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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:** U1111-1200-2164, NCT03350191, 2017-001789-23 **Study code:** PDY15264
Title of the study: A PET/CT study to assess the receptor occupancy by SAR425899 after repeat dosing using radiolabeled tracers for the glucagon and GLP-1 receptor in overweight to obese T2DM patients	
Study center(s): 1, CTC, Uppsala, Sweden	
Study period: Date first patient enrolled: 17/Jan/2018 Date last patient completed: 07/Jun/2018 Study enrollment stopped in June 2018 and study stopped 6 September 2018.	
Phase of development: Phase 1b	
Objectives: To assess in overweight to obese Type 2 diabetes mellitus (T2DM) patients: • The glucagon receptor occupancy of SAR425899 at 2 dose levels in the human liver with positron emitting tomography (PET) imaging using [68Ga]Ga DO3A VS-Cys40-Tuna-2 as a tracer compound • The GLP-1 receptor occupancy of SAR425899 at 2 dose levels in the human pancreas with PET imaging using [68Ga]Ga-DO3A-VS-Cys40-Exendin-4 as a tracer compound • Pharmacodynamic effects on fasting plasma glucose and biomarkers of lipid metabolism • Pharmacokinetic parameters for SAR425899 measured in plasma after repeated SC doses • Safety and tolerability of SAR425899	
Methodology: Phase 1, single-center, open-label, 20 days once daily repeated subcutaneous (SC) injection doses of SAR425899 with 2 different dose regimens, PET and computed tomography (CT) scans.	

Number of patient:

Planned: 12 to 14 overweight to obese male and female patients with T2DM to achieve 12 evaluable patients

Randomized: 13

Treated: 13

Evaluated:

Pharmacodynamics: 6

Safety: 13

Pharmacokinetics: 13

Diagnosis and criteria for inclusion:

Overweight to obese male and female patients aged between 18 and 75 years diagnosed with T2DM at least 1 year before inclusion with a body mass index (BMI) between 28 and 38 kg/m2, fasting plasma glucose (FPG) ≥90 mg/dL, glycosylated hemoglobin ≥6.5% and ≤9%, and no antidiabetic treatment except stable metformin and sulphonylureas.

Study treatments

Investigational medicinal product(s): Bamadutide (SAR425899)

Formulation: Cartridges containing 3 mL solution for injection at a concentration of 0.5 mg/mL in sodium dihydrogen phosphate dihydrate, di-sodium 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® injector was used to deliver the SC doses.

Dose regimen: Repeated once daily SC doses administered after breakfast in the morning. Treatment duration was 20 days with following dose levels and units per dose:

Group A:

- 0.06 mg (12 units [U]), Days 1 to 4
- 0.12 mg (24 U), Days 5 to 8
- 0.16 mg (32 U), Days 9 to 12
- 0.2 mg (40 U), Days 13 to 20

Group B:

- 0.06 mg (12 U), Days 1 to 4
- 0.12 mg (24 U), Days 5 to 20

Any patients assigned to Group A who experienced gastrointestinal (GI) side effects (nausea, vomiting, diarrhea etc) that prevented dose increase from 0.12 to 0.16 mg or from 0.16 to 0.2 mg, or continuation of treatment with 0.16 or 0.2 mg may have been re-assigned to Group B and continued at a dose level of 0.12 mg except when 6 patients in Group B already completed treatment or the patient was already treated with 0.2 mg SAR425899 for ≥2 days. Patients who did not tolerate 0.06 or 0.12 mg SAR425899 had to be withdrawn and could be replaced.

Non investigational medicinal product (1): [^{68}Ga]Ga-DO3A-VS-Cys40-Tuna-2 as a glucagon receptor tracer

Formulation: Solid powder

Route(s) of administration: Intravenous (IV) bolus

Dose regimen: <0.2 µg/kg containing 30-50 MBq

Non investigational medicinal product (2): [^{68}Ga]Ga-DO3A-VS-Cys40-Exendin-4 as a GLP-1 receptor tracer

Formulation: Solid powder

Route(s) of administration: IV bolus

Dose regimen: <0.15 µg/kg containing 30-50 MBq

Duration of treatment: 20 days of treatment

Duration of observation: 55 days

Screening within 28 days (Days -28 to -1)

Treatment period:

- 20 days of treatment (Days 1 to 20)
- An end-of-study (EOS) visit 7 days after dosing (Day 27)

Criteria for evaluation: The current report is an abbreviated report.

Pharmacodynamics: Pharmacodynamic assessments consisted of:

- PET/CT scans
  - The PET images were co registered with the individual CT anatomical scans and the ROI analyses were performed to determine the localization of glucagon and GLP-1R occupancies within the liver (glucagon), pancreas (GLP-1), spleen (both) and aorta (both).
- Glycemic parameters
- Fasting plasma glucose (FPG)
- Lipid biomarkers
- Ketone bodies

Safety:

Baseline demographic characteristics consisted of age, height, BMI, gender, race, diabetes history and dates and dose of background treatment. Laboratory testing included serology testing, urine drug screen, alcohol breath and plasma testing, and follicle-stimulating hormone in postmenopausal females.

Safety investigations at baseline and during the study: Safety assessments consisted of adverse events, physical examinations, measurement of vital signs and body weight, laboratory tests including hematology and biochemistry parameters, urinalysis, pregnancy testing in females, and 12-lead electrocardiograms (ECGs).

Pharmacokinetics:

SAR425899 concentrations were measured in plasma samples collected at the following times:

- On Day 1 and all ambulatory visits predose in the morning (trough)
- Day 20: Predose, 1, 2, 4, 6, 7, 7.5, 8, 9 and 10 hours after dosing

Statistical methods:

Pharmacodynamic parameters

All analyses were explorative. Descriptive statistics and graphs were provided on raw data and change from baseline, as appropriate.

Safety parameters

The safety analysis was conducted on the safety population 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), Treatment Emergent Adverse Events (TEAEs) were tabulated (counts and percent). Descriptive statistics were generated by 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.

Pharmacokinetic parameters

Pharmacokinetic parameters of SAR425899 were summarized by descriptive statistics.

Summary:

Population characteristics:

A total of 13 patients were treated, of whom 7 patients completed the 20-day once daily treatment with SAR425899. Six (46.2%) patients discontinued treatment permanently due to TEAEs.

Overall, the patients had a median body weight of 98.00 kg, a median body mass index of 30.59 kg/m2, and the majority were male (12 [92.3%] of 13 patients).

Pharmacodynamic results:

The results of GCG tracer distribution, elimination and receptor binding were subject to different modeling approaches (compartmental modeling, graphical analyses like Patlak or Logan). Patlak graphical analysis was finally preferred over the Logan graphical analysis and compartmental models. Although having the best goodness-of-fit of the tested models, the Patlak graphical analysis did not provide an improvement in precision compared to the simpler standard uptake value at 55 minutes (SUV55min) assessment. It was therefore decided to estimate receptor occupancy based on SUV data, with SUV55min (at the end of PET scan) as primary endpoint, while compartmental model (volume of distribution, Vt) or Patlak (net uptake rate, Ki) derived parameters were not used to calculate receptor occupancy.

Glucagon tracer binding in the liver: Plasma GCG (Figure 3) and liver volume values both decreased under treatment with SAR425899. In addition, GCG PET tracer liver uptake (measured as SUV55min) at the baseline examination had a small correlation with the levels of GCG in plasma (slope of linear relationship -0.01). This is expected to some degree, as the tracer engages the same binding site as endogenous GCG. Thus, if the baseline tracer binding value is to be compared to an assessment in which the subject exhibited lower or higher endogenous GCG levels, an adjustment for plasma GCG levels had to be performed.

PET tracer binding was also corrected for changes in liver volume. Mean decrease of liver volume from baseline until end of treatment under 0.2 mg SAR425899 was around 10 % (see Table 1).

Table 1 - Liver volume on Day 17 relative to baseline - descriptive statistics per last dose - PD population

	Raw data for relative liver volume (Ratio)						
Last dose of SAR425899 (mg)	**N**	**Mean**	**SD**	**SEM**	**Median**	**Min**	**Max**
0.12	1	0.99	NC	NC	0.99	1.0	1.0
0.2	5	0.90	0.06	0.027	0.88	0.8	1.0

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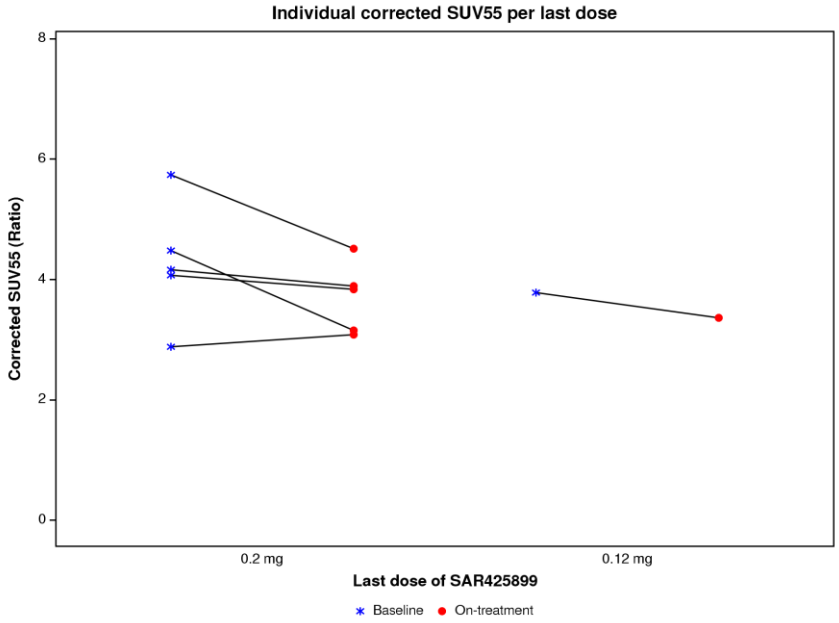
Individual SUV55min values for the GCG tracer in the liver, corrected/adjusted for GCG levels and liver volume, at baseline on Day 17 are shown in Figure 1.

Figure 1 - Corrected individual SUV55min values for glucagon tracer at baseline and Day 17



SUV55 on-treatment is corrected for liver volume
SUV55 at baseline is adjusted for glucagon level
SUV55 = Standard Uptake Value 55 minutes into PET scan
PGM=PRODOPS/SAR425899/PDY15264/CSR/REPORT/PGM/pd_isuv_pd_g.sas OUT=REPORT/OUTPUT/pd_isuv_pd_g_1_i.rtf (26OCT2018 - 16:24)

Descriptive statistics for the percentage SAR425899 GCG receptor occupancy in the liver at the Day 17, calculated from the change of tracer binding between baseline and Day 17, are provided in Table 2.

At a dose of 0.2 mg SAR425899, the average occupancy rate on the GCG receptor was 11.21% (median 6.51%, N=5) with standard deviation of 14.38, indicating no clear receptor occupancy. The individual receptor occupancy values ranged between 29.6% and zero (as a negative value has no biological meaning).

Table 2 - Percentage occupancy for the glucagon receptor - Descriptive statistics per last dose - PD population

	Raw data for glucagon receptor occupancy (%)						
Last dose of SAR425899 (mg)	**N**	**Mean**	**SD**	**SEM**	**Median**	**Min**	**Max**
% GCGR occupancy based on SUV55							
0.12	1	11.08	NC	NC	11.08	11.1	11.1
0.2	5	11.21	14.38	6.433	6.51	-7.1	29.6

Occupancy = 100 * (1 - SUV55OT / SUV55BL), OT = On-treatment, BL = Baseline
SUV55OT = SUV55 on-treatment, corrected for liver volume
SUV55BL = SUV55 at baseline, adjusted for glucagon level
SUV55 = Standard Uptake Value 55 minutes into PET scan
Note: Individual occupancy below zero is a mathematical result from the adjustment and does not have a biological meaning.
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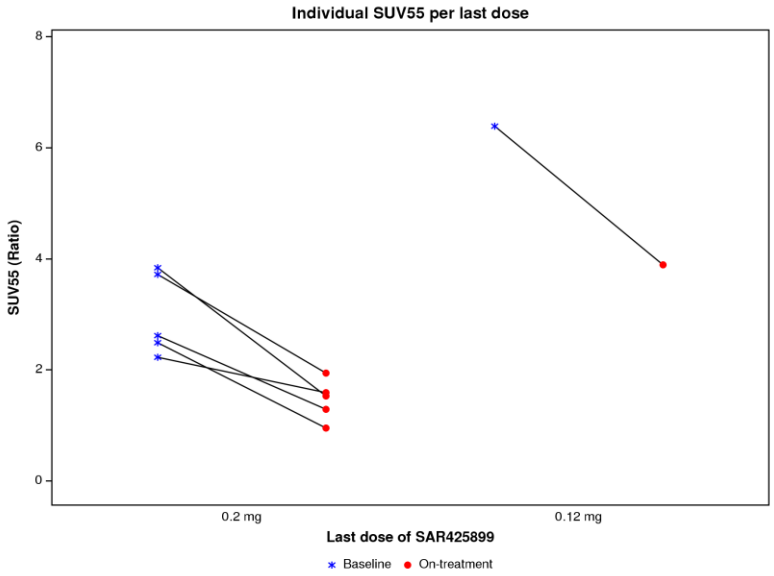
GLP-1 Tracer binding in pancreas: Individual SUV55min values for the GLP-1 tracer in the pancreas at baseline and end Day 20 are shown in Figure 2.

Figure 2 - Corrected individual SUV55min values for GLP-1 tracer at baseline and end of treatment



SUV55 = Standard Uptake Value 55 minutes into PET scan
PGM=PRODOPS/SAR425899/PDY15264/CSR/REPORT/PGM/pd_isuv_pd_g.sas OUT=REPORT/OUTPUT/pd_isuv_pd_g_2_i.rtf (26OCT2018 - 16:24)

Descriptive statistics for the % SAR425899 GLP-1 receptor occupancy in the pancreas at the end of treatment (Day 20), calculated from the change of tracer binding between baseline and Day 20. Results show the receptor occupancy based on the Patlak derived variable K_i and SUV55min. At a dose of 0.2 mg SAR425899, the average occupancy rate on the GLP-1 receptor was estimated as 49.89% (SUV55min, standard deviation [SD]: 13.25) and 61.64% (K_i; SD: 8.34). The inter-individual variability of receptor occupancy was acceptable for both parameters (Table 3).

Table 3 - Percentage occupancy for the GLP-1 receptor - descriptive statistics per last dose - PD population

	Raw data for GLP-1 receptor occupancy (%)						
Last dose of SAR425899 (mg)	**N**	**Mean**	**SD**	**SEM**	**Median**	**Min**	**Max**
% GLP-1R occupancy based on KI							
0.12	1	31.52	NC	NC	31.52	31.5	31.5
0.2	5	61.64	8.34	3.729	62.14	50.1	69.6
% GLP-1R occupancy based on SUV55							
0.12	1	39.12	NC	NC	39.12	39.1	39.1
0.2	5	49.86	13.25	5.926	50.76	28.7	61.8

OT = On-treatment, BL = Baseline
Occupancy based on KI = 100 * (1 - KIOT / KIBL)
Occupancy based on SUV55= 100 * (1 - SUV55OT / SUV55BL)

KI = Net Uptake Rate

SUV55 = Standard Uptake Value 55 minutes into PET scan

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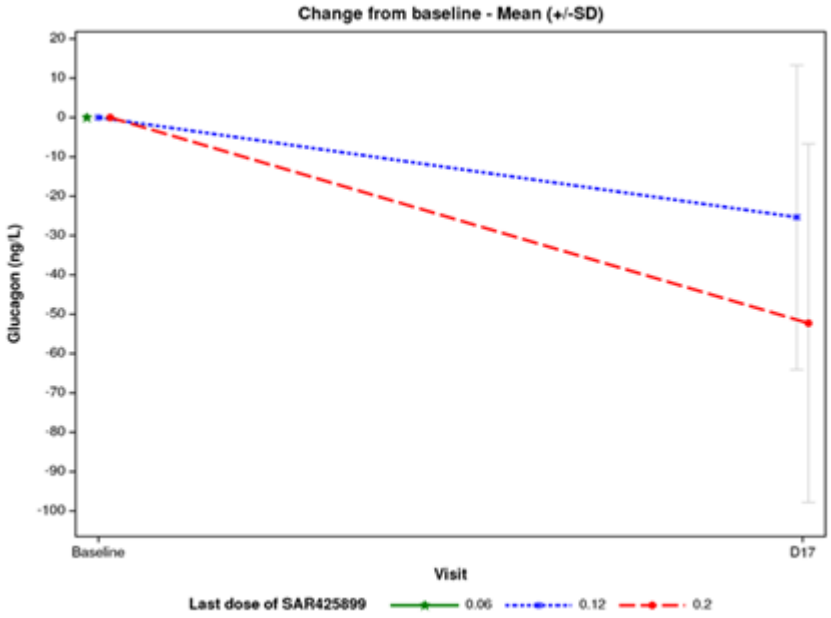
Glucagon: GCG plasma concentrations decreased under treatment with SAR425899, as shown in Figure 3, though the variability was high. Mean absolute change from baseline was -52.23ng/L between baseline and Day 17 (SD: 45.58) at a dose of 0.2 mg SAR425899.

Figure 3 - Plasma glucagon change from baseline – mean -



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Other PD parameters: Descriptive data for body weight (raw data and change from baseline) over time are provided in

Table 4. Mean change from baseline on Day 20 at a dose of 0.2 mg SAR425899 was -3.87% (SD: 0.87). Other PD parameters will be provided in the clinical study report.

Table 4 - Percent change in body weight - Descriptive statistics per last dose - PD population

Last dose of SAR425899 (mg)	Percent change from baseline						
	N	Mean	SD	SEM	Median	Min	Max
0.12							
Baseline							
D5	1	-3.00	NC	NC	-3.00	-3.0	-3.0
D13	1	-4.00	NC	NC	-4.00	-4.0	-4.0
D17	1	-4.00	NC	NC	-4.00	-4.0	-4.0
D20	1	-5.00	NC	NC	-5.00	-5.0	-5.0
End of study	1	-4.00	NC	NC	-4.00	-4.0	-4.0
0.2							
Baseline							
D5	5	-0.80	1.14	0.510	-1.01	-2.1	1.1
D13	5	-2.43	1.08	0.481	-2.13	-3.8	-1.0
D17	5	-3.86	1.28	0.572	-4.12	-5.2	-2.0
D20	5	-3.87	0.87	0.389	-3.81	-5.2	-3.0
End of study	5	-2.64	1.35	0.603	-2.08	-4.3	-1.0

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Safety results:

One serious AE (SAE) (pyelonephritis) was reported. This SAE was considered not to be related to the SAR425899 treatment by the Investigator. Six subjects prematurely discontinued treatment due to a AEs, namely: lipase increased, discomfort, pyelonephritis, constipation, nausea, and presyncope.

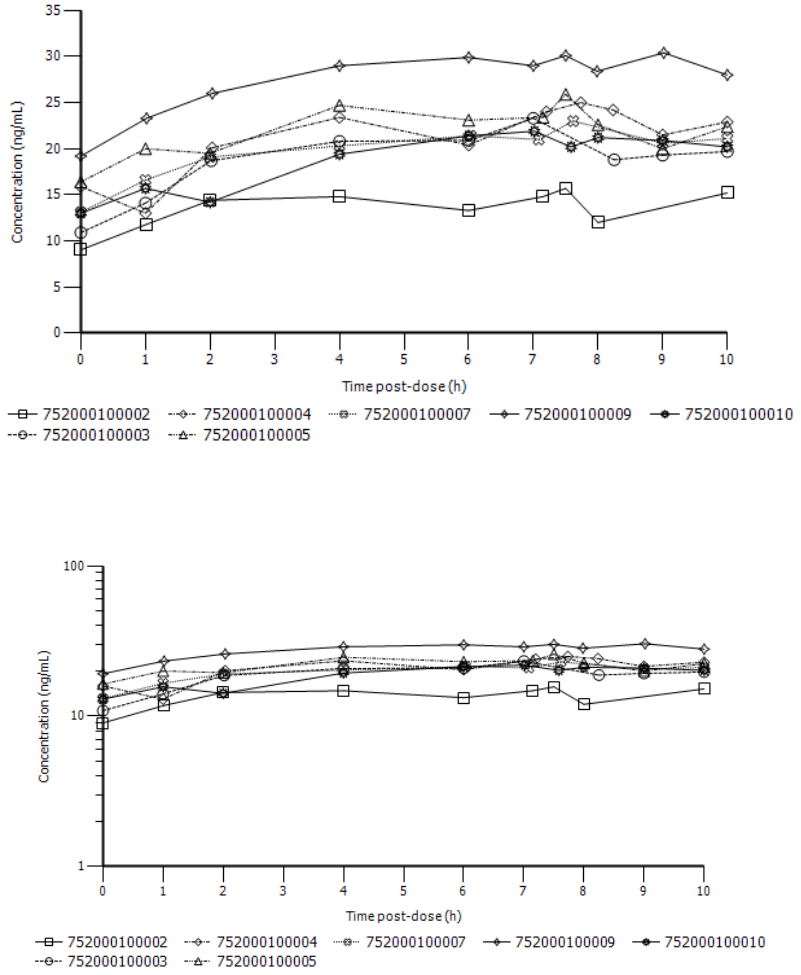
The most frequently reported TEAEs, by PT, reported by ≥2 patients were:

- Decreased appetite and nausea in 7 (53.8%) patients each
- Fatigue in 4 (30.8%) patients
- Headache and eructation in 3 (23.1%) patients each
- Constipation, dyspepsia, gastritis, vomiting, and malaise in 2 (15.4%) patients

Pharmacokinetic results:

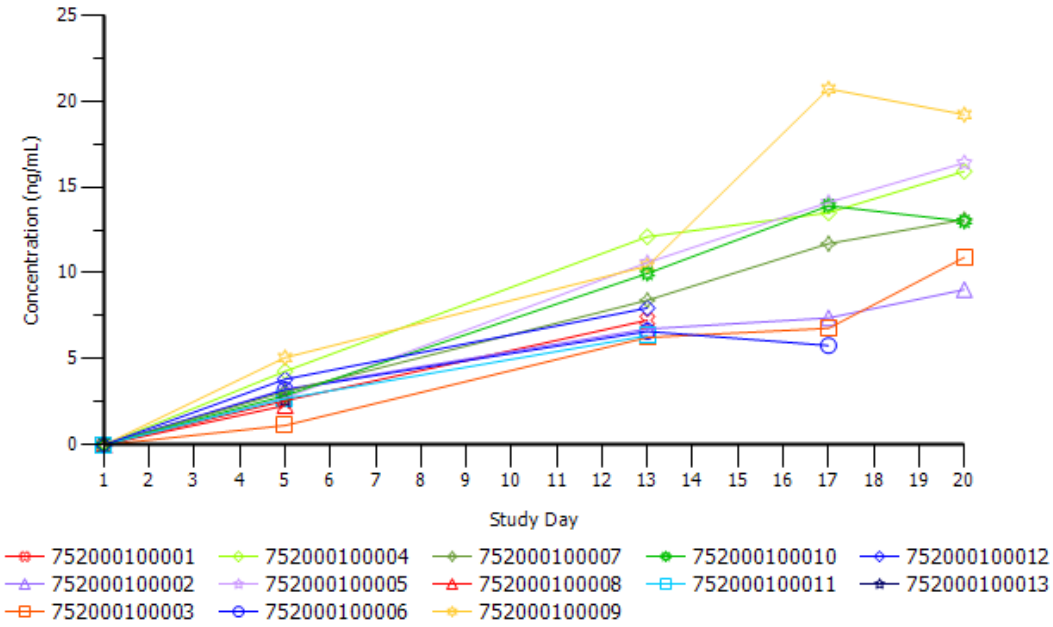
Individual subject plasma concentrations of SAR425899 on Day 20 following once daily SC administration of SAR425899 to overweight to obese T2DM patients are presented in Figure 4. Individual subject trough plasma concentrations of SAR425899 following once daily SC administration of SAR425899 are presented in Figure 5.

Figure 4 - Individual subject plasma concentrations of SAR425899 on Day 20 following repeated SC administration of SAR425899 to overweight to obese T2DM patients (linear and semi-logarithmic)



Notes: Patient 752000100002 was the only patient who completed the 0.12 mg dose regimen (highest SAR425899 dose received was 0.12 mg)
Patient 752000100003 was excluded from PK parameter descriptive statistics for 0.2 mg SAR425899 due a major protocol deviation (dosing titration irregularity)

Figure 5 - Individual subject trough plasma concentrations of SAR425899 following repeated SC administration of SAR425899 to overweight to obese T2DM patients (linear and semi-logarithmic scales)



A summary of the PK parameters of SAR425899 following administration of the 0.2 mg SAR425899 dose regimen is presented in Table 5.

Table 5 Pharmacokinetic parameters of SAR425899 following administration of the 0.2 mg SAR425899 dose regimen to overweight to obese T2DM patients

	0.2 mg SAR425899 dose regimen				
	C_{max} (ng/mL)	C_{trough}* (ng/mL)	t_{max} (h)	$AUC_{0\text{-}last}$ (ng.h/mL)	t_{last} (h)
N	5	5	5	5	5
Mean	25.2	15.5	7.78	219	10.00
SD	3.29	2.58	0.74	34.7	0.00
SE	1.47	1.15	0.33	15.5	0.00
Min	21.9	13.0	7.02	188	10.00
Median	25.0	15.9	7.62	210	10.00
Max	30.4	19.2	9.02	277	10.00
CV%	13	17	10	16	0
Geometric Mean	25.1	15.4	7.75	217	10.00

* Day 20 pre-dose concentration

Patient 752000100002 was excluded from descriptive statistics as patient completed the 0.12 mg dose regimen.

Patient 752000100003 was excluded from descriptive statistics due to a major protocol deviation (dosing titration irregularity).

On Day 20 following administration of the 0.2 mg SAR425899 dose regimen, SAR425899 was steadily absorbed, with a median time to reach maximum concentration (t_{max}) of 7.62 hours postdose (individual range: 7.02 to 9.02 hours postdose). Plasma concentration-time profiles remained relatively flat until the last scheduled PK timepoint of 10 hours postdose, at which SAR425899 was still quantifiable in all patients.

Although the limited number of patients should be taken into account, the between-patient variability in $AUC_{0\text{-last}}$ and maximum concentration (C_{max}) was low based on CV% values of 16% and 13%, respectively.

The Day 20 measured concentration at the end of a dosing at steady state (C_{trough}) values were similar across patients, with individual results ranging from 13.0 to 19.2 ng/mL, and a geometric mean value of 15.4 ng/mL, accounting for 61% of the geometric mean C_{max}.

Issue date: 20-Nov-2019