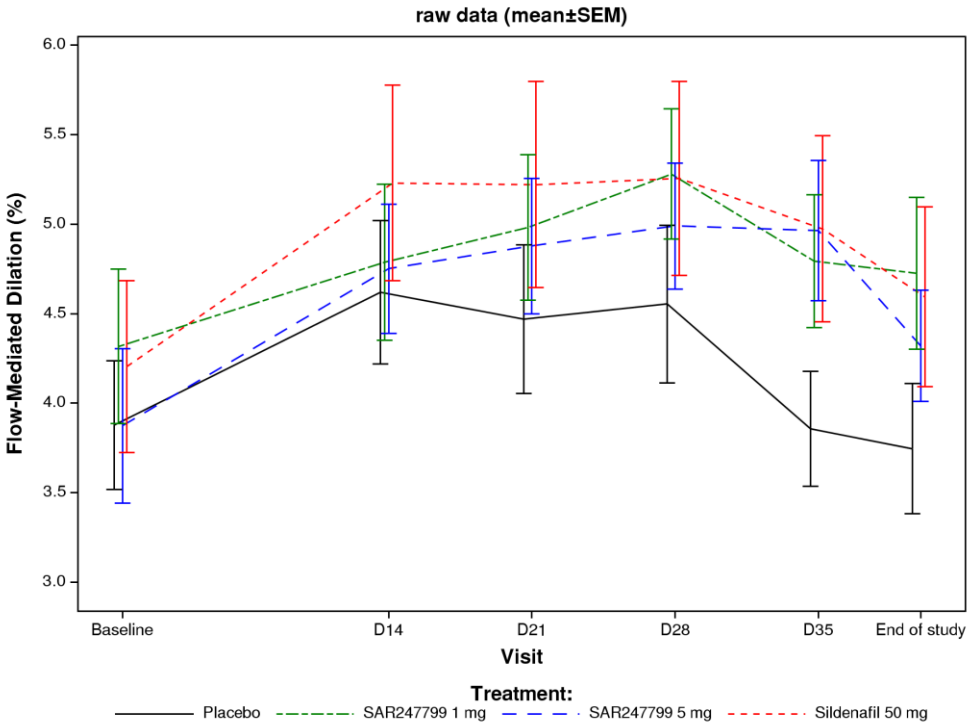
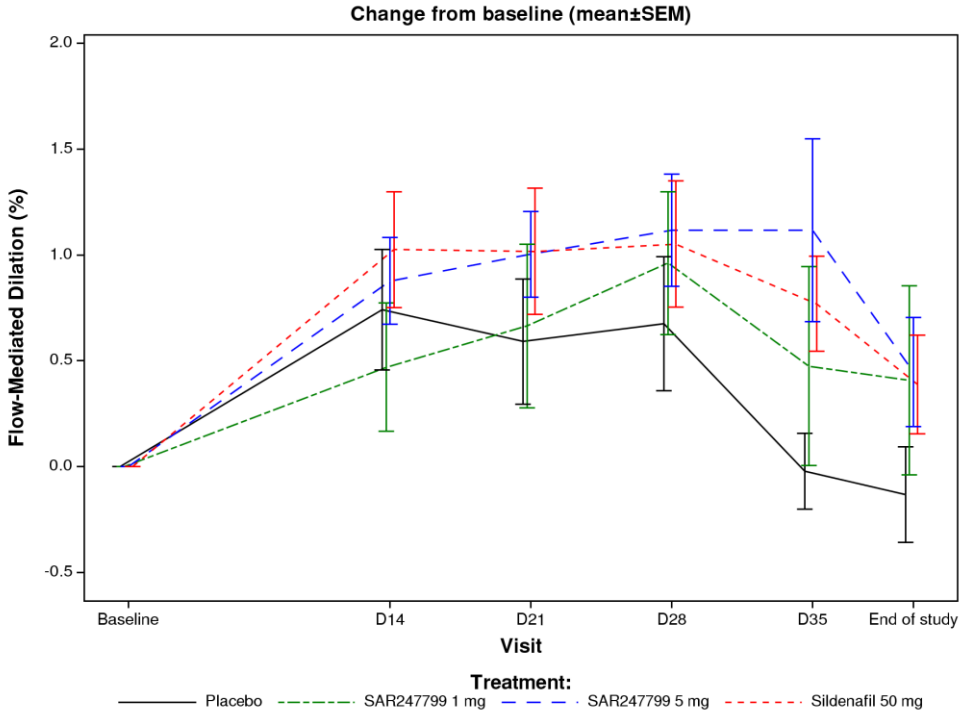


Figure 2: Summary plot of FMD (%) following SAR247799 1 and 5 mg, sildenafil 50 mg and placebo measured at screening, baseline, Days 14, 21, 28, 35 and 42 (EoS); change from baseline – PD population



Laser Doppler perfusion monitoring system assessment (secondary endpoint)

Two patients of the PD population were excluded from the Laser Doppler analyses; 1 patient had a baseline value too high to interpret and 1 patient was excluded because the baseline Laser Doppler measurement could not be performed after several attempts.

Plots of Laser Doppler signal (perfusion unit) after acetylcholine 200 µA iontophoresis in raw data and changes from baseline are presented in Figures 3 and 4 below.

Descriptive statistics show that the placebo changes from baseline values were generally higher or equivalent to those seen in any of the treatment groups at most time points.

No treatment effect could be concluded considering the effect of placebo and the variability.

Similar conclusions can be drawn from Laser Doppler signal data following acetylcholine 80 µA and 140 µA iontophoresis.

Figure 3: Summary plot of Laser Doppler following SAR247799 1 and 5 mg, sildenafil 50 mg and placebo measured at screening, baseline, Days 14, 21, 28, 35 and 42 (EOS); raw data – PD population

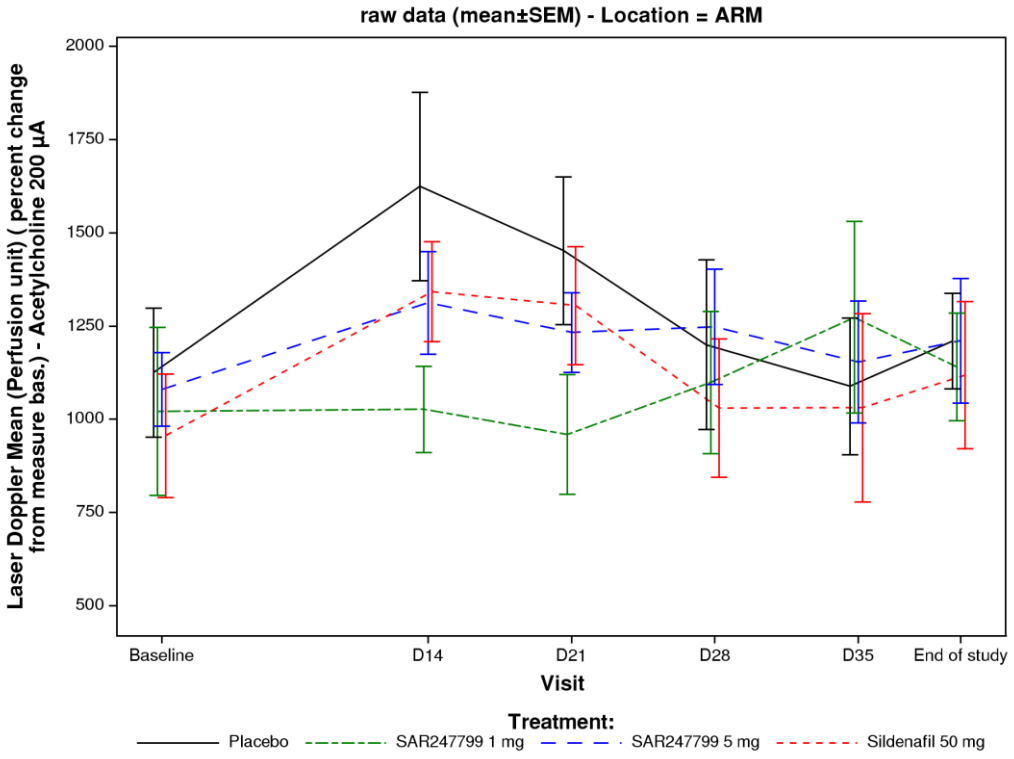
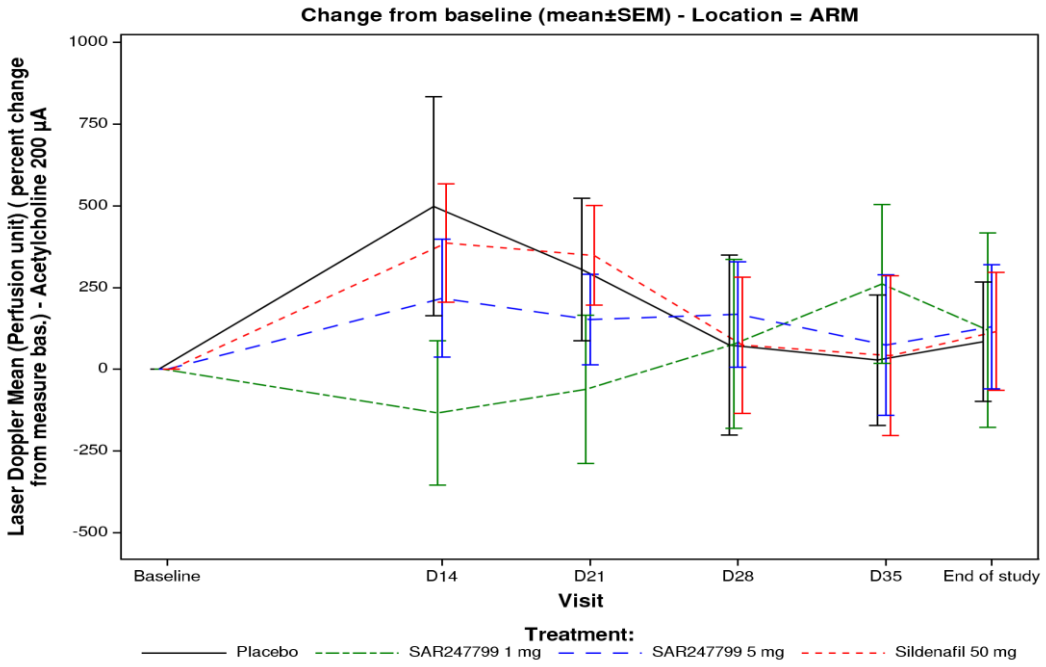


Figure 4: Summary plot of Laser Doppler following SAR247799 1 mg and 5 mg, sildenafil 50 mg and placebo measured at screening, baseline, Day 14, Day 21, Day 28, Day 35 and Day 42 (EOS); change from baseline – PD population



Safety results (secondary endpoint):

There were no deaths, severe TEAEs, or AEs of special interest reported during the study, and no SAEs were reported during the on-treatment period of the study. There was 1 SAE pretreatment for a screen fail patient (silent anterior myocardial infarction) and 1 SAE during the post treatment period (back pain). There was 1 TEAE of ventricular extrasystoles reported during the study, which led to the discontinuation of treatment and the patient did not complete the study.

A total of 19 patients reported mild to moderate TEAEs, with 5 (33.3%) patients of the SAR247799 1 mg treatment group, 6 (40.0%) patients of the SAR247799 5 mg treatment group, 5 (41.7%) patients of the sildenafil 50 mg, and 3 (25.0%) patients of the placebo treatment group. All TEAEs were recovered/resolved.

There were no clinically relevant abnormalities in clinical laboratory parameters.

Overall, the number of patients with vital sign PCSAs was low. A reduction in orthostatic systolic blood pressure was reported in 1 patient, which was associated with a TEAE of dizziness.

In addition to the TEAE that led to treatment discontinuation in the sildenafil group (ventricular extrasystoles), some patients had ECG PCSAs but the number of patients across the treatment groups, including placebo, was similar.

Pharmacokinetic results (secondary endpoint):

Descriptive statistics of plasma PK parameters obtained in T2DM patients receiving oral administration of 1 and 5 mg SAR247799 as a single dose or repeated once daily doses are presented by dose level on Day 1 and Day 14 below.

Descriptive statistics of plasma pharmacokinetic parameters following 1 and 5 mg SAR247799 repeated once daily oral administration by dose level on Day 1 and Day 14

Day	Parameter	Dose	N	Mean	Median	SD	CV%	Min	Max
1	t_{max} (h)	1	15	2.68	2.50	0.320	11.9	2.25	3.25
		5	15	2.42	2.50	0.122	5.05	2.25	2.5
	C_{max} (µg/mL)	1	15	0.0574	0.0538	0.0131	22.8	0.0403	0.0907
		5	15	0.310	0.315	0.0635	20.5	0.207	0.414
	AUC_{0-24} (µg.h/mL)	1	15	1.03	0.983	0.232	22.5	0.750	1.69
		5	15	5.31	5.31	0.955	18.0	3.75	6.87
14	t_{max} (h)	1	15	2.24	2.25	0.0969	4.32	2.00	2.50
		5	15	2.15	2.25	0.116	5.40	2.00	2.25
	C_{max} (µg/mL)	1	15	0.152	0.147	0.0419	27.6	0.0998	0.271
		5	15	0.779	0.760	0.186	23.9	0.500	1.13
	AUC_{0-24} (µg.h/mL)	1	15	2.97	2.78	0.902	30.4	1.84	5.46
		5	15	14.9	14.8	4.03	27.0	8.74	22.3
	Rac_AUC_{0-24}[a]	1	15	2.86	2.70	0.432	15.1	2.10	3.56
		5	15	2.79	2.73	0.492	17.6	2.10	3.64
	Rac_C_{max}[a]	1	15	2.66	2.50	0.443	16.7	1.89	3.41
		5	15	2.54	2.46	0.468	18.4	1.86	3.49

a Rac: accumulation ratio

Median t_{max} was observed from 2.25 to 2.5 hours postdose with no apparent dose effect.

At steady-state, SAR247799 exposure increased as expected by dose proportionality between 1 and 5 mg, with a 5-fold increase in dose resulting in an approximately 5.1- and 5.0-fold in increase in C_{max} and AUC_{0-24}, respectively. Similarly, SAR247799 exposure increased as expected by dose proportionality on Day 1 between 1 and 5 mg.

SAR247799 steady-state conditions were reached on average between Day 9 and Day 10. Mean accumulation ratio (Day14/Day 1) was approximately 2.6 for C_{max} and 2.8 for AUC_{0-24}, with no apparent dose-dependent effect.

Issue date: 06-Jan-2020