PRODUCT REGISTRY REPORT

Compound(s): **Lyxumia®**

Registry Title**:**
The effectiveness of Lyxumia use in type 2 diabetic patients in actual medical practice in Czech Republic and Slovakia

Registry number: LIXISL06943

Registry name: SALY

Registry initiation date [date first patient in (FPI)]: 12-May-2014

Registry completion date [last patient out (LPO)]: 15-Dec-2015

Registry design: An international, multicenter, observational, non-interventional, 6-month prospective product registry in subjects with Type 2 diabetes mellitus (T2DM) who are initiating therapy with lixisenatide.

Report date: 11-Oct-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'.

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SYNOPSIS

Title of the registry:	The effectiveness of Lyxumia® use in type 2 diabetic patients in actual medical practice in Czech Republic and Slovakia
Design:	An multinational, multicenter, observational, non-interventional, 6-month prospective product registry in subjects with Type 2 diabetes mellitus (T2DM) who are initiating therapy with lixisenatide. This study was aimed to evaluate the effectiveness and safety of lixisenatide.
Objectives:	**Primary Objectives:** ▪ To describe the change in HbA1c from baseline to Month 6. **Secondary Objectives:** To describe: ▪ percentage of patients reaching HbA1c goal < 7% DCCT (< 53 mmol/mol), ▪ percentage of patients with decrease in HbA1c by at least 0.4% from baseline, ▪ change in FPG from baseline to Month 6, ▪ change in body weight from baseline to Month 6, ▪ incidence of adverse events, ▪ frequency and severity of symptomatic and severe hypoglycemia, ▪ patients' satisfaction with treatment (reported by TRIM-D questionnaire), ▪ physicians' assessment of treatment.
Treatment:	All patients were treated with lixisenatide, which was administered subcutaneously. The patients were selected from those for whom the participating physician had decided to prescribe lixisenatide irrespective of the study participation. For this study, the drug was not provided.
Scientific committee and members:	Not applicable.
Publications (reference):	Not published yet. Initiatives for any local communication in participating countries/regions: Not applicable.
Introduction - Background/rationale:	Lyxumia® (lixisenatide) is a new once-daily injectable prandial GLP-1 receptor agonist that was approved by the European Medicines Agency in Feb-2013 for the management of T2DM. It is indicated for the treatment of adults with T2DM, to achieve glycaemic control, in combination with oral glucose-lowering medicinal products and/or basal insulin, when these, together with diet and exercise, do not provide adequate glycaemic control [1]. The efficacy and safety of lixisenatide were assessed in the clinical phase III program GetGoal. In this program, lixisenatide was evaluated in a broad range of type 2 diabetic patients, in combination with oral hypoglycaemic agents or basal insulin. Lixisenatide demonstrated a significant reduction in HbA1c, fasting and postprandial plasma glucose levels and body weight, when compared with the placebo, in patients failing on oral therapy. When added to basal insulin, it provided a significant reduction in HbA1c and postprandial plasma glucose levels and a beneficial effect on body weight [2]. Lixisenatide was generally well tolerated, and associated with a low risk of hypoglycaemia. The most frequently reported adverse reactions during the clinical study GetGoal were nausea, vomiting, and diarrhoea. These reactions were mostly mild and transient, and occurred mainly during the first 3 weeks of treatment [1]. In comparison with exenatide twice daily, lixisenatide once daily in T2DM patients,

	inadequately controlled with metformin, demonstrated comparable improvements in HbA1c, a better gastrointestinal tolerability and a lower risk of hypoglycaemia [3]. Since Lyxumia® was first launched in 2013, there are no available data about its effectiveness in everyday clinical practice in the Czech and Slovak Republic. The objective of this non-interventional observational study was to observe the therapeutic benefit of treatment with Lyxumia® for six months in actual medical practice in the Czech republic and Slovakia after the marketing of this product in the mentioned countries. In this project, patients were stratified by country. **References:** 1) SPC Lyxumia SPC Lyxumia, available online [04-08-2013] http://www.ema.europa.eu/docs/cs_CZ/document_library/EPAR_-_Product_Information/human/002445/WC500140401.pdf 2) Raccah D. Efficacy and safety of lixisenatide in the treatment of type 2 diabetes mellitus: a review of phase III clinical data. Expert Rev Endocrinol Metab 2013;8:105–21. 3) Rosenstock J et al. Efficacy and Safety of Lixisenatide Once Daily Versus Exenatide Twice Daily in Type 2 Diabetes Inadequately Controlled on Metformin. Diabetes Care 2013;36(10):2945-2951.
Methodology:	**(a) Site and patient selection:** In total, 826 patients were recruited for this study (622 in the Czech Republic and 204 in the Slovak Republic) in 156 centers (121 in the Czech Republic and 35 in the Slovak Republic). The participating physicians were randomly chosen from the diabetologists who were familiar with GLP-1 receptor agonists therapy. The participating diabetologists proposed to include each consecutive patient who met the inclusion criteria and did not meet any of the exclusion criteria to participate in the registry (with a target of 4-5 patients per site and a maximum of 8 patients). This consecutive recruitment of patients was aimed to limit the selection bias. *Inclusion criteria:* • type 2 diabetes mellitus, • male or female, at least 18 years of age, • GLP-1 receptor agonist naive patients, not adequately controlled (HbA1c > 7% DCCT; >53 mmol/mol), for whom the participating diabetologists decided to initiate lixisenatide treatment within the 4 weeks before the inclusion, • written informed consent signed. *Exclusion criteria:* • Type 1 diabetes mellitus, • pregnancy and lactation, • actual participation in another clinical trial, • patients not able to attend follow-up visits. **(b) Data collection:** The data were recorded prospectively during inclusion visit and two follow-up visits within 6 months. Available data obtained as close as possible to visits scheduled in month 3 and 6 were recorded.

Data collected on patients at inclusion visit (Visit 1):

- date of visit,
- date of informed consent,
- demographic data (age [years] and gender),
- inclusion and exclusion criteria,
- physical measurements and vital signs (height [cm], weight [kg], blood pressure [mmHg], pulse rate [bpm], body mass index [$kg.m^{-2}$],
- medical history,
- history and complications of diabetes,
- previous and current therapy with OADs and insulin (type of OAD/ insulin, start date of treatment, current daily dose, changes in therapy after start with lixisenatide),
- concomitant therapy for diabetes,
- lixisenatide therapy at treatment start (start date of therapy, daily dose [µg], time of administration),
- the most recent value of HbA1c [mmol/mol or %DCCT] and FPG [mmol/L] (max. 1 month before lixisenatide initiation),
- Patient Reported Outcome: TRIM-D questionnaire.

Data collected during the follow-up visits: Visit V2 (month 3)and Visit V3 (month 6):

- date of visit,
- information about lixisenatide therapy (actually used dose [µg], prescribed dose [µg], and time of administration),
- physical measurements and vital signs (weight [kg], blood pressure [mmHg] and pulse rate [bpm]),
- value of HbA1c [mmol/mol or %DCCT], and FPG [mmol/l] on day of visit (or ± 7 days),
- daily glycaemic profile (including two-hour postprandial glycaemia),
- change in therapy with insulin/ OADs since previous visit,
- change in concomitant therapy for diabetes,
- occurrence of adverse events,
- occurrence of hypoglycemia (the total number of hypoglycaemia occurrences since the previous visit, the number of documented symptomatic hypoglycaemia occurrences and severe hypoglycaemia occurrences),
- patient reported outcome: TRIM-D questionnaire (only at Visit 3),
- physicians' satisfaction with treatment (only at visit 3).

(c) Safety data collection:

Adverse events and concomitant medications were recorded throughout the project after signing an informed consent until the last visit.

Adverse events were recorded in Adverse Event Form. Serious adverse events were recorded in Adverse Event Form and Safety Complementary Form by completion of relevant parts of eCRF.

(d) Data management, review, validation:

Data were anonymously documented on electronic CRFs. If inspection of the data revealed potential inconsistencies, additional queries were sent to the investigator who was asked to respond by confirming or modifying the data questioned. Data quality control was performed in at least 5% of active centers chosen at random, with at least one patient included. The database was locked on 26th Feb, 2016.

Further information on data collection, validation and quality is given in the study manual.

(e) Statistical considerations:

Primary endpoint

The primary evaluation criterion of the study was change in glycaemic control (HbA1c) after 6 months of treatment with lixisenatide in the overall population (change in mean HbA1c from most recent value obtained at inclusion visit to the end of the study).

Secondary endpoint

The secondary evaluation criteria were as follows:

- percentage of patients with HbA1c <7% DCCT (<53 mmol/mol) after 6 months,
- percentage of patients with decrease in HbA1c by at least 0.4%,
- mean change in FPG,
- mean change in body weight,
- incidence of adverse events,
- rates of symptomatic (plasma glucose level ≤ 3,9 mmol/l), and severe (requires active help of another person) hypoglycaemia occurrences,
- Change in patients' satisfaction with the treatment (reported by TRIM-D questionnaire) from baseline to end of the study,
- physicians' assessment of treatment at the end of the study.

Statistical methods

Statistical methods commonly used for the analysis of epidemiological data were applied. All collected assessments were presented by means of descriptive analysis and calculation of confidence intervals. Descriptive analysis was carried out respecting the type of variable:

- Continuous variables (e.g. age, HbA1c): number of available data (N), arithmetic mean, standard deviation (SD), median, minimum (Min), maximum (Max), lower quartile, upper quartile, and 95% confidence interval (if appropriate).
- Categorical or discrete variables (e.g. number of AEs or hypoglycaemia occurrences): absolute and relative frequencies.
- Binary variables (e.g. sex): absolute and relative frequencies.

The number of missing values was presented for continuous variables (if needed). In case of missing data for categorical or binary variables percentages were calculated from the total number of patients included in the analysis (i.e. missing data or unknown responses were not counted in the percentages).

Confidence intervals and statistical tests were computed in accordance with assumptions required by those statistical methods. Normal distribution of all tested continuous variables was assessed. Normal distribution was assessed on the basis of Shapiro-Wilks test.

If variables were normally distributed, parametric tests (paired t-test for analysis of changes from baseline) were applied. If variables were not normally distributed nonparametric tests were applied (Wilcoxon signed rank test for analysis of changes from baseline).

For all statistical tests the significance level was fixed at $\alpha = 0.05$ and 95% confidence interval was calculated.

The analyses were performed globally and by country (unless otherwise specified).

Sample size determination

It was planned to include a total of 828 patients. The sample size was estimated in order to achieve a width of 95% confidence interval for a mean change in HbA1c of at least 0.25% which is half of the clinically relevant change.

	Planned ratio of enrolment in the Czech Republic and the Slovak Republic was 3:1 (621 patients in CZ and 207 patients in SK). Assuming the same variability of data and 20% drop-out in both countries, the numbers of patients were considered as sufficient for analyses per country with the following justification. Width of confidence interval 0.29% was expected in analysis of data from the Czech Republic. In analysis of data from the Slovak Republic the width of confidence interval 0.51%, which is very close to clinical important difference of 0.5%, was expected. *Analysis populations* Two analysis populations were defined: a) Eligible population The eligible patient population consisted of the patients who have fulfilled inclusion criteria and who have received at least one dose of lixisenatide and with at least one follow-up visit, and who were not excluded according to the decisions taken during the data review. In case of missing HbA1c value after 6 months of therapy with lixisenatide the Last Observation Carried Forward (LOCF) method was applied (a value of HbA1c after 3 months of therapy with lixisenatide was used for analysis of primary endpoint). b) Per protocol population The per protocol population was defined by eligible patients who have available values for primary analysis (values of HbA1c at baseline and after 6 months). Per protocol population was employed for sensitivity analysis of primary endpoint.
RESULTS	
Participants (actual):	a) Overall participation status: A total of 156 physicians recruited 826 patients in the Czech Republic and Slovakia. The participating investigators were randomly selected from diabetologists who had experience with GLP-1 receptor agonists therapy. b) Participation per period of the registry: 826 patients were screened and enrolled into the study. Out of them, 54 patients were excluded, constituting an eligible population of 772 patients. Out of the excluded patients, 38 patients were excluded due to missing HbA1c values at both follow-up visits, 12 patients were excluded due to missing baseline HbA1c values, and 4 patients were excluded for not fulfilling the inclusion criteria. From the eligible population, 35 patients were excluded due to missing HbA1c data for the primary analysis, constituting a per protocol population of 737 patients eventually. 30 patients prematurely discontinued the study - in 9 patients, it was due to the physician's decision, in 8 patients, it was due to the withdrawal of the patient, in 5 patients, it was due to the loss of the follow-up, in 3 patients, it was due to a non-compliance with the study drug, and in 5 patients, it was due to unknown reason. (Figure 1, Table 1-4).

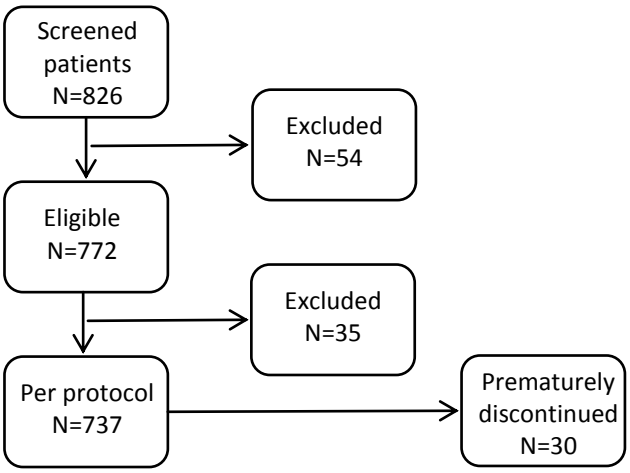

Figure 1. Patients flow

Table 1. Disposition of patients and analysis populations

Analysis population	n (%)
Patients enrolled into the study	826 (100.0 %)
Eligible population	772 (93.5 %)
Per protocol population	737 (89.2 %)

Data are presented as n (%).

Table 2. Prematurely discontinued patients and reasons for discontinuation

Reasons for discontinuation	Eligible population (N=772) n (%)
Non-compliance with study drug	3 (0.4 %)
Withdrawal by patient	8 (1.0 %)
Lost to follow-up	5 (0.6 %)
Physician decision	9 (1.2 %)
Unknown reason	5 (0.6 %)
Total	30 (3.9 %)

Data are presented as n (%).

Table 3. Participating physicians and disposition of patients by country

	Overall	Czech Republic	Slovak Republic
Participating physicians	156	121	35
Patients enrolled into the study	826	622	204
Eligible population	772	585	187
Per protocol population	737	562	175

Table 4. Disposition of eligible population at each visit

Visit	Eligible population (N=772) n (%)
Visit 1 (baseline)	772 (100.0 %)
Visit 2 (3 months after start with lixisenatide)	769 (99.6 %)
Visit 3 (6 months after start with lixisenatide)	742 (96.1 %)

Data are presented as n (%).

Participant characteristics and primary analyses:

Demographics and baseline characteristics

The mean age of the study population was 56.7 years The age of the participants ranged between 22 and 77 years, with no difference in gender distribution: males (51.4%) and females (48.6%). The patients were classified as obese according to WHO classification (mean ± SD weight was 110.0 ± 19.11 kg and mean ± SD BMI was 37.6 ± 5.89 kg/m^2). (Table 5)

Table 5. Demographic and baseline characteristics – Eligible population

Parameter	Statistics	Visit 1 (baseline)
Age [years]		N=772
	Mean (SD)	56.7 (9.32)
	Median (range)	58 (22 – 77)
Sex		N=772
Male	n (%)	397 (51.4)
Female	n (%)	375 (48.6)
Weight [kg]		N=772
	Mean (SD)	110.0 (19.11)
	Median (range)	109 (56 – 225)
BMI [kg/m^2]		N=772
	Mean (SD)	37.6 (5.89)
	Median (range)	37.1 (24.9 - 68.7)
Systolic BP [mmHg]		N=772
	Mean (SD)	138.7 (13.20)
	Median (range)	140.0 (100 – 191)
Diastolic BP [mmHg]		N=772
	Mean (SD)	82.2 (8.93)
	Median (range)	80 (58 – 110)

SD = Standard deviation

Diabetic medical history

The mean duration of disease was 7.7 years, mean duration of OAD treatment was 6.8 years, and the duration of insulin treatment was 3.4 years. (Table 6)

The most frequent complications were diabetic neuropathy in 130 patients (16.8%), followed by diabetic nephropathy in 93 patients (12.0%), diabetic retinopathy in 62 patients (8.0%), and myocardial infarction in 44 patients (5.7%). The most frequent concomitant diseases were hypertension in 666 patients (86.3%), and dyslipidemia in 587 patients (76.0%). The patients were concomitantly treated mostly with RAS blockers (68.8%), statins (54.5%), and beta-blockers (43.9%). (Table 7)

Table 6. History of diabetes – Eligible population

Parameter	Statistics	Visit 1 (baseline)
Duration of T2DM [years]		N=644
	Mean (SD)	7.7 (5.45)
	Median (range)	6.58 (0.05 - 36.0)
Duration of OAD treatment [years]		N=659
	Mean (SD)	6.8 (4.85)
	Median (range)	5.68 (0.05 - 33.4)
Duration of insulin treatment [years]		N=154
	Mean (SD)	3.4 (3.72)
	Median (range)	2.18 (0.03 - 22.7)

SD = Standard deviation

N = number of patients with available information about the duration

Table 7. Diabetic complications – Eligible population

Complication	Overall
Microvascular complication	N = 772
Diabetic nephropathy	93 (12.0 %)
Diabetic neuropathy	130 (16.8 %)
Diabetic retinopathy	62 (8.0 %)
Without microvascular complications	559 (72.4 %)
Macrovascular complication	N = 772
Myocardial infarction	44 (5.7 %)
Stroke	10 (1.3 %)
Transient ischemic attack	8 (1.0 %)
Chronic lower extremity ischemia	26 (3.4 %)
Diabetic foot	9 (1.2 %)
Without macrovascular complications	687 (89.0 %)
Without any diabetic complications	506 (65.5 %)

Data are presented as n (%).
N = number of patients with available information about complications ("Yes"/ "No")

Previous and current therapy with OADs and insulin

Patients were classified into subgroups based on the number of OADs used or the number of OADs used in combination with insulin. In this setting, most patients used 2 OADs (n=269; 34.8%) followed by patients who used only one OAD (n=187; 24.2%). In patients taking OADs with insulin, it was most frequently 1 OAD and 1 insulin (n=77; 10.0%) followed by patients taking 2 OADs and 1 insulin (n=61; 7.9%). (Table 8)

Table 8. Previous and current therapy with OADs and insulin – Eligible population

	Overall
Number of patients with OAD/insulin	N = 772
Only OAD	
1 OAD	187 (24.2 %)
2 OADs	269 (34.8 %)
3 OADs	148 (19.2 %)
4 OADs	6 (0.8 %)
Combination of OAD and insulin	
1 OAD + 1 insulin	77 (10.0 %)
2 OADs + 1 insulin	61 (7.9 %)
3 OADs + 1 insulin	22 (2.8 %)
4 OADs + 1 insulin	2 (0.3 %)

Data are presented as n (%); OAD = oral antidiabetics

Types of concomitantly used OADs

All patients were taking OADs. Metformin was the most frequent OAD (n=738; 95.6%) followed by sulphonylureas (n=407; 52.7%), and inhibitors of DPP IV (n=249; 32.3%). (Table 9)

Table 9. Types of concomitantly used OADs – Eligible population

OAD	n (%)	Daily dose [mg] Mean (SD)
Number of patients with OAD	N = 772	
Metformin	738 (95.6 %)	2047.4 (610.49)
Sulfonylurea	407 (52.7 %)	NA
Inhibitors of DPP IV	249 (32.3 %)	NA
Glitazon	42 (5.4 %)	NA
Glinid	17 (2.2 %)	NA
Inhibitors of SGLT2	9 (1.2 %)	NA
Inhibitors of alpha-glucosidase	4 (0.5 %)	212.5 (103.08)

OAD = oral antidiabetics; SD = Standard deviation

Types of concomitantly used insulin

The most frequently used insulin was glargine (n/N=100/162; 61.7%) followed by detemir (n=39; 24.1%), and NPH insulin (n=23; 14.2%). (Table 10)

Table 10. Types of concomitantly used insulin

Insulin	n (%)	Daily dose [IU] Mean (SD)
Number of patients with insulin	N = 162	
Human insulin type NPH	23 (14.2 %)	29.7 (17.97)
Insulin detemir	39 (24.1 %)	27.2 (15.38)
Insulin glargine	100 (61.7 %)	31.5 (12.76)

SD = Standard deviation

Changes in insulin therapy

At each visit, there could have been changes in insulin therapy including: the initiation of insulin therapy, insulin dose increase or decrease, or insulin discontinuation. The most frequently newly prescribed insulin was glargine in 30 patients followed by detemir in 15 patients, and the least frequently prescribed insulin was human NPH insulin in 4 patients. (Table 11)

Table 11. Summary of changes in insulin therapy – Eligible population

	At visit 1[1]	Between visit 1 and visit 2	Between visit 2 and visit 3	During the study[2]
	n (%)	n (%)	n (%)	n (%)
	N = 772	N = 769	N = 743	N = 743
Any change	48 (6.2%)	62 (8.1%)	65 (8.7%)	133 (17.9%)
No change	724 (93.8%)	707 (91.9%)	678 (91.3%)	610 (82.1%)

N = number of patients at each visit
[1]Change in insulin therapy at visit 1 due to initiation of lixisenatide therapy
[2]Occurrence of at least one change in insulin therapy between visit 1 and visit 3

Changes in OAD therapy

Changes in the concomitant OAD medications were also observed during the course of the study. The most frequently newly prescribed OAD was sulphonylureas in 32 patients followed by inhibitors of SGLT2 in 16 patients. The most frequent OAD changes concerned the discontinuation of DPP IV at Visit 1 (191 patients). (Table 12)

Table 12. Summary of changes in OAD therapy – Eligible population

	At visit 1[1]	Between visit 1 and visit 2	Between visit 2 and visit 3	During the study[2]
	n (%)	n (%)	n (%)	n (%)
	N = 772	N = 769	N = 743	N = 743
Any change	288 (37.3%)	98 (12.7%)	77 (10.4%)	361 (48.6%)
No change	484 (62.7%)	671 (87.3%)	666 (89.6%)	382 (51.4%)

N = number of patients at each visit
[1]Change in OAD therapy at visit 1 due to initiation of lixisenatide therapy
[2]Occurrence of at least one change in OAD therapy between visit 1 and visit 3 (inclusive)

Daily dose of lixisenatide

The mean prescribed dose was 10.1 ± 0.80 µg daily at baseline with a further increase to 19.5 ± 2.23 µg daily at Visit 2, and 19.7 ± 1.68 µg daily at Visit 3. (Table 13)

Table 13. Daily dose of lixisenatide – Eligible population

	Daily dose [µg]		
Statistics	Visit 1 (baseline)	Visit 2 (after 3 months)	Visit 3 (after 6 months)
N	772	746	689
Mean (SD)	10.1 (0.80)	19.5 (2.23)	19.7 (1.68)
Median	10	20	20
Q1-Q3	10 - 10	20 - 20	20 - 20
Min-Max	10 - 20	10 - 20	10 - 29

N = number of patients with available value
SD = standard deviation; Q1 = lower (25%) quartile; Q3 = upper (75%) quartile

Primary analysis

Primary analysis has been performed on eligible population (with LOCF method applied for missing HbA1c values) and on per protocol population as well.

Absolute values of levels of HbA1c (mmol/mol and %DCCT) and change from baseline after 6 months of treatment with lixisenatide

The primary outcome variable of this study was the change in HbA1c between the baseline, when the patient was started on lixisenatide treatment, and the last follow-up visit (6 months). In the eligible population, the mean ± SD change was -9.25 ± 14.49 mmol/mol (-0.85 ± 1.33 %DCCT) (Table 14) and in the per protocol population the mean ± SD change was -9.72 ± 14.35 mmol/mol (-0.89 ± 1.31 %DCCT) (Table 15). All the changes from the baseline were statistically significant (p<0.001). A higher decrease from the baseline in the values of HbA1c was observed in the group which achieved a target HbA1c levels of less than 53 mmol/mol by visit 3 (Figure 2). It was also observed that the patients who didn't achieve a decrease in the levels of HbA1c by at least 0.4% by visit 3, experienced an increase in the levels of HbA1c (Figure 3). Based on the analysis performed on the subgroups of this study, it was observed that patients who were younger, with higher BMI and who had a shorter duration of diabetes were the ones to achieve a target HbA1c levels of less than 53 mmol/mol by the end of the study. It was also observed, based on the analysis of the subgroups, that the population which achieved a target HbA1c levels of less than 53 mmol/mol were less likely to experience microvascular and macrovascular diabetic complications, suffered from less concomitant conditions, were less likely to have a change in insulin therapy and OAD treatment and achieved a bigger reduction in body weight by the end of the study (not adjusted for age and diabetes duration).

Table 14. Absolute values of levels of HbA1c (mmol/mol) and change from baseline after 6 months of treatment with lixisenatide (eligible population)

	HbA1c [mmol/mol]				
	---------- Absolute value ----------			-------Change from baseline ------	
Visit*	N	Mean (SD)	Median (range)	Mean (SD)	Median (range)
Visit 1	772	74.09 (13.03)	71.58 (54.0 – 131.0)		
Visit 3	772	64.84 (14.91)	62.84 (30.1 – 126.0)	-9.25 (14.49)	-8.95 (-80.0 – 51.0)

SD = standard deviation
* Visit 1 = baseline, Visit 3 = after 6 months of treatment with lixisenatide; LOCF method applied for missing HbA1c values

Table 15. Absolute values of levels of HbA1c (mmol/mol) and change from baseline after 6 months of treatment with lixisenatide (per protocol population)

	HbA1c [mmol/mol]				
	---------- Absolute value ----------			-------Change from baseline ------	
Visit*	N	Mean (SD)	Median (range)	Mean (SD)	Median (range)
Visit 1	737	74.10 (13.06)	71.58 (54.0 – 131.0)		
Visit 3	737	64.38 (14.75)	62.00 (30.1 – 126.0)	-9.72 (14.35)	-9.00 (-80.0 – 51.0)

SD = standard deviation
* Visit 1 = baseline, Visit 3 = after 6 months of treatment with lixisenatide

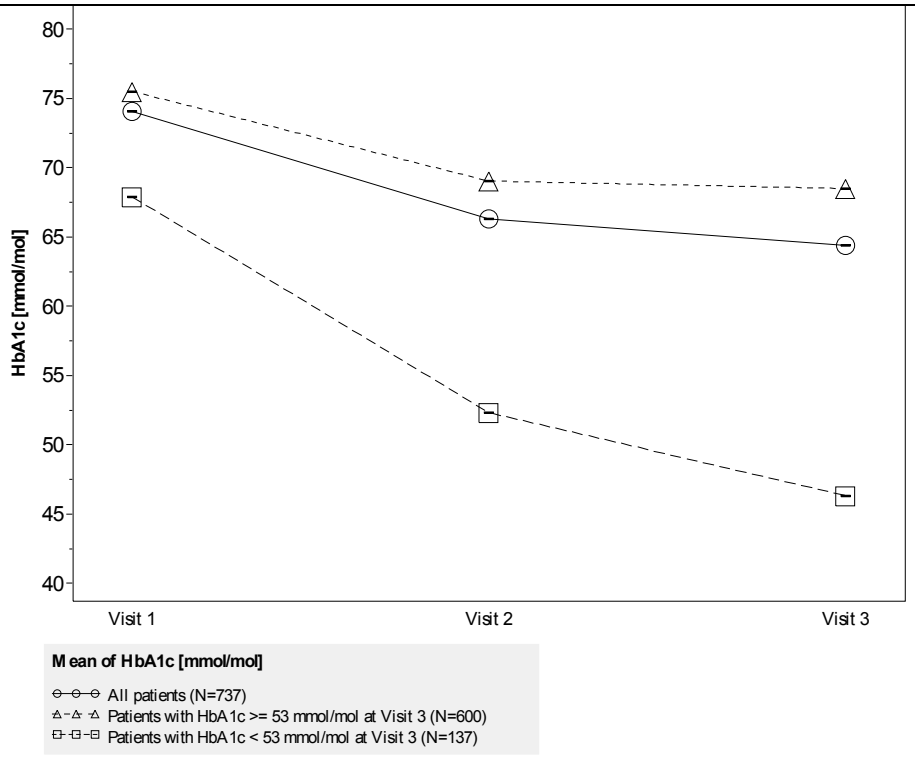

Figure 2. HbA1c values [mmol/mol] during lixisenatide therapy (subgroups by achievement target value of HbA1c at Visit 3)

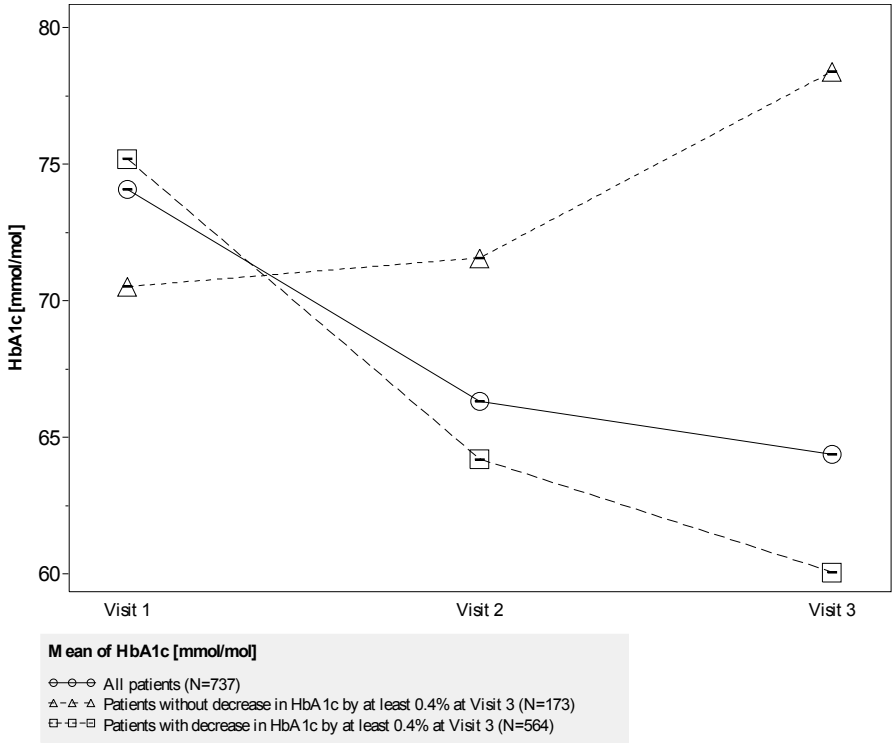

Figure 3. HbA1c values [mmol/mol] during lixisenatide therapy (subgroups by decrease in HbA1c by at

least 0.4% at Visit 3)

Other analyses:

Secondary analysis

Proportion of patients with HbA1c < 7% DCCT (< 53 mmol/mol) after 6 months of therapy with lixisenatide

137 patients (18.6%) achieved HbA1c < 7% DCCT (< 53 mmol/mol) after 6 months of therapy with lixisenatide, in the PP-Population. (Table 16)

Table 16. Proportion of patients with level of HbA1c < 7% DCCT (< 53 mmol/mol) after 6 months of therapy with lixisenatide (PP-Population)

		Proportion of patients at target	
Level of HbA1c after 6 months	**N**	**n (%)**	**95% Wald confidence interval**
HbA1c < 7% DCCT (< 53 mmol/mol)	737	137 (18.6 %)	15.71 % - 21.47 %

N = number of patients with available values of HbA1c at 6 months after start with lixisenatide therapy
(n (%) = number (percentage) of patients with level of HbA1c <53 mmol/mol (glycemic controlled patients))

Proportion of patients with decrease in HbA1c by at least 0.4% from baseline after 6 months of therapy with lixisenatide

564 patients (76.5%) achieved a decrease in HbA1c by at least 0.4% from the baseline after 6 months of therapy with lixisenatide, in the PP-Population. (Table 17, Figure 3)

Table 17. Proportion of patients with decrease in HbA1c by at least 0.4% from baseline after 6 months of therapy with lixisenatide (PP-Population)

	N	**n (%)**	**95% Wald confidence interval**
Decrease in HbA1c by at least 0.4% from baseline after 6 months	737	564 (76.5 %)	73.40 % - 79.65 %

N = number of patients with available values of HbA1c at 6 months after start with lixisenatide therapy
n (%) = number (percentage) of patients with decrease in HbA1c by at least 0.4% from baseline after 6 months

Absolute values of levels of FPG and change from baseline to the last follow-up visit

The mean ± SD change in FPG at the last follow-up visit was -1.76 ±2.8 mmol/l in the PP-Population and this decrease was statistically significant (p<0.001). (Figure 4)

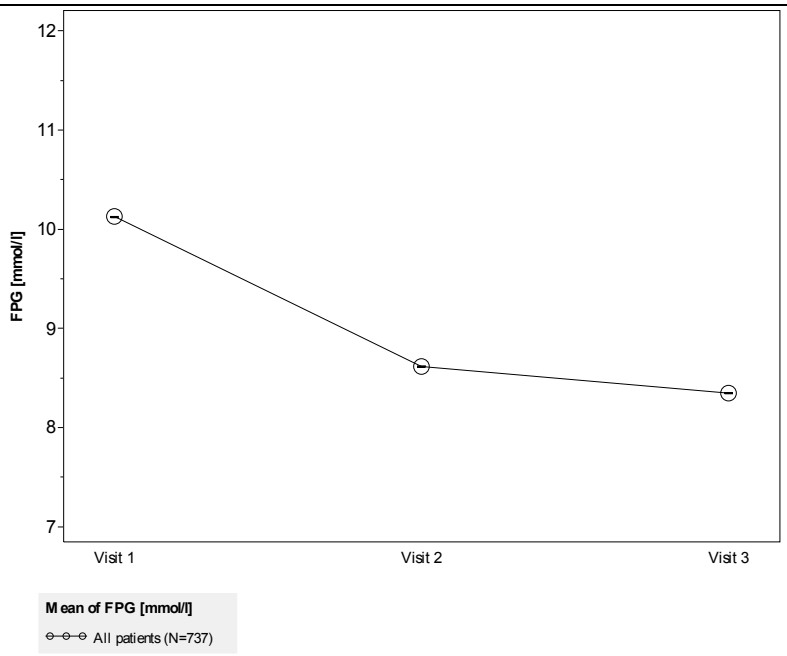

Figure 4. Values of FPG [mmol/l] during lixisenatide therapy

Absolute values of body weight and change from baseline to the last follow-up visit

A significant reduction in the mean body weight was observed over the study period. At last follow-up visit, the mean ± SD was -3.52 ±5.42 kg and this decrease was statistically significant (p<0.001). (Figure 5)

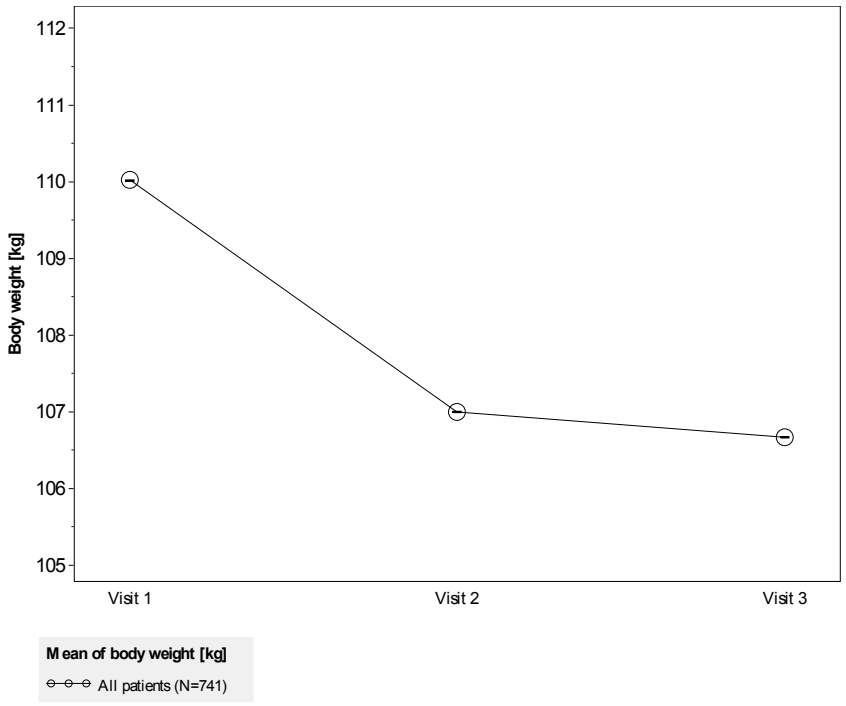

Figure 5. Values of body weight [kg] during lixisenatide therapy

Adverse events

In the eligible population, a total of 25 adverse events (AEs) occurred in 23 patients (3.0%) during the course of the study and led to the discontinuation of the study drug in 7 patients. The most frequent adverse events were gastrointestinal disorders (14 patients), followed by infections in 3 patients. The gastrointestinal disorders included: nausea, vomiting, digestive difficulties, upper dyspeptic syndrome, epigastric cramps, belching, colitis acuta, feeling of fullness in the stomach, dyspepsia, gastrointestinal intolerance and epigastric pain. 22 AEs occurred in 20 patients in the Czech republic and led to the discontinuation of the study drug in 5 patients, while 3 AEs occurred in 3 patients in the Slovak Republic and led to the discontinuation of the study drug in 2 patients (Table 18). 13 AEs were related to study treatment, of which 11 occurred in CZ, and 2 in SK. In one patient who was on OAD, the AE was related to the OAD and to the study drug. No AEs were reported as related to insulin. The intensity of the adverse events was most frequently moderate (15 patients) (Table 19). Moreover, 5 additional AEs occurred in the non-eligible population; 1 of which was an SAE. Three of them were mild and 2 were moderate. All of them were gastrointestinal disorders and all were recovered at the end of the study.

Serious adverse reactions

A total of 3 serious adverse events occurred in 3 patients (0.4%). In one patient, it was lower urinary tract infection and in another, it was moderately differentiated rectal adenocarcinoma, while in the third patient it was bariatric surgery – laparoscopic gastric banding. No SAEs were related to the study drug. All SAEs were recovered at the end of the study. No deaths were documented during the course of this study.

Table 18. The incidence of adverse events

Country		Statistics	Incidence of AE
Overall	Number of patients with at least one AE	n (%)	23 (3.0 %)
	Number of AEs	n	25
	Number of patients with at least one SAE	n (%)	3 (0.4 %)
	Number of SAEs	n	3
Czech Republic	Number of patients with at least one AE	n (%)	20 (3.4 %)
	Number of AEs	n	22
	Number of patients with at least one SAE	n (%)	2 (0.3 %)
	Number of SAEs	n	2
Slovak Republic	Number of patients with at least one AE	n (%)	3 (1.6 %)
	Number of AEs	n	3
	Number of patients with at least one SAE	n (%)	1 (0.5 %)
	Number of SAEs	n	1

% = (n*100)/N; N = Number of patients in the eligible population (Overall: N = 772 / Czech Republic: N = 585 / Slovak Republic: N = 187)

Table 19. The incidence of adverse events by intensity

Country	Intensity of AE	n (%)
Overall	Mild	9 (36.0 %)
	Moderate	15 (60.0 %)
	Severe	1 (4.0 %)
Czech Republic	Mild	9 (40.9 %)
	Moderate	13 (59.1 %)
Slovak Republic	Moderate	2 (66.7 %)
	Severe	1 (33.3 %)

% = (n*100)/N; N = Number of adverse events (AEs) in the corresponding country

Patients with symptomatic and severe hypoglycaemia occurrences

14 patients experienced at least one episode of symptomatic hypoglycaemia, confirmed by PG ≤ 70mg/dL (3.9mmol/L) during the course of this study. No episodes of severe hypoglycaemia were documented. The incidence of symptomatic hypoglycaemia occurrences was more frequent between visit 1 and visit 2 (1.3%) compared to the interval between visit 2 and visit 3 (0.7%).

Physicians' satisfaction with treatment

A total number of 149 physicians evaluated their satisfaction with the treatment in 741 patients. The majority of participating physicians were satisfied with the treatment with 37.9% of them who described the treatment as very good and 29.6% as good. Less than 1% of the physicians described the treatment as very poor. The physicians selected their scores mainly based on the influence of the treatment on HbA1c levels and the body weight of the patients. (Figure 6, Table 20)

Table 20. Physicians' satisfaction with treatment

Score of physicians' satisfaction	n (%)
	N = 741
Very good	281 (37.9 %)
Good	219 (29.6 %)
Fair	164 (22.1 %)
Poor	70 (9.4 %)
Very poor	7 (0.9 %)

N = number of patients with available physicians' evaluation

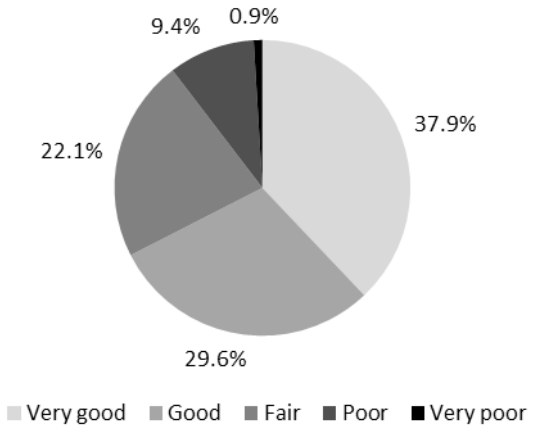

Figure 6. Physicians' satisfaction with treatment

Results of the TRIM-D questionnaire

The TRIM-D questionnaires obtained from 652 patients at visit 1 and from 549 patients at visit 3 were evaluated. The patients' overall satisfaction with the ease and convenience of their medication improved between visit 1 and 3 (0.2 improvement in the mean; missing data for 103 patients). The biggest change, however, was in the patient's satisfaction with their medication's ability to manage their weight (0.6 improvement in the mean between visit 1 and visit 3). There was also a tangible improvement between visit 1 and 3 in indicators such as the patient's satisfaction with their medication's ability to control diabetes and prevent hypoglycaemia/hyperglycaemia (0.4 improvement in the mean), the medication's interference with the patients' meal planning and social activities (0.2 improvement in the mean), the medication's influence on the patients' daily activities and relationships with family and friends (0.2 improvement in the mean) and the negative feelings associated with diabetes medication (0.2 improvement in the mean). The overall compliance of the patients to their medication also improved between visit 1 and 3 (0.2 improvement in the mean).

Discussions:

a) Key results

The primary objective of the study was to evaluate the effectiveness of lixisenatide over a six-month observational period in T2DM patients. This objective was assessed based on the changes in HbA1c levels in comparison to the baseline. Out of 826 patients included into the study, 737 were available for the primary analysis. The mean prescribed dose was at 10µg daily at baseline with a further increase to 20 µg at visit 2, and 20 µg at visit 3.

Over the six-month follow-up period, a significant decrease (p<0.001) of HbA1c was observed. The mean ±SD change in HbA1c levels was -9.72±14.35 mmol/mol (-0.89±1.31% DCCT).

At the last follow-up visit, 137 patients (18.6%) achieved a target HbA1c<7% DCCT (<53 mmol/mol) and 564 patients (76.5%) achieved a target decrease in HbA1c levels by at least 0.4%. This improvement in glycaemic control was accompanied by a parallel reduction in the mean FPG of -1.76±2.8 mmol/l (p<0.001) with a low reported number of hypoglycaemia. Changes in mean ±SD body weight during the follow-up period were -3.52 ±5.42 kg and this decrease was statistically significant (p<0.001).

25 adverse events were reported in 23 patients and in 7 patients they led to discontinuation of the drug. The most frequent adverse events were gastrointestinal disorders. 13 AEs were related to study drug. The intensity of the adverse events was most frequently moderate (15

patients). Three severe adverse events occurred in 3 patients. In one patient, it was lower urinary tract infection, and in another it was moderately differentiated rectal adenocarcinoma, while in the third patient it was bariatric surgery – laparoscopic gastric banding. No SAEs were related to the study drug.

14 patients experienced at least one episode of symptomatic hypoglycaemia, confirmed by PG ≤ 3.9mmol/l during the course of this study. No episodes of severe hypoglycaemia were documented. The incidence of symptomatic hypoglycaemia occurrences was more frequent between visit 1 and visit 2 (1.3%) compared to the interval between visit 2 and visit 3 (0.7%).

The participating physicians expressed an overall satisfaction with the treatment (37.9% of them described the treatment as very good and 29.6% described it as good. Less than 1% of the physicians described the treatment as very poor).

In patients who had a questionnaire available at Visit 1 and Visit 3, the patients's satisfaction with the treatment improved between visit 1 and 3 with the biggest improvements being in the patient's satisfaction with their medication's ability to manage their weight (0.6 improvement in the mean between visit 1 and visit 3) and the patient's satisfaction with their medication's ability to control diabetes and prevent hypoglycaemia/hyperglycaemia (0.4 improvement in the mean).

b) Interpretation

This study showed that treatment with lixisenatide was effective in providing improvement in glycaemic control and weight loss over the period of 6 months. The improvements were observed with the measured HbA1c, FPG, and body weight at the 3rd month of treatment and lasted for the time of the study (up to 6 months).

The evaluation of the safety profile of lixisenatide was also an objective of this study. Adverse events were reported at a very low frequency (in 3.0% patients) and in 7 patients, led to the discontinuation of the drug. The most frequent adverse events were gastrointestinal disorders, which in 13 patients were related to the study drug. The intensity of the adverse events was most frequently moderate. Three SAEs were reported not related to the study medication. 14 patients experienced at least one episode of symptomatic hypoglycaemia and no episodes of severe hypoglycaemia were documented. No new safety concerns were identified in this study that calls into question the established safety profile of lixisenatide.

The results of the study also showed a good satisfaction level in the majority of participating physicians, and an improvement in the patients' satisfaction with the addition of lixisenatide to their therapy regimen was reported in patients who answered the TRIM-D questionnaire at Visit 1 and Visit 3.

c) Generalizability

This study addressed the therapeutic options for patients with T2DM, in which the treatment with OADs and/or basal insulin together with lifestyle modifications, does not provide adequate control of the disease. The results of this study suggests that patients who were younger, with higher BMI and who suffered from diabetes for a less period of time may benefit the most from the addition of lixisenatide to the therapy regimen. This study suggets that at the initiation of an intensive insulin regimen (basal-bolus), the physicians could consider the option to initiate a combination of OADs with lixisenatide or OADs and basal

	insulin with lixisenatide, at least in this particular population (cited before). As in all studies requiring active physician participation, it cannot be excluded that the quality of care provided by the diabetologists who agreed to participate in this study and those who declined may differ.
Conclusions:	This prospective observational study performed in everyday clinical practice in the Czech Republic and Slovakia showed that the initiation of treatment with lixisenatide in patients with T2DM, whose glycemic profile was inadequately controlled on their antidiabetic therapy, resulted in a clinically relevant improvement of glycaemic control, with a low incidence of symptomatic hypoglycaemia and gastrointestinal side effects, and a weight loss. Switching to lixisenatide represents an effective and safe therapeutic option in patients with inadequate glycaemic control, especially in younger, with higher BMI and shorter diabetes duration.
Date of report:	11-Oct-2016