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/company:	sanofi-aventis	**ClinicalTrials.gov Identifier:**	NCT00174642
		Study Code:	HMR1964A_3506
Generic drug name:	Insulin Glulisine	**Date:**	4 December 2009

Title of the study:	Comparison of Three Therapeutic Strategies for Treating Type 2 Diabetes Mellitus Patients Poorly Controlled With Basal Insulin Associated With Oral Antidiabetic Drugs OSIRIS STUDY: Opposing Step-by-step Insulin Reinforcement to Intensified Strategy - HMR1964A/3506	
Investigator(s):	Prof Denis Raccah, CH Ste Marguerite, Maladies Métaboliques, 270 boulevard Ste Marguerite, 13274 Marseille Cedex 09, France.	
Study center(s):	103 active centers (hospital and independent diabetologists) in 18 countries: Belgium, France, Germany, Greece, Hungary, Ireland, Italy, Korea, Lituania, Mexico, Netherlands, Poland, Russia, Spain, Sweden, Taiwan, Turkey and United Kingdom.	
Publications (reference):	None	
Study period: Date first subject enrolled: Date last subject completed:	 16 December 2004 01 December 2008	Phase of development: IIIb
Objectives:	<u>Primary objectives</u>: To show the non-inferiority in terms of efficacy (change in HbA1c) of insulin glargine plus metformin combined with 1 to 3 bolus of insulin glulisine introduced progressively (Arm 2) compared with insulin glargine plus metformin combined with 3 bolus of insulin glulisine (Arm 1), in Type 2 diabetes mellitus subjects poorly controlled on basal insulin therapy with oral antidiabetic drugs (OAD). To show the non-inferiority in terms of efficacy (change in HbA1c) of insulin glargine plus metformin combined with 1 to 3 bolus of insulin glulisine introduced progressively (Arm 2) compared with insulin glargine plus metformin and insulin secretagogue (IS) (sulfonylurea or glinide) combined with 1 to 3 bolus of insulin glulisine introduced progressively (Arm 3), in Type 2 diabetes mellitus subjects poorly controlled on basal insulin therapy with OADs. <u>Secondary objectives</u>: To compare between the 3 treatment arms: evolution of HbA1c over time, percentage of subjects with HbA1c $\leq$7% at the end of the study, evolution of blood glucose profiles, incidence of hypoglycemia, insulin doses, evolution of body weight and treatment satisfaction.	

<table>
<tr><td>Methodology:</td><td>International, multicenter, comparative, open, randomized 3-arm parallel group study consisting of 1 to 3 weeks of selection followed by an 18-month treatment period comprising an initial 6-month nonrandomized treatment period and a 12-month randomized treatment period. During the initial nonrandomized 6-month period, the subjects were treated with insulin glargine in a single daily injection in the evening together with their previous OAD treatment. At the end of the initial period, subjects whose HbA1c was >7% and whose mean fasting blood glucose (FBG) was ≤120 mg/dL (6.7 mmol/L) were randomized to one of the following 12-month treatment arms:
Arm 1: insulin glargine + 3 bolus of insulin glulisine + metformin
Arm 2: insulin glargine + 1 to 3 bolus of insulin glulisine + metformin
Arm 3: insulin glargine + 1 to 3 bolus of insulin glulisine + metformin + IS.</td></tr>
<tr><td>Number of subjects:</td><td>The planned number of subjects to be included was 776 of whom 388 would be randomized.
Actual number of subjects enrolled, randomized and analyzed for efficacy and or safety are summarized in the following table:
<table>
<tr><th></th><th>Arm 1
N

n (%)</th><th>Arm 2
N

n (%)</th><th>Arm 3
N

n (%)</th><th>All
N

n (%)</th></tr>
<tr><td>Screened subjects</td><td>-</td><td>-</td><td>-</td><td>942</td></tr>
<tr><td>Included subjects</td><td>-</td><td>-</td><td>-</td><td>811</td></tr>
<tr><td>Treated subjects in initial period</td><td>-</td><td>-</td><td>-</td><td>804</td></tr>
<tr><td>Randomized subjects</td><td>153</td><td>199</td><td>124</td><td>476</td></tr>
<tr><td>Randomized and treated population</td><td>144 (94.1)</td><td>197 (99.0)</td><td>123 (99.2)</td><td>464 (97.5)</td></tr>
<tr><td>ITT population for primary criterion</td><td>140 (91.5)</td><td>190 (95.5)</td><td>116 (93.5)</td><td>446 (93.7)</td></tr>
<tr><td>PP population for primary criterion</td><td>120 (78.4)</td><td>165 (82.9)</td><td>100 (80.6)</td><td>385 (80.9)</td></tr>
<tr><td>Safety population of randomized period</td><td>144 (94.1)</td><td>197 (99.0)</td><td>123 (99.2)</td><td>464 (97.5)</td></tr>
</table>
ITT = intent to treat; PP = per protocol</td></tr>
<tr><td>Diagnosis and criteria for inclusion:</td><td>Type 2 diabetic men or women; aged 18 to 75 years; body mass index (BMI) ≤40 kg/m^2; HbA1c >7%; treated with basal insulin (NPH, Insulin Zinc, insulin glargine or insulin detemir), and at least, 2 OADs including an IS (sulfonylurea or glinide at any dosage) and metformin (at the maximum tolerated dosage), for more than 6 months; informed consent obtained in writing for all subjects prior to enrollment into the study.</td></tr>
</table>

Investigational product:	Insulin glulisine in cartridges of 3 mL (100 U/mL)
Dose:	The initial dose of insulin glulisine was calculated as post-prandial blood glucose (PPBG) in mmol/L divided by 2. Then insulin glulisine was to be titrated every 3-4 days to obtain a PPBG of between 110 mg/dL and 160 mg/dL (6.1 mmol/L and 8.9 mmol/L). Arm 1: 3 daily bolus (1 injection immediately before each meal). Arm 2 and Arm 3: initially 1 daily bolus immediately before the meal corresponding to the highest PPBG, possibly adjusted to 2 daily bolus before the 2 meals with highest PPBG after 4 months and to 3 daily bolus after 8 months. Subjects in Arm 1 and Arm 2 also received one injection of insulin glargine in the evening and oral metformin. Subjects in Arm 3 also received one injection of insulin glargine in the evening and oral metformin + an IS (sulfonylurea or glinide).
Administration:	Subcutaneous injection with a blue or green OptiPen® Pro1 only during the 12-month randomized treatment period.
Duration of treatment: 12 months	Duration of observation: 18 months including a 6-month nonrandomized treatment period and a 12-month randomized treatment period.
Combined therapy:	Insulin glargine (Lantus®) cartridges of 3 mL (100 U/mL).
Dose:	The initial dose of insulin glargine was calculated as the dose of previous basal insulin if 1 daily injection or total dose of previous insulin -20% if more than 1 daily injection. Then insulin glargine was to be titrated every 3-4 days to obtain a FBG of between 80 mg/dL and 110 mg/dL (4.4 mmol/L and 6.1 mmol/L). Initial 6-month period: 1 single daily injection at dinner or at bedtime. Initial OAD treament was maintained (at least metformin + IS). 12-month randomized treatment period: same dosage + 3 daily bolus of insulin glulisine + metformin (Arm 1) or + 1 to 3 daily bolus of insulin glulisine + metformin (Arm 2) or + 1 to 3 daily bolus of insulin glulisine + metformin + IS (Arm 3).
Administration:	Subcutaneous (SC) injection with a white OptiPen Pro1 in the evening at dinner or at bedtime.
Criteria for evaluation:	
Efficacy:	Primary efficacy variable: • Change in HbA1c between measurements at the randomization visit (Month 6) and at endpoint (the last available value during the randomized on-treatment period). Secondary efficacy variables: • Change in HbA1c measured before randomization at V6 (the randomization visit) and at Months 10 (V8), 14 (V10) and 18 (V12).

Safety:	• Percentage of subjects with HbA1c ≤7% at the endpoint. • In Arms 2 and 3, percentage of completed subjects remaining with fewer than 3 bolus of insulin glulisine at the end of the randomized treatment period (V12), and with HbA1c ≤7%. • 6-point blood glucose (BG) profiles (before and 2 hours after each meal) at inclusion (V2), at the randomization visit, at visits V8, V10, V12, and at endpoint • Mean daily BG levels at V2, the randomization visit, V8, V10, V12, and at last available BG profile. • Symptomatic hypoglycemia, nocturnal symptomatic hypoglycemia, severe symptomatic hypoglycemia and severe nocturnal symptomatic hypoglycemia. • The doses of insulin glargine at each visit from V2 and insulin glulisine at each visit from the randomization visit: the daily insulin doses and the daily doses per kilogram of body weight. <u>Treatment satisfaction</u>: • Treatment satisfaction at V2, the randomization visit, V8, V10, and V12 assessed using the Diabetes Treatment Satisfaction Questionnaires, DTSQs and DTSQc. • Adverse events (AEs) during the initial period and treatment-emergent adverse events (TEAE), ie, adverse events (AE) beginning or worsening during the treatment period with insulin glargine + insulin glulisine. • Vital signs: systolic blood pressure (SBP), diastolic blood pressure (DBP) at V2, the randomization visit, V10, V12, and at endpoint. • Weight at V2, the randomization visit, V10, V12, and at endpoint.
Statistical methods:	<u>Primary analysis of efficacy</u> The following primary analysis of efficacy was carried out in the PP population: Calculation of the change in HbA1c from randomization (V6) to endpoint. Construction of the 95% confidence interval (CI; two-sided) of the differences of the adjusted means (Arm 2 – Arm 1; Arm 2 – Arm 3), obtained by an analysis of covariance (ANCOVA), with the change in HbA1c as the dependent variable, the treatment (3 levels) as the fixed effect and the value of HbA1c before randomization as the covariate. Conclusion to the non-inferiority of Arm 2 to Arm 1 if the upper limit of the CI of the difference (Arm 2 - Arm 1) was ≤0.4% [statistical test therefore performed at the 2.5% level (one-sided)].
	IF AND ONLY IF the non-inferiority of Arm 2 to Arm 1 was proven, the same test was performed to establish the non-inferiority of Arm 2 to Arm 3.

	The analysis was also carried out in the ITT population for the primary criterion to assess the robustness of the results. Secondary analyses of efficacy: • Evolution of HbA1c (PP population): Descriptive statistics at each visit (V1 to V12) and at endpoint, and in subjects having a measurement of HbA1c after at least 10 months of exposure to insulin glulisine. • Change in HbA1c measured at V8, V10 and V12 (ITT population): Between-arm comparisons of the change in HbA1c during the study using an analysis of variance (ANOVA) model with repeated measurements in which the treatment effect and the time effect were included. • Percentage of subjects achieving HbA1c $\leq$7% at the end of the randomized period (ITT population): Assessment of the 95% CI of the between-arm differences. In Arm 2 and Arm 3, calculation of the percentage of subjects treated with less than 3 bolus of glulisine at V12 and with HbA1c $\leq$7% at V12, and of the illustrative 95% CI on subjects having a measurement of HbA1c after at least 10 months of exposure to insulin glulisine. • Blood glucose profile (ITT population): Descriptive analysis on the mean BG profile (at each timepoint), and on the daily mean value at V2, randomization, V8, V10, V12 and for the last valid profile. Between-arm comparisons of the changes of mean BG profile at each timepoint from randomization to the last valid profile using an ANCOVA, with the value at randomization as the covariate. A similar model was used for the analysis of daily mean BG levels. • Variability on the 3 profiles at each timepoint (between-day variability) (ITT population): Descriptive analysis at randomization and for the last valid profile, and daily variability at V2, randomization, V8, V10, V12 and for the last valid profile. For the last valid profile, between-arm comparisons of between-day variability at each timepoint using a rank ANCOVA with the ranked randomization variability as covariate. A similar model was used for the analysis of daily variability of BG levels. • Doses of insulin glargine and insulin glulisine (ITT population): Descriptive analysis of the daily dose and the daily dose per kilogram of body weight for insulin glargine at V2, V3, V4, V5 and randomization, for each insulin and in total at each visit. Change from randomization to the last available dose.

Statistical methods (continued):	• Hypoglycemia (Safety population): Number and percentage of subjects with at least one symptomatic hypoglycemia and rate of symptomatic hypoglycemia per subject-year calculated for the initial period and for each randomized arm. Comparisons of the 3 contrasts (Arm 2 versus Arm 1, Arm 2 versus Arm 3, and Arm 3 versus Arm 1) using a Fisher's exact test for the number of subjects with at least one event during the randomized period and a Wilcoxon rank sum test for the rate of symptomatic hypoglycemia per subject-year during the randomized period. Safety analysis: • AEs/TEAEs: Frequencies of all AEs and TEAEs, deaths, serious AE (SAE), serious TEAEs, withdrawals due to AE/TEAE by system organ class (SOC) and by treatment arm (for the randomized safety population). Severe hypoglycemia was counted as a SAE. • Vital signs: Descriptive analysis for the initial and randomized period. • Weight: For weight measured during the randomized period, construction of the 95% CIs (two-sided) of the differences of the adjusted means (Arm 2 – Arm 1; Arm 2 – Arm 3; Arm 3 – Arm 1), obtained by an ANCOVA, with the value of weight at randomization as the covariate.

	Treatment satisfaction analysis: • DTSQs questionnaire: Descriptive statistics by visit (from V2 to V12 and endpoint) for the score at each question, for global score (the sum of the scores for the 8 questions) and for changes from V2 and from randomization (for the randomized period) at each visit. For the global score, between-arm comparisons of the ranked variations from randomization to endpoint using an ANCOVA, with the ranked value of DTSQs at randomization as the covariate. Between-arm comparisons using the Tukey method, if significant treatment effect This analysis was also performed for each of the 8 questions separately. • DTSQc questionnaire: Descriptive statistics at V12 for the score at each question and for the global score (sum of the scores for the 8 questions). For the global score, between-arm comparisons of the ranked values at V12 using an ANCOVA, with the ranked value of DTSQs at randomization as the covariate. Between-arm comparisons using the Tukey method, if significant treatment effect. This analysis was also performed for each of the 8 questions separately.

Summary: Demography:	Of the 811 subjects included for the initial period, 476 were randomized. Twelve of the randomized subjects were not treated. The randomized and treated population comprised 464 subjects. A total of 37 subjects withdrew from the study. The main causes of withdrawal was "subject did not wish to continue in the study" (11 subjects), "non compliance with treatment procedure" (8 subjects), "adverse event" (4 subjects), "protocol violation" (4 subjects) and "lost to follow-up" (4 subjects). Thus, 427 subjects completed the study (134 in Arm 1, 182 in Arm 2 and 111 in Arm 3). The study population of the initial period (N = 811) was composed of 44.5% male and 55.5% female subjects. Mean age (SD) was 58.6 years (8.9). Mean (SD) HbA1c was 9.1% (1.4) and mean fasting blood glucose (FBG) over 7 days was 146.6 mg/dL (42.7). At the end of the initial period, mean (SD) HbA1c was 8.3% (1.3) and mean FBG was 112.3 mg/dL(22.5). 63 subjects prematurely withdrew during the initial period. At the end of this period, 272 subjects were not randomized (mainly because of a mean FBG >120 mg/dL).
Demography:	The safety population of the randomized period (randomized and treated subjects) (N = 464) was composed of 40.5% male and 59.5% female subjects. Mean age (SD) was 58.5 years (8.7). Mean (SD) HbA1c at randomization was 8.4% (1.1) and mean FBG over 7 days was 105.0 mg/dL(10.7). The mean (SD) daily dose of insulin glargine at randomization was 33.8 U (16.1) in Arm 1, 33.9 U (19.2) in Arm 2 and 37.1 U (21.4) in Arm 3. Overall mean duration (SD) of diabetes was 12.6 years (6.9). Overall mean duration (SD) of treatment with OADs was 11.4 years (6.7) and was similar in the 3 treatment arms. Overall mean duration of treatment with insulin was 3.1 years (3.4), with similar durations in Arm 1 and Arm 2 (2.9 years) and slighly higher duration in Arm 3 (3.5 years).
Efficacy results:	Primary efficacy variable The change in HbA1c from randomization to endpoint in the PP population (the primary criterion) is summarized in the following table

		Arm 1 N = 120	Arm 2 N = 165	Arm 3 N = 100
HbA1c at randomization (%)	Mean (SD)	8.5 (1.1)	8.4 (1.1)	8.3 (1.1)
Endpoint HbA1c (%)	Mean (SD)	7.7 (1.2)	7.9 (1.2)	7.9 (1.3)
Change in HbA1c (%)	Adjusted mean (SE)	-0.69 (0.09)	-0.47 (0.08)	-0.43 (0.10)
Comparison Arm 2 versus Arm 1				
Adjusted mean difference (SE)			0.228 (0.125)	
95% CI			[-0.018 ; 0.473]	

SE = standard error; 95% CI = 95% confidence interval

	The upper limit of the 95% CI of the Arm 2 - Arm 1 mean difference of the change from randomization in HbA1c exceeded 0.4%, therefore the non-inferiority of Arm 2 to Arm 1 was not demonstrated. This precluded the analysis of the Arm 2 - Arm 3 difference. In the analysis in the ITT population for the primary criterion, the 95% CI of the Arm 2 - Arm 1 difference was (-0.144; 0.358) showing non-inferiority of Arm 2 to Arm 1. Secondary efficacy variables • Changes in HbA1c from randomization to V8, V10 and V12 in the ITT population: The adjusted mean (SE) change from randomization at V12 was -0.58% (0.08) in Arm 1, -0.25% (0.07) in Arm 2 and -0.38% (0.09) in Arm 3. The comparison of Arm 2 versus Arm 1 was significant (p = 0.0021), reflecting the smaller decrease in HbA1c in Arm 2 than in Arm 1 at V8 and V10. The comparisons of Arm 2 versus Arm 3 (p = 0.2674) and Arm 3 versus Arm 1 (p = 0.0912) were not significant.

Efficacy results (continued):	• Percentages (95% CI) of subjects achieving HbA1c ≤7% at endpoint were 27.1% (19.8; 34.5) in Arm 1, 18.4% (12.9; 23.9) in Arm 2 and 22.4% (14.8; 30.0) in Arm 3. The highest percentage of subjects achieving HabA1c ≤7% at endpoint was in Arm 1. However, the Arm 2 - Arm 1 difference was not significant [difference (95% CI) of -8.72% (-17.92; 0.48)]. The Arm 2 - Arm 3 difference was not significant either [difference of -3.99 (-13.37; 5.39)]. • Blood glucose (mg/dL) profiles at endpoint and changes from randomization are summarized in the following table:

	Arm 1		Arm 2		Arm 3		
	N	Mean (SD)	N	Mean (SD)	N	Mean (SD)	
Endpoint							
Before breakfast	138	110.8 (23.4)	186	107.5 (21.5)	115	110.1 (21.0)	
After breakfast	137	141.4 (29.3)	185	148.5 (33.3)	115	153.2 (38.6)	
Before lunch	137	124.9 (29.2)	184	129.1 (33.8)	114	124.1 (30.7)	
After lunch	137	146.4 (29.9)	185	157.0 (39.8)	115	152.0 (39.8)	
Before dinner	137	131.0 (29.2)	182	138.8 (35.2)	114	132.4 (35.4)	
After dinner	137	147.1 (27.1)	185	159.8 (43.2)	115	159.4 (43.1)	
	N	Adjusted mean (SE)	N	Adjusted mean (SE)	N	Adjusted mean (SE)	p-value for treatment effect
Change (endpoint - randomization)							
Before breakfast	138	6.0 (1.9)	186	2.8 (1.6)	115	5.2 (2.1)	0.3889
After breakfast	136	-31.7 (2.7)	185	-25.9 (2.3)	115	-21.3 (2.9)	0.0332
Before lunch	137	-12.3 (2.6)	182	-8.7 (2.3)	114	-13.9 (2.8)	0.3076
After lunch	136	-35.9 (3.1)	185	-27.7 (2.6)	114	-31.4 (3.3)	0.1269
Before dinner	137	-17.6 (2.7)	181	-10.1 (2.4)	114	-16.4 (3.0)	0.0791
After dinner	137	-42.0 (3.2)	183	-31.0 (2.8)	115	-31.0 (3.5)	0.0185

p-value obtained from an ANCOVA analysis

	Overall, subjects nearly reached the blood glucose targets defined in the protocol (FBG ≤110 mg/dL and post-prandial BG value ≤160 mg/dL) at endpoint. A significant difference between treatment arms was observed at endpoint for post-breakfast change from randomization and for post-dinner change from randomization in favor of Arm 1. • Mean daily BG levels decreased steadily between randomization and endpoint in the 3 treatment arms. No statistically significant difference between treatment arms was found in the extent of decrease of daily mean BG levels over the randomized treatment period. • A ranked ANCOVA at endpoint showed a treatment effect (p = 0.0035) in favor of a lower variability of BG levels in Arm 1: at last available profile, mean daily variability (SD) was 28.1 mg/dL (12.8) in Arm 1, 34.9 mg/dL (16.9) in Arm 2 and 35.0 mg/dL (18.1) in Arm 3. • From randomization to endpoint, the mean (SD) daily dose of insulin glargine increased from 33.8 U (16.1) to 36.6 U (16.7) in Arm 1, from 33.9 U (19.2) to 39.6 U (22.6) in Arm 2 and from 37.1 U (21.4) to 40.4 U (24.6) in Arm 3. The mean daily dose of insulin glulisine increased steadily from randomization to endpoint: from 14.2 U (4.0) to 29.2 U (17.0) in Arm 1; from 5.5 U (1.8) to 19.7 U (14.4) in Arm 2 and from 5.5 U (1.8) to 16.8 U (13.7) in Arm 3. The higher values for insulin glulisine in Arm 1 reflect the protocol-specified injection of 3 glulisine bolus from the start of the randomized period. Glulisine doses in Arm 2 and Arm 3 showed similar increases. • There was no statistically significant difference between treatment arms in the rate per subject-year of overall symptomatic hypoglycemia confirmed by a BG ≤70 mg/dL. However, the rate of nocturnal symptomatic hypoglycemia confirmed by a BG ≤70 mg/dL was significantly lower in Arm 2 [0.66 (2.37)] than in Arm 3 [0.92 (2.37); p = 0.0460]. Severe hypoglycemia was reported in only 1 subject in each treatment arm.
Safety results:	During the initial period, 227 (28.2%) of the 804 subjects of the safety population of the initial period experienced at least 1 AE. • The most frequently involved SOCs (≥1.5% of subjects with AEs) included infections and infestations (10.8%), musculoskeletal and connective tissues disorders (4.2%), gastrointestinal disorders (4.1%), nervous system disorders (3.4%), injury poisoning and procedural complications (2.0%), skin and subcutaneous tissues disorders (2.0%), vascular disorders (1.9%), cardiac disorders (1.7%) and psychiatric disorders (1.5%). • There were 3 deaths during this initial period. There were 44 subjects (5.5%) with SAEs, mostly cardiovascular SAEs (21 subjects, 2.6%), including cardiac disorders (10 subjects), vascular disorders (2 subjects), vascular-disorder-related nervous system disorders (3 subjects with transient ischemic attack; 2 subjects with cerebral infarction and 2 subjects with cerebrovascular accident), and retinopathy (2 subjects). Infections and infestations (7 subjects (0.9%)] were the second most frequent class of SAEs. Severe symptomatic hypoglycemia was experienced by 3 subjects (0.4%). • Ten subjects (1.2%) withdrew from the study due to AEs.

	During the randomized period, mean duration (SD) of treatment with insulin glulisine was 346.3 days (66.1) overall with similar duration in each of the 3 treatment arms. Of the 464 subjects of the safety population of the randomized period, 202 (43.5%) experienced at least 1 TEAE. Percentages of subjects with TEAE were similar in the 3 treatment arms (42.4% in Arm 1, 41.6% in Arm 2 and 48.0% in Arm 3). • A large number of TEAEs were isolated cases occurring in only 1 subject overall. The most frequently reported TEAEs (in >1% of the subjects) were hypertension (3.7%), nasopharyngitis (3.0%), bronchitis, influenza (2.4% each), upper respiratory tract infection (1.9%), arthralgia, back pain, and urinary tract infection (1.5% each), musculoskeletal pain, peripheral edema (1.3% each), diabetic neuropathy, headache, and wrong drug administered (1.1% each), with similar percentages in the 3 treatment arms. • Only 8 non-serious TEAEs experienced by 7 subjects (1.5%) were considered to be possibly treatment related: wrong drug administration (3 subjects), peripheral edema (1 subject), edema (1 subject), fatigue (1 subject) hyperhydrosis (1 subject), and injection site irritation (1 subject). • There were 2 deaths (pancreatic carcinoma and sepsis). • Overall, 42 subjects (9.1%) experienced at least 1 serious TEAE. Most frequent serious TEAEs [SOCs with ≥2 subjects (0.4%) with at least 1 serious TEAE] included cardiac disorders (2.2%), injury, poisoning and procedural complications (1.5%), metabolism and nutrition disorders (1.1%), nervous system disorders (1.1%), infections and infestations (0.9%), musculoskeletal and connective tissue disorders (1.1%), eye disorders (0.6%), gastrointestinal disorders (0.4%), and neoplasms benign, malignant, and unspecified (0.4%). • Only 4 of the serious TEAEs [4 subjects (0.4%)] were considered to be possibly treatment-related, including 1 case of hypoglycemia (in Arm 2), 1 case of hypoglycemic seizure (in Arm 1) and 2 cases of wrong drug administration (both in Arm 2). • Six subjects (1.3%) withdrew from the randomized treatment period due to TEAEs: in Arm 1, 1 subject with fatigue and 1 subject with gastroenteritis and acute renal failure; in Arm 2, 1 subject with osteoarthritis, diarrhea, asthenia and edema, 1 subject with aortic valve stenosis and 1 subject with pancreatic carcinoma; in Arm 3, 1 subject with sepsis. Fatigue was a non-serious TEAE considered as possibly treatment related. The other events were SAEs not treatment-related. • Mean weight gain (SD) during the initial period in the safety population of the initial period was 0.6 kg (2.8). A moderate weight gain from randomization to endpoint was observed in the 3 treatment arms; adjusted mean weight gain (SE) was 2.03 kg (0.27) in Arm 1, 1.29 kg (0.23) in Arm 2, and 1.92 kg (0.30) in Arm 3. Weight gain in Arm 2 was significantly smaller than in Arm 1 (p = 0.0399). The 2 other arm comparisons were not significant
Quality of life results:	Satisfaction of the randomized and treated subjects for their antidiabetic treatment as assessed from the DTSQs questionnaire showed some improvement during the initial period, then, from randomization to V12, DTSQs global score decreased slightly. There was no significant difference between arms. As assessed from the DTSQc global score, overall treatment satisfaction was similar in the 3 treatment arms.
Date of report:	02 December 2009