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Sponsor/company:	sanofi-aventis	**ClinialTrials.gov Identifier:**	NCT00046462
		Study Code:	HOE901_4022
Generic drug name:	Insulin Glargine	**Date:**	17/Dec/2008

GCP non-compliance

Efficacy data from 36 randomized subjects at two (2) investigator sites were excluded due to GCP non-compliance/scientific misconduct in other clinical trials. Datasets with these 2 sites included and excluded were generated and the outputs examined to ensure that the results of the study were non-compromised. Results excluding data from these 36 subjects are provided in the main efficacy analysis sections, and results including data from these 36 subjects are provided in the additional efficacy analysis section. All randomized subjects were included in the safety analysis in the amended CSR.

Title of the study: Substituting Lantus® (Insulin glargine [rDNA origin] injection) for a thiazolidinedione vs. a third oral agent as add-on therapy in patients failing a thiazolidinedione and sulfonylurea or Glucophage® (metformin) combination: a multicenter, controlled, randomized, open-label study

Investigator(s): Multicenter (107 investigators) Coordinating Investigator: Priscilla Hollander, MD Baylor University Medical Center, 3600 Gaston Avenue, 656 Wadley, Dallas, TX 75246

Study center(s): 101 active sites in the United States

Publications (reference): none

Study period:

Date first patient enrolled: 09 Oct 2001

Date last patient completed: 30 Nov 2004

Phase of development: A Phase 3b, prospective study to compare the effect of glycemic control with insulin glargine (GLAR) as replacement therapy for thiazolidinedione (TZD) and a third oral agent (SU or metformin) as add-on therapy in patients whose existing therapy with 2 oral agents (TZD and a SU or metformin) has failed.

Objectives: The primary objective was to determine the difference in glycemic control (as measured by glycosylated hemoglobin [HbA1c]) between substituting a TZD with GLAR and adding a third oral agent in patients who failed on TZD/SU or TZD/metformin combination therapy.

The secondary objectives were to compare several parameters (occurrence of hypoglycemia, change in fasting plasma glucose [FPG], percentage of patients achieving HbA1c ≤ 7%, time to glycemic control, change in body weight, and change in serum lipid profile) between the treatment groups, and to determine if discontinuing a TZD and substituting GLAR was an appropriate alternative therapy in patients inadequately controlled by combination therapy with a TZD.

Methodology: This was a multicenter, controlled, randomized (1:1), 2-arm, parallel-group, open-label study comparing treatment with GLAR as a substitute for a TZD and the addition of a third oral agent. There was a screening period that was up to 2 weeks in duration followed by a 48-week treatment period. Patients were stratified according to prior antidiabetic therapy.

Number of patients:

Planned: approximately 320 patients

Randomized: 167 in the GLAR group and 170 in the third oral agent group
149 in the GLAR group and 152 in the third oral agent group, excluding data from two Good Clinical Practice (GCP) non-compliant sites

Treated : 165 in the GLAR group and 169 in the third oral agent group were treated in the 24-week analysis population

Evaluated:

Efficacy: Change from baseline in HbA1c values, fasting plasma glucose (FPG), body mass index (BMI), body weight, and lipids (total cholesterol [TC], non-high-density lipoprotein [HDL], HDL, low-density lipoprotein [LDL], triglycerides [TG], and free fatty acids [FFA]); proportions of patients with HbA1c values ≤ 7% and ≤ 6.5%; time to achievement and maintenance of response (HbA1c ≤ 7%).

Safety: Evaluations included adverse events, physical examinations, clinical laboratory tests, vital signs, and 12-lead electrocardiograms, and assessments of hypoglycemic events.

Pharmacokinetics: Not applicable

Pharmacokinetic sampling times and bioanalytical methods: Not applicable

Criteria for Evaluation: Male and female patients who were between 18 and 79 years of age, inclusive, had a diagnosis of type 2 diabetes mellitus for at least 6 months and were inadequately controlled (HbA1c between 7.5% and 12.0%, inclusive) on continuous treatment with at least half-maximally labeled dose of TZD (rosiglitazone or pioglitazone) and at least 1000 mg metformin or half-maximally labeled dose of SU daily for at least 3 months prior to the screening week visit (Visit 1).

Investigational product: Insulin glargine injection, 10 mL vial, 100 IU/mL

Dose: The starting dose for GLAR was 10 IU/day, administered subcutaneously at bedtime for 7 days. After the first 7 days, dose adjustments were made every 7 days over a 24-week period until the average of the last 2 days fasting self-monitored blood glucose (SMBG) values was between 72 mg/dL and 100 mg/dL, inclusive. From week 26 onwards dose adjustments were made every 7 days until the mean fasting SMBG was ≤ 94 mg/dL and ≥ 70 mg/dL.

Administration: subcutaneous injection

Duration of treatment: 24 weeks before and 48 weeks after Amendment 2, issue date 27-Nov-2002.

Duration of observation: up to 26 weeks (up to a 2-week screening/stabilization period followed by a 24-week study period) before Amendment 2; up to 50 weeks (up to a 2-week screening/stabilization period and a 48-week study period) after Amendment 2.

Reference therapies: Metformin tablets, Metformin XR tablets, Glyburide tablets

Metformin tablets; 500 mg/tablet

Dose: The starting dose for add-on metformin was 1000 mg/day, administered as 500 mg twice a day. The dose was titrated upward in 500-mg increments weekly until the glycemic target was achieved or a maximum dose of 2000 mg/day or the maximum tolerated dose was reached.

Administration: oral

Metformin extended-release (XR) tablets; 500 mg/tablet

Dose: The starting dose for add-on metformin XR was 500 mg/day titrated upward in 500-mg increments weekly to a maximum dose of 2000 mg/day.

Administration: oral

Glyburide tablets; 2.5 and 5 mg/tablet

Dose: The starting dose for add-on glyburide was 5 mg/day titrated upward in 2.5-mg increments every 2 weeks to a maximum dose of 10 mg/day.

Administration: oral

Criteria for evaluation:

Efficacy: HbA1c, FPG, lipid (TC, non-HDL, HDL, LDL, TG, and FFA) measurements; body weight, BMI.

Safety: Adverse events reported by the patient or noted by the investigator; standard hematology, blood, chemistry, and urinalysis, 12-lead electrocardiogram, vital signs, and hypoglycemic events.

Statistical methods: Amendment 2 extended the study an additional 24 weeks based on the key learning from another study showing declining trend of A1c levels even after 24 weeks of treatment utilizing the FBG target of ≤100 mg/dl. Revision of the algorithm (FBG target ≤ 94 mg/dl) and an extension of additional 24 weeks were deemed appropriate to allow subjects to fully optimize their treatment and reach better glycemic control. Because a number of subjects had already completed the study or withdrew early prior to the implementation of Amendment 2, and a different dosing algorithm was implemented during the last half of the study, under Amendment 2, two major analysis populations became necessary for this study: the 24-week analysis population (all patients who entered the study, ie, signed informed consent, whether or not they continued beyond the implementation of Amendment 2) and the 48-week analysis population (all patients who entered the study after the implementation of Amendment 2, or continued in the study for at least 2 visits after Amendment 2 was implemented). A complete set of analyses was performed for each analysis population.

The primary hypothesis was one of noninferiority (α=0.025, 1-sided), the primary efficacy analysis populations were the 24-week and 48-week completers populations, and the primary efficacy variables were the mean change in HbA1c from baseline to study week 24 (24-week analysis population) and week 48 (48-week analysis population). The primary efficacy analysis was conducted using ANCOVA with treatment and antidiabetic therapy at baseline as factors, treatment by baseline antidiabetic therapy and treatment by baseline interactions, and baseline HbA1c as the covariate. Ninety-five percent confidence intervals were computed for the adjusted mean difference between the treatment groups from the ANCOVA to test for noninferiority. The non-inferiority of GLAR to the comparator was demonstrated if the upper boundary for the 95% CI for the difference in the adjusted mean changes from baseline to endpoint for HbA1c was < 0.5%. Noninferiority was also assessed for the 24-week and 48-week modified intent-to-treat (mITT) populations based on the change in HbA1c from baseline to the last on therapy observation. In the event the hypothesis of noninferiority was accepted for a study population and endpoint, the superiority hypothesis would be tested for that population. Conclusions of noninferiority were based on the results from the completer's population. Conclusions of superiority were based on the results of the mITT population. The results for all time points and population were reported.

The analysis of continuous variables (changes from baseline HbA1c, FPG, serum lipids, BMI and weight) was conducted using analysis of covariance (ANCOVA) with treatment and stratification level as main effects, and baseline value as covariate. The proportion of responders (ie, patients with HbA1c ≤ 7.0% and patients with HbA1c ≤ 6.5% at week 48 or the last on-therapy observation), and the incidence of hypoglycemia were compared using the Cochran-Mantel-Haenszel test. The time to response was analyzed using the log-rank statistic. The hypoglycemia rates per patient year were compared between the 2 treatment arms using Poisson regression accounting for overdispersion and adjusting for randomization stratum. Adverse events and the results of laboratory assessments, physical examinations, and vital signs assessments were reviewed for clinically significant abnormalities.

The 48-week efficacy analysis population included patients enrolled in GCP compliant sites that were randomized after the implementation of Amendment 2, or continued in the study for at least 2 visits after the implementation of Amendment 2. The 24-week efficacy analysis population included all patients enrolled in GCP compliant sites who entered the study, ie, signed informed consent, whether or not they continued beyond the implementation of Amendment 2, dated 27-Nov-2002, but no data collected after study week 24. To ensure the results of the study are non-compromised, the sponsor ran analyses excluding (Sections 8.1 and 8.2) and including (Section 8.3) the GCP non-compliant patients, and compared the results of the analyses. All randomized patients who were dispensed study medication are included in the safety analysis population

Summary: Patient population:

In the overall study, a total of 337 patients were randomized (167 patients were randomized to the GLAR group and 170 patients were randomized to third oral agent group). Of these, 250 patients were included in the 48-week analysis (119 in the GLAR group and 131 in the third oral agent group). The 2 treatments groups were comparable with respect to baseline demography and disease state in the efficacy analysis population. There were no significant differences between treatments groups in study duration or patient year of treatment.

The following table summarizes the disposition of patients in the all randomized population.

All Randomized Population	GLAR (N = 167)	Third Oral (N = 170)
24-week analysis population [N]	167	170
Completed [n (%)][a]	146 (87.4)	145 (85.3)
Withdrawn prior to week 26 [n (%)] [a]	21 (12.6)	25 (14.7)
Reason for withdrawal [n (%)] [c]		
Adverse event	3 (14.3)	1 (4.0)
Patient died	0 (0.0)	1 (4.0)
Patient did not meet entry criteria	1 (4.8)	2 (8.0)
Treatment failure	0 (0.0)	3 (12.0)
Patient did not wish to continue	9 (42.9)	5 (20.0)
Protocol violation	1 (4.8)	2 (8.0)
Patient lost to follow-up	6 (28.6)	7 (28.0)
Other reason	1 (4.8)	4 (16.0)
48-week analysis population [N]	119[b]	131[b]
Completed [n (%)][a]	90 (75.6)	98 (74.8)
Withdrawn prior to week 48 [n (%)] [a]	29 (24.4)	33 (25.2)
Reason for withdrawal [n (%)] [c]		
Adverse event	5 (17.2)	3 (9.1)
Patient died	0 (0.0)	1 (3.0)
Patient did not meet entry criteria	0 (0.0)	2 (6.1)
Treatment failure	0 (0.0)	4 (12.1)
Patient did not wish to continue	8 (27.6)	6 (18.2)
Protocol violation	4 (13.8)	2 (6.1)
Patient lost to follow-up	7 (24.1)	10 (30.3)
Other reason	5 (17.2)	5 (15.2)

[a] Percent based on number of patients in analysis population.
[b] Among total 291 24-week completed patients (Glargine: 146, Third Oral: 145), 215 patients (Glargine: 104, Third Oral: 111) enrolled in 48-week analysis population. The other 35 patients in 48-weeks analysis population did not have complete efficacy data for week 24. Among 76 24-week completed patients who did not enroll in 48-week analysis population (Glargine: 42, Third Oral: 34), there are 64 patients (Glargine: 35, Third Oral: 29) who completed 24-week study before amendment 2 , and were not eligible to participate in the extension.
GLAR = insulin glargine
[c] For analysis reason, "Withdrawn Prior to Week 26" and "Withdrawn Prior to Week 48" taken into account multiple variables (specially CRF answers to "Withdrawn Prior to Week 26", "Withdrawn Prior to Week 48" and day of last contact)

Excluding data from sites 25 and 55, a total of 301 patients were randomized (149 patients were randomized to the GLAR group and 152 patients were randomized to the third oral agent group). Of these, 232 patients were included in the 48-week analysis (110 patients in the GLAR group and 122 patients in the third oral agent group). The 2 treatments groups were comparable with respect to baseline demography and disease state in the efficacy analysis population. No differences in the 2 treatments groups in study duration or patient year of treatment were observed in all patients randomized, excluding data from sites 25 and 55. The following table provides a summary of the disposition of patients in the all randomized population, excluding data from sites 25 and 55.

All Randomized Population, Excluding Sites 25 and 55	GLAR (N = 149)	Third Oral (N = 152)
24-week analysis population [N]	149	152
Completed [n (%)] [a]	130 (87.2)	130 (85.5)
Withdrawn prior to week 26 [n (%)] [a]	19 (12.8)	22 (14.5)
Reason for withdrawal [n (%)] [c]		
Adverse event	3 (15.8)	1 (4.5)
Patient died	0 (0.0)	1 (4.5)
Patient did not meet entry criteria	0 (0.0)	2 (9.1)
Treatment failure	0 (0.0)	3 (13.6)
Patient did not wish to continue	8 (42.1)	3 (13.6)
Protocol violation	1 (5.3)	2 (9.1)
Patient lost to follow-up	6 (31.6)	6 (27.3)
Other reason	1 (5.3)	4 (18.2)
48-week analysis population [N]	110[b]	122[b]
Completed [n (%)][a]	82 (74.5)	90 (73.8)
Withdrawn prior to week 48 [n (%)][a]	28 (25.5)	32 (26.2)
Reason for withdrawal [n (%)] [c]		
Adverse event	5 (17.9)	3 (9.4)
Patient died	0 (0.0)	1 (3.1)
Patient did not meet entry criteria	0 (0.0)	2 (6.3)
Treatment failure	0 (0.0)	4 (12.5)
Patient did not wish to continue	7 (25.0)	5 (15.6)
Protocol violation	4 (14.3)	2 (6.3)
Patient lost to follow-up	7 (25.0)	10 (31.3)
Other reason	5 (17.9)	5 (15.6)

[a] Percent based on number of patients in analysis population.
[b] Among total 260 24-week completed patients (Glargine: 130, Third Oral: 130), 199 patients (Glargine: 96, Third Oral: 103) enrolled in 48-week analysis population. The other 33 patients in 48-weeks analysis population did not have complete efficacy data for week 24. Among 61 24-week completed patients who did not enroll in 48-week analysis population (Glargine: 34, Third Oral: 27), there are 56 patients (Glargine: 30, Third Oral: 26) who completed the 24-week study before amendment 2, and were not eligible to participate in the extension
GLAR = insulin glargine
[c]."For analysis reason, "Withdrawn Prior to Week 26" and "Withdrawn Prior to Week 48" taken into account multiple variables (specially CRF answers to "Withdrawn Prior to Week 26", "Withdrawn Prior to Week 48" and day of last contact

Pharmacokinetics and Pharmacodynamics:

No bioanalytical variable analysis and pharmacokinetic – pharmacodynamics (PK-PD) analysis were performed in this study.

Efficacy results:

This study was designed to compare the effect of glycemic control with GLAR as replacement therapy for TZD and a third oral agent (SU or metformin) as add-on therapy in patients whose existing therapy with 2 oral agents (TZD and a SU or metformin) had failed.

Primary

In the 48-week completers population, excluding sites 25 and 55, treatment with GLAR and 1 oral agent failed to meet the non-inferiority criterion compared with the addition of a third oral agent in controlling HbA1c at study endpoint. Similar results were obtained in all other analysis populations (48-week mITT and 24-week mITT and completers populations).

The results of the primary efficacy analysis in the 48-week completers population, excluding sites 25 and 55, were consistent with those for the 48-week mITT and 24-week mITT and completers populations, including sites 25 and 55.

Secondary

The results of the secondary efficacy analysis in the 48-week mITT and completers populations, excluding sites 25 and 55, were consistent with those for the 48-week mITT and completer's populations, including sites 25 and 55, with the exception of the responder analysis (see below).

Change from baseline in HbA1c

Both treatments, GLAR and a third oral agent were effective in improving HbA1c in both the 48 week completers and mITT populations, excluding sites 25 and 55, at the end of the study. ANCOVA revealed that patients in both treatment groups achieved statistically significant ($p < 0.0001$) reduction of HbA1c values from baseline as early as week 12, the earliest assessment time point, and the effect was sustained throughout the 48-week treatment duration.

For both the 48-week completers and mITT populations, excluding sites 25 and 55, the trend of significantly better glycemic control (reduction in HbA1c) by the addition of a third oral agent over GLAR was observed at week 12, and this trend was sustained throughout the 48-week study duration.

Change from baseline in FPG

Both treatment groups were effective in reducing FPG from baseline to endpoint for the 48-week completers and mITT patients, excluding sites 25 and 55. The reductions from baseline in FPG were greater in the third oral agent group than in the GLAR group at week 2 through week 12, with statistically significant between-group ($p < 0.05$) differences at weeks 2 and 6. However by week 18, this trend began to reverse. With the implementation of the more aggressive GLAR dose-titration regimen after week 26 (Amendment 2), patients in the GLAR group had greater reductions in FPG compared to patients in the third oral agent group in the 48 week completers population, excluding sites 25 and 55. ANCOVA revealed statistically significant ($p < 0.05$) between-group differences, in favor of GLAR, at weeks 30, 42, and 48. A similar pattern was observed for the 48-week mITT population; ANCOVA revealed statistically significant ($p < 0.05$) between-group differences, in favor of GLAR, at weeks 36, 42, 48 and at endpoint.

Responder analyses

In the 48-week completers and mITT populations, excluding sites 25 and 55, a greater proportion of patients in the third oral agent group had HbA1c values ≤ 7.0% at the end of treatment compared with patients in the GLAR group. The proportions of patients with HbA1c values ≤ 6.5% at the end of treatment were more comparable between the 2 treatment groups in the 48-week completers and mITT populations, excluding sites 25 and 55.

The results of the responder analyses in the 48-week mITT and completers populations, excluding sites 25 and 55, were consistent with those including sites 25 and 55, with the exception of the between-group difference for patients with HbA1c values ≤ 7%, which was not significant in the analysis excluding sites 25 and 55 ($p = 0.1056$), but was significant in analysis including sites 25 and 55 ($p = 0.0389$).

Time to response

In the 48-week completers and mITT populations, excluding data from sites 25 and 55, patients in the GLAR group, took a longer time to achieve and maintain HbA1c values ≤ 7% compared with patients in the third oral agent group. Log rank test revealed a statistically significant between-group difference for the 48-week mITT population, but not for the 48-week completer's population.

Changes from baseline in body weight and BMI

In the 48-week safety population, patients in the GLAR group gained less weight and had smaller increases in BMI at each study visit and at endpoint. ANCOVA revealed a statistically significant ($p < 0.05$) between-group difference at week 12 for weight and BMI.

Changes from baseline in lipids

There were no clinically relevant between-group differences in the change from baseline in TC, non-HDL, HDL, LDL, or FFA. ANCOVA revealed that patients treated with GLAR had statistically significant reductions in TG from baseline at weeks 12, 24, 36, and endpoint compared with patients treated with the third oral agent.

Dosing

In the 48-week safety population, the overall mean baseline dose of GLAR dosing was 10.02 IU, glyburide dosing was 4.66 mg, and glucophage/glucophage XR was 520.83 mg.

In the 48-week safety population, the overall mean last dose of GLAR was 78.03 IU. Endpoint daily GLAR doses were 81.58 IU for the GLAR + SU and 75.99 IU the GLAR + metformin treatment strata. The mean daily doses for add-on oral agents in the third oral agent group at endpoint were 8.49 mg for SU and 1770.83 mg for metformin. In the 48-week mITT population, the overall mean last dose of GLAR was 81.33 IU. Endpoint daily GLAR doses were 86.55 IU for the GLAR + SU and 78.43 IU for the GLAR + metformin treatment strata. The mean daily doses for add-on oral agents in the third oral agent group at endpoint were 8.73 mg for SU and 1782.61 mg for metformin. For the 48-week safety population, the average daily doses of study medications were: GLAR [54.98 (33.109) IU], glyburide [8.09 (2.273) mg], glucophage [1940.68 (NA) mg], and glucophage XR [1673.78 (403.276) mg].

The following table provides the changes from baseline to endpoint for HbA1c and FPG in the 48-week completer population, excluding data from sites 25 and 55, and the change from baseline to endpoint for the lipid profile, BMI, and weight in the 48-week safety population, which included data from sites 25 and 55.

	GLAR		Third Oral		GLAR – Third Oral	
Efficacy Variable	Mean (SE) at Baseline	Adjusted Mean (SE) Change from Baseline to Endpoint	Mean (SE) at Baseline	Adjusted Mean (SE) Change from Baseline to Endpoint	95% CI	Prob[a]
HbA1c (%)	8.89 (0.145)	-1.65 (0.126)	8.96 (0.138)	-1.90 (0.120)	(-0.09 , 0.60)	0.1478
FPG (mg/dL)	188.2 (6.40)	-72.2 (5.27)	199.6 (6.10)	-57.3 (5.01)	(-29.3, -0.5)	0.0421
TC (mmol/L)	5.315 (0.1334)	-0.149 (0.0908)	5.165 (0.1262)	-0.041 (0.0858)	(-0.355, 0.138)	0.3873
Non-HDL (mmol/L)	4.132 (0.1339)	-0.083 (0.0922)	4.050 (0.1256)	-0.021 (0.0864)	(-0.310, 0.188)	0.6272
HDL (mmol/L)	1.181 (0.0298)	-0.060 (0.0178)	1.115 (0.0280)	-0.017 (0.0166)	(-0.091, 0.005)	0.0809
LDL (mmol/L)	3.024 (0.1172)	0.069 (0.0771)	2.966 (0.1095)	0.028 (0.0720)	(-0.167, 0.249)	0.6964
TG (mmol/L)	2.471 (0.1743)	-0.373 (0.1024)	2.392 (0.1649	-0.062 (0.0969)	(-0.589, -0.033)	0.0284
FFA (mmol/L	0.60 (0.034)	-0.13 (0.019	0.56 (0.032)	-0.10 (0.018)	(-0.08, 0.02)	0.2949
Weight (kg)	98.99 (2.433)	2.00 (0.704)	100.31 (2.276)	2.74 (0.658)	(-2.64, 1.15)	0.4410
BMI (kg/m^2)	35.03 (0.723)	0.66 (0.241)	34.92 (0.677)	1.01 (0.225)	(-1.00, 0.30)	0.2925

[a]Prob = probability. Data presented at each visit were generated from an ANCOVA model including the main effects of treatment and previous oral diabetic medication, baseline value as a covariate, and the interactions between treatment and previous oral diabetic medication, and treatment and baseline value (**). The p-value assesses significance of the difference in the adjusted means.

BMI = body mass index; CI = confidence interval; FFA = free fatty acids; FPG = fasting plasma glucose; GLAR = insulin glargine; HbA1c = glycosylated hemoglobin; HDL = high-density lipoprotein; LDL = low-density lipoprotein; SE = standard error; TC = total cholesterol; TG = triglyceride.

Strata effect

HbA1c

In the TZD + SU stratum, ANCOVA revealed significantly ($p < 0.05$) greater reductions in HbA1c in the third oral agent group than in the GLAR group at weeks 12, 24, 36, and 48 for the completers population and at weeks 12, 34, and 48 for the mITT population.

Change in HbA1c (%) for collapsed strata: 48-week completers and mITT population, excluding data from sites 25 and 55

Time Points	GLAR			Third Oral			Difference: GLAR - Third Oral			
	N	Adjusted Mean	SE	N	Adjusted Mean	SE	Adjusted Mean	95% CI	SE	Prob[a]
48-week completers population, excluding data from sites 25 and 55										
Week 12										
TZD + SU	27	-0.82	0.173	29	-1.73	0.167	0.91	(0.44 , 1.39)	0.237	0.0002
TZD + Metformin	51	-1.26	0.126	53	-2.03	0.124	0.77	(0.42 , 1.12)	0.176	<0.0001
Week 24										
TZD + SU	27	-1.11	0.189	28	-1.86	0.185	0.75	(0.22 , 1.27)	0.260	0.0054
TZD + Metformin	51	-1.86	0.137	54	-2.16	0.133	0.29	(-0.08 , 0.67)	0.191	0.1264
Week 36										
TZD + SU	26	-1.20	0.192	29	-1.86	0.181	0.66	(0.14 , 1.18)	0.260	0.0134
TZD + Metformin	51	-2.12	0.137	54	-2.11	0.133	-0.01	(-0.38 , 0.37)	0.190	0.9749
Week 48										
TZD + SU	28	-1.16	0.197	30	-1.81	0.190	0.65	(0.11 , 1.20)	0.270	0.0181
TZD + Metformin	52	-2.10	0.144	55	-2.02	0.141	-0.09	(-0.49 , 0.31)	0.201	0.6614
48-week mITT population, excluding data from sites 25 and 55										
Week 12										
TZD + SU	35	-1.07	0.161	42	-1.67	0.146	0.61	(0.18 , 1.03)	0.215	0.0058
TZD + Metformin	66	-1.08	0.117	67	-1.95	0.116	0.87	(0.55 , 1.20)	0.164	<0.0001
Week-24										
TZD + SU	32	-1.31	0.178	37	-1.93	0.166	0.61	(0.13 , 1.09)	0.241	0.0127
TZD + Metformin	60	-1.81	0.130	65	-2.15	0.125	0.34	(-0.02 , 0.69)	0.180	0.0639
Week-36										
TZD + SU	30	-1.40	0.185	34	-1.81	0.174	0.41	(-0.10 , 0.91)	0.251	0.1124
TZD + Metformin	56	-2.07	0.136	59	-2.18	0.132	0.11	(-0.26 , 0.49)	0.189	0.5557
Week-48										
TZD + SU	28	-1.15	0.197	30	-1.81	0.190	0.65	(0.11 , 1.19)	0.270	0.0180
TZD + Metformin	53	-2.08	0.143	55	-2.01	0.140	-0.07	(-0.47 , 0.32)	0.200	0.7124
Endpoint										
TZD + SU	36	-1.38	0.181	43	-1.78	0.166	0.40	(-0.09 , 0.88)	0.244	0.1079
TZD + Metformin	67	-1.90	0.133	70	-1.97	0.130	0.07	(-0.30 , 0.44)	0.185	0.7073

[a]Prob = probability. Analysis by study week is limited to data in the study window as defined in the statistical analysis plan. Data presented at each visit were generated from an ANCOVA model including the main effects of treatment and previous oral diabetic medication, baseline value as a covariate, and the interactions between treatment and previous oral diabetic medication, and treatment and baseline value (**). CI = confidence interval; GLAR = insulin glargine; SE = standard error; SU = sulfonylurea; TZD = thiazolidinedione.

For patients treated with GLAR in the 48-week completers and mITT populations, reductions in HbA1c were numerically greater for patients in the metformin stratum than for patients in the TZD + SU stratum at all study visits.

In the TZD + metformin stratum, ANCOVA revealed significantly ($p < 0.0001$) greater reductions in HbA1c in the third oral agent group than in the GLAR group at week 12 for the 48-week completers and mITT populations, but by week 36, GLAR was shown to be statistically non-inferior to the third oral for reduction in HbA1c (upper CI of the adjusted mean difference was < 0.5% from week 46 through endpoint).

FPG

In the TZD + SU stratum in the 48-week completers population, excluding data from sites 25 and 55, the reductions in FPG were greater in the third oral agent group than in the GLAR group at weeks 2, 6, 12, 18, 24, 36 and 48. ANCOVA revealed statistically significant between-group differences at weeks 2 and 6 ($p < 0.05$). Thereafter, the changes from baseline in FPG were generally similar between the 2 groups. A similar trend was noted for the 48 week mITT population.

In the TZD + metformin stratum, ANCOVA revealed statistically significant ($p < 0.05$) greater reductions in the third oral agent group than in the GLAR group at weeks 2 and 6 for the 48 week completers, excluding data from sites 25 and 55. By week 24, the trend had reversed. ANCOVA revealed significantly ($p < 0.05$) greater reductions from baseline in FPG in the GLAR group than in the third oral agent group at weeks 30, 36, 42 and 48. A similar trend was noted for the 48 week mITT population.

For patients treated with GLAR in the 48-week completers and mITT populations, excluding data from sites 25 and 55, reductions in FPG were numerically greater for patients in the TZD + metformin stratum than for patients in the TZD + SU stratum at all study visits.

Weight and BMI

ANCOVA revealed no statistically significant ($p \geq 0.05$) between-group differences in the TZD + SU stratum. In the TZD + metformin stratum, patients in the GLAR group gained less weight than patients in the third oral agent group at each study visit and at endpoint. ANCOVA revealed a statistically significant between-group difference in the change in weight from baseline at week 12, 24 and 36. In the TZD + metformin strata, patients in the GLAR group had smaller changes from baseline in BMI compared with patients in the third oral agent group throughout the study. ANCOVA revealed a statistically between-group difference in BMI at week 12 (GLAR: 0.03 kg/m^2, third oral agent 0.61 kg/m^2; $p = 0.0013$).

Adjusted mean difference in BMI (kg/m^2) by strata (48-week safety population)

Time-Points	Difference: GLAR - Third Oral			
	Adjusted Mean	95% CI	SE	Prob[a]
Week 12				
TZD + SU	-0.32	(-0.86 , 0.23)	0.273	0.2504
TZD + Metformin	-0.79	(-1.21 , -0.38)	0.211	0.0002
Week 24				
TZD + SU	0.25	(-0.65 , 1.15)	0.452	0.5909
TZD + Metformin	-0.93	(-1.61 , -0.24)	0.345	0.0080
Week 36				
TZD + SU	0.39	(-0.62 , 1.40)	0.506	0.4479
TZD + Metformin	-0.98	(-1.73 , -0.23)	0.378	0.0104
Week 48				
TZD + SU	-0.27	(-1.41 , 0.87)	0.571	0.6408
TZD + Metformin	-0.94	(-1.77 , -0.12)	0.416	0.0252
Endpoint				
TZD + SU	0.13	(-0.88 , 1.15)	0.509	0.7944
TZD + Metformin	-0.70	(-1.47 , 0.07)	0.388	0.0729

[a]Prob = probability. Analysis by study week is limited to data in the study window as defined in the statistical analysis plan. Data presented at each visit were generated from an ANCOVA model including the main effects of treatment and previous oral diabetic medication, baseline value as a covariate, and the interactions between treatment and previous oral diabetic medication, and treatment and baseline value (**). The p-value assesses significance of the difference in the adjusted means.

CI = confidence interval; GLAR = insulin glargine; SE = standard error; SU = sulfonylurea; TZD = thiazolidinedione.

Lipid Profile

There were few between-group differences in the TZD + SU stratum for changes in TC, HDL, non-HDL, LDL, TG and FFA. In the TZD + metformin stratum, patients in the GLAR group had statistically significantly ($p < 0.05$) greater improvements in TC, LDL, and FFA values compared with patients in the third oral agent group at all visits, except week 24 for LDL and weeks 12 and 24 for FFA.

TC: Throughout the study, GLAR-treated patients in the TZD + metformin stratum displayed numerically greater reductions from baseline in TC values compared with GLAR-treated patients in the TZD + SU stratum. At endpoint, the adjusted mean reduction from baseline in TC for GLAR-treated patients was -0.344 ± 0.1053 mmol/L in the metformin stratum and 0.009 ± 0.1413 mmol/L in the TZD + SU stratum.

HDL: There were no statistically significant between-group differences in either strata (TZD + SU or TZD + metformin), except at week 12 in the TZD + SU stratum. In the TZD + SU stratum, ANCOVA revealed that patients in the GLAR group had statistically significant reduction ($p = 0.0323$) in HDL values compared with patients in the third oral agent group at week 12. Throughout the study, the adjusted mean reductions from baseline in HDL values were similar for GLAR-treated patients in the 2 strata (TZD + metformin and TZD + SU). At endpoint, the adjusted mean HDL reduction from baseline was -0.057 ± 0.0203 mmol/L in the TZD + metformin and -0.053± 0.0277 mmol/L in the TZD + SU stratum.

Non-HDL: In the TZD + SU stratum, ANCOVA revealed that patients in the GLAR group had statistically significantly greater increase ($p = 0.0135$) in non-HDL values compared with patients in the third oral agent group at week 24. There were no other statistically significant between-group differences in the TZD + SU stratum. In the TZD + metformin stratum, ANCOVA revealed that patients in the GLAR group had statistically significantly greater reductions ($p \leq 0.05$) in non-HDL values compared with patients in the third oral agent group at weeks 12, 24, 36, 48, and at endpoint.

LDL: In the TZD + SU stratum, ANCOVA revealed that patients in the GLAR group had statistically significant increases ($p < 0.05$) in LDL values compared with patient in the third oral agent group at week 24 and at endpoint. In the TZD + metformin stratum, patients in the GLAR group had statistically significant reductions ($p < 0.05$) in LDL values compared with patients in the third oral agent group for all visit weeks, except week 24. Throughout the study, GLAR-treated patients in the TZD + metformin stratum displayed numerically greater reductions from baseline in LDL values compared with GLAR-treated patients in the TZD + SU stratum. At endpoint, the adjusted mean reduction from baseline in LDL for GLAR-treated patients was -0.091 ± 0.0898 mmol/L in the TZD + metformin stratum and 0.195 ± 0.1191 mmol/L in the TZD + SU stratum.

TG: In the TZD + SU stratum, patients in the GLAR group had numerically greater reductions in TG values compared with patients in the third oral agent group for all visit weeks. ANCOVA revealed statistically significant between-group differences at week 12 ($p = 0.0024$). A similar trend in favor of GLAR was observed in the metformin stratum; however, none of the between-group differences was statistically significant. Throughout the study, the reductions from baseline in TG values for GLAR-treated patients were numerically similar between the 2 strata. At endpoint, the adjusted mean reduction from baseline in TG was -0.347± 0.1182 mmol/L in the TZD + metformin and -0.414 ± 0.1585 mmol/L in the SU stratum.

FFA: ANCOVA revealed no statistically significant between-group differences in the TZD + SU strata. In the TZD + metformin stratum, ANCOVA revealed that patients in the GLAR group had statistically significant ($p < 0.05$) greater reductions in FFA values compared with patients in the third oral agent group at week 36, week 48, and at endpoint. Throughout the study, the reductions from baseline in FFA values for GLAR-treated patients were numerically similar between the 2 strata. At endpoint the adjusted mean FFA reduction from baseline was -0.17 ± 0.022 mmol/L in the metformin stratum and -0.09± 0.030 mmol/L in the SU stratum.

Safety results:

Both treatments were safe and tolerable. In the GLAR group, 73.9% (122/165) of patients reported at least 1 TEAE and 5.5% (9/165) of patients had TEAEs that were considered possibly related to treatment. Similarly in the third oral agent group, 69.2% (117/169) patients reported at least 1 TEAE but the percentage of patients who had TEAEs that were considered possibly related to treatment was higher (14.8%, 25/169). Serious TEAEs were reported for 7.9% (13/165) of patients in the GLAR group and 8.3% (14/169) of patient in the third oral agent group. The percentage of patients who discontinued treatment because of an adverse event was small in the GLAR (3.6%, 6/165) and third oral agent groups (1.2%, 2/169). There were no deaths reported for patients in the GLAR group. One patient in the third oral agent group died due to hypoglycemic coma, which was considered to be possibly related to treatment.

THE FOLLOWING TABLE SUMMARIZES THE TEAES DURING THE STUDY DURATION IN THE ALL-SAFETY POPULATION.

All Safety Population	GLAR (N = 165)		Third Oral (N = 169)	
	TEAE	Possibly Related TEAE	TEAE	Possibly Related TEAE
Reported at least 1 TEAE [n (%)]	122 (73.9)	9 (5.5)	117 (69.2)	25 (14.8)
Reported at least 1 serious TEAE [n (%)]	13 (7.9)	0 (0.0)	14 (8.3)	3 (1.8)
Patients discontinued due to a TEAE [n (%)]	6 (3.6)	0 (0.0)	2 (1.2)	0 (0.0)
Patients who died during the study [n (%)]	0 (0.0)	0 (0.0)	1 (0.6)	1 (0.6)

GLAR = insulin glargine; TEAE = treatment-emergent adverse event.

Hypoglycemic events:

There were no statistically significant differences between the two groups in the percentage of patients with 1 or more hypoglycemic events, all types (46.1% for the GLAR group and 51.5% for the third oral agent group) or any category of hypoglycemic event. When the rate of hypoglycemic events was adjusted for years of exposure, Poisson regression revealed that the event rate was statistically significantly lower in the GLAR group than in the third oral agent group for hypoglycemic events, all types (3.36 for GLAR vs 5.23 for the third oral agent group; p = 0.0485), confirmed clinically relevant hypoglycemic events (2.54 vs 4.15, respectively; p = 0.0362), and moderate to severe hypoglycemic events (0.39 vs 0.93, respectively; 0.0069). The event rate for severe hypoglycemic events was significantly greater in the GLAR group than in the third oral agent group (0.13 vs 0.05; p = 0.0474)

The following table summarizes the hypoglycemic events in the all safety population.

Type of hypoglycemia – All Safety Population		GLAR (N = 165)		Third Oral (N = 169)		
		N	%	N	%	Prob[a]
All types	Patients with ≥ 1 episode	76	46.1	87	51.5	0.3365
	Episodes reported	394		644		
Confirmed clinically relevant	Patients with ≥ 1 episode	68	41.2	71	42.0	0.9109
	Episodes reported	301		515		
Moderate to severe	Patients with ≥ 1 episode	30	18.2	37	21.9	0.3951
	Episodes reported	51		131		
Severe	Patients with ≥ 1 episode	13	7.9	6	3.6	0.0885
	Episodes reported	15		6		
Unconfirmed non-severe	Patients with ≥ 1 episode	43	26.1	48	28.4	0.6691
	Episodes reported	93		129		
Nocturnal	Patients with ≥ 1 episode	35	21.2	25	14.8	0.1216
	Episodes reported	107		63		
Symptomatic	Patients with ≥ 1 episode	73	44.2	84	49.7	0.3370
	Episodes reported	369		590		
Asymptomatic	Patients with ≥ 1 episode	11	6.7	16	9.5	0.3239
	Episodes reported	25		54		

[a] Prob = probability. P-value comparing the percentage of patients with event between treatment groups using the CMH test controlling for previous oral diabetic medication.
GLAR = insulin glargine.

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