# Clinical Study Report

## Study title: “Comparative investigation of efficacy and safety of Insulin glargine versus Metformin as first line drug in treatment of early Type 2 Diabetes (GLORY)”
## [Vergleichende Untersuchung zur Effizienz und Sicherheit von Insulin glargin versus Metformin als first line drug zur Behandlung des frühen Typ 2 Diabetes]

**Name of test drug/ investigational product:** Lantus (Insulin glargine) vs. Metformin

**Indication:** Type 2 diabetes

**Study design:** Randomized, prospective, open-label, active-controlled, two arm parallel study

**Sponsor:** GWT-TUD GmbH

**Protocol identification:** GWT-2008-1

**Development phase of study:** Phase 4

**Study initiation date:** 09.03.2009

**Study completion date:** 14.07.2011

**Responsible medical officer:** Prof. Markolf Hanefeld

**Name of company/sponsor signatory:** Dr. Carsta Köhler

**Date of report:** 23.12.2011

**The study was performed in compliance with Good Clinical Practices (GCP).**

# 1 Synopsis

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| Title of Study:<br>Comparative investigation of efficacy and safety of Insulin glargine versus Metformin as first line drug in treatment of early Type 2 Diabetes (GLORY)<br>Amendment 01: 16.03.2009<br>Amendment 02: 03.03.2010<br>All data refers to the study protocol from Amendment 02. |
| Sponsor:<br>GWT-TUD GmbH |
| Principal Investigator:<br>Prof. Markolf Hanefeld from the Center for Clinical Studies of the GWT-TUD GmbH in Dresden/Germany |
| Study center(s):<br>- Center for Clinical Study, GWT-TUD GmbH, Dresden – principal investigator: Prof. Markolf Hanefeld (site 1)<br>- Ikfe, Mainz – principal investigator: Prof. Thomas Forst (site 2)<br>- Diabetes Center Neuwied, Neuwied – principal investigator: Dr. Thomas Behnke (site 3)<br>- Group practice Becker-Preuße-Schaefer-Sanuri, Essen – principal investigator: Dr. Mazin Sanuri (site 4) |
| Studied period:<br>09.03.2009-14.07.2011 |
| Primary objective is Area Under the Curve (AUC) in mmol/l/time measured in the subcutaneous abdominal fat after a standardized test meal (TM) after 2 hours. AUC was measured via continous glucose monitoring system (CGMS). The TM was taken in as breakfast on the second day of CGM.<br>• AUC [mmol/l/time] 2h pp<br><br>Secondary objectives are:<br>• Protection of the b-cell via early insulin therapy<br>• Glycemic variability<br>• Antiinflammatory effect by insulin<br>• Effect on endothelial function<br>• Effect on renal function<br>• Risk of hypoglycemia<br>• Free fatty acids |
| Number of patients (planned and analyzed): 100 planned and 75 analyzed |
| Test product, dose and mode of administration:<br>Lantus (Insulin glargine), titration to target |
| Duration of treatment: 36 weeks |
| Reference therapy, dose and mode of administration, batch number:<br>Metformin; 1000 mg titrated to 2000 mg |
| Criteria for evaluation:<br>Efficacy:<br>• Change of AUC 2hpp after test meal (mean (SD)) |

- Protection beta cell function
- Effect on glycemic variability

Safety:

- Risk of hypoglycemia
- Change of weight, blood pressure and plasma glucose over all visits

Statistical methods:
All continuous parameters were tested for normal distribution by Kolmogorov-Smirnov-test. Non-normal distributed variables will be log-transformated. When no normal distribution was obtained, Mann-Whitney-U-test will be used instead of T-test. Paired T-test (first vs. last visit) for each treatment arm and T-test for independent samples at the time of last visit between the treatment arms. The analysis of the effect of study treatment on the primary endpoint is performed using an analysis of covariance (ANCOVA), considering the initial values for the AUC TM.

**EFFICACY RESULTS:**
Insulin glargine treatment resulted in a better interstitial glucose control compared to metformin. Insulin glargine also reduced postprandial interstitial glucose concentrations compared to the corresponding baseline values, however the reduction of the incremental AUC was identical between both treatments.
Furthermore we did not find significant differences of markers of glycemic variability between different treatments as demonstrated by MAGE or SD. In accordance with these interstitial measurements, insulin glargine treatment resulted in significantly lower fasting plasma glucose, whereas changes of postprandial plasma glucose 2 hr after ingestion of the test meal or HbA1c were not significantly different between both treatments.
Fasting proinsulin as marker of beta cell dysfunction could be reduced more pronounced in the glargine group. Fasting endogenous insulin secretion – assessed by c-peptide - could be reduced due to the bedtime insulin administration whereas the postprandial endogenous insulin secretion was preserved. Insulin glargine treatment resulted in a significantly greater change of the ratio between proinsulin and c-peptide. This finding indicates an improvement of postprandial beta cell function too.

**SAFETY RESULTS:**
Insulin treated patients gained weight and become more abdominally obese despite an intensive dietary counselling during the study;
Hypoglycemic events by patient self assessment defined as any symptomatic hypoglycaemia or blood glucose below 3.9 mmol/l during the study occurred more often in the glargine group; however there was only one symptomatic but not severe hypoglycaemia.
A comparison of the interstitial glucose values after 36 wk of did not reveal any differences of glucose concentrations below 3.9 mmol/l between metformin and Insulin glargine treated patients.

**CONCLUSION:**
In conclusion we demonstrated that Insulin glargine as first line treatment in type 2 diabetic patients provided a better interstitial glucose control and a better fasting plasma glucose control compared to the standard treatment with metformin. This improved glycemic control was associated with an improved beta cell function. Both treatments were well tolerated and Insulin glargine did not increase the risk of symptomatic hypoglycaemia but was associated with a significant weight gain which could be problematic during longer treatment. Of course we now need studies of longer duration to evaluate the clinical relevance of the observed improvement of glucose control for progression of type 2 diabetes.