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Sponsor / Company: sanofi-aventis **Drug substance(s):** Insulin Glargine	**Study Identifier:** NCT00950534 **Study code:** LANTU_L_04264
Title of the study: A Randomised, Multicentre, Open-Label, Parallel-Group, 24-Week Phase IV Study Comparing the Effectiveness and Safety of Two Approaches to the Management Of Type 2 Diabetes Mellitus in Australian Primary Care: General Practitioner Initiation of Insulin Glargine versus the Usual Standard of Care (RELIANCE)	
Study center(s): Trial performed in Australia. 33 initiated study centers. 12 centers randomised at least 1 patient.	
Study period: Date first subject/patient enrolled: 29 July 2009 Date last subject/patient completed: 25 August 2010	
Phase of development: IV	
Objectives: **- Primary:** To demonstrate the improvement in HbA_{1c} levels after general practitioner (GP) initiation and management of Type 2 Diabetes Mellitus (T2DM) with insulin glargine compared with their usual clinical practice. **- Main Secondary:** To demonstrate the importance of GP initiation of insulin glargine for the treatment of T2DM.	
Methodology: Prospective, randomised, multicentre, open-label, two-arm, parallel-group 24-week phase IV study. Patients will be randomised using a 1:1 ratio to one of the following two treatment arms: - Arm A: GP initiation with insulin glargine. - Arm B: Usual standard of care.	
Number of subjects: **Planned:** 400 **Randomized:** 25 (Arm A=12, Arm B=13) Due to poor recruitment, the study was prematurely discontinued.	

Diagnosis and criteria for inclusion:

A patient was eligible if they met all of the following inclusion criteria:

- Age ≥ 18 and ≤ 80 years
- Diagnosed with T2DM
- HbA_{1c} levels ≥ 7.5% and ≤ 10%
- Continuous Oral Anti Diabetics (OAD) treatment for ≥ 3 months before randomisation with stable daily doses of one or more OADs (if on two or more OADs, one must be ≤ half maximum tolerated dose)
- Willing and able to perform blood glucose monitoring using a blood glucose meter
- Willing and able to keep a daily patient diary
- Willing and able to provide written informed consent before enrolment in the study

A patient was not eligible for inclusion if they met any of the following:

- Type 1 Diabetes Mellitus (T1DM)
- Body mass index > 45 kg/m^2
- Works night shifts
- History of ketoacidosis or hyperosmolar hyperglycaemic state, stroke, myocardial infarction, angina pectoris, coronary artery bypass graft or percutaneous transluminal coronary angioplasty within the previous 12 months, congestive heart failure
- Hypoglycaemia unawareness
- Have had more than 1 episode of hypoglycaemia (per protocol definition) within 24 weeks before screening
- Impaired renal function defined as, but not limited to, serum creatinine ≥ 1.5 mg/dL (133 µmol/L) [males] or ≥ 1.4 mg/dL (124 µmol/L) [females]
- Active liver disease (alanine transaminase [ALT] greater than two times the upper limit of the reference range, as defined by the local laboratory)
- Have any condition (including known substance or alcohol abuse or psychiatric disorder) that precludes the patient from following and completing the study protocol
- Had a blood transfusion or severe blood loss within the 3 months before screening, or have known haemoglobinopathy, haemolytic anaemia or sickle cell anaemia
- Current or previous use of insulin
- Known hypersensitivity / intolerance to insulin glargine or any of its excipients
- Have taken exenatide in the six weeks before screening or for a total of 30 days or more in the 24 weeks before screening
- Currently receiving treatment with non-selective ß-blockers
- Currently receiving chronic (longer than two weeks) systemic glucocorticoid therapy (excluding topical or inhaled preparations) or have received such therapy within the four weeks preceding the screening visit
- Currently undergoing therapy or planned radiological examinations requiring the administration of contrasting agents for malignancy (other than non-metastatic / early stage basal cell or squamous cell carcinoma).
- Currently participating in another investigational study or recent study participation ending < 30 days before screening

Female patients who are pregnant, breastfeeding, of childbearing potential not willing to agree to use a medically accepted contraceptive regimen for the duration of the study.

Investigational product: Insulin glargine

Dose: Titration

Administration: Subcutaneous injection to the abdomen, thigh or upper arm using the SoloSTAR® pen.

Duration of treatment: 24 weeks

Duration of observation: 25 weeks

Reference therapy: N/A, commercially available OAD at Physician's discretion.

Dose: N/A, commercially available OAD at Physician's discretion.

Administration: N/A, commercially available OAD at Physician's discretion.

Criteria for evaluation:

Efficacy/pharmacodynamic:

- % of patients who achieved HbA_{1c} levels ≤ 7.0%
- Time required to reach target HbA_{1c} level of ≤ 7%
- % of patients who achieved 2 consecutive on treatment HbA_{1c} measurements of ≤ 7.0%
- A decrease in mean HbA_{1c} level at end of study
- A decrease in mean Fasting Plasma Glucose (FPG) at end of study
- Mean change in body weight at end of study
- GP satisfaction of diabetes treatment with initiation of insulin glargine
- GP satisfaction with insulin initiation

Safety:

- Safety of GP initiation of insulin glargine
- Frequency and severity of Adverse Events, including the incidence, type (e.g., nocturnal or symptomatic) and severity of hypoglycaemia
- Physical examination findings and vital signs

Statistical methods:

It was determined that a sample of 400 patients (GP initiation of insulin glargine: n = 200 [Arm A]; Usual standard of care: n = 200 [Arm B]) will provide 80% power to detect a hazard ratio of 1.5 for achievement of target on insulin glargine compared with standard care; if 44% of the standard care group achieved target (as observed in the Canadian INSIGHT [Implementing New Strategies with Insulin Glargine for Hyperglycaemia Treatment] trial[1]) this will correspond to an absolute difference between the two study arms of 14% in the percentage of patients achieving an HbA1c ≤ 7.0%.

The sample size was calculated based on the assumption that the analysis will be undertaken using a log-rank test with 44% of the control group (standard care arm) and 58% of the insulin glargine group achieving target HbA1c levels (giving a hazard ratio of 1.5). A drop-out rate of 0.0021 in each group was used (corresponding to a 5% drop-out rate). The effect size described is based on the results observed in the Canadian INSIGHT trial.

The sample size estimation was performed using SAS and confirmed using NQuery Advisor (V4.0) and PASS 2008 software.

Summary:

The feasibility of this study was reviewed extensively on 5 March 2010. Strategies employed towards recruitment was examined and discussed with Steering Committee members. Due to poor recruitment, the decision was made to discontinue the study. Following is a summary of all activities used to address recruitment.

Between June 2009 and December 2009, a total of 45 sites were selected for study participation. 11 sites withdrew prior to site initiation. Of sites initiated, 11 sites withdrew prior to Ethical Review Committee (ERC) approval. Of all sites that were initiated, 12 sites recruitment at least 1 patient.

A total of 42 patients signed consent with 25 patients randomised.

Recruitment initiatives in selection and assistance of Investigators included:

- Direct phone contact to ~ 600 GPs
- Mailout to ~5500 GPs
- Contact with GP Divisions / GP Network Groups
- Contact with sanofi-aventis Pasteur
- Advertisement in GP Magazines & Divisions
- Review of alternative 'insulin initiation training' programs
- Provision of additional GP training for SoloStar pen
- Distribution of flyers to Investigator clinics
- Liaison with 10 Clinical Research Organisations who have GP network

Recruitment initiatives in patient recruitment included:

- Posters in GP waiting rooms
- Diabetes Information Brochure (aim to ease fear of needles/insulin)
- Provision of Patient Recall Letter
- Increased screening range for A1c
- Provision of study coordinators to review all T2D patients at each clinic
- Recruitment tools to help site staff (visit calculator, eligible patient tracking list, screening & randomisation worksheets, OAD max dose list, study pocket guide etc…)
- Provision of clinical papers on insulin initiation (e.g. How to inject insulin, **K**eep **I**t **S**imple for user**S** [KISS] paper)
- Provision of SoloStar Instruction brochures and NDSS brochures
- Continuation of 'Recruitment Drive' (min weekly contact with sites & regular visits)
- Minimum weekly contacts with Contract Research Organizations (CROs) [including provision of weekly reports]
- Regular teleconference discussions with Steering Committee members
- Distribution of monthly newsletters (including status update, note from Dr Graham [lead recruiter], helpful hints for informed consent / recruitment / needle phobia etc)
- Follow-up of 'Non-confident' GPs via GP Specialist Advice program

Reminder to sites to follow-up patients that have had recent OAD changes / slightly outside HbA1c range

Efficacy/pharmacodynamic results:

Not performed (with only 25 patients randomized to the study, it was not possible to answer any of the primary efficacy objectives).

Safety results:

Of the 25 patients enrolled into the study:

- 1 patient experienced 4 Adverse Events (AEs) [severe] prior to randomization & withdrew from the study.

- Of patients randomized to Insulin Glargine, 13 were non serious AEs; 1 was serious as it was related to other medically important event (squamous cell carcinoma of Trachea) and was unrelated to Insulin Glargine. There were no reports of Hypoglycaemia within this group.

- Of patients randomized to Standard of Care regimen, 16 non-serious AEs were reported, 1 was deemed related to therapy; the event was hypoglycaemia.

Below is a summary of AEs reported:

	Overall **N (%)** **N = 24**	**Insulin Glargine** **N (%)** **N = 12**	**Standard of Care** **N (%)** **N = 12**
Number of adverse events (AEs)	34 (100%)	14 (100%)	16 (100.0%)
non-serious	29 (85.3%)	13 (92.9%)	16 (100.0%)
serious	5 (14.7%)	1 (7.1%)	0 (0%)
treatment related	1 (2.94%)	0 (0%)	1 (6.3%)
mild intensity	19 (55.9%)	11 (78.6%)	8 (50.0%)
moderate intensity	11 (32.4%)	3 (21.4%)	8 (50.0%)
severe intensity	4 (11.8%)	0 (0%)	
Life threatening, hospitalization, other medical event	1 (2.9%)	0 (0%)	0 (0%)
Prolonged hospitalization	3 (8.8%)	0 (0%)	0 (0%)
Other medically important event	1 (2.9%)	1 (7.1%)	0 (0%)

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