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Sponsor: Sanofi **Drug substance(s):** Bamadutide (SAR425899)	**Study Identifiers:** U1111-1191-5658, IND 136429, NCT03376802 **Study code:** PDY15012

Title of the study: A randomized, double-blind, placebo-controlled study to assess the effect of repeated subcutaneous doses of SAR425899 on energy expenditure and safety in overweight to obese male and female subjects

Study center(s): 2 (United States)

Study period:

Date first subject enrolled: 17/Apr/2018

Date last subject completed: 14/Dec/2018

Phase of development: Phase 1b

Objectives:

Primary

To assess in overweight to obese subjects the change in sleep energy expenditure after repeated SC doses of SAR425899.

Secondary

To assess in overweight to obese subjects

- The change in resting, basal and total daily energy expenditure.
- The change in respiratory quotient.
- The change in body composition and core temperature.
- Pharmacodynamic effects on fasting plasma glucose, biomarkers of lipid metabolism and HbA1c.
- Pharmacokinetic parameters for SAR425899 after repeated SC doses.
- Safety and tolerability.

Methodology: Multicenter study, placebo controlled, double-blind, 1:1 randomly allocated ratio, 2-parallel groups (active/placebo), repeated once daily subcutaneous (SC) dosing study with a 7-day run-in period and dose escalation for SAR425899 after 4, 8 and 12 days of treatment.

Number of subjects: Planned: 30 (15 subjects per group)

Randomized: 35

Treated: 35

Evaluated:

Pharmacodynamics: 28

Safety: 35

Pharmacokinetics: 17

Diagnosis and criteria for inclusion: Overweight to obese, male and female subjects, aged 18 to 50 years old (inclusive), with a body mass index between 28.0 and 40.0 kg/m^2 (inclusive), fasting plasma glucose $\leq$125 mg/dL, glycosylated hemoglobin (HbA1c) $\leq$6.5% who were certified as healthy (obesity associated mild concomitant diseases allowed) not receiving any concomitant medication other than stable treatment with statins or antihypertensive drugs (except β-blocker).

Study treatments

Investigational medicinal product: Bamadutide (SAR425899)

Formulation: Cartridges containing 3 mL solution for injection at a concentration of 0.5 mg/mL SAR425899 in sodium dihydrogen phosphate dihydrate, disodium hydrogen phosphate dodecahydrate, sodium chloride, m-cresol, HCl/NaOH and water for injection.

Route(s) of administration: Subcutaneous injection using a pen-type injector (Tactipen).

Dose regimen: 0.06 mg (12U) from Day 1 until Day 4

0.12 mg (24U) from Day 5 until Day 8

0.16 mg (32U) from Day 9 until Day 12

0.2 mg (40U) from Day 13 until Day 19

For subjects not tolerating a dose of 0.2 mg SAR425899 the dose was reduced to 0.16 mg and they continued at this dose level until the end of treatment (Day 19).

Investigational medicinal product: Placebo

Formulation: Cartridges containing 3 mL solution for injection of sodium dihydrogen phosphate dihydrate, disodium hydrogen phosphate dodecahydrate, sodium chloride, m-cresol, HCl/NaOH and water for injection.

Route(s) of administration: Subcutaneous injection using a pen-type injector (Tactipen).

Dose regimen: Equivalent volumes to SAR425899, the amount of volume of 1 injection was adapted accordingly in order to keep the blinding of the study.

Duration of treatment: 19 days

Duration of observation: Total study duration of up to a maximum of 55 days (Screening period: up to 21 days [Days -29 to -8], run-in period 7 days [Days -7 to -1] including 3 chamber days [Days -3 to -1], Treatment period: 19 days [Days 1 to 19] including 3 chamber days [Days 17 to 19] and an end-of-study visit 7 days after the last dosing [Day 26 ± 1 day]. Subjects were confined to the metabolic ward between Day -4 and 20.

Criteria for evaluation:

Pharmacodynamics:

Primary:

- Sleep energy expenditure (EE_{sleep}).

Secondary:

- Total daily energy expenditure (EE_{total}), resting energy expenditure (EE_{rest}), basal energy expenditure (EE_{basal}), 24-hour, sleep, resting and basal respiratory quotient (RQ), fat mass and fat free mass (by dual energy x-ray absorptiometry [DEXA] scan), Diet Induced Thermogenesis (DIT), fasting plasma glucose, HbA1c, lipid biomarker (free fatty acids, triglycerides, total cholesterol, high-density lipoprotein/low-density lipoprotein-cholesterol) and ketone bodies (blood and urine).

Safety:

- Assessment of Adverse Events (AEs) / Treatment-Emergent Adverse Events (TEAEs), vital signs (supine and standing blood pressure, heart rate), physical examination, core body temperature, clinical laboratory evaluations including hematology, biochemistry, coagulation, urinalysis, urinary cortisol, 12-lead electrocardiogram (ECG; automatic reading), 24-hours average heart rate, amylase / lipase and antibody status.

Pharmacokinetics:

- SAR425899 pharmacokinetic (PK) parameters including C_{max}, t_{max}, C_{trough}, AUC, AUC_{0-24}, AUC_{last}, $t_{1/2z}$, and CL/F

Statistical methods:

Pharmacodynamics:

The pharmacodynamic (PD) analyses were conducted on all subjects with no major or critical deviations related to investigational medicinal product and/or PD measurements, for whom PD data were considered sufficient and interpretable. Descriptive statistics and graphs were provided on raw data and change from baseline for selected parameters of interest.

The EE_{sleep} and EE_{total} in kcal/d were measured by indirect calorimetry repeatedly on 3 consecutive days during run-in (baseline) and at the end-of-treatment period. Values were extrapolated to a 24-hours period.

In order to achieve a metabolic condition during which body weight loss and body weight loss mediated metabolic adaptation of energy expenditure (EE) is similar in both treatment arms, the effect of energy intake on body weight loss should be neutralized. This was achieved through a homogenous reduction of energy intake in placebo and treatment groups, which is a 1000 kcal deficit per day. Furthermore, EE data was adjusted for the changes in body weight and body composition as measured by DEXA in the analysis (see below).

Primary PD analysis:

Change in EE_{sleep}:

Analysis of EE_{sleep} change from baseline was based on a linear model with treatment and stratification factors (site and gender) as a class effect, EE_{sleep} at baseline and change in body weight as covariates and on-treatment study days as repeating factor. Treatment difference, in change from baseline was based on corresponding contrasts and reported with point estimate, 2-sided 90% confidence interval, and corresponding 1-sided p-value. Primary endpoint (EE_{sleep}) was tested 1-sided at a Type 1 error level of alpha=0.05 for an effect between treatments.

Sensitivity analyses were performed adjusting the response on baseline body weight or change from baseline in body composition: ie; fat free mass and fat mass, instead of the change in body weight.

Secondary PD analyses:

Change in EE_{total}:

The EE based secondary endpoint was analyzed with a method corresponding to the primary analysis (without sensitivity analyses). Due to the explorative character of the secondary endpoints, no adjustment for multiple testing was performed.

Exploratory analyses

Change in metabolic adaptation for EE_{sleep} and EE_{total}:

Metabolic adaptation is defined as a decrease in EE beyond what is predicted based on the change in body composition. Predicted EE values at each time point were derived from a linear regression at baseline including body composition and gender as covariates. Difference between predicted and observed EE was calculated for run-in and end-of-treatment periods. Then, change from baseline of the residuals (residual difference) was analyzed through linear model with treatment and stratification factors (site and gender) as class effects, baseline residual as covariate and study day as repeating factor. Treatment difference for change from baseline was based on corresponding contrasts and reported with point estimate, 2-sided 90% confidence interval, and corresponding 1-sided p-value. Treatment difference was further tested 1-sided at a Type 1 error level of alpha=0.05.

Safety:

The safety analysis was conducted on all subjects who received at least 1 dose of IMP and was based on the review of the individual values (clinically significant abnormalities) and descriptive statistics (summary tables and plots if appropriate). Individual values were flagged for potentially clinically significant abnormalities (PCSAs) and TEAEs were tabulated (counts and percent).

Descriptive statistics were generated by treatment and timepoint for selected parameters of interest. In addition, raw data and changes from baseline for selected parameters were summarized in descriptive statistics and summary plots.

Pharmacokinetics:

The PK analysis was conducted on all subjects with no major or critical deviations related to the investigational medicinal product (eg, missing or incorrect SC injection) and for whom PK data were considered sufficient and interpretable. Subjects having received only placebo was not included in the analyses. Plasma SAR425899 concentrations and PK parameters (where applicable) were summarized using descriptive statistics.

During the PK analysis the calculated PK parameters were changed as the sampling schedule didn't allow for reliable determination of some of the planned parameters and they were not suitable for steady state data. The AUC, $t_{1/2z}$, and CL/F were not calculated. Steady state CL/F (CL_{ss}/F) was calculated instead. The PK parameter CL_{ss}/F was calculated as $Dose/AUC_{0-24}$, which is appropriate for steady state data. The AUC was not calculated as this is steady state data and was therefore not appropriate. The $t_{1/2z}$ was not calculated due to the short sampling schedule resulted in the terminal elimination phase not being accurately captured.

Summary:

Population characteristics:

Thirty-five (35) healthy obese subjects were randomized and treated (safety population) with SAR425899 (N=17) or placebo (N=18). Twenty-eight (28) subjects completed the treatment and the full study period while 7 subjects prematurely discontinued the study, 6 of them because of an adverse event. All 28 completers were included in the PD population. The number of evaluable completers was 11 for SAR425899 and 17 for placebo.

Mean (±standard deviation [SD]) age and weight at baseline was 36.5 (±7.1) years and 91.94 (±10.48) kg, respectively, for the safety population. Of the 35 subjects included 24 (68.6%) subjects were males and 11 (31.4%) subjects were females. Age, weight and gender were equally distributed between both treatment arms.

Pharmacodynamic results:

- Sleep energy expenditure (EE_{sleep})

Mean (±SD) EE_{sleep} (in kcal/day) at baseline (BL) was comparable between both treatment groups (SAR425899: 1553.2 [±254.6], placebo: 1598.2 [±270.4]).

As expected under a diet with a high caloric deficit resulting in a substantial body weight loss (see section below) EE_{sleep} declined in both treatment arms from baseline until end of treatment as a consequence of metabolic adaptation. But while subjects in the SAR425899 group lost more body weight than in the placebo group, the decrease from BL for EE_{sleep} on Days 17, 18, and 19 (on-treatment chamber days, ±SD) was larger in the placebo group (-139.3 ± 45.3, -95.4 ± 75.3, and -145.4 ±86.3) compared to SAR425899 (-48.6 ± 102.1, -48.1 ± 94.1, and -82.0 ± 87.5).

As EE is linked to body weight (reduction of BW decreases EE) and body composition, the change of EE_{sleep} was adjusted to changes in BW and body composition (as measured by DEXA scan). The point estimates for the treatment difference between SAR425899 and placebo adjusted for body weight and body composition are shown in Table 1 and Table 2.

Table 1 - EE_{sleep} adjusted to change in body weight: Point estimate, two-sided 90% and one-sided p-values of the model of treatment difference for change from baseline in sleep energy expenditure - PD population

Parameter	Treatment difference	Estimate	90% CI	DF	t-statistic	p-value
Sleep Energy Expenditure (kcal/day)	SAR425899 - placebo	114.19	(55.15 to 173.23)	22.0	3.32	0.002

Parameter denotes change from baseline.
The linear model includes treatment and stratification factors (site and gender) as fixed effects and sleep energy expenditure at run-in period and change from baseline in body weight as covariates.
Estimate: a positive value indicates a larger decrease from baseline in placebo group than in treatment group.
Null hypothesis: decrease from baseline is equal or larger in treatment group than in placebo group; null hypothesis is rejected if p-value is lower than 0.05.
PGM=PRODOPS/SAR425899/PDY15012/CSR/REPORT/PGM/pd_diff_ee_primary.sas OUT=REPORT/OUTPUT/pd_diff_ee_primary_k_t_5_i.rtf (22AUG2019 - 15:42)

Table 2 - EEsleep adjusted to change in body composition: Point estimate, two-sided 90% and one-sided p-values of the model of treatment difference for change from baseline in sleep energy expenditure - PD population

Parameter	Treatment difference	Estimate	90% CI	DF	t-statistic	p-value
Sleep Energy Expenditure (kcal/day)	SAR425899 - placebo	76.58	(20.44 to 132.72)	20.8	2.35	0.014

Parameter denotes change from baseline.
The linear model includes treatment and stratification factors (site and gender) as fixed effects and sleep energy expenditure at run-in period and change from baseline in body composition as covariates.
Estimate: a positive value indicates a larger decrease from baseline in placebo group than in treatment group.
Null hypothesis: decrease from baseline is equal or larger in treatment group than in placebo group; null hypothesis is rejected if p-value is lower than 0.05.
PGM=PRODOPS/SAR425899/PDY15012/CSR/REPORT/PGM/pd_diff_ee_primary.sas OUT=REPORT/OUTPUT/pd_diff_ee_ss_bc_k_t_5_i.rtf (22AUG2019 - 15:45)

The EE_{sleep} decrease from baseline for SAR4256899 adjusted for change in body weight or body composition was statistically significantly smaller than for placebo (point estimate = 114.19, 1-sided p-values: 0.002 [adjusted to change in body weight] and point estimate = 76.58, 0.014 [adjusted to change in body composition]).

Similar results were obtained when adjusting for baseline body weight (point estimate = 57.38, p-value = 0.034) or when analyzing residual EE_{sleep} (a function of metabolic adaptation; point estimate = 77.17, p-value = 0.002).

- Total energy expenditure (EE_{total})

Mean EE_{total} (in kcal/day) at baseline was comparable between both treatment groups (SAR425899: 2095.5, placebo: 2081.2).

In contrast to EE_{sleep}, the EE_{total} decrease from BL (±SD) for Days 17, 18 and 19 was smaller in the placebo group (-191.8 ± 66.4, -162.7 ± 70.9, and -161.4 ± 72.4) than for SAR425899 (-218.5 ± 108.2, -233.3 ± 107.9, and -244.6 ± 85.2).

The point estimate for the treatment difference between SAR425899 and placebo for EE_{total} adjusted to body weight is shown in Table 3. When adjusting for change in body weight the EE_{total} decrease from baseline in the SAR4256899 group was not statistically smaller than from placebo (1-sided p-value: 0.825).

Table 3 - EEtotal adjusted to change in body weight: Point estimate, two-sided 90% and one-sided p-values of the model of treatment difference for change from baseline in sleep energy expenditure - PD population

Parameter	Treatment difference	Estimate	90% CI	DF	t-statistic	p-value
Energy Expenditure 24h (kcal/day)	SAR425899 - placebo	-38.11	(-106.73 to 30.52)	22.1	-0.95	0.825

Parameter denotes change from baseline.
The linear model includes treatment and stratification factors (site and gender) as fixed effects and total daily energy expenditure at run-in period and change from baseline in body weight as covariates.
Estimate: a positive value indicates a larger decrease from baseline in placebo group than in treatment group.
Null hypothesis: decrease from baseline is equal or larger in treatment group than in placebo group; null hypothesis is rejected if p-value is lower than 0.05.
PGM=PRODOPS/SAR425899/PDY15012/CSR/REPORT/PGM/pd_diff_ee_secondary.sas OUT=REPORT/OUTPUT/pd_diff_ee_secondary_k_t_5_i.rtf (22AUG2019 - 15:20)

- Resting energy expenditure (EE_{rest})

Mean EE_{rest} (in kcal/day) at baseline was comparable between both treatment groups. Similar to EE_{sleep}, EE_{rest} declined in both treatment groups from baseline until end of treatment as a consequence of body weight loss and metabolic adaptation, but decrease from baseline for EE_{rest} was again larger in the placebo group compared to SAR425899 on 2 out of 2 on-treatment chamber days.

- Basal energy expenditure (EE_{basal})

Mean EE_{basal} (in kcal/day) at baseline and change from baseline was comparable between both treatment groups.

- Body weight (PD population, N=28)

At baseline the means (±SD) of body weight were comparable between placebo (90.39 ± 12.08 kg) and SAR425899 (92.68 ± 9.89 kg).

Mean change from baseline for body weight on Days 5, 9, 16 and 20 was -1.07, -1.55, -2.22 and -2.83 kg for placebo, and -0.91, -1.76, -3.39, and -4.30 kg for SAR425899.

- Body composition

At baseline the means (±SD) of fat and fat free mass were comparable between placebo and SAR425899 (fat mass: placebo 33.6 ± 6.1 kg, SAR425899 35.3 ± 6.7 kg; fat free mass: placebo 57.3 ± 11.4 kg, SAR425899 57.9 ± 9.2 kg).

Mean change from baseline (±SD) for fat- and fat free mass (kg) was -1.5 ± 0.5 and -2.4 ± 1.2 kg for SAR425899, and -1.0 ± 0.5 and -1.8 kg ± 0.8 for placebo, respectively.

- Respiratory quotient

The RQ calculated from the ratio of carbon dioxide produced by the body to oxygen consumed by the body. The RQ value indicates which macronutrients are being metabolized, as different energy pathways are used for fats, carbohydrates, and proteins. If metabolism consists solely of lipids, the RQ is 0.7, for proteins it is 0.8, and for carbohydrates it is 1.0. Most of the time, however, energy consumption is composed of both fats and carbohydrates. The approximate RQ of a mixed diet is 0.8.

Total mean daily RQ at baseline was comparable between both treatment groups. It decreased in both groups toward end of treatment suggesting a shift to more lipid metabolization. Change from baseline was roughly 2-fold higher under treatment with SAR425899 compared to placebo.

Sleep RQ at baseline was comparable between both treatment groups but change from baseline was slightly higher under treatment with SAR425899 compared to placebo.

Resting RQ at baseline was comparable between both treatment groups but change from baseline was roughly 2-fold higher under treatment with SAR425899 compared to placebo. Similar to total daily RQ, resting RQ was closer to 0.8 in the SAR425899 group at the end of treatment, suggesting a shift to more lipid metabolization.

Results obtained for basal RQ are similar as described for resting RQ.

- Body weight

At baseline the mean (±SD) of body weight were comparable between placebo (90.39 ± 12.08 kg) and SAR425899 (92.68 ± 9.89 kg).

Mean change from baseline for body weight on Days 5, 9, 16 and 20 was -1.07, -1.55, -2.22, and -2.83 kg for placebo, and -0.91, -1.76, -3.39, and -4.30 kg for SAR425899.

- Glycemic parameters, blood lipids, and ketone bodies

Ketone bodies tended to be higher at end of treatment in the SAR425899 treatment group as compared to placebo.

Safety results:

Overall, 16 (94.1%) subjects treated with SAR425899 (16 [94.1%] subjects) and 15 (83.3%) subjects treated with placebo experienced at least 1 TEAE during the study. Two subjects in the SAR425899 group and 1 subject in the placebo group were permanently discontinued by the Investigator due to a TEAE. Three subjects in the in the SAR425899 group decided to withdraw from treatment because of a TEAE. An AE of special interest was reported in 1 subject each in the SAR425899 and placebo group. In both cases this was an alanine aminotransferase increase >2 x the upper limit of normal.

More subjects reported TEAEs in the system organ classes (SOCs) of gastrointestinal disorders and nervous system disorders compared to the other SOCs. Gastrointestinal TEAEs ie, nausea and vomiting observed in this study were comparable to known effects of the glucagon-like peptide-1 class.

Treatment-emergent AEs in the SOC of Gastrointestinal disorders were reported by 15 (88.2%) subjects in the SAR425899 group and 9 (50.0%) subjects in the placebo group. The TEAEs reported by more subjects were constipation (SAR452899: 12 [70.6%] subjects, placebo: 5 [27.8%] subjects), nausea (SAR452899: 11 [64.7%] subjects, placebo: 4 [22.2%] subjects), vomiting (SAR452899: 10 [58.8%] subjects, placebo: 0 subjects), abdominal distention: (SAR452899: 5 [29.4%] subjects, placebo: 1 [5.6%] subject), and dyspepsia: (SAR452899: 5 [29.4%] subjects, placebo: 0 subjects). Vomiting, decreased appetite, diarrhea and dehydration was reported in the SAR425899 group by 10 (58.8%) subjects, 4 (23.5%) subjects, 3 (17.6%) subjects, and 1 (5.9%) subjects, respectively, but not at all in the placebo group.

Potentially clinically significant abnormalities reported for clinical laboratory evaluations and vital signs were low, with no obvious differences between treatment groups. None of the reported PCSAs were considered to be clinically significant. Body weight was decreased for both treatment groups, with the SAR452899 showing a greater decrease than the placebo group.

Regarding the ECG parameters, the total number of PCSAs reported were low with no obvious difference between the treatment groups, except for a PCSA of >90 beats/min reported for 7 subjects in the SAR425899 group along with a PCSA of >90 beats/min and increase from baseline ≥20 beats/min reported for 6 subjects in the SAR425899 group.

For the anti-SAR425899 antibody, all subjects in the SAR425899 group tested negative.

Pharmacokinetic results:

On Day 16 following administration of 0.2 mg SAR425899, geometric mean values for SAR425899 AUC_{0-24} and C_{max} were 421 ng.h/mL and 25.0 ng/mL, respectively, and the median t_{max} was 6.50 hours. Steady state had been achieved by the morning of Day 16, with a geometric mean C_{trough} value of 11.4 ng/mL, representing approximately 46% of C_{max}.

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