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Sponsor / Company: Sanofi **Drug substance(s):** Insulin Glargine (HOE901) Insulin Glulisine (HMR1964)	**Study Identifiers:** NCT01013571 **Study code:** LANTU_L_04695
Title of the study: A Canadian, Phase IV, multicenter, comparative, open-label study evaluating 2 approaches of blood glucose monitoring and insulin titration (patient-managed vs healthcare professional) in T2DM (type 2 diabetic mellitus) patients while receiving the addition of 1 injection insulin glulisine at breakfast following optimization of insulin glargine. (START)	
Study center(s): There were 47 active study centers in Canada.	
Study period: Date first patient enrolled: 07 OCT 2009 Date last patient completed: 31 JAN 2012	
Phase of development: Phase IV	
Objectives: The primary objective of this study was to demonstrate non-inferiority of a patient-managed titration algorithm (including blood glucose monitoring) for the addition of a single dose of insulin glulisine at breakfast in Canadian patients with inadequately controlled T2DM after optimization of basal insulin, compared with an health care professional (HCP) managed titration algorithm. The primary endpoint for assessment of this objective is the percentage of patients reaching a target HbA1c ≤7.0% without severe hypoglycemia at the end of the study. Secondary objectives of the study were to compare the effect of the two different insulin glulisine titration algorithms (patient-managed versus HCP-managed) on different parameters of glycemic control, patient-reported outcomes and resource utilization.	
Methodology: This was a randomized, parallel group, comparative, open-label study.	
Number of patients: Screened: 669 Run-in: 641 (planned ≈ 640) Randomized: 316 (planned ≈ 320) Follow-up: 170 (planned ≈ 150)	
Evaluated: Efficacy: Run-in analyses (324 Insulin naïve and 317 Previous insulin) Randomized analyses (154 patient (PAT) managed and 162 HCP-managed) Follow-up analyses (Randomized 316 and Follow-up 170) Safety: Run-in safety 641 Randomized population: inslulin glargine safety 316 insulin glulisine safety 314 Follow-up safety 170	
Diagnosis and criteria for inclusion: Patients with type 2 diabetes mellitus who were ≥30 years of age and who had been treated for at least 3 months with a basal insulin (insulin glargine, NPH, detemir) ± oral anti-hyperglycemic drugs (OADs) with an HbA1c >7.0% **or** insulin naïve (2-3 OADs) with an HbA1c ≥7.8%. Signed informed consent was required.	

Study treatments

Insulin glargine and insulin glulisine

Insulin glargine was added to insulin naïve patients treatment following the screening visit, beginning with 10U. Patients previously treated with basal insulins other than insulin glargine were switched to insulin glargine, while patients previously treated with insulin glargine continued their insulin glargine. During the run-in phase, all patients were asked to increase the dose of insulin glargine by 1U/day until their fasting blood glucose was <5.5 mmol/L.

Patients added a once-daily dose of insulin glulisine in the morning to the fixed dose of insulin glargine (established during Run-in) and OADs.

- Patient (PAT)-managed titration algorithm: The starting dose was 2U and patients were to titrate 1U/day to reach a 2-hour post breakfast glucose target between 5.0 mmol/L and 8.0 mmol/L. Maintenance included weekly titration based on the monitoring of 2 readings per week of 2-hour post breakfast glucose.
- HCP-managed titration algorithm: The recommended starting dose for insulin glulisine was 2U. The titration algorithm and blood glucose monitoring were left to the HCP's discretion. The patient was required to contact the HCP prior to any dose adjustment.

Formulation: Insulin glargine: LANTUS® SoloSTAR 3-mL pre-filled pen
Insulin glulisine: APIDRA® SoloSTAR 3-mL pre-filled pen

Route(s) of administration: subcutaneous for both insulin glargine and insulin glulisine

Dose regimen: Insulin glargine: once daily in the evening. Titration to fasting blood glucose (FBG) ≤5.5 mmol/L
Insulin glulisine: once daily in the morning at breakfast. Titration to 2-hr post breakfast glucose between 5.0mmol/L and 8.0 mmol/L

Duration of treatment: Insulin glargine: Run-in phase for 12 weeks plus Randomized or Follow-up phase for 24 weeks
Insulin glulisine: Randomized phase for 24 weeks

Duration of observation: 36 weeks from screening to end of treatment

Criteria for evaluation:

- Efficacy:

  Primary
  • Percentage of subjects reaching target HbA1c ≤7.0% without severe hypoglycemia at Week 36 (study end)

  Secondary
  • Change in HbA1c from Week 12 (randomization) to Week 24 and Week 36
  • Change in 7-point glucose profile parameters of before breakfast FBG, area under the curve (AUC), and difference between blood glucose values prior to breakfast and value 2 hours after breakfast, from Week 12 (randomization) to Week 24 and Week 36
  • Change in insulin glulisine dose from Week 12 (randomization) to Week 24 and Week 36
- Safety:
  • Adverse events
  • Incidence of hypoglycemia
  • Change in weight from Week 12 (randomization) to Week 24 and to Week 36
- Other:
  • Treatment satisfaction (Diabetes Treatment Satisfaction Questionnaire (DTSQ) for patient from Week 12 to Week 36 and HCP questionnaire at Week 36)
  • Resource utilization (glucose test strips, HCP visits, telephone calls) between study visits

Statistical methods:

Primary

For the primary efficacy endpoint, the percentage of PAT-managed patients with an HbA1c ≤7.0% and no severe hypoglycemia was said to be non-inferior to the percentage of HCP-managed patients with an HbA1c ≤7.0% and no severe hypoglycemia if the lower end of the 95% CI for the difference was ≥ -5.0%. The percent of patients achieving the endpoint was estimated from the generalized linear model with treatment and pooled site as the classified independent variables with binomial distribution and identity link function.

Secondary efficacy endpoints were all changes from randomization and were analyzed using analysis of covariance (ANCOVA). Means were estimated with the change from randomization as the dependent variable, with treatment and pooled site as the classified independent variables and randomization value as covariate. Differences between the titration algorithm groups were considered significant if p<0.05.

Summary: Only results for the primary study population, the Randomized population, are presented in the synopsis.

- Demographics, Disease characteristics and Patient withdrawal Results:

  Patients had a median age of 61 years, most were male (60.8%) and White (88.3%), with a median height of 170 cm, a median weight of 95.3 kg, and a median body mass index (BMI) of 33.0 kg/m^2. There were no statistical differences between titration arms with the exception of race, with more White patients in the PAT-managed arm (92.2% PAT-managed versus 84.6% HCP-managed; p = 0.0347). Patients had a mean duration of diabetes of 10.4 years, a mean historical HbA1c of 9.01%, and 49.4% were insulin naïve at study entry; there were no statistical differences between titration arms.

  All post-randomization patient withdrawals are presented in table S1 below for the Randomized population by titration algorithm and there was no significant difference between the groups.

Table S1: Patients who withdrew from study for Randomized population by titration algorithm (ITT patients)

Characteristic		N (%) PAT managed	N (%) HCP managed	P-value
Number of patients		154	162	
Withdrew from study	No	144 (93.5)	144 (88.9)	0.1816
	Yes	10 (6.5)	18 (11.1)	
Reason for withdrawal	Adverse event	3 (30.0)	3 (16.7)	0.8029
	Lack of efficacy	1 (10.0)	1 (5.6)	
	Protocol violation	1 (10.0)	0 (0.0)	
	Lost to follow-up	1 (10.0)	3 (16.7)	
	Did not wish to continue	2 (20.0)	9 (50.0)	
	Other reason	2 (20.0)	2 (11.1)	

HCP = Healthcare professional; PAT = Patient

- Efficacy results:

  Primary endpoint

  The percent of patients with an HbA1c ≤7.0% and with no severe hypoglycemia at the end of the Randomization phase was 28.4% for the PAT-managed algorithm versus 21.2% for the HCP- managed algorithm (see table S2 below). The lower end of the 95% confidence interval for the difference between the two groups was ≥-5.0% (-3.2%), indicating that the PAT strategy was non-inferior to the HCP strategy. The p-value for non-inferiority was 0.0105.

Table S2: Primary efficacy endpoint: Percent of patients with an HbA1c ≤7.0% and with no severe hypoglycemia for Randomized population by titration algorithm (ITT patients)

PAT managed				HCP managed				Difference: PAT managed - HCP managed		
N	%	SE	95% CI	N	%	SE	95% CI	%	SE	95% CI
154	28.4	3.70	(21.2; 35.7)	162	21.2	3.57	(14.2; 28.2)	7.2	5.31	(-3.2; 17.7)

CI = confidence interval; HCP = healthcare professional; N = number of patients; PAT = patient; SE = standard error

Secondary endpoints:

There were no significant differences between titration algorithms for any of the secondary endpoint measures of glycemic control (see table S3 below). The PAT-managed patients did increase their dose of insulin glulisine significantly higher than the HCP-managed patients (p=0.0018).

Table S3: Change from Randomization visit (Week 12) to End of treatment for Secondary efficacy endpoints for Randomized population by titration algorithm (mITT patients)

Endpoint	PAT managed		HCP managed		Difference: PAT managed – HCP managed			
	N	Adjusted mean	N	Adjusted mean	Adjusted mean	SE	95% CI	P-value
HbA1c (%)	154	-0.59	159	-0.51	-0.08	0.099	(-0.27; 0.12)	0.4361
Before breakfast FBG (mmol/L)	121	0.69	129	0.47	0.21	0.276	(-0.33; 0.76)	0.4380
24-hour AUC (mmol*h)	121	-17.92	129	-17.51	-0.41	5.080	(-10.42; 9.60)	0.9351
BG before breakfast – BG 2h after breakfast (mmol/L)	121	-2.66	129	-2.34	-0.32	0.412	(-1.13; 0.49)	0.4348
Insulin glulisine dose (U)	148	14.9	151	9.3	5.6	1.77	(2.1; 9.1)	0.0018

HbA1c = glycosylated hemoglobin; AUC = area under the 7-point glucose profile curve; BG = blood glucose; CI = confidence interval; FBG = fasting blood glucose; HCP = healthcare professional; N = number of patients; PAT = patient; SE = standard error

- Safety results:

Adverse events

An overview of the adverse event profile for the Randomized population is presented in the table S4 and S5 below. There were no notable differences between study arms, with 54 (35.1%) of the PAT-managed patients having a treatment emergent adverse event (TEAE) and 60 (37.5%) of patients in the HCP-managed arm reporting a TEAE from randomization until the end of treatment. The same can be said for TEAEs related to insulin glulisine. The proportion of patients with serious TEAEs was also similar, as was the proportion of patients with any TEAE leading to permanent treatment discontinuation. There were no deaths in the Randomized population.

Table S4: Overview of adverse event profile: all TEAEs – Randomized population by titration algorithm from Randomization visit (Week 12) to end of treatment (Insulin glulisine Safety patients)

	N (%)	
	PAT managed (N=154)	HCP managed (N=160)
Patients with any TEAE	54 (35.1%)	60 (37.5%)
Patients with any treatment emergent SAE	7 (4.5%)	8 (5.0%)
Patients with any TEAE leading to death	0 (0.0%)	0 (0.0%)
Patients with any TEAE leading to permanent treatment discontinuation	3 (1.9%)	4 (2.5%)

HCP = healthcare professional; N = number of patients; PAT = patient; SAE = serious adverse event;

Table S5: Overview of adverse event profile: all TEAEs related to insulin glulisine – Randomized population by titration algorithm from Randomization visit (Week 12) to end of treatment (Insulin glulisine Safety patients)

	N (%)	
	PAT managed (N=154)	HCP managed (N=160)
Patients with any related TEAE	7 (4.5%)	5 (3.1%)
Patients with any related treatment emergent SAE	2 (1.3%)	0 (0.0%)
Patients with any related TEAE leading to death	0 (0.0%)	0 (0.0%)
Patients with any related TEAE leading to permanent treatment discontinuation	2 (1.3%)	2 (1.3%)

HCP = healthcare professional; N = number of patients; PAT = patient; SAE = serious adverse event;
TEAE = treatment-emergent adverse event

Hypoglycemia

The incidence and annualized rates for hypoglycemic events are presented for the Randomized population by titration algorithm in table S6. There was no significance between titration groups in either the percentage of patients who experienced hypoglycemia or the annualized rate of hypoglycemia.

Table S6: Incidence and annualized rate for each type of hypoglycemic event for Randomized population by titration algorithm patients from Randomization visit (Week 12) to end of treatment (All Safety patients)

	PAT managed N = 154		HCP managed N = 162		Difference (PAT managed – HCP managed)			
					Incidence (%)		Annualized Rate	
Type of hypoglycemia	**%**	**Rate**	**%**	**Rate**	**95% CI**	**P-value**	**95% CI**	**P-value**
All	67.5	8.93	61.1	8.09	(-17.0, 4.1)	0.2324	(0.62, 1.32)	0.6061
All confirmed	63.6	7.07	58.6	6.20	(-15.7, 5.7)	0.3618	(0.60, 1.29)	0.5074
Nocturnal	26.0	0.91	28.4	0.84	(-7.4, 12.2)	0.6285	(0.53, 1.58)	0.7521
Severe	1.9	0.02	1.9	0.03	(-3.1, 2.9)	0.9501	(0.24, 9.32)	0.6759

CI = confidence interval; HCP = healthcare professional; PAT = patient

Weight

Change in weight and BMI from the Randomization visit to the end of treatment is presented for the Randomized population by titration algorithm in the table S7 below. Although patients in the PAT-managed group gained more weight than patients in the HCP-managed group (p=0.0494), the change in body mass index (BMI) was not significantly different between titration groups at the end of treatment.

Change from Randomization visit (Week 12) to end of treatment for weight (kg) and BMI (kg/m^2) for Randomized population by titration algorithm (mITT patients)

	PAT managed		HCP managed		Difference: PAT managed – HCP managed			
Visit	**N**	**Adjusted mean**	**N**	**Adjusted mean**	**Adjusted mean**	**SE**	**95% CI**	**P-value**
Weight (kg)	147	1.91	150	1.04	0.87	0.439	(0.00; 1.73)	0.0494
BMI (kg/m^2)	147	0.64	149	0.35	0.29	0.155	(-0.02; 0.59)	0.0624

BMI = body mass index; CI = confidence interval; HCP = healthcare professional; N = number of patients; PAT = patient; SE = standard error

- Treatment satisfaction results:

The changes in treatment satisfaction scores for the DTSQc are presented for the Randomized population by titration algorithm in the table below. There were no significant differences between titration algorithm groups in any of the measures of satisfaction with treatment from Randomization to the end of treatment.

Table S7: Change in scores in DTSQ from Randomization visit (Week 12) to end of treatment for Randomized population by titration algorithm (mITT patients)

	PAT managed		HCP managed		Difference: PAT managed – HCP managed			
DTSQ measure	**N**	**Adjusted mean**	**N**	**Adjusted mean**	**Adjusted mean**	**SE**	**95% CI**	**P-value**
Total score	122	13.37	111	13.59	-0.22	0.706	(-1.61; 1.17)	0.7557
Perceived frequency of hyperglycemia	121	-0.68	111	-0.65	-0.03	0.251	(-0.53; 0.46)	0.9004
Perceived frequency of hypoglycemia	121	-0.36	110	-0.25	-0.11	0.226	(-0.56; 0.33)	0.6231
Wish to continue	121	2.39	111	2.44	-0.05	0.150	(-0.34; 0.25)	0.7501

CI = confidence interval; DTSQ = diabetes treatment satisfaction questionnaire; HCP = healthcare professional; N = number of patients; PAT = patient; SE = standard error

Mean scores for the 7 items on the HCP satisfaction questionnaire are presented below for the 41/47 sites (87%) who responded. The mean total satisfaction score was 14.0 ± 7.21 with a range from -6 to 21.

Table S8: Healthcare professional satisfaction questionnaire: means (SD) for all 41 sites

Characteristic	Mean (SD)
1. Basal plus treatment easy to implement	2.3 (0.91)
2. Basal plus treatment effective	2.1 (1.09)
3. PAT-managed titration simple and easy	2.0 (1.24)
4. satisfied with outcome in patients using PAT-managed titration	1.7 (1.32)
5. Patient-managed titration increased belief that patients actively participate	2.2 (1.05)
6. Would use the START PAT-managed titration in their practice	1.9 (1.33)
7. Would recommend the use of START PAT-managed titration	1.7 (1.38)
TOTAL HCP SCORE	14.0 (7.21)

HCP = healthcare professional; N = number of sites; PAT= patient; SD = standard deviation
Items score range -3 (totally disagree) to +3 (totally agree)

- Resource utilization results:

  Health resource utilization at end of treatment is presented for the Randomized population by titration algorithm in the table S9 below. There was no significant difference between titration algorithms in the number of gluocometer strips used or visits to their healthcare professional. The PAT-managed patients had significantly fewer telephone calls to the site about their diabetes than the HCP-managed patients (p=0.0001).

Table S9: Resource utilization since last visit for end of treatment for Randomized population by titration algorithm (mITT patients)

Number of:	PAT managed		HCP managed		Difference: PAT managed – HCP managed			
	N	Adjusted mean	N	Adjusted mean	Adjusted mean	SE	95% CI	P-value
Glucometer strips used	143	161.00	145	164.18	-3.18	8.136	(-19.20; 12.84)	0.6965
Visits to HCP	152	1.24	154	1.28	-0.04	0.178	(-0.39; 0.31)	0.8110
Telephone calls to site	152	0.95	154	1.70	-0.74	0.201	(-1.14; -0.35)	0.0001

CI = confidence interval; HCP = healthcare professional; N = number of patients; PAT = patient; SE = standard error

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