PRODUCT REGISTRY REPORT

Compound(s):

lixisenatide/LYXUMIA®

Registry Title:

Therapeutic benefit of the addition of the once time daily prandial GLP-1-Receptor agonist lixisenatide in patients being poorly controlled on Basal insulin +/- oral antidiabetic drug

Registry number: LIXISL06702

Registry name: ISIS

Registry initiation date [date first patient in (FPI)]: 15-Mar-2013

Registry completion date [last patient completed/last patient out (LPO)]: 26-Jun-2014

Registry design: Prospective, non-interventional study with lixisenatide in patients with poorly controlled diabetes type 2 over a 24-weeks period

Date of interim report: 08-Sep-2014

Report date: 15-Apr-2015 (12-Jan-2015 first draft, 24-Feb-2015 local approvement, 24-Apr-2015 global approvement)

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

LIST OF ABBREVIATIONS

ADR	Adverse drug reaction
AE	Adverse event
AESI	Adverse event of special interest
AMG	German Drug Law (Arzneimittelgesetz)
AMNOG	German Pharmaceutical Market Reorganisation Act (Arzneimittelneuordnungsgesetz)
BG	Blood glucose
BMI	Body Mass Index
CI	Confidence interval
CRF	Case report form
CRO	Contract research organization
DPP-4	Dipeptidyl peptidase 4
FAS	Full Analysis Set
FBG	Fasting blood glucose
GLP-1	Glucagon-like-peptide-1
MedDRA	Medical Dictionary for Regulatory Activities
NIS	Non-interventional study
NPH	Neutral Protamine Hagedorn
OAD	Oral anti-diabetics
PPS	Per-Protocol Set
SAE	Serious adverse event
SAS	Safety-Analysis-Set
SD	Standard deviation
SmPC	Summary of product Characteristics
STROBE	Strengthening the Reporting of Observational studies in Epidemiology
T2DM	Type 2 diabetes mellitus

SYNOPSIS

Title of the registry:	Therapeutic benefit of the addition of the once time daily prandial GLP-1-Receptor agonist Lixisenatide in patients being poorly controlled on Basal insulin +/- oral antidiabetic drug. Registry number: LIXISL06702
Design:	ISIS was an open, non-controlled, non-interventional, multi-centric observational and prospective 24 weeks study conducted in Germany, according to § 67,6 AMG (Arzneimittelgesetz, German Drug Law). In the context of patients' selection, the physician received no specifications with regard to diagnostics, therapy or follow-up examinations. The study consisted in only observing and documenting parameters related to diagnostics and therapy that were already reported by the physician in the context of usual patients' care, or that were available from other sources (e.g. hospital discharge reports during observation period). Patient selection Inclusion criteria: • Type 2 diabetes mellitus • Treatment with basal insulin for at least 6 months (additional OAD were allowed) • GLP-1 receptor agonists naïve (Glucagon like Peptide 1) • FBG (Fasting Blood Glucose) ≤ 140 mg/dl (≤ 7.8 mmol/l) • HbA1c ≥ 7.5% • Age ≥ 18 years • Blood glucose self-monitoring capability • Patient information delivered • Signed patient informed consent Exclusion criteria: • Type 1 diabetes mellitus • Preexisting and concomitant treatment with DPP-4 inhibitor • Existing treatment with sulfonylurea
Objectives:	Primary objective: • Change in HbA_{1c} value from baseline to week 24. Secondary objectives: • HbA_{1c} target response rates. • Change in FBG from baseline to week 24. • Change in four-point diurnal glucose profile from baseline to week 24. • Change in body weight from baseline to week 24. • Basal insulin dosage at baseline and at week 24. • Frequency of confirmed hypoglycemic events (BG value ≤ 60 mg/dl), confirmed nocturnal hypoglycemic events (between 10:00 p.m. and 6:00 a.m.), severe hypoglycemic events (< 36 mg/dl and external help needed) and severe nocturnal hypoglycemic events. • Frequencies of adverse events (AE) and adverse drug reactions (ADR) during treatment with lixisenatide.
Treatment:	According to the SmPC it was recommended to administer Lyxumia® (lixisenatide) as follows: • Starting dose: Dosing is initiated at 10 mcg Lyxumia® once daily for 14 days. • Maintenance dose: A fixed maintenance dose of 20 mcg Lyxumia® once daily is started on day 15.

Scientific committee and members:	Not applicable.
Publications (reference):	Not applicable.
Introduction – Background / rationale:	In case a therapy with oral anti-diabetics (OAD) should fail (HbA_{1c} value after 3 - 6 months still > 6.5% [1] or > 7.0% [2]) a combination therapy with basal insulin and OAD should be started according to the national and international guidelines. In case the HbA_{1c} value lies above 7.5% after a basic therapy (diet change and physical activity) plus metformin, basal insulin can be administered in combination with metformin. [1], [2], [3] The administration of basal insulin influences mainly the fasting blood glucose (FBG) levels in type 2 diabetes (T2DM) patients. The pathophysiological foundation of the FBG decrease is an inhibition of the liver glucose production as well as a decrease of the hepatic resistance [4]. Especially with higher initial HbA_{1c} values the decrease of the FBG plays an important role for the improvement of the HbA_{1c} value [5]. Additionally, new studies have shown that the additional administration of basal insulin can improve the secretion of the beta cells and with that increases the level of endogenous insulin after meals. This results in the decrease of postprandial blood glucose levels in general and in a decrease of the postprandial peaks (decrease of the cardio vascular risk) [6]. These measures however are not sufficient to keep the HbA_{1c} value within the norm over a longer period of time even in addition to oral anti-diabetic drugs [7]. In these cases rapid acting insulin [8] or prandial GLP-1 receptor agonist [9] as a combination partner to the basal insulin can be a therapeutic option. The two substances differ from each other in terms of hypoglycemic risk and body weight changes [8], [9]. In accordance with the national and international guidelines, diabetes type 2 therapies should have a minimized risk for adverse events such as hypoglycemia and weight gain [1], [2], [3]. Due to this the prandial GLP-1 receptor agonists are a preferred combinational partner. New controlled studies have shown that in combination with basal insulin the prandial GLP-1 receptor agonist does not increase the rate of hypoglycemia and a weight reduction is possible [10], [11]. Several publications have additionally confirmed the meaningfulness of this combination [12], [13], [14]. However, data on the use of the prandial GLP-1 receptor agonist like lixisenatide in combination with basal insulin under real-life conditions are insufficient.
Methodology:	(a) Site and patient selection: To ensure a valid statistical evaluation it was intended to document 7,500 evaluable patients in this study. With these 7500 patients the statistical precision for the estimated mean change from baseline in HbA1c [%] can be reached assuming a mean HbA1c change from baseline of absolute 0.4% and a standard deviation of 1.5%. The planned number of participating sites amounted to approx. 3,400 if like normally two patients per site should be documented. The observational study was carried out by office based doctors (general practitioners and internists) distributed throughout Germany. (b) Data collection: Each site received an investigator site file containing a non-interventional study (NIS) contract, an observational plan, a patient identification list and two paper-based case report forms (CRF) including patient information, patient informed consent and two adverse event (AE) / serious adverse event (SAE) forms for each patient. Each patient planned to be enrolled in the study was informed by the physician about the objectives and the conduct of the observational study. Each patient willing to participate in the study had to sign the informed consent form. (c) Safety data collection: All AEs/SAEs including hypoglycemic events occurring during the course of the study had to be documented on (serious) adverse event forms and forwarded to the pharmacovigilance department of Sanofi-Aventis by fax. (d) Data management, review, validation: The completed CRFs were sent back to the NIS management department of *Sanofi-Aventis Deutschland GmbH*. After a check of completeness and hidden AEs, the CRFs were forwarded to the contract research organization (CRO) *factum GmbH* for data entry. The data entry was performed according to the parameters and units of the case report form using the data management program DMSys® Version 5.1. The data entry was carried out by two persons. After completion of the data entry, both entries were compared automatically, differences were listed, the

correct entry was verified comparing with the CRF by a third person and corrected in the data base accordingly (data verification). The captured data were validated according to check rules defined in the data validation plan (DVP)

(e) Statistical considerations: The statistical analyses were performed by factum GmbH, Offenbach. Here, all tables were calculated using the statistical program package SPSS for Windows (Release 15.0.0).

The conducted analysis was of exploratory character. Absolute frequency, relative frequency and adjusted relative frequency were specified for categorical variables. For continuous variables mean, standard deviation, minimum, maximum, median, 25th and 75th percentile were determined. Exact 95%-confidence intervals (CI) were calculated for mean changes from baseline to end of study of HbA_{1c} and FBG.

Continuous parameters were collected at baseline and at week 24 (longitudinal data), base statistics were calculated including absolute differences between both time-points. For value pairs with one missing entry no substitution was carried out (e.g. according to the last-observation-carried-forward-method). Only the patients with complete value pairs were considered in the analysis (available case analysis), resulting in different sample sizes in the analysis of the longitudinal data.

Three HbA_{1c} response rates are defined:

- Percentage of patients with an HbA_{1c} value < 6.5% at final visit.
- Percentage of patients with an HbA_{1c} value < 7.0% at final visit.
- Percentage of patients who reached the individual HbA_{1c} treatment goal at final visit.

Verification of the inclusion/exclusion criteria

If possible the information concerning the selection criteria were verified with further data from the CRF. The following six criteria were verified: treatment with basal insulin, GLP-1RA naïve, HbA1c ≥ 7.5% at baseline, Age ≥ 18 years, no pre-treatment or treatment with DPP-4 inhibitor (e.g.: linagliptine, saxagliptine, sitagliptine, vildagliptine) and no treatment with sulfonylurea at baseline. Since fasting blood glucose is a punctual value with daily fluctuations, the selection criterion FBG≤ 140 mg/dl were not verified with the documented FBG value at baseline.

Analyzed populations:

The Full Analysis Set (FAS) was composed of all patients for whom a CRF was available and who received at least one dose of lixisenatide. The FAS was used for effectiveness analysis.

The Per-Protocol Set (PPS) was composed of all treated patients who complied with the protocol. The PPS was used to provide supplementary analysis for the primary outcome parameter $HbA1_c$.

The Safety Analysis Set (SAS) was composed of all patients of the FAS and additionally patients with documented AEs or SAEs but without an available CRF.

RESULTS

Participants (actual):

Participants (actual)

A total of 526 physicians (internists and general practitioners) throughout Germany took part in this study. CRFs were available for a total of 1,437 patients. Data were collected from January 24, 2013 (first-patient-in) until May 26, 2014 (last-patient-out). The number of included patients (FAS: 1,437) was considerably less than planned (7,500 patients). One main reason for this was the difficult price negotiations under the AMNOG law which finally led to a withdrawal of Lyxumia® from the german market and to a premature end of patients' recruitment. All 1,437 patients were included in the Full Analysis Set (FAS). Additionally, for three patients without a submitted CRF, at least one AE or SAE was reported. Therefore, the Safety Analysis Set (SAS) contains a total of 1,440 patients. The Per-protocol Set (PPS) includes all patients of the FAS who did not violate the documentation criteria (N = 1,194, table 1, 2, 3).

Table 1: Analysis sets

	N	% of FAS
Full Analysis Set (FAS)	1437	100.00

Per Protocol Set (PPS)	1194	83.09	
Safety Analysis Set (SAS)	1440	------	

Table 2: Patient selection: inclusion criteria
Sample: FAS

	Yes	No	No data	Total
	N (%)	N (%)	N (%)	N (%)
Diabetes mellitus type 2	1434 (99.79)	1 (.07)	2 (.14)	1437 (100.00)
Treatment with a basal insulin for at least 6 months +/- OAD	1391 (96.80)	11 (.77)	35 (2.44)	1437 (100.00)
GLP-1 RA naive	1371 (95.41)	19 (1.32)	47 (3.27)	1437 (100.00)
FBG ≤ 140 mg/dl (≤ 7,8 mmol/l)	1406 (97.84)	19 (1.32)	12 (.84)	1437 (100.00)
HbA_{1C} ≥ 7.5%	1353 (94.15)	83 (5.78)	1 (.07)	1437 (100.00)
Age ≥ 18 years	1430 (99.51)	2 (.14)	5 (.35)	1437 (100.00)
Capacity/ability for blood glucose self-measurement	1432 (99.65)	3 (.21)	2 (.14)	1437 (100.00)
Patient information delivered	1427 (99.30)	2 (.14)	8 (.56)	1437 (100.00)
Patient consent	1430 (99.51)	0 (.00)	7 (.49)	1437 (100.00)

(see appendix II – 2.1)

Table 3: Patient selection: exclusion criteria
Sample: FAS

	Yes	No	No data	Total
	N (%)	N (%)	N (%)	N (%)
Diabetes mellitus Type 1	1 (.07)	1434 (99.79)	2 (.14)	1437 (100.00)
Preexisting and concomitant treatment with DPP-4-inhibitors	44 (3.06)	1339 (93.18)	54 (3.76)	1437 (100.00)
Existing treatment with sulfonylurea	7 (.49)	1368 (95.20)	62 (4.31)	1437 (100.00)

(see appendix II – 2.1)

Participant characteristics and primary analyses:

Demographic and morphometric data

Overall, 51.91% of the patients were male, 47.25% female (table 4). Most of the patients (57.41%) were between 46 and 65 years old (table 6). The mean age was 59.8 ± 10.5 (SD) years for men and 60.6 ± 11.5 (SD) years for women (table 5). The majority of patients were significantly overweight, according to WHO definition. The mean body weight was 107.73 ± 20.16 (SD) kg for men and 95.70 ± 19.61 (SD) kg for women (table 7). The mean body mass index was 34.22 ± 5.81 (SD) kg/m² for men and 35.36 ± 7.17 (SD) kg/m² for women (table 8).

Table 4: Gender of patients
Sample: FAS

Gender	N	%
Male	746	51.91

Female	679	47.25
Not reported	12	.84
Total	1437	100.00

(see appendix II – 2.2.1)

Table 5: Age of patients by gender (continuous)
Sample: FAS

Gender	Mean	SD	Minimum	25. Perc.	Median	75. Perc.	Maximum	N
Male	59.8	10.5	28.0	52.0	60.0	68.0	100.0	735
Female	60.6	11.5	19.0	53.0	61.0	69.0	89.0	660
Not reported	54.5	10.9	35.0	45.0	55.0	65.0	70.0	11
Total	60.2	11.0	19.0	52.0	61.0	68.0	100.0	1406

(see appendix II – 2.2.2)

Table 6: Age of patients (categorical)
Sample: FAS

	N	%
Up to 45 years	129	8.98%
> 45 - 65 years	825	57.41%
> 65 years	452	31.45%
No data	31	2.16%
Total	1437	100.00%

(see appendix II – 2.2.2)

Table 7: Weight of patients (kg) by gender
Sample: FAS

	Mean	SD	Minimum	25. Perc.	Median	75. Perc.	Maximum	N
Male	107.73	20.16	65.00	93.00	104.00	120.00	194.00	743
Female	95.70	19.61	46.00	82.00	92.00	105.00	180.00	676
Not reported	98.98	17.22	73.80	82.00	99.50	112.00	128.00	12
Total	101.98	20.75	46.00	88.00	99.00	115.00	194.00	1431

(see appendix II – 2.2.4)

Table 8: Body Mass Index (kg/m^2) by gender
Sample: FAS

	Mean	SD	Minimum	25. Perc.	Median	75. Perc.	Maximum	N
Male	34.22	5.81	22.23	30.00	33.04	37.74	57.30	742
Female	35.36	7.17	19.53	30.47	34.06	39.01	68.89	672
Not reported	34.40	5.54	26.46	30.59	33.36	37.96	44.08	12
Total	34.76	6.50	19.53	30.27	33.30	38.27	68.89	1426

(see appendix II – 2.2.5)

Diagnosis and baseline characteristics

The mean duration of diabetes was 9.04 ± 6.47 (SD) years. The patients have been treated with insulin for 2.92 ± 3.22 (mean ±SD) years (table 9).

Table 9: Duration of diabetes (years) and time since first insulin therapy; continuous
Sample: patient with explicit documentation of date
Sample: FAS

	Mean	SD	Minimum	25. Perc.	Median	75. Perc.	Maximum	N
Time since primary manifestation (years) of diabetes	9.04	6.47	.00	4.00	8.00	12.00	53.00	1081
Time since first insulin therapy (years) of diabetes	2.92	3.22	.00	1.00	2.00	4.00	20.00	1035

(see appendix II – 2.3.1.1, 2.3.2.1)

The mean HbA_{1c} value was 8.59% ± 1.19% at baseline (table 10). Patients with an HbA_{1c} value of < 7.5% should not be documented in this NIS. However, a total of 5.78% (N = 83) of the patients with a baseline value of < 7.5% were documented (table 2). The mean ±SD fasting blood glucose (FBG) level was 161.89 ± 52.74 mg/dL. The last two 4-point blood glucose profiles before initiating the treatment with lixisenatide were supposed to be documented, if available. The data showed minimal differences between both profiles (mean differences between pre-prandial values -2.41 and postprandial values -4.61 to -6.12 mg/dL). Table 10 shows the last measured 4-point blood glucose profile before lixisenatide: morning pre-prandial 152.48 ± 45.56 mg/dL, morning 2 h postprandial 197.23 ± 47.27 mg/dL, lunch 2 h postprandial 188.11 ± 50.48 mg/dL and evening 2h postprandial 189.99 ± 52.40 mg/dL.

Table 10: Relevant metabolic parameters at baseline
Sample: FAS

	Mean	SD	Minimum	25. Perc.	Median	75. Perc.	Maximum	N
$HbA1_c$ (%)	8.59	1.19	5.40	7.80	8.30	9.00	15.90	1383
FBG (mg/dL)	161.89	52.74	64.87	131.00	142.36	182.00	600.07	1338
Blood glucose profile (last measurement at baseline)								
Morning pre-prandial	152.48	45.56	70.00	128.00	140.00	168.00	595.00	735
Morning 2 h postprandial	197.23	47.27	77.00	167.00	192.00	218.02	500.00	637
Lunch 2 h postprandial	188.11	50.48	101.00	156.00	178.00	210.00	486.00	621
Evening 2 h postprandial	189.99	52.40	81.00	156.76	180.18	207.21	547.75	658

(see appendix II – 4.1.1.3, 4.1.2.3, 4.1.3.2)

Treatment with lixisenatide

The planned duration of observation was "approximately 24 weeks". As table 11 shows, the mean actual observation period was 27.01 ± 5.60 weeks.

Table 11: Duration of observation period (weeks)
Sample: FAS

	Mean	SD	Minimum	25. Perc.	Median	75. Perc.	Maximum	N
Duration of observation period (weeks)	27.01	5.60	1.71	24.43	27.29	29.71	53.71	1371

(see appendix II – 3.1)

In 81.84% of the patients the treatment with lixisenatide was continued beyond the recorded end of observation. In 14.61% the treatment was discontinued during the observation period and for 3.55% of the

patients no data on continuation of lixisenatide were available. Main reason for discontinuation of treatment was insufficient blood glucose control (10.16% of all patients). In 2.92% of the patients adverse events led to a discontinuation of treatment and in 2.85% no reasons were given (table 12).

Table 12: Continuation / discontinuation of lixisenatide
Sample: FAS

	N	%
Continuation of lixisenatide	1176	81.84%
Discontinuation	210	14.61%
Reason for discontinuation*:		
Insufficient blood glucose control	146	10.16%
Adverse Event	42	2.92%
No data for reason of discontinuation	41	2.85%
No data on continuation of lixisenatide	51	3.55%
Total	1437	100.00%

(see appendix II – 3.2.1.1, 3.2.1.2)

* multiple responses possible

Diabetes treatment with basal insulin and oral antidiabetic drugs (OAD)

All patients were receiving basal insulin at baseline. Thereof, 87.27% received the same basal insulin at final visit. A total of 9.67% of the patients changed to another basal insulin or the basal insulin treatment was permanently terminated. For 3.90% a sufficient blood glucose control could be achieved without application of basal insulin. For 3.55% the basal insulin regime had to be changed due to insufficient blood glucose control. In two patients (0.14%) adverse events led to discontinuation or change of the current basal insulin treatment and in 0.28% of the patients other reasons for discontinuation or change were given (table 13).

Table 13: Continuation / discontinuation of current basal insulin treatment
Sample: FAS

	N	%
Continuation of current basal insulin treatment	1254	87.27%
Discontinuation or change	139	9.67%
Reason for discontinuation/change*:		
Insufficient blood glucose control	51	3.55%
Sufficient blood glucose control without basal insulin	56	3.90%
Adverse Event	2	.14%
Other	4	.28%
No data for reason of discontinuation/change	28	1.95%
No data on continuation of current basal insulin	44	3.06%

Total	1437	100.00%

(see appendix II – 3.2.2.1, 3.2.2.2)

* multiple responses possible

Insulin glargine was the most common used basal insulin at baseline and at final visit (63.54% / 59.71%, respectively), followed by NPH insulin (18.93% / 16.28%, respectively) and insulin detemir (13.57% / 11.69 %, respectively) (table 14).

Table 14: Basal insulin: preparations
Sample: FAS

	Baseline N (%)	Final visit N (%)
Insulin glargine	913 (63.54)	858 (59.71)
NPH insulin	272 (18.93)	234 (16.28)
Insulin detemir	195 (13.57)	168 (11.69)
No data	57 (3.97)	177 (12.32)
Total	1437 (100.00)	1437 (100.00)

(see appendix II – 3.3.1.1.1, 3.3.2.1.1)

The table 15 and table 16 show the daily dosage for all basal insulins (total) and for the different basal insulins types at baseline and at final visit. The mean total basal insulin dosages at final visit did not differ from the baseline dosages. The mean total basal insulin dosage was 25.18 ± 15.09 (SD) units at baseline and 25.77 ± 14.30 (SD) units at final visit.

Table 15: Basal insulin: daily dose (units) by preparation; baseline
Sample: FAS

	Mean	SD	Minimum	25. Perc.	Median	75. Perc.	Maximum	N
Insulin glargine	25.91	15.35	2.00	16.00	22.00	32.00	140.00	898
NPH insulin	23.54	15.38	4.00	12.00	20.00	30.00	100.00	268
Insulin detemir	23.68	13.36	6.00	14.00	20.00	30.00	72.00	195
No data*	28.65	13.02	12.00	18.00	26.00	34.00	72.00	23
Total	25.18	15.09	2.00	14.00	22.00	32.00	140.00	1384

* concerning kind of basal insulin

(see appendix II – 3.3.1.3)

Table 16: Basal insulin: daily dose (units) by preparation; week 24
Sample: FAS

	Mean	SD	Minimum	25. Perc.	Median	75. Perc.	Maximum	N
Insulin glargine	26.37	14.39	2.00	16.00	24.00	32.00	110.00	535
NPH insulin	24.89	14.81	6.00	14.00	20.00	33.00	90.00	129

Insulin detemir	22.88	13.24	8.00	12.00	20.00	28.00	72.00	82
No data*	27.50	10.84	12.00	20.00	24.00	33.00	52.00	16
Total	25.77	14.30	2.00	16.00	24.00	32.00	110.00	762

* concerning kind of basal insulin

(see appendix II – 3.3.2.3)

Before initiating the treatment with lixisenatide, 79.82% of the patients were pretreated with other antidiabetics than insulin - usually oral anti-diabetics (OAD). Metformin was the most common used OAD - alone (73.97%) or in fixed combination with pioglitazone (0.90%) -, followed by sulfonylureas (10.30%). According to the observational plan, for most of the patients the treatment with sulfonylureas was terminated at baseline. Thus, only 0.21% / 1.25% received sulfonylureas at baseline and at final visit, respectively. A total of 84.27% (baseline) and 83.72% (final visit) received metformin (table 17).

Table 17: Type of antidiabetic treatment, except insulin
Sample: FAS

	Previous	Baseline	Final visit
	N (%)	N (%)	N (%)
Antidiabetic treatment, except insulin*	1147 (79.82)	1253 (87.20)	1261 (87.75)
Metformin	1063 (73.97)	1211 (84.27)	1203 (83.72)
Pioglitazone	13 (.90)	6 (.42)	8 (.56)
Metformin/Pioglitazone	28 (1.95)	21 (1.46)	32 (2.23)
Alpha glucosidase inhibitor	44 (3.06)	16 (1.11)	9 (.63)
Sulfonylureas**	148 (10.30)	3 (.21)	18 (1.25)
Glinides	20 (1.39)	16 (1.11)	15 (1.04)
GLP1 receptor agonist***	3 (.21)	0 (.00)	0 (.00)
DPP4 inhibitor***	28 (1.95)	19 (1.32)	28 (1.95)
Other antidiabetic treatment	11 (.77)	8 (.56)	20 (1.39)
No treatment documented	290 (20.18)	184 (12.80)	176 (12.25)
Total	1437 (100.00)	1437 (100.00)	1437 (100.00)

(see appendix II – 3.4.1.1, 3.4.2.1, 3.4.2.2)

* multiple entries possible

** According to observational plan: should be terminated before initiation treatment with lixisenatide.
*** According to observational plan: patients should be GLP1 receptor agonist / DPP4 inhibitor naïve.

Primary effectiveness variables

The mean target HbA_{1c} value in the Full Analysis Set (FAS) was 6.98 ± .52% (SD) and 7.01 ± .50% (SD) in the Per-Protocol Set (PPS; table 18). Most frequently, the individual target values were between >6.5% and 7.0% (FAS: 43.63% of patients; PPS: 45.73%). For 26.37% (FAS) and 24.87% (PPS) of the patients the target values were between > 6.05 – 6.5% and for 19.14% (FAS) and 20.69% (PPS) between >7.0% - 7.5%. Lower limits were specified for 2.02% and 1.17%, respectively, and higher limits for 5.64% and 5.53%, respectively (table 19).

Table 18: Target HbA_{1c} value (%; continuous)

	Mean	SD	Minimum	25. Perc.	Median	75. Perc.	Maximum	N

Sample: FAS	6.98	.52	5.50	6.50	7.00	7.20	12.00	1391
Sample: PPS	7.01	.50	5.90	6.50	7.00	7.20	12.00	1170

(see appendix II – 4.1.1.2)

Table 19: Target HbA_{1c} value (%; categorical)

	Sample: FAS N (%)	Sample: PP N (%)
>5.0 – 6.0%	29 (2.02)	14 (1.17)
>6.0 - 6.5%	379 (26.37)	297 (24.87)
>6.5 - 7.0%	627 (43.63)	546 (45.73)
>7.0 - 7.5%	275 (19.14)	247 (20.69)
>7.5 – 12.0%	81 (5.64)	66 (5.53)
No data	46 (3.20)	24 (2.01)
Total	1437 (100.00)	1194 (100.00)

(see appendix II – 4.1.1.2)

The mean (± SD) HbA_{1c} value of all FAS patients with valid data at both visits (n =1,320) decreased from 8.59% ± (1.19%) at baseline to 7.58% (± 1.15%) at final visit (after 24 weeks), corresponding to a mean (± SD) change of -1.01% (± 1.16%) (95% CI: -.95% to -1.08%) (table 20). In the PPS the mean (± SD) HbA_{1c} value decreased from 8.66% (± 1.11%) to 7.60% (±1.09%), corresponding to a mean change of -1.06% (± 1.14%) (95% CI: -.99% to -1.13%), based on 1,111 patients with valid data on both visits (table 21).

Table 20: HbA_{1c} (%); change final (week 24) visit vs. baseline
Sample: patients with both values available
Sample: FAS

	Mean	SD	Minimum	25. Perc.	Median	75. Perc.	Maximum	N
Baseline	8.59	1.19	5.40	7.80	8.30	9.00	15.90	1320
Final visit	7.58	1.15	4.60	6.90	7.40	8.00	18.70	1320
Change	-1.01	1.16	-7.80	-1.50	-.90	-.40	7.00	1320

(see appendix II – 4.1.1.5.1.1)

95% confidence interval for mean change: -.95; -.1.08

Table 21: HbA_{1c} (%); change final visit (week 24) vs. baseline
Sample: patients with both values available
Sample: PPS

	Mean	SD	Minimum	25. Perc.	Median	75. Perc.	Maximum	N
Baseline	8.66	1.11	7.50	7.90	8.40	9.00	15.90	1111
Final visit	7.60	1.09	4.60	7.00	7.40	8.10	18.70	1111
Change	-1.06	1.14	-7.80	-1.50	-1.00	-.50	7.00	1111

(see appendix II – 4.1.1.5.2.1)

95% confidence interval for mean change: -.99; -.1.13

Other analyses:

Secondary effectiveness variables

HbA_{1c} response rates

The following three response rates were defined:

- Proportion of patients with an HbA_{1c} level <6.5% at final visit.
- Proportion of patients with an HbA_{1c} level <7.0% at final visit.
- Proportion of patients who reached the individual HbA_{1c} level.

In the FAS (N = 1,437), the response criterion target HbA_{1c} <6.5% was achieved at week 24 in 9.26% of the patients and 25.12% of the patients achieved the response criterion target HbA_{1c} <7.0%. The individual HbA_{1c} target value was obtained at week 24 in 26.10% of the patients at the end of the

observation period (table 22).

In the PPS (N = 1,194), the response criterion target HbA_{1c} <6.5% was achieved at week 24 in 8.21% of the patients and 23.12% of the patients achieved the response criterion target HbA_{1c} <7.0%. The individual HbA_{1c} target value was obtained at week 24 in 26.38% of the patients at the end of the observation period (table 22).

Table 22: HbA1c target response rates at week 24
Sample FAS

	HbA_{1c} < 6.5% N (%)	HbA_{1c} < 7.0% N (%)	Individual HbA_{1c} target value N (%)
Sample: FAS			
Reached	133 (9.26)	361 (25.12)	375 (26.10)
Not reached	1234 (85.87)	1006 (70.01)	954 (66.39)
No data	70 (4.87)	70 (4.87)	108 (7.52)
Total	1437 (100.0)	1437 (100.0)	1437 (100.0)
Sample: PPS			
Reached	98 (8.21)	276 (23.12)	315 (26.38)
Not reached	1051 (88.02)	873 (73.12)	811 (67.92)
No data	45 (3.77)	45 (3.77)	68 (5.70)
Total	1194 (100.0)	1194 (100.0)	1194 (100.0)

(see appendix II – 4.1.1.6.1.1 to 4.1.1.6.2.2)

Change in FBG

The mean (±SD) FBG of all patients with valid data at both visits (n = 1,279; FAS) decreased from 161.47 (± 52.3) mg/dl (baseline) to 133.63 (±36.23) mg/dl (final visit, week 24), corresponding to a mean change of -27.85 (± 51.91) mg/dl (95% CI: -25.00 mg/dl to -30.69 mg/dl) (table 23).

Table 23: Fasting blood glucose (mg/dl); change final visit (week 24) vs. baseline
Sample: patients with both values available
Sample: FAS

	Mean	SD	Minimum	25. Perc.	Median	75. Perc.	Maximum	N
Baseline	161.47	52.30	64.87	131.00	142.36	182.00	600.07	1279
Final visit	133.63	36.23	59.00	111.72	126.00	145.00	412.00	1279
Change	-27.85	51.91	-499.07	-46.85	-20.00	-5.00	218.04	1279

(see appendix II – 4.1.2.4.1)

95% confidence interval for mean change: -25.00; -30.69

Change in four-point diurnal glucose profile

Table 24 shows the changes in the four-point glucose profile for patients (FAS) with valid values on both visits. The mean (±SD) morning pre-prandial blood glucose (BG) levels decreased from 152.07 (±46.54) mg/dl (baseline) to 124.64 (±30.65) mg/dl (final visit), corresponding to a mean change of -27.43 (± 47.11) mg/dl. The mean (±SD) morning 2-hours postprandial BG value decreased from 197.41 (±48.07) mg/dl to 157.09 (±36.76) mg/dl, corresponding to a mean change of -40.32 (± 49.22) mg/dl. The mean (±SD) lunch 2-hours postprandial BG value decreased from 187.18 (±49.11) mg/dl to 151.45 (±34.19) mg/dl, corresponding to a mean change of -35.73 (± 46.08) mg/dl. The mean (±SD) evening 2-hours postprandial BG value decreased from 189.75 (±52.95) mg/dl to 153.83 (±38.22) mg/dl, corresponding to a mean change of -35.92 (± 52.09) mg/dl.

Table 24: 4-point blood glucose profile; change final visit week 24 (last measurement) vs. baseline (last measurement)
Sample: patients with measurements available at both visits
Sample: FAS

	Mean	SD	Minimum	25. Perc.	Median	75. Perc.	Maximum	N
Morning pre-prandial								
Baseline	152.07	46.54	73.87	127.00	139.00	168.00	595.00	587
Final visit	124.64	30.65	72.00	107.00	119.00	134.00	424.00	587
Change	-27.43	47.11	-440.00	-41.00	-19.82	-5.41	243.00	587
Morning 2h postprandial								
Baseline	197.41	48.07	77.00	166.00	191.00	218.02	500.00	495
Final visit	157.09	36.76	82.00	134.00	151.00	175.00	338.00	495
Change	-40.32	49.22	-395.00	-64.00	-37.00	-13.00	146.00	495
Lunch 2h postprandial								
Baseline	187.18	49.11	101.00	156.76	178.00	205.41	486.00	487
Final visit	151.45	34.19	68.00	129.73	147.00	168.00	273.00	487
Change	-35.73	46.08	-366.00	-55.86	-31.00	-9.01	142.00	487
Evening 2h postprandial								
Baseline	189.75	52.95	81.00	157.00	180.00	205.70	547.75	520
Final visit	153.83	38.22	84.00	130.00	145.00	168.00	373.00	520
Change	-35.92	52.09	-346.75	-57.00	-30.00	-9.01	167.00	520

(see appendix II – 4.1.3.5)

Change in body weight

The mean (±SD) body weight of all patients with valid data at both visits (n = 1,379) decreased from 101.92 (±20.57) kg (baseline) to 98.3 (±19.9) kg (final visit, week 24), corresponding to a mean change of -3.60 (± 4.97) kg (95% CI: -3.34 kg to -3.86 kg) (table 25).

Table 25: Weight (kg); change final visit (week 24) vs. baseline
Sample: patients with both values available
Sample: FAS

	Mean	SD	Minimum	25. Perc.	Median	75. Perc.	Maximum	N
Baseline	101.92	20.57	46.00	88.00	98.00	115.00	194.00	1379
Final visit	98.3	19.9	50.0	84.1	95.0	109.0	199.0	1379
Change	-3.60	4.97	-50.00	-5.00	-3.00	-1.00	15.00	1379

(see appendix II – 4.2.2.1)

95% confidence interval for mean change: -3.34; -3.86

Safety analysis

Hypoglycemic events

Hypoglycemia was defined as a symptomatic hypoglycemic event confirmed by a blood glucose level ≤ 60 mg/dl. The hypoglycemia was rated as severe, if the measured blood glucose level was ≤ 36 mg/dl and external help was required.

Symptomatic hypoglycemic events occurred only in nine patients (0.65%, 95%-CI: 0.30%; 1.23%; table 26). Two patients each had one night-time hypoglycemia and two night-time hypoglycemic events (table

27, 28). Severe hypoglycemic events were not observed (95-CI: 0.00%; 0.22%) (table 29).

Table 26: Frequency of patients with at least one hypoglycemic event during observation period
Sample: FAS

	N	%
Yes	9 (10 events)	.65*
No	1377	99.35
Total	1386	100.00

(see appendix II – 6.1.1)

* 95% confidence interval: 0.30%; 1.23%
No data: n = 51

Table 27: Frequency of patients with at least one night-time hypoglycemia during observation period
Sample: patients with missing data excluded
Sample: FAS

	N	%
Yes	4	.29
No	1381	99.71
Total	1437	100.00

(see appendix II – 6.1.2)

No data: n = 52

Table 28: Number of night-time hypoglycaemic events since last visit; final visit
Sample: patients with hypoglycaemic events
Sample: FAS

	Mean	SD	Minimum	25. Perc.	Median	75. Perc.	Maximum	N
Number of night-time hypoglycaemic events since last visit	1.50	.58	1.00	1.00	1.50	2.00	2.00	4

(see appendix II – 6.1.2)

Table 29: Frequency of patients with at least one severe hypoglycemia during observation period
Sample: patients with missing data excluded
Sample: FAS

	N	%
With severe hypoglycaemic events	0	.00*
Without severe hypoglycaemic events	1385	100.00
Total	1385	100.00

(see appendix II – 6.1.3)

* 95% confidence interval: 0.00%; 0.22%
No data: n = 52

Adverse events and adverse drug reactions

The safety analysis set was based on 1,440 patients. The safety analysis considers adverse events (AE) classified as primary symptoms (e.g. hypoglycemia) and documented in the context of the Lyxiumia® application. For additional information concerning secondary symptoms (e.g. sweating associated with hypoglycemia) and adverse events occurring due to other pharmaceutical products of Sanofi-Aventis please refer to appendix 3.6.1.1 Adverse events.

A total of 106 AEs occurred in 73 patients (5.07%; table 30). According to the Sanofi-Aventis pharmacovigilance department a causal relationship to Lyxumia® (lixisenatide) was to be suspected in 93 events occurring in 63 patients (4.38%; table 31). These cases are called "adverse drug reactions (ADR)", to be differentiated from "adverse events (AE)"; in these cases a causal relationship is not implied.

Table 30: Frequency of adverse events (AE)
Safety Analysis Set

	N	%
Patients with adverse events (AE)	73	5.07
Patients without adverse events (AE)	1367	94.93
Total	1440	100.00

(see appendix II – 6.2.1.1.1)

Table 31: Frequency of adverse drug reaction (ADR)
Safety Analysis Set

	N	%
Patients with adverse drug reactions (ADR)	63	4.38
Patients without adverse drug reactions (ADR)	1377	95.63
Total	1440	100.00

(see appendix II – 6.2.1.2.1)

The tables 32 and 33 show the frequency rates of AE/ADR according to MedDRA primary system organ class. Rates of patients with at least one AE/ADR of the corresponding system organ class are listed. Most frequently AEs/ADRs referred to the MedDRA primary system organ class "gastrointestinal disorders" (2.08%/2.08% of all patients), "investigations" (1.39%/1.39%) and "metabolism and nutrition disorders" (1.04%/0.97%).

Table 32: Frequency of adverse events (AE) by MedDRA Primary System Organ Class (multiple entries possible)
Safety Analysis Set

	N	%
Cardiac disorders	2	.14
Gastrointestinal disorders	30	2.08
General disorders and administration site conditions	9	.63
Injury, poisoning and procedural complications	2	.14
Investigations	20	1.39
Metabolism and nutrition disorders	15	1.04
Nervous system disorders	6	.42
Psychiatric disorders	3	.21
Skin and subcutaneous tissue disorders	1	.07
Surgical and medical procedures	1	.07
Patients with adverse events (AE)	73	5.07
Patients without adverse events (AE)	1367	94.93

Total	1440	100.00

(see appendix II – 6.2.1.1.3)

Table 33: Frequency of adverse drug reactions (ADR) by MedDRA Primary System Organ Class (multiple entries possible)
Safety Analysis Set

	N	%
Gastrointestinal disorders	30	2.08
General disorders and administration site conditions	8	.56
Investigations	20	1.39
Metabolism and nutrition disorders	14	.97
Nervous system disorders	3	.21
Psychiatric disorders	1	.07
Skin and subcutaneous tissue disorders	1	.07
Patients with adverse drug reactions (ADR)	63	4.38
Patients without adverse drug reactions (ADR)	1377	95.63
Total	1440	100.00

(see appendix II – 6.2.1.2.3)

The tables 34 and 35 show the frequencies of AE/ ADR by MedDRA preferred term sorted according to frequencies. The most frequently reported AEs were nausea (1.94%, n = 28), followed by abnormal blood glucose (0.97%, n = 14) and hypoglycemia (0.69%, n = 10). The most frequently reported ADRs were nausea (1.94%, n = 28), followed by abnormal blood glucose (0.97%, n = 14) and hypoglycemia (0.63%, n = 9).

Table 34: Frequency of adverse events (AE) by MedDRA Preferred Term (multiple entries possible)
Safety Analysis Set

	N	%
Nausea	28	1.94
Blood glucose abnormal	14	.97
Hypoglycaemia	10	.69
Vomiting	5	.35
Abdominal distension	4	.28
Decreased appetite	4	.28
Diarrhoea	3	.21
Weight increased	3	.21
Anxiety	2	.14
Blood glucose fluctuation	2	.14
Blood glucose increased	2	.14

Diabetes mellitus inadequate control	2	.14
Drug effect decreased	2	.14
Headache	2	.14
Malaise	2	.14
Abdominal discomfort	1	.07
Adverse event	1	.07
Agitation	1	.07
Cerebrovascular accident	1	.07
Coronary artery disease	1	.07
Dementia	1	.07
Dizziness	1	.07
Dysgeusia	1	.07
Dyspepsia	1	.07
Exposure during pregnancy	1	.07
General physical health	1	.07
Injection site erythema	1	.07
Injection site pain	1	.07
Injection site pruritus	1	.07
Insomnia	1	.07
Pruritus	1	.07
Retching	1	.07
Tachycardia	1	.07
Thirst	1	.07
Vascular graft	1	.07
Wrong technique in drug	1	.07
Patients with adverse events (AE)	73	5.07
Patients without adverse events (AE)	1367	94.93
Total	1440	100.00

(see appendix II – 6.2.1.1.2)

Table 35: Frequency of patients with adverse drug reactions (ADR) by MedDRA Preferred Term (multiple entries possible)
Safety Analysis Set

	N	%
Nausea	28	1.94
Blood glucose abnormal	14	.97
Hypoglycaemia	9 (10 events)	.63
Vomiting	5	.35
Abdominal distension	4	.28
Decreased appetite	4	.28
Diarrhoea	3	.21
Weight increased	3	.21
Blood glucose fluctuation	2	.14

Blood glucose increased	2	.14
Diabetes mellitus inadequate control	2	.14
Drug effect decreased	2	.14
Malaise	2	.14
Abdominal discomfort	1	.07
Anxiety	1	.07
Dizziness	1	.07
Dysgeusia	1	.07
Dyspepsia	1	.07
General physical health	1	.07
Headache	1	.07
Injection site erythema	1	.07
Injection site pain	1	.07
Injection site pruritus	1	.07
Pruritus	1	.07
Retching	1	.07
Thirst	1	.07
Patients with adverse drug reactions (ADR)	63	4.38
Patients without adverse drug reactions (ADR)	1377	95.63
Total	1440	100.00

(see appendix II – 6.2.1.2.2)

The tables 36 and 37 show the frequencies of serious and non-serious AEs/ADRs. Rates of patients with at least one AE/ADR of the respective category are listed (patients with both serious and non-serious events were counted in both categories).

In six patients (0.42%) eight serious AEs occurred. In three patients (0.21%) four serious ADRs (decreased appetite (n=1), diabetes mellitus inadequate control (n=1) and nausea (n=2)) occurred.

Table 36: Frequency of serious adverse events (AE) by MedDRA Preferred Term
Safety Analysis Set

	Event	Patients
	N	N (%)
Cerebrovascular accident	1	1 (.07)
Coronary artery disease	1	1 (.07)
Decreased appetite	1	1 (.07)
Dementia	1	1 (.07)
Diabetes mellitus inadequate control	1	1 (.07)
Nausea	2	2 (.14)
Vascular graft	1	1 (.07)

Serious AE	8	6 (.42)
Total	106	1440 (100.00)

(see appendix II – 6.2.4.1)

Table 37: Frequency of serious adverse drug reactions (ADR) by by MedDRA Preferred Term
Safety Analysis Set

	Event	Patients
	N	N (%)
Decreased appetite	1	1 (.07)
Diabetes mellitus inadequate control	1	1 (.07)
Nausea	2	2 (.14)
Serious ADR	4	3 (.21)
Total	93	1440 (100.00)

(see appendix II – 6.2.4.1)

Tables 38 and 39 show the frequencies of AEs/ADRs labelled 'unlisted/listed' according to the company core data sheet of Lyxumia®. In 1.94% (n = 28) of the patients unlisted AE were observed (table 38) and in 1.60% (n = 23) unlisted ADRs were observed (table 39).

Table 38: Frequency of adverse events (AE) 'unlisted/listed' (Core Safety Information) (multiple entries possible)
Safety Analysis Set

	N	%
Patients with 'unlisted' adverse events (AE)	28	1.94
Patients with 'listed' adverse events (AE)	54	3.75
Patients with 'listed/unlisted' not available*	4	.28
Patients with adverse events (AE)	73	5.07
Patients without adverse events (AE)	1367	94.93
Total	1440	100.00

* Imprecise designations of events (e.g. "insufficient blood glucose control") were not classified.

(see appendix II – 6.2.1.1.5)

Table 39: Frequency of adverse drug reactions (ADR) 'unlisted/listed' (Core Safety Information) (multiple entries possible)
Safety Analysis Set

	N	%
Patients with 'unlisted' adverse drug reactions (ADR)	23	1.60
Patients with 'listed' adverse drug reactions (ADR)	51	3.54
Patients with 'listed/unlisted' not available*	2	.14
Patients with adverse drug reactions (ADR)	63	4.38

	Patients without adverse drug reactions (ADR) 1377 95.63 Total 1440 100.00 * Imprecise designations of events (e.g. "insufficient blood glucose control") were not classified. (see appendix II – 6.2.1.5) No patient died during the observation period of the study.
Discussions:	Diabetes is one of the most common chronic diseases in the industrialized countries. And more than 90% of the diabetes cases are type 2 diabetes. The glycemic control in these patients has become more complex, since a broad spectrum of pharmacological agents is available today. As a consequence, several international and national scientific diabetes associations (e.g.: American Diabetes Association, European Association for the Study of Diabetes, German Diabetes Association) has published guidelines for antihyperglycemic treatment in patients with type 2 diabetes. GLP-1 receptor agonists are recommended, if basal insulin supported oral therapy has not lead to a sufficient glycemic control. Treatment with GLP-1 receptor agonists can reduce the HbA_{1c} value by 1.0% to 1.5% [3]. Additional advantages are weight reduction and lower risk of hypoglycemic events. The present ISIS study is a prospective non-interventional study to document the treatment with lixisenatide in adult diabetes type 2 patients over a period of about 24 weeks. Inclusion criteria were treatment with basal insulin since at least six months (additional treatment with OADs was allowed), GLP-1 receptor agonists' naïve, FBG ≤ 140 mg/dl and HbA_{1c} ≥ 7.5%; patients with pre-treatment and actual treatment with DPP-4 inhibitors were excluded. According to the SmPC, a triple therapy with lixisenatide, basal insulin and sulfonylurea was not allowed. To ensure the representativeness of the data, the observational study was carried out by diabetologists (general practitioners and internists) distributed throughout Germany. A data quality review was performed in approximately 5% of the participating centers. The number of included patients (FAS: 1,437) was considerably less than planned (approx. 7,500 patients). One main reason for this was the difficult price negotiations under the AMNOG law which finally led to a withdrawal of Lyxumia® from the market and to a premature end of patients' recruitment. The mean age was 59.8 ± 10.5 (SD) years for men and 60.6 ± 11.5 (SD) years for women. The majority of patients were significantly overweight. The mean body mass index was 34.22 ± 5.81 (SD) kg/m² for men and 35.36 ± 7.17 (SD) kg/m² for women. Before initiating the treatment with lixisenatide the most common used treatment regime contained basal insulin and metformin (73.97%). A total of 20.18% received no OAD. Basal insulin plus metformin was also the most preferred combination during the treatment with lixisenatide (baseline: 84.27%, final visit: 83.72%). Whereas only 12.80% and 12.25% of the patients were not receiving any OAD at baseline and end of study, respectively. The mean total basal insulin dosages at final visit did not differ from baseline dosages. The mean total basal insulin dosage was 25.18 ± 15.09 (SD) units at baseline and 25.77 ± 14.30 (SD) units at final visit. In the FAS the mean HbA_{1c} value improved from 8.59% at baseline to 7.58% at final visit (after 24 weeks), corresponding to a mean decrease of -1.01%. For 9.26% of the patients the target HbA_{1c} value was < 6.5% and for 25.12% the target HbA_{1c} value <7.0%. The individual HbA_{1c} target value was obtained in 26.10% of the patients. In the PPS the mean HbA_{1c} value improved from 8.66% to 7.60%, corresponding to a mean decrease of -1.06%. These results are in line with clinical trial data [10], [15]. For 8.21% of the patients the HbA_{1c} value was < 6.5% and for 23.12% of the patients the HbA_{1c} value was <7.0%. The individual HbA_{1c} target value was obtained in 26.38% of the patients. The mean ± SD FBG (baseline: 161.47 mg/dl) improved by -27.85 ± 51.91 mg/dl. Changes in the four-point glucose profile were as follows: The mean ± SD morning pre-prandial BG improved by -27.43 ± 47.11 mg/dl. The mean ± SD improvements of postprandial BG values were between -35.73 ± 46.08

	mg/dl to -40.32 ± 49.22 mg/dl. Overall, a weight reduction could be observed. The mean ± SD body weight was reduced by -3.60 ± 4.97 kg from baseline. Symptomatic hypoglycemic events occurred only in nine patients (0.65% of all patients). Two patients each had one and two night-time hypoglycemic events. In none of the patients severe hypoglycemic events (< 36 mg/dl and external help needed) occurred. A total of 106 adverse events (AE) occurred in 73 patients (5.07% of the SAS (N = 1,440)). According to the pharmacovigilance department a causal relationship (= ADR) to Lyxumia® (lixisenatide) was to be suspected in 93 events occurring in 63 patients (4.38%). The most frequently reported AEs were nausea (1.94%, n = 28), followed by abnormal blood glucose (0.97%, n = 14) and hypoglycemia (0.69%, n = 10). The most frequently reported ADRs were nausea (1.94%, n = 28), followed by abnormal blood glucose (0.97%, n = 14) and hypoglycemia (0.63%, n = 9). In six patients (0.42%) serious AEs occurred and in three patients (0.21%) serious ADRs occurred. No patient died during the observation period of the study. In summary, the treatment with Lyxumia® can be considered as safe in daily routine practice.
Conclusions:	The results from the present study conducted in Germany, show that the GLP-1-receptor agonist lixisenatide adding to a pre-existing antidiabetic treatment containing basal insulin can improve glycemic control in previously poorly controlled T2DM patients. The frequencies of hypoglycemic events and other adverse events were low. In conclusion, the results suggest that Lyxumia® (lixisenatide) is an effective and safe treatment option in patients with type 2 diabetes who are inadequately controlled with basal insulin +/- OAD.
Date of report:	15-Apr-2015

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

SANOFI

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Product Code:	Lyxumia® INN: Lixisenatide
Study Code / Name:	LIXIS-L-06702
Study Title:	Therapeutic benefit of the addition of the once time daily prandial GLP-1-Receptor agonist lixisenatide in patients being poorly controlled on Basal insulin +/- oral antidiabetic drug
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)	[redacted]

THE STUDY REPORT / SYNOPSIS

Final Draft dated 15-Apr-2015

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	[redacted]	[redacted] Signature Date: 24.04.2015

1 APPENDIX IV - PUBLICATIONS

1.1 REFERENCES

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1.2 PUBLICATIONS/ABSTRACTS OF THE REGISTRY RESULTS

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