Reduced Hypoglycemia Risk With Insulin Glargine

A meta-analysis comparing insulin glargine with human NPH insulin in type 2 diabetes

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OBJECTIVE — Insulin glargine (LANTUS) is a once-daily basal insulin analog with a smooth 24-h time-action profile that provides effective glycemic control with reduced hypoglycemia risk (particularly nocturnal) compared with NPH insulin in patients with type 2 diabetes. A recent "treat-to-target" study has shown that more patients on insulin glargine reached HbA_{1c} levels ≤7.0% without confirmed nocturnal hypoglycemia compared with NPH insulin. We further assessed the risk for hypoglycemia in a meta-analysis of controlled trials of a similar design for insulin glargine versus once- or twice-daily NPH insulin in adults with type 2 diabetes.

RESEARCH DESIGN AND METHODS — All studies were 24–28 weeks long, except one 52-week study, for which interim 20-week data were used.

RESULTS — Patient demographics were similar between the insulin glargine (n = 1,142) and NPH insulin (n = 1,162) groups. The proportion of patients achieving target HbA_{1c} (≤7.0%) was similar between insulin glargine– and NPH insulin–treated patients (30.8 and 32.1%, respectively). There was a consistent significant reduction of hypoglycemia risk associated with insulin glargine, compared with NPH insulin, in terms of overall symptomatic (11%; P = 0.0006) and nocturnal (26%; $P < 0.0001$) hypoglycemia. Most notably, the risk of severe hypoglycemia and severe nocturnal hypoglycemia were reduced with insulin glargine by 46% (P = 0.0442) and 59% (P = 0.0231), respectively.

CONCLUSIONS — These results confirmed that insulin glargine given once daily reduces the risk of hypoglycemia compared with NPH insulin, which can facilitate more aggressive insulin treatment to a HbA_{1c} target of ≤7.0% in patients with type 2 diabetes.

Diabetes Care **28:950–955, 2005**

The emerging clinical paradigm is to add insulin replacement early as a "treat-to-target" strategy when oral agents are insufficient to meet the increasingly stringent glycemic targets currently recommended for type 2 diabetes management (1,2). Hypoglycemia and fear of hypoglycemia, however, remain a major barrier to treating patients with type 2 diabetes to target HbA_{1c} <7.0% (3,4). Furthermore, there is a growing awareness of the previously underrecognized risk of hypoglycemia, particularly nocturnal as well as severe hypoglycemia (5), and a pressing need for the prevention of hypoglycemic episodes in these patients (6,7).

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Received for publication 17 September 2004 and accepted in revised form 1 January 2005.

J.R., G.D., M.M.-B., and A.F. have received honoraria, consulting fees, and grant/research support from Aventis.

Abbreviations: ITT, intent to treat.

For many years, the most common insulin used to provide a basal insulin supply has been NPH insulin, but this intermediate-acting insulin often results in nocturnal hypoglycemia due to unwanted plasma insulin peaks, particularly during the night, as well as higher fasting glucose levels (8). Insulin glargine (LANTUS) is a long-acting basal human insulin analog with a smooth time-action profile and no pronounced peak (9). Insulin glargine appears to mimic normal physiologic basal insulin concentrations more closely compared with currently available intermediate- and long-acting insulins (10,11). In clinical trials, insulin glargine has been shown to provide an effective basal insulin supply when administered once daily in patients with type 2 diabetes (8,12). In addition, insulin glargine substantially reduces the risk of nocturnal hypoglycemia compared with NPH insulin with at least equivalent glycemic control in type 2 diabetes (8,13).

The treat-to-target insulin glargine versus NPH insulin trial (13), in insulin-naive patients with type 2 diabetes, showed that insulin glargine therapy was superior to NPH insulin with respect to a primary composite end point involving both glycemic control and hypoglycemia (HbA_{1c} ≤7.0% with no single episode of confirmed nocturnal hypoglycemia or severe nocturnal hypoglycemia). Indeed, insulin glargine trials have consistently demonstrated a decrease in overall and nocturnal hypoglycemia, but the numbers of severe hypoglycemic events were insufficient in the individual trials to reach statistical significance (13–16). To more accurately assess hypoglycemic risk reduction in a broader patient population in type 2 diabetes, a meta-analysis of the hypoglycemia profile and glycemic control seen in patients with type 2 diabetes from all insulin glargine– versus NPH insulin–controlled studies was performed. This meta-analysis enables the application of uniform methods in the data collection, analysis, and reporting of results from

Table 1—*Studies included in the integrated analysis*

Study (ref. no.)	Number of randomized and treated patients	Study duration	Prestudy treatment	Study treatment	Additional antidiabetic treatment
3002 (8,14)	570	52 weeks*	OAD and once-daily insulin or OAD alone	Once daily at bedtime: insulin glargine or NPH insulin	OAD(s)
3006 (12,15)	518	28 weeks	Insulin for >3 months (no OAD)	Insulin glargine once daily at bedtime or NPH once or twice daily	Regular human insulin
4001 (16)†	460	28 weeks	OAD for >6 months	Once daily at bedtime: insulin glargine or NPH insulin	OAD (glimepiride)
4002 (13)	756	24 weeks	OAD alone	Once daily at bedtime: insulin glargine or NPH insulin	OAD(s)

*The 20-week data used for the original study were included in this analysis. †In this study, insulin glargine was given once daily at breakfast or bedtime. Only those receiving insulin glargine at bedtime are included in this analysis. OAD, oral antidiabetic drug.

various clinical trials into a single analysis to assess all hypoglycemia-related variables in patients with type 2 diabetes treated with insulin glargine or NPH insulin.

RESEARCH DESIGN AND METHODS

— Four open-label, randomized, parallel-group studies, conducted in Europe and North America, were identified in the Aventis research and development database using a predefined search criteria: insulin glargine–controlled studies with NPH insulin in patients with type 2 diabetes. Each study compared insulin glargine administered at bedtime with NPH insulin administered once or twice daily in patients with type 2 diabetes. A summary of all studies included in the analysis is shown in Table 1; all studies were of a similar design, consisting of a 1- to 4-week screening phase and a 24- to 28-week treatment phase with similar end points. It should be noted that while study 1 was a 52-week study, a complete interim analysis of the study was performed for the database at 20 weeks for the original U.S. New Drug Application. These interim data were used in the integrated analysis in order to compare patients with a similar treatment duration. The intent-to-treat (ITT) population was used in the integrated analysis. Individual study definitions for the ITT population varied slightly but essentially included all patients who were randomized and treated with at least one dose of study medication. There was no post hoc definition of the ITT population. This applied to all hypoglycemia-related end points, in addition to HbA_{1c}- and glycemic control–related end points.

A total of 2,304 patients with type 2 diabetes were included in these studies: 1,142 in the insulin glargine and 1,162 in the NPH insulin treatment groups. They were enrolled from a total of 318 study centers predominantly in Europe and North America. Inclusion criteria included patients who had type 2 diabetes for at least 2 years, were aged <80 years, had HbA_{1c} levels >7.5% but <12%, and had BMI values <40 kg/m^2. Exclusion criteria included significant hepatic or renal impairment.

The primary aim of the current analysis was to compare hypoglycemia-related variables in patients with type 2 diabetes treated with insulin glargine or NPH insulin. The secondary aims were to compare HbA_{1c} and other glycemic control variables and hypoglycemia-related safety in patients with type 2 diabetes treated with insulin glargine or NPH insulin.

Efficacy measures

The primary end points were the incidences of hypoglycemia, including symptomatic hypoglycemia, nocturnal hypoglycemia, nonnocturnal (diurnal) hypoglycemia, severe hypoglycemia, severe nocturnal hypoglycemia, and severe nonnocturnal (diurnal) hypoglycemia. Consistent with the treat-to-target study, hypoglycemia in patients achieving the HbA_{1c} target goal of ≤7.0% was also evaluated. Symptomatic hypoglycemia was defined as an event with clinical symptoms consistent with hypoglycemia. Nocturnal hypoglycemia was defined as symptomatic hypoglycemia occurring while the patient was asleep, after the evening insulin injection, and before getting up in the morning. Confirmed or documented hypoglycemia was determined at plasma glucose levels of ≤72 mg/dl (≤4.0 mmol/l) and ≤56 mg/dl (≤3.1 mmol/l) for each type of hypoglycemic episode described above. Severe hypoglycemia was defined as an event with symptoms consistent with hypoglycemia in which the patient required the assistance of another person and was associated with either a plasma glucose level ≤56 mg/dl (≤3.1 mmol/l) or prompt recovery after oral carbohydrate, intravenous glucose, or glucagon administration.

The secondary efficacy variables of glycemic control included the percentage of patients reaching target HbA_{1c} (≤7.0%), change in fasting plasma glucose levels, and insulin dose (basal and total). For studies with blood glucose measurements, instead of plasma glucose measurements, the blood glucose values were converted to plasma glucose equivalent for pooled analysis using the following formula provided by the manufacturer of the glucometer used in the treat-to-target study (plasma glucose result [mg/dl] = 1.104 × blood glucose result [mg/dl] − 4.5).

Safety variables

Safety variables analyzed included the percentage of patients who reported hypoglycemia-related serious adverse

Table 2—*Baseline demographics and characteristics and baseline to end point changes in the glycemic control variables of the analysis population*

	Insulin glargine	NPH insulin
Sex		
Men	636 (56)	652 (56)
Women	506 (44)	510 (44)
Age (years)	58.0 ± 9.8	58.4 ± 9.3
BMI (kg/m^2)	30.5 ± 4.9	30.5 ± 6.4
Age at onset of diabetes (years)	48.4 ± 9.7	48.4 ± 9.7
Diabetes duration (years)	10.2 ± 7.0	10.6 ± 6.9
Type of previous treatment		
OAD only	815 (71)	826 (71)
Insulin only	259 (23)	259 (22)
Duration of insulin treatment (years)*	7.1 ± 6.7	6.8 ± 7.3
Duration of OAD treatment (years)	7.4 ± 5.4	8.0 ± 5.2
HbA_{1c} level (%)		
Baseline	8.8 ± 1.1	8.7 ± 1.1
End point	7.8 ± 1.3	7.7 ± 1.2
Fasting plasma glucose level (mg/dl [mmol/l])		
Baseline	199 ± 2 [11 ± 0.1]	199 ± 2 [11 ± 0.1]
End point	155 ± 2 [8 ± 0.1]	161 ± 2 [9 ± 0.0]†

Data are means ± SD or *n* (%). *Only patients in study 3006 (100%) and study 3002 (25%) were on insulin prior to study initiation. †$P = 0.0233$ for the insulin glargine versus NPH insulin group at end point. OAD, oral antidiabetic agent.

events, experienced hypoglycemia resulting in death, or experienced hypoglycemic adverse events resulting in withdrawal from the study.

Statistical methods

Primary statistical methods prespecified for each of the individual studies were used for this meta-analysis. For continuous variables, an ANOVA or ANCOVA was conducted, with treatment and (pooled) center (within a study) as fixed factors and the corresponding baseline value as the covariate if the baseline value was assessed for the variable. Center pooling was prespecified for centers with few patients before database lock of the individual studies for stratified analyses, and the same pooling method was used in this meta-analysis. There were a total of 84 pooled study centers from the four clinical studies. Analysis for categorical variables was made using the Cochran-Mantel-Haenszel test stratified by (pooled) center. All tests were two-sided with statistical significance when $P \leq 0.05$, if not otherwise specified. The above ANCOVA model and Cochran-Mantel-Haenszel test are widely accepted statistical methods in handling continuous and categorical data. They were consistently documented in the study protocols and/or analysis plans, and we utilized these methods in the meta-analysis to avoid selection bias. Treatment-by-center (pooled) interaction was tested for the key efficacy variables (hypoglycemia variables and HbA_{1c} at end point) for consistency of results between the strata.

Analysis of demographics, baseline characteristics, study medication exposure, and study completion status. Descriptive statistics were computed for continuous variables. Between-treatment comparisons were performed using the ANOVA model. Categoric variables were summarized by frequency distributions; between-treatment comparisons were made using the Cochran-Mantel-Haenszel test.

Analysis of hypoglycemia. Between-treatment comparisons of the incidence of patients with at least one episode of symptomatic hypoglycemia (overall and by time of day) were performed using the Cochran-Mantel-Haenszel test stratified by (pooled) center.

Analysis of glycemic control parameters. The percentage of patients who reached target HbA_{1c} values was compared between treatment groups using the Cochran-Mantel-Haenszel test. HbA_{1c} change from baseline and the clinical laboratory–determined fasting plasma glucose data were summarized in terms of means ± SD and analyzed using the ANCOVA model.

Analysis of safety variables. The percentage of patients reporting each safety variable was summarized by treatment group; no inferential statistical analyses were performed.

RESULTS

Patients

A total of 2,304 patients were randomized and treated (1,142 with insulin glargine and 1,162 with NPH insulin). There were no significant between-treatment differences with respect to baseline demographics (Table 2). Greater than 90% of patients in each treatment arm completed the treatment phase of the study: 1,057 (93%) in the insulin glargine and 1,064 (92%) in the NPH insulin groups.

Glycemic control

Glycemic control was similar between the two treatment groups at both baseline and end point with respect to the proportion of patients reaching target $HbA_{1c} \leq 7.0\%$ (insulin glargine group: 3.1 vs. 30.8%; NPH insulin group: 3.3 vs. 32.1%, at baseline versus end point). Fasting plasma glucose levels were similar in both treatment groups at baseline but were significantly lower at end point in the insulin glargine group than in the NPH insulin group ($P = 0.0233$; Table 2).

Insulin dose

Insulin glargine– and NPH insulin–treated patients had similar mean basal and total insulin doses at baseline and end point. Basal insulin levels were 21 ± 20 and 38 ± 25 IU in the insulin glargine group and 21 ± 20 and 37 ± 27 IU in the NPH insulin group, at baseline and end point, respectively, for both insulins. In study 3006, where 399 patients received basal and human regular insulin, total daily insulin levels in the insulin glargine group were 64 ± 32 and 74 ± 41 IU at baseline and end point, respectively, and 67 ± 32 and 80 ± 50 IU in the NPH insulin group at baseline and end point, respectively. Baseline to end point changes in basal and total insulin doses were similar between the two treatment groups.

Hypoglycemia

The incidence of overall symptomatic hypoglycemia, nocturnal hypoglycemia, and severe hypoglycemia was signifi-

Table 3—*Incidence (percentage of patients reporting one or more hypoglycemic episode) and percentage risk reduction of symptomatic, nocturnal, and nonnocturnal hypoglycemia and severe, severe nocturnal, and severe nonnocturnal hypoglycemia in patients receiving insulin glargine versus NPH insulin*

Type of symptomatic hypoglycemia	Insulin glargine (% of patients)	NPH insulin (% of patients)	*P*	Insulin glargine significant % risk reduction
Overall documented	54.2	61.2	0.0006	11
Plasma glucose ≤72 mg/dl (≤4.0 mmol/l)	46.0	53.3	0.0004	14
Plasma glucose ≤56 mg/dl (≤3.1 mmol/l)	29.9	37.0	0.0002	19
Nocturnal documented	28.4	38.2	<0.0001	26
Plasma glucose ≤72 mg/dl (≤4.0 mmol/l)	23.9	33.9	<0.0001	29
Plasma glucose ≤56 mg/dl (≤3.1 mmol/l)	16.3	23.1	<0.0001	29
Nonnocturnal documented	49.6	51.7	0.4642	—
Plasma glucose ≤72 mg/dl (≤4.0 mmol/l)	40.1	42.9	0.2553	—
Plasma glucose ≤56 mg/dl (≤3.1 mmol/l)	22.8	25.4	0.1545	—
Severe documented	1.4	2.6	0.0442	46
Plasma glucose ≤72 mg/dl (≤4.0 mmol/l)	1.1	2.0	0.1089	—
Plasma glucose ≤56 mg/dl (≤3.1 mmol/l)	0.9	1.5	0.1735	—
Severe nocturnal documented	0.7	1.7	0.0231	59
Plasma glucose ≤72 mg/dl (≤4.0 mmol/l)	0.6	1.5	0.0416	60
Plasma glucose ≤56 mg/dl (≤3.1 mmol/l)	0.5	1.3	0.0461	62
Severe nonnocturnal documented	0.8	0.9	0.7296	—
Plasma glucose ≤72 mg/dl (≤4.0 mmol/l)	0.6	0.6	0.9042	—
Plasma glucose ≤56 mg/dl (≤3.1 mmol/l)	0.4	0.3	0.4669	—

cantly lower with insulin glargine compared with NPH insulin (Table 3). With the exception of overall severe hypoglycemia, this remained the case when hypoglycemia was confirmed by plasma glucose levels. The incidence of severe and severe nocturnal hypoglycemia was also significantly lower with insulin glargine versus NPH insulin. There were no significant between-treatment differences in symptomatic or severe hypoglycemia during nonnocturnal (diurnal) periods. The reduction in nocturnal hypoglycemia observed with insulin glargine was supported by an analysis of symptomatic hypoglycemia by time of day (Fig. 1). The percentages of patients reporting symptomatic, nocturnal, nonnocturnal, severe, severe nocturnal, and severe nonnocturnal hypoglycemia are summarized in Table 3.

Incidence of hypoglycemia in patients achieving target HbA_{1c} levels

In those patients who reached target HbA_{1c} ≤7.0%, there was a significantly lower incidence of nocturnal hypoglycemia in the insulin glargine versus NPH insulin group (39 vs. 49%; $P < 0.01$). The incidence of all other types of hypoglycemia was similar between the insulin glargine– and NPH insulin–treated patients for symptomatic (71 vs. 75%), severe (2.0 vs. 2.2%), and severe nocturnal (0.9 vs. 0.5%) hypoglycemia in this group of patients.

Robustness of results

Efficacy results were generally consistent across individual studies and across the analysis strata (pooled study centers). No significant treatment-by-strata interaction was found for key efficacy variables (hypoglycemia variables and HbA_{1c} at end point). The analysis of hypoglycemia incidence was also supported by an analysis of hypoglycemia monthly rate (number of hypoglycemia episodes per month per patient). This supporting analysis was consistently prespecified for each study,

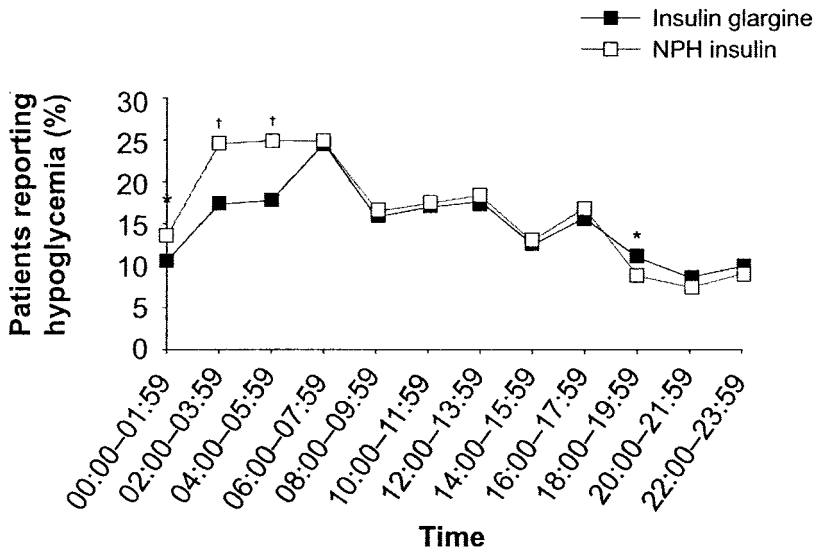

Figure 1— *Incidence (%) of patients reporting symptomatic hypoglycemia during a 24-h treatment period. *P < 0.05; †P ≤ 0.0001 insulin glargine vs. NPH insulin.*

and the results were very consistent with those based on the incidence rate.

Safety

Since the focus of this integrated analysis was hypoglycemia, only hypoglycemia-related treatment-emergent adverse events are presented (10.2% in the insulin glargine group versus 9.1% in the NPH insulin group). There were no statistically significant between-treatment differences in the incidence of hypoglycemia reported as a serious event (life threatening, hospitalization, or medically important). No hypoglycemia in either group in any of the studies resulted in death. Only a single patient in all of the studies reported hypoglycemia that resulted in study withdrawal in the NPH insulin group.

CONCLUSIONS — Tight glycemic control is central to reducing the risk of long-term complications of diabetes but must be achieved with a minimal risk of hypoglycemia (4). This meta-analysis compared the effects of insulin glargine with NPH insulin on hypoglycemia in large studies of insulin glargine in type 2 diabetes reported to date. A meta-analysis was used for this purpose as it allows the reporting of results from various compatible clinical trials into a single analysis of the largest available population. In each individual study, consistent decreases in nocturnal hypoglycemia were observed with insulin glargine.

Traditionally, severe hypoglycemia in type 2 diabetes was not considered a problem because the incidence was much lower than that observed in type 1 diabetes (17). This is due, in part, to the fact that glycemic control is often not tight enough in type 2 diabetes because the major barrier to achieving target glycemic control is, in fact, the fear of hypoglycemia by patients and physicians. However, a recent population analysis in the U.K. suggests that severe hypoglycemia in patients with type 2 diabetes results in more morbidity and medical expenses than those occurring in type 1 diabetes (5). Hypoglycemia can result in severe morbidity or, in the worst case, mortality. Prolonged hypoglycemia, in particular, represents a significant risk since it can cause cerebral damage, seizure, coma, or death (18). Hence, there is a tangible need to minimize both the fear and the actual occurrence of nocturnal and severe hypoglycemia in patients with type 2 diabetes. New therapies with enhanced efficacy and safety are required to reduce large medical costs that are associated with hypoglycemia-associated complications.

The results of this meta-analysis support the findings of the treat-to-target study in a larger population of patients with type 2 diabetes by confirming that once-daily insulin glargine affords equivalent glycemic control to once- or twice-daily NPH insulin but with significantly less symptomatic hypoglycemia, particularly nocturnal episodes (12–14). In addition, consistent with previous data, fasting plasma glucose levels were significantly lower in those patients treated with insulin glargine compared with those receiving NPH insulin. While it should be noted that no differences occurred in the proportion of patients affected by severe nonnocturnal (diurnal) hypoglycemia, substantial risk reductions were demonstrated for severe and severe nocturnal hypoglycemia in insulin glargine–treated patients compared with those treated with NPH insulin. The lower incidence of hypoglycemia can be explained by the differences in the time-action profiles of the two insulins: while NPH insulin acts maximally during the night, peaking 4–6 h after a bedtime injection, insulin glargine has a flat time-action profile with no pronounced peak (9), which would facilitate maintenance of euglycemia with less blood glucose fluctuations. This also explains why, in this analysis, the most significant reductions in hypoglycemia were seen during nighttime periods with insulin glargine. Moreover, in those patients who achieved target glycemic control, the incidence of nocturnal hypoglycemia was significantly lower with insulin glargine, which is especially important from a clinical perspective. The reduced risk of hypoglycemia was achieved with similar basal and total daily insulin dosing in insulin glargine– and NPH insulin–treated patients, with basal insulin and total daily insulin doses increasing similarly from baseline to end point in both treatment groups. Regarding safety, there were no significant differences between insulin glargine– and NPH insulin–treated patients in the incidence of serious adverse events such as death, coma, and hospitalizations.

The results of this analysis support the use of insulin glargine as first choice for once-daily basal insulin therapy. There is a growing trend toward more aggressive treatment regimens, and insulin supplementation is being used earlier to achieve target HbA_{1c} levels (≤6.5–7.0%) in order to reduce long-term complications in type 2 diabetes. As more evidence-based data emerge, the target HbA_{1c} may be progressively lowered toward normal with the obvious concomitant increase in the risk of hypoglycemia. At present, the most sensible approach to treatment targets is to achieve and sustain the lowest HbA_{1c} level possible with the lesser risk of hypoglycemia (4). Indeed, the risk of hypoglycemia, particularly nocturnal episodes, has been a hindrance to attaining this goal, and there is a great need for safer antidiabetic agents that can achieve glycemic control without increasing the risk of hypoglycemia. The results reported here strongly support a role for insulin glargine in overcoming this barrier toward achieving near-normoglycemic control. As such, compared with NPH insulin, insulin glargine can potentially allow greater increases in insulin doses without necessarily increasing the risk of hypoglycemia.

In summary, this meta-analysis in type 2 diabetes shows that with regard to attempting to improve glycemic control while avoiding severe and nocturnal hypoglycemia, insulin glargine provides a safer basal insulin supply than NPH insulin. Insulin glargine may, therefore, be especially suited to aggressive treatment regimens to bring more patients within the stringent levels of glycemic control recommended by current treatment guidelines.

Acknowledgments — This study was sponsored by Aventis Pharma.

Data from this manuscript have been published in abstract form (*Diabetes* 52 [Suppl. 1]:A444, 2003 [Abstract 1925]; *Diabetologia* 46 [Suppl. 2]:A305, 2003 [Abstract 880]) at the American Diabetes Association and International Diabetes Federation (IDF) 2003 congresses and presented as a poster at IDF 2003.

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