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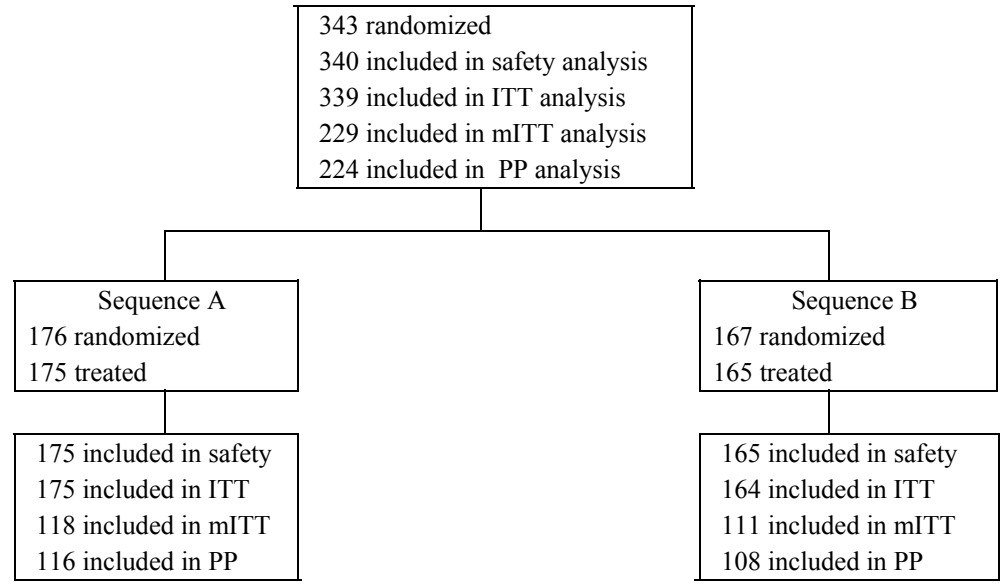
Prescribing decisions should be made based on the approved package insert in the country of prescription.

Sponsor / Company: Sanofi **Drug substance(s):** Insulin Glargine (HOE901)	**Study Identifiers:** NCT00941369, EudraCT 2009-019013-59 **Study code:** LANTU_L_04079
Title of the study: *H*ealth *A*ssessment, *P*atient treatment satisfaction and Quality-of-Life in insulin-naive type 2 diabetes *P*atients uncontrolled on OHA treatment initiating basal insulin therap*y* with either insulin glargine or NPH insulin added to therapies with oral hypoglycemic agents (HAPPY).	
Study center(s): 39 centers in Germany (internists and diabetologists)	
Study period: Date first patient enrolled: 18-Jun-2009 Date last patient completed: 16-Oct-2012	
Phase of development: 4	
Objectives: The primary objective was to investigate the impact of insulin glargine vs. NPH basal insulin on a composite Diabetes Related Quality of Life score (DRQoL), consisting of a standardized and unweighted Insulin Treatment Experience Score (ITEQ), the Problem Areas in Diabetes Questionnaire Score (PAID) and the mental health score of the SF 12® Health Survey (SF 12®). The treatments consisted of a combination therapy of oral antidiabetic agents and either insulin glargine or NPH basal insulin.	
Methodology: This was a multicenter, prospective, cross-over, open, randomized clinical trial.	
Number of patients: Planned: 332 Randomized: 343 Treated: 340 Evaluated:  Efficacy: 229 patients in modified Intention-To-Treat (mITT) population (primary endpoint); 339 patients in ITT population Safety: 340	

Diagnosis and criteria for inclusion: Insulin naïve type 2 diabetic patients, who failed to have sufficient metabolic control, with HbA_{1c} values ≥ 7.0% and ≤ 10.0% in spite of treatment with oral antidiabetic agents

Study treatments

Investigational medicinal products: Insulin glargine (Lantus®) given once daily at any time but every day the same time; NPH basal insulin (Insuman® Basal) given OD or BID at the discretion of the investigator. Basal insulin was initiated with 10 units per day and titrated with the same algorithm for both insulins to target FBG values ≤100 mg/dL (5.5 mmol/L).

Formulation: 100 U/ml in TactiPen® reusable pen

Route of administration: Subcutaneous injection

Duration of treatment: Two 24-weeks periods (cross-over design without wash-out period)

Duration of observation: 51 weeks (2 weeks screening phase, followed by two 24 weeks treatment periods and 1 week follow-up phase)

Criteria for evaluation:

Efficacy:

Primary endpoint: The mean score of Diabetes Related Quality of Life score (DRQoL, primary endpoint) calculated as mean of three sub-scores (ITEQ, PAID, and SF-12®), in each sequence and each period.

Secondary endpoints: The mean scores of patient questionnaires (ITEQ [Insulin Treatment Experience Questionnaire], DTSQs [Diabetes Treatment Satisfaction Questionnaire], PAID [Problem Areas in Diabetes Questionnaire], SF-12® [Health Survey Short Form 12], EQ-5D [Euro Q5 Questionnaire]), treatment preference at end of treatment, mean changes in lab parameters (HbA_{1c}, fasting blood glucose, total cholesterol, HDL, LDL, triglycerides), 7-point blood glucose profile, hypoglycemia episodes, anthropometric data (body weight, waist circumference), and total daily insulin dose.

Safety: Frequency of adverse events reported by the patient or noted by the Investigator, as well as abnormal standard hematology and blood chemistry and vital signs.

Statistical methods:

The primary endpoint was Diabetes Related Quality of Life score (DRQoL) calculated as mean of three sub-scores (ITEQ, PAID, and SF-12®). The primary endpoint was analyzed for the modified intent-to-treat population including randomized patients with valid values for DRQoL for both treatment periods. A variance analytical model (ANCOVA) was calculated including fixed effects for treatment, sequence and period (treatment by sequence interaction), as well as a random effect to account for subjects within sequence. Tests were performed at a significance level of 0.05.

Based on α=0.05 (two-sided) and ß=0.10, 265 patients were needed to detect an effect size of d=0.20 on the DRQoL total score, using a paired t-test. With an expected non-evaluable rate of 20%, a total number of 332 patients were planned to be enrolled.

Secondary endpoints were analyzed for the intent-to-treat population including all randomized patients. Wherever possible, changes from baseline to end of treatment phase were analyzed. As there was no wash-out phase, values assessed at cross-over visit were used twice: as value for end of period for period 1 and baseline value for period 2. Two-sided 95%-confidence intervals for all estimated parameters were calculated. Secondary endpoints were analyzed in an explorative manner. If applicable, treatment comparisons for secondary efficacy variables were done by the variance analytical approach as described above for the primary efficacy endpoint. McNemar test was used to analyze hypoglycemia rates.

Subgroup analyses were performed for primary and secondary endpoints: within patient comparisons in subgroups by treatment sequence and between patient comparisons regarding the single treatment periods.

Summary:

Population characteristics: Overall, the treatment sequences (Sequence A: insulin glargine then switching to NPH insulin; Sequence B: NPH insulin then switching to insulin glargine) were well balanced with regard to age, gender and race. Median age for all patients was 62.6 with a range between 31 and 80 years. More male patients were randomized (60.5%) than female. All patients were Caucasian except for one Asian patient.

Disease characteristics at baseline were comparable between the two treatment sequences. Overall, the median time since diagnosis of type 2 diabetes mellitus was 104 months. Median time since start of first OHA treatment was 58.6 months. At the time of the screening visit 90% of the patients received metformin, 56% received sulfonylurea, and 24% received DPP-IV inhibitors.

A total of 47 patients (25 in sequence A, 22 in sequence B) discontinued trial treatment prematurely. The most common reason for premature discontinuation was 'Patient does not wish to continue' which was reported by 16 patients. Furthermore, 'Other reason' was stated by 14 patients, 'Adverse event' by 11 patients, 'Poor compliance to protocol' by 5 patients and 'Lost to follow-up' by 1 patient.

Efficacy results: The results for DRQoL scores were very similar for the two treatment sequences and the two periods. On a 0-100 scale, the mean scores (±std) in period 1 were 69.7 (±8.45) in sequence A and 69.8 (±9.81) in sequence B. In the second treatment period the mean scores (±std) were 70.1 (±9.04) in sequence A and 69.4 (±9.66) in sequence B. Neither treatment nor period effect could be observed in ANCOVA or subgroup analyses.

In patient reported outcomes (patient questionnaires) no differences between the two insulin treatments could be observed. For PAID and DTQS an increase in Quality of Life in the first treatment period could be equally demonstrated for both treatments.

Regarding the effects on the glucose metabolism again no differences between the two insulin types could be observed. Mean HbA_{1c} values were decreased by -1.17% in the first treatment period for insulin glargine and NPH basal insulin. In the second period HbA_{1c} values slightly increased again compared to the cross-over visit (0.21% and 0.09% in sequence A and B, respectively). Similarly, mean fasting blood glucose was reduced in the first period and slightly reduced in the second period by both treatments.

Rates of patients with confirmed hypoglycemia (being defined as events with related blood glucose measurement below 3.1 mmol/L) were 12.2% during insulin glargine and 14.9% during NPH basal insulin treatment. A total of 17 (5.2%) and 21 (6.5%) patients reported nocturnal confirmed hypoglycemia, respectively. Two patients, one in each treatment group, reported events that fulfilled the criteria for confirmed severe hypoglycemia as well as for serious hypoglycemia.

Although there were some period effects (reduction of total cholesterol and triglycerides; slight increase of HDL cholesterol) in mean change of lipid profile during insulin treatment no differences between the two treatments were observed.

No essential changes during the study or differences between the treatments were observed for anthropometric data.

Concerning treatment preference more patients continued the insulin treatment they received at the end of the study (in period 2). However, more patients changed from NPH basal insulin at study end back to insulin glargine than vice versa. Thus, in sequence A 47.4% of patients continued on NPH basal insulin after the study while 39.4% switched back to insulin glargine. In sequence B 67.7% continued on insulin glargine and only 17.7% switched back to NPH basal insulin.

Safety results: The overall profile of treatment-emergent adverse events (TEAEs) was similar for the two insulin treatments. Overall, 46.2% and 43.2% of the patients experienced at least one TEAE during treatment with insulin glargine and NPH basal insulin, respectively. Treatment-emergent SAEs were reported for 7.3% and 5.2% of the patients, respectively.

Four patients died during the study: 3 patients during treatment with insulin glargine and one patient during treatment with NPH basal insulin. None of the AEs leading to death were considered as possibly related to the investigational product by the investigator. The reported reasons for death were multiple organ failure, pancreatic cancer, cardiovascular failure, and 'natural' death.

A total of 12 TEAEs leading to discontinuation were reported for 6 patients (1.8%) during treatment with insulin glargine. During NPH basal insulin treatment a total of 6 TEAEs leading to discontinuation were reported for 5 patients (1.5%).

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