Lixisenatide reduces glycemic variability in insulin-treated patients with type 2 diabetes

Short running title: Reduced glycemic variability in type 2 diabetics treated with lixisenatide.

Guillermo Umpierrez MD[1], David O'Neal MD[2], Andres DiGenio MD, PhD[3], Ronald Goldenberg MD[4], Eric Hernandez-Triana MD[5], Jay Lin PhD[6], Cheol-Young Park MD,PhD[7], Eric Renard MD, PhD[8–10] and, Boris Kovatchev PhD[11]

[1]Emory University of Medicine, Atlanta, GA, USA

[2] University of Melbourne Department of Medicine, St Vincent's Hospital, Melbourne, Australia

[3]AKCEA Therapeutics, Cambridge, MA, USA

[4]LMC Diabetes and Endocrinology, Thornhill, ON, Canada

[5]Endocare Research Institute, Universidad del Rosario, Bogota, Colombia

[6]Novosys Health, Green Brook, NJ, USA

[7]Division of Endocrinology and Metabolism, Department of Internal Medicine, Kangbuk Samsung Hospital, Sungkyunkwan University School of Medicine, Seoul, South Korea

[8]Department of Endocrinology, Diabetes, Nutrition, Montpellier University Hospital, Montpellier, France

[9]INSERM Clinical Investigation Centre 1411, Montpellier, France

[10]Institute of Functional Genomics, CNRS UMR-5203, INSERM U1191, University of Montpellier, Montpellier, France

[11]University of Virginia Health System, Center for Diabetes Technology. Charlottesville, VA, USA

Corresponding author:

G. E. Umpierrez, Emory University of Medicine, Atlanta, GA, USA (geumpie@emory.edu).

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Abstract

Chronic hyperglycemia and glucose variability are associated with the development of chronic diabetes-related complications. We conducted a pooled analysis of patient-level data from three 24-week, randomized, phase 3 clinical trials to evaluate the impact of lixisenatide (LIXI) on glycemic variability (GV) vs. placebo as add-on to basal insulin. The main outcome GV measures were standard deviation (SD), mean amplitude of glycemic excursions (MAGE), mean absolute glucose (MAG), area under the curve-fasting glucose (AUC-F), and high and low blood glucose indices (HBGI/LBGI). The change in GV metrics over 24 weeks, and relationships between baseline GV, patient characteristics, and outcomes were assessed. Data were pooled from 1198 patients (665 LIXI, 533 placebo). SD, MAG, MAGE, HBGI and AUC-F significantly decreased with LIXI vs. placebo while LBGI was unchanged. Higher baseline GV measures correlated with older age, longer T2D duration, lower body mass index, higher baseline A1C, greater reduction in postprandial glucose (PPG), and higher rates of symptomatic hypoglycemia. These data demonstrate that LIXI added to basal insulin significantly reduced GV and PPG excursions vs. placebo, without increasing the risk of hypoglycemia (LBGI).

KEYWORDS

lixisenatide, glycemic variability, insulin, type 2 diabetes

1 Introduction

Management of dysglycemia in type 2 diabetes (T2D) has two major goals: correction of chronic hyperglycemia and reduction of glucose variability, both of which are associated with the development of diabetes-related chronic complications.[1] Glycemic control is usually assessed using glycated hemoglobin (A1C) levels. This measure, however, only reflects the average blood glucose levels (fasting, pre-meal, and postprandial) over the 1–3 months prior to testing, and gives little indication of daily fluctuations in blood glucose.[2] Patients with similar A1C values can have markedly different daily glucose profiles, with differences in the number and magnitude of glycemic excursions; even patients with optimal A1C levels can have significant variations in blood glucose levels and postprandial hyperglycemia.[3] Glycemic variability (GV) is the term generally used to define intra-day or day-to-day variability in blood glucose levels and includes both periods of hyper- and hypoglycemia.[1] Studies suggest that it is GV, particularly with excursions into the hyperglycemic range, rather than chronic sustained hyperglycemia, that has the greater role in promoting these complications.[1] Risk-based GV measures have also been associated with an increase in the frequency and severity of hypoglycemia.[2,4] Given these findings, GV is an emerging consideration in the management of patients with T2D.

Glucagon-like peptide-1 receptor agonists (GLP-1 RAs) complement the effects of basal insulin by potentiating endogenous insulin responses to hyperglycemic excursions, suppressing elevated glucagon secretion, promoting satiety, and (for some agents) slowing gastric emptying, therefore blunting postprandial hyperglycemia.[5] GLP-1 RA therapy has been shown to improve A1C, with a low incidence of hypoglycemia,[6] and decrease postprandial glucose (PPG) excursions.[7] Although this profile suggests that GLP-1 RAs will decrease GV, there are currently few studies assessing the direct impact of GLP-1 RAs on GV in patients with T2D.

Lixisenatide (LIXI) is a once-daily short-acting GLP-1 RA that has demonstrated improvement in both A1C and postprandial hyperglycemia when used in combination with

basal insulin, with or without oral antidiabetic drugs (OADs).[8-10] The objective of this pooled analysis of patient-level data from three phase 3 clinical trials was to evaluate the impact of LIXI on GV vs. placebo as add-on therapy to basal insulin in patients with T2D.

2 Methods

2.1 Study design and patients

Analysis was conducted using pooled patient-level data from three 24-week, randomized, placebo-controlled, phase 3, multicenter clinical trials: GetGoal-L (NCT00715624)[8], GetGoal-Duo1 (NCT00975286)[9], and GetGoal-L-Asia (NCT00866658)[10], the full details of which have been published elsewhere.[8-10] Each trial evaluated the efficacy and safety of adding LIXI (taken before breakfast) or placebo to basal insulin or basal insulin together with OADs among patients with T2D, baseline A1C 7.0%-10.0% and duration of diabetes ≥ 1 year. Patient baseline demographics and clinical characteristics across studies are shown in table S1.

Patients included in the pooled analysis were the modified intent-to-treat (mITT) population, which included adult patients with baseline A1C 7.0%-10.0% and duration of diabetes ≥ 1 year who received at least one dose of double-blind study drug from the three trials and had both baseline and endpoint A1C measurements.

2.2 Study measures

GV[2,4] was assessed from 7-point, self-monitored, plasma-referenced glucose (SMPG) profiles using global measures including; standard deviation (SD), mean amplitude of glycemic excursions (MAGE), mean absolute glucose (MAG) change per unit time, area under the curve-fasting glucose (AUC-F), risk-based high and low blood glucose indices (HBGI and LGBI) as measures of the extent of hyper- and hypoglycemia, and average daily risk range (ADRR). Methods used for calculating these metrics are shown in table S2.

Efficacy was measured using the change in GV parameters for the LIXI vs. placebo cohorts over the 24-week study period.

Endpoints included the percentage of patients achieving A1C < 7.0% and composite endpoints; A1C < 7.0% without symptomatic hypoglycemia, A1C < 7.0% without severe hypoglycemia, A1C < 7.0% without weight gain (defined as change in weight [endpoint – baseline weight] ≤ 0), A1C < 7.0% without weight gain or symptomatic hypoglycemia, and A1C < 7.0% without weight gain or severe hypoglycemia.

Symptomatic hypoglycemia was defined as an event with clinical symptoms that were considered to result from a hypoglycemic episode with an accompanying blood glucose of < 60 mg/dl (3.3 mmol/l) or associated with prompt recovery after oral carbohydrate administration if no blood glucose value was available. Symptoms with an associated blood glucose ≥ 60 mg/dl (3.3 mmol/l) were not reported as hypoglycemia. Severe symptomatic hypoglycemia was defined as a hypoglycemic event in which the patient required assistance from another individual due to neurological impairment and either had a blood glucose level of < 36 mg/dl (2.0 mmol/l) or the patient recovered quickly after oral carbohydrate, intravenous glucose, or glucagon administration.

2.3 Statistical analyses

Clinical characteristics and patient demographics were reported using descriptive statistics. Continuous variables were analyzed using analysis of variance, and categorical variables were analyzed using Chi-squared tests. Paired t-tests were used for comparison of baseline and endpoint measurements. Partial correlations, accounting for treatment group assignment, were used to test correlations between baseline GV measurements, patient characteristics, and study outcomes. All descriptive statistical analyses were carried out using SAS version 9.2.

3 Results

The pooled dataset (N = 1198) included 665 patients from LIXI treatment arms and 533 patients from placebo arms. Patient demographics and clinical characteristics at baseline are shown in table S3.

There were no significant differences at baseline between LIXI and placebo in measurements of GV except for AUC-F, which was lower in the placebo group (mean 750.8 vs. 647.8 mg/dl*h, respectively; p = .036) (Table 1). GV was significantly reduced from baseline to week 24 in the LIXI group compared with the placebo group, irrespective of the measure used. This reduction in GV was primarily associated with a significant reduction in HBGI in the LIXI group; GV fell from an HBGI of 10.63 (representing a high risk for hyperglycemia) to 6.99 (representing a moderate risk for hyperglycemia).[4] LBGI was unchanged from baseline to week 24 in both groups (0.41 and 0.44 at baseline and week 24, respectively, in the LIXI group; 0.38 and 0.38 at baseline and week 24, respectively, in the placebo group), representing an overall low risk for hypoglycemia.[4]

Higher baseline GV measures were found to correlate with older age, a longer T2D duration, lower body mass index (BMI), and higher baseline PPG and A1C (Table 2A). Higher baseline GV measures were also correlated with higher week 24 PPG and week 24 A1C levels, a greater PPG reduction and higher rates of symptomatic hypoglycemia during follow-up (Table 2B).

Patients in the LIXI group also experienced a greater mean (SD) change in A1C from baseline to week 24 compared with the placebo group [−0.68% (1.03) vs. −0.19% (0.88), respectively); p < .0001] while significantly more patients in the LIXI group achieved the target A1C of < 7.0% at endpoint compared with the placebo group. Furthermore, more patients in the LIXI group achieved the composite endpoints related to target A1C, hypoglycemia and weight gain (Table S4).

The overall mean change (SD) in the 2-hour post-breakfast SMPG value from baseline to week 24 was significantly greater with LIXI than with placebo; mean change (SD) was

−51.61 (81.42) mg/dl in the LIXI group vs. −1.17 (68.13) mg/dl in the placebo group ($p < .0001$) (Figure S1). The LIXI group showed a significantly greater decrease in SMPG levels from baseline to endpoint at 2 hours post-breakfast, lunch, and dinner, as well as before lunch and bedtime compared with the placebo group (Table S5).

4 Conclusions

This analysis revealed that LIXI added to basal insulin with or without OADs significantly reduced GV and PPG excursions compared with placebo. In addition, more patients who received LIXI achieved target A1C as well as composite safety and efficacy endpoints compared with placebo, including target A1C without symptomatic or severe hypoglycemia or weight gain.

One of the strengths of this analysis was the use of seven different measures of GV, all of which have been shown to provide clinical information relevant to treatment intensification.[4] While both fasting plasma glucose (FPG) and PPG levels contribute to glycemic control, their relative influence on glycemic exposure as estimated by A1C varies; PPG levels may be a more important contributor to A1C levels than FPG, particularly in patients with better glycemic control.[11] In the patient population described in this study, LIXI had a significant impact on PPG excursions at all three meals, as well as beneficial effects on both GV and A1C. These findings are clinically important as both GV and PPG have been reported as independent risk factors for cardiovascular disease that are predictive of cardiovascular events and all-cause mortality in patients with T2D.[12] In addition, GV has been associated with additional complications, such as diabetic peripheral neuropathy and stroke.[13,14]

This reanalysis suggests that therapy with LIXI in patients with T2D managed with basal insulin offers an effective strategy that reduces GV as well as A1C. This could potentially be beneficial in the management of patients' with T2D and builds on a pre-existing body of knowledge.[15] In addition, although patients with T2D are a highly heterogeneous population,

the higher incidence of GV observed in older patients, those with a longer duration of diabetes, and those with a lower body weight suggests that treatment with an agent which can reduce GV might be of benefit in some of these high-risk patients.

Overall a significant reduction in GV and PPG excursions compared with placebo was observed when LIXI was added to basal insulin, with or without OADs, in patients with T2D. The consistent results from this analysis and other published studies indicate that LIXI is a suitable antihyperglycemic agent for patients with T2D who have increased GV and those at risk of postprandial hyperglycemia; however, there is a need for further prospective studies to address the clinical outcomes of improved GV.

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Conflict of Interest

A. D was employed at Sanofi US when the study was conducted. R. G has received research support from Abbott, AstraZeneca, Boehringer Ingelheim, Bristol-Myers Squibb, Eli Lilly, GlaxoSmithKline, Janssen, Medtronic, Merck, Novartis, Novo Nordisk, Roche, Sanofi, and Takeda; served on advisory panels for AstraZeneca, Boehringer Ingelheim, Bristol-Myers Squibb, Eli Lilly, Janssen, Merck, Novo Nordisk, Roche, Sanofi, and Takeda; participated in speaker bureaus for Abbott, AstraZeneca, Boehringer Ingelheim, Bristol-Myers Squibb, Eli Lilly, Merck, Novo Nordisk, Sanofi, and Servier; and is consultant for AstraZeneca, Boehringer Ingelheim, Bristol-Myers Squibb, Eli Lilly, Janssen, Novo Nordisk, and Takeda. E. H-T has received research support from, Boehringer Ingelheim, Janssen, Novartis, Roche, and Sanofi; served on advisory panels for AstraZeneca, Boehringer Ingelheim, Eli Lilly, Merck, and Sanofi; and participated in speaker bureaus for AstraZeneca,

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J. L is an employee of Novosys Health, which received research funding from Sanofi US, Inc. D. O has received research support, travel grants, and honoraria from Sanofi, Medtronic, Novo Nordisk, Roche, Bristol-Myers Squibb, and Merck.C-Y. P has no conflicts of interest to disclose. E. R is a consultant/advisor for A. Menarini Diagnostics, Abbott, Cellnovo, Dexcom, Eli-Lilly, Johnson & Johnson (Animas, LifeScan), Medtronic, Novo Nordisk, Roche Diagnostics, and Sanofi, and has received research grant/material support from Abbott, Dexcom, Insulet, and Roche Diagnostics. G. E. U has served on advisory board for Sanofi and received grant support (to Emory University) from Sanofi, Merck, Boehringer Ingelheim, Astra Zeneca, and Novo Nordisk. B. K. reports grants from Sanofi and consulting fees from Sanofi outside of the submitted work; research support from Dexcom, Inc., Roche Diagnostics and Tandem Diabetes Care; patent royalties from Johnson & Johnson and Sanofi; and is a board member and shareholder in TypeZero Technologies.

All authors confirm they meet the International Committee of Medical Journal Editors (ICJME) uniform requirements for authorship and that they have participated in reviewing and interpreting the data, providing comments and revisions of the manuscript. All authors approved the final manuscript and the decision to submit it for publication.

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TABLE 1 Summary of GV at baseline, week 24, and the absolute change from baseline to week 24 in GV by measurement used

GV measure	LIXI			Placebo			p value*
	Baseline	Week 24	Change	Baseline	Week 24	Change	
SD, mg/dl	n = 630 51.41 (24.44)	n = 657 43.18 (22.76)	n = 630 −8.28 (25.17)	n = 500 52.01 (24.07)	n = 525 48.69 (22.31)	n = 500 −3.89 (23.61)	.0028
MAGE, mg/dl	n = 622 92.57 (46.27)	n = 649 76.62 (42.95)	n = 616 −16.02 (50.97)	n = 493 94.78 (45.98)	n = 522 88.62 (42.20)	n = 492 −7.02 (47.55)	.0027
MAG, mg/dl	n = 545 24.50 (13.26)	n = 635 17.73 (9.39)	n = 545 −6.80 (12.96)	n = 428 24.57 (13.10)	n = 498 23.43 (11.78)	n = 428 −1.48 (12.51)	< .0001
AUC-F, mg/dl*h	n = 480 750.8 (699.0)	n = 591 480.7 (580.0)	n = 461 −298.5 (715.9)	n = 370 647.8 (725.4)	n = 466 713.5 (650.9)	n = 355 −15.5 (714.1)	< .0001
HBGI	n = 631 10.63 (8.64)	n = 657 6.99 (6.59)	n = 631 −3.65 (8.23)	n = 500 10.01 (8.39)	n = 525 9.37 (8.05)	n = 500 −0.88 (7.16)	< .0001
LBGI	n = 631 0.41 (0.93)	n = 657 0.44 (0.77)	n = 631 0.04 (1.13)	n = 500 0.38 (0.81)	n = 525 0.38 (0.99)	n = 500 −0.03 (1.03)	.2773
ADRR	n = 665 24.2 (16.32)	n = 665 19.4 (13.61)	n = 665 −4.74 (16.16)	n = 533 23.4 (16.10)	n = 533 23.39 (15.76)	n = 533 −0.06 (17.19)	< .0001

ADRR, average daily risk range; AUC-F, area under the curve-fasting glucose; GV, glycemic variability; HBGI, high blood glucose index; LIXI, lixisenatide; LBGI, low blood glucose index; MAG, mean absolute glucose; MAGE, mean amplitude of glycemic excursions; SD, standard deviation.

*Comparison LIXI change vs. placebo change.

Data are mean (SD).

TABLE 2 Relationship between baseline GV and baseline patient characteristics and outcomes

	A: Relationship between baseline GV and baseline patient demographics and clinical characteristics						B: Relationship between baseline GV and clinical outcomes						
	Age	**Baseline BMI**	**T2D duration**	**Baseline FBG**	**Baseline PPG**	**Baseline A1C**	**Endpoint FBG**	**FBG change from baseline**	**Endpoint PPG**	**PPG change from baseline**	**Endpoint A1C**	**A1C change from baseline**	**Number of symptomatic hypoglycemic events[§]/year**
Baseline SD	0.1167*	−0.2876*	0.2254*	0.0043	0.5180*	0.3003*	−0.0217	−0.0236	0.1769*	−0.3169*	0.1671*	−0.0594	0.1033*
Baseline MAGE	0.1018*	−0.2749*	0.1889*	0.0063	0.5416*	0.2765*	−0.0206	−0.0242	0.1557*	−0.3547*	0.1315*	−0.0803	0.0836
Baseline MAG	0.0852	−0.3145*	0.1838*	−0.0006	0.5807*	0.2464*	0.0089	0.0087	0.2031*	−0.3611*	0.1486*	−0.0332	0.0719
Baseline AUC-F	0.1503*	−0.1609*	0.0928	−0.1137*	0.3522*	0.1827*	−0.0622	0.0378	0.1098	−0.2330*	0.1284*	−0.0036	0.0430
Baseline HBGI	0.0492	−0.1959*	0.1476*	0.3486*	0.7667*	0.5652*	0.2114*	−0.0966	0.2834*	−0.4556*	0.3744*	−0.0413	−0.0080
ADRR	0.0417	−0.2215*	0.1586*	0.1685*	0.6656*	0.3792*	0.0803[†]	−0.0671[†]	0.1853*	−0.4127*	0.2389*	−0.0451	0.0970*
LBGI	0.0400	−0.0764[†]	0.0698[†]	−0.2725*	−0.2042*	−0.1907*	0.1411*	0.0979[†]	−0.0865[†]	0.1137*	−0.1108[†]	0.0323	0.2151*

A1C, glycated hemoglobin; ADRR, average daily risk range; AUC-F, area under the curve-fasting glucose; BMI, body mass index; FPG, fasting plasma glucose; GV, glycemic variability; HBGI, high blood glucose index; LBGI, low blood glucose index; MAG, mean absolute glucose;

MAGE, mean amplitude of glycemic excursions; OAD, oral antidiabetic drug; PPG, postprandial glucose; SD, standard deviation; T2D, type 2 diabetes.

Data presented are partial correlation coefficients accounting for treatment group assignment.

*p < .001.

†p < .05.

§ Defined as an event with clinical symptoms considered to result from a hypoglycemic episode with an accompanying blood glucose of < 60 mg/dl (3.3 mmol/l) or associated with prompt recovery after oral carbohydrate administration if no blood glucose value available.

Author/s:
Umpierrez, GE; O'Neal, D; DiGenio, A; Goldenberg, R; Hernandez-Triana, E; Lin, J; Park, C-Y; Renard, E; Kovatchev, B

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