SYNOPSIS

Compound(s): Lantus®/Insulin glargine

Registry Title:

TIP - Therapeutic benefits of patients on Insulin Glargine vs. NPH-Insulin being poorly controlled on prior short time basal-insulin supported therapy with NPH insulin or Insulin glargine

Registry number: LANTU_L_05713

Date first patient in (FPI): 01-Jul-2011

Date last patient out (LPO): 25-Jun-2013

Registry design: Open, non-controlled, non-interventional, multi-centric observational study of 24 weeks conducted in Germany

Report date: 24-Apr-2014 (13-Mrz-2014 first draft, 24-Mrz-2014 local approvement, 23-Apr-2014 regional approvement, 24-Apr-2014 global approvement)

This registry was performed in compliance with the guidelines for Good Epidemiology Practice. This report has been prepared based on the publication 'Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) – Guidelines for reporting observational studies – Ann Intern Med. 2007'.

Date: 24-Apr-2014 **Total number of pages: 17**

SYNOPSIS

Title of the registry:	TIP: Therapeutic benefits of patients on Insulin Glargine vs. NPH-Insulin being poorly controlled on prior short time basal-insulin supported therapy with NPH insulin or Insulin glargine – LANTU_L_05713
Design:	This was an open, non-controlled, non-interventional, multi-centric observational study of 24 weeks conducted in Germany, according to § 67,6 AMG.
Objectives:	This observational study had two main objectives: • Documentation of the therapy adjustment with a combination therapy consisting of OAD and Lantus® or NPH in regard to a better metabolic profile and lower hypoglycemic risk. The study was conducted during an approximately 24week long observation period according to the guidelines and documented under daily conditions. • Documentation of the satisfaction with the therapy using the ITEQ (insulin treatment experience questionnaire) in the beginning and at the end of the 24 week duration period.
Treatment:	Type 2 diabetes patients on basal supported oral therapy using insulin glargine (Lantus®) or NPH insulin.
Steering Committee:	N.N. N.N.
Publications (reference):	Not applicable.
Introduction - Background/rationale:	Due to its high prevalence, type II diabetes mellitus (T2DM) has become one of the most common diseases in the daily practice. It is therefore of an increasing concern for the health system [1]. In order to avoid the rising costs connected with diabetic concomitant diseases a sufficient antidiabetic therapy is required [2], [3]. Immediately after the diagnosis patients are recommended a basic therapy consisting of a course of instruction, diet and physical activity including an oral anti diabetic medication therapy with metformin. In case the HbA_{1c} value remains at 6.5% or higher within the first three to six months of therapy there are certain possibilities to intensify the therapy. In case the HbA_{1c} value persists at ≥ 7.5% an insulin therapy is recommended. If the HbA_{1c} value is < 7.5% it is also recommended that a second oral antidiabetic drug (OAD) or a GLP-1 analog is prescribed. In case the HbA_{1c} value still remains at 6.5% or higher within the next three to six months insulin is recommended in order to intensify the therapy [2]. During this phase of the disease the patients fasting blood glucose levels usually remain above 100 mg/dl or 5.6 mmol/l. This is due to the insufficient suppression of endogenous glucose production through endogenous insulin [4]. In order to compensate for the basic insulin deficiency a therapy with basal insulin is appropriate. The insulin is injected before bedtime and suppresses the glucose production during the night (so called basal insulin supported oral therapy, BOT) [5]. Unfortunately the insulin titration necessary to stabilize the fasting blood glucose levels is often not properly completed due to frequent hypoglycemia or fear of hypoglycemia [6]. Different clinical studies and meta- analyses showed that the long acting basal insulin Glargine (Lantus®) has a lower hypoglycemia risk combined with the same

	efficacy as NPH insulin [7]. The current TIP observational study was designed based on the implications mentioned above. Its goal was to document the guideline suited therapy adaptation under daily conditions of T2DM patients, who had started a therapy consisting of BOT with Insulin glargine (Lantus®) or NPH insulin within the past 3 to 6 months, and whose anti-hyperglycemic therapy was not yet properly adjusted ($HbA_{1c} \geq 7.5\%$). Since there are no current ambulatory health care data concerning the adaptation of the insulin dose in regard to avoiding hypoglycemia and achieving the aimed blood glucose level, it was of medical importance to collect such data.
Methodology:	**Site and patient selection**: In order to guarantee a valid statistical analysis approx. 4,200 patients had to be enrolled into this observational study. The aim of this study was to compare the rates of patients reaching FPG ≤ 120mg/dl without symptomatic hypoglycemia between Lantus® and NPH-Insulin treatment groups. The comparison is conducted for the total sample and for a matched sample (half the size of the total sample). A two group chi-square test with a 0.05 two-sided significance has 99% / 90% power to detect the difference between an expected response rate for Insulin glargine of 33% and an expected response rate for NPH-Insulin of 26% (odds ratio of 0.713) when the sample size in each treatment group is 1780 (total sample) / 890 (matched sample), i.e. (a total of 3560 / 1780 evaluable patients necessary). Assuming a non-evaluable rate of 15%, about 4188 patients had to be enrolled into the study. The response rates were concluded from the Treat-to-Target trail of Riddle MC et al. 2003. Approximately 1,000 centers (64,51% General practitioners and 35,23 % office based internal medics) - distributed nationwide - were asked to participate in this study. **Data collection:** Data were collected on a standardized paper case report form (CRF). The patients had to meet the following criteria in order to be documented in the study: • Type 2 diabetes mellitus, diabetes duration ≤ 10 years • Under treatment with BOT of NPH insulin or Lantus® at least during the last 3 to 6 months • $HbA_{1c} \geq 7,5\%$ • Age ≥ 18 years • Patient informed consent Not documented were patients with: • Cardio-vascular events in the past (myocardial infarction, stroke) • Anamnestic severe hypoglycemia (blood glucose ≤ 56 mg/dl or ≤ 3,1 mmol/l) • Therapy with GLP-1 agonists • Contraindication to the therapy with Lantus® or NPH insulin • Alcohol or drug abuse • Dementia or general incapability to understand the content of this observational study **Data management, validation:** The observational study was placed by Sanofi-Aventis Deutschland GmbH staff in accordance with the VFA recommendations [8] for the conduct of NIS. The centers were informed

	about the aims of the study, its background and the procedure. There was no stratification of the center according to the type of treatment. The staff and project management of Sanofi-Aventis Deutschland GmbH were available in case of queries. The centers sent the filled out case report form (CRF) to the NIS-management of Sanofi-Aventis. Through signing the contract the attending centers gave their consent to make all the data accessible to the pharmaceutical company for the purpose of quality control. Such on-site quality controls, in which data from the CRF were compared with the data in the patient files, were performed in 5,2% of the participating centers during the course of the observational study. The electronic data entry in a database and the analyses were performed by the CRO factum GmbH. The data entry was carried out by two persons. After completion of the data entry, both entries were compared automatically, differences were listed, the correct entry was verified with the CRF by a third independent person and corrected in the data base accordingly (data verification). **Statistical methods:** The statistical analysis of all collected data (sample size justification see above) was performed using descriptive measures. The biometrical analysis was carried out after determination of a statistical analysis plan being defined prior to database closure. To control imbalances in this not randomized observational study in predefined potential confounders at the beginning of the study, a propensity score matching was carried out for the effectiveness analyses. Statistical analyses were performed for the total sample and for the matched sample. **Variables and evaluation criteria:** Included patients were observed for approx. 24 weeks. Three-part documentation was scheduled for the observation: • Baseline visit (documentation 1) • Control visit after approx.12 weeks (documentation 2) • Control visit after approx.12 weeks after documentation 2 (documentation 3) The following parameters were collected: <u>Baseline</u> • General patient data and patient informed consent • Medical history of diabetes • Bogy height and body weight • HbA_{1c}, fasting blood glucose (FBG), 7-point blood glucose profile • Current anti-diabetic treatment (oral, insulin) • Patient questionnaire (ITEQ) • Blood glucose measuring characteristics <u>Documentation 2 after approx. 12 weeks</u> • Body weight • HbA_{1c}, fasting blood glucose (FBG), 7-point blood glucose profile • Current anti-diabetic treatment • Occurrence of new micro- or macrovascular complications

	• Confirmed hypoglycemias • Adverse events • Dosage adjustment (insulin) • Blood glucose measuring characteristics <u>Documentation 3 after further approx. 12 weeks</u> • Body weight • HbA_{1c}, fasting blood glucose (FBG), 7-point blood glucose profile • Current anti-diabetic treatment • Occurrence of new micro- or macrovascular complications • Confirmed hypoglycemias • Adverse events • Dosage adjustment (insulin) • Blood glucose measuring characteristics In case of change in anti-diabetic treatment: • New insulin treatment scheme (preparation, dose and frequency • Concomitant oral anti-diabetics • Reason for change in anti-diabetic treatment • Occurrence of new micro- or macrovascular complications • Blood glucose measuring characteristics **Primary and secondary evaluation criteria:** <u>Primary outcome</u> Number of patients with FBG ≤ 120 mg/dl and number of patients with FBG ≤ 120 mg/dl or HbA_{1c} ≤ 7.0% at endpoint and without occurrence of symptomatic hypoglycemias during treatment with Lantus® or NPH insulin (clinical benefit I and II). The clinical benefit I was defined as the documented FBG value was ≤ 120 mg/dl at last visit and no symptomatic hypoglycemia was documented during observation period. The clinical benefit II was definded as the documented FBG value was ≤ 120 mg/dl or the HbA1c value was ≤ 7.0% at last visit and no symptomatic hypoglycemia was documented during observation period. <u>Secondary outcomes</u> • Incidence of confirmed hypoglycemias (BG value ≤ 70 mg/dl), severe hypoglycemia's (< 56 mg/dl) and nocturnal hypoglycemia's. • Change in body weight from baseline to endpoint. • Change in HbA_{1c} and FBG from baseline to endpoint. • Treatment satisfaction and quality of life (ITEQ). • Change in daily insulin dose from start of insulin treatment to endpoint including frequency of dose adjustments. • Incidence of micro- and macrovascular complications. • Frequency of change in insulin therapy and reasons for change.

	Safety parameter • Frequencies of adverse events during treatment with Lantus® (abs./rel.) or Insuman® basal (abs.). **Data analyses:** The analyses concerning description of patients, treatment, effectiveness and lab values (see chapter 5.6 Outcome parameters) were carried out for two (primary) populations: • EAS (Effectiveness analysis set): total sample: The complete population of all included and treated patients with evaluable data. • EAS: PSM (Propensity score matching patients): The "matched" population resulting from a propensity score matching of the EAS. Continuous data were described by mean, standard deviation, median, minimum, maximum, 25th and 75th percentile. Categorical data were described using absolute and relative frequencies. If continuous parameters were collected at several times (longitudinal data), for each time-point base statistics were calculated including absolute differences between the values measured at the respective time-point and at baseline. For value pairs with one missing entry no substitution was carried out (e.g. according to the last-observation-carried-forward-method). Only the patients with complete value pairs were considered in the analysis (available case analysis), resulting in different sample sizes in the analysis of the longitudinal data. The results are presented per treatment group (Lantus®, NPH insulin) and for all patients (total EAS). **Analyses of safety:** Adverse events (AE) were supposed to be documented only if they occurred under a Sanofi-Aventis medication (Lantus® or Insuman® Basal). In case the AE occurred under a medication from a different manufacturer, it was reported to either the Drug Commission of the German Physician's Board (AKdÄ), the Federal Institute for Drugs and Medical Products (BfArM) or to the manufacturer. Thus a group comparison concerning the safety data between the Lantus® and NPH groups is not possible. Furthermore due to the fact that only the total number of patients who were treated with NPH was known, and not the total number of patients who were treated with Insuman® Basal, only the absolute frequencies will be stated, and not the empirical probability. The safety analyses were carried out for three samples: • Disposition to Lantus®: Patients who received at least once Lantus® during observation period, irrespective of whether insulin they received at start of observation. • Patients with AE under treatment with Insuman® basal. • Patients with ADR under treatment with Insuman® basal.
RESULTS	
Participants (actual):	**Patients:** A total of 2,629 CRFs were available for this non-interventional study. Only 2,629 CRFs of planned 4200 were available due to a good control of BOT treated patients after at least 3-6 month treatment (HbA1c below 7.5%). With 2629 evaluable patients (about 1314 in each group) and

	with the same assumptions as planned, the power would have been still 97% for the total sample and 79% for the matched sample. According to the objectives of this non-interventional study patients were included in the analysis of effectiveness only if the selection criteria were met. For 698 out of a total of 2,629 patients at least one selection criteria was not met (Mostly 11% longer diabetes duration, 11% lower HbA1c, 7% insulin usage shorter than 3-6 month) . Thus, the analysis of the remaining parameters such as patient data, treatment data and effectiveness parameters is based on a sample size of N = 1,931 (effectiveness analysis set; total sample). At baseline a total of 1,614 patients received a basal supported oral therapy with Lantus® (Lantus® group) and only 303 patients received NPH insulin as part of BOT at baseline (NPH group). Due to the unbalanced distribution between Lantus® group (N = 1,614) and the NPH insulin group (N = 303) in the total sample, the theoretical maximum of the PSM sample was only 2 x 303 patients. Actually, 285 statistical twin pairs were found through the method of propensity score matching. The inbalance between usage of Lantus or NPH-Insulin for BOT is representive according of nationwide market share for this treatment option. The safety analysis set based on all available 2,629 CRFs. A total of 2,387 patients receiving at least one dose of Lantus® dose during the observation and 242 patients receiving solely other basal insulins were included in the safety analysis. (Some patients switched from Lantus to NPH and many patients switched from NPH to Lantus during the observation period). Adverse events were supposed to be documented only if they occurred under a Sanofi-Aventis medication. **Centers:** Actual a total of 534 centers took part in this non-interventional study. The mean number of patients treated per center was 4.9. Most of the patients were treated by general practitioners (61.01%) and internists (34.80%). Only 3.50% were treated by practitioners without specialization and 0.53% by physicians with two specializations (internal and general medicine). For 0.15% of the patients the specialization was unknown.
Participant characteristics	**Demographics** **EAS - total sample:** The male-female distribution was 52.35% / 47.15% in the Lantus® group and 53.80% / 45.54% in the NPH insulin group. The age (mean ± SD) was 64.4 ± 10.7 years in the Lantus® group and 64.2 ± 11.0 years in the NPH insulin group. The mean body mass index (BMI) was 30.82 ± 5.30 (SD) kg/m² in the Lantus® group and 30.73 ± 4.76 (SD) kg/m² in the NPH insulin group. **EAS - PSM patients:** The male-female distribution was 52.63% / 47.37% in the Lantus® group and 54.39% / 45.61% in the NPH insulin group. The age (mean ± SD) was 63.7 ± 11.2 years in the Lantus® group and 64.4 ± 10.7 years in the NPH insulin group. The mean BMI was 31.12 ± 6.02 (SD) kg/m² in the Lantus® group and 30.80 ± 4.76 (SD) kg/m² for in the NPH insulin group. **Diagnosis** All patients suffered from type 2 diabetes mellitus. **EAS - total sample:** The mean diabetes duration was 5.31 ± 2.76 (SD) years in the Lantus® group and 5.24 ± 2.65 (SD) years in the NPH insulin group. For both groups the most frequently mentioned diabetic

	complications and comorbidities were diabetic neuropathy (Lantus® group: 22.55% / NPH group: 21.45%), microalbuminuria (22.30% / 27.06%) and coronary heart disease (15.55% / 13.20%). **EAS - PSM patients:** The mean diabetes duration was 5.47 ± 2.56 (SD) years in the Lantus® group and 5.28 ± 2.62 (SD) years in the NPH insulin group. For both groups the most frequently mentioned diabetic complications and comorbidities were diabetic neuropathy (Lantus® group: 23.51% / NPH group: 20.70%), microalbuminuria (17.89% / 27.37%) and coronary heart disease (14.74% / 12.98%). **Treatment** **EAS - total sample:** The start of the insulin treatment was markedly earlier in the NPH group comparing to Lantus® group. In the Lantus® group insulin treatment was initiated (mean ± SD) 22.27 ± 49.78 weeks before baseline (N = 1,406), whereas in the NPH insulin group insulin treatment started 47.70 ± 89.24 (mean ± SD) weeks before baseline (N = 275). In both groups (Lantus®, NPH insulin), patients received basal insulin mostly once per day and mainly at evening or at bedtime. During observation the proportion of Lantus® patients who injected their insulin once daily decreased from 91.95% (baseline) to 84.26% (24-week visit). An opposite trend was observed in the NPH insulin group: the proportion of patients who injected their insulin once daily increased from 63.37% (baseline) to 76.57% (24-week visit). The daily insulin dose (mean ± SD) at baseline was 16.89 ± 10.07 units in the Lantus® group (N = 1,585) and 22.33 ± 14.02 units in the NPH group (N = 300). In both groups the insulin dose was increased during observation. At 24-week visit the daily insulin dose (mean ± SD) was 25.22 ± 11.82 units in the Lantus® group (N = 1,503) and 27.97 ± 14.76 units in the NPH insulin group (N = 285). The vast majority of patients received metformin as an oral antidiabetic drug in an oral monotherapy or in combination. At baseline, metformin was prescribed to 88.85% of the patients in the Lantus® group and to 91.75% in the NPH insulin group. Further commonly prescribed OADs were DPP IV-inhibitors (Lantus® group 26.08% / NPH insulin group 18.81%) and sulfonylureas (19.70% / 14.52%). **EAS - PSM patients:** The start of the insulin treatment was markedly earlier in the NPH group comparing to Lantus® group. In the Lantus® group insulin treatment was initiated (mean ± SD) 23.86 ± 46.72 weeks before baseline (N = 256), whereas in the NPH insulin group insulin treatment started 47.68 ± 89.71 (mean ± SD) weeks before baseline (N = 268). In both groups (Lantus®, NPH insulin), patients received basal insulin mostly once per day and mainly at evening or at bedtime. During observation the proportion of Lantus® patients who injected their insulin once daily decreased from 90.88% (baseline) to 85.26% (24-week visit). An opposite trend was observed in the NPH insulin group: the proportion of patients who injected their insulin once daily increased from 63.16% (baseline) to 76.84% (24-week visit). The daily insulin dose (mean ± SD) at baseline was 17.02 ± 11.54 units in the Lantus® group (N = 281) and 22.57 ± 14.05 units in the NPH group (N = 283). In both groups the insulin dose was increased during observation. At 24-week visit the daily insulin dose (mean ± SD) was 24.92 ± 12.04 units in the Lantus® group (N = 269) and 28.11 ± 14.78 units in the NPH insulin group (N = 268).

	As in the total sample, the vast majority of the PSM patients received metformin as an oral antidiabetic drug in an oral monotherapy or in combination. At baseline, metformin was prescribed to 89.47% of the patients in the Lantus® group and to 91.23% in the NPH insulin group. Further commonly prescribed OADs were sulfonylureas (18.25% / 13.68%) and DPP IV-inhibitors (17.54% / 18.60%). **Continuation / change of antidiabetic therapy** **EAS - total sample:** Most of the patients in the Lantus® group continued their BOT with Lantus® during the observation period (95.29%). Only 0.68% of the patients switched from Lantus® to NPH insulin within the BOT and 3.53% changed to a different antidiabetic therapy (no data: 0.50%). In the NPH insulin group only 42.24% of the patients continued their BOT with NPH insulin up to 24-week visit, but 52.81% of the patients switched from NPH insulin to Lantus®. Additionnaly 4.95% of the NPH insulin patients changed to a different antidiabetic therapy. In both treatment groups the most given reason for change of the basal insulin was "insufficient blood glucose modulation" (Lantus® group: 83.33% of those who changed insulin; NPH insulin group: 92.59%). Adverse events did not lead to a switch in the Lantus® group and was a rarely mentioned reason in the NPH insulin group (1.85%). **EAS – PSM patients:** Most of the patients in the Lantus® group continued their BOT with Lantus® during the observation period (95.79%). Only 1.40% of the patients switched from Lantus® to NPH insulin within the BOT and 2.46% changed to a different antidiabetic therapy (no data: 0.35%). In the NPH insulin group only 40.70% of the patients continued their BOT with NPH insulin up to 24-week visit, but 54.39% of the patients switched from NPH insulin to Lantus®. Additionaly 4.91% of the NPH insulin patients changed to a different antidiabetic therapy. In both treatment groups the most given reason for change of the basal insulin was "insufficient blood glucose modulation" (Lantus® group: 75.00%; NPH insulin group: 92.99%). Adverse events did not lead to a switch in the Lantus® group and was a rarely mentioned reason in the NPH insulin group (1.91%).
Primary analyses:	Two definitions have been applied for the **clinical benefit**: **Clinical benefit I**: The documented FBG value was ≤ 120 mg/dl at last visit and no symptomatic hypoglycemia was documented during observation period. **Clinical benefit II**: The documented FBG value was ≤ 120 mg/dl or the HbA1c value was ≤ 7.0% at last visit and no symptomatic hypoglycemia was documented during observation period. For the total sample 1,380 out of 1,614 patients of the Lantus® group and a total of 279 out of 303 patients of the NPH insulin group could be considered in the analysis of the clinical benefit I and II. The corresponding sample sizes for the matched patients group were 245 out of 285 patients (Lantus®) and 266 out of 285 patients (NPH insulin). **Clinical benefit I (FBG ≤ 120 mg/dl and no hypoglycemia)** **EAS – total sample:** For 41.52% out of 1,380 Lantus® patients the last documented FBG value was ≤ 120 mg/dl. In all, 93.70% of the Lantus® patients had no symptomatic hypoglycemia during the observation. A clinical benefit (I) was achieved in 38.04% of the Lantus® patients.

	For 43.73% out of 279 NPH insulin patients the last documented FBG value was ≤ 120 mg/dl and 80.29% had no symptomatic hypoglycemia during the observation. A clinical benefit (I) could be observed in 33.33% of the NPH patients. With this number the statistical power was only 31%. For patients with valid data (Lantus®: N =1,358; NPH insulin: N = 276) the clinical benefit (I) response was 38.66% vs. 33.70% (Odds ratio: 1.24, 95%-CI: 0.94 – 1.63). **EAS – PSM patients:** For 44.08% out of 245 Lantus® patients the last documented FBG value was ≤ 120 mg/dl. In all, 92.65% of the Lantus® patients had no symptomatic hypoglycemia during the observation. A clinical benefit (I) was achieved in 38.78% of the Lantus® patients. For 44.36% out of 266 NPH insulin patients the last documented FBG value was ≤ 120 mg/dl and 80.08% had no symptomatic hypoglycemia during the observation. A clinical benefit (I) could be observed in 33.83% of the NPH patients. For patients with valid data (Lantus®: N = 240; NPH insulin: N = 263) the clinical benefit (I) response was 39.58% vs. 34.22% (Odds ratio: 1.26, 95%-CI: 0.88 – 1.81). The probability of achieving a FBG value ≤ 120 mg/dl without symptomatic hypoglycemic events was highest in the Lantus® group compared to the NPH group. **Clinical benefit II (FBG ≤ 120 mg/dl or HbA_{1c} ≤ 7.0% and no hypoglycemia)** **EAS – total sample:** For 55.00% out of 1,380 Lantus® patients the last documented FBG value was ≤ 120 mg/dl or the last documented HbA1c value was ≤ 7.0%. A clinical benefit (II) was achieved in 50.58% of the Lantus® patients. For 56.99% out of 279 NPH insulin patients the last documented FBG or HbA1c value was within the specified limits (≤ 120 mg/dl or ≤ 7.0%, respectively). A clinical benefit (II) could be observed in 42.65% of the NPH patients. For patients with valid data (Lantus®: N =1,368; NPH insulin: N = 277) the clinical benefit (II) response was 51.02% vs. 42.96% (Odds ratio: 1.38, 95%-CI: 1.07 – 1.79). **EAS – PSM patients:** For 53.06% out of 245 Lantus® patients the last documented FBG value was ≤ 120 mg/dl or the last documented HbA_{1c} value was ≤ 7.0%. A clinical benefit (II) was achieved in 47.35% of the The probability of achieving a FBG value ≤ 120 mg/dl or an HbA1c value ≤ 7.0 without symptomatic hypoglycemic events was highest in the Lantus® group compared to the NPH group. For patients with valid data (Lantus®: N =1,368; NPH insulin: N = 277) the clinical benefit (II) response was 51.02% vs. 42.96% (Odds ratio: 1.38, 95%-CI: 1.07 – 1.79). Lantus® patients. For 57.52% out of 266 NPH insulin patients the last documented FBG or HbA_{1c} value was within the specified limit (≤ 120 mg/dl or ≤ 7.0%, respectively). A clinical benefit (II) could be observed in 43.23% of the NPH patients. For patients with valid data (Lantus®: N = 243; NPH insulin: N = 264) the

	clinical benefit (II) response was 47.74% vs. 43.56% (Odds ratio: 1.18, 95%-CI: 0.83 – 1.68). The probability of achieving a FBG value ≤ 120 mg/dl or an HbA_{1c} value ≤ 7.0 without symptomatic hypoglycemic events was highest in the Lantus® group compared to the NPH group.
Secondary analyses:	**Incidence of hypoglycemias** **EAS – total sample:** In the total sample of the EAS symptomatic hypoglycemias (< 70 mg/dl) occurred in 6.01% of the Lantus® patients and in 18.81% of the NPH insulin patients. In 1.61% of the Lantus® patients and in 10.23% of the NPH patients the hypoglycemia occurred at night-time. Severe hypoglycemias (BG ≤ 56 mg/dl) occurred in 0.31% of the Lantus® patients and in 1.98% of the NPH insulin patients. In 0.19% of the Lantus® patients and in 0.66% of the NPH patients the severe hypoglycemias occurred at night-time. **EAS – PSM patients:** For the matched patients symptomatic hypoglycemias occurred in 7.37% of the Lantus® patients and in 19.30% of the NPH insulin patients. In 1.40% of the Lantus® patients and in 10.53% of the NPH patients the hypoglycemias occurred at night-time. Severe hypoglycemia (BG ≤ 56 mg/dl) occurred only in one (0.35%) of the Lantus® patients and in 2.11% (N = 6) of the NPH insulin patients. One severe night-time hypoglycemia occurred in one (0.35%) of the Lantus® patients. Severe night-time hypoglycemias were present in 0.70% (N = 2) of the NPH insulin patients. **Change in body weight** **EAS – total sample:** In both treatment groups a slight decrease in body weight was observed. In the Lantus® group the mean body weight decreased from 89.31 kg (baseline) to 88.66 kg (24-week visit; based on N = 1,568), corresponding to a mean change of -0.65 ± 4.23 (SD) kg. In the NPH insulin group the mean body weight decreased from 89.12 kg (baseline) to 88.01 kg (24-week visit; based on N = 288), corresponding to a mean change of -1.11 ± 3.69 (SD) kg. **EAS – PSM patients:** In both treatment groups a slight decrease in body weight was observed. In the Lantus® group the mean body weight decreased from 90.17 kg (baseline) to 89.34 kg (24-week visit; based on N = 279), corresponding to a mean change of -0.83 ± 3.72 (SD) kg. In the NPH insulin group the mean body weight decreased from 89.40 kg (baseline) to 88.30 kg (24-week visit; based on N = 272), corresponding to a mean change of -1.10 ± 3.61 (SD) kg. **Change in HbA_{1c} and FBG** **EAS – total sample:** For the Lantus® group the mean HbA_{1c} decreased from 8.50% (baseline) to 7.38% (last visit), corresponding to a mean change of -1.13% ± 1.14% (N = 1,524). For the NPH insulin group the mean HbA_{1c} decreased from 8.46% to 7.40%, corresponding to a mean change of -1.06% ± 0.92% (N = 285). For the Lantus® group the mean FBG decreased from 167.27 mg/dl (baseline) to 130.41 mg/dl (last visit), corresponding to a mean change of -36.86 ± 51.39 mg/dl (N = 1,538). For the NPH insulin group the mean FBG decreased from 172.02 mg/dl to 128.00 mg/dl, corresponding to a mean change of -44.02 ± 50.99 mg/dl (N = 291). **EAS – PSM patients:** For the Lantus® group the mean HbA_{1c} decreased from 8.54% (baseline) to 7.37% (last visit), corresponding to a mean change

	of -1.18% ± 1.10% (N = 270). For the NPH insulin group the mean HbA_{1c} decreased from 8.46% to 7.39%, corresponding to a mean change of -1.07% ± 0.93% (N = 274). For the Lantus® group the mean FBG decreased from 171.10 mg/dl (baseline) to 127.84 mg/dl (last visit), corresponding to a mean change of -43.25 ± 56.87 mg/dl (N = 271). For the NPH insulin group the mean FBG decreased from 172.46 mg/dl to 127.54 mg/dl, corresponding to a mean change of -44.92 ± 51.66 mg/dl (N = 278). **ITEQ: baseline vs. end of observation** At the end of observation the patients were more satisfied with the actual diabetes treatment comparing to the treatment at baseline. In both treatment groups the ITEQ scores increased in all domains. **EAS – total sample:** For the Lantus® group the mean score for the "overall treatment satisfaction" increased from 70.64 ± 20.10 (SD) at baseline to 80.32 ± 16.69 at 24-week visit, corresponding to a mean change of 9.68 ± 20.27 (N = 1,354). The mean "total score" increased from 65.94 ± 17.35 (SD) to 73.49 ± 14.64, corresponding to a mean change of 7.56 ± 13.55 (N = 1,382). For the NPH insulin group the mean score for the "overall treatment satisfaction" increased from 63.16 ± 22.48 (SD) at baseline to 80.55 ± 17.23 at 24-week visit, corresponding to a mean change of 17.39 ± 22.69 (N = 266). The mean "total score" increased from 60.11 ± 17.32 (SD) to 72.03 ± 13.77, corresponding to a mean change of 11.92 ± 15.61 (N = 258). **EAS – PSM patients:** For the Lantus® group the mean score for the "overall treatment satisfaction" increased from 70.42 ± 20.06 (SD) at baseline to 80.42 ± 15.74 at 24-week visit, corresponding to a mean change of 10.00 ± 17.98 (N = 240). The mean "total score" increased from 65.34 ± 15.76 (SD) to 73.94 ± 14.27, corresponding to a mean change of 8.60 ± 13.38 (N = 240). For the NPH insulin group the mean score for the "overall treatment satisfaction" increased from 63.94 ± 22.36 (SD) at baseline to 81.18 ± 16.02 at 24-week visit, corresponding to a mean change of 17.23 ± 22.12 (N = 251). The mean "total score" increased from 60.33 ± 17.25 (SD) to 72.13 ± 13.92, corresponding to a mean change of 11.80 ± 14.92 (N = 244). **ITEQ: Lantus® vs. NPH insulin** **EAS – total sample:** The mean "total score" was 73.45 ± 14.60 (SD) in the Lantus® group and 71.94 ± 13.97 (SD) in the NPH insulin group. The highest mean score was obtained in the domain leisure activities (81.08 / 78.38) and the lowest mean score was calculated for the domain weight control (62.25 / 61.62). In an effort to provide standard estimates of the difference between both treatment groups the effect sizes were calculated using Cohen's d. In the total sample at least a small effect size (d = 0.2) was observed for the domain leisure activities (d = 0.15; p = 0.002) and for sleep (d = 0.21; p = 0.003). **EAS – PSM patients:** The mean "total score" was 74.13 ± 14.04 (SD) in the Lantus® group and 72.06 ± 14.15 (SD) in the NPH insulin group. The highest mean score was obtained in the domain leisure activities (82.00 / 78.28) and the lowest mean score was calculated for the domain weight

	control (61.95 / 61.98). In the total sample at least a small effect size (Cohen's d = 0.2) was observed for sleep (d = 0.26; p = 0.004), leisure activities (d = 0.21; p = 0.004) and for the total score (d = 0.15; p = 0.049). **Micro- and macrovascular complications** **EAS – total sample:** In the total sample new micro- or macrovascular complications during observation were observed for 1.92% in the Lantus® group and for 2.31% in the NPH insulin group. **EAS – PSM patients:** For the matched patients new micro- or macrovascular complications during observation were observed for 1.40% in the Lantus® group and for 2.46% in the NPH insulin group.
Other analyses:	**Adverse events and adverse drug reactions** **Lantus®:** A total of 90 adverse events (AE) occurred in 69 patients (2.89%) of the 2 387 Lantus® patients of the safety sample. In 7 patients (0.29%) with a total of 8 events a causal relationship to Lantus® could not be excluded. The most frequently reported AEs were hypoglycemia (0.54%, n = 13), diabetic neuropathy (0.38%, n = 9), microalbuminuria (0.34%, n = 8) and diabetic nephropathy (0.21%, n = 5). Reported ADRs were hypoglycemia (0.25%, n =6), albuminuria and increased appetite (0.04%, n = 1 for each). Two of the 2,387 Lantus® patients died during this non-interventional study. For both patients a causal relationship with Lantus® was excluded. The corresponding cases are described in detail in chapter 6.8.1. **Insuman® basal:** Only the absolute frequencies can be presented for the events which occurred during the Insuman® basal treatment: Overall, 11 AE occurred in 7 patients and for 4 events concerning 2 patients a causal relationship to Insuman® basal was to be suspected (ADR). Hypoglycemia was the most mentioned AE (n = 5) and ADR (n = 2). Serious AEs were observed for 3 patients, whereas none of the observed ADRs were serious. No deaths were reported for patients treated with Insuman® basal.
Discussions:	This non interventional study saught to answer the question whether the use of insulin glargine (Lantus®) contributes to a better metabolic profile with a lower hypoglycemic risk in comparison to NPH insulin. Only 2,629 CRFs of planned 4200 were available doe to a good control of BOT treated patients after at least 3-6 month treatment (HbA1c below 7.5%). Non interventional studies are implicitly non randomized observational studies. The choice of the patients and their therapy is made by the physician. Due to that the distribution of factors which can influence the results (confounder) can be unbalanced throughout the treatment groups and the measured differences in the effect variables can not necessarily be connected to the different treatments. In order to test the robustness of the results in the total sample, predefined potentially uneven distributed variables (gender, age, OAD treatment, baseline HbA_{1c}, diabetes duration and BMI) were controlled in the matched population using the propensity score matching method (PSM patients). Concerning the blood glucose control no clinically significant differences were shown. At the last visit the HbA_{1c} value in the Lantus® group was 7.37% and in the NPH insulin group 7.39%. The FBG values were 127.84 mg/dl and 127.54 mg/dl, respectively (EAS-PSM patients). Significant differences in the frequencies of hypoglycemia were found in the total sample as well as in the matched population. The hypoglycemia rate in the NPH insulin group was markedly higher during the 24-week

	observational period in comparison with the Lantus® group (EAS-PSM patients: 19.30% vs. 7.37%). Even though severe hypoglycemia occurred seldom in both groups, the rate hypoglycemia rate was lower in the Lantus® group. The primary outcome (clinical benefit I and II) was achieved in the Lantus® group more often as in the NPH insulin group (Odds ratios between 1.18 and 1.26). The treatment satisfaction, which was measured with the ITEQ questionnaire, was slightly better in the Lantus® group in comparison with the NPH insulin group. A small effect size (Cohen's d = 0.2) was observed only in the domains leisure activities and sleep. It is possible that these minor differences are the result of a lower therapy adherence in the NPH insulin group. More than a half of the patients from the NPH group (total sample) switched to a BOT with Lantus® due to an insufficient blood glucose modulation during the observation period. This means that a considerable part of the patients of the NPH group evaluated their treatment satisfaction under a Lantus® treatment at end of observation.
Conclusions:	In the present non-interventional study, conducted in Germany, the diabetes control in T2DM patients with Lantus® and NPH insulin was compared as a part of basal supported oral treatment (BOT) under daily practice conditions. The response rates for the clinical benefit I (documented FBG value ≤ 120 mg/dl at last visit and no symptomatic hypoglycemia was documented during observation period) and for the clinical benefit II (documented FBG value ≤ 120 mg/dl or the HbA1c value ≤ 7.0% at last visit and no symptomatic hypoglycemia was documented during observation period) were higher for the Lantus patients for the total sample and for the matched sample. In addition the Lantus® patients show lower incidence of hypoglycemic events which is in line with the results of different clinical studies [1], [2], [3]. **Benefit-risk-profile:** The results of this routine evaluation have no new evidence that could change the assessment of the benefit-risk-profile of Lantus®.
Date of report:	**Fehler! Verweisquelle konnte nicht gefunden werden.** .

1 ABBREVIATIONS

ADR	Adverse drug reaction
AE	Adverse events
AMG	German Medical Act (Arzneimittelgesetz)
BG	Blood glucose
BMI	Body mass index
BOT	Basal supported oral therapy
CI	Confidence interval
CRF	Case report form
CRO	Contract Research Organization
EAS	Effectiveness analysis set
EASD	European Association for the Study of Diabetes
ESC	European Society of Cardiology
FBG	Fasting blood glucose
FPI	First patient in
IC	Informed consent
ICF	Informed consent form
ITEQ	Insulin treatment experience questionnaire
LPO	Last patient out
NIS	Non-interventional study
NPH	Neutral Protamine Hagedorn
OAD	Oral antidiabetic drug

OR	Odds Ratio
PAOD	Peripheral arterial occlusive disease
PSM	Propensity score matching
SAP	Statistical Analysis Plan
SAS	Safety analysis set
SD	Standard deviation
TIA	Transitory ischemic attack
T2DM	Type 2 diabetes mellitus
UKPDS	United Kingdom Prospective Diabetes Study
VFA	German Association of Research-based Pharmaceutical Companies (Verband forschender Arzneimittelhersteller)
YR(S)	Year(s)

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