GLUCOSE CONTROL, SAFETY AND IMMUNOGENICITY IN PEOPLE WITH T1DM USING SAR342434 OR INSULIN LISPRO (U100) ON MDI WITH BASAL INSULIN GLARGINE (U100): SORELLA 1 STUDY

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INTRODUCTION

- SAR342434 (Sanofi insulin lispro; 100 units/mL; SAR ILis), a rapid-acting insulin, has been developed as a follow-on product to Humalog (100 units/mL; ILis) in the USA, and as a biosimilar in the European Union (EU).
- SAR ILis has an identical amino acid sequence as ILis. SAR ILis is produced by recombinant DNA technology utilizing a nonpathogenic strain of *Escherichia coli.*
- Similarity between SAR ILis and ILis was demonstrated in physico-chemical analyses, non-clinical and clinical pharmacology[1] studies and in clinical efficacy and safety studies, including immunogenicity.[2]
- In addition to the results from the overall population we analyzed efficacy and safety data from subgroups of special interest: Elderly (≥65 – <75 years), obese (BMI ≥30 kg/m²), patients with long duration of diabetes (≥10 years) and poor glycemic control (HbA1c ≥8%) and in ethnic groups such as Black, Asian/Oriental and Hispanics. These subgroups were defined in the statistical analysis plan.

OBJECTIVE

The overall objective of the study was to demonstrate non-inferiority (with a 0.3% margin) of SAR ILis versus ILis on glycemic control as measured by change in hemoglobin A1c (HbA1c) from baseline to Week 26 in adults with T1DM. Here we show efficacy results of subgroup analyses with the corresponding safety results.

MATERIALS AND METHODS

Study design

- **Ethics:** The study was conducted in compliance with international and local laws and regulations, including approval by Health Authorities and Ethics Committees prior to initiation. All subjects provided written informed consent prior to participation.
- **Design:** 6-month, multicenter, randomized (1:1), open-label, 2-arm parallel group study (NCT02273180) conducted in 8 countries (Europe, Japan and North America) followed by a 6-month safety extension period.
- **Participants:** Adults with T1DM for ≥1 year pre-treated with insulin glargine (GLA-100) and insulin lispro or insulin aspart for ≥6 months and with HbA1c ≥7.0 % (≥53 mmol/mol) and ≤10.0 % (≤86 mmol/mol) at screening.
- **Treatment:** Participants were randomized to SAR ILis or ILis while continuing basal insulin GLA-100. Rapid-acting insulins were titrated to achieve 2-hour postprandial plasma glucose in the range of 120-160 mg/dL (6.7-8.9 mmol/L) while avoiding hypoglycemia; GLA-100 was to be titrated to achieve fasting pre-breakfast plasma glucose of 80-130 mg/dL (4.4-7.2 mmol/L).

Study endpoints

Primary efficacy endpoint was change from baseline to Week 26 in HbA1c. Secondary efficacy endpoints were percentage of patients with HbA1c <7 % at Week 26; change in fasting plasma glucose (FPG); change in mean 24-hour plasma glucose concentration, based on the 7-point self-measured plasma glucose (SMPG) profile taken before and 2 hours after each main meal, and at bedtime; change in 2 hour postprandial plasma glucose excursions from baseline to Week 26 and insulin dose. Safety endpoints included injection site reactions; hypersensitivity reactions; hypoglycemia (according to ADA categories); adverse events; serious adverse events and body weight during main 6-month period.

Data analysis and statistics

- **Randomization and sample size:** randomization was stratified by HbA1c at the screening visit (<8.0%, ≥8.0%), prior use of Humalog (Yes, No) and geographical region (Japan, non-Japan). The sample size (240 patients in each group) was chosen to ensure sufficient power for the primary endpoint analysis (change in HbA1c from baseline to Week 26).
- **Efficacy analyses:** non-inferiority on the primary efficacy endpoint was tested in the intent-to-treat (ITT) population (all randomized patients) at the 0.3% margin, with alpha level of 0.025 (one-sided). If non-inferiority of SAR ILis over ILis was demonstrated, using a hierarchical step-down testing procedure, the inverse non-inferiority (of ILis over SAR ILis) was tested.
- **Safety analyses:** descriptive statistics on the safety population (all randomized patients who received investigational medicinal product [IMP]).

RESULTS

Study population

- 507 patients were randomized to SAR ILis (n=253) or to ILis (n=254) (ITT population [efficacy population]); 506 patients (SAR ILis [n=252], ILis [n=254]) received IMP (safety population).

Baseline characteristics

- Demographics were similar in both treatment groups.[2]

Glycemic control

- **HbA1c** decreased similarly in both treatment groups from baseline to Week 26. Non-inferiority of SAR ILis versus ILis was demonstrated at the 0.3% non-inferiority margin (upper bound of the 95% CI of the difference between SAR ILis and ILis <0.3%) in the ITT population. The inverse non-inferiority (of ILis versus SAR ILis) was also demonstrated (lower bound of the 95% CI of the difference between SAR ILis and ILis >-0.3%). In all subgroups reported HbA1c decreased with no relevant differences between treatment groups (Table 1). Remarkably, patients with BMI ≥ 30 kg/m², with HbA1c ≥ 8% and with age ≥65 – <75 years had a more pronounced decrease in HbA1c than the overall population.
- For FPG, post-prandial glucose excursions and patients achieving HbA1c <7 % no between-treatment differences were observed in the overall study population.[2]

Table 1 - Change in HbA1c (%) from baseline to Week 26 – ITT population

Subgroup Treatment group	n[a]	Change in HbA1c (%) from baseline to Week 26 Baseline Mean	M6 endpoint Mean	LS Mean (SE) from MMRM[b]	LS Mean Difference (SE) vs. Lispro (95% CI) from MMRM[b]
All patients					
SAR342434	247	8.08	7.62	-0.42 (0.051)	0.06 (0.071)
Lispro	249	7.99	7.53	-0.47 (0.050)	(-0.084 to 0.197)
Age ≥65 – <75 years[c]					
SAR342434	25	7.86	7.37	-0.50 (0.162)	0.02 (0.261)
Lispro	15	7.79	7.37	-0.52 (0.205)	(-0.491 to 0.533)
Black					
SAR342434	16	8.39	8.06	-0.19 (0.198)	-0.08 (0.342)
Lispro	8	8.16	8.00	-0.11 (0.279)	(-0.751 to 0.592)
Asian / Oriental					
SAR342434	32	8.14	7.95	-0.14 (0.140)	0.21 (0.200)
Lispro	31	7.80	7.55	-0.35 (0.142)	(-0.181 to 0.604)
Hispanic					
SAR342434	16	7.72	7.27	-0.58 (0.199)	0.07 (0.331)
Lispro	9	7.97	7.34	-0.66 (0.264)	(-0.580 to 0.721)
BMI <30 kg/m²					
SAR342434	201	8.08	7.65	-0.39 (0.056)	0.08 (0.079)
Lispro	204	7.95	7.51	-0.47 (0.056)	(-0.074 to 0.238)
BMI ≥30 kg/m²					
SAR342434	46	8.06	7.49	-0.55 (0.119)	-0.05 (0.168)
Lispro	45	8.18	7.63	-0.50 (0.120)	(-0.383 to 0.278)
Duration of diabetes ≥10 years					
SAR342434	184	8.11	7.67	-0.39 (0.059)	0.12 (0.083)
Lispro	186	8.02	7.51	-0.51 (0.058)	(-0.038 to 0.288)
HbA1c < 8%					
SAR342434	95	7.41	7.28	-0.14 (0.084)	0.12 (0.118)
Lispro	97	7.43	7.18	-0.25 (0.083)	(-0.113 to 0.351)
HbA1c ≥8%					
SAR342434	152	8.49	7.84	-0.62 (0.067)	-0.03 (0.095)
Lispro	152	8.35	7.76	-0.59 (0.067)	(-0.217 to 0.154)

MMRM=Mixed-effect model for repeated measures, LS=Least-squares
a Number of patients included in the MMRM analysis
b For all patients: MMRM with treatment group (SAR ILis, ILis), randomization strata of screening HbA1c (<8.0, ≥8.0%), prior use of Humalog (Yes, No), and geographical region (Japan, Non-Japan), visit (Week 12, Week 26), treatment-by-visit interaction as fixed categorical effects, and baseline HbA1c value and baseline HbA1c value-by-visit interaction as continuous fixed covariates. For subgroups: same model with subgroup, subgroup-by-treatment interaction, subgroup-by-visit interaction and subgroup-by-visit-by-treatment interaction as additional fixed categorical effects, and without adjustment on randomization strata of geographical region.
c Number of patients in subgroup ≥ 75 years is too small (2 patients on SAR ILis,1 patient on ILis) to present data

Hypoglycemia

- Almost all the patients had at least one episode of hypoglycemia (regardless of the category and the time of day) and a similar percentage of SAR ILis and ILis treated patients reported predefined categories of hypoglycemia.
- In all subgroups no clinically meaningful differences were observed between treatments (Table 2).
- Also, severe hypoglycemia and documented symptomatic hypoglycemia were reported by a similar number of patients with SAR ILis and ILis.
- The differences in some subgroups have to be interpreted with caution due to the small number of patients per subgroup.

Table 2 - Number (%) of patients with at least one hypoglycemia by category during the main 6-month on-treatment period – Safety population

Subgroup Treatment group	Patients with at least one hypoglycemia[a] Any hypoglycemia, n(%)	Severe hypoglycemia, n(%)	Documented symptomatic hypoglycemia, n(%) [≤3.9 mmo/L (70 mg/dL)]
All patients			
SAR342434	249/252 (98.8 %)	20/252 (7.9 %)	214/252 (84.9 %)
Lispro	253/254 (99.6 %)	19/254 (7.5 %)	225/254 (88.6 %)
Age ≥65 – <75 years[b]			
SAR342434	25/25 (100.0 %)	3/25 (12.0 %)	19/25 (76.0 %)
Lispro	16/16 (100.0 %)	0	15/16 (93.8 %)
Black			
SAR342434	16/16 (100.0 %)	3/16 (18.8 %)	14/16 (87.5 %)
Lispro	8/8 (100.0 %)	1/8 (12.5 %)	6/8 (75.0 %)
Asian / Oriental			
SAR342434	30/32 (93.8 %)	0	23/32 (71.9 %)
Lispro	31/31 (100.0 %)	2/31 (6.5 %)	24/31 (77.4 %)
Hispanic			
SAR342434	17/17 (100.0 %)	2/17 (11.8 %)	16/17 (94.1 %)
Lispro	10/10 (100.0 %)	0	7/10 (70.0 %)
BMI <30 kg/m²			
SAR342434	202/205 (98.5 %)	16/205 (7.8 %)	173/205 (84.4 %)
Lispro	209/209 (100.0 %)	17/209 (8.1 %)	184/209 (88.0 %)
BMI ≥30 kg/m²			
SAR342434	47/47 (100.0 %)	4/47 (8.5 %)	41/47 (87.2 %)
Lispro	44/45 (97.8 %)	2/45 (4.4 %)	41/45 (91.1 %)
Duration of diabetes ≥10 years			
SAR342434	187/189 (98.9 %)	16/189 (8.5 %)	162/189 (85.7 %)
Lispro	188/189 (99.5 %)	18/189 (9.5 %)	168/189 (88.9 %)
HbA1c <8%			
SAR342434	98/98 (100.0 %)	8/98 (8.2 %)	83/98 (84.7 %)
Lispro	99/99 (100.0 %)	7/99 (7.1 %)	86/99 (86.9 %)
HbA1c ≥8%			
SAR342434	151/154 (98.1 %)	12/154 (7.8 %)	131/154 (85.1 %)
Lispro	154/155 (99.4 %)	12/155 (7.7 %)	139/155 (89.7 %)

a Number (%) of patients with at least one treatment-emergent hypoglycemia during the main 6-month on-treatment period – Safety population
b Number of patients in subgroup ≥ 75 years is too small (2 patients on SAR ILis,1 patient on ILis) to present data

Adverse events

- In the overall safety population, a similar percentage of patients reported any TEAE or serious TEAE.[2]
- One patient in each treatment group discontinued IMP permanently due to TEAE.
- There was one death in the SAR ILis treatment group due to a cardiovascular event, not associated with hypoglycemia and not considered related to IMP. One pregnancy was reported in the ILis group and the patient was discontinued from the study.
- In most subgroups a similar percentage of patients reported TEAEs (Table 3). However, more Asian/Oriental patients reported TEAEs in the SAR ILis group (23/32 [71.9%]) compared to ILis (13/31 [41.9%]), whereas more Hispanics reported TEAEs while on ILis treatment (6/10 [60.0%]) compared to SAR ILis treatment (6/17 [35.3%]).

Table 3 - Number (%) of patients with treatment-emergent adverse events during the main 6-month on-treatment period – Safety population

Subgroup Treatment group	Patients with TEAE(s)[a] Any TEAE n(%)
All patients	
SAR342434	108/252 (42.9%)
Lispro	106/254 (41.7%)
Age ≥65 – <75 years[b]	
SAR342434	14/25 (56.0%)
Lispro	10/16 (62.5%)
Black	
SAR342434	6/16 (37.5%)
Lispro	3/8 (37.5%)
Asian / Oriental	
SAR342434	23/32 (71.9%)
Lispro	13/31 (41.9%)
Hispanic	
SAR342434	6/17 (35.3%)
Lispro	6/10 (60.0%)
BMI <30 kg/m²	
SAR342434	85/205 (41.5%)
Lispro	84/209 (40.2%)
BMI ≥30 kg/m²	
SAR342434	23/47 (48.9%)
Lispro	22/45 (48.9%)
HbA1c <8%	
SAR342434	53/98 (54.1%)
Lispro	46/99 (46.5%)
HbA1c ≥8%	
SAR342434	55/154 (35.7%)
Lispro	60/155 (38.7%)

TEAE: Treatment-emergent adverse events; defined as AEs that developed or worsened or became serious from the first IMP administration up to 1 day after the last administration.
IMP: Investigational medicinal product
a Number (%) of patients with at least one TEAE during the main 6-month on-treatment period – Safety population
b Number of patients in subgroup ≥ 75 years is too small (2 patients on SAR ILis,1 patient on ILis) to present data

Body weight

- A similar increase in body weight was noted from baseline to Week 26 in both treatment groups (mean change SAR ILis 0.69 kg and ILis 0.67 kg).

SUMMARY

In patients with T1DM

- SAR ILis was non-inferior to ILis for change in HbA1c. The inverse non-inferiority of ILis versus SAR ILis was also demonstrated.
- In all subgroups HbA1c decreased with no differences between treatment groups.
- In most subgroups no clinically meaningful differences in the number of hypoglycemia of the different categories were observed. The only differences were seen in subgroups with a low number of patients and have thus to be interpreted with caution.
- In general adverse events were similar for SAR ILis and ILis across subgroups. Only differences occurred in Asian/Oriental and in Hispanics subgroups.

CONCLUSIONS

- SAR342434 (SAR ILis) was similarly effective, well tolerated with similar safety profile as Humalog® (ILis) in patients with type 1 diabetes treated for 6 months regardless of the subgroup.

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DISCLOSURE

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