PRODUCT REGISTRY REPORT

Title: Non-interventional, open, *P*rospective observ*A*tional study to obse*R*ve efficacy and *T*olerability of a basal-bolus therapy regime*N* in type 2 diabetes subjects pretreated eith*ER* with Lantus® in a BOT regimen or with Apidra® at meal times

PARTNER Observational Study

Original Title: Nicht-interventionelle, *P*rospektive Beob*A*chtungsstudie zur Wi*R*ksamkeit und Verträglichkeit einer Basal-Bolus-*T*herapie bei Patienten mit Typ 2-Diabetes mellitus u*N*ter einer Vorth*ER*apie mit Lantus® in der BOT oder Apidra® zu den Mahlzeiten

PARTNER-Beobachtungsstudie

Study code: PARTNER (LANTU_L_04724)

Date first patient in (FPI): 17-Jan-2011 (Apidra®) and 03-Jan-2011 (Lantus®)

Registry completion date: 08-Mar-2013 (date of last CRF received)

Report Date: 08-Jan-2014 (Update of version 0.3 (27-Nov-2013); 03-Dec-2013 local approval, 11-Dec-2013 regional approval, 08-Jan-2014 global approval)

This study 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: 08-Jan-2014 Total number of pages: 13

SUMMARY

Title of the registry:	Original title: Nicht-interventionelle, *P*rospektive Beob*A*chtungsstudie zur Wi*R*ksamkeit und Verträglichkeit einer Basal-Bolus-*T*herapie bei Patienten mit Typ 2-Diabetes mellitus u*N*ter einer Vorth*ER*apie mit Lantus® in der BOT[1] oder Apidra® zu den Mahlzeiten PARTNER-Beobachtungsstudie Non-interventional, open, *P*rospective observ*A*tional study to obse*R*ve efficacy and *T*olerability of a basal-bolus therapy regime*N* in type 2 diabetes subjects pre-treated eith*ER* with Lantus® in a BOT regimen or with Apidra® at meal times PARTNER Observational Study
Design:	Non-interventional study (NIS), multicenter observational study according to § 67 (6) German Drug Law (AMG)
Objectives:	a) Documentation of changes in HbA_{1c} following intensification of insulin therapy in routine clinical practice during approximately 12 and 24 weeks of observation. Patients were pretreated either with Lantus® in a basal insulin-supported oral therapy regimen (BOT; "intensified Lantus® BOT group" (= Lantus® group)) OR with Apidra® in a prandial supplementary insulin therapy (SIT; "intensified Apidra® prandial group" (= Apidra® group)). Intensification was either with a shofrt-acting insulin analogue (at least 3-times daily (TID); = Lantus® group) OR with a basal insulin (= Apidra® group). b) Documentation of therapy effects for type 2 diabetes (T2DM) patients under conditions of routine clinical practice - including tolerability and adverse events - during approximately 12- and 24-week observation periods, when insulin therapy was intensified to a basal-bolus therapy regimen.
Treatment:	Observation over periods of approximately 12 and 24 weeks of type 2 diabetes patients with poor glycemic control as assessed by HbA_{1c}, after intensification of their insulin treatment regimen. EITHER - Lantus® BOT regimen intensified to a basal-bolus insulin regimen by adding a rapid acting insulin analogue (at least TID) OR - Apidra® SIT (at least TID) intensified to a basal-bolus insulin regimen by adding a long acting basal insulin. Only routine therapeutic data were documented. It was the sole decision of the investigator to intensify the BOT or SIT regimen to a basal-bolus insulin regimen.
Participants as of 08 Mar 2013 last CRF received:	A maximum of 2,700 patients were planned to be documented, 1,350 within the Lantus® group and 1,350 within the Apidra® group. These were to be recruited by approx. 450 centers specializing in diabetes mellitus (diabetologists; ≤6 patients per center; 3 in each treatment group) all over Germany. Patients had to be on insulin glargine (Lantus®) in a BOT regimen or on insulin glulisine (Apidra®) in an SIT regimen. A total of 1,530 patients screened were documented from 258 German centers. 1,490 (97.4%) patients fulfilled all inclusion criteria, but 40 patients (2.6%) did not.

[1] Basalunterstützte orale Therapie, basal insulin-supported oral therapy

	Inclusion criteria: • T2DM patients aged ≥18 years receiving insulin therapy for at least 3 months, either as a BOT regimen with Lantus® or as an SIT regimen with Apidra® TID • HbA_{1c} ≥6.5% • No known malignant disease in medical history • Ability to perform self-monitored blood glucose assessment • Use of the injection devices SoloStar®, ClikStar® or TactiPen®, respectively • Informed consent Exclusion criteria: • Contraindication for a therapy with Lantus® or Aprida® • Known alcohol or drug abuse • Dementia or general incapability to comprehend the content of this observational study
Scientific lead and study group:	Scientific lead: Dr. med. Berndt von Stritzky Sanofi-Aventis Deutschland GmbH Potsdamer Str. 8 10785 Berlin Phone: +49(0)30-2575-2529 Project leader: Miriam Fehr Clinical Study Unit Sanofi-Aventis Deutschland GmbH Potsdamer Str. 8 10785 Berlin Phone: +49(0)30-2575-2257 Fax: +49(0)30-2575-2518 Karlheinz Theobald Biostatistics & Epidemiologoy/EbM & Health Economy Sanofi-Aventis Deutschland GmbH Industriepark Höchst, K 703 65926 Frankfurt am Main Phone: +49(0)69-305-3861 Fax: +49(0)69-305-17963 Contract Research Organisation: CSG Clinische Studien Gesellschaft mbH Friedrichstr. 180 10117 Berlin Phone: +49(0)30-230809-20 Fax: +49(0)30-230809-22 NIS Management: Martina John Clinical Study Unit Sanofi-Aventis Deutschland GmbH Industriepark Höchst, H 831 65926 Frankfurt am Main Phone: +49(0)69-305-80746

	Fax: +49(0)69-305-25730
Publications (reference):	Not applicable, but a future publication is planned.
Introduction - Background/rationale:	As T2DM is a chronic progressive disease, antidiabetic drugs need to be continuously adapted, depending on the patient's metabolic status, in order to impede long-term complications [1, 2]. Therefore, in patients with advanced T2DM and HbA_{1c} ≥6.5% after insulin pretreatment for 3–6 months (BOT or SIT), insulin therapy should be intensified. The 10-years follow-up data of the UKPD study as well as a meta-analysis on the impact of anti-hyperglycemic therapy on macrovascular events in T2DM patients convincingly demonstrated the long-term benefit of intensified therapy in reducing long-term diabetic complications, e.g. myocardial infarction [3, 4]. While the use of conventional insulin therapy (CT) is now declining, the efficacy of intensified conventional insulin therapy (ICT) has been repeatedly demonstrated [2, 5]. With this basal-bolus therapy the patient achieves greater flexibility in his/her daily activities and diet and improves his/her quality of life. ICT using Lantus® and Apidra® is superior to conventional insulin therapy. This has been shown in clinical trials and in the outpatient setting; moreover, patient satisfaction was markedly improved after switching from inadequately controlled ICT to a combination of Lantus® and Apidra® [6, 7]. The PARTNER observational study was conducted in order to document intensification of conventional insulin therapy in T2DM patients pretreated with insulin (BOT or SIT), who had elevated HbA_{1c} values. The procedure was in accordance with the guidelines of the German Diabetes Association (DDG) and part of daily clinical practice. The characteristics of the patients in both pretreatment groups were documented, both before and after intensification. The following questions were examined in the present study: 1) Were there differences between the patients in the two treatment groups (Lantus® in a BOT regimen, Apidra® in an SIT regimen)? 2) How successful were these pretreatments? 3) How successful was the intensification in each group? 4) How satisfied were the patients with the relatively new injection devices SoloStar®, ClicStar® and TactiPen®, respectively?
Methodology:	(a) Site and patient selection: Equally distributed all over Germany, resident physicians specialized in diabetes mellitus (diabetologists) and who were representative for German diabetologists were selected. Those physicians cared for T2DM patients pre-treated with insulin glargine (Lantus®) or insulin glulisine (Apidra®) according to their respective labeling in a BOT or SIT regimen for at least 3 months, using the injection devices SoloStar®, ClikStar® or TactiPen® and who failed to achieve glycemic target parameters under the respective treatment and for whom the attending physician had decided to intensify their insulin treatment to an ICT regimen, before initiating the study. The decision was completely independent of any possible participation in the PARTNER observational study. Each center was asked to document up to 6 T2DM patients (3 in each group). No site replacement methodology was described in the study protocol. (b) Data collection: Paper documentation. (c) Data management, review, validation: The NIS management of Sanofi-Aventis Deutschland GmbH was responsible for the distribution and collection of the documentation,

	including completeness and plausibility control, as well as for source data verification at approximately 3% of the centers and discrepancy management by clarification through queries to the centers. The contract research organization (CRO) was responsible for data entry into the clinical database by double data entry. All data management processes are detailed in a data management plan (DMP). No queries were generated by the CRO. All collected data were validated after the end of data capture by running check programs in SAS. (d) Statistical considerations: Data were evaluated descriptively and are regarded as purely explorative. Statistical analyses were performed separately for the two groups, Lantus® group and Apidra® group. The sample size determination of 2,700 patients was based on a return (without dropout) of 90% (Lantus® group; n=1,215 of 1,350 patients) and 85% (Apidra® group; n=1,147 of 1,350 patients) assuming a mean clinically significant absolute reduction in HbA_{1c} of 0.4% with an SD of 1.2% from baseline to endpoint. The estimated 95% CIs for evaluable 1,215 patients (Lantus® group) and 1,147 patients (Apidra® group) were 0.333–0.467% and 0.331–0.469%, respectively. The corresponding 95% probability to detect at least one AE in both cohorts was calculated to be 1:406 and 1:383, respectively. Variables and evaluation criteria: The primary study endpoint was: - Mean change in HbA_{1c} from baseline after approximately 12 and 24 weeks on an ICT regimen in T2DM patients pretreated with Lantus® (BOT) or Apidra® (SIT), separately evaluated for each insulin pretreatment group The secondary study endpoints were: - Mean change in fasting blood glucose (FBG), separately evaluated for each pretreatment group - Mean change in peri-prandial blood glucose levels (preprandial, 1-hour (1h-) and 2-hours (2h-) postprandial) at 3 time points (breakfast, lunch, dinner), separately evaluated for each pretreatment group - Percentage of patients achieving the target HbA_{1c} of ≤6.5% or ≤7.0% at baseline and under ICT treatment, separately evaluated for each insulin pretreatment group - Percentage of patients achieving the target FBG of ≤5.6 mmol/L (≤100 mg/dL) at baseline and under ICT treatment, separately evaluated for each insulin pretreatment group - Percentage of patients achieving the target 2h-postprandial blood glucose of <140 mg/dL (<7.8 mmol/L) once, twice and at all time points (morning, lunch and evening) at baseline and under ICT treatment, separately evaluated for each insulin pretreatment group - Mean daily dose (U/day) and dose per kg body weight (BW; U/kg BW) of Lantus® (BOT) or Apidra® (SIT) during pretreatment and after intensification to an ICT; separately evaluated for each pretreatment group in total as well as per subgroups reaching FBG target of ≤100 mg/dL (≤5.6 mmol/L) and/or 2h-postprandial glucose of <140 mg/dL (<7.8 mmol/L) - Ratio of Lantus® dosage and total prandial insulin dosage per day at study end for patients pretreated with Lantus® and of Apidra® dosage and total basal insulin dosage per day at study end for patients pretreated with Apidra®

	- Preferred time of Lantus® and Apidra® administration in ICT - Change in body weight from baseline, separately evaluated for each pretreatment group - Percentage of patients that maintained, reduced or increased their body weight from baseline after approximately 12 and 24 weeks on ICT - Percentage distribution of the injection devices SoloStar®, ClikStar® and TactiPen® in each pretreatment group - Percentage distribution of satisfaction parameters for given pen properties in each pretreatment group Safety parameters: - Incidence of confirmed symptomatic hypoglycemia with a blood glucose level of ≤70 mg/dL (≤3.9 mmol/L) or severe confirmed hypoglycemia with a blood glucose level of ≤56 mg/dL (≤3.1 mmol/L) during an ICT with Lantus® and Apidra® - Incidence of adverse events (AEs) during an ICT with Lantus® and Apidra® Data analyses: Descriptive statistics for continuous variables including patient numbers, mean, standard deviation (SD), median, minimum (min), maximum (max) and selected percentiles were calculated. For categorical variables, absolute, percent and adjusted percent frequencies were determined. For estimated frequencies and, if possible, for other parameters 95% confidence intervals (CIs) were calculated. All statistical analyses were performed separately for each of the two treatment groups, i.e. Lantus® group and Apidra® group and, if reasonable, also for the total group. No specific actions were made to address potential sources of bias. There were no changes made to the study analyses, objectives or conduct compared with initial planned procedures and protocol. The following data were obtained for evaluation at baseline: • Demographic data and informed consent • Body height and weight • Medical history data regarding T2DM including duration of T2DM • Concomitant oral anti-diabetic therapy (compound group, dose) • HbA_{1c} and FBG • Preprandial and 2h-postprandial daily blood glucose profiles • Duration of BOT with Lantus® or SIT with Apidra® • Application times, frequency and doses of Lantus® and Apidra®, respectively, and of newly added insulins at the start of ICT treatment • Consumption of blood glucose test strips and needles prior to start of the ICT • Satisfaction with the injection devices SoloStar®, ClikStar® or TactiPen® (1=best score; 6=worst score) The following data were obtained for evaluation after approximately 12 and 24 weeks: • Body weight • HbA_{1c} and FBG • Pre-prandial and 2h-postprandial daily blood glucose profiles • Application times, frequency and doses of Lantus® and Apidra®, respectively, and of the respective concomitant insulin during ICT treatment • Concomitant oral anti-diabetic therapy (compound group, dose) • Consumption of blood glucose test strips and needles during the ICT

	• Confirmed hypoglycemia • Adverse events
Study period (planned):	This report includes data from 8 months reported to the Apidra® and Lantus® registry as of last CRF received date 08-Mar-2013 for the full, enrolled and safety analysis set.

RESULTS	
Participants:	A total of 258 sites throughout Germany took part in this study. These were representative for German diabetologists. N=1,530 patients were screened for participation in this observational study during the screening phase from July 1, 2011, until July 31, 2012. N=1,301 of 1,530 screened patients were included in the full analysis set (FAS), 1,515 patients in the safety analysis set (SAS) and 1,403 patients in the enrolled analysis set (EAS). Among screened patients, insulin pretreatment was Apidra® (n=258; 16.9%), Lantus® (n=1,198; 78.3%) or both (n=44; 2.9%), with missing data for n=30 (2.0%). The most common oral antidiabetic drug was metformin in 161 of 229 patients (Apidra® group) and in 844 of 1,072 patients (Lantus® group) (FAS). To avoid bias due to the large difference in group size between Apidra® group (n=258) and Lantus® group (n=1,198) no direct comparisons between both groups are made.
Participant characteristics and primary analyses:	Intensification of insulin treatment for FAS patients was initiated at baseline and was continued until the 24-week visit for a total of 235 patients pretreated with Apidra® and 1,103 patients pretreated with Lantus®. Pre-intensification daily doses (mean±SD) of the short-acting insulin Apidra® (36.44±24.61 U/d) were higher than for the long-acting insulin Lantus® (22.96±14.40 U/d). However, doses of the pretreatment insulins were not further recorded during ICT. Therefore, it was not possible to calculate ratios of the basal and prandial insulins used in ICT. At study end total daily doses of additional insulins in the ICT were higher in the Lantus® group (33.62 U/d) than in the Apidra® group (22.43 U/d). Insulin doses per kg bodyweight of the respective additional insulins at study end were 0.24 U/kg in the Apidra® group and 0.36 U/kg in the Lantus® group. After cautious introduction of additional prandial or basal insulins for ICT at baseline in both groups, final assessment at the 24-week visit showed similar daily doses for these additional insulins as had been used for the respective pretreatment insulin class (short- or long-acting insulin) at baseline. This suggests a similar balance between short- and long-acting insulins in the two treatment groups during ICT. However, no final conclusions can be drawn, because final values of insulin doses of the pretreatment insulins during ICT are missing. Evaluation of HbA_{1c} concentrations HbA_{1c} decreased from baseline 8.67% (Lantus® group) and 8.46% (Apidra® group) to 7.73% and 7.66%, respectively, at 12-week visit and further to 7.38% and 7.30%, respectively, at 24-week visit, resulting in a statistically significant mean difference of -0.94% and -0.80%, respectively, at 12-week visit vs baseline and of -1.29% and -1.15%, respectively, at 24-week visit vs baseline (all p<0.0001). During intensification of insulin treatment, HbA_{1c} decreased in most patients of both groups already after 12 weeks (from baseline until 12-week visit) and in even more patients until 24 weeks (24-week visit); i.e. in 185 (80.7%) and 191 (83.4%) of patients in the Apidra® group and in 894 (83.3%) and 934 (87.1%) of patients in the Lantus® group, respectively. The proportion of patients showing an increase in HbA_{1c} was 15.7% (n=36) at 12-week visit and 13.5% (n=31) at 24-week visit in the Apidra® group and slightly lower in the Lantus® group with 12.2% (n=131) at 12-week visit and 10.4% (n=112) at 24-week visit. No changes in HbA_{1c} were observed in the Apidra® group in 8 (3.5%; 12-week visit) and 7 (3.0%; 24-week visit) patients and in the Lantus® group in 47 (4.4%; 12-week visit)

	and 26 (2.4%; 24-week visit) of patients. Evaluation of FBG concentrations In line with the significant decrease in HbA_{1c} there were also clinically and statistically significant decreases in FBG values. Similar decreases from baseline were shown for both groups, i.e. –35 mg/dL (–1.9 mmol/L; Apidra® group) and –37 mg/dL (–2.1 mmol/L; Lantus® group), at 12-week visit, and –46 mg/dL (–2.6 mmol/L; Apidra® group) and –47 mg/dL (–2.6 mmol/L; Lantus® group), at 24-week visit. All subgroup analyses for BMI, age, gender and diabetes duration revealed similar, statistically significant FBG decreases (all p<0.0001). Patients aged <65 years generally exhibited tighter blood glucose control. Patients with BMI ≥30 kg/m² and those with diabetes duration ≥6 years were better controlled with respect to FBG in the Apidra® group, while in the Lantus® group decreases in FBG were greatest in patients with diabetes duration of 3 –<6 years. Evaluation of post-prandial glucose concentrations Information about peri-prandial blood glucose profiles during pretreatment with Apidra® in an SIT regimen was available from only a very small proportion of patients at baseline and even less after 12 and 24 weeks. Peri-prandial blood glucose levels from patients of the Lantus® group were available from less than 10% of the patients. Therefore, no sufficiently valid analysis of these data was possible to allow for interpretation of the results. HbA_{1c} target achievement A total of 17.9% and 47.1% of patients in the Apidra® group achieved the strict or less strict HbA_{1c} target of ≤6.5% and ≤7.0% at study end (24-week visit), and 18.6% and 43.0% in the Lantus® group. Subgroup analyses revealed that in patients with BMI <30 kg/m² HbA_{1c} targets of ≤6.5% and ≤7.0% at 24-week visit were achieved by 20.7% and 54.4% (n=101; Apidra® group) and by 20.8% and 48.8% (n=466; Lantus® group), respectively. Percentages were lower in patients with BMI ≥30 kg/m²; i.e. 15.8% and 42.0% (n=126; Apidra® group) and 16.9% and 38.9% (n=603; Lantus® group), respectively. In the Apidra® and the Lantus® group, similar proportions of patients aged <65 years achieved the target of HbA_{1c} ≤6.5% at 24-week visit (18.6%, n=24 and 19.4%, n=104), compared with patients aged ≥65 years (16.6%, n=16 and 17.5%, n=92). The respective figures for achieving an HbA_{1c} of ≤7.0% were 46.5% (n=60) and 43.0% (n=230) for patients aged <65 years and 47.9% (n=46) and 43.2% (n=226) for those aged ≥65 years, respectively. The proportions of females who achieved an HbA_{1c} of ≤6.5% and ≤7.0% were 20.2% (n=20) and 45.5% (n=45; Apidra® group) and 15.6% (n=76) and 40.2% (n=195; Lantus® group), respectively, vs 16.4% (n=21) and 49.2% (n=63; Apidra® group) and 20.9% (n=122) and 45.2% (n=264; Lantus® group), respectively, in males. Overall, subgroup analyses pointed to better glycemic control in patients with shorter diabetes duration. For example, in the Apidra® group, 20.7% (n=16) and 51.9% (n=40) of patients with diabetes duration of 3 months to 1 year achieved the limits of HbA_{1c} of ≤6.5% and ≤7.0%, in contrast to 11.6% (n=7) and 36.6% (n=22) of patients with diabetes duration of 3 to 6 years, respectively. In the Lantus® group, 21.6% (n=80) and 45.6% (n=169) of patients with diabetes duration of 3 months to 1 year achieved the limits of HbA_{1c} of ≤6.5% and ≤7.0%, in contrast to 17.4% (n=41) and 39.5% (n=93)

	of patients with diabetes duration of 3 to 6 years, respectively. FBG target achievement FBG control (≤100 mg/dL) was achieved in lower proportions of patients at study end (24-week visit; 14.8% (Apidra® group), 13.4% (Lantus® group)) than those achieving the HbA_{1c} target of ≤6.5% (~18–19%). However, the lower number of patients with good FBG control may have been biased by a higher percentage of missing data for FBG at study end (3.5-7.9%) than for HbA_{1c} (0%). Subanalyses for BMI, age, gender and diabetes duration did not reveal any significant differences in achievement of the FBG target. Results for elderly were similar to those for younger patients in both groups. Stricter control appeared to be achieved for females in the Apidra® group, but in the Lantus® group for men. Based on the results of rather small subgroups it appears that patients with long diabetes duration showed greater benefits from intensification of a therapy based on Lantus® pretreatment, while those with shorter diabetes duration tended to benefit from Apidra® based pretreatment. Weight changes In the Apidra® group, the mean body weight at baseline was 92.54 kg (N=228; 95% CI 89.88–95.20 kg). In the Lantus® group, the mean body weight at baseline was 92.07 kg (N=1,071; 95% CI 90.95–93.19 kg). There were essentially no changes in body weight in either group during ICT (mean weight change after 24 weeks vs baseline: 0.16 kg (N=224; 95% CI -0.25–0.68 kg) in the Apidra® group and 0.26 kg (N=1,054; 95% CI -0.07–0.58 kg) in the Lantus® group). Assessment of satisfaction with the pens As assessed at baseline, SoloStar® was the pen device most frequently used and also had the highest rating for satisfaction (1=best score, 6=worst score), followed by TactiPen®. Only a few patients used the ClikStar® pen. Besides ranking of the patient's satisfaction with the pen in use, several features (i.e. look/design, handling, dose adjustment, effort for dose injection and size) of the respective pen could be marked by the participating physician, if particularly positive for the respective patient. Most patients (82-90%) in both groups were satisfied with the handling of the pens. More than half of the patients were also satisfied with the dose adjustment and the effort for dose injection of the pen they used. The feature "size" was not important for the majority of patients, irrespective of the pen in use. Very few patients (1–25) in either group reported problems with their device; therefore, no conclusions can be drawn from these limited data.
Other analyses:	Safety Safety analyses included adverse events (AEs), blood pressure (BP) and blood lipids within the safety analysis set (SAS) of 1,515 patients, including a patient subset who received both, Apidra® and Lantus®, at baseline. FBG and HbA_{1c} values within the SAS did not show any noteworthy difference compared to the data reported for the FAS population shown above. Overall, there were 24 reported AEs in 24 patients. Among those 14 were reported as serious AEs (SAEs). The most frequent AE was hypoglycemia (n=9), which was reported as a SAE in 8 patients (Apidra® pretreatment (n=2), Lantus® pretreatment (n=5) and pretreatment with both (n=1)) and as a non-serious AE in one patient in

	the Lantus® group. In the Lantus® group all 6 cases of hypoglycemia (5 severe hypoglycemia, one non-severe), 2 cases of arthralgia and one hypersensitivity reaction were considered treatment-related by the sponsor. The AEs in the Apidra® group were hypoglycemia (n=2), hypertensive encephalopathy (n=1), epicondylitis (n=1) and arthralgia (n=1). Only the 2 cases of severe hypoglycemia were considered treatment-related by the sponsor. Also one severe hypoglycemia in a patient receiving both at baseline, Apidra® and Lantus®, was considered treatment-related by the sponsor. The overall 14 SAEs included 4 deaths unrelated to treatment; 2 of these patients died from natural course of the disease, one patient died from neoplasm, and one from myocardial infarction (Lantus® group). There was one serious case of pancreatic cancer (Lantus® group) and one serious case of hypertensive encephalopathy (Apidra® group). Blood pressure (BP) values were available for >92.5% of patients in both groups. BP slightly decreased during the observation period, from an average of 138/81 mm Hg in the Apidra® and 139/82 mm Hg in the Lantus® group, respectively, at baseline to an average of 135/79 mm Hg and 135/80 mm Hg, respectively, at 24-week visit. Mean changes were -3.12/-2.07 mm Hg and -2.30/-1.75 mm Hg, respectively, with 95% CIs for the change at 24-week visit of [-5.10; -1.14/-3.41; -0.73 mm Hg] for the Apidra® group and [-4.21; -2.44/-2.33; -1.16 mm Hg] for the Lantus® group. Blood lipids values were available for <50% of patients at both visits after baseline. In the Lantus® group, the 95% CIs for subjects with data at 24-week visit indicate that total cholesterol changed by a mean of - 9.82 [-13.6; -6.04] mmol/l and LDL by -5.98 [-8.83;-3.13] mmol/l, while HDL slightly increased by 1.49 [0.51; 2.48] mmol/l. In the smaller Apidra® group, however, the mean change for total cholesterol was only -3.24 [-10.0; 3.54] mmol/l, for LDL -2.35 [-8.02; 3.32] and for HDL 1.85 [-0.03; 3.73] mmol/l. Similarly, triglyceride concentrations showed a pronounced change of -30.72 [-39.7; -21.7] mmol/l in the Lantus® group, but only a trend towards lower values in the Apidra® group (-10.21 [-25.4; 5.00] mmol/l).
Discussion:	The PARTNER study was an open, prospective non-interventional study in T2DM patients with uncontrolled blood glucose on insulin pretreatment to evaluate the efficacy and safety of an intensification of a BOT pretreatment with insulin glargine (Lantus®) and a prandial SIT pretreatment with insulin glulisine (Apidra®) to a basal-bolus therapy by adding a bolus insulin at least TID and a basal insulin, respectively, to the pretreatment insulin under daily clinical practice conditions in Germany. A total of 1,530 patients were screened, 834 males and 689 females aged 19–93 (median: 64) years, with a BMI range of 16.5–62.9 (median: 31) kg/m^2. Of those, 1,301 patients were included in the FAS, 229 on Apidra® pretreatment and 1,072 on Lantus® pretreatment, whereas 1,515 were included in the SAS and 1,403 in the EAS. High rates of long-term diabetes complications were observed, likely due to a high proportion of patients with a long diabetes duration of >10 years (>40% of patients in both treatment groups). Complications were most frequently neuropathy (~40% of patients), cardiovascular diseases and nephropathy (<20%) and retinopathy (~15%). Pretreatment duration with either Apidra® or Lantus® ranged from 0.25 to <1 year in ~34% of patients, from 1 to <3 years in 30% (Apidra® group) and 28% (Lantus® group) and from 3 to <6 years in 26% (Apidra® group) and 22% (Lantus® group). Over 6 years of pretreatment duration were seen in 5% (Apidra® group) and 6% (Lantus® group) of patients. As per inclusion criterion (HbA_{1c} ≥6.5%), glycemic control was suboptimal in all patients.

	Pretreatment Apidra® daily doses (mean±SD) were higher (36.44±24.61 U/d) than pretreatment Lantus® daily doses (22.96±14.40 U/d). At 24-week visit final daily doses of long-acting insulins of 22.43±11.18 U/d were added to Apidra® and final daily doses of short-acting insulins of 33.62±19.47 U/d were added to Lantus®. Therefore, balance between short- and long-acting insulins in the two groups seemed to be similar at study end, when assuming no changes in dosing of the pretreatment insulin. HbA_{1c} as the *primary study endpoint* showed a clinically and statistically significant reduction at 12-week visit, with an incremental decrease at 24-week visit as expected. The mean reduction at 24-week visit was -1.15% (95% CI [-1.34; -0.97%]) in the Apidra® group (N=229) and -1.29% (95% CI [-1.38; -1.20%]) in the Lantus® group (N=1,072). Within subgroups, younger patients <65 years exhibited lower HbA_{1c}. The results for males were slightly more favorable than for females. Patients with a BMI ≥30 kg/m² had a similar decrease in HbA_{1c} levels as patients with BMI <30 kg/m². There was a trend for lower HbA_{1c} in patients with shorter diabetes duration. Among the *secondary study endpoints*, the percentage of patients achieving the target HbA_{1c} of ≤6.5% increased similarly from ~1% at baseline to ~18% at 24-week visit in both groups and for the target HbA_{1c} of ≤7.0% from ~10% (Lantus® group) and ~11% (Apidra® group) at baseline to ~43% and ~47%, respectively, at 24-week visit. Thus, slightly more patients starting an ICT from a prandial SIT based regimen achieved HbA_{1c} targets than those starting from basal insulin in a BOT regimen. However, the study duration may have been too short to uncover the true rate of long-term glycemic control with an ongoing dose adjustment after the 24-week visit. In both treatment groups, fasting blood glucose was markedly and statistically significantly reduced; by ~-36 mg/dL at 12-week visit and ~-46 mg/dL at 24-week visit. The decrease in FBG was also statistically significant in all subgroups analyses. The proportion of patients achieving target FBG ≤5.6 mmol/L (≤100 mg/dL) increased from 3.7% (baseline) to 13.4% (24-week visit) in the Lantus® group and from 2.6% (baseline) to 14.8% (24-week visit) in the Apidra® group. Subgroup analyses revealed no clear pattern in patients achieving FBG control. Safety analyses included 24 reported AEs with 4 cases of death, which were unrelated to treatment. There were 6 hypoglycemic AEs (5 SAEs) related to treatment as well as 2 cases of arthralgia and one hypersensitivity reaction (Lantus® group); 2 hypoglycemic AEs (2 SAEs) related to treatment (Apidra® group) as well as 1 hypoglycemic AE (1 SAE) related to treatment in a patient pretreated with both insulins. Systolic and diastolic BP statistically significantly decreased in both treatment groups. The results obtained from the present study show an improvement in glycemic control in a previously poorly controlled, unselected T2DM patient population from a daily clinical practice setting in Germany and may be considered representative for a Caucasian population.
Conclusions:	The PARTNER observational study, conducted in Germany, showed improvements in glycemic control by intensifying insulin treatment to a basal-bolus regimen in patients pretreated with the short-acting insulin glulisine (Apidra®) and to a slightly higher extent for those pretreated with long-acting insulin glargine (Lantus®), as indicated by a mean decrease in HbA_{1c} of -1.15% and -1.29%, respectively. This improvement was

	accompanied by a marked decrease in FBG of >46 mg/dL (>2.6 mmol/L) in both treatment groups at 24-week assessment compared to baseline. According to the reported AEs, safety analyses overall indicated that the ICT was well tolerated, with very few serious adverse events or severe hypoglycemic episodes. The improved glycemic control was accompanied by a statistically significant reduction in systolic and diastolic BP in both treatment groups. Therefore, insulin glargine (Lantus®) and insulin glulisine (Apidra®) appear to be a well-tolerated and effective treatment option for intensifying a BOT regimen with insulin glargine or a SIT regimen with insulin glulisine to an ICT treatment regimen.
Date of report:	08-Jan-2014
References:	1. Köster I, Ferber L von, Ihle P, Schubert I, Hauner H. The cost burden of diabetes mellitus: the evidence from germany – the CoDiM Study. Diabetologia 2006; 49 (7): 1498 – 1504 2. Matthaei S, Bierwirth R, Fritsche A, Gallwitz B, Häring H-U, Joost H-G, Kellerer M, Kloos Ch, Kunt T, Nauck M, Schernthaner G, Siegel E, Thienel F. Medikamentöse antihyperglykämische Therapie des Diabetes mellitus Typ 2. Update der Evidenzbasierten Leitlinie der DDG. Diabetologie 2009; 4: 32 – 64 3. Holman RR, Paul SK, Bethel, MA, Matthews DR, Neil HAW: 10-year follow-up of intensive glucose control in type 2 diabetes. N Engl J Med 2008; 359: 1577 – 1589 4. Stettler C, Allemann S, Jüni P, Cull CA, Holmann RR, Egger M, Krähenbühl S, Diem P. Glycemic control and macrovascular disease in types 1 and 2 diabetes mellitus: metaanalysis of randomized trials. Am Heart J 2006; 152: 27 – 38 5. Ryden L, Standl E, Bartnik M, Van den Berghe G, Betteridge J, de Boer MJ, Cosentino F, Jönsson B, Laakso M, Malberg K, Priori S, Östergren J, Tuomilehto J, Thrainsdottir I. Guidelines on diabetes, prediabetes, and cardiovascular disease: executive summary. Eur Heart J 2007; 28: 88 – 136 6. Fritsche A, Larbig M, Böhler S, Häring HU; GINGER study group. Comparison between a basal-bolus and a premixed insulin regimen in individuals with type 2 diabetes – results of the GINGER study. Diabetes Obes Metab 2010; 12: 115 – 123 7. Daikeler R, Högy B, Donaubauer B. Effects of an Intensified Insulin Therapy (ICT) with Insulin Glargine and Insulin Glulisine on Patient Reported Outcomes (PRO) in Diabetes Mellitus. Diabetologie 2007; 2: 308 – 314

Study report or synopsis Sponsor approval form for local/regional Medical Affairs studies

SANOFI

Product Code:	HOE901 Insulin glargine
Study Code / Name:	LANTU_L_04724 PARTNER observational study
Study Title:	Non-interventional, open, prospective observational study to observe efficacy and tolerability of a basal-bolus therapy regimen in type 2 diabetes subjects pretreated either with Lantus® in a BOT regimen or with Apidra® at meal times (PARTNER)
Document Type: (Tick appropriate box)	☐ Clinical Study Report / ☐ Synopsis ☐ Product Registry Report / ☒ Synopsis ☐ Disease Registry Report / ☐ Synopsis ☐ Compassionate Use Cohort Study Report / ☐ Synopsis
Name of Medical Director (i.e. individual responsible for medical oversight of the report)	W. Dieter Paar

THE STUDY REPORT / SYNOPSIS

Final Draft dated 08-Jan-2014

is APPROVED*.

*Note: to approve the document, the Medical Director should ensure that the local PV responsible has reviewed the document and comments have been incorporated

Sponsor's responsible medical officer:		
☒ Medical Director	W. Dieter Paar	D. P. 8.1.14 Signature Date: