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

Sponsor: Sanofi **Drug substance(s):** Bamadutide (SAR425899)	**Study Identifiers:** U1111-1205-1368, IND 124931, NCT03414736 **Study code:** TDR15516
Title of the study: A randomized, comparative, open label study to assess the safety and tolerability of 3-arm, parallel, repeated subcutaneous dose regimens of SAR425899 in overweight to obese subjects and T2DM patients not requiring anti-diabetic pharmacotherapy, with an optional 6-month safety extension period	
Study center(s): 3 (United States)	
Study period: **Main study** Date first patient enrolled: 19/Jan/2018 Date last patient completed: 17/Apr/2018 **Optional 6-month safety extension period** Date first patient enrolled: 31/Mar/2018 Date last patient completed: 05/Oct/2018	
Phase of development: Phase 1b	
Objectives: **<u>Main study period</u>** **Primary objective** To assess in overweight to obese subjects and type-2 diabetes mellitus (T2DM) patients not requiring anti-diabetic pharmacotherapy the safety and tolerability of 3 different dose escalation regimens of SAR425899 in terms of the relative and absolute frequency and severity gastrointestinal (GI) adverse event (AE)s.	

Secondary objectives

To assess in overweight to obese subjects and T2DM patients not requiring anti-diabetic pharmacotherapy:

- The effect of once daily (QD) dosing of SAR425899 on body weight (BW) and fasting plasma glucose (FPG) and glycosylated hemoglobin (HbA1c) over 8 weeks.
- Safety and tolerability.

Other objectives

Pharmacokinetics (PK) parameters of SAR425899

Optional 6-month safety extension period

Primary objective

To assess the safety and tolerability of SAR425899 after 6 months treatment at the maximum dose that was individually well tolerated during the main part of the study in terms of the relative and absolute frequency and severity of GI AEs.

Secondary objectives

To assess in overweight to obese subjects and T2DM patients not requiring anti-diabetic pharmacotherapy:

- The effect of QD dosing of SAR425899 on BW, FPG and HbA1c over 8 months.
- Safety and tolerability.

Other objectives

Pharmacokinetic parameters of SAR425899.

Methodology: A multi-center, open label,1:1:1 ratio randomized, 3-arms, parallel group, dose escalation, subcutaneous (SC) injections, duration of 12-weeks with optional 6-months safety extension.

At randomization subjects were prescribed a 500 kcal per day deficient diet and were encouraged to exercise regularly (recommended 150 minutes per week of brisk walking).

Number of patient:	Planned: 60
	Randomized: 60
	Main study period:
	Treated: 60
	Optional 6-month safety extension period:
	Included: 26
	Treated: 26
Evaluated:	
	Main study period:
	Safety: 60
	Pharmacodynamics: 57
	Pharmacokinetics: 50
	Optional 6-month safety extension period:
	Safety: 26
	Pharmacodynamic: 23
	Pharmacokinetics: 21

Diagnosis and criteria for inclusion: Male and female, overweight to obese subjects, T2DM patients not requiring anti-diabetic pharmacotherapy, aged between 18 and 75 years (inclusive), body mass index of ≥27 kg/m^2.

Study treatments

Investigational medicinal product(s): Bamadutide (SAR425899)

Formulation: Cartridges containing 3 mL solution for injection, at a concentration of 0.5 mg/mL SAR425899

Route(s) of administration: Subcutaneous doses via a Tactipen injector

Dose regimen:

Main Study period

Three dose escalation regimens (cohorts)

Cohort 1: Daily dose escalation

Starting dose of 20 µg (4 units [U]) with daily 5 µg (1 U) increments to 200 µg (40 U).

- Escalation phase 20 µg (4 U) to 195 v (39 U): Day 1 to Day 36.
- 200 µg (40 U) from Day 37 to Day 56.

In Cohort 1, in the case of unwanted GI side effects (nausea, diarrhea, vomiting, bloating etc), the treatment was continued at the same dose level until the symptoms disappeared before administration of the next dose level or until the total treatment duration of 8 weeks was reached.

Cohort 2: Weekly dose escalation in 6 escalation steps (7 dose levels)

Starting dose of 20 µg (4 U) with weekly 30 µg (6 U) increments to 200 µg (40 U).

- 20 µg (4 U) from Day 1 to Day 7.
- 50 µg (10 U) from Day 8 to Day 14.
- 80 µg (16 U) from Day 15 to Day 21.
- 110 µg (22 U) from Day 22 to Day 28.
- 140 µg (28 U) from Day 29 to Day 35.
- 170 µg (34 U) from Day 36 to Day 42.
- 200 µg (40 U) from Day 43 to Day 56.

Cohort 3: Weekly dose escalation in 4 escalation steps (5 dose levels)

Starting dose of 40 µg (8 U) with weekly 40 µg (8 U) increments to 200 µg (40 U).

- 40 µg (8 U) from Day 1 to Day 7.
- 80 µg (16 U) from Day 8 to Day 14.
- 120 µg (24 U) from Day 15 to Day 21.
- 160 µg (32 U) from Day 22 to Day 28.
- 200 µg (40 U) from day 29 to Day 56.

In Cohort 2 and 3, where unwanted GI side effects were experienced, and the side effects did not resolve before the next dose escalation, treatment on the same dose level was continued for another 7 days. In the case of persistent side effects, treatment at the same dose level continued at 7-day intervals until symptoms resolved or until the total treatment duration of 8 weeks was reached.

Optional 6-month safety extension period

Subjects continued to receive treatment with QD SAR425899 at the maximum dose that was individually well tolerated during the main part of the study (any dose ≤200 µg [40 U]). This dose was kept stable throughout the 6-month extension period.

Main study and optional 6-month safety extension period

Doses of SAR425899 were injected in the morning at the same time every day except on clinical visit days. On clinical visit days, the SAR425899 injection time was after blood test/electrocardiogram (ECG) measurement in the morning and was to be coordinated with PK sampling time.

Duration of treatment/participation:

Main study period: 56 days

Optional 6-month safety extension period: 8 months (from first investigational medicinal product [IMP] administration during the main study period to last assessment).

Duration of observation:

Main study period: Maximum duration for main study: 12 weeks per patient (up-to 3-weeks screening period, 8-week treatment period, 3-day post treatment follow-up period).

Optional 6-month safety extension period: Maximum study duration including screening: 9 months (12 weeks main study and 6 months safety extension period, 3-day post treatment follow-up period).

Criteria for evaluation:

Safety:

Main study period

Primary

- Relative and absolute frequency and severity of GI AEs (for example nausea and vomiting).

Secondary

- Assessment of AEs/treatment emergent adverse (TEAEs) and AEs of special interest (AESI), like hypoglycemia (severe, documented, asymptomatic, probable, relative). Vital signs (blood pressure, heart rate), physical examination, clinical laboratory evaluations including hematology, biochemistry, urinalysis and amylase/lipase, 12-lead ECG (automated reading), and anti-SAR425899 antibodies.

6-month safety extension period

Primary

- Relative and absolute frequency and severity of GI AEs (for example nausea and vomiting) during the 6-month safety study extension period.

Secondary

- Assessment of AEs/TEAEs and AESIs, hypoglycemia (severe, documented, asymptomatic, probable, relative). Vital signs (blood pressure, heart rate), physical examination, clinical laboratory evaluations including hematology, biochemistry, urinalysis, and amylase/lipase, 12-lead ECG (automatic reading) and antidrug antibodies.

Pharmacodynamics:

Main study period

Secondary

- Change in BW, FPG and HbA1c from baseline to Week 8.
- Circumference of waist and hip measurement.

Optional 6-month extension period

Secondary

- Change in BW, FPG and HbA1c from baseline (Week 0) and start of the extension period (Visit 11 EXT) to Month 8, respectively.

Pharmacokinetics:

- SAR425899 concentrations measured in plasma.

Statistical methods:

Safety

Assessment of AEs, TEAEs and AESI, like hypoglycemia (severe, documented, asymptomatic, probable, relative). Vital signs (blood pressure, heart rate), physical examination, clinical laboratory evaluations including hematology, biochemistry, urinalysis and amylase/lipase, ECG (automated reading), and anti-SAR425899 antibodies.

Adverse events were coded using the Medical Dictionary for Regulatory Activities (Version 20.1).

Pharmacodynamics

Analyses for FPG and BW were summarized by descriptive statistics and mean plots on raw data and change from baseline over time, by cohort assigned for main study and additionally pooled over all cohorts.

Pharmacokinetics

Plasma concentration of SAR425899 was determined by Covance.

Summary:

Safety:

Main study

The maximum maintenance dose of 200 µg was reached in 38 (63.3%) of all patients, of which 12 (63.2%), 10 (47.6%) and 16 (80.0%) were randomized to Cohort 1, Cohort 2, and Cohort 3, respectively.

A higher percentage of patients in Cohort 3 (90%) reported at least 1 TEAE, followed by Cohort 2 (85.7%) and Cohort 1 (84.2%). More patients reported severe TEAEs in Cohort 2 (5 [23.8%] patients), followed by Cohort 1 (2 [10.5%] patients) and Cohort 3 (1 [5.0%] patients). Treatment emergent AEs leading to permanent treatment discontinuation by the Investigator was reported in all 3 cohorts, and AESIs in Cohort 1 (1 [5.3%] patients) and Cohort 2 (2 [9.5%] patients).

The primary endpoint of this study was GI AEs reported by patients or observed by the Investigator.

There was no obvious difference in tolerability between the 3 dose escalation regimens. However, comparing the totality of data, there was a trend that Cohort 3 (4 escalation steps) was better tolerated, compared to Cohort 1 (daily dose escalation) and Cohort 2 (6 escalation steps) for the following reason:

- In Cohort 3, 80% of the patients reached the maximum maintenance dose of 200µg compared to 63.2% patients from Cohort 1 and 47.6% from Cohort 2
- Number of early treatment discontinuations was lower in Cohort 1 and 3 (3 patients in both cohorts) compared to Cohort 2 (5 patients)
- In Cohort 3 no AESI was reported compared to 1 AESI in Cohort 1 (lipase increased) and 2 AESI in Cohort 2 (urticaria and alanine aminotransferase increased)

Even though the total number of patients with GI TEAEs was higher in Cohort 3 (85.0%) compared to Cohort 1 (68.4%) and 2 (81.0%), the number of patients that reported GI TEAEs being as of moderate or severe intensity was lower in Cohort 3 compared to Cohort 1 and Cohort 2. Vomiting rated as severe in intensity was reported in 4 patients (2 patients in Cohort 1 and 2 patients in Cohort 2). Severe diarrhea was reported in 2 patients in Cohort 2.

Withdrawal due to GI AEs mainly occurred within the first 3 weeks of treatment (5 out of the 8 patients). The incidence of nausea was highest during Week 2 and Week 3 and declined thereafter.

Higher percentage of patients reported TEAEs in the system organ class of GI disorders and general disorders and administration site conditions. Gastrointestinal TEAEs ie, nausea and vomiting observed in this study were comparable to known effects of the GLP-1 class. Most of the GI AEs were graded as Grade 1 in severity.

Gastrointestinal AEs were reported by 2 (10.5%) patients in Cohort 1 (severe vomiting) and 4 (19.0%) patients in Cohort 2 (severe vomiting [2 patients] and severe diarrhea [2 patients]) as Grade 3 severity.

Four patients, 1 (5.3%) patient in Cohort 1 (injection site reaction), 1 (4.8%) patient in Cohort 2 (urticaria) and 2 (10.0%) patients in Cohort 3 (injection site erythema and nausea) reported TEAEs leading to permanent treatment discontinuation as per the Investigators' decision.

Potentially clinically significant abnormalities were reported for clinical laboratory evaluations and vital signs were low, with no obvious differences between cohorts, and none were considered to be clinically significant.

For the anti-SAR425899 antibody a total of 20 (33.3%) patients converted from negative at baseline to positive status and among them all were treatment-induced.

6-Month safety extension period

Overall, a total of 26 patients participated in the study extension period. Eighteen (69.2%) of these patients were at an individual maintenance dose of 200 µg at the end of the extension period. No maintenance dose could be determined for 5 (19.2%) patients.

No SAEs or AESI were reported during the 6-month safety extension period. Four subjects prematurely discontinued treatment, but none were due to AEs.

In the 6-month safety extension period, the most frequently observed TEAEs by SOC were GI disorders (11[42.3%] patients), followed by infections and infestations, respiratory, thoracic and mediastinal disorders, musculoskeletal and connective tissue disorders, and general disorders and administration site conditions (all 2 [7.7%] patients). Gastrointestinal disorders were reported in 2 (28.6%) patients in Cohort 1, 3 (37.5%) patients in Cohort 2, and 6 (54.5%) patients in Cohort 3. The majority of patients experiencing GI TEAEs reported GI events of mild intensity.

In general, more patients reported onset of first vomiting in the first 2 to 4 weeks. Small differences in the first onset between the 3 cohorts should be interpreted with caution due to the low patient number per cohort. Around Day 140 after 5 months of treatment there appears to be a striking increase in the onset of vomiting in Cohort 3. However, at this time point only 4 patients who were originally randomized to Cohort 3 were still in the study. In addition, this increase is less pronounced for the subset of events of vomiting that were considered as possible related to IMP.

Potentially clinically significant abnormalities were reported for clinical laboratory evaluations and vital signs were low, with no obvious differences between cohorts, and none were considered to be clinically significant.

For the anti-SAR425899 antibody by Week 32 (Month 8), more than 70% of the patients had converted from negative to positive status from baseline.

Pharmacodynamics:

Main Study

Mean BW change (kg) (±standard deviation [SD]) between baseline and Week 8 were as follows:

- Cohort 1: -6.91 (±4.11) kg (n=14).
- Cohort 2: -4.37 (±2.88) kg (n=15).
- Cohort 3: -5.05 (±2.26) kg (n=17).

Mean FPG (mmol/L) (±SD) between baseline and Week 8 were as follows:

- Cohort 1: -0.55 (±0.49) mmol/L (n=14).
- Cohort 2: -0.47 (±0.51) mmol/L (n=15).
- Cohort 3: -0.23 (±0.49) mmol/L (n=17).

6-Month safety extension period

For the pharmacodynamic extension population, the mean BW change (kg) (±SD) and corresponding median between baseline and Week 32 (Month 8) were as follows:

- Cohort 1 assigned for main study: -8.70 (±8.73) kg (n=5; median= -10.00 kg).
- Cohort 2 assigned for main study: -9.34 (±10.66) kg (n=8; median= -5.90 kg).
- Cohort 3 assigned for main study: -8.75 (±6.61) kg (n=8; median= -10.00 kg).
- All cohorts: -8.96 (±8.39) kg (n=21; median= -9.20 kg).

The mean BW for the pharmacodynamic extension population was 100.35 ±18.05 kg (n=23; median=97.8 kg) at baseline and dropped to 89.27 ±15.38 kg (n=21; median=91.9 kg) at Week 32 (Month 8).

Mean FPG change (mmol/L) (±SD) and corresponding median between baseline and Week 32 (Month 8) were as follows:

- Cohort 1 assigned for main study: -0.64 (±0.67) mmol/L (n=5; median= -0.61).
- Cohort 2 assigned for main study: -0.46 (±0.72) mmol/L (n=8; median= -0.33).
- Cohort 3 assigned for main study: -0.44 (±0.61) mmol/L (n=8; median= -0.33).
- All cohorts: -0.50 (±0.64) mmol/L (n=21; median= -0.39).

Pharmacokinetic:

- Following escalating SC administrations of SAR425899, plasma trough concentrations of SAR425899 were roughly similar across the 3 different dose escalation regimens by the final visit of the main study period (Visit 11, Week 8, Day 56), with arithmetic mean Ctrough values of 18.7, 12.8 and 16.6 ng/mL for Cohorts 1, 2 and 3, respectively. Arithmetic mean C6h values at Visit 11 also appeared similar across Cohorts 1, 2 and 3, with respective values of 29.8, 25.7 and 27.8 ng/mL.
- Based on pooled cohort data due to limited number of subjects in each cohort participating in the 6-month safety extension period, arithmetic mean Ctrough values were roughly similar between Visits 14 and 17 (30.9 and 37.8 ng/mL, respectively) and appeared slightly higher than the arithmetic mean Ctrough values observed in each cohort at Visit 11.
- Comparisons using Ctrough should be interpreted with caution due to the high between-subject variability observed in all cohorts (CV% ranging from 48% to 153%). The between-subject variability in C6h was lower than that for Ctrough, with CV% ranging from 38% to 41%.

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