These results are supplied for informational purposes only.
Prescribing decisions should be made based on the approved package insert in the country of prescription.

Sponsor: Sanofi **Drug substance(s):** SAR438544	**Study Identifiers:** U1111-1172-1152, NCT02625636 **Study code**: TDU14518

Title of the study: A randomized, double-blind, glucagon and placebo-controlled study to assess the safety, pharmacokinetics and pharmacodynamics of single escalating doses of SAR438544 administered by subcutaneous route in healthy subjects (TDU14518) and patients with type 1 diabetes mellitus (PDY14452).

Study center: 1 center in the USA.

Study period:

Date first subject enrolled: 01/Dec/2015

Date last subject last visit: 29/Jan/2016

Study Status: The study was definitely and prematurely stopped after completion of dose cohorts 1 (SAR438544; 50 µg) and 2 (SAR438544; 150 µg) in healthy subjects, when at the 150 µg the pre-set exposure limit was met per the study protocol. The study was not stopped due to safety concerns.

Phase of development: Phase 1

Objectives:

To assess in healthy subjects and in type 1 diabetes mellitus (T1DM) patients:

- The tolerability and safety of SAR438544 after single ascending subcutaneous (SC) doses.
- The pharmacokinetic (PK) parameters of SAR438544 after single ascending SC doses.
- The preliminary pharmacodynamics (PD) of SAR438544 after single ascending SC doses.

Methodology: Double-blind, randomized, placebo-controlled, sequential single ascending dose study with glucagon as a positive control.

Number of subjects: Planned: from 30 to 60 healthy subjects and 10 T1DM patients

Randomized: 20 healthy subjects

Treated: 20 healthy subjects

Evaluated:

Pharmacodynamics: 20 healthy subjects

Safety: 20 healthy subjects

Pharmacokinetics (if applicable): 20 healthy subjects

Diagnosis and criteria for inclusion:

- **Healthy subjects**: Male and female healthy subjects ages 18 to 45 years inclusive.
- **T1DM patients**: Male or female patients, between ages 18 and 60 years inclusive, with T1DM at least one year, as defined by the American Diabetes Association, otherwise healthy.

Study treatments

Investigational medicinal product: SAR438544

Formulation: Glass vials of 500 µg/mL aqueous solution containing histidine, mannitol, L-arginine, hydrochloric acid, sodium hydroxide (1 mL solution in 2 mL vial).

Route of administration: Subcutaneous.

Dose regimen:

- Healthy subjects: single dose of 50 µg, 150 µg or 450 µg (up to 1000 µg/mL optional) under fasting condition.
- Type 1 diabetes mellitus patients: to be determined after completion of the dose escalation in healthy subjects and not to be higher than the highest dose tested in healthy subjects, under fasting condition.

Investigational medicinal product: SAR438544 placebo.

Formulation: Glass vials of aqueous solution containing histidine, mannitol, L-arginine, hydrochloric acid, sodium hydroxide (1 mL solution in 2 mL vial).
Route(s) of administration: Subcutaneous.
Dose regimen: Single administration, as per corresponding SAR438544 volume, under fasting condition.

Investigational medicinal product: Glucagon (recombinant DNA origin) GlucaGen® HypoKit Novo Nordisk provided by the clinical site.

Formulation: 1 mg dry powder to be solubilized with 1 mL sterile water in order to achieve a 1 mg/mL solution for administration (as per prescribing information).
Route(s) of administration: Subcutaneous.
Dose regimen: 1 mg, single dose under fasting conditions.

Duration of treatment: 1 treatment day (1 single dose) of SAR438544, SAR438544 placebo, or glucagon.

Duration of observation:

- Healthy subjects: total duration up to 4.5 weeks including screening (Day -21 to Day -2), 1 treatment day (single administration on Day 1), evaluation period (Day -1 to Day 2), and end-of-study visit (7 days ± 1 day after investigational medicinal product [IMP] administration).

Criteria for evaluation:

Safety: Adverse events (AEs) including treatment emergent adverse events (TEAEs); physical examination and body weight; clinical laboratory evaluations including hematology, biochemistry, coagulation, urinalysis; vital signs (supine blood pressure [BP], heart rate [HR] and respiratory rate), 12-lead electrocardiogram (ECG), ECG telemetry and Holter ECG; and local tolerability.

Pharmacodynamics: No pharmacodynamic (PD) parameters were considered as primary. The following 2 secondary PD parameters were derived individually from smoothed fasting blood glucose (BG) levels: BG maximum observed concentration (BG-C_{max}), and BG time to reach the maximum concentration (BG-T_{max}). BG area under the concentration versus time curve using the trapezoidal method from time 0 to time t (BG-AUC_{0-t}) was calculated from unsmoothed fasting BG levels.

Pharmacokinetics: Plasma concentrations of SAR438544 and glucagon were used to calculate the following PK parameters using noncompartmental methods: C_{max}, area under the concentration versus time curve calculated using the trapezoidal method from time 0 to the real time t_{last} (time corresponding to the last observed concentration above the limit of quantification) (AUC_{last}), area under the concentration versus time curve extrapolated to infinity (AUC), partial AUCs (AUC_{0-t}), t_{max}, t_{last}, and half-life ($t_{1/2z}$).

Pharmacokinetic/Pharmacodynamics sampling times and bioanalytical methods:

Pharmacodynamic sampling times and bioanalytical methods:

Arterialized venous blood was drawn continuously at a rate of 2 mL/hour for the determination of arterial BG concentration from about 6.0 hours prior to medication up to 6 hours after IMP dosing.

In addition, arterialized venous blood samples (approximately 0.2 mL) for concurrent Biostator® calibration were collected at least every 30 minutes after connection to the Biostator up to 6 hours after IMP dosing.

***Pharmacokinetic sampling time and bioanalytical methods**:*

Blood samples for the determination of plasma SAR438544 or glucagon concentrations following administration of SAR438544 or glucagon were collected on Day 1 to Day 2 at the following time points: 0H (directly predose), 0H05, 0H10, 0H15, 0H30, 0H45, 1H, 1H30, 2H, 4H, 6H, 12H, 24H postdose. SAR438544 was analyzed using a validated liquid chromatography with tandem mass spectrometry (LC-MS/MS) based method specific to SAR438544 (does not detect endogenous glucagon) with a lower limit of quantification of 0.1 ng/mL (100 pg/mL). Glucagon was analysed with the validated commercial Mercodia® glucagon ELISA kit. The lower limit of quantification was 33.6 pg/mL (0.0336 ng/mL). The Mercodia assay is unspecific and also detects endogenous glucagon.

Statistical methods:

Results for placebo and glucagon were pooled across dose-cohorts within study population (healthy subjects).

Safety

The safety analysis was conducted on the safety population, ie, all healthy subjects who received 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 and summarized for potentially clinically significant abnormalities (PCSAs). Treatment-emergent adverse events were tabulated (counts and percentages). Descriptive statistics were generated by treatment and dose level for SAR438544, and time point for selected parameters of interest.

Pharmacodynamics

Descriptive statistics and graphs were provided on raw data and change from baseline BG level reached at 0, 7, 15, 30, 45, 60, 90 minutes, 2, 4, and up to 6 hours after dosing (based on smoothed profiles) for each treatment and time point.

AUCs were calculated based on unsmoothed BG profiles. BG-C_{max} and corresponding BG-T_{max} were calculated based on smoothed BG profiles (smoothing factor 0.06). Descriptive statistics were derived for BG-C_{max}, BG-T_{max} and BG-AUC_{0-t} between IMP dosing and time t (with t = 7, 15, 30, 45, 60 and 90 minutes, 2, 4, 6 hours after IMP dosing) per treatment group.

Pharmacokinetics

Concentration of SAR438544 and glucagon in plasma were summarized by dose level.

Pharmacokinetic parameters were summarized using descriptive statistics.

Summary:

Population characteristics:

Twenty (20) healthy male and female subjects were enrolled in 2 dose cohorts of 10 subjects each (6 active, 2 placebo and 2 glucagon as a positive control). In total, 4 subjects received a single dose of placebo, 6 subjects received a single dose of 50 µg of SAR438544, 6 subjects received 150 µg of SAR438544 and 4 subjects received 1 mg glucagon in fasting conditions as subcutaneous injection in the abdomen.

All subjects completed the study treatment period as per protocol and no protocol safety stopping rules were met.

All 20 subjects were included in the safety, PK, PD and PK/PD populations.

No subjects were exposed to other SAR438544 doses (eg, 450 µg) and no T1DM patients were finally enrolled in the study.

Safety results:

Adverse events

There were no deaths, no severe or serious TEAEs, and no adverse events of special interest reported during the study.

Overall, a total of 6 TEAEs were reported in 6 subjects. Most were of mild intensity except for one, consisting of a catheter site extravasation of moderate intensity in the glucagon group. There were more subjects presenting with TEAEs in the SAR438544 150 µg dose as compared to the other groups with 1 of 4 (25.0%), 1 of 6 (16.7%), 3/6 (50.0%) and 1 of 4 (25.0%) subjects with AEs following placebo, SAR438544 at 50 and 150 µg and glucagon administration, respectively. Of note, 1 mild nausea and 1 mild abdominal pain were reported in 2 subjects of the 150 µg group. They occurred around 2 to 3 hours post dose for a duration of 2 hours 55 minutes for nausea and 20 minutes for the abdominal pain.

No injection site reaction or hypersensitivity reaction were observed in any treatment group.

Potentially clinically significant abnormalities

There was 1 of 6 subjects in the SAR438544 50 µg group with systolic blood pressure ≤ 95 mmHg and decrease from baseline ≥20 mmHg, versus no subject in the other groups. This PCSA was asymptomatic.

Except hemoglobin decrease reported in 1 of 6 subjects in the SAR438544 50 µg group (value of 118 g/L, decrease from baseline of 28 g/L at end of study visit), no PCSA were reported in hematology parameters in any other group.

Except CPK increase >3 ULN reported in 1 of 4 subjects of the placebo group with documented physical exercise and creatinine increase >30% from baseline reported in 1 of 4 subjects in the glucagon group, no other PCSA were reported in biochemistry parameters, including liver function.

Regarding ECG evaluations (automatic reading), there were 1 of 6 and 2 of 6 subjects in SAR438544 50 µg and 150 µg groups, respectively, with HR <50 bpm versus 2 of 4 subjects in the placebo group and none in the glucagon group. Increased HR >90 bpm was only observed in 1 of 4 subjects in the glucagon group. There were 2 of 6 subjects in SAR438544 50 µg groups with PR >200 ms (none above 220 ms) versus none in the other groups. There were no subjects presenting with PCSA for prolonged QT or QTc in the SAR438544 groups whereas 1 of 4 subjects from the placebo group experienced a QTc increase greater than 30 ms but less than 60 ms.

None of the above PCSAs were reported as clinically relevant by the investigator. Overall, 50 µg and 150 µg single SC doses of SAR438544 were safe and well-tolerated in healthy volunteers.

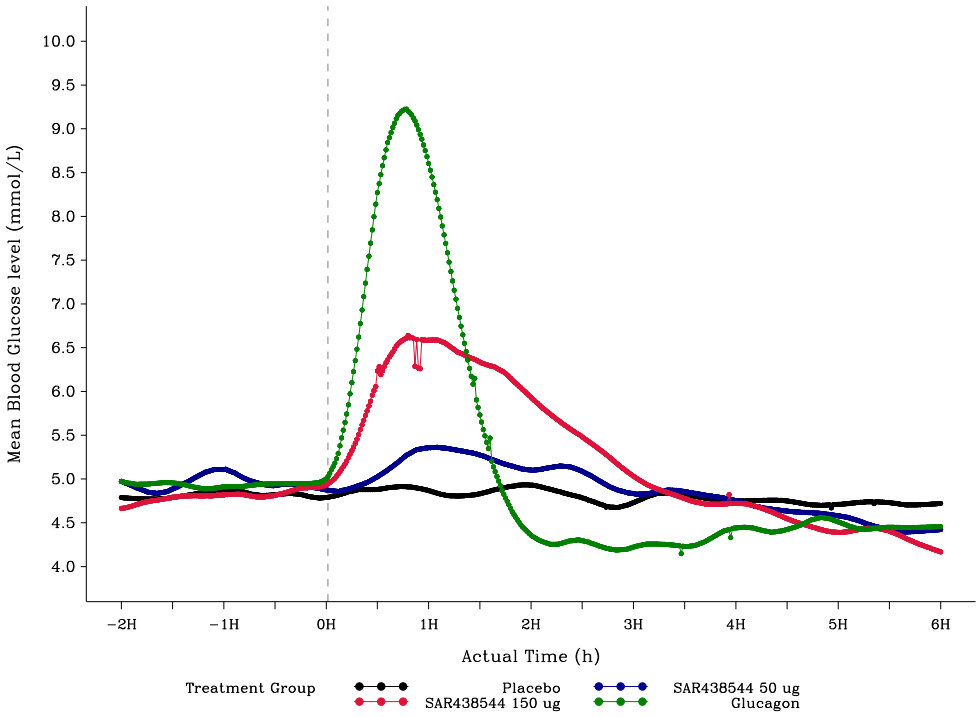
Pharmacodynamic results:

The PD response was evaluated by direct assessment of fasting BG concentrations. BG was assessed continuously from time -6H before dosing and up to time 6H after dosing on Day 1 using the Biostator to assess the response after placebo, SAR438544 50 µg, or 150 µg, or 1 mg glucagon single administration.

The increase in mean BG-C_{max} (mmol/L) was dose-dependent between SAR438544 at 50 and 150 µg with higher concentrations at 150 µg. There was no BG response in the placebo group. The response observed in the 1 mg glucagon group was greater than the one observed in the SAR438544 groups. The mean BG-C_{max} (mean change from baseline) were 5.07 (0.19), 5.45 (0.49), 7.21 (2.37) and 9.26 (4.25) mmol/L for the placebo, SAR438544 50 µg, SAR438544 150 µg, and glucagon, respectively. The BG concentrations in the 2 SAR438544 dose groups were close to baseline at about 3 to 4 hours post dose whereas subjects from the glucagon group showed a rebound between 3 to 5 hours, with values below baseline. At 6 hours post dose (end of BG monitoring) only the placebo subjects showed a mean BG value similar to baseline. The variability of the response was higher in the SAR438544 groups. Refer to Figure 1 below for the mean smoothed blood glucose concentrations over time by treatment and figures 2 to 5 for individual plots of smoothed blood glucose concentrations by treatment.

Corresponding time to reach BG-C_{max} (BG-T_{max}, h) was shorter in the glucagon group as compared to the SAR438544 groups, showing a quicker onset of action. There was a slightly shorter median BG-T_{max} in SAR438544 150 µg versus 50 µg groups. The median BG-t_{max} were 1.22, 1.08 and 0.78 hour for SAR438544 50 µg, SAR438544 150µg, or glucagon, respectively. Using the median BG-T_{max} , the delay in BG-T_{max} in SAR438544 50 µg and 150 µg groups versus glucagon was about 27 and 18 minutes, respectively. The variability of the BG-T_{max} was higher in the SAR438544 150 µg group as compared to the SAR438544 50 µg and glucagon groups with mean (SEM) of 1.21 (0.086), 1.15 (0.220) and 0.77 (0.028) hours for SAR438544 50 µg, SAR438544 150 µg, and glucagon, respectively. From the visual inspection of the plots, the offset of action appears to occur about 1.5 hour later in the SAR438544 groups as compared to glucagon. The slope of the increase in BG in the first 30 minutes appears steeper with SAR438544 at 150 µg as compared to SAR438544 at 50 µg, but not as steep as with 1 mg glucagon. Refer to Figure 1 below.

Figure 1 - Mean smoothed blood glucose concentrations over time by treatment



Smoothing factor is 0.06

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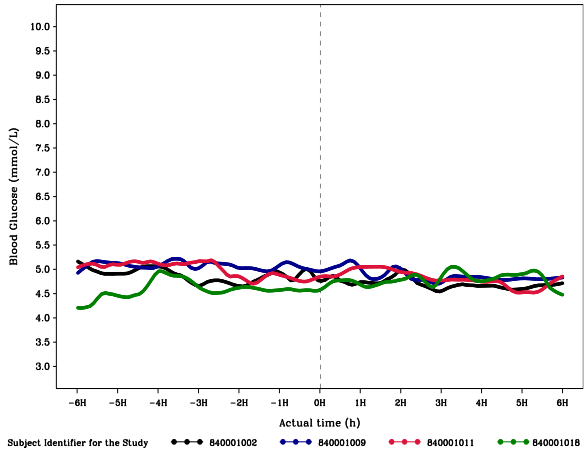
Figure 2 - Individual plot of smoothed blood glucose concentrations for placebo



Smoothing factor is 0.06

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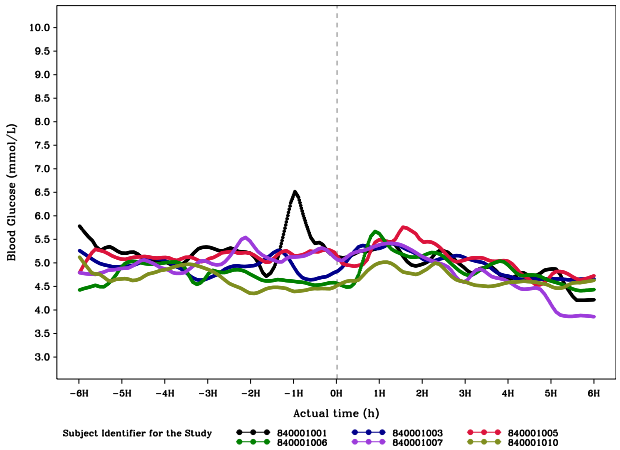
Figure 3 - Individual plot of smoothed blood glucose concentrations for SAR438544 50 µg



Smoothing factor is 0.06

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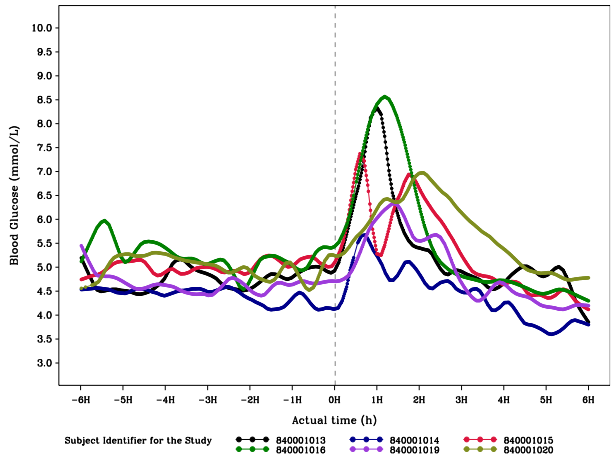
Figure 4 - Individual plot of smoothed blood glucose concentrations for SAR438544 150 µg



Smoothing factor is 0.06

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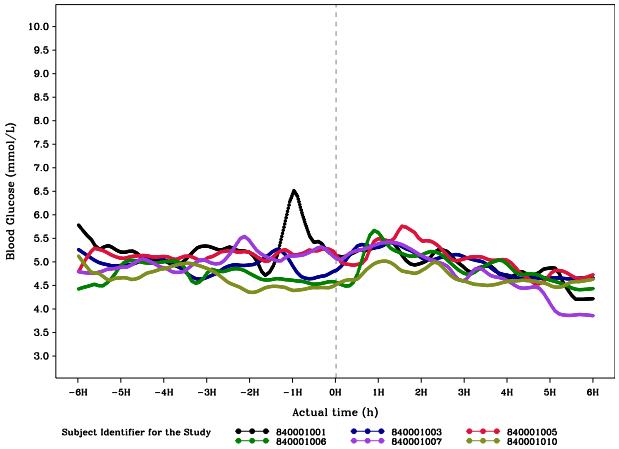
Figure 5 - Individual plot of smoothed blood glucose concentrations for glucagon



Smoothing factor is 0.06

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Consistent with the above BG-C_{max} and BG-T_{max} data, the area under the concentration versus time curve (AUC) of BG at different time points (BG-AUC_{0-t}) appeared greater in the glucagon group as compared with the SAR438544 50 µg and 150 µg groups. This was especially obvious for the early baseline-adjusted AUCs when the BG response is expected to have reached a clinically relevant increase from baseline. Of note, a greater variability was observed in early BG-$_{adj}AUC_t$ in the SAR438544 50 µg and 150 µg groups as compared with glucagon with a coefficient of variation (CV) of about 262, 56 and 26% respectively for BG-$_{adj}AUC_{0-30m}$ and of about 149, 52 and 14% respectively, for BG-$_{adj}AUC_{0-60m}$. See Table 1 below.

Table 1 - Descriptive statistics of baseline adjusted BG-$_{adj}AUC_{0-t}$ (mmol*min/L) by treatment

	Raw data						
	N	**Mean**	**SD**	**SEM**	**Median**	**Min**	**Max**
Placebo							
BG-$_{adj}AUC_{0-7m}$	4	-0.94	0.33	0.165	-0.96	-1.3	-0.5
BG-$_{adj}AUC_{0-15m}$	4	-0.56	1.58	0.790	-0.70	-2.1	1.3
BG-$_{adj}AUC_{0-30m}$	4	-0.90	3.62	1.809	-1.23	-5.0	3.8
BG-$_{adj}AUC_{0-45m}$	4	-0.79	5.43	2.715	-2.35	-5.4	6.9
BG-$_{adj}AUC_{0-60m}$	4	0.06	6.71	3.354	-1.75	-5.6	9.4
SAR438544 50 ug							
BG-$_{adj}AUC_{0-7m}$	6	-0.98	0.66	0.269	-0.98	-2.1	-0.0
BG-$_{adj}AUC_{0-15m}$	6	-1.73	1.66	0.676	-1.80	-3.5	0.2
BG-$_{adj}AUC_{0-30m}$	6	-1.87	4.91	2.004	-3.00	-7.3	4.8
BG-$_{adj}AUC_{0-45m}$	6	0.29	7.76	3.166	-0.70	-10.2	11.5
BG-$_{adj}AUC_{0-60m}$	6	6.42	9.59	3.917	8.27	-6.0	17.0
SAR438544 150 ug							
BG-$_{adj}AUC_{0-7m}$	6	0.23	1.48	0.603	0.57	-2.7	1.3
BG-$_{adj}AUC_{0-15m}$	6	2.05	3.92	1.600	3.53	-5.2	5.4
BG-$_{adj}AUC_{0-30m}$	5	15.87	8.87	3.966	17.30	4.1	25.5
BG-$_{adj}AUC_{0-45m}$	6	39.91	21.01	8.576	38.93	15.4	66.3
BG-$_{adj}AUC_{0-60m}$	6	66.60	34.48	14.077	58.95	34.8	117.4
Glucagon							
BG-$_{adj}AUC_{0-7m}$	4	-0.60	0.66	0.331	-0.84	-1.1	0.4
BG-$_{adj}AUC_{0-15m}$	4	-0.54	2.15	1.073	-0.27	-3.3	1.7
BG-$_{adj}AUC_{0-30m}$	4	33.58	8.79	4.393	35.17	21.8	42.2
BG-$_{adj}AUC_{0-45m}$	4	96.06	16.30	8.151	100.35	74.3	109.3
BG-$_{adj}AUC_{0-60m}$	4	158.43	22.35	11.175	165.18	127.0	176.4

N corresponds to the count of subjects with available data

Baseline adjusted AUC is calculated based on unsmoothed baseline adjusted blood glucose values using the trapezoidal rule.

Unsmoothed baseline adjusted blood glucose value is defined as the baseline value minus the mean of unsmoothed blood glucose value from T-6H to T0H on Day1.

PGM=PRODOPS/SAR438544/TDU14518/CSR/REPORT/PGM/pd_bgblauc_s_t.sas OUT=REPORT/OUTPUT/pd_bgblauc_s_t_i.rtf (30SEP2016 - 10:27)

Pharmacokinetic results:

Descriptive statistics of PK parameters and concentration time profiles of SAR435544 following a single SC dose of 50 µg and 150 µg and glucagon following a single SC dose 1 mg are provided in Table 2 and Figures 6 and 7 below.

Table 2 - Pharmacokinetic parameters of SAR438544 and Glucagon in plasma

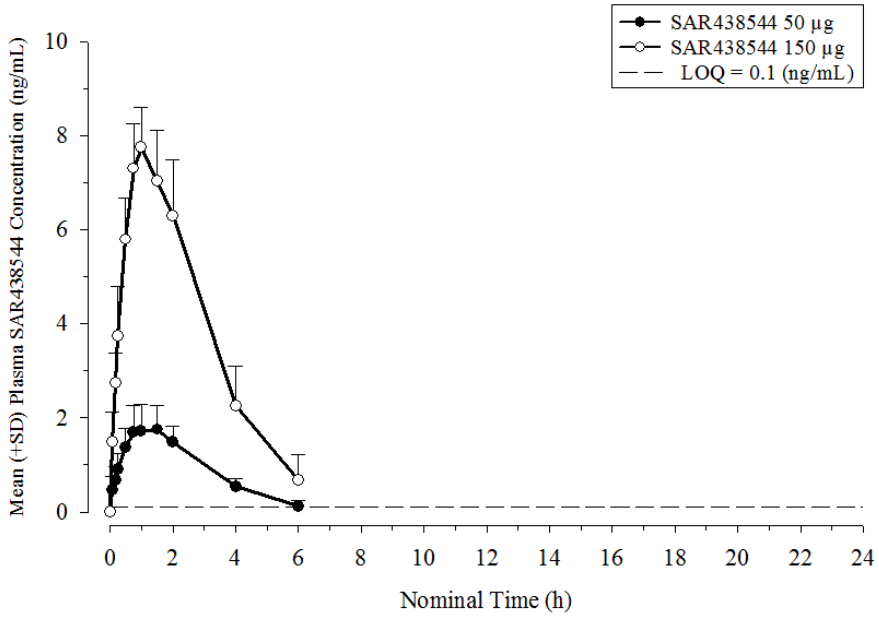
Mean ± SD (Geometric Mean) [CV%]	**Plasma Glucagon**	**Plasma SAR438544**	
	Glucagon 1 mg	**SAR438544 50 µg**	**SAR438544 150 µg**
N	4	6	6
C_{max} (ng/mL)	4.37 ± 1.47 (4.21) [33.7]	1.82 ± 0.531 (1.76) [29.2]	8.05 ± 0.749 (8.02) [9.3]
t_{max}[a] (h)	0.13 (0.08 - 0.17)	1.25 (1.00 - 1.50)	1.00 (0.75 - 2.00)
$t_{1/2z}$ (h)	0.795 ± 0.0676 (0.793) [8.5]	1.34 ± 0.281 (1.31) [21.1]	1.22 ± 0.367 (1.19) [30.0]
$AUC_{0\text{-}7min}$ (ng•h/mL)	0.304 ± 0.124 (2.88) [40.9]	0.0381 ± 0.0231 (0.0327) [60.5]	0.129 ± 0.0479 (0.123) [37.1]
$AUC_{0\text{-}15\ min}$ (ng•h/mL)	0.730 ± 0.133 (0.721) [18.2]	0.131 ± 0.0602 (0.121) [45.9]	0.508 ± 0.121 (0.496) [23.7]
$AUC_{0\text{-}30min}$ (ng•h/mL)	1.45 ± 0.224 (1.44) [15.4]	0.414 ± 0.152 (0.391) [36.7]	1.70 ± 0.280 (1.68) [16.5]
$AUC_{0\text{-}45min}$ (ng•h/mL)	2.04 ± 0.365 (2.02) [17.9]	0.797 ± 0.270 (0.762) [33.9]	3.34 ± 0.411 (3.32) [12.3]
$AUC_{0\text{-}60min}$ (ng•h/mL)	2.50 ± 0.481 (2.46) [19.3]	1.22 ± 0.409 (1.17) [33.4]	5.22 ± 0.585 (5.19) [11.2]
$AUC_{0\text{-}90min}$ (ng•h/mL)	3.10 ± 0.734 (3040) [23.6]	2.09 ± 0.675 (2.01) [32.3]	8.92 ± 0.793 (8.89) [8.9]
$AUC_{0\text{-}2\ hours}$ (ng•h/mL)	3.36 ± 0.896 (3.26) [26.7]	2.90 ± 0.880 (2.80) [30.3]	12.3 ± 1.00 (12.2) [8.2]
$AUC_{0\text{-}4\ hours}$ (ng•h/mL)	3.62 ± 0.985 (3.51) [27.2]	4.93 ± 1.23 (4.81) [24.9]	20.9 ± 2.08 (20.8) [9.9]
$AUC_{0\text{-}6\ hours}$ (ng•h/mL)	3.69 ± 0.996 (3.59) [26.9]	5.62 ± 1.28 (5.50) [22.8]	23.8 ± 2.92 (23.7) [12.3]
AUC (ng•h/mL)	4.06 ± 1.28 (3.90) [31.6]	5.98 ± 1.31 (5.86) [22.0]	25.3 ± 4.29 (25.0) [17.0]

[a] Median (Min - Max)
Source = PKS Study : TDU14518; Scenario: P-GLU-A-EV-OD, Version 8

Date/Time = 5/9/2016;
Results for Glucagon converted from pg/mL to ng/mL

[a] Median (Min - Max)
Source = PKS Study : TDU14518; Scenario: P-D-A-EV-OD, Version 7
Date/Time = 5/9/2016

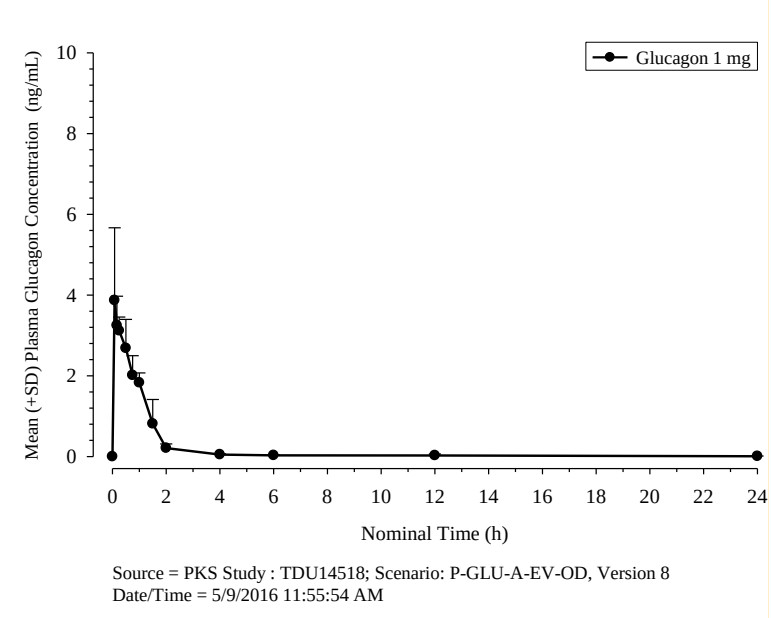
Figure 6 - Mean (+ SD) SAR438544 plasma concentration-time profiles in linear scale by dose



Source = PKS Study : TDU14518; Scenario: P-D-A-EV-OD, Version 7
Date/Time = 5/9/2016

The pharmacokinetic profiles of SAR438544 show exposure for both dose groups administered until 6 hours post dosing. The exposure of SAR438544 expressed by C_{max} and partial AUCs, increase by a factor of about 4 by tripled dosing. The time to reach the maximum concentration (t_{max}) is reached at 1.25 hour for 50 µg SAR438544 and at 1 hour for 150 µg SAR438544 dose administered respectively. The apparent terminal half-life is comparable for both dose groups administered.

Figure 7 - Mean (+ SD) baseline corrected Glucagon plasma concentration-time profile in linear scale



Source = PKS Study : TDU14518; Scenario: P-GLU-A-EV-OD, Version 8
Date/Time = 5/9/2016 11:55:54 AM

The exposure of baseline corrected glucagon expressed by C_{max} is 4.37 ng/mL after a SC administration of 1mg glucagon. The time to reach the maximum concentration (t_{max}) is 0.13 hours respectively. The apparent terminal half-life is about 0.8 hours.

For SAR438544 the exposure after 2 hours post dosing (AUC0-2) reached about 50% and after 4 hours post dosing (AUC0-4) the exposure presents 80% of the AUC to infinity for both dose groups administered. For glucagon, the exposure after 2 hours post dosing (AUC0-2) reached about 80% and after 4 hours post dosing (AUC0-4) the exposure presents 90% of AUC, respectively. For both compounds administered, about 90% of the overall exposure were reached after 6 hours post dosing (AUC0-6).

Issue date: 16-Nov-2020