Non-interventional trial (NIT) according to § 67(6) AMG with

Lantus®

Blood glucose regulation with Lantus® and DPP-4 inhibitor in the context with BOT combination therapy in diabetes type 2 patients

GOLD - observational trial

LANTU_L_05196

Report - Final version - 19-OCT-2012

1 SYNOPSIS

Sanofi-Aventis Deutschland GmbH

Non-interventional trial number: LANTU_L_05196

Trade name: LANTUS®

Active ingredient: Insulin glargine

Title of non-interventional trial:

GOLD

Blood glucose regulation with Lantus® and DPP-4 inhibitor in the context with BOT combination therapy in diabetes type 2 patients

Duration of the observational period: January 1, 2010 (start of NIT) to January 9, 2012 (date of last visit documented)

Aim of the non-interventional trial:

The GOLD-observation study (Blood glucose re**G**ulati**O**n with **L**antus® and a **D**PP-4 inhibitor in BOT in type 2 diabetes patients) has two main objectives:

a) Documentation of changes in the FBG, HbA_{1c} and the insulin dose during an approx. 20 week-long observation period, through a guideline-based initiation/adjustment of the patients treated with Lantus® in a BOT under daily conditions.

b) Documentation of therapy effects (tolerability, adverse events) in connection with initiating Lantus® in addition to a metformin/DPP-4 inhibitor combination therapy in early T2DM patients over an approx. 20 week observation period with regard to the metabolism control under daily conditions.

Participating physicians: 650 physicians with own practice. Most of the patients were treated by general practitioners (62.51%) and internists (33.04%).

Diagnosis and documentation criteria:

The patients had to meet the following conditions in order to be included in the study:

- Insulin-naive type-2 diabetes mellitus
- Metformin/DPP-4 inhibitor combination therapy for at least three months
- $7.5\% \leq HbA_{1c} \leq 10\%$
- Age ≥18 years
- Capability of self-blood glucose monitoring
- Patient informed consent

Not documented were patients with:

- A therapy during the last six months with insulin, sulfonylurea, glitazones, GLP-1 analogues or acarbose
- Severe hypoglycaemia during the course of the disease (blood glucose < 56 mg/dl or < 3.1 mmol/l)

- A contradiction for a therapy with Lantus®
- Known alcohol or drug abuse
- Dementia or a general incapability to understand the contents of the study

Effectiveness parameters:

Primary outcome measurements:

- Change in HbA_{1C} value from start of BOT with Lantus® to endpoint
- Change in FBG value from start of BOT with Lantus® to endpoint
- Number and proportion of patients with glycaemic target achievement (HbA_{1c} < 6.5%) at endpoint
- Number and proportion of patients with glycaemic target achievement (HbA_{1c} < 7.0%) at endpoint
- Number and proportion of patients with glycaemic target achievement (FBG < 100 mg/dl / 5.6 mmol/l) at endpoint

Secondary outcome measurements:

- Individual treatment goals for FBG value
- Change in insulin dosage per day from start of insulin treatment to endpoint
- Change in number of daily insulin injections day from start of insulin treatment to endpoint
- Change in application time point of insulin from start of insulin treatment to endpoint
- Change in metformin and DPP-4 inhibitor dosage from start of insulin treatment to endpoint
- Change in body weight from start of insulin treatment to endpoint
- Number of insulin dosage adjustments during the first 4 to 6 months after start of insulin treatment
- Consumption of blood glucose stripes per day and per month at endpoint
- Consumption of pen needles per day and per month at endpoint

Safety parameters:

- Incidence of confirmed symptomatic hypoglycaemias with blood glucose levels ≤ 70 mg/dl (3.9 mmol/I) during BOT with Lantus®
- Incidence of confirmed severe hypoglycaemias with blood glucose levels < 56 mg/dl (3.1 mmol/I) during BOT with Lantus®
- Incidence of adverse events during BOT with Lantus®

Statistical methods:

The statistical analysis of all collected data was performed using descriptive measures. The biometrical analysis was carried out after determination of a statistical analysis plan being defined prior to database closure. Continuous data were described by mean, standard deviation, median, 1^{st}, 25^{th}, 75^{th} and 99^{th} percentile. The 95% confidence intervals (CI) will be reported for the changes in HbA_{1c} and in FBG. Categorical data were described using

absolute and relative frequencies.

Results

Data sets:

The safety analysis set included all patients for whom a case report form was available. According to the objectives of this non-interventional trial patients were included in the analysis of effectiveness only if the selection criteria were met. For 221 patients at least one selection criteria was not met. This results in the following sample sizes:

- Efficacy analysis set: N = 1,262
- Safety analysis set: N = 1,483

Demographic data and baseline characteristics:

Demographic data

55.15% of the patients were male, 44.53% female. The mean age was 63.2 ± 10.5 (SD) years for men and 65.5 ± 10.9 (SD) years for women. The mean body weight was 95.16 ± 16.05 (SD) kg for men and 82.92 ± 15.19 (SD) kg for women. The mean body mass index was 30.63 ± 4.70 (SD) kg/m² for men and 30.91 ± 5.44 (SD) kg/m² for women.

Type 2 diabetes mellitus and complications/comorbidities

The diabetes was known since less than one year in 0.79% of the patients, since 1 to < 3 years in 10.46%, since 3 to < 5 years in 16.48%, since 5 years and more in 71.71%. For 64.90% of the patients complications and comorbidities were specified. 24.88% of the patients have one complication or comorbidity and 40.02% have more than one complication or comorbidity. The most frequent complications / comorbidities were microalbuminuria (31.85%), neuropathy (30.19%), coronary heart disease (26.62%), nephropathy (13.87%) and retinopathy (13.87).

HbA_{1c} and FBG at baseline

At baseline the mean HbA_{1c}-value was 8.50% ± 0.98% (SD) and the mean fasting blood glucose (FBG) value was 173.96 ± 46.57 (SD) mg/dl.

Antidiabetic pretreatment

8.08% of the patients received metformin since less than one year before start of BOT with Lantus®, 21.00% since 1 to < 3 years, 22.90% since 3 to 5 years and 42.55% since 5 years and more (no data: 5.47%).

30.11% of the patients received a DPP-4 inhibitor since less than 6 months before start of BOT with Lantus®, 31.93% since 6 months to < one year, 30.90% since one year to < 3 years and 4.12% since 3 years and more (no data: 2.93%).

Basal insulin supported oral therapy (BOT) with Lantus®:

Lantus®

The treatment with Lantus® started 1.05 ± 11.23 (SD) days (mean) before documentation 1 (baseline). The mean initial dosage administered was 13.35 ± 7.04 (SD) Units per day. During the approximately 20 weeks treatment (baseline up to documentation 2) the dosage

of Lantus® increased from 13.43 Units/day to 20.39 Units/day (based on N = 1,180), corresponding to a mean change of 6.96 ± 7.70 (SD) Units/day. For 20.92% (N = 264) of the patients the dosage was increased again on day of documentation 2. Mean increment was 3.74 ± 2.42 SD) Units/day (from 19.92 Units/day to 23.66 Units/day).

The frequency of insulin dose adjustments decreased during the approximately 20 weeks observation period. In the first month after initiating Lantus® treatment 1.35 ± 1.24 (SD) insulin adjustments were made. The mean frequencies of dose adjustments in the following months were (mean ± SD): 1.04 ± 0.93 (month 2), 0.72 ± 0.87 (month 3), 0.52 ± 0.79 (month 4) and 0.39 ± 0.75 (month 5).

Mostly Lantus® was injected once per day. A once daily dose was taken for 96.59% of the patients at start of BOT and for 90.33% after approximately 20 weeks treatment. 1.82% / 2.93% of the patients injected Lantus® twice daily. Only 17 patients switched from a once daily regimen at baseline to a twice daily regimen after approx. 20 weeks treatment and only one patient switched from twice daily to once daily application. The preferred application time points were at night (start of BOT: 42.63%; after approx. 20 weeks: 40.10%) and in the evening (36.69% / 34.31%).

Concomitant oral antidiabetic treatment

According to the selection criteria all patients had already received metformin and DPP-4 inhibitor since at least 3 months before intensifying the antidiabetic treatment with Lantus®. With the initiation of BOT the metformin dosage was decreased for 5.07% and increased for 3.33% of the patients. Overall, the mean metformin dosage was slightly reduced from 1903.49 mg/d to 1889.54 mg/d (based on N = 1,241 patients with entries for both time points), corresponding to a mean change of -13.94 ± 217.56 (SD) mg/d. After approx. 20 weeks treatment the metformin dosage was decreased for 1.98% and increased for 1.35% of the patients. The mean metformin dosage decreased from 1888.56 mg/d on day after documentation 1 to 1881.41 mg/d (based on N = 1,182 patients with entries for both time points), corresponding to a mean change of -7.15 ± 145.19 (SD) mg/d.
For 1.82% of the patients the DPP-4 dosage was changed on start with BOT. For 1.51% of the patients the dosage was decreased and for 0.32% the dosage was increased). The prescribed drugs were not inquired, thus a presentation of dosages does not make sense.

Discontinuation of BOT
In 92.63% of the patients the BOT with Lantus® was continued beyond the end of observation period, 3.17% (N = 40) discontinued or switched to another therapy scheme and for 4.20% no data were available. Main reason for discontinuation of BOT with Lantus® was "insufficient blood glucose levels" (1.35% / N = 17) of all patients), 0.08% (N = 1) discontinued the BOT due to adverse event and for 1.19% (N = 15) no reason for discontinuation of BOT was documented.

Effectiveness results:

HbA_{1c}

The mean HbA_{1c} value of all patients with valid data at both visits (N = 1,210) decreased from 8.51% to 7.36%, corresponding to a mean change of -1.15% ± 0.91% (95% CI: -1.20% to -1.10%). For 8.24% of the patients an HbA_{1c} level of < 6.5% was achieved and a total of 31.46% achieved an HbA_{1c} level of < 7.0%. For 65.53% of the patients the measured HbA_{1c} value was ≥ 7.0% after approx. 20 weeks BOT).

For a total of 1 149 patients HbA_{1c} levels between 7.5% and 10% were explicitly documented at baseline. The HbA_{1c} value decreased from 8.42% to 7.32% (based on N = 1,102 with data on both visits), corresponding to a mean change of -1.10% ± 0.74% (95% CI: -1.14% to -1.05%; Table 40). For 7.66% of the patients an HbA_{1c} level of < 6.5% was achieved and a total of 31.24% achieved an HbA_{1c} level of < 7.0%. For 65.88% of the patients the measured HbA_{1c} value was ≥ 7.0% after approx. 20 weeks BOT.

Fasting blood glucose (FBG)

The mean FBG value of all patients with valid data at both visits (N = 1,197) decreased from 174.13 to 126.88 mg/dl, corresponding to a mean change of -47.25 ± 44.05 mg/dl (95% CI: -49.75 mg/dl to -44.76 mg/dl). For 11.89% of the patients an FBG level of < 100 mg/dl was achieved and for 83.91% the FBG level was ≥ 100 mg/dl after approx. 20 weeks BOT (no data: 4.20%).

For the patients with explicitly documented HbA_{1c} levels between 7.5% and 10% at baseline, the FBG value decreased from 171.38 mg/dl to 125.30 mg/dl (based on N = 1,092 with data on both visits), corresponding to a mean change of -46.08 mg/dl ± 40.07 mg/dl (95% CI: -48.46 mg to -43.70 mg/dl). For 12.36% of the patients an FBG level of < 100 mg/dl and for 83.55% the FBG value was ≥ 100 mg/dl after approx. 20 weeks BOT (no data: 4.09%).

Individual treatment goal

The treatment goal (mean) for FBG was 117.54 ± 14.02 (SD) mg/dl. The most frequent documented FBG values ranged from 100 mg/dl to < 130 mg/dl (74.88%). For 4.83% the treatment goal was < 100 mg/dl and for 16.01% the treatment goal was ≥ 130 mg/dl (no data: 4.28%).

For 35.90% of the patients the treatment goal for FBG was reached and for 56.58% the goal was not reached (no data: 7.53%).

Number of FBG measurements

The frequency of FBG measurements decreased during the approx. 20 weeks treatment with Lantus®. In the first month of treatment FBG measurements were performed 4.86 ± 2.15 (SD) times per week, in the second month 4.44 ± 2.15 (SD) times, in the third month 4.06 ± 2.20 (SD) times, in the fourth month 3.94 ± 2.21 (SD) times and in the fifth month 3.81 ± 2.21 (SD) times per week.

Consumption of blood glucose (BG) tests strips

Before start of BOT with Lantus® the mean consumption of blood glucose (BG) test strips was 41.87 ± 38.01 (SD) strips per month (N = 1,123). After approx. 20 weeks treatment with Lantus® the mean consumption of BG test strips was 44.11 ± 35.44 (SD) strips per month (N = 1,191). For 22 patients with change from BOT to another treatment regimen the mean consumption of BG test strips was 85.98 ± 48.80 (SD) strips per month. In the patients with valid data at start of BOT and at the end of observation (N = 1,067) the mean consumption of BG strips increased from 41.59 to 45.06 strips per month, corresponding to a mean change of 3.47 ± 36.46 (SD) strips per month.

Consumption of pen needles

The mean consumption of pen needles after approx. 20 weeks BOT with Lantus® was 24.58 ± 14.75 (SD) needles per month (based on N = 1,183). For 19 patients with change from BOT to another treatment regimen the mean consumption of pen needles was 77.34 ± 42.19 (SD) needles monthly.

Changes in body weight

The mean body weight slightly decreased from 89.56 kg (baseline) to 88.58 kg (after 20 weeks; based on N = 1,227), corresponding to a mean change of -0.98 ± 3.90 (SD) kg (95% CI: -1.19; -0.76).

Safety results:

Hypoglycaemias

Hypoglycaemias (BG < 70 mg/dl) were observed for 2.30% of the patients during the approx. 20 weeks BOT. Thereof nocturnal hypoglycaemia were documented for 0.48% and for 0.32% severe hypoglycaemias (BG < 56 mg/dl) were observed. The mean number of hypoglycaemias were 1.88 ± 1.03 (SD; N = 24), the mean number of nocturnal hypoglycaemias were 1.67 ± .082 (SD; N= 6) and the mean number of severe hypoglycaemias were 1.00 ± 0.00 (SD; N = 4).

Adverse events (AE) and adverse drug reactions (ADR)

A total of 29 adverse events (AE) occurred in 13 patients (0.88%) of the 1 483 patients of the safety sample. In 2 patients (0.13%) with a total of 5 events a causal relationship to Lantus® could not be excluded. The most frequently reported AE were hypoglycaemia (0.20%, N = 3), dizziness, erysipelas, hyperhidrosis and weight increased (0.13%, N = 2 for each; Table 66). Reported ADR were hypoglycaemia (0.13%, N =2), convulsion, hyperhidrosis and weight increase (0.07%, N = 1 for each). Serious AE were observed for 0.40% (N = 6) of the patients. Serious ADR were observed in one patient (0.07%; hypoglycaemia and convulsion). One patient died during this non-interventional trial. For this patient a causal relationship with Lantus® could be excluded.

Summary and conclusion:

- Aim of this non-interventional trial was to observe the adjustment of type 2 diabetes mellitus patients from a metformin/DPP-4 inhibitor combination therapy to a basal insulin supported oral therapy (BOT) with Lantus® under conditions of daily clinical routine.
- BOT with Lantus® led to reductions in HbA_{1c} (-1.15%) and in FBG (-47.25 mg/dl) during a approx. 20 weeks-long observation period.
- Hypoglycaemias (BG < 70 mg/dl) were only observed for 2.30% and severe hypoglycaemias (BG < 56 mg/dl) for 0.32% of the patients.
- Adverse drug reactions (ADR) occurred in 2 patients (0.13%) and serious adverse events (hypoglycaemia and convulsion) were observed in only one patient.

Benefit-risk-profile: The results of this routine evaluation have no evidence to change the assessment of the benefit-risk-profile of Lantus®.