PRODUCT REGISTRY REPORT

Compound(s): Lantus®/Insulin glargine

Registry Title: Titration and OPtimization trial for insulin glargine in patients with type 2 diabetes with poor glycaemic control on OADs or on basal insulin plus OADs

Registry number: LANTU_L_05715

Registry name: TOP

Registry initiation date [date first patient in (FPI)]: 16-Sep-2013

Registry completion date [last patient completed/last patient out (LPO)]: 21-Oct-2015

Registry design: Non-interventional, open, prospective study

Report date: 22-Aug-2016

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'.

TABLE OF CONTENTS

SYNOPSIS

Title of the registry:	Titration and OPtimization (TOP) trial for insulin glargine in patients with type 2 diabetes with poor glycemic control on oral antidiabetic drugs (OADs) or on basal insulin plus OADs
Design:	Non-interventional, open, prospective study. The study was conducted by pooling the participating patients into three subgroups of titration algorithms (titration algorithm according to Fritsche et al., according to Davies et al. or individual algorithm (any other titration algorithm according to the discretion of the physician)) according to the physician's preferred algorithm for titrating insulin glargine in daily clinical practice to reflect the distribution of different dosing algorithms in daily clinical practice.
Objectives:	The two main objectives of this registry were: 1. To assess the dosing algorithm(s) of basal insulin glargine in type 2 diabetes patients in Germany in routine daily clinical practice when glargine is added to OAD and titrated to individualized targets over one year of observation and to have a snapshot of the distribution of the different dosing algorithms actually used in Germany in routine daily clinical practice 2. To assess how to optimize glycemic control in these patients by evaluating the different titration algorithms used in daily clinical practice in Germany
Treatment:	Product name: Lantus® INN: Insulin glargine Source of drug: prescription Route of administration: s.c.
Scientific committee and members:	A scientific steering committee was asked for scientific advice during set-up, conduction and evaluation of the study results. Members of the scientific steering committee are: [redacted]
Publications (reference):	Poster abstracts: 1. Fritsche A, Pfohl M, Pscherer S, Anderten H, Pegelow K, Seufert J. *T*itrations- und *Op*timierungsstudie (TOP) für die Initiierung von Insulin glargin 100 E/ml (Gla-100) bei Typ-2-Diabetespatienten mit unzureichender Blutzuckereinstellung – 6-Monats-Ergebnisse (Translation: Titration and OPtimization (TOP) study on initiation of insulin glargine 100 U/mL in patients with type 2 diabetes and poor glycemic control – 6 months results). Diabetologie & Stoffwechsel 2016; 11: S14, abstr. P46. Presented as poster oral at the annual meeting of the German Diabetes Association at 05.05.2016 in Berlin, Germany. 2. Seufert J, Pscherer S, Fritsche A, Anderten H, Pegelow K, Pfohl M. *T*itrations- und *Op*timierungsstudie (TOP) für die Initiierung von Insulin glargin 100 E/ml (Gla-100) bei Typ-2-Diabetespatienten mit unzureichender Blutzuckereinstellung unter oralen Antidiabetika – Baseline-Daten (Translation: Titration and OPtimization (TOP) trial for initiation of insulin glargine 100 U/mL in patients with type-2 diabetes with poor glycemic control on oral antidiabetic drugs - baseline data). Diabetologie & Stoffwechsel 2016; 11: S39, abstr. P138. Presented as poster oral at the annual meeting of the German Diabetes Association at 06.05.2016 in Berlin, Germany.

	3. Fritsche A, Pfohl M, Pscherer S, Anderten H, Pegelow K, Seufert J. Titration and OPtimization (TOP) study on initiation of insulin glargine 100 U/mL in patients with type 2 diabetes and poor glycemic control – 6 month results. Abstr. P10-11. Presented as poster at the D.A.CH congress in Munich, Germany, 26.-28.05.2016. 4. Seufert J, Pscherer S, Fritsche A, Anderten H, Pegelow K, Pfohl M. Titration and OPtimization (TOP) trial for initiation of insulin glargine 100 U/mL in patients with type-2 diabetes with poor glycemic control on oral antidiabetic drugs - baseline data. Abstr. P10-12. Presented as poster at the D.A.CH congress in Munich, Germany, 26.-28.05.2016. 5. Seufert J, Fritsche A, Pscherer S, Anderten H, Pegelow K, Pfohl M. Titration and OPtimization (TOP) trial for initiation of insulin glargine 100 U/mL in type-2 diabetes patients poorly controlled on oral antidiabetic drugs. Diabetes 2016; 65 (Suppl. 1): abstr. 923-P. Presented as poster oral at the 76th Scientific Sessions of the American Diabetes Association at 12.06.2016 in New Orleans, USA Initiatives for any local communication in participating countries/regions: Not applicable.
Introduction - **Background/rationale:**	Initiating insulin is recommended if OADs fail to control blood glucose levels to achieve the HbA_{1c} goal <7.0 %. The preferred option to initiate insulin therapy in addition to oral therapy recommended by the evidence based treatment guidelines (EBG) of the German diabetes association (DDG) is to add basal insulin once daily. [1] There is no recommendation in German EBG regarding starting dose and titration algorithms, respectively, for initiating insulin treatment in patients with type 2 diabetes. However, for long acting insulins, US and European EBG [2] propose to start with 10 units per day or 0.1 to 0.2 units per kg body weight per day. Furthermore, several starting doses and titration algorithms for insulin glargine 100 units/mL (U100; Lantus®) have been proposed and used in randomized controlled trials and have been proposed for daily clinical practice. [3-7] There are recommendations in the Summary of Product Characteristics (SmPC) for insulin glargine U100 (Lantus®) regarding switching from other basal insulins to insulin glargine U100, i.e. to switch to the same amount of units if the former basal insulin was injected once daily and to reduce total daily dose by 20-30%, if the former basal insulin was injected twice a day. [8] However, no titration algorithm is recommended. With the intent to support the basal insulin supported oral therapy (BOT) concept in Germany, a titration algorithm based on the titration algorithm that was used in the study of Fritsche et al.[3] has been proposed to diabetologists as well as primary care professionals, i.e. general practitioners, family doctors, and internists acting as general practitioners, during the last years for initiating insulin glargine U100 in addition to OAD. A second algorithm was added in 2005 to support patient-driven treatment management based on the patient-driven algorithm used in the AT.LANTUS trial. [4] The aim of this non-interventional study (NIS) was to assess the dosing algorithms frequently used in Germany by health care professionals (HCP) in daily clinical practice when insulin glargine U100 is added to OAD or the patient is switched from another basal insulin plus OAD to insulin glargine U100 plus OAD and titrated to individualized targets. In addition, the study aimed to describe the frequency of use of these dosing algorithms in German daily clinical practice, and to suggest how to optimize glycemic control in these patients by evaluating efficacy of these different titration algorithms.

Methodology:

All data were collected three times during this NIS; at baseline, approximately 6 and approximately 12 months after starting insulin glargine U100 (Lantus®) therapy. Baseline documentation (documentation 1) had to start immediately after adding insulin glargine U100 (Lantus®) to OAD or after switching to insulin glargine U100 (Lantus®) from another basal insulin. This had to occur after the physician had independent of the participation in this study decided to prescribe insulin glargine U100 (Lantus®) and when thereafter the physician and the patient had decided the participation of the latter in this study. Next measurements were documented approximately 6 months thereafter (documentation 2), and the last measurement was documented approximately 12 months thereafter (documentation 3). Besides this, all fasting blood glucose (FBG) measurements available were collected on a monthly base asking for documentation of changes during the last four weeks each month. Also dosing informations were captured every month; i.e. actual dose and frequency of dose changes during the last four weeks. Data had to be generated during daily clinical routine of the HCPs. Any change in the patient's antidiabetic therapy regimen was strictly left at the physician's discretion. No therapeutic decision of the physician should have been based upon this NIS. Participating HCPs were distributed equally all over Germany to allow for a representative sample of German type 2 diabetes patients initiating or switching basal insulin therapy as add-on to their oral antidiabetic treatment.

Before starting the inclusion of patients, the participating physicians indicated, which insulin glargine U100 (Lantus®) titration algorithm they preferentially use for their patients: An algorithm based on Fritsche's scheme (Fritsche), an algorithm based on the patient-centered approach in Davies' AT.LANTUS study (Davies) or an individual titration algorithm (IT). The two specified titration algorithms were as follows:

Fritsche's scheme

Initiation with 10 U/d insulin glargine 100 U/ml or 0.1-0.2 U/kg body weight OD; maintain OAD as appropriate; fasting blood glucose (FBG) treatment target: 90-110 mg/dL (5.0-6.1 mmol/L)

Dose adjustment every 3-5 days based on FBG (mean of 3 measurements) according to the following scheme:

FBG (mg/dL)	FBG (mmol/L)	Dose adaption
>180 mg/dL	>10.0 mmol/L	+8 U/d
>160 mg/dL	>8.9 mmol/L	+6 U/d
>140 mg/dL	>7.8 mmol/L	+4 U/d
>110 mg/dL	>6.1 mmol/L	+2 U/d
90-110 mg/dL	5.0-6.1 mmol/L	No change
<90 mg/dL	<5.0 mmol/L	-2 U/d

Davies' scheme

Dose adjustment every 3 days based on FBG (mean of 3 measurements) according to the following scheme:

FBG (mg/dL)	FBG (mmol/L)	Dose adaption
>110 mg/dL	>6.1 mmol/L	+2 U/d
90-110 mg/dl	5.0-6.1 mmol/l	No change
<90 mg/dL	<5.0 mmol/L	-2 U/d

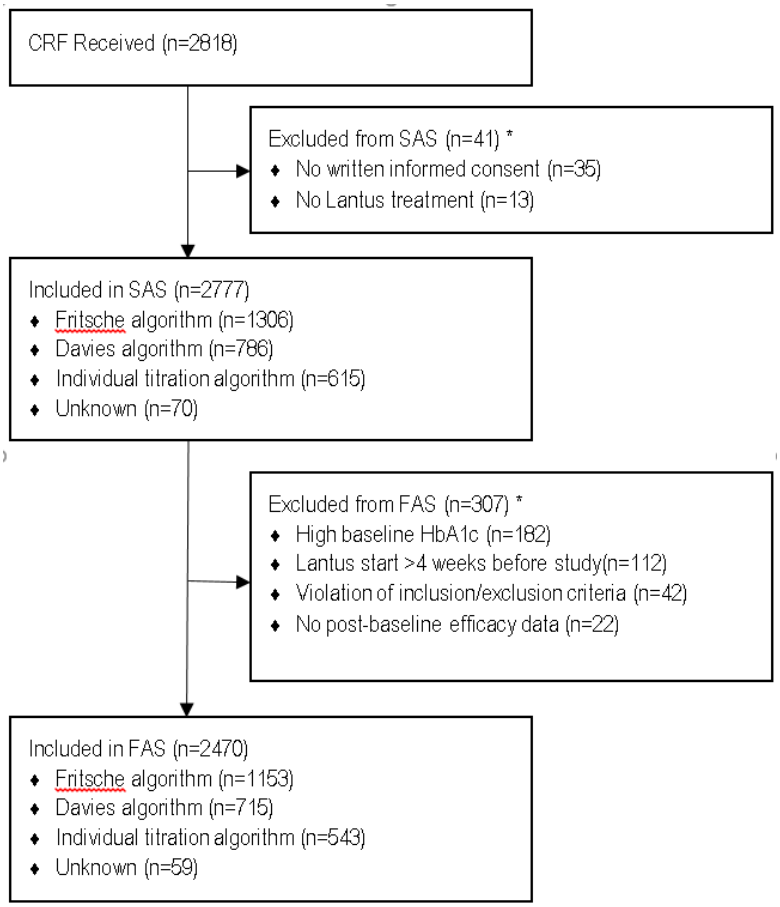
Check FBG values regularly and adjust dose accordingly

Based on this indication, the patients of the physicians were pooled to the respective titration algorithm group to allow for predefined subgroup analysis. No indication of intended titration for each patient was done. In order to allow for a valid statistical analysis even in smaller subgroups of 500 patients (as distribution of the different pre-indicated dosing algorithms may be not equal) it was planned to document and analyze about 6,000 patients in this NIS. The planned number of participating sites was 1,500. Participating doctors were mostly to be general practitioners, as the kind of physician who usually start basal insulin therapy in Germany. Also diabetologists practicing as general practitioners were to be included in the study. The practices were to be distributed equally all over Germany to allow for geographical representativeness.

Two analysis sets were defined for this NIS. The Safety Analysis Set (SAS) included patients who provided written informed consent and who received insulin glargine U100 (Lantus®) at any time during the study. The SAS was used for analyses of safety parameters. The Full Analysis Set (FAS) was a subset of the SAS excluding patients without post-baseline assessment, patients who started insulin glargine U100

	(Lantus®) more than four weeks before study, and patients who did not fulfill both, all inclusion and no exclusion criteria, including patients with strongly increased baseline HbA_{1c} (>10%). Main inclusion criteria were type 2 diabetes mellitus, oral antidiabetic therapy ± basal insulin (other than insulin glargine U100 (Lantus®)), age ≥18 years, and 7.5% ≤ HbA_{1c} ≤ 10.0%; main exclusion criteria were type 1 diabetes mellitus, contraindications for a therapy with insulin glargine, insulin glargine U100, and existing insulin therapy with a mealtime insulin (i.e. basal-bolus insulin therapy, premixed insulin therapy). All in- and exclusion criteria can be found in the protocol of the study (cf. appendix 3.1). Efficacy parameters were analyzed for the FAS. All analyses including statistical tests are exploratory and can be interpreted descriptively only. All tests were two-tailed and statistically relevant results were declared at the 0.05 level of significance without adjustment for multiplicity. The combined primary efficacy parameter of this NIS was response rates during month 1-6 and month 1-12 after start of insulin glargine U100 (Lantus®) treatment, response being defined as achieving a predefined individual target HbA_{1c} or a FBG ≤110 mg/dL (≤6.1 mmol/L). Target HbA_{1c} was predefined individually at the inclusion visit and had to be stated in the CRF before or directly at start of documentation. In addition, response rates for month 7-12 were calculated. Patients were considered as responders if at least two FBG values ≤110 mg/dL or at least one HbA_{1c} value less or equal to the individual target value were reported within the respective observation period. Response rates were summarized by pre-indicated titration groups and for the whole population with frequency distribution and, in addition, adjusted frequency distribution considering only patients with non-missing data. Exact 95% confidence intervals (CI) according to Pearson-Clopper were calculated. Comparisons of the adjusted response rates among the pre-indicated titration groups were performed by chi-square tests. In case of a p value <0.1 in the overall treatment comparison, pairwise chi-square tests were applied. Secondary efficacy parameters were: • Absolute change in HbA_{1c} • Absolute change in FBG • Response rate 6 and 12 months after start of insulin glargine U100 (Lantus®) treatment defined by o Reaching a FBG value ≤110 mg/dL (≤6.1 mmol/L) o Reaching the predefined individual HbA_{1c} target value o Reaching a FBG value ≤110 mg/dL (≤6.1 mmol/L) and the predefined individual HbA_{1c} target value • Time from start of insulin glargine U100 (Lantus®) treatment to response for each of the response endpoints (see definitions above) was analyzed using Kaplan-Meier methods and plots of the Kaplan-Meier estimates for each pre-indicated titration group were produced. Reaching a response criterion for the first time was considered as event in these analyses. Patients without response were censored at the date of last measurement of FBG or HbA_{1c}, respectively. For pairwise comparison of the pre-indicated titration groups, log-rank tests were performed and Cox proportional hazards models were used to estimate the hazard ratio including 95% CIs. • Duration (persistence) of response for each of the response endpoints (see definitions above) was analyzed using Kaplan-Meier methods and plots of the Kaplan-Meier estimates for each pre-indicated titration group were produced. Only patients with documented response and valid duration time (not missing, not negative) were included in these analyses. End of response was defined as one of the following:

	• the second FBG value >110 mg/dL (>6.1 mmol/L) after start of FBG response • the first HbA_{1c} value above the individual predefined target • change of insulin therapy Patients without documented end of response were censored at the date of last measurement of FBG or HbA_{1c}, respectively. For pairwise comparison of the pre-indicated titration groups (descriptively), log-rank tests were performed and Cox proportional hazards models were used to estimate the hazard ratio including 95% CIs. • Incidence rates and rates per patient year were calculated for symptomatic, confirmed symptomatic, nocturnal, severe, and severe nocturnal hypoglycaemia as reported in the CRF. Confirmation of symptomatic hypoglycaemia was defined as self-measured blood glucose (SMBG) measurement ≤70 mg/dL (≤3.9 mmol/L). Severe hypoglycaemia was defined as necessity of the assistance of another person or a SMBG measurement of ≤56 mg/dL (≤3.1 mmol/L). Nocturnal hypoglycaemia was defined as hypoglycaemia occurring during the night, while the patient was asleep (symptomatic or confirmed by SMBG measurement ≤70 mg/dL [≤3.9 mmol/L]). Severe nocturnal hypoglycaemia were those nocturnal hypoglycaemia fulfilling the definition of a severe hypoglycaemia. 95% CIs for incidence rates were calculated according to Pearson-Clopper. Rates per patient year were calculated as cumulative number of hypoglycaemia events for all patients divided by the cumulative duration of insulin glargine U100 (Lantus®) therapy in years, whereas patients with missing treatment duration or missing number of hypoglycaemia events were excluded. Details for calculation are provided in the SAP. • Absolute change in body weight • Absolute change in daily insulin doses In order to ensure as much balance as possible between the pre-indicated titration groups with respect to the distribution of pre-defined factors that might have an influence on efficacy parameters, additional pairwise comparisons were done using propensity score methods. Those factors were age, gender, body mass index (BMI), time since first diagnosis of type 2 diabetes mellitus, number of OADs at baseline and baseline HbA_{1c} value. For these pairwise comparisons of the pre-indicated titration groups patient pairs were selected by 1:1 matching using propensity scores: 685 pairs for comparison of Fritsche vs Davies group, 511 pairs for comparison of Frische vs IT group and 511 pairs for comparison of Davies vs IT group. Of note, different patient subsets of each titration group were selected for the different comparisons. McNemar tests were performed for response rates in the paired observations. For HbA_{1c} and FBG values paired t-test were performed. Safety parameters were incidences of adverse events (AE) and serious adverse events (SAE). Safety parameters were analyzed for the SAS. For detailed description of planned analyses including handling of missing data, subgroup and additional analyses refer to the Statistical Analysis Plan (SAP), see section 3.2.1. Interim analyses of baseline characteristics and primary and selected secondary endpoints were performed on a regular basis. A Steering Committee was involved in the study, for details refer to section 1.7.

RESULTS	
Participants (actual):	A total of 2,818 patients were documented in this NIS. The titration was pre-indicated to follow Fritsche's algorithm for 1,327 patients (47.1%), Davies' algorithm for 796 patients (28.2%) and an individual titration (IT) algorithm for 623 patients (22.1%). For 72 patients (2.6%) no data were provided about the preferred titration algorithm. In the SAS, a total of 2,777 patients (98.5%) were included: 1,306, 786 and 615 patients in the Fritsche, Davies and IT group, respectively (70 patients with unknown titration group). Of the 41 patients excluded from SAS, 35 (1.2%) did not provide written informed consent and 13 (0.5%) did not receive insulin glargine U100 (Lantus®) treatment (more than one reason could apply per patient). The FAS was defined as a subset of the SAS and included 2,470 patients (87.7%): 1,153, 715 and 543 patients in Fritsche, Davies and IT group, respectively (59 patients with unknown titration group). Reasons for excluding SAS patients from the FAS were: high baseline HbA_{1c} (>10%) for 182 patients (6.5%), start of insulin glargine U100 (Lantus®) treatment more than 4 weeks prior to study start for 112 patients (4.0%), violation of other inclusion/exclusion criteria for 42 patients (1.5%), and no documentation of post-baseline efficacy data for 22 patients (0.8%); more than one reason could apply per patient. Patients excluded from at least one of the analysis populations are listed in DIS01L_ALL. **Figure 1: Overview of analysis populations**  ** Note: More than one reason could apply*

	Source: DIS01T_ALL, DIS03_ALL Considering patients in the FAS, a total of 2,251 patients (91.1%) continued their BOT therapy with insulin glargine U100 (Lantus®) at documentation 2 with similar rates ranging between 89.5% and 92.7% in the different titration groups. Ten patients (0.4%) switched to BOT therapy with another basal insulin and 48 patients (1.9%) switched to another form of insulin therapy. No data about continuation status was provided for 167 patients (6.8%) and for 6 patients (0.2%) both boxes (for continuation and for switch) were ticked. At documentation 3 a total of 2,121 patients (85.9%) continued their BOT therapy with insulin glargine U100 (Lantus®): 85.9%, 87.6% and 83.1% in the Fritsche, Davies and IT group, respectively. Ten patients (0.4%) switched to BOT therapy with another basal insulin (reason for switch being blood glucose for 9 patients, adverse event [AE] for one patient and other reason for 8 patients; multiple reasons per patient possible), and 63 patients (2.6%) switched to another form of insulin therapy (reason for switch being blood glucose for 41 patients, AE for 2 patients and other reason for 23 patients; multiple reasons per patient possible). No data about continuation status was provided for 284 patients (11.5%) and for 8 patients (0.3%) both boxes (for continuation and for switch) were ticked. Basal insulin therapy after switch from insulin glargine U100 (Lantus®) was specified for 17 patients: insulin degludec in seven patients (0.3%), insulin glargine U300, insulin detemir and NPH insulin in three patients each (0.1%), premixed insulin and short-acting analogue insulin in one patient each (<0.1%); one patient reported two insulin therapies. To evaluate if the pre-indicated titration groups correspond to the actual titration algorithms used, actual titration groups were post-hoc defined by the number of titration steps applied in the first month of titration. Fritsche's titration algorithm is based on one to two titration steps per week, i.e. 4-8 titration steps per month. Davies' titration algorithm is based on one titration step every three days, i.e. about 10 titration steps per month. However, the majority of participating physicians (approx. 95%) applied ≤3 titration steps during the first month only. Therefore, actual titration groups were post-hoc defined by the dose change within the first four weeks of the study. A dose increase of ≤5 units was considered as a slow titration algorithm, a dose increase of 6 units was considered as following a Davies algorithm, a dose increase of 7-18 units was considered as following a Fritsche algorithm and a dose increase of ≥19 units was considered as a tight titration algorithm. In the FAS population the actual titration algorithm was slow titration for 1,634 patients (66.2%), Davies algorithm for 229 patients (9.3%), Fritsche algorithm for 393 (15.9%) and tight titration for 52 patients (2.1%). For a total of 162 patients (6.6%) no dose increase was reported in the first four weeks of the study. More than 60% of patients in all three pre-indicated titration strata used slow titration (Fritsche 66.0%, Davies 68.8%, IT 63.7%), followed by Fritsche algorithm (Fritsche 16.1%, Davies 14.8%, IT 16.8%) and Davies algorithm (Fritsche 10.3%, Davies 9.4%, IT 6.4%). Only 2.2% (Fritsche), 1.5% (Davies) and 2.8% (IT) used tight titration. No obvious differences in actual algorithms were observed between the pre-indicated titration groups (p=0.3549, Kruskal-Wallis test). More details are listed in DIS02T_FAS and AHDIS02Tests_FAS. Results of the main endpoints analyzed for the actual treatment algorithms used are shown in TOP_final_analysis_ATRT_2016-04-22.
Participant characteristics and primary analyses:	**Demographic data and baseline characteristics** The FAS consisted of 52.9% male and 46.4% female patients with a mean (±SD) age of 65.4 (±11.3) years. For 0.7% of patients no gender was reported. The mean (±SD) weight was 90.2 (±17.7) kg, and 53.2% of patients had a BMI of 30 kg/m^2 or more at

	baseline while 45.7% of patients had a BMI less than 30 kg/m^2. The mean (±SD) HbA_{1c} value before study was 8.5 (±0.78)% and mean FBG (±SD) before study was 183.2 (±40.36) mg/dL. The individual target value for HbA_{1c} had a mean (±SD) of 6.9 (±0.48)%. Demographic data and baseline characteristics were comparable among the three pre-indicated titration groups (statistical tests showed only p-values <0.05 for baseline FBG values (Fritsche 185.9±40.24 mg/dL, Davies 181.0±40.78 mg/dL, IT 181.4±40.40 mg/dL; p=0.0243, ANOVA) and individual predefined HbA_{1c} target values (Fritsche 6.9±0.47%, Davies 6.9±0.48%, IT 7.0±0.51%; p=0.0137, ANOVA, see AHDM01Tests_FAS)). The median start day of insulin glargine U100 (Lantus®) treatment was day 0, i.e. the day of documentation 1 (both quartile (Q) 1 and Q3 being 0). The application time point for insulin glargine U100 (Lantus®) start was in the morning for 19.6% of patients, in the evening for 33.6% of patients and at bedtime for 47.8% of patients. Only 1.1% of patients received insulin glargine U100 (Lantus®) at lunch time. More details are listed in MT01T_FAS. **Disease history** In the FAS (±SD) mean time since first diagnosis of type 2 diabetes mellitus was 8.4 (±6.3) years. Time since first diagnosis was less than 3 years for 330 patients (13.4%), 3-5 years for 477 patients (19.3%), 5-10 years for 1,109 patients (44.9%) and more than 10 years for 533 patients (21.6%). Comparing the three pre-indicated titration groups, a slightly higher diabetes duration was observed in the IT group with a mean (±SD) duration of 8.8 (±6.9) years and 26.0% of patients with a duration of more than 10 years (p=0.3714, Kruskal-Wallis test). Less than 1% of FAS patients reported symptomatic hypoglycaemia cases within the last 12 weeks prior to study. **Previous and concomitant diseases** At baseline (documentation 1), 86.4% of FAS patients reported concomitant diseases with comparable rates in the three pre-indicated titration groups (84.4%, 89.7% and 85.8% in Fritsche, Davies and IT group, respectively). The most commonly reported System Organ Classes (SOC) were nervous system disorders (80.1%), metabolism and nutrition disorders (19.6%), cardiac disorders (15.8%), respiratory, thoracic and mediastinal disorders (13.4%) and vascular disorders (10.4%). Other SOC were reported for less than 10% of FAS patients. MedDRA preferred terms (PT) reported in at least 5% of FAS patients were: hypertonia (75.5%), neuropathy peripheral (29.9%), hyperlipidaemia (9.6%), myocardial infarction (9.4%), chronic obstructive pulmonary disease (7.9%), peripheral arterial occlusive disease (7.9%), cerebrovascular accident (5.5%) and sleep apnoea syndrome (5.3%). At documentation 3, overall 63.5% of FAS patients reported concomitant disease (62.3%, 67.7% and 59.5% in pre-indicated Fritsche, Davies and IT group, respectively) with most commonly reported SOCs and PTs being the same as for baseline. **Previous and concomitant antidiabetic treatments** At documentation 1, a total of 59.8% of FAS patients received an OAD therapy with metformin (60.3%, 62.9%, 54.5% in pre-indicated Fritsche, Davies, IT group, respectively, p=0.0093, chi-square test), 28.6% received a combination of metformin and a dipeptidyl peptidase 4 (DPP4) inhibitor (27.7%, 27.8%, 30.9%, p=0.3440), 27.0% received DPP4 inhibitors (27.7%, 26.4%, 25.2%, p=0.5567), 17.1% received sulfonylureas (15.0%, 16.8%, 22.7%, p=0.0005), 6.2% received a glinide (6.2%, 4.9%, 7.9%, p=0.0890), 3.0% received sodium-glucose co-transporter 2 (SGLT2) inhibitors (2.3%, 3.1%, 3.9%, p=0.2063), 1.6% received a glitazone (1.7%, 1.5%, 1.1%, p=0.6161), and 1.3% received glucagon-like peptide-1 receptor agonists (GLP-1 RA)

	(1.3%, 0.6%, 2.2%, p=0.0364). Other antidiabetic therapies were reported for less than 1% of FAS patients. At documentations 2 and 3, lower frequencies for OADs were reported. However, the most frequently reported drugs remained metformin (55.1% and 50.2% of FAS patients in documentation 2 and 3, respectively), combination of metformin and a DPP4 inhibitor (32.2% and 29.8%), DPP4 inhibitors (25.5% and 22.6%), sulfonylureas (12.6% and 10.6%), a glinide (5.3% and 4.9%), and SGLT2 inhibitor (4.6% and 4.5%). Comparison of frequencies between the pre-indicated titration groups showed p-value (chi-square tests) <0.05 for metformin (p=0.0007 and p=0.0011 for documentation 2 and 3, respectively) and sulfonylurea (p=0.0009 and p=0.0045). Within the FAS population 215 patients (8.7%) received previous basal insulin therapy: 7.5% in the pre-indicated Fritsche group, 9.8% in the pre-indicated Davies group and 10.1% in the pre-indicated IT group. Of those, 127 patients (5.1%) received NPH insulin (4.4%, 5.7%, 6.1% in Fritsche, Davies and IT group, respectively) and 50 patients (2.0%) received insulin detemir (2.0%, 2.2%, 1.8%). Other therapies were reported for less than 1% of FAS patients. **Primary efficacy analysis – response rates defined as FBG ≤110 mg/dL (≤6.1 mmol/L) or HbA_{1c} ≤ individual predefined target (combined primary endpoint)** A total of 1,109 patients (unadjusted frequency: 44.9% [95% CI: 42.9% to 46.9%]; adjusted frequency (only patients with data available included): 45.6% [95% CI: 43.6% to 47.6%]) achieved the combined primary endpoint (i.e. had a response in FBG or HbA_{1c}) within the first 6 months after start of insulin glargine U100 (Lantus®) treatment. Response rates for the combined primary endpoint (adjusted frequencies) were 44.6% in the pre-indicated Fritsche group, 45.6% in the pre-indicated Davies group and 48.1% in the pre-indicated IT group with widely overlapping CIs (p=0.3979, chi-square test). Considering only month 7-12 data, for a total of 1,341 patients (unadjusted: 54.3%; adjusted: 59.3%) response in FBG or HbA_{1c} was reported. Response rates for the combined primary endpoint were similar within the pre-indicated titration groups (adjusted: 58.7%, 58.8% and 60.7% for Fritsche, Davies and IT group, respectively; p=0.7271, chi-square test). Overall 1,610 patients (unadjusted: 65.2% [95% CI: 63.3% to 67.1%]; adjusted: 65.9% [95% CI: 64.0% to 67.8%]) achieved the combined primary endpoint (i.e. had a response in FBG or HbA_{1c}) within 12 months after start of insulin glargine U100 (Lantus®). No difference was observed for these response rates within the pre-indicated titration groups (adjusted: 65.4%, 64.7%, 67.7% in Fritsche, Davies and IT group, respectively; p=0.5138, chi-square test). Results of the primary analysis are presented in Table 1. Response rates for the combined primary endpoint were compared between patients for whom a defined titration algorithm was pre-indicated (pooled Fritsche/Davies) and patients with a pre-indicated individual titration. Response rates in FBG or HbA_{1c} were 65.2% (adjusted, 95% CI: 62.9% to 67.3%) in the pooled Fritsche/Davies group compared to 67.7% (adjusted, 95% CI: 63.6% to 71.7%) in the IT group (p=0.2696, chi-square test). Looking at actual titration groups, the adjusted response rates for the combined primary endpoint (response in FBG or HbA_{1c}) within 12 months after start of insulin glargine (Lantus®) were 66.4% [95% CI: 64.1% to 68.7%] for slow titration, 70.4% [95% CI: 63.9% to 76.2%] for Davies, 63.2% [95% CI: 58.2% to 68.0%] for Fritsche and 59.6% [95% CI: 45.1% to 73.0%] for tight titration algorithm (p=0.2241, chi-square test). No obvious differences in the response rates for the combined primary endpoint (i.e. achieving FBG ≤110 mg/dL (≤6.1 mmol/L) or HbA_{1c} ≤ individual predefined target)

	were observed for subgroups by age or baseline OAD treatment compared to overall FAS. Of note, in patients receiving a combination of metformin and a DPP-4 inhibitor at baseline response rates were higher in the pre-indicated IT group compared to pre-indicated Fritsche and Davies group particularly for month 1-6 (adjusted frequencies IT group: 57.4% [95% CI: 49.6% to 65.0%]; Fritsche: 43.8% [95% CI: 39.0% to 48.6%], p=0.0027, pairwise chi-square test; Davies: 44.8% [95% CI: 38.5% to 51.2%], p=0.0113, pairwise chi-square test). Patients who had a basal insulin therapy prior to this study showed higher response rates (FBG or HbA_{1c}) during month 1-6 (adjusted frequencies: 56.6% [95% CI: 49.6% to 63.4%], compared to 44.5% [95% CI: 42.5% to 46.6%] in insulin naïve patients, p=0.0008, chi-square test). However, the difference was smaller for month 1-12 (68.4% [95% CI: 61.7% to 74.5%], compared to 65.6% [95% CI: 63.6% to 67.6%] in insulin naïve patients, p=0.4188). In total, response rates for the combined primary endpoint (i.e. achieving FBG or HbA_{1c} targets) were lower in patients with higher baseline BMI (≥30 kg/m^2, adjusted frequencies: 41.8%, 54.7%, and 60.6% for month 1-6, 7-12, and 1-12, respectively) compared to patients with lower BMI (<30 kg/m^2, 49.9%, 64.8%, 72.2%; p<0.0001, chi-square tests for response during month 1-6 and month 1-12). Of note, in patients with higher baseline BMI response rates were higher in the pre-indicated IT group compared to pre-indicated Fritsche and Davies group (adjusted frequencies during month 1-12 in IT group: 66.6% [95% CI: 60.9% to 71.9%]; Fritsche: 59.3% [95% CI: 55.2% to 63.2%], p=0.0348, pairwise chi-square test; Davies: 57.0% [95% CI: 51.8% to 62.1%], p=0.0117, pairwise chi-square test).

Table 1: Response rates defined as FBG ≤110 mg/dL (≤6.1 mmol/L) or HbA_{1c} ≤ individual predefined target (combined primary endpoint)

Observation Period Statistics	Fritsche group* (N=1153)	Davies group* (N=715)	IT group* (N=543)	Unknown titration* (N=59)	Total (N=2470)
Month 1-6					
Response [1]	509 (44.1%)	320 (44.8%)	256 (47.1%)	24 (40.7%)	1109 (44.9%)
No response	633 (54.9%)	381 (53.3%)	276 (50.8%)	33 (55.9%)	1323 (53.6%)
No data	11 (1.0%)	14 (2.0%)	11 (2.0%)	2 (3.4%)	38 (1.5%)
N	1153	715	543	59	2470
95% CI [3]	[41.3, 47.1]	[41.1, 48.5]	[42.9, 51.4]	[28.1, 54.3]	[42.9, 46.9]
Response [2]	509 (44.6%)	320 (45.6%)	256 (48.1%)	24 (42.1%)	1109 (45.6%)
No response	633 (55.4%)	381 (54.4%)	276 (51.9%)	33 (57.9%)	1323 (54.4%)
N	1142	701	532	57	2432
95% CI [3]	[41.7, 47.5]	[41.9, 49.4]	[43.8, 52.5]	[29.1, 55.9]	[43.6, 47.6]
p-value [4]					0.3979
Month 7-12					
Response [1]	619 (53.7%)	390 (54.5%)	297 (54.7%)	35 (59.3%)	1341 (54.3%)
No response	436 (37.8%)	273 (38.2%)	192 (35.4%)	20 (33.9%)	921 (37.3%)
No data	98 (8.5%)	52 (7.3%)	54 (9.9%)	4 (6.8%)	208 (8.4%)
N	1153	715	543	59	2470
95% CI [3]	[50.8, 56.6]	[50.8, 58.2]	[50.4, 58.9]	[45.7, 71.9]	[52.3, 56.3]
Response [2]	619 (58.7%)	390 (58.8%)	297 (60.7%)	35 (63.6%)	1341 (59.3%)
No response	436 (41.3%)	273 (41.2%)	192 (39.3%)	20 (36.4%)	921 (40.7%)
N	1055	663	489	55	2262
95% CI [3]	[55.6, 61.7]	[55.0, 62.6]	[56.3, 65.1]	[49.6, 76.2]	[57.2, 61.3]
p-value [4]					0.7271
Month 1-12					
Response [1]	750 (65.0%)	456 (63.8%)	363 (66.9%)	41 (69.5%)	1610 (65.2%)
No response	396 (34.3%)	249 (34.8%)	173 (31.9%)	16 (27.1%)	834 (33.8%)
No data	7 (0.6%)	10 (1.4%)	7 (1.3%)	2 (3.4%)	26 (1.1%)
N	1153	715	543	59	2470
95% CI [3]	[62.2, 67.8]	[60.1, 67.3]	[62.7, 70.8]	[56.1, 80.8]	[63.3, 67.1]
Response [2]	750 (65.4%)	456 (64.7%)	363 (67.7%)	41 (71.9%)	1610 (65.9%)
No response	396 (34.6%)	249 (35.3%)	173 (32.3%)	16 (28.1%)	834 (34.1%)
N	1146	705	536	57	2444
95% CI [3]	[62.6, 68.2]	[61.0, 68.2]	[63.6, 71.7]	[58.5, 83.0]	[64.0, 67.8]
p-value [4]					0.5138

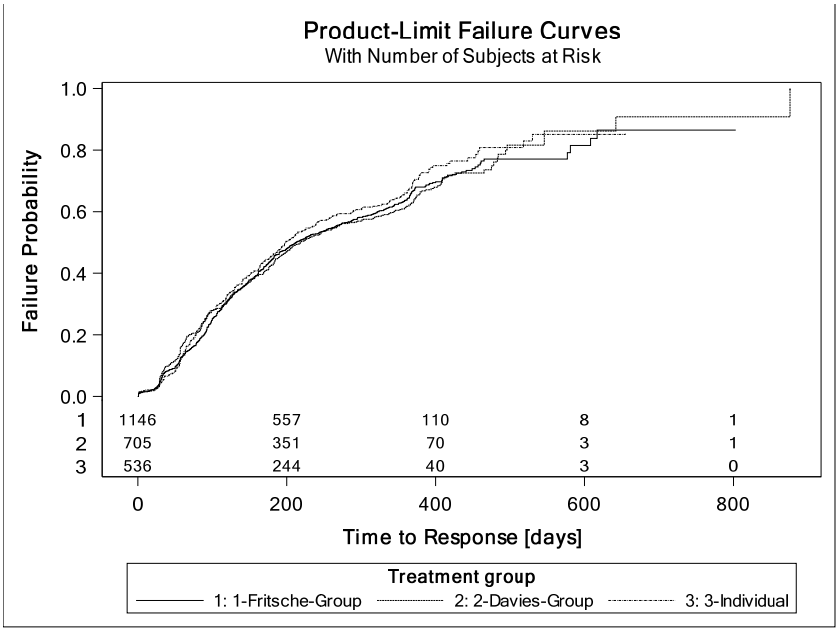
* Pre-indicated titration groups
[1] Denominator for calculation of percentages is the number of patients in the titration group.
[2] Denominator for calculation of percentages is the number of patients in the titration group with non-missing values.
[3] Exact 95% confidence intervals for rate of responders according to Pearson-Clopper.
[4] Results of chi-square tests for adjusted frequencies excluding patients with unknown group.
Response month 1-6: at least 2 FBG values <=110mg/dL or 1 HbA_{1c} value <= individual target before/at documentation 2.
Response month 7-12: at least 2 FBG values <=110mg/dL or 1 HbA_{1c} value <= individual target after documentation 2.
Response month 1-12: at least 2 FBG values <=110mg/dL or 1 HbA_{1c} value <= individual target before/at/after documentation 2.
Only FBG values measured at monthly visits contribute to analysis.
Exception: missing FBG values at monthly visit were replaced by last value reported in interim documentation (LOCF).
Source: RR01T_RR1_FAS

Other analyses:	**Change in HbA_{1c} and FBG values** Within the FAS population, mean (±SD) HbA_{1c} value at baseline was 8.49 (±0.783) %. Mean (±SD) changes from baseline were -1.14 (±0.898) % points in documentation 2 and -1.37 (±0.966) % points in documentation 3. Between the three pre-indicated titration algorithms only small differences were observed with mean changes from baseline being -1.14% points and -1.37% points at documentation 2 and 3 in the Fritsche group, -1.11% points and -1.36% points in the Davies group and -1.19% points and -1.38% points in the IT group. In the total FAS population, mean (±SD) FBG value at baseline was 183.2 (±40.36) mg/dL. Mean (±SD) changes from baseline were -54.5 (±43.25) mg/dL in documentation 2 and -59.2 (±44.05) mg/dL in documentation 3. Between the three titration algorithms only small differences were observed with mean FBG values of 129.6 mg/dL, 127.5 mg/dL, 130.3 mg/dL (documentation 2) and 125.4 mg/dL, 120.7 mg/dL, 125.1 mg/dL (documentation 3) in pre-indicated Fritsche, Davies and IT group, respectively. Summary tables for HbA_{1c} and FBG absolute values and changes from baseline by titration group and visit are provided in LB01T_HBA1C_FAS and LB01T_FBG_FAS. **Primary endpoint component response rates for FBG, HbA_{1c} and a combination of FBG and HbA_{1c}** In addition to the combined primary efficacy parameter, response rates were analyzed for • response defined by achieving a FBG value ≤110 mg/dL (≤6.1 mmol/L) • response defined by achieving the individual predefined target value for HbA_{1c} • response defined by achieving a FBG value ≤110 mg/dL (≤6.1 mmol/L) and the individual predefined target value for HbA_{1c} Response for FBG was observed for 690 patients (adjusted: 28.7% [95% CI: 26.9% to 30.5%]) in month 1-6, 872 patients (adjusted: 39.4% [95% CI: 37.3% to 41.4%]) in month 7-12 and for 1,104 patients (adjusted: 45.6% [95% CI: 43.6% to 47.6%]) in month 1-12 with no notable difference among the pre-indicated titration groups. For month 7-12 higher response rates were observed in Davies group (adjusted: 43.5% [95% CI: 39.7% to 47.5%]) compared to Fritsche (adjusted: 38.5% [95% CI: 35.5% to 41.5%], p=0.0404, pairwise chi-square test) and IT group (adjusted: 35.5% [95% CI: 31.3% to 40.0%], p=0.0066, pairwise chi-square test). Response for HbA_{1c} was observed for 701 patients (adjusted: 30.9% [95% CI: 29.0% to 32.8%]) in month 1-6, 976 patients (adjusted: 46.7% [95% CI: 44.5% to 48.9%]) in month 7-12 and for 1,184 patients (adjusted: 50.7% [95% CI: 48.6% to 52.7%]) in month 1-12. For all observation periods the highest response rates were observed for the IT group (adjusted: 33.4%, 50.2% and 54.2% at month 1-6, 7-12 and 1-12, respectively) and the lowest response rates were observed for the Davies group (adjusted: 27.9%, 44.4% and 48.1%, respectively). However, p-values (chi-square tests) for overall comparison of pre-indicated titration groups were >0.1 for all periods. For response defined by FBG and HbA_{1c} at target the response episodes for FBG and HbA_{1c} had to be overlapping. Response was observed for 249 patients (adjusted: 11.1% [95% CI: 9.8% to 12.5%]) in month 1-6, 423 patients (adjusted: 20.7% [95% CI: 19.0% to 22.5%]) in month 7-12 and for 498 patients (adjusted: 21.5% [95% CI: 19.9% to 23.2%]) in month 1-12 with no notable differences among the pre-indicated titration groups for all periods.

Time to response

For response defined by FBG or HbA_{1c} at target (as defined for the combined primary endpoint) the median time to response was 210 days (95% CI: 199 to 226 days) without obvious differences among pre-indicated titration groups (213, 218, and 198 days in Fritsche, Davies, and IT groups, respectively). Response rates (Kaplan-Meier estimates) were 45% (95% CI: 43% to 47%) at month 6 and 65% (95% CI: 63% to 67%) at month 12. Kaplan-Meier curves of the pre-indicated titration groups were largely overlapping (see Figure 2) and pairwise log-rank tests did not reveal notable differences. For further details see tables RR02T_TTR1_FAS - RR02T_TTR4_FAS.

Figure 2: Kaplan-Meier plot for time to response defined as FBG or HbA_{1c} at target

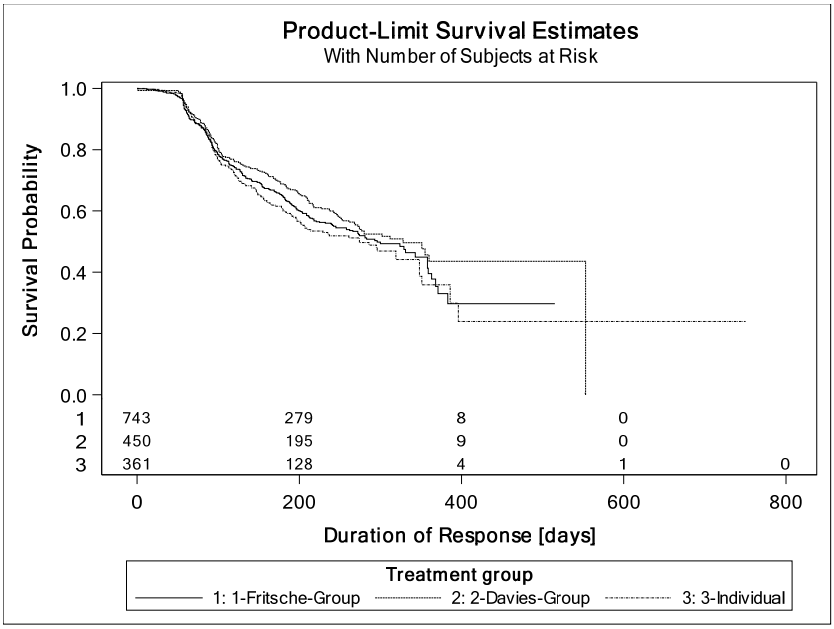


For time to response defined as FBG ≤110 mg/dL (≤6.1 mmol/L) only or HbA_{1c} at predefined individual target only the median was not reached within 12 months after start of insulin glargine U100 (Lantus®) treatment.

Duration of response

For response defined as FBG or HbA_{1c} at target (as defined for the combined primary endpoint) 1,595 patients were included in this analysis (743 pre-indicated Fritsche, 450 pre-indicated Davies, 361 pre-indicated IT, 41 unknown pre-indicated titration group). Of those 617 patients (38.7%) documented end of response (38.5%, 37.1%, and 41.0% in Fritsche, Davies, and IT group, respectively). Median duration of response was 296 days (95% CI: 273 to 343 days) without obvious differences among pre-indicated titration groups (296, 328, and 274 days in Fritsche, Davies, and IT groups, respectively; pairwise log-rank tests: p=0.1953 Fritsche vs Davies group, p=0.3908 Fritsche vs IT and p=0.0646 Davies vs IT). Event-free rate (i.e., no end of response) at month 6 (Kaplan-Meier estimate) was 64% (95% CI: 61% to 67%). The highest event-free rate was observed in the Davies group (68% [95% CI: 63% to 73%]) as compared to Fritsche (63% [95% CI: 59% to 67%]) and IT group (60% [95% CI: 54% to 65%]). Kaplan-Meier curves are provided in Figure 3. For further details see tables RR02T_DR1_FAS - RR02T_DR4_FAS.

Figure 3: Kaplan-Meier plot for duration of response defined as FBG or HbA_{1c} at target



Hypoglycaemia rates

An overview for hypoglycaemia incidence rates is provided in Table 2.

Of note: Due to the high number of hypoglycaemia events reported in one single patient (patient ID: 150002, pre-indicated Fritsche group) analyses of hypoglycaemia rates were repeated excluding this patient.

Symptomatic hypoglycaemia: Overall 45 patients (1.8% [95% CI: 1.3% to 2.4%]) reported at least one symptomatic hypoglycaemic event: 20 patients (1.7% [95% CI: 1.1% to 2.7%]) in the pre-indicated Fritsche group, 11 patients (1.5% [95% CI: 0.8% to 2.7%]) in the Davies group, and 14 patients (2.6% [95% CI: 1.4% to 4.3%]) in the IT group (no patient in unknown titration group) with no obvious differences between the pre-indicated titration groups (p=0.3574, chi-square test). Rates per patient year were lower in the Davies group (0.03 [95% CI: 0.01 to 0.04]) compared to Fritsche (0.06 [95% CI: 0.05 to 0.08]) and IT group (0.06 [95% CI: 0.04 to 0.08]). Excluding patient 150002 who had reported 38 symptomatic hypoglycaemic events, the rate per patient year in the Fritsche group (0.03 [95% CI: 0.02 to 0.04]) was similar to the rate in the Davies group.

Confirmed symptomatic hypoglycaemia: Overall 38 patients (1.5% [95% CI: 1.1% to 2.1%]) reported at least one confirmed symptomatic hypoglycaemic event: 15 patients (1.3% [95% CI: 0.7% to 2.1%]) in the pre-indicated Fritsche group, 9 patients (1.3% [95% CI: 0.6% to 2.4%]) in the Davies group, 13 patients (2.4% [95% CI: 1.3% to 4.1%]) in the IT group, and one patient (1.7% [95% CI: 0.0% to 9.1%]) with unknown titration group with no obvious differences between the pre-indicated titration groups (p=0.1780, chi-square test). Rates per patient year were lower in the Davies group (0.03 [95% CI: 0.02 to 0.04]) compared to Fritsche (0.05 [95% CI: 0.04 to 0.07]) and IT group (0.05 [95% CI: 0.04 to 0.08]). Excluding patient 150002 who had reported 38 confirmed symptomatic hypoglycaemic events, the rate per patient year in the Fritsche group was 0.02 [95% CI: 0.01 to 0.03].

Nocturnal hypoglycaemia: Overall 16 patients (0.6% [95% CI: 0.4% to 1.0%]) reported at least one nocturnal hypoglycaemic event: 5 patients (0.4% [95% CI: 0.1% to 1.0%]) in the pre-indicated Fritsche group, 5 patients (0.7% [95% CI: 0.2% to 1.6%]) in the Davies group, 5 patients (0.9% [95% CI: 0.3% to 2.1%]) in the IT group, and one

patient (1.7% [95% CI: 0.0% to 9.1%]) with unknown titration group with no obvious differences between the pre-indicated titration groups (p=0.4646, Fisher exact test). Rates per patient year were higher in the pre-indicated Fritsche group (0.02 [95% CI: 0.02 to 0.03]) compared to Davies (0.01 [95% CI: 0.00 to 0.01]) and IT group (0.01 [95% CI: 0.00 to 0.02]). Excluding patient 150002 who had reported 24 nocturnal hypoglycaemic events, the rate per patient year in the Fritsche group was 0.00 [95% CI: 0.00 to 0.01].

Severe hypoglycaemia: Overall 9 patients (0.4% [95% CI: 0.2% to 0.7%]) reported at least one severe hypoglycaemic event: 3 patients (0.3% [95% CI: 0.1% to 0.8%]) in the pre-indicated Fritsche group, 3 patients (0.4% [95% CI: 0.1% to 1.2%]) in the Davies group, 2 patients (0.4% [95% CI: 0.0% to 1.3%]) in the IT group, and one patient (1.7% [95% CI: 0.0% to 9.1%]) with unknown titration group with no obvious differences between the pre-indicated titration groups (p=0.7326, Fisher exact test). Rates per patient year were 0.00 in all pre-indicated titration groups (95% CI: 0.00 to 0.00 in Fritsche and 0.00 to 0.01 in Davies and IT groups).

Severe nocturnal hypoglycaemia: Overall 6 patients (0.2% [95% CI: 0.1% to 0.5%]) reported at least one severe nocturnal hypoglycaemic event: two patients (0.2% [95% CI: 0.0% to 0.6%]) in the pre-indicated Fritsche group, two patients (0.3% [95% CI: 0.0% to 1.0%]) in the Davies group, one patient (0.2% [95% CI: 0.0% to 1.0%]) in the IT group, and one patient (1.7% [95% CI: 0.0% to 9.1%]) with unknown titration group with no obvious differences between the pre-indicated titration groups (p=0.8545, Fisher exact test). Rates per patient year were 0.00 in all pre-indicated titration groups (95% CI: 0.00 to 0.00 in Fritsche and 0.00 to 0.01 in Davies and IT groups).

A cross-tabulation of presence or absence of hypoglycaemia at baseline and during study with p-values (McNemar tests) for the comparison of rates at baseline vs during study is provided by pre-indicated titration group and hypoglycaemia category in Tables 3-5.

Table 2: Hypoglycaemia incidence rates during study (FAS)

	Fritsche group* (N=1153)	Davies group* (N=715)	IT group* (N=543)	Unknown titration* (N=59)	Total (N=2470)
Symptomatic	20 (1.7%)	11 (1.5%)	14 (2.6%)	-	45 (1.8%)
Confirmed symptomatic	15 (1.3%)	9 (1.3%)	13 (2.4%)	1 (1.7%)	38 (1.5%)
Nocturnal	5 (0.4%)	5 (0.7%)	5 (0.9%)	1 (1.7%)	16 (0.6%)
Severe	3 (0.3%)	3 (0.4%)	2 (0.4%)	1 (1.7%)	9 (0.4%)
Severe nocturnal	2 (0.2%)	2 (0.3%)	1 (0.2%)	1 (1.7%)	6 (0.2%)

* Pre-indicated titration groups
Denominator for calculation of percentages is the number of patients in the titration group.
Source: HG01T_1_FAS, HG01T_2_FAS, HG01T_3_FAS, HG01T_4_FAS, HG01T_5_FAS

Table 3: Hypoglycaemia changes from baseline (FAS) – pre-indicated Fritsche group

		Baseline		p-value
	During study	Yes	No	(McNemar test)
Symptomatic	**Yes**	0	20	
	No	6	1098	0.0060
Confirmed symptomatic	**Yes**	0	15	
	No	3	1107	0.0047
Nocturnal	**Yes**	0	5	
	No	2	1118	0.2568
Severe	**Yes**	0	3	
	No	2	1120	0.6547
Severe nocturnal	**Yes**	0	2	
	No	2	1121	1.0000

Source: AHHG01Tests_FAS

Table 4: Hypoglycaemia changes from baseline (FAS) – pre-indicated Davies group

		Baseline		p-value
	During study	Yes	No	(McNemar test)
Symptomatic	**Yes**	0	11	
	No	7	692	0.3458
Confirmed symptomatic	**Yes**	0	9	
	No	4	697	0.1655
Nocturnal	**Yes**	0	5	
	No	3	702	0.4795
Severe	**Yes**	0	3	
	No	2	705	0.6547
Severe nocturnal	**Yes**	0	2	
	No	1	707	0.5637

Source: AHHG01Tests_FAS

Table 5: Hypoglycaemia changes from baseline (FAS) – pre-indicated IT group

		Baseline		p-value
	During study	Yes	No	(McNemar test)
Symptomatic	**Yes**	1	13	
	No	5	511	0.0593
Confirmed symptomatic	**Yes**	0	13	
	No	1	516	0.0013
Nocturnal	**Yes**	0	5	
	No	2	523	0.2568
Severe	**Yes**	0	2	
	No	1	527	0.5637
Severe nocturnal	**Yes**	0	1	
	No	1	528	1.0000

Source: AHHG01Tests_FAS

Change in body weight

The mean (±SD) body weight at baseline was 90.2 (±17.7) kg. The mean (±SD) change of body weight was -0.6 (±5.0) kg at month 6 and -1.0 (±6.3) kg at month 12. There were no notable differences observed for body weight at baseline or change in body weight among the pre-indicated titration groups. A decrease in mean body weight was observed in all pre-indicated titration groups ($p<0.0001$ in Fritsche and Davies group, $p=0.0037$ in IT group, paired t-test for comparison of baseline and month 12 values).

In patients with response in FBG or HbA_{1c} during month 1-6 (N=1,109) the mean (±SD) body weight at baseline was 88.8 (±17.4) kg and mean (±SD) changes were -1.1 (±5.6) kg at month 6 and -1.2 (±7.0) kg at month 12. Similar results were observed for patients with response during month 1-12 (N=1,610): mean (±SD) body weight at baseline was 88.7 (±17.1) kg and mean (±SD) changes were -0.9 (±5.0) kg and -1.2 (±6.3) kg at month 6 and 12, respectively.

In patients without response during month 1-6 (N=1,323) the mean (±SD) body weight at baseline was 91.3 (±17.9) kg and mean (±SD) changes were -0.2 (±4.4) kg and -0.7 (±5.6) kg at month 6 and 12, respectively. In patients without response during month 1-12 (N=834) the mean (±SD) body weight at baseline was 93.0 (±18.6) kg and mean (±SD) changes were -0.1 (±5.0) kg and -0.3 (±6.3) kg at month 6 and 12, respectively. Of note, for non-responder an increase of mean±SD body weight was observed in the pre-indicated IT group (0.4±3.4 kg at month 6, 0.3±4.7 kg at month 12). Compared to patients with response (during month 1-12) there was less weight decrease in non-responders ($p=0.0029$, t-test).

In patients with response in FBG or HbA_{1c} and documented end of response (N=630) no obvious difference to the overall population was observed: mean (±SD) body weight at baseline was 89.3 (±18.2) kg and mean (±SD) changes were -0.7 (±6.4) kg and -0.7 (±7.8) kg at month 6 and 12, respectively.

Change in daily insulin doses

Mean insulin glargine U100 (Lantus®) doses based on the pre-indicated titration groups are presented in Table 6. Overall the mean (±SD) insulin glargine (Lantus®) dose increased from 11.7 (±6.25) units at baseline to 20.7 (±10.43) units at month 6 and 22.2 (±11.02) units at month 12.

In addition, insulin glargine U100 (Lantus®) doses were summarized in units per kg body weight (see Table 7). Overall the mean (±SD) insulin glargine U100 (Lantus®) doses were 0.13 (±0.070) units/kg body weight at baseline, 0.23 (±0.121) units/kg body weight at month 6 and 0.25 (±0.136) units/kg body weight at month 12.

Table 6: Insulin glargine U100 (Lantus®) doses [units] by visit

Visit Statistics	Fritsche group* (N=1153)	Davies group* (N=715)	IT group* (N=543)	Unknown titration* (N=59)	Total (N=2470)
Documentation 1					
N	1149	710	534	59	2452
Mean	11.8	11.3	12.1	10.4	11.7
Std	6.30	5.82	6.80	4.22	6.25
Documentation 2					
N	1094	689	511	58	2352
Mean	21.1	19.7	21.1	19.5	20.7
Std	10.46	9.55	11.61	8.09	10.43
Documentation 3					
N	1027	648	481	54	2210
Mean	22.8	20.9	22.8	20.9	22.2
Std	10.82	10.36	12.30	9.16	11.02

Baseline value (documentation 1) calculated as sum of morning, lunch, evening and bedtime units. Implausible doses (<0 or >800 units) are set to missing. Zero doses are included.
* Pre-indicated titration groups
Source: MT03T_FAS

Table 7: Insulin glargine U100 (Lantus®) doses [units/kg body weight] by visit

Visit Statistics	Fritsche group* (N=1153)	Davies group* (N=715)	IT group* (N=543)	Unknown titration* (N=59)	Total (N=2470)
Documentation 1					
N	1141	704	531	59	2435
Mean	0.13	0.13	0.14	0.12	0.13
Std	0.071	0.067	0.075	0.045	0.070
Documentation 2					
N	1094	685	511	58	2348
Mean	0.24	0.23	0.24	0.22	0.23
Std	0.114	0.130	0.124	0.094	0.121
Documentation 3					
N	1027	644	481	54	2206
Mean	0.26	0.24	0.26	0.24	0.25
Std	0.116	0.165	0.136	0.109	0.136

Baseline value (documentation 1) calculated as sum of morning, lunch, evening and bedtime units. Implausible doses (<0 or >800 units) are set to missing. Zero doses are included. Last Observation Carried Forward method applied for body weight assessed at documentation 1, 2 and 3.
* Pre-indicated titration groups
Source: MT04T_FAS

Propensity score analyses

Comparison pre-indicated Fritsche vs Davies group:

- Response rate for achieving the FBG target for month 1-6 was lower in the Fritsche group (23.9% vs 31.2%, p=0.0039, McNemar test). However, this difference was not confirmed for month 1-12 (43.9% vs 48.0%, p=0.1425, McNemar test).

	• Response rate for achieving an individual predefined HbA_{1c} was higher in the Fritsche group (month 1-6: 32.8% vs 27.2%, p=0.0455, McNemar test; month 1-12: 50.7% vs 46.6%, p=0.1482, McNemar test). • There were no obvious differences observed for response according to the combined primary endpoint (FBG or HbA_{1c} at target, month 1-6: 43.9% vs 44.8% in Fritsche and Davies group, month 1-12: 65.9% vs 64.3%) or the secondary endpoint defined as FBG and HbA_{1c} at target (month 1-6: 9.9% vs 10.9%, respectively, month 1-12: 19.2% vs 22.6%, respectively). • HbA_{1c} values were reduced more in Fritsche compared to Davies group from baseline to month 6 (mean difference between titration groups=0.18 [95% CI: 0.067 to 0.298], p=0.0021, paired t-test) and to month 12 (mean difference=0.16 [95% CI: 0.026 to 0.287], p=0.0185, paired t-test). • No obvious differences for change in FBG values were observed. <u>Comparison pre-indicated Fritsche vs individual titration group</u>: • Lower response rates were observed in the Fritsche group compared to IT group for o the combined primary endpoint (response defined as achieving FBG or HbA_{1c} target) during month 1-6 (39.8% vs 47.8%, p=0.0131, McNemar test) and for month 1-12 (62.4% vs 68.1%, p=0.0511, McNemar test). o Response defined as achieving the FBG target during month 1-6 (23.3% vs 29.2%, p=0.0438, McNemar test). However, this difference was not confirmed for month 1-12 (40.8% vs 44.4%). o Response defined as achieving an individual predefined HbA_{1c} during month 1-6 (25.8% vs 32.6%, p=0.0245, McNemar test) and for month 1-12 (44.7% vs 54.2%, p=0.0030, McNemar test). • No obvious difference was observed for response in the secondary endpoint defined as FBG and HbA_{1c} at target (month 1-6: 8.6% vs 10.4%, month 1-12: 18.1% vs 20.7%). • For change from baseline to month 12 HbA_{1c} values were reduced more in Fritsche compared to IT group (mean difference between titration groups=0.22 [95% CI: 0.062 to 0.385], p=0.0069, paired t-test). • No obvious differences for change in FBG values were observed. <u>Comparison pre-indicated Davies vs individual titration group</u>: • Lower response rates were observed in the Davies group compared to IT group for o the combined primary endpoint (response defined as achieving the FBG or HbA_{1c} target) during month 1-6 (42.3% vs 48.6%, p=0.0458, McNemar test) and during month 1-12 (62.1% vs 68.6%, p=0.0272, McNemar test). o Response defined as achieving an individual predefined HbA_{1c} during month 1-6 (30.7% vs 32.6%, p=0.5637, McNemar test) and during month 1-12 (47.1% vs 54.0%, p=0.0302, McNemar test). • No obvious differences were observed for response in the secondary endpoint FBG and HbA_{1c} at target (month 1-6: 11.2% vs 10.8%, month 1-12: 19.8% vs 20.4%) or for response defined as achieving the FBG target (month 1-6: 26.0% vs 30.0%, month 1-12: 41.9% vs 45.0%). • No obvious differences for change in HbA_{1c} or FBG values were observed.

	Safety Analyses Summary tables for AEs and SAEs by MedDRA SOC and PT are shown in TOP_final_analysis_safety_2016-05-03. An overview for adverse events is provided in Table 8. Overall, AEs were reported for 349 patients (12.6%) with a higher incidence rate in the pre-indicated IT group (15.6%) compared to Fritsche (11.3%) and Davies (12.5%) group. Most frequently reported SOCs were investigations (3.8%, 4.3%, 5.7% in pre-indicated Fritsche, Davies, IT groups, respectively), metabolism and nutrition disorders (4.1%, 3.6%, 5.0%), nervous system disorders (2.0%, 2.9%, 2.6%) as well as general disorders and administration site conditions (1.3%, 1.7%, 3.1%). For other SOCs AEs were reported for less than 2% of patients in all pre-indicated titration groups. MedDRA PT for AEs that were reported for at least 2% of patients were (sorted in descending frequency): • Blood glucose increased (SOC: investigations, 2.3%, 2.2%, 3.6% in pre-indicated Fritsche, Davies, IT groups, respectively) • Hypoglycaemia (SOC: metabolism and nutrition disorders, 2.1%, 1.8%, 2.6%) • Glycosylated haemoglobin increased (SOC: investigations, 1.4%, 2.0%, 2.3%) • Diabetes mellitus inadequate control (SOC: metabolism and nutrition disorders, 1.6%, 1.3%, 2.1%) Related AEs were defined as events that were considered associated to treatment with insulin glargine U100 (Lantus®) by the reporter or the sponsor. Related AEs were reported for 97 patients (3.5%): 35 patients in Fritsche group (2.7%), 27 patients in Davies group (3.4%), 34 patients in IT group (5.5%) and one patient (1.4%) with unknown titration group. MedDRA PTs for related AEs that were reported for at least 1% of patients were (sorted in descending frequency): • Blood glucose increased (SOC: investigations, 0.9%, 1.4%, 2.1% in pre-indicated Fritsche, Davies, IT groups, respectively) • Glycosylated haemoglobin increased (SOC: investigations, 0.6%, 1.4%, 2.1%) • Hypoglycaemia (SOC: metabolism and nutrition disorders, 0.6%, 1.1%, 1.1%) SAEs were reported for 95 patients (3.4%): 2.9%, 3.8% and 4.4% in pre-indicated Fritsche, Davies and IT groups, respectively. Most frequently reported SOCs were cardiac disorders (0.7%, 1.0%, 0.5% in pre-indicated Fritsche, Davies, IT groups, respectively), nervous system disorders (0.2%, 1.4%, 0.8%), general disorders and administration site conditions (0.3%, 0.5%, 1.0%), renal and urinary disorders (0.5%, 0.6%, 0.3%), infections and infestations (0.5%, 0.5%, 0.3%) and gastrointestinal disorders (0.1%, 0.1%, 1.3%). For other SOCs SAEs were reported for less than 10 patients overall. MedDRA PT for SAEs that were reported for at least 5 patients overall were (sorted in descending frequency): • Condition aggravated (SOC: general disorders and administration site conditions, 2 patients each in pre-indicated Fritsche, Davies and IT group) • Cerebrovascular accident (SOC: nervous system disorders, 4 patients in Davies and 1 patient in IT group) • Renal failure (SOC: renal and urinary disorders, 3 patients in Fritsche and 2 patients in Davies group) Related SAEs were reported for 13 patients (0.5%): 6 patients in Fritsche group (0.5%), 4 patients in Davies group (0.5%) and 3 patients in IT group (0.5%). Most

	frequently reported MedDRA SOCs for related SAEs were nervous system disorders (5 patients) and metabolism and nutrition disorders (4 patients). Other SOCs were reported for less than 3 patients. A summary for related SAEs is provided in AE01T_SREL_SAF. A total of 16 AEs with fatal outcome were reported for 12 patients (0.4%): 3 patients in pre-indicated Fritsche group (0.2%), 5 patients in pre-indicated Davies group (0.6%) and 4 patients in pre-indicated IT group (0.7%). MedDRA preferred terms for fatal AEs were cardiac arrest, death and cerebrovascular accident each reported for 2 patients overall, and cardiac failure, cardiac failure acute, myocardial infarction, multi-organ failure, senile dementia, infection, sepsis, bronchial carcinoma, renal failure and pneumonia aspiration each reported for single patients. None of the fatal AEs were considered associated to treatment with insulin glargine U100 (Lantus®) by the reporter or the sponsor. Fatal AEs are listed in AE01L_DTH_SAF. The narratives are listed in Appendix II.

Table 8: Overview of adverse events

Visit Statistics	Fritsche group* (N=1306)	Davies group* (N=786)	IT group* (N=615)	Unknown titration* (N=70)	Total (N=2777)
All adverse events (incl. SAE)					
Any AE	147 (11.3%)	98 (12.5%)	96 (15.6%)	8 (11.4%)	349 (12.6%)
Related AE	35 (2.7%)	27 (3.4%)	34 (5.5%)	1 (1.4%)	97 (3.5%)
Serious adverse events					
Any SAE	38 (2.9%)	30 (3.8%)	27 (4.4%)	-	95 (3.4%)
Related SAE	6 (0.5%)	4 (0.5%)	3 (0.5%)	-	13 (0.5%)
Fatal AE **	3 (0.2%)	5 (0.6%)	4 (0.7%)	-	12 (0.4%)

Denominator for calculation of percentages is the number of patients in the titration group. Numbers are for patients with at least one event. Related events defined as events that were considered associated to insulin glargine U100 (Lantus®) treatment by the reporter or sponsor.
* Pre-indicated titration groups
** None of the AEs with fatal outcome was considered as related AE.
Source: AE01T_SAF, AE01T_SER_SAF, AE01T_REL_SAF, AE01T_SREL_SAF, AE01T_DTH_SAF, AE01L_DTH_SAF

Discussions:	Titration of insulin glargine U100 (Lantus®) was pre-indicated to follow the Fritsche algorithm for 1,327 patients (47.1%), the Davies algorithm for 796 patients (28.2%) and an individual titration algorithm for 623 patients (22.1%). Post-hoc definition of actual titration behavior based on the insulin glargine U100 (Lantus®) dose increase within the first four weeks of the study revealed that actual titration defined as slow titration (≤5 units) was applied in 66.2% of FAS patients, titration defined as following a Davies algorithm (6 units) in 9.3%, titration defined as following a Fritsche algorithm (7-18 units) in 15.9% and actual titration defined as tight titration (≥19 units) in 2.1% of FAS patients. Demographic data and baseline characteristics were comparable among the different pre-indicated titration groups and were representative for German type 2 diabetes patients on OAD therapy starting basal insulin therapy. Within 12 months after start of insulin glargine U100 (Lantus®) response based on the combined primary endpoint (achieving FBG or HbA_{1c} target) occurred for 65.9% (adjusted frequency) of FAS patients with no obvious differences observed between the pre-indicated titration groups (adjusted frequencies: 65.4%, 64.7%, 67.7% in Fritsche, Davies and individual titration group, respectively). Similarly, no notable differences were observed among the pre-indicated titration groups for response defined as achieving FBG target alone, HbA_{1c} target alone and for the secondary endpoint of achieving FBG and HbA_{1c} targets combined. HbA_{1c} and FBG levels were lowered considerably during the first 12 months of insulin glargine U100 (Lantus®) treatment by -1.37% points and -59.2 mg/dL, respectively. However, only small differences between the three pre-indicated titration algorithms

	were observed regarding FBG and HbA_{1c} mean changes from baseline. The observed small differences between the three pre-indicated titration groups (Fritsche, Davies, IT) may be due to the fact that actual titration of basal insulin glargine U100 (Lantus®) was individualized for each patient and was done much slower (in approx. 95% of patients ≤3 titration steps during the first month of titration were applied) and with smaller dose increases (in 66.2% of patients ≤5 units were added in the first month of titration) in the majority of patients. Furthermore, differences in the amount of units added during the first month of titration were rather equally distributed within the three pre-indicated titration groups. Therefore, although participating physicians indicated certain preferences of given or individual dosing algorithms for titrating insulin glargine U100 (Lantus®) in their type 2 diabetes patients, in clinical practice each patient was treated very individually and in most cases dose increases were handled very reluctantly. Several reasons might apply to explain the difference between pre-indicated and actual dosing behavior; among others fear of hypoglycaemia, especially nocturnal hypoglycaemia, fear of weight gain due to insulin therapy, or fear of overdosing insulin therapy. Further investigations are necessary to evaluate the actual reasons for this “inertia” to necessary timely and sufficient basal insulin dose increases. Confirmed symptomatic (0.04 events/patient year [E/pty; 95% CI: 0.04-0.05 E/pty]), nocturnal (0.01 E/pty [95% CI: 0.01-0.02 E/pty]) or severe hypoglycaemia event rates (0.00 E/pty [95% CI: 0.00-0.00 E/pty]) were low and no obvious difference was observed between the pre-indicated titration groups. Overall AEs were reported for 349 patients (12.6%) with a slightly higher incidence rate in the IT group (15.6%) compared to Fritsche (11.3%) and Davies (12.5%) group. Most frequently reported SOCs were investigations, metabolism and nutrition disorders, nervous system disorders and general disorders and administration site conditions. MedDRA PT for AEs that were reported for at least 2% of patients were blood glucose increased, hypoglycaemia, glycosylated haemoglobin increased and diabetes mellitus inadequate control. Related AEs were reported for 97 patients (3.5%): 35 patients in Fritsche group (2.7%), 27 patients in Davies group (3.4%), 34 patients in IT group (5.5%) and one patient (1.4%) with unknown titration group. SAEs were reported for 95 patients (3.4%): 2.9%, 3.8% and 4.4% in Fritsche, Davies and IT group, respectively. Most frequently reported SOCs were cardiac disorders, nervous system disorders, general disorders and administration site conditions, renal and urinary disorders, infections and infestations and gastrointestinal disorders. MedDRA PT for SAEs that were reported for at least 5 patients overall were condition aggravated, cerebrovascular accident and renal failure. Related SAEs were reported for 13 patients (0.5%): 6 patients in Fritsche group (0.5%), 4 patients in Davies group (0.5%) and 3 patients in IT group (0.5%). AEs with fatal outcome were reported for 12 patients (0.4%) overall. MedDRA preferred terms for fatal AEs were cardiac arrest, death and cerebrovascular accident each reported for 2 patients, and cardiac failure, cardiac failure acute, myocardial infarction, multi-organ failure, senile dementia, infection, sepsis, bronchial carcinoma, renal failure and pneumonia aspiration each reported for single patients. None of the fatal AEs were considered associated to treatment with insulin glargine U100 (Lantus®) by the reporter or the sponsor. Reported AEs did not reveal any safety signal for insulin glargine U100 (Lantus®) and correspond to the expected risk profile for the drug substance which is reflected in the SmPC of Lantus®. The results obtained from the present observational study show an improvement in glycemic control after introducing basal insulin therapy with insulin glargine U100 (Lantus®) in a previously poorly controlled, unselected T2DM patient population from a daily clinical practice setting in Germany and may be considered representative for

	German type 2 diabetes patients.
Conclusions:	The TOP observational study, conducted in Germany, showed improvements in glycemic control by initiating basal insulin therapy with insulin glargine U100 (Lantus®) in type 2 diabetes patients pretreated with oral antidiabetic drugs (plus another basal insulin in 8.7% of patients), as indicated by a mean decrease in HbA_{1c} of -1.37% points after 12 months of treatment. This improvement was accompanied by a marked decrease in FBG of -59.2 mg/dL (-3.3 mmol/L) at 12-month assessment compared to baseline. With insulin glargine U100 (Lantus®) 65.9% of the type 2 diabetic patients achieved the combined primary endpoint defined as reaching their individual HbA_{1c} target or a FGB ≤110 mg/dL within 12 months. Within 12 months 50.7% of the patients achieved their individual HbA_{1c} target, and 45.6% of the patients achieved a target FBG ≤110 mg/dL. Improvement of glycemic control seemed to be independent of the pre-indicated titration algorithm to be applied; this might be due to the small and slow steps in dose increase seen in the majority of patients during the first 4 weeks of treatment. Reasons for this reluctant dosing behavior remain to be assessed, especially in view of the very low rates of hypoglycaemia and no weight gain observed in this study. According to the reported AEs, safety analyses overall indicated that the BOT with insulin glargine U100 (Lantus®) was well tolerated, with very few serious adverse events or severe hypoglycaemic episodes. Therefore, insulin glargine U100 (Lantus®) appears to be a well-tolerated and effective treatment option for initiating insulin therapy in a BOT regimen, independent of the treatment algorithm chosen.
Date of report:	22-Aug-2016
References:	[1] Bundesärztekammer (BÄK), Kassenärztliche Bundesvereinigung (KBV), Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften (AWMF). Nationale VersorgungsLeitlinie Therapie des Typ-2-Diabetes – Langfassung, 1. Auflage. Version 4. 2013, zuletzt geändert: November 2014. Available from: www.dm-therapie.versorgungsleitlinien.de; [cited: 24.05.2016]; DOI: 10.6101/AZQ/000213 [2] Inzucchi SE, Bergenstal RM, Buse JB, Diamant M, Ferrannini E, Nauck M et al. Management of Hyperglycemia in Type 2 Diabetes, 2015: A Patient-Centered Approach. Diabetes Care 2015; 38: 140–149 [3] Fritsche A, Schweitzer MA, Häring HU; 4001 Study Group. Glimepiride combined with morning insulin glargine, bedtime neutral protamine hagedorn insulin, or bedtime insulin glargine in patients with type 2 diabetes. A randomized, controlled trial. Ann Intern Med 2003; 138: 952-959 [4] Davies M, Storms F, Shutler S, Bianchi-Biscay M, Gomis R; AT.LANTUS Study Group et al. Improvement of glycemic control in subjects with poorly controlled type 2 diabetes: comparison of two treatment algorithms using insulin glargine. Diabetes Care 2005; 28: 1282-1288

	[5] Yki-Järvinen H, Juurinen L, Alvarsson M, Bystedt T, Caldwell I, Davies M et al. Initiate Insulin by Aggressive Titration and Education (INITIATE): a randomized study to compare initiation of insulin combination therapy in type 2 diabetic patients individually and in groups. Diabetes Care 2007; 30: 1364-1369 [6] Gerstein HC, Yale JF, Harris SB, Issa M, Stewart JA, Dempsey E. A randomized trial of adding insulin glargine vs. avoidance of insulin in people with Type 2 diabetes on either no oral glucose-lowering agents or submaximal doses of metformin and/or sulphonylureas. The Canadian INSIGHT (Implementing New Strategies with Insulin Glargine for Hyperglycaemia Treatment) Study. Diabet Med 2006; 23: 736-742 [7] Riddle MC, Rosenstock J, Gerich J; Insulin Glargine 4002 Study Investigators. The treat-to-target trial: randomized addition of glargine or human NPH insulin to oral therapy of type 2 diabetic patients. Diabetes Care 2003; 26: 3080-3086 [8] SmPC Lantus®, effective February 2016. Available at: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/000284/WC500036082.pdf