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Sponsor / Company: Sanofi **Drug substance(s):** insulin glargine/insulin glulisine	**Study Identifiers:** NCT00965549, EudraCT 2008-007026-19 **Study code:** Lantu_L_04211
Title of the study: Comparison of a basal plus one insulin regimen (insulin glargine/insulin glulisine) with a biphasic insulin regimen (insulin aspart/insulin aspart protamine 30/70) in type 2 diabetes patients following basal insulin optimisation (Lantu_L_04211).	
Study center(s): The study was conducted in the UK (54 active sites) and Australia (12 active sites) where active sites were those where one or more patients were screened.	
Study period: Date first patient enrolled: 22/Jul/2009 Date last patient completed: 20/Dec/2012	
Phase of development: Phase 4	
Objectives: **Primary Objective:** Demonstrate non-inferiority at 6 months of a basal plus one insulin regimen (Lantus® plus one injection of Apidra®) compared with a biphasic insulin regimen (NovoMix® 30) at controlling glycosylated haemoglobin (HbA_{1c}) in type 2 diabetes. **Secondary Objectives:** 1. To compare the proportion of patients in each treatment group reaching HbA_{1c} target (<7%) at the end of the treatment period. 2. To compare the incidence rates of hypoglycaemia (total, severe, nocturnal). 3. To compare the change in body weight from Randomisation to End of Study. 4. To compare the change in diabetes specific quality of life and other patient reported outcomes from Randomisation to End of Study: • Diabetes Treatment Satisfaction Questionnaire - status and change ($DTSQ_{s+c}$). • Audit of Diabetes-Dependent Quality of Life (ADDQoL) questionnaire. • Insulin Treatment Satisfaction Questionnaire (ITSQ). • EuroQoL 5 Dimensions (EQ-5D) questionnaire. 5. To record the change in the daily dose of insulin from Visit 2 (start of Run-in) to Randomisation and Randomisation to End of Study.	
Methodology: An active controlled, open-label, comparative, randomised, parallel group study.	

Number of patients:	Screened: 600
	Run-in period: 480
	Randomised: 360
	Treated: 360 (324 completed)
Evaluated:	
	Efficacy: 288 Per Protocol (PP), 335 Intention-to-Treat (ITT)
	Safety: 334

Diagnosis and criteria for inclusion: Men or women (non-child bearing potential), age 18 to 75 inclusive, with type 2 diabetes mellitus and being treated with Lantus® (once daily), Levemir (once or twice daily) or Neutral Protamine Hagedorn (NPH) insulin (once or twice daily) as a single insulin ≥3 months, with 11.0% ≥ HbA_{1c} ≥7.5% and body mass index (BMI) ≤40 kg/m^2.

Study treatments

Investigational medicinal product(s):

Run-In Period

Lantus® (insulin glargine)

Randomised Period

Either:

Basal Plus One: Lantus® and Apidra® (insulin glulisine)

or:

Biphasic: (NovoMix® 30 [insulin aspart/insulin aspart protamine 30/70])

Formulation: Lantus®: Clear, colourless, aqueous solution for injection. 100 U/mL in a prefilled pen (SoloStar®)

Apidra®: Clear, colourless, aqueous solution for injection. 100 U/mL in a prefilled pen (SoloStar®)

NovoMix® 30: White aqueous suspension for injection. 100 U/mL in a prefilled pen (FlexPen®)

Route(s) of administration: subcutaneous injection

Dose regimen:

Run-In Period

Lantus® once daily, at any time of the day but the same time each day. The dose of Lantus® was individually titrated once a week to obtain fasting glucose between 4.3 and 6.1 mmol/L.

Randomised Period

Either:

Basal Plus One:

Lantus® once daily, at any time of the day but the same time each day. The dose of Lantus® was individually titrated once a week for four weeks, then fortnightly, to obtain fasting glucose between 4.3 and 6.1 mmol/L, and

Apidra® once daily immediately before the main meal. The dose of Apidra® was individually titrated once a week for four weeks, then fortnightly, to obtain post-prandial glucose of ≤7.5 mmol/L.

or:

Biphasic:

NovoMix® 30 twice daily immediately before breakfast and immediately before the evening meal. The dose of NovoMix® 30 was individually titrated once a week for four weeks, then fortnightly, to obtain pre-meal glucose between 4.3 and 6.1 mmol/L.

Duration of treatment: 24 weeks

Duration of observation: Screening period 1-2 weeks followed by a standard 8-week or extended 12-week Run-in period and 24-week Treatment period. Therefore, the total duration of observation was 34 weeks assuming a 2-week Screening period if patients completed the standard Run-in period and 38 weeks if patients completed the extended Run-in period.

Criteria for evaluation:

Efficacy:

Primary

- Change in HbA_{1c} between Visit 9 or 9a (pre-randomisation – defined as "Baseline" throughout the Synopsis) and End of Study.

Secondary

- Proportion of patients reaching the $HbA1_c$ target of <7.0% at End of Study.
- Change in weight from Randomisation to End of Study.
- Change in diabetes specific quality of life and other patient reported outcomes from Randomisation to End of Study.

Safety:

- Hypoglycaemia (total, severe, and nocturnal): incidence rates of hypoglycaemic episodes for the Run-in period and the Treatment period.
- Vital signs (heart rate, systolic blood pressure, diastolic blood pressure): the change from Visit 2 (start of Run-in) to Randomisation and Randomisation to the last measurement on treatment was calculated.
- Adverse events (AEs): Treatment-emergent adverse events (TEAE) were summarised: AEs beginning or worsening during the Treatment period.

Statistical methods:

The main aim of the study based on the primary outcome measure was to demonstrate non-inferiority of the basal plus one regime relative to the biphasic insulin with respect to change in HbA1c from Randomisation to End of Study. Non-inferiority was assumed if the upper one-sided 97.5% confidence limit <0.4%. A total of 162 completers in each arm would give 80% power to show non-inferiority with an observed standard deviation (SD) of 0.8 and a difference in favour of biphasic insulin of 0.15 (as per Protocol Amendment 05, dated 20-Jan-2012). Since the primary analysis population was the PP population, allowing for a 10% dropout rate during the study, required 360 patients to be randomised. To allow for a dropout rate during the Run-in of between 20% and 25% and screen failure rate of between 20% and 25%, the target for screening was 600 patients. This figure was revised from the original target after a planned (Protocol Amendment 04) blinded interim analysis was conducted on the first 75 patients who had completed the study. The original estimate of standard deviation (of the primary outcome measure) was updated with observations from the first 75 patients (treatment allocation remaining concealed), resulting in the lower sample size.

For the purpose of analysis of HbA_{1c}, when a patient had entered the Run-in extension phase, data from Visit 9a was used as the baseline (pre-randomisation) value rather than Visit 9.

The primary efficacy analysis was analysis of covariance (ANCOVA) with covariates comprising baseline (as defined above), country and whether patients were randomised under the original criteria, or under the criteria defined in Protocol Amendment 04 (dated 06-Jul-2010). The PP population provided the primary population for analysis, but any differences between that and the ITT population was fully explored. There was only one primary efficacy variable and final assessment, so there were no multiplicity issues. Similar methods were used for the analyses of the secondary endpoints, namely the change in body weight, the change in diabetes specific quality of life, and other patient reported outcomes from Randomisation to End of Study using the ITT population. A logistic regression was used to compare between treatment proportion of patients reaching the HbA_{1c} target of <7.0% at the End of Study.

The primary safety analysis was the analysis of the event rate of hypoglycaemic episodes, overall and nocturnal. Adjusted mean hypoglycaemia event rates were obtained from a negative binomial regression model with treatment and randomisation criteria as explanatory variables. The log of the duration of hypoglycaemia monitoring period was used as the offset variable. AEs were summarised in tables and graphs but no formal statistical analysis was conducted.

Summary:

Population characteristics: A total of 602 patients were screened. A total of 462 patients entered the standard Run-in period, of which 70 patients entered the extended Run-in period. Mean age of those entering the Run-in phase was 61.2 years and 71.2% were male. Mean HbA_{1c} was 8.80% and mean fasting glucose (FG) was 8.76 mmol/L at Screening; mean pre -randomisation HbA_{1c} was 8.62%. The majority of patients who entered the Run-in period (n = 335, 72.5%) were randomised, of which 298 patients (89.0%) completed the study. The main reason for patients not meeting the randomisation criteria at Visit 9/9a was that the mean FG ≥7.0 mmol/L (18.0% of all patients). Once randomised, the main reason for patients being prematurely withdrawn from the investigational product was because the patient did not wish to continue (4.5%) with a similar proportion in each treatment group (4.1% versus 4.8%; basal plus one versus biphasic insulin). Overall, the majority of randomised patients were male (72.5%) and Caucasian (89.5%), with a mean age of 61.6 years, mean weight of 91.10 kg and mean BMI of 31.09 kg/m^2. Mean overall pre-randomisation HbA_{1c} was 8.6%. At Screening, patients had an overall mean duration of diabetes of 12.94 years, and overall mean duration of current therapy of 2.26 years, with the majority of patients (97.9%) taking insulin plus an oral anti-diabetic drug. The demography of the two treatment groups was similar. The investigator's assessment of compliance with the titration algorithm was recorded. Summary data have not been produced. During Run-in (Visit 2 to Randomisation), a similar mean change in insulin dose was seen across the basal plus one and biphasic insulin groups (20.0 U/mL versus 18.2 U/mL; basal plus one versus biphasic insulin). Between Randomisation and End of Study, the mean change in insulin dose was higher in both treatment groups compared with the mean changes seen during Run-in. A higher mean change (35.6 U/mL) was seen in the biphasic insulin group compared with the basal plus one group (25.5 U/mL).

Efficacy results: The primary objective of this study was achieved with non-inferiority demonstrated between the basal plus one and biphasic insulin groups: the upper one-sided 97.5% confidence interval (CI) for the adjusted mean change in HbA_{1c} (between Baseline and End of Study) was <0.4% (the pre-defined non-inferiority margin) for the PP population. Data from the same analysis of the ITT population supported the PP data. There was no statistically significant difference between the basal plus one group and biphasic insulin group in relation to reaching target HbA_{1c} (<7.0%). Baseline HbA_{1c}, baseline FG, and randomisation criteria had no significant impact on patient withdrawal. These data further supported the interim analysis outcomes and the assumptions made with respect to sample size calculations.

As expected following the administration of insulin, an anabolic hormone, body weight increased from Baseline to End of Study for patients in the basal plus one group and the biphasic insulin group with no statistical significance shown between the two treatments.

In both treatment groups, an increase in patient satisfaction was observed with respect to their diabetes treatment (total $DTSQ_c$) but a decrease in patient satisfaction was seen with respect to their insulin treatment (total ITSQ) relative to baseline. Statistically significant differences between the treatment groups in favour of the basal plus one group were observed for overall change in diabetes treatment satisfaction at End of Study (total $DTSQ_c$), perceived frequency of hyperglycaemia (from $DTSQ_c$), overall "present quality of life" (ADDQoL overview item I score) and insulin treatment satisfaction (total ITSQ). No statistically significant differences were observed in relation to either the perceived frequency of hypoglycaemia ($DTSQ_c$ item 3) or in relation to ADDQoL "average weighted impact" (AWI) score. In both treatment groups, the mean impact score for the question, "freedom to eat as I wish" was negative at Randomisation. Between baseline and the end of study, a small reduction in the impact of diabetes on "freedom to eat as I wish" was observed in the basal plus one group compared to slightly increased impact in the biphasic insulin group. No statistically significant differences were seen between the basal plus one and biphasic insulin treatments in relation to either the patients' perception of health status (EQ-VAS) or the utility values, both of which showed little change in either group with mean levels of around 75% (0.75) throughout.

Safety results: There was no statistically significant difference between the basal plus one and biphasic insulin treatments in relation to overall hypoglycaemic incidence rate, however, there was a statistically significant difference between the two treatment groups in relation to nocturnal hypoglycaemic incidence rate (basal plus one [56.5%], biphasic [39.6%]) favouring the biphasic insulin treatment regimen.

Similar numbers of patients experienced AEs and TEAEs across the basal plus one and biphasic insulin treatment groups, with a low number of withdrawals (a total of 3 patients) overall due to TEAEs. Treatment-related serious adverse events (SAEs) of hypoglycaemia and accidental overdose were experienced by patients in the basal plus one group but not by those in the biphasic insulin group. For patients who experienced accidental overdoses, the majority were assessed to be related to Apidra®. During the study, two patients experienced fatal treatment-emergent SAEs, one patient in the basal plus one group due to cardiac failure, and one patient in the biphasic insulin group due to a serious malignant lung neoplasm; both SAEs were considered not related to the study drug.

Overall the basal plus one and biphasic insulin treatments were well tolerated with no changes of significant clinical concern observed in the other safety parameters that were assessed.

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