Current Therapeutic Research 89 (2018) 37–42

Contents lists available at ScienceDirect

Current Therapeutic Research

journal homepage: www.elsevier.com/locate/curtheres

Intensification of Basal Insulin Therapy with Lixisenatide in Patients with Type 2 Diabetes in a Real-World Setting: The BASAL-LIXI Study

Diego Bellido, MD, PhD[1,*], Pablo Abellán, MD, PhD[2,3], José Manuel Ruiz Palomar, MD[4], Rogelio Álvarez Sintes, MD[5], Andreu Nubiolae, MD[6], Virginia Bellido, MD, PhD[7], Gracia Romero, PhD[8], for the Basal Lixi Study investigators[†]

[1] *Department of Endocrinology and Nutrition, Ferrol Universitary Hospital Complex (CHUF), Ferrol, Spain*
[2] *Department of Endocrinology and Nutrition, Castellón General Universitary Hospital, Castellón de la Plana, Spain; Department of Medicine, Universidad Cardenal Herrera-CEU University, CEU Universities, Castellón, Spain*
[3] *Department of Endocrinology and Nutrition, Elda Hospital, Elda, Spain*
[4] *Department of Endocrinology and Nutrition, Quirón Health, Miguel Domínguez Hospitals Group, Pontevedra, Spain*
[5] *Department of Endocrinology and Nutrition, Medigroup Nubiola Center, Barcelona, Spain*
[6] *Department of Endocrinology and Nutrition, Cruces Universitary Hospital, Barakaldo, Spain*
[7] *Medical department, Sanofi Barcelona, Barcelona, Spain*
[8] *Sanofi Barcelona, Barcelona, Spain*

ARTICLE INFO

Article history:
Received 1 May 2018
Revised 27 September 2018
Accepted 28 September 2018

Key words:
basal insulin
GLP-1 RA
hypoglycemia
intensification therapy
lixisenatide
type 2 diabetes

ABSTRACT

Background: Basal insulin reduces fasting blood glucose levels, but postprandial blood glucose levels may remain higher. Traditional strategies with rapid insulin intensification can cause hypoglycemic episodes and weight gain. Glucagon-like peptide-1 receptor agonists, such as the short-acting lixisenatide, are able to control postprandial excursions, without weight gain, and with a low risk of hypoglycemic events.
Objective: Due to the limited data on the combination of lixisenatide with basal insulin (with or without oral antidiabetes drugs) in clinical practice, this study evaluated changes in parameters associated with glycemic control and anthropometric data after 24 weeks of this therapy intensification.
Methods: This was a multicenter, retrospective observational study of 129 patients with type 2 diabetes that was uncontrolled by basal insulin. Their treatment was intensified by the addition of lixisenatide at least 24 weeks before being included in the study. Data were retrospectively collected to determine changes in glycated hemoglobin (HbA1c) levels, blood glucose levels, weight, and body mass index. Adverse reactions and hypoglycemic events were also recorded.
Results: After 24 weeks of therapy intensification with lixisenatide, a significant reduction in HbA1c levels was observed (−1.1%; $P < 0.001$). An HbA1c <7% was achieved in 30.2% of patients, and 17.1% reached an HbA1c <6.5%. There was a reduction in fasting blood glucose (31.8 [60.3] mg/dL; $P < 0.001$) and postprandial blood glucose (55.0 [49] mg/dL; $P < 0.001$) levels, as well as body weight (4.0 [5.4] kg; $P < 0.001$) and body mass index (1.5 [1.9]; $P < 0.001$). The most commonly observed adverse reactions were nausea (n = 9), in line with previous studies. Hypoglycemia events were rare; only reported in 2 patients.
Conclusions: Intensification strategy based on lixisenatide added to basal insulin (with or without oral antidiabetes drugs) can be an effective treatment option in patients with uncontrolled type 2 diabetes. In this small, selected population, glycemic control was significantly improved in terms of HbA1, fasting blood glucose levels, and postprandial glucose levels, with a reduction of body weight and low risk of hypoglycemic events. (*Curr Ther Res Clin Exp.* 2018; 79:XXX–XXX)
© 2018 The Authors. Published by Elsevier Inc.
This is an open access article under the CC BY-NC-ND license.
(http://creativecommons.org/licenses/by-nc-nd/4.0/)

Introduction

The natural course of type 2 diabetes is characterized by a progressive deterioration of beta-cell function. Patients need lifelong monitoring and treatment adjustments with subsequent dose

* Address correspondence to: Diego Bellido, MD, PhD, Complejo Hospitalario Universitario de Ferrol, C/ Hospital n° 29-31 (4°-A), 15401-Ferrol (A Coruña), Spain.
E-mail addresses: diegobellido@gmail.com, diegobellido@endofer.com (D. Bellido).
† The BASAL-LIXI Study investigators are listed in the Acknowledgments.

https://doi.org/10.1016/j.curtheres.2018.09.001
0011-393X/© 2018 The Authors. Published by Elsevier Inc. This is an open access article under the CC BY-NC-ND license. (http://creativecommons.org/licenses/by-nc-nd/4.0/)

intensification to achieve glycemic control.[1] Patients with type 2 diabetes who do not respond to combination therapy with oral antihyperglycemic drugs (OADs) have traditionally received intensification therapy with basal and rapid-acting insulins. These strategies have been shown to effectively reduce glycosylated haemoglobin (HbA1c) and fasting blood glucose (FBG), but usually result in unwanted side effects such as weight gain and episodes of hypoglycemia.[2–4]

The current American Diabetes Association and the European Association for the Study of Diabetes consensus statement recommends the addition of glucagon-like peptide-1 (GLP-1) receptor agonist (RA) to basal insulin (combination injectable therapy) as an option to improve metabolic control in patients with type 2 diabetes.[5] These agents achieve a physiologic blood glucose-insulin response with low risk of hypoglycemia, by mimicking the effect of the endogenous GLP-1 hormone, enhancing insulin secretion and reducing glucagon release.[6]

Lixisenatide is a once-daily, short-acting GLP-1 RA that is associated with a delay in gastric emptying and, as a result, mediates particularly pronounced reductions in postprandial blood glucose (PPG). It is crucial that PPG, and not only FBG, is adequately controlled to achieve target HbA1c levels and potentially prevent cardiovascular risk. The use of a short-acting GLP-1 RA, such as lixisenatide, targeting predominantly PPG, in combination with a basal insulin, controlling mainly FBG, exploits the complementary effects of both of these therapies.[7]

Despite a number of clinical studies that have demonstrated effective reductions in HbA1c and blood glucose levels with lixisenatide combined with basal insulin in comparison with placebo,[8–10] or prandial insulin glulisine,[11] there are limited data available regarding real-world settings. For this reason, we performed the current retrospective observational study, involving patients with type 2 diabetes who had initiated treatment with lixisenatide in combination with basal insulin due to poor glycemic control in routine clinical practice conditions.

Materials and Methods

Study design

The BASAL-LIXI Study was a retrospective, multicenter study, carried out in 33 endocrinology and internal medicine departments across Spain between October 2014 and May 2015. The study was conducted in accordance with the Declaration of Helsinki, including all amendments, and was approved by the Independent Research Ethics Committee at Hospital Costa del Sol (Málaga, Spain). All patients provided their written informed consent before being included in the study.

Patients

Eligible patients were all adults with a documented diagnosis of type 2 diabetes who were initiated on lixisenatide treatment in combination with basal insulin (with or without OADs) due to poor glycemic control at least 24 weeks before study inclusion. Those patients with other types of diabetes (eg, type 1 or gestational), severe concomitant diseases, or who had participated in a clinical trial 1 year before the study were excluded. Each investigator selected a maximum of 8 patients who met all the selection criteria and had given their written informed consent.

Study objectives

The primary objective was to document the change in HbA1c associated with the addition of lixisenatide to basal insulin (considered as baseline) from baseline to Week 24. Secondary objectives were to determine HbA1c response rates (<7% and <6.5%), and changes in FBG level, PPG level, body weight, body mass index (BMI), and daily basal insulin dose. Further objectives were to document the frequency of hypoglycemic events (blood glucose levels < 70 mg/dL) and adverse drug reactions (ADRs) related to lixisenatide.

Table 1
Patient characteristics at baseline (N = 129).*

	Result
Demographic data	
Age, y	58.7 (10.0)
Male sex	68 (52.7)
Anthropometric data	
Body weight, kg	97.6 (16.3)
Body mass index	35.8 (5.0)
Waist perimeter,† cm	112.7 (14.6)
Time of diabetes evolution, y	10.2 (6.4)
Glycemic control parameters	
Glycated hemoglobin, %	8.7 (1.5)
Fasting plasma glucose, mg/dL	175.4 (58.5)
Postprandial glucose† mg/d	218.9 (56.2)

* Value for male sex are presented as n (%); other values are presented as mean (SD).
† Missing data for n = 21 patients.
‡Missing data for n = 9 patients.

Statistical considerations

A descriptive analysis was carried out on the study variables using measures of central tendency and dispersion for quantitative variables, and valid frequencies and percentages for qualitative variables. When an inferential analysis was required, parametric tests were used for continuous variables and nonparametric tests in the case of ordinal or categorical or nonparametric variables. For variables not fitting a normal (or parametric) distribution, the Mann-Whitney test (for unpaired data) and the Wilcoxon test (paired data) were used. Missing data were not imputed and were left as lost. Statistical analyses were performed using the Statistical Package for the Social Sciences version 17.0 software package (IBM-SPSS Inc, Armonk, NY). All hypothesis tests were 2-sided and with a significance level of 0.05.

Results

Patient population

A total of 134 patients were included in the study. Five patients were excluded due to screening failures. Therefore, the evaluable population comprised 129 patients (Table 1). Mean (SD) age was 58.7 (10) years, 52.7% were men, and most patients were obese, with a mean (SD) BMI of 35.8 (5.0). Patients had a mean (SD) diabetes duration of 10.2 (6.4) years and showed mean (SD) HbA1c levels of 8.7% (1.5%).

Effectiveness of intensification therapy with lixisenatide

Following 24 weeks of intensification therapy with lixisenatide, a significant reduction of 1.1% ($P < 0.001$) of the mean HbA1c levels was achieved (Figure 1). A significant increase in the percentage of patients achieving HbA1c ≤7.0% (9.3% vs 30.2%; $P < 0.001$) and HbA1c ≤6.5% (3.1% vs 17.1%; $P < 0.001$) were also observed. The mean (SD) FBG level decreased significantly by 31.8 (60.3) mg/dL ($P < 0.001$) (from 175.4 [58.5] to 143.5 [46.7] mg/dL; $P < 0.001$) and the PPG level by 55.0 [49] mg/dL ($P < 0.001$) (from 218.9 [56.2] to 163.9 [39.8] mg/dL; $P < 0.001$). (Table 2).

Additionally, mean (SD) body weight decreased 4.0 (5.4) kg ($P < 0.001$) and the BMI decreased with a mean (SD) difference

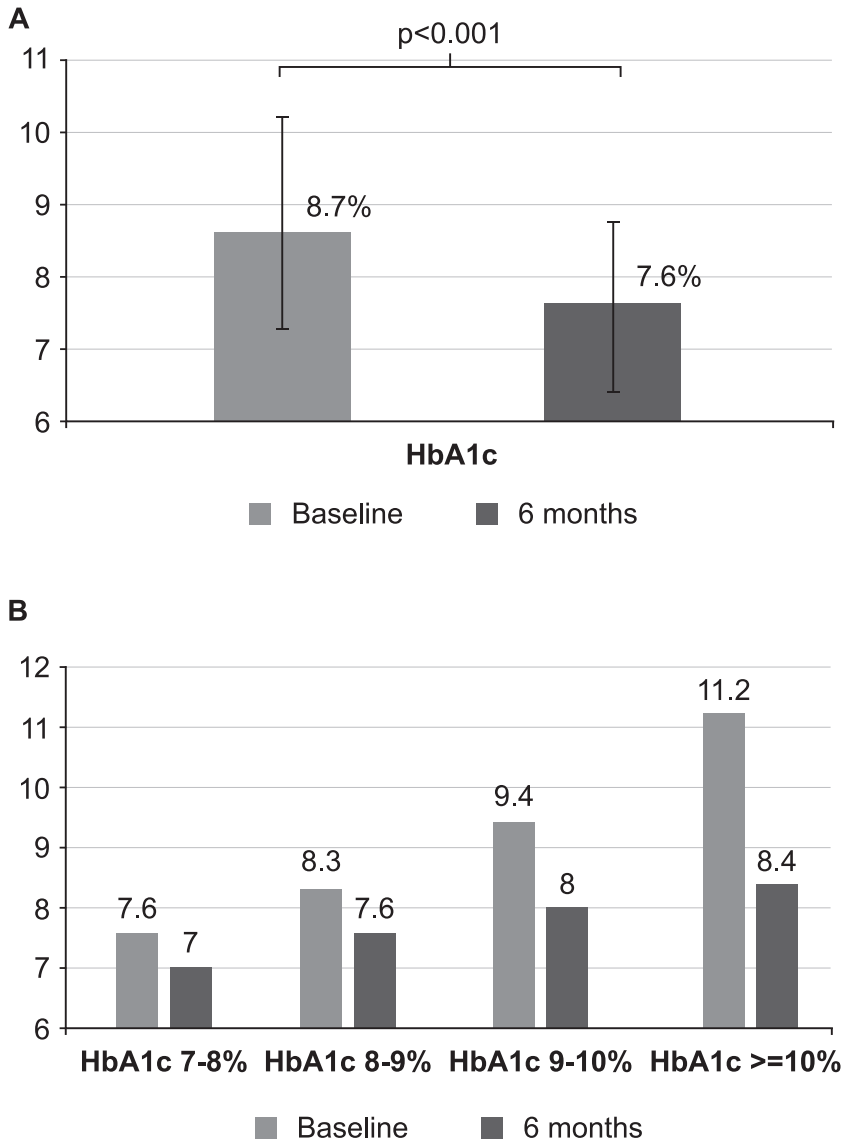

Figure 1. Evolution of glycated hemoglobin (HbA1c) levels following 24 weeks of intensification of basal insulin therapy with lixisenatide.

Table 2
Evolution of anthropometric data and glycemic control parameters from baseline to Week 24 after intensification therapy with lixisenatide.

	Baseline*	Week 24*	*P* value
Anthropometric data			
Body weight (kg)	97.6 (16.3)	93.6 (15.7)	< 0.001
Body mass index	35.8 (5.0)	34.4 (4.9)	< 0.001
Glycemic control parameters			
Glycated hemoglobin (%)	8.7 (1.5)	7.6 (1.2)	< 0.001
Fasting plasma glucose (mg/dL)	175.4 (58.5)	143.5 (46.7)	< 0.001
Postprandial glucose† (mg/d)	218.9 (56.2)	163.9 (39.8)	< 0.001

* Values for baseline and Week 24 are presented as mean (SD).
† Missing data for n = 9 and n = 7 patients at the initiation of therapy and Week 24, respectively.

of 1.5 (1.9) ($P < 0.001$) (from 35.8 [5] to 34.4 [4.9]; $P < 0.001$) (Table). A simultaneous decrease in values of HbA1c and weight was observed in 72.9% of patients at 6 months (Figure 2).

Diabetes treatment

Most patients (99.2%) initiated lixisenatide at the starting dosage of 10 µg once daily. After 14 days, 128 patients (99.2%) reached the maintenance dosage of 20 µg once daily and only 1 (0.8%) patient maintained 10 µg a day. Six months later, 127 patients (98.4%) continued with the maintenance dosage of 20 µg once daily and 2 patients (1.6%) were taking 10 µg lixisenatide once daily due to nausea.

At baseline, the vast majority of patients (83.7%) were receiving insulin glargine as the basal insulin. The percentage of patients receiving detemir was 10.9%, regular insulin 8.5%, and neutral protamine Hagedorn insulin 6.2%. From baseline to 6 months of treatment, no significant differences were found in the mean (SD) doses of glargine (30.8 [16.8] IU vs 31.9 [17.1] IU; $P = 0.348$) or detemir (44.5 [32.6] IU vs 50.8 [27.3] IU; $P = 0.449$), which represents just a slight increase in both cases. Regarding therapy with OADs, most patients were receiving biguanides (76%), followed by glinides (11.6%), and sulphonylureas (8.5%). Following 24 weeks of intensification therapy with lixisenatide, nonsignificant changes in the proportion of patients receiving these combinations were observed.

Safety

Thirteen patients (10%) reported having experienced at least 1 ADR. Nausea was the most frequently reported ADR, with 12

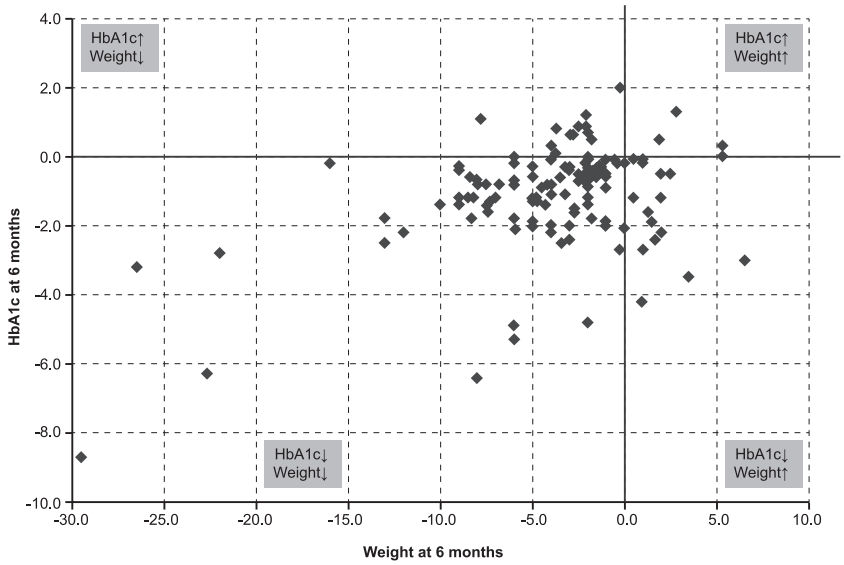

Figure 2. Glycated hemoglobin (HbA1c) and weight changes at 6 months.

Table 3
Reported adverse drug reactions during the 6-month intensification therapy with lixisenatide and basal insulin.

Reaction	Mild		Moderate		Total	
	E	n (%)	E	n (%)	E	n (%)
Hypoglycaemia	2	2 (1.6)	0	0 (0.0)	2	2 (1.6)
Nausea	4	4 (3.1)	8	8 (6.2)	12	12 (9.3)
Stomach disturbances	1	1 (0.8)	0	0 (0.0)	1	1 (0.8)
Hunger	1	1 (0.8)	0	0 (0.0)	1	1 (0.8)
Total	8	8 (6.2)	8	8 (6.2)	16	16 (12.4)

E = number of reactions.

patients (9.3%) experiencing at least 1 such event. One patient reported stomach disturbances and 1 patient reported hunger; hypoglycemia was rare, with 2 patients reporting an episode. No severe ADRs were reported during the study. Table 3 shows ADRs.

Discussion

The results of this study in this small, selected population suggest that intensification therapy with lixisenatide in combination with basal insulin (with or without OADs) when used in real-world clinical practice settings, is not only associated with an improvement in glycemic control, but also with significant reductions in FBG, PPG, and body weight at 24 weeks.

The decrease in HbA1c of 1.1% found, accompanied by achievements of optimal metabolic control (HbA1c $\leq$6.5% and $\leq$7%) and reduction of glucose levels, support a number of previous placebo-controlled clinical studies that demonstrated effective reductions in HbA1c and blood glucose levels when lixisenatide was administered once daily in combination with basal insulin.[8–10] In the GetGoal-Duo2 trial, Rosentock et al[11] reported comparable improvements of HbA1c levels (a decrease of 1.3%), as well as body weight reductions and lower incidence of hypoglycemia events in patients randomized to lixisenatide once daily added to glargine in comparison to those taking insulin glulisine once daily or 3 times daily. Similarly, the analysis of data from 5 randomized, controlled trials comparing addition of either insulin glulisine or lixisenatide to basal insulin showed that both combinations are effective in terms of HbA1c reductions, but patients being treated with lixisenatide presented lower risk of hypoglycemia and weight gain.[12] In an attempt to gain data on treatment with lixisenatide in real-life situations, a study published by Fleischmann et al[13] addressed the effectiveness of adding lixisenatide to basal insulin in patients with uncontrolled diabetes finding that following 6 months of treatment, a significant decrease in HbA1c level (0.94%; $P \leq 0.001$) was achieved along with significant reductions in glucose levels and a marked decrease in the PPG excursions during the whole day. Similarly, findings from the study conducted by Roca-Rodríguez et al[14] to evaluate the effect of lixisenatide on metabolic control parameters and body weight in obese patients with type 2 diabetes concluded that lixisenatide was an effective treatment option in this group of patients, leading to similar HbA1c and FBG levels and body weight reductions in a real-world setting.

A well-known advantage of the addition of lixisenatide to basal insulin (with or without OADs) is the potential for weight loss. Indeed, following 24 weeks of intensification therapy with lixisenatide, we observed a large change in mean body weight (–4 kg), which may be explained by the higher baseline body weight of the patients included. This value is consistent with the value recorded in the aforementioned noninterventional observational study (3.1 [4.1] kg; $P \leq 0.001$).[13] However, our value is higher than those reported in the clinical trials, with mean changes ranging from –1.3 kg ($P < 0.0001$)[8] to the modest, albeit significant, –0.89 kg ($P = 0.0012$).[9]

Type 2 diabetes is a chronic metabolic disease commonly related to obesity that can lead to serious cardiovascular complications.[15] A recent systematic analysis comparing GLP-1 RAs to other glucose-lowering agents on cardiovascular risk factors showed favorable effects on systolic and diastolic blood pressure and total cholesterol levels, as well as a small but significant increase in heart rate.[16] The Evaluation of Lixisenatide in Acute Coronary Syndrome trial[17] assessed the effect of lixisenatide on cardiovascular outcomes in patients with type 2 diabetes who had had a recent acute coronary syndrome event, showing that the addition of lixisenatide to conventional therapy did not increase the risk of major cardiovascular events. Nonetheless, further prospective studies are required to study the long-term effect of intensification therapy with lixisenatide on cardiovascular events.

Gastrointestinal side effects are the most frequently reported adverse event with GLP-1 RAs and they are related to dose and background medication.[18] We found that <10% of patients experienced gastrointestinal ADRs, nausea being the most commonly encountered event. This follows a similar pattern to that obtained in previous clinical studies,[8,9] although with lower rates. The combination of basal insulin with a GLP-1 RA has gained significant

interest these days, based on the complementary effects, the mitigating effect on body weight and hypoglycemia, and the reduction of gastrointestinal adverse effects in comparison when administered individually. The recently published results of the study led by Aroda et al[19] have shown that the delivery of a titratable fixed ratio combination of insulin glargine and lixisenatide appears to lessen the gastrointestinal intolerance typically associated with stepped titration of GLP-1 RAs while it confers advantages by simplifying and intensifying more efficiently basal insulin treatment in this group of patients.

Another benefit of the intensification therapy with lixisenatide is the low incidence of hypoglycemic events,[20] which were present in only 1.6% of patients, therefore confirming the findings obtained in controlled clinical trials. Patients with a long evolution of type 2 diabetes that have an insufficient glycemic control with previous therapies and that require insulin, will need another add-on agent such as GLP-1 RAs.[21] The advantages of a prandial/postprandial control with GLP-1 RAs instead of short-acting insulin taken during the main meals are that there is a lower risk of hypoglycemia, a body weight reduction,[22] and relief from the burden of frequent self-monitoring of blood glucose.[12,23–25]

In this study, we observed an improved glycemic control with significant reductions of postprandial excursions, weight control, and low rate of hypoglycemic events, although no patient satisfaction data were collected. A meta-analysis of the GetGoal program after 76 weeks of treatment shows that these beneficial effects in terms of glycemic control and weight reduction with a good safety profile are maintained with time[26] regardless of BMI category.[27]

There are some limitations to the study that should be considered when interpreting the results. Because this was an observational study, recording of hypoglycemic episodes and gastrointestinal side effects were self-reported by patients and collected retrospectively, leading perhaps to an underdiagnosis bias or failure to collect data. Similarly, the enthusiasm of starting a new treatment may lead patients to increase their physical activity and change their eating habits, therefore amplifying the observed effects. The absence of a control group means that the information extracted does not provide sufficient evidence to establish cause–effect relationships. Another limitation is the duration of the study—24 weeks—which is insufficient to determine clinical long-term benefits. However, the performance of this type of study is of the utmost relevance to determine the conditions derived from routine clinical practice.

Conclusions

The addition of short-acting lixisenatide to advance basal insulin therapy can be an effective treatment option in terms of glycemic control and body weight reduction with a low risk of hypoglycemia in patients with uncontrolled type 2 diabetes. These findings acquired in a real-world clinical setting support the evidence obtained from previous controlled clinical trials.

Acknowledgments

D. Bellido contributed with study design. D. Bellido, P. Abellán, J.M. Ruiz Palomar, R. Álvarez Sintes and A. Nubiola contributed with data collection. All the authors contributed with data interpretation and writing, with special dedication of V. Bellido. As sponsor of the study, sanofi contracted a CRO to conduct the study and writing the manuscript and supported the decisions of the authors to submit the manuscript for publication.

Principal investigators for the BASAL-LIXI Study:

Site	City	Principal investigator
Hospital Universitario Insular de Gran Canaria	Gran Canaria	Rosa María Sánchez Hernández
Hospital Universitario de Canarias	Tenerife	María Isabel Mascareño Pérez
Private practice	Zaragoza	Ana Isabel Ilundain González
Private practice	Zaragoza	Francisco Javier Acha Pérez
Hospital de Basurto	Bilbao	Fernando Goñi Goicoechea
Hospital de Donostia	San Sebastián	Alfredo Yoldi Arrieta
Hospital Universitario Infanta Leonor	Madrid	Cristina Sevillano Collantes
Private practice	Alcorcón (Madrid)	Juan Carlos Percovich Hualpa
Private practice	Ourense	Maria Jesús Blanco Rodríguez
Gerencia de Gestión Integrada H. Juan Canalejo	A Coruña	Alfonso Soto González
Complejo Hospitalario Universitario de Pontevedra	Pontevedra	Pablo Fernández Catalina
Private practice	Pontevedra	Rogelio Álvarez Sintes
Complejo Asistencial de Ávila	Ávila	Demetrio Sánchez Fuentes
Hospital Regional Universitario de Málaga	Málaga	Sergio Valdés Hernández
Agencia Sanitaria Costa del Sol	Marbella (Málaga)	Maria Dolores García de Lucas
Hospital Universitario Virgen de la Victoria	Málaga	Araceli Muñoz Garach
Hospital Universitario Infanta Elena	Huelva	Manuel Jesús Romero Jiménez
Hospital Quiron Marbella	Marbella (Málaga)	Jose Andrés Maldonado Muñoz
Hospital Universitari de Bellvitge	L'Hospitalet de Llobregat (Barcelona)	Jordi Caballero Corchuelo
Hospital Parc Taulí de Sabadell	Sabadell (Barcelona)	Assumpta Caixàs Pedragós
Hospital Universitari Germans Trias i Pujol	Badalona (Barcelona)	Berta Soldevila
Hospital Clínico Universitario San Carlos	Madrid	Alejandra Durán Rodríguez-Hervada
Medigrup Nubiola	Barcelona	Andreu Nubiola Calonge
Hospital Universitario de Getafe	Getafe (Madrid)	José Antonio Rosado Sierra
Hospital General Universitario de Castellón	Castellón	Pablo Abellán Galiana
Private practice	Castellón	Marián Bennasar Remolar
Private practice	Valencia	Jordi Ferri Císcar
Hospital Internacional Medimar	Alicante	José Manuel Ruiz Palomar
Private practice	Alicante	Luis López Penabad
Private practice	Madrid	Carlos Gorospe Pérez-Jauregui
Hospital Universitari Germans Trias i Pujol	Badalona (Barcelona)	Silvia Pellitero Rodríguez
Hospital de Toledo	Toledo	Esther Maqueda Villaizan
Clínica Endofer Dr. Bellido	Ferrol	Diego Bellido Guerrero

Conflict of Interest Statement

This study was sponsored by Sanofi, which also funded the medical writing and editorial support.

D. Bellido has received honoraria for consulting and/or speaking (Sanofi, NovoNordisk, Lilly, Novartis, Astra-Zeneca, Jansen, and Boehringer) and for advising and lecturing (Sanofi, NovoNordisk, Lilly, Novartis, AstraZeneca, Jansen, Boehringer, and Nestle HC Nutrition). A. Nubiola has received honoraria for consulting and/or speaking (NovoNordisk, AstraZeneca, Lilly, Sanofi, Esteve, Almirall, Janssen-Cylag, MSD, and Novartis). P. Abellán has received honoraria for consulting and/or speaking (Sanofi, NovoNordisk, Lilly, Boehringer, AstraZeneca, Janssen, Novartis, Almirall, Abbot, and Esteve) and for advising and lecturing (Sanofi, NovoNordisk, Lilly, Boehringer, AstraZeneca, Janssen, Novartis, Almirall, Abbot, and Esteve). R. A. Sintes has received honoraria for consulting and/or speaking (Almirall, Bayer Healthcare, Boehringer, Glaxo Smithkline, Menarini, Lilly, Rovi, Ordesa, Novartis, Ferrer, Recordati, AstraZeneca, Mundipharma, Tedec-Meiji Farma, Grunenthal, Pfizer, Chiesi, Sanofi, NovoNordisk, Abbott, and Jansen y Zambon). J. M. Ruiz Palomar has received honoraria for consulting and/or speaking (Sanofi). V. Bellido has received honoraria for consulting and/or speaking (Sanofi, NovoNordisk, Lilly, Astra-Zeneca, Janssen, Boehringer, MSD, Abbott, and Esteve). G. Romero is employed by Sanofi-Aventis. The authors have indicated that they have no other conflicts of interest regarding the content of this article.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.curtheres.2018.09.001.

References

1. Turner RC, Cull CA, Frighi V, Holman RR. Glycemic control with diet, sulfonylurea, metformin, or insulin in patients with type 2 diabetes mellitus: progressive requirement for multiple therapies (UKPDS 49). UK Prospective Diabetes Study (UKPDS) Group. *Jama*. 1999;281:2005–2012.
2. Goldenberg R. Insulin plus incretin agent combination therapy in type 2 diabetes: a systematic review. *Current medical research and opinion*. 2014;30:431–445.
3. Lane W, Weinrib S, Rappaport J, Hale C. The effect of addition of liraglutide to high-dose intensive insulin therapy: a randomized prospective trial. *Diabetes, obesity & metabolism*. 2014;16:827–832.
4. Russell-Jones D, Khan R. Insulin-associated weight gain in diabetes–causes, effects and coping strategies. *Diabetes, obesity & metabolism*. 2007;9:799–812.
5. Inzucchi SE, Bergenstal RM, Buse JB, et al. Management of hyperglycaemia in type 2 diabetes, 2015: a patient-centred approach. Update to a position statement of the American Diabetes Association and the European Association for the Study of Diabetes. *Diabetologia*. 2015;58:429–442.
6. Trujillo JM, Nuffer W. GLP-1 receptor agonists for type 2 diabetes mellitus: recent developments and emerging agents. *Pharmacotherapy*. 2014;34:1174–1186.
7. Hanefeld M, Raccah D, Monnier L. Individualized, patient-centered use of lixisenatide for the treatment of type 2 diabetes mellitus. *Expert Opinion on Drug Metabolism & Toxicology*. 2017. doi:10.1080/17425255.2017.1251579.
8. Riddle MC, Aronson R, Home P, et al. Adding once-daily lixisenatide for type 2 diabetes inadequately controlled by established basal insulin: a 24-week, randomized, placebo-controlled comparison (GetGoal-L). *Diabetes care*. 2013;36:2489–2496.
9. Riddle MC, Forst T, Aronson R, et al. Adding once-daily lixisenatide for type 2 diabetes inadequately controlled with newly initiated and continuously titrated basal insulin glargine: a 24-week, randomized, placebo-controlled study (GetGoal-Duo 1). *Diabetes care*. 2013;36:2497–2503.
10. Seino Y, Min KW, Niemoeller E, Takami A. Randomized, double-blind, placebo-controlled trial of the once-daily GLP-1 receptor agonist lixisenatide in Asian patients with type 2 diabetes insufficiently controlled on basal insulin with or without a sulfonylurea (GetGoal-L-Asia). *Diabetes, obesity & metabolism*. 2012;14:910–917.
11. Rosenstock J, Guerci B, Hanefeld M, et al. Prandial Options to Advance Basal Insulin Glargine Therapy: Testing Lixisenatide Plus Basal Insulin Versus Insulin Glulisine Either as Basal-Plus or Basal-Bolus in Type 2 Diabetes: The GetGoal Duo-2 Trial. *Diabetes care*. 2016;39:1318–1328.
12. Raccah D, Lin J, Wang E, et al. Once-daily prandial lixisenatide versus once–daily rapid-acting insulin in patients with type 2 diabetes mellitus insufficiently controlled with basal insulin: analysis of data from five randomized, controlled trials. *Journal of diabetes and its complications*. 2014;28:40–44.
13. Fleischmann H, Goke R, Bramlage P. Addition of once daily prandial lixisenatide to basal insulin therapy in patients with type-2 diabetes results in a reduction of HbA1c as an effect of postprandial glucose lowering. *Diabetes & metabolic syndrome*. 2016.
14. Roca-Rodríguez MM, Muros de Fuentes MT, Piédrola-Maroto G, et al. Lixisenatida en pacientes con diabetes tipo 2 y obesidad: más allá del control glucémico. *Aten Primaria*. 2017;49:294–299.
15. Padwal RS, Sharma AM. Prevention of cardiovascular disease: obesity, diabetes and the metabolic syndrome. *Can J Cardiol*. 2010;26:18C–20C.
16. Levin PA, Nguyen H, Wittbrodt ET, Kim SC. Glucagon-like peptide-1 receptor agonists: a systematic review of comparative effectiveness research. *Diabetes, metabolic syndrome and obesity: targets and therapy*. 2017;10:123–139.
17. Pfeffer MA, Claggett B, Diaz R, et al. Lixisenatide in Patients with Type 2 Diabetes and Acute Coronary Syndrome. *N Engl J Med*. 2015;373:2247–2257.
18. Bettge K, Kahle M, Abd El Aziz MS, Meier JJ, Nauck MA. Occurrence of nausea, vomiting and diarrhoea reported as adverse events in clinical trials studying glucagon-like peptide-1 receptor agonists: A systematic analysis of published clinical trials. *Diabetes, obesity & metabolism*. 2017;19:336–347.
19. Aroda VR, Rosenstock J, Wysham C, et al. Efficacy and Safety of LixiLan, a Titratable Fixed-Ratio Combination of Insulin Glargine Plus Lixisenatide in Type 2 Diabetes Inadequately Controlled on Basal Insulin and Metformin: The LixiLan-L Randomized Trial. *Diabetes care*. 2016;39:1972–1980.
20. Liu SC, Tu YK, Chien MN, Chien KL. Effect of antidiabetic agents added to metformin on glycaemic control, hypoglycaemia and weight change in patients with type 2 diabetes: a network meta-analysis. *Diabetes, obesity & metabolism*. 2012;14:810–820.
21. Forst T. Lixisenatide as add-on to insulin glargine for the treatment of type 2 diabetes mellitus. *Expert opinion on pharmacotherapy*. 2016;17:1703–1708.
22. Scholz GH, Fleischmann H. Basal insulin combined incretin mimetic therapy with glucagon-like protein 1 receptor agonists as an upcoming option in the treatment of type 2 diabetes: a practical guide to decision making. *Therapeutic advances in endocrinology and metabolism*. 2014;5:95–123.
23. Darmon P, Raccah D. Options for intensification of basal insulin in type 2 diabetes: Premeal insulin or short-acting GLP-1 receptor agonists? *Diabetes & metabolism*. 2015;41:6S21–26S27.
24. Hirsch IB, Buse JB, Leahy J, et al. Options for prandial glucose management in type 2 diabetes patients using basal insulin: addition of a short-acting GLP-1 analogue versus progression to basal-bolus therapy. *Diabetes, obesity & metabolism*. 2014;16:206–214.
25. Porcellati F, Lucidi P, Bolli GB, Fanelli CG. GLP-1 RAs as compared to prandial insulin after failure of basal insulin in type 2 diabetes: lessons from the 4B and Get-Goal DUO 2 trials. *Diabetes & metabolism*. 2015;41:6S16–16S20.
26. Broglio F, Mannucci E, Napoli R, et al. Beneficial effect of lixisenatide after 76 weeks of treatment in patients with type 2 diabetes mellitus: A meta-analysis from the GetGoal programme. *Diabetes, obesity & metabolism*. 2017;19:248–256.
27. Eto K, Naito Y, Seino Y. Evaluation of the efficacy and safety of lixisenatide add-on treatment to basal insulin therapy among T2DM patients with different body mass indices from GetGoal trials. *Diabetology & metabolic syndrome*. 2015;7:106.