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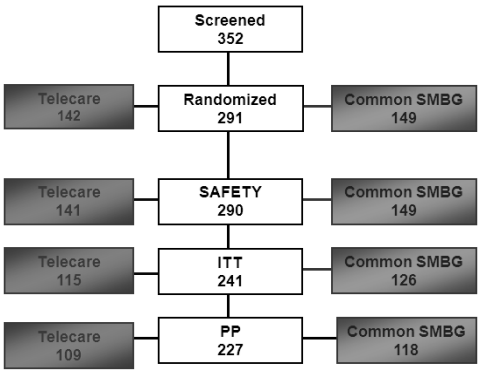
Sponsor/company:	sanofi-aventis	**Clinicaltrials.gov Identifier:**	NCT00272064
		Study Code:	HMR1964A_3514
Generic drug name:	Insulin Glulisine	**Date:**	19/May/2009

Title of the study:	OPTIMISATION OF INSULIN TREATMENT OF TYPE 2 DIABETES MELLITUS BY TELECARE ASSISTANCE FOR SELF MONITORING OF BLOOD GLUCOSE – ELEONOR STUDY (Study Code: HMR1964A/3514)
Investigator(s):	Multicentric study Coordinating Investigator: Prof. Stefano Del Prato Presidio Ospedaliero di Cisanello - Unità Operativa Malattie Metaboliche e Diabetologia Universitaria. Via Paradisa, 2 - 56124 Pisa, Italy
Study center(s):	35 centers in Italy
Publications (reference):	N/A

Study period: Date first patient enrolled: 26-Oct-2005 Date last patient completed: 14-May-2008	**Phase of development:** IIIb

Objectives:	The primary objective of the study was to verify the superiority of Telecare program vs. standard SMBG program in terms of mean HbA1c value (expected difference: - 0,5%) at end-point, in patients with type 2 diabetes mellitus (T2DM). The secondary objectives of the study were the assessment of: changes in glycaemic and lipid profile, frequency of hypoglycaemias, changes in weight, with Telecare program vs. common ambulatory program; general safety (adverse event profile, other routine laboratory parameters), changes in health related Quality of Life		
Methodology:	Open label, national, multicentre, randomised (1:1), controlled, parallel-group study comparing a Telecare program with the standard self monitoring of blood glucose (SMBG program) in the evaluation of the blood glucose values		
Number of patients:	Planned: 380 (190 in each arm) Sample size re-estimated: 190 patients (95 in each arm)	Screened: 352 Randomized: 291 (142 to Telecare; 149 to Common SMBG)	Treated: 290 (141 to Telecare; 149 to Common SMBG). One patient never treated
Evaluated:	Efficacy : Intention-To-Treat (ITT) population: 241 (115 to Telecare; 126 to Common SMBG) Per-protocol (PP) population: 227 (109 to Telecare; 118 to Common SMBG group)		Safety: 290

	ITT population: randomised patients known to have taken at least one dose of study drugs and providing enough data to assess the primary variable (i.e. having completed at least 12 weeks of treatment). PP population: all patients in the ITT population adhering to protocol conditions, i.e. patients without major protocol violations. Safety population: all randomised patients known to have taken at least one dose of study drug
Diagnosis and criteria for inclusion:	male / female patients (35-70 years) with type 2 diabetes mellitus (T2DM) on treatment with combined oral antidiabetic drugs (OAD) or metformin at maximal doses for at last 3 months. BMI > 25 Kg/m^2; HbA1c range of ≥ 7.5 % and ≤ 11 %
Investigational product:	insulin glargine (3 ml cartridges containing 100 U/ml)
Dose:	Individualized, once daily, dose to reach mean fasting plasma glucose (FPG) ≤ 126 mg/dl (7.0 mmol/l), since randomization
Administration:	subcutaneous
Investigational product:	insulin glulisine (3 ml Optisets containing 100 U/ml)
Dose:	Individualized, once daily, dose aiming at 2h post-prandial plasma glucose goal < 140 mg/dl (7.8 mmol/l), in the optimized treatment phase, since visit 3
Administration:	subcutaneous
Non investigational product:	metfomin (tab 1000 mg)
Dose:	1000 mg b.i.d., since the qualification phase
Administration:	oral
Duration of treatment: 4-week qualification phase with metformin (visit 1 to visit 2); 8-week (up to 16-week) titration phase of insulin glargine in addition to metformin (visit 2 to visit 3 - baseline); 24-week optimised treatment with insulin glulisine added to insulin glargine and metformin (visit 3 to visit 5); 2-week follow-up (visit 5 to visit 6)	**Duration of observation**: approximately 38 weeks
Reference therapy:	N/A (the study compares the effectiveness of the Telecare program vs. Common SMBG program)
Criteria for evaluation:	
Efficacy:	Primary: changes of glycosilated haemoglobin (HbA1c) from baseline to endpoint Secondary: other changes in glucidic profile (fasting plasma glucose; plasma insulin levels; pre- and post-prandial glycaemic values; Mean Amplitude Glucose Excursions - MAGE) and lipidic profile (total and HDL cholesterol; tryglicerides); Health related Quality of Life; changes in weight
Safety:	Frequency of patients with hypoglycaemias and frequency of hypoglycaemia overall Adverse events' profile, standard laboratory parameters, vital signs.
Statistical methods:	The primary analysis was based on the change of mean glycosilated haemoglobin (HbA1c [%]) from baseline (visit 3) to endpoint in the ITT population, to verify the superiority of Telecare program vs standard SMBG program. The difference in mean changes was estimated using the associated standard error and 95% confidence interval from the ANCOVA model including treatment group as factor and baseline value as linear covariate. Comparison within group of treatment (Telecare or Common SMBG) from baseline to endpoint was performed using t-test based on ANCOVA model.

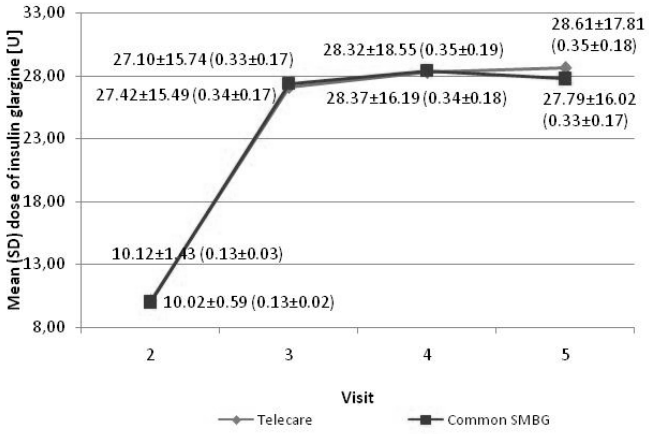
Summary:	This study selected patients with T2DM on treatment with metformin alone (10 % of patients) or in combination with other antidiabetic agents (90 % of patients) 291 patients were randomized in the study. The safety population is represented by 290 patients because one patient randomized in the Telecare group was never treated. 241 patients provided data for the primary variable and represent the ITT population. Because of protocol violations the PP population is represented by 227 patients. There were no differences between the two groups as for the incidence of violations. Protocol violations were mostly represented by study continuation in the presence of FPG levels out of the allowed range at visit 3 (end of titration/start of treatment), two violations of the inclusion/exclusion criteria, three cases of temporary study drug discontinuation > 5 days (titration phase) or > 10 days (treatment phase). 

The two groups (Telecare and Common SMBG) were well balanced as for demographic characteristics and medical history.

ITT population baseline characteristics	Telecare (N=115)	Common SMBG (N=126)
Male	60 (52.2%)	66 (52.4%)
Female	55 (47.8%)	60 (47.6%)
Mean age [years]	57.9	58.7
Ethnic group: white	114 (99.1%)	126 (100.0%)
BMI [kg/m^2]	30.0	30.3
duration of T2DM (years)	10.5	11.3
HbA1c	8.83	8.89
Absence of microalbuminuria	77.5 %	78.2 %
Average calories [kal] in diet	1620.3	1590.0

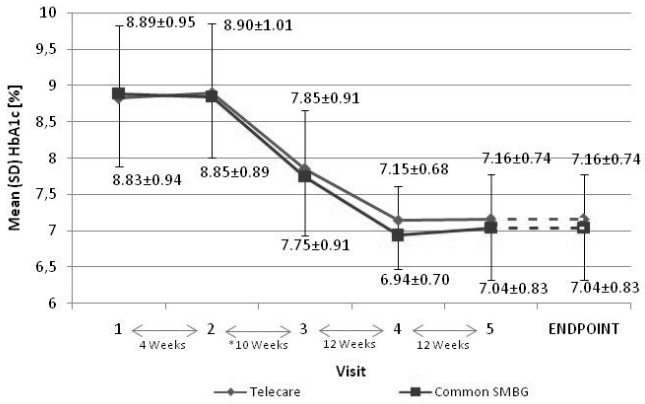
238 of the 291 randomized patients completed the study (80.3% in the Telecare arm and 83.2% in the Common SMBG arm). Main reason for study interruption was high FPG levels (> 126 mg/dL) at the end of the titration phase.

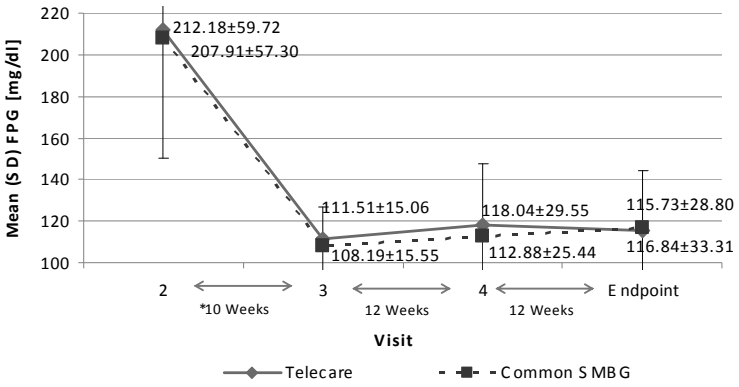
Mean insulin glargine daily doses were not different between the two groups, as shown in the following figure (data reported as Units and as U/kg/day in parenthesis):



The administration of insulin glulisine was forseen only for patients with a mean FPG after breakfast or lunch or dinner over the cut-off limit of 140 mg/dL.

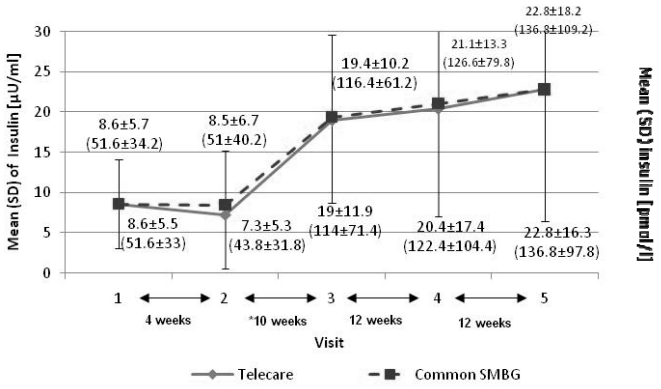
Insulin glulisine was taken by all patients but 13 and 14 patients of the Telecare and common SMBG groups, respectively. Mean daily doses escalated from 4.2 – 4.4 U (Telecare and common SMBG groups, respectively, at visit 3) to 9.5 U (both groups, at visit 5).

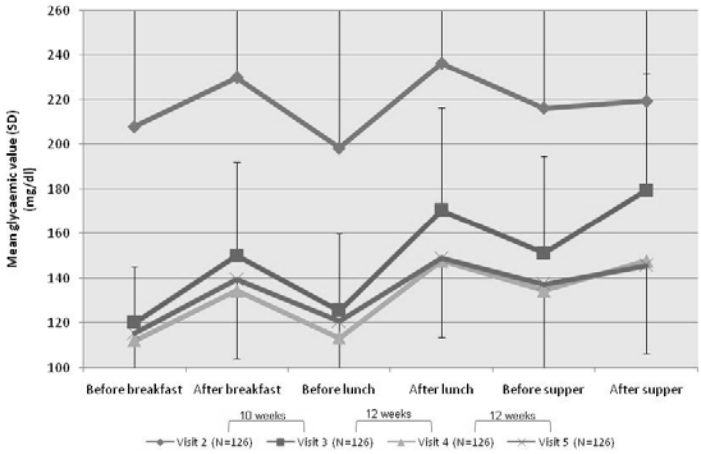
Efficacy results:	ITT population - HbA1c (%): the change in the adjusted mean (SE) of glycated hemoglobin from baseline (visit 3) to endpoint was -0.65 (0.06) % in the Telecare group (p<.0001) and -0.73 (0.06) % in the Common SMBG group (p<.0001). No statistically significant difference was found between groups (95% CI: -0.1; 0.25). The overall course of HbA1c (%) in the two groups is represented in the following figure:  Changes between visits were significant from visit 2 to visit 3 and from visit 3 to visit 4 within either groups (p<.0001). 50.2% of the total patients' population achieved HbA1c ≤ 7% at the end of study. Mean glycated hemoglobin in remaining patients (49.8 % of patients with HbA1c > 7%) was 7.68 % PP population - HbA1c (%): changes observed in the PP population (-0.66 (0.06)% in the Telecare group and -0.72 (0.06)% in the Common SMBG group) were similar to those in the ITT population, with highly significant differences within groups (p<.0001) from baseline to endpoint and no difference between groups (95% CI: -0.12; 0.24). ITT population – fasting plasma glucose (mg/dL): in both groups, mean FPG significantly decreased during the insulin titration phase (p <.0001) and was kept in both groups over the following course of the study at mean values ranging between 108 and 118 mg/dL, as represented in the next figure:



The adjusted mean change of FPG between visit 2 and visit 3 was statistically significant in both groups (-98.54 $\pm$ 1.39 (SE) mg/dl in the Telecare group, p <.0001; -102.88 $\pm$ 1.37 (SE) mg/dl in the Common SMBG group, p <.0001). Also the difference between the two groups (4.33 mg/dl) was statistically significant (p=0.027).

ITT population – plasma insulin (microU/ml): plasma insulin significantly increased during the titration phase in both groups (p<.0001) and showed a progressive increase during the optimised treatment phase, without significant differences between the two groups (values in microU/ml and pmol/l in parenthesis).



	ITT population – Self-monitoring of Blood Glucose (SMBG - mg/dL): glycaemic profiles based on 6-point assessments (values measured before and 2 hours after meals) were taken into consideration from 126 patients (52 in the Telecare and 74 in the Common SMBG) having monitored at least 50% of the planned assessments within the same day (i.e. $\geq$ 3 assessments) and with at least one glycaemic profile (complete or partial) at all visits (e.g. visit 2, visit 3, visit 4 and visit 5. Considerable and progressive improvement of the glycaemic profiles was obtained from the randomization (visit 2) to the end of study (visit 5), after the start of treatment with insuline glargine (since visit 2) and the introduction of insulin glulisine (since visit 3), as shown in the next figure:  The change of SMBG was not statistically significant between treatments at any daily measurements considered. ITT population – Mean Amplitude Glucose Excursion (MAGE): mean MAGE (SD) was reduced from 82.6 (34.9) mg/dl (visit 3) to 71 (36.8) mg/dl (visit 5) in the Telecare group and from 83.4 (35.3) mg/dl (visit 3) to 76.6 (26.9) mg/dl (visit 5) in the Common SMBG group (no statistically significant differences between groups). ITT population – post-hoc analysis: the MODD index : MODD is an index of between-day blood glucose variability calculated as the mean of daily differences of paired blood glucose values on successive days. The MODD showed stable values, indicating very low variability of blood glucose over time.

	ITT population – Health related Quality of Life: when comparing SF-36 scores at V5 versus the start of insulin glargine (V2), similar improvements were seen within Telecare Program and SMBG groups in all domains evaluated, as well as in summary physical (49.3 vs 47.8; p=0.04 and 49.8 vs 47.2; p<0.0001) and mental (50.5 vs 47.4; p<0.0001 and 51.2 vs 47.6; p=0.04) component scores. Treatment satisfaction improved in the Telecare Program and SMBG groups (DTSQ score: 30.1 vs 25.6 and 30.4 vs 24.7; both p<0.0001), with a reduced frequency of perceived hyperglycemic episodes (2.4 vs 4.7 and 2.4 vs 4.2; both p<0.0001) and a mildly increased frequency of perceived hypoglycemic episodes (1.7 vs 0.8 and 1.8 vs 0.6; both p<0.0001). No difference emerged between groups. ITT population – Lipid profile: No significant changes were observed for total cholesterol during the study. HDL cholesterol and tryglicerides significantly increased in both groups (p<.0001) without significant differences between treatments. ITT population – Body weight; Body Mass Index: No significant changes were observed for body weight and BMI during the study. Body weight slightly increased from 79.3 ± 14.1 to 81.0 ± 14.8 kg in the Telecare Program and from 81.0 ± 15.0 to 82.2 ± 15.4 Kg in the SMBG group, at baseline (V3) vs endpoint (V5), respectively (mean ± SD).
Safety results:	Treatment Emergent Adverse Events (TEAEs) in the Safety population were reported from 25 patients (17.7%) of the Telecare group and 39 patients (26.2%) of the Common SMBG group. Serious events were reported in 2.8% and 4.7 % of patients of the Telecare group and Common SMBG group, respectively. Two patients in each treatment group experienced TEAEs considered by the investigator as treatment-related; these were non-serious. One patient (0.7%) in the Telecare and two patients (1.3%) in the Common SMBG reported TEAEs leading to withdrawal of the study treatment. No deaths were reported. Overall, 343 episodes of hypoglycaemia (plasma glucose <72 mg/dl, or symptomatic episode) were reported (172 in the Telecare and 171 in the Common SMBG), with an incidence (number of patients with any hypoglycaemia / total number of patients within group) of 0.21 in the Telecare and 0.23 in the Common SMBG. 316 hypoglycemic events occurred during insulin titration and treatment phase, 157 in the Telecare and 159 in the Common SMBG, corresponding to an incidence of 1.89 and 1.76 hypoglycaemic events/patient/year in the Telecare and SMBG groups, respectively. 32% of symptomatic hypoglycemia episodes occurring over the entire study period in the Telecare and 19.9% in the Common SMBG were nocturnal (33.8 % and 19.5 %, respectively, during titration and treatment phase).

	Overall, 30 patients (21.3%) in the Telecare group and 35 patients (23.5%) in the Common SMBG experienced episodes of symptomatic hypoglicaemia during the study. These were severe in 4 (2.8%) and 3 (2.0%) patients, respectively. Out of the 157 episodes of symptomatic hypoglycaemia during titration and treatment phase in the Telecare group, 12.7 % occurred between V2 and V3 (titration period with insulin glargine only) and 87.3 % between V3 and V5 (treatment period with the combination of insulin glargine and glulisine). In the Common SMBG (159 episodes of symptomatic hypoglycaemia during titration or treatment period), 13.2 % of episodes occurred between V2 and V3 (titration period with insulin glargine only) and 86.8 % between V3 and V5 (treatment period with the combination of insulin glargine and glulisine). Episodes of symptomatic nocturnal hypoglycemia occurred at a rate of 5.1 % vs 3.1 % during the titration period of treatment with insulin glargine only (Telecare vs Common SMBG, respectively), and at a rate of 28.7 % vs 16.4 % during the period of treatment with insulin glargine and glulisine (Telecare vs Common SMBG, respectively). The episodes of symptomatic severe hypoglycemia occurred only during the period of treatment with insulin glargine and glulisine (V3 to V5) and were 1.9% in the Telecare and 1.3% in the Common SMBG, corresponding to a rate of 0.04 events/patient/year in the Telecare vs 0.02 events/patient/year in the Common SMBG. Also the episodes of severe nocturnal hypoglycemia occurred only during the period of treatment with insulin glargine and glulisine (V3 to V5) and were 1.3% in the Telecare and 0.6% in the Common SMBG, corresponding to a rate of 0.02 events/patient/year in the Telecare vs 0.01 events/patient/year in the Common SMBG. No correlation was found between the time of injection of glulisine with hypoglycaemic episodes. Standard hematology and biochemistry showed no relevant changes during the study.
Date of report:	05-MAR-2009